Tailored reperfusion therapy of patients with evolving myocardial infarction

- Models to guide clinical decision making -

Reperfusie therapie op maat in patienten met een zich ontwikkelend myocard infarct

- Beslismodellen ten behoeve van klinische besluitvorming -

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... van vele boeken te maken is geen einde ...
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voor Margrit
en mijn ouders

INTRODUCTION

Chapter 1

USEFULNESS OF DECISION MODELS TO GUIDE REPERFUSION THERAPY IN PATIENTS WITH EVOLVING MYOCARDIAL INFARCTION

Myocardial infarction is one of the leading causes of death among adults in the Western World. In The Netherlands, yearly approximately 20,000 men and 10,000 women are admitted with this disease, which is responsible for circa 12% of annual mortality (figure).[1,2] Myocardial infarction is an acute coronary syndrome, which may happen during the chronic process of coronary atherosclerosis.[3,4] At a certain stage in this process fissuring and disruption of the growing atherosclerotic plaque may occur, initiating intraluminal thrombus formation. Such thrombi may cause total occlusion of the coronary artery, so that oxygen delivery to the myocardium is blocked. If this situation persists for more than 30 minutes, irreversible damage to the myocardium, i.e. myocardial infarction, will occur.[5] Prolonged duration of coronary occlusion results in a progressive increase of the infarcted area, until the whole area at risk becomes necrotic. Generally, after approximately six hours of continuous occlusion the infarct has reached its full extension.[5]

Although the notion that myocardial infarction is caused by acute coronary thrombosis was already advanced in the beginning of this century,[6] the correctness of this idea was demonstrated only in the early 1980s, by studies of DeWood et al.[7] Since that time, treatment strategies have been introduced that aimed at rapid and lasting restoration of the coronary blood circulation. The overall benefits of these 'reperfusion' strategies have been established unequivocally.[8] Timely reperfusion therapy interrupts the process of evolving myocardial necrosis, which results in salvage of viable myocardium, preservation of left ventricular function and, consequently, improved survival. Nowadays, physicians can choose among different thrombolytic drug regimens based on streptokinase, reteplase and alteplase. In some hospitals also direct angioplasty is an alternative.

The beneficial effect of reperfusion therapy depends on patient's demographic characteristics, the location and extend of the jeopardised myocardium, and the duration of the coronary occlusion.[9] Furthermore, the different treatment options have their intrinsic properties, effects and costs. Key questions in clinical practice are therefore, how widely thrombolytic therapy should 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. Since the first six hours of symptom onset are of vital importance in treatment of myocardial infarction patients,[10] time to weight potential benefits, risks and

costs in individual patients is fairly limited. In this situation a decision model which integrates all relevant aspects might be very useful.

The present thesis reflects the development of such clinical decision models, with the foundation laid in the 'Premises' and the upshot given in the part on 'Practical decision models'. Chapter 2 presents an overview of the most relevant randomised trials which studied the effects of various reperfusion strategies in myocardial infarction. Chapter 3 describes the relationship between treatment delay and -benefit. Chapter 4 evaluates to which degree consensus exists about factors that determine efficacy and applicability of reperfusion therapy in clinical practice among several groups of investigators. In chapters 5 and 6 the ingredients as described in the 'Premises' are moulded into reperfusion treatment models. Sets of tables are presented which summarise treatment effects in individual patients. These can be implemented in clinical care for rapid and consistent decision making. Distribution of available resources with help of these tables is evaluated in an actual cohort of

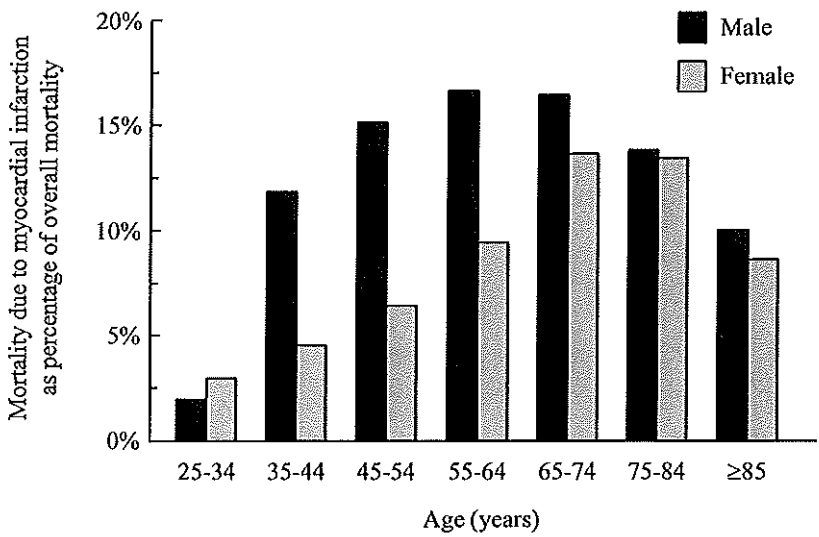

Figure: **Mortality due to myocardial infarction as a percentage of overall mortality, according to age, in the Dutch population of 1993**

Dutch myocardial infarction patients. Sensitivity analyses are performed. In chapter 7 the importance of very early, pre-hospital reperfusion therapy is recognised. Benefits and risks of several pre-hospital thrombolysis strategies are studied. A general discussion of the results is presented in chapter 8, in which also practical and ethical consequences of medicine according to protocol are addressed.

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PREMISES

Chapter 2

AN OVERVIEW OF THE CLINICAL EFFICACY OF CURRENTLY AVAILABLE REPERFUSION TREATMENT OPTIONS IN MYOCARDIAL INFARCTION

Boersma E, Simoons ML
Evidence-based cardiology. Reperfusion strategies in acute myocardial infarction
Eur Heart J 1997; 18: 1703-11

INTRODUCTION

The understanding that a myocardial infarction is usually caused by an acute thrombotic obstruction of a coronary artery has led to a major change in the approach of this disease.[1] Since the early 1980s, pharmacological and mechanical interventions have been introduced that aimed at rapid and sustained restoration of blood flow in the occluded artery. This approach has been successful, and considerable progress has been achieved since that time. In The Netherlands, in 1980, in-hospital mortality after myocardial infarction was approximately 15.6% (24.3%) in male (female) patients, whereas nowadays this figure is markedly reduced to about 11.3% (18.5%).[2]

The effects of various treatment strategies have been evaluated in a number of randomised trials. Specially attention was paid to the properties of thrombolytic, antiplatelet and anticoagulant therapy, alone and in combination, and more recently direct angioplasty was studied. The present paper presents a survey of the most relevant results observed in these trials, and reviews whether and to what extent evidence for benefit can be claimed for different reperfusion strategies. An overview of other review articles is presented in table 1.

THROMBOLYTIC THERAPY

Treatment within six hours of symptom onset

Restoration of blood flow to the jeopardised myocardium within 6 h of symptom onset preserves viable myocardial tissue, which protects left ventricular function, and consequently reduces mortality (we appreciate, that this reasoning simplifies complex biochemical processes, and disregards the paradoxical fact that early reperfusion might also cause some cellular injury, even though the overall effects are clearly beneficial).[3] By intracoronary infusion of streptokinase recanalisation can be achieved in approximately 80% of patients.[4,5] At the same time the enzymatic infarct size is reduced by 20%-35% compared with control therapy, and left ventricular function is preserved.[6,7] Mortality after intracoronary streptokinase was evaluated in a couple of relatively small randomised controlled clinical trials. Pooled analysis of the results of these trials (including approximately 1,000 patients) indicate that use of intracoronary streptokinase results in a non-significant 15% relative

Theme of the overview	Keywords	Author	Year of publication
Mortality, reinfarction and adverse events after intracoronary and intravenous thrombolysis	thrombolytic therapy, intracoronary infusion, intravenous infusion	Yusuf et al.[8]	1985
Development of routine medical management	thrombolytic therapy, aspirin, heparin, beta-blockers, calcium blockers, nitrates	Yusuf et al.[57]	1990
All randomised trials between fibrinolytic and control therapy which include at least 1,000 patients	thrombolytic therapy, overall evidence, subgroup analysis	Fibrinolytic Therapy Trialists' Collaborative Group[20]	1994
Prolonged antiplatelet therapy (in myocardial infarction patients among others)	antiplatelet therapy, vascular death, reinfarction, stroke	Antiplatelet Trialists' Collaboration[41]	1994
Effects of anticoagulant therapy in coherence with antiplatelet treatment	heparin, aspirin, reinfarction, stroke, pulmonary embolism	Collins et al.[39]	1996
Effects of thrombolytic treatment delay on mortality in randomised trials which include at least 100 patients	thrombolytic therapy, time to treatment	Boersma et al.[21]	1996
Randomised clinical trials of aspirin, heparin and fibrinolytic therapy	thrombolytic therapy, aspirin, heparin	Collins et al.[36]	1997
Comparison of thrombolytic therapy vs. primary coronary angioplasty	thrombolytic therapy, angioplasty	Weaver et al.[49]	1997

Table 1: **Review-articles which address mortality based on randomised trials on reperfusion therapy in acute myocardial infarction**

Comparison	Study	N	Antiplatelet therapy	Anticoagulant therapy	Time to therapy	Follow-up	Year of publication
IV-SK vs. standard therapy	GISSI-1[10]	11,806	no	no	0-12 h	21 days	1986
IV-SK vs. placebo and ASA vs. placebo	ISIS-2[11]	17,187	ASA (50%)	no	0-24 h	35 days	1988
IV-SK vs. placebo	ISAM[9]	1,741	ASA	IV-Hep(1)	0-6 h	21 days	1986
	EMERAS[23]	4,534	ASA	no	>6-24 h	in hospital	1993
APSAC vs. placebo	AIMS[16] (2)	1,254	no	IV-Hep	0-6 h	30 days	1988
rt-PA vs. placebo	ASSET[17]	5,012	no	IV-Hep	0-6 h	1 month	1988
	LATE[24]	5,711	ASA	IV-Hep (64%)(3)	>6-24 h	35 days	1993
IV-UK vs. standard therapy	USIM[59]	2,201	no	IV-Hep(4)	0-6 h	in hospital	1991
IV-SK vs. rt-PA (ISIS-3: vs. APSAC) and Hep vs. non-Hep	GISSI-2[28,29]	20,749	ASA	SC-Hep (50%)	0-6 h	in hospital	1990
	ISIS-3[30] (5)	41,299	ASA	SC-Hep (50%)	0-24 h	35 days	1992
IV-SK vs. rt-PA vs. combination	GUSTO-1[33] (6)	41,021	ASA	Hep (SC 25% and IV 75%)	0-6 h	30 days	1993
IV-SK vs. r-PA	INJECT[37]	6,010	ASA	IV-Hep	0-12 h	35 days	1995
rt-PA vs. immediate PTCA	GUSTO-2b[48] (7)	1,138	ASA	IV-Hep (50%) Hirudin (50%)	0-12 h	30 days	1996
rt-PA vs. r-PA	GUSTO-3 [38] (8)	15,100	ASA	IV-Hep	0-6 h	30 days	1996

Table 2: **Characteristics of all randomised trials on short-term mortality after reperfusion therapy in acute myocardial infarction that include at least 1,000 patients**

SK = streptokinase; APSAC = anisoylated plasminogen streptokinase activator; UK = urokinase; rt-PA = alteplase; r-PA = reteplase; PTCA = percutaneous transluminal coronary angioplasty; ASA = aspirin; Hep = heparin; IV = intravenous; SC = subcutaneous

If no comments are made, treatment schedules were used as follows: SK: 1.5 MU over 1 h; UK: 1 MU bolus, repeated after 1 h; rt-PA: 10 mg bolus + 50 mg over 1 h + 20 mg over each of next 2 h; APSAC: 30 U over 3-5 min; r-PA: two boluses of 10U given 30 min apart; ASA: 160-325 mg/day; SC-Hep: 12,500 U twice dayly; IV-Hep: 5,000 U bolus + 800-1,200 U/h.

(1) Additional oral anticoagulant therapy; (2) AIMS planned to include 2,000 patients, but terminated prematurely because of an extreme mortality reduction by APSAC observed in an interim analysis half-way the trial; no Hep bolus was given, but instead 1,000-1,500 U/h; additional oral anticoagulant therapy; (3) after protocol amendment; some patients received 2 boluses of 5,000 U; (4) 10,000 U bolus; (5) rt-PA regimen: 0.04 MU/kg bolus + 0.36 MU/kg over 1 h + 0.067 MU/kg over next 3 h; (6) comparison of 4 groups: IV-SK, SC-Hep vs. IV-SK, IV-Hep vs. rt-PA (15 mg bolus + 0.75 mg/kg over 30 min + 0.5 mg/kg over next h), IV-Hep vs. rt-PA (0.1 mg/kg bolus + 0.9 mg/kg over 1 h), IV-SK (1.0 MU over 1 h), IV-Hep; (7) primary study endpoint was a composite of death, non-fatal reinfarction and non-fatal disabling stroke; the rt-PA regimen is equal to GUSTO-1; patients were randomised to IV-Hep or hirudin (0.1 mg/kg bolus + 0.1 mg/kg/h); (8) the rt-PA regimen is equal to GUSTO-1.

reduction in one-year mortality, from 14.7% to 12.5% [odds ratio (OR) 0.82 and 95% confidence interval (CI) 0.56-1.19; chi-square-test for 2x2 contingency table $p=0.32$].[8]

Intracoronary drug infusion requires angiography, which is laborious, expensive and causes further treatment delay. Therefore, subsequent investigations concentrated on intravenous infusion of streptokinase. The largest trials in this context, GISSI-1, ISAM and ISIS-2, comprehend 30,600 patients, who were randomised to either intravenous streptokinase or control therapy (table 2).[9-11] In the patients treated within 0-6 h of onset of symptoms ($N=22,200$), mortality at one month was significantly reduced by intravenous streptokinase from 12.0% to 9.2% [23% reduction; OR 0.74 and 95% CI 0.68-0.81; $p<0.0001$], figure 1.

The most feared complication related to thrombolytic therapy is the occurrence of intracranial haemorrhage, which leads to death in half of the cases and to severe disability in another quarter.[12] Embolic stroke rates are reduced in patients receiving thrombolytic therapy. The occurrence of any cerebrovascular accident in the GISSI-1, ISAM and ISIS-2 trials was slightly, but not significantly increased, from 0.74% in the control group to 0.79% in the intravenous streptokinase group (figure 1).

Other intravenous thrombolytic drugs have been developed that might produce more rapid thrombolysis than streptokinase, resulting in higher early coronary patency rates.[13-15] One such second-generation drug, anisoylated plasminogen streptokinase activator (APSAC), has the additional advantage of a relative long half life, so that a single injection would be sufficient. This thrombolytic was evaluated in the placebo controlled AIMS study (1,000 patients randomised within 0-6 h; table 2),[16] which reported a 6.4% mortality at one month in the APSAC group compared with 12.2% in placebo [48% reduction; OR 0.48 and 95% CI 0.30-0.70; $p=0.001$]. No excess cerebrovascular accidents occurred in the active group. The ASSET trial (table 2) studied recombinant tissue-type plasminogen activator (rt-PA),[17] which has the advantage over streptokinase and APSAC of being non-antigenic. Approximately 5,000 patients were randomised within 0-6 h, and mortality at one month was 26% reduced, from 9.8% to 7.2% by rt-PA compared with placebo [OR 0.72 and 95% CI 0.58-0.88; $p=0.001$]. Stroke rates were similar in both groups.

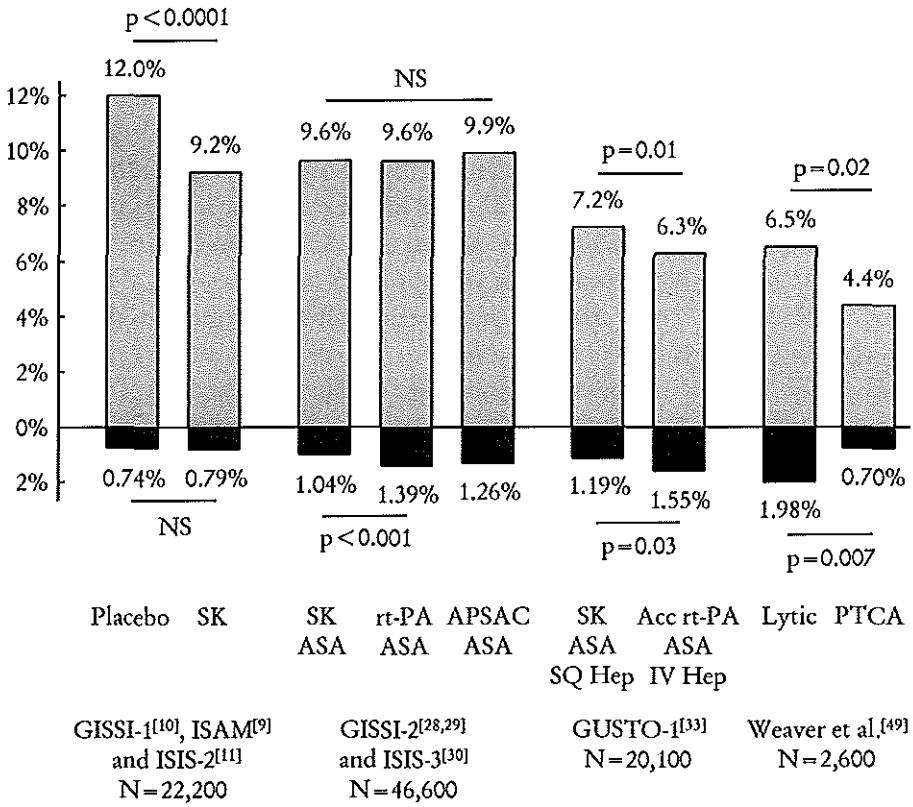

Figure 1: **One-month mortality and stroke rates after thrombolytic therapy or immediate angioplasty in patients with suspected myocardial infarction treated within 0-6 h of onset of symptoms**

Grey bars represent mortality in the 0-6 h patients. Black bars represent stroke-rates (haemorrhagic or embolic) in all patients. Mortality data from the overview of Weaver et al. is also not restricted to the 0-6 h cohort.

SK = streptokinase; APSAC = anisoylated plasminogen streptokinase activator; rt-PA = recombinant tissue type plasminogen activator; PTCA = percutaneous transluminal coronary angioplasty; ASA = aspirin; Hep = heparin

Very early treatment

Experimental data and measurements of myocardial enzymes in humans suggest that most of the irreversible damage to the myocardium occurs between 1 and 2 h after coronary occlusion.[18,19] Thus, appreciable additional benefit might be expected from very early thrombolytic therapy. However, in a pooled analysis of the large trials (N=58,600) by the Fibrinolytic Therapy Trialists (FTT analysis) there was no marked discontinuity in mortality reduction as a result of thrombolytic therapy with regard to time of symptom onset.[20] Recently, this analysis has been criticised, and it has been demonstrated that the beneficial effect of fibrinolytic therapy is indeed substantially higher in patients presenting within 2 h of symptom onset compared to those presenting later.[21] This 'golden hour' concept, however, is still controversial.[6]

Treatment after six hours

Thrombolytic treatment after 6 h of continuous coronary occlusion is unlikely to prevent myocardial necrosis. Nevertheless, there are some reasons for a beneficial effect on post-infarct survival in patients presenting relatively late after onset of symptoms.[6,22] One argument is, that many patients suffer from intermittent occlusions rather than one continuous occlusion - coronary thrombus formation and resolution is a dynamic process - so that partial salvage of ischaemic myocardium may still be achieved. Furthermore, existing collaterals may preserve some blood flow to the jeopardised area. Finally, even relatively late opening of the occluded artery will improve the healing process of the infarction and reduce left ventricular remodelling and dilatation.

The combined results of the GISSI-1, ISIS-2 and EMERAS trials indicate that treatment with intravenous streptokinase within 6-12 h after onset of symptoms (N=8,100) will reduce one-month mortality by 11% compared with control therapy, from 13.9% to 11.9% [OR 0.87 and 95% CI 0.76-0.99; p=0.04],[10,11,23] which is half the reduction observed in the 0-6 h period. The LATE trial of rt-PA vs. placebo (table 2) reported a 26% mortality reduction, from 12.0% to 8.9% [OR 0.72 and 95% CI 0.53-0.96; p=0.02] in the relatively small 6-12 h cohort (N=2,100).[24] In patients randomised within 12-24 h of symptom onset (N=9,000 in the FTT-analysis) no significant reduction in one-month mortality was observed following thrombolytic therapy.[20]

Overall clinical benefit of thrombolytic therapy

From 1980 over 61,000 patients with suspected myocardial infarction participated in trials that randomised between thrombolytic therapy and control, within 24 h of onset of symptoms. The FTT analysis, which covers about 95% of the data, indicates a highly significant 17% one-month mortality reduction by thrombolysis from 11.5% to 9.6% [OR 0.82 and 95% CI 0.78-0.87; $p<0.0001$], which corresponds to an avoidance of 18 [SD 3] deaths per 1,000 patients treated.[6,20] Thrombolytic therapy increases the occurrence of cerebrovascular accidents from 0.76% to 1.16% [OR 1.52 and 95% CI 1.28- 1.81; $p<0.0001$], reflecting a small excess of about 4 [1] strokes (mainly intracranial bleedings) per 1,000 treated. It should be realised that half of this excess is already accounted for in the mortality data. Follow-up studies show that the mortality reduction produced by thrombolytic therapy is sustained throughout at least four to ten years.[25,26,27]

Comparison of thrombolytic regimens

Superficial comparison of the results described above suggests, that APSAC (single injection of 30 U) and, to a lesser extent, rt-PA (100 mg infusion over 3 h) might be more effective than streptokinase (infusion of 1.5 MU over 1 h). However, direct comparisons in patients randomised within 0-6 h in the GISSI-2 (streptokinase vs. rt-PA, N=20,800) and ISIS-3 trials (streptokinase vs. rt-PA vs. APSAC, N=25,800; table 2),[28-30] showed no significant difference in one-month mortality between streptokinase and non-streptokinase regimens (figure 1). On the other hand, cerebrovascular accidents were slightly, but significantly, more frequent in the non-streptokinase groups [stroke rate 1.39% in rt-PA vs. 1.04% in streptokinase; OR 1.37 and 95% CI 1.15-1.62; $p<0.001$]. Thus, the chosen rt-PA and APSAC regimens in GISSI-2 and ISIS-3 appeared not to be superior to streptokinase. There were some indications, however, that a so-called 'accelerated' rt-PA infusion - i.e. over 1.5 h, with two thirds of the dose given in the first 30 min - will lead to greater infarct artery patency, which can be sustained with intravenous heparin infusion.[31,32] The accelerated rt-PA regimen has been evaluated in the GUSTO-1 trial, which randomly assigned 41,000 patients (within 0-6 h of symptom onset) to four different thrombolytic strategies (table 2). Treatment with accelerated rt-PA and intravenous heparin significantly reduced one-month mortality compared with streptokinase and subcutaneous heparin, the 'standard' streptokinase regimen, from 7.2% to 6.3% [13% reduction; OR 0.87 and 95% CI 0.78-0.97;

p=0.01], figure 1.[33] This mortality reduction was sustained throughout at least one year.[34] Left ventricular function was also better in patients randomised to accelerated rt-PA.[35] Conversely, the incidence of cerebrovascular accidents was increased from 1.19% to 1.55% [OR 1.31 and 95% CI 1.02-1.67; p=0.03].[12] Thus, the accelerated rt-PA regimen produces a clear, albeit modest, overall clinical benefit compared with 'standard' streptokinase. This conclusion, however, is not shared by all investigators in the field.[6,36]

Nowadays, to prove that new thrombolytic agents significantly reduce mortality compared with established strategies, trials require inclusion of tens of thousands of patients. To demonstrate, however, that the properties of new drugs are similar to established therapies, considerably fewer patients are needed. One such 'equivalence' trial is INJECT (N=6,000; table 2). This trial demonstrated that the two boluses of 10 MU reteplase regimen is at least equivalent to 'standard' streptokinase: mortality at one month was 9.0% and 9.5%, respectively, whereas stroke rates were 1.23% and 1.00%.[37] The recent GUSTO-3 trial (N=15,100; table 2) compared reteplase with the GUSTO-1 accelerated rt-PA regimen, and observed no statistically significant differences in 30-day mortality (7.2% after accelerated rt-PA and 7.4% after reteplase) or cerebral complications (stroke rates were 1.83% and 1.67%, respectively).[38] Thus, clinical effects of reteplase seem to be in between 'standard' streptokinase and accelerated rt-PA.

ANTIPLATELET AND ANTICOAGULANT THERAPY

Immediate and temporary use

ISIS-2 (N=17,200) assessed the value of antiplatelet therapy in acute myocardial infarction.[11] Patients were randomised not only to intravenous streptokinase or placebo, but also to oral aspirin (162.5 mg daily for one month) or placebo (table 2). Aspirin significantly reduced one-month mortality from 11.8% to 9.4% [20% reduction; OR 0.77 and 95% CI 0.70-0.85; p<0.0001], figure 2. The occurrence of cerebrovascular accidents was also significantly reduced, from 0.94% to 0.55% [41% reduction; OR 0.58 and 95% CI 0.40-0.84; p=0.003], while intracranial haemorrhage rates were similar. In patients allocated both intravenous streptokinase and aspirin one-month mortality was 8.0% compared with 13.2% in those allocated both placebo

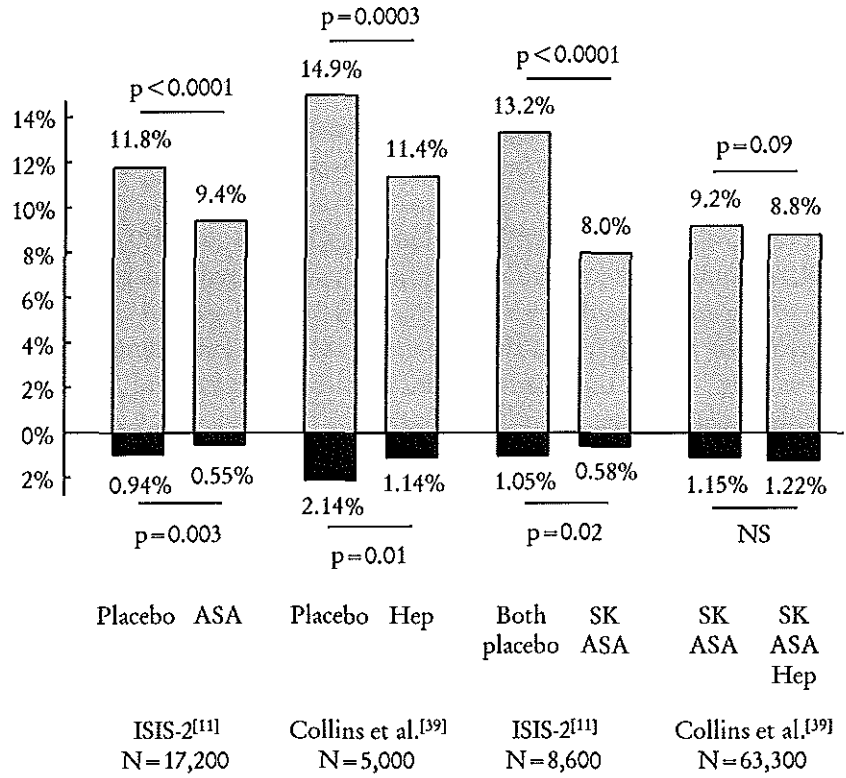

Figure 2: **One-month mortality and stroke rates after antiplatelet or anticoagulant therapy in patients with suspected myocardial infarction**

Grey bars represent mortality and black bars represent stroke rates (haemorrhagic or embolic).

SK = streptokinase; APSAC = anisoylated plasminogen streptokinase activator; rt-PA = recombinant tissue type plasminogen activator; PTCA = percutaneous transluminal coronary angioplasty; ASA = aspirin; Hep = heparin

[39% reduction; OR 0.56 and 95% CI 0.48-0.66; $p<0.0001$], figure2. Thus, streptokinase and aspirin show additive effects.

The properties of anticoagulant therapy in the absence of antiplatelet therapy are evaluated in a couple of randomised trials, covering about 5,000 patients (all of them received heparin, but doses and mode of administration varied).[39] Heparin decreased short-term mortality to 11.4% compared with 14.9% after control treatment [23% reduction; OR 0.74 and 95% CI 0.62-0.87; $p=0.0003$], figure 2, and cerebral complications were reduced from 2.14% to 1.14% [47% reduction; OR 0.53 and 95% CI 0.31-0.90; $p=0.01$]. These results are comparable with aspirin in the absence of anticoagulant therapy. There are very few data about the combination of thrombolytic and anticoagulant therapy in non-aspirin patients.[39]

The value of anticoagulant treatment added to the combination of thrombolytic and antiplatelet therapy was evaluated in about 63,300 patients, who were randomised to subcutaneous heparin (the GISSI-2 and ISIS-3 regimen, table 2) or control therapy.[39] A small non-significant 4% short-term mortality reduction was observed in the heparin group (mortality 8.8% in the heparin group and 9.2% in controls [OR 0.95 and 95% CI 0.90-1.01; $p=0.09$], figure 2). Stroke rates were 1.22% and 1.15% in heparin vs. non-heparin patients, respectively [OR 1.07 and 95% CI 0.92-1.24; $p=0.37$]. In the GUSTO-1 study, no significant difference was observed between subcutaneous and intravenous heparin in patients treated with streptokinase. Thus, it may be concluded from the GISSI-2, ISIS-3 and GUSTO-1 studies that neither subcutaneous nor intravenous heparin adds much to the outcome in streptokinase patients. Therefore, recent guidelines do not recommend heparin as adjunctive therapy in myocardial infarction patients treated with streptokinase and aspirin.[40]

Angiographic studies indicate that coronary patency is improved by adding intravenous heparin to rt-PA.[31,32] As described above, the GUSTO-1 accelerated rt-PA regimen, which included intravenous heparin, was significantly better than 'standard' streptokinase. Thus, although there are no large randomised trials that assess the clinical benefit of adding heparin to rt-PA, the available data support the use of intravenous heparin for two or three days in patients receiving rt-PA.

Secondary prevention

Approximately 19,800 patients with recent myocardial infarction participated in trials that randomised between prolonged use, i.e. at least for one month, of aspirin or other antiplatelet agents (such as dipyridamole and sulfinpyrazone) and control therapy.[41] Antiplatelet therapy significantly reduced long-term mortality by 12%, from 10.4% to 9.2% [OR 0.88 and 95% CI 0.80-0.96; p=0.006], non-fatal myocardial reinfarction by 28%, from 6.5% to 4.7% [OR 0.70 and 95% CI 0.62-0.80; p<0.0001] and non-fatal stroke by 33%, from 1.5% to 1.0% [OR 0.63 and 95% CI 0.47-0.84; p<0.001].

Two recent randomised trials evaluated the value of long-term oral anticoagulant treatment (warfarin or coumadin vs. placebo) in about 4,600 survivors of myocardial infarction.[42,43] Mortality at three years was 11.4% in the anticoagulant group and 13.5% in the placebo group, which implies a reduction of 15% [OR 0.83 and 95% CI 0.69-0.99; p=0.03]. Recurrence of myocardial infarction was reduced by 46%, from 15.8% to 8.5% [OR 0.49 and 95% CI 0.41-0.60; p<0.0001], as was the occurrence of cerebrovascular accidents, from 4.6% to 2.5% [OR 0.53 and 95% CI 0.37-0.74; p=0.0001].

Thus, prolonged use of aspirin or coumadin prevent reinfarction, stroke and mortality after myocardial infarction. The salutary effects of coumadin seem somewhat larger, but direct comparisons of antiplatelet and anticoagulant therapy are lacking. One trial recently reported that aspirin and low-dose coumadin resulted in similar effects.[44] However, that trial was stopped prematurely because outcomes in the two groups were virtually identical. Other trials comparing high dose coumadin and aspirin are ongoing.

IMMEDIATE ANGIOPLASTY

The most important conceptual deficit of thombolytic therapy in patients with evolving myocardial infarction is, that such pharmacological intervention only aims to dissolve the acute coronary thrombus. On the other hand, mechanical intervention by means of immediate coronary angioplasty also treats the underlying atherosclerotic plaque. Thus, recurrence of ischaemia and reocclusion are less likely after angioplasty than after thrombolysis. Additionally, less serious (cerebral) bleeding complications are to be expected. Whereas routine angioplasty after thrombolytic therapy appeared not be successful,[14,45] clinical trials that randomised between direct angioplasty and

thrombolytic therapy initially reported excellent (extreme) results in support of the invasive strategy.[46,47] However, results of the recent larger GUSTO-2b angioplasty substudy (N=1,100; table 2), which applied the GUSTO-1 accelerated rt-PA regimen, were less favourable.[48] Overall, among the 2,600 patients randomised in all of the angioplasty trials, short term mortality was significantly reduced from 6.5% after thrombolytic treatment to 4.4% after primary angioplasty [33% reduction; OR 0.66 and 95% CI 0.46-0.95; p=0.02], figure 1.[49] The risk of stroke was reduced from 1.98% to 0.70% [65% reduction; OR 0.35 and 95% CI 0.14-0.77; p=0.007]. The wide confidence intervals reflect the relative small number of patients randomised, which necessitates a careful interpretation of the estimates of benefit. Furthermore, it should be realised that these results are obtained by high volume angioplasty operators and experienced teams. Nevertheless, direct angioplasty might be considered the treatment of choice, particularly in patients at high risk of death or cerebral haemorrhage.

Current trials address the issue whether implantation of coronary stents is associated with additional benefits.[50] Trials are also ongoing to establish the value of special catheter devices designed to remove thrombotic material by section or ultrasound in selected patients with a high clot burden.

FUTURE DIRECTIONS

Direct thrombin inhibitors

Heparin is an indirect thrombin inhibitor, requiring the presence of anti-thrombin III. Direct thrombin inhibitors, like hirudin and hirulog, do not require this enzyme and might therefore be expected to be more effective. Direct thrombin inhibitors also act on platelet bound thrombin. However, two large randomised studies in patients with evolving myocardial infarction (TIMI-9 and GUSTO-2) did not show a significant advantage of hirudin over heparin in combination with thrombolysis.[51,52] The high dose of hirudin initially used in these trials resulted in an unacceptable high rate of intracranial haemorrhage, which was also observed in the HIT trial.[53] The subsequently low doses used, largely avoided these complications, but had little (GUSTO-2b) or no (TIMI-9b) effect on survival.[54,55] Studies with other thrombin inhibitors in combination with thrombolytic therapy are ongoing.

Platelet glycoprotein IIb/IIIa receptor blockers

Aspirin is a weak inhibitor of platelet aggregation. More extensive, or even full inhibition of platelet aggregation can be achieved with the new platelet glycoprotein IIb/IIIa receptor blockers. The first such agent, abciximab, has been shown to be very effective in patients undergoing coronary angioplasty, including angioplasty for myocardial infarction. Pre-treatment with abciximab while preparing for direct angioplasty may resolve the occlusive clot in some patients.[56] In animal experiments combined treatment with glycoprotein IIb/IIIa receptor blockers and thrombolytics has been shown to facilitate clot lysis. Studies assessing the clinical value of such treatment in patients with evolving myocardial infarction are ongoing. Again, it is possible that such combination treatment will improve reperfusion and reduce reocclusion rates, but it might also increase the bleeding risk.

CONCLUSIONS

- Thrombolytic treatment of suspected myocardial infarction within 0-6 h of onset of symptoms will avoid approximately 25 deaths per 1,000 patients, while 4 cerebrovascular complications will be caused.
- The beneficial effect of thrombolytic therapy very much depends on the time of symptom onset. However, thrombolytic therapy is generally beneficial up to 12 h after the onset of symptoms, and in some patients (those with ongoing ischaemia) even up to 24 h.
- Administration of antiplatelet or anticoagulant therapy will avoid about 20 deaths and 5 cerebrovascular accidents per 1,000 patients. The beneficial effects of thrombolytic therapy and aspirin are largely independent. Subcutaneous heparin adds little to combination therapy with a thrombolytic agent and aspirin, while intravenous heparin is recommended in patients treated with (accelerated) alteplase.
- There are moderate, but significant differences in outcome between several reperfusion strategies: direct angioplasty being most effective, and accelerated alteplase (with intravenous heparin) being slightly superior to streptokinase. However, most emphasis should be on rapid installation of some effective therapy without worrying overmuch about which strategy to choose.

- Secondary prevention with either antiplatelet or anticoagulant therapy has a modest effect on mortality, but substantially reduces the risk of recurrent myocardial infarction.

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Chapter 3

RELATIONSHIP BETWEEN TREATMENT DELAY AND TREATMENT BENEFIT

Boersma E, Maas ACP, Deckers JW, Simoons ML
Early thrombolytic treatment in acute myocardial infarction: reappraisal of the 'golden hour'
Lancet 1996; 348: 771-75

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 continuous to be debated. This paper discusses whether or not appreciable additional gain can be achieved with very early treatment.

Methods and findings

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.

Benefit of fibrinolytic therapy was 65 [SD 14], 37 [9], 26 [6] and 29 [5] lives saved per 1,000 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 1,000 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).

Conclusion

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

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.[1] Although earlier reperfusion yields a better clinical outcome, the relation between treatment delay and mortality reduction is still controversial. A key question is whether or not a substantial additional reduction of the mortality risk can be achieved with very early treatment, i.e. within 2 to 3 h after onset of symptoms. The concept of a 'first golden hour'[2] is supported both by experimental studies and randomised trials comparing pre-hospital with in-hospital therapy.[2,3] By contrast, the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group, in a pooled dataset of randomised trials of more than 1,000 patients,[4] 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.[5-7] 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.[6,7] Thus, necrosis can be prevented provided reperfusion is achieved within this period.[8] A small area of necrosis usually occurs with reperfusion after 45 min occlusion, while the mid-endocardial and sub-endocardial zones are still viable.[6] 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 point.[3,6] Six hours 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.[9]

Pre-hospital versus in-hospital thrombolysis

Various clinical trials have shown that early restoration of coronary patency improves survival.[10-13] Later recanalisation may also be beneficial, particularly in patients with sufficient collateral flow and those with stuttering infarction. Randomised trials comparing pre-hospital with in-hospital therapy[14-21] 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.[2,22] The largest EMIP trial, with 5,469 randomised patients, reported 15 [SD 8] additional patients alive at 30 days per 1,000 patients as a result of one hour earlier treatment.[21] Figure 1 shows the weighted regression line of all 8 randomised studies.[14-21] In these studies, the average delay from symptom onset to initiation of therapy was 2.1 h in the pre-hospital patients and 3.1 h in the in-hospital patients.[22] One hour earlier treatment within 3 h of symptom onset is associated with a benefit of 21 [6] lives per 1,000 treated (p = 0.002).

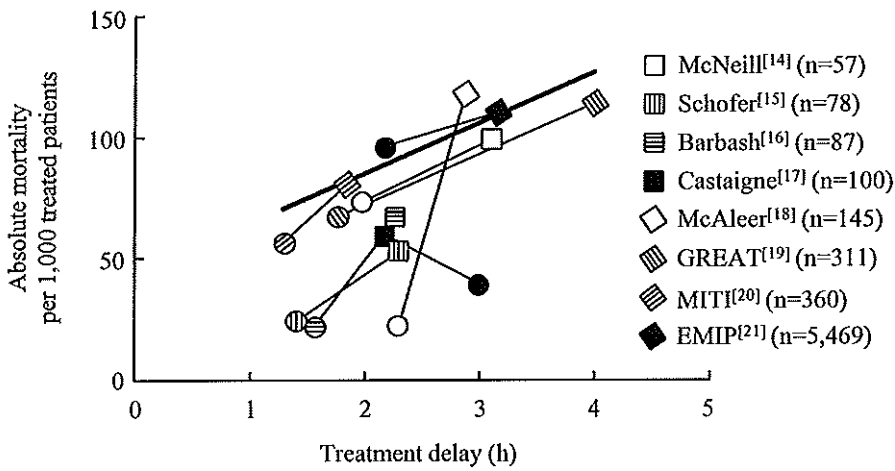

Figure 1: **Mortality at 35 days in randomised studies comparing pre-hospital (circles) with in-hospital (squares) thrombolytic therapy**

All trials (except Castaigne) showed a trend favouring pre-hospital thrombolysis. The regression line (bold, weighted by the number of patients included in the mortality result) was mainly determined by the EMIP[21] study.

FTT analysis

The Fibrinolytic Therapy Trialists' Collaborative Group presented a systematic analysis of the pooled data from all unconfounded trials of fibrinolytic therapy vs. control or placebo that randomised at least 1,000 patients with suspected myocardial infarction.[4] Nine trials were included with 58,600 patients, among whom 6,177 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 5 subgroups according to the delay from symptom onset to randomisation (0-1, ≥1-3, ≥3-6, ≥6-12 and ≥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 1,000 treated. In patients presenting ≥1-3 and ≥3-6 h the benefits were 25 [5] and 19 [5] additional alive patients per 1,000 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 1,000 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 1,000 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 achieved very early, pre-hospital therapy.

Alternative presentation of the trial data

Since the FTT analysis is at variance with the experimental data, and with the larger benefit found in direct, randomised comparison of pre-hospital with in-hospital therapy, an alternative presentation of the trial data may be 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 1,000 patients for each of the 9 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 three hours (at average delay times of 0.98 and 2.50 h, respectively). In this way, part of a potential large effect in the first two hours 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.[23] 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 vs. placebo or control which included at least 100 patients. These trials were reported between 1983 and 1993 and were indexed in the MEDLINE information system.[24] There are 22 such trials.[12,13,25-44] 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;[43,44] these patient subgroups are unlikely to benefit from fibrinolysis.[45-47] The USIM and ISIS-3 trials included 4,250 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.[12,13,27,29,31-33,41-44] Patients were subsequently allocated to six subgroups according to treatment delay (0-1, ≥1-2, ≥2-3, ≥3-6, ≥6-12 and ≥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. 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.[4] 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.

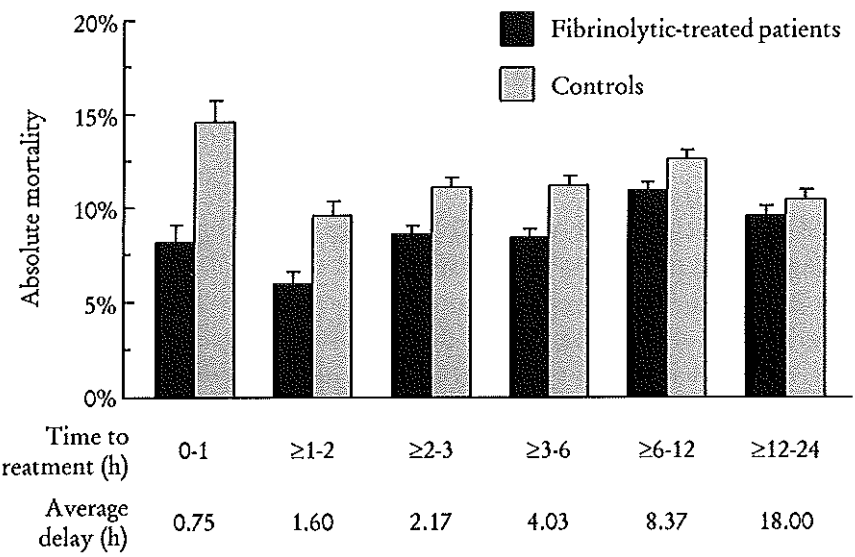

Figure 2: **Mortality at 35 days among fibrinolytic-treated and control patients, according to treatment delay**

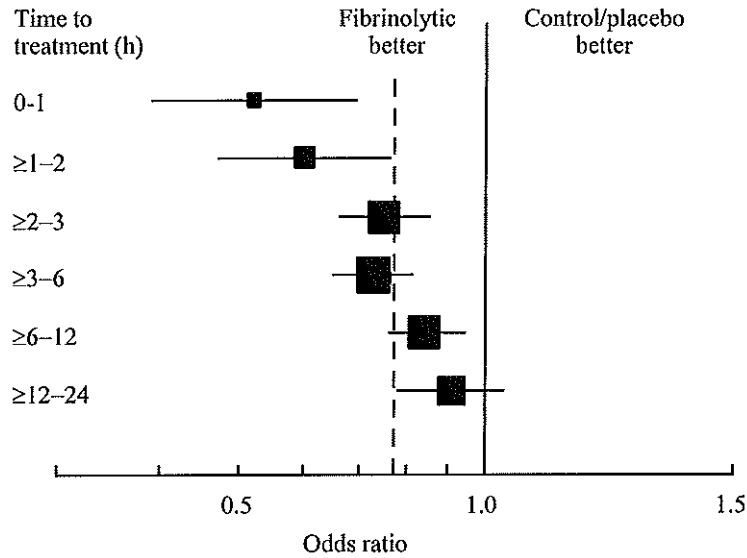

Figure 3: **Proportional effect of fibrinolytic therapy on 35-day mortality according to treatment delay**

Odds ratios, plotted with their 95% CI on a log scale, are significantly different over the six groups (Breslow-Day test, p=0.001) The areas of the black squares are proportional to the amount of statistical information.[4]

RESULTS

The 22 trials included a total of 50,246 patients, of whom 5,762 (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 1,000 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 1,000 treated). The benefit per 1,000 treated in the subgroups presenting at ≥2-3, ≥3-6, ≥6-12 and ≥12-24 was respectively 26 [6; 14-37], 29 [5; 19-40], 18 [6; 7-29] and 9 [7; -5-22].

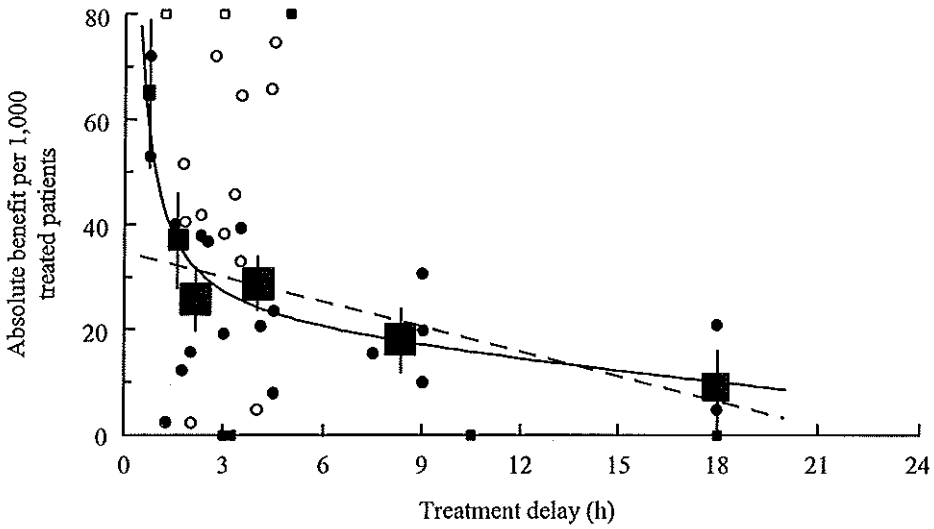

Figure 4: **Absolute 35-day mortality reduction versus treatment delay**

Small closed dots: information from trials included in the FTT analysis; open dots: information from additional trials; small squares: data beyond the scale of the 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 the inverse of the variance of the absolute benefit in each datapoint.[4] Black squares: average effects in six time-to-treatment groups (the areas of these squares are inversely proportional to the variance of absolute benefit described.

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 1,000 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 γx^2 (H_0: $\gamma=0$ not rejected; $p=0.29$; $R^2=0.25$). However, the component γx^{-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 (WWashIC and ICIN)[26,28] did not essentially change these findings. Further analyses were performed including all trials with at least 1,000 (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 1,334 patients with evolving myocardial infarction.[9] The cumulative release of myocardial α-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, pre-hospital initiation of therapy and delayed, in-hospital therapy (figure 1).[2,22]

This advantage of very early therapy in the pre-hospital studies is much larger than the effect of 1 h earlier treatment reported by the FTT investigators (1.6 lives per 1,000 treated), who compared in-hospital thrombolytic with placebo or conventional therapy.[4] 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)[48] report early, whereas elderly patients tend to wait longer.[49,50] Therefore, the randomised comparisons of

earlier vs. 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 (e.g. the GISSI-1 clinical trial)[12] were considered hypothesis-generating, whereas the outcomes of experimental and pre-hospital trials were dismissed.[4] 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 pre-hospital data (figure 4). A large reduction in mortality was detected in patients treated within 1 h of symptom onset (65 [SD 14] per 1,000 treated). The decrease in benefit in the 0.75-1.6 h interval (51 min) was roughly 33 lives per 1,000 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 one month per 1,000 treated compared with conventional therapy. The benefit of therapy within 1-3 h is in the range 30-50 per 1,000 treated.

From a clinical standpoint, the challenge is to initiate fibrinolytic treatment within the first 2 to 3 h after onset of symptoms. 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.[51] 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.[52]

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Chapter 4

FACTORS THAT DETERMINE EFFICACY AND APPLICABILITY OF REPERFUSION THERAPY IN CLINICAL PRACTICE: A SEARCH FOR CONSENSUS

The Reperfusion Therapy Consensus Group
Clinical perspectives:
Selection of reperfusion therapy for individual patients with evolving myocardial infarction
Eur Heart J 1997; 18: 1371-81

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 hours - 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 summarised. 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.

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 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%-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 randomised 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 randomised 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 1,000 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 the 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 1,000 treated aged <55 years, 21 [5] aged 55-64, 37 [6] aged 65-74 and 13 [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 relative 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 [5] fewer deaths per 1,000 treated patients, while the absolute benefit was 28 [7] fewer deaths per 1,000 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 randomised within 0-3 or ≥3-6 h of symptom onset (48 [13] and 18 [12], respectively) were similar to those at day 35 (44 [9] and 25 [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 [11] and 62 [15] fewer deaths per 1,000 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 as least as great among these patients (45 [19] lives saved per 1,000) as among those aged less than 70 years (23 [7] lives saved per 1,000). 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]

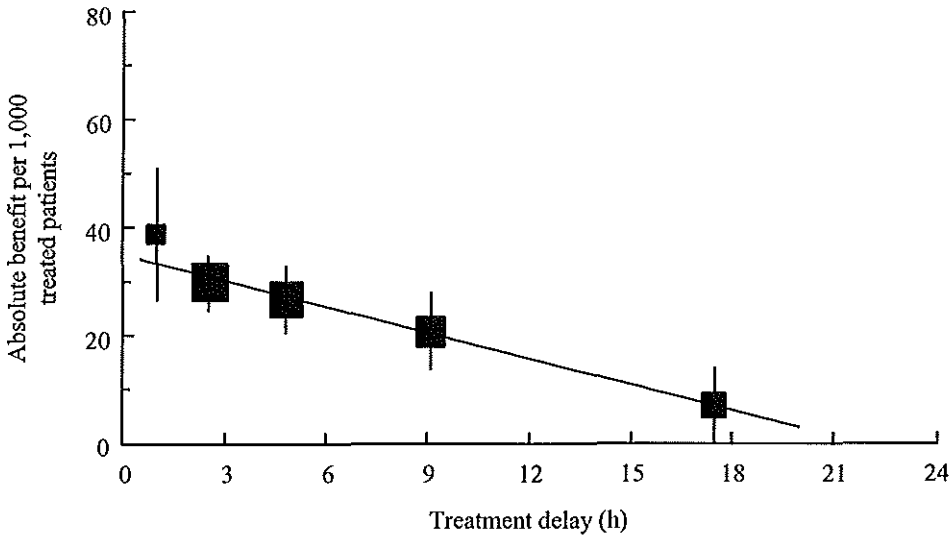

Figure 1: **Absolute reduction in 35-day mortality versus treatment delay as reported by the FTT investigators**[12]

The loss of benefit per hour of delay to randomisation was estimated at 1.6 [SD 0.6] per 1,000 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 1,000 patients (involving a total of 46,000 randomised 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 (figure 1).[12] A retrospective subgroup analysis of GISSI-1 had suggested that fibrinolytic therapy might be especially effective when started within one hour 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 randomised in hours 0-1 was slightly below the sloping line in figure 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 [0.6] deaths per 1,000 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 2 (or even 3) extra deaths per 1,000, 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 randomised 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 randomised 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 1,000, 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 one hour earlier treatment in the largest trial (EMIP) was observed in those randomised 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 1,000 treated at a median of 2.2 h instead of 3.2 h after onset of symptoms (95% CI: 27 fewer deaths to 1 additional death per 1,000 treated, not significant), albeit that most of this benefit was realised in patients treated between 3-6 h after onset of symptoms.[26] Although the pre-hospital trials were relatively small and the individual results 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 randomised patients between fibrinolytic therapy and control.[35] This analysis showed that the delay/benefit relation could be significantly better described with a non-linear than with a linear function (see figure 2). The decrease in benefit up to approximately 1.5 h from symptom

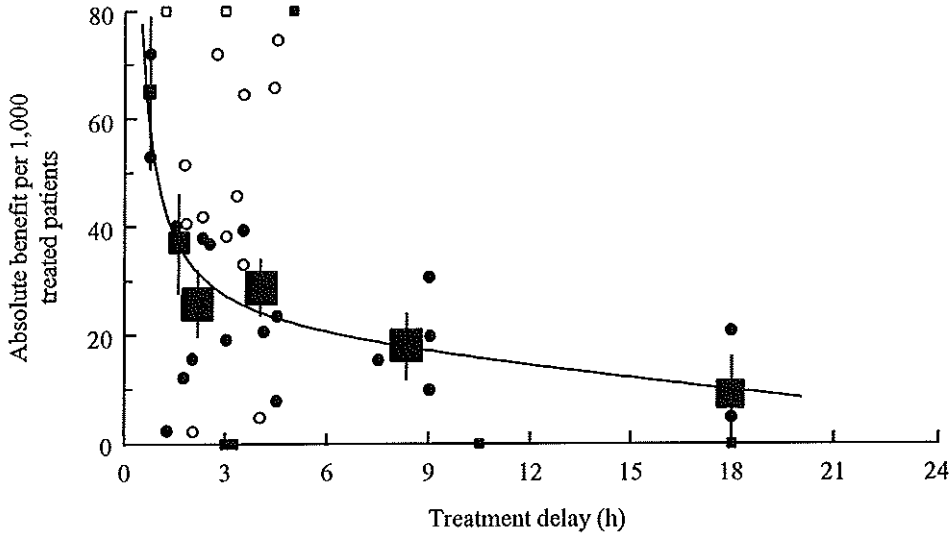

Figure 2: **Absolute 35-day mortality reduction versus treatment delay as reported by a re-analysis of the FTT data in combination with data from smaller trials (at least 100 patients) that randomised between fibrinolytic therapy and control or placebo[35]**

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 ($19.4-0.6x+29.3x^{-1}$) 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.

onset was about 30 lives per 1,000 treated per hour, and declined rapidly to approximately 3 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 optimisation 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 hours - 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, 7,000 patients with ST elevation or bundle branch block presenting between 12 and 24 h from symptom onset have been randomised between fibrinolytic therapy and control.[11,22,36,39] Although the absolute benefit of 7 [7] fewer deaths per 1,000 treated observed among these patients was non-significant,[12] benefit with earlier treatment and the gradual diminution of benefit with later treatment (see figures 1 and 2) does suggest that worthwhile net benefits may await discovery among patients who present within 12-18 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 recombinant tissue plasminogen activator (rt-PA).[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 4 [0.8] per 1,000 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 including 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 mm Hg) 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 randomised 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 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 4 extra strokes per 1,000 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) rt-PA 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 rt-PA (alteplase/duteplase infused over 3-4 h, also with or without heparin).[39,44,45] The GUSTO-1 investigators, however, reported a significant reduction in 30-day mortality of 10 [3] per 1,000 patients treated with *accelerated* administered rt-PA (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.A. and non-U.S.A. 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 rt-PA compared with streptokinase. In GUSTO-1, a significant absolute increase in total stroke was reported of 2.6 [1.5] per 1,000 patients treated with accelerated rt-PA. Nevertheless, the absolute net clinical benefit, of the combined end point of 30-day mortality or non-fatal stroke was still 9

[3] patients per 1,000 treated with accelerated rt-PA. Thus, *accelerated* rt-PA has been shown to be clearly superior to streptokinase.

In spite of the favourable outcome with accelerated rt-PA, 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 rt-PA compared with streptokinase at $27,369 per life year added, based on the cost of rt-PA in the U.S.A..[49] Accordingly, accelerated rt-PA 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 do 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 of more intensive thrombolytic regimens outweigh any cerebrovascular disadvantages.

In the three large trials of the 'standard' 1 h 1.5 MU streptokinase regimen vs. rt-PA-based fibrinolytic regimens, patients were entered on an average of 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 rt-PA-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 rt-PA-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 rt-PA-alone regimen and 78 mg of alteplase with the other rt-PA-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 [0.8] strokes per 1,000 treated with rt-PA compared with streptokinase.[50] Most of this excess occurred within the first day of giving rt-PA, and was attributed to

an even more definite excess of 2.9 [0.5] cerebral haemorrhages per 1,000. These excesses with the rt-PA regimens increased with increasing age and blood pressure. Overall, the rt-PA-based regimens were associated with 4.9 [1.8] fewer non-stroke deaths per 1,000 compared with streptokinase, but the 95% CI for this estimate spans a wide range from about 1 to about 9 fewer non-stroke deaths per 1,000. When taken all together, the directly randomised comparisons suggest such rt-PA-based regimens might confer a non-significant improvement of only one or two per 1,000 in net clinical outcome. But, whereas the hazard is definite (about 3 additional cerebral haemorrhages per 1,000) 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 rt-PA and 149 streptokinase) vs. angioplasty (394 patients) indicated a favourable outcome of the latter strategy (6.4% vs. 2.6% in-hospital mortality; reduction of 39 per 1,000, with 95% CI of 10-68, $p=0.01$).[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 rt-PA 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 95% CI of 15 more to 40 fewer deaths per 1,000 angioplasties). The combined 30-day endpoint of death, re-infarction or disabling stroke was significantly lower in patients treated with direct PTCA (9.6%) compared with thrombolytic therapy (13.7%; reduction of 41 per 1,000, but with 95% CI of 3-78, $p=0.033$).[55]

The initial costs of an angioplasty procedure are relative 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 practical 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 rt-PA 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) of rt-PA 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 rt-PA 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 unclear due to the relatively small number of randomised patients studied. Primary angioplasty may be offered as an alternative of 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 organisational 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 can not 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 one month is reduced by approximately 30 deaths per 1,000 patients treated within 6 h from symptom onset, despite a small excess of cerebral bleeding complications (approximately 4 per 1,000).

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 pre-hospital 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 regimens, 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 glycoprotein IIb/IIIa 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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APPENDIX

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PRACTICAL DECISION MODELS

Chapter 5

A TREATMENT SCHEME TO GUIDE DECISION MAKING IN INDIVIDUAL MYOCARDIAL INFARCTION PATIENTS, BASED ON ESTIMATED RESIDUAL LIFE EXPECTANCY

Boersma H, Vlugt van der MJ, Arnold AER, Deckers JW, Simoons ML
Estimated gain in life expectancy. A simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction
Eur Heart J 1996; 17: 64-75

SUMMARY

Background

Currently several modes of reperfusion therapy for acute myocardial infarction are available. Streptokinase, accelerated alteplase and direct angioplasty are the most frequently used. These options are increasingly effective, but also increasingly complex and costly. Since, unfortunately, physicians are often restricted by budget limitations, choices must be made in clinical practice to provide optimal therapy to individual patients.

Methods and findings

In order to guide such decision making, we developed a model to predict the expected benefit of therapy in terms of gain in life expectancy. Patients' life expectancy will decrease after infarction. Part of this loss can be prevented by early reperfusion therapy. This clinical benefit of therapy ranges from negligible gain in patients with small infarcts treated relatively late to an expected gain of more than 2 years in patients with extensive infarction treated within 3 h of onset of symptoms.

The expected benefits are presented in a set of tables and depend on age, previous infarction, estimated infarct size, treatment delay and intracranial bleeding risk. With the help of these tables, resources will be allocated in such a manner, that patients who will benefit most will receive the most effective therapy. Patients with similar expected treatment benefit will be offered the same mode of therapy. Future life years were discounted at 5% per year. The arbitrary thresholds currently applied for decision making at the Thoraxcentre are: no reperfusion therapy when the estimated gain in discounted life expectancy was <1 month, streptokinase for 1-4 months and accelerated alteplase for a gain ≥ 5 months. Direct angioplasty is recommended in patients with an estimated gain ≥ 12 months, and in patients with an increased risk of intracranial bleeding. In this way, approximately 80% of our patients will be treated with thrombolytics (40% streptokinase and 40% accelerated alteplase), while in 10% direct angioplasty will be initiated. Patients with small infarcts presenting late will not receive reperfusion therapy.

Conclusions

These threshold values have been chosen arbitrarily, and different thresholds may be selected in other centres. However, the developed model would guarantee that treatment decisions are made in a consistent manner, to provide optimal therapy for patients with evolving myocardial infarction, in spite of limited resources.

INTRODUCTION

The necessity of early reperfusion to improve survival in acute myocardial infarction patients has clearly been demonstrated.[1-12] Such reperfusion can be achieved using one of several regimens of thrombolytic drug therapy, or by direct percutaneous transluminal coronary angioplasty. Various pharmacological strategies have been compared in separate trials. The regimens studied in the GISSI-2 and ISIS-3 studies appeared to be equally effective: streptokinase, anistreplase, alteplase rt-PA and duteplase, each administered with aspirin and either without or with subcutaneous heparin started a few hours after thrombolysis.[8,13] In addition, a bolus injection with reteplase was shown to be equivalent to streptokinase.[14] In contrast, the GUSTO trial demonstrated improved survival by accelerated administration of rt-PA with aspirin and immediate intravenous heparin: one additional survivor at 30 days and at one year for 100 patients treated with accelerated rt-PA in comparison with streptokinase.[15,16] The combined results of three recently presented studies indicated superior survival following direct angioplasty compared with thrombolysis. The 42-day mortality rates were 2.2% [95% CI: 0.6-3.8] and 5.8% [3.3-8.3], respectively.[17-19] Furthermore, fewer intracranial haemorrhages and a lower rate of recurrent infarction were reported in the angioplasty group.

The gradient of efficacy of the three accepted and most widely used modes of reperfusion therapy (streptokinase, accelerated rt-PA and direct angioplasty) runs parallel to a gradient of costs and complexity. For example, the initial, direct costs of treatment of a patient with rt-PA in The Netherlands are approximately five times higher than if streptokinase were used (Dfl. 2,000 vs. Dfl. 400, respectively), while an angioplasty procedure requires more complex organisation and is even more expensive: approximately Dfl. 5,000 to 8,000. Other regimens for reperfusion therapy are being evaluated, including combined thrombolytic and anti-thrombotic therapy,[20-22] and thrombolytic therapy with platelet fibrinogen receptor blockers.[23] The clinical benefits of these and other approaches have yet to be determined. Again, more effective therapy will often be more costly than current available therapy.

A gradient of treatment benefit is also apparent when subsets of patients with evolving myocardial infarction are compared. The benefit of reperfusion therapy depends on age, the area at risk, treatment delay and the risk of intracranial bleeding.[1,5,24-29] Accordingly, in clinical practice physicians must choose the most suitable mode of therapy for individual patients.

Unfortunately, this choice is often limited by a budget, such that the most effective therapy cannot be offered to all patients. Given this constraint, it is appropriate to offer more effective, more expensive and more complex modes of therapy to patients who are likely to benefit most from treatment, and to provide slightly less effective, but considerably less expensive modes of therapy to patients whose expected benefits from treatment are lower. To facilitate such decision making, we present a model which predicts the benefit of reperfusion therapy in individual patients through assessment of the gain in life expectancy. An earlier model expressed treatment benefit in terms of number of cardiac deaths prevented in the first year.[29] However, that model did not account for differences in life expectancy in different age categories. For example, elderly patients may have considerable initial benefit from intensive therapy, but their life expectancy remains limited, and the cost-efficacy ratio may be unsatisfactory. In contrast, a smaller initial benefit in younger or middle-aged patients with a longer life expectancy may result in a more favourable cost-efficacy ratio.

In the proposed model, life expectancy was estimated from age- and gender- specific mortality and follow-up data from different groups of patients after myocardial infarction. The influence of various parameters in the model was evaluated by a sensitivity analysis using data from a recent cohort of 500 consecutive patients admitted with evolving myocardial infarction. Finally, a set of simple tables is presented, which provides an overall estimate of the effects of reperfusion therapy in patient subgroups to assist clinical decision making in a consistent manner. The present model may be used to choose between four currently available treatment options: no reperfusion therapy, streptokinase, accelerated rt-PA with intravenous heparin and direct angioplasty. It may be adapted to other treatment regimens when these become available in the future.

DESIGN OF THE MODEL

A cost-efficacy analysis, comparing outcome and costs of *each regimen* in different subsets of patients is a formal way to choose between different treatment regimens in an individual patient.[30] This would require assessment of the initial and subsequent costs associated with the different modes of treatment as well as survival analysis. However, a complete cost-efficacy model applicable to individual patients would need extensive computations with an appropriately

programmed computer system, and would be difficult to handle for immediate decision-making in clinical practice. Also the design of such a detailed model would require precise knowledge of differences (if any) in long-term effects of various treatment modalities, knowledge that is not currently available. Therefore we sought an alternative approach, which provides an *overall estimate* of the effects of reperfusion therapy in patient subgroups, presented in a set of tables.

The chosen approach is based on the assumption that differences in expected benefits between treatment regimens are greater in groups of patients with a greater overall benefit from reperfusion therapy. Indeed, currently

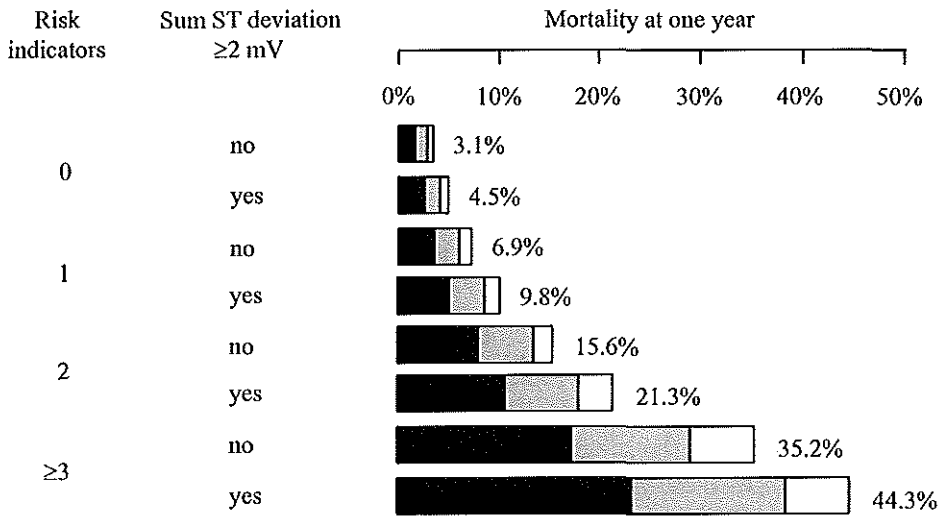

Figure 1: Estimated one-year mortality in different patient subgroups

Results are based on a multivariate analysis of data from 3,179 patients from three studies.[29] Risk factors for one-year mortality were: advanced age, previous infarction, anterior infarction, inferior location with right ventricular involvement, heart failure and bundle branch block. Patients are devided into groups according to their increasing number of risk factors, either without or with extensive ST segment deviation. The length of each bar represents estimated mortality without reperfusion therapy (no treatment). Early treatment (within 3 h of symptom onset) is assumed to reduce mortality in each group by 50% (grey area), while only 12.5% mortality reduction is achieved by late treatment (6-12 h of symptom onset, white area).

1.	Mortality in the first year after infarction can be predicted from age, history of infarction, infarct location and indicators of infarct size.
2.	Mortality reduction by reperfusion therapy is proportional to predicted mortality and related age, and to time to treatment.
3.	Differences in efficacy of various modes of reperfusion therapy are proportional to the overall mortality reduction.
4.	The risk of intracranial haemorrhage can be predicted from age, blood pressure, body weight and the mode of reperfusion therapy.
5.	Survival curves of myocardial infarction patients without and with reperfusion therapy run parallel after the first year, and exceed mortality rates of the 'normal' reference populations with a constant difference.
6.	Late mortality rates are proportional to one-year mortality after infarction: patients with a large infarct have both greater initial and greater subsequent mortality rate (i.e. larger differences relative to the reference population).
7.	The utility of future life years is discounted at 5% per year.

Table 1: **Assumptions made in the models to assess the benefit of reperfusion therapy in patients with evolving myocardial infarction**

available data indicate that both the benefit of reperfusion therapy compared to conventional therapy, as well as the incremental benefit of more intensive therapy (for example accelerated rt-PA versus streptokinase) are proportional to the mortality risk in patient subgroups. Thus, to identify patients whose additional benefit from intensive therapy would be considerable, it would be sufficient to identify the subgroups with the highest overall one-year mortality risk (figure 1). In these groups, classified according to the initial mortality risk, the expected benefit of reperfusion therapy will be expressed as gain in life expectancy (years or months).

In the following paragraphs the model will be developed and explained in a stepwise manner. The model assumptions have been summarised in table 1.

INITIAL TREATMENT BENEFIT

Initial treatment benefit can be expressed as the 'numbers of lives saved' within the first year after myocardial infarction. As described previously, treatment

benefit is related predominantly to mortality risk without therapy and to the time to intervention.[1,5,29] Factors determining mortality risk include age, previous infarction and indicators of the expected infarct size: infarct location, the total amount of ST-segment deviation in the ECG, the presence or absence of heart failure and presence or absence of bundle branch block (figure 1).[1,29]

THE RISK FOR INTRACRANIAL HAEMORRHAGE

The initial benefit of thrombolytic therapy is lost in some patients who have an increased risk of intracranial haemorrhage.[31] On the other hand, the risk of embolic stroke is diminished. No increase in total stroke was observed in large studies with streptokinase,[2,5] while a small excess of intracranial haemorrhage and stroke was observed after administration of accelerated rt-PA. Nevertheless, excess stroke after accelerated rt-PA is only 10% of the additional survival benefit.[15] Previous studies have identified risk factors for intracranial haemorrhage: increased age, elevated blood pressure at admission, low body-weight and the use of rt-PA vs. streptokinase.[32-34] Patients with other risk factors for intracranial haemorrhage were generally excluded from trials: those with a known history of cerebrovascular disease or other intracranial abnormalities and patients with a recent head trauma. These contraindications for thrombolytic therapy should be respected in clinical practice, and direct angioplasty should be considered in patients with increased bleeding risk.

LIFE EXPECTANCY OF THE REFERENCE POPULATION

Using age- and sex-specific mortality data from The Netherlands in 1990, life expectancy was estimated of an imaginary, average reference person in the normal population. Since 80% of the infarct patients admitted to coronary care units in The Netherlands are male, mortality risks were weighted according to this sex distribution. Reference life expectancies calculated for different age categories were 30.9 years at the age of 45, and 22.0, 14.3 and 8.4 years at ages 55, 65 and 75 respectively (figure 2a). Yearly mortality of a 55 year old reference subject would be approximately 1.0% to 1.5% during the first 5 years.

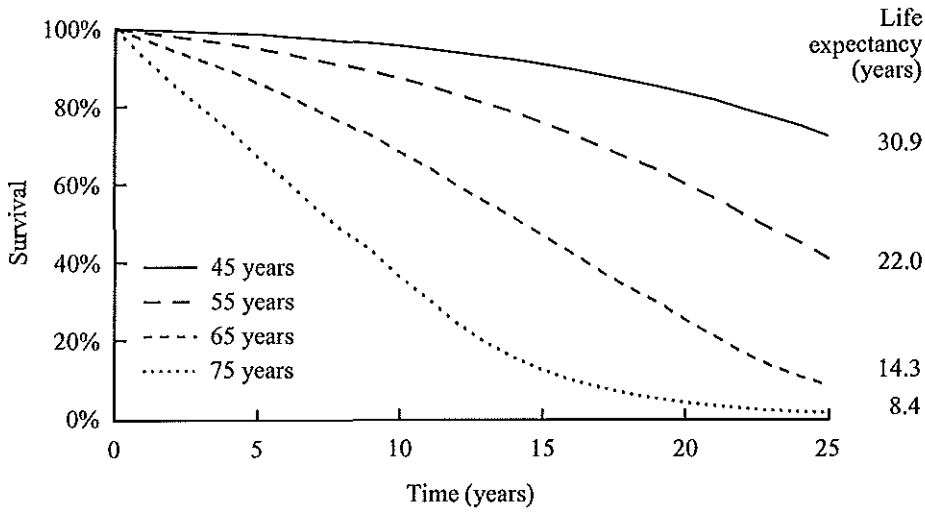

Figure 2(a): Life expectancy in the Dutch reference population. A comparison of four age groups

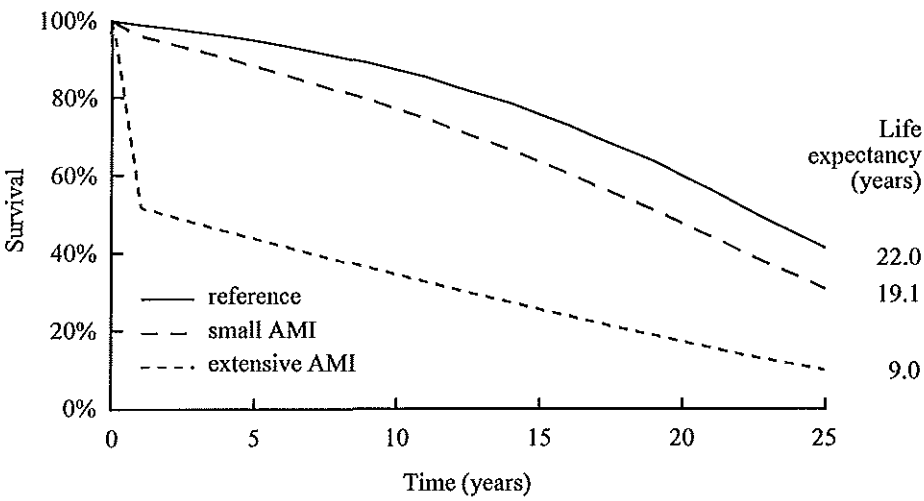

Figure 2(b): Life expectancy of a 55 year old myocardial infarction patient after conven-tional therapy

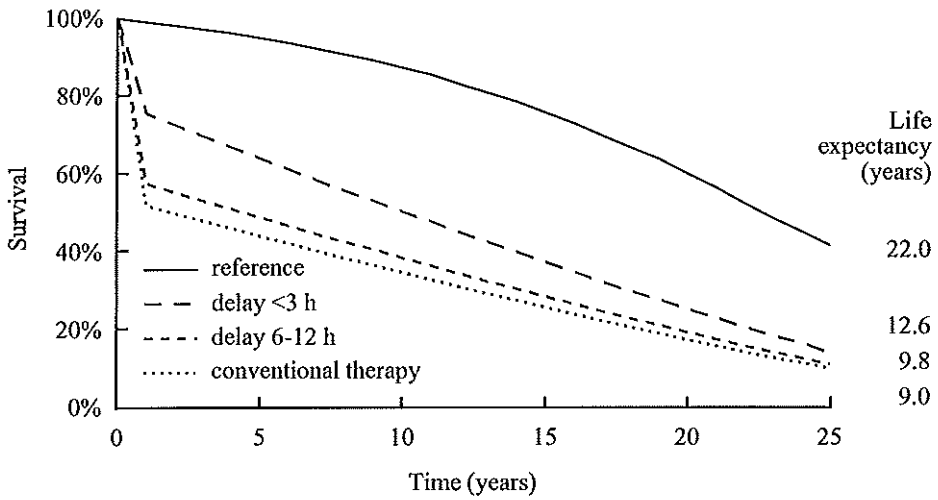

Figure 2(c): **Life expectancy of a 55 year old patient with extensive myocardial infarction patient after conventional as well as reperfusion therapy**

Figure 2: **Life expectancy (a) in a reference population as well as in myocardial infarction patients after (b) conventional and (c) reperfusion therapy**

(a) Reference life expectancies for different age categories. (b) Survival curves of a 55 year old reference subject as well as the curves of two conventionally treated patients of the same age. After a small infarction, life expectancy (the area under the curve) will be reduced from 22.0 to 19.1 years, a loss of 2.9 years (35 months). An extensive infarction would result in a loss of 13 years and a remaining life expectancy of only 9 years ((c), see also table 2(a)). Part of this loss can be regained by reperfusion therapy, as shown by the survival curve of a patient whose large myocardial infarction was treated early. Assuming no risk factors for intracranial haemorrhage, reperfusion therapy within 3 h of onset of symptoms regains 3.6 life years (43 months): from 9.0 to 12.6 years. The benefit of treatment initiated between 6 and 12 h would be 0.8 year (10 months): from 9.0 to 9.8 years. In the presence of risk factors for intracranial haemorrhage the treatment benefit in similar patients would be reduced by approximately 0.1 years (1 month).

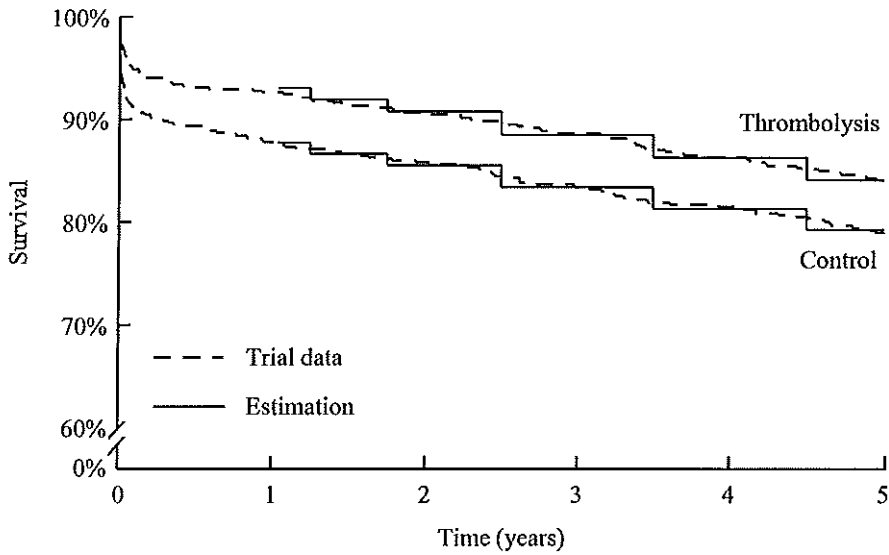

Figure 3: **Estimated and observed long-term mortality effects of reperfusion therapy in myocardial infarction**

Computed survival curves according to the proposed model were compared with observed survival in the combined data from 1,254 patients in trials by the Inter-university Cardiology Institute of The Netherlands and the European Cooperative Study Group.[35,37] The mean age of the patients was 55 years; the one-year mortality rate without thrombolysis was 12.5%. This corresponds to the mortality of a patient in the model of the same age with an anterior infarction and a total ST segment deviation exceeding 2.0 mV. Indeed, the estimated survival curves (dotted line) are superimposed on the observed curves (straight line) in the trials.

LIFE EXPECTANCY AFTER MYOCARDIAL INFARCTION

To assess life expectancy after myocardial infarction, with or without reperfusion therapy, follow up data were analysed from different trials of thrombo-lytic therapy. In all trials the reduction in mortality after one year was maintained during follow-up, for at least during 3 to 8 years.[29,35-37] Survival curves of patients without or with thrombolytic therapy were approximately parallel. This implies a sustained absolute survival benefit and a similar or slightly lower relative mortality after thrombolytic therapy compared with conventional treatment.

In the early study of intracoronary streptokinase conducted by the Inter-university Cardiology Institute of The Netherlands (ICIN), mortality rates after the first year were 3.2% and 2.1% in conventionally treated and reperfused treated patients respectively.[35] In the Western Washington intracoronary streptokinase studies these figures were 3.3% and 4.8%, respectively, and in the studies by the European Cooperative Study Group (ECSG) 2.0% and 1.8%.[36,37] The mean age of the patients in these studies was approximately 55 years. A recent observational study in a London district general hospital revealed a yearly mortality rate after the first year of follow-up of 4.2% in conventionally treated and 3.8% in thrombolysis treated patients at a median age of 62 years.[38] Thus, mortality in survivors of a myocardial infarction is in the range of 2% to 5% per year, which is 0.5% to 4.0% higher than mortality in the reference population as presented above. Late mortality rates are similar among patients with and without reperfusion therapy. We assumed that an average excess in mortality rate of approximately 1.5% will also occur in other age categories, and that this will be maintained beyond the reported follow-up. The accuracy of this estimation for a 55 year old patient is illustrated in figure 3, in which computed and observed survival curves are presented.

Survivors of a small infarct will have a better prognosis than those patients surviving a large infarction. In fact, predictors of late mortality are similar to factors determining early mortality.[37] We analysed late mortality rates in subgroups of patients with low, middle or high tertiles of initial mortality risk, employing the combined data of the ICIN and ECSG trials. In the low risk group, late mortality rate was 1.9% [95% CI 1.4-2.4] per year, whereas these figures were 2.5% [1.7-3.4] and 4.1% [2.5-5.6] in the medium and high risk groups, respectively. To account for these differences in our model, we assumed an excess in mortality of 1.0%, 2.0% and 3.0% compared with the reference population, for patients with a one-year mortality risk of less than 10%, between 10% and 30% and more than 30%, respectively (figure 1).

OVERALL BENEFIT OF REPERFUSION THERAPY

Part of the potential loss in life years from myocardial infarction can be regained by timely reperfusion therapy. The expected gain from reperfusion therapy in different subgroups of patients is presented in table 2(a) taking into account age, estimated infarct size and its modification by reperfusion therapy, and treatment

Number of risk indicators	ST deviation ≥2.0 mV	Life expect. (years) without therapy	Benefit: life expectancy (months) added by reperfusion therapy			Discounted Life expect. (years) without therapy	Benefit: discounted life expectancy (months) added by reperfusion therapy		
			<3 h	3-6 h	6-12 h		<3 h	3-6 h	6-12 h
Age <50 years									
0	no	25.6	5	2	0	13.6	3	1	0
0	yes	25.2	8	3	1	13.4	4	2	<1
1	no	24.6	13	6	2	13.1	7	3	1
1	yes	23.8	19	9	4	12.7	10	5	2
2	no	19.2	27	13	6	10.8	15	7	3
2	yes	18.0	37	18	8	10.1	20	10	5
≥3	no	13.0	53	26	13	7.7	30	15	7
≥3	yes	11.2	67	33	16	6.7	39	19	9
Age 50-59 years									
0	no	19.1	3	1	0	11.6	2	<1	0
0	yes	18.8	5	2	0	11.5	3	1	0
1	no	18.4	8	3	1	11.2	5	2	<1
1	yes	17.8	11	5	2	10.9	7	3	1
2	no	14.9	16	8	3	9.4	10	5	2
2	yes	13.9	22	11	5	8.8	14	7	3
≥3	no	10.4	34	16	8	6.8	21	11	5
≥3	yes	9.0	43	21	10	5.9	27	13	6

Age 60-69 years									
0	no	12.6	3	1	0	8.8	2	<1	0
0	yes	12.2	5	2	1	8.6	3	1	0
1	no	10.6	8	3	2	7.6	6	3	1
1	yes	9.9	11	5	2	7.1	8	4	1
≥2	no	7.6	18	8	4	5.6	12	6	3
≥2	yes	6.6	22	11	5	4.9	16	8	3
Age 70-79 years									
0	no	6.9	3	1	0	5.5	2	<1	0
0	yes	6.4	4	2	0	5.1	3	1	0
≥1	no	5.1	7	3	1	4.2	5	2	<1
≥1	yes	4.5	8	4	2	3.6	7	3	1

Table 2(a): **Estimated gain in life expectancy** Table 2(b): **Gain in discounted life expectancy**

Estimated gain in life expectancy (a) in different patient subgroups depending on age, indicators of increased mortality risk (risk indicators, see figure 1) and total ST segment deviation in the 12 standard ECG leads. Reference life expectancies in the different age groups are 30.9, 22.0, 14.3 and 8.4 years, respectively. The expected benefit of reperfusion therapy is estimated depending on baseline risk and treatment delay. See text for further explanation. The double line (in the right-hand column) separates patients whose expected benefit is less than the 50th percentile (above the line) from those exceeding the 50th percentile (below the line). The single line indicates patients with a very limited expected treatment benefit: less than the 10th percentile. The value of reperfusion therapy in such patients may be questioned. The underscored numbers indicate patients in whom the expected treatment benefit would be lost if risk factors for intracranial haemorrhage were present (apart from age): high blood pressure, low body weight and treatment with alteplase.[34] Discounting future life years at 5% per year results in values as presented in (b). The 50th percentile and 10th percentile lines are indicated as in (a). Note the similar position of the double lines in (a) and (b), with only a one position shift downward for early treatment in the youngest age group.

delay. In patients between 50 and 59 years of age the expected gain varied from less than 1 month to more than 2 years, respectively, in those with small infarcts arriving late and those with extensive infarction treated within 3 h of symptom onset. In all subgroups at younger age the expected gain in life years was somewhat greater, due to their longer life expectancy. The expected gain was also greater in patients between 60 and 69 years of age, as a result of the greater initial benefit due to the high mortality risk without therapy. In the elderly patients, aged 70 years or over, reperfusion therapy was less effective, and consequently the expected gain decreased. It should be appreciated that the available data[29] did not allow a more comprehensive analysis of expected benefits in patients at advanced age with extensive infarctions (multiple mortality risk factors) since such patients have a low life expectancy anyhow. The reduction of expected gain by intracranial bleeding was less than 1 month in the youngest age groups, and less than 1.6 and 2.2 months in patients aged 60-69 and 70-79 years, respectively.

In cost-efficacy analysis it is customary to discount future life years, to account for the greater value given to the near future, when compared with the value of the more uncertain, more distant future.[30] Discounting also compensates for the lesser accuracy of predicted long-term survival. In table 2(b) the discounted life expectancies (discounting factor 5% per year) are presented for different patient groups. In patients with the longest life expectancy - those in the youngest age group - values are reduced relative to elderly patients (compare tables 2(a) and (b)). The loss in discounted life expectancy from increased bleeding risk was less than 0.7, 0.6, 1.1 and 1.7 months in the respective groups of patients with increasing age.

The proposed model (table 2(a) and (b)) provides a scale to rank patients with greater or smaller expected treatment benefit. In order to analyse the distribution of patients with different levels of expected treatment benefit in clinical practice, data were collected from a series of 500 consecutive patients with myocardial infarction admitted to different hospitals (table 3). One third of these patients were above the age of 70, and only one sixth were less than 50 years of age. The distribution - in percentiles - of expected gain in life years among the different age groups is presented in figure 4(a). Patients with the greatest expected benefit were predominantly represented in the younger age groups. The 25% of patients with the greatest predicted benefit were within those younger than 70 years of age. Computation of discounted life expectancies resulted in some shift of the 50th percentile of expected benefits towards the

elderly. The greatest expected benefit according to the discounting principle was observed in patients between 60 and 70 years of age (figure 4(b)). This shift towards greater expected benefit in the elderly was even more pronounced if decisions were based on the initial treatment effect: reduction in one-year mortality. The distribution in figure 4(c) indicates that the 50% of patients with greatest expected benefit, who would warrant the most intensive mode of therapy, would be mainly among those above the age of 60 according to this approach, although none of the elderly would be above the 90th percentile.

Baseline characteristics	Number (%)
Male sex	373 (75)
Mean age (years)	63
Age (years)	
<50	73 (15)
50 - 59	124 (25)
60 - 69	145 (29)
≥70	158 (32)
Prior infarction	119 (24)
Localisation	
anterior	205 (41)
inferior and right ventricle	120 (24)
QRS time > 120 msec	31 (6)
Congestive heart failure	61 (12)
Symptom onset (h)	
<3	330 (66)
3 - 6	117 (23)
6 - 12	53 (11)
ST deviation ≥2.0 mV	195 (39)
Mean RR at admission ≥160/90 mmHg	140 (28)
Body weight <70 kg	151 (30)
Mean number of MI risk factors	1.1
Mean number of ICH risk factors	0.6

Table 3: **Baseline characteristics of 500 patients with evolving myocardial infarction admitted consecutively to six hospitals in The Netherlands during predefined periods in 1993 and 1994**

MI = myocardial infarction; ICH = intracranial haemorrhage

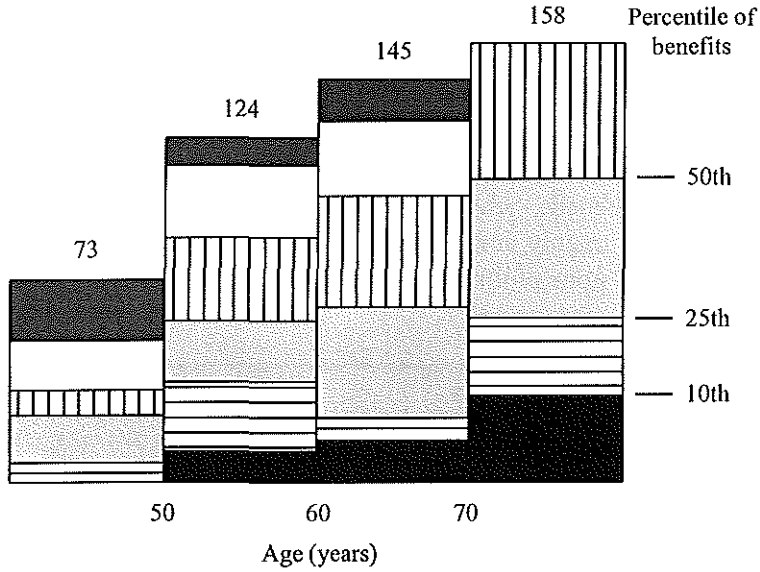

Figure 4(a): **Distribution based on gain in life expectancy (no discounting)**

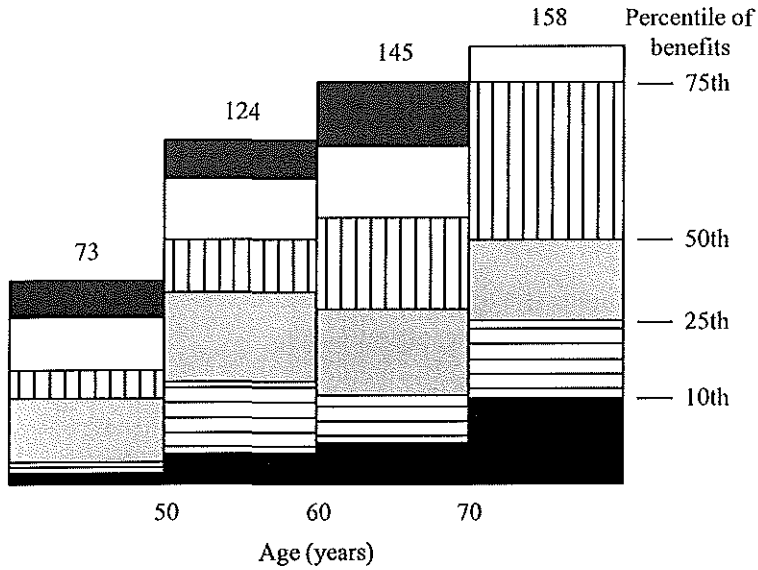

Figure 4(b): **Distribution based on gain in life expectancy (future life years discounted at 5% per year)**

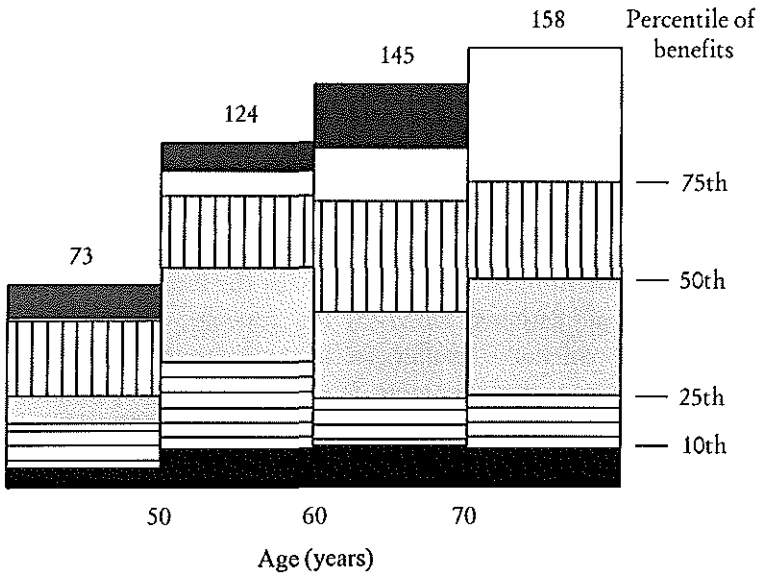

Figure 4(c): **Distribution based on reduction of one-year mortality**

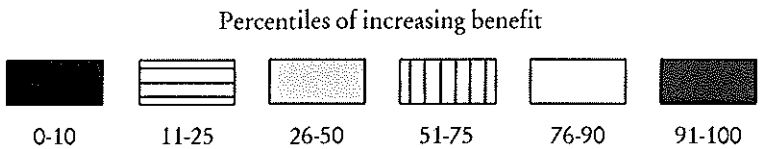

Figure 4: **Distribution of patients with different levels of estimated treatment benefit in clinical practice**

Three different models were applied to data from 500 consecutive patients from six different hospitals (table 3). The bars represent the actual patient numbers in four age groups. The different shadings represent patients with estimated benefit within the specified percentiles of the distribution. Note: (I) A marked shift of the centre of the distribution - 50th percentile - of models accounting for life expectancy (a) and (b) vs. reduction of one-year mortality (c). (II) The 25% of patients with greatest predicted benefit according to the full life expectancy model (a) was found in those younger than 70 years of age. (III) Discounting life years resulted in some shift of the 50th percentile of expected benefits towards the elderly (compare (a) and (b)). (IV) The greatest expected benefit according to the discounting principle was observed in patients between 60 and 70 years of age.

DISCUSSION AND SENSITIVITY ANALYSIS

The purpose of the current analysis was to develop a simple tool for clinical decision making in patients with evolving myocardial infarction. In most hospitals in Europe, as well as in other continents, physicians have to select the best available reperfusion therapy for individual patients, given that (1) several modes of therapy are available, which differ in efficacy, costs and complexity, while (2) resources are limited, which implies that the most effective therapy can not be offered to all patients. Since (3) the expected benefit differs among various groups of patients - smaller vs. larger infarcts, younger vs. elderly patients, early vs. late treatment (table 2) - it will be appropriate to offer the most effective (costly) therapy to those with the greatest expected benefit. At the same time, patients with similar expected benefits should be treated in a similar manner. Selection criteria, mainly based on age, financial situation or social status - better therapy for the younger, wealthy and powerful - are considered undesirable.

In order to choose the optimal therapy following this principle, the physician must be able to assess the expected treatment benefit, and to rank patients according to this expected benefit. Table 2, as presented in this report, provides such measures of expected benefit expressed in 'gain of (discounted) life years'. Since the available follow-up data are limited, a model had to be developed to estimate the expected gain in life years (or months) for different groups of patients which can easily be identified in clinical practice. The assumptions made in the model (table 1) will be discussed below and the effects of alternative assumptions on the outcome (i.e. ranking of patients according to the expected treatment benefit) will be presented where appropriate (sensitivity analysis).

Initial benefit: one-year survival

Predictors of one-year survival were obtained by multivariate logistic regression analysis in a series of 3,179 patients from different trials.[29] More recently a detailed analysis was performed by the GUSTO investigators, predicting 30-day mortality from patient characteristics as available upon admission, and by the Fibrinolytic Therapy Trialists.[1,39] In all three studies the characteristics which appeared to predict mortality were similar, which supports the validity of the proposed model for initial benefit of reperfusion therapy.

The duration of coronary occlusion preceding reperfusion is a major determinant of the extent of myocardial necrosis and infarct mortality. In the model it was assumed that initiation of reperfusion therapy within 3 h would reduce mortality in the first year by 50%, and therapy after 3-6 h and 6-12 h by 25% and 12.5%, respectively. This represents a simplification of the curvilinear relation between time to treatment and myocardial salvage as observed in experimental studies as well as clinical studies measuring infarct size (figure 5).[40,41] Within each time interval, the *relative* benefits of reperfusion therapy were assumed to be constant, thus the *absolute* benefits depend on, and are proportional to the mortality risk in patient subgroups. This is consistent with findings in all larger trials comparing thrombolytic therapy vs. placebo or controls, and with the GUSTO data.[1-10,15]

Overall benefit: life expectancy

Life expectancy in subgroups of patients was assessed from a survival table of the reference population in The Netherlands, with adjusted (higher) yearly mortality rates after myocardial infarction. The major determinants of life expectancy were initial - one-year - survival rates (as discussed above) and the difference between reference mortality and late mortality rates after infarction. Benefit of reperfusion therapy was defined as the number of regained future life years (months) which otherwise would have been lost after infarction. The effects of late mortality on prediction of treatment benefit in several age categories was evaluated for different model assumptions.

In the model, increased late mortality was related to mortality in the first year: 1.0%, 2.0% and 3.0% higher than the reference group, respectively, in three groups of patients with low, intermediate and high one-year mortality. This reflects the notion that patients with a large infarct will have both increased early (one year) and late mortality due to impaired ventricular function. In addition a more simple model was tested assuming similar late mortality rates, independent of infarct size, 1.5% greater than reference mortality. These two approaches yielded similar distributions of the expected gain (the data of the second model not shown). A shift in late mortality rates within the models had little effect, neither on the estimation of treatment benefit nor on the ranking of patients according to the expected treatment benefit.

There was a modest reduction in estimated treatment benefit in patients at increased risk for intracranial haemorrhage. However, this hardly affected the

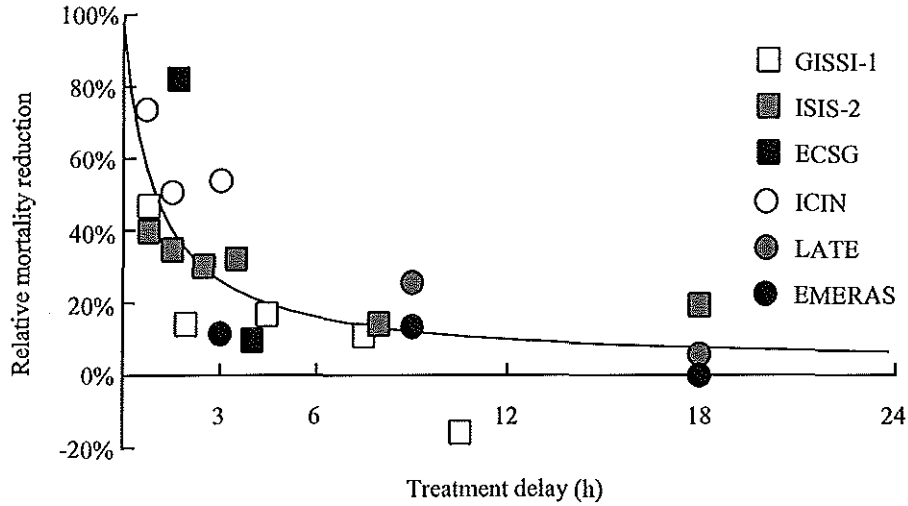

Figure 5: Relationship between treatment delay and mortality reduction as reported in clinical trials

The exact relationship is still debatable. The dotted curvelinear line presents the assumed relationship based on animal experiments.[41] Although no statistical curve fitting was used, the line appears to match data from different patient studies as indicated.

ranking of patients groups with increasing treatment benefit (table 2). The ranking of patients according to expected treatment benefit was determined predominantly by the introduction of life expectancy vs. reduction in one-year mortality in the model (compare figures 4(a) and (c)). Furthermore, the centre of the distribution (50th percentile line) was slightly affected by the discounting factor of 5% per year (compare figures 4(a) and (b)). The top end of the distribution (90th percentile) also shifted slightly, implying greatest benefit in patients between 60 and 70 years of age using the latter concept. The identification of patients with the smallest expected benefit (below 10th percentile) was also influenced by the design of the model (figure 4).

A PROPOSED DECISION RULE

The model which has been developed estimates the gain in life expectancy by reperfusion therapy depending on patient characteristics, predicted infarct size and time to treatment (table 2). This resulted in a gradient of expected benefits ranging from a negligible benefit <1 month in patients with small infarcts treated late, to an increased life expectancy of more than 2 years in patients with large infarctions treated within 3 h of symptom onset, or within 6 h in the youngest age group.

Each physician or each hospital must select the *best available* therapy for each patient. If a choice were made to treat all patients with one mode of therapy (e.g. streptokinase as being the less expensive drug, or rt-PA, it being the most effective), decisions in individual patients can be avoided. In clinical practice, however, individual decisions are usually required because of budgetary and/or organisational (direct angioplasty) constraints. At the Thoraxcentre we elected to allocate the resources as follows: 5% to 10% of the patients will not receive thrombolytic therapy, if estimated benefit is very small or even absent (e.g. in those with a small infarct, presenting late); 5% to 10% of patients with a large expected treatment benefit will be treated with direct angioplasty, including patients with a markedly increased risk for intracranial haemorrhage. In the remaining 80% to 90% of patients, half will receive streptokinase and the other half accelerated rt-PA. The life expectancy model (table 2(b)) is used to rank patients according to expected treatment benefit, while discounting future life years. The model with discounting was chosen, because it seems to be the best theoretical approach, and because of its intermediate position between the expected one-year benefit (figure 4(c)) and life expectancy without discounting (figure 4(a), table 2(a)). It should be appreciated, that the latter choice has only modest influence on the distribution of the use of the two thrombolytic regimens (table 2). According to the chosen model (table 2(b), figure 4(b)), direct angioplasty will be offered only to patients younger than 70 years of age.

The use of the two thrombolytic regimens in patient groups of similar size has been based on the recent cost effectiveness analysis of the GUSTO trial.[42] In that analysis, based on U.S.A. data, the incremental costs per life year gained by using accelerated rt-PA vs. streptokinase were estimated at $27,400. After adjustment for differences in price levels between the U.S.A. and The Netherlands the incremental costs of rt-PA per year of life gained amounts to approximately Dfl. 25,000. We elected to use this more effective but more

expensive therapy in half of the patients: those with the greatest expected gain in life years. In these patients the incremental costs will be less than Dfl. 25,000. Patients in whom incremental costs for rt-PA would be in excess of Dfl. 25,000 were recommended to be treated with streptokinase.

The thresholds currently applied for decision making at the Thoraxcentre are (based on the model of our choice as described above): no reperfusion therapy when the gain in discounted life expectancy was <1 month, streptokinase for 1-4 months and accelerated rt-PA for a gain ≥ 5 months. Direct angioplasty is recommended in patients with an increased intracranial bleeding risk and in those with estimated gain ≥ 12 months. Indeed, application of this decision rule to the 500 patients resulted in 54 patients (10.8%) being recommended conventional therapy, 197 (39.4%) SK, 199 (39.8%) accelerated rt-PA and 50 (10%) direct angioplasty. It should be appreciated that this choice for allocation of recourses is wholly arbitrarily. Other centres may elect to apply another model, or to provide the available therapies in different proportions and use, for example, direct angioplasty more frequently or never. This would imply other threshold values, while the same principles could still be applied.

CLINICAL IMPLICATIONS : ARBITRARY BUT CONSISTENT DECISIONS

Currently available follow-up after reperfusion therapy is limited, and lacks power to allow a definite choice between the approaches presented above. However, the physician often has to make his choices, at night, with little time for reflection. Patients previously treated with streptokinase or anistreplase preferably should not receive such drug a second time because of development of streptokinase antibodies.[43] Patients in cardiogenic shock should be offered direct angioplasty, when available. For most patients, however, models like the one presented here may guide the physician to be consistent, and to offer the same mode of therapy to patients with similar expected treatment benefits. Benefit always will be greatest in patients with extensive infarction, treated early after the onset of symptoms. All efforts should be made to promote early treatment by whichever regimen available, whether it be streptokinase, accelerated rt-PA or direct angioplasty.[43]

Patients with the greatest expected treatment benefit deserve the most effective therapeutic regimen, regardless of costs and complexity. If such decision were based predominantly on the initial treatment benefit, then such

intensive and expensive therapy would be reserved mainly for elderly patients (figure 4(c)). However, the most intensive therapy should be given to younger patients if the decision is weighted by the expected long-term survival after successful intervention (figure 4(a)). This reasoning may also be reversed : A physician who, intuitively, applies direct angioplasty (the assumed most effective therapy) to predominantly younger patients logically assumes a significant long term benefit of the intervention.

At the Thoraxcentre, we have opted for the intermediate approach (table 2(b), figure 4(b)), but others may be inclined to base their decisions on other models. It should be appreciated that our preference will change when new, more effective treatment regimens become available in which either the risk of intracranial haemorrhage or the costs would be lower. Nevertheless, a model as described above does ensure that treatment decisions are made in an organised and consistent manner, to provide optimal treatment for patients with evolving myocardial infarction, given the existing financial - and organisational restrictions.

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Chapter 6

ALLOCATION OF REPERFUSION TREATMENT RESOURCES IN INDIVIDUAL PATIENTS: A FURTHER ANALYSIS

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Reperfusion therapy for acute myocardial infarction: which strategy for which patient?
Submitted

INTRODUCTION

Large randomised trials have demonstrated the benefit of reperfusion therapy in treatment of patients with evolving myocardial infarction.[1,2] Reperfusion therapy dissolves (pharmacological approach) or removes (mechanical procedure) the occluding coronary thrombus, thus recovering blood flow and oxygen delivery to the jeopardised myocardium. If such therapy is initiated within 6 h from coronary occlusion, which event usually coincides with onset of chest pain, part of the viable myocardial tissue will be preserved,[3] which has favourable impact on patient's prognosis.

Results of randomised investigations apply by necessity to a patient *population*, whose characteristics are defined by the trial in- and exclusion criteria. In clinical practice, however, physicians will treat *individual* patients, in whom the benefits, risks and cost/effectiveness of reperfusion therapy are not always clear at once, let alone differences in efficacy between specific reperfusion strategies. Since benefits of therapy rapidly fall off with time,[4] opportunities for reflection are limited at the moment of presentation of the patient. Therefore, it might be wise to determine in advance which patient will receive which therapy (if any), and to reflect decisions in treatment guidelines. In this paper, we summarise the key aspects which should be considered in this respect.

REPERFUSION THERAPY OPTIONS

Over the last 15 years several reperfusion treatment strategies have been developed. Table 1 summarises the properties of the most relevant options.

Streptokinase and aspirin

The clinical effectiveness of intravenous streptokinase has been demonstrated by the GISSI-1 (N=11,802), ISAM (N=1,741) and ISIS-2 (N=17,187) investigations.[5-7] In these trials patients were randomised to either a streptokinase infusion of 1.5 MU units over 1 h or placebo treatment (open control in GISSI). Short term mortality among the streptokinase patients was 20% reduced compared to those allocated control therapy (35-day mortality 9.6% vs. 12.1%; $p<0.0001$). This beneficial effect of streptokinase is maintained for at least 4 years.[8] The smaller ICIN trial (N=533) of

	Streptokinase	Reteplase	Alteplase	Angioplasty
Recommended dose	1.5 MU over 1 h	2 boluses of 10 MU given 30 min apart	15 mg bolus; 0.75 mg/kg over 30 min; 0.5 mg/kg over next 60 min (total dose ≤100 mg)	Does not apply
Accompanying medication	Aspirin[1]	Aspirin and intravenous Heparin[2]	Aspirin and intravenous Heparin	Aspirin and intravenous Heparin
Price[3]	$250 - $270	Not on the market yet	$1,260 - $2,220	$5,040 - $6,200
Patency[4]	57%	83%	81%	98%
Intracranial bleeding	0.5%	0.7%	0.7%	<0.1%
Complexity	Allergic reaction Hypotension	Relative high reocclusion rate (need heparin, see above)	Relative high reocclusion rate (need heparin, see above)	Complex procedure, need excellent medical staff; only in hospitals with catheterisation laboratory
Strength	Effective thrombolytic drug with low complication rate and broad applicability	Bolus administration	High early patency rate	Angioplasty not only removes occluding thrombus, but also treats underlying coronary artery disease

Table 1: **Characteristics of the most relevant reperfusion treatment strategies**

(1) Aspirin dose 160-325 mg/day for at least 1 month; (2) heparin dose 5000U bolus; 1000-1200U/h for 3-5 days; (3) the lowest values represent European prices,[45] whereas the highest values correspond with US prices[44]; (4) represents the percentage of patients with TIMI-grade 2 or 3 flow at 90 min.[16,56,57]

intracoronary streptokinase reported a sustained effect even at 10 years follow-up.[9] The stroke rate was in balance between the two groups (0.79% vs. 0.74%). There was a difference in the rate of intracranial bleeding complications, which event was documented in 22 out of 15,356 streptokinase patients, 17 of whom died, and in none of the 15,378 controls. It should be realised, however, that these numbers represent only part of the true incidence of intracranial haemorrhage, since most of the strokes were not classified as either ischaemic or embolic.

In ISIS-2 patients were further randomised to either oral aspirin (162.5 mg daily for one month) or placebo. Mortality among patients randomised to both streptokinase and aspirin was 39% reduced compared with both placebo (8.0% vs. 13.2%; $p<0.0001$), whereas the incidence of cerebral complications was almost halved (0.58% vs. 1.05%; $p<0.0001$), thus demonstrating the clinical efficacy of combined thrombolytic and antiplatelet therapy to reopen the occluded coronary artery and keep it open.

Accelerated alteplase and intravenous heparin

A disadvantage of streptokinase is the production of antibodies, which limits it's efficacy and applicability on repeated use. Recombinant tissue-type plasminogen activator (rt-PA), on the other hand, is a non-antigenic agent, which directly activates the lytic process, and is potentially more powerful than streptokinase. The relative efficacy of rt-PA (100 mg infusion over 3 h) over streptokinase was studied in the GISSI-2 (N=20,768) and ISIS-3 (N=41,299) trials, but no clinical benefit was observed.[10-12] In contrast, in the GUSTO-1 trial (N=41,021), the combination regimen of *accelerated* rt-PA (100 mg infusion over 1.5 h) and intravenous heparin yielded a statistically significant ($p=0.001$) 14% relative reduction in 30-day mortality compared with 'standard' streptokinase (combined with either subcutaneous or intravenous heparin) from 7.3% to 6.3% on the absolute scale. The difference was still present at one year.[13,14] The rate of intracranial complications was slightly, but significantly ($p<0.001$) increased from 1.29% to 1.55%, which was mainly caused by a difference in cerebral bleeding complications.

Reteplase

Recombinant plasminogen activator (reteplase, r-PA) is a mutant of rt-PA with a markedly increased half-life, which allows bolus administration. Angiographic evaluations of the r-PA regimen of 2 boluses of 10 MU given 30

min apart showed relatively high early coronary patency rates compared with rt-PA.[15,16] Two large mortality studies with r-PA have been reported. The INJECT trial (N=6,010) demonstrated that the reteplase regimen is at least equivalent to 'standard' streptokinase.[17] Mortality at one month was 9.0% and 9.5% in patients randomised to r-PA and streptokinase, respectively, whereas stroke rates were 1.23% and 1.00% (these differences were not significant, while it should be realised that INJECT was designed to show equivalence, and not superiority of reteplase). The GUSTO-3 study (N=15,060) compared r-PA with the GUSTO-1 accelerated rt-PA regimen.[18] This trial has a power of 70% (90%) to demonstrate a 15% (20%) relative reduction in 30-day mortality after r-PA. However, no significant difference was observed: mortality was 7.2% after accelerated rt-PA and 7.4% after r-PA. Stroke rates were also comparable: 1.83% and 1.67%, respectively. These results suggest that the clinical effects of r-PA are in between 'standard' streptokinase and accelerated rt-PA.

Other agents

Other thrombolytic regimens based on agents from the class of plasminogen activators are currently being studied. Angiographic investigations with saruplase and lanoteplase indicated that the efficacy and safety profile of these drugs is comparable with alteplase.[19,20] More promising results have been reported from staphylokinase. In a small randomised trial (N=100) staphylokinase appeared to be at least as effective for early recanalisation as accelerated rt-PA, while it was significantly more fibrin-specific.[21] The improved fibrin specificity will avoid a systemic fibrinolytic state, and may very well reduce the risk of haemorrhages. Larger studies are necessary to determine the clinical properties of this drug.

Angioplasty

Another way to repair the perilous coronary occlusion is an *immediate* mechanical intervention. Direct coronary angioplasty has been compared with several thrombolytic regimens in a couple of randomised trials. Among the patients enrolled in all of these trials (N=2,606) short term mortality after primary angioplasty was 33% reduced compared with thrombolysis (4.4% vs. 6.5%; p=0.018).[2] The risk of stroke was also significantly reduced (0.70% vs. 1.98%; p=0.007; intracranial haemorrhage: 0.07% vs. 1.14%; p=0.0005). So far, there are no reports on long term outcome. It should be realised, that the

major part of the observed reduction in cerebral bleeding complications is already accounted for in the mortality results, since 50% to 70% of cerebral bleeds will lead to death.[22,23] This indicates, that direct angioplasty is especially an alternative for, and probably superior to thrombolysis in patients with high risk for cerebral bleeding complications.

Several trials (N≈7,000) investigated the value of systematic *additional* angioplasty after thrombolytic therapy.[24] No benefit of this approach was observed if the combined endpoint of mortality and non-fatal reinfarction at 6 weeks was considered, as compared with thrombolysis alone (12.1% vs. 11.6%; NS). Among the 6 weeks survivors, however, angioplasty seemed to be associated with a lower one-year mortality rate (2.1% vs. 2.6%, which implies a 19% relative reduction; NS). Longer follow-up is necessary to determine whether this survival difference will emerge. So far, however, it is not recommended to perform *routine* angioplasty as an adjunct to thrombolytic therapy. On the other hand, results of the DANAMI trial (N=1,008) indicate that angioplasty or coronary bypass surgery is warranted and beneficial in patients with recurrent ischaemia prior to discharge.[25]

Only few randomised investigations evaluated the merits of *rescue* angioplasty after failed thrombolysis. The limited data indicate that such approach might have some benefit (mortality at 6 weeks was 5.4% among 93 patients randomised to rescue angioplasty vs. 12.9% among 85 controls; $p=0.078$),[24] but more evidence is definitely needed.

Antithrombotic agents

Antithrombotic treatment as an adjunct to thrombolytic and antiplatelet (aspirin) therapy was evaluated in the GISSI-2 and ISIS-3 trials.[10-12] Both trials together, 62,067 patients were randomised to either subcutaneous heparin or control therapy. Mortality at one month was slightly, but not significantly reduced in the heparin group (8.8%) compared with controls (9.2%), whereas stroke rates were slightly higher (1.22% and 1.15%, respectively). In the GUSTO-1 study no significant difference was observed between subcutaneous and intravenous heparin in patients treated with streptokinase.[13] Thus, it can be concluded that neither subcutaneous nor intravenous heparin adds much to the outcome in streptokinase patients. The additional value of intravenous heparin added to accelerated rt-PA (one of the GUSTO-1 treatment arms) cannot be quantified with data from existing randomised controlled clinical trials. There are, however, strong indications from angiographic studies that

intravenous heparin considerably contributes to sustained infarct-artery patency.[26]

As opposed to heparin, hirudin directly acts on platelet bound thrombin and might therefore be expected to be more effective. However, two randomised trials in patients with evolving myocardial infarction (TIMI-9a, N=757 and GUSTO-2a, N=2,564)[27,28] did not show a significant advantage of intravenous hirudin over intravenous heparin in combination with thrombolysis, while the high dose of hirudin used in these trials resulted in an unacceptable high rate of intracranial haemorrhage. The subsequently used low dose largely avoided these complications, but had little (GUSTO-2b, N=12,142) or no (TIMI-9b, N=3,002) effect on survival.[29,30] Studies with other thrombin inhibitors, such as hirulog and argatroban, in combination with thrombolytic therapy are ongoing.

Future directions: glycoprotein IIb/IIIa receptor blockers

Current investigations focus on the development of reperfusion strategies which may result in more *rapid* (new fibrinolytic agents), more *complete* (direct angioplasty) and more *sustained* (intracoronary stents) coronary patency compared with existing options.[31] The introduction of platelet glycoprotein IIb/IIIa receptor blockers may improve treatment of patients with evolving myocardial infarction in all three aspects. glycoprotein IIb/IIIa forms the final common pathway in platelet aggregation, which may lead to the formation of a 'white', platelet-rich thrombus. Use of glycoprotein IIb/IIIa receptor blockers will lead to extensive or even full inhibition of this process, and may thus facilitate clot lysis and prevent early reocclusion.

The first agent developed for clinical use, abciximab, has been shown to be beneficial in the prevention of thrombotic complications following coronary angioplasty in patients at high risk for acute vessel closure, including those with evolving myocardial infarction.[32,33] Results of the CAPTURE trial (N=1,265) indicate, that abciximab can stabilise patients to such level that subsequent coronary intervention might be postponed or even cancelled.[33] The clinical efficacy of another glycoprotein IIb/IIIa receptor blocker, eptifibatide, has been evaluated in the recent large PURSUIT randomised trial (N=10,948). In patients with unstable angina or suspected non-Q-wave myocardial infarction eptifibatide showed a significant 10% relative reduction in the combined endpoint death or non-fatal myocardial (re)infarction at 30 days compared with placebo (14.2% vs. 15.7%; p=0.042; 17.8% vs. 19.8% in

the myocardial infarction patients).[34] Similar results have been shown for tirofiban and lamifiban in several studies reported recently.[35-37] A small dose-ranging study in patients with acute myocardial infarction suggested that the incidence and speed of reperfusion can be enhanced when eptifibatide is combined with accelerated rt-PA, aspirin and heparin.[38] Large randomised trials assessing the clinical value of such treatment will be launched soon.

TIME FROM ONSET OF SYMPTOMS TO TREATMENT

The beneficial effect of reperfusion therapy depends on time from symptom onset, although the nature of the treatment benefit/delay relationship is subject to discussion.[1,4,39] Generally, it is agreed, that initiation of therapy within 6 h of symptom onset will *directly* save left ventricular muscle cells, and consequently improve survival. Treatment within 6 to 12 h from continuous coronary occlusion will have *indirect* salutary effects on left ventricular function (reduction of left ventricular remodelling and dilatation)[40] and improved survival after such delays is therefore less pronounced. Considering the results of experimental studies, combined with randomised comparisons between pre- and in-hospital thrombolysis on about 6,600 patients, and larger randomised clinical trials, we are convinced of the importance of reperfusion treatment within 1 to 2 h from onset of symptoms, the time window in which cell death just commences. In the first hour a 50% mortality reduction is conceivable,[4] whereas this figure is approximately 30%, 25% and 12.5% in the respective ≥1-3, ≥3-6 and ≥6-12 h intervals. In an earlier study,[41] a 50% reduction was assumed for treatment in the first 3 h period, which was based on an analysis of 3,362 patients,[42] but this seems overoptimistic in view of current evidence from clinical trials.

COMPLICATIONS

While early thrombolytic therapy considerably reduces mortality in patients with evolving myocardial infarction, some complications may occur. The most feared complication is intracranial haemorrhage, which happened in between 0.3% and 1.0% of patients who participated in randomised trials, and led to death in more than half of those cases, while only about 10% recovered

without significant disability.[22,23] It should be appreciated, that these deaths were reckoned in the overall mortality figures, which were clearly in favour of thrombolytic therapy compared with conservative treatment. Furthermore, the rate of embolic strokes was reduced due to thrombolytic therapy, so that the overall rate of cerebrovascular complications as a whole was only marginally increased. Among each 1,000 patients with ST elevation or new Bundle Branch Block treated within 6 h of symptom onset, thrombolytic therapy will prevent approximately 30 deaths compared with control therapy, due to early reperfusion of the occluded coronary artery, and cause about 2 deaths as well as lasting disability in another 2 patients, due to cerebral complications.[39] Thus, the benefits of thrombolytic therapy far exceed the risks in these patients.

Rates of haemorrhage other than intracranial as reported in randomised trials of thrombolysis are difficult to interpret, because of varying definitions, different intensities of data collection and differences in use of invasive revascularisation procedures. Overall in the placebo-controlled trials, there is a two to three fold increased incidence of severe haemorrhage after thrombolytic therapy (0.4% among controls vs. 1.1% among patients randomised to active treatment).[1]

Immunologic reactions may occur if streptokinase is applied, which drug is derived from group C streptococci. Determination of the true incidence of these reactions is difficult, since symptoms of allergy, such as fever, hypotension and shortness of breath are often indistinguishable from symptoms that may be caused by the myocardial infarction itself. Nevertheless, in several trials, mild allergic reactions were reported in approximately 4% of patients treated with streptokinase. True anaphylactic shock is very rare, perhaps occurring in 0.1%. Hypotension may occur in about 6%.[23]

Reperfusion therapy may also induce ventricle fibrillation, especially if treatment is initiated in an early stage of the infarction.[43] This complication should therefore be watched, particularly in pre-hospital thrombolysis programs. Thrombolytic treatment is only warranted if first aid (defibrillator) is immediately available.

Feature	Fibrinolytic Therapy Trialists' Collaborative Group					GUSTO-1 randomised trial				
	No. patients		Deaths during first 35 days			No. patients		Deaths during first 30 days		
	Fibrin	Contr	Fibrin	Contr	Benefit per 1,000 (SD)	Acc t-PA	SK	Acc t-PA	SK	Benefit per 1,000 (SD)
Location										
inferior	6,556	6 484	493 (7.5%)	542 (8.4%)	8 (5)	5 931	11 575	277 (4.7%)	592 (5.1%)	4 (3)
anterior	6,587	6 642	868 (13.2%)	1 120 (16.9%)	37 (6)	4 019	7 829	352 (8.8%)	822 (10.5%)	17 (6)
Hours from onset										
0-1	1,678	1,670	159 (9.5%)	217 (13.0%)	35 (11)	239	505	18 (7.5%)	24 (4.8%)	-28 (20)
≥1-3	8,297	8,315	683 (8.2%)	889 (10.7%)	25 (5)	5,204	10,369	238 (4.6%)	619 (6.0%)	14 (4)
≥3-6	8,294	8,195	802 (9.7%)	945 (11.5%)	19 (5)	4,255	7,912	318 (7.5%)	637 (8.1%)	6 (5)
0-6	18,269	18,180	1,644 (9.0%)	2,051 (11.3%)	23 (3)	9,698	18,786	574 (5.9%)	1,288 (6.9%)	9 (3)
≥6-12	6,478	6,404	719 (11.1%)	813 (12.7%)	16 (6)	330	715	30 (9.1%)	66 (9.2%)	1 (19)
Age (years)										
<55	8,082	8,158	278 (3.4%)	373 (4.6%)	11 (3)	3,232	6,389	58 (1.8%)	126 (2.0%)	2 (3)
55-64	9,911	9,678	709 (7.2%)	864 (8.9%)	18 (4)	2,989	5,792	108 (3.6%)	275 (4.8%)	11 (4)
65-74	8,487	8,496	1,144 (13.5%)	1,372 (16.1%)	27 (5)	2,789	5,553	230 (8.3%)	575 (10.4%)	21 (7)
≥75	2,835	2,953	689 (24.3%)	748 (25.3%)	10 (13)	1,326	2,394	254 (19.2%)	490 (20.5%)	13 (14)
Gender										
male	22,353	22,412	1,835 (8.2%)	2,258 (10.1%)	19 (3)	7,721	15,049	383 (5.0%)	884 (5.9%)	9 (3)
female	6,962	6,873	985 (14.1%)	1,099 (16.0%)	18 (6)	2,622	5,090	270 (10.3%)	587 (11.5%)	12 (7)

SBP (mmHg)										
<100	1,263	1,182	365 (28.9%)	415 (35.1%)	62 (18)	959	1,973	162 (16.9%)	362 (18.4%)	15 (15)
100-149	17,979	18,063	1,731 (9.6%)	2,081 (11.5%)	19 (3)	7,301	14,112	394 (5.4%)	895 (6.3%)	9 (3)
150-174	7,907	8,005	569 (7.2%)	694 (8.7%)	15 (4)	1,777	3,454	84 (4.7%)	167 (4.8%)	1 (6)
≥175	2,166	2,035	155 (7.2%)	167 (8.2%)	11 (8)	304	603	13 (4.3%)	47 (7.8%)	35 (16)
HR (bpm)										
<80	12,922	12,965	926 (7.2%)	1,097 (8.5%)	13 (3)	6,488	12,593	314 (4.8%)	723 (5.7%)	9 (3)
80-99	6,268	6,221	579 (9.2%)	706 (11.3%)	21 (5)	2,913	5,684	197 (6.8%)	454 (8.0%)	12 (6)
≥100	3,095	3,126	537 (17.4%)	646 (20.7%)	33 (10)	942	1,864	142 (15.1%)	294 (15.8%)	7 (14)
Prior MI										
no	22,468	22,635	,993 (8.9%)	2,467 (10.9%)	20 (3)	8,596	16,798	463 (5.4%)	1,050 (6.3%)	9 (3)
yes	5,719	5,577	717 (13.6%)	784 (14.1%)	15 (6)	1,726	3,294	180 (10.4%)	399 (12.1%)	17 (9)
Diabetes										
no	19,423	19,424	1,697 (8.7%)	1,981 (10.2%)	15 (3)	8,828	17,075	504 (5.7%)	1,100 (6.4%)	7 (3)
yes	2,236	2,260	1,981 (10.2%)	391 (17.3%)	37 (11)	1,498	3,024	140 (9.4%)	343 (11.3%)	20 (9)
All patients	29,315	29,285	2,820 (9.6%)	3,357 (11.5%)	18 (3)	10,348	20,162	653 (6.3%)	1,475 (7.3%)	10 (3)

Table 2: **Short-term mortality observations from randomised clinical trials of thrombolytic therapy versus placebo/control and of more effective therapy (accelerated rt-PA) versus 'standard' therapy (streptokinase)**

Fibrin = fibrinolytic therapy; Contr = control or placebo; Acc t-PA = accelerated t-PA; SK = streptokinase; SBP = systolic blood pressure; HR = heart rate; MI = myocardial infarction

Observations are derived from the Fibrinolytic Therapy Trialists' Collaborative analysis[1] and an analysis of the GUSTO-1[13] data.

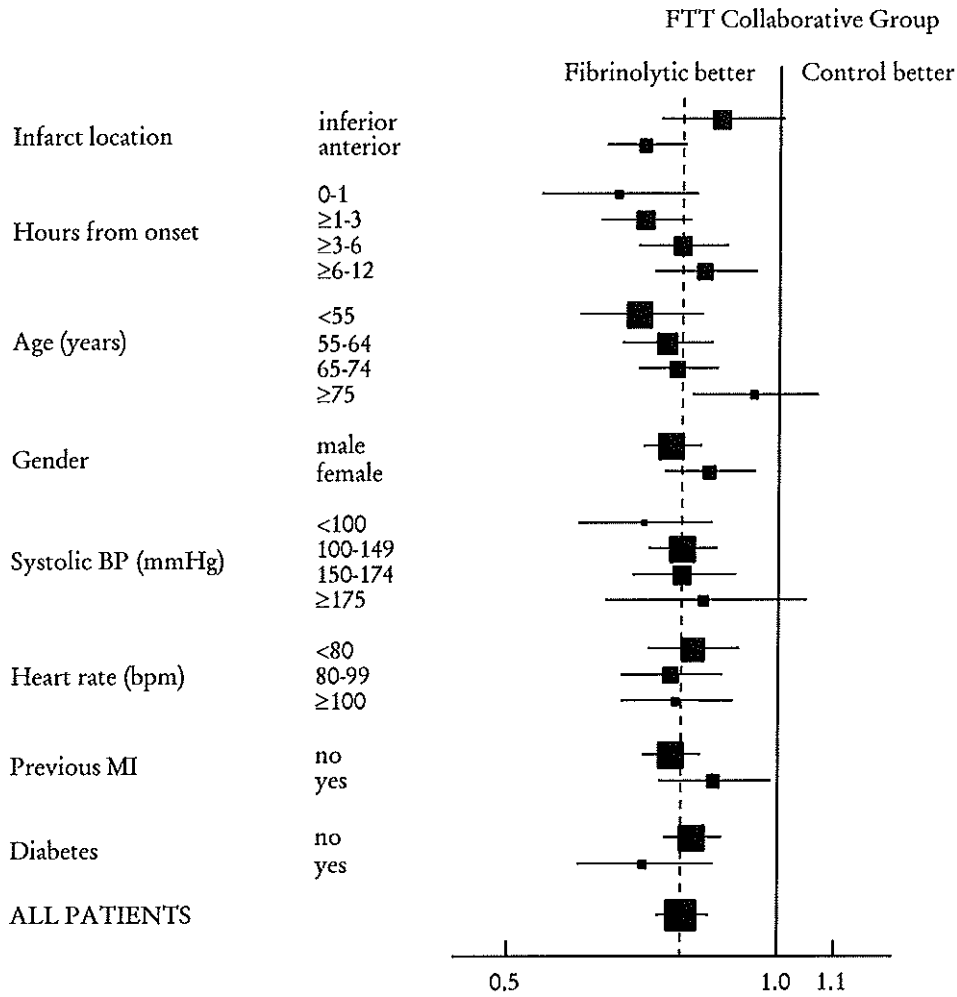
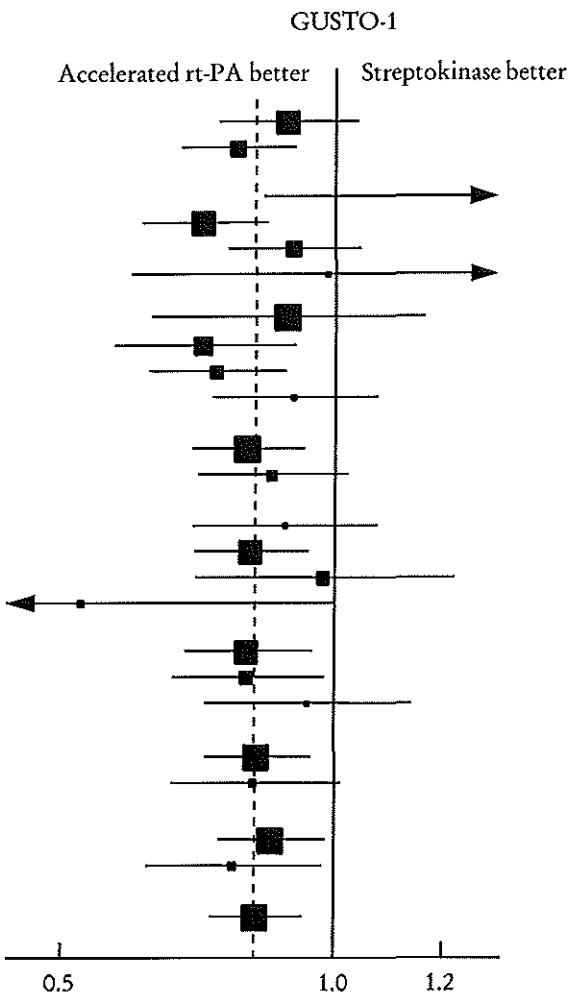


Figure 1: **Relative effects of thrombolytic therapy compared with control, and of more effective therapy (accelerated rt-PA) compared with 'standard' therapy (streptokinase) on short-term mortality in several subgroups of patients**



Data represent odds ratio's and corresponding 95% confidence intervals. The areas of the black squares are proportional to the amount of 'statistical information' contributed by the trials.[1] Observations are derived from the Fibrinolytic Therapy Trialists' Collaborative analysis,[1] which included patients randomised up to 24 h after onset of symptoms, and an analysis of the GUSTO-1 data,[13] in which most patients were randomised within 6 h.

COSTS

Besides differences in clinical efficacy between the reperfusion strategies discussed above, there are major differences in costs. Streptokinase therapy initially requires about $250, whereas rt-PA treatment costs approximately $2000 (USA prices, see table 1).[44,45] A cost-effectiveness analysis of the GUSTO-1 data showed, that these initial differences will not be recovered by savings during follow-up (the incremental cost-effectiveness ratio was about $27,400 per year of life saved by rt-PA compared with streptokinase).[44] Immediate angioplasty is even more expensive, with initial costs around $6000. Investigations of data from randomised trials indicated that these costs are recovered in part by a decrease in subsequent revascularisation procedures compared with thrombolysis.[45,46] Observational data, however, contradict these findings.[47]

The considerable higher costs of rt-PA and angioplasty compared with streptokinase will limit their availability, especially in an era of shrinking health care budgets, while angioplasty is by nature limited to hospitals with a catheterisation laboratory and excellent trained and experienced medical staff. Therefore, these options should be applied, when available, in patients who are expected to benefit most from therapy.

TREATMENT EFFECTS IN SUBGROUPS OF PATIENTS

Table 2 and figure 1 present the effects of thrombolytic therapy on 35-day mortality compared with control as observed in an analysis of all trials that randomised at least 1,000 patients (altogether 58,600 patients).[1] No apparent deviations from the average *relative* mortality reduction are observed, except for subgroups according to time from symptom onset (as discussed above) and, to a lesser extent, age.[1,39] Consequently, the *absolute* number of deaths avoided by thrombolytic treatment appears to be greater in those groups with a higher mortality. The relative and absolute reductions were maintained during follow-up, but there was no further divergence observed. As far as age is concerned, there was a significant trend towards larger *relative* mortality reductions among younger patients. However, *absolute* reductions were comparable, since mortality greatly increases with age.

Table 2 and figure 1 also demonstrate detailed data on 30-day mortality of 30,510 GUSTO-1 patients randomised to either streptokinase (with either subcutaneous or intravenous heparin) or accelerated rt-PA.[13] Again, there is no significant heterogeneity between the relative mortality reductions in the different subgroups of patients studied. Thus, also the additional effect of more intensive and effective therapy (rt-PA) upon 'standard' therapy (streptokinase) is most pronounced in the patient groups at high mortality risk.[48] The GUSTO-2b angioplasty substudy (1,138 patients) presented some subgroup analyses, which indicated, that this argumentation also holds for angioplasty vs. accelerated rt-PA, although it should be appreciated that the latter data is fairly limited.[49]

BENEFITS AND RISKS IN INDIVIDUAL PATIENTS

From the above it is apparent, that reperfusion therapy *generally* reduces mortality after myocardial infarction. The absolute effect of therapy compared with control treatment, as well as the additional effect of more effective therapy upon 'standard' therapy is most prominent in subgroups of patients with high mortality rates. Nevertheless, it should be realised that reperfusion therapy (especially thrombolytic therapy) may lead to life-threatening cerebral bleeding complications, which would not have occurred without treatment. Accordingly, to evaluate treatment efficacy in an *individual* patient, the risk reduction of cardiac death (i.e. death not due to haemorrhagic stroke) should be weighed against the introduced risk for adverse cerebral bleeding complications.

Determinants of mortality not due to haemorrhagic stroke

Analysis of the GUSTO-1 data showed that patient's 30-day mortality risk after thrombolysis is largely determined by the independent presenting features: age (most important), systolic blood pressure, Killip class, heart rate, infarct location and history of myocardial infarction.[50] A young, haemodyamically stable patient with a small inferior infarction is at low risk, while an elderly patient presenting with signs of heart failure and an extensive anterior infarction is at high risk of early death.[9,51]

In the GUSTO-1 trial 268 patients suffered from a primary intracranial bleeding complication, and 160 (60%) of them subsequently died within the

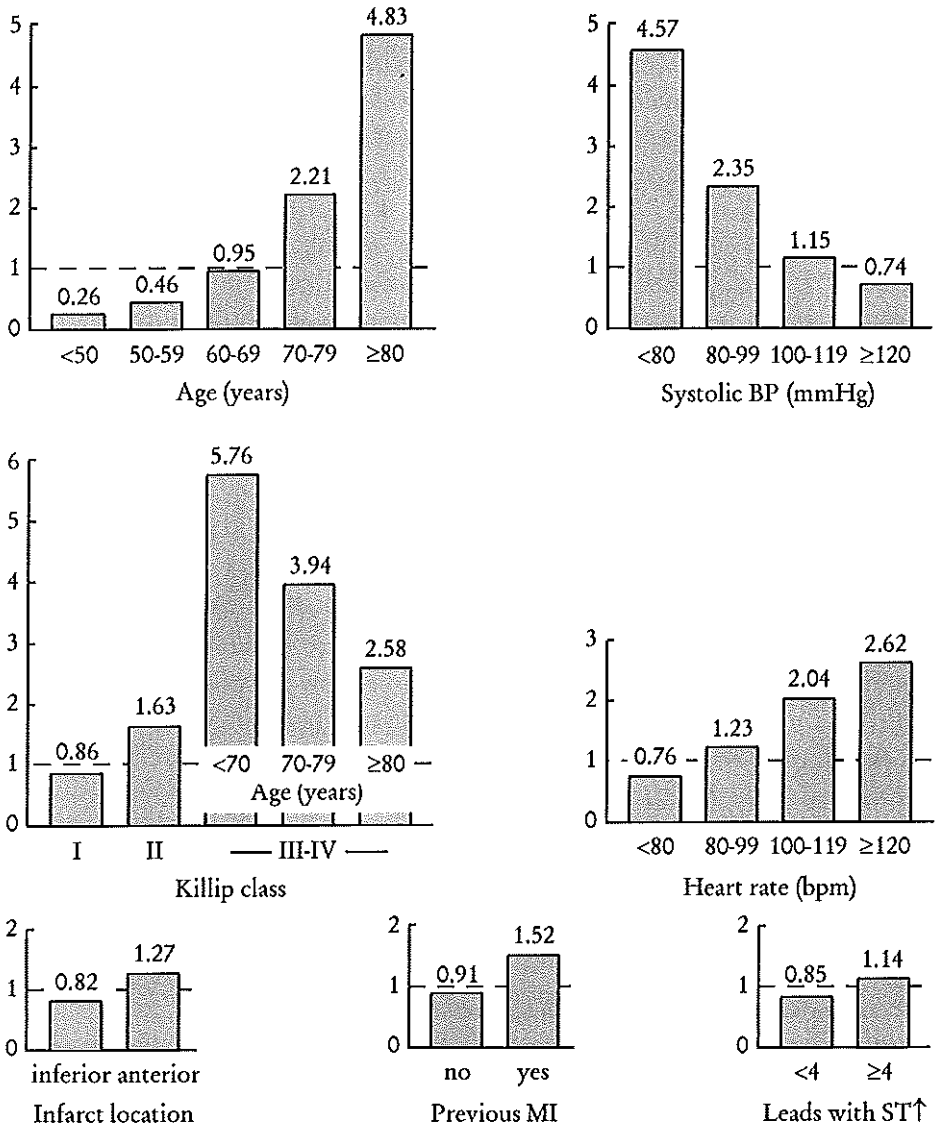


Figure 2: **Graphical representation of the independent contribution of several presenting features to determine cardiac mortality after reperfusion therapy in patients with evolving myocardial infarction**

Mortality (in odds form, see appendix) of an average patient is indexed at value 1. To calculate the mortality index of a particular patient, characterised by given presenting features, deviations from this average should be multiplied.

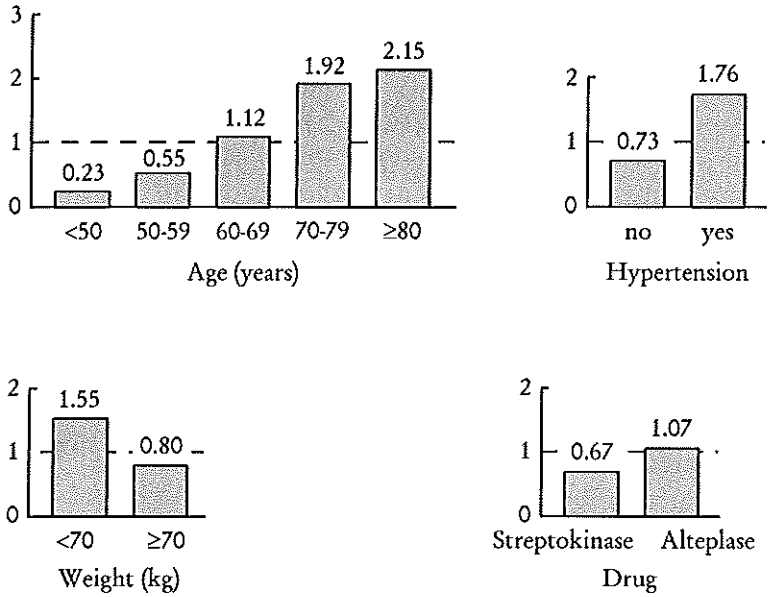


Figure 3: **Graphical representation of the independent contribution of several presenting features to determine the risk of haemorrhagic stroke after thrombolytic therapy in patients with evolving myocardial infarction**

The haemorrhagic stroke rate (in odds form, see appendix) of an average patient is indexed at value 1. To calculate the haemorrhagic stroke index of a particular patient, characterised by given presenting features, deviations from this average should be multiplied.

30-day follow-up period.[22] To estimate the magnitude of the above mentioned risk factors in predicting *cardiac* death, we performed a subsequent multivariate logistic regression analysis on the GUSTO-1 data, excluding patients with fatal cerebral haemorrhage. Results of this analysis are summarised in figure 2 (see also the appendix).

The developed regression model may, strictly speaking, only be applied to estimate patient's individual 30-day probability of cardiac death in a 'GUSTO-1 alike' population. However, since the model appeared to be practically independent from the population mortality (appendix), it may also be used in populations with different (higher) mortality rates. Furthermore, although all GUSTO-1 patients received thrombolytic therapy, the model can

be employed to estimate the risk for dying without reperfusion therapy, since the relative effect of such therapy is almost equal for each patient (see above), and, consequently, the ratio between the individual- and the population risk will not be influenced by therapy. Finally, the model may be applied to assess individual one-year mortality rather than 30-day mortality, because almost all of the infarct-related mortality occurs in the first month, whereas the hazard of mortality remains stable after this period.[14,52]

Determinants of intracranial haemorrhage

In general cerebral events are hard to predict, although there are some well recognised predictive factors for intracranial haemorrhage after thrombolytic therapy, including advanced age, low body weight, elevated blood pressure at time of presentation and use of rt-PA instead of streptokinase.[53] To quantify the individual contribution of these risk factors in prediction of the adverse bleeding complication, we again performed a multivariate logistic regression analysis in the GUSTO-1 dataset. Results are presented in figure 3 (see also the appendix). The developed regression model estimates patient's individual risk for intracranial haemorrhage after initiation of thrombolytic therapy. Since cerebral bleeding complications are very rare (<0.1%) among myocardial infarction patients who do not receive thrombolysis,[1] the model may also be used to estimate the excess bleeding risk caused by therapy.

Life expectancy

Due to increased mortality risk, life expectancy (appendix) of a myocardial infarction patient is decreased compared with an 'average' person of the same community at the same age. With the help of reperfusion therapy part of this potential loss can be regained. The impact of changes in early survival on patient's life expectancy is age dependent.[41] For example, a one-year mortality reduction from 12% to 10% in a 45 year old patient will save approximately 4 months, while a similar early mortality reduction yields less than 2 months in a 75 year old (these savings reflect so-called 'discounted' values, see appendix). Therefore, we prefer to concentrate on the effects of treatments on life expectancy rather than on one-year mortality, since the long-term perspective may be most appropriate for medical decision making.[54]

Integration of benefits and risks in individual patients

Table 3 may help to integrate benefits and risks in potential candidates for reperfusion therapy. The average (population) probability of dying within one year after a conventional treated myocardial infarction (i.e. without reperfusion therapy) is assumed to be 12.5%. Dependent on the described presenting features (figure 2) patient's individual mortality risk without therapy may vary from less than 2% to even more than 50% (upper panel in table 3). Consequently, remaining life expectancies range from almost 14 years in young patients at low risk to about 4 years in the elderly at high risk. Due to reperfusion therapy cardiac mortality at one year will decrease. The magnitude of this reduction depends on the time expired from onset of symptoms (see paragraph about time to treatment). Consequently, remaining life expectancy will increase. Most benefits of reperfusion therapy are to be expected in young, high-risk patients treated within 1 h after symptom onset (average gain up to 39 months).

The risk for cerebral bleeding complications can be estimated using the lower panel of table 3. We presumed a 0.75% population probability for intracranial haemorrhage after thrombolytic therapy. In individual patients this may range from a negligible $<0.2\%$ to even 3.5%. The probability of intracranial haemorrhage should be weighed against the expected reduction in cardiac death. If both are (almost) equal, one should refrain from reperfusion therapy, although in some case immediate angioplasty still might be an option.

Advantage of the described model

Over the years several models have been developed to identify which patients benefit most from reperfusion therapy,[9,14,41,48,51] and some of these are incorporated in treatment protocols which are applied in clinical practice.[9,41] Therefore, the question is justified as to what is the advantage of the current model. Does it lead to 'better' estimations of treatment effects in individual patients than existing ones?

The problem with answering this question is, that there is no uniform starting-point in the different models and also no clear definition of 'better'. The effects of reperfusion therapy are quantified in terms of one-month mortality,[48] one-year mortality,[9] as well as life expectancy.[41] Is the latter approach 'better' than the first one? We do take this view (see paragraph about life expectancy), but agree that a focus on the more short term effects is also

Mortality index	No reperfusion therapy		Benefit from reperfusion therapy: months added (absolute mortality reduction in %)			
	One year mortality (%)	Life expectancy (years)	0-1 h	1-3 h	3-6 h	6-12 h
Age < 50 years						
0.125	2	13.6	3 (0.9)	2 (0.5)	1 (0.4)	0 (0.3)
0.25	3	13.4	4 (2.5)	2 (1.5)	2 (1.3)	< 1 (0.8)
0.5	7	13.1	7 (4.1)	4 (2.5)	3 (2.0)	1 (1.2)
0.75	10	12.7	10 (5.6)	6 (3.3)	5 (2.8)	2 (1.7)
1.0	12.5	10.8	15 (7.6)	8 (4.5)	7 (3.8)	3 (2.3)
1.5	18	10.1	20 (11.1)	11 (6.7)	10 (5.6)	5 (3.3)
2.5	26	7.7	30 (17.4)	17 (10.5)	15 (8.7)	7 (5.2)
5.0	42	6.7	39 (23.6)	22 (14.2)	19 (11.8)	9 (7.1)
Age 50-59 years						
0.125	2	11.6	2 (0.9)	1 (0.5)	< 1 (0.4)	0 (0.3)
0.25	3	11.5	3 (2.5)	1 (1.5)	1 (1.3)	0 (0.8)
0.5	7	11.2	5 (4.1)	3 (2.5)	2 (2.0)	< 1 (1.2)
0.75	10	10.9	7 (5.6)	4 (3.3)	3 (2.8)	1 (1.7)
1.0	12.5	9.4	10 (7.6)	6 (4.5)	5 (3.8)	2 (2.3)
1.5	18	8.8	14 (11.1)	8 (6.7)	7 (5.6)	3 (3.3)
2.5	26	6.8	21 (17.4)	13 (10.5)	11 (8.7)	5 (5.2)
5.0	42	5.9	27 (23.6)	16 (14.2)	13 (11.8)	6 (7.1)
Age 60-69 years						
0.5	7	8.8	2 (4.1)	1 (2.5)	< 1 (2.0)	0 (1.2)
0.75	10	8.6	3 (5.6)	1 (3.3)	1 (2.8)	0 (1.7)
1.0	12.5	7.6	6 (7.6)	4 (4.5)	3 (3.8)	1 (2.3)

1.5	18	7.1	8 (11.1)	5 (6.7)	4 (5.6)	1 (3.3)
2.5	26	5.6	12 (17.4)	7 (10.5)	6 (8.7)	3 (5.2)
5.0	42	4.9	16 (23.6)	10 (14.2)	8 (11.8)	3 (7.1)
Age 70-79 years						
1.0	12.5	5.5	2 (7.6)	1 (4.5)	<1 (3.8)	0 (2.3)
1.5	18	5.1	3 (11.1)	1 (6.7)	1 (5.6)	0 (3.3)
2.5	26	4.2	5 (17.4)	3 (10.5)	2 (8.7)	<1 (5.2)
5.0	42	3.6	7 (23.6)	4 (14.2)	3 (11.8)	1 (7.1)

ICH index	0.125	0.25	0.5	1.0	1.5	2.5	5.0
ICH complications							
Probability (%)	0.1	0.2	0.4	0.8	1.1	1.9	3.6
Death (%)	±0.1	±0.1	0.2-0.3	0.4-0.6	0.6-0.8	1.0-1.3	1.8-2.5

Table 3: **Estimated benefits and risks of reperfusion therapy in individual patients with evolving myocardial infarction**

The upper panel shows one year mortality rates and life expectancies in several categories of patients in case reperfusion therapy is not installed. Also the expected, time-dependent benefits from such therapy are presented. The average one year mortality without reperfusion therapy is estimated at 12.5%. Patient's individual mortality index can be determined with help of figure 2; the individual mortality probability follows by multiplication of this index with the average mortality (in odds form, see appendix).

The lower panel presents the risk for intracranial haemorrhage after reperfusion therapy. The average probability is estimated at 0.75%. Patient's intracranial haemorrhage index can be determined with help of figure 3; the individual probability follows by multiplication of this index with the average probability (in odds form).

ICH = intracranial haemorrhage

valid, and may very well match with physician's first aim: discharge a patient in a good clinical condition.

On the other hand, models which apply more detailed information (e.g. age and blood pressure as continuous values)[48] may better distinguish low risk from high risk patients than models using more rough data (e.g. age categorised as <65 or ≥ 65 years, and blood pressure as 'hypertension' or 'no hypertension').[41] Further, since multivariate analyses were performed on a very large data set (GUSTO-1), parameter estimates are more precise than those used in an earlier version of the life-expectancy model, which was based on a much smaller data set.[42] Another advantage is, that the quantified positive and negative aspects of reperfusion therapy are presented separately (table 3), which may lead to a more accurate weighing in individual patients. The models presented contain well-known and readily-available patient characteristics and are expected to be valid for new patients. The effects of reperfusion therapy on mortality and intracranial haemorrhage were considered separately from the influence of these patient characteristics, which makes our approach transparent and suitable for clinical use.

WHICH TREATMENT FOR WHICH PATIENT?

To satisfy the requirements of cost-effective clinical practice, costly therapy should be reserved for patients with substantial expected benefit, while relative cheap, but slightly less effective therapy might be allocated to those with lower expected profits. Now that an instrument has been developed to estimate the effect of reperfusion therapy, the question still remains as to what is 'low' and what is 'high' benefit? Which thresholds should be used to equitably allocate scarce reperfusion resources?

Patient-driven decision making

Some physicians opt for an allocation policy which can be called 'patient-driven'. In such situation, patients in whom expected benefits from reperfusion therapy do not exceed the threshold of certain X_1 months to be gained will receive streptokinase, being an effective and relative cheap treatment option (obviously, in those with a negligible gain no reperfusion therapy will be initiated). Patients with an expected benefit in the range X_1 to Y_1 months might be treated with rt-PA, which is slightly more effective, but

also more expensive than streptokinase (also r-PA might be considered in such patients). If the expected gain goes beyond Y_1 months immediate angioplasty might be performed. Angioplasty might also be considered in patients with more modest gain in life expectancy, but increased risk for intracranial haemorrhage. The essence of this policy is that the fixed thresholds X_1 and Y_1 are determined in advance by the team of treating cardiologists on the basis of their insight in what is *cost-effective treatment of their individual myocardial infarction patient.*

Budget-driven decision making

The advantage of the patient-driven policy is that decision thresholds are determined by the professional group on account of their knowledge. However, a major problem arises when reperfusion resources are limited to such extent that at some point in time the preferred option is not available. This situation may very well happen in case of closed (e.g. yearly) budgets, and is very undesirable, since it is at variance with the ethical rule of 'equivalent treatment in equivalent cases'.[55] Therefore, others defend a 'budget-driven' allocation-policy. Point of departure is the available amount of separate reperfusion treatment options (*supply*), and the expected number of patients that will consume these resources (the population, e.g. all myocardial infarction patients that will be admitted on the coronary care unit in a certain year; *demand*). Availability of reperfusion resources is determined in consultation with health care policy makers, representatives of insurance companies, hospital boards and treating cardiologists. Characteristics of the population can be obtained from analyses of data from the recent past. These former patients can be ordered according to what their gain in life expectancy from reperfusion therapy would have been. Based on this order, it is possible to reliably agree upon treatment allocation in future patients. Patients belonging to the lower X_2%, middle X_2% to Y_2% or upper 100%-Y_2% of estimated gain will be allocated streptokinase, rt-PA or angioplasty, respectively, in which X_2 and Y_2 are dependent on the ratio of demand and supply (e.g. in the Thoraxcentre Rotterdam $X_2=50$ and $Y_2=90$). Thus, the budget-driven policy concentrates on *cost-effective treatment of a certain population of myocardial infarction patients* rather than individual patients.

CONCLUDING REMARKS

In the first part of this paper the most important results are summarised as observed in randomised trials of reperfusion therapy in patients with evolving myocardial infarction for different treatment strategies. Benefits and complications are described, and the direction for future investigations is indicated. In the second part it has been discussed in which way this information can be applied for decision making in individual patients. A set of tables is presented which might be applied on a coronary care unit. It should be realised, however, that the intention of this article is to arrange thoughts rather than to dictate the 'final' solution to the question of equitable allocation of scarce reperfusion resources. We definitely appreciate the importance of an attentive treating cardiologist, who cannot be replaced by a 'paper clinician'. Conversely, we are also convinced of the usefulness of guidelines or protocols in clinical practice, especially if rapid decision making is of vital importance. These views, however, are not mutually exclusive. Individual patients as well as the community will profit from skilful physicians who use treatment guidelines in a sensible way.

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APPENDIX

Logistic regression model for prediction of 30-day cardiac mortality

Probability of cardiac death within 30 days = $(1 + \exp(\alpha)\ \Pi_i \exp(-\beta_i))^{-1}$, where $\alpha = 5.406$;

$\beta_1 = 0$, 0.569, 1.290, 2.138 or 2.919 if age <50, 50-59, 60-69, 70-79 or ≥ 80 years;

$\beta_2 = 0$, 0.447, 1.162 or 1.825 if systolic blood pressure ≥ 120, 100-119, 80-99 or <80 mmHg;

$\beta_3 = 0$, 0.635 or 1.898 if Killip class is I, II or III/IV; $\beta 3 = 1.519$ or 1.094 if Killip class is III/IV and age 70-79 or ≥ 80 years (age is an effect modifier for the relation between Killip class and mortality);

$\beta_4 = 0$, 0.484, 0.987 or 1.239 if heart rate <80, 80-99, 100-119 or ≥ 120 bpm;

$\beta_5 = 0$ if infarct location is non-anterior or 0.436 if location is anterior;

$\beta_6 = 0$ if there is no history of infarction or 0.518 in case of previous infarction;

$\beta_7 = 0$ if total ST elevation <0.4 mV or 0.295 if ST elevation ≥ 0.4 mV.

This model is developed in 38,814 GUSTO-1 patients with complete data on mortality, intracranial haemorrhage, age, blood pressure, Killip class, heart rate, infarct location, infarct history, electrocardiographic infarct size and weight.

Probability and odds

Given a probability (risk) of X%, the odds is defined as X% / (100% - X%). Two patients with equal risk profile for early cardiac death, except for one predictive variable (e.g. age) will have different odds. The ratio of these odds is called odds ratio, and can be interpreted as a relative risk. The components $\exp(\beta_i)$ in the cardiac mortality model represent independent odds ratio's corresponding with the different predictive features. For each feature, the

index-group is determined by $\beta_i = 0$. For example, a patient in the age category 50-59 years has an odds ratio of exp(0.569) = 1.8, which implies an almost two fold risk of cardiac death compared to an, otherwise comparable, patient of less than 50 years (the index-group). A patient aged 80 years has a exp(2.919) = 18.5 times higher risk.

Mortality index

Cardiac death within 30 days occurred in 2,493 of the 38,814 patients, which implies a population risk (probability) of 6.4% and an odds of 0.069. In other words: each patient of the population has a prior odds of 0.069. With help of the mortality model, the risk (and thus the odds) of an individual patient can be determined. The ratio of this so-called posterior (individual) odds and the prior (population) odds is the likelihood ratio (we avoid mentioning this term in the text and do call it mortality index). Thus, the index-value with regard to the likelihood ratio is related to an *average* patient from the population, whereas the index-value in the mortality model is related to the patient with the *best* perspectives (lowest mortality probability).

The likelihood ratio an also be considered as a multiplicative composition of factors corresponding with the different independent predictive features. These factors are presented in figure 2, and can be determined as follows. Consider each presenting feature F_i ($i = 1,.., 7$) separately. F_i has k ($k=1,..,K_i$) mutually exclusive categories. There are N_k patients in category k, who each have a probability of cardiac death P_k estimated by $(1 + \exp(\alpha_i) \exp(-\beta_{ik}))^{-1}$, with β_{ik} as described above, and α_i such that $\Sigma_k N_k P_k = 2{,}493$ (the total number of cardiac deaths in the population). The ratio between P_k and the population probability (in odds form) gives the factor at issue.

We assume that the relative risks corresponding with the described features ($\exp(\beta_i)$) are independent from the population risk. In that case, mortality indices appeared to be insensible for moderate changes in the population risk, and may thus be applied in populations with higher underlying mortality. In figure 2 a 12.5% mortality probability is assumed.

Logistic regression model for prediction of the risk of intracranial haemorrhage

Probability of intracranial haemorrhage = $(1 + \exp(\alpha) \Pi_i \exp(-\beta_i))^{-1}$, where

$\alpha = 6.919$;

$\beta_1 = 0$, 0.857, 1.567, 2.111 or 2.224 if age <50, 50-59, 60-69, 70-79 or ≥ 80 years;

β_2 = 0 in case of normal tension (systolic blood pressure <165 and diastolic blood pressure <95 mmHg) or 0.881 in case of hypertension (systolic blood pressure ≥165 or diastolic blood pressure ≥95 mmHg);
β_3 = 0 or 0.660 if weight ≥70 or <70 kg.

This model is developed in 38,814 GUSTO-1 patients with complete data on mortality, intracranial haemorrhage (N=251), age, blood pressure, Killip class, heart rate, infarct location, infarct history, electrocardiographic infarct size and weight.

Haemorrhagic bleeding indices can be calculated with help of figure 3 (see paragraph about mortality index for the theoretical background). The underlying population risk is estimated at 0.75%.

Life expectancy and discounting principle

Life expectancy of an average reference person in the normal population is based on age and sex specific mortality data from The Netherlands in 1990. Compared with this average person, life expectancy after myocardial infarction is decreased due to (a) a higher mortality risk at one year, which can be calculated with help of the model in figure 2, and (b) a higher subsequent mortality risk; we assumed a yearly mortality excess of 1.0%, 2.0% and 3.0% for patients with a one-year mortality risk of <10%, 10% - 30% and ≥30%, respectively.

In cost-effectiveness analyses it is customary to discount future life years, thus accounting for the greater value given to treatment effects in the near future compared with the more distant future. Discounting also compensates for the moderate accuracy of predicted long term survival. The presented life expectancies in this manuscript are discounted by 5% per year.

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Chapter 7

BENEFITS AND RISKS OF POSSIBLE PRE-HOSPITAL THROMBOLYSIS STRATEGIES

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The benefits of thrombolytic therapy exceed the risks, even in patients with somewhat uncertain diagnosis of myocardial infarction. Implications for pre-hospital programs
Submitted

SUMMARY

Background

Effectiveness and safety of pre-hospital thrombolysis in myocardial infarction patients depends on possibilities for rapid and correct diagnosis. The Rotterdam pre-hospital treatment program utilises an automated electrocardiogram for confirmation of infarction. To prevent inaccurate diagnosis and inappropriate treatment, current electrocardiographic criteria are very strict. We investigated whether these criteria could safely be widened, to increase the number of patients eligible for pre-hospital therapy.

Methods and findings

The benefit of pre-hospital thrombolysis is defined as the number of lives saved in true infarctions compared with in-hospital therapy (approximately 10 to 20 per 1,000 treated). The risk is determined by the number of cerebral bleeds caused in inappropriately treated patients without infarction (5 to 10 per 1,000 inappropriate treatments).

Automated 12-lead electrocardiograms were recorded in 1,072 consecutive patients with symptoms suggestive of acute coronary syndrome. Myocardial infarction was diagnosed in 371 (35%) cases, 128 (35%) of whom were confirmed by the current criteria for pre-hospital therapy (total ST-deviation ≥1.0 mV). False positive diagnosis occurred in 6 non-infarctions. This corresponds with a benefit/risk ratio ranging from 21 to 85. The criteria usually applied for in-hospital confirmation of infarction were satisfied by 214 infarctions and 49 non-infarctions (benefit/risk ratio 4 to 17). The maximal net benefit per 1,000 patients screened (1.6 to 3.7 lives saved) was observed at a ST-elevation level of 0.6 (0.4) mV in probable anterior (inferior) infarctions (benefit/risk ratio 5 to 22).

Conclusions

The benefits of rapid, pre-hospital thrombolysis far exceed the risks, even in patients with somewhat uncertain diagnosis of myocardial infarction. Therefore, initiation of such therapy should be considered in a greater amount of patients.

INTRODUCTION

The sequelae of myocardial infarction, particularly heart failure and death, are largely avoided by very early reperfusion therapy.[1,2] Such therapy, whether by thrombolysis or angioplasty, is recommended in all patients with a diagnosis of evolving myocardial infarction, especially in those with ST segment elevation or a new Bundle Branch Block.[1,3] Physicians are reluctant, however, to initiate thrombolytic therapy in patients in whom the diagnosis 'evolving infarction' is somewhat uncertain. This reluctance is caused by fear for bleeding complications, above all intracranial haemorrhage.

Pre-hospital thrombolytic therapy is particularly effective since it allows very early therapy. In the pre-hospital 'REPAIR' program (REPerfusion for Acute Infarction in Rotterdam) 73% of patients recognised with large infarctions are treated within 2 hours after onset of symptom onset, resulting in high survival rates.[4,5] In this program, initiated in 1988, an automated 12-lead ECG analysis is used for confirmation of evolving myocardial infarction in patients with chest pain, to support the General Practitioner in decision making. Paramedics on the scene are allowed to start thrombolytic therapy in eligible patients in the absence of a physician.[4,6] In the early stage of the program the limited diagnostic facilities in the pre-hospital setting were appreciated and considerations of patient safety prevailed. At that time the protocol was designed to identify patients with extensive evolving myocardial infarction, in whom the additional benefit of very early therapy would be large,[7] and to minimise the risk of intracranial haemorrhage. Accordingly, ECG criteria to confirm evolving myocardial infarction were very strict and pre-hospital therapy was restricted to patients less than 70 (until 1991) or 75 (since 1991) years of age, with extensive ST segment elevation (total ST deviation over all 12 leads $\geq$1.0 mV).[6] Consequently, the number of patients who benefit from out of hospital therapy was limited, averaging 120 per year, which is approximately 40% to 50% of patients who ultimately received thrombolytic therapy.

Currently, pre-hospital thrombolysis has proven to be safe, without major complications outside the hospital.[4,6] In the REPAIR program, over 1,000 patients have been treated, in only 1% of whom infarction was not confirmed by subsequent ECG evolution and enzyme elevations in hospital. One-year survival was 97% and 5-year survival 92%.[4] In view of this experience it would be appropriate to offer immediate, pre-hospital therapy to

a larger proportion of patients with evolving infarction. Therefore, we investigated whether the criteria for enrolment and immediate thrombolytic therapy could be widened, to increase the number of patients to be treated without excessive risk.

The occurrence of ST-segment deviation (ST-segment elevation and concomitant depression) on the ECG is the most specific electrocardiographic measure for confirmation of evolving myocardial infarction.[8] The percentage of myocardial infarctions to be confirmed (sensitivity) and of non-infarctions to be excluded (specificity) is related to the selected thresholds for ST-deviation. The choice of these thresholds for pre-hospital thrombolysis is arbitrary and depends on the perceived benefits of appropriate and risks of inappropriate treatment. A quantitative analysis is performed to estimate benefit/risk ratio's at several ST-deviation thresholds. Results are applicable not only to the pre-hospital setting, but also to the emergency room in many hospitals.

METHODS

Patients and electrocardiographic data

From January 1992 to April 1994 standard 12-lead ECG's were recorded prior to hospital admission in 1,072 patients with chest pain suggestive of acute coronary pathology, transported by the ambulance service in the Rotterdam region (table 1). Patients above the age of 80 years and those with chest pain existing for more than 6 h were excluded from our analysis. For each lead amplitude and time measurements were computed and interpreted by Siemens' Sicard P+ ECG analysis system.[9] These measurements were subsequently stored for off-line analysis. Thrombolytic therapy was initiated on site in patients with symptoms of evolving myocardial infarction, without contraindications, in whom this pattern was confirmed by the automated ECG interpretation (table 2). All chest pain patients were hospitalised. Final diagnoses were gathered from the hospital medical records. Definite myocardial infarction was diagnosed by enzyme rise and/or evolving Q waves on the ECG in 371 patients (table 1).

Number of patients	1,072
Male sex	622 (58)
Mean age, years (range)	63 (30-80
History of coronary artery disease(1)	531 (50)
History of myocardial infarction	291 (27)
Time from symptom onset	
< 1 hour	182 (17)
1-3 hours	681 (64)
3-6 hours	209 (19)
Diagnosis	
Myocardial infarction	371 (35)
Anterior	149 (40)
Inferior	176 (47)
Unknown	46 (12)
Unstable angina pectoris	187 (17)
Stable angina pectoris	90 (8)
ECG criteria for pre-hospital thrombolysis satisfied	134 (13)
Myocardial infarction	128 (96)
Unstable angina pectoris	0 (0)
Stable angina pectoris	2 (1)
Other diagnosis	4 (3)
Immediate thrombolytic therapy in infarctions	84 (23)
Thrombolysis initiated in-hospital in infarctions	25 (7)
Immediate thrombolytic therapy in non-infarctions	1 (0)

Table 1: **Characteristics of chest pain patients admitted within 6 h from symptom onset. The age limit in the analysis was 80 years. The numbers between brackets represent percentages**
(1) Myocardial infarction, angina pectoris, bypass surgery or percutaneous transluminal coronary angioplasty.

Benefit/risk analysis

In Western Europe and the USA pre-hospital initiation of thrombolytic treatment reduces the call-to-needle-time with about 1 h compared to in-hospital therapy.[10-13] Pooled analyses of all trials that compared pre-hospital and in-hospital thrombolysis indicated that this gain of time results in about 15 to 21 additional survivors at 30 days per 1,000 treated.[2,10,13] The gain of earlier

Indications

- chest pain ≥30 minutes and <6 hours duration suggestive of myocardial infarction
- no relief by nitro-glycerine

Main contraindications

- age ≥75 years; for women <55 years to avoid any bleeding risk during menstruation or pregnancy
- cardiac massage, history of cerebrovascular accident, major trauma or surgery in the previous 3 months

ECG criteria

- ≥0.3 mV ST elevation in ≥2 leads of V1-V6, or ≥0.2 mV in ≥2 leads of II/III/aVF
- total ST elevation ≥1.0 mV
- excluded: left bundle branch block, Wollf-Parkinson-White pattern, intraventricular conduction delay and pacemaker rhythm

Table 2: **In- and exclusion criteria for pre-hospital thrombolytic therapy in patients with evolving myocardial infarction according to the Rotterdam triage protocol**

therapy is time-dependent. The average gain per hour earlier treatment is approximately 60, 10 and 2 lives saved per 1,000 treated patients in the respective 0-1 h, >1-3 h and >3-6 h intervals after onset of symptoms.[2] Since most patients in our series were visited within 3 h of symptom onset (table 1), mortality reduction in definite myocardial infarction patients - the *benefit* of a pre-hospital thrombolysis program - can reliably be estimated at 10 to 20 lives saved per 1,000 treated.

In some patients an intracranial bleeding may occur as a consequence of thrombolytic therapy, which will lead to death in more than half of the cases and to severe disability in another quarter.[14] The risk for intracranial haemorrhage can be estimated at 5 to 10 per 1,000 patients treated.[1,14] In patients with evolving myocardial infarction this risk is partly compensated by a reduction of the risk for embolic stroke (strokes of any type occur in approximately 4 to 8 per 1,000 treated patients).[1,14] Moreover, the expected mortality reduction far exceeds the expected risk of intracranial haemorrhage.[1] However, in

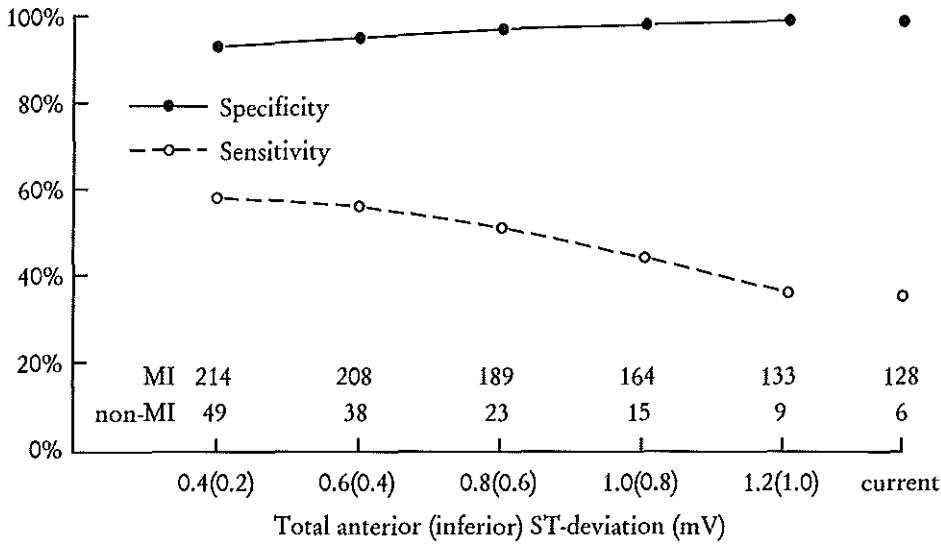

Figure 1: Sensitivity and specificity in confirmation of myocardial infarction at several thresholds of ST-deviation on the presenting electrocardiograms

All 263 (=214+49) patients in this figure met the classical criteria for in-hospital confirmation of infarction (≥2 leads of V1-V6 show ≥0.2 mV ST-elevation or ≥2 leads of II,III,aVF show ≥0.1 mV ST-elevation).

ST-deviation is defined as: (a) in case of anterior ST-elevation: the total sum of ST-elevation in V1-V6 plus ST-depression in II,III,aVF and (b) otherwise (said to be inferior): the total sum of ST-elevation in I,II,III,aVF,aVL,V5,V6 plus ST-depression in V1-V4.

'Current' represents the strict criteria as applied in the original Rotterdam program.

patients without infarction who (erroneously) receive thrombolytic therapy the benefits are absent, while the bleeding risk prevails. Hence, the *risk* of a pre-hospital thrombolysis program can be estimated at 5 to 10 intracranial bleeding complications per 1,000 treated non-infarctions.

We evaluated the benefit/risk relation of initiation of thrombolytic therapy at several levels of ST deviation on the automated ECG's. Reported are the number of myocardial infarction patients and non-infarctions that reach certain ST-deviation thresholds, the corresponding sensitivity and specificity, the benefit/risk ratio and the estimated net benefit. The latter is

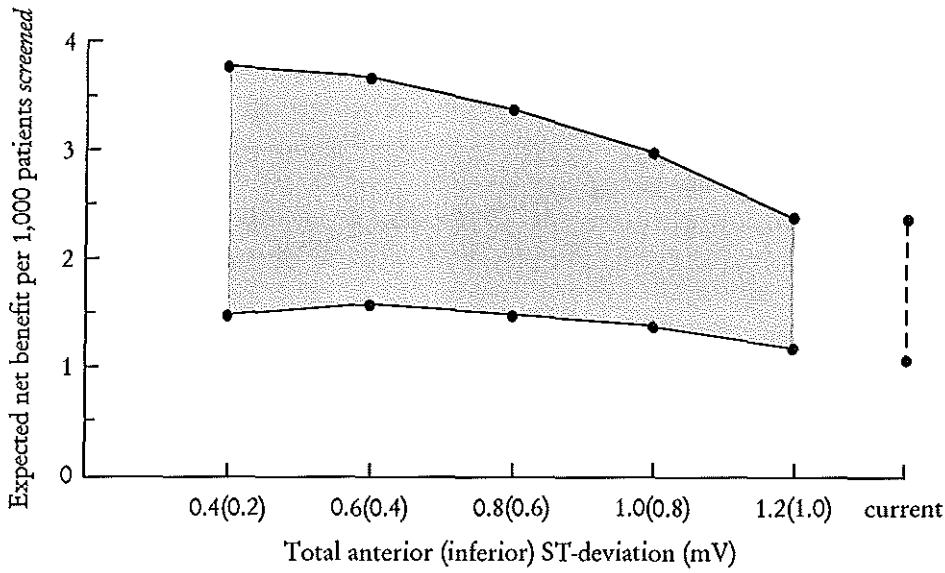

Figure2: **Expected net benefit per 1,000 patients screened at several thresholds of ST-deviation on the presenting electrocardiogram**

Only the 263 patients that met the classical in-hospital criteria (figure 1) for confirmation of infarction are potential candidates for pre-hospital thrombolysis. These patients contribute in the benefit/risk estimations. See figure 1 for definition of ST-deviation.

defined as the difference between estimated benefit and risk, and is to be interpreted as the additional number of lives saved by pre-hospital therapy without additional cerebral bleeding complications. In order to emphasise that estimates of benefits and risks are necessarily imprecise, results are presented by a bandwidth, based on above described estimates, rather than point estimates.

RESULTS

The current pre-hospital program identified extensive ST-segment elevation in 128 out of 371 patients with definite myocardial infarction (sensitivity 35%; figure 1), and thrombolytic therapy was initiated immediately in 84 of these (21 patients were excluded due their age: 14 patients were >75 years and 7

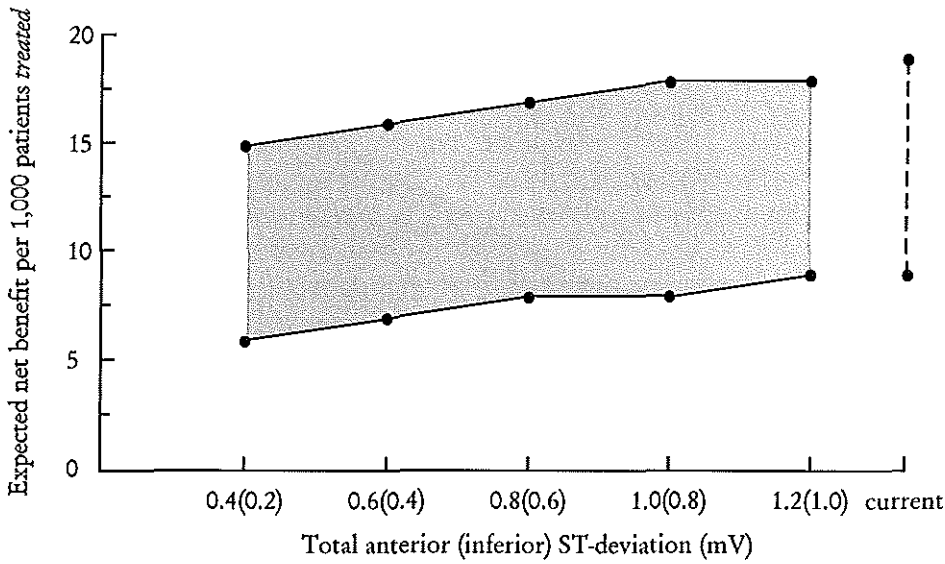

Figure 3: **Expected benefit per 1,000 patients treated at several thresholds of ST-deviation on the presenting electrocardiograms**

Only the 263 patients that met the classical in-hospital criteria (figure 1) for confirmation of infarction are potential candidates for pre-hospital thrombolysis. These patients contribute in the benefit/risk estimations. See figure 1 for definition of ST-deviation.

women were <55 years; 23 patients met other exclusion criteria). Large ST elevation was also observed in 6 patients in whom myocardial infarction was not confirmed (specificity 99%). Only 1 of these patients was actually treated with thrombolytics. In-hospital thrombolytic therapy was installed in 99 additional patients, so that overall 183 (49%) infarctions received reperfusion therapy.

The classical criteria for in-hospital electrocardiographic confirmation of evolving myocardial infarction comprehend ≥0.2 mV of ST-elevation in two or more contiguous precordial leads (V1-V6; anterior location) or ≥0.1 mV in two or more limb leads (II,III,aVF; inferior location).[15,16] These criteria were met in 214 patients with confirmed infarction, implying a sensitivity of 58% (figure 1). The benefit of pre-hospital thrombolytic treatment of these patients would be in the range of 10 to 20 lives saved per 1000 patients treated one hour earlier (see methods), corresponding to 2.1 to 4.3 additional lives saved in

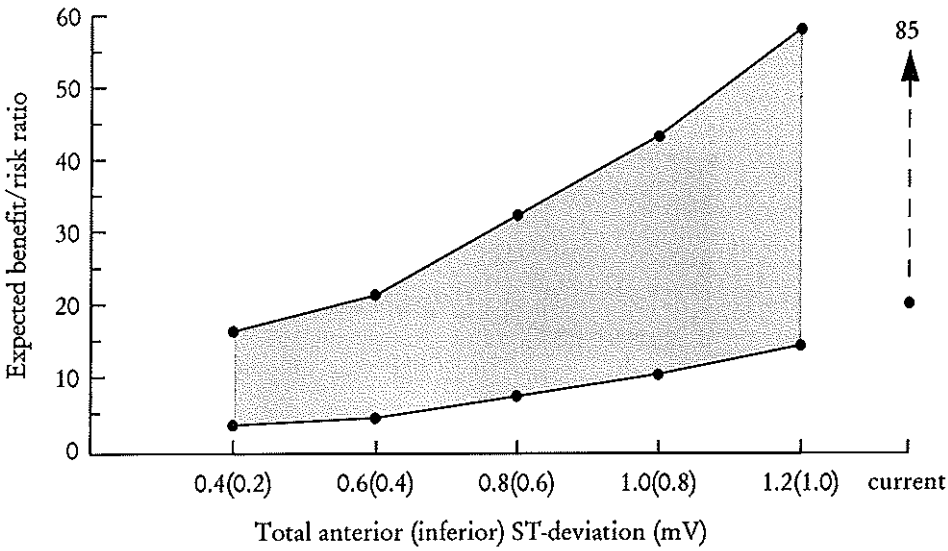

Figure 4: **Expected benefit/risk ratio at several thresholds of ST-deviation on the presenting electrocardiograms**

Only the 263 patients that met the classical in-hospital criteria (figure 1) for confirmation of infarction are potential candidates for pre-hospital thrombolysis. These patients contribute in the benefit/risk estimations. See figure 1 for definition of ST-deviation.

this series (214/1,000 times 10 to 20 lives expected to be saved). The criteria were also satisfied in 49 non-infarctions (specificity 93%), so the risk of installing pre-hospital therapy at the mentioned ST-elevation thresholds would be 0.25 to 0.49 intracranial bleeding complications (49/1,000 times a risk of 5 to 10 expected intracranial haemorrhages). Consequently, the expected net benefit would range from 1.6 (lowest benefit minus highest risk) to 4.0 (highest benefit minus lowest risk). The estimated net benefit per *1,000 patients screened* ranges from 1.5 to 3.8 (multiplication factor 1,000/1,072; figure 2), and per *1,000 patients treated* from 6 to 15 (multiplication factor 1,000/(214+49); figure 3).

For each 4 infarctions that met the classical ST-thresholds one non-infarction did so, resulting in a benefit/risk ratio of 4 to 17 (figure 4). This ratio can be improved by introducing additional criteria for total ST-deviation, which simultaneously increase specificity but reduce sensitivity for confir-

mation of myocardial infarction. Consequently, the expected net benefit of pre-hospital thrombolytic therapy per 1000 *patients treated* will increase (figure 3). However, the benefit per 1000 patients *screened* will decrease (figure 2), due to the decreasing number of confirmed infarctions that satisfy the more strict criteria (decreasing sensitivity). The benefit/risk ratio can also be improved if more strict criteria for ST-elevation in separate leads would be employed (e.g. ≥0.3 mV for precordial leads and ≥0.2 mV for limb leads). In this situation sensitivity is low (less than 38%) and specificity high (99%), resulting in a relative high benefit/risk ratio (more than 14) and low net benefit per 1,000 patients screened (between 1.1 and 2.6).

DISCUSSION

Physicians have been educated with the principle 'primum non nocere' ('first do no harm', 'better be safe than sorry'). This principle does apply to most modes of therapy, however, such attitude may be too strict in patients with possible evolving myocardial infarction. Myocardial infarction is a life threatening disease. The high mortality-rate can be considerably reduced by early (particularly very early) reperfusion therapy.[1,2] In patients with ST-elevation or Bundle Branch Block this benefit is estimated at 30 fewer deaths per 1,000 patients treated early after symptom onset compared with conventional therapy.[3] Yet, most myocardial infarction patients do not timely receive such life saving therapy, partly because diagnosis is initially uncertain, and partly because significant delays occur in those who ultimately appeared to be eligible. Treatment delays can be reduced by immediate, pre-hospital initiation of thrombolytic treatment,[4,10-12] though pre-hospital diagnosis may be somewhat uncertain. The current analysis implies, however, that thrombolytic therapy could be, and should be, initiated even in patients with some diagnostic uncertainty!

Thrombolytic therapy carries some risk for cerebral haemorrhage (estimated at 5 to 10 per 1,000 treated patients). *Pre-hospital* thrombolysis carries *additional* risk, since, due to limited diagnostic facilities, such treatment might be installed in patients without infarction and subsequently cause a cerebral bleed in some if them. Given this risk, the question arises whether all patients should be withheld pre-hospital therapy? If not, what would be an acceptable benefit/risk ratio? First of all, it should be accepted that the risk of causing cerebral haemorrhage in somebody without infarction can never be

Final diagnosis	Patients that satisfy 'optimal' ST threshold[1] (N=246)	EMIP[10] (N=5,469)
Myocardial infarction[2]	208 (84.5%)	4,892 (89.4%)
Unstable angina pectoris	19 (7.7%)	390 (7.1%)
Pericarditis	2 (0.8%)	21 (0.4%)
Aortic dissection	0 (0%)	9 (0.2%)
Other cardiac disease[3]	15 (6.1%)	57 (1.0%)
Noncardiac disease	2 (0.8%)	100 (1.8%)

Table 3: **Final diagnosis among 246 patients that satisfy extended electrocardiographic criteria compared with the 5,469 patients from the EMIP[10] trial**

(1) At the 'optimal' threshold (0.6 mV anterior or 0.4 mV inferior total ST-deviation) the net benefit per 1,000 patients screened reached it's maximum; (2) including patients with diagnosis 'probable infarction' (EMIP); (3) including patients with final diagnosis 'atypical chest pain'.

eliminated completely, even not in-hospital by an experienced cardiologist. The diagnosis of myocardial infarction cannot be made with complete certainty at an early stage.[17,18] Enzyme rise and new Q-waves on the electrocardiogram appear only hours after symptom onset, at a stage where thrombolytic therapy has lost most of its value.

In the pre-hospital setting, the balance between appropriate and inappropriate treatment depends on the available diagnostic tools. Automated electrocardiography on site might be very useful, since clinical symptoms of evolving myocardial infarction usually are accompanied by manifest ST elevations. Our investigation focused on these electrocardiographic measures. It should be realised, however, that the decision whether or not to install thrombolytic therapy was only considered in patients with manifest symptoms of evolving myocardial infarction, which were systematically checked by the visiting physician by means of a standardised questionnaire. The electro-cardiogram was used to *confirm* clinical signs of acute coronary pathology.

It has been argued by others, that an acceptable benefit/risk ratio for in-hospital thrombolysis would be obtained if such therapy is initiated in all patients with symptoms suggestive of evolving myocardial infarction, accompanied by classical ST abnormalities in the presenting

electrocardiogram.[18] In the present series this implies a positive predictive value of 81% (214 out of 263 ECG's that satisfy the classical in-hospital electrocardiographic criteria were infarct-related, see figure 1), which can be considered the directive for a pre-hospital diagnostic system. However, as figure 2 suggests, a better threshold seems to be 0.6 mV ST deviation in case of anterior and 0.4 mV in inferior infarction, as at that point the lower estimate of the net benefit per 1,000 patients screened seems to reach its maximum value, though it is appreciated that differences in this lower estimate are small. Table 3 shows hospital diagnoses of all 246 patients that satisfy this more strict threshold. In 208 patients (85%) myocardial infarction was confirmed, which is slightly lower than in the large EMIP trial of pre-hospital thrombolytic therapy.[10] Among the 38 non-infarction patients, 18 showed significant anterior ST elevation, with total ST elevation ranging from 0.4 to even 2.4 mV. Inferior ST elevation were observed in the remaining 20 patients, with totals in the range 0.3 to 0.9 mV. One of the false positives with extensive anterior ST elevations received thrombolytic therapy in-hospital. Since no enzyme elevations occurred, the final diagnosis was unstable angina pectoris, but actually, in this patient an evolving infarction was aborted. Only very few (0.8%) patients were suffering from cardiac disorders with an increased life-threatening bleeding risk, such as pericarditis. In the present series there were no cases of aortic dissection, while in EMIP 0.2% of treated patients appeared to suffer from this disease. It should be noticed, that aortic dissection may well be associated with evolving infarction, so the diagnosis might also be overlooked in-hospital.

The initial electrocardiographic criteria in the Rotterdam pre-hospital program were clearly risk-avoiding (the estimated benefit/risk ratio is in the range 21 to 85), and were satisfied only by 35% of the myocardial infarction patients. Consequently, the expected net benefit per 1,000 patients screened is relatively low. In our opinion, we are now at the stage that a less risk-avoiding strategy would be acceptable, and electrocardiographic criteria might be widened. Using the described 'optimal' thresholds, estimated benefits are 5 to 22 times higher than the risks, thus for each intracranial bleed caused in non-infarction patients at least 5 lives are expected to be saved in true infarctions. In patients with a reduced risk for intracranial bleeding (e.g. the younger patients and those with a normal blood pressure)[19] an even higher number can be expected. These insights have been translated into an revised program, which is currently being evaluated.

Administration of thrombolytic therapy to patients who do not have an evolving infarction carries unnecessary costs in addition to the risk involved. In our opinion these costs are acceptable, particularly when using streptokinase as thrombolytic drug in the pre-hospital setting (REPAIR).

Despite the awareness of the importance of rapid thrombolysis, 25% of treatment delay is caused by time-consuming in-hospital procedures, including time spend by nursing, emergency physician evaluation and cardiologist bedside consultation.[20] One way to reduce this delay is to improve diagnostic tools in the emergency room, for example by using automated an 12-lead ECG system, and to allow nurses to initiate life-saving thrombolytic therapy in typical myocardial infarction patients. The results described above are derived from ECG's in the pre-hospital setting, but are similarly applicable in the emergency room situation, to the benefit of many patients with evolving myocardial infarction in whom treatment delay might be reduced, and with little risk to other patients without a final diagnosis of infarction.

CONCLUSION

Although the question of the optimal ratio between benefits and risks in pre-hospital thrombolysis can not be answered unambiguously, the quantitative analysis as presented in this paper does contribute to a better understanding of the choices. In general, additional mortality reduction among patients with extensive myocardial infarction - due to the simple fact that they are treated in time - far outweighs the risk of causing major complications in erroneously treated non-infarct patients. Therefore, initiation of thrombolytic therapy prior to hospital admission should be considered in a greater amount of patients. At the same time, in-hospital logistics should be improved by introducing of automated diagnostic tools in the emergency room.

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GENERAL DISCUSSION

Chapter 8

PRACTICAL AND ETHICAL CONSEQUENCES OF MEDICINE ACCORDING TO PROTOCOL

INTRODUCTION

'All effective treatment must be free' was the slogan of Archie Cochrane, eminent founder of evidence based medicine, when he was a medical student in the 1930s.[1] About four decades later he developed this perception in his book 'Effectiveness and Efficiency: Random Reflections on Health Services'.[1] Cochrane's principles were straightforward: since resources are always limited, they should be applied to provide *equitably* those forms of health care which had been shown *effective* in properly designed investigations. Clearly, two major questions arise: what is 'effective' medical treatment? and what is an 'equitable' distribution of resources? Actually, these problems occur both at society (macro) and hospital or department (micro) level. The first decision to be made at the macro-level is how much of the Gross National Product should be allocated to health care.[2] After the general health care budget has been settled, it has to be determined what percentage should be allocated for preventive care, acute care, long-term care, and for specific patient populations. Given the financial scope for treatment of a specific disease, at micro-level decisions are to be made as to which patients will receive which mode of available therapies.

The problem as dealt with in this thesis is an example of medical decision making on micro-level. Myocardial infarction is an acute life-threatening disease which can be treated with several modes of reperfusion therapy. The properties of these treatment options and the *effects* on mortality and morbidity are studied and discussed in the 'Premises'. Based on these materials, in the part 'Practical decision models' treatment guidelines are developed for *equitable* allocation of scarce reperfusion resources in daily clinical practice. In this final chapter premises are briefly recapitulated, and ethical principles and practical consequences of evidence based medicine are discussed.

PREMISES

Measurements of evidence

The first issue is that of evaluating to what extent different reperfusion treatment options improve clinical prognosis of individual myocardial infarction patients. It is commonly accepted, that clinical evidence can be measured objectively by means of a randomised controlled investigation.[3] In

such setting, patients are allocated based on random numbers to one of several treatment options. Preferably, neither the physician nor the patients know which of the treatments is being given ('double blind' randomisation). This technique guarantees that baseline characteristics in all treatment arms are comparable (if not, differences are per definition due to chance) and eliminates the possibility of observer bias. Thus, differences in outcome between the treatment arms can entirely be accredited to the treatment itself. Almost all of the evidence as stated in this thesis is derived from randomised comparisons. Sometimes additional non-randomised comparisons of groups of patients and experimental observations are used to make the point (chapter 3).

Reperfusion therapy in evolving myocardial infarction

Since it became accepted that myocardial infarction is generally caused by an acute thrombotic obstruction of a coronary artery, several pharmacological and mechanical interventions were introduced that aimed at rapid and sustained restoration of local blood flow (chapter 2). Nowadays, intravenous infusion of streptokinase (1.5 MU over 1 h) is the cheapest (and most widely used) therapeutic alternative. Randomised investigations involving more than 30,000 patients indicate that mortality at one month is 23% reduced if such therapy is initiated within 6 h from onset of symptoms.[4-7] In combination with aspirin an even higher (almost 40%) mortality reduction can be achieved.[6] Streptokinase therapy does increase the rate of intracranial haemorrhage. On the other hand, embolic stroke rates are slightly reduced. Overall, the excess of any stroke (haemorrhagic or embolic) with thrombolytic therapy in the large trials (in 90% the agent in concern was streptokinase) appeared to be small compared with the achieved mortality reduction: about 4 strokes caused as against 30 fewer deaths (including 2 fatal strokes) per 1,000 myocardial infarction patients treated within 6 h.[8]

Recombinant tissue-type plasminogen activator (rt-PA) is a thrombolytic agent which directly activates the lytic process, and is therefore potentially more powerful than streptokinase. However, rt-PA is also more expensive. Randomised clinical investigations that compared effects of streptokinase with rt-PA showed contradictory results. In two trials the relative slow infusion of rt-PA (100 mg infusion over 3 h) appeared not to be more effective than streptokinase in terms of short-term mortality reduction (in these investigations 38,000 patients were randomised within 6 h).[9-11] On the other hand, combination therapy of so-called accelerated rt-PA (100 mg infusion

over 1.5 h) and intravenous heparin resulted in a 14% mortality reduction at one month compared with streptokinase in combination with heparin (results are based on 30,600 randomised patients).[12] Both rt-PA regimens produced a higher rate of haemorrhagic strokes than streptokinase. Investigators in question did not reach consensus as to whether there was a net difference in clinical outcome between the two different thrombolytic agents (chapter 4).[8] One group argued that, to avoid selective emphasis on particular trial results, all randomised investigations on rt-PA versus streptokinase should be considered together.[13] Such analysis does not indicate superiority of rt-PA over streptokinase. Others stated, that the combination therapy of accelerated rt-PA and intravenous heparin is an apparently different regimen than 'slow' rt-PA alone, and combined analysis is therefore inappropriate. In this thesis the last opinion is preferred (chapters 5 and 6).

Recombinant plasminogen activator (reteplase, r-PA) is a mutant of rt-PA with an increased half-life, which allows administration via bolus injection. So far, the r-PA regimen of 2 boluses of 10 MU given 30 min apart has been evaluated in two large randomised trials.[14,15] The results of these investigations indicate that the clinical effects of r-PA are in between 'standard' streptokinase and accelerated rt-PA.

Direct coronary angioplasty is another way to treat the coronary occlusion. This technique has been compared with several thrombolytic regimens in a couple of randomised trials, including about 2,600 patients.[16] Short term mortality after primary angioplasty was 33% reduced compared with thrombolysis, while the risk of stroke was also remarkably decreased. In view of the relative small amount of available data, these observations should be interpreted cautiously. Nevertheless, direct angioplasty is an alternative for thrombolysis, especially in patients with increased risk for cerebral bleeding complications. The initial costs related with the invasive procedure are high and it is yet uncertain whether these are counterbalanced by a decrease in revascularisation procedures during follow-up.[17-19]

Perspectives

As far as future developments in treatment of myocardial infarction patients are concerned, investigations focus on strategies which will result in more rapid and sustained coronary patency compared with existing options. This includes introduction of new thrombolytic agents as well as application of coronary stents to optimise the result of direct angioplasty. Also platelet

glycoprotein IIb/IIIa receptor blockers are nowadays subject of examination. Drugs from this class inhibit the process of platelet aggregation, and may thus prevent the occurrence of occluding 'white', platelet-rich thrombi. Promising results are observed in a small dose-ranging study.[20]

Time from symptom onset to treatment

The beneficial effect of reperfusion therapy depends on time from symptom onset. The nature of the treatment benefit/delay relationship is subject to discussion (chapter 4).[8] In this thesis the importance of very early reperfusion treatment is emphasised (chapters 3 and 7).[21] The beneficial effect of such therapy is thought to be substantially higher in patients presenting within 2 h after symptom onset compared to those presenting later (chapters 3, 5, 6 and 7).

Treatment effects in subgroups of patients

The risk of death from acute myocardial infarction can be predicted at the time of hospital admission. Most important mortality determinants are: age, blood pressure, Killip class, heart rate, history of infarction and site of the current infarct (chapters 4, 5 and 6). Systematic overview of the large randomised trials showed that there was no significant heterogeneity between the proportional mortality reductions in the different subgroups of patients studied.[22] Consequently, the absolute number of deaths avoided by reperfusion treatment appears to be greater in those groups with a higher baseline mortality risk. Also the additional benefit of more intensive therapy upon 'standard' therapy is most pronounced in patients at high baseline risk (chapter 6).

Long term effects of reperfusion therapy

Most randomised investigations planned only evaluation of the short-term (one month) effects of reperfusion therapy. Some trials reported also results at long term follow-up (up to 10 years; 4 year data is available in about 18,300 randomised patients), and showed a sustained survival benefit of reperfusion therapy (chapters 4 and 5).[23-25] The larger absolute benefits observed at one month in patients at higher risk of death were also sustained.

PRACTICAL DECISION MODELS

Ethical principles with respect to allocation of scarce resources

Medical resources are often scarce in relation to human wants,[26] which implies that a physician may not always be able to pursue patient's best interests. At the bedside these individual interests may come into conflict with the social benefits from fairly resource allocation. To arrive at an equitable resource allocation, three general ethical principles should be considered.[27] The first principle focuses on maximising patient welfare, which can be quantified with help of (quality adjusted) life years. The fact that a certain treatment option produces greater increase in patient welfare than another is a reason to choose that option. The other way around, patients in whom greater welfare increase can be expected from certain treatment are more suitable candidates than others with a more limited gain. The second principle indicates that patients with equal benefit from therapy should be given an equal chance. The third principle says that the aim of health care is not to produce as many quality adjusted life years as possible (in that case all stakes should be thrown on fertility programs).[28] Sometimes the acute medical need justifies interventions which will not be cost-effective.

Equitable allocation of reperfusion resources among patients with evolving myocardial infarction

As has been outlined above, there are several modes of reperfusion therapy for patients with evolving myocardial infarction. These options are increasingly effective, but also increasingly costly and complex. In most hospitals in Western-Europe and the United States reperfusion resources are limited (especially, direct angioplasty is only possible in hospitals with catheterisation laboratory and excellent trained and experienced medical staff). To equitably allocate these resources, in this thesis a two-step approach is described (chapters 5 and 6).

In the first step, based on patient's presentation features, one year mortality risks are determined, both with and without reperfusion therapy. Subsequently, life expectancies are calculated, using Dutch life tables. The difference between patient's life expectancy with and without treatment is defined to be the treatment benefit. No quality of life adjustments are performed, except for the occurrence of intracranial haemorrhage. This event may be caused by thrombolytic therapy, and will lead to death in more than

half of the cases. Therefore, the probability of intracranial bleeding due to treatment has been judged as undesirable as the occurrence of death after refrained treatment. The concept of life expectancy is refined by introduction of the discounting principle (chapter 5). With help of this technique a greater value can be given to treatment results in the near future, compared with the more distant future, which is in concordance with physician's opinion of good clinical practice. For several categories of patients the estimated benefits of reperfusion therapy - gain in future life years, both 'crude' and discounted - are presented in sets of tables (chapters 5 and 6).

In the second step, treatment allocation policies are discussed, with the estimated gain in life-expectancy in individual patients being the bench mark. Patients with a negative or negligible gain will not be offered reperfusion therapy (treatment will likely be harmful). In those with a relative small expected gain 'standard' therapy is the preferred option (nowadays: streptokinase), whereas more effective, but more expensive options (in rising order: reteplase, accelerated rt-PA and angioplasty) are recommended in patients with higher awaited benefits. The question as of what is 'small' and 'high' benefit cannot be answered unambiguously. Some physicians defend a so-called 'patient-driven' treatment definition. In such case, treating cardiologists determine fixed decision-thresholds on the basis of their insight in what is cost-effective treatment in individual *patients*. They do not aim in the first place at cost-effective treatment of the *population* of myocardial infarction patients. Others opt for a more 'budget-driven' definition. Thresholds are determined in consultation with hospital boards and treating cardiologists on the basis of the expected demand (patients to be treated) and supply (available resources). In the Thoraxcentre Rotterdam this latter policy is preferred, and current thresholds are chosen in such way that approximately 50% of patients will receive 'standard' therapy and 50% more advanced therapy (chapter 5).

The developed decision model generally answers the first and second ethical principles outlined above. In some cases, however, application of the model may yield spurious results. Patients with a high underlying mortality risk usually benefit most from reperfusion therapy (also in terms of expected life years to be gained), and are consequently candidates for intensive treatment. However, in a patient presenting in a terminal stage (e.g. an elderly patient with extensive infarction complicated by severe heart failure, low blood-pressure and increased heart rate), who has also an extreme high mortality risk, reperfusion therapy will not be useful, and good terminal care

should be considered instead. Undeserved initiation of reperfusion treatment as suggested by the model (chapters 5 and 6) in such patient may be to the disadvantage of those who will really benefit. At the other hand one might argue that in this typical situation the acute need requires some action (third ethical principle). Obviously, the decision model can not replace the physician's clinical judgement, and should consequently not be used compulsively. In individual cases protocol deviations are allowed for sure, although these variations are not encouraged.

Doing more good than harm

Another dilemma discussed in this thesis is, whether it is allowed to initiate thrombolytic therapy in patients with somewhat uncertain diagnosis of myocardial infarction (chapter 7). Thrombolytic therapy is especially effective very early after onset of symptoms, and therefore several attempts are made to initiate treatment prior to hospital admission. Since thrombolysis also carries some risk for life-threatening cerebral bleeding complications, correct diagnosis is essential, to prevent inappropriate treatment of non-infarction patients. No diagnostic tool, however, has a specificity of one hundred percent. Thus the question arises as to what is an optimal balance between sensitivity and specificity.

Generally, it is appreciated that medicine may do harm as well as good, and only medical treatments of which one can be reasonably sure of doing more good than harm are agreed to be permitted.[29] This principle refers to treatment of patients who definitely suffer from a certain disease. In the described situation, however, diagnosis is uncertain. Treatment will be very beneficial in patients with true infarctions, but can only be harmful in the non-infarctions. It is questionable whether the 'more good than harm' principle still holds. Actually, no entirely satisfactory solution can be given in this situation. The decision not to treat patients before hospital admission because of diagnostic uncertainty may be fatal for approximately 1% to 2% of those with true infarction (mind that the focus is on very early treatment). On the other hand, a generalised treatment decision may lead to cerebral bleed in about 0.5% to 1.0% and subsequent death in 0.3% to 0.7% of patients without infarction. In this thesis it is argued that the diagnosis of myocardial infarction cannot be made with complete certainty at an early stage, even not in-hospital by an experienced cardiologist. 'To treat or not to treat' depends on the expected ratio between true- and false positive diagnoses. Treatment was

judged permissible and indispensable in case estimated benefits are at least 5 times higher than the risks.

FINAL REMARKS

This thesis is a typical product of the modern scientific method. On the basis of axioms, observations, experimental results (randomised clinical trials), mathematical techniques (calculation of life expectancy) and rational reasoning an answer is formulated to the problem of optimal, equitable allocation of scarce resources in reperfusion treatment of patients with evolving myocardial infarction. So far, observations, results and techniques are extensively discussed, while axioms are underexposed. Nevertheless, it might be useful to pay some attention to the underlying fundamental assumptions.

The most conspicuous and dominating assumption is that the natural course of a disease, the effects of medical interventions and the distribution of resources can be determined according the theory of probabilities. A particular myocardial infarction patient was thought to run a certain 'risk' (or 'probability') of early death. Results of 'randomised' clinical trials indicate a 'risk-reduction' after reperfusion therapy, with different effects of distinct treatment options. Treatment effects are summarised in terms of 'life-expectancy' (a measure constructed with help of estimated future mortality probabilities). Finally, resource allocation is based on 'distribution' of estimated treatment benefit within a certain patient population. This narrowing of reality was essential for solution of the central problem, but passes over patient's experience of the disease (e.g. the faith that God does guide his life) and his endured emotions (e.g. uncertainty about the final outcome, doubt whether the goal he hoped to achieve is still attainable). To overcome this gap in the 'scientific solution' a good, human patient-doctor relationship is essential (also pastoral support may be considered in this respect). The listening ear of an observant treating physician can therefore not be replaced by the developed treatment protocol. The combination of both, however, may lead to equitable allocation of medical resources and improved patient care.

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APPENDICES

SUMMARY

INTRODUCTION

Chapter 1

Several modes of reperfusion therapy for evolving myocardial infarction have been developed, which differ in terms of effectiveness, complexity and costs. Resources are often restricted by budgetary constraints or logistic circumstances, and therefore cost-benefit considerations will play a prominent part in the decision as to which therapy to provide to an individual patient. Since the first hours of symptom onset are of vital importance, time to estimate and weigh benefits, risks and costs of different options is fairly limited. In this situation a decision model which integrates all relevant aspects might be very useful. The present thesis reflects the development of such clinical decision models. The foundation is laid in the 'Premises' and the upshot given in the part on 'Practical decision models'.

PREMISES

Chapter 2

The clinical effects of various reperfusion treatment strategies, especially streptokinase, accelerated alteplase and direct coronary angioplasty have been studied in a number of randomised trials. This chapter presents a survey of the most relevant results observed in these investigations. Reperfustion therapy of suspected myocardial infarction within 6 h of onset of symptoms does avoid approximately 25 deaths per 1,000 patients compared with control therapy. On the other hand, thrombolytic treatment will cause a slight excess in cerebrovascular complications: 4 per 1,000 treatments, 2 of these are fatal (and are already accounted for in the mortality result). Thus, reperfusion therapy is clearly beneficial in these patients. There are moderate, but significant differences in outcome between several reperfusion strategies: direct angioplasty being most effective, followed by accelerated alteplase (with intravenous heparin) and streptokinase. In clinical practice, however, most emphasis should be on rapid installation of some reperfusion therapy without worrying overmuch about which option to choose.

Chapter 3

Mortality-reduction by reperfusion therapy is related to the time elapsing between onset of symptoms and commencement of treatment. In this chapter the nature of this relationship is studied, using tabulated data from randomised trials reported within the 1983-1993 period which compared fibrinolytic therapy with control (including a total of 50,246 randomised patients). The absolute as well as the proportional mortality reduction by thrombolytic therapy was significantly higher in patients treated within 2 h compared to those treated later. The relation between treatment delay and mortality reduction was expressed significantly better by a non-linear than a linear regression equation. This analysis emphasises the importance of early (pre-hospital) thrombolytic therapy.

Chapter 4

In February 1995, a colloquium involving several groups of investigators was organised to discuss several questions with regard to selection of reperfusion therapy for individual myocardial infarction patients. This chapter provides a summary of that discussion. There was a consensus on most topics, and the most important conclusions were:

- Almost all patients with evolving myocardial infarction presenting up to at least 12 h from symptom onset will benefit from reperfusion 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 will benefit most from such therapy.
- The absolute mortality reduction produced by reperfusion therapy is sustained after the first year.
- The beneficial effect of reperfusion therapy depends on the time expired from the onset of symptoms.

Consensus could not be reached with respect to two issues:

- There was no agreement about the shape of the association between treatment delay and treatment benefit.
- Some investigators were convinced that the use of accelerated alteplase with intravenous heparin yields a significant net clinical benefit over streptokinase, while others considered that whereas the hazard with rt-PA is definite any excess of benefit over hazard is uncertain.

The occurrence of these contrasting viewpoints can partly be explained by differences in emphasis on pathophysiological concepts and results of large trials. These differences, however, do not lead to major differences in routine treatment strategies.

PRACTICAL DECISION MODELS

Chapter 5

Patients' life expectancy will decrease after myocardial infarction. By early reperfusion therapy part of this loss can be prevented. The magnitude of the clinical benefit depends on several factors, among which patient's age, the infarct size and treatment delay are the most important. In this chapter, treatment benefit is quantified in terms of 'gain in life expectancy' for several categories of patients and presented in a set of tables. These can be used for allocation of reperfusion resources in clinical practice. For cost-effectiveness reasons, patients in whom the largest benefits are awaited, will receive the most effective (expensive) therapy. Medical ethics require, that patients with similar expected treatment benefit will be offered the same mode of therapy.

Currently at the Thoraxcentre in Rotterdam streptokinase is installed when the estimated gain in life expectancy is 1-4 months and accelerated alteplase for a gain ≥5 months (future life years were discounted with 5% per year). Direct angioplasty is recommended in patients with an estimated gain ≥12 months, and in those with an increased risk of intracranial bleeding. In this way, approximately 80% of the patients will be treated with thrombolytics (40% streptokinase and 40% accelerated alteplase), while in 10% direct angioplasty will be initiated. These threshold values have been chosen based on the actual situation in the Thoraxcentre. Different thresholds may be selected in other centres. Nevertheless, the developed model guarantees that treatment decisions will be made in a consistent manner, and that, within the margins of the available budget, optimal therapy will be provided for individual patients.

Chapter 6

In this chapter an alternative model for the estimation of treatment benefit is presented, which is mainly based on an analysis of the GUSTO-1 randomised trial. Since more detailed information is applied as compared with the model presented in chapter 5, this alternative potentially better distinguishes low

risk- from high risk patients. A further advantage is, that the quantified positive and negative aspects of reperfusion therapy are presented separately, which generally will lead to a more accurate weighing in individual patients.

Chapter 7

One way to avoid unnecessary treatment delay, is initiation of thrombolytic therapy prior to hospital admission. The effectiveness and safety of pre-hospital thrombolysis depends on possibilities for rapid and correct diagnosis. The Rotterdam pre-hospital treatment program utilises a standardised and computer-interpreted electrocardiogram for confirmation of infarction. To prevent false positive diagnosis and inappropriate treatment, current electrocardiographic criteria are very strict: a total ST-deviation ≥1.0 mV is required among other things. In this chapter it is investigated whether these criteria can safely be widened, to increase the number of patients eligible for pre-hospital therapy.

Myocardial infarction was definite in 371 (35%) out of 1,072 studied patients with symptoms suggestive of acute coronary syndrome. In 128 (35%) of these cases the pre-hospital electrocardiogram satisfied the current criteria for immediate thrombolysis, which was also the case in 6 (1%) of the non-infarctions. This corresponds with a benefit/risk ratio of at least 20. The maximal net benefit per 1,000 patients screened is reached if pre-hospital thrombolysis would be installed above the 0.6 (0.4) mV ST-elevation level in probable anterior (inferior) infarctions. In that case, the benefit/risk will be approximately 5. On the basis of these results, pre-hospital thrombolysis should be considered in a greater amount of patients.

GENERAL DISCUSSION

Chapter 8

This final chapter provides a general discussion of the results described in this thesis. Practical and ethical consequences of medicine according to protocol are addressed. Finally it is stated, that the use of a clinical decision model by an attentive treating physician may lead to both an equitable allocation of medical resources and improved patient care.

SAMENVATTING

INLEIDING

Hoofdstuk 1

Voor de behandeling van patiënten met een zich ontwikkelend myocard infarct zijn diverse reperfusie therapieën ontwikkeld, die verschil vertonen in effectiviteit, complexiteit en kostbaarheid. Om budgettaire en organisatorische redenen zijn in de klinische praktijk meestal niet alle opties onbeperkt voorhanden, zodat de kosten-baten verhouding een belangrijke rol speelt in het opstellen van een behandel-plan voor de individuele patiënt. Aangezien het van levensbelang is de reperfusie behandeling zo snel mogelijk na het onstaan van de klachten te beginnnen, is er weinig tijd om de baten, risico's en kosten van verschillende opties in te schatten en tegen elkaar af te wegen. In deze situatie kan het bijzonder zinvol zijn, gebruik te maken van een beslismodel dat alle relevante aspecten integreert. Dit proefschrift beschrijft de ontwikkeling van zulke klinische beslismodellen, waarbij de basis wordt gelegd in de 'Premissen' en de uitwerking volgt in het gedeelte over 'Praktische beslismodellen'.

PREMISSEN

Hoofdstuk 2

De klinische effecten van verschillende reperfusie therapieën, met name streptokinase, alteplase en directe coronaria-angioplastiek, zijn bestudeerd in diverse gerandomiseerde studies. In dit hoofdstuk wordt een overzicht gepresenteert van de belangrijkste resultaten zoals die in deze onderzoeken zijn behaald. Reperfusie behandeling van elke 1.000 patiënten met een vermoedelijk myocard infarct binnen 6 uur na het onstaan van de klachten leidt tot een reductie van ongeveer 25 sterfgevallen in vergelijking met controle-behandeling. Daartegenover staat een geringe toename van het aantal cerebro-vasculaire complicaties: 4 per 1.000 behandelingen, waarvan er 2 fataal zijn (deze zijn reeds verwerkt in het sterfte-cijfer). Dus, reperfusie therapie is duidelijk nuttig in deze groep patiënten. Er zijn kleine, maar significante verschillen in uitkomst tussen de verschillende reperfusie therapieën: directe angioplastiek is het effectiefst, gevolgd door alteplase (in zogenaamd 'versneld' toegediende vorm en in combinatie met intraveneuze heparine) en streptokinase. In de klinische praktijk echter, moet de nadruk liggen op het zo

snel mogelijk beginnen van enige reperfusie therapie. De vraag wélke optie te kiezen, komt pas in tweede instantie aan de orde.

Hoofdstuk 3

De sterfte-reductie die bereikt wordt door reperfusie therapie is gerelateerd aan de tijd die verstreken is sinds het ontstaan van de klachten. In dit hoofdstuk wordt de aard van deze relatie bestudeerd aan de hand van getabuleerde gegevens van gerandomiseerde studies uit de periode 1983-1993 waarin thrombolytische therapie werd vergeleken met controle-behandeling (totaal 50.246 gerandomiseerde patiënten). De absolute zowel als de proportionele sterfte-reductie ten gevolge van thrombolytische therapy was significant groter onder patiënten die binnen 2 uur werden behandeld dan onder hen die later werden geholpen. De relatie tussen behandelings-vertraging en sterfte-reductie kon significant beter worden beschreven met een niet-lineaire dan met een lineaire regressie vergelijking. Deze analyse benadrukt het belang van vroege (pre-hospitale) thrombolytische therapie.

Hoofdstuk 4

In februari 1995 is er een colloquium georganiseerd, waarin verschillende groepen onderzoekers met elkaar van gedachten wisselden over vragen met betrekking tot de selectie van reperfusie therapie in patiënten met een zich ontwikkelend myocard infarct. In dit hoofdstuk wordt een samenvatting van die discussie gegeven. Over het antwoord op de meeste vragen bestond overeenstemming. De belangrijkste conclusies waren:

- Nagenoeg alle patiënten met een zich ontwikkelend myocard infarct die binnen 12 uur na het ontstaan van de klachten behandeld worden, hebben baat bij reperfusie therapie.
- De proportionele verbetering in korte-termijn overleving ten gevolge van reperfusie therapie is nagenoeg gelijk in diverse subgroepen van patiënten. In absolute zin is de sterfte-reductie dus het grootst onder patiënten met een hoog onderliggend sterfte-risico.
- De absolute sterfte-reductie ten gevolge van reperfusie therapie blijft ook na het eerste jaar behouden.
- De omvang van het heilzame effect van reperfusie therapie is afhankelijk van de tijd die verstreken is sinds het onstaan van de klachten.

Twee vragen konden niet eensluidend worden beantwoord:

- Er was geen overeenstemming over de aard van de relatie tussen behandelings-vertraging en behandelings-effect.
- Sommige onderzoekers waren ervan overtuigd dat de combinatie van 'versneld' toegediende alteplase en intraveneuze heparine tot een significant beter resultaat leidt dan behandeling met streptokinase. Anderen, daarentegen, waren van mening dat het onzeker is of het onweerlegbaar toegenomen risico uiteindelijk opweegt tegen de baten.

Het bestaan van deze tegenstrijdige standpunten kan gedeeltelijk worden verklaard door verschillen in het omgaan met pathofysiologische concepten en resultaten van grote gerandomiseerde studies. In de klinische praktijk hebben deze verschillen van inzicht echter geen grote consequenties.

PRAKTISCHE BESLISMODELLEN

Hoofdstuk 5

De levensverwachting van een patient zal afnemen ten gevolge van een doorgemaakt myocard infarct. Door vroegtijdige reperfusie therapie kan dit verlies in levensjaren gedeeltelijk worden voorkomen. De omvang van het behandelings-effect is afhankelijk van diverse factoren, waaronder de leeftijd van de patiënt, de omvang van het bedreigde myocard weefsel en de tijd die verstreken is sinds het ontstaan van de klachten de belangrijkste rol spelen. In dit hoofdstuk wordt voor diverse categorieën van patienten de 'winst in levensverwachting' na reperfusie therapie uitgerekend en gepresenteerd in een aantal tabellen. Deze kunnen worden gebruikt voor het verdelen van beschikbare middelen in de klinische praktijk, waarbij om redenen van kosten-effectiviteit de effectiefste (kostbaarste) optie wordt toegewezen aan patiënten waarin de grootste winst kan worden verwacht. Om ethische redenen dienen patiënten met een onderling vergelijkbare winst voor dezelfde behandeling in aanmerking te komen.

Momenteel worden in het Thoraxcentrum in Rotterdam patiënten met een geschatte winst in levensverwachting in de orde 1-4 maanden behandeld met streptokinase, terwijl 'versnelde' alteplase wordt toegediend bij een winst ≥5 maanden (hierbij zijn toekomstige levensjaren met 5% per jaar gekort). Directe coronaria-angioplastiek wordt aanbevolen in patiënten met een geschatte winst ≥12 maanden en in patiënten met een verhoogd risico op een

cerebrale bloeding. Op deze manier wordt ongeveer 80% van de populatie behandeld met een thrombolyticum (40% streptokinase en 40% 'versnelde' alteplase), terwijl 10% een directe angioplastiek ondergaat. Genoemde drempelwaarden zijn gekozen op basis van de huidige situatie in het Thoraxcentrum. Andere centra komen mogelijk tot afwijkende drempels. Desondanks garandeert het ontwikkelde model dat er consistente keuzes worden gemaakt, en dat, binnen de marges van het beschikbare budget, patiënten optimaal worden behandeld.

Hoofdstuk 6

In dit hoofdstuk wordt een alternatief model beschreven voor het schatten van het effect van reperfusie therapie, voornamelijk gebaseerd op een analyse van de GUSTO-1 studie. Aangezien de gegevens die hierin worden gebruikt gedetailleerder zijn dan die in het model uit hoofdstuk 5, leidt dit alternatief tot een betere onderscheiding van laag- en hoog-risico patiënten. Een bijkomend voordeel is, dat de geschatte positieve en negatieve gevolgen van reperfusie therapie gescheiden worden gepresenteerd, hetgeen over het algemeen zal leiden tot een nauwkeuriger afweging in individuele gevallen.

Hoofdstuk 7

Een manier om onnodige behandelings-vertraging te voorkomen, is het toedienen van een thrombolyticum voor opname in het ziekenhuis. De effectiviteit en veiligheid van zo'n procedure is afhankelijk van de mogelijkheden voor snelle en correcte diagnose. In het Rotterdamse programma voor pre-hospitale thrombolyse wordt voor de bevestiging van het myocard infarct gebruik gemaakt van een gestandaardiseerd en computer-geïnterpreteerd electrocardiogram. Ter voorkoming van een vals positieve diagnose en ongepaste thrombolytische behandeling zijn de huidige electrocardiografische criteria erg streng: onder andere is een totale ST-deviatie $\geq$1,0 mV vereist. In dit hoofdstuk wordt onderzocht of deze criteria op een veilige wijze kunnen worden versoepeld teneinde meer patiënten reeds voor ziekenhuisopname te kunnen behandelen.

Myocard infarct was de definitieve diagnose in 371 (35%) van de 1.072 bestudeerde patiënten met symptomen passend bij een acute coronaria aandoening. Van 128 (35%) patiënten uit deze groep voldeed het pre-hospitale electrocardiogram aan de huidige criteria voor directe thrombolyse, hetgeen ook het geval was bij 6 (1%) patiënten met een uiteindelijke diagnose anders

dan myocard infarct. De hiermee corresponderende baten-risico verhouding was groter dan 20. De maximale winst per 1.000 geëvalueerde patiënten wordt behaald indien pre-hospitale thrombolytische therapie zou worden toegediend aan hen met een totale ST-deviatie ≥0,6 (0,4) mV bij een mogelijk voorwand (onderwand) infarct. De baten-risico verhouding is dan ongeveer 5. Op grond van dit onderzoek zou een groter aantal patiënten voor pre-hospitale behandeling in aanmerking kunnen komen dan nu het geval is.

ALGEMENE DISCUSSIE

Hoofdstuk 8

Dit laatste hoofdstuk bevat een algemene discussie van de in dit proefschrift beschreven resultaten. Aandacht wordt besteed aan praktische en ethische consequenties van protocollaire geneeskunde. Uiteindelijk wordt gesteld, dat een klinisch beslismodel in handen van een terzake kundige arts een goed middel kan zijn om tot een rechtvaardige verdeling van beschikbare middelen te komen, waarbij tegelijkertijd de kwaliteit van de patiëntenzorg wordt verbeterd.

Dankwoord

Wie ben ik, dat ik dit doen mag?
Koningin Juliana tijdens de rede ter gelegenheid van haar inhuldiging in 1948

Het verschijnen van dit proefschrift is het resultaat van een vormingsproces waaraan diverse personen hun bijdrage hebben geleverd. Wanneer ik hierna enige van hen met name noem, is dat in de erkenning dat het de Heere God was Die mij het verstand, de krachten en de gelegenheid schonk dit werk te verrichten.

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Curriculum vitae

Hendrik (Eric) Boersma is op 20 juli 1966 te 's Gravenhage geboren.

In 1992 is hij gehuwd met Margrit de Jager. Samen kregen zij drie kinderen: Ardjan (1993), Marianne (1995) en Arno (1997).

In de periode 1978 - 1985 volgde hij onderwijs aan het ongedeeld lyceum 'Guido de Brès' te Rotterdam. Het V.W.O.-diploma behaalde hij in 1985.

Gedurende 1985 - 1990 studeerde hij wiskunde aan aan de Technische Universiteit te Delft. Deze studie rondde hij onder leiding van Prof. dr F.A. Lootsma in 1990 af met het diploma Wiskundig Ingenieur.

In 1990 - 1991 vervulde hij zijn militaire dienstplicht.

Vanaf 1991 is hij werkzaam als biomedisch statisticus en wetenschappelijk onderzoeker bij het Academisch Ziekenhuis te Rotterdam, op de afdeling Klinische Epidemiologie van het Thoraxcentrum.

Vanaf 1997 is hij tevens hoofd van deze afdeling.

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