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Reperfusion Therapy for Acute Myocardial Infarction

Which Strategy for Which Patient?

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Abstract

Several modes of reperfusion therapy for evolving myocardial infarction (MI) have been developed, which differ in terms of effectiveness, complexity and costs. Reperfusion resources are often restricted by budgetary or logistical circumstances. To arrive at an equitable distribution of treatment options, physicians should therefore consider which treatment to apply in which patient. Two major questions which arise in this respect are discussed here: what is the treatment effect in an individual patient, and what is an equitable resource allocation?

Currently, the most relevant treatment options are: streptokinase (1.5MU over 1h), reteplase (2 boluses of 10MU), alteplase (tissue plasminogen activator; t-PA)

[100mg over 1.5 hours] and immediate angioplasty. In combination with aspirin, streptokinase leads to an almost 40% mortality reduction at 1 month compared with placebo [from 13.2 to 8.0%; Second International Study of Infarct Survival (ISIS-2) trial]. The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-1) study demonstrated a further mortality reduction by early combination therapy of aspirin, intravenous heparin and alteplase *vs* aspirin, heparin (either intravenous or subcutaneous) plus streptokinase (from 7.3 to 6.3%). The clinical effects of reteplase fall somewhere between those of streptokinase and alteplase. Combined analysis of the angioplasty trials suggests that angioplasty is superior to thrombolysis, especially in patients with a high cerebral bleeding risk. The noticed gradient of efficacy runs parallel to a gradient of costs and complexity: streptokinase is the least costly treatment option while direct angioplasty is the most expensive and complex.

Subgroup analyses indicate that there are neither apparent deviations in the relative effect of reperfusion therapy as compared to control treatment, nor in the additional effect of more intensive therapy (alteplase) upon 'standard' therapy (streptokinase). Consequently, the absolute number of deaths avoided by reperfusion therapy appears to be greatest in those groups with a high mortality risk without therapy. There is one major exception: in patients treated early after symptom onset a much greater relative mortality reduction is observed than in those treated later.

Owing to the higher mortality risk, the life expectancy of a patient with MI is shorter than that of an 'average' person of the same community and the same age. Since mortality reduction by reperfusion therapy is maintained at long term follow-up, part of this potential loss can be regained. This 're-gain of lost years' is judged to be the ultimate treatment effect in an individual patient. An equitable treatment allocation should be such that patients who will benefit most will receive the most effective therapy, while patients with similar expected benefit will be offered the same mode of therapy.

The conclusion is that treatment guidelines or protocols can be very useful in clinical practice, especially if rapid decision making is of vital importance.

Large randomised trials have demonstrated the benefit of reperfusion therapy in treating patients with evolving myocardial infarction (MI).[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 hours of a coronary occlusion, which usually coincides with the onset of chest pain, part of the viable myocardial tissue will be preserved,[3] which has a favourable impact on the patient's prognosis.

Results of randomised investigations apply by necessity to a patient population whose characteristics are defined by the trial inclusion and exclusion criteria. In clinical practice, however, physicians will treat individual patients, in whom even the benefits, risks and cost/effectiveness of reperfusion therapy are not always immediately clear, to say nothing of the differences in efficacy between specific reperfusion strategies. Since the benefits of therapy fall off rapidly 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 deci-

sions in treatment guidelines. In this article, we summarise the key aspects which should be considered in this respect.

1. Options for Reperfusion Therapy

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

1.1 Streptokinase and Aspirin

The clinical effectiveness of intravenous streptokinase has been demonstrated by the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto miocardico (GISSI-1) [n = 11 802], Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) [n = 1741] and Second International Study of Infarct Survival (ISIS-2) [n = 17 187] investigations.[10-12] In these trials patients were randomised to either a streptokinase infusion of 1.5MU over 1 hour or placebo (open control in GISSI). Short term mortality among the streptokinase patients was reduced by 20% compared with controls (35-day mortality 9.6 *vs* 12.1%; $p < 0.0001$). This beneficial effect of streptokinase is maintained for at least 4 years.[13] The smaller ICIN trial (n = 533) of intracoronary streptokinase reported a sustained effect even at 10 years' follow-up.[14] The stroke rate was in balance between the 2 groups (0.79 *vs* 0.74%). There was a difference in the rate of intracranial bleeding complications, an event which was documented in 22 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 162.5mg daily for 1 month or placebo. Mortality among patients randomised to both streptokinase and aspirin was reduced by 39% compared with double 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

Table I. Characteristics of the most relevant reperfusion treatment strategies

Characteristic	Streptokinase	Reteplase	Alteplase	Angioplasty
Recommended dose	1.5MU over 1h	2 boluses of 10MU given 30 min apart	15 mg bolus; 0.75 mg/kg over 30 min; 0.5 mg/kg over next 60 min (total dose ≤100mg)	Not applicable
Accompanying medication	Aspirin 160-325 mg/day × at least 1mo	Aspirin 160-325 mg/day × at least 1mo + IV heparin 5000U bolus; 1000-1200 U/h × 3-5 days	Aspirin 160-325 mg/day × at least 1mo + IV heparin 5000U bolus; 1000-1200 U/h × 3-5 days	Aspirin 160-325 mg/day × at least 1mo + IV heparin 5000U bolus; 1000-1200 U/h × 3-5 days
Price[a]	$US250-270	Currently not on the market	$US1260-2220	$US5040-6200
Patency[b]	57%	83%	81%	98%
Intracranial bleeding	0.5%	0.7%	0.7%	<0.1%
Complexity	Allergic reaction Hypotension	Relatively high reocclusion rate (need heparin, see above)	Relatively 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

a Lowest values represent European prices;[5] highest values correspond to US prices.[6]

b Percentage of patients with TIMI grade 2 or grade 3 flow at 90 min.[7,8,9]

IV = intravenous; **TIMI** = Thrombolysis and Thrombin Inhibition in Myocardial Infarction trial.

combined thrombolytic and antiplatelet therapy to reopen the occluded coronary artery and keep it open.

1.2 Accelerated Alteplase and Intravenous Heparin

A disadvantage of streptokinase is the production of antibodies, which limits its efficacy and applicability on repeated use. Alteplase [recombinant tissue-type plasminogen activator (rt-PA)], on the other hand, is a nonantigenic agent which directly activates the lytic process, and is potentially more powerful than streptokinase. The relative efficacy of alteplase 100mg infused over 3 hours compared with streptokinase was studied in the GISSI-2 (n = 20 768) and ISIS-3 (n = 41 299) trials, but no clinical benefit was observed.[15-17] In contrast, in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-1) trial (n = 41 021), the combination regimen of accelerated alteplase 100mg infused over 1.5 hours 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 1 year.[18,19] 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.

1.3 Reteplase

Reteplase (recombinant plasminogen activator; r-PA) is a mutant of rt-PA with a markedly increased half-life, which allows bolus administration. Angiographic evaluations of the reteplase regimen of 2 boluses of 10MU given 30 minutes apart showed relatively high early coronary patency rates compared with alteplase.[7,20]

Two large mortality studies with reteplase have been reported. The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial (n = 6010) demonstrated that the reteplase regimen is at least equivalent to 'standard' streptokinase.[21] Mortality at 1 month was 9.0 and 9.5% in patients randomised to reteplase and streptokinase, respectively, whereas stroke rates were 1.23 and 1.00% (these differences were not significant; it should be realised that INJECT was designed to show equivalence, and not the superiority of reteplase). The GUSTO-3 study (n = 15 060) compared reteplase with the GUSTO-1 accelerated alteplase regimen.[22] This trial had a power of 70% and 90% to demonstrate a 15% and 20% relative reduction in 30-day mortality after reteplase, respectively. However, no significant difference was observed: mortality was 7.2% after accelerated alteplase and 7.4% after reteplase. Stroke rates were also comparable: 1.83 and 1.67%, respectively. These results suggest that the clinical effects of reteplase are in between those of 'standard' streptokinase and accelerated alteplase.

1.4 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 profiles of these drugs are comparable with those of alteplase.[23,24] 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 alteplase, while it was significantly more fibrin-specific.[25] 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.

1.5 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 few randomised trials. Among the patients enrolled in all of these trials (n = 2606), short term mortality after primary angioplasty was reduced by 33%

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). To date, there are no reports on long term outcome. It should be realised that the major part of the reduction seen in cerebral bleeding complications is already accounted for in the mortality results, since 50 to 70% of cerebral bleeds will lead to death.[26,27] This indicates that direct angioplasty in particular is an alternative for, and probably superior to, thrombolysis in patients with high risk for cerebral bleeding complications. It should be appreciated, however, that there may be logistical obstacles to immediate performance of this invasive procedure (e.g. the availability of cardiac catheterisation facilities, as well as surgical backup).

Several trials involving a total of approximately 7000 patients have investigated the value of systematic additional angioplasty after thrombolytic therapy.[28] No benefit of this approach was observed if the combined end-point of mortality and nonfatal reinfarction at 6 weeks was considered, compared with thrombolysis alone (12.1 *vs* 11.6%, not significant). Among the 6-week survivors, however, angioplasty seemed to be associated with a lower 1 year mortality rate (2.1 *vs* 2.6%, which implies a 19% relative reduction; not significant). Longer follow-up is necessary to determine whether a statistically significant survival difference will emerge. At present, however, it is not recommended that angioplasty be routinely performed as an adjunct to thrombolytic therapy. On the other hand, the results of the Danish Trial in Acute Myocardial Infarction (DANAMI) trial (n = 1008) indicate that angioplasty or coronary bypass surgery is warranted and beneficial in patients with recurrent ischaemia prior to discharge.[29]

Only a few randomised investigations have evaluated the merits of rescue angioplasty after failed thrombolysis. The limited data indicate that such an 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),[28] but more evidence is definitely needed.

1.6 Antithrombotic Agents

Antithrombotic treatment as an adjunct to thrombolytic and antiplatelet (aspirin) therapy was evaluated in the GISSI-2 and ISIS-3 trials.[15-17] Taking both trials together, 62 067 patients were randomised to either subcutaneous heparin or control therapy. Mortality at 1 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.[18] Thus, it can be concluded that heparin by either route does not do much to improve the outcome in streptokinase patients. The additional value of intravenous heparin added to accelerated alteplase (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.[30]

In contrast to heparin, hirudin directly acts on platelet-bound thrombin and might therefore be expected to be more effective. However, 2 randomised trials in patients with evolving MI [Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI)-9a (n = 757) and GUSTO-2a (n = 2564)][31,32] 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 unacceptably high rate of intracranial haemorrhage. The low dose subsequently used largely avoided these complications, but had little (GUSTO-2b, n = 12 142) or no (TIMI-9b, n = 3002) effect on survival.[33,34] Studies with other thrombin inhibitors, such as bivalirudin (hirulog) and argatroban, in combination with thrombolytic therapy are ongoing.

1.7 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.[35] The introduction of platelet glycoprotein IIb-IIIa receptor blockers may improve treatment of patients with evolving MI in all 3 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 MI.[36,37] Results of the C7E3 Antiplatelet Therapy for Unstable Refractory Angina (CAPTURE) trial (n = 1265) indicate that abciximab can stabilise patients to such a degree that subsequent coronary intervention might be postponed or even cancelled.[37]

The clinical efficacy of another glycoprotein IIb-IIIa receptor blocker, eptifibatide, has been evaluated in the recent large Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) randomised trial (n = 10 948). In patients with unstable angina or suspected non–Q-wave MI, eptifibatide showed a significant 10% relative reduction in the combined end-point death or nonfatal myocardial (re)infarction at 30 days compared with placebo (14.2 *vs* 15.7%, p = 0.042; 17.8 *vs* 19.8% in the MI patients).[38] Similar results have been shown for tirofiban and lamifiban in several studies reported recently.[39-41] A small dose-ranging study in patients with acute MI suggested that the incidence and speed of reperfusion can be enhanced when eptifibatide is combined with accelerated alteplase, aspirin and heparin.[42] Large randomised trials assessing the clinical value of such treatment are due to be started soon.

2. 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.[1,4,43] Generally, it is agreed that initiation of therapy within 6 hours from symptom onset will directly save left ventricular muscle cells, and consequently improve survival. Treatment within 6 to 12 hours from continuous coronary occlusion will have only indirect salutary effects on left ventricular function (reduction of left ventricular remodelling and dilatation)[44] and improved survival after such delays is therefore less pronounced.

Randomised trials which compared prehospital with in-hospital therapy have shown a substantial additional beneficial effect of very early thrombolysis.[4] Pooled analysis of the data, comprising about 6600 patients, indicate that as a result of treatment being initiated 1 hour earlier, 21 ± 6 additional patients will be alive at 30 days per 1000 treated. These findings, as well as observations from experimental studies and larger randomised clinical trials,[4] emphasise the importance of reperfusion treatment within 1 to 2 hours from the onset of symptoms, the time window in which cell death is just starting. In the first hour a 50% mortality reduction is conceivable,[4] whereas this figure is approximately 30, 25 and 12.5% in the periods between 1 and 3, 3 and 6, and 6 and 12 hours after onset, respectively. In an earlier study,[45] a 50% reduction was assumed for treatment in the first 3-hour period, which was based on an analysis of 3362 patients,[46] but this seems overoptimistic in view of current evidence from clinical trials.

3. Complications

While early thrombolytic therapy considerably reduces mortality in patients with evolving MI, some complications may occur. The most cata-

strophic of these is intracranial haemorrhage, which occurred 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.[26,27] It should be appreciated that these deaths were taken into consideration 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 1000 patients with ST elevation or new bundle branch block treated within 6 hours from 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).[43] 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 2- to 3-fold increased incidence of severe haemorrhage after thrombolytic therapy (0.4% among controls *vs* 1.1% among patients randomised to active treatment).[1]

Immunological reactions may occur if the patient receives streptokinase, which 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 MI itself. Nevertheless, in several trials, mild allergic reactions were reported in approximately 4% of patients treated with streptokinase. True anaphylactic shock is very rare, occurring in perhaps 0.1%. Hypotension may occur in about 6%.[27]

Reperfusion therapy may also induce ventricular fibrillation, especially if treatment is initiated in an early stage of the infarction.[47] This complication should therefore be watched, particularly in prehospital thrombolysis programmes. Thrombolytic treatment is only warranted if first aid (a defibrillator) is immediately available.

4. Costs

Besides differences in clinical efficacy between the reperfusion strategies discussed above, there are major differences in costs. Streptokinase therapy initially requires about $US250, whereas alteplase treatment costs approximately $US2000 (US prices, see table I).[5,6] 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 $US27 400 per year of life saved by alteplase compared with streptokinase) [1995 costings].[6] Immediate angioplasty is even more expensive, with initial costs of up to around $US6000. Investigations of data from randomised trials indicated that these costs are recovered in part by a decrease in subsequent revascularisation procedures compared with thrombolysis.[5,48] Observational data, however, contradict these findings.[49]

The considerably higher costs of alteplase and angioplasty compared with streptokinase will limit their availability, especially in an era of shrinking healthcare 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.

5. Treatment Effects in Subgroups of Patients

Table II 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 1000 patients (altogether 58 600 patients).[1] No apparent deviations

Table II. Short term mortality observations from randomised clinical trials of thrombolytic therapy versus placebo/control and of more effective therapy (accelerated t-PA) versus standard therapy (streptokinase) [data from Fibrinolytic Therapy Trialists' Collaborative[1] (reprinted with permission) and GUSTO-1[18]]

	Fibrinolytic Therapy Trialists' Collaborative Group					GUSTO-1 randomised trial				
	no. of patients		deaths during first 30 days			no. of patients		deaths during first 30 days		
	fibrinolytic	control	fibrinolytic [no. (%)]	control [no. (%)]	benefit per 1000 (± SD)	accelerated t-PA	streptokinase	accelerated t-PA [no. (%)]	streptokinase [no. (%)]	benefit per 1000[a] (± SD)
Infarct 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)	1120 (16.9)	37 (6)	4 019	7 829	352 (8.8)	822 (10.5)	17 (6)
Time from onset (h)										
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	1644 (9.0)	2051 (11.3)	23 (3)	9 698	18 786	574 (5.9)	1288 (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 (y)										
<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	1144 (13.5)	1372 (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)
Sex										
male	22 353	22 412	1835 (8.2)	2258 (10.1)	19 (3)	7 721	15 049	383 (5.0)	884 (5.9)	9 (3)
female	6 962	6 873	985 (14.1)	1099 (16.0)	18 (6)	2 622	5 090	270 (10.3)	587 (11.5)	12 (7)
Systolic BP (mm Hg)										
<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	1731 (9.6)	2081 (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)
Heart rate (beats/min)										
<80	12 922	12 965	926 (7.2)	1097 (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)
Previous MI										
no	22 468	22 635	1993 (8.9)	2467 (10.9)	20 (3)	8 596	16 798	463 (5.4)	1050 (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	1697 (8.7)	1981 (10.2)	15 (3)	8 828	17 075	504 (5.7)	1100 (6.4)	7 (3)
yes	2 236	2 260	1981 (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	2820 (9.6)	3357 (11.5)	18 (3)	10 348	20 162	653 (6.3)	1475 (7.3)	10 (3)

a Benefit of accelerated t-PA over streptokinase.

BP = blood pressure; **MI** = myocardial infarction; **t-PA** = alteplase.

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.[1,43] 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 II 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 alteplase.[18] Again, there is no significant hetero-

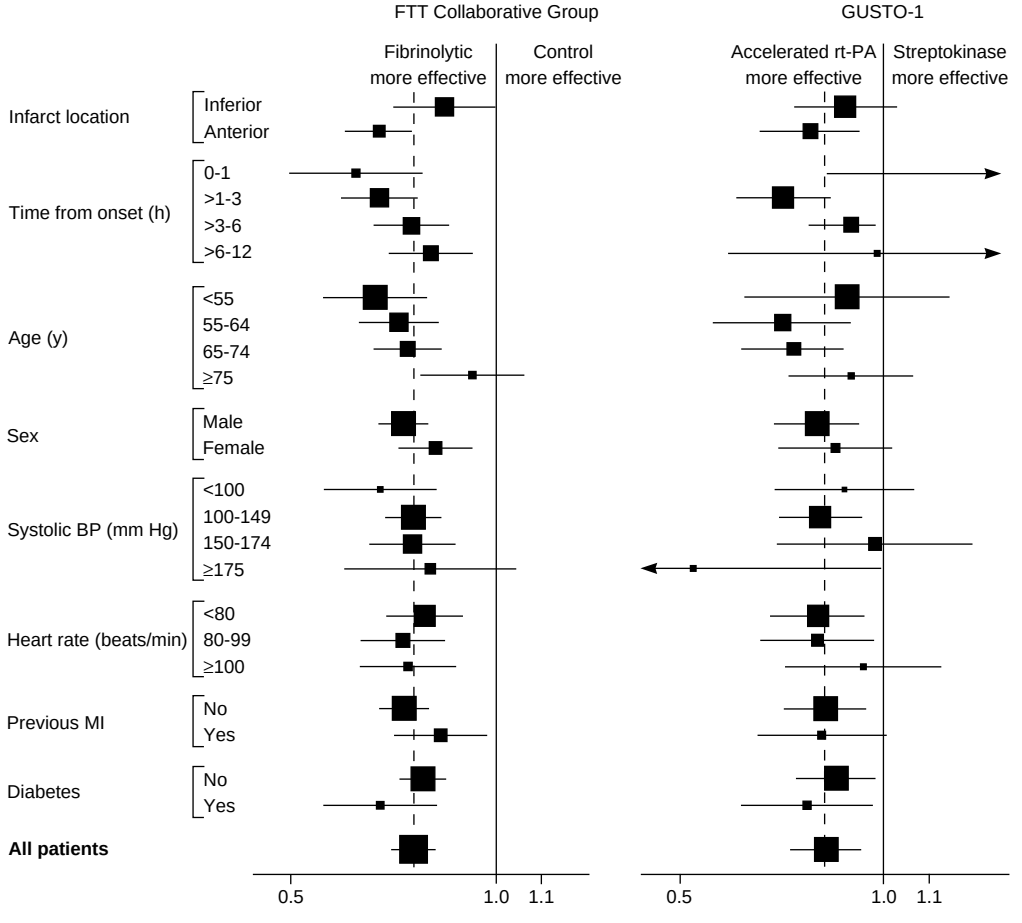

Fig. 1. Relative effects of thrombolytic therapy compared with control, and of more effective therapy [alteplase; accelerated recombinant tissue-type plasminogen activator (rt-PA)] compared with 'standard' therapy (streptokinase) on short term mortality in several subgroups of patients. Data represent odds ratios 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' (FTT) Collaborative Group analysis,[1] which included patients randomised up to 24 hours after the onset of symptoms, and an analysis of the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-1)[18] data, in which most patients were randomised within 6 hours. Data from the Fibrinolytic Therapy Trialists' Collaborative Analysis reprinted with permission.[1] **BP** = blood pressure; **MI** = myocardial infarction.

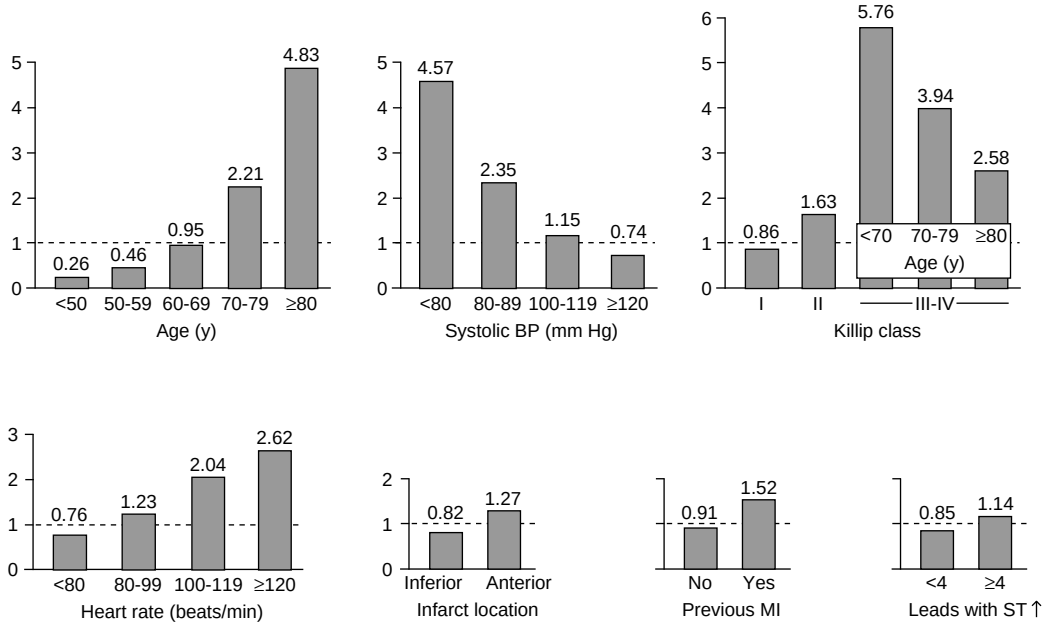

Fig. 2. Graphical representation of the independent contribution of several presenting features to determine cardiac mortality after reperfusion therapy in patients with evolving myocardial infarction. Mortality (in odds form, see Appendix) of an average patient is indexed at value 1. To calculate the mortality index of a particular patient, characterised by given presenting features, deviations from this average should be multiplied. **BP** = blood pressure; **MI** = myocardial infarction.

geneity between the relative mortality reductions in the different subgroups of patients studied. Thus, the additional effect of more intensive and effective therapy (alteplase) upon 'standard' therapy (streptokinase) is also most pronounced in the patient groups at high mortality risk.[50] The GUSTO-2b angioplasty substudy (1138 patients) presented some subgroup analyses, which indicated that this argument also holds for angioplasty *vs* accelerated alteplase, although it should be appreciated that data on the latter are fairly limited.[51]

6. Benefits and Risks in Individual Patients

From the above (sections 1.1 through 1.6), it is apparent that reperfusion therapy generally reduces mortality after MI. 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.

6.1 Determinants of Mortality Not Due to Haemorrhagic Stroke

Analysis of the GUSTO-1 data showed that patients' 30-day mortality risk after thrombolysis is largely determined by the independent presenting features: age (most important), systolic blood pressure, Killip class (which provides a quantification of the pump function of the heart), heart rate, infarct location and history of MI.[52] A young,

haemodynamically 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.[14,53]

In the GUSTO-1 trial 268 patients suffered from a primary intracranial bleeding complication, and 160 (60%) of those subsequently died within the 30-day follow-up period.[26] To estimate the magnitude of the abovementioned risk factors in predicting cardiac death, we performed a subsequent multivariate logistical 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 patients' individual 30-day probability of cardiac death in a 'GUSTO-1–like' 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 population risk will not be influenced by therapy. Finally, the model may be applied to assess individual 1-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.[19,54]

6.2 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 bodyweight, elevated blood pressure at time of presentation and use of alteplase instead of streptokinase.[55] To quantify the individual contribution of these risk factors in predicting the adverse bleeding complication, we again performed a multivariate logistical regression analysis in the GUSTO-1 dataset. The results are presented in figure 3 (see also the Appendix). The developed regression model estimates patients' individual risk for intracranial haemorrhage after initiation of thrombolytic therapy. Since cerebral bleeding complications are very rare (<0.1%) among MI patients who do not receive thrombolysis,[1] the model may also be used to estimate the excess bleeding risk caused by therapy.

6.3 Life Expectancy

Due to increased mortality risk, the life expectancy (Appendix) of a patient with MI is lessened compared with that of 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 patients' life expectancy is age-dependent.[45] For example, a 1-year mortality reduction from 12 to 10% in a 45-year-old patient will save approxi-

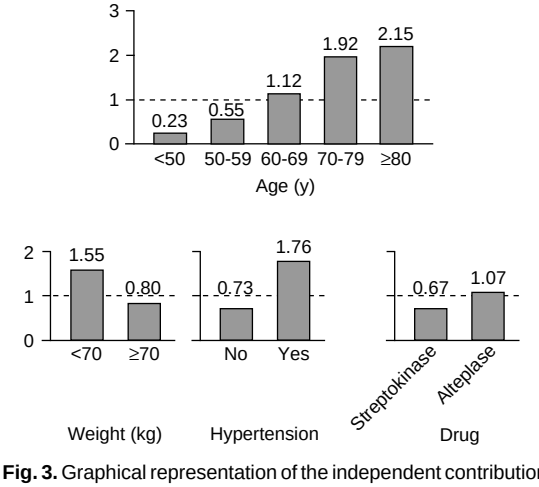

Fig. 3. Graphical representation of the independent contribution of several presenting features to determine the risk of haemorrhagic stroke after thrombolytic therapy in patients with evolving myocardial infarction. The haemorrhagic stroke rate (in odds form, see Appendix) of an average patient is indexed 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.

Table III. Estimated benefits and risks of reperfusion therapy in individual patients with evolving myocardial infarction, showing 1y mortality rates and life expectancies (discounted values, see Appendix) in several categories of patients in the case where reperfusion therapy is not initiated. Also showing are the expected time-dependent benefits from such therapy. The average 1y mortality without reperfusion therapy is estimated at 12.5%. Patients' individual mortality index can be determined with the help of figure 2; the individual mortality probability follows by multiplication of this index with the average mortality (in odds form, see Appendix)

Mortality index	No reperfusion therapy		Benefit from reperfusion therapy: months added [absolute mortality reduction (%)]			
	1y mortality (%)	life expectancy (y)	<1h	1-3h	3-6h	6-12h
Age <50y						
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 50-59y						
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 60-69y						
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 ≥70y						
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)

mately 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 the Appendix). We prefer to concentrate on the effects of treatment on life expectancy rather than on 1-year mortality, since the long term perspective may be most appropriate for medical decision making.[56]

6.4 Integration of Benefits and Risks in Individual Patients

Tables III and IV may help to integrate the benefits and risks in potential candidates for reperfusion therapy. The average (population) probability of dying within 1 year after a conventionally treated MI (i.e. without reperfusion therapy) is as-

sumed to be 12.5%. Depending on the described presenting features (fig. 2), patients' individual mortality risk without therapy may vary from less than 2% to even more than 50% (table III). 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 (note again we use 'discounted' values). Due to reperfusion therapy, cardiac mortality at 1 year will decrease. The magnitude of this reduction depends on the time expired from onset of symptoms (see section 2). Consequently, remaining life expectancy will increase. Most benefits of reperfusion therapy are to be expected in young, high-risk patients treated within 1 hour after symptom onset (average gain up to 39 months).

The risk for cerebral bleeding complications can be estimated with the aid of table IV. 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 as much as 3.5%. The probability of intracranial haemorrhage should be weighed against the expected reduction in cardiac death. If both are (almost) equal, the practitioner should refrain from reperfusion therapy, although in some case immediate angioplasty still might be an option.

Table IV. Risk for cerebral bleeding complications after reperfusion therapy. The average probability is estimated at 0.75%. Patients' individual bleeding index can be determined with the help of figure 3; the individual cerebral bleeding probability follows by multiplication of this index with the average probability (in odds form).

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

ICH = intracranial haemorrhage.

6.5 Advantage of the Model Described

Over the years, several models have been developed to identify which patients benefit most from reperfusion therapy,[14,19,45,50,53] and some of these are incorporated in treatment protocols which are applied in clinical practice.[14,45] Therefore, the question as to what is the advantage of the current model is justified. Does it lead to 'better' estimates of treatment effects in individual patients than existing models?

The problem in 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 1-month mortality,[50] 1-year mortality[14] and life expectancy.[45] Is the latter approach 'better' than the first? We do take this view (see section 6.3), but agree that a focus on the more short term effects is also valid, and may very well match with the physician's first aim: to 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)[50] may better distinguish low risk from high risk patients than models using rougher data (e.g. age categorised as '<65' or '≥65' years, and blood pressure as 'hypertension' or 'no hypertension').[45] 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.[46]

Another advantage is that the quantified positive and negative aspects of reperfusion therapy are presented separately (tables III and IV), 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.

7. 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 relatively inexpensive but less effective therapy might be allocated to those with lower expected benefit. 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? In discussing these issues, the differences in use of reperfusion therapy between nations should be appreciated.[57] These differences can largely be explained by differences in socioeconomic and cultural circumstances.

7.1 Patient-Driven Decision Making

Some physicians opt for an allocation policy which can be called 'patient-driven', since it is mainly based on estimations of costs and effects of therapy in a particular patient (rather than on cost-effective treatment of a population: the so-called 'population-driven' or 'budget-driven' policy). In such situations, patients in whom the 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 inexpensive 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 alteplase, which is slightly more effective, but also more expensive than streptokinase (reteplase might also 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 who have an 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 into what is cost-effective treatment of the individual patient with MI.

7.2 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 expertise. However, a major problem arises when reperfusion resources are limited to such extent that at some point the preferred option is not available. This situation may very well happen in the 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'.[58] Therefore, other practitioners defend a 'budget-driven' allocation policy. The point of departure is the available amount of separate reperfusion treatment options ('supply'), and the expected number of patients who will consume these resources (the population, e.g. all MI patients who will be admitted to the coronary care unit in a certain year; 'demand').

Availability of reperfusion resources is determined in consultation with healthcare policy makers, representatives of insurance companies, hospital boards and treating cardiologists. Population characteristics can be obtained from analysis of data from the recent past. These former patients can be ranked according to what their gain in life expectancy from reperfusion therapy would have been. From this ranking 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 minus Y_2% of estimated gain will be allocated streptokinase, alteplase or angioplasty, respectively, where X_2 and Y_2 are dependent on the ratio of demand and supply (e.g. in the Thoraxcenter Rotterdam, $X_2 = 50$ and $Y_2 = 90$). Thus, the budget-driven policy concentrates on cost-effective treatment of a certain population of MI patients, rather than individual patients.

8. Conclusion

The intention of this article has been 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.

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 is ≥120, 100-119, 80-99 or <80mm Hg;

$\beta_3 = 0, 0.635$ 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 is 70-79 or ≥80 years, respectively (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 is <80, 80-99, 100-119 or ≥120 beats/min;

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

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

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

This model has been 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 are 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 the odds ratio, and can be interpreted as a relative risk. The components $\exp(\beta_i)$ in the cardiac mortality model represent independent odds ratios 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 2-fold risk of cardiac death compared with an otherwise comparable patient of less than 50 years (the index group). A patient aged 80 years has an $\exp(2.919) = 18.5$ times higher risk.

Mortality Index

Cardiac death within 30 days occurred in 2493 of the 38 814 patients, which implies a population risk (probability) of 6.4% and odds of 0.069. In other words, each patient of the population has prior odds of 0.069. With the help of the mortality model, the risk (and thus the odds) for an individual patient can be determined. The ratio of this so-called posterior (individual) odds and the prior (population) odds is the likelihood ratio (referred to as the mortality index in the main body of this article). 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 prognosis (lowest mortality probability).

The likelihood ratio can 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 $\Sigma_k\ N_k\ P_k = 2493$ (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

α = 6.919;

β_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 the case of normotension (systolic blood pressure <165 and diastolic blood pressure <95mm Hg) or 0.881 in the case of hypertension (systolic blood pressure ≥165 or diastolic blood pressure ≥95mm Hg);

β_3 = 0 or 0.660 if weight ≥70 or <70kg.

This model has been 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 Mortality Index above 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 MI is decreased due to (a) a higher mortality risk at 1 year, which can be calculated with the 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 1-year mortality risk of <10, 10 to 29 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 life expectancies presented in this article are discounted by 5% per year.

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