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Estimated gain in life expectancy

A simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction

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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 are 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. 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. The 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 the 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 Thoraxcenter 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 $\geqslant 5$ months. Direct angioplasty is recommended in patients with an estimated gain $\geqslant 12$ 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. 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.
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Key Words: Myocardial infarction, thrombolysis, direct PTCA, decision making, life expectancy.

Introduction

The necessity of early reperfusion to improve survival in acute myocardial infarction patients has been clearly demonstrated[1–12]. Such reperfusion can be achieved using one of several regimens of thrombolytic drug therapy, or by direct percutaneous transluminal coronary angioplasty (PTCA). Various pharmacological-strategies have been compared in separate trials. The regimens studied in the GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) and ISIS-3 (Third International Study of Infarct Survival) studies appeared to be equally effective: streptokinase, anistreplase, alteplase (t-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, GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries trial) demonstrated improved survival by accelerated administration of t-PA with aspirin and immediate intravenous heparin: one additional survivor at 30 days and at one year for

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100 patients treated with accelerated t-PA in comparison with streptokinase[15,16]. The combined results of three recently presented studies indicated superior survival following direct PTCA 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 PTCA group.

The gradient of efficacy of the three accepted and most widely used modes of reperfusion therapy (streptokinase, accelerated t-PA and direct PTCA) runs parallel to a gradient of costs and complexity. For example, the initial, direct costs of treating a patient with t-PA in the Netherlands are approximately five times higher than if streptokinase were used (Dfl. 2000 versus Dfl. 400 respectively), while a PTCA procedure requires more complex organization and is even more expensive: approximately Dfl. 5000 to 8000. 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 should be 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 was evaluated by 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 t-PA with intravenous heparin and direct PTCA. 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 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 t-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 (Fig. 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 summarized 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

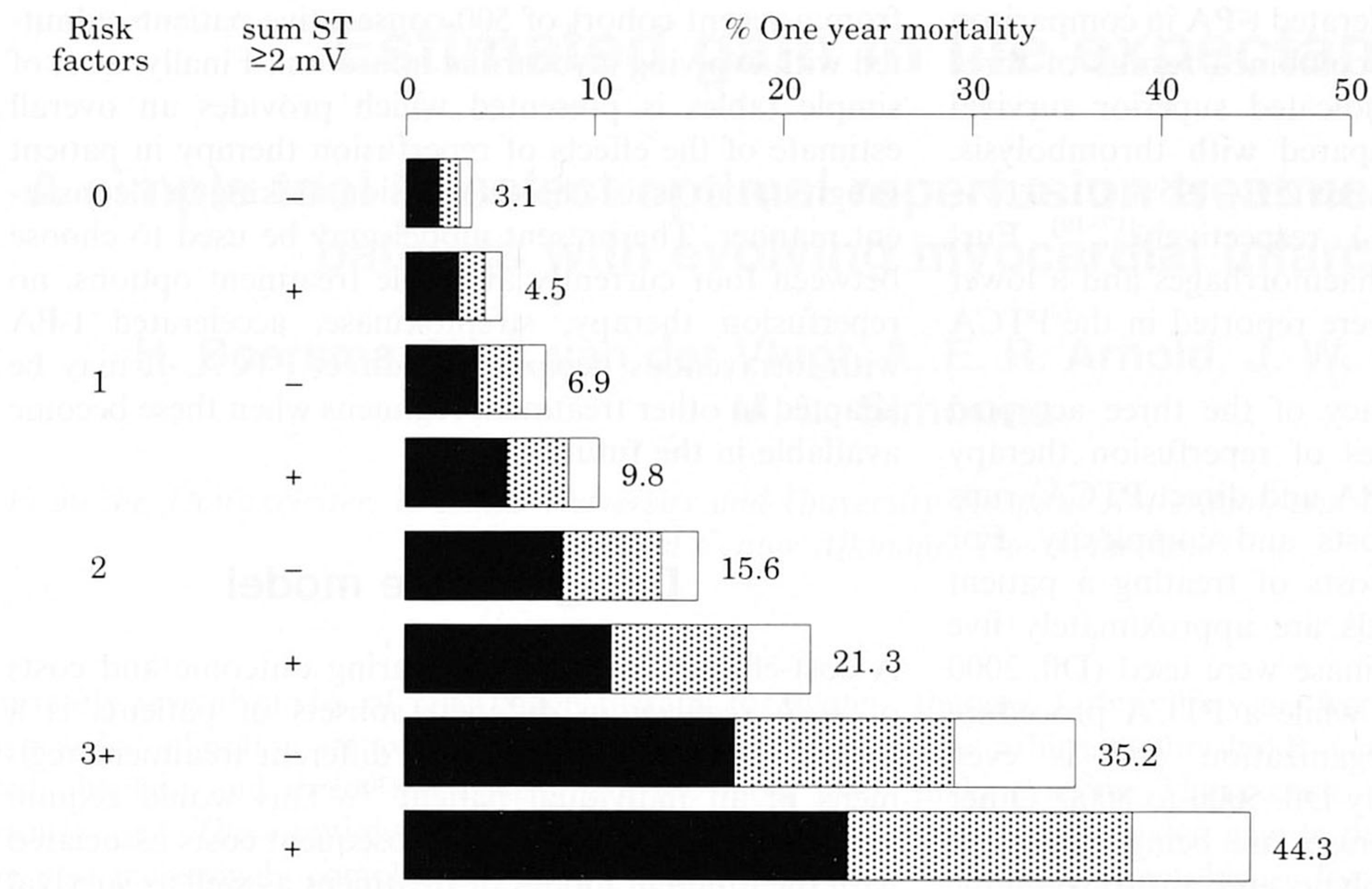

Figure 1 **Estimated one year mortality in different patient subgroups, based on multivariable analysis of data from 3179 patients from three studies[29]. Risk factors for one year mortality were: advanced age, previous infarction, anterior location, inferior location with right ventricular involvement, heart failure and bundle branch block. Patients are divided 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% (hatched area), while only 12·5% mortality reduction is achieved by late treatment (6–12 h after symptom onset, white area).**

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 (Fig. 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 t-PA. Nevertheless, excess stroke after accelerated t-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 t-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 PTCA should be considered in patients with increased bleeding risk.

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

1.	Mortality in the first year after infarction can be predicted from age, history of previous infarction, infarct location and indicators of infarct size.
2.	Mortality reduction by reperfusion therapy is proportional to predicted mortality and related to 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.

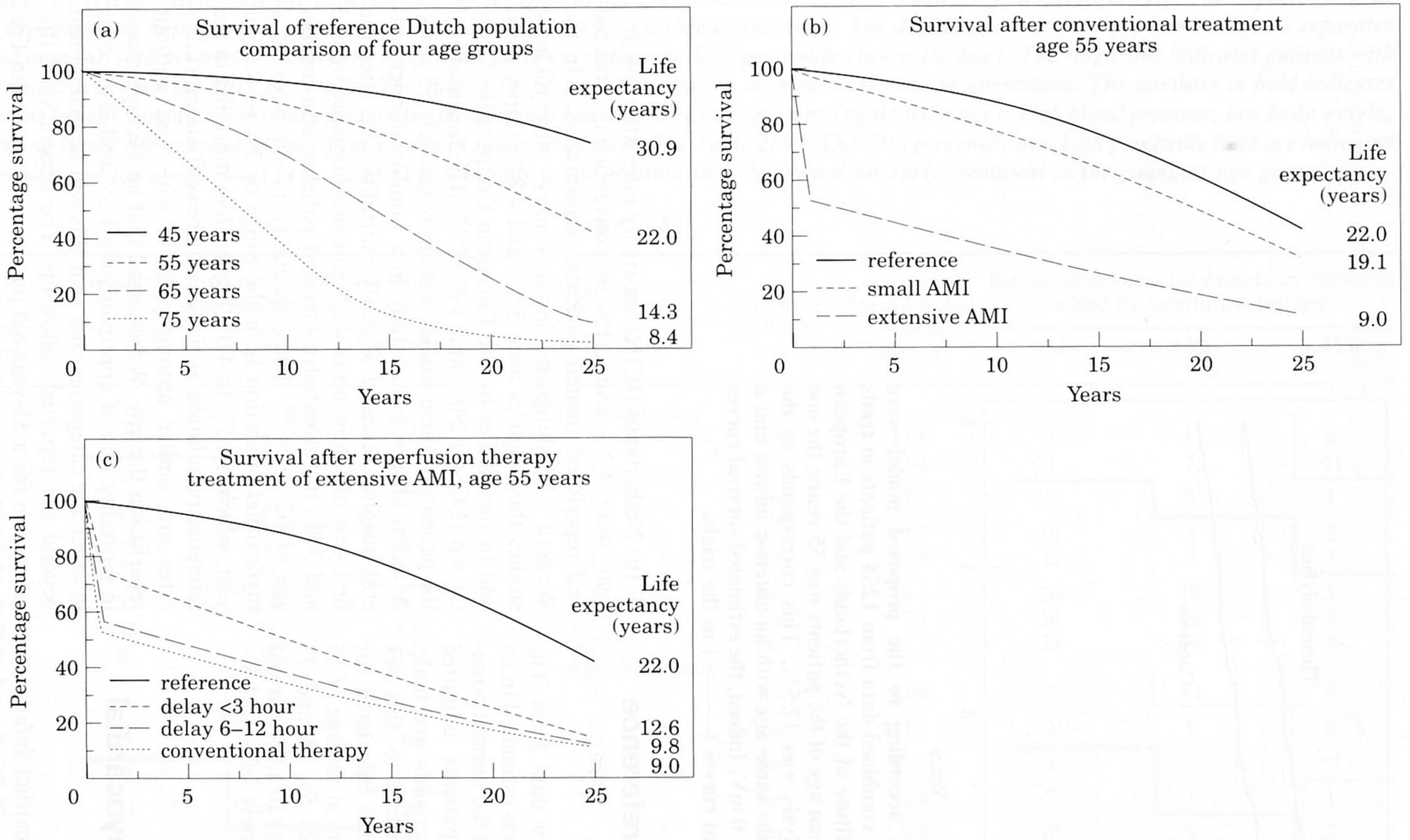

Figure 2 **(a) Reference life expectancies for different age categories (b) Survival curves of a 55-year-old reference subject as well as the curves of two conventionally treated patients of the same age. After a small infarction, life expectancy (the area under the curve) will be reduced from 22·0 to 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 from 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).**

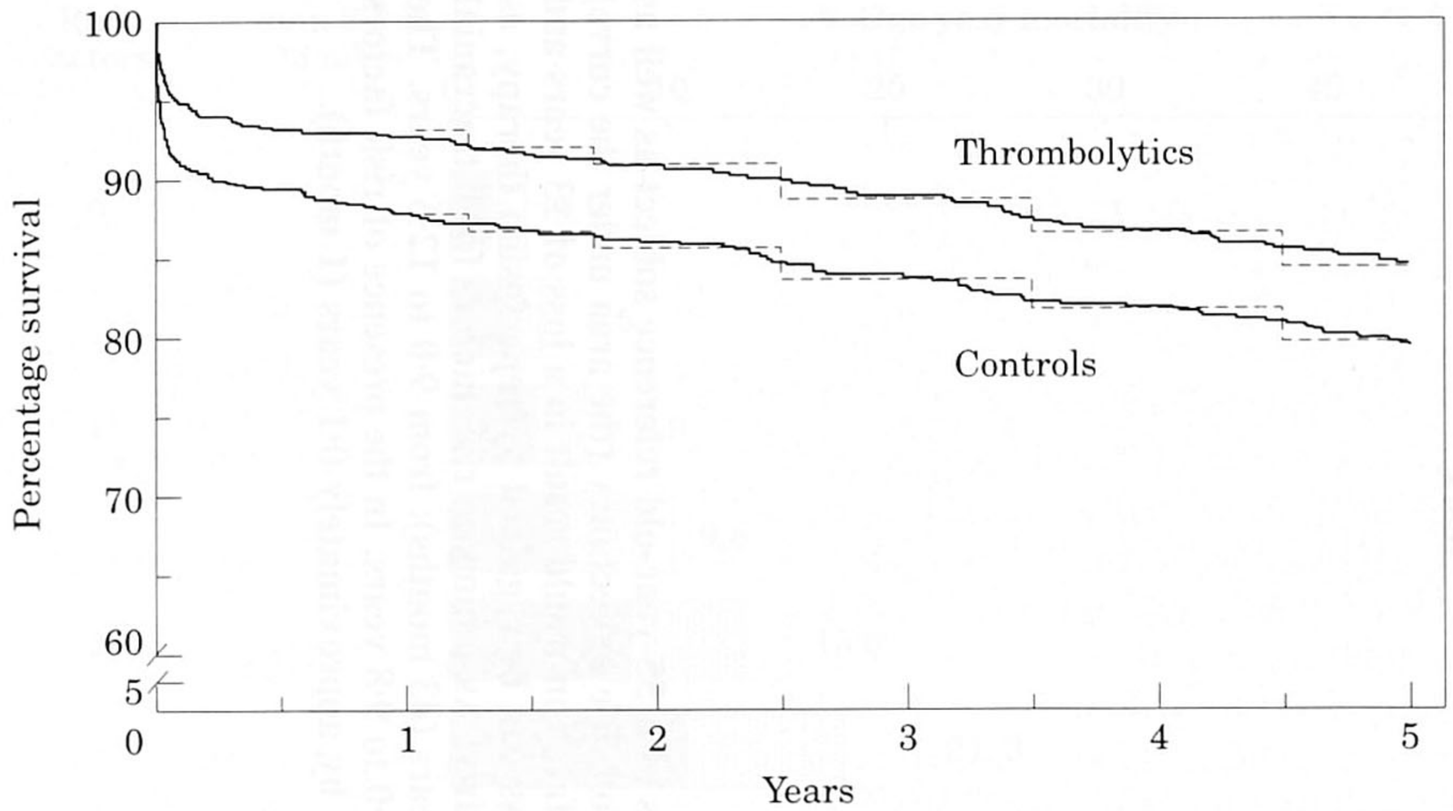

Figure 3 **Computed survival curves according to the proposed model were compared with observed survival in the combined data from 1254 patients in trials by the Inter-university Cardiology Institute of the Netherlands and the European Cooperative Study Group[35,37]. The mean age of the patients was 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 infarct and a total ST-segment deviation exceeding 2·0 mV. Indeed, the estimated survival curves (– –) are superimposed on the observed curves (———) in the trials.**

Life expectancy of the reference population

Using age- and sex-specific mortality data from The Netherlands in 1990, life expectancy was estimated in 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 (Fig. 2(a)). Yearly mortality in a 55-year-old reference subject would be approximately 1·0% to 1·5% during the first five years.

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 thrombolytic 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 with or without 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 Fig. 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 and 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

***Table 2** Estimated gain in life expectancy (a) in different patient subgroups depending on age, indicators of increased mortality risk (AMI RF, see Fig. 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 numbers in bold indicates 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, treatment with alteplase[1341]. Discounting future life years at 5% per year results in values as presented in Table 2(b). The 50th percentile and 10th percentile lines are indicated as in Table 2(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*

Table 2(a)

Number of AMI RF	ST dev ≥2·0mV	Life exp (years) without therapy	Benefit: life expectancy (months) added by reperfusion therapy		
			<3 h	3–6 h	6–12 h
Age <50 years					
0	no	25·6	5	**2**	0
0	yes	25·2	8	3	1
1	no	24·6	13	6	**2**
1	yes	23·8	19	9	4
2	no	19·2	27	13	6
2	yes	18·0	37	18	8
≥3	no	13·0	53	26	13
≥3	yes	11·2	67	33	16
Age 50–59 years					
0	no	19·1	3	1	0
0	yes	18·8	5	**2**	0
1	no	18·4	8	3	1
1	yes	17·8	11	5	**2**
2	no	14·9	16	8	3
2	yes	13·9	22	11	5
≥3	no	10·4	34	16	8
≥3	yes	9·0	43	21	10
Age 60–69 years					
0	no	12·6	3	1	0
0	yes	12·2	5	**2**	1
1	no	10·6	8	3	**2**
1	yes	9·9	11	5	**2**
≥2	no	7·6	18	8	4
≥2	yes	6·6	22	11	5
Age 70–79 years					
0	no	6·9	**3**	1	0
0	yes	6·4	4	**2**	0
≥1	no	5·1	7	**3**	1
≥1	yes	4·5	8	4	**2**

Table 2(b)

Number of AMI RF	ST dev ≥2·0 mV	Discounted life exp (years) without therapy	Benefit: discounted life expectancy (months) added by reperfusion therapy		
			<3 h	3 6 h	6–12 h
Age <50 years					
0	no	13·6	3	**1**	0
0	yes	13·4	4	2	<1
1	no	13·1	7	3	**1**
1	yes	12·7	10	5	2
2	no	10·8	15	7	3
2	yes	10·1	20	10	5
≥3	no	7·7	30	15	7
≥3	yes	6·7	39	19	9
Age 50–59 years					
0	no	11·6	2	<1	0
0	yes	11·5	3	**1**	0
1	no	11·2	5	2	<1
1	yes	10·9	7	3	**1**
2	no	9·4	10	5	2
2	yes	8·8	14	7	3
≥3	no	6·8	21	11	5
≥3	yes	5·9	27	13	6
Age 60–69 years					
0	no	8·8	2	<1	0
0	yes	8·6	3	**1**	0
1	no	7·6	6	3	**1**
1	yes	7·1	8	4	**1**
≥2	no	5·6	12	6	3
≥2	yes	4·9	16	8	3
Age 70–79 years					
0	no	5·5	**2**	<1	0
0	yes	5·1	3	**1**	0
≥1	no	4·2	5	**2**	<1
≥1	yes	3·6	7	3	**1**

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 (Fig. 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 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 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 lower 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

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

Baseline characteristics	Number (percentage) of patients
Male sex	373 (75%)
Mean age	63 years
Age	
<50 years	73 (15%)
50–59 years	124 (25%)
60–69 years	145 (29%)
>70 years	158 (32%)
Prior infarction	119 (24%)
Localization	
anterior	205 (41%)
inferior+RV	120 (24%)
QRS time >120 ms	31 (6%)
Congestive heart failure	61 (12%)
Symptom onset	
<3 h	330 (66%)
3–6 h	117 (23%)
6–12 h	53 (11%)
ST deviation ≥2·0 mV	195 (39%)
Mean RR at admission ≥160/90	140 (28%)
Body weight <70 kg	151 (30%)
Mean number of AMI risk factors	1·1
Mean number of ICH risk factors	0·6

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 (Fig. 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 Fig. 4(c) indicates that the 50% of patients with the 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.

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

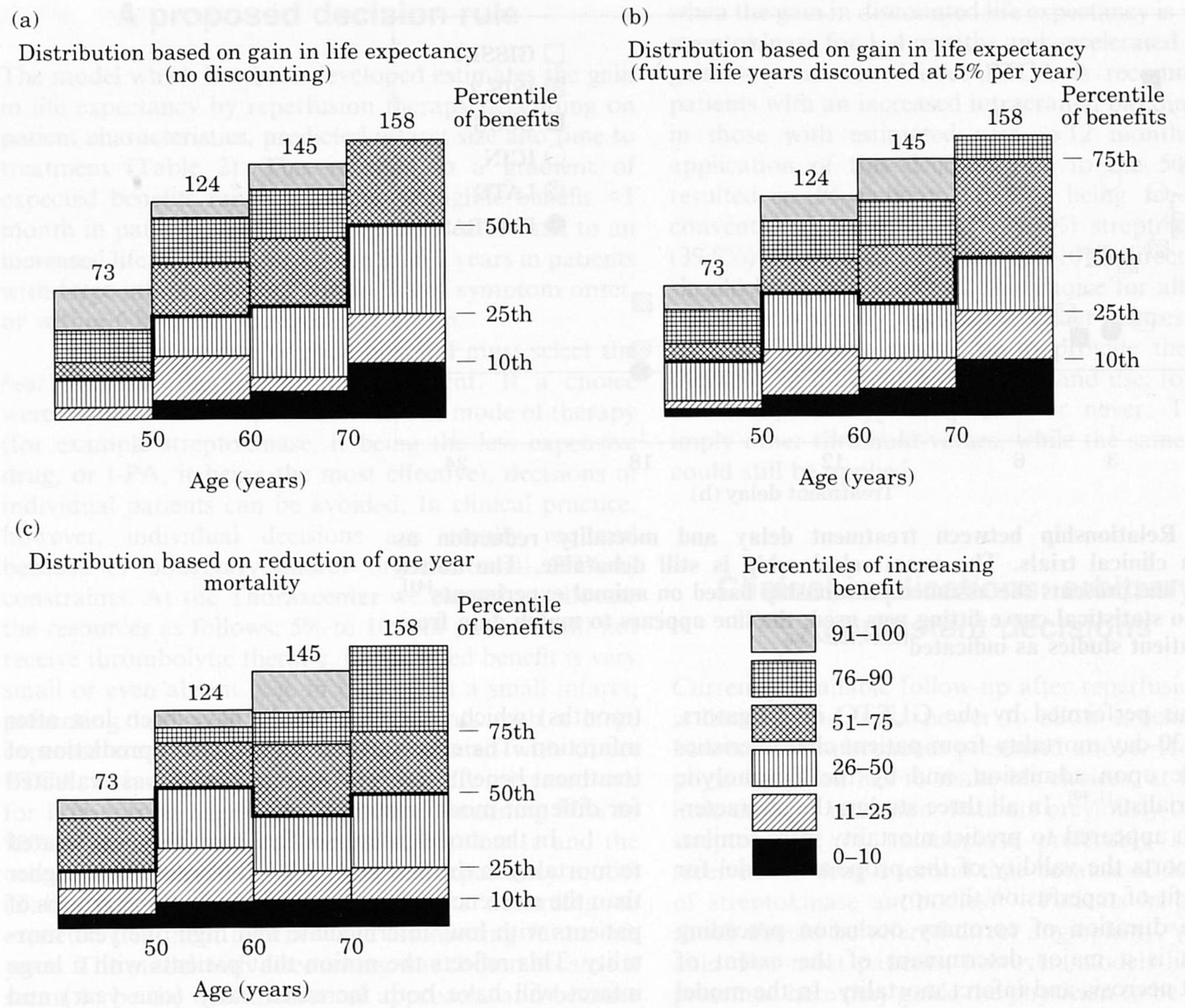

Figure 4 **Distribution of patients with different levels of estimated treatment benefit in clinical practice. Three different models were applied to data from 500 consecutive patients from six different hospitals (Table 3). The bars represent the actual patient numbers in four age groups. The different 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 the 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.**

complexity, while (2) resources are limited, which implies that the most effective therapy cannot 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 young, 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 3179 patients from different trials[29]. More recently a detailed

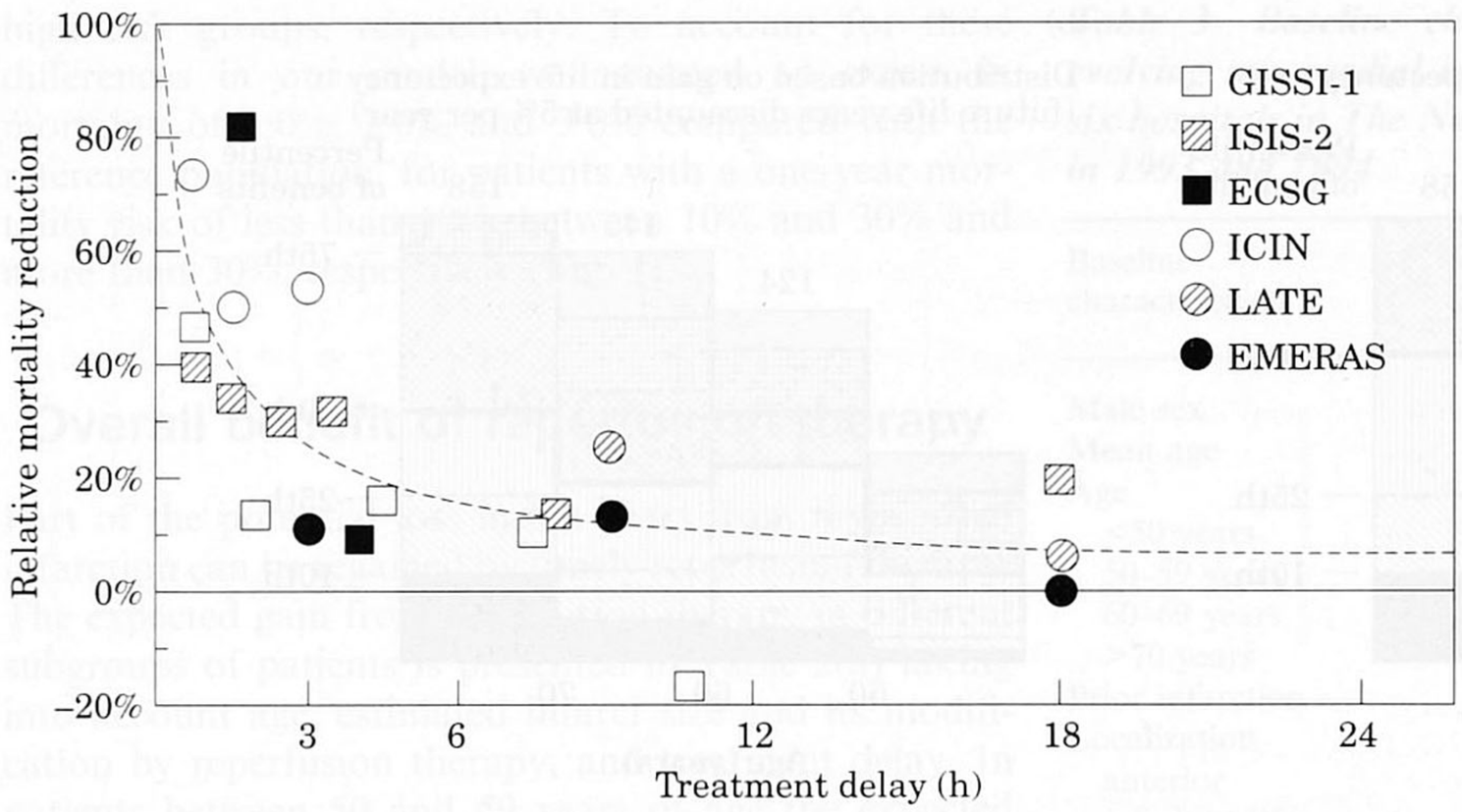

Figure 5 **Relationship between treatment delay and mortality reduction as reported in clinical trials. The exact relationship is still debatable. The dotted curvelinear line presents the assumed relationship based on animal experiments[41]. Although no statistical curve fitting was used, the line appears to match data from different patient studies as indicated[2,5,9,10,24,44].**

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 relationship between time to treatment and myocardial salvage as observed in experimental studies as well as in clinical studies measuring infarct size (Fig. 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 intercranial haemorrhage. However, this hardly affected the ranking of patient 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 Figs 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 Figs 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 (Fig. 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 infarcts 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 (for example streptokinase, it being the less expensive drug, or t-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 organizational (PTCA) constraints. At the Thoraxcenter we elected to allocate the resources as follows: 5% to 10% of 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 PTCA, 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 t-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 (Fig. 4(c)) and life expectancy without discounting (Fig. 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), Fig. 4(b)), direct PTCA 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 t-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 t-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 t-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 Thoraxcenter are (based on the model of our choice as described above): no reperfusion therapy when the gain in discounted life expectancy is <1 month, streptokinase for 1–4 months and accelerated t-PA for a gain $\geqslant 5$ months. Direct PTCA is recommended in patients with an increased intracranial bleeding risk and in those with estimated gain $\geqslant 12$ months. Indeed, application of this decision rule to the 500 patients resulted in 54 patients (10·8%) being recommended conventional therapy, 197 (39·4%) streptokinase, 199 (39·8%) accelerated t-PA and 50 (10%) direct PTCA. It should be appreciated that this choice for allocation of resources 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 PTCA 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 is available, whether it be streptokinase, accelerated t-PA or direct PTCA[43].

Patients with the greatest expected treatment benefit deserve the most effective therapeutic regimen, regardless of costs and complexity. If such a decision were based predominantly on the initial treatment benefit, then such intensive and expensive therapy would be reserved mainly for elderly patients (Fig. 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 (Fig. 4(a)). This reasoning may also be reversed: a physician who, intuitively, applies direct PTCA (the assumed most effective therapy) to predominantly younger patients logically assumes a significant long-term benefit from the intervention.

At the Thoraxcenter, we have opted for the intermediate approach (Table 2(b), Fig. 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 organized and consistent manner, to provide optimal treatment for patients with evolving myocardial infarction, given the existing financial — and organizational — restrictions.

The data on 500 consecutive patients presented in Table 3 were collected by: C. Burgersdijk (*Medisch Centrum Alkmaar, Alkmaar*), M. J. Veerhoek (*St. Franciscus Gasthuis, Rotterdam*), C. van der Zwaan (*University Hospital Rotterdam, Dijkzigt, Rotterdam*), L. G. P. M. van Zeijl (*Havenziekenhuis, Rotterdam*), L. R. van der Wieken (*Onze Lieve Vrouwe Gasthuis, Amsterdam*), P. H. van der Burgh (*Medisch Spectrum Twente, Enschede*).

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