Tailored Thrombolytic Therapy

A Perspective

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Background. **In contrast with current standard regimens, it seems more appropriate to tailor thrombolytic therapy to individual patient characteristics. A proposed model for such tailored therapy is based on individual assessment of benefits and risks of thrombolytic therapy, taking into account the response of individual patients to the therapy given.**

Methods and Results. **Potential benefits of thrombolysis in individual patients can be predicted by use of demographic patient characteristics (age, sex, history of previous infarction) together with indicators of the ischemic area at risk (total ST segment deviation) and treatment delay. Using these parameters, the number of "lives saved" by thrombolytic therapy for specific patient characteristics can be estimated. Similarly, the risk of intracranial hemorrhage during thrombolytic therapy can be estimated from the patient's age, blood pressure at admission, and body weight. Depending on benefit/risk estimates, a choice can be made between regimens with high, medium, or modest thrombolytic efficacy. Continuous multilead ECG ischemia monitoring and rapid assays of myocardial proteins in serum can be used to assess the occurrence or absence of reperfusion and to detect signs of reocclusion. Such data help to decide whether thrombolytic therapy should be continued or intensified or might be discontinued in individual patients before the total standard dose has been administered. Such tailored reduction of the total thrombolytic dose will reduce the risk for bleeding complications in some of the patients.**

Conclusions. **The concept of tailoring thrombolytic therapy and the models presented for benefit/risk assessment should be tested in clinical studies and may subsequently help the physician to select the optimal approach in individual patients. (*Circulation*. 1993;88:2556-2564.)**

KEY WORDS • risk factors • hemorrhage • ischemia

The efficacy of thrombolytic therapy for evolving myocardial infarction has been documented by a number of medium-size and megatrials using different drug regimens.[1-8] Accordingly, in recent years, the indications for thrombolytic therapy have been extended to include most patients with evolving infarction who can be treated within 12 hours after the onset of symptoms.[9,10] It has been shown that the salutary effects of thrombolytic therapy can be improved by addition of an antiplatelet drug.[6,11-13] The addition of aspirin to either streptokinase or alteplase improves coronary patency within the first day, at 1 week,[13] and at 3 months,[12] and the addition of aspirin to streptokinase further improves survival.[6] The value of anticoagulation with heparin is still under debate. Sustained coronary patency was improved by concomitant intravenous heparin in patients receiving alteplase,[14,15] particularly if the level of anticoagulation was adequate.[16,17] Nevertheless, little or no improvement in survival was observed by addition of subcutaneous heparin to either streptokinase, anistreplase, alteplase, or duteplase.[18,19]

The lack of difference in survival between large groups of patients treated with streptokinase, alteplase, duteplase, or anistreplase in combination with aspirin and either with or without subcutaneous heparin has resulted in a debate between advocates of various pharmacological approaches.[20-22] This controversy has been resolved by the recent GUSTO trial,[23] which demonstrated a strong association between the proportion of patients with early coronary reperfusion and survival. The accelerated alteplase regimen in GUSTO resulted in more rapid reperfusion than the other regimens tested and in further reduction of mortality.

The various clinical trials were designed either to test a specific therapeutic regimen[2-10] or to compare several regimens so as to define the optimal mode of therapy.[14,15,18,19,23] Subsequently, the investigators recommend a "standard" regimen for all patients who qualify for thrombolytic therapy.[24,25] In contrast to this uniform approach, we propose that thrombolytic therapy might be tailored to patient characteristics and a patient's response so as to optimize the benefit as well as safety in individual patients. The background and a stepwise approach to such tailored thrombolytic therapy are presented in this perspective and summarized in Table 1.

Step 1: Assessment of the Potential Benefit of Thrombolytic Therapy

The long-term benefits of thrombolytic therapy are illustrated in Fig 1. In this study, in which intracoronary streptokinase and aspirin were used as intervention, a reduction of both early (in hospital to 1 year) and late

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TABLE 1. Tailored Thrombolytic Therapy

Step 1	Assess benefits of thrombolytic therapy from patient characteristics, the estimated myocardial area at risk, and treatment delay
Step 2	Determine risk of intracranial hemorrhage
Step 3	Select regimen for reperfusion therapy Intensive thrombolytic therapy Medium-intensity (moderate) thrombolytic therapy Low-intensity (gentle) thrombolytic therapy Direct PTCA None Optimize therapy to prevent reocclusion Aspirin or other antiplatelet agent Heparin intravenously or other anticoagulant (guided by coagulation measurements)
Step 4	Monitor effect of intervention by continuous multilead ECG ischemia monitoring and/or by rapid assays of myocardial proteins in plasma Consider discontinuation of thrombolytic drug infusion when coronary patency has (probably) been achieved, as assessed by ischemia monitoring Consider rescue thrombolysis (addition of other thrombolytic agent) or angiography with rescue PTCA for persistent pain plus ST elevation
Step 5	Continue monitoring to detect reischemia In case of clinical signs of reocclusion, consider Second dose of thrombolytic drug (same or other) Angiography and PTCA

PTCA indicates percutaneous transluminal coronary angioplasty.

Proposed 5-step approach to tailor thrombolytic therapy to individual patient characteristics and to the observed response in patients. Additional studies should be performed to test the applicability of this approach in clinical practice.

(up to 8 years) mortality was observed. After the first year, mortality averaged 3% per year in the conventionally treated group and only 2% per year in the thrombolysis group. Mortality after hospital discharge appeared to be related to left ventricular function as well as to the extent and degree of coronary artery disease.[26] Thus, long-term outcome appeared to be determined predominantly by the status of the patient at the time of hospital discharge (left ventricular function, coronary anatomy) and not by the preceding events per se.[26,27] The status of the myocardium and of the coronary vessels in patients after myocardial infarction will depend on different factors, some of which can be modified by therapy: demographic characteristics, "predicted infarct size" or the "area at risk," and the duration of coronary occlusion (Table 2).

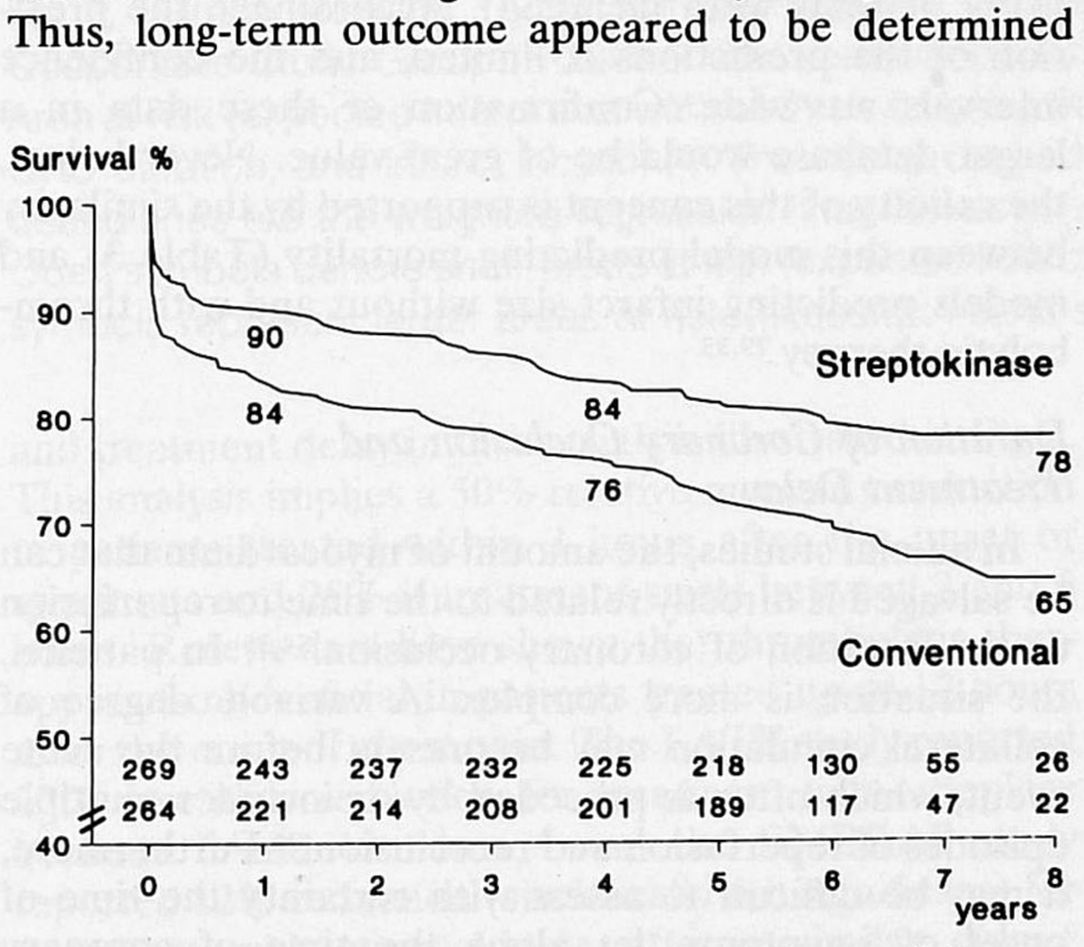

FIG 1. Graph showing follow-up data (8 years) from a trial including 533 patients treated either conventionally or with intracoronary streptokinase.[26] In this trial, thrombolytic therapy was associated with limitation of infarct size, preservation of left ventricular function (ejection fraction), and improved 1-year survival. After the first year, mortality averaged 3% per year in the control group and only 2% per year in patients originally allocated to thrombolytic therapy. Thus, the survival difference increased over subsequent years, reflecting the better left ventricular function and more favorable anatomy of the coronary arteries after intracoronary streptokinase therapy.[26]

Patient Characteristics (Demographics)

Mortality in elderly patients with myocardial infarction is higher than in younger patients with or without thrombolytic therapy.[6] Furthermore, survival is lower in patients with impaired left ventricular function before the event, eg, caused by a previous infarction. At the same age, mortality in women with myocardial infarction exceeds mortality in men.[6] Obviously, these premorbid demographic characteristics cannot be altered by thrombolytic therapy. Nevertheless, the number of patients "saved" by thrombolytic therapy appears to be greater in those groups with a higher mortality risk. This is illustrated by the analysis of various subgroups within ISIS-2, which demonstrated a relative mortality reduc-

TABLE 2. Determinants of Outcome of Myocardial Infarction

Demographics	Predicted Infarct Size (Area at Risk)	Duration of Coronary Occlusion
Sex	Total ST deviation	Treatment delay
Age	Anterior MI	Thrombolytic regimen
Baseline LV Function	Heart failure/shock	
(Previous MI)	Wide QRS	

LV indicates left ventricular and MI, myocardial infarction.

TABLE 3. Prediction of 1-Year Mortality After Myocardial Infarction

Number of Risk Factors	Prevalence (%)	ST Deviation ≥2.0 mV	Probability of Death (%) Without Thrombolysis	Lives Saved by Thrombolytic Therapy (%)		
				<3 hours	3-6 hours	6-12 hours
0	25	−	3.1 (1.9-5.2)	1.6	0.8	0.4
		+	4.5 (2.6-7.6)	2.2	1.1	0.6
1	42	−	6.9 (4.7-10.1)	3.5	1.7	0.9
		+	9.8 (6.6-14.4)	4.9	2.4	1.2
2	24	−	15.6 (10.8-21.9)	7.8	3.9	1.9
		+	21.3 (14.9-29.4)	10.6	5.3	2.7
3+	9	−	35.2 (25.4-46.4)	17.6	8.8	4.4
		+	44.3 (33.0-56.3)	22.2	11.1	5.5
Relative mortality reduction (%)				50	25	12.5

Probability of death without thrombolysis (95% confidence intervals in parentheses) in eight subgroups of patients. Factors associated with increased mortality risk were advanced age, a history of previous infarction, anterior location of the current infarct, heart failure, QRS duration >120 milliseconds, and the total ST segment deviation in the ECG. From these data, increased 1-year survival ("lives saved") by thrombolytic therapy was predicted, assuming 50% and 25% mortality reduction for treatment within 3 hours and 3 to 6 hours after symptom onset,[6] respectively (Fig 2) and 12.5% mortality reduction for treatment starting between 6 and 12 hours.[10,11] 3+ indicates three or more risk factors; −, absent; and +, present.

tion of approximately 25% in most subgroups.[6] Thus, the gain in survival by thrombolytic therapy appears to be proportional to the baseline risk.

Area at Risk: Expected Infarct Size Without Therapy

In patients with evolving myocardial infarction, part of the ischemic myocardium (area at risk) can be salvaged through timely reperfusion. The amount salvaged will depend on the extent of ischemia, on the collateral circulation during coronary occlusion, and on the duration of coronary occlusion until the time of reperfusion.[28] In a detailed analysis comparing patients treated conventionally with those treated with intracoronary streptokinase, the salutary effects of thrombolysis on infarct size, left ventricular function, and 3-month mortality could be predicted from the amount of ST segment deviation on admission, the presence of severe heart failure or shock, and treatment delay.[29] Similarly, the GISSI investigators identified the number of leads with ST segment elevation as a predictor of mortality risk, and extensive ST segment elevation in GISSI was associated with greater benefit from thrombolytic therapy.[30]

Prediction of Mortality Without Thrombolysis

A model to predict 1-year mortality after myocardial infarction was derived from a combined analysis of data from the ICIN,[2] ECSG,[31,32] and ISAM[5] studies. In a multivariate regression model, advanced age, a history of previous infarction, anterior location of the current infarct, heart failure during admission, intraventricular conduction delay, and the sum of ST segment deviation in the ECG were identified as independent predictors of 1-year mortality. The results of this analysis are summarized in Table 3.[33] In younger patients with a first inferior infarction and a small predicted infarct size (total ST deviation <2.0 mV), without heart failure, predicted 1-year mortality without thrombolytic therapy would be 3.1%. Patients with either extensive ST segment elevation or one other characteristic as listed above have a 4.5% to 6.9% predicted 1-year mortality without thrombolysis. The highest mortality would be expected in elderly patients with extensive anterior wall infarction and heart failure or with other combinations of three clinical risk indicators (35.2% to 44.3%).

It should be appreciated that this model is somewhat simplified. To obtain a model that can be used easily in clinical practice, several characteristics were combined as shown in Table 3. Furthermore, the number of patients on which this analysis was based was limited (3179 patients were included). Accordingly, the precision of the predictions is limited, and the confidence intervals are wide. Confirmation of these data in a larger database would be of great value. Nevertheless, the validity of this concept is supported by the similarity between this model predicting mortality (Table 3) and models predicting infarct size without and with thrombolytic therapy.[29,33]

Duration of Coronary Occlusion and Treatment Delay

In animal studies, the amount of myocardium that can be salvaged is directly related to the time to reperfusion or the duration of coronary occlusion.[34,35] In patients, the situation is more complex. A variable degree of collateral circulation may be present before the acute event, which often is preceded by or includes multiple episodes of reperfusion and reocclusion.[36] Furthermore, it may be difficult to assess with certainty the time of onset of symptoms, let alone the time of coronary occlusion. Nevertheless, limitation of infarct size[19,28,33,37] and reduction of mortality by thrombolytic therapy[4,6,31,33] are clearly related to treatment delay. In patients with symptom duration (duration of coronary occlusion) <30 minutes, usually no myocardial damage can be detected. Most damage can be prevented if treatment is initiated within the first hour after onset of symptoms.[4,29] In subsequent hours, the benefits of thrombolytic therapy diminish, although some benefit may be apparent even in patients treated up to 12 hours after the onset of symptoms.[6,9,10] The interplay between area at risk (expected infarct size without thrombolysis)

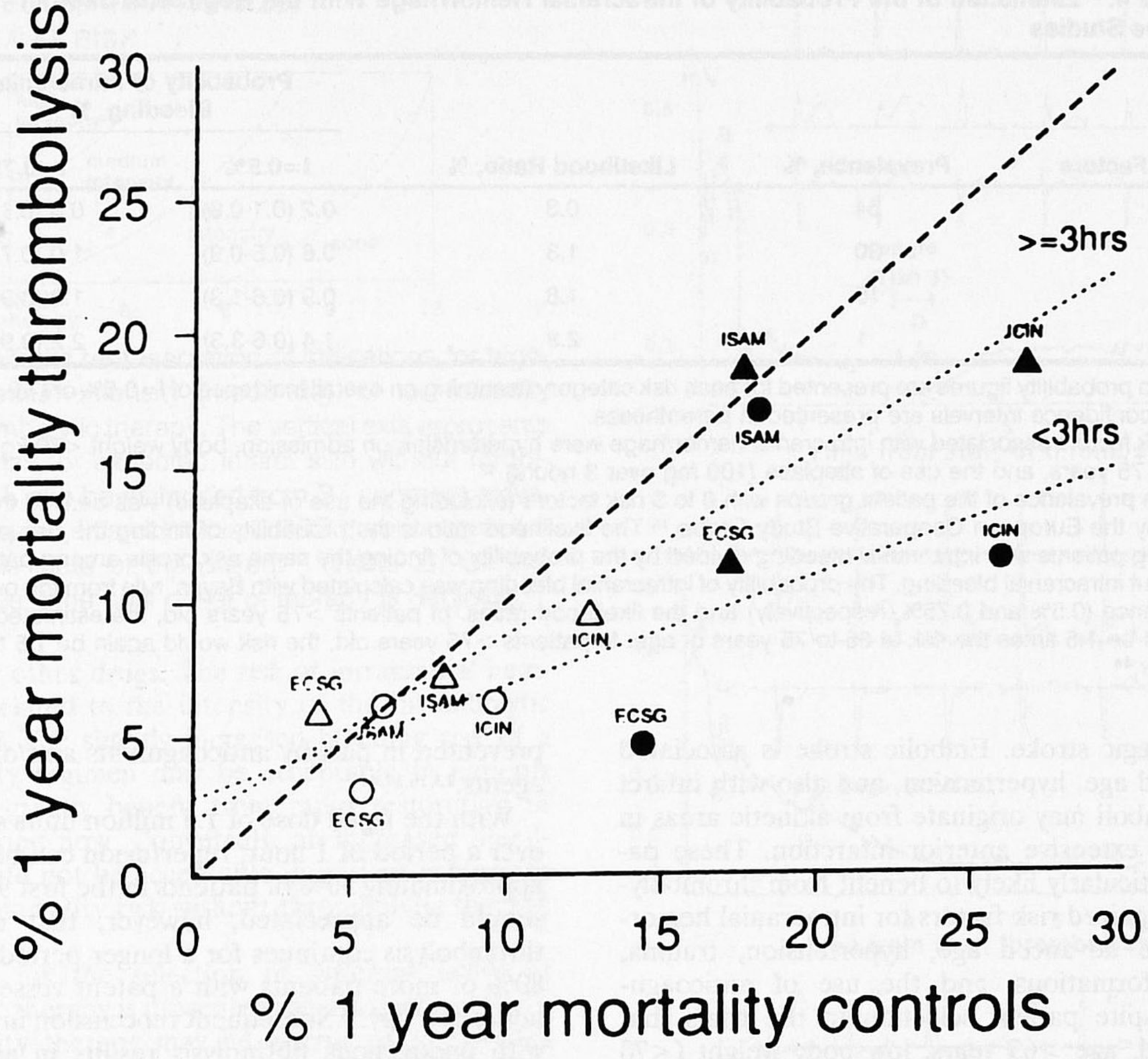

FIG 2. Graph showing 1-year mortality stratified for area at risk and treatment delay for the trials by the European Cooperative Study Group (ECSG),[31] the Netherlands Interuniversity Cardiology Institute (ICIN),[2] and the ISAM study.[5] Area at risk (expected infarct size without thrombolysis) was predicted from the sum of ST segment elevation, Killip class, QRS duration, and infarct location.[33] The heavy dashed line represents the line of "no treatment effect." The lighter dotted lines are the weighted regression lines for early (≤3 hours, circles) and later (3 to 6 hours, triangles) treatment. Open symbols denote small areas at risk (expected infarct size <1000 U/L hydroxybutyrate dehydrogenase), and closed symbols represent larger areas at risk (expected infarct size ≥1000 U/L hydroxybutyrate dehydrogenase).

and treatment delay in three trials is illustrated in Fig 2. This analysis implies a 50% relative mortality reduction in patients treated within 3 hours after the onset of symptoms and 25% if treatment starts between 3 and 6 hours. Recent data have shown that thrombolytic therapy is also beneficial in patients treated up to 12 hours after the onset of chest pain. The LATE study reported 27% mortality reduction for treatment with alteplase between 6 and 12 hours,[10] and the EMERAS study reported 12% reduction (statistically not significant) for treatment with streptokinase after a similar delay.[9] Taken together with data from GISSI[4] and ISIS-2,[6] this results in 14% mortality reduction at 1 month in patients treated between 6 and 12 hours after symptom onset. This corresponds to approximately 12.5% reduction of 1-year mortality.

Benefits of Thrombolysis

The data presented so far are summarized in Table 3. The benefits of thrombolytic therapy, expressed as percentage increase in 1-year survival ("lives saved"), vary between <1% for patients with small infarcts treated after 3 hours to >10% for elderly patients with large infarcts treated within 3 hours after onset of symptoms. This implies that stronger measures and a more aggressive thrombolytic regimen might be used in high-risk patients, despite a possibly higher complication rate, whereas a milder regimen with fewer complications should be used in patients with a lower risk of mortality without thrombolytic therapy.

Step 2: Risks of Thrombolytic Therapy

The inherent risk of thrombolytic therapy is bleeding. Most bleeding complications occur at arterial or venous puncture sites and can easily be controlled. In some patients, extensive retroperitoneal hemorrhage may occur. The most feared complication is the occurrence of intracranial hemorrhage. Although patients with a recognized increased risk for intracranial hemorrhage were not included, either because of protocol requirements or by prudent physicians, intracranial hemorrhage has been reported in 0.5% to 1.6% of patients in larger studies.[4,6,38-42] Approximately half of the patients with intracranial hemorrhage die, and many others remain disabled. It should be appreciated that a distinction must be made between risk factors for embolic stroke

TABLE 4. Estimation of the Probability of Intracranial Hemorrhage With the Regimens Used in These Studies

Risk Factors	Prevalence, %	Likelihood Ratio, %	Probability of Intracranial Bleeding, %	
			I=0.5%	I=0.75%
None	54	0.3	0.2 (0.1-0.3)	0.3 (0.1-0.4)
1	30	1.3	0.6 (0.5-0.9)	1.0 (0.7-1.3)
2	15	1.8	0.9 (0.6-1.3)	1.3 (0.9-1.9)
3	1	2.9	1.4 (0.6-3.3)	2.2 (0.9-4.8)

Two probability figures are presented for each risk category assuming an overall incidence of I=0.5% or I=0.75%. 95% confidence intervals are presented in parentheses.

Risk factors associated with intracranial hemorrhage were hypertension on admission, body weight <70 kg, age 65 to 75 years, and the use of alteplase (100 mg over 3 hours).[42]

The prevalence of the patient groups with 0 to 3 risk factors (excluding the use of alteplase) was derived from a trial by the European Cooperative Study Group.[15] The likelihood ratio is the probability of finding the risk profile among patients with intracranial bleeding divided by the probability of finding the same risk profile among patients without intracranial bleeding. The probability of intracranial bleeding was calculated with Bayes' rule from the overall incidence (0.5% and 0.75%, respectively) and the likelihood ratios. In patients >75 years old, the estimated risk would be 1.5 times the risk at 65 to 75 years of age. In patients >75 years old, the risk would again be 1.5 times higher.[44]

and hemorrhagic stroke. Embolic stroke is associated with advanced age, hypertension, and also with infarct size, since emboli may originate from akinetic areas in patients with extensive anterior infarction. These patients are particularly likely to benefit from thrombolysis.[6,29,30] Recognized risk factors for intracranial hemorrhage include advanced age, hypertension, trauma, vascular malformations, and the use of anticoagulants.[43,44] Despite patient selection in the trials that were analyzed, age >65 years, low body weight (<70 kg), hypertension on hospital admission, and the use of alteplase were associated with increased risk of intracranial hemorrhage with thrombolytic therapy.[39-42]

Table 4 presents a model for assessment of the probability of intracranial hemorrhage for current treatment regimens. This model was developed using multivariable logistic regression analysis (BMDP statistical package) and Bayes' rule.[42] In low-risk patients, this probability is <.5%, even if the overall probability would be .75%. Conversely, intracranial hemorrhage may be expected in 2.2% of elderly patients with hypertension and low body weight if 1.5 million units streptokinase were given and even more frequently after administration of 100 mg alteplase.

Combination of the data in Tables 3 and 4 enables the clinician to decide whether the expected benefits of thrombolysis (Table 3) exceed the estimated risk (Table 4) in a given patient.

Step 3: Selection of a Thrombolytic Regimen

Myocardial infarction usually occurs as the result of an occlusive thrombus formation in a previously diseased coronary segment. Such thrombus can be resolved by thrombolytic agents that promote plasmin activity, resulting in degradation of fibrin. The goals of therapy in patients with occlusive coronary thrombosis are twofold: first, restoration of patency by clot lysis and second, maintenance of patency by prevention of reocclusion. The speed of clot resolution depends on the choice and the concentration (ie, amount administered) of the thrombolytic agent,[45] whereas reocclusion can be prevented in part by anticoagulants and/or antiplatelet agents.[13,16,17,45]

With the usual dose of 1.5 million units streptokinase over a period of 1 hour, reperfusion can be achieved in approximately 50% of patients in the first 90 minutes. It should be appreciated, however, that drug-induced thrombolysis continues for a longer period, resulting in 80% or more patients with a patent vessel after a few hours or 1 day.[45] Subsequent reocclusion in combination with endogenous fibrinolysis results in approximately 74% patency after 1 to 3 weeks. In fact, patency after 1 to 3 weeks as achieved by initial thrombolytic therapy is only marginally higher than patency in patients receiving aspirin and heparin only.[45] For example, in the ECSG-5 study, patency after 10 to 24 days was 78% in patients receiving heparin and aspirin without thrombolytic drug and 83% after alteplase.[31]

More rapid thrombolysis can be achieved by alteplase,[45] particularly if a front-loaded regimen is used,[46,47] or by saruplase.[48] The rate of thrombolysis achieved by alteplase is clearly dose dependent. A schedule of 50 mg administered in 1.5 hours results in 90-minute patency figures similar to those with streptokinase (1.5 million units in 1 hour), whereas more rapid reperfusion is achieved by initially higher dosages.[49] Similar dose-response relations have been shown for anistreplase,[50] but no systematic dose-response studies for streptokinase are available. Unfortunately, the one study that addressed this issue was hampered by excessive variation of timing of angiography and yielded inconclusive data.[51]

On the basis of these early patency figures, thrombolytic regimens may be developed with different levels of initial thrombolytic activity. A high-intensity or rapid regimen would include a relatively large dose of alteplase or saruplase initially, such as the so-called front-loaded or accelerated alteplase regimens.[46,47] A medium-intensity or modest regimen might be the widely used 1.5 million units streptokinase in 1 hour (or 20 000 IU/kg in 1 hour) or 50 mg alteplase (0.67 mg/kg) in 1.5 hours. Finally, low-intensity regimens might be developed using lesser amounts of either streptokinase,

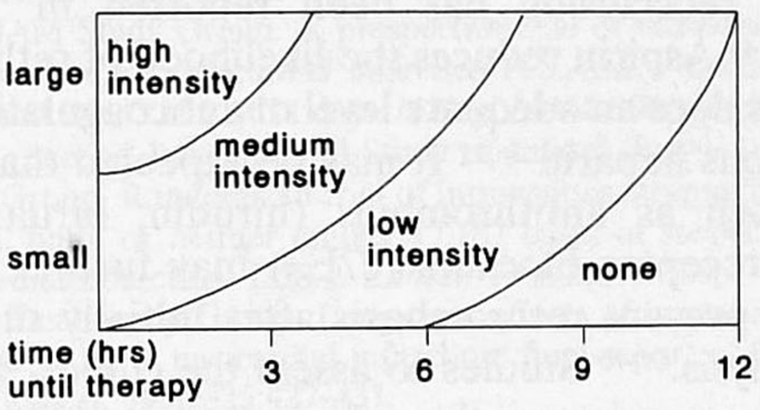

FIG 3. Schematic representation of indications for high-intensity, medium-intensity (moderate), or low-intensity (gentle) thrombolytic therapy. The vertical axis represents the area at risk, or expected infarct size without thrombolysis, which can be estimated from ST segment elevation on admission, infarct location, QRS duration, and the hemodynamic state of the patient[32] (Table 2). On the horizontal axis, time until onset of therapy is depicted.

alteplase, or other drugs. The risk of intracranial hemorrhage is related to the intensity of the thrombolytic regimen.[39-42] The slightly increased bleeding risk of a high-intensity regimen may be acceptable in patients who would greatly benefit from rapid restoration of coronary blood flow. Conversely, an increased bleeding risk would not be acceptable in patient subgroups with a low mortality risk without thrombolytic therapy (Table 3).

A model for the selection of different levels of thrombolytic therapy is presented schematically in Fig 3. High-intensity therapy may be warranted in patients with a large "area at risk" or "expected infarct size" who can be treated early. Conversely, low-intensity thrombolytic therapy would be appropriate in patients with either a small expected infarct size or a larger expected infarct size when treatment is delayed. In these patients with limited benefit from thrombolysis, bleeding risk should be minimized. Finally, a group of patients can be identified in whom no thrombolytic therapy will be warranted because the bleeding risk exceeds the potential benefits of such intervention. In addition to the assessment of clinical benefit (survival) and risk (bleeding), economic cost-efficacy analysis may also be taken into account for the selection of therapy. Thus, a more expensive regimen (accelerated alteplase) will be more appropriate in patients with a large expected clinical benefit, whereas a less expensive regimen (streptokinase) may be selected in other patients. This concept has been confirmed by the GUSTO trial. As reported recently, the accelerated alteplase regimen resulted in a lower mortality than the streptokinase regimens in all patient subgroups.[23] Nevertheless, the cost-efficacy ratio was lowest in patients with a large evolving infarct, particularly with a short treatment delay.

Direct Percutaneous Transluminal Coronary Angioplasty

In hospitals with facilities for angiography and percutaneous transluminal coronary angioplasty (PTCA), direct PTCA may be offered as an alternative for thrombolytic therapy. In patients receiving alteplase, an invasive strategy with systematic PTCA does not improve outcome and may in fact increase mortality.[32,52,53] The lack of benefit of additional PTCA in these randomized studies is probably related to activation of

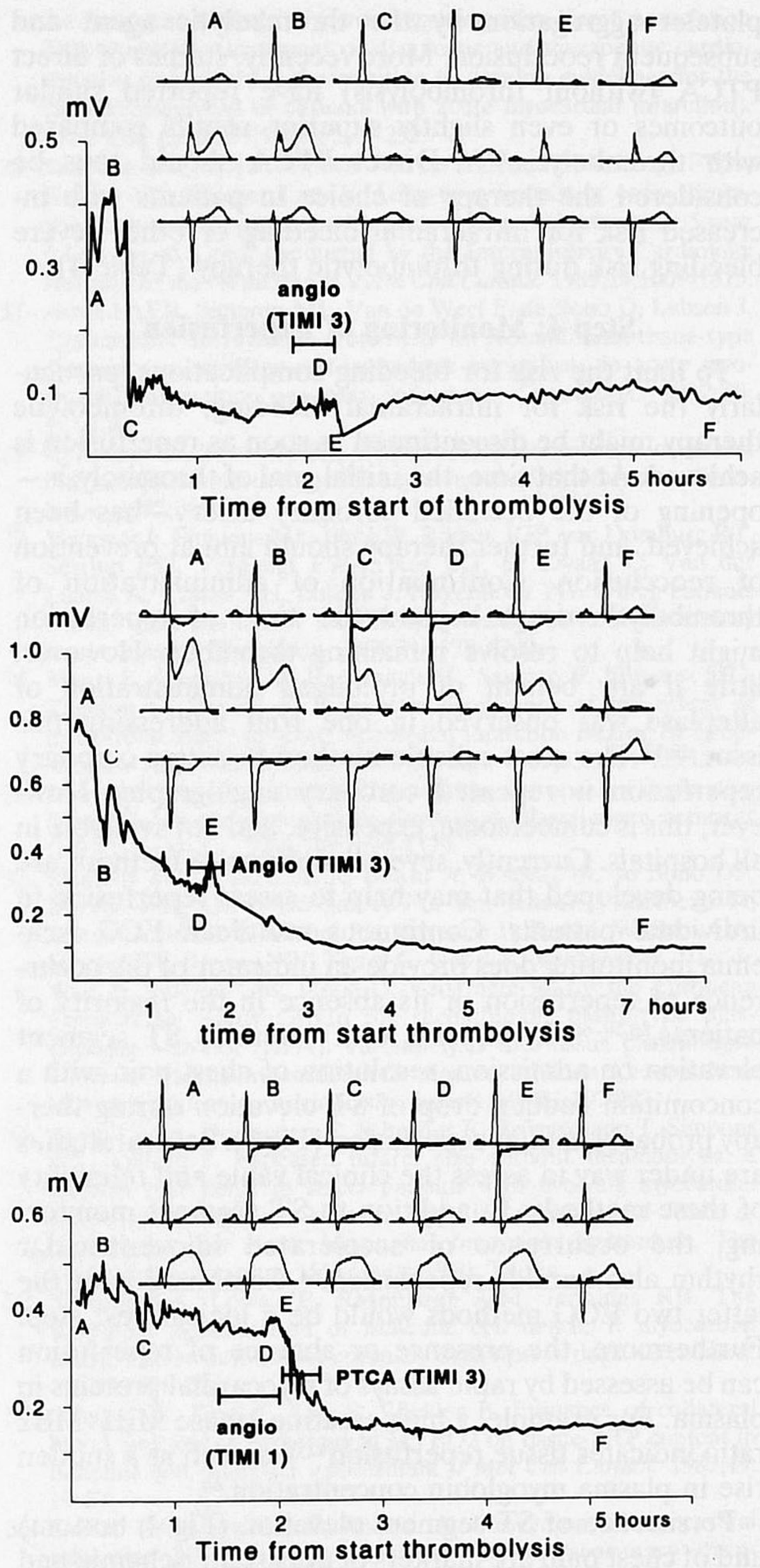

FIG 4. Tracings of continuous ECG ST segment monitoring in three patients receiving thrombolytic therapy. Patient A (top) shows ST segment elevation that suddenly recovers after 22 minutes of therapy. This represents reperfusion, as verified by angiography at 2 hours (TIMI grade 3). Patient B (middle) has a more gradual but consistent decrease of ST segment elevation over the first hour, again representing reperfusion. Coronary angiography showed TIMI grade 3 perfusion at 100 minutes. Patient C (bottom) shows no recovery of ST segment elevation over the first 2 hours. At angiography, an occluded vessel (TIMI grade 0) was found, which was opened by percutaneous transluminal coronary angioplasty (PTCA). After reperfusion by rescue PTCA, the ST segment elevation resolved.

platelet aggregation by the thrombolytic agent and subsequent reocclusion. More recently, studies of direct PTCA (without thrombolysis) have reported similar outcomes or even slightly superior results compared with thrombolysis.[54,55] Direct PTCA should thus be considered the therapy of choice in patients with increased risk for intracranial bleeding or other severe bleeding risk during thrombolytic therapy (Table 4).

Step 4: Monitoring of Reperfusion

To limit the risk for bleeding complications, particularly the risk for intracranial bleeding, thrombolytic therapy might be discontinued as soon as reperfusion is achieved. At that time, the initial goal of thrombolysis—opening of the occluded coronary artery—has been achieved, and further therapy should aim at prevention of reocclusion. Continuation of administration of thrombolytic drugs beyond the time of reperfusion might help to resolve remaining thrombus. However, little if any benefit of prolonged administration of alteplase was observed in one trial addressing this issue.[56,57] The most reliable method to assess coronary reperfusion is repeated coronary angiography. However, this is cumbersome, expensive, and not available in all hospitals. Currently, several noninvasive methods are being developed that may help to assess reperfusion in individual patients. Continuous multilead ECG ischemia monitoring does provide an indicator of the occurrence of reperfusion or its absence in the majority of patients.[36,58-60] In patients with extensive ST segment elevation on admission, resolution of chest pain with a concomitant sudden drop of ST elevation during therapy probably implies reperfusion (Fig 4). Several studies are under way to assess the clinical value and reliability of these methods. In addition to ST segment monitoring, the occurrence of accelerated idioventricular rhythm also heralds reperfusion.[61] Combination of the latter two ECG methods would be a logical next step. Furthermore, the presence or absence of reperfusion can be assessed by rapid assays of myocardial proteins in plasma. For example, a high creatine kinase MB1:MB2 ratio indicates tissue reperfusion[62,63] as well as a sudden rise in plasma myoglobin concentration.[64]

Persistence of ST segment elevation (Fig 4, bottom) and of chest pain are markers of persistent ischemia and probably failed thrombolysis. In such patients, reperfusion may yet be achieved by addition of another thrombolytic agent. For example, in 14 patients with persistent occlusion despite 1.5 million units streptokinase and contrast injections, patency was achieved in 8 (57%) by the addition of alteplase in one study.[65] Obviously, such "rescue thrombolysis" does carry an increased bleeding risk. Accordingly, rescue PTCA may be a more prudent approach to failed thrombolysis,[66] particularly if a potent platelet aggregation inhibitor can be used. The methods for noninvasive assessment of perfusion of the ischemic myocardium (and coronary patency) are still under development. Nevertheless, these methods are likely to offer a tool to tailor thrombolytic therapy in individual patients in the near future.

Step 5: Prevention, Detection, and Treatment of Reocclusion

Reocclusion after thrombolysis has been observed in a number of studies using repeated coronary angiography. Early reocclusion occurs on average in 8% of patients treated with streptokinase. After alteplase therapy, reocclusion has been reported in 14% of patients.[45] Aspirin reduces the likelihood of rethrombosis,[12,13] as does an adequate level of anticoagulation with intravenous heparin.[16,17] It may be expected that newer drugs such as antithrombins (hirudin, hirulog) and IIb/IIIa receptor blockers (c7E3) may further help to delay or prevent rethrombosis after initially successful thrombolysis.[67-70] Studies to assess the clinical value of these drugs are currently under way. Late reocclusion, between 1 to 5 days and 3 months, has been reported in 8% to 32% of patients with an initially patent artery.[12,71] Again, aspirin may reduce the late reocclusion rate.[12]

Methods to tailor initial therapy after thrombolysis may include continuous ECG ST segment monitoring to detect recurrent ischemia and measurement of hemostasis parameters. If signs of reocclusion occur, either treatment with a new (second) dose of a thrombolytic[72,73] or PTCA should be considered.

Conclusions

In this overview, a concept of tailored thrombolytic therapy has been developed. Currently, several different thrombolytic regimens are used, which are claimed to be effective for (virtually) all patients with evolving myocardial infarction. In contrast, we propose that it might be more appropriate to tailor therapy to the characteristics of individual patients and their responses, as summarized in Table 1. This approach should take into account premorbid characteristics that are associated with high or low mortality risk, the area at risk or expected infarct size without thrombolysis, the time since symptom onset at which therapy can be commenced, and the risk of intracerebral hemorrhage in a given patient. In Tables 3 and 4 and Fig 3, models have been presented that might help the physician to select the optimal approach in individual patients. Further studies are required to verify and to expand these models. In contrast to the current simple approach ("one size fits all"), tailored therapy will require attention to many details and continuous monitoring of the course of events in each patient. Continuous ECG ischemia monitoring may be particularly useful to determine whether the therapy is indeed successful or whether an alternative approach should be selected, such as the addition of another thrombolytic drug or rescue PTCA. Data that have been collected in the GUSTO trial[23] and a meta-analysis of data from previous trials may help to further define the precise patient characteristics that can be used to tailor thrombolytic therapy.

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