Thrombolysis for Acute Myocardial Infarction
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Abstract—Thrombolytic therapy has been a major advance in the management of acute myocardial infarction. Unfortunately, it continues to be underused or is administered later than is optimal. Thrombolytic therapy works by lysing infarct artery thrombi and achieving reperfusion, thereby reducing infarct size, preserving left ventricular function, and improving survival. The most effective thrombolytic regimens achieve angiographic epicardial infarct-artery patency in only $\sim50\%$ of patients within 90 minutes. Bleeding requiring transfusion occurs in $\sim5\%$ of patients and stroke in $\sim1.8\%$ with these regimens, which include adjunctive aspirin and intravenous heparin. There are several ways in which reperfusion rates and thus patient outcomes might be improved, such as different dosing regimens of established agents; combinations of different agents; improved adjunctive therapy such as direct antithrombin agents, low-molecular-weight heparin, or glycoprotein IIb/IIIa receptor antagonists; or the development of novel thrombolytic agents with enhanced fibrin specificity, resistance to native inhibitors, or prolonged half-lives allowing bolus administration. All of these strategies are being tested in clinical trials. The best approach currently is to administer thrombolytic therapy as soon as possible to all patients without contraindications who present within 12 hours of symptom onset and have ST-segment elevation on the ECG or new-onset left bundle-branch block, unless an alternative reperfusion strategy is planned. (Circulation. 1998;97:1632-1646.)

Key Words: myocardial infarction • plasminogen activators • streptokinase • thrombolysis

A short distance from its origin the left coronary artery was completely obliterated by a red thrombus that had formed at a point of great narrowing. . .

Thus did James Herrick describe the autopsy of his first patient in his seminal paper in 1912, attributing myocardial infarction to coronary artery thrombus. He went on to state, “The hope for the damaged myocardium lies in the direction of securing a supply of blood.” Over the next 68 years, controversy raged as to whether coronary artery thrombus was a cause of myocardial infarction or whether the clot formed after death and was merely a postmortem finding. In 1980, DeWood and colleagues reported finding thrombus in the infarct-related arteries of $\sim90\%$ of patients undergoing acute coronary artery surgery in the first few hours after the onset of acute myocardial infarction. Although Herrick was referring to collateral blood flow when he wrote of “securing a supply of blood,” his original insight forms the basis for the use of thrombolytic therapy.

The most important therapeutic goal in the management of acute myocardial infarction is early restoration of complete infarct artery perfusion after the occurrence of an acute coronary occlusion. More than 200 000 patients have been randomized in clinical trials of thrombolytic therapy, and in no other area of medicine has a therapy been so extensively investigated. Each year between 1.5 and 2 million patients worldwide are admitted to hospital with acute myocardial infarction. Unfortunately, many of these patients do not receive thrombolytic therapy, and countless lives are lost despite the best scientific evidence of its safety and efficacy. Underusage and delay in administering thrombolytic therapy are the two greatest challenges facing physicians caring for patients with acute myocardial infarction.

The first use of thrombolytic therapy in patients with acute myocardial infarction was reported by Fletcher and colleagues in 1958. In the early 1960s and 1970s, 24 trials were performed evaluating the efficacy of intravenous streptokinase. By modern standards, these trials had major design flaws. For instance, patients were randomized up to 72 hours after the onset of myocardial infarction, and low doses of streptokinase (50 000 to 150 000 IU) were used. The theoretical basis for the administration of thrombolytic therapy was also not yet established, and this, together with lack of evidence of efficacy in a single trial, led to the abandonment of further investigation into this mode of treatment.

In 1969, Chazov administered intracoronary streptokinase in Russia, and it is now nearly 20 years since Rentrop et al reported its use, thereby rejuvenating interest in reperfusion as a treatment modality for the management of acute myocardial infarction. Since then, several new thrombolytic agents, including tissue plasminogen activator (alteplase or reteplase), and adjunctive antiplatelet and antithrombotic regimens have been...
Selected Abbreviations and Acronyms

ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent
ASSET = Anglo-Scandinavian Study of Early Thrombolysis
COMPASS = Comparison of Saruplase and Streptokinase in Acute Myocardial Infarction
FTT = Fibrinolytic Therapy Trialists
GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico
GISSI-2 = Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico
GUSTO-I = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
GUSTO-III = Global Use of Strategies to Open Occluded Coronary Arteries
INJECT = International Joint Efficacy Comparison of Thrombolytics
InTIME = Intravenous n-PA for Treating Infarcting Myocardium Early
ISIS-3 = Third International Study of Infarct Survival
ISIS-4 = Fourth International Study of Infarct Survival
LATE = Late Assessment of Thrombolytic Efficacy
n-PA = novel plasminogen activator: lanoteplase
RAPID-2 = Reteplace Versus Alteplase Patency Investigation During Acute Myocardial Infarction
SESAM = Study in Europe with Saruplase and Alteplase in Myocardial Infarction
TIMI = Thrombolysis in Myocardial Infarction
TNK-TPA = TNK-tissue plasminogen activator
USIM = Urochinasi per via Sistemica nell’Infarto Miocardico

Importance of Infarct Artery Patency

The primary goal of thrombolytic therapy is rapid, complete, and sustained restoration of infarct artery blood flow. The GUSTO-I angiographic substudy strongly correlated 90-minute patency of the infarct-related artery with the mortality reduction achieved with accelerated alteplase.7 Regardless of the thrombolytic agent used, an occluded infarct-related artery (ie, TIMI grade 0 or 1 flow)8 at 90 minutes was associated with an 8.9% 30-day mortality rate, and “normal” perfusion (TIMI grade 3 flow) with a 4.0% mortality rate. Patients with “partial” perfusion (TIMI grade 2 flow, ie, infarct-related artery fills to full length but more slowly than adjacent normal vessels) had an intermediate mortality rate of 7.4%. In addition, at 5 to 7 days, left ventricular ejection fractions were higher, end-systolic volumes were smaller, and regional wall motion in the infarct zone was less depressed in patients with TIMI grade 3 flow than in those with lesser TIMI flow grades,9 confirming the hypothesis that early perfusion at 90 minutes results in preservation of left ventricular function and reduced mortality.

The benefits of early reperfusion may, however, be reduced by subsequent reocclusion of the infarct-related artery. Early reocclusion causes loss of ventricular function and doubles the mortality rate.10 The incidence of reocclusion varies from 4.9% to 25%, depending on the thrombolytic and adjunctive therapies used.9,11 Late reocclusion (occurring up to 1 year after reperfusion) may occur in 25% to 30% of patent infarct-related arteries.12,13 Because long-term patency of the infarct-related artery has been shown to be an independent prognostic factor,14,15 even silent late reocclusion may be associated with a poor outcome.

Eligibility

The proportion of patients presenting with myocardial infarction who are eligible for thrombolytic therapy has varied in reports because of differing eligibility criteria, and depends partly on whether “eligibility” is based on the admission ECG and time window criteria (Table 1) or on a discharge diagnosis of myocardial infarction. In ISIS-4, 70% of patients who presented with suspected acute myocardial infarction received thrombolytic therapy.31 This figure, however, may represent only a subset of patients presenting with myocardial infarction, because only a few patients per month were randomized in the trial in each hospital.

In a recent prospective study, 53% of patients presenting to four coronary care units in Auckland were eligible for reperfusion therapy on the basis of ECG criteria (ST-segment elevation or new left bundle-branch block) and a 12-hour time window.32 Thirty-three percent of the patients had ST-segment depression, paced rhythms, or T-wave inversion, and 14% presented after 12 hours.

The goal should be to treat all eligible patients with reperfusion therapy as soon as possible. Contraindications against thrombolytic therapy exist in 7% to 10% of patients.32,23 Ineligibility for thrombolysis does not mean that the patient is ineligible for reperfusion, and percutaneous revascularization should be considered in such cases.

Time

The timing of the onset of ischemic symptoms is only a crude measure for determining when the infarct-related artery occluded and myocyte necrosis began. This is because occlusion may occur intermittently,34 myocardial demands may vary, and the presence and function of collateral circulation may play an important role. In animals, myocardial necrosis begins within 15 minutes of the onset of a coronary artery occlusion, with a “wave front” of myocyte necrosis proceeding from the endocardium to the epicardium.35 After 40 minutes of occlusion, necrosis is 38% complete; at 3 hours it is 57% complete; at 6 hours 71% complete; and at 24 hours 85% complete. Depletion of ATP occurs over a similar time frame.36 In humans, the time window is likely to be longer because of the factors mentioned above, and ischemic preconditioning may also extend the time during which myocardial salvage may occur.37

Early Treatment

Streptokinase therapy was associated with a 51% reduction in mortality (SD, 12%) at 21 days in a retrospective subgroup analysis of patients randomized to streptokinase or control treatment within 1 hour of symptom onset in the GISSI-1 trial. This observation was considered “hypothesis-generating” by the FTT Collaborative Group,38 who analyzed nine trials of fibrinolytic therapy that had randomized more than 1000 patients each (n=58 600). They concluded that there
TABLE 1. Eligibility Criteria for Thrombolytic Therapy in Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time From Symptom Onset, h</th>
<th>Limb Leads (n)</th>
<th>Leads V1 to V3 (n)</th>
<th>Leads V4 to V6 (n)</th>
<th>ST-Segment Depression</th>
<th>Other Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Washington</td>
<td>≤12</td>
<td>≥1 mm (2)</td>
<td>≥1.5 mm (2)</td>
<td>≥1 mm (2)</td>
<td>Not eligible</td>
<td>One lead with ST elevation if no Q waves or hyperacute T waves</td>
</tr>
<tr>
<td>Interuniversity</td>
<td>≤4</td>
<td>≥1 mm (1)</td>
<td>≥2 mm (1)</td>
<td>≥2 mm (1)</td>
<td>Not eligible</td>
<td>...</td>
</tr>
<tr>
<td>GISSI-1</td>
<td>≤12</td>
<td>≥1 mm (1)</td>
<td>≥2 mm (1)</td>
<td>≥2 mm (1)</td>
<td>As for ST elevation</td>
<td>...</td>
</tr>
<tr>
<td>ISAM28</td>
<td>≤6</td>
<td>≥1 mm (1)</td>
<td>≥2 mm (1)</td>
<td>≥2 mm (1)</td>
<td>Not eligible</td>
<td>...</td>
</tr>
<tr>
<td>ECGS20</td>
<td>≤5</td>
<td>≥2 mm (2)</td>
<td>≥3 mm (2)</td>
<td>≥2 mm (2)</td>
<td>Yes if other criteria</td>
<td>...</td>
</tr>
<tr>
<td>AIMS31</td>
<td>≤6</td>
<td>≥1 mm (2)</td>
<td>≥2 mm (2)</td>
<td>≥2 mm (2)</td>
<td>Not eligible</td>
<td>...</td>
</tr>
<tr>
<td>ASSET22</td>
<td>≤5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ISIS-23</td>
<td>≤24</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>White et al24,25</td>
<td>≤6</td>
<td>≥1 mm (2)</td>
<td>≥2 mm (2)</td>
<td>≥1 mm (2)</td>
<td>Not eligible</td>
<td>...</td>
</tr>
<tr>
<td>USIM26</td>
<td>≤4</td>
<td>≥1 mm (1)</td>
<td>≥2 mm (1)</td>
<td>≥2 mm (1)</td>
<td>As for ST elevation</td>
<td>...</td>
</tr>
<tr>
<td>ISIS-327</td>
<td>≤24</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>EMERAS28</td>
<td>6–24</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>GUSTO-129</td>
<td>≤6</td>
<td>≥1 mm (2)</td>
<td>≥2 mm (2)</td>
<td>≥2 mm (2)</td>
<td>Not eligible</td>
<td>...</td>
</tr>
<tr>
<td>LATE30</td>
<td>6–24</td>
<td>≥1 mm (2)</td>
<td>≥2 mm (2)</td>
<td>≥2 mm (2)</td>
<td>≥2 mm in 2 leads</td>
<td>Abnormal Q or T waves in 2 leads</td>
</tr>
</tbody>
</table>

Aims indicates Anistreplase in Acute Myocardial Infarction; ECSG, European Cooperative Study Group; EMERAS, Estudio Multicentrico Estreptokinase Republicas de America del Sur; and ISAM, Intravenous Streptokinase in Acute Myocardial infarction. Modified with permission from Reference 32.

![Figure 1](https://example.com/figure1.png)  

Figure 1. Mortality among fibrinolytic-treated and control patients according to treatment delay. Reproduced with permission from Reference 39.

was no marked discontinuity at 0 to 1 hours and only a gradual diminution of benefit with delay (30% reduction at 0 to 1 hours [SD, 9%]; 25% reduction at 2 to 3 hours [SD, 5%]; and 18% reduction at 4 to 6 hours [SD, 5%]). For each hour of delay in administering thrombolytic therapy, 1.6 additional lives were lost for every 1000 patients treated.

Boersma and colleagues99 recently analyzed 22 trials that had compared fibrinolytic therapy with placebo or control treatment in at least 100 patients (n=50 246). They came to a different conclusion, namely, that the relation between treatment delay and mortality reduction was expressed significantly better by a nonlinear than a linear regression equation (P=.03) (Fig 1). Their analysis excluded 4250 patients from the USIM and ISIS-3 trials, both of which were included in the FITT analysis. USIM included patients with unstable angina (32%), and ISIS-3 included patients without or with only minor ST-segment elevation. The proportional mortality reduction was 48% in patients treated within 1 hour (95% CI, 31% to 61%), and patients treated within 2 hours had a significantly greater mortality reduction (44%; CI, 32% to 53%) than those treated later (20%; CI, 15% to 25%). These benefits exceed the FITT linear finding of 1.6 lives saved per 1000 patients for each hour of earlier treatment. The implied benefit from treatment 1 hour earlier in GUSTO-I, five lives saved per 1000 patients treated, was also greater than the FITT finding.

These analyses are from nonrandomized comparisons of patients treated earlier versus those treated later and need to be interpreted cautiously. Patients who present earlier may have larger infarcts, and those presenting later are more often elderly, female, diabetic, or hypertensive or have had previous infarctions or bypass surgery.40

The greatest delay between symptom onset and thrombolytic therapy is due to late presentation by patients, and this accounted for 55% of the total treatment delay in GUSTO-I.40 Unfortunately, public education programs aiming to reduce these delays have had variable results.41

In GUSTO-I, the delay between hospital admission and treatment—the “door-to-needle” time—was 64 minutes. Patients in the United States faced slightly longer delays (median, 66 minutes) than those outside the United States (median, 60 minutes).40 It is disappointing to note that in the GUSTO-III trial, which commenced randomization 5 years after GUSTO-I, the median delay was 54 minutes. Whichever thrombolytic regimen is used, it is important that treatment delays be reduced for the benefit of all eligible patients.
Age

Older age is associated with increasing rates of mortality and intracerebral hemorrhage after thrombolytic therapy, regardless of the thrombolytic agent used. Concerns about increasing hemorrhagic risk caused a number of the early thrombolytic trials to impose an upper age limit for randomization,21,22,24,43 and physicians became reluctant to use thrombolytic therapy in patients >75 years of age. Indeed, the 1990 American College of Cardiology/American Heart Association guidelines for the early management of patients with acute myocardial infarction stated that physicians should be judicious in the selection of older patients for thrombolysis and suggested that treatment of patients >75 years old was not well established by the available evidence.44 The elderly have potentially the most to gain from reperfusion strategies because of their high absolute mortality rate. Almost half of all deaths after acute myocardial infarction occur in patients >75 years old,45 and older age is the most important prognostic factor after myocardial infarction.46,47 No randomized, placebo-controlled thrombolytic trial has been designed specifically to assess benefits and risks in the elderly. However, the FTT overview showed that mortality was significantly lower in patients 65 to 74 years old who had received thrombolytic therapy than in control patients (16.1% versus 13.5%; P < .00001), and there was a nonsignificant trend toward a reduction in mortality in patients ≥75 years old (25.3% versus 24.3%).38

The GUSTO-I trial had no upper age limit for randomization, and the oldest patient enrolled was 110 years of age.48 Multivariate analysis confirmed that older age was the most important adverse prognostic factor, with a 30-day mortality rate of 1.1% in patients <45 years and 20.5% in those >75 years old.47 All but the oldest patients (those >85 years of age) had a lower mortality rate, and the net clinical benefit (death plus nonfatal disabling stroke) was greater in patients randomized to receive accelerated alteplase.48

Thrombolytic therapy remains underused in the elderly. Patients >75 years of age are six times less likely to receive thrombolytic therapy than younger patients.30 In a North American registry of the GUSTO-I trial, 30.1% of patients presenting with acute myocardial infarction were >75 years old, but only 17.8% were randomized in the study.51 There are several possible reasons why elderly patients are less likely to receive thrombolytic therapy, including the higher frequency of anginal equivalents, more nondiagnostic ECGs, later presentation, a higher incidence of comorbid disease, and relative contraindications against the use of thrombolytic therapy. With regard to cost-effectiveness, the elderly are likely to obtain greater benefit from thrombolytic therapy because the average number of life-years added by treatment with accelerated alteplase is greater than in younger patients (Table 2).52 For example, among patients <65 years of age, there were 5 fewer deaths or disabling strokes per 1000 patients treated with accelerated alteplase than in those given streptokinase. In patients between the ages of 75 and 85 years, there were 17 fewer deaths or disabling strokes with accelerated alteplase.

It might be expected that a more aggressive thrombolytic regimen, such as accelerated alteplase, would cause more intracerebral hemorrhage in elderly patients and that the net clinical benefit (death plus nonfatal disabling stroke) would be lessened. However, because mortality from intracerebral hemorrhage increases dramatically with age, intracerebral hemorrhage contributes more to the mortality component of the net clinical benefit, and few patients survive with disabling strokes (Fig 2). The greater cardiac benefit of alteplase in the elderly maintains the advantage of this therapy up to the age of 85 years. For patients >85 years old, the best regimen in GUSTO-I appeared to be streptokinase plus subcutaneous heparin.49

Infarct Site

Patients with anterior or inferior infarcts should receive thrombolytic therapy. Although inferior infarcts are usually smaller, the GISSI-1 trial showed that the benefit of thrombolytic therapy was related to the amount of ST-segment elevation rather than the site of the infarct.53 Forty percent of thrombolytic-eligible patients have inferior ST-segment elevation on the presenting ECG.44 In the FTT overview, patients with inferior ST-segment elevation who were randomized within 12 hours of symptom onset had a mortality reduction of 13% (95% CI, −24% to 0%). Patients with inferior infarcts are a heterogeneous group, and adverse prognostic factors may not be apparent on admission when the decision as to whether or not to give thrombolytic therapy must be made. Before the thrombolytic era, the incidence of second- or third-degree heart block complicating inferior infarction was ~19%,54 but nowadays the incidence is ~11.8% with thrombolytic therapy, and the need for temporary pacemakers is uncommon.55 Right ventricular infarction occurs in ~30% of patients with inferior infarcts, and those with ECG evidence of right ventricular infarction have a mortality rate of 30%.55 In the FTT overview, patients with acute inferior infarction and a previous infarction had a mortality rate of 13%. Patients with inferior infarction and anterior ST-segment depression are

<table>
<thead>
<tr>
<th>Age of Patient, y</th>
<th>Anterior Infarction</th>
<th>Inferior Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40</td>
<td>123 609</td>
<td>203 071</td>
</tr>
<tr>
<td>41–60</td>
<td>49 877</td>
<td>74 896</td>
</tr>
<tr>
<td>61–75</td>
<td>20 601</td>
<td>27 873</td>
</tr>
<tr>
<td>&gt;75</td>
<td>13 410</td>
<td>16 246</td>
</tr>
</tbody>
</table>

Figure 2. Incidence of mortality, stroke, and nonfatal disabling stroke with increasing age.
also at high risk. All of these patient groups are at high absolute risk and are likely to benefit substantially from thrombolysis, which reduces mortality and preserves left ventricular function. A patent infarct-related artery has the potential to provide collaterals to another infarct zone in the event of subsequent coronary occlusion and can decrease arrhythmogenesis and remodeling of the left ventricle. Treatment of elderly patients with inferior infarcts has been shown to be particularly cost-effective compared with other widely used treatments (Table 2).

Patients with lateral or circumflex artery infarcts not involving the inferior surface of the heart have usually been excluded from randomized trials because of the requirement for 2 mm of ST-segment elevation in leads V4 to V6 (Table 1), even though these leads are not usually affected by repolarization abnormalities. It would seem logical that patients with occlusive thrombus in a circumflex artery would benefit from thrombolytic therapy, and these patients could be identified by 1 mm of ST-segment elevation in the lateral precordium or lead aVL or by an echocardiogram showing a lateral wall motion abnormality. True posterior infarcts should also be treated. The FTT overview showed that patients with bundle-branch block patterns also benefit from thrombolytic therapy. The trials that included such patients did not specify that the bundle-branch block must be new. ST-segment elevation is easily recognized in the presence of right bundle-branch block, and new infarction can also be detected in the presence of left bundle-branch block. If the diagnosis is uncertain and an old ECG is not readily available, echocardiography may help to determine whether there is a regional wall motion abnormality. Although sequential examinations may be required to determine whether this was due to acute ischemia, stunning, previous long-standing necrosis, or myocardial disease, the absence of myocardial thinning and the presence of contralateral wall hyperkinesis would be supportive evidence for an acute ischemic event. Bedside measurement of cardiac proteins such as myoglobin or troponin T may also aid management.

If patients have a good history of prolonged ischemic chest pain and a normal ECG, they should have another ECG 30 minutes later, because it may take time for significant ST-segment abnormalities to manifest.

### Contraindications

As thrombolytic therapy has become more widely used and the results of the megatrials have confirmed its efficacy and safety, the contraindications have widened in some instances and narrowed in others. In many circumstances, however, no data are available and recommendations must be based on reasonable judgments. Depending on patient demographics and the regimen used, thrombolysis is associated with an increase in the stroke rate of ~0.4% to 0.8%; and there is bleeding requiring transfusion in ~5% of cases, depending on the number of invasive procedures performed. Table 3 lists major contraindications and Table 4 relative contraindications against the use of thrombolytic therapy. For the individual patient, the size of the infarct, the hemodynamic status, any history of previous infarction, the time elapsed since symptom onset, and the patient’s age, etc, must be weighed against the risk of bleeding to determine the likelihood of benefit or harm. If percutaneous revascularization procedures are available, the threshold for administering thrombolytic therapy in the presence of contraindications should be higher. However, if thrombolytic therapy is the only option available, then contraindications in very sick patients may outweigh the possibility of benefit.

### Oral Anticoagulants and Known Bleeding Disorders

Some authorities and most recent trials have considered oral anticoagulants to be an absolute contraindication against the use of thrombolytic therapy. In a multivariate logistic regression analysis of 2469 patients with acute myocardial infarction, those on oral anticoagulants before admission had a significantly higher risk of intracranial hemorrhage after thrombolysis. Theoretically, these patients would be at increased risk of bleeding because of depletion of the vitamin K–dependent clotting factors (factors II, VII, IX, and X). However, if the international normalized ratio is subtherapeutic, it may be reasonable to administer thrombolytic therapy as indicated and to delay or reduce the first dose of heparin. If the international normalized ratio is in the therapeutic range, one approach would be to administer thrombolytic therapy simultaneously with fresh frozen plasma to replenish.

### TABLE 3. Major Contraindications Against the Use of Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any previous history of hemorrhagic stroke</td>
</tr>
<tr>
<td>History of stroke, dementia, or central nervous system damage</td>
</tr>
<tr>
<td>within 1 year</td>
</tr>
<tr>
<td>Head trauma or brain surgery within 6 months</td>
</tr>
<tr>
<td>Known intracranial neoplasm</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
</tr>
<tr>
<td>Internal bleeding within 6 weeks</td>
</tr>
<tr>
<td>Active bleeding or known bleeding disorder</td>
</tr>
<tr>
<td>Major surgery, trauma, or bleeding within 6 weeks</td>
</tr>
<tr>
<td>Traumatic cardiopulmonary resuscitation within 3 weeks</td>
</tr>
</tbody>
</table>

### TABLE 4. Relative Contraindications Against the Use of Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulant therapy</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Pregnancy or within 1 week postpartum</td>
</tr>
<tr>
<td>Active peptic ulceration</td>
</tr>
<tr>
<td>Transient ischemic attack within 6 months</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>Active cavitating pulmonary tuberculosis</td>
</tr>
<tr>
<td>Advanced liver disease</td>
</tr>
<tr>
<td>Intracardiac thrombi</td>
</tr>
<tr>
<td>Uncontrolled hypertension (systolic blood pressure &gt;180 mm Hg, diastolic blood pressure &gt;110 mm Hg)</td>
</tr>
<tr>
<td>Puncture of noncompressible blood vessel within 2 weeks</td>
</tr>
<tr>
<td>Previous streptokinase therapy</td>
</tr>
</tbody>
</table>
the clotting factors. It should be acknowledged, however, that these approaches have not been formally evaluated.

Little information is available about the safety of thrombolytic therapy in patients with common abnormalities such as von Willebrand's disease, which affects 0.1% of the population. The clinical manifestations of this disorder are variable. If patients have had only mild bleeding associated with trauma, it may be reasonable to administer thrombolysis, whereas if transfusion has been required, thrombolysis would be contraindicated.

Other Contraindications

Hemorrhagic pancreatitis could be aggravated by thrombolytic therapy and is therefore considered a relative contraindication against the use of thrombolytic therapy.

There are no data on fetal safety when thrombolytic therapy is administered during pregnancy, and there is also a risk of maternal bleeding in the first week postpartum.

Recent bleeding from peptic ulceration in the previous 6 weeks is considered a contraindication against the use of thrombolytic therapy, but "vague" indigestion should not prevent patients from receiving thrombolytic therapy.

In a case-control study from GUSTO-I, the risk of intracerebral hemorrhage in patients who had previously suffered transient ischemic attacks was 2.8 times that of control cases.60 Patients with a history of dementia had 3.4 times the risk of intracerebral hemorrhage. This may relate to the known increased bleeding risk associated with cerebral amyloid angiopathy.

Myotic aneurysms associated with infective endocarditis may bleed, and because of this possibility, endocarditis is considered a contraindication against the use of thrombolytic therapy.

Catastrophic hemoptysis may occur with cavitating pulmonary tuberculosis, and thrombolytic therapy is therefore contraindicated.

Because the liver produces coagulant factors and there is a possibility of portal hypertension and esophageal varices with the propensity for uncontrollable hematemesis, thrombolytic therapy is contraindicated in cases of advanced liver disease.

Percutaneous revascularization is preferable to thrombolytic therapy if there is a strong possibility of systemic embolism from a fresh left atrial thrombus or a protuberant left ventricular thrombus.

Patients with acute myocardial infarction and a history of hypertension or elevated blood pressure on admission have a greater risk of intracranial hemorrhage after thrombolysis.46 In general, patients with a previous history of hypertension represent a higher-risk group (older age, more women, higher incidence of diabetes, and Killip class >1). They therefore have a worse clinical outcome, including both a higher cardiac death rate and higher total and hemorrhage stroke rates.61 In GUSTO-I, the risk of death in patients with a high systolic blood pressure at entry was similar to that in normotensive patients (excluding patients with a systolic pressure of <120 mm Hg, in whom the risk of death was higher).62 The risk of intracranial hemorrhage, however, increased with systolic blood pressure, especially at systolic pressures of >170 mm Hg, although there was no clear threshold for this effect.62 The rate of intracranial hemorrhage was doubled if the systolic pressure was ≥175 mm Hg at study entry. The effect of elevated diastolic blood pressure at entry on clinical outcomes is less striking. In GUSTO-I, there was a slight increase in the rates of intracranial hemorrhage with increasing diastolic blood pressure, but no significant increase in mortality was observed in patients with high diastolic blood pressures on admission (≥100 mm Hg). It is unknown whether acute treatment of high blood pressure on admission reduces the risk of intracranial hemorrhage after thrombolysis. However, in patients for whom coronary angioplasty is inappropriate or unavailable, it would seem reasonable to lower the blood pressure immediately and then administer thrombolytic therapy.46 In some patients with a very high blood pressure on admission and a low risk of dying of cardiac causes, the risk of hemorrhagic stroke may outweigh the potential reduction in mortality and morbidity.

Sufficient anti-streptokinase antibodies develop to neutralize a standard dose of streptokinase within 3 to 4 days after initial administration. At 4 years, 50%63 of patients still have elevated levels of antibodies. Because of concerns mainly about efficacy but also about allergy,64 streptokinase should not be readministered except in the first 24 to 48 hours.

Factors That Should Not Be Considered Contraindications

Menstruation

Active bleeding at the time of presentation with acute myocardial infarction is usually considered a contraindication against the use of thrombolytic therapy. However, menstrual bleeding is not due to hematological abnormalities but rather to high local concentrations of native plasminogen activator and decreased procoagulants in the endometrial fluid, together with active sloughing of the endometrium induced by prostaglandin-mediated arteriolar spasm. Although menstrual bleeding could theoretically be increased during the first 12 to 18 hours of menstruation, this has not been observed in the few women who have received thrombolytic therapy on day 1 of their menstrual cycle. There have been reports of 24 women who have safely received thrombolytic therapy during menstruation, although moderate bleeding may be increased, requiring transfusion.65 Thus, the risk of bleeding is not a sufficient reason to deny women the benefits of thrombolytic therapy.

Nontraumatic Cardiopulmonary Resuscitation

Small series of patients have reported no significant complications from resuscitation lasting <10 minutes.66-68 No significant bleeding has been reported even when resuscitation was continued for 2 hours or when patients with rib fractures were given thrombolytic therapy.70 Nontraumatic cardiopulmonary resuscitation should therefore not be considered a contraindication against the use of thrombolytic therapy.

Diabetes

Diabetic patients have been less frequently treated with thrombolytic agents because of concerns about the increased risk of bleeding complications. The 1990 American College of Cardiology/American Heart Association guidelines for the
management of acute myocardial infarction classified diabetic hemorrhagic retinopathy as an absolute contraindication against the use of thrombolytic therapy. In the FTT analysis, however, the incidence of stroke and major bleeding complications after thrombolytic therapy was only slightly higher in diabetic patients (stroke, 1.9% versus 1.0%; major bleeding, 1.3% versus 1.0%). In the GISSI-2/International Study Group trial, the incidence of these complications was similar among diabetic and non-diabetic patients. Intraocular hemorrhage and, more specifically, retinal bleeding are extremely uncommon complications of thrombolytic therapy. In the GUSTO-I study, 300 of the 6011 diabetic patients were estimated to have proliferative retinopathy, but none had intraocular hemorrhages, and the calculated upper 95% confidence limit of the possible occurrence of intraocular hemorrhage was only 0.05%. It is unlikely that thrombolytic therapy would increase vitreous hemorrhage, which is due to vitreous detachment, in patients with diabetic retinopathy. Also, the few non-diabetic patients reported have shown no limitation of visual acuity at follow-up. Thus, the concerns many clinicians have about bleeding complications after thrombolysis in diabetic patients are not supported by the results of large-scale clinical trials.

With regard to efficacy, the GUSTO-I angiography substudy showed that thrombolytic therapy is equally efficacious in restoring early coronary artery patency in patients with and without diabetes. In the FTT analysis, diabetics had a 21% reduction in 35-day mortality with thrombolytic therapy compared with control therapy, which corresponds to 37 lives saved per 1000 patients treated versus 15 lives in nondiabetic patients. Thus, diabetic patients with acute myocardial infarction are just as eligible for thrombolytic therapy as nondiabetics, but their early mortality rates remain high even after adjustment for both clinical and angiographic variables. A higher reocclusion rate and reduced compensatory hyperkinesis of the noninfarct zones have been proposed as explanations for this excess in early mortality.

Subgroups
Although thrombolysis has become the mainstay of acute treatment in the majority of patients with suspected acute myocardial infarction, uncertainties still remain with regard to the clinical benefit of this therapy in certain subgroups of patients.

ST-Segment Depression
Patients without ST-segment elevation are currently not given thrombolytic therapy. In the FTT analysis, mortality at 35 days in such patients was nonsignificantly higher after thrombolysis (15.2%) than after control treatment (13.8%). A possible explanation for this negative outcome is the procoagulant effect of fibrinolytic agents, which may cause progression of a non-obstructive mural thrombus to complete occlusion. Theoretically, thrombolytic therapy could worsen a coronary artery stenosis by causing intraplaque hemorrhage, and lysis of a subocclusive thrombus could also cause distal embolism and infarction.

Patients with ischemic chest pain and ST-segment depression are a heterogeneous group. Some patients with ST-segment depression in the anterior leads may actually be developing a true transmural posterior infarction. Others may develop non-Q-wave infarction or may have unstable angina without myocardial necrosis. In general, the deeper the ST-segment depression and the greater the number of leads involved, the greater the likelihood of myocardial necrosis and thus non-Q-wave infarction. In the LATE study, mortality rates in 528 patients with confirmed non-Q-wave infarction and ST-segment depression of ≥2 mm were significantly lower in those who received alteplase (8.6% versus 16.6% at 35 days [P<.006] and 20.1% versus 31.9% at 1 year [P<.006]). This post hoc analysis of patients treated late suggests that thrombolytic therapy may be beneficial in selected patients with typical symptoms and deep ST-segment depression (≥2 mm), because these patients are most likely developing a true posterior wall infarction or non-Q-wave infarction. The overall outcomes in patients with ST-segment depression observed in the FIT study may represent a net benefit in patients with posterior wall infarction or non-Q-wave infarction and harm in those patients with unstable angina. New prospective trials in patients with ischemic chest pain and deep ST-segment depression are needed.

Cardiogenic Shock
Thrombolytic therapy may be less effective in patients with cardiogenic shock. In the GISSI-1 trial, hospital mortality rates in Killip class IV patients were high, with no difference between control patients and those treated with streptokinase (69.9% versus 70.1%, respectively). Also, in the FTT overview, patients with both a systolic blood pressure of <100 mm Hg and a heart rate of >100 bpm had high mortality rates at 35 days, with a statistically nonsignificant difference in favor of thrombolysis (53.8% versus 61.1%). In view of these observations, cardiogenic shock is considered an indication for primary angioplasty, although there are also no randomized data showing benefit. If primary angioplasty is unavailable, thrombolytic therapy, preferably using a non-fibrin-specific agent such as streptokinase, should be given. Lower mortality rates were observed in Killip class IV patients given streptokinase than in those given alteplase in both the GISSI-2/International Study Group trial (64.9% with streptokinase versus 78.1% with alteplase; P<.05) and the GUSTO-I trial (55.6% with streptokinase versus 62% with alteplase; P=.06). A possible explanation for these observations is that a sufficiently high coronary perfusion pressure is needed for local fibrin-specific clot lysis, whereas the induction of a general lytic state with subsequent local clot lysis can occur at low arterial blood pressures with a non-fibrin-specific agent. Although hypotension may occur during administration of streptokinase, this is unrelated to the initial blood pressure and is usually rapidly reversible with administration of fluids and cessation of the streptokinase infusion. It is important that a full dose of a thrombolytic agent is given when the patient is hemodynamically stable, either by recommencement of streptokinase at a lower infusion rate or by administration of alteplase or reteplase; otherwise, angioplasty should be considered.
Prior Coronary Artery Bypass Graft Surgery

In GUSTO-I, prior bypass surgery was an independent predictor of a higher 30-day mortality rate.47

The poor outcome in these patients may be explained by a higher prevalence of multivessel disease and impaired left ventricular function.51,52 Most patients had a low to moderate ejection fraction and a high prevalence of diabetes and hypertension.51,52 A lower 90-minute coronary artery patency rate after thrombolysis,53,54 most likely because of the presence of large thrombi when a vein graft is the infarct-related vessel. This probably also explains the greater benefit observed in these patients when they are given a more potent lytic agent such as alteplase.55,56 Indeed, although the difference was not significant, this group had one of the largest treatment differences in GUSTO-I: the 30-day mortality rate was 11% in patients who received streptokinase and 8.3% in those randomized to receive alteplase.

Prehospital Treatment

Eight trials have randomized patients to receive prehospital or in-hospital thrombolytic therapy. When combined, these trials show a significant 17% reduction in early mortality with prehospital treatment (21 lives saved per 1000 patients treated; P=.02) (Fig 3).38,39,40 Complication rates are similar in both community-initiated and hospital-initiated thrombolysis, although ventricular fibrillation may occur more frequently in the community with prehospital administration, necessitating well-trained staff and the availability of defibrillators. These benefits arise from earlier treatment, and similar benefits would be expected if patients were able to be evaluated expeditiously and treated quickly in hospital. Prehospital administration of thrombolytic therapy has been shown to be of the greatest value in sparsely populated communities with transport delays to hospital of >1 hour. However, several studies31,32 have shown that ~20 patients with chest pain require evaluation for every patient found to be eligible for thrombolytic therapy. Each community needs to define the best approach for expedient delivery of reperfusion therapy on the basis of local transportation times, resources, and available expertise.

Late Treatment

A 12-hour time window for administration of thrombolytic therapy is now widely accepted.37 The FTT overview showed that thrombolytic therapy reduced mortality by 14% (SD, 5%) in patients randomized between 7 and 12 hours after symptom onset (P=.005),38 and there was a nonsignificant 5% reduction in mortality among the 9000 patients who presented after 12 hours. Because patients from the LATE and ASSET studies were not subdivided by ECG criteria in this analysis, the benefit in patients presenting between 13 and 18 hours with ST-segment elevation or bundle-branch block could be of the order of 10 lives saved per 1000 patients treated.

Patients who present late may have stuttering infarcts, or the infarct-related artery may have been patent at some stage after the initial occlusion, enabling salvage of myocardium beyond 6 hours. The major benefit of late treatment, however, is probably not due to myocardial salvage but rather to other mechanisms (Table 5).35

Choice of Agent

Three megatrials randomizing a total of 103 069 patients have compared the effects on mortality of various thrombolytic agents. In the GISSI-2/International Study,33,34 20 891 patients were randomized to receive either streptokinase or alteplase infused over a period of 3 hours in a factorial design, followed by randomization at 12 hours to either no heparin or subcutaneous heparin (12 500 IU) given twice daily. Mortalities at 30 days were similar (8.9% with streptokinase versus 8.5% with alteplase).

The ISIS-3 trial randomized 41 299 patients to receive either streptokinase, anistreplase, or duteplase (a form of tissue plasminogen activator not commercially available) infused over a period of 4 hours. As in GISSI-2, there was a factorial design

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Time Difference (min)</th>
<th>Mortality</th>
<th>Odds Ratio and CI</th>
</tr>
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<tbody>
<tr>
<td>CASTLE II (ref 41)</td>
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<td>Anistreplase (30u, IV bolus)</td>
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<td>60.0%</td>
<td>4.0%</td>
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<tr>
<td>Morrisey (ref 42)</td>
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<td>Alteplase (150mg over 6 hours)</td>
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<td>7.4%</td>
<td>10.0%</td>
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<td>6.8%</td>
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<tr>
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<tr>
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<td>Streptokinase (1.5 million u over 30 minutes)</td>
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<td>10.9%</td>
</tr>
<tr>
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<td>5549</td>
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<td>11.1%</td>
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<tr>
<td>MITI (ref 48)</td>
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<td>8.1%</td>
</tr>
<tr>
<td>Crude Sub Total</td>
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<td></td>
<td>9.1%</td>
<td>10.9%</td>
</tr>
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</tr>
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Test for homogeneity: Chi square = 4.69

Figure 3. Results of trials comparing prehospital with in-hospital administration of thrombolytic therapy. Relative risk of early death (in hospital or within 30 days, except for the Barbash trial,40 which used a 60-day end point) and 95% CIs are shown. Red indicates reduction.

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TABLE 5. Potential Benefits of Late Reperfusion

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Odds Ratio and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in infarct size</td>
<td></td>
</tr>
<tr>
<td>Improved scar formation and healing</td>
<td></td>
</tr>
<tr>
<td>Decreased infarct zone remodeling</td>
<td></td>
</tr>
<tr>
<td>Decreased left ventricular volumes</td>
<td></td>
</tr>
<tr>
<td>Reduced mural thrombus formation</td>
<td></td>
</tr>
<tr>
<td>Lower incidence of arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Provision of collateral blood flow to another infarct zone</td>
<td></td>
</tr>
</tbody>
</table>
with subcutaneous heparin or control therapy beginning 4 hours after initiation of thrombolytic therapy. Mortality was similar with all three thrombolytic regimens: 10.5% with streptokinase, 10.3% with duteplase, and 10.6% with anistreplase. The GUSTO-I trial randomized 41,021 patients to receive one of four thrombolytic regimens. The lowest mortality rate at 30 days (6.3%) was achieved with accelerated alteplase infused over a period of 90 minutes with immediate administration of intravenous heparin, compared with 7.2% for streptokinase plus subcutaneous heparin (as administered in ISIS-4), although 36% of patients in GUSTO-I also received intravenous heparin), 7.4% for streptokinase plus immediate intravenous heparin, and 7.9% for combination therapy with streptokinase plus alteplase plus intravenous heparin. At 30 days, the reduction in mortality was 14% in the accelerated alteplase group compared with the combined streptokinase groups, equating to an extra 10 lives saved per 1000 patients treated. For the combined end point of death plus nonfatal disabling stroke, there were 11 fewer events per 1000 patients treated. The benefit was consistent across most subgroups, including patients with anterior or inferior infarcts and those presenting earlier or later. The greatest benefit was seen in patients with higher-risk baseline characteristics.

Why did ISIS-3 and GISSI-2 fail to demonstrate any mortality differences between streptokinase and tissue plasminogen activator, as the GUSTO-I trial did? First, the failure to use intravenous heparin in the former trials may have disadvantaged duteplase in GISSI-2 and alteplase in ISIS-3. Second, a 3-hour infusion of alteplase has been shown to produce less 90-minute patency than an accelerated alteplase regimen, which delivers substantially more of the drug to an average-weight patient in the first 60 minutes, as in GUSTO-I, and the absolute improvement in TIMI grade 3 flow with an accelerated alteplase regimen is of the order of 13%.

Cost-effectiveness
Several studies have used retrospective data and varying assumptions to show that thrombolytic therapy is very cost-effective compared with other accepted medical therapies. An international issue is the appropriate allocation of scarce healthcare resources, and many hospitals worldwide use streptokinase because it is 7 to 8 times cheaper than alteplase. The GUSTO-I study prospectively gathered details of hospital and medical charges in a subgroup of US patients. Compared with streptokinase therapy, the additional cost of accelerated alteplase per extra life-year saved was US $27,382 (in 1992 dollars). The cost-effectiveness of preferentially using alteplase varied according to the age of the patients and the site of infarction (Table 2).

Long-term Follow-up
Early and sustained coronary artery patency after thrombolysis has many beneficial effects. Some of these are very much time-dependent (eg, salvage of ischemic myocardium with preservation of left ventricular function), whereas other are less affected by the time of recanalization (eg, attenuation of infarct expansion, left ventricular remodeling, enhanced electrical stability, and provision of collateral flow). One would expect that these favorable effects would result in survival benefits not only during the hospital stay but also afterward. Surprisingly, no extra survival benefit after hospital discharge has been observed in patients given intravenous thrombolytic therapy. A meta-analysis performed by the FTT Collaborative Group of more than 40,000 patients participating in placebo-controlled trials of intravenous thrombolysis indicated that the risk of death after 1 month was equal in survivors of acute myocardial infarction whether or not intravenous thrombolytic therapy was given on admission and irrespective of the time this treatment was started.

There are many explanations for the absence of any extra long-term benefit. Only a minority of patients are treated within a time window that allows substantial salvage of ischemic myocardial tissue. The incidence of optimal reperfusion with the present fibrinolytic agents is only ~50%, and even in patients who receive treatment early and have TIMI grade 3 flow, adequate tissue reperfusion is often not achieved ("no reflow" or "impaired reflow"). Furthermore, reocclusion and reinfarction are frequently observed after hospital discharge, and late mortality rates are high in patients with very poor residual left ventricular function who survive the hospital phase because of successful thrombolysis. Thrombolytic therapy may have other important benefits besides mortality reduction, such as preservation of left ventricular function, which can improve exercise tolerance and quality of life. There have been surprisingly few studies evaluating these potential benefits.

New Agents
New fibrinolytic agents are being developed to improve the efficacy of clot lysis and/or ease of administration. Novel plasminogen activators have been designed or purified from natural sources with one or more of the following properties: a prolonged half-life (allowing bolus administration), enhanced fibrin specificity, or resistance to natural inhibitors such as plasminogen activator inhibitor-1. The following novel plasminogen activators are in different stages of clinical development or marketing or will enter clinical testing very soon: mutants of native tissue plasminogen activator (reteplase, lanoteplase, TNK-tPA); Desmodus salivary plasminogen activator-α, derived from the saliva of the vampire bat, Desmodus rotundus; saruplase (recombinant single-chain urokinase plasminogen activator); and staphylokinase, produced by Staphylococcus aureus. Combinations of different fibrinolytic agents (chimeric plasminogen activators consisting of various portions of tissue plasminogen activator and urokinase) have also been investigated, without any clear evidence that their benefit-to-risk ratio will outperform the single-agent regimens. Murine monoclonal anti-human fibrin antibodies conjugated with fibrinolytic agents have not been tested in patients, although there is evidence of increased thrombolytic potency in animals. Table 6 compares the properties of five new fibrinolytic agents that have been or will be approved for clinical use over the next few years with those of alteplase and streptokinase. Each of these new agents will be briefly discussed.
TABLE 6. New Versus Established Fibrinolytic Agents in Acute Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase</th>
<th>Alteplase</th>
<th>Staphylokinase</th>
<th>TNK-tPA</th>
<th>Reteplase</th>
<th>Lanoteplase</th>
<th>Saruplase</th>
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</thead>
<tbody>
<tr>
<td><strong>Molecular weight, D</strong></td>
<td>47 000</td>
<td>70 000</td>
<td>16 500</td>
<td>70 000</td>
<td>39 000</td>
<td>53 500</td>
<td>46 500</td>
</tr>
<tr>
<td><strong>Plasma half-life, min</strong></td>
<td>23–29</td>
<td>4–8</td>
<td>6</td>
<td>20</td>
<td>15</td>
<td>23</td>
<td>±</td>
</tr>
<tr>
<td><strong>Fibrin specificity</strong></td>
<td>Indirect</td>
<td>Direct</td>
<td>Indirect</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Plasminogen activation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Direct</td>
<td>Direct</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>1.5 MIU/60 min</td>
<td>100 mg/90 min</td>
<td>20–30 mg/30 min</td>
<td>0.5 mg/kg bolus</td>
<td>2×10 IU boluses</td>
<td>30 min apart</td>
<td>120 IU/kg bolus</td>
</tr>
<tr>
<td><strong>Antigenicity</strong></td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td><strong>Patency at 90 minutes</strong></td>
<td>+</td>
<td>++</td>
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<td>++</td>
<td>+++ (+?)</td>
<td>+++ (+?)</td>
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<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>+</td>
<td>++</td>
<td>?</td>
<td>+ or ++</td>
<td>+</td>
<td>?</td>
<td>+ (+)</td>
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<tr>
<td><strong>Mortality reduction</strong></td>
<td>+</td>
<td>++</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+ (+)</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>+</td>
<td>+++ (+?)</td>
<td>++ (?))</td>
<td>+++ (?))</td>
<td>+ (+)</td>
<td>++ (?))</td>
<td>++ (?))</td>
</tr>
<tr>
<td><strong>Concomitant heparin†</strong></td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

MIU indicates million units.

*Most frequently used/tested.
†With the exception of streptokinase, and to some extent alteplase, the need for concomitant heparin has not been formally tested.

Retepase

Retepase (Boehringer Mannheim) is a deletion mutant of alteplase (Fig 4) and represents the first of the third-generation fibrinolytics to become commercially available. The kringle-2 and protease domains of native tissue plasminogen activator have been maintained, but the kringle-1, finger, and epidermal growth factor domains have been deleted, as have the carbohydrate side chains. Elimination of the kringle-1 and epidermal growth factor domains reduces hepatic receptor binding, which, along with the lack of carbohydrate groups, prolongs plasma clearance. Retepase has a half-life approximately twice that of alteplase (Table 6) but less fibrin specificity because of the deletion of the finger domain. In two angiographic trials, reteplase (given as two 10-IU boluses 30 minutes apart) yielded more TIMI grade 3 flow at 90 minutes than a 3-hour (62.7% versus 49.0%; P<.05)113 or 90-minute (59.9% versus 45.2%; P=.01) infusion of alteplase.114 However, the same dose of reteplase showed only a small (and not statistically significant) benefit over streptokinase in the INJECT trial115 and no benefit over alteplase in the GUSTO-III trial.16 In the latter trial, the absolute difference in 30-day mortality between reteplase and alteplase was 0.23% in favor of alteplase, with a 95% CI of −1.11% to 0.66%. These results do not support the equivalence of reteplase and accelerated alteplase if a 1% absolute difference in mortality is considered an appropriate boundary of equivalence. On the other hand, for the secondary end point of death or disabling stroke, the 95% CIs were <1%, suggesting that the two treatments were interchangeable. Stroke occurred in 1.64% of patients treated with reteplase and 1.79% of those treated with alteplase (P=.5). These results clearly indicate the importance of defining boundaries for equivalence in any future clinical evaluation of new plasminogen activators.

Why did the enhanced patency rates with reteplase at 60 and 90 minutes not translate into lower mortality? This might have...
been due to chance, because the observed patency difference at 90 minutes would have been expected to produce a mortality difference of <15%.

Alternatively, it may be that patency rates with each agent fluctuate at different time points. In a small group (96 patients) in the RAPID-2 angiographic study, alteplase produced higher patency rates at 30 minutes than reteplase (39.0% versus 27.3%; P=NS), and this very early advantage might have offset the later patency advantage of reteplase. Another possible explanation is that reocclusion rates might have been higher with reteplase.

**TNK-tPA**

TNK-tPA is a genetically engineered triple-combination mutant of native tissue plasminogen activator with amino acid substitutions at the following sites: a threonine (T) is replaced by an asparagine, which adds a glycosylation site to position 103; an asparagine (N) is replaced by a glutamine, thereby removing a glycosylation site from site 117; and four amino acids, lysine (K), histidine (H), and arginine (R), are replaced by four alanines (A) at sites 296–299. (Fig 4). These substitutions result in reduced plasma clearance, increased fibrin specificity, and resistance to plasminogen activator inhibitor-1.

In the TIMI-10B study, a large, phase II efficacy trial in 886 patients, a single 40-mg bolus of TNK-tPA produced TIMI grade 3 flow rates at 90 minutes that were identical to those seen with accelerated alteplase (63% in both groups). Furthermore, TIMI frame counting in TIMI-10B suggested faster and more complete reperfusion with 40 mg of TNK-tPA than with accelerated alteplase. The best angiographic results were obtained with a dose/weight ratio of ±0.5 mg/kg. In the ASSENT-1 trial in 3325 patients, an intracranial hemorrhage rate of 0.76% was observed with the 40-mg dose of TNK-tPA. This incidence was considered acceptable, because 14.6% of the patients in ASSENT-1 were >75 years old. On the basis of the results of TIMI-10B and ASSENT-1, 16 500 patients with acute myocardial infarction are being randomized in a double-blind manner to receive weight-adjusted TNK-tPA or alteplase in the ASSENT-2 phase III mortality trial. The results are expected in early 1999.

**Lanoteplase**

Like reteplase, lanoteplase, or n-PA, is a deletion mutant of alteplase in which one amino acid is substituted in position 117 (Fig 4). In the InTIME-1 trial, a single 120-IU/kg bolus of lanoteplase produced TIMI grade 3 flow in 57.1% of patients compared with 46.4% in patients treated with alteplase. There were also fewer adverse events with lanoteplase.

At 30 days, the combined incidence of death, infarction, heart failure, and major bleeding (including one intracranial hemorrhage in a patient treated with alteplase) was 11% with lanoteplase and 24% with alteplase. Lanoteplase will be compared with alteplase in a large mortality trial (InTIME-2), and the results should be available in early 1999.

**Saruplase**

Saruplase, or prourokinase, is a naturally occurring glycoprotein that is rapidly converted into urokinase by plasmin but appears to have some intrinsic plasminogen activating potential. In a comparative trial with streptokinase, recombinant saruplase was associated with earlier reperfusion, higher patency rates, and slightly less fibrinogen breakdown.

In the SESAM study, similar TIMI grade 2 and 3 flows were observed with saruplase and a 3-hour infusion of alteplase.

In the COMPASS equivalence trial (n=3089 patients), 30-day mortality rates were lower with saruplase (80 mg/h) than with streptokinase (5.7% versus 6.7%), but there was also an increased rate of intracranial hemorrhage (0.7% versus 0.3%). Single-bolus administration (80 mg) of saruplase is being explored as well. This agent is expected to be approved for use in Europe this year.

**Staphylokinase**

Staphylokinase, a 136-amino-acid protein produced by certain strains of *Staphylococcus aureus*, has a unique mechanism of fibrin selectivity. In two angiographic studies, recombinant staphylokinase (in doses between 20 and 30 mg) was at least as potent as alteplase and significantly more fibrin-specific.

As a bacterial protein, staphylokinase induces antibody formation and resistance to repeated administration. However, preliminary studies suggest that the immunogenicity of staphylokinase can be reduced by site-directed mutagenesis. Large comparative trials are needed to determine the safety and full clinical potential of this agent.

**The Future**

A number of new therapeutic strategies may achieve greater early and, consequently, greater long-term benefits in patients with an acute myocardial infarction. Greater reductions of infarct size are possible by earlier administration of more effective thrombolytic regimens, eg, prehospital bolus administration of new fibrinolytic agents with equal or higher potency for clot lysis, such as TNK-tPA, lanoteplase, or staphylokinase, and better conjunctive antithrombotic therapies (eg, direct antithrombins or glycoprotein IIb/IIIa receptor antagonists). Reocclusion and reinfarction in the days or weeks after the acute event may be better prevented by new antiplatelet agents (eg, oral glycoprotein IIb/IIIa receptor antagonists), prolonged subcutaneous antithrombin therapy (eg, low-molecular-weight heparin or direct antithrombins), better selection of patients for additional revascularization, lipid-modifying agents (eg, statins), and plaque-stabilizing agents. Reperfusion damage may also be diminished by earlier treatment and by therapies that improve the microcirculation (eg, inhibition of neutrophil chemotaxis or adhesion or enhancement of endogenous adenosine activity). Greater attenuation of left ventricular remodeling (eg, using ACE inhibitors) and better antiarrhythmic treatment may also increase the long-term clinical benefit of successful thrombolysis.

The risk of bleeding complications, particularly hemorrhagic stroke, must also be decreased. There is a need for more careful selection of patients for thrombolysis, and it may be just as effective and safer to administer a reduced dose of a fibrinolytic agent in conjunction with a more potent antithrombotic agent (eg, abciximab or other glycoprotein IIb/IIIa receptor antagonists).

Each of the strategies mentioned above needs to be tested in large clinical trials. Because it is unethical to conduct these trials with a placebo control, it is likely that in the future,
investigators will increasingly seek to demonstrate equivalence of treatments. Second.

Equivalence of new thrombolytic regimens should be established first in terms of mortality, the primary efficacy outcome.

Secondary aspects of innovative treatments, such as side effects, ease of use, and cost, also need to be evaluated. It is generally accepted that in the field of thrombolysis, a 1% absolute difference in mortality, if still demonstrable at long-term follow-up, is clinically important. As shown in the GUSTO-I trial, this 1% difference (or a relative 14% difference) may prevent 1 of every 7 deaths. For a disease with a high prevalence and mortality rate, this reduction is relevant at the population level. If a 1% absolute difference is chosen as the limit of a range of equivalence, it is important that the population of randomized patients includes those at high risk, for example, elderly patients, as in the GUSTO-I trial. Otherwise, if a low-risk population with, say, a baseline mortality of 5% is studied or if patients less likely to benefit, such as those treated late, are included, the chance of showing "equivalence" is much higher. An alternative approach would be to use an odds reduction as the prespecified limit of the range of equivalence, because the mortality rates in the standard treatment arm may vary depending on the selection criteria. Either a 1% absolute difference or a 14% relative difference (whichever is the smallest), as shown between streptokinase and alteplase in the GUSTO-I trial, could be regarded as appropriate boundaries for equivalence. This flexible definition of equivalence has the advantage of keeping the boundaries for equivalence narrow, as illustrated in the following example. If 30-day mortality in the standard treatment group is 5%, the upper boundary for equivalence should be 5.7% (5% plus 14% of 5%) and not 6% (1% absolute difference). On the other hand, if 30-day mortality in the control group is 10%, the upper boundary for equivalence should be 11% (1% absolute difference) and not 11.4% (10% plus 14% of 10%). This dual definition is being used in the ongoing ASSENT-2 trial comparing the new thrombolytic, TNK-TPA, with an accelerated infusion of alteplase, whereas an odds reduction definition for equivalence has been used in the COMPASS trial comparing streptokinase with saruplase.

It should be stressed that, although the statistics involved are rather complex, it remains the responsibility of clinical investigators to define the equivalence (interchangeability) of two alternative treatments. It is possible that in the future, other definitions of equivalence of reperfusion strategies will emerge if, for example, newer and more reliable surrogate endpoints for efficacy, such as infarct size, become better validated.

In conclusion, many improvements in pharmacological reperfusion seem possible. Not only can higher initial patency rates be achieved and maintained, but the net clinical benefit resulting from successful reperfusion can probably also be increased. The "ideal" thrombolytic agent has not yet been developed (Table 7). Further refinements of molecules, with carefully performed dose-ranging studies to choose the best dose for achievement of TIMI grade 3 flow (or corrected TIMI frame counts) with an acceptable safety profile, are needed to improve on the results of large clinical trials to assess clinical end points and safety. Adjunctive therapies with glycoprotein IIb/IIIa receptor antagonists, direct thrombin inhibitors, and low-molecular-weight heparins also need to be tested. Data on cost-effectiveness compared with current therapies will also be required.

### References


### TABLE 7. Characteristics of an "Ideal" Thrombolytic Agent

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Rapid reperfusion (15–30 min)</td>
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<td>Close to 100% efficacy for reperfusion</td>
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<td>Can be given as a rapid intravenous bolus</td>
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<td>Low rate of intracranial hemorrhage</td>
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<tr>
<td>Low rate of systemic bleeding</td>
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<tr>
<td>Specific for recent thrombi</td>
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<tr>
<td>Low rate of early reocclusion</td>
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<tr>
<td>Sustained patency long-term</td>
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<tr>
<td>No effect on blood pressure</td>
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<tr>
<td>No antigenicity</td>
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<tr>
<td>No negative interactions with adjunctive treatment</td>
<td></td>
</tr>
<tr>
<td>No other significant side effects</td>
<td></td>
</tr>
<tr>
<td>Acceptable cost</td>
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</table>

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18. Van de Werf F, Arnold AER, for the European Cooperative Study Group for Recombinant Tissue Type Plasminogen Activator. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. BMJ. 1988;297:1347-1349.


84. White HD, Van der Werf April 28, 1998

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