Intravenous Thrombolysis in Acute Myocardial Infarction

E. Magnus Ohman, MD, FCCP; Robert A. Harrington, MD; Christopher P. Cannon, MD; Giancarlo Agnelli, MD; John A. Cairns, MD; and J.Ward Kennedy, MD

Abbreviations: APTT = activated partial thromboplastin time; ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent; CI = confidence interval; FTT = Fibrinolytic Therapy Trialists' Collaborative Group; GISSI = Gruppo Italiano per lo Studio Streptokinasi nell'Infarto Miocardico; GP = glycoprotein; GUSTO = Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries; HIT = Hirudin for the Improvement of Thrombolysis; INJECT = International Joint Efficacy Comparison of Thrombolytics; ISIS = International Study of Infarct Survival; MI = myocardial infarction; n-PA = lanoteplase; NS = not significant; RAPID = Retepase Angiographic Phase II International Dose-finding; r-PA = reteplase; rt-PA = recombinant tissue-type plasminogen activator; scu-PA = single-chain urokinase-type plasminogen activator; TIMI = Thrombosis in Myocardial Infarction; TNK-tPA = tenecteplase; t-PA = tissue plasminogen activator

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Fibrinolytic therapy for acute myocardial infarction (MI) has been one of the most potent treatments ever developed for a condition that kills more patients worldwide than any other. This review will focus on approved agents and the randomized trials that have led to their widespread use. The use of adjunctive antithrombotic therapies, such as aspirin and heparin, also will be discussed, but a more complete discussion of these therapies is located in other sections of this supplement. A brief overview of new adjunctive therapies, such as platelet glycoprotein (GP) IIb/IIIa inhibitors and direct thrombin inhibitors, will be provided. This section also will explore how therapeutic success can be evaluated, cost-effectiveness analysis, and complications with this therapy. Finally, we will provide a set of recommendations for the use of fibrinolytic therapy in acute MI based on the published literature.

Brief History of Reperfusion Therapy for Acute MI

The first description of the use of a prolonged infusion of streptokinase for patients with acute MI appeared in 1958.1 Several smaller studies followed, but they generally showed no clear therapeutic advantage over standard therapy. When these early trials were combined in a meta-analysis2 in the mid-1980s, a significant reduction in mortality was revealed. This observation, coupled with early angiographic observations of reperfusion among patients receiving intracoronary streptokinase,3 ushered in the modern era of reperfusion therapy for acute MI. It was soon recognized that intracoronary fibrinolytic therapy could salvage myocardium and that earlier restoration of patency of the infarct-related artery resulted in better preservation of left ventricular function.1-6

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This discovery led to the transition from intracoronary therapy (with its inherent delay in establishing coronary reperfusion) back to IV therapy.

The use of large clinical trials, which focused on mortality and safety profiles through adequate sample sizes, led to worldwide adoption of IV thrombolysis for acute MI.7-10 Observations from these trials made it possible to define the therapeutic windows and risk/benefit ratios for an array of patient subgroups. The importance of therapy that could be administered rapidly and easily to allow earlier treatment also became evident.11 Continued evaluation of mechanistic components of therapy served as an underpinning for the large mortality trials and led to development of adjunctive therapies to enhance reperfusion rates and safety profiles.12 Although adjunctive therapies such as aspirin and IV heparin have been found to be important to reduce mortality and to maximize therapeutic efficacy, other approaches to these ends, including direct thrombin inhibition and complete platelet pacification by GP IIb/IIIa inhibitors, remain to be realized. The future of reperfusion therapies, for example, should include strategies compatible with primary angioplasty, which has shown improved mortality over IV thrombolysis in a meta-analysis of 10 small trials13 but is limited by a lack of widespread availability and expertise.

Pharmacology of Fibrinolytic Agents

The term thrombolytic agents really is a misnomer when applied to plasminogen activators. All of these agents convert plasminogen to plasmin that then degrades fibrin, a major structure component of the thrombus; thus, the more correct term is fibrinolytic therapy. The agents can be grouped into direct and indirect plasminogen activators (Table 1). The relatively nonspecific agents include streptokinase, anistreplase (anisoylated plasminogen streptokinase activator complex), and urokinase. The newer (or second-generation) plasminogen activators include recombinant tissue-type plasminogen activator (rt-PA) (alteplase or duteplase) and several variants of tissue-type plasminogen activator: reteplase (r-PA), tenecteplase (TNK-tPA), and lanoteplase (n-PA).

Streptokinase

Streptokinase is an indirect fibrinolytic agent that binds to plasminogen, thereby converting plasminogen into a plasmin-like molecule capable of converting plasminogen to plasmin because streptokinase activates both circulating and fibrin-bound plasminogen to plasmin; it produces systemic plasminemia with resultant depletion of fibrinogen, plasminogen, and factors V and VIII. This “systemic lytic state” creates a sustained hypocoagulable state that may reduce the risk of rethrombosis. Patients who receive streptokinase can develop antistreptococcal antibodies. The rate has varied in the literature, but it has been well documented that patients treated with streptokinase have allergic reactions. In the milder form, these include chills, fever, and rigo. In more severe forms, anaphylaxis has been described. Generation of bradykinin also may contribute to the hypotension that occurs in patients receiving streptokinase. This hypotensive reaction usually responds.
well to vasopressors and IV fluids. Because of these reactions and serologic confirmation of antibodies, there has been some controversy about the repeat administration of streptokinase. It has been suggested that patients should not receive a second dose of streptokinase within 1 year of initial therapy. However, many patients have received a second dose of streptokinase without suffering severe allergic or anaphylactic reactions.

**Anistreplase**

Anistreplase is a modified streptokinase molecule, bound to lys-plasminogen to form an activator complex. Because lys-plasminogen has affinity for fibrin, it was hoped that the complex would be more fibrin specific than streptokinase. The modified streptokinase undergoes activation after deacylation, providing a much longer half-life (approximately 100 min) and allowing single-bolus dosing. The antigenicity and side effects profile of anistreplase are similar to those seen with streptokinase.

**Urokinase**

This naturally occurring plasminogen activator has been used to treat acute MI for > 30 years. Urokinase is significantly less antigenic than streptokinase, and, unlike streptokinase, urokinase directly activates plasminogen. Despite its years of use, however, it has not been developed as a standard treatment for acute MI. Although urokinase was used extensively for treating peripheral vascular occlusions, production problems have curtailed its availability.

**Saruplase (Prourokinase)**

This agent, also known as single-chain urokinase-type plasminogen activator (scu-PA), is a single-chain precursor to urokinase that has little intrinsic enzymatic activity. scu-PA has relative fibrin specificity similar to tissue plasminogen activator (t-PA). The amino-acid sequence of scu-PA resembles that of t-PA, and thus this agent has a very short half-life. Scu-PA circulates bound to a specific inhibitor; under this condition, the catalytic activity of scu-PA is inactivated. In the presence of fibrin, the complex between scu-PA and its specific inhibitor is dissociated and thus scu-PA is able to express its fibrinolytic activity.

**rt-PAAs**

rt-PAAs are naturally occurring, serine proteases that are physiologically identical to the naturally occurring endogenous plasminogen activator in humans. In its natural state, t-PA is produced by vascular endothelium. Plasminogen activator inhibitors counteract its effect in humans. The rt-PA molecule was cloned by Pennica and colleagues14 and is produced by recombinant DNA technology. Two forms have been manufactured commercially. Alteplase is predominantly a single-chain rt-PA molecule. In the mid-1980s, manufacturing began for a predominantly two-chain rt-PA molecule, duteplase. Although these drugs never were compared directly in trials, the latter compound was dropped after large trials failed to show its superiority over streptokinase.

As opposed to streptokinase, alteplase is not antigenic and appears not to be associated with allergic reactions. The fibrin specificity of alteplase is considerably greater than that of streptokinase. Nevertheless, alteplase produces mild fibrinogen depletion. Another theoretical advantage of alteplase over streptokinase is its ability to lyse more highly cross-linked fibrin. This theoretical advantage is more of a consideration among patients who have had symptoms for a longer duration.

**r-PA**

Truncated forms of rt-PA have been developed; the first was r-PA. This is a single-chain deletion mutant that lacks the finger, epidermal growth factor, and Kringle-1 domains (Fig 1). This mutation results in a half-life about twice that of native t-PA, permitting double-bolus therapy of 10 U, 30 min apart. The fibrinogen depletion with r-PA is greater than that with alteplase but less than that with streptokinase. Because the finger domain mediates the high-affinity interaction of rt-PA with fibrin, r-PA has lower affinity for fibrin than rt-PA. No antigenicity has been reported with this compound. Its mode of action otherwise is similar to that of naturally occurring t-PA.

**TNK-tPA**

TNK-tPA is similar to wild-type t-PA, but has amino acid substitutions at three sites (Fig 1). A threonine is replaced by asparagine, which adds a glycosylation site to position 103; an asparagine is replaced by a glutamine, thereby removing a glycosylation site at position 117; and four amino acids in the protease domain (lysine, histidine, arginine, and arginine) are replaced by four alanine residues. These mutations, in animal models, produce a prolonged half-life, increased fibrin specificity, and increased resistance to inhibition by plasminogen activator inhibitors-1 compared with naturally occurring t-PA. In humans, TNK-tPA has shown slower plasma clearance relative to values for alteplase; its plasma elimination half-life ranges from 11 to 20 min compared with 3.5 min reported for alteplase. TNK-tPA is more fibrin-specific than alteplase, which itself is more fibrin specific than streptokinase or r-PA. Systemic fibrinogen and plasminogen levels fell by only 5 to 15% over the first 6 h of TNK-tPA dosing of 30 to 50 mg, compared with 40 to 50% reductions after alteplase dosing. Similarly, the consumption of α2-antiplasmin, the fluid-phase inhibitor of plasmin, and the resultant increase in plasmin-α2-antiplasmin complexes were four to five times greater with alteplase versus TNK-tPA. The greater fibrin specificity of TNK-tPA compared with alteplase helps explain its efficacy when given as a 5-s to 10-s single bolus, and the fact that it does not induce the “plasminogen steal” phenomenon.

**n-PA**

n-PA is another deletion mutant of naturally occurring t-PA. It combines deletions of the finger and epidermal growth factor domains with substitution of the asparagine residue at position 117 with a glycine residue to remove the glycosylation site in the first Kringle domain. It has one of the longest half-lives of the mutant t-PA molecules.
### Table 1—Characteristics of Fibrinolytic Agents

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Cost/Dose</th>
<th>Molecular Source</th>
<th>Half-life, min</th>
<th>Mode of Action</th>
<th>Specific Metabolism</th>
<th>Other Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Group A streptococci</td>
<td>18-23</td>
<td>Activator</td>
<td>Yes</td>
<td>1-h infusion</td>
<td>$300</td>
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<tr>
<td>Urokinase</td>
<td>Recombinant, human</td>
<td>35-55</td>
<td>Direct</td>
<td>No</td>
<td>1-h infusion</td>
<td>$2,000</td>
</tr>
<tr>
<td>Anistreplase</td>
<td>Group A streptococci</td>
<td>11</td>
<td>Direct</td>
<td>No</td>
<td>Bolus, 90-min infusion</td>
<td>$2,200</td>
</tr>
<tr>
<td>t-PA</td>
<td>Recombinant, human</td>
<td>70-120</td>
<td>Direct</td>
<td>No</td>
<td>Bolus</td>
<td>$2,200</td>
</tr>
<tr>
<td>r-PA</td>
<td>Recombinant, human</td>
<td>39</td>
<td>Direct</td>
<td>No</td>
<td>Bolus</td>
<td>$2,200</td>
</tr>
<tr>
<td>TNK-tPA</td>
<td>Recombinant plus Point mutations</td>
<td>111</td>
<td>Direct</td>
<td>No</td>
<td>Single bolus</td>
<td>$2,200</td>
</tr>
<tr>
<td>n-PA</td>
<td>Recombinant plus Domain deletion</td>
<td>30-45</td>
<td>Direct</td>
<td>No</td>
<td>Single bolus</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Agents**

- Streptokinase
- Urokinase
- Anistreplase
- t-PA
- r-PA
- TNK-tPA
- n-PA

**Molecular Weight (kDa)**

- Streptokinase: 47
- Urokinase: 35-55
- Anistreplase: 131
- t-PA: 63-70
- r-PA: 39
- TNK-tPA: 111
- n-PA: 30-45

**Structure**

- F, E, K domains
- Lacks F, E, K1 domains
- Lacks F, E, K domains
- Lacks F, E, K domains
- Lacks F, E, K domains
- Lacks F, E, K domains
- Lacks F, E, K domains

**Specific Metabolism**

- Hepatic
- Renal
- Hepatic
- Hepatic
- Hepatic
- Hepatic
- Hepatic

**Dosing**

- 1-h infusion
- 1-h infusion
- 1-h infusion
- Direct
- Direct
- Direct
- Direct

**Other Properties**

- Antigenic
- Non-Antigenic
- Resistance to PAI-1
- Resistance to PAI-1
- Resistance to PAI-1
- Resistance to PAI-1
- Resistance to PAI-1

**Note**: The completeness and success of reperfusion therapy have been extensively studied, as measured by angiography and ST-segment resolution on the 12-lead ECG. In addition, the therapeutic risk/benefit ratio has been well established in large mortality trials. The field of thrombolysis developed traditionally; that is, the first studies evaluated a new agent vs a placebo or an established treatment, in trials that tested for superiority. After the first large, placebo-controlled trials showed an unequivocal benefit with fibrinolytic therapy, it became unethical to test newer therapies against placebo therapy. Further, agents that may have shown similar efficacy in superiority trials appeared to have other characteristics that could offer a clinical advantage (such as bolus therapy vs infusion). Thus, a different trial method was developed. This statistical approach, called equivalence testing, is based on the assumption that differences between outcomes with two treatments should be less than a certain predetermined value to be considered equivalent. Recent studies suggest that this threshold should be defined as a < 1% absolute difference in mortality or a relative difference of < 14% between the agents. This threshold is based on the half of the benefit on mortality observed with fibrinolytic therapy over placebo in placebo-controlled trials (a 2% absolute difference in mortality) and the full benefit observed with alteplase over streptokinase (1% absolute mortality difference). To establish equivalence, the 95% confidence intervals (CIs) are calculated based on the absolute difference in mortality rates. A new therapy that has an absolute rate and 95% CI within the 1% is deemed to be of equivalent efficacy to an established therapy. This concept will hold true only if a similar safety profile is observed.

To establish equivalence, a number of different statistical approaches have been taken in randomized clinical trials. There appears not to be any consensus on the exact boundaries to accept. However, it should be recognized that the rationale might differ among different clinical trials depending on what the goal is with the intended therapy. In the International Joint Efficacy Comparison of Thrombolitics (INJECT) trial, in which noninferiority with r-PA was tested against streptokinase, a 1% absolute difference (half of the benefit) in mortality was used as the lower boundary (see section on r-PA), the assumption being that streptokinase is associated with a 2% lower mortality against placebo. However, in a study comparing two different ways of administration of t-PA, a much tighter 95% boundary of 0.4% was used, the assumption being that with similar therapies, half of the benefit that was observed with a bolus plus infusion of t-PA over streptokinase (1%) should be maintained. In this particular case, the observed 95% CI extended to 0.49%, suggesting that the modes of administrations of t-PA were not equivalent (see section on alteplase). Another approach permitting a single bolus administration. Because it lacks the finger domain, it exhibits lower affinity for fibrin than t-PA.
has been to use an odds ratio of < 1.5 (less than a relative 50% increase in mortality) compared with streptokinase (see section on scu-PA).

Angiographic Evaluation

Since the mid-1980s, the angiographic assessment of epicardial coronary flow has been critical in the development of new reperfusion strategies, as seen in Tables 2–4.25–75 The angiographic substudy of the Global Utilization of Streptokinase and TPA (alteplase) provided the link between Thrombosis in Myocardial Infarction (TIMI) grade 3 flow (normal antegrade flow) and 30-day survival; Simes and colleagues76 showed that the superior survival with alteplase vs streptokinase resulted from the superior epicardial blood flow provided by alteplase. In the 1990s, Gibson and colleagues77 moved us beyond a fixation on epicardial coronary flow with the development of concepts such as the corrected TIMI frame count and the myocardial perfusion blush score, which take into consideration both epicardial and microvascular flow. As the field moves toward combining fibrinolytic therapy with antiplatelet therapy, the notion of improved myocardial perfusion through improvement in microcirculatory flow has become an important tenet of reperfusion investigation.

ECG Evaluation

Investigation over the last 25 years into the concepts of reperfusion and myocardial salvage have now come full circle. Work by Braunwald and colleagues77 in the mid-1970s concentrated on the importance of restoring myocardial perfusion with the goal of preserving left ventricular function. There was a shift in the 1980s, as investigation of acute MI came to focus on the restoration of epicardial coronary flow. Quantification of this flow during initial work by the TIMI investigators formed the basis of much investigation over the next 10 to 12 years. With the introduction of the platelet GP IIIb/IIIa inhibitors into clinical practice, we have witnessed a shift back to actual myocardial perfusion, and investigation now centers on not only restoration of epicardial coronary flow but also preservation of microcirculatory flow. As fibrinolytic therapy moved from clinical investigation (with its reliance on angiography to determine therapeutic success) into clinical practice, clinical measures of reperfusion were needed to gauge the success or failure of therapy. Unfortunately, simple measures of reperfusion, such as resolution of chest pain and of ECG findings, were noted to be unreliable in their predictive accuracy.78 Investigators reported that although complete resolution of chest pain with complete resolution of ST-segment elevation was highly predictive of a patent coronary artery, this combination of findings was extremely unusual and thus of relative little clinical utility among patients being treated with fibrinolytic therapy.

Braunwald and others78a championed the use of the 12-lead ECG as a way to quantify left ventricular dysfunction after MI. It was not until the mid-1990s, however, that Schroder and colleagues79 more completely characterized ST-segment resolution and its relationship to clinical outcomes. Data from five recent randomized trials of almost 6,000 patients, outlining the relationship between ST-segment resolution after fibrinolytic therapy and 30-day mortality, are shown in Table 5.79–82 Clearly, there is a linear relationship between the degree of ST-segment resolution and later mortality that is highly statistically significant and very relevant clinically, as this is an easily employed bedside technique. Observations from primary angioplasty experiences have confirmed the value of the static ECG as a tool to predict clinical outcomes after reperfusion. While rapid early resolution of ST-segment elevation is better than later resolution, the optimal timing of static ECG tracings is unknown. Furthermore, the ECG undoubtedly provides important information about tissue perfusion and not just epicardial coronary flow; however, how best to incorporate serial tracings into the acute evaluation of these patients requires further investigation.

Continuous ST-segment monitoring has evolved over the last 10 to 15 years as an alternative to static ECG measurement in the evaluation of reperfusion. The obvious advantage is that it provides insight into the continuum of reperfusion, providing information on cyclic flow, reperfusion, and reocclusion. The main limitation is that it requires special equipment. Until recent technical improvements, its use was limited by the fact that patients were required to be at bed rest. Continuous ST-segment monitoring can provide predictive information about patency of the epicardial infarct artery, but there are complexities because of the issues of tissue-level perfusion and collateral blood flow. The ST-segment evaluation appears to be best at providing data reflecting myocardial perfusion rather than epicardial coronary flow. Work from the Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries (GUSTO)-1 trial83 has shown that this technique can be used to predict clinical outcomes. Additionally, it is an important tool in the noninvasive evaluation of new drugs and reperfusion strategies. Use of this technology may allow a smaller sample size than angiographic trials typically require.

Mortality and Intracranial Hemorrhage End Points

The large amount of information available from fibrinolytic mortality trials has provided ample opportunity to
create outcome models based on patient characteristics. Lee and colleagues have used the GUSTO-1 trial to provide insight into the predictors of 30-day mortality among patients being treated with fibrinolytic therapy for acute MI (Table 6). Certain patient characteristics (age, Killip class, and infarct location) are associated with much higher 30-day mortality.

The major risk of fibrinolytic therapy is intracranial hemorrhage, which usually occurs in the first 24 h after starting therapy. Several patient characteristics are associated with a higher risk of intracranial bleeding (Table 7). The level of concomitant anticoagulation with IV heparin, as measured by activated partial thromboplastin time (APTT), also can influence the rate of intracranial hemorrhage. An APTT of between 50 s and 75 s, measured between 6 h and 24 h after starting fibrinolytic therapy and IV heparin therapy, appears to offer the best balance between optimal outcomes and the risk of intracranial hemorrhage.

1. **Fibrinolytic Therapy**

**Trials of Streptokinase**

The field of IV fibrinolytic therapy was transformed when it became possible to examine the efficacy of therapy with angiography during the acute phase of MI. The initial trials of urokinase and streptokinase were carried out with dosages established on a theoretical basis. In fact, IV streptokinase was not subjected to a true form of dose-ranging angiographic trial until well into the 1980s. Nevertheless, the placebo-controlled trials of streptokinase were very powerful in showing a significant mortality reduction with IV streptokinase for acute MI.

Several trials have reported patency of the infarct-related artery at different time points among patients not receiving fibrinolytic therapy (Table 2). Most patients did receive aspirin and heparin, although aspirin was not standard therapy for acute MI until the International Study of Infarct Survival (ISIS)-2 trial results were published in 1988.

Several angiographic trials also were undertaken to explore the patent and recanalization rates with IV streptokinase. The first trials explored rates of recanalization. In those studies, patients underwent urgent angiography. If the vessel was occluded (TIMI grade 0 or 1 flow), IV fibrinolytic therapy was given and the rate of opening was established. The delays inherent in this approach, however, suggested adverse effects on left ventricular function, as described. Thus patency trials were developed, wherein patients with acute MI were given fibrinolytic therapy as soon as possible and then underwent angiography, where patency (defined as TIMI grade 2 or 3 flow) was examined. The results for both patenty and recanalization trials of streptokinase are shown in Table 3. Overall, the angiographic data suggest patency rates with streptokinase of approximately 44% at 60 min and 48% at 90 min. Approximately 2 to 3 h after beginning therapy, patency rates were 72%, achieving a rate of between 75% and 85% at 24 h to 21 days after therapy from a pooled meta-analysis. These rates are substantially higher than those of control patients (Fig 2), but less than those with accelerated alteplase and similar to those with anistreplase or alteplase given > 3 h.

The efficacy of streptokinase with regard to mortality was evaluated in four large, placebo-controlled trials (Table 8). The first true mortality trial for streptokinase was the Gruppo Italiano per lo Studio Streptokinasi nell’Infarto Miocardico (GISSI-1) trial. This was an open-label, randomized trial of 11,806 patients. Of note, only 14% of patients received aspirin and only 62% received any heparin in this study; all adjunctive therapies were at the investigator’s discretion. Nevertheless, in-hospital mortality (14 to 21 days) was reduced by 18% compared with standard therapy (10.7% vs 13.0%; p = 0.002). The reduction in mortality was time dependent, decreasing from a 47% reduction in patients treated within 1 h, to 23% for those treated within 3 h, and to 17% for those treated within 6 h of symptom onset. The reduction in mortality was maintained > 12 months (17.2% with streptokinase vs 19.0% for control subjects; p = 0.008). The Intravenous Streptokinase in Acute Myocardial infarction study was a double-blind, randomized trial of streptokinase vs placebo in 1,741 patients with ST-segment-elevation MI. Consistent with the GISSI-1 findings, there was an 11% reduction in 21-day mortality, although this did not achieve statistical significance.

The second ISIS trial was a large, double-blind, placebo-controlled study of IV streptokinase in patients with suspected MI. There were no specific entry criteria other than the physician’s clinical suspicion of an acute MI. Most patients, however, had ST-segment elevation or left bundle-branch block on the presenting ECG. In all, 17,187 patients were randomized in 417 hospitals worldwide. Patients were enrolled up to 24 h after symptom onset, but most were randomized in the first 12 h. The study used a 2 × 2 factorial design testing aspirin alone (162.5 mg/d for 1 month), streptokinase alone (1.5 MU > 1 h), both, or neither. Patients randomized to streptokinase had a 25% reduction in 35-day vascular mortality compared with those who received placebo (9.2% vs 12.0%; p < 0.001). The study also showed that aspirin alone could reduce mortality by a relative 23% (p < 0.001). The most important part of this trial was the synergistic effects of aspirin with streptokinase, which produced a 42% reduction in vascular mortality (8.0% vs 13.2%; p < 0.001). Additional benefits with aspirin in this trial included reduced rates of reinfarction, cardiac arrest, cardiac rupture, and stroke. Similar to the GISSI-1 study, there was clear evidence of time dependency for treatment benefit. Patients treated within 6 h of symptoms had significantly improved survival, and this benefit persisted for treatment that began within up to 12 h after symptom onset.

A smaller, South American trial (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) also was a double-blind, placebo-controlled trial of streptokinase. This study was altered to include only patients who presented at least 6 h after but within 24 h of symptom onset, once the ISIS-2 results were reported. Mortality at
35 days did not differ significantly in the 3,568 patients enrolled between 6 h and 24 h (11.2% for streptokinase vs 11.8% for placebo).

Consistent across these trials was that the treatment benefit observed in the first 21 to 42 days was maintained up to 1 year. The Fibrinolytic Therapy Trialists’ Collaborative Group (FTT) combined these and other trials in a meta-analysis.24 The overall benefit was observed among patients with ST-segment elevation or bundle-branch block irrespective of age, sex, BP, heart rate, prior MI, or diabetic status. Furthermore, the treatment benefit was greater the earlier that treatment began. For patients treated within 6 h, the absolute reduction in mortality was 30 lives saved for 1,000 patients treated; for patients treated within the first 7 to 12 h after symptom onset, it was 20 lives saved per 1,000 treated. For patients treated between 13 h and 18 h after symptom onset, there was an uncertain trend toward mortality reduction of approximately 10 lives saved per 1,000 treated. Fibrinolytic therapy was associated with approximately four extra strokes per 1,000 patients treated; most of that occurred within 2 days. Approximately 50% were associated with an early death and so were already accounted for in the overall mortality reduction. Of the remaining patients with stroke, 25% were moderately or severely disabled and the other 25% were not. The overview thus suggested a treatment benefit for most patients who present with acute MI within 12 h of symptom duration.

Trials of Alteplase

After two small series of patients had been treated with alteplase,93,94 the first comparative trial was conducted between alteplase and streptokinase. In the TIMI-1 trial,95 290 patients with acute MI underwent diagnostic coronary angiography and then were treated with either streptokinase or alteplase, in addition to IV heparin. The primary end point, reperfusion of an initially occluded coronary artery after 90 min, was achieved in 62% of alteplase-treated patients compared with 31% of streptokinase-treated patients (p = 0.001; Fig 3).22,26,95 The patency rate at 90 min, independent of findings on the baseline angiogram, was 70% for alteplase vs 43% for streptokinase (p < 0.001). The European Study Group reported nearly identical results.44 Alteplase was then studied in numerous angiographic trials, 26,31,32,35,36,38,40,42,44,53–55,60–75 as reviewed by Granger and colleagues (Table 4).96 These early trials observed that the 3-h dosing regimen of alteplase resulted in superior patency and TIMI grade 3 flow results at both 60 min and 90 min compared with streptokinase or anistreplase.96 Neuhaus and colleagues97 developed an “accelerated” 90-min dosing regimen for alteplase, which

### Table 2—Infarct-Artery Patency Without Fibrinolytic Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No.</th>
<th>Time to Treatment, † min</th>
<th>Mean Catheterization Time</th>
<th>Patency, % (No./Total Patients)</th>
<th>95% CI, %</th>
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<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anderson et al25</td>
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<td>0 min</td>
<td>20 (57/289)</td>
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<tr>
<td>Pooled</td>
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<td>20 (70/352)</td>
<td>16–24</td>
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<td>1 h</td>
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<tr>
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<td>68 min</td>
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*NHFA = National Heart Foundation of Australia Coronary Thrombosis Group. Reprinted from Granger et al42 with permission.

†Time from symptom onset to start of thrombolytic or control treatment.
was found to achieve even higher rates of early reperfusion than did the 3-h regimen of alteplase, anistreplase treatment, or streptokinase treatment. Given the importance of rapid reperfusion, a fibrinolytic regimen that achieves a higher rate of early infarct-artery patency would be expected to be associated with lower mortality. This notion was called into question with the disappointing results of the GISSI-2 and International Study Group and the ISIS-3 trial. The lack of benefit seen in these trials, however, may have been because of the use of subcutaneous heparin (rather than IV heparin) and the use of duteplase as opposed to alteplase, as will be discussed.

The relationship of early reperfusion and improved survival was strongly supported by the results of GUSTO-1 trial, which set out to evaluate several promising fibrinolytic regimens. The reference arms of the trial both used streptokinase, one with subcutaneous heparin (12,500 U q12h beginning at 4 h) and one with IV heparin, as noted earlier in this article. The third arm was front-loaded (accelerated) alteplase and IV heparin. The fourth arm was combination fibrinolytic therapy, which involved about two thirds of the typical doses of alteplase and streptokinase with IV heparin. All patients received aspirin, 325 mg/d.

A total of 41,021 patients were enrolled in GUSTO-1, of which the primary end point was 30-day mortality (Table

<table>
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<tr>
<th>Study†</th>
<th>Patients, No.</th>
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<th>Time to Treatment</th>
<th>Mean Catheterization Time</th>
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<th>95% CI, %</th>
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<td>24 h</td>
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<tr>
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<td>180 min</td>
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<td>30 min</td>
<td>60 min</td>
<td>80</td>
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*PRIMI = Pro-Urokinase in Myocardial Infarction trial; PAIMS = Plasminogen Activator Italian Multicentre Study. Adapted from Granger et al, with permission.
†Studies with streptokinase dose ≥ 1.0 MU.
‡Percent with recanalization.
Mortality at 30 days was significantly lower in the accelerated alteplase arm compared with each of the three other arms. The improvement in mortality was present as early as 24 h after treatment began, with alteplase-treated patients having a significantly lower mortality rate. Other major complications also were reduced in patients treated with alteplase, including less cardiogenic shock, congestive heart failure, and ventricular arrhythmias.

Some physicians have stated that the relative 14% reduction in mortality with alteplase vs streptokinase (an absolute 1% difference) is a small, clinically irrelevant improvement. Thrombolysis itself, however, widely considered to be a revolution in the treatment of acute MI, led to a 25% relative (or approximately 2% absolute) improvement in mortality compared with placebo. In counting the absolute benefit in terms of the number of lives saved, standard fibrinolysis is estimated to save 26 lives per 1,000 patients treated compared with placebo.

### Table 4—Patency With IV Alteplase

<table>
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<tr>
<th>Study†</th>
<th>Patients, No.</th>
<th>Dose</th>
<th>Time to Treatment</th>
<th>Mean Catheterization Time</th>
<th>Patency, % (No./Total Patients)</th>
<th>95% CI, %</th>
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<td>156 min</td>
<td>42 min</td>
<td>60 (108/180)</td>
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<td>Smalling et al40</td>
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<td>56 min</td>
<td>45 (40/88)</td>
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<td>168 min</td>
<td>62 min</td>
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<td>216 min</td>
<td>68 min</td>
<td>57 (40/70)</td>
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<td>120 min</td>
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<td>24 h</td>
<td>78 (82/105)</td>
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<td>100 mg</td>
<td>168 min</td>
<td>33 h</td>
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<td>76 (64/84)</td>
</tr>
<tr>
<td></td>
<td>NHFA58</td>
<td>73</td>
<td>100 mg/3 h</td>
<td>195 min</td>
<td>5–7 d</td>
<td>70 (43/61)</td>
</tr>
<tr>
<td></td>
<td>TIMI-HA63</td>
<td>359</td>
<td>100–150 mg/6 h</td>
<td>174 min</td>
<td>7–10 d</td>
<td>79 (240/303)</td>
</tr>
<tr>
<td></td>
<td>Thompson et al74</td>
<td>241</td>
<td>100 mg/3 h</td>
<td>155 min</td>
<td>7–10 d</td>
<td>80 (157/196)</td>
</tr>
<tr>
<td></td>
<td>Neuhaus et al10</td>
<td>124</td>
<td>70 mg/3 h</td>
<td>&lt; 4 h</td>
<td>10 d</td>
<td>73 (63/86)</td>
</tr>
<tr>
<td></td>
<td>Cherif et al44</td>
<td>59</td>
<td>100 mg/3 h</td>
<td>312 min</td>
<td>10–14 d</td>
<td>77 (23/30)</td>
</tr>
<tr>
<td></td>
<td>Rapold et al73</td>
<td>34</td>
<td>100 mg/3 h</td>
<td>186 min</td>
<td>12.5 d</td>
<td>81 (25/31)</td>
</tr>
<tr>
<td></td>
<td>de Bono38</td>
<td>367</td>
<td>100 mg/3 h</td>
<td>156 min</td>
<td>15 d</td>
<td>87 (283/327)</td>
</tr>
<tr>
<td></td>
<td>White et al35</td>
<td>135</td>
<td>100 mg/3 h</td>
<td>150 min</td>
<td>21 d</td>
<td>76 (94/124)</td>
</tr>
<tr>
<td></td>
<td>O’Rourke et al40</td>
<td>74</td>
<td>100 mg/3 h</td>
<td>120 min</td>
<td>21 d</td>
<td>81 (55/68)</td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>2,327</td>
<td></td>
<td></td>
<td></td>
<td>80 (1,520/1,906)</td>
</tr>
</tbody>
</table>

*See Table 2 for abbreviation. Reprinted from Granger et al.42 with permission.
†Studies with 0.75- to 1.5-mg/kg or 70- to 100-mg alteplase.
patients with ST-segment elevation. Treatment with accelerated alteplase and IV heparin saves an additional 10 lives per 1,000 treated, representing a 40% improvement over standard fibrinolytic regimens. Otherwise stated, the use of alteplase instead of streptokinase prevents one of the seven deaths that would have occurred among 100 patients treated. As such, accelerated alteplase does afford an important benefit over previous standard fibrinolytic regimens.

Despite the aggressive regimens of thrombolysis, aspirin, and heparin, intracranial hemorrhage occurred only rarely in GUSTO-1. For each of the streptokinase arms, intracranial hemorrhage occurred only in 0.7% of patients treated with accelerated alteplase compared with 0.9% of patients treated with combination alteplase and 0.9% of patients treated with accelerated alteplase and IV heparin, intracranial hemorrhage occurred only rarely in GUSTO-1. As such, accelerated alteplase does afford an important benefit over previous standard fibrinolytic regimens.

The benefit of accelerated alteplase was seen in nearly every subgroup analyzed, including patients with anterior or inferior MI and in the young and the elderly. The absolute benefit was greater in higher-risk patients, for example, those with anterior MI.

To fully understand the benefits of the various fibrinolytic regimens, an angiographic substudy was carried out. Over 2,400 patients were randomized to undergo angiography at 90 min, 180 min, 24 h, or 5 days. At the important, 90-min time point, the alteplase-treated patients had a significantly higher patency rate and a much higher rate of TIMI grade 3 flow, which, as noted above, is associated with the best outcomes (Table 10). At the other three time points, there were no significant differences among the four fibrinolytic regimens. Thus the benefit of accelerated alteplase was associated with early opening of the infarct-related artery. The improved patency at 90 min was associated with improved survival at both 24 h and at 30 days, thus highlighting the benefits of rapid reperfusion.

TIMI-4: The TIMI-4 trial was a double-blind trial comparing accelerated alteplase, anistreplase, and their combination. All patients received aspirin and IV heparin. Accelerated alteplase was found to have a 78% patency rate after only 60 min compared with only 60% for anistreplase or combination fibrinolytic therapy. At 90 min, patency and TIMI grade 3 flow rates both were significantly better in the accelerated alteplase arm. Overall clinical outcomes, using a composite end point and 1-year survival, also were better with alteplase. Thus, this double-blind trial confirmed the results found in the GUSTO-1 trial.

### Table 5—Mortality Prediction With ST-Segment Resolution After Fibrinolysis*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, No.</th>
<th>Time of Analysis, min</th>
<th>Follow-up, d</th>
<th>Resolution of ST-Segment Elevation, † %</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAM&lt;sup&gt;79&lt;/sup&gt;</td>
<td>1,516</td>
<td>180</td>
<td>35</td>
<td>Complete 2.8, Partial 4.3, None 9.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>INJECT&lt;sup&gt;90&lt;/sup&gt;</td>
<td>1,398</td>
<td>180</td>
<td>35</td>
<td>Complete 2.5, Partial 4.3, None 17.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HIT-4&lt;sup&gt;91&lt;/sup&gt;</td>
<td>998</td>
<td>180</td>
<td>35</td>
<td>Complete 2.8, Partial 6.0, None 14.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GUSTO-III&lt;sup&gt;92&lt;/sup&gt;</td>
<td>1,577</td>
<td>90</td>
<td>30</td>
<td>Complete 2.7, Partial 4.8, None 13.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI-1&lt;sup&gt;4&lt;/sup&gt;</td>
<td>444</td>
<td>90</td>
<td>30</td>
<td>Complete 1.0, Partial 4.2, None 5.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Reprinted from Roe et al<sup>82</sup> with permission.
†Complete resolution was ≥ 70% of baseline; partial resolution was 31 to 69% of baseline; no resolution was ≤ 30% of baseline.

### Table 6—Predictors of 30-d Mortality After Fibrinolysis for Acute MI: the GUSTO-1 Model*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted χ²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>717†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>550</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Killip class</td>
<td>350 (3 df)†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>272 (2 df)†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Location of infarction</td>
<td>143 (2 df)†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>64†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Age-by-Killip class interaction</td>
<td>29†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>31 (4 df)‡</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Time to treatment</td>
<td>23†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>16†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (2 df)†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Choice of fibrinolytic therapy</td>
<td>15 (3 df)†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Previous bypass surgery</td>
<td>16†</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Prior cerebrovascular disease</td>
<td>10†</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Adapted from Lee et al<sup>84</sup> with permission; df = degrees of freedom.
†p < 0.00001.
‡p < 0.0001.
§p < 0.001.

### Table 7—Predictors of Intracranial Hemorrhage After Fibrinolysis for Acute MI: the GUSTO-1 Model<sup>93</sup>*

<table>
<thead>
<tr>
<th>Variables</th>
<th>χ²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.94</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight</td>
<td>34.63</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prior cerebrovascular disease</td>
<td>20.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>14.07</td>
<td>0.0002</td>
</tr>
<tr>
<td>Combination alteplase-streptokinase therapy</td>
<td>14.01</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.44</td>
<td>0.0065</td>
</tr>
<tr>
<td>Hypertension times age interaction term</td>
<td>5.90</td>
<td>0.0152</td>
</tr>
<tr>
<td>Accelerated alteplase treatment</td>
<td>3.98</td>
<td>0.0460</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>3.88</td>
<td>0.0488</td>
</tr>
</tbody>
</table>

*C-index value, 0.53; adapted from Gore et al<sup>89</sup> with permission.
The benefits of accelerated alteplase seen in the GUSTO-1 and TIMI-4 trials vs the lack of benefit seen in GISSI-2 and ISIS-3 reflects two factors: the alteplase regimen and the heparin dosing. The former trials used the accelerated alteplase regimen, which results in a higher rate of early patency compared with the older, 3-h regimen and early, IV heparin, which improves late infarct-artery patency. In contrast, the GISSI-2 and ISIS-3 trials used the slower infusion of alteplase or duteplase and delayed, subcutaneous heparin, which does not elevate the APTT level until approximately 24 h after the start of treatment. Reocclusion of an open infarct-related artery, which is associated with a threefold increase in mortality, occurs most often during this period. Thus, a subcutaneous heparin regimen cannot prevent this important predictor of poor outcomes.

The benefits of accelerated alteplase and IV heparin, then, are based on the ability to achieve rapid, sustained infarct-artery patency after acute MI. This link between early reperfusion, especially achievement of TIMI grade 3 flow, and improved survival was established in the GUSTO-1 angiographic substudy. If newer regimens, such as fibrinolytic therapy plus platelet GP IIb/IIIa inhibition, can further improve early reperfusion, further reductions in mortality can be expected.

Double-Bolus Alteplase: Initial interest in a double-bolus regimen of alteplase came from a series of patients to whom two 50-mg boluses of alteplase were given 30 min apart. TIMI grade 3 flow was achieved in 88% of patients, a considerably higher rate than in previous studies. In a later randomized trial, however, double-bolus alteplase resulted in TIMI grade 3 flow in only 58% of patients.

---

**Table 8—Placebo-Controlled Mortality Trials of Streptokinase**

<table>
<thead>
<tr>
<th>Variables</th>
<th>GISSI-1*</th>
<th>ISAM**</th>
<th>ISIS-2**</th>
<th>EMERAS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>11,806</td>
<td>1,741</td>
<td>17,187</td>
<td>3,568</td>
</tr>
<tr>
<td>Sites, No.</td>
<td>176</td>
<td>38</td>
<td>417</td>
<td>236</td>
</tr>
<tr>
<td>Dose/duration</td>
<td>1.5 MU/1 h</td>
<td>1.5 MU/1 h</td>
<td>1.5 MU/1 h</td>
<td>1.5 MU/1 h</td>
</tr>
<tr>
<td>Placebo blinding</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age criteria</td>
<td>All</td>
<td>&lt; 75 yr</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Symptom duration, h</td>
<td>&lt; 12</td>
<td>&lt; 6</td>
<td>&lt; 24</td>
<td>6–24</td>
</tr>
<tr>
<td>ECG criteria</td>
<td>ST-segment ↑ or ↓</td>
<td>ST-segment ↑</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Aspirin</td>
<td>±</td>
<td>Yes</td>
<td>Randomized</td>
<td>Yes</td>
</tr>
<tr>
<td>Heparin</td>
<td>±</td>
<td>IV</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Mortality follow-up, d</td>
<td>In-hospital</td>
<td>21</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

*EMERAS = Estudio Multicentrico Estreptocinasa Republicas de America del Sur.
compared with a 66% rate in patients treated with the accelerated, 90-min infusion of alteplase. Further, the Continuous Infusion vs Double-Bolus Administration of Alteplase trial,109 which compared double-bolus vs accelerated infusion dosing of alteplase, was terminated early because of concern about the safety of the double-bolus regimen. Thirty-day mortality tended to be higher in the double-bolus group than in the accelerated-infusion group (7.98% vs 7.53%). Statistically, double-bolus alteplase was not equivalent to the infusion regimen. Rates of hemorrhagic stroke were 1.12% after double-bolus alteplase compared with 0.81% after accelerated infusion of alteplase (p = 0.23).109 Based on these data, double-bolus alteplase is not recommended for general clinical use, and the accelerated, 90-min infusion remains the current standard dosing for alteplase treatment of acute MI.

Cost-Effectiveness of Alteplase: A formal cost-effectiveness analysis was incorporated into the GUSTO-I protocol as a substudy to be carried out in the United States and Canada.110 At 1 year, alteplase-treated patients had both higher costs ($2,845) and higher survival (an absolute 1.1% higher rate, or 11 more patients surviving per 1,000 patients treated) compared with streptokinase-treated patients. The incremental cost-effectiveness ratio was $32,678 per year of life saved.110 The use of alteplase in patients with anterior MI yielded even more favorable cost-effectiveness values but less in inferior infarction and young patients. Thus, the cost-effectiveness of alteplase compared with streptokinase compares favorably with that of other therapies, such as hemodialysis for end-stage renal disease ($35,000 to $50,000 per year of life saved).

Potential Advantages of Bolus Fibrinolytic Agents

Administration of fibrinolytic agents as a bolus has several potential advantages. First, its ease of administration could aid in more rapid treatment of acute MI, which has been shown to improve survival.5,111 Reducing the time to treatment, particularly the “door-to-drug” time, has been identified as a critical target by the National Heart Attack Alert Program.112 An increased door-to-drug time has recently been shown to relate directly to increased mortality.113 The time from “the decision” to “the start of drug” can be reduced if a simple, bolus fibrinolytic agent is available. The advantage of single-bolus therapy in relation to compliance was established in ISIS-3, in that 95% of patients assigned to anistreplase treatment actually received the drug compared with only 89% and 90% of patients in the alteplase and streptokinase groups, respectively.101 Further, in a study by Hilleman and Seyedrondbari,114 patients given double-bolus r-PA therapy received the drug 15 min sooner than did those treated with alteplase infusion.

Second, bolus fibrinolytic may make more feasible the promising strategy of prehospital therapy.115-117 In an overview of all trials, a 19% reduction in mortality with prehospital treatment compared with standard, hospital-based treatment was observed.115 In a single study,117 using bolus anistreplase treatment, mortality was reduced by > 50% when given before patients arrived at the hospital.

Another potential advantage of bolus fibrinolytic is fewer medication errors, which are associated with adverse outcomes and longer hospital stays in this population.118-120 With the bolus-plus-infusion regimen for alteplase, for example, there is a surprisingly high percentage of patients with medication errors (an incorrect dose or infusion duration). In GUSTO-I, 12% of the 41,021 patients treated with alteplase or streptokinase infusion had a medication error, although the 30-day mortality was significantly higher in patients with a medication error than in those given the correct dose (for alteplase, 7.7% vs 5.5%; for streptokinase, 11.3% vs 6.4%; both p < 0.001). This observation is limited by the difficulty in adjusting for risk factors for adverse events in this population.121 In the National Registry of Myocardial Infarction involving > 71,000 patients, patients who received a dose of alteplase > 1.5 mg/kg had a 2.3-fold increase in intracranial hemorrhage, with a multivariate risk ratio of 1.49, suggesting that medication errors with bolus and infusion fibrinolytic therapy may be important.88

In the Intravenous n-PA for Treatment of Infarcting Myocardium Early (InTIME)-II trial,122 there were more dosing errors in the alteplase group than in the single-bolus n-PA group (7.3% vs 5.7%; p < 0.001). As was seen in GUSTO-I, mortality was higher among alteplase-treated patients with medication errors vs those receiving the correct alteplase dose (12.5% vs 5.9%; p < 0.001). Interestingly, the same relationship was not seen for weight-adjusted n-PA. Intracranial hemorrhage also was significantly increased among alteplase-treated patients with medication errors (1.4% vs 0.6% with the correct alteplase dose).122 For the double-bolus agent r-PA, the rate of medication errors also has been low; only 1% of patients did not receive the full r-PA dose in one study compared with 4% for alteplase (p = 0.03).114

In summary, these data from several large trials show that (1) bolus fibrinolytic therapy can reduce the rate of medication errors, and (2) medication errors may be associated with increased rates of both mortality and intracranial hemorrhage.

Trials of r-PA

r-PA was one of the first mutant t-PA molecules to undergo extensive clinical testing. Early observations suggested that optimal therapeutic efficacy resulted when r-PA was divided into two boluses (10 U + 10 U) given 30 min apart.123 This was followed by two angiographic trials comparing alteplase with r-PA. The first, the Reteplase Angiographic Phase II International Dose-finding (RAPID)-1 trial, examined three dosing strategies for r-PA (Table 11).124 These were compared with an infusion of alteplase (100 mg delivered > 3 h). The TIMI grade 3 flow rate at 90 min was 63% with r-PA compared with 49% with alteplase (p < 0.05). A second, larger trial (RAPID-2) compared the best regimen from RAPID-1 with accelerated alteplase.125 Once again, r-PA was found to be superior to accelerated alteplase. When these two trials were combined, the rate of TIMI grade 3 flow at 90 min was 61% for r-PA (10 U + 10 U) compared with 45% for the accelerated alteplase regimen (p < 0.01). The 16%
absolute increase in TIMI grade 3 rate with r-PA over accelerated alteplase was less than the 24% increase seen with alteplase over streptokinase in the GUSTO-I angiographic substudy, but this smaller difference translated into a much larger difference in mortality in the RAPID trials (3.1% for r-PA vs 8.4% for alteplase) in the two RAPID trials.

The INJECT study125a examined whether double-bolus r-PA was at least equivalent to streptokinase in reducing mortality (Table 12). The 35-day mortality rate with r-PA was 9% compared with 9.5% with streptokinase. The 95% CIs for the absolute mortality difference (0.5%; 95% CI, −1.98 to 0.96) did not extend to a possible 1% higher mortality rate with r-PA compared with streptokinase. This would suggest that r-PA is at least equivalent to streptokinase and therefore superior to placebo in this study. These findings served as the basis for US Food and Drug Administration approval for r-PA.

The GUSTO-3 study 126 compared double-bolus r-PA with accelerated alteplase. This was a superiority trial to test whether the reported 16% increase in TIMI grade 3 flow with r-PA compared with t-PA would translate into improved 30-day mortality. A total of 15,059 patients presenting within 6 h of MI symptom onset were enrolled. The primary end point of 30-day mortality was reached in 7.47% of r-PA-treated patients and in 7.24% of alteplase-treated patients.

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Table 9—Results From the GISSI-2/International Study and the ISIS-3 Trial*

<table>
<thead>
<tr>
<th>Trials</th>
<th>Streptokinase, sq Heparin</th>
<th>Streptokinase, No Heparin</th>
<th>Alteplase, sq Heparin</th>
<th>Alteplase, No Heparin</th>
<th>Anistreplase, sq Heparin</th>
<th>Anistreplase, No Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-2/International Study100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
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<td>10,372</td>
<td>10,361</td>
<td>10,407</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>35-d mortality, %</td>
<td>9.2</td>
<td>9.6</td>
<td>9.3</td>
<td>9.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total stroke, %</td>
<td>1.0</td>
<td>1.3</td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intracranial hemorrhage, %</td>
<td>0.3</td>
<td>0.4</td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ISIS-3101†</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients, No.</td>
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<td>13,746</td>
<td>13,773</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-d mortality, %</td>
<td>10.6</td>
<td>10.3</td>
<td>10.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stroke, %</td>
<td>1.1</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage, %</td>
<td>0.25</td>
<td>0.22</td>
<td>0.72</td>
<td>0.59</td>
<td>0.71</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*sq = subcutaneous.
†In the ISIS-3 study, the mortality in patients randomized to subcutaneous heparin therapy across the three arms was similar to those randomized to no heparin therapy (10.3% vs 10.6%). When ISIS-3 and GISSI-2 were combined, the 35-day mortality was identical with t-PA and streptokinase (10.0% vs 10.0%).
‡3-h infusion; duteplase was used in ISIS-3.
Table 10—Results From the GUSTO-I Trial*

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase Plus Heparin</th>
<th>Streptokinase Plus IV Heparin</th>
<th>Accelerated Alteplase Plus IV Heparin</th>
<th>Combination Therapy Plus IV Heparin†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>9,796</td>
<td>10,377</td>
<td>10,344</td>
<td>10,328</td>
<td>—</td>
</tr>
<tr>
<td>30-d mortality</td>
<td>7.2</td>
<td>7.4</td>
<td>6.4†</td>
<td>7.0</td>
<td>0.005†</td>
</tr>
<tr>
<td>Net clinical benefit¶</td>
<td>7.7</td>
<td>7.9</td>
<td>6.9†</td>
<td>7.6</td>
<td>0.006†</td>
</tr>
<tr>
<td>24-h mortality</td>
<td>2.8</td>
<td>2.9</td>
<td>2.3†</td>
<td>2.8</td>
<td>0.005†</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.5</td>
<td>0.5</td>
<td>0.7†</td>
<td>0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>17.5</td>
<td>16.8</td>
<td>15.2†</td>
<td>16.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>6.9</td>
<td>6.3</td>
<td>5.1</td>
<td>6.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Angiographic substudy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
<td>293</td>
<td>283</td>
<td>292</td>
<td>299</td>
<td>—</td>
</tr>
<tr>
<td>Infarct-artery patency, 90 min</td>
<td>54</td>
<td>60</td>
<td>81</td>
<td>73</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI grade 3 flow, 90 min</td>
<td>29</td>
<td>32</td>
<td>54</td>
<td>38</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Data are presented as % unless otherwise indicated.
†Reduced-dose alteplase and reduced-dose streptokinase.
‡For alteplase vs both streptokinase arms combined.
¶Death or nonfatal disabling stroke.
§Net clinical benefit.

Treated patients (p = 0.6; Table 12). Therefore r-PA was not superior to alteplase in this study. The 95% CI for the absolute mortality difference of 0.23% ranged from 1.11% in favor of alteplase to 0.66% in favor of r-PA. Using the 1% cutoff, these observations did not prove the equivalence of the two agents. The mortality rates were similar when patients were categorized into subgroups, including by age, infarct location, and enrolling region. There was an interaction between symptom duration and outcomes with r-PA vs alteplase, which was of borderline significance (p = 0.05). The rates of stroke, bleeding, and intracranial hemorrhage did not differ significantly. The lack of superiority of r-PA over alteplase in clinical outcome is consistent with the concept that at least a 20% absolute increase in TIMI grade 3 flow incidence is required to substantially improve mortality in acute MI.

Trials of TNK-tPA

Clinical testing of TNK-tPA began in the TIMI-10A trial,16 with doses ranging from 5 to 50 mg. The trial showed a greater incidence of TIMI grade 3 flow at 90 min (57 to 64%) in patients given 30 to 50 mg of TNK-tPA than those treated with lower doses (p = 0.032). In TIMI-10B,22 a total of 886 patients were randomized to receive either accelerated alteplase or a 5-s to 10-s bolus of 30 mg or 50 mg of TNK-tPA. The 50-mg dose was discontinued because of increased bleeding and replaced with a 40-mg dose. The 40-mg dose of TNK-tPA produced an incidence of TIMI grade 3 flow at 90 min similar to that with alteplase (Fig 4)127; the 30-mg dose produced a significantly lower rate (54.6%, p = 0.04 vs alteplase), and the 50-mg dose produced a rate of 65.8% (p = not significant [NS]).22 The rate of TIMI grade 2 or 3 flow and TIMI frame counts at 90 min were similar between TNK-tPA and alteplase. At 60 min, there was no difference in the rates of TIMI grade 3 flow or overall patency.

Weight-Adjusted Dosing: Both TIMI-10B and the Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT)-1 study called for prospectively defined, weight-based analyses of efficacy.22,128,129 The rate of TIMI grade 3 flow was 62 to 63% for doses of TNK-tPA of approximately 0.5 mg/kg or higher, but was only 51 to 54% at lower doses (p = 0.028 across quintiles). When dose/weight was stratified into tertiles, the median corrected TIMI frame count was significantly lower (that is, coronary flow was faster) in patients who received the higher “weight-corrected” dose.129

Safety Results in TIMI-10B: During the first phase of the trial (that is, before the reduction in heparin dosage described below), there were three intracranial hemorrhages among 78 patients (3.8%; 95% CI, 0.8 to 10.8%) treated with the 50-mg dose of TNK-tPA. In the parallel ASSENT-1 trial, however, no intracranial hemorrhages occurred at this dose. This dose was dropped from further testing in TIMI-10B, and, at the same time, the doses of heparin were reduced. Further analysis showed that the concomitant heparin dose could have played a larger role than that of the TNK-tPA dose in defining the rate of intracranial hemorrhage.

Initially in TIMI-10B and ASSENT-I, heparin dosing was at the discretion of the treating physicians. However, a protocol amendment mandated that patients receive the after dose of heparin: for patients > 67 kg, a 5,000-U bolus and 1,000 U/h infusion; for patients weighing ≤ 67 kg, a 4,000-U bolus and 800 U/h infusion. The amendment also mandated that the heparin dose be adjusted according to the nomogram beginning with the 6-h APTT.

The rates of both intracranial hemorrhage and serious bleeding were lower after the protocol amendment, from 2.2 to 0% for the 30-mg dose of TNK-tPA (p = 0.047), and from 2.8 to 1.2% for alteplase (p = 0.29; overall combined p = 0.04).22 The rates of intracranial hemorrhage were similarly and significantly reduced in the overall TNK-tPA experience, combining the TIMI-10B and ASSENT-I data.130 Severe bleeding also decreased with the reduced heparin dosing; from 3 to 0% for the 30-mg dose of
TNK-tPA (p = 0.02), and from 8 to 2% for alteplase (p = 0.01; combined, p = 0.001).\textsuperscript{22} Thus, the subsequent phase-III trial, ASSENT-2, used the lower-dose heparin regimen.

The rate of serious bleeding (noncerebral bleeding requiring transfusion) was lower with TNK-tPA compared with alteplase in TIMI-10B. For alteplase, 7.0% of patients required transfusion compared with 1.0% of patients treated with 30 mg of TNK-tPA (p < 0.001) and 1.3% of those treated with 40 mg of TNK-tPA (p < 0.01).\textsuperscript{131} Similar low rates were observed in the ASSENT-1 trial.\textsuperscript{131} Thus, there was early evidence that the very fibrin-specific agent TNK-tPA might be associated with lower rates of bleeding than alteplase.

ASSENT-I: ASSENT-I was a randomized trial of three doses of TNK-tPA, with its primary goal to determine the rate of intracranial hemorrhage with each dose, to assist in determining the appropriate dose for a large, phase III trial. A total of 3,298 patients were randomized to receive 30 mg of TNK-tPA (n = 1,705), 40 mg of TNK-tPA (n = 1,457), or 50 mg of TNK-tPA (n = 73).\textsuperscript{128} As noted above, the 50-mg dose was discontinued and replaced by 40 mg because of increased bleeding observed in the TIMI-10B study. Intracranial hemorrhage occurred in 0.77% of patients overall: 0.94% in the 30-mg arm and 0.62% in the 40-mg arm. No strokes were found in the 73 patients treated with 50 mg of TNK-tPA. Among patients treated within 6 h of symptom onset, the rates of intracranial hemorrhage were 0.56% with 30 mg of TNK-tPA and 0.55% with 40 mg of TNK-tPA. Death, nonfatal stroke, or severe bleeding complications occurred in low proportions of patients: 6.4%, 7.4%, and 2.8%, in the 30-mg, 40-mg, and 50-mg arms, respectively.

ASSENT-2: TNK-tPA was compared with accelerated alteplase in this large equivalence mortality trial of patients with acute ST-segment elevation MI presenting within 6 h of the onset of chest pain. The study enrolled 16,950 patients worldwide. TNK-tPA was given as a weight-adjusted dose of 0.53 mg/kg given in 5-mg increments, ranging from 30 to 50 mg.\textsuperscript{127}

Overall mortality essentially was identical between the two agents: 6.17% for TNK-tPA vs 6.15% for alteplase. This trial was an “equivalence” trial,\textsuperscript{132} and under its prospectively defined criteria, TNK-tPA was shown to be equivalent to alteplase. The relative risk of 30-day mortality was 1.00 for TNK-tPA vs alteplase (90% CI, 0.91 to 1.10; p value for equivalence = 0.028). The equivalence of the agents in reducing mortality was shown in nearly every subgroup tested.

Interestingly, patients treated > 4 h after symptom onset had improved outcomes compared with such patients treated with alteplase. This benefit may relate to the greater fibrin specificity of TNK-tPA. The first observation of a benefit of greater fibrin specificity in patients treated > 4 h came from the TIMI-1 trial, in that 90-min patency was preserved in patients treated with alteplase, whether treated before or after 4 h of symptoms, but patency was significantly worse in patients who received streptokinase after 4 h rather than before.\textsuperscript{26,65} Similar findings were seen in an analysis of German angiographic fibrinolytic trials.\textsuperscript{133,134} The same pattern favoring the more fibrin-specific agent was seen in the GUSTO-III trial, in that patients treated > 4 h after symptom onset had significantly lower mortality with alteplase compared with r-PA, a less fibrin-specific agent.\textsuperscript{126} The occlusive clot may be more resistant the longer it has been able to mature, and the greater fibrin specificity of a fibrinolytic agent may enhance its ability to lyse the clot.

Safety Observations: In ASSENT-2, the rates of intracranial hemorrhage were nearly identical for TNK-tPA and alteplase (0.93% and 0.94%, respectively), as were the overall rates of stroke (1.78% and 1.66%).\textsuperscript{127} Of note, patients aged > 75 years showed a trend toward reduced intracranial hemorrhage with TNK-tPA vs alteplase treatment (1.7% vs 2.6%). The group at the highest risk for intracranial hemorrhage was elderly female patients weighing ≤ 67 kg,\textsuperscript{135} which has been noted in two previous multivariable analyses.\textsuperscript{68,136} It is encouraging that the rate of intracranial hemorrhage in this high-risk group was only 1.1% after treatment with TNK-tPA compared with 3.0% for those treated with alteplase (multivariate adjusted odds ratio, 0.30; 95% CI, 0.09 to 0.98; p < 0.05).\textsuperscript{135} In all other patients, the intracranial hemorrhage rates were similar between the two groups.

These benefits with regard to intracranial hemorrhage were paralleled by significantly lower rates of major bleeding. In the trial as a whole, the rates of major bleeding were 4.7% for TNK-tPA and 5.9% for alteplase (p = 0.0002).\textsuperscript{127} Overall bleeding likewise occurred in fewer patients treated with TNK-tPA (p = 0.0003).\textsuperscript{127,135} Similarly, the rate of bleeding requiring transfusion was significantly lower with TNK-tPA.

In summary, the single-bolus agent TNK-tPA shows promise based on the data from the ASSENT-2 trial. Mortality with this agent is similar to that with alteplase, and major bleeding is lower. The US Food and Drug Administration recently approved TNK-tPA for use.

Other Fibrinolytic Agents

A number of other fibrinolytic agents have been tested in humans. The agents described in this section are generally not approved for use or are in limited use around the world. However, some of these agents have been extensively tested and some are currently being evaluated.

Urokinase: This agent was one of the first tested fibrinolytic agents in humans. Despite this, it has undergone relatively sparse clinical trials evaluation. A number of smaller angiographic trials were carried out in the 1980s.\textsuperscript{65,70,137,138} These collectively showed angiographic patency and TIMI grade 3 flow rates that in general were superior to streptokinase and similar to those observed with t-PA, particularly when the higher dose of 3 million units was used. Urokinase was tested in a trial of 2,201 patients with a dose of 2 million units of urokinase plus heparin against heparin alone.\textsuperscript{139} At 16 days, the mortality was 8% in the urokinase plus heparin group and 8.3% in the heparin-alone group. This agent therefore offers little clinical advantage over existing agents and is predominantly used for peripheral vascular thrombotic occlusions.

scu-PA: scu-PA is a naturally occurring protein that is produced through recombinant DNA technology. It has a
site 117 has been used. These changes have led to a factor domains deleted. In addition, a point mutation at had the fibronectin finger-like and the epidermal growth extensive testing. It is a modified t-PA molecule that has therapy.43 The effect was only modest at the 90-min angiography (71% vs 64%). An angiographic trial comparing it against 3 h of t-PA was also carried out in 473 patients with acute MI.140 At 60 min, the patency rates were similar with either regimen (scu-PA, 80%; t-PA, 75%). This was followed by a randomized equivalence trial.141 A total of 3,089 patients were randomized to treatment with either 80 mg of scu-PA or 1.5 million units of streptokinase with IV heparin in both groups.142 The 30-day mortality rates were 5.7% for scu-PA and 6.7% for streptokinase (absolute difference, 1.01%; 95% CI, −2.78% to 0.75%). The CIs do not extend to 1%; therefore, a placebo response can be excluded. However, there was a significant higher rate of intracranial hemorrhage with scu-PA (0.9%) compared with streptokinase (0.3%; p = 0.038), calling into question the validity in calling scu-PA equivalent to streptokinase.142

n-PA: This is a single-bolus agent that has undergone extensive testing. It is a modified t-PA molecule that has had the fibronectin finger-like and the epidermal growth factor domains deleted. In addition, a point mutation at site 117 has been used. These changes have led to a substantial longer half-life compared with other agents.143 It was initially tested in an angiographic trial144 with doses ranging from 15 to 120 KU/kg in 602 patients with MI. At the highest dose, the patency rate was higher with n-PA compared with accelerated t-PA (83% vs 71%; p < 0.05). There was a trend toward higher TIMI grade 3 flow rates (57% vs 46%, respectively). n-PA was also tested in a large phase-III randomized equivalence trial.144 A total of 15,078 patients were treated with n-PA using the 120-KU/kg dose vs accelerated t-PA. Overall 30-day mortality was similar between the two agents (n-PA, 6.7% vs t-PA, 6.6%; p < 0.05 for equivalence). However, intracranial hemorrhage was significantly higher with n-PA compared with t-PA (1.13% vs 0.62%; p < 0.003). This agent is not being developed for commercial use.

Staphylokinase: Recombinant staphylokinase is a 136 amino acid single chain that activates plasminogen to plasmin with high fibrin specificity, which has undergone limited testing in humans.145 In a randomized angiographic trial,146 45 patients were allocated to staphylokinase (double bolus of either 10 mg or 20 mg) and had a TIMI grade 3 flow rate of 62% compared with 58% for 52 patients given t-PA. The highest dose (20 mg) had the highest TIMI grade 3 rate (74%). In a further study of 82 patients, a bolus and infusen were tested (15 mg, 30 mg, or 45 mg). The 90-min TIMI grade 3 flow rates showed no evidence of a dose response, with rates from 62% with the lowest dose to 63% with the highest dose.147

Complications of IV Fibrinolytic Therapy

The main complication of fibrinolytic therapy is bleeding, with the most severe bleeding complication being intracranial hemorrhage. The FTT reported, in their overview of nine trials that randomized 55,600 patients, an excess of 3.9 strokes per 1,000 patients treated with fibrinolysis vs placebo (Table 13).24 The excess stroke risk associated with fibrinolytic therapy largely is attributable to the excess risk of intracranial hemorrhage that occurs in the first day after such treatment. In the GUSTO-1 trial of 41,021 patients, 265 patients suffered an intracranial hemorrhage, of whom 160 patients (59.7%) died by 30 days.89,148 Clinical predictors of intracranial hemorrhage are shown in Table 7.89 Multivariable predictors of mortality after an intracranial hemorrhage included Glasgow coma scale score, shorter time from fibrinolytic therapy to stroke onset, and total hemorrhage volume,148 baseline clinical predictors of overall mortality in this population,24 of that age of the patient was the most important.

Regarding noncerebral bleeding, the FTT24 defined major bleeding events as those that were considered life threatening or required blood transfusion. They reported a 1.1% incidence among patients receiving fibrinolytic therapy compared with 0.4% among those receiving placebo, an increase of seven major bleeds per 1,000 patients so treated.24 In the most comprehensive report on noncerebral bleeding after fibrinolytic therapy to date, Berkowitz and other GUSTO-1 colleagues149 defined severe bleeding as that causing substantial hemodynamic compromise requiring intervention, and moderate bleeding as that requiring transfusion but without associated hemodynamic compromise. Table 14 displays bleeding according to treatment assignment in GUSTO-1. The most common cause of bleeding in GUSTO-1 was the use of coronary revascularization procedures. The most powerful multivariable predictors of moderate or severe bleeding in GUS-

<table>
<thead>
<tr>
<th>Study</th>
<th>Fibrinolytic Agent</th>
<th>Patients, No.</th>
<th>Patency at 90 min, %</th>
<th>TIMI Grade 3 Flow at 90 min, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smalling et al124</td>
<td>r-PA 15 U</td>
<td>146</td>
<td>63</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>r-PA 10 U plus 5 U</td>
<td>152</td>
<td>67</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>r-PA 10 U plus 10 U</td>
<td>154</td>
<td>85</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Alteplase 100 mg/3 h</td>
<td>154</td>
<td>77</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>r-PA 10 U plus 10 U</td>
<td>169</td>
<td>83</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Alteplase (accelerated)</td>
<td>155</td>
<td>73</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 11—Dosing Regimens and Results of the RAPID-1 and RAPID-2 Trials
TO-1 were advanced age, lighter body weight, and female sex (Table 15). These variables remained the most potent predictors of bleeding risk even among patients who did not undergo an in-hospital cardiac procedure. Regarding the issue of fibrin specificity, even after adjustment for the APTT level, the bleeding was greater with streptokinase use than with alteplase use. More recently, similar observations have been made with TNK-tPA over alteplase.

2. Adjunctive Treatment With Direct Thrombin Inhibitors

Antithrombin Agents

Thrombin plays a central role in arterial thrombosis. It converts fibrinogen to fibrin in the final common pathway for clot formation, it is a powerful stimulus for platelet aggregation, and it activates factor XIII, which leads to cross-linking and stabilization of the fibrin clot. Thrombin molecules are incorporated into coronary thrombi and can form the nidus of rethrombosis (that is, reocclusion or reinfarction) as the thrombus undergoes fibrinolysis.

Heparin: Heparin is unable to inhibit clot-bound thrombin, largely because the heparin-binding site of thrombin is not accessible when it is bound to the fibrin clot. Nevertheless, heparin is an important adjunctive agent after treatment with t-PA-derived agents (TNK-tPA, alteplase, and r-PA) to maintain infarct-related artery patency. An important lesson learned in the TIMI-10B and ASSENT-2 trials, also evident in TIMI-9 and GUSTO-2 studies, is that lower doses of heparin with thrombolysis are associated with reduced rates of intracranial and major hemorrhage. A recent overview of all major fibrinolytic trials, and of detailed information from the TIMI and InTIME-2 trials, confirmed that lower doses of heparin are associated with reduced intracranial hemorrhage. Based on the emerging data, the 1999 update to the American College of Cardiology/American Heart Association guidelines for the management of acute MI recommends a new, lower dose of heparin: a bolus of 60 U/kg (up to 4,000 U) and an initial infusion of 12 U/kg/h (up to 1,000 U/h).

Clinical trials involving unfractionated heparin have used universal therapeutic APTT ranges—typically

<table>
<thead>
<tr>
<th>Study</th>
<th>Fibrinolytic Agent</th>
<th>Patients, No.</th>
<th>Mortality at 30–35 d, %</th>
<th>Intracranial Hemorrhage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>INJECT</td>
<td>r-PA 10 U plus 10 U</td>
<td>3,004</td>
<td>9.02</td>
<td>0.77</td>
</tr>
<tr>
<td>GUSTO-3</td>
<td>r-PA 10 U plus 10 U</td>
<td>10,138</td>
<td>7.47</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Figure 4. Dosing schedule of weight-adjusted TNK-tPA used in the ASSENT-2 trial. Reprinted with permission from *Lancet*. 

16 949 patients with ST-segment elevation after acute myocardial infarction of <6h

8461 assigned single-bolus, weight-adjusted, tenecteplase
< 60 kg - 30 mg
60.0–69.9 kg - 35 mg
70.0–79.9 kg - 40 mg
80.0–89.9 kg - 45 mg
> 90 kg - 50 mg

8488 assigned accelerated infusion of alteplase
15 mg bolus followed by: 0.75 mg/kg (up to 50 mg) infusion over 30 min.
0.50 mg/kg (up to 35 mg) infusion over 60 min.

289 received no study treatment 3 vital status at 30 days unknown

236 received no study treatment 3 vital status at 30 days unknown

8458 completed follow-up of 30 days

8485 completed follow-up of 30 days
Consortium Pathologists, 164 and the American College of Chest Physicians, 165 and other sources 159,161,162,166 have recommended against generalization of therapeutic APTT ranges. There is wide agreement that therapeutic APTT ranges should be customized for the specific thromboplastin reagent in use. Because clinical trials have failed to do so, evidence-based recommendations for use of unfractionated heparin for cardiac indications are difficult to make. We have made recommendations based on the APTT ranges as they are described in published studies. However, institutions that have established therapeutic APTT ranges in the recommended fashion are encouraged to continue using them. The implementation of a discrepant universal therapeutic range at such an institution will likely lead to systematic errors in heparin dosing.

2.2. Direct Thrombin Inhibitors: Direct thrombin inhibitors also have undergone extensive evaluation in conjunction with fibrinolytic therapy. The prototypic agent is hirudin, a 65-amino-acid polypeptide derived from the leech Hirudo medicinalis, which acts as a potent, selective thrombin inhibitor compared with heparin. 166 Hirudin selectively binds in a 1:1 fashion to thrombin at two sites: the carboxy-terminus of hirudin binds to the substrate recognition site, the domain of thrombin that recognizes fibrinogen 167 or the platelet, 168 and the amino-terminus of hirudin binds to the catalytic site of thrombin. 167 Hirudin does not inhibit other enzymes in the coagulation or fibrinolytic pathways, such as factor Xa, factor IX, kalikrein, activated protein C, plasmin, or t-PA. 166 Hirudin does not bind covalently to thrombin; however, the dissociation rate is extremely slow, making hirudin an essentially irreversible inhibitor of thrombin. 166,169 Hirudin is produced in yeast by recombinant DNA technology. Several different hirudin preparations are available, including desirudin and lepirudin. 170 Other direct thrombin inhibitors also are available, including bivalirudin, 171-173 argatroban, 174 efegatran, 175 and inogatran. 176 Bivalirudin, which is being tested in a large mortality trial with streptokinase, contains three domains: the 12-amino-acid carboxy-terminus derived from hirudin; a four-amino-acid sequence (D-Phe-Pro-Arg-Pro), which binds to the catalytic site of thrombin; and a linker region with the optimal length to allow binding of both inhibitory sites. 171

Direct thrombin inhibitors inhibit all the major actions of thrombin, including thrombin-induced generation of fibrin, thrombin-induced platelet activation, and the autocatalytic reaction of thrombin. 166,177 Potential advantages of hirudin over heparin are that hirudin can inhibit clot-bound thrombin, 150 it is not inhibited by activated platelets, 179 and it does not require a cofactor. Thus, it may provide a more stable anticoagulant response. 177

The effects of desirudin with thrombolysis were tested in the TIMI-5, TIMI-6, TIMI-9, and GUSTO-2 trials. 99,155,156,179 Hirudin provided a more stable APTT, which was within the target range almost twice as often. No episodes of thrombocytopenia were reported for hirudin.

In TIMI-5, a lower rate of reinfarction was observed with hirudin than heparin (4.3% vs 11.9% for heparin; p = 0.03) and a trend toward less reocclusion (1.6% vs 6.7%; p = 0.07). 99 In the phase III, TIMI-9B trial, a similar trend toward less reinfarction was noted during hospitalization (2.3% vs 3.4%; p = 0.07), but there was no difference in the primary end point of death, MI, severe congestive heart failure, or shock at 30 days (12.9% for hirudin vs 11.9% for heparin; p = NS). 155 Similarly, the incidence of death or MI did not differ between the two anticoagulants (9.7% vs 9.5% for heparin; p = NS). Hirudin was tested in > 12,000 patients across the spectrum of acute coronary syndromes in the GUSTO-2b trial. There was significantly less reinfarction with hirudin (5.4% vs 6.3% for heparin; p = 0.04), but only a trend toward reduction in death or MI at 30 days (8.9% vs 9.8%; p = 0.06). 156 In patients with ST-segment elevation MI, the incidence of death or MI was slightly lower with hirudin (9.9% vs 11.3%; p = 0.13). There was an intriguing trend toward a greater benefit of hirudin in patients treated with streptokinase vs alteplase in GUSTO-2b, 180 but this was not observed in TIMI-9B. 155

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Table 13—Incidence and Etiology of Stroke With Fibrinolytic Therapy*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fibrinolytic (n = 29,315), No. (%)</th>
<th>Control (n = 29,285), No. (%)</th>
<th>Excess per 1,000 treated, No. (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 or 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable hemorrhage</td>
<td>78 (0.3)</td>
<td>4 (0.0)</td>
<td>2.5 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>88 (0.3)</td>
<td>35 (0.1)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>166 (0.6)</td>
<td>39 (0.1)</td>
<td>4.3 (0.5)</td>
</tr>
<tr>
<td>Days 2 to 35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable hemorrhage</td>
<td>31 (0.1)</td>
<td>11 (0.0)</td>
<td>0.7 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>139 (0.5)</td>
<td>172 (0.6)</td>
<td>– 1.1 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>170 (0.6)</td>
<td>183 (0.6)</td>
<td>– 0.4 (0.7)</td>
</tr>
<tr>
<td>Days 0 to 35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable hemorrhage</td>
<td>111 (0.4)</td>
<td>16 (0.1)</td>
<td>3.2 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>229 (0.8)</td>
<td>208 (0.7)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>340 (1.2)</td>
<td>224 (0.8)</td>
<td>3.9 (0.8)</td>
</tr>
</tbody>
</table>

*Adapted with permission by Lancet. 24
In the Hirudin for the Improvement of Thrombolysis (HIT)-3 trial, excess intracranial hemorrhage was observed with lepirudin (3.4% vs 0%). In the HIT-4 trial, which enrolled 1,208 patients and used a lower dose of lepirudin, TIMI flow grade 3 was observed in 40.7% in the lepirudin and in 33.5% in the heparin group (p = 0.16). No differences were seen between lepirudin and heparin in the rate of hemorrhagic stroke (0.2% vs 0.3%), reinfarction (4.6% vs 5.1%), or mortality (6.8% vs 6.4%) at 30 days. Thus, lepirudin in conjunction with streptokinase did not significantly improve reperfusion or clinical outcomes in this study.

Angiographic trials with other direct thrombin inhibitors also have been conducted. In a pilot study and the Hirulog Early Reperfusion/Occlusion trial, a trend toward greater early (90 to 120 min) TIMI grade 3 flow was observed with the higher dose of bivalirudin compared with heparin in patients receiving streptokinase. Testing with other agents found modest or no improvements compared with heparin.

Thus, there has not been a dramatic improvement in clinical outcomes with direct thrombin inhibitors as adjuncts to fibrinolytic therapy in acute MI. Nevertheless, a large trial now is evaluating the direct thrombin inhibitor bivalirudin, which is being compared with heparin as an adjunctive agent to streptokinase in the ongoing Hirulog Early Reperfusion/Occlusion-2 study.

### Adjunctive Therapy With GP IIb/IIIa Receptor Blockers

The platelet GP IIb/IIIa receptor antagonists have been shown to be effective and safe in reducing the ischemic complications of percutaneous coronary intervention and reducing the composite of death or MI among patients presenting with acute coronary syndromes without ST-segment elevation. The success of these agents in these groups of patients has led to a number of investigations combining GP IIb/IIIa-receptor blockers with fibrinolytic therapy. Initial trials were performed with full doses of both agents (Table 16). These trials uniformly showed improvement in the angiographic or ECG measures of reperfusion, but concerns were raised about bleeding risks with this combination therapy. More recently, data have been reported on two trials that have combined the monoclonal antibody GP IIb/IIIa inhibitor, abciximab, with half-doses of fibrinolytic therapy (Table 17). These investigations have been very promising in showing that reperfusion can be achieved rapidly beyond what is seen with fibrinolysis alone, and that myocardial perfusion can be improved as measured by ECG findings. Several similar, dose-finding trials are evaluating the small-molecule inhibitors of GP IIb/IIIa in conjunction with reduced-dose fibrinolysis. Larger mortality trials will need to be performed to provide definitive evidence as to whether such combination therapies improve mortality without increasing the risk of intracranial hemorrhage to an unacceptable level.

### Table 14—Moderate and Severe Bleeding by Fibrinolytic Assignment in GUSTO-1*

<table>
<thead>
<tr>
<th>Bleeding Rate</th>
<th>Streptokinase Plus Subcutaneous Heparin (n = 9,608)</th>
<th>Streptokinase Plus IV Heparin (n = 10,387)</th>
<th>Alteplase Plus IV Heparin (n = 10,366)</th>
<th>Combination† Plus IV Heparin (n = 10,341)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or severe</td>
<td>1,160 (11.8)</td>
<td>1,451 (14.0)</td>
<td>1,155 (11.1)</td>
<td>1,388 (13.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>117 (1.2)</td>
<td>151 (1.5)</td>
<td>92 (0.9)</td>
<td>135 (1.3)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%). Adapted from Berkowitz et al149 with permission.
†Reduced-dose alteplase and streptokinase infusions.

### Table 15—Multivariable Baseline Predictors of Moderate or Severe Bleeding from GUSTO-1

<table>
<thead>
<tr>
<th>Variables</th>
<th>χ²</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment in the United States</td>
<td>520.78</td>
<td>1.76 (1.08–2.85)</td>
</tr>
<tr>
<td>Age (60 yr vs 50 yr)</td>
<td>222.05</td>
<td>1.30 (1.26–1.35)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>163.88</td>
<td>—</td>
</tr>
<tr>
<td>100 vs 90</td>
<td>—</td>
<td>0.83 (0.73–0.95)</td>
</tr>
<tr>
<td>85 vs 75</td>
<td>—</td>
<td>0.81 (0.78–0.85)</td>
</tr>
<tr>
<td>Female sex</td>
<td>72.84</td>
<td>1.42 (1.31–1.53)</td>
</tr>
<tr>
<td>Streptokinase/IV heparin therapy†</td>
<td>32.82</td>
<td>—</td>
</tr>
<tr>
<td>US patients</td>
<td>—</td>
<td>1.13 (1.01–1.26)</td>
</tr>
<tr>
<td>Non-US patients</td>
<td>—</td>
<td>1.63 (1.36–1.95)</td>
</tr>
<tr>
<td>Combination fibrinolytic therapy†</td>
<td>31.15</td>
<td>—</td>
</tr>
<tr>
<td>US patients</td>
<td>—</td>
<td>1.02 (0.92–1.14)</td>
</tr>
<tr>
<td>Non-US patients</td>
<td>—</td>
<td>1.66 (1.39–1.95)</td>
</tr>
<tr>
<td>Diastolic BP (90 mm Hg vs 80 mm Hg)</td>
<td>28.51</td>
<td>0.94 (0.92–0.96)</td>
</tr>
<tr>
<td>Black race</td>
<td>10.17</td>
<td>1.33 (1.12–1.57)</td>
</tr>
<tr>
<td>Alteplase treatment†</td>
<td>9.20</td>
<td>—</td>
</tr>
<tr>
<td>US patients</td>
<td>—</td>
<td>0.85 (0.76–0.96)</td>
</tr>
<tr>
<td>Non-US patients</td>
<td>—</td>
<td>1.14 (0.94–1.38)</td>
</tr>
</tbody>
</table>

*Adapted from Berkowitz et al149 with permission.
†vs streptokinase with subcutaneous heparin.
†Reduced-dose alteplase and streptokinase infusions.

### Recommendations

1. **Fibrinolytic Therapy**

   1.1. We recommend that all patients with acute MI who receive fibrinolytic therapy receive aspirin (165 to 325 mg) on arrival to the hospital and daily thereafter (grade 1A).

   1.2. We recommend that patients with ischemic symptoms characteristic of acute MI for ≤ 12 h who have ST-segment elevation or left bundle-branch block on the ECG receive IV fibrinolytic therapy unless they have contraindications (grade 1A).
1.3. For patients with symptoms characteristic of acute MI and duration of 12 to 24 h who have ST-segment elevation or left bundle-branch block on the ECG, we recommend that IV fibrinolytic therapy should be considered (grade 2B).

1.4. We recommend that in patients with prior intracranial hemorrhage, any stroke within the past year, or active bleeding, clinicians do not administer IV fibrinolytic therapy (grade 1B).

1.5. We recommend that all patients with acute MI who are candidates for fibrinolytic therapy receive it within 30 min after arrival to the hospital (grade 1A). For patients with symptom duration $\leq$ 12 h, we recommend administration of one of the fibrinolytic agents: streptokinase, anistreplase, or alteplase (all grade 1A in comparison to placebo).

Remark: r-PA is equivalent to streptokinase.

1.6. For patients with symptom duration 6 h, we recommend the administration of alteplase over streptokinase (grade 1A).

Remark: TNK-tPA is equivalent to alteplase.

1.7. We recommend that patients with known allergy or sensitivity to streptokinase receive alteplase, TNK-tPA, or r-PA (grade 1C†).

2. Adjunctive Treatment With Thrombin Inhibitors

2.1. Heparin

2.1.1. For patients receiving streptokinase, we recommend administration of subcutaneous unfractionated heparin (12,500 U q12h for 48 h) (grade 2A).

2.1.2. For patients given streptokinase or anistreplase, we recommend administration of alteplase or streptokinase (all grade 1A in comparison to placebo).

Remark: r-PA is equivalent to streptokinase.

2.1.3. For patients receiving alteplase, TNK-tPA, or r-PA, we recommend administration of IV unfractionated heparin for 48 h (grade 1B).

2.1.4. For patients receiving IV heparin with alteplase, r-PA, or TNK-tPA, we recommend administration of either standard-dose unfractionated heparin (5,000-U bolus followed by 1,000 U/h) (grade 2A) or weight-adjusted dosing (60-U/kg bolus [4,000 U maximum] followed by 12 U/kg/h [1,000 U/h maximum]) (grade 2C), both adjusted to maintain an APTT of 50 to 70 s.

2.2. Direct Thrombin Inhibitors

2.2.1. For patients with known or suspected heparin-induced thrombocytopenia or thrombosis who are receiving fibrinolytic therapy (either alteplase or streptokinase), we recommend administration of IV hirudin (lepirudin 0.1-mg/kg bolus followed 0.15-mg/h infusion) (grade 2A).

REFERENCES


2 Yusuf S, Collins R, Peto R, et al. Intravenous and intracoronary heparinated heparin only if they are at high risk of systemic or venous thromboembolism (anterior MI, existing heart failure, previous embolus, atrial fibrillation, or left ventricular thrombus) (grade 1C). Remark: Heparin should be given not earlier than 4 h after therapy and when the APTT is < 70 s. The target APTT should be 50 to 70 s, and the infusion should continue for $\approx 48$ h.

2.1.3. For patients receiving alteplase, r-PA, or TNK-tPA, we recommend administration of IV unfractionated heparin for 48 h (grade 1B).

2.1.4. For patients receiving IV heparin with alteplase, r-PA, or TNK-tPA, we recommend administration of either standard-dose unfractionated heparin (5,000-U bolus followed by 1,000 U/h) (grade 2A) or weight-adjusted dosing (60-U/kg bolus [4,000 U maximum] followed by 12 U/kg/h [1,000 U/h maximum]) (grade 2C), both adjusted to maintain an APTT of 50 to 70 s.

2.2. Direct Thrombin Inhibitors

2.2.1. For patients with known or suspected heparin-induced thrombocytopenia or thrombosis who are receiving fibrinolytic therapy (either alteplase or streptokinase), we recommend administration of IV hirudin (lepirudin 0.1-mg/kg bolus followed 0.15-mg/h infusion) (grade 2A).

Table 16—Clinical Trials of Full-Dose Fibrinolytic Therapy With Platelet GP IIb/IIIa Inhibition*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Patients, No.</th>
<th>GP IIIb/IIIa Agent</th>
<th>Fibrinolytic Agent</th>
<th>Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleiman et al\textsuperscript{83}</td>
<td>1993</td>
<td>68</td>
<td>m7E3</td>
<td>Alteplase</td>
<td>First test of concept; ↑ angiographic patency</td>
</tr>
<tr>
<td>Ohman et al\textsuperscript{96}</td>
<td>1997</td>
<td>180</td>
<td>Eptifibatide</td>
<td>Alteplase</td>
<td>↑ acute TIMI grade 3 flow and faster ECG resolution vs alteplase alone</td>
</tr>
<tr>
<td>PARADIGM\textsuperscript{187}</td>
<td>1998</td>
<td>345</td>
<td>Lamifiban</td>
<td>Alteplase or streptokinase</td>
<td>↑ bleeding at highest doses but also faster ST-segment resolution vs fibrinolytic alone</td>
</tr>
</tbody>
</table>

*Adapted from Topol\textsuperscript{38} with permission; PARADIGM = Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction.

Table 17—Completed Trials of Reduced-Dose Fibrinolysis and Platelet GP IIb/IIIa Inhibition*

<table>
<thead>
<tr>
<th>Trials</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Primary Treatment</th>
<th>Adjunctive Heparin Bolus Plus Infusion</th>
<th>TIMI Grade 3 Flow at 90 min, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman et al\textsuperscript{106}</td>
<td>1999</td>
<td>888</td>
<td>Alteplase plus abciximab</td>
<td>60-U/kg bolus; 7-U/kg/h infusion</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alteplase plus abciximab</td>
<td>30-U/kg bolus; 4-U/kg/h infusion</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alteplase alone</td>
<td>70-U/kg bolus; 15-U/kg/h infusion</td>
<td>62</td>
</tr>
<tr>
<td>SPEED\textsuperscript{105}</td>
<td>2000</td>
<td>528</td>
<td>Abciximab plus r-PA</td>
<td>60-U/kg boluses</td>
<td>611</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abciximab plus r-PA</td>
<td>40-U/kg boluses</td>
<td>511</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>r-PA alone</td>
<td>70-U/kg boluses</td>
<td>471</td>
</tr>
</tbody>
</table>

*SPEED = Strategies for Patency Enhancement in the Emergency Department.

†60-min angiography.
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