Bolus Fibrinolytic Therapy in Acute Myocardial Infarction

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THE FOUNDATION OF MODERN therapy for acute myocardial infarction (AMI) with ST-segment elevation is based on the demonstration that, in its early stage, AMI is frequently associated with thrombotic coronary artery occlusion.1 One approach to the treatment of occlusive thrombosis consists of pharmacological dissolution of the blood clot by intravenous infusion of plasminogen activators that activate the fibrinolytic system.2,3 Fibrinolytic agents activate plasminogen to the active enzyme plasmin, which in turn digests fibrin to soluble degradation products (FIGURE 1).

The benefit of reperfusion therapy is early achievement of artery patency; rapid coronary reperfusion limits infarct size, decreases left ventricular dysfunction, and improves survival.4,5 More complete reperfusion has been facilitated by more potent fibrinolytic regimens.6,7 Simpler effective treatments, such as single- or double-bolus injection, may potentially offer additional benefits through rapid time to treatment and reduction of dosing errors.

Over the last decade, there have been numerous trials evaluating various bolus fibrinolytic agents. Anistreplase, a streptokinase (SK)-based bolus fibrinolytic agent, was initially evaluated but its early patency profile and clinical outcome were inferior to that of accelerated infusion alteplase (recombinant tissue-type plasminogen activator [tPA]).8,9 Subsequently, a double-bolus regimen of recombinant tPA was tested, but clinical outcomes tended to be worse compared with accelerated infusion recombinant tPA.10,11 Recent attention has focused mainly on 3 new bolus fibrinolytic drugs derived from tPA: reteplase (rPA), lanoteplase (nPA), and tenecteplase (TNK-tPA) (FIGURE 2). The angiographic and clinical efficacy of these new bolus fibrinolytic agents has been studied recently in phase 2 and phase 3 trials.

Context New bolus fibrinolytics derived from the human tissue-type plasminogen activator (tPA) have emerged as a means of dissolution of occlusive thrombosis associated with acute myocardial infarction.

Objective To review the new bolus fibrinolytic drugs derived from tPA: reteplase, lanoteplase, and tenecteplase.

Data Sources The MEDLINE, EMBASE, and Current Contents databases were searched for articles from 1983 to 2001, using the index terms pharmacokinetics, pharmacodynamics, plasminogen activator, reteplase, lanoteplase, and tenecteplase. Additional data sources included bibliographies of articles identified on MEDLINE, EMBASE, and Current Content, inquiry of experts and pharmaceutical companies, and preliminary data presented at recent national and international cardiology conferences.

Study Selection We selected for review studies that evaluated the pharmacokinetics and pharmacodynamics of reteplase, lanoteplase, and tenecteplase, and assessed the effects of these bolus fibrinolytic drugs on the angiographic and immediate and long-term outcomes of patients. Of 138 articles identified, 38 were analyzed.

Data Extraction Data quality was determined by publication in the peer-reviewed literature or presentation at an official cardiology society–sponsored meeting.

Data Synthesis Tenecteplase and reteplase are comparable with accelerated infusion recombinant tPA in terms of efficacy and safety but more convenient because they are administered by bolus injection. Lanoteplase and hirgin bolus plus infusion is as effective as tPA with regard to mortality, but the rate of intracranial hemorrhage is significantly higher.

Conclusion Given the ease of administration and the similar outcomes compared with accelerated infusion recombinant tPA, it is likely that a key component of contemporary reperfusion will include a bolus fibrinolytic.

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stracts from the annual meetings of the American College of Cardiology, and the European Society of Cardiology were reviewed. We selected for review studies that evaluated the pharmacokinetics and pharmacodynamics of rPA, nPA, and TNK-tPA, and assessed the effects of these bolus fibrinolytic drugs on angiographic and immediate and long-term clinical outcomes. Data quality was determined by publication in peer-reviewed literature or presentation at an official cardiology society meeting. Of 138 articles identified, 38 were analyzed. GraphPad Prism version 2.01 (GraphPad Software Inc, San Diego, Calif) was used for statistical analyses. Incomplete or inconsistent data were verified through direct correspondence with the primary author.

The INJECT (International Joint Efficacy Comparison of Thrombolytics), InTIME (Intravenous nPA for Treatment of Infarcting Myocardium Early)-II, and ASSENT (Assessment of the Safety and Efficacy of a New Thrombolytic)-II, trials were designed as equivalence trials; P < .05 for equivalence in these studies is considered statistically significant and indicates that the bolus fibrinolytic is as good as the positive control (tPA) within a predefined margin. For InTIME-II and ASSENT-II, the Food and Drug Administration-supported criterion of an upper bound of the 95% confidence interval (CI) of the risk ratio (RR) ≤1.143 was used, while for INJECT, an upper bound of the 1-sided 90% CI of the absolute risk difference of <1% was the equivalence criterion used.

RESULTS

Biological Characterization

Alteplase. Tissue-type plasminogen activator is a 70-kd serine protease composed of a single polypeptide chain of 527 amino acids. It is converted by plasmin to a 2-chain form by hydrolysis of the arginine275-isoleucine276 peptide bond. The NH2-terminal region is composed of several domains with homologies to other proteins: a finger domain comprising residues 4-50, a growth factor domain comprising residues 50-87, and 2 kringle domains comprising residues 87-176 and 176-262. The region comprising residues 276-527 constitutes the serine protease part with the catalytic site, which is composed of histidine322, aspartate371, and serine478. These distinct domains in tPA are involved in several functions of the enzyme (Figure 2). The human tPA gene has been localized on chromosome 8 and consists of 14 exons. Variants of tPA have been constructed with altered pharmacokinetic properties or with altered functional properties, including binding to fibrin, fibrin-specific plasminogen activation, and resistance to plasma protease inhibitors (eg, plasminogen activator inhibitor [PAI-1]). Variants of tPA with deletion of the fibronectin finger, epidermal growth factor domains, and/or kringle-1 domains have shown significantly reduced plasma clearance. This reduced plasma clearance, however, is frequently associated with a reduced fibrin-specific activity. A prolonged half-life also has been obtained by substitution or deletion of one or a few selected amino acids in the finger, epidermal growth factor, or kringle-1 domains.

Retepase. Retepase is a recombinant plasminogen activator derived from tPA, with the finger, epidermal growth factor, and kringle-1 domains removed (Figure 2). Because it is produced in Escherichia coli cells, rPA also lacks carbohydrate side chains. The single-chain rPA molecule consists of 355 amino acids, starting with Ser1 and ending with proline527 of the original tPA sequence and lacking the amino acids valine4 through glutamate175. The molecular weight is thus decreased to 39 kDa. Retepase can be converted to the double-chain form during fibrinolysis.

Lanoteplase. Lanoteplase is a fibrinolytic agent derived from tPA by deleting its fibronectin finger and epidermal growth factor domains and mutating asparagine117 to glutamine117 (designated Ghn36 in nPA) (Figure 2). The deletion involves the removal of PAI-1 residues cysteine6 through Ile86. The

Figure 1. The Fibrinolytic System

Fibrin Surface

<table>
<thead>
<tr>
<th>Fibrinolytic System Products</th>
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<tbody>
<tr>
<td>Alpha2-Antiplasmin (a2-APl)</td>
</tr>
<tr>
<td>Plasminogen Activator Inhibitor-1 (PAI-1)</td>
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<tr>
<td>Plasmin</td>
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Fluid Phase

<table>
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<tr>
<th>Fibrinolytic System Products</th>
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</thead>
<tbody>
<tr>
<td>Nonfibrin-Specific or Less Fibrin-Specific Plasminogen Activators</td>
</tr>
<tr>
<td>Alpha2-Antiplasmin (a2-APl)</td>
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<tr>
<td>Plasminogen</td>
</tr>
<tr>
<td>Plasmin</td>
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</tbody>
</table>

Plasminogen is converted by either intrinsic or extrinsic activators to plasmin, which in turn degrades fibrin. More fibrin-specific activators preferentially activate plasminogen at the fibrin surface, whereas nonfibrin or less specific plasminogen activators induce extensive systemic plasminogen activation, with degradation of several plasma proteins including fibrinogen, factor V, and factor VIII. Plasminogen activator inhibitor (PAI) 1 and a2-antiplasmin are serine protease inhibitors (members of the serpin superfamily) that are the main inhibitors of plasminogen activator and plasmin, respectively, in human plasma.

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Asn117→Gln mutation results in the elimination of an N-linked glycosylation site. This change was made based on previous findings that nonglycosylated wild-type tPA binds to fibrin better than glycosylated wild-type tPA.17

Lanoteplase is produced by cell culture fermentation using a Chinese hamster ovary cell line. The purified protein is primarily a single-chain molecule with the plasmin cleavage site intact. Of the 2 potential sites for glycosylation, one site is variably occupied (Asn103), while the other (Asn370) is fully occupied. The species with a single carbohydrate moiety at Asn370 predominates over the species with moieties at both Asn370 and Asn103. The molecular weight of nPA, which includes carbohydrate content, is 53.6 kd. Tenecteplase. Tenecteplase is a fibrinolytic drug that results from modification of native tPA at 3 sites.18-20 A threonine is replaced by an Asn in position 103, which adds a glycosylation site in kringle 1. An Asn is replaced by a Gln in position 117, thereby removing a glycosylation site from kringle 1 (Figure 2). These variations substantially decrease the clearance of TNK-tPA from plasma. In addition, the amino acids lysine296, His297, Arg298, and Arg299 are replaced by 4 alanines. This tetra-alanine substitution confers enhanced fibrin specificity and resistance to PAI-1 inhibition. The molecular weight of TNK-tPA is approximately 75 kd.

**Pharmacology**

These 3 derivatives (rPA, nPA, TNK-tPA) of tPA have a reduced plasma clearance and a prolonged half-life compared with tPA (Table 1). Lanoteplase and TNK-tPA are administered as a single bolus and have hepatic excretion, whereas rPA is administered as a double bolus (30 minutes apart) and is excreted by both renal and hepatic routes. The antigenic profiles of these agents are similar to that of tPA.

Tenecteplase is the most fibrin-specific, reducing systemic fibrinogen and plasminogen levels by only 3% and 13% respectively, at 1 hour after administration (Table 1).21 Less fibrin-specific plasminogen activators induce more extensive systemic plasminogen activation, and after saturation of α2-antiplasmin, excess plasmin may degrade several proteins including fibrinogen, factor V, and factor VIII (Figure 1).23 The clinical implication is that administration of a less fibrin-specific agent may cause a greater systemic coagulopathy, with the potential for more bleeding.

**Angiographic Evaluation**

Reteplase, nPA, and TNK-tPA were all evaluated in phase 2 angiographic trials, yielding promising results (Figure 3).22-27 In RAPID (Reteplase vs Alteplase in Acute Myocardial Infarction)-II, 324 patients with AMI were randomized to receive either a double bolus (10 U plus 10 U) of rPA or accelerated infusion tPA. Infarct-related coronary artery patency (Thrombolysis in Myocardial Infarction [TIMI] grade 2 or 3 flow)28 and complete patency (TIMI grade 3 flow) at 90 minutes after the start of fibrinolytic therapy were significantly higher in the rPA-treated patients (TIMI grade 2 or 3 flow: 83.4% vs 73.3% for accelerated infusion tPA, P=.03; TIMI grade 3 flow: 59.9% vs 45.2%, P=.01).25 At 60 min-
utes, the incidences of both patency and complete patency were also significantly higher in rPA-treated patients (rPA vs tPA, TIMI grade 2 or 3: 81.8% vs 66.1%, P=.01; TIMI grade 3: 51.2% vs 37.4%, P=.006). There were no significant differences between rPA and tPA in bleeding requiring transfusion or in hemorrhagic stroke.

Lanoteplase, in doses ranging from 15 kU/kg to 120 kU/kg, was evaluated in 602 patients in the InTIME-I trial.²⁶ The proportion of patients achieving TIMI grade 3 flow increased with an increasing dose of nPA at both 60 and 90 minutes. At 90 minutes, TIMI grade 2 or 3 flow with a 120-KU/kg dose was 83% compared with 71.4% for accelerated infusion recombinant tPA (P=.04). TIMI grade 3 flow also tended to be higher with nPA at 90 minutes (57.1% vs 46.4%, P=.14). Major and moderate bleeding did not differ in patients receiving nPA and recombinant tPA.

In the TIMI-10B trial, a total of 886 patients presenting to the hospital within 12 hours of symptom onset were randomized to receive either accelerated infusion recombinant tPA or a single 5- to 10-second bolus of TNK-tPA (30 or 50 mg).²⁷ The 50-mg dose was discontinued due to increased bleeding and was replaced with a 40-mg dose of TNK-tPA. The 40-mg dose of TNK-tPA produced a similar rate of TIMI grade 3 flow at 90 minutes compared with recombinant tPA (62.8% vs 62.7%, P=.99), whereas the 30-mg dose had a significantly lower rate of TIMI grade 3 flow at 90 minutes than recombinant tPA (54.6% vs 62.7%, P=.04).

### Phase 2 Safety Trial

The rationale for performing a large phase 2 safety study is that phase 2 efficacy studies do not allow reliable evaluation of the risk of bleeding complications (especially intracranial hemorrhage [ICH]) associated with a new thrombolytic regimen. In ASSENT-I,²⁹ a total of 3235 patients were randomized to receive 30 mg (n=1705), 40 mg (n=1457), or 50 mg (n=73) of TNK-tPA to further understand the safety of this agent. The 50-mg dose was discontinued and replaced with 40 mg because of increased bleeding observed in the TIMI-10B study. Death at 30 days occurred in low proportions of patients: 6.9% (30 mg) and 6.0% (40 mg). Intracranial hemorrhage occurred in 0.77% (95% CI, 0.50%-1.14%) overall. A reduced, weight-based heparin dosing with more careful attention to dose adjustment based on early aPTT assessment introduced early in the trial was associated with a lower incidence of ICH (1.25% vs 0.72%, P=.49).³⁰

Prespecified analyses from ASSENT-I and TIMI-10B revealed that efficacy and safety could be improved with weight-based dosing (0.53 mg/kg), and that no ICH occurred in patients weighing more than 90 kg who received 50 mg of TNK-tPA in these studies. Thus a weight-based dosing regimen for TNK-tPA (Table 2) was selected for study in the phase 3 trials and became the dosing regimen approved for use in clinical practice.

### Clinical Efficacy and Safety

Based on the favorable angiographic results obtained with rPA, nPA, and TNK-tPA, as well as the safety information obtained in ASSENT-I with TNK-tPA,
large-scale phase 3 mortality trials were designed to compare these agents with accelerated infusion recombinant tPA or SK (Table 3).31-34

Reteplace. The INJECT trial was designed as an equivalency study of rPA and SK.32 Mortality in the rPA group was lower than that of SK-treated patients (9.02% vs 9.53%; risk difference, −0.51%; 90% CI, −1.74% to 0.73%; *P* <.001 for equivalency), but this difference was not statistically significant (*P* = 0.51) for superiority of rPA compared with SK. At 6 months, mortality was 11.02% for rPA vs 12.05% for SK (*P* = .22).

Reteplace was also compared with accelerated infusion recombinant tPA in the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries)-III trial. This multicenter, randomized, open-label study was designed to test the primary hypothesis that rPA would significantly reduce 30-day mortality compared with accelerated infusion tPA in patients with AMI treated within 6 hours from symptom onset.32 Adjunctive therapy included aspirin and heparin (5000 U bolus and 1000 U/h infusion [800 U/h if patient weighed <80 kg]). Mortality (7.47% vs 7.24%, *P* = .54), ICH (0.91% vs 0.87%, *P* = .84), and net clinical benefit (death or disabling stroke: 7.89% vs 7.91%, *P* = .98) were very similar between double-bolus rPA and tPA bolus plus infusion, respectively. However, several predefined patient subgroups, including patients older than 75 years, those with anterior infarction, and those in whom treatment was initiated more than 4 hours after symptom onset, exhibited trends toward worse outcome with rPA compared with recombinant tPA. When applying post hoc criteria for equivalence (evaluating the upper boundary of the 95% CI) rPA was statistically equivalent for death or disabling stroke using a 1% absolute boundary (derived from the difference observed between SK and recombinant tPA in the GUSTO-I trial). Mortality alone, however, was not strictly equivalent using either the 1% absolute difference definition or the 14.3% relative difference rule proposed by the Food and Drug Administration, because the 95% CI in each case did not exclude the null hypothesis that a meaningful difference existed (absolute difference: RR, −0.23%; 95% CI, −1.11% to 0.66%; relative difference: RR, 1.03; 95% CI, 0.91-1.18).

Lanoteplase. The InTIME-II trial33 was a randomized, double-blind, multicenter equivalence trial that was designed to test whether 120-kU/kg single-bolus nPA was equivalent to 100 mg of accelerated recombinant tPA in reducing mortality and major morbidity in patients with suspected AMI presenting within 6 hours of symptom onset. A total of 15078 patients were enrolled at 855 hospitals in 35 countries. Patients also received aspirin and heparin (70-U/kg bolus [maximum 4000 U], and 15-U/h infusion [maximum 1000 U]). At 30 days, nPA was equivalent to tPA with regard to mortality (6.75% vs 6.61%, *P* = .04 for equivalence). Reinfarction, severe cardiac failure, and emergency revascularization occurred less often with nPA. Overall, the incidence of stroke was similar in the 2 treatment groups (1.53% [tPA] vs 1.87% [nPA], *P* = .14). However, the rate of ICH was significantly higher in nPA-treated patients (0.64% vs 1.12%, *P* = .004), possibly related to higher early activated partial thromboplastin times (aPTTs) and use of bolus heparin (see below) or due to an excessive dose of nPA. Further development of nPA has been halted.

Lanoteplase administered without a heparin bolus was studied in the open-label registry InTIME-IIb, and preliminary results revealed an absence of the early aPTT spike observed in the main InTIME-II trial, as well as a lower ICH rate (0.50%; 95% CI, 0.20%-1.02%, per protocol cohort).35,36 The 30-day mortality rate was 6.97% (95% CI, 5.69%-8.43%), which in a multivariable model adjusting for differences in the baseline characteristics of the patients enrolled was not different from that observed with nPA plus heparin bolus and infusion in InTIME-II (odds ratio, 0.99; 95% CI, 0.75-1.32).35,36

Tenecteplase. ASSENT-II34 was a randomized, double-blind, international study designed to demonstrate equivalence in 30-day mortality between bolus administration of TNK-tPA (30 or 50 mg, weight-adjusted dosing) (Table 2) and accelerated infusion recombinant tPA in patients with AMI presenting to the hospital within 6 hours of symptom onset. A total of 16949 patients were randomized into the study at 1021 hospitals in 29 countries. All patients received aspirin and intravenous heparin (5000-U bolus and 1000-U/h infusion for patients weighing >67 kg; 4000-U bo-

### Table 2. Weight-Based Dosing Regimen for Tenecteplase

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>TNK-tPA Bolus Dose, mg</th>
</tr>
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<tbody>
<tr>
<td>&lt;60</td>
<td>30</td>
</tr>
<tr>
<td>≥60 to &lt;70</td>
<td>35</td>
</tr>
<tr>
<td>≥70 to &lt;80</td>
<td>40</td>
</tr>
<tr>
<td>≥80 to &lt;90</td>
<td>45</td>
</tr>
<tr>
<td>≥90</td>
<td>50</td>
</tr>
</tbody>
</table>

### Table 3. Clinical Outcomes at 30 Days in Multicenter Phase 3 Trials With Bolus Fibrinolytics Derived From tPA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agents Compared</th>
<th>Death, %</th>
<th>Death and Disabling Stroke, %</th>
<th>Total Stroke, %</th>
<th>ICH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>COBALT,18 1997</td>
<td>tPA/nPA†</td>
<td>7.53/7.89</td>
<td>NA</td>
<td>1.53/1.92</td>
<td>0.81/1.12</td>
</tr>
<tr>
<td>INJECT,19 1995</td>
<td>SK/nPA†</td>
<td>9.53/9.02†</td>
<td>9.79/9.19†</td>
<td>1.00/1.23†</td>
<td>0.37/0.77†</td>
</tr>
<tr>
<td>GUSTO-II,31 1997</td>
<td>tPA/nPA</td>
<td>7.24/7.47</td>
<td>7.91/7.89</td>
<td>1.79/1.64</td>
<td>0.87/0.91</td>
</tr>
<tr>
<td>InTIME-II,32 2000</td>
<td>tPA/nPA†</td>
<td>6.61/6.75</td>
<td>7.00/7.23</td>
<td>1.53/1.87</td>
<td>0.64/1.12</td>
</tr>
<tr>
<td>ASSENT-II,33 1999</td>
<td>TNK/nPA†</td>
<td>6.15/6.18</td>
<td>6.05/6.21§</td>
<td>1.66/1.78</td>
<td>0.94/0.93</td>
</tr>
</tbody>
</table>

*†*tPA indicates tissue-type plasminogen activator (alteplase); ICH, intracranial hemorrhage; COBALT, Continuous Infusion versus Double-Bolus Administration of Alteplase; NA, not available; INJECT, International Joint Efficacy Comparison of Thrombolytics; SK, streptokinase; rPA, reteplase; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; InTIME, Intravenous rPA for Treatment of Infarcting Myocardium Early; nPA, lanoteplase; ASSENT, Assessment of the Safety and Efficacy of a New Thrombolytic; and TNK-tPA, tenecteplase.

†Day 35 outcomes.

‡In-hospital stroke or ICH.

§In single bolus.

-35-Day outcomes.

P<.05 for equivalence.
lus and 800-U/h infusion for patients weighing ≤67 kg). Tenecteplase was equivalent to tPA in terms of 30-day mortality (6.18% vs 6.15%, P = .006 for equivalence). There were no significant differences in mortality in subgroup analyses, except in those patients treated after 4 hours of chest pain onset, which favored TNK-tPA (7.04% vs 9.19%, P < .02). The incidences of ICH and total stroke were similar in the 2 treatment groups, as was the combined end point of death or nonfatal stroke (7.11% [TNK-tPA] vs 7.04% [tPA]).

Fewer noncerebral bleeding complications (26.43% vs 28.95%, P < .001) were observed and fewer blood transfusions (4.25% vs 5.49%, P < .002) were required in the TNK-tPA group than in the tPA group, and this clinical advantage is probably related to the higher fibrin specificity of TNK-tPA. However, the nearly identical rates of ICH with TNK-tPA and tPA in this trial suggest that, in contrast with noncerebral bleeding complications, greater fibrin specificity may not lower the risk of cerebral bleeding.

**COMMENT**

**Advantages of Bolus Fibrinolysis**

A key advantage of bolus fibrinolysis is ease of administration. A simple bolus administration should shorten the time between onset of pain and treatment (onset-to-needle time) and facilitate prehospital fibrinolysis, both of which can reduce mortality.5-7

The link between rapid time to treatment and improved survival was initially observed in the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico)-1 trial,8 the first AMI megatrial, and was subsequently confirmed by other studies.7,37,38 Improved outcomes in patients treated early has led to the consideration of prehospital administration of fibrinolysis. Several trials of prehospital fibrinolysis have demonstrated reductions in both time to treatment and mortality, especially in areas where the historical time to hospital arrival was prolonged.38-40

Another potential advantage of bolus fibrinolytic therapy compared with more complicated regimens is a reduction in medication errors.80 Although the relationship between fibrinolytic dosing errors and morbidity and mortality is complex,41-42 the use of simpler bolus agents should reduce medication errors, and consequently may potentially improve clinical outcomes.

**Improving Safety**

Intracranial bleeding is the most serious complication of fibrinolytic therapy and its major disadvantage compared with primary percutaneous coronary intervention. Individual risk assessment,43 weight-adjusted regimens, dose reduction of associated antithrombotic therapy,28-30,35,36,44-47 and careful aPTT monitoring35,36,48 may reduce this devastating complication. Reduced doses of heparin have been associated with lower rates of ICH in several trials36,39-40,35,36,44-47 without compromising the angiographic efficacy.27 Unfortunately, the importance of the heparin dose has been underappreciated, and its contribution to the risk of ICH may be as important as the formulation and method of administration of the fibrinolytic agent.49-51

Post hoc analyses of the aPTT values and ICH rates in the InTIME-II trial revealed that 120-KU/kg single-bolus nPA was associated with significantly higher aPTTs at 7 to 12 hours than recombinant tPA,37 perhaps owing to the lesser fibrin specificity of nPA. This in turn was hypothesized as a potential explanation for the higher rate of ICH with nPA in the main InTIME-II trial (with heparin bolus and infusion) but not in the InTIME-IIB registry (heparin infusion only). The notion that higher doses of heparin are associated with increased ICH risk is consistent with observations from an experimental model of spontaneously hypertensive rats receiving recombinant tPA that revealed a potentiation of ICH by heparin.52 The increased risk of ICH in this rat model was dependent on the heparin dose and proportional to the prolongation of the aPTT. Such a mechanism may also explain the increased risk of ICH as aPTT levels increased beyond 70 seconds in GUSTO-I.68

Recently, a meta-analysis99 of phase 3 megatrials involving several different fibrinolytic agents used for AMI suggested that agents administered as a bolus are associated with an excessive risk of ICH.99,101 However, we do not believe that clinically reliable information can be derived from these analyses since this approach disregards the heterogeneity of the pharmacological properties and dosing of the fibrinolytic agents used and fails to consider the dosing and monitoring of concurrent antithrombotic therapy.32,51 Separate and combined analyses demonstrate that neither tPA nor TNK-tPA seems to increase the risk of ICH when compared with accelerated recombinant tPA.42

Because ICH is a rare event, the safety profile of a fibrinolytic regimen cannot be adequately assessed with the number of patients currently studied in phase 2 angiographic trials. Important but rare safety issues may not emerge until about more than 1000 patients have been exposed to a fibrinolytic agent.49,95,96 Therefore, to better define the safety profile of a new reperfusion regimen, a large (approximately 1500 patients per dose group) phase 2 safety trial (eg, ASSENT-I) was performed to more accurately assess the risk of ICH and other rare events. However, to ensure that clinically important differences in ICH are not missed, large phase 3 megatrials are still essential.49,100

**Improving Efficacy**

The thrombus obstructing the infarct-related artery in ST-segment–elevation AMI consists of multiple elements, including platelets, thrombin, and a fibrin mesh. Although fibrinolytic agents target the fibrin mesh component of the thrombus, their use is associated with both heightened thrombin activity and platelet activation.24-57 In response to stimulation by thrombin, platelets express platelet glycoprotein IIb/IIIa complex (GP IIb/IIIa) receptors on their surface, promoting cross-linking by ligands such as fibrinogen, thereby providing a greater surface area for formation of the prothrombinase complex and additional thrombin generation. Other con-
sequences of platelet activation that promote thrombus formation include release of PAI-1 and vasoconstrictor substances. The platelet-rich thrombus is not only more resistant to thrombolysis, but additional platelet activation after initially successful thrombolysis may promote reocclusion. At the microcirculatory level, distal embolization of platelet aggregates formed at the ruptured plaque release vasoconstrictive platelet mediators and may compromise the recovery of perfusion. Thus, more effective platelet inhibition using a GP IIb/IIIa inhibitor is a logical addition to existing reperfusion regimens. The TIMI-14 trial demonstrated that the combination of abciximab with half-dose recombinant tPA was superior to full-dose accelerated recombinant tPA as determined by the speed and extent of angiographic reperfusion and the degree of ST-segment resolution. In the HART trials, the combination of enoxaparin with TNK-tPA is under investigation in 2 clinical studies (ASSENT-3, ASSENT-3-PLUS), the latter in a prehospital setting. Meanwhile, enoxaparin with TNK-tPA and with and without a GP IIb/IIIa antagonist is being evaluated in the ENTIRE/TIMI-23 angiographic study.

Possible novel approaches for developing better bolus fibrinolytic agents are the use of antibodies to target the agent to specific components of the thrombus, the use of less immunogenic polyethylene glycol–derived staphylokinase variants, or new structural tPA variants with altered functional properties. Assessment of the use of these new agents awaits clinical studies.

**ADDENDUM**

Following the final acceptance of this manuscript, results from the GUSTO V trial were published. At 30 days, there was no difference in mortality between half-dose rPA plus abciximab compared with standard-dose rPA alone (P = .43; RR, 0.95; 95% CI, 0.84-1.08), and combination therapy was not inferior (upper 95% CI of RR, <1.10). Rates of ICH were similar (0.62% vs 0.59%, P = .79), but more patients receiving combination therapy experienced noncerebral bleeding (severe bleeding, 1.1% vs 0.5%; spontaneous moderate or severe bleeding, 4.3% vs 1.9%; any bleeding, 24.6% vs 13.7%), with an increased need for transfusion of whole blood (5.0% vs 3.7%) and platelets (1.7% vs 0.8%) (P < .001). Combination therapy reduced the odds of major cardiac complications by 14%, including a 17% reduction in the odds of infarction (P < .001 for both). Post hoc analyses demonstrated reductions in the composite of death or infarction (7.4% vs 8.8%, P = .001) and death, reinfarction, or urgent percutaneous revascularization (16.2% vs 20.6%, P < .001) in patients randomized to combination half-dose rPA plus abciximab.

Whether the reduction in recurrent MIs and urgent PCI will have an impact on longer-term mortality awaits further follow-up.

**REFERENCES**