TNK–Tissue Plasminogen Activator Compared With Front-Loaded Alteplase in Acute Myocardial Infarction

Results of the TIMI 10B Trial

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Background—Bolus thrombolytic therapy is a simplified means of administering thrombolysis that facilitates rapid time to treatment. TNK-tissue plasminogen activator (TNK-tPA) is a highly fibrin-specific single-bolus thrombolytic agent.

Methods and Results—In TIMI 10B, 886 patients with acute ST-elevation myocardial infarction presenting within 12 hours were randomized to receive either a single bolus of 30 or 50 mg TNK-tPA or front-loaded tPA and underwent immediate coronary angiography. The 50-mg dose was discontinued early because of increased intracranial hemorrhage and was replaced by a 40-mg dose, and heparin doses were decreased. TNK-tPA 40 mg and tPA produced similar rates of TIMI grade 3 flow at 90 minutes (62.8% versus 62.7%, respectively, \(P=NS\)); the rate for the 30-mg dose was significantly lower (54.3%, \(P=0.035\)) and was 65.8% for the 50-mg dose (\(P=NS\)). A prespecified analysis of weight-based TNK-tPA dosing using median TIMI frame count demonstrated a dose response (\(P=0.001\)). Similar dose responses were observed for serious bleeding and intracranial hemorrhage, but significantly lower rates were observed for both TNK-tPA and tPA after the heparin doses were lowered and titration of the heparin was started at 6 hours.

Conclusions—TNK-tPA, given as a single 40-mg bolus, achieved rates of TIMI grade 3 flow similar to those of the 90-minute bolus and infusion of tPA. Weight-adjusting TNK-tPA appears to be important in achieving optimal reperfusion; reduced heparin dosing appears to improve safety for both agents. Together with the safety results from the parallel Assessment of the Safety of a New Thrombolytic: TNK-tPA (ASSENT I) trial, an appropriate dose of this single-bolus thrombolytic agent has been identified for phase III testing. (Circulation. 1998;98:2805-2814.)

Key Words: thrombolysis myocardial infarction plasminogen activators

Bolus thrombolysis is a new means of administering thrombolytic agents that has several potential advantages. First, its ease of administration could facilitate more rapid treatment, which has been shown to improve survival in acute myocardial infarction (MI).1-2 Second, bolus thrombolysis may make more feasible the promising strategy of prehospital treatment with thrombolysis.3-4 Finally, the simplicity of dosing may reduce medication errors, which were associated with increased mortality in the Global Use of Streptokinase and Tissue Plasminogen Activator to Open Occluded Arteries (GUSTO)-I trial.5

TNK–tissue plasminogen activator (TNK-tPA) is a genetically engineered variant of tPA. TNK-tPA is similar to wild-type tPA but has amino acid substitutions at 3 sites: a threonine (T) is replaced by asparagine, which adds a glycosylation site to position 103; an asparagine (N) is replaced by a glutamine, thereby removing a glycosylation site from site 117; and 4 amino acids, lysine (K), histidine, and two arginines, are replaced by 4 alanines at the third site. Together, these substitutions lead to a longer half-life of the molecule,6,7 increased fibrin specificity,8 and increased resistance to inhibition by plasminogen activator inhibitor 1 in

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animal models compared with wild-type iPA. The Thrombolysis in Myocardial Infarction (TIMI) 10A trial demonstrated that TNK-iPA has a prolonged half-life, permitting administration as a single bolus; that it was highly fibrin-specific; and that the 30- to 50-mg doses warranted further investigation. The purpose of the TIMI 10B trial was to compare prospectively the angiographic efficacy and safety of several doses of TNK-iPA and iPA to identify an appropriate dose for testing in a large mortality trial.

Methods

Study Population

Patients were screened for enrollment at 76 hospitals (see Appendix) between March 1996 and March 2, 1997. Inclusion criteria for the trial were the presence of ischemic pain lasting ≥30 minutes, associated with ST-segment elevation ≥0.1 mV in ≥2 contiguous leads, and the ability to be randomized within 12 hours of symptom onset. An amendment in September 1996 added an upper age limit of <80 years (see below). Exclusion criteria were prior stroke, transient ischemic attack, or central nervous system structural damage; a history of dementia or major cognitive deficit; a reliably obtained blood pressure >180/110 mm Hg; significant bleeding disorder within 6 months; cardiogenic shock; treatment of acute MI with thrombolytic therapy within the previous 4 days; major surgery, biopsy, or trauma (including head trauma associated with the presenting MI) within 3 months; prolonged (>2 minutes) cardiopulmonary resuscitation within 2 weeks; recent noncompressible vascular puncture; previous coronary artery bypass surgery; inability to undergo cardiac catheterization; therapeutic oral anticoagulation; pregnancy, current lactation, or women of childbearing potential not using adequate birth control; allergy to heparin or history of multiple allergies; current cocaine abuse; other serious illness; current participation in another experimental drug or device protocol; previous treatment with TNK-iPA; inability to follow the protocol; or any other condition that the investigator felt would pose a significant hazard to the patient if the investigational therapy were initiated. The use of abciximab within the preceding 96 hours was added to the amendment.

Randomization

Patients were randomized in a central, computerized, telephone randomization system (Leuven Coordinating Center, Leuven, Belgium). Initially, patients were randomized to receive either TNK-iPA 30 or 50 mg or front-loaded iPA in a 1:1:1 ratio. The 50-mg dose of TNK-iPA was suspended (see below) on August 22, 1996, leaving randomization between 30 mg versus iPA. After approval of a protocol amendment at each hospital, a 40-mg dose of TNK-iPA was added, with a randomization to 40 mg TNK-iPA, 30 mg TNK-iPA, or iPA in a 4:1:1 ratio.

Treatment Regimen

Patients were randomized to receive either a single bolus of TNK-iPA (Genentech) administered over 5 to 10 seconds or iPA (Activase, Genentech) given as a 15-mg bolus, a 0.75-mg/kg (up to 50 mg) infusion over 30 minutes, followed by 0.50-mg/kg (up to 35 mg) infusion over 60 minutes. All patients received 150 to 325 mg of oral or intravenous aspirin daily. Lipid-lowering medication was begun within 60 minutes after the start of study drug at selected centers. For patients weighing ≤67 kg, a 6400 U bolus and 1440 U · kg⁻¹ · h⁻¹ infusion (eg, 6400 U bolus and 1440 U · kg⁻¹ · h⁻¹ infusion for an 80-kg patient). In addition, patients were noted to have undergone rescue angioplasty more often (50% versus 26% in the final cohort, P = 0.04) and consequently received more heparin (see Results). Because of the previously observed interaction of heparin, thrombolytic therapy, and intracranial hemorrhage in TIMI 9A/B, a protocol amendment was instituted that mandated the following doses of heparin: for patients weighing >67 kg, a 5000-U bolus and 1000 U/h infusion, and for patients weighing ≤67 kg, a 4000-U bolus and 800 U/h infusion. In addition, adjustment of the heparin dose according to the nomogram was mandated to begin with the 6-hour aPTT. The amendment also specified that no additional heparin be administered for diagnostic catheterization if the patient was already receiving intravenous heparin. If rescue angioplasty was performed, the recommended target activated clotting time was 300 seconds, and to achieve this activated clotting time, boluses of heparin were to be administered in increments of ±2500 U, so as to reduce the likelihood of overshooting the target. Finally, the Data and Safety Monitoring Board made 2 other recommendations based on the potential for increased risk (not observed in the trial): an upper age limit of 80 years was added, and the use of abciximab was proscribed in the first 96 hours after randomization.

Heparin Dosing

Heparin dosing was initially specified to be at the discretion of the treating physician. The protocol did, however, offer a guideline for heparin dosing: a 5000-U bolus and an initial intravenous infusion of 1000 U/h (for patients weighing >67 kg) or 800 U/h (for patients ≤67 kg) for 48 to 72 hours. Heparin was to be given before or as soon as possible after administration of thrombolytics. Heparin was titrated to an activated partial thromboplastin time (aPTT) of 55 to 80 seconds, and a suggested heparin nomogram was provided. aPTT was measured at 6, 12, and 24 hours after the start of thrombolysis and daily while the patient was on heparin, as well as 6 hours after a change in dose.

Early in the trial, it was noted that the heparin doses in some patients who experienced intracranial hemorrhage were higher than the suggested dose; for example, patients had received a weight-adjusted regimen of 80 U/kg bolus and 18 U · kg⁻¹ · h⁻¹ infusion (eg, 6400 U bolus and 1440 U · kg⁻¹ · h⁻¹ infusion for an 80-kg patient). In addition, patients were noted to have undergone rescue angioplasty more often (50% versus 26% in the final cohort, P = 0.04) and consequently received more heparin (see Results). Because of the previously observed interaction of heparin, thrombolytic therapy, and intracranial hemorrhage in TIMI 9A/B, a protocol amendment was instituted that mandated the following doses of heparin: for patients weighing >67 kg, a 5000-U bolus and 1000 U/h infusion, and for patients weighing ≤67 kg, a 4000-U bolus and 800 U/h infusion. In addition, adjustment of the heparin dose according to the nomogram was mandated to begin with the 6-hour aPTT. The amendment also specified that no additional heparin be administered for diagnostic catheterization if the patient was already receiving intravenous heparin. If rescue angioplasty was performed, the recommended target activated clotting time was 300 seconds, and to achieve this activated clotting time, boluses of heparin were to be administered in increments of ±2500 U, so as to reduce the likelihood of overshooting the target. Finally, the Data and Safety Monitoring Board made 2 other recommendations based on the potential for increased risk (not observed in the trial): an upper age limit of 80 years was added, and the use of abciximab was proscribed in the first 96 hours after randomization.

Protocol

Patients underwent coronary angiography at 90 minutes and, when feasible, at 60 and 75 minutes. Percutaneous transluminal coronary angioplasty (PTCA) with a Food and Drug Administration (FDA)–approved device was performed at the discretion of the treating physician after the 90-minute angiogram was obtained. Cardiac enzymes were obtained at baseline and 8 and 16 hours and for symptoms suggestive of recurrent MI. Samples for coagulation/fibrinolysis parameters (eg, fibrinogen, plasminogen) were obtained at baseline and 1, 3, and 6 hours after start of study drug for measurement in a core laboratory. Blood samples for pharmacokinetics were obtained at baseline and 2, 30, 60, 90, 120, 180, and 360 minutes after the start of study drug at selected centers. For patients who received TNK-iPA, a blood sample was obtained at baseline and at 30 days to evaluate for the formation of TNK-iPA antibodies. Patient follow-up was obtained at 30 days. The study protocol and amendment were reviewed and approved by each hospital’s Institutional Review Board, and written informed consent was obtained from each patient before enrollment.

Patient Cohorts

A total of 886 patients were randomized into the trial. Six patients did not give informed consent, and thus their data were not included in the database. Two cohorts were prespecified for analyses: the safety cohort comprised patients who received any amount of study drug (856 patients), and the “efficacy-eligible” cohort comprised patients who received study drug and had an evaluable 90-minute angiogram (837 patients). The 24 patients not treated with study drug were evenly distributed among the 4 treatment groups; 11 received other thrombolytic therapy, 2 underwent primary angioplasty, 9 did not give informed consent, and thus their data were not included in the database. A total of 886 patients were randomized into the trial. Six patients did not give informed consent, and thus their data were not included in the database. Two cohorts were prespecified for analyses: the safety cohort comprised patients who received any amount of study drug (856 patients), and the “efficacy-eligible” cohort comprised patients who received study drug and had an evaluable 90-minute angiogram (837 patients). The 24 patients not treated with study drug were evenly distributed among the 4 treatment groups; 11 received other thrombolytic therapy, 2 underwent primary angioplasty, 9 did not give informed consent, and thus their data were not included in the database.

Study End Points

The primary end point of the trial was the rate of TIMI grade 3 flow at 90 minutes. Secondary end points included TIMI grade 3 flow at 60 and 75 minutes, TIMI grade 2 or 3 flow and TIMI frame count at all time points, pharmacokinetics, coagulation parameters, recur-
rent MI, and serious bleeding. All angiograms were analyzed by the angiographic core laboratory, which was blinded to treatment assignment. Pharmacokinetics of TNK-tPA were characterized by standard methods. Coagulation assays were collected and assayed as in previous TIMI trials. Plasmin-α2-antiplasmin complexes were assayed with an ELISA assay. Antibodies to TNK-tPA were analyzed as in the TIMI 10A trial. Serious bleeding was defined according to FDA guidelines as bleeding that was either fatal or life-threatening, required or prolonged hospitalization, resulted in significant disability, or necessitated medical or surgical intervention to preclude permanent impairment of a body function or structure. Clinical end points were defined as in previous TIMI trials.

Statistical Considerations

The primary end point and other categorical variables were analyzed by the Pearson χ2 test. Dose response across TNK-tPA doses was calculated by the Mantel-Haenszel test. Continuous variables were compared by the Wilcoxon rank-sum test. Confidence intervals were produced by the exact binomial method. Pharmacokinetic data were analyzed by use of a compartmental model for TNK-tPA and a noncompartmental model for tPA. The sample size was determined by use of the Fleiss sample-size algorithm for proportions and rates of TIMI grade 3 flow as observed in the GUSTO I trial. It was calculated that 150 evaluable patients per group were necessary to provide 80% power of detecting a TIMI grade 3 flow rate of ≥38% or ≥69% in the TNK-tPA groups compared with the tPA group with a 5% significance level. No adjustments were made for multiple comparisons.

Results

Patient Population

The mean age of the 837 patients in the efficacy-evaluable cohort was 59.6 years, 76.0% were male, 38.7% presented with anterior MI, 21.5% weighed ≤67 kg, and 47.2% were current smokers at the time of randomization (Table 1). The median time from symptom onset to treatment was 2.9 hours (25th and 75th percentiles, 2.0 and 4.2 hours). There were no significant differences in the baseline characteristics of the treatment groups.

Angiographic Results

The 40-mg dose of TNK-tPA produced a rate of TIMI grade 3 flow at 90 minutes after the start of thrombolysis (62.8%; 95% CI, 54.5% to 70.6%) similar to that of tPA (62.7%; 95% CI, 57.1% to 68.1%; P = NS) (Figure 1). The 30-mg dose of TNK-tPA had a significantly lower rate of TIMI grade 3 flow than tPA (54.3%, P = 0.035), whereas the 50-mg dose achieved 65.8% TIMI grade 3 flow (P = 0.030 for trend across TNK-tPA doses). TIMI grade 2 or 3 flow (patency) showed a similar increasing trend of 81.7% for tPA versus 76.8%, 79.1%, and 88.2% for the 30-, 40-, and 50-mg doses of TNK-tPA, respectively.

![Figure 1. TIMI flow grade at 60 and 90 minutes by dose group.](http://circ.ahajournals.org/)

*P = 0.015 vs tPA, P = 0.05 vs TNK-tPA 50 mg. No other differences between groups were statistically significant.*
40-, and 50-mg doses of TNK-tPA, respectively \((P \text{ for trend}=0.044)\). At 60 minutes, there were no significant differences in the rates of TIMI grade 3 flow or patency (Figure 1).

The rates of TIMI grade 3 flow or TIMI grade 2 or 3 flow combined were similar for patients treated within 6 hours from symptom onset versus ≥6 hours in each treatment arm. Right coronary arteries displayed higher rates of TIMI grade 3 flow, 68.9%, compared with left anterior descending (48.5%) or left circumflex infarct-related arteries (57.4%) in each of the treatment groups (overall \(P<0.001\)). However, TIMI grade 2 or 3 flow was similar among the 3 arteries in each treatment group (79.3%, 83.7%, and 73.0%, respectively, \(P=\text{NS}\)). No differences in TIMI flow grades were observed when patients enrolled before versus after implementation of the protocol amendment with lower heparin dosing were compared.

### TIMI Frame Count

The TIMI frame count results by treatment group are shown in Table 2. The percentages of patients with corrected TIMI frame count <40 (previously noted to be a useful cut point to define TIMI grade 3 flow) quantitatively corroborated the lower rate of full reperfusion with TNK-tPA 30 mg compared with tPA. There were no differences between TNK-tPA and tPA in the rate of “normal” flow, as defined by a corrected TIMI frame count <28 frames.\(^4\) The median TIMI frame count at 60 minutes was slightly, but not significantly, lower for TNK-tPA 40 mg than for tPA (34 versus 40 frames, \(P=0.33\)).

#### Weight-Based Dosing Analysis

For all patients who received TNK-tPA, a “weight-corrected” dose was calculated as the dose of TNK-tPA in mg divided by the patient’s weight. As shown in Figure 2, the rate of TIMI grade 3 flow was 62% to 63% for doses of 0.5 mg/kg and higher but was 51% to 54% at doses lower than this (\(P=0.028\) across quintiles). Further analysis into covariates of degree of perfusion achieved revealed that when dose/weight was stratified into tertiles, the median corrected TIMI frame count was significantly lower (ie, faster flow) in patients who received the higher weight-corrected dose (Figure 3).

#### Pharmacokinetics

Among the 159 patients with pharmacokinetic samples, the plasma clearance of TNK-tPA ranged from 98.4±42 to

![Figure 2](image_url)  
**Figure 2.** TIMI flow grade at 90 minutes among TNK-tPA–treated patients, with dose expressed in mg TNK-tPA per patient body weight. Data shown are quintiles of weight-corrected dose of TNK-tPA. \(P\) for trend=0.028 across quintiles.

![Figure 3](image_url)  
**Figure 3.** Cumulative distribution and median corrected TIMI frame counts (CTFC) at 90 minutes among TNK-tPA–treated patients, according to tertile of weight-based dose, expressed as mg TNK-tPA per patient body weight.
119.0±49 mL/min across the 30-, 40-, and 50-mg doses, compared with 453±170 mL/min for tPA. The corresponding plasma elimination half-life of TNK-tPA ranged from 5.5±5.5 to 21.5±8.2 minutes. The corresponding half-life for tPA is 3.5±1.4 minutes.22 Figure 4 shows the TNK-tPA plasma levels over time for the 3 doses of TNK-tPA and tPA. As shown, after a single bolus of TNK-tPA, the plasma concentration was initially higher, but the area under the curve approximates that of tPA given as a bolus and 90-minute infusion.

Coagulation Assays

The effects on systemic coagulation/fibrinolytic factors over the first 6 hours for TNK-tPA and tPA are shown in Figure 5. There was a 5% to 10% drop in fibrinogen over the first 6 hours at the 30- to 50-mg doses of TNK-tPA, compared with a 40% drop after tPA. The fall in plasminogen was only 10% to 15% after TNK-tPA, compared with a 50% drop in plasminogen for tPA. The consumption of α2-antiplasmin, the fluid-phase inhibitor of plasmin, and a consequent increase in plasmin–α2-antiplasmin complexes was 4 to 5 times greater with tPA than with TNK-tPA at any of the 3 doses.

Safety Results

During the initial phase of the trial, ie, before the reduction of heparin dosage described above, there were 3 intracranial hemorrhages among the 78 patients (3.8%; 95% CI, 0.8% to 10.8%) treated with the 50-mg TNK-tPA dose. Balancing these results was a favorable mortality rate for TNK-tPA 50 mg, 3.8%, and the resultant net clinical benefit (death or nonfatal intracranial hemorrhage) was 5.1%. (Table 3). The corresponding rate for tPA in the GUSTO-I trial was 6.6%. Nonetheless, on the recommendation of the Data and Safety Monitoring Board, this arm was suspended and replaced by 40 mg with a protocol amendment. At the same time, the doses of heparin were reduced, as noted above.

Overall, the rates of intracranial hemorrhage were 1.0% for 30 mg TNK-tPA, 1.9% for 40 mg, and 1.9% for tPA (Table 3). Serious bleeding followed a similar “dose response” occurring in 1.9%, 5.2%, and 11.5% (P<0.001) of patients treated with the 30-, 40-, and 50-mg doses of TNK-tPA, compared with 8.5% for tPA (Table 4). Analyses of serious bleeding and intracranial hemorrhage with weight-corrected doses of TNK-tPA are shown in Figure 6. Significantly more serious bleeding (P=0.001) and intra-
cranial hemorrhages \((P=0.033)\) were observed at the highest weight-corrected dose \((\geq 0.55 \text{mg/kg})\) (Figure 6A). Even after the protocol amendment to use lower doses of heparin, significantly higher intracranial hemorrhage \((P=0.014)\) and serious bleeding \((P=0.002)\) remained at the higher weight-corrected dose (Figure 6B).

### Effect of Heparin Dosing

The protocol amendment reduced the dose of heparin received: The total dose received was reduced from an average of 13 258 to 12 326 U over the first 6 hours \((P=0.01)\) and from 18 784 to 17 898 U over the first 12 hours \((P=0.04)\). The doses of heparin received for patients undergoing rescue PTCA were higher, 15 957 versus 11 644 U without PTCA, but each group had a reduction in the dose of heparin received, to 14 613 and 10 962 U in patients with and without rescue PTCA, respectively. The median aPTT values at 6 and 12 hours tended to be lower after the protocol amendment, 100 versus 94 seconds at 6 hours \((P=0.12)\) and 67 versus 64 seconds at 12 hours \((P=0.15)\) for the group as a whole.

The rates of both intracranial hemorrhage and serious bleeding were lower after the protocol amendment: For TNK-tPA 30 mg, intracranial hemorrhage fell from 3 of 134 patients (2.2%) to 0 of 174 (0%) \((P=0.047)\), and for tPA from 4 of 143 patients (2.8%) to 2 of 173 (1.2%) \((P=0.29)\) (overall combined \(P=0.04)\). Similar observations and statistically significant reductions in intracranial hemorrhage were observed in overall TNK-tPA experience when the TIMI 10B and ASSENT I trials were combined.\(^24\) Severe bleeding also was reduced with the lower heparin dosing: Severe bleeding fell from 3.0% to 0% \((P=0.02)\) for 30 mg TNK-tPA and from 8.4% to 2.3% \((P=0.01)\) for tPA (combined \(P=0.001)\).

### Clinical Outcome

Mortality at 30 days was 4.9% overall, without significant differences between TNK-tPA doses and tPA (Table 3).

### TABLE 3. Strokes, Mortality, and Clinical Events to 30 Days
(Safety-Evaluable Cohort)

<table>
<thead>
<tr>
<th></th>
<th>TNK-tPA 30 mg, %</th>
<th>TNK-tPA 40 mg, %</th>
<th>TNK-tPA 50 mg, %</th>
<th>tPA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>308</td>
<td>154</td>
<td>78</td>
<td>316</td>
</tr>
<tr>
<td>ICH (95% CI)</td>
<td>1.0 (0.2–2.8)</td>
<td>1.9 (0.4–5.6)</td>
<td>3.8 (0.8–10.8)</td>
<td>1.9 (0.7–4.1)</td>
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<tr>
<td>Total stroke</td>
<td>1.9</td>
<td>2.6</td>
<td>5.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Death</td>
<td>3.6</td>
<td>6.5</td>
<td>3.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Death or nonfatal</td>
<td>4.2 (2.3–7.1)</td>
<td>6.5 (3.2–11.6)</td>
<td>5.1 (1.4–12.6)</td>
<td>6.6</td>
</tr>
<tr>
<td>ICH (95% CI)</td>
<td>3.9 (2.0–6.7)</td>
<td>6.5 (3.2–11.6)</td>
<td>5.1 (1.4–12.6)</td>
<td>6.0</td>
</tr>
<tr>
<td>Disabling stroke (95% CI)</td>
<td>5.2 (2.3–7.1)</td>
<td>6.5 (3.2–11.6)</td>
<td>5.1 (1.4–12.6)</td>
<td>6.0</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>5.2</td>
<td>6.5</td>
<td>2.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
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<td>3.2</td>
<td>1.3</td>
<td>4.1</td>
</tr>
<tr>
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<td>5.5</td>
<td>4.5</td>
<td>1.3</td>
<td>4.1</td>
</tr>
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</table>

ICH indicates intracranial hemorrhage.

### TABLE 4. Serious Bleeding Events to 30 Days
(Safety-Evaluable Cohort)

<table>
<thead>
<tr>
<th></th>
<th>TNK-tPA 30 mg, %</th>
<th>TNK-tPA 40 mg, %</th>
<th>TNK-tPA 50 mg, %</th>
<th>tPA, %</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>308</td>
<td>154</td>
<td>78</td>
<td>316</td>
</tr>
<tr>
<td>Serious bleed</td>
<td>1.9*</td>
<td>5.2</td>
<td>11.5†</td>
<td>8.5</td>
</tr>
<tr>
<td>Severe bleed</td>
<td>1.3‡</td>
<td>3.2</td>
<td>9.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Moderate bleed</td>
<td>0.7§</td>
<td>1.9</td>
<td>5.1</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Severity categories of bleeding events not mutually exclusive.

*\(P<0.001\) across TNK-tPA doses, \(P=0.001\) vs tPA; †\(P=0.001\) vs TNK-tPA 30 mg, \(P=0.055\) vs TNK-tPA 40 mg; ‡\(P=0.002\) across TNK-tPA doses, \(P=0.01\) vs tPA; §\(P=0.02\) across TNK-tPA doses, \(P=0.005\) vs tPA.

Figure 6. Rates of intracranial hemorrhage and serious bleeding (including intracranial hemorrhage) among TNK-tPA–treated patients, according to quintile of weight-based dose, expressed as mg TNK-tPA per patient body weight in all patients and in patients enrolled after protocol amendment with reduced heparin dosing. \(P\) values shown evaluate rates of bleeding across 5 weight-corrected dose quintiles.
Reinfarction was observed in 5.4% of patients overall, without differences between TNK-tPA or tPA (Table 3). New-onset pulmonary edema and cardiogenic shock also were similar between TNK-tPA and tPA. Antibodies to TNK-tPA were detected in 1 of 364 patients (0.3%) at 30 days, although no antibodies were detected in this patient at 90 days.

Discussion

In this randomized, dose-ranging angiographic trial of TNK-tPA, we observed a clear dose-response in the achievement of reperfusion at 90 minutes by TNK-tPA given as a single bolus (Figure 1). Notably, a bolus of 40 mg TNK-tPA achieved 90-minute TIMI grade 3 flow similar to that of the bolus and 90-minute infusion of tPA. TNK-tPA was observed to have a prolonged half-life (Figure 4) and to be very fibrin-specific compared with tPA (Figure 5), features that help explain its efficacy when administered as a 5- to 10-second bolus, and the absence of induction of the “plasminogen steal” phenomenon.25

Weight adjustment of TNK-tPA appears to be important in achieving optimal reperfusion, assessed by both TIMI flow grade and the TIMI frame count (Figures 2 and 3). Serious bleeding showed a similar increasing trend at the highest range of the weight-corrected doses (>0.55 mg/kg) (Figure 6, top), even among patients with the lower-dose heparin regimen (Figure 6, bottom). Together with the safety results from the parallel ASSENT I trial (F.V.d.W., unpublished results), a “stepped” weight-adjusted dose of 0.5 mg/kg TNK-tPA was selected for phase III testing.

Phase II Dose-Ranging Trial Design

For phase II dose-ranging, the TIMI Investigators collaborated with the Leuven Coordinating Center to conduct 2 trials simultaneously to evaluate 2 important aspects of a new thrombolytic agent: To study efficacy, an angiographic study (TIMI 10B) was conducted, and for safety, focused on intracranial hemorrhage, ASSENT I was carried out. This parallel design is focused on providing adequate sample size to assess each of these 2 critical features. Thus, in the angiographic trial, 150 to 300 patients per dose provide adequate power to determine relative efficacy compared with the control arm. However, because intracranial hemorrhage is a rare event, the safety profile cannot be assessed adequately by reliance on such a sample size, as learned in previous trials (TIMI 5 and 6, GUSTO II Pilot).18,26,27 Experience from previous large trials (TIMI 2, TIMI 9A, GUSTO IIA) indicates that safety problems often emerge after ~750 to 1000 patients.10,11,28 Therefore, a new type of phase II program was used for TNK-tPA to have both an angiographic trial studying several hundred patients per dose and, in parallel, to evaluate safety in 1500 patients per dose group. In this fashion, the angiographic efficacy and safety profile could be defined better before we embarked on a large phase III trial.

Clinical Significance of Fibrin Specificity

TNK-tPA was designed and proved to be very fibrin-specific compared with tPA (Figure 5), which itself is more fibrin-specific than streptokinase.29 However, despite the hope that fibrin specificity would allow selective clot lysis of a coronary thrombus and not cause intracerebral hemorrhage, this trial documents that marked fibrin specificity does not prevent intracranial hemorrhage, and the incidence of intracranial hemorrhage was, in fact, similar for TNK-tPA and tPA. This is consistent with the hypothesis that intracranial hemorrhage is caused by thrombolytic-induced lysis of microthrombi in diseased cerebral vessels. Further support for this hypothesis is that both elderly patients and those with established cerebrovascular disease are at 5 to 10 times increased risk of intracranial hemorrhage, as documented in the TIMI 2 trial30 and other trials.31,32 Alternatively, direct effects of plasmin (generated by all plasminogen activators) on the cerebral vasculature may induce intracranial hemorrhage. Similarly, the comparability in rates of TIMI grade 3 flow and all other measures of reperfusion between TNK-tPA, a very fibrin-specific agent, and tPA, a moderately fibrin-specific agent, suggests that further increases in fibrin specificity above that of tPA do not improve thrombolytic efficacy.

Adjunctive Heparin Dosing

We observed an improvement in the safety profiles of both TNK-tPA and tPA after the protocol amendment, which lowered the doses of heparin used initially and with rescue PTCAs. The overall rates of intracranial hemorrhage were higher in this trial, and in other angiographic trials,33 than in nonangiographic trials.23 Because additional heparin is usually given for cardiac catheterization, this observation is consistent with the hypothesis that adjunctive heparin increases the risk of intracranial hemorrhage. In addition, when the initial doses of heparin (and hirudin) were reduced slightly from the TIMI 9A and GUSTO IIA trials to the TIMI 9B and GUSTO IIB trials, the rates of intracranial and major hemorrhage fell by >50%.11,12,28,34

In this trial, we lowered the initial dose of heparin to slightly less than the conventional dose of 5000 U bolus and 1000 U/h infusion. This change affected primarily the lower-body-weight patients, who are at increased risk of intracranial hemorrhage and major bleeding.11,32,35 The reduction in heparin dosing in the trial led to a lower dose of heparin received and a reduction in bleeding complications (without compromising angiographic efficacy). The adjustment of heparin dosing according to the aPTT result was also begun at 6 hours in the protocol amendment, which may have contributed to the overall safety, although it should be noted that the majority of intracranial hemorrhages occur in the first 6 to 10 hours,11,12,28,34 thus implicating the initial heparin dose as a very important target for reducing bleeding complications. Thus, as observed with platelet glycoprotein IIb/IIIa inhibitors,36,37 use of lower doses of heparin appears to improve the safety profile without compromising the efficacy of tPA and TNK-tPA. Our data suggest that lower doses of heparin, like those used in this trial, should be used with fibrin-specific thrombolytic agents. Based on these and other data,38 we have proposed a revision to the heparin dosing recommendation in the ACC/AHA Acute MI Guidelines:9: a weight-adjusted regimen of 70 U/kg bolus, with a
5000-U maximum, and a 15-U \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{ infusion, with a 1000-U \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{ maximum.}}

Conclusions

TNK-tPA is a promising new single-bolus thrombolytic agent. At a 40-mg dose, the rate of TIMI grade 3 flow was comparable to that with the 90-minute regimen of tPA. Weight-adjustment of the dose appears to be important in optimizing reperfusion and safety. There appeared to be an important influence of the adjunctive heparin dosing on bleeding complications for both TNK-tPA and tPA, with a favorable safety (and efficacy) profile when using a modestly reduced heparin dose. Together with the safety results from the parallel ASSENT I trial, the efficacy and safety profile of an appropriate dose of TNK-tPA have been established, and this agent is currently being compared with tPA in a large mortality trial, ASSENT II, designed to show equivalence between the 2 drugs.

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Appendix


Myocardial Infarction Triage and Intervention (MITI) Coordinating Center: University of Washington, Seattle: W.D. Weaver, J.S. Martin, C. Schaff.


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