Survival Outcomes 1 Year After Reperfusion Therapy With Either Alteplase or Reteplase for Acute Myocardial Infarction

Results From the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) III Trial

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Background—New recombinant plasminogen activators have been developed to simulate the fibrinolytic action of the physiological serine protease tissue plasminogen activator (alteplase, t-PA), and have prolonged half-life features permitting bolus administration. One such activator, reteplase (r-PA), was compared with t-PA in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-III Trial.

Methods and Results—At 1-year follow-up, survival status was ascertained in 97.4% of the 15 059 patients enrolled in the GUSTO-III trial. At 1 year, the mortality rate for the t-PA–assigned group was 11.06%, and for r-PA it was 11.20% (P=0.77). The absolute mortality difference of 0.14% has 95% CIs of −1.21% to 0.93%. There were no significant differences in outcome by intention-to-treat for the 2 different plasminogen activators in the prespecified groups (age, infarct location, time-to-treatment). The absolute difference in mortality rates between t-PA and r-PA progressively narrowed over the predetermined observation times after random assignment; it was 0.31% at 24 hours, 0.26% at 7 days, 0.23% at 30 days, and 0.14% at 1 year. Of note, mortality rate in the trial between 30 days and 1 year was 4.02% and did not differ between the treatment groups. However, this mortality rate was substantially greater than in GUSTO-I, in which mortality rate for t-PA versus streptokinase between 30 days and 1 year was 2.97% (heart rate 1.36, 95% CI 1.23, 1.50, P<0.001).

Conclusions—The r-PA and t-PA strategies yielded similar survival outcomes after 30 days in this trial. The increase in mortality rate during extended follow-up compared with previous trials may reflect higher-risk patients and highlights the need for improved secondary prevention strategies. (Circulation. 2000;102:1761-1765.)

Key Words: reperfusion • myocardial infarction • plasminogen activators

Fibrinolytic therapy for acute myocardial infarction (MI) is the most intensively studied medical intervention, with >200 000 patients enrolled in worldwide trials. After validation that streptokinase and tissue plasminogen activator (alteplase, t-PA) improved survival as compared with placebo,1-3 the stage was set for the development of improved fibrinolytic strategies. A large trial that we previously conducted showed that t-PA given in an accelerated infusion over a period of 90 minutes provided improved infarct vessel patency and survival compared with streptokinase.4 Alteplase t-PA is a serine protease and the principal physiological plasminogen activator; it has been the subject of extensive bioengineering efforts to create molecular mutants with improved features. The first of these mutants to undergo

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comprehensive clinical evaluation was reteplase (r-PA), which lacks the finger, kringle-1, and epidermal growth factor domains of t-PA. These properties create a molecule with a longer half-life, and one with a lesser extent of fibrin specificity. The primary end point of the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-III Trial was superiority of r-PA compared with t-PA at 30 days. Compared with accelerated t-PA in the GUSTO III trial at 30-day follow-up, there was a 0.23% absolute difference of mortality rate favoring t-PA. This difference was not statistically significant (P=0.54). Furthermore, there is debate as to what constitutes criteria for equivalency of agents in fibrinolytic trials and clinical trials in general. One further means of providing illumination on the relative performance of t-PA compared with r-PA is to extend the follow-up interval, as was prospectively planned in the GUSTO-III trial. In this report, we present the findings of survival outcomes at 1 year after enrollment and compare the outcomes for survivors at 30 days in the present trial with the large cohort in the GUSTO-I trial.

Methods
The protocol and clinical entry criteria are summarized in the primary report. Briefly, patients were eligible if they had >30 minutes of chest discomfort but <6 hours from symptom onset, accompanied by electrocardiographic ST-segment elevation or new bundle-branch block. The upper limit exclusion for blood pressure at any time after hospital arrival was 200 mm Hg systolic and 110 mg Hg diastolic. A 2:1 randomization for r-PA (Centocor subsidiary of Johnson and Johnson) or t-PA (Genentech) was used, with the assignment made by telephone. No masking of the study drug was performed. The dose of t-PA was 100 mg given over a period of 90 minutes and for r-PA 20 MU given as 2 boluses of 10 MU, each 30 minutes apart.

One-year follow-up survival was determined in 14,674 patients, which represents 97.4% of the entire cohort. The completeness was balanced in the treatment arms: 97.3% for t-PA, 97.5% for r-PA. Follow-up after 365 days was censored at 365 days.

Statistical Analysis
The overall trial tested the superiority of r-PA compared with t-PA, with 85% power to detect a 20% reduction of mortality rate at 30 days. Mortality rate during the 365-day observation period was characterized by Kaplan-Meier curves. Odds ratios and 95% CIs were used to compare the death rates between the treatment groups and among subgroups. The protocol specified comparisons for the key subgroups including age, infarct location, time to treatment, and geographic origin from within or outside the United States. All tests of significance were 2-tailed, and treatment comparisons were according to the intention-to-treat principle.

Results
The demographics for the patients with 1-year follow-up, along with those in whom follow-up was not obtained, are provided in Tables 1 and 2, respectively. Baseline characteristics for the patients entered into the trial but not available for 1-year follow-up did not differ significantly as compared with the majority (97%) of patients who completed follow-up. The Kaplan-Meier event rates are summarized in Figure 1. At 1 year, the mortality rate for t-PA was 11.06% and for the r-PA group 11.20% (P=0.77). For the 4 major subgroups of age, site of infarction, time to treatment, or geographic origin, there were no significant differences in treatment. As shown in Figure 2, patients receiving either treatment who were <75 years old had a similar mortality rate (8.16% versus 8.08%, respectively, P=0.88), as did those >75 years of age (29.6% and 30.9%, respectively, P=0.46).

For infarct location, patients with inferior MI had mortality rates of 7.95% and 7.92% for t-PA and r-PA, respectively (P=0.95). The death rate among patients with anterior MI was also similar: 14.18% and 14.39%, respectively (P=0.74).

The time-to-treatment subgroup analysis did not demonstrate a significant treatment interaction. For treatment 0 to 2 hours, the mortality rates were 8.33% and 8.94% (P=0.25). For 2 to 4 hours, the rates were 11.05% and 11.37% (P=0.67) and for >4 hours 12.70% versus 14.34% (P=0.18, Figure 3). By Cox proportional hazards, time to treatment was highly significant for predicting mortality rates (P=0.001), but there was no significance for the interaction of time to treatment and thrombolytic assignment (P=0.25). The results are at some variance with the 30-day data, which showed a significant time-to-treatment and drug interaction. However, the trend of the maximal difference between the drugs (if a difference does exist) for patients treated beyond 4 hours is consistent (Figure 3).

For patients within the United States, the mortality rates were 10.15% and 9.59% for t-PA and r-PA, respectively (P=0.57). Outside the United States, the mortality rates were 11.46% and 11.96%, respectively (P=0.44). The pattern of survival after 30 days is shown in Figure 4. The mortality

<table>
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<th>Characteristic</th>
<th>Reteplase (N=9885)</th>
<th>Alteplase (N=4789)</th>
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<tr>
<td>Age, y</td>
<td>61.3 (52.9, 71.4)</td>
<td>63.1 (53.2, 71.8)</td>
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<td>Age &gt;75 y, %</td>
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<td>13.7</td>
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<tr>
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<td>27.7</td>
<td>27.3</td>
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<td>Hypercholesterolemia, %</td>
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<td>3.9</td>
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<td>134 (119, 150)</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<td>80 (70, 90)</td>
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<tr>
<td>Heart rate, bpm</td>
<td>73 (62, 86)</td>
<td>73 (62, 86)</td>
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<td>Location of infarction, %</td>
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<tr>
<td>Anterior</td>
<td>47.2</td>
<td>47.4</td>
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<td>Inferior</td>
<td>48.8</td>
<td>48.4</td>
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<tr>
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<td>Killip class, %</td>
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<tr>
<td>I</td>
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<td>85.4</td>
</tr>
<tr>
<td>II</td>
<td>12.2</td>
<td>12.8</td>
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<tr>
<td>III</td>
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</tr>
<tr>
<td>IV</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td>Symptom onset to treatment, h</td>
<td>2.7 (1.8, 3.8)</td>
<td>2.7 (1.9, 3.9)</td>
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</table>
curves do not separate but in fact fully converge (and cross) at several points. The 1-year mortality rates for survivors at 30 days were 4.07% for t-PA and 3.99% for r-PA (P = 0.81).

The death rate between 30 and 365 days in GUSTO-III is markedly disparate from GUSTO-I (Figure 5). The mortality rate after 30 days in GUSTO-I was 2.97%, whereas in the current trial it was 4.02% (P < 0.001). In GUSTO-I, the rate did not vary by treatment assignment: accelerated t-PA (n = 9670), 2.86%; streptokinase and intravenous heparin (n = 9579), 2.92%; t-PA and streptokinase (n = 9575), 3.04%; and streptokinase with subcutaneous heparin (n = 9057), 3.07%. As previously published with the primary GUSTO-III findings, the patients in the current trial were older, proportionately aged >75 years, 13.6% versus 10.5%, more likely to be female (27.4% versus 25.2%), more likely to have anterior MI (47.5% versus 39.1%), and had higher blood pressure on admission (median systolic blood pressure of 135 mm Hg versus 130 mm Hg).5

**Discussion**

The extended follow-up of the current trial provides several insights about reperfusion therapy, in general, and the direct comparison of t-PA versus r-PA, in particular. Overall, the results indicate that there is consistency of the findings at 30 days, which is quite similar to the extended follow-up reports of 10 years from the Gruppo Italiano Streptochiania, Suravivenza Infarto (GISSI-1) and the International Studies of Infarct Survival (ISIS-2).7,8 In these two trials with a decade of follow-up, there was remarkable durability of the initial findings documenting an advantage of streptokinase over conventional or placebo therapy for acute MI. This represents an outgrowth of near “parallelism” of the follow-up event curves after the primary end point was determined.

In the present trial there was indeed durability of the early findings, but the criteria of “parallelism” of the mortality curves was different than the prior inactive (placebo or conventional care) control trials. Unlike the GUSTO-I com-
comparison of accelerated t-PA and streptokinase at 1 year, there was a narrowing of the gap in the point estimates of mortality. As shown in Figure 6, the absolute difference narrowed throughout the trial, with the maximum noted at 24 hours and the minimum at 365 days. The mechanism for the observed reduction in the difference between the plasminogen activators is unknown but quite interesting to consider.

An angiographic trial that directly compared r-PA and accelerated t-PA showed better early infarct vessel patency for r-PA. From this observation and the association of early infarct vessel patency and improved survival outcomes, the GUSTO-III hypothesis of superiority of survival outcomes was generated. Quite unexpectedly, there was no evidence of superiority for r-PA, and the absolute point estimate was 0.23%, nonsignificantly in favor of t-PA at 30 days. Interestingly, this absolute difference was nearly halved at the 1-year follow-up point and represents a reverse trend than expected if the early angiographic benefit had been manifest in improved survival by such outcomes as 24-hour mortality rates. In contrast, in the GUSTO-I comparison of t-PA and streptokinase, the reduced mortality rate of t-PA was significant at 24 hours and tended to narrow slightly at each subsequent point of reassessment until 1 year. The mechanism, therefore, to explain the current findings is unlikely to stem from early infarct vessel patency. The finding that the Kaplan-Meier curves cross each other several times for the 30-day survival cohort (Figure 4) suggests that any differences are due to chance rather than complex multifactional biology. It remains possible that there are differences of less subsequent reocclusion or late reperfusion related to the more extensive fibrinogen breakdown with r-PA than t-PA (ie, “fibrin selectivity”) or less platelet activation. On the latter point, there have been conflicting data thus far reported on the relative effects on platelet activation between r-PA and t-PA.

The new data set offers the opportunity to readdress whether r-PA and t-PA can be viewed as “equivalent.” This is a controversial topic in clinical trial methodology and it is virtually impossible to prove that two different therapies are truly “equivalent.” This becomes a matter of interpretation, and the term “noninferiority” has been advocated as being more accurately descriptive. For fibrinolytic trials of acute MI, we have advocated that the 95% CI of 1.0% be used, since this was the absolute difference, denoting superiority, demonstrated in GUSTO-I for t-PA compared with streptokinase at 30 days. The findings at 1 year in the current trial indicate that although there is a trend toward less difference at 1 year compared with 30 days (0.14% versus 0.23%), the CI for the difference is wider as a result of the higher 1-year event rates. GUSTO III was not powered to address the question of “noninferiority” under an assumption of equal efficacy at 1 year. At the studied sample size, the lower 95% CI still overlaps the 1.0% absolute boundary, which would not be interpretable as “noninferior” with the use of these stringent standards. However, the 1.0% CI boundaries were suggested for 30 days, and no standard or consensus has emerged for differences at 1 year between reperfusion strategies.

Finally, the excess of out-of-hospital mortality rates in the present trial compared with GUSTO-I is a disturbing finding. In light of more intensive pharmacological intervention after MI with aspirin, statins, β-blockers, and ACE inhibitors, the 35% increase in late deaths is surprising. While this likely reflects a higher-risk population who were enrolled in GUSTO-III, it further highlights the challenges in the future to improve long-term outcomes after myocardial reperfusion.
References


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