**Editorial Comment**

**Thrombolytic Therapy and Equivalence Trials**

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The Fibrinolytic Therapy Trialists’ (1) overview of 58,600 patients randomized to receive either fibrinolytic or control treatment reported a 23% mortality reduction with fibrinolytic therapy among patients who presented with myocardial infarction with ST segment elevation and were randomized within 6 h of symptom onset. These data are compelling, and it is no longer ethical to withhold fibrinolytic therapy from patients with these demographics. The mortality rate in the Global Utilization of Streptokinase and TPA [tissue plasminogen activator] for Occluded Coronary Arteries (GUSTO-I) trial was 6.3% with aspirin, tissue-type plasminogen activator (t-PA) and intravenous heparin. The intracranial hemorrhage rate was 0.72%, and the total stroke rate was 1.55%. These figures are too high, and would not be accepted in other areas of medicine. More effective thrombolytic regimens are therefore required, and these new regimens will preferably be safer, more easily administered or cheaper. It is therefore incumbent on cardiologists to continue to explore ways of improving patient outcomes after myocardial infarction and to test these in appropriately designed trials—but how can this be done if it is unethical to use placebo-controlled trials? In this issue of the Journal, Tebbe et al. (2) use an equivalence design to test whether saruplase was “equivalent” to streptokinase in a randomized trial of 3,081 patients.

Saruplase is unglycosylated single-chain urokinase-type plasminogen activator, produced by genetically transformed *Escherichia coli*. It is converted into active two-chain urokinase-type plasminogen activator by plasmin, and it also activates plasminogen directly, largely in the presence of fibrin. Saruplase has been associated with high patency rates in angiographic studies (3) and may be cheaper than other currently available fibrin-specific thrombolytic agents. This trial is much smaller than the Gruppo Italiano per lo Studio della Sopravvenienza nell’Infarto Miocardico (GISSI-2) trial, the Third International Study of Infarct Survival (ISIS-3) or the GUSTO-I trial, which together randomized between 20,000 and 40,000 patients to detect whether t-PA was superior to streptokinase. In this commentary, the trial design and interpretation and issues of superiority, equivalence and sufficiency trials are discussed.

The mechanism of benefit of thrombolytic therapy is the opening of occluded infarct-related arteries (4). Maximal benefit is obtained when reperfusion is achieved early and flow in the infarct-related artery is brisk and sustained. Is it appropriate to assume that this paradigm will translate into a mortality reduction if a new agent is shown to achieve greater rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow (5) or a lower corrected TIMI frame count (6) than an established agent, thus avoiding the need for megatrials?

Two recent, large megatrials evaluating mortality outcomes have not confirmed the promising findings of pilot patency trials. TIMI grade 3 flow with t-PA was reported to be 88% when given as a double bolus (7) compared with 54% when administered over 90 min in the GUSTO-I trial (8). However, the Continuous Infusion Versus Double-Bolus Administration of Alteplase (COBALT) trial (9) in 7,169 patients showed that double-bolus t-PA was “equivalent” to t-PA in its effects on mortality. In the Reteplase Angiographic Phase II International Dose-Finding (RAPID-I and RAPID-II) trials, which were the pilot studies for the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) trial, reteplase was shown to be superior to t-PA in achieving 90-min TIMI grade 3 flow (reteplase 63% vs. accelerated t-PA 49%, p < 0.05) (10,11). In the GUSTO-III trial, which enrolled 15,059 patients, reteplase was judged not to be superior to t-PA (12). Thus, angiographic patency at 90 min is not necessarily a perfect surrogate for mortality benefit and clearly cannot predict intracranial hemorrhage rates with new thrombolytic regimens. Larger trials are required to define benefit and risk.

The COBALT and GUSTO-III trials had different aims. GUSTO-III used the reference standard in clinical research (i.e., a double-blind, placebo-controlled design) with the hypothesis that reteplase was superior to t-PA, and the statistical testing was done to reject the null hypothesis of no treatment difference. The COBALT trial was designed as a positive-control “equivalence” trial, which aimed to demonstrate the therapeutic equivalence of double-bolus administration and accelerated administration of t-PA by testing the null hypothesis that the absolute mortality difference at 30 days would be >0.4% with double-bolus t-PA. This value is the lower 95% confidence limit of the 1% mortality difference between t-PA and streptokinase shown in GUSTO-I (8). If this boundary was not exceeded, superiority of double-bolus t-PA over streptokinase would have been claimed. This design is methodologically very different from a “null-control” trial.

In equivalence trials the new thrombolytic agent should be proved superior to control (i.e., nonthrombolytic) treatment, and these trials generally need to be larger than superiority trials, not smaller (13). Given the streptokinase mortality rate of 6.7% in the current trial, it would take 10,000 patients to show a 20% superiority of saruplase with a power of 80% and p < 0.05. The current trial has only a 32% power to show a

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20% superiority. Failure to detect a difference in a statistically underpowered superiority trial does not prove equivalence, and “lack of evidence of difference” is not the same as “evidence of a lack of difference.” The current trial was designed to exclude a mortality increase of 50% with saruplase over streptokinase and to claim equivalence if the difference in mortality was $<50\%$.

The choice of a prespecified absolute difference to define equivalence has been used in other trials (9,14). This approach increases the chance of showing equivalence if a low risk population is studied. For example, it would be much more difficult to show a 1% absolute difference between a new agent and t-PA if the baseline mortality were 5% than if the baseline mortality were 10%. In the present trial, the mortality rate at 30 days was 6.7% in patients randomized to receive streptokinase, which compares with a mortality rate of 12% in previous streptokinase versus control trials (15–20) and a 42% higher mortality of 9.5% in the International Joint Efficacy Comparison of Thrombolytic's (INJECT) trial (14), a previous equivalence trial of reteplase versus streptokinase.

Rather than using absolute reductions, the preferred approach may be to use a prespecified percentage or odds reduction for limits of the range of equivalence, as in the current trial, in which a prespecified odds ratio of 1.5 was chosen. According to this definition, if the 95% confidence limits do not overlap this boundary, the new treatment can be regarded as equivalent (13) (Fig. 1).

Six previous trials of streptokinase versus control treatment in patients randomized with ST segment elevation within 6 h of symptom onset showed a 24% reduction in mortality (odds ratio 0.76, 95% confidence interval 18% to 31%) (15–20). If exclusion of an 18% increase in mortality with saruplase over streptokinase had been chosen in the current trial (i.e., to exclude overlapping the lower boundary of the confidence interval), the statistical power would have been only 23%.

Figure 2 depicts the results of the current trial, which shows a 16% mortality reduction with saruplase versus streptokinase, with an upper 95% confidence limit of 1.09 (i.e., there could be a 9% increase in mortality with saruplase) not overlapping the confidence limits of the previous streptokinase versus control trials. Saruplase has therefore been shown to be equivalent to streptokinase, but not superior. It would also have been informative to explore the consistency of this effect across subgroups, such as the elderly, patients with anterior infarction, patients presenting before and after 6 h and those actually receiving the treatments.

It is very important that a population similar to that in the previous streptokinase versus control trials be used if assumptions are to be made about superiority to control treatment. Age is the most important adverse prognostic factor for mortality and stroke (21), and it is surprising that the first 800 patients enrolled in the current study excluded those $>75$ years old. One cannot therefore confidently apply the trial results to elderly patients, in whom streptokinase may be preferred because of its lower rate of intracranial hemorrhage.

There were also imbalances between the patients random-
ized to receive saruplase and those randomized to receive streptokinase. The two significant imbalances would count against streptokinase. Patients who received streptokinase were, on average, 1.1 years older than those who received saruplase, and 4.2% more patients in the saruplase group were current smokers, who have been shown to have a lower 30-day mortality rate than that of nonsmokers or ex-smokers (22).

When comparing a new thrombolytic agent with an established agent it is necessary to show that the new agent is “clinically” indistinguishable from the old agent (i.e., similar enough to be clinically accepted as equivalent). This type of trial has been termed a “sufficiency trial.” Do the results of the current trial enable us to declare that saruplase and streptokinase are clinically similar? The investigators of the saruplase trial provide supportive, but not compelling, evidence that saruplase is a suitable alternative to streptokinase. The intracranial hemorrhage rates were 0.9% and 0.3% for saruplase and streptokinase, respectively (p < 0.05). The 95% confidence interval includes an absolute increase of 0.3% to 1.4% in intracranial hemorrhage with saruplase. However, the numbers of patients with total stroke and nonfatal disabling strokes were similar, but again the confidence intervals are wide, with the possibility of a 0.8% reduction in stroke or a 0.9% absolute increase with saruplase.

Conclusions. There are three approaches for improving on the current thrombolytic regimens. The first is to attempt to improve on nature with a more effective mutant or chimeric of native t-PA. To date this improvement has not been achieved. The drugs being tested in current megatrials—lanoteplase and TNK-t-PA—have several features with the potential to improve patient care. However, in small trials without the power to draw definitive conclusions, the stroke rates with these agents have been similar to those with t-PA, which was associated with a stroke rate of 1.83% in the GUSTO-III trial. A second approach is to reduce the dose of the thrombolytic agent and add a glycoprotein IIb/IIIa receptor antagonist. A third approach is to add an adjunctive therapy, such as hirulog, to streptokinase, the aim being to improve patient outcome by improving infarct-related artery patency without increasing the stroke rate (22). All three approaches are presently being evaluated in equivalence or superiority trials that will total >50,000 patients worldwide, including areas of Eastern Europe, Latin America and Asia that have not previously participated in large cardiologic trials. The collaboration and enthusiasm of the investigators is impressive, and it is hoped that this research will improve patient care.

References