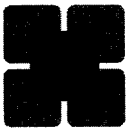

Breaking the thrombolytic gridlock: insights from the GUSTO trial

THE RECENTLY completed Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial[1] compared four thrombolytic strategies for acute myocardial infarction in 41 021 patients in 15 countries. We found that an accelerated regimen of tissue plasminogen activator (t-PA) was superior to the other strategies in improving survival at 30 days. Beyond advancing our knowledge of how to treat patients with acute myocardial infarction, the trial contributed to our understanding of the importance of early and sustained myocardial reperfusion, how cost may affect progress in biotechnology, and how to conduct large-scale cooperative randomized projects. I will review the trial's principal results and give my perspective on each of these three topics.

GUSTO DESIGN AND MAIN FINDINGS

Patients who had symptoms of acute myocardial infarction of less than 6 hours' duration with significant ST-segment elevation were eligible for thrombolytic therapy. They were randomly assigned to one of four strategies: streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, t-PA given on an accelerated basis and intravenous heparin, or the combination of t-PA and streptokinase with intravenous heparin. All patients received aspirin; intravenous or oral beta-blockade was recommended if there were no contraindications to it. The remainder of the treatment plan was left to the discretion of the attending physician, including decisions about other medical therapies and whether or not to perform angiography or coronary revascularization.

Mortality at 30 days was the primary endpoint. In addition, a subset of 2431 patients underwent coronary angiography at 90 minutes, 3 hours, 24 hours, and 5 to 7 days on a randomized, systematic basis to better define the patency of the infarcted vessel and to establish the correlation between patency and survival. The major hypothesis was that early, complete, and sustained reperfusion would be associated with reduced mortality.

At 30 days, 6.3% of the patients who received the accelerated t-PA regimen had died, compared with 7.3% of the patients who received either of the two streptokinase regimens, a 14% reduction ($P < .001$). The accelerated t-PA regimen also offered a significant advantage over the combination of t-PA and streptokinase, which was associated with a mortality rate of 7.0% ($P = .04$).

There was an excess of one disabling stroke per 1000 patients treated with the accelerated t-PA regimen. The majority (70%) of the hemorrhagic strokes were fatal and were included in the mortality data. Accordingly, there was a "net" benefit of accelerated t-PA treatment of 10 lives saved per 1000 compared with the other regimens, outweighing the risk of stroke by a 10-to-1 ratio.

IMPROVED MYOCARDIAL REPERFUSION

The angiographic trial elucidated how accelerated t-PA therapy reduced mortality.[2] The key effect was a more rapid and complete restoration of patency of the infarcted vessels: after 90 minutes of t-PA therapy, 81% of the vessels were patent, compared with 60% with streptokinase regimens ($P < .001$). More importantly, complete reperfusion (defined as grade 3 by the criteria of the Thrombolysis in Myocardial Infarction [TIMI] trial[3]) occurred 70% more frequently with accelerated t-PA treat-

ment than with the other three thrombolytic treatments: 55% of patients given accelerated t-PA treatment achieved TIMI grade 3 flow at 90 minutes compared with 32% of patients treated with other regimens. With respect to therapy, vessel patency proved to be the single most important determinant of survival. In fact, no matter what therapy was given, only 4% of patients died if TIMI grade 3 flow was restored, whereas between 8% to 9% died if the flow was less.

This has been a valuable lesson for the future of myocardial reperfusion therapy. For the past 8 years we have been in a "thrombolytic gridlock" wherein two large-scale trials failed to demonstrate any advantage of one thrombolytic regimen compared with another.[4-6] Many experts believed that it would not be possible to further reduce mortality with alterations of thrombolytic therapy. GUSTO has changed this perception by providing incontrovertible evidence that early and complete restoration of coronary blood flow is the primary explanation for improving survival. However, only 55% of patients achieved complete reflow by 90 minutes of therapy. Surely, we will be able to do better in the future: we hope, eventually, to be able to achieve more than 90% complete reflow by 30 minutes. Further improvements are likely to emanate from novel, potent thrombolytic agents, targeted platelet glycoprotein IIb/IIIa integrin antagonists, or direct thrombin inhibitors.[7] In GUSTO II, recombinant hirudin, the prototypic thrombin inhibitor, will be compared with heparin in 12 000 patients with acute coronary syndromes.

COST OF THERAPY AND HEALTH CARE RATIONING

The impact of the GUSTO results on practice exemplifies the collision of an advance in biotechnology with an economic crisis in health care. How can t-PA be paid for, when it costs over $2300 per dose, and nearly 200 000 patients per year in the United States are candidates for it? The media and peers responded quickly with questions such as "how much is a life worth," and "is $200 000 per life saved acceptable?"[8] The medical community has reacted by using subgroup analysis to attempt to determine which patients would benefit most, so that therapy could be rationed. For example, it has been advocated that only patients younger than age 75 who present within 4 hours with large or anterior myocardial infarctions be considered for accelerated t-PA.[8]

However, it is quite problematic to make recommendations for therapy on the basis of subgroup analysis, considering the GUSTO trial was designed to assess the overall population only. Such subgroup analyses are fraught with problems: they often lack statistical power, they are univariate comparisons representing only an "ice-pick" view of the data, and they can engender spurious results because of multiple comparisons.

A better way to interpret the subgroups from GUSTO is to consider consistency of the effect of accelerated t-PA with respect to absolute or relative survival benefit. Of 200 subgroups in GUSTO, 198 show advantage for accelerated t-PA in reducing mortality—a remarkably consistent finding. In fact, the most extensive benefit of accelerated t-PA was noted in the very patients who had the most to gain from thrombolytic therapy in all of the past trials—those presenting early with the highest risk. Were it not for health care rationing, there would be a global recommendation for accelerated t-PA in patients receiving thrombolytic therapy for acute myocardial infarction. Surely the rationing that we are seeing with t-PA will epitomize what is to come when expensive therapies that have proven lifesaving effects are introduced into clinical practice.

CONDUCTING LARGE-SCALE TRIALS

The scope of participation in GUSTO was extraordinary. Over 1100 hospitals in 15 countries spanning four continents participated, and the spirit of cooperation (some have referred to this as "gusto") was unprecedented in my career as a clinical investigator. Many investigators have written to me about their "GUSTO withdrawal syndrome" since the trial was completed in February 1993. In order for critical questions in medical research to be addressed in a timely, efficient, and rigorous way, simple, international, large-scale cooperative trials will be increasingly important in years to come. The GUSTO project was unique in incorporating a mechanistic study within the framework of a mortality reduction trial.[9] Previously, trials of this scope have been organized in Europe, notably the United Kingdom and Italy, but GUSTO has shown that a trial organized in the United States and performed collaboratively worldwide can be quite successful. Such a model may be useful to study future therapeutic strategies, not only in cardiovascular medicine, but also in oncology, acquired immunodeficiency syndrome (AIDS) ther-

apy, and other medical disciplines in which significant advances are needed.

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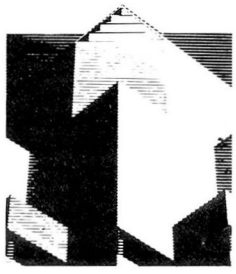
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