The publication of the 10-year follow-up from the GISSI-1 study in this issue of Circulation heralds an important event in the evolution of cardiovascular medicine worthy of a pause for reflection.1 The follow-up to the trial demonstrates that a 1-hour infusion of streptokinase in patients with ST-segment–elevation myocardial infarction reduced the risk of death over the ensuing 10 years from 469 per 1000 patients treated to 450 per 1000. These figures result in a net benefit of 19 lives saved per 1000 patients treated over that time. In patients who presented for medical attention within 1 hour of the onset of symptoms, this benefit is dramatically magnified (80 lives saved per 1000 patients treated). In contrast, in the elderly and in patients with ST-segment depression at admission, the treatment effect went in the wrong direction, confirming previous results in the ST-segment depression group and raising an interesting issue for the elderly. In patients with nonanterior myocardial infarction, the benefit was relatively small.

Combined with the 10-year follow-up from ISIS-2, these data present a clear and impressive picture of what a simple and well-timed intervention can do to improve clinical outcome.2 Furthermore, the GISSI project raises a number of interesting technical points about fibrinolytic therapy as well as critical issues in the development of therapeutic strategies for patients with acute coronary syndromes.

What is the mechanism of the sustained benefit? Only by mechanistic understanding can we improve on future therapy. The GISSI study itself provides no direct pathophysiological insight, but the fabric of other trials in this therapeutic arena points to the critical importance of sustained coronary patency in improving outcome. A variety of mechanisms, including prevention of left ventricular remodeling, improved electrical stability, and scaffolding of the myocardium, have been demonstrated to be potentially important.

Why did the survival curves not continue to widen? If reperfusion reduced infarct size and led to better left ventricular function, one would expect that patients treated with streptokinase would be more likely to survive beyond 30 days; unfortunately, this did not happen. Perhaps the benefit of less remodeling was offset by a higher risk of reocclusion of the infarct-related artery, an event associated with a doubling of mortality. Another potential explanation is that reperfusion saved the lives of patients with impaired left ventricular function who would have died without reperfusion. Van de Werf called this the “reperfusion paradox,” and it would result in a higher-risk population remaining alive at 30 days in the streptokinase-treated patients compared with those treated with standard care.3 In effect, the benefits of less remodeling and greater electrical stability could be counteracted by the risk of reocclusion and the differential survival of higher-risk patients.

The plight of patients with suspected myocardial infarction and without ST-segment elevation remains a dilemma. Although survival is higher in patients treated without streptokinase, the numbers of patients are small, and we are far from certain about the true mortality effect. In addition, the special subpopulations of the subgroup, including those with posterior infarction or severe symptoms and dramatic ST-segment depression, are not specifically addressed, because this amount of detail was not collected. Small pathophysiological studies have suggested that these patients may have a great thrombus burden that is responsive to fibrinolytic therapy.4

Perhaps the thorniest clinical issue raised by the study concerns treatment of the elderly. The current ACC/AHA guidelines point out the absence of definitive proof of survival benefit in patients >75 years old.5 Two points of view on this issue are rational. The argument could be made that the observed results in this relatively small subgroup are due to random effects; alternatively, perhaps the higher risk of bleeding and the presence of more severe multivessel disease in the elderly negates the benefit of fibrinolytic therapy. A strategy of catheter-based mechanical reperfusion may be preferable in older patients.

How do we place these results in perspective? The treatment has an early hazard (excess risk of death on the first day) and a subsequent benefit that is fully realized within 30 days. After 30 days, deaths accrue equally in both groups all the way to 10 years. This result in a maintenance of the absolute benefit of the treatment but a gradual decline in the relative reduction in risk. We usually wish for more dramatic treatment benefits, but we rarely see them. On balance, the definite and sustained benefit of this simple therapy is one of the most important developments in modern medicine.

The broader perspective on the GISSI collaboration may be more important than the specific data from this report. The broad-scale clinical research collaboration initiated by the ISIS and GISSI groups has changed the fate of cardiovascular medicine.6–12 Before the demonstration by these 2 collaborative groups that large numbers of patients could be entered into randomized trials of acutely ill patients, assessment of the impact of therapies on true clinical outcomes was considered to be impossible. With very little investigator payment and strict adherence to the principle of focus on

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Ten Years of Benefit From a One-Hour Intervention

Robert M. Califf, MD
simplicity, these groups opened the field to the dramatic benefits of evidence-based medicine.

Therapeutic benefits are typically modest, and the adverse side of pharmacological intervention cannot be predicted. The modest nature of observed treatment benefits requires large sample sizes to eliminate random effects. In this particular example, the accurate quantification of the intracranial hemorrhage risk requires a similarly large sample size. The demonstration that large trials not only were necessary but could actually be performed constitutes the most important contribution of the GISSI organization.

One critical aspect of the effort has been the focus on avoiding unnecessary bureaucracy in these trials. Keeping the entry criteria broad, focusing on data that serve a useful purpose, and measuring hard clinical outcomes allowed the answer to be obtained unambiguously. Unfortunately, the current interpretation of government regulations for trials sponsored by the medical products industry has led to a huge increase in the collection of data that have no practical value and to the design of elaborate and expensive systems to report safety data to regulatory authorities in real time. The dramatic advances of fibrinolytic therapy, β-blockers, and ACE inhibitors happened with simple case report forms and relatively inexpensive trials. There is no evidence that the increased data collection in recent trials has made a substantial difference.

Before the modern era, we were in an age of therapeutic inefficacy; available medications provided little benefit but had little risk. Over the past 20 years, we have been blessed with a golden era of therapeutic efficacy. Government and industry investment in medical sciences has paid off with a host of beneficial therapies. Demonstration of benefit was straightforward compared with placebo or conventional care. The GISSI and ISIS studies represent the best of this era.

We have now entered an era of therapeutic cacophony. We have many effective therapies for most medical conditions, yet few are curative, and much improvement is necessary to reduce poor clinical outcomes. The advent of combinatorial chemistry, high-throughput screening, and the human genome project will increase the number of new therapies exponentially.

The practice community and our patients are facing a dilemma created by the tremendous success of medicine: among the many proven beneficial therapies, which ones should we use? In the treatment of acute coronary syndromes in late 1998, we have a choice among 6 fibrinolytic agents (streptokinase, urokinase, alteplase, anistreplase, TNK-tPA, and lanetopla), 8 antithrombin agents (unfractionated heparin, 4 types of low-molecular-weight heparin, Hirulog, and 2 types of hirudin), and 6 antiplatelet agents (aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide, and tirofiban). Healthcare systems are increasingly overwhelmed by the panoply of new therapies, each with a small incremental benefit. We cannot afford to pay for all possibly beneficial therapies, and without clinical outcome trials, we have no rational method of making choices.

How do we combine these agents? Combinations in different doses might lead to multiplicative, additive, neutral, or detrimental effects; the magnitude of these combined effects could exceed the effects of any of these therapies independently.

Unfortunately, there is no apparent mechanism to clarify these issues. There is little incentive for industry to fund directly comparative studies, and with the current mechanisms of clinical trial operations, the cost of comparative trials exceeds the investment that government is willing to make. Only when the physician community insisted were directly comparative trials done with fibrinolytic agents. The GUSTO-I effort represented an extension of the megatrial concept combined with the use of information technology and pathophysiological substudies. Yet, the potential for societal harm from arbitrary combinations of potent therapies and the great possibility of benefit from rational combinations of effective therapies demand that we reevaluate our approach to clinical trials and the interaction of the clinical community and the medical products industry.

When the GISSI and ISIS groups broke the megatrial barrier, the issue was whether the purported benefits of therapies based on surrogate measures translated into real effects. In some cases (fibrinolytics, direct angioplasty, ACE inhibitors), the purported benefits were proven; in other cases (type I antiarrhythmics, oral milrinone, flosequinon, epoprostenol, fluosol), the purported benefits were proved to be incorrect, and the therapies were actually detrimental. As a result, we no longer can accept surrogate measures in most cardiovascular conditions. The new barrier in an active-control comparative era is much more complicated, but the availability of internet-based data systems and the globalization of cardiovascular medicine provide an opportunity to approach this new era in a rational manner. The enduring lessons of GISSI provide us with guidance about how to proceed: Focus trials aimed at drug development on questions that will inform clinical practice. Keep the mechanisms and bureaucracy of trials to a minimum. Capitalize on the clear mandate of healthcare providers to act on behalf of patients by participating in clinical trials that will provide the information we need to care for our patients. The spirit of the GISSI organization must be replicated to provide a mechanism that can deliver the evidence for the practice of evidence-based medicine.

References


**Key Words:** Editorials • trials • myocardial infarction • streptokinase
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