Perspectives gained from large-scale thrombolytic comparative trials

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Four thrombolytic comparative trials without a placebo arm have each been conducted in populations of more than 1000 patients: GISSI-2 International, ISIS-3, GUSTO, and INJECT. The treatment strategy associated with use of intravenous heparin and the accelerated regimen of tissue plasminogen activator (t-PA) accounts for the differences between the results of GUSTO and those of the earlier studies of GISSI-2 International and ISIS-3. Using analysis of predefined parameters, it is possible to identify those subsets of patients most likely to benefit from accelerated administration of t-PA. A useful profile of patients at risk for intracranial haemorrhage has also been derived; this profile enhances efficient, sensible, individualized decision making.

Results from the angiographic substudy of GUSTO highlight the fundamental importance of early coronary artery patency as a determinant of improved left ventricular function and survival and reaffirm the usefulness of left ventricular function as a surrogate measure for assessing the efficacy of novel reperfusion strategies. In addition, the opportunity to evaluate international differences in practice patterns, coupled with measures of quality of life and return to work, has given new insight into the importance of these issues in the care of patients with acute myocardial infarction.

Future investigation must address the challenge of optimal use of resources in assessing novel therapies. Strategies include logistic modelling, surrogate end-points, sample enrichment with high-risk subsets, blended end-points, and uneven randomization.

Key Words: Thrombolytics, myocardial infarction, t-PA, heparin, streptokinase, retapase.

Introduction

Results of large-scale clinical trials have had a profound impact on evaluation of the efficacy of thrombolytic therapy in the management of acute myocardial infarction (AMI). Establishing that thrombolytic therapy substantially reduces the morbidity and mortality due to AMI resulted in a worldwide change in the management of this common and important syndrome. The Second International Study of Infarct Survival (ISIS-2) unequivocally established the importance of aspirin and streptokinase administration in reducing mortality; this trial ended the era of randomized placebo-controlled trials of thrombolytic therapy for AMI. Nine placebo-controlled randomized trials of thrombolytic therapy each included more than 1000 patients; a summary of these trials represents composite information in about 58,600 patients. Despite an overall mortality benefit of this therapy equal to 18 lives saved per 1000 patients treated, a residual mortality rate of 9.6% in the treated patients was seen, highlighting the importance of continuing to strive for earlier delivery of thrombolytic therapy and more effective reperfusion strategies, including the use of complementary adjunctive anti-thrombotic agents.

New era of reperfusion trials in AMI

A new era of non-placebo-controlled trials of reperfusion strategies in AMI emerged in the 1990s. It is the purpose of this review to present an evaluation of these trials and the lessons to be learned from their execution. Following the tradition of the Fibrinolytic Therapy Trialists' Collaborative Group, only trials randomizing more than 1000 patients have been considered: the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico and International Study Group (GISSI-2 International), ISIS-3, Global Utilization of Streptokinase and t-PA (tissue plasminogen activator) for Ocluded Coronary Arteries (GUSTO), and the International Joint Efficacy Comparison of Thrombolitics (INJECT) trials. These four trials involve the study of more than 100,000 cases of AMI and ST-segment elevation worldwide. Table 1 presents an overview of patient mortality in these trials and provides...
Table 1 Overview of mortality in comparative trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Heparin use</th>
<th>Associated mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-2</td>
<td>s.c.</td>
<td>t-PA</td>
</tr>
<tr>
<td>n=12,490</td>
<td>None</td>
<td>9.2</td>
</tr>
<tr>
<td>ISIS-3</td>
<td>s.c.</td>
<td>t-PA</td>
</tr>
<tr>
<td>n=41,299 (36,381)</td>
<td>None</td>
<td>9.1</td>
</tr>
<tr>
<td>GUSTO</td>
<td>i.v.</td>
<td>Acc t-PA</td>
</tr>
<tr>
<td>n=41,021</td>
<td>s.c.</td>
<td>6.3</td>
</tr>
<tr>
<td>INJECT</td>
<td>i.v.</td>
<td>r-PA</td>
</tr>
<tr>
<td>n=6000</td>
<td>s.c.</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Acc = accelerated (front-loaded) t-PA; APSAC = anisoylated plasminogen streptokinase activator complex (anistreplase); COMB = combined t-PA and SK; i.v. = intravenous; r-PA = recombinant tissue plasminogen activator (reteplase); s.c. = subcutaneous; SK = streptokinase; t-PA = tissue plasminogen activator.

GISSI-2 = Gruppo Italiano per lo Studio della Soprawivenza nell’Infarto Miocardico and International Study Group.
GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Arteries.
INJECT = International Joint Efficacy Comparison of Thrombolytics.
ISIS-3 = Third International Study of Infarct Survival.

their sample size, design features, and adjunctive heparin strategy.

Methods

The composite results of GISSI-2 International and ISIS-3, large trials of simple design aimed at randomizing as many patients as possible in a timely fashion, suggested that administration of t-PA was not associated with a greater benefit than that of streptokinase, despite prior demonstration of differences in the coronary thrombolytic efficacy of these agents\(^{17}\). Although findings of the APSAC (anisoylated plasminogen streptokinase activator complex) Intervention Mortality Study (AIMS) suggested the superior thrombolytic efficacy of APSAC over other agents studied to that point, the results of ISIS-3 emphasize the importance of direct comparisons of different agents and re-emphasize the likelihood that intervention trials terminated prematurely for reasons of efficacy may over-estimate the true treatment effect\(^{18}\).

Treatment strategies

In an effort to maintain simplicity of the treatment strategy, investigators in both the GISSI-2 International and ISIS-3 trials elected to administer heparin subcutaneously (at 12 and 4 h, respectively) after administration of the thrombolytic agent. This heparin strategy for t-PA use was contrary to that used in earlier dose-finding coronary thrombolytic trials and was not aligned to conventional clinical use\(^{7,9,10}\).

Notably, the GUSTO trial was designed not only to incorporate optimal adjunctive anticoagulation with heparin, but also to maintain a streptokinase-subcutaneous heparin arm to provide a standard for comparison with the ISIS-3 trial. In addition, GUSTO incorporated an accelerated t-PA regimen shown to have thrombolytic efficacy superior to that of the conventional 3-h mode of t-PA administration used in GISSI-2 and ISIS-3\(^{11}\). Both of these protocol features in GUSTO most likely account for the greater mortality benefit evident with the t-PA treatment strategy than with streptokinase. Recognizing the potential differences in risk associated with the treatment strategies evaluated in GUSTO, the designers of this trial both identified the primary end-point of all-cause mortality at 30 days and prospectively defined and assessed a composite end-point of death and non-fatal stroke of different categories. This design allowed the determination of a greater mortality benefit associated with t-PA than with streptokinase, equal to 10 lives saved per 1000 patients treated; for the
prevention of death and disabling stroke, this benefit was 9 per 1000 patients treated, highlighting the precise quantitative trade-off between safety and efficacy.

Subsequently, using composite data from five sources, Simoons and his colleagues conducted a study in 150 patients with documented intracranial haemorrhage as a result of thrombolytic therapy; to identify predictors of intracranial haemorrhage, these investigators then used multivariate analysis to compare the findings in these patients with those of 294 matched controls. Four predictive factors were identified: age >65 years (adjusted odds ratio [OR] 2.2), weight <70 kg (OR 2.1), hypertension on admission (OR 2.0), and use of t-PA (OR 1.6). Assuming an overall intracranial haemorrhage rate of 0.75%, it is possible to evaluate the risk to individual patients. Thus, in some patients, risk of haemorrhage may be as low as 0.26%, whereas with all four risk factors, the predicted incidence is unacceptably high, i.e. 3.5%.

**Variations between trials**

**Cost benefit**

Because of substantial differences in the cost of diverse thrombolytic strategies, extraordinary attention has been paid to cost-benefit implications. This has generated healthy debate on the appropriateness of more expensive strategies, the definition of their benefit according to cost per life-years saved, and the development of a clinical context in which to evaluate thrombolytic therapy in comparison with other treatments both within and outside the cardiovascular arena. The potential for substantial financial gains to industrial sponsors has placed unwarranted focus on claims of efficacy and safety and led to hyperbole, especially in advertising and non-peer-reviewed publications. These issues, coupled with the importance of monitoring patient safety, motivated the GUSTO investigators to go to unusual lengths in defining and publishing their approach before beginning the GUSTO trial.

**Informed consent**

Other differences between these trials that warrant comment include contrasting attitudes toward informed consent. In the GISSI-2 study, as in GISSI-1, informed consent was perceived as unnecessary, since the Ethics Committee recommended that ‘informed consent should not be required, mainly because the patients’ conditions were too acute for satisfactory application of the procedure’ for elicitation of detailed written, informed consent.

**Identification of high-risk subsets**

The absolute benefits achievable by new advances are understandably attenuated, since they must be incrementally over established effective therapy. Therefore, investigators have been searching for high-risk subsets in which novel advances may be particularly useful.

In the GUSTO trial, patients with anterior MI who were younger than 75 years of age tended to achieve greater absolute benefit than others. Importantly, the relationship between 90-min patency and 30-day mortality was secured by the revelation that the Thrombolysis in Myocardial Infarction degree of perfusion (TIMI) 0 or 1 patency was associated with a mortality rate of 8.9%, whereas individuals with TIMI 3 perfusion had a mortality rate of 4.4% \((P=0.009)\). Moreover, in a model developed from the angiographic substudy of GUSTO, a close relationship is observed between predicted and observed 30-day mortality rates, further consolidating the relationship between the success of early reperfusion and 30-day mortality. The reaffirmation of the relationship between early coronary patency, left ventricular function, and mortality is an important implication for future comparative trials: surrogate measures of coronary thrombolytic efficacy can be utilized.

**International data exchange**

Data resulting from these large international trials have stimulated examination of practice patterns within and between participating countries. The acquisition of carefully documented time-to-treatment data among individual institutions and provision of comparative data stimulate enhanced, more efficient delivery of this therapy, thereby providing important secondary gains. Examination of the patterns of ancillary technical procedures, adherence to evidence-based medicine, quality of life, and return-to-work measures have been important subsidiary objectives that provide evidence useful in the debate on the adequacy and disposition of health care funding between countries. Although thrombolytic therapy is still under-utilized in clinical practice in many countries, significant improvements have occurred as a result of the publicity and communication of trial evidence. Notably, centres participating in these trials use effective therapy more frequently in clinical care, highlighting the value of community ‘grassroots’ participation in clinical investigation.

**New concepts in investigative design**

Most important, comparative trials have raised questions regarding the future of investigative strategies concerning innovative therapy in the setting of AMI. To be determined are the parameters constituting a reasonable margin of benefit in the absence of a permissible placebo-controlled group for comparison. Establishing the relative benefits of innovative therapy will be increasingly difficult to achieve; it is potentially feasible only when the additive or synergistic effects of more than one treatment regimen are examined, as was the case in the GUSTO trial. Alternatively, a new treatment
strategy might represent a meaningful therapeutic advance — despite a lack of significant improvement in mortality rate — if it offers a simpler regimen for administration; is less amenable to error, with potential safety benefits; or incorporates a delivery strategy allowing for earlier administration or cost reduction.

The INJECT trial was undertaken in an effort to avoid the huge sample sizes and costs associated with conducting a trial designed to demonstrate superiority of one novel thrombolytic agent over another. This trial compared use of the agent reteplase with conventional streptokinase therapy in 6000 patients, with the primary objective of showing the ‘equivalence’ of these two treatments in relation to their effect on mortality. The authors argued that equivalence could be ascertained if reteplase was not more than 1% less effective than streptokinase, based on 90% confidence limits of ±1% around their estimates. Patients treated with reteplase achieved a mortality rate slightly lower (0.5%) than streptokinase-treated patients (Table 1). Although the difference was not statistically significant, the 90% confidence limits ranged from -1.74% to +0.73%: this translates into a 76% probability that reteplase is more effective than streptokinase. Since approximately 20% of patients were treated more than 6 h following symptom onset, further subgroup analysis based on the interval from onset to treatment would be revealing. However, the ability to provide precise confidence limits around the frequency of a haemorrhagic stroke with reteplase is limited by the 3000-patient sample size. The ultimate role of equivalence testing in comparative trials remains to be determined; however, this concept represents a meaningful therapeutic advance — despite a lack of significant improvement in mortality rate — if it offers a simpler regimen for administration; is less amenable to error, with potential safety benefits; or incorporates a delivery strategy allowing for earlier administration or cost reduction.

Innovated various design strategies in an attempt to economize on the resources required (Table 2). It is likely that these concepts will be increasingly developed.

### Conclusion

As the dawn of a new millennium approaches, clinical investigation focusing on the treatment of AMI enters an exciting and challenging era. Creative, thoughtful engineering is required to realize the opportunities provided by the novel treatments available and to utilize these treatments widely for patients at risk.

### References


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