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Scientific Update™

Towards Optimal Outcomes with Myocardial Reperfusion: The GUSTO III Trial

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The final results of the GUSTO III trial comparing reteplase (rPA) and alteplase (tPA) showed no statistical difference in mortality, stroke, or net clinical benefit. While the data argue strongly for similarity between rPA and tPA, "equivalence" is a relative, quantitative term that is extremely difficult to prove. Potential advantages of rPA (ease of administration) were placed into context with the use of tPA (the previous gold standard of thrombolytic treatments). Important additional information from GUSTO III – including the significance of early resolution of ST segment elevation, insights on time to treatment, and the prognostic value of troponin T in ST segment elevation infarction – was also discussed.

Rationale for GUSTO III: The RAPID studies

The GUSTO III trial was based on two randomized pilot studies: RAPID I and II.[1,2] RAPID I was designed to compare three bolus or double-bolus dosage regimens of reteplase (rPA) with one of alteplase (tPA) with respect to producing coronary artery patency 90 minutes after initiation of thrombolytic treatment following an infarction. Of the four treatment regimens, a 10+10 Unit double bolus of rPA separated by 30 minutes produced greater 90-minute and 5-14 day TIMI III flow than did any tPA regimen (63% vs 49%, p<0.02; and 88% vs 71%, p<0.01 respectively). Both the global ejection fraction and regional wall motion were also superior in the rPA 10+10 U group at hospital discharge, and bleeding complications were similar among the groups.

While RAPID I was in progress, the GUSTO I study employed a front-loaded, "accelerated" regimen of tPA (100 mg over 90 minutes as compared to over 3 hours) as the regimen of choice for this agent, since it produced greater reduced mortality than did intravenous streptokinase.[3] Furthermore, the angiographic sub-study of the GUSTO trial suggested that the superiority of front-loaded tPA was linked to a higher percentage of early (90-minute) patency and more complete (TIMI III flow) reperfusion.[4]

The RAPID II study then compared the 10+10 U rPA regimen to the accelerated tPA regimen among 324 patients with acute myocardial infarctions (MI). Again, complete patency (TIMI III) at 90 minutes was significantly higher in the rPA-treated patients than in the tPA-treated patients (59.9% vs 45.2%, p=0.01). Although the study was not powered to evaluate clinical events, rPA-treated patients required fewer additional coronary interventions (13.6% vs 26.5%, p<0.01), and 35-day mortality was somewhat lower (4.1% vs 8.4%, p=NS) for rPA-treated patients.

Around the same time that the RAPID studies were being performed, a large-scale, randomized, double-blind comparison of double-bolus rPA with intravenous streptokinase (SK) in acute MI was undertaken by the International Joint Efficacy Comparison of Thrombolytics (INJECT) Investigators.[5] In this study designed to evaluate the equivalence of the two thrombolytic regimens, the 30-day mortality was 0.5% lower among those who received rPA as compared to those receiving streptokinase (95% CI: -1.74,

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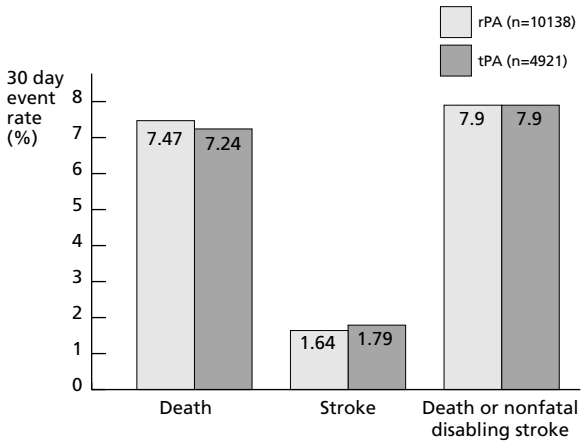
0.73). This positive – but not statistically significant – survival difference was maintained at six months (rPA mortality 11.02% vs SK mortality 12.05%). Although mortality was not significantly lower with rPA, significant reductions in the incidence of congestive heart failure (23.6% vs 26.3%), shock (4.7% vs 6.0%), hypotension (15.5% vs 17.6%), and atrial fibrillation (7.2% vs 8.8%) were seen (all comparisons $p<0.05$).

Therefore, based on the RAPID and INJECT study results, a larger mortality trial comparing rPA and accelerated tPA was undertaken in GUSTO III. In view of the greater ease of administration of two boluses of rPA as compared to a bolus and then continuous infusion of tPA, it was anticipated that fewer patients would have thrombolytic administration terminated prematurely because of early death or bleeding complications, and patients could potentially receive therapy more quickly. This in turn could enhance infarction-related artery patency, improving clinical outcome.

GUSTO III trial design and patient demographics

The primary hypothesis of the GUSTO III trial was that 30-day mortality after acute MI would be significantly reduced with rPA in comparison with accelerated tPA. To test this hypothesis 15,060 patients presenting within 6 hours of symptom onset, and with ST segment elevation, were enrolled at 807 hospitals in 15 countries; they were randomly assigned in a 2:1 ratio to receive rPA or accelerated tPA. Upon arrival, 97% of the patients received 160 mg acetylsalicylic acid (ASA), and during the period of thrombolytic therapy, these patients also received intravenous heparin bolus of 5,000 U followed by an infusion adjusted to maintain an activated partial thromboplastin time (aPTT) of 50-70 seconds. No differences were found in the baseline characteristics of the two treatment groups. In comparison with GUSTO I, the patients enrolled in GUSTO III tended to be older, included a higher percentage of females, had higher blood pressures at enrollment, and had a greater prevalence of anterior MI and history of previous MI.

Figure 1: GUSTO III 30-day event rates



Efficacy results

The total mortality at day 30 (the primary end-point of the study) was 7.47 in rPA- and 7.24 in tPA-treated patients (-0.23% difference, 95% CI: -1.12%, 0.66%). The 30-day rate of stroke was 1.64% in the rPA- and 1.79 in the tPA-treated groups. Additional secondary end-points, including bleeding, in-hospital recurrent ischemia, reinfarction, and congestive heart failure, were similar among the two treatment groups.

Therefore, the hypothesis of the GUSTO III trial that 30-day mortality would be significantly reduced with rPA as compared to tPA was not realized. Taking into account the small – but not statistically significant – differences in mortality (favoring tPA) and stroke (favoring rPA), the net clinical benefit as defined by 30-day mortality or non-fatal disabling stroke was 7.9% in both treatment groups (see Figure 1). The GUSTO III Steering Committee concluded that, with 95% confidence, they could not exclude that the absolute mortality for accelerated tPA is 1.1% better than for rPA, or that mortality for rPA is 0.7% better than for accelerated tPA. The Steering Committee felt that there was still

Figure 2: GUSTO III – 30-day mortality according to ST segment resolution

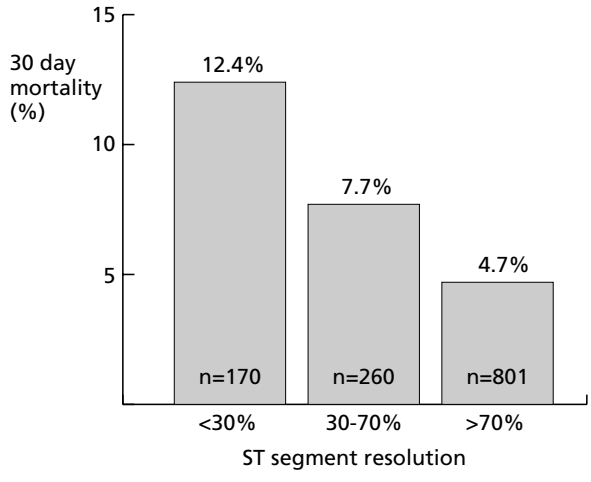
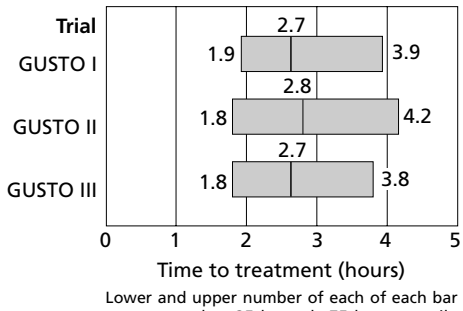


Figure 3: Time to treatment



Lower and upper number of each of each bar represent the 25th and 75th percentile respectively. The middle line represents the median time to treatment.

some uncertainty as to whether these two fibrinolytic drugs can be regarded as equivalent, and they suggested that the choice of treatment will depend on the ease of use, cost of drug, and other issues as perceived by the treating physician.

Early resolution of ST segment elevation: A non-invasive marker of reperfusion and prognosis

A sub-study was done on 3,057 GUSTO-III patients who had a 12-lead electrocardiogram performed at baseline and at 90 minutes and/or 180 minutes after the start of either rPA or tPA. Electrocardiograms were categorized according to <30%, 30-70%, and >70% decrease in the sum of ST segment elevations between baseline and the 90/180-minute electrocardiograms.

Investigators from three previous large-scale thrombolytic trials (including INJECT) had found a very powerful relationship between the degree of ST segment resolution and the 30- to 35-day mortality rate, regardless of the therapy received. The highest early mortality was seen among those with the least amount of ST segment resolution. In the GUSTO III sub-study, 30-day mortality, according to the ST segment resolution category at 180 minutes, was indeed highest among the group that had <30% resolution (see Figure 2). In a similar fashion, both 24-hour mortality and in-hospital reinfarction were highest within the group with the least amount of ST segment resolution. Consistent with the over-all GUSTO III results, administration of rPA or tPA resulted in resolution of ST segment elevation to an equal extent and with similar speed. Thus, evaluation of early ST segment resolution by 12-lead electrocardiography is an inexpensive and useful non-invasive marker of reperfusion and prognosis.

Time to treatment

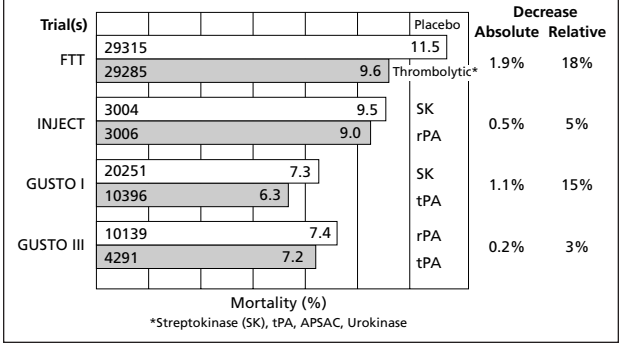
Comparison of GUSTO III with the two previous GUSTO trials revealed that time to treatment was almost identical in all three trials (see Figure 3). However, the time to treatment in the United States declined in GUSTO III as compared with GUSTO I: 2.3 hours (25th-75th percentile ranges 1.6-3.3) vs 2.7 hours (1.9-3.8) (p=0.0001), whereas there was no change among non-US patients: 2.9 hours (2.0-4.1) vs 2.9 hours (2.1-4.0). This decline in time to treatment within the US cohort was secondary to a reduction of in-hospital time to treatment from 1.1 hours (0.82-1.55) to 0.82 hours (0.60-1.18) (p=0.0001) from GUSTO I to GUSTO III. The over-all impact of time to treatment on 30-day mortality in GUSTO III was remarkably similar to that observed in GUSTO I. Thus, delay from symptom onset to treatment remains a major public health issue; however, advances in hospital process of care have contributed to shortened time to treatment within, but not outside, the United States.

Of interest, and consistent with the concept that administration of rPA (double bolus) would be easier than that of tPA (bolus followed by continuous infusion), a smaller percentage of rPA-treated patients required thrombolytic treatment termination early on (0.77% vs 1.88%, p<0.0001).

Prognostic markers in acute MI

The major limitation in using serum cardiac markers for risk stratification at admission has been the delay in obtaining results. However, a qualitative assay for troponin T has recently been developed, and this point-of-care assay can be performed in 20 minutes at the bedside and requires no centrifuging. Since GUSTO III patients presented with chest pain and ST segment elevation, the troponin T was measured

Figure 4: Absolute and relative mortality decrease in selected thrombolytic trials.



*Streptokinase (SK), tPA, APSAC, Urokinase

for prognosis and not diagnosis in over 13,000 of the total 15,000 patients. It's important to note that, in a model predicting 30-day mortality, a positive troponin T was an independent marker in addition to age, systolic blood pressure, heart rate, MI location, and Killip class at baseline. In other words, beyond the use of age and other factors to stratify patients into low and high risk for subsequent morbidity and mortality, troponin T assay at the bedside was able to provide important prognostic information.

GUSTO III in the context of other clinical trials

The 30-35 day mortality of more than 110,000 patients in randomized trials was drawn from the previous Fibrinolytic Therapy Trials (FTT) collaboration (meta-analysis of all placebo-controlled trials of more than 1,000 patients), and from the INJECT, GUSTO I, and GUSTO III trials. (See Figure 4.) The comparative (two active treatments) trials of INJECT, GUSTO I, and GUSTO III produced a difference of only one absolute percent, with results ranging from a low of 0.2% (GUSTO III) to a maximum of 1.1% (a 15% relative reduction in GUSTO I). Clearly, the 0.2% mortality difference in GUSTO III, in which rPA and tPA were compared, is quite small, especially when compared to the absolute 1.9% difference between thrombolytics and placebo in the FTT meta-analysis. Thus, the GUSTO III data argue strongly for similarity between rPA and tPA; however, equivalence is extremely difficult to prove and represents a relative, quantitative term.

Conclusion

We have accumulated significant experience in thrombolytic treatment of patients with acute MI. GUSTO III adds to this knowledge with the addition of an easy-to-administer, potent thrombolytic agent: rPA. Whether to treat patients presenting in under 12 hours with ST elevation or new bundle branch block is no longer a question; however, significant challenges remain with respect to patient education and shortening of time to treatment, increasing ease and safety of thrombolytic administration, and maintenance of early patency. Additional and important challenges relate to risk stratification and optimal management of patients with acute MI who are not eligible for thrombolytic therapy.

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