Clinical Investigation and Reports

Link Between the Angiographic Substudy and Mortality Outcomes in a Large Randomized Trial of Myocardial Reperfusion

Importance of Early and Complete Infarct Artery Reperfusion

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Background The Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) trial was designed to test whether thrombolytic strategies achieving more complete, early, sustained coronary artery patency would lead to further reductions in mortality in patients with acute myocardial infarction. An angiographic substudy within GUSTO-I provided a unique opportunity to examine the relation between mortality and degrees of patency among the regimens.

Methods and Results Four thrombolytic strategies were compared in 41 021 patients in GUSTO-I: streptokinase with subcutaneous or intravenous heparin, accelerated tissue plasminogen activator (TPA) with intravenous heparin, and combination streptokinase plus TPA with intravenous heparin. Accelerated TPA was associated with lower 30-day mortality (6.3%) than the other strategies (7.2%, 7.4%, and 7.0%, respectively). Among the 1210 patients in the angiographic substudy randomized to angiography 90 minutes after starting treatment, there was improved patency, particularly Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, with accelerated TPA over the other regimens ($P<.0001$). Coronary artery perfusion (TIMI grade 3) at 90 minutes was also a significant predictor of 30-day survival ($P<.01$). To determine whether differences in mortality among the four strategies matched differences in 90-minute patency, a model was developed for predicting mortality differences in the main trial from the angiographic substudy. The model assumed that any differences in treatment effects on 30-day mortality were mediated through differences in 90-minute patency for the four treatments. The predicted rates were then compared with observed mortality rates of the remaining patients in the main trial for each treatment group. The predicted and observed 30-day mortality rates of the four treatments were streptokinase with subcutaneous heparin, 7.46% versus 7.28%; streptokinase with intravenous heparin, 7.26% versus 7.39%; accelerated TPA, 6.31% versus 6.37%; and streptokinase plus TPA, 6.98% versus 6.96%. The correlation between predicted and observed results was .97, and the proportion of squared error explained (R^2) was .92.

Conclusions The close relation between the predicted and observed 30-day mortality rates supports the concept that an important mechanism for improved survival with thrombolytic therapy is achievement of early, complete perfusion. The close match provides a strong biological explanation for the mortality differences seen in GUSTO-I and a sound rationale for the additional survival advantage of the accelerated TPA regimen. Irrespective of which treatment is used, early and complete restoration of infarct artery perfusion represents an essential goal of myocardial reperfusion therapy. **(*Circulation*. 1995;91:1923-1928.)**

Key Words • reperfusion • myocardial infarction • mortality • angiography • clinical trials • thrombolysis

The rationale for giving thrombolytic therapies in patients with evolving myocardial infarction is to reopen an occluded coronary artery, hence minimizing myocardial injury, preserving cardiac function, and ultimately improving overall survival. Angiographic studies have clearly demonstrated that total coronary artery occlusion early in the course of an evolving myocardial infarction occurs in the vast majority of patients[1] and that thrombolysis is able to achieve reperfusion in many cases[2]; animal studies have demonstrated that early reperfusion may limit infarct size.[3] The effectiveness of thrombolytic therapies on patient outcome is also now well established, resulting in an ≈25% reduction in short-term mortality.[4-7]

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Despite a strong rationale for thrombolytic therapy, the importance of early perfusion in achieving mortality reduction was called into question by the results of the international GISSI-2 and ISIS-3 trials.[8-10] In these studies, tissue-type plasminogen activator (TPA) given over 3 hours was compared with streptokinase given with or without subcutaneous heparin. Despite the promise

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TABLE 1. Classification of TIMI Flow in the Infarct-Related Coronary Artery

TIMI grade 0	Absent antegrade flow
TIMI grade 1	Partial contrast penetration; incomplete distal filling
TIMI grade 2	Patent with opacification of the entire distal artery; delayed contrast filling or washout
TIMI grade 3	Patent with normal flow

TIMI indicates Thrombolysis in Myocardial Infarction.

of further reductions in mortality from TPA (due to anticipated higher levels of early patency), no survival advantage was demonstrated.

The Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) trial was designed specifically to test strategies aimed at improving both early and sustained coronary artery patency and to determine whether these would lead to reductions in mortality. An angiographic substudy, designed to examine any differences in coronary perfusion, provided an opportunity to explore the relation between mortality differences and the underlying angiographic findings. The GUSTO-I trial was unique in this regard, because it was the first megatrial of thrombolytic therapies that enabled underlying treatment mechanisms and effects on total mortality to be examined directly.

To test whether the magnitude of the mortality differences seen in the main trial could be explained on the basis of differences in 90-minute coronary artery patency, a model was developed from the substudy (which assumed that treatment was operating only through this mechanism) to predict mortality differences in the main trial.

Methods

The GUSTO-I Trial

The GUSTO-I trial has been described in detail.[11] In brief, 41 021 patients with evolving acute myocardial infarction were randomized to one of four thrombolytic regimens: streptokinase with subcutaneous or intravenous heparin, accelerated TPA with intravenous heparin, or a combination of streptokinase plus TPA with intravenous heparin. Eligible patients had ST-segment elevation of >0.1 mV in two or more limb leads (or >0.2 mV in two or more contiguous precordial leads), onset of ischemic chest pain within 6 hours of randomization, and no contraindications to thrombolysis. The primary outcome of the trial was all-cause 30-day mortality.

Angiographic Substudy

The angiographic substudy involved 2431 patients randomized among 75 GUSTO-I centers. In this substudy, described in detail previously,[12] patients were randomized to undergo angiography at one of four times: 1210 patients (50%) at 90 minutes, 403 (16.6%) at 3 hours, 405 (16.6%) at 24 hours, and 413 (16.6%) at 7 days. Patency was classified according to standard criteria: TIMI flow grade 0, 1, 2, or 3 (Table 1).[13] Data from the 1210 patients randomized to 90-minute angiography were used to develop the mortality prediction model.

Risk Factors for 30-Day Mortality

The relations of TIMI grade flow at 90 minutes and baseline risk factors to 30-day mortality were explored in logistic regression analyses. Patient factors examined in the angiographic substudy were the most significant predictors of mortality in the main trial: sex, age, previous myocardial infarction, site of infarction, height, systolic blood pressure, and heart rate.[14] The effect of TIMI grade on 30-day mortality, adjusted for these prognostic factors, was also examined. Mortality rates were compared for each TIMI grade by means of the χ^2 test.

Mortality Prediction Model

Predicted mortality for each thrombolytic strategy was calculated by assuming that thrombolytic therapy obtained its effect only through increasing coronary artery patency at 90 minutes and not through other mechanisms. Consequently, mortality was predicted for each therapy from the proportion of patients achieving each patency level and from the mortality rate (averaged over all four treatments) associated with each patency level.

We defined P_{ij} as the probability of each patient having TIMI grade i at 90 minutes if given treatment j. Then the mortality rate for each patient was assumed to depend on the TIMI grade level i obtained at 90 minutes but not on the treatment j, except through this mechanism. This meant that the predicted mortality for each treatment (m_j) was a weighted average of mortality rates for each TIMI grade (m_i) weighted by the proportion of patients at each TIMI level (0, 1, 2, and 3), given by

$$(1) \qquad m_j = \sum_i P_{ij} m_i$$

Mortality rates (m_i) were estimated by combining the observed mortality rates of all four treatments at each TIMI grade level. Thirty-three patients did not have an angiogram, and several early deaths were seen in such patients before an angiogram could be done. We assumed that the chance of each patient not having a 90-minute angiogram and the 30-day mortality of such patients were not treatment dependent. Then the predicted mortality rate for each treatment incorporating unknowns became

$$(2) \qquad m_j^* = m_j(1-\theta) + \theta m$$

where m was the mortality rate among proportion θ of those without angiographic results.

To determine whether differences in mortality among the four treatments were consistent with differences in the patency results, an adjusted predicted mortality was obtained for each treatment by setting the average adjusted predicted mortality equal to the average observed mortality:

$$(3) \qquad m_j^{**} = m_j^* \times \overline{m}/\overline{M}$$

where $\overline{m}$ and $\overline{M}$ were the average (unadjusted) predicted and observed mortality rates, respectively. The adjusted predicted mortality rates provided a better test of whether differences in the main trial were consistent with the model and, in effect, incorporated adjustment for differences in patient risk factors between the substudy and the main trial. Nevertheless, unadjusted predicted mortality rates are also presented.

Analysis

The mortality prediction model was developed to test the prespecified hypothesis that strategies achieving better early patency would be associated with greater survival. While the specific model and analyses undertaken were not prespecified, the primary analysis and methods used for handling missing data were specified without knowledge of their effects on the results. Sensitivity analyses were then done to show that the initial assumptions made did not affect the conclusions.

The primary analysis was based on results of the first angiogram for all patients randomized to a 90-minute angiogram (the "intent-to-treat" analysis). Secondary analyses were done on only those patients who had an initial angiogram before 3 hours or before 2 hours. All patients without an angiogram done at this time were included in the "unknown" category of the analysis. To ensure that the two data sets were quite independent, only those patients in the main trial not

TABLE 2. Coronary Artery Patency at 90 Minutes by Thrombolytic Therapy and 30-Day Mortality*

TIMI Grade	Total	SK-SQ n=296	SK-IV n=286	TPA n=292	TPA+SK n=302	30-Day Mortality, %
0	285	97 (33)	83 (29)	41 (14)	64 (21)	8.4
1	98	38 (13)	29 (10)	14 (5)	17 (6)	9.2
2	341	75 (25)	80 (28)	79 (27)	107 (35)	7.9
3	452	86 (29)	94 (33)	158 (54)	114 (38)	4.0
Unknown	34	7	6	11	10	18.2
Total	1210	303	292	303	312	

TIMI indicates Thrombolysis in Myocardial Infarction; SK-SQ, streptokinase with subcutaneous heparin; SK-IV, streptokinase with intravenous heparin; TPA, accelerated tissue-type plasminogen activator with IV heparin; and TPA+SK, tissue-type plasminogen activator plus streptokinase with intravenous heparin. Values are numbers (percentages) of patients receiving each treatment at each TIMI grade who also had angiographic results.

*For the 1210 patients randomized to the 90-minute angiographic substudy. Results are of the first angiogram irrespective of time done. Those without any angiogram are given as unknown.

included in the angiographic substudy at 90 minutes were included for the observed mortality results.

An alternative analysis for handling the patients with unknown patency considered the proportion of patients with TIMI flow unknown, p*j, for each treatment j as an additional category in Equation 1 rather than adjusting for the unknowns in Equation 2. This analysis assumed that the chance of whether an angiogram was actually done depended on the thrombolytic given but that the mortality of each patient with unknown TIMI flow was still independent of treatment.

Measures of association between the predicted and observed mortality results were based on Pearson's correlation coefficient and the proportion of squared error explained (an R^2 measure).[15] The proportion of squared error explained is a measure of the amount of variation in mortality differences in the main trial that could be explained through differences in 90-minute patency results.

Results

90-Minute Angiographic Findings

Results of angiography planned for 90 minutes are shown in Table 2. A total of 1176 patients (97%) had at least one angiogram and were included in the primary analysis. Of these, 1124 (96%) had an angiogram within 3 hours and 1021 (87%) had an angiogram within 2 hours of starting treatment. Secondary analyses based on only those who had an angiogram within 3 hours or within 2 hours gave very similar conclusions. Accelerated TPA was associated with the highest TIMI grades at 90 minutes, particularly grade 3 flow (54% of the TPA patients, $P<.001$). Overall patency (TIMI grades 2 and 3) for the combination arm was similar, but less TIMI grade 3 flow was seen in this group than with accelerated TPA. There were no significant differences in clinical characteristics between patients in the angiographic substudy and the main trial.

90-Minute Angiography Results and 30-Day Mortality

Table 2 also shows the 30-day mortality associated with each patency level among the four treatment arms combined. Mortality was significantly lower in patients with TIMI grade 3 flow (4.0%, $P<.01$) than other TIMI grades. Importantly, TIMI grade 2 flow was not associated with a significant survival advantage compared with TIMI grade 0 or 1. The sample described here is slightly larger than that of the initial report of the GUSTO-I Angiographic Substudy[12] owing to collection of previously unavailable outcome data. The relation between patency and 30-day mortality remained within 0.5% in each TIMI grade, comparing the current edited and more complete database with the earlier report.

The relation between TIMI flow at 90 minutes and mortality at 30 days was explored further in a logistic regression analysis (Fig 1). This showed a significant reduction in 30-day mortality for TIMI grade 3, with an odds ratio of 0.44 (95% CI, 0.24 to 0.79) relative to TIMI 0 or 1 ($P=.007$). To determine whether angiographic findings predicted mortality independent of known patient risk factors, the regression analysis was repeated, adjusting for the most important prognostic factors determined from the main trial: sex, age, previous myocardial infarction, myocardial infarction location, height, systolic blood pressure, and heart rate.[14] After adjustment for these prognostic factors, TIMI grade 3 flow remained a significant predictor of 30-day survival ($P=.015$), with an odds ratio of 0.46 (95% CI, 0.25 to 0.86).

Predicted Versus Observed Mortality Results

The predicted mortality for each treatment is shown relative to the observed 30-day mortality of the other patients in the main trial in Fig 2. Since the predicted mortality results were adjusted so that the average predicted mortality and the average observed mortality were equal, differences among the mortality results are of most importance. The degree of correlation between observed and predicted mortality was very high ($r=.97$).

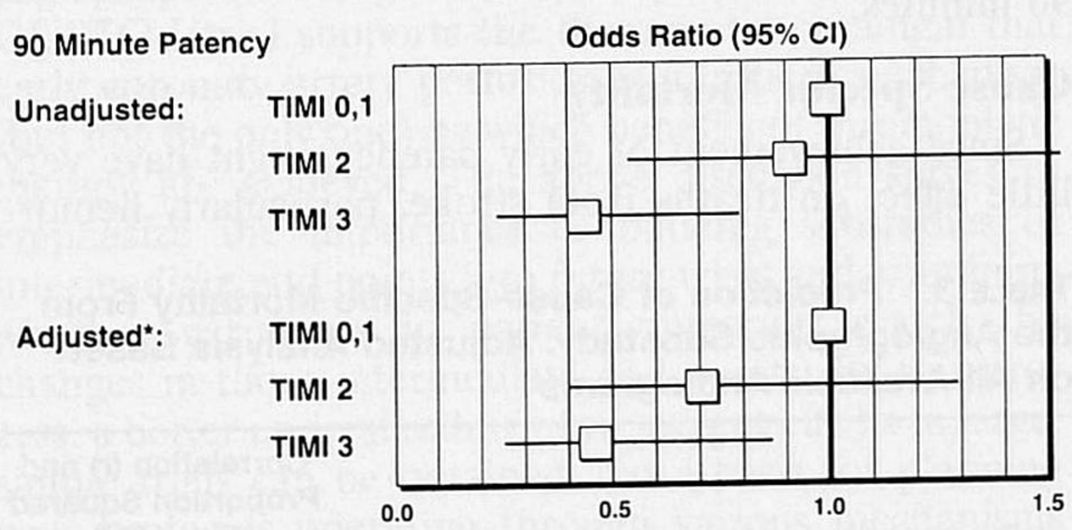

FIG 1. Graph showing relationship between TIMI grade flow and 30-day mortality. Odds ratios and 95% CIs are shown, both unadjusted and adjusted for the major prognostic factors identified from the main study: sex, age, previous myocardial infarction, location of infarction, height, systolic blood pressure, and heart rate.[14]

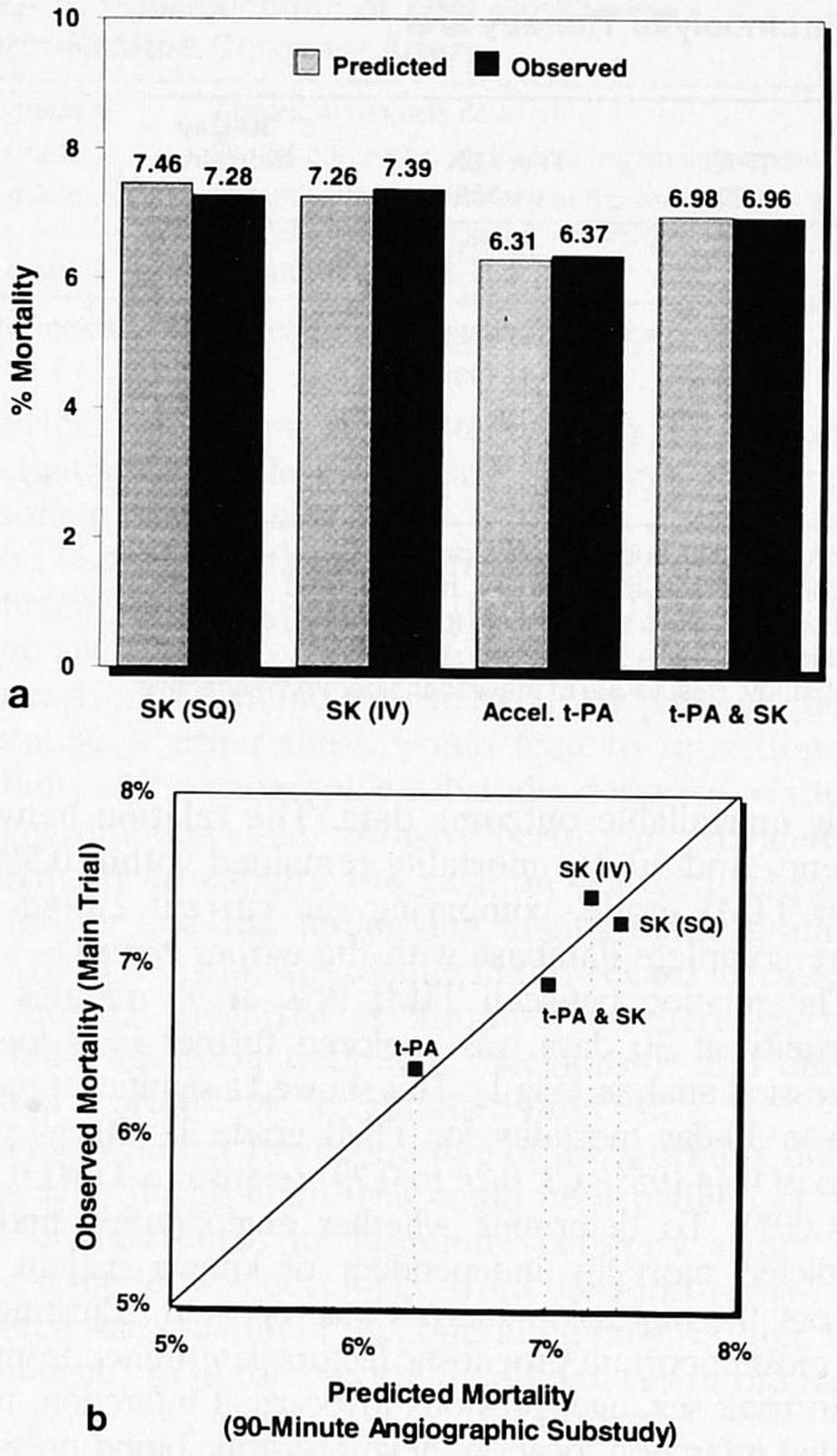

FIG 2. Graphs showing predicted versus observed 30-day mortality results by treatment assignment. Predicted results are based on the 1210 patients randomized to angiography at 90 minutes. Observed results refer to the remaining 39 811 patients in the main trial. a, Histogram of mortality results. b, Plot of predicted versus observed mortality, where points lying on the diagonal represent a perfect match. Proportion of squared error explained (R^2) is .92. SK (SQ) indicates streptokinase with subcutaneous heparin; SK (IV), streptokinase with intravenous heparin; Accel. t-PA, accelerated tissue-type plasminogen activator (TPA) with intravenous heparin; t-PA & SK, TPA plus streptokinase with intravenous heparin.

The proportion of squared error explained was also high (R^2=.92), suggesting that approximately 92% of the variation in mortality among the four treatments could be explained on the basis of differences in TIMI flow at 90 minutes.

Cause-Specific Mortality

Since achievement of early patency might have very little effect on deaths from stroke, particularly hemorrhagic stroke, a repeat analysis tested the ability of the model to predict cause-specific mortality with all fatal strokes or fatal hemorrhagic strokes excluded (Table 3). These results were very similar, with the degree of correlation at least .97 and the proportion of squared error explained still ≥92%.

TABLE 3. Prediction of Cause-Specific Mortality From the Angiographic Substudy: Adjusted Analysis Based on All Available Angiograms

	Correlation (*r*) and Proportion Squared Error (R^2)	
Cause-Specific Mortality	***r***	***R*²**
All-cause mortality	.97	.92
Excluding fatal strokes	.97	.92
Excluding fatal hemorrhagic strokes	.98	.96

Sensitivity Analysis

The results above were based on an analysis of the first angiogram in each patient, irrespective of time performed. When angiograms performed only within 3 hours or within 2 hours were examined (patients without early angiograms specified as unknown), similar results were obtained. Table 4 shows the degree of correlation and proportion of squared error explained for varying assumptions. The match was marginally greater when the predicted mortality results were adjusted according to the average mortality observed in the main trial. The match was not quite as strong when the alternative analysis was used to handle unknowns. Overall, the correlation was still .95 and the proportion of squared error explained ≥88%.

Discussion

The mortality differences predicted from the early patency data of the angiographic substudy closely matched the actual mortality results of the main trial. This suggests that the mortality rates were certainly consistent with a treatment effect operating through this mechanism. The ability of the model to predict cause-specific mortality, with fatal strokes excluded, was just as strong, and the sensitivity analyses indicated that this conclusion was robust when a number of assumptions used in the model were varied. Consequently, most of the mortality differences among the treatments in GUSTO-I could be accounted for by differences in early, complete perfusion.

The logistic regression model emphasized the importance of TIMI grade 3 flow at 90 minutes in predicting subsequent mortality. These results, essentially unaltered after adjustment for known patient risk factors, suggest that the relation is not simply a reflection of different patient groups but rather adds support to the hypothesis that treatment effects are mediated through restoration of coronary artery blood flow. The importance of TIMI grade 3 (but not grade 2) flow in

TABLE 4. Sensitivity Analysis: Varying the Assumptions Used in Predicting Mortality From the Angiographic Substudy

	Correlation (*r*) and Proportion Squared Error (R^2)			
	Primary Analysis		Alternative Analysis*	
Type of Analysis	***r***	***R*²**	***r***	***R*²**
Adjusted				
All available angiograms	.97	.92	.95	.90
Angiograms within 3 hours	.98	.95	.96	.92
Angiograms within 2 hours	.97	.91	.96	.90
Unadjusted				
All available angiograms	.97	.91	.95	.88
Angiograms within 3 hours	.98	.94	.96	.90
Angiograms within 2 hours	.97	.89	.96	.88

*See "Methods."

predicting mortality may provide an explanation for some of the inconsistencies between patency and outcome seen in earlier studies.

Although the findings from this analysis make a strong case for a biological explanation of treatment effect, they should not be overinterpreted. First, the analysis does not prove that treatment operates through this mechanism but rather that the size of the observed mortality effect is what one would predict through this mechanism. Second, the analysis relates only to the importance of early and complete perfusion in achieving differences in mortality among the therapies rather than the importance of this mechanism in achieving an absolute effect common to all four regimens.

The question posed earlier as to why ISIS-3 and GISSI-2 failed to demonstrate mortality differences when differences in coronary artery perfusion were anticipated is difficult to answer without an angiographic substudy built into these two large trials. How often early TIMI grade 3 flow was achieved in these trials is unknown, but it was most likely less for the standard-dose TPA or duteplase used in these trials than was achieved with accelerated TPA in GUSTO-I, based on angiographic findings from such trials as the Rapid Administration of Alteplase in Myocardial Infarction study (RAAMI),[16] TPA-APSAC Patency Study (TAPS),[17] and Thrombolysis and Myocardial Infarction (TAMI-7) study.[18] A pooled (nonrandomized) analysis of angiographic results from trials using standard versus accelerated TPA suggests that early TIMI grade 3 flow occurs in roughly an extra 13% of patients with accelerated TPA.[19] Hence, a smaller mortality reduction might have been expected with standard-dose TPA over streptokinase, but any reduction may have been offset by other factors, such as heparin dosing or the failure to use intravenous heparin in these trials, an important component of TPA regimens for sustained perfusion.[20-23]

Since accelerated TPA appears to achieve greater mortality reduction through early perfusion of the infarct-related artery (attaining complete perfusion of the infarct-related artery up to about 2 hours earlier in an extra 25% of patients), the GUSTO-I trial provides indirect support for the need for early thrombolytic treatment, a concept also supported by several other studies.[24-27] The fibrinolytic overview,[7] which reviewed all major controlled trials evaluating thrombolytic treatments, suggested that an additional 1.6 lives per thousand might be saved for every hour earlier that patients were randomized to treatment and perhaps 2 lives per thousand for every hour earlier that patients were treated (the benefit of earlier treatment will be underestimated when time-from-randomization data are used because of the variable delay from randomization to treatment, which results in regression dilution bias). This is less than the implied benefit of thrombolytic therapy in GUSTO-I, which suggested that roughly an additional 5 lives per 1000 were saved for each hour earlier that treatment began.

This apparent discrepancy may be explained if the benefit of early opening of the coronary artery were disproportionately greater within the first few hours of symptom onset, corresponding more closely with the size of the benefit of early treatment implied from GUSTO-I. The close match between patency and mortality differences in GUSTO-I and the fact that comparisons within GUSTO-I are direct and randomized lend some support to this notion.

Whatever the magnitude of the benefit of earlier treatment, the result from GUSTO-I that early, complete perfusion is associated with mortality reductions serves to emphasize the importance of beginning thrombolytic therapy as early as possible. While accelerated TPA leads to further reductions in mortality over other regimens, steps to improve time to treatment are important for all patients irrespective of which thrombolytic drug is given.

The angiographic patency-mortality model presented here is based only on patients randomized to angiography at 90 minutes. This is because results showed significant differences in complete perfusion at 90 minutes but few differences in perfusion at the subsequent times of 3 hours, 24 hours, and 7 days.[12] In fact, models based on the substudy at these times had no ability to predict 30-day mortality differences. Coronary reocclusion rates were low and similar for all four strategies and hence also unlikely to explain differences in 30-day mortality seen in the main trial. This does not imply that thrombolytic strategies that achieve late patency are not important in achieving mortality reductions but rather that this mechanism is highly unlikely to account for the mortality differences seen in GUSTO-I, in which all four therapies had similar late patency results.

Despite the reduction in 30-day mortality of 14% with accelerated TPA over the streptokinase regimens in GUSTO-I, the absolute mortality of 6.3% and early complete perfusion rate of 54% leave room for further improvement. If the goal of achieving nearly 100% early complete perfusion could be attained, then further reductions in mortality to as low as ≈4% (the rate associated with TIMI grade 3 flow in GUSTO-I) might be realized. Studies of immediate angioplasty for evolving myocardial infarction demonstrate that rates of early complete perfusion as high as 95% are possible,[28-30] and an overview of the randomized trials suggests that a 35% reduction in mortality for angioplasty over conventional thrombolytic strategies is possible.[31] This is the subject of ongoing studies such as the angioplasty substudy of the GUSTO-II trial.[32] Irrespective of which strategy is used in the treatment of evolving myocardial infarction, early restoration of complete infarct artery perfusion should be an essential therapeutic goal.

In conclusion, the picture within GUSTO-I provides a strong, internally consistent association between early angiographic findings and subsequent mortality. The GUSTO-I trial supports the therapeutic paradigm that early coronary artery perfusion is a critical mechanism (but not the only one) by which benefits of thrombolytic therapy are achieved. The above discussion serves to emphasize the importance of building substudies of intermediate end points into future trials and examining whether variations in patient outcomes match the changes in those intermediate end points. By this process, a better understanding of treatment effects in large, simple trials can be obtained and a basis for planning new strategies operating through various mechanisms can be developed.

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