Mortality at 1 Year With Combination Platelet Glycoprotein IIb/IIIa Inhibition and Reduced-Dose Fibrinolytic Therapy vs Conventional Fibrinolytic Therapy for Acute Myocardial Infarction
GUSTO V Randomized Trial

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Context Among patients with acute myocardial infarction, combination reperfusion therapy with a platelet glycoprotein IIb/IIIa receptor inhibitor (abciximab) and a half dose of a plasminogen activator (reteplase) did not significantly reduce mortality at 30 days compared with a full dose of reteplase. Rates of nonfatal ischemic complications were significantly diminished.

Objective To determine if the beneficial effects of abciximab and reteplase (combination therapy) on early nonfatal complications would translate into a reduction in the risk of death by 1 year.

Design, Setting, and Patients One-year follow-up of a randomized controlled trial (Global Use of Strategies To Open Coronary Arteries [GUSTO] V). Of 16588 patients who had been treated in 820 community and referral hospitals in 20 countries between July 1999 and February 2001, mortality data were available for 16453 (99.2%).

Intervention Patients were randomly assigned to receive (intravenously) a standard dose of reteplase (two 10-U boluses, 30 minutes apart) or the combination of a standard dose of abciximab (0.25 mg/kg bolus, 0.125 µg/kg per minute infusion [maximum 10 µg/min for 12 hours]) and a half dose of reteplase (two 5-U boluses, 30 minutes apart).

Main Outcome Measure One-year all-cause mortality rates.

Results All-cause mortality at 1 year occurred in 692 (8.38%) of 8260 patients in the reteplase group and 698 (8.38%) of the 8328 patients in the combination therapy group (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.90–1.11; P = .99). Reinfarction within the first 7 days occurred in 3.5% of patients in the reteplase group and 2.3% of patients in the combination therapy group, and was significantly associated with 1-year mortality (22.6% in patients with reinfarction vs 8.0% in patients without reinfarction; HR, 3.08; 95% CI, 2.53–3.75; P < .001). However, treatment assignment did not significantly influence time of mortality regardless of reinfarction status.

Conclusion Combination therapy (abciximab and reteplase) did not reduce mortality over 1 year compared with fibrinolytic therapy with reteplase alone.

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The primary efficacy end point was all-cause mortality by 30 days after randomization. Other early end points included the incidence of myocardial reinfarction, as evidenced by new electrocardiographic changes or elevation in cardiac enzyme levels with recurrent chest pain, during the hospitalization or within 7 days (whichever came first). Mortality at 1 year was a prospectively defined secondary analysis.

**Statistical Analysis**

The protocol required that patients be contacted by the study sites via telephone or written questionnaire at or after 365 days postrandomization for assessment of vital status. For analysis purposes, confirmed vital status information on or after day 335 postrandomization was accepted. The Kaplan-Meier method was used to calculate event rates and treatment groups were compared using the log-rank statistic. Treatment effects in subgroups are displayed as hazard ratios (HRs) and 95% confidence intervals (CIs) calculated using univariable Cox proportional hazards regression models. Analyses were conducted according to the intention-to-treat principle using SAS statistical software (Version 8; SAS Institute Inc, Cary, NC) and P<.05 was the level of significance.

**RESULTS**

The 1-year follow-up database was finalized on April 23, 2002. Mortality status at or beyond 335 days after randomization was available for 8196 (99.2%) of 8260 patients in the reteplase group and for 8257 (99.1%) of 8328 patients in the abciximab and reteplase group (FIGURE I). Baseline characteristics were balanced and did not differ between the 2 treatment groups (TABLE). The patients’ mean (SD) age was 61.3 (12.1) years. Twenty-five percent of the patients were women and 16% had diabetes mellitus. The mean (SD) time from onset of symptoms to randomization was 2.7 (2.0) hours. Thirty-seven percent of MIs were anterior in location and 98% of patients were classified as Killip class I or II. Aspirin had been administered before ran-

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domination to 71% of patients, β-adrenergic receptor blockers to 19%, and angiotensin-converting enzyme inhibitors to 14%. Rates of revascularization by hospital discharge were significantly lower in the combination therapy group, due entirely to the reduced need for percutaneous intervention within the first 6 hours (8.6% for reteplase alone vs 5.6% for abciximab and reteplase; P < .001).

All-cause mortality at 1 year occurred in 692 (8.38%) of 8260 patients in the reteplase group compared with 698 (8.38%) of 8328 patients in the abciximab and reteplase group (HR, 1.00; 95% CI, 0.90-1.11; P > .99). The nonsignificant absolute mortality difference of 0.3% observed at 30 days in favor of combination therapy (5.9% for reteplase vs 5.6% for abciximab and reteplase) was maintained until approximately 90 days (6.9% for reteplase vs 6.6% for abciximab and reteplase), after which the mortality curves converged and remained superimposed beyond 180 days (Figure 2). One-year mortality rates at 30 days and 1 year in the prespecified subgroups are compared in Figure 3. Although trends had been observed at 30 days for a mortality advantage with abciximab and reteplase in patients aged 75 years or younger or those with anterior infarction, diabetes, or time to treatment of more than 4 hours, differences in outcome were less apparent in those subgroups by 1 year.

Reinfarction within 7 days of randomization had occurred in 285 patients (3.5%) in the reteplase group and 194 patients (2.3%) in the abciximab and reteplase group (P < .001). The rate of subsequent mortality by 1 year was significantly higher among patients who had experienced reinfarction (22.6%) than among those who did not (8.0%) (HR, 3.08; 95% CI, 2.53-3.75; P < .001). When only those deaths occurring after the 7-day period for assessment of the reinfarction end point were considered, the excess risk of 1-year mortality associated with reinfarction was even more marked (HR, 6.65; 95% CI, 5.43-8.16; P < .001). Treatment assignment (reteplase vs abciximab and reteplase) did not significantly influence time of mortality regardless of reinfarction status (reinfarction: 20.4% vs −25.8%; without reinfarction: 8.0% vs 8.0%, respectively).

**Comment**

The GUSTO V trial was the first large-scale study to test an alternative strategy for pharmacologic reperfusion during acute MI, in which a reduced-dose fibrinolytic agent was combined with a potent antithrombotic adjunct. Although a mortality advantage of abciximab and reteplase relative to reteplase alone had not been observed at 30 days, the combination regimen had been associated with a decreased incidence of reinfarction and other nonfatal complications. In this follow-up analysis of GUSTO V, mortality rates at 1 year were the same among patients treated with abciximab and reteplase compared with reteplase alone, demonstrating that the combination regimen does not lead to a superior long-term survival benefit despite the early protection it affords from ischemic events.

The efficacy of fibrinolytic therapy for acute MI remains limited by incom-
complete restoration of infarct vessel patency, persistent cyclical coronary flow, reocclusion, or impaired tissue level reperfusion in a substantial proportion of patients. Although bioengineered with improved fibrin specificity, circulating half-lives, or resistance to inhibitors, the “third generation” plasminogen activators have nonetheless failed to produce incremental clinical benefit in large-scale mortality trials. Moreover, pharmacologic reperfusion therapy continues to be associated with disturbingly high rates of intracranial hemorrhage and other bleeding complications. Alternatively, direct percutaneous coronary revascularization has been shown in randomized trials to reduce composite end points of death, reinfarction, or stroke compared with fibrinolysis. Concerns regarding the potential for bleeding with the combination of a potent platelet inhibitor and a full-dose thrombolytic agent motivated the current investigation of low-dose fibrinolytic regimens with glycoprotein IIb/IIIa blockade. Phase 2 studies provided preliminary evidence that doses of reteplase or alteplase could be reduced by half when abciximab was also given, providing not only better infarct vessel patency relative to conventional fibrinolytic therapy, but also more complete resolution of electrocardiographic ST-segment elevations. It was perhaps somewhat surprising, then, that when tested in the large-scale GUSTO V mortality trial, this reperfusion strategy resulted in only a nonsignificant 0.3% decrease in the rate of death by 30 days relative to conventional reteplase monotherapy. More encouraging, however, was the finding of an apparent improved stability of reperfusion with combination therapy, as evidenced by significant reductions in rates of reocclusion.

The unequivocal efficacy of aspirin among patients with acute MI suggested that the clinical benefit derived from fibrinolytic therapy might be improved by adjunctive use of more potent platelet inhibitors. In small pilot trials, administration of a glycoprotein IIb/IIIa receptor antagonist during thrombolysis appeared to increase the speed and completeness of infarct vessel recanalization and reduce reocclusion. Concerns regarding the potential for bleeding with the combination of a potent platelet inhibitor and a full-dose thrombolytic agent motivated the current investigation of low-dose fibrinolytic regimens with glycoprotein IIb/IIIa blockade. Phase 2 studies provided preliminary evidence that doses of reteplase or alteplase could be reduced by half when abciximab was also given, providing not only better infarct vessel patency relative to conventional fibrinolytic therapy, but also more complete resolution of electrocardiographic ST-segment elevations. It was perhaps somewhat surprising, then, that when tested in the large-scale GUSTO V mortality trial, this reperfusion strategy resulted in only a nonsignificant 0.3% decrease in the rate of death by 30 days relative to conventional reteplase monotherapy. More encouraging, however, was the finding of an apparent improved stability of reperfusion with combination therapy, as evidenced by significant reductions in rates of reocclusion.

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farction, recurrent ischemia, and early urgent revascularization procedures. The subsequent Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT) 3 trial confirmed this observation, wherein the combination of abciximab and half dose of tenecteplase was associated with 37% to 51% relative reductions in the risks of reinfarction, refractory ischemia, or urgent percutaneous revascularization compared with tenecteplase alone.\(^{15}\)

Given that nonfatal ischemic complications, particularly reinfarction, have been associated with increased long-term mortality following acute MI,\(^{16}\) it was anticipated that the early beneficial effects of abciximab and reteplase in GUSTO V might translate to a significant reduction in the risk of death over extended follow-up. The 1-year analysis of GUSTO V failed to confirm this hypothesis. Rates of mortality were identical in the 2 treatment groups at 1 year, with superimposition of the time-to-event curves after the first 6 months.

Reasons for the lack of a survival benefit with combination therapy in GUSTO V despite apparent improvements in epicardial vessel recanalization and tissue level reperfusion in earlier trials remain unclear. It is possible that the 13% increase in infarct vessel patency observed in the angiographic pilot study with abciximab and reteplase compared with reteplase alone (55% vs 48%, respectively)\(^{16}\) was not of sufficient magnitude to produce an improvement in mortality. It may be relevant to note that the significant reduction in mortality obtained with alteplase vs streptokinase in the GUSTO I trial\(^{17}\) was accompanied by more than a 74% relative increase in the rate of 90-minute angiographic coronary patency (54% vs 31%, respectively; \(P < .001\)).\(^{16}\) The potential for modest improvements in angiographic end points to influence mortality may have been diminished in GUSTO V by the high use rates of other therapies (aspirin, \(\beta\)-blockers, and angiotensin-converting enzyme inhibitors), which have been proven to enhance clinical outcome following MI. It is also unknown if and how the difference in use of early percutaneous interventions affected long-term survival. Moreover, baseline characteristics suggest that the population of patients enrolled in GUSTO V may have been at relatively low risk for mortality, further limiting the ability of the trial to discriminate a benefit of combination therapy. Finally, the extent to which any improvement in myocardial reperfusion can impact long-term survival is likely to remain suboptimal when delays of approximately 3 hours between the onset of symptoms and treatment have allowed substantial irreversible myocardial necrosis to occur.

Should this therapy have any role in the contemporary management of acute MI? Although a survival benefit cannot be expected, abciximab and reteplase combination therapy may be a useful reperfusion strategy because of its effect on nonfatal end points. Notably, the results of GUSTO V confirmed that inhospital reinfarction has an unfavorable long-term prognosis, with a 3- to 6-fold increase in the risk of death by 1 year among patients who experienced reinfarction compared with those who did not. Data regarding cause of death were not collected within this trial format, and thus these findings do not elucidate the mechanisms of mortality risk associated with reinfarction. Previous analyses of smaller trials, however, have demonstrated that coronary reoclusion is associated with impaired recovery of global and infarct-zone regional left ventricular function,\(^{19}\) suggesting a potential hazard arising from pump dysfunction or arrhythmias.

It is nevertheless remarkable that even with contemporary medical therapies, nearly one quarter of patients who experience reinfarction can be expected to die within the following year. However, the absolute reduction of 1.2% in reinfarction rates observed with the combination therapy in this trial would be extrapolated to reduce mortality at 1 year by only approximately 0.18% (derived from the 14.6% absolute mortality reduction per patient with reinfarction), an effect that is too small to significantly influence overall 1-year mortality event rates. Nevertheless, prevention of reinfarction and other ischemic events may be a worthwhile objective for an individual patient and provides a rationale for considering combination therapy.

Potential benefits of the abciximab and reteplase combination therapy must be weighed against the near doubling of rates of nonintracranial bleeding observed in the primary analysis,\(^{8}\) especially since other combination fibrinolytic regimens under investigation may entail less hemorrhagic risk.\(^{15,20}\) Preliminary analyses suggest that older patients are at particular risk for bleeding with abciximab and reteplase, although clinically important hemorrhage in younger patients appears to be infrequent with this regimen (unpublished data, 2002). Moreover, multivariate modeling has demonstrated an interaction between the risk of intracranial hemorrhage and age, whereby patients older than 75 years are at increased risk, while those younger than 55 years may have significant protection against intracranial bleeding with combination therapy relative to reteplase alone.\(^{21}\) Although a formal economic analysis of GUSTO V is under way, it is unlikely that drug acquisition costs will prove to be a crucial factor in choosing between combination and conventional fibrinolytic therapies. The cost of abciximab is largely offset by the savings using a half dose of the thrombolytic agent reteplase.

The potential for combination therapy to unite the current dichotomy between mechanical and pharmacologic means of reperfusion for acute MI remains. Complementarity is suggested by the favorable trial experience with abciximab during primary percutaneous coronary revascularization for acute MI.\(^{22-24}\) The rationale for pretreatment with the combination of abciximab and reteplase in patients undergoing primary intervention would be to restore epicardial vessel patency and microvascular reperfusion during the time delay inherent in mobilizing the cardiac catheterization laboratory. GUSTO V did not test such an approach because early percutaneous revascularization was reserved for clinical indications of failed reperfusion.
and was not used routinely. Trials are currently under way to specifically evaluate this concept of “facilitated” percutaneous coronary intervention.

In conclusion, the 30-day and 1-year results of the GUSTO V trial together validate the regimen of abciximab with a half dose of reteleplase as the first alternative reperfusion strategy that is at least as effective as traditional fibrinolysis for acute MI. Although the combination of this glycoprotein IIb/IIIa receptor antagonist with a reduced-dose fibrinolytic is neither superior nor inferior to reteplase monotherapy with regard to short-term or long-term mortality, it represents an incremental therapeutic advance with regard to nonfatal outcomes. Selection of combination therapy for clinical use must be based on the perceived balance of benefit from reduced nonfatal ischemic complications vs risk of increased bleeding in individual patients.

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Author Contributions: Dr Lincoff, as principal investig ator of the GUSTO V study, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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