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Long-Term Results After the Glycoprotein IIb/IIIa Inhibitor Abciximab in Unstable Angina

One-Year Survival in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV—Acute Coronary Syndrome) Trial

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Background—This study was designed to investigate long-term effects of the glycoprotein IIb/IIIa inhibitor abciximab in patients with acute coronary syndrome without ST elevation who were not scheduled for coronary intervention.

Methods and Results—A total of 7800 patients were included with an acute coronary syndrome without ST elevation, documented by either elevated cardiac troponin or transient or persistent ST-segment depression. They were randomized to abciximab bolus and 24-hour infusion, abciximab bolus and 48-hour infusion, or matching placebo. The overall 1-year mortality rate was 8.3% (649 patients). One-year mortality was 7.8% in the placebo group and 8.2% in the 24-hour and 9.0% in the 48-hour abciximab infusion group. Compared with placebo, the hazard ratio for the 24-hour infusion of abciximab was 1.1 (95% CI 0.86 to 1.29), and for the 48-hour infusion, it was 1.2 (95% CI 0.95 to 1.41). The lack of benefit of abciximab was observed in every subgroup studied. Patients with negative troponin or elevated C-reactive protein had a higher mortality rate after treatment with abciximab for 48 hours than with placebo: 8.5% versus 5.8% in those with negative troponin ($P=0.02$), 16.3% versus 12.1% in those with elevated C-reactive protein ($P=0.04$).

Conclusions—Compared with placebo, abciximab did not provide any survival benefit at 1 year in patients admitted with an acute coronary syndrome with ST depression and/or elevated troponin who were not scheduled to undergo early coronary revascularization. In subgroups of patients, in particular those with low cardiac troponin or elevated C-reactive protein, abciximab was associated with excess mortality. (*Circulation*. 2003;107:437-442.)

Key Words: coronary disease ■ acute coronary syndromes ■ prognosis

The initiating event of an acute coronary syndrome (ACS) is thought to be rupture or erosion of an atherosclerotic plaque in a coronary artery due to inflammation followed by thrombosis.¹ Of the patients who present with ACS without ST-segment elevation, as many as 10% to 15% develop acute myocardial infarction or death within 1 year after admission. Medical therapy includes β -blockers, nitrates, calcium channel blockers, and antithrombotic therapy: aspirin, heparin, IIb/IIIa inhibitors, and clopidogrel.²⁻⁴ Coronary revascularization by either PTCA or CABG can be considered and is recommended in high- and intermediate-risk patients.^{2,3}

There are several randomized studies about the use of glycoprotein (GP) IIb/IIIa inhibitors in the treatment of ACS.⁵⁻⁹ Beneficial effects of GP IIb/IIIa inhibitors in patients

with ACS have been demonstrated with abciximab in patients with refractory angina who subsequently underwent a percutaneous coronary intervention (PCI)⁵ and with eptifibatid⁶ and tirofiban⁷ in studies in which a proportion of patients underwent early revascularization. In contrast, after 30 days of follow-up in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV—Acute Coronary Syndrome) study, no benefit was observed with abciximab⁸ in patients who were not scheduled for early coronary revascularization. A recent meta-analysis of all major trials of IIb/IIIa inhibitors in ACS, including GUSTO IV-ACS, demonstrated a modest but significant (relative risk [RR] 0.91, 95% CI 0.85 to 0.98) reduction in death and myocardial infarction at 30 days.¹⁰ The greatest benefit was observed in

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patients with elevated troponin, although data on troponin levels were missing in many patients in those trials. In most studies, follow-up data were available at 30 days and 6 months. In this report, we present the 1-year follow-up data of 7800 patients in GUSTO IV-ACS and relate these outcomes to baseline characteristics, including concentrations of cardiac troponin and C-reactive protein (CRP) at enrollment.

Methods

Study Design and Study Population

Design, methods, and 30-day main results of GUSTO IV-ACS have been described previously.⁸ In short, it was a multicenter, international, randomized trial of patients with ACS without persistent ST-segment elevation, including non-ST-elevation myocardial infarction and unstable angina. Eligible patients were aged 21 years or older and should have had 1 or more episodes of angina lasting at least 5 minutes within 24 hours before admission. They had either an abnormal cardiac troponin T or I test or at least 0.5 mm of transient or persistent ST-segment depression.

Drug Regimen

Patients were randomly assigned to 1 of 3 treatment groups: abciximab for 24 hours (0.25 mg/kg bolus followed by a 0.125- $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion up to a maximum of 10 $\mu\text{g}/\text{min}$ for 24 hours), followed by 24 hours of placebo infusion; abciximab for 48 hours (same bolus and infusion for total duration of 48 hours); or matching placebo (bolus and 48-hour infusion). All patients were to receive aspirin for at least 30 days if not contraindicated. Furthermore, all patients received an unfractionated heparin bolus and infusion of low-molecular-weight heparin (dalteparin) subcutaneously every 12 hours for 5 to 7 days or until a revascularization procedure or discharge. Coronary angiography was not recommended during or within 12 hours after completion of the study-agent infusion (ie, within 60 hours after randomization) unless the patient had recurrent or continuing ischemia at rest associated with ischemic ST-T changes that were unresponsive to intensive medical therapy.

Blood Sampling

Venous blood samples were collected at baseline and 8, 16, 24, 36, and 48 hours after randomization. Levels of CRP were determined at baseline. An elevated CRP was defined as a CRP value ≥ 10 mg/L. Elevated troponin was defined as cardiac troponin T or I above the upper limit of normal for the local qualitative or quantitative assay. Quantitative levels of troponin T were also determined centrally by a third-generation assay on an Elecsys (Roche Diagnostics), with the detection limit 0.01 $\mu\text{g}/\text{L}$.

Follow-Up Evaluation and End Points

The primary end point in the trial was the occurrence, within 30 days after randomization, of death (of any cause) or myocardial infarction, adjudicated by the Clinical End Point Committee. Follow-up data were obtained on vital status up to 1 year after randomization and were completed for 7746 patients (99.3%). Deaths were reported by the investigator at each site. Follow-up data were collected via the register office, the general practitioner, or direct contact with patients or their relatives by telephone.

Statistical Analysis

All analyses were by intention to treat. Differences between group means were tested by 2-tailed Student's *t* test. A χ^2 statistic was calculated to test differences between proportions. Survival functions were calculated with the Kaplan-Meier product limit method.¹¹ Mantel-Cox (or log-rank) test was applied to evaluate differences between survival functions. Categories for subgroup analyses included age, sex, diabetes, elevated troponin, ST depression, and CRP status. The effects of troponin on survival were assessed on both the local (qualitative) values and the central measured quantitative values. Quantitative troponin

TABLE 1. Baseline Characteristics

| Characteristic | Placebo (n=2598) | 24-h Abciximab (n=2590) | 48-h Abciximab (n=2612) |
|--|---------------------|----------------------------|----------------------------|
| Men | 1609 (62) | 1594 (62) | 1667 (64) |
| Age, y | 65.2 (11.1) | 65.1 (11.3) | 65.3 (11.5) |
| Previous MI | 788 (30) | 796 (31) | 830 (32) |
| Diabetes | 562 (22) | 551 (21) | 564 (22) |
| ST depression | 2073 (80) | 2094 (81) | 2082 (80) |
| Raised troponin* | 1329 (58) | 1361 (60) | 1351 (59) |
| Both ST depression and raised troponin | 815 (31) | 875 (34) | 823 (32) |
| Elevated CRP† | 580 (22) | 582 (22) | 545 (21) |
| Both CRP and raised troponin | 334 (13) | 339 (13) | 318 (12) |

Values are n (%), except for age, which is mean (SD).

*Cardiac troponin T or I above the upper limit of normal for local qualitative or quantitative assay.

†CRP value >10 mg/L.

nin values were divided into quartiles. Statistical significance was defined as a probability value of less than 0.05.

Results

Baseline Characteristics

Between July 17, 1998, and April 21, 2000, a total of 7800 patients were randomized. All baseline characteristics were similar among the 3 treatment groups (Table 1). Centrally measured quantitative troponin T levels ranged from 0.01 to 17.3 $\mu\text{g}/\text{L}$, and quartile limits were 0.01, 0.12, and 0.47 $\mu\text{g}/\text{L}$.

One-Year Mortality

Total mortality was 6.6% (516 patients) after 6 months and 8.3% (649 patients) after 1 year. Mortality was not significantly different between the 3 treatment groups: 1-year mortality was 7.8% in the placebo group, 8.2% in the 24-hour abciximab-infusion group, and 9.0% in the 48-hour abciximab-infusion group (Figure 1). Compared with placebo, the hazard ratio for the 24-hour infusion of abciximab was 1.1 (95% CI 0.86 to 1.29), and for the 48-hour infusion of abciximab, it was 1.2 (95% CI 0.95 to 1.41). When all patients treated with abciximab (both 24 and 48 hours) were compared with those treated with placebo, the hazard ratio was 1.1 (95% CI 0.94 to 1.29).

Predictors of Mortality

Increasing age and diabetes were strong predictors of 1-year mortality. Patients with body weight ≤ 75 kg had 1-year mortality of 9.6% compared with 7.4% in patients with body weight 75 to 90 kg and 6.6% in patients with weight ≥ 90 kg ($P<0.001$). The 1104 patients who were included in North America had 1-year mortality of 9.1% compared with 8.8% of those included in Eastern Europe and 7.9% of those included in Western Europe ($P=0.28$). Of the 4041 patients with positive local measurement of troponin at baseline, 1-year mortality was 9.1% (369 patients) compared with 6.9% in patients with negative troponin at baseline ($P<0.001$). There was a gradual increase of 1-year mortality with an increase in the quantitative troponin level: 1-year mortality in the ascending quartiles of troponin was 3.8%,

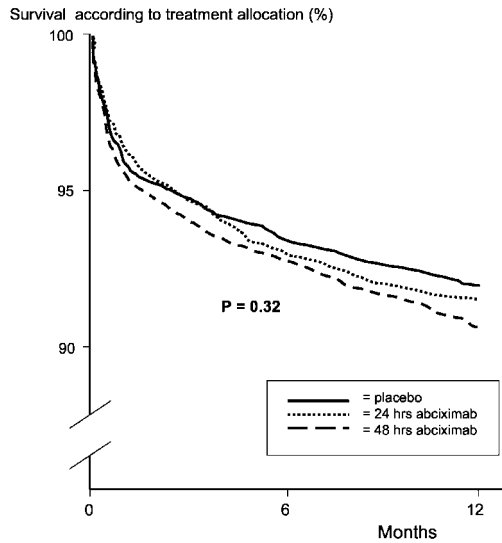


Figure 1. Proportion of patients who survived up to 1 year after randomization to placebo, 24-hour infusion of abciximab, and 48-hour abciximab. There was no significant difference between the 3 groups ($P=0.32$).

7.7%, 8.8%, and 13.3%, respectively. Of the 1707 patients with elevated CRP, 1-year mortality was 13.9% (237 patients) compared with 6.5% in patients without elevated CRP ($P<0.001$). Although positive troponin was a stronger predictor of mortality than an elevated CRP level, both determinants had independent additional value in predicting 1-year survival.

Effects of Abciximab in Subgroups

In Figure 2, the association between treatment with placebo, 24-hour abciximab, or 48-hour abciximab and 1-year mortality according to several subgroups is summarized. There was no subgroup in which patients treated with abciximab had significantly lower 1-year mortality compared with placebo. However, there were 3 subgroups in which 48-hour infusion of abciximab was associated with increased 1-year mortality: patients with body weight <75 kg and those with negative troponin or positive CRP at baseline. In patients with elevated troponin, an early mortality benefit was suggested for 24-hour abciximab; however, the survival curves of all 3 treatment groups with elevated troponin overlapped beyond 5 months (Figure 3). In contrast, a gradient with better outcome in the placebo group and worse outcome with 48-hour abciximab was apparent throughout in patients with a negative troponin value (Figure 4, log-rank test 0.04, P for trend=0.02). In the 2842 patients without elevated troponin, 1-year mortality was 5.8% in the placebo group compared with 8.5% in the 48-hour infusion group (hazard ratio 1.5, 95% CI 1.1 to 2.1). This effect was particularly apparent in females with negative troponin (hazard ratio 1.7, 95% CI 1.0 to 3.0) and was less clear in men (hazard ratio 1.4, 95% CI 0.9 to 2.1). In none of the quantitative troponin quartiles was a significant difference between the 3 treatment groups found. A consistent pattern of increased mortality with 48-hour abciximab compared with 24-hour abciximab and placebo was also apparent in patients with elevated CRP (log-rank test 0.1, P for trend=0.04),

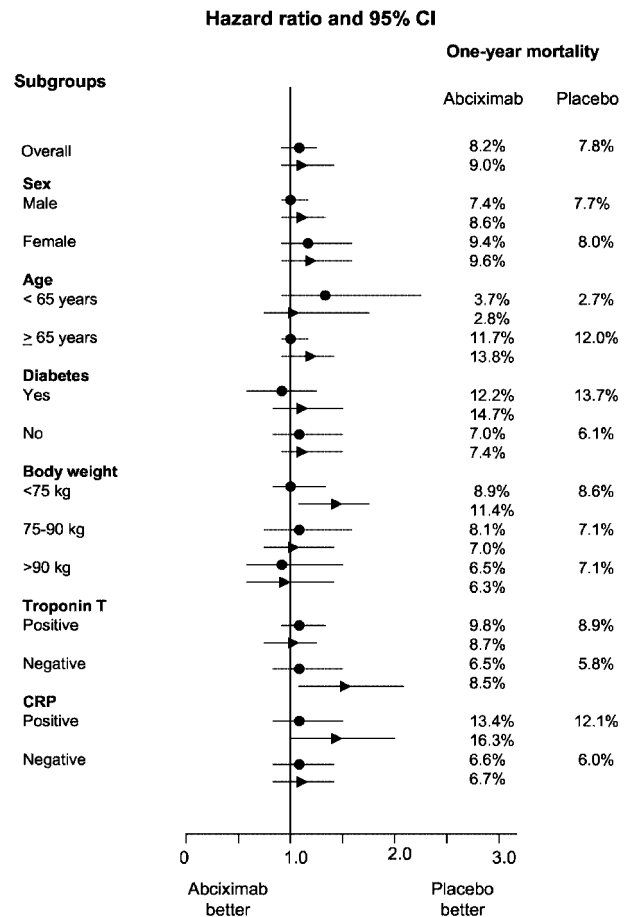


Figure 2. Subgroup analysis of 1-year mortality, hazard ratio, and 95% CI: placebo vs 24-hour abciximab, ●; placebo vs 48-hour abciximab, ▶.

whereas mortality was low and event curves overlapped in patients with a low CRP level at enrollment (Figure 5). In patients with an elevated CRP level, 1-year mortality was 12.1% in the placebo group compared with 16.3% in the 48-hour infusion group (hazard ratio 1.4, 95% CI 1.0 to 2.0).

A total of 128 patients (1.6%) had percutaneous revascularization within 48 hours, whereas 1509 patients had PCI within 30 days. In patients undergoing PCI within 30 days, there was no significant difference in the 1-year mortality rate among the 3 treatment groups, although there was a nonsignificant trend favoring abciximab therapy: 4.2% in the placebo group, 3.8% in the 24-hour abciximab group, and 3.6% in the 48-hour abciximab group (P for trend=0.6).

Discussion

The main findings at 1-year follow-up in GUSTO IV-ACS were that in patients with ACS who are not scheduled for early revascularization, routine use of abciximab did not provide a survival benefit. In some subgroups, a statistically significant excess mortality was apparent with 48-hour abciximab infusion, particularly in patients with elevated CRP, normal cardiac troponin, and low body weight. The results extend the previously reported findings of the primary and secondary end points at 30 days.⁸

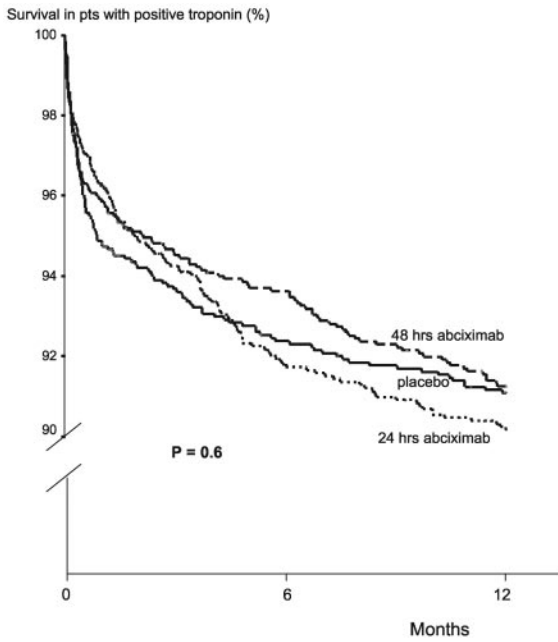


Figure 3. Proportion of patients (pts; n=4041) with positive local troponin who survived up to 1 year after randomization to either placebo, 24-hour infusion of abciximab, or 48-hour abciximab.

Comparison With Previous Trials

The lack of mortality benefit at 1 year with prolonged administration of abciximab in patients not undergoing early revascularization is in contrast with the survival benefit reported at follow-up of 5154 patients receiving abciximab during and after PCI.¹² In that meta-analysis, mortality after an average follow-up of 1 year was 3.4% with abciximab and 4.3% with placebo ($P=0.031$). The trend in patients under-

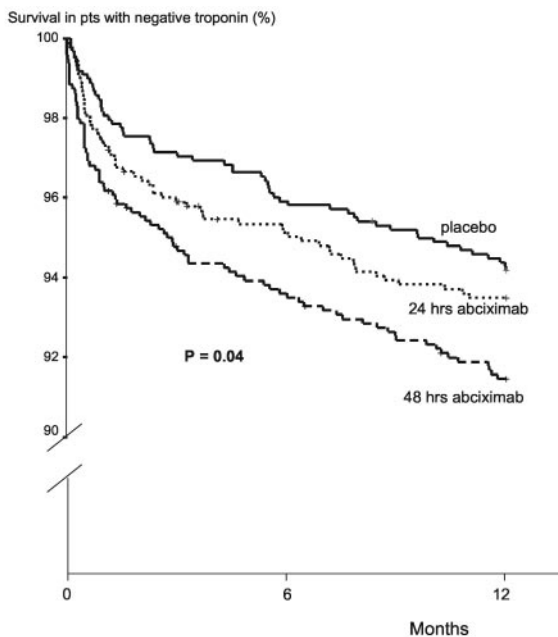


Figure 4. Proportion of patients (pts; n=2842) with negative local troponin who survived up to 1 year after randomization to either placebo, 24-hour infusion of abciximab, or 48-hour abciximab.

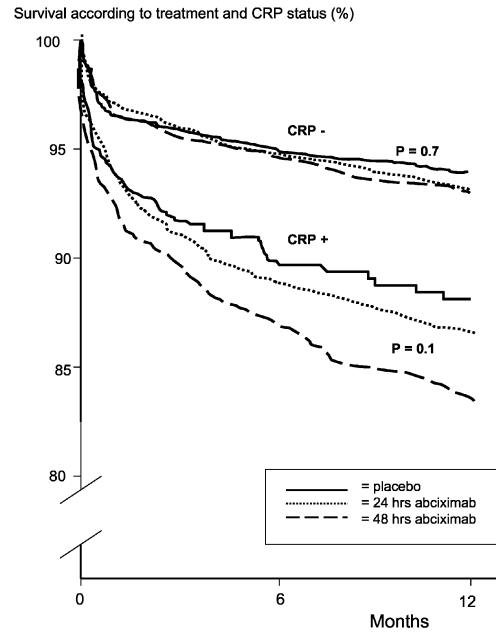


Figure 5. Proportion of patients with either elevated or normal CRP randomized to placebo, 24-hour abciximab, or 48-hour abciximab.

going PCI within 30 days in GUSTO IV-ACS was similar, although not statistically significant. The interpretation of the latter observation remains uncertain, however, because it was not recorded whether patients received a GP IIb/IIIa inhibitor at the time of the PCI. Studies with other GP IIb/IIIa inhibitors in ACS also showed no survival benefit after a follow-up period of 6 months,¹³ although GUSTO IV-ACS is the only one of these trials in which the estimate of the treatment effect favored placebo. The higher mortality in the several subgroups in GUSTO IV-ACS after 48-hour abciximab infusion are not fully explained. These subgroups may provide insight into effects of abciximab separate from platelet inhibition, as will be discussed below, but they may also be chance findings, particularly since the overall findings in the trial were not significantly different among the treatment groups.

Excess Mortality in Subgroups

In GUSTO IV-ACS, an excess in mortality with abciximab was observed in patients with negative cardiac troponin levels, and an unfavorable trend was seen in patients with signs of inflammation at enrollment, as reflected by elevated CRP levels. Elevated troponin may be a marker of extended intracoronary thrombosis in many patients, and without such thrombosis, aggressive platelet inhibition may be less important, and negative effects of antiplatelet therapy in general or abciximab in particular may prevail. The association of elevated CRP at enrollment and impaired outcome with prolonged (48 hours) administration of abciximab suggests that this particular GP IIb/IIIa receptor blocker may interfere with and enhance an inflammatory response in a subgroup of patients.

There is some evidence that GP IIb/IIIa inhibitors may, under certain circumstances, increase the incidence of ad-

TABLE 2. Clinical End Points

| Characteristic | Placebo (n=2598) | 24-h Abciximab (n=2590) | 48-h Abciximab (n=2612) |
|-------------------|---------------------|----------------------------|----------------------------|
| 30 Days | | | |
| Death | 102 (3.9) | 88 (3.4) | 111 (4.3) |
| MI | 133 (5.1) | 146 (5.6) | 153 (5.9) |
| Death or MI | 209 (8.0) | 212 (8.2) | 238 (9.1) |
| 30 Days to 1 year | | | |
| Death | 101 (4.0) | 124 (5.0) | 123 (4.9) |
| 1 Year | | | |
| Death | 203 (7.8) | 212 (8.2) | 234 (9.0) |

Values are n (%). There were no statistically significant differences.

verse events. The long-term oral GP IIb/IIIa inhibitors did increase mortality.¹⁴ Furthermore, there are some biological explanations for untoward effects¹⁵: antagonist-induced platelet activation, insufficient level of platelet inhibition, and proinflammatory effects. That the excess of mortality was particularly observed in patients with 48-hour abciximab may be explained by low levels of platelet inhibition during the later parts of the infusion.

During PCIs, abciximab reduced the number of leukocyte-platelet aggregates,¹⁶ and it diminished the rise in inflammatory markers after PCI.¹⁷ However, it is possible that these effects were secondary to the antithrombotic effects of abciximab. It has also been shown that abciximab may enhance leukocyte adhesion¹⁸ and that low dosages of abciximab may cause platelet activation and shedding of CD40 ligands.¹⁵ These may be interpreted as proinflammatory effects. Accordingly, the clinical importance of the effects of abciximab on inflammation, and the duration of these effects, should be further investigated.

Differences in Design Between Previous Trials

In the first report of GUSTO IV-ACS⁸ and the accompanying commentary,¹⁹ several suggestions were made for design-related causes of the unexpected lack of benefit with abciximab as observed: the patient selection, the dose and duration of abciximab, and statistical issues.⁸ None of these appeared to be fully satisfactory.¹⁹ The new information presented in this 1-year follow-up report indicates that the lack of benefit with abciximab is authentic and is not due to statistical chance.

An important difference from most previous studies of GP IIb/IIIa inhibitors in unstable angina was that in GUSTO IV-ACS, early angiography and subsequent revascularization were discouraged. Benefits of inhibition of platelet aggregation with abciximab and other GP IIb/IIIa receptor blockers have been demonstrated particularly in patients undergoing percutaneous (balloon or stent) coronary intervention.^{5,20–25} In this setting, disruption at the arterial wall may result in extensive intracoronary thrombosis, which can be prevented to a large extent by intensive antiplatelet therapy. In GUSTO IV-ACS, revascularization was performed within 48 hours in only a very few patients (0.3% CABG, 1.6% PCI), and abciximab would have been of particular benefit in these patients.⁸ Furthermore, of the 36 patients in the placebo group who underwent PCI within 48 hours, 24 (66%) received

abciximab (leaving only 12 patients with PCI within 48 hours on placebo, without abciximab), which may have masked potential beneficial effects of abciximab versus placebo. The observed better outcome at 1 year in patients with PCI within 30 days in GUSTO IV-ACS is in agreement with the results of previous trials, demonstrating the benefits of an invasive approach.^{26,27} However, the better prognosis of patients with PCI in GUSTO IV-ACS may be caused by selection bias.

It has been suggested that the absence of treatment benefit with abciximab might be related to selection of a low-risk patient population. This contention clearly is not supported by our 1-year observations. Overall mortality in GUSTO IV-ACS was 6.6% at 6 months and 8.3% at 1 year, which is comparable to that of the PURSUIT (Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial (5.8% at 6 months) and much higher than the 1-year mortality in FRISC II (Fragmin and/or early Revascularization during InStability in Coronary artery disease), which was 2.2% in the invasive group and 3.9% in the noninvasive group.²⁶ In fact, the 1-year mortality rate in the present trial was comparable to recent trials with fibrinolysis in patients with ST-elevation myocardial infarction.^{28–30} This may imply that the patients in the present trial consist of a relatively high-risk population compared with other ACS trials.

Although overall cardiovascular risk in GUSTO IV-ACS patients was not low, with a high proportion of ST-segment depression (80%) or positive troponin (52%) at baseline and a relatively high 1-year mortality, patients may still have been enrolled with a false-positive diagnosis of ACS. For example, positive troponin in GUSTO IV-ACS was allowed as a single objective inclusion criterion in patients with chest pain, but this may have been caused by renal failure, congestive heart failure, hypertension, or liver disease in some of the patients. Moreover, positive troponin may have been caused by an infarct several days before admission, because troponin may remain high for several days.

There were also differences between the ECG inclusion criteria of GUSTO IV-ACS and previous trials. In GUSTO IV-ACS, ECG ST depression had to be at least 0.5 mm, compared with at least 1.0 mm in the PRISM and PRISM-PLUS trials. Patients admitted with ACS with at least 0.5 mm of ST depression have an increased risk of mortality and infarction compared with patients with normal ECGs, although the severity of the ST depression is strongly associated with a poor prognosis.^{31,32} However, ECGs with ST-segment depression of 0.5 mm may have included nonspecific abnormalities. It is therefore possible that a proportion of the patients who were included in GUSTO IV-ACS did not have a real ACS. This is particularly of interest because an abnormal ECG was more often the reason for inclusion in women than in men. Indeed, women in other trials more often had nonsignificant coronary artery disease than men,³³ with a lack of treatment benefit. In fact, a significantly increased risk of death and myocardial infarction at 30 days in women was also observed with GP IIb/IIIa inhibitors in the recently published meta-analysis.¹⁰ However, it is difficult to demonstrate whether different patients were included in GUSTO IV-ACS because of the differences in inclusion criteria between GUSTO IV-ACS and previous trials and whether this may have influenced results. Head-to-

head comparisons are needed between the different GP IIb/IIIa inhibitors to guide medication choice.

Conclusions

GUSTO IV-ACS demonstrated that patients with ACS with ST depression and/or elevated troponin who were not scheduled to undergo early coronary revascularization while taking the study drug had a relatively high 1-year mortality. Troponin and CRP had additive value in predicting 1-year mortality. Compared with placebo, abciximab did not provide any survival benefit at 1 year. Patients without troponin elevation tended to do worse with abciximab, which is consistent with findings in other GP IIb/IIIa inhibitors.¹⁰ Those with CRP elevation also tended to do worse with abciximab, and this may represent a different pathophysiological mechanism that should be explored. The percentage of patients with early revascularization while taking study drug in GUSTO IV-ACS was very low, which may have contributed to the lack of benefit of abciximab. In patients with documented ACS, abciximab should be reserved for those patients undergoing PCI or who do not respond to medical therapy and in whom a PCI is planned within 24 hours.

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