Abciximab-Supported Infarct Artery Stent Implantation for Acute Myocardial Infarction and Long-Term Survival

A Prospective, Multicenter, Randomized Trial Comparing Infarct Artery Stenting Plus Abciximab With Stenting Alone

David Antoniucci, MD; Angela Migliorini, MD; Guido Parodi, MD; Renato Valenti, MD; Alfredo Rodriguez, MD; Albrecht Hempel, MD; Gentian Memisha, MD; Giovanni Maria Santoro, MD

Background—The impact on survival of routine use of abciximab as adjunctive treatment to routine infarct artery stenting for acute myocardial infarction is not defined. We sought to determine the effect of abciximab on 1-year survival and other major adverse cardiac events of patients with acute myocardial infarction undergoing routine infarct artery stenting.

Methods and Results—The Abciximab and Carbostent Evaluation (ACE) Trial is an unblinded, randomized, controlled trial that compared abciximab with placebo in patients undergoing routine infarct artery stent implantation for acute myocardial infarction. At 1 year, the survival rate was 95±2% in the abciximab group and 88±2% in the stent-alone group (P=0.017). The reinfarction rate was 1% in the abciximab group and 6.0% in the stent-alone group, whereas there were no differences between groups in target vessel revascularization rate (16.5% in the abciximab group, 17.5% in the stent-alone group).

Conclusions—Abciximab as adjunctive treatment to routine infarct artery stenting for acute myocardial infarction resulted in improved 1-year survival and lower reinfarction rates. (Circulation. 2004;109:1704-1706.)

Key Words: myocardial infarction ■ stents ■ glycoproteins

Abciximab provides well-established clinical benefits in several percutaneous coronary intervention trials by virtue of its antiplatelet and antiinflammatory effects that decrease target vessel failure and optimize reperfusion at the myocardial tissue level.1,2 However, previous concluded randomized trials comparing abciximab with placebo in patients undergoing infarct artery stenting for acute myocardial infarction (AMI) have produced conflicting results, and no individual trial detected a significant mortality benefit.3–5 The ACE (Abciximab and Carbostent Evaluation) Trial demonstrated a strong benefit of abciximab as adjunctive treatment to infarct artery stenting for AMI at 1- and 6-month follow-up, with a lower rate of the composite of death and reinfarction at 6 months (5.5% versus 13.5%, P=0.006).6 This effect was related in part to the already-established protective effect against early target vessel failure and in part to better myocardial reperfusion, as shown by the more frequent early ST-segment resolution and smaller infarcts in abciximab-treated patients as compared with placebo. We performed the 1-year follow-up of the ACE trial patients to determine if the beneficial effect of abciximab on myocardial reperfusion would translate into improved long-term survival.

Methods

Patients and Treatment

The ACE Trial design has been previously reported.6 The study is a multicenter, international, unblinded, randomized trial comparing abciximab plus stenting with stenting alone in 400 patients with ST-segment elevation AMI. The study was conducted from January 2001 to August 2002. Patients with AMI were randomly assigned to abciximab or placebo after baseline coronary angiography. The most relevant figure of the study design is that broad inclusion criteria were used to enroll a population representative of the “real world” of AMI. Patients with cardiogenic shock caused by predominant ventricular failure were included, as were patients with high-risk coronary anatomy (massive coronary thrombus, diffuse disease, a major branch involved in the culprit lesion, left main disease, or severe vessel tortuosity were not considered contraindications to stenting). The angiographic criteria for exclusion from random assignment included (1) infarct artery reference diameter <2.5 mm on visual assessment at baseline angiography, (2) previous stented infarct artery, (3) stenosis of the infarct artery <70% associated with Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow,7 and (4) inability to identify the infarct artery.

Follow-Up

The 1-year follow-up data were obtained from hospital charts and interviews with the patients or the primary physicians. The end points were death from any cause, nonfatal reinfarction, and target...
Analyses were performed with the software package SPSS 8.0 (SPSS Inc). A probability value of 0.05 was considered significant. The χ² test was used for comparison of categorical variables. The Mann-Whitney U test was used for comparison of continuous variables. Survival curves were generated by use of the Kaplan-Meier method, and the difference between curves was assessed by the log-rank test. Forward stepwise multivariate Cox regression analysis was performed to identify independent correlates of 1-year survival. All analyses were conducted according to the intention-to-treat principle. A probability value <0.05 was considered significant. Analyses were performed with the software package SPSS 8.0 (SPSS Inc).

### Statistical Analysis

The χ² test was used for comparison of categorical variables. The Mann-Whitney U test was used for comparison of continuous variables. Survival curves were generated by use of the Kaplan-Meier method, and the difference between curves was assessed by the log-rank test. Forward stepwise multivariate Cox regression analysis was performed to identify independent correlates of 1-year survival. All analyses were conducted according to the intention-to-treat principle. A probability value <0.05 was considered significant. Analyses were performed with the software package SPSS 8.0 (SPSS Inc).

### Results

Of 485 consecutive patients with ST-segment elevation AMI, 400 (82%) underwent random assignment. The 6-month follow-up data were available for all patients, and the 1-year follow-up data were available for 394 of 400 randomly assigned patients (98.5%).

The 2 groups of patients were well matched in all baseline characteristics, and the majority of the patients (66%) were “not low risk,” according to the TIMI criteria (Table 1). The 1-month mortality rates were similar in the 2 groups (3.5% in the abciximab group, 4% in the stent-alone group). At 6 months, the mortality rate increased to 4.5% in the abciximab group and to 8% in the stent-alone group; this difference did not reach significance (P=0.148).

Table 2 summarizes the 1-year follow-up data. At 1 year, the survival rate was 95±2% in the abciximab group and 88±2% in the stent-alone group (P=0.017). The cardiovascular mortality rate was 5.0% in the abciximab group and 10.5% in the stent-alone group (P=0.040), with a relative difference in cardiovascular mortality rate of 52%. There were 5 noncardiac deaths: 1 in the abciximab group and 4 in the stent-alone group; all noncardiac deaths were neoplastic. The Kaplan-Meier survival curves were nearly identical in the first month and progressively diverged during the following 11 months as a consequence of the greater increase in mortality rates in the stent-alone group (Figure). All cardiovascular deaths but one were cardiac (a fatal nonhemorrhagic stroke occurred in a patient in the stent-alone group). In the abciximab group, 7 of 10 cardiac deaths occurred within 1 month of random assignment, whereas in the stent-alone group, the majority of the cardiac deaths occurred after 1 month from random assignment (12 of 21 deaths). Heart failure accounted for the majority of deaths in both groups (5

### TABLE 1. Baseline Characteristics of Patients and Procedural Results

<table>
<thead>
<tr>
<th></th>
<th>Stenting Alone (n=200)</th>
<th>Stenting Plus Abciximab (n=200)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63</td>
<td>64</td>
<td>0.473</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>53–74</td>
<td>55–74</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>157 (79)</td>
<td>152 (76)</td>
<td>0.551</td>
</tr>
<tr>
<td>Hypertension</td>
<td>94 (47)</td>
<td>92 (46)</td>
<td>0.841</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>78 (39)</td>
<td>80 (40)</td>
<td>0.838</td>
</tr>
<tr>
<td>History of smoking</td>
<td>82 (41)</td>
<td>78 (39)</td>
<td>0.683</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (19)</td>
<td>33 (17)</td>
<td>0.699</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>25 (12)</td>
<td>20 (10)</td>
<td>0.279</td>
</tr>
<tr>
<td>Anterior acute myocardial infarction</td>
<td>92 (46)</td>
<td>81 (40)</td>
<td>0.267</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>21 (10)</td>
<td>16 (8)</td>
<td>0.388</td>
</tr>
<tr>
<td>Not low-risk patients</td>
<td>134 (67)</td>
<td>129 (65)</td>
<td>0.588</td>
</tr>
<tr>
<td>Symptom onset to reperfusion, h</td>
<td>4.2</td>
<td>3.7</td>
<td>0.080</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3.1–5.5</td>
<td>2.9–5.5</td>
<td></td>
</tr>
<tr>
<td>TIMI grade flow 0–1</td>
<td>149 (75)</td>
<td>156 (78)</td>
<td>0.411</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>115 (57)</td>
<td>108 (54)</td>
<td>0.481</td>
</tr>
<tr>
<td>Primary failure</td>
<td>2 (1)</td>
<td>1 (0.5)</td>
<td>0.511</td>
</tr>
<tr>
<td>Infarct artery stenting</td>
<td>197 (99)</td>
<td>198 (99)</td>
<td>0.653</td>
</tr>
<tr>
<td>Abciximab treatment</td>
<td>22 (11)</td>
<td>200 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postprocedural TIMI grade 3 flow</td>
<td>192 (96)</td>
<td>194 (97)</td>
<td>0.719</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise indicated.

### TABLE 2. One-Year Outcome

<table>
<thead>
<tr>
<th></th>
<th>Stenting Alone (n=200)</th>
<th>Stenting Plus Abciximab (n=200)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year survival, %</td>
<td>88±2</td>
<td>95±2</td>
<td>0.017</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>21 (10.5)</td>
<td>10 (5)</td>
<td>0.040</td>
</tr>
<tr>
<td>Heart failure or shock</td>
<td>14</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>4 (2)</td>
<td>1 (0.5)</td>
<td>0.159</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>12 (6)</td>
<td>2 (1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>35 (17.5)</td>
<td>33 (16.5)</td>
<td>0.790</td>
</tr>
<tr>
<td>Composite of death, reinfarction, and target vessel revascularization</td>
<td>72 (36)</td>
<td>46 (23)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise indicated.

vessel revascularization within 1 year of random assignment. Patients with more than 1 event were assigned the highest ranked event according to the previous list. Cardiovascular death was defined as sudden death or death caused by reinfarction, heart failure, arrhythmia, or fatal vascular disease. Reinfarction was defined as recurrent chest pain with ST-segment or T-wave changes and recurrent elevation of cardiac enzymes. Target vessel revascularization was defined as coronary angioplasty or coronary surgery performed for restenosis or reocclusion of the infarct artery.

The Kaplan-Meier survival curves were nearly identical in the first month and progressively diverged during the following 11 months as a consequence of the greater increase in mortality rates in the stent-alone group (Figure). All cardiovascular deaths but one were cardiac (a fatal nonhemorrhagic stroke occurred in a patient in the stent-alone group). In the abciximab group, 7 of 10 cardiac deaths occurred within 1 month of random assignment, whereas in the stent-alone group, the majority of the cardiac deaths occurred after 1 month from random assignment (12 of 21 deaths). Heart failure accounted for the majority of deaths in both groups (5
deaths in the abciximab group and 14 in the stent-alone group were due to heart failure). By Cox analysis, random assignment to abciximab resulted in an unadjusted hazard ratio (HR) of 0.43 (95% CI, 0.21 to 0.88; \( P=0.020 \)). The variables independently related to 1-year survival were age (HR, 1.07; 95% CI, 1.03 to 1.10; \( P<0.001 \)), cardiogenic shock (HR, 7.27; 95% CI, 3.44 to 15.39; \( P<0.001 \)), and time to reperfusion (HR, 1.12; 95% CI, 1.01 to 1.23; \( P=0.027 \)). At 1 year, early ST-segment resolution maintained a strong predictive value of cardiovascular survival (HR, 0.46; 95% CI, 0.22 to 0.96; \( P=0.040 \)).

The 1-month difference in reinfarction rates (0.5% in the abciximab group, 4.5% in the stent-alone group) was maintained at 1 year (1% in the abciximab group, 6% in the stent-alone group; \( P=0.006 \)).

There were no differences between groups in target vessel revascularization rates (16.5% in the abciximab group, 17.5% in the stent-alone group).

**Discussion**

Abciximab has consistently shown clinical benefits in PCI-AMI trials.\(^3\)\(^–\)\(^5\)\(^,\)\(^9\) However, all studies showed that the benefit is mainly due to the decrease in post-PCI early coronary complications such as myocardial infarction or the need for urgent target vessel revascularization, and no individual study could demonstrate a decrease in mortality rates. A recent meta-analysis of 4 PCI-AMI trials shows that abciximab therapy results in a significant decrease in the need for urgent target vessel revascularization but not in reductions of death or recurrent myocardial infarction.\(^10\) The lack of a significant effect of abciximab on survival in these studies may be explained at least in part by the low risk of the enrolled populations or the small number of patients.\(^11\)

The ACE trial shows that abciximab may prevent target vessel failure in the early phase by virtue of its antiplatelet effect and provide a better myocardial reperfusion by virtue of its dethrombotic and antiinflammatory effects. The latter effects have the potential for reduction of microvessel disruption caused by embolization and of reperfusion injury. The improved myocardial salvage in the early phase may translate into improved survival in the long-term follow-up.

Some limitations of the study should be acknowledged. The study was not sufficiently powered to assess differences in mortality rates, and the 1-year mortality rate was not a prespecified end point. Nevertheless, it is unlikely that the strong difference in mortality rates between groups was generated by chance. Early ST-segment resolution, a strong marker of the effectiveness of reperfusion and myocardial salvage, was more frequent in the abciximab group and maintained at 1 year a strong predictive value of survival at multivariate analysis, suggesting a mechanistic link between the treatment and improved late survival.

**Acknowledgments**

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**References**

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