Effect of Glycoprotein IIb/IIIa Receptor Blockade With Abciximab on Clinical and Angiographic Restenosis Rate After the Placement of Coronary Stents Following Acute Myocardial Infarction
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OBJECTIVES
In the Intracoronary Stenting and Antithrombotic Regimen-2 trial (ISAR-2), we sought to investigate the effect of abciximab on angiographic and clinical restenosis after stenting following acute myocardial infarction (AMI). We also intended to assess the impact of abciximab on clinical outcome in this setting.

BACKGROUND
It is unclear whether abciximab reduces neointima formation after stenting. Such an effect may be particularly prominent in thrombus-containing lesions.

METHODS
Patients undergoing stenting within 48 h after onset of AMI were randomly assigned to receive either standard-dose heparin or abciximab plus reduced-dose heparin. Of 401 patients randomized, 366 without 30-day adverse events were eligible for six-month angiographic follow-up. Scheduled angiography was performed in 80% of these patients.

RESULTS
By 30 days, the composite clinical end point of death, reinfarction, and target lesion revascularization (TLR) was reached in 5.0% of the abciximab group and in 10.5% of the control group (p = 0.038). At one year, absolute reduction in the composite clinical end point by abciximab was still 5.7% but had lost its statistical significance. Our primary end point, late lumen loss, was 1.26 ± 0.85 mm with abciximab and 1.21 ± 0.74 mm with standard heparin (p = 0.61), and binary angiographic restenosis rates were 31.1% and 30.6%, respectively (p = 0.92).

CONCLUSIONS
In patients undergoing stenting following AMI, abciximab exerted beneficial effects by substantially reducing the 30-day rate of major adverse cardiac events. During one-year follow-up, there was no additional benefit from a reduction in TLR nor did abciximab reduce angiographic restenosis. (J Am Coll Cardiol 2000;35:915–21) © 2000 by the American College of Cardiology

Glycoprotein IIb/IIIa receptor blockade with abciximab reduces the early hazard of ischemic complications after percutaneous coronary interventions by about one-half (1,2). It is currently unclear whether abciximab offers additional long-term benefit by reducing neointima formation.

In animal models, platelet deposition and aggregation at the site of vessel injury promote neointima formation (3–5). This concept is also supported by the clinical finding of an association between the PA polymorphism of platelet glycoprotein IIIa and the risk of angiographic restenosis after coronary stent placement (6). Potent platelet inhibition by abciximab may reduce neointima formation by blockade of not only glycoprotein IIb/IIIa but also vitronectin receptors and Mac-1. These integrins are known to play a key role in neointima formation (7–9).

Nevertheless, in angiographic studies of in-stent restenosis, binary restenosis rates were not reduced by abciximab, and the effect of abciximab on other indices of neointima formation was either marginal or absent (10,11). The inability of abciximab to prevent angiographic or clinical restenosis in unselected patient populations, however, does not exclude reduction of neointima formation in specific groups. For example, in EPISTENT (Evaluation of IIb/IIIa Platelet Inhibition for Stenting), abciximab markedly
Reduced clinical restenosis rate after stenting in diabetics (12). Patients with thrombus containing lesions may constitute another group in whom abciximab could be particularly effective in preventing neointima formation. This is suggested by animal models of restenosis indicating that the severity of intracoronary thrombosis after vessel injury predicts subsequent lumen narrowing (13).

Based on these findings, we hypothesized that potential inhibition of angiographic or clinical restenosis by abciximab was most pronounced in the most thrombogenic lesions; that is, in those of acute myocardial infarction (AMI). We, therefore, conducted the Intracoronary Stenting and Antithrombotic Regimen-2 trial (ISAR-2). This prospective randomized study on patients undergoing stenting following AMI investigated the effect of abciximab on angiographic restenosis as the primary end point. In addition, we assessed the effect of abciximab on clinical restenosis and on the composite rate of death, recurrent myocardial infarction and target lesion revascularization (TLR).

METHODS

Study cohort. The study included patients with AMI undergoing revascularization by stent placement within 48 h after onset of pain. Inclusion criteria were (a) typical anginal pain lasting >30 min, (b) ST-segment elevation of at least 1 mm in two or more contiguous leads, (c) elevation in creatine kinase to at least three times the upper limit of normal with a concomitant rise in MB isoenzyme, and (d) coronary artery occlusion with angiographic appearance of fresh thrombus. We recruited patients who met the first criterion plus at least one of the other criteria. Exclusion criteria were inability to give informed consent and contraindications to one of the study drugs. All eligible patients who gave written, informed consent were randomized by means of sealed envelopes. Patients, but not physicians, were blinded to the assignment of treatment. The study was carried out according to the Declaration of Helsinki and was approved by our institutional ethics committee.

Study protocol. Before catheterization, all patients received heparin, 5,000 U, and aspirin, 500 mg, intravenously. Once the decision was made for stent placement, patients were randomized to one of two treatment regimens. Patients assigned to treatment with glycoprotein IIb/IIIa receptor blockade received a bolus of abciximab, 0.25 mg/kg of body weight, followed by continuous infusion, 10 μg/min for 12 h plus an additional dose of heparin, 2,500 U, intraarterially. In patients assigned to usual care, we administered heparin, 10,000 U, intra-arterially, followed by IV heparin infusion, 1,000 U/h, for the first 12 h after sheath removal. Stent placement was performed as described previously (14). We used different types of slotted-tube stents, which were evenly distributed between the study groups (Table 1). In both groups, postinterventional antithrombotic therapy consisted of ticlopidine (250 mg bds) for four weeks and aspirin (100 mg bds) throughout the study. During hospital stay, creatine kinase was routinely monitored at intervals of 8 h until it returned to normal or at least for the first 24 h and daily thereafter. Patients with successful intervention (TIMI [thrombolysis in myocardial infarction] flow grade ≥2, residual stenosis <25%) and no adverse cardiac event within the first month were eligible for angiographic follow-up. Follow-up angiography was performed at six months or earlier if the patient had recurrent symptoms or signs of ischemia. Patients who had undergone angiography at <4 months after recruitment without meeting the criteria for a clinical endpoint were encouraged to undergo repeat angiography at six months.

Measures of clinical outcome. We monitored major adverse cardiac events, including death, nonfatal reinfarction, and TLR. Diagnosis of recurrent infarction was based on typical chest pain, new ST-segment changes and an increase in creatine kinase of at least 50% over the previous trough level in at least two samples reaching ≥240 U/liter. The TLR was defined as coronary artery bypass surgery (CABG) or repeat PTCA (percutaneous transluminal coronary angiography) involving the stented segment. It was performed for symptoms or signs of ischemia in the presence of angiographic restenosis.

Quantitative angiography and definitions. Angiographic images (Hicor; Siemens) were stored on compact discs and analyzed off-line by operators unaware of the study groups to which the patients were assigned. The TIMI flow grades before and after the intervention were assessed visually. Quantitative analysis was performed as described previously (14,15). We obtained minimal luminal diameter (MLD), reference diameter, percent diameter stenosis and the diameter of the maximally inflated balloon from the analysis system (MEDIS Medical Imaging Systems, Leiden, The Netherlands).

Acute gain was calculated as the difference between post-stenting and predilation MLD, late loss as the difference between post-stenting MLD and MLD at follow-up, net gain as the difference between MLD at follow-up and predilation MLD, and loss index was calculated as the ratio of late loss to acute gain. Angiographic restenosis was defined as diameter stenosis >50%.

Abbreviations and Acronyms

Abbreviations and Acronyms

- AMI = acute myocardial infarction
- CABG = coronary artery bypass surgery
- EPISTENT = Evaluation of IIb/IIIa Platelet Inhibition for Stenting
- MLD = minimal luminal diameter
- PTCA = percutaneous transluminal coronary angiography
- RAPPORT = ReoPro in Acute MI Primary PTCA Organization and Randomized Trial
- TIMI = thrombolysis in myocardial infarction
- TLR = target lesion revascularization
Study cohort, procedural and clinical outcome. The study enrolled 401 consecutive patients; 200 were assigned to usual care and 201 to abciximab treatment. The study groups were homogeneous with respect to baseline demographic, clinical and angiographic characteristics (Table 1).

In one patient of the abciximab group and three patients of the control group, the intervention was unsuccessful. The reasons were failure to recanализ the infarct-related occlusion and no-reflow (TIMI flow grade 1) despite recanalization in two patients, respectively. In 14 patients of the control group, the operators administered abciximab to deter imminent failure of the procedure. In 10 of these patients the intervention was completed with TIMI flow grade 3. There were no crossovers to higher-dose heparin in the abciximab group.

At 30-day follow-up, adverse cardiac events were significantly fewer in the abciximab group than in the usual-care group, with a relative risk reduction by abciximab of 53% (Table 2, Fig. 1). The beneficial effect of abciximab affected all components of the clinical end point almost equally. The absolute reduction in the incidence of adverse cardiac events was 5.5% at 30 days. During one-year follow-up, this absolute reduction persisted (5.7%), but was no longer statistically significant (Fig. 2). Noncardiac events occurred at a similar rate in both study groups (Table 2).

Angiographic and clinical indices of restenosis. Lesion characteristics, technical details of the stenting procedure and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). 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In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3). In particular, MLD after stenting and procedural results were comparable in both study groups (Tables 1 and 3).
follow-up (p = 0.80). The median time interval from the initial intervention was 194 days in the abciximab group and 193 days in the control group (p = 0.75).

At six-month follow-up, none of the angiographic indices of restenosis showed a significant difference between the two treatment groups (Table 3). Specifically, the primary end point of late loss was similar in both groups (Fig. 3). Similarly, loss index, net gain and MLD at follow-up were not significantly different between treatment groups. Binary restenosis rates were 31.1% in the abciximab group and 30.6% in the control group. Between 30 days and one year, 26 patients of the abciximab group and 27 patients of the control group required TLR (p = 0.87).

With respect to the effect of abciximab on angiographic restenosis rates, stratified analysis according to stent type did not show any significant interaction between stent type and abciximab (p = 0.56). When we removed patients with crossover to abciximab from the analysis, the point estimate for angiographic restenosis rate remained essentially unchanged (30.8%).

**DISCUSSION**

Our prospective randomized trial investigated the effect of abciximab on clinical outcome and angiographic restenosis after stenting following AMI. Compared with the reference treatment, abciximab reduced the early risk of adverse cardiac events within 30 days after stenting following AMI by more than one-half. Abciximab thereby achieved an absolute reduction in the cardiac event rate of 5.5% during the acute phase. This reduction in event rate was essentially maintained during the one-year follow-up. Contrary to our study hypothesis, we did not find an additional late benefit from abciximab through inhibition of restenosis development. Angiographically, none of the indices of neointima

### Table 2. Clinical Events During First 30 Days After Intervention

<table>
<thead>
<tr>
<th>Event</th>
<th>Abciximab (n = 201)</th>
<th>Usual Care (n = 200)</th>
<th>p Value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiac event</td>
<td>10 (5.0)</td>
<td>21 (10.5)</td>
<td>0.038</td>
<td>0.47 (0.25–0.88)</td>
</tr>
<tr>
<td>Death or repeat MI</td>
<td>5 (2.5)</td>
<td>12 (6.0)</td>
<td>0.08</td>
<td>0.41 (0.17–1.00)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (2.0)</td>
<td>9 (4.5)</td>
<td>0.16</td>
<td>0.44 (0.17–1.18)</td>
</tr>
<tr>
<td>Nonfatal MI*</td>
<td>1 (0.5)</td>
<td>3 (1.5)</td>
<td>0.62</td>
<td>0.33 (0.01–4.09)</td>
</tr>
<tr>
<td>TLR</td>
<td>6 (3.0)</td>
<td>10 (5.0)</td>
<td>0.30</td>
<td>0.60 (0.27–1.33)</td>
</tr>
<tr>
<td>PTCA</td>
<td>5 (2.5)</td>
<td>9 (4.5)</td>
<td>0.27</td>
<td>0.55 (0.23–1.33)</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any noncardiac event</td>
<td>7 (3.5)</td>
<td>9 (4.5)</td>
<td>0.79</td>
<td>0.77 (0.25–2.29)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery at access site</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>7 (3.5)</td>
<td>9 (4.5)</td>
<td>0.79</td>
<td>0.77 (0.25–2.29)</td>
</tr>
</tbody>
</table>

Data are expressed as number of patients (percentage). CI = confidence interval; MI = nonfatal reinfarction; RR = relative risk; TLR = target lesion revascularization.

*Occurring at day 11 in the abciximab group and at days 1, 17, and 29 in the usual-care group.

### Table 3. Quantitative Angiographic Data

<table>
<thead>
<tr>
<th>Event</th>
<th>Abciximab (n = 148)</th>
<th>Usual Care (n = 144)</th>
<th>p Value</th>
<th>Vessel size, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before stenting</td>
<td></td>
<td></td>
<td></td>
<td>3.13 ± 0.49</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>0.26 ± 0.39</td>
<td>0.28 ± 0.41</td>
<td>0.69</td>
<td>3.13 ± 0.51</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>91.2 ± 12.6</td>
<td>91.1 ± 12.5</td>
<td>0.92</td>
<td>3.13 ± 0.51</td>
</tr>
<tr>
<td>Balloon-to-vessel-ratio</td>
<td>1.07 ± 0.09</td>
<td>1.07 ± 0.09</td>
<td>0.96</td>
<td>3.13 ± 0.51</td>
</tr>
<tr>
<td>Inflation pressure, atm</td>
<td>14.4 ± 3.0</td>
<td>13.9 ± 3.0</td>
<td>0.12</td>
<td>3.13 ± 0.51</td>
</tr>
<tr>
<td>After stenting</td>
<td></td>
<td></td>
<td></td>
<td>3.04 ± 0.47</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>3.04 ± 0.47</td>
<td>3.04 ± 0.47</td>
<td>0.98</td>
<td>3.04 ± 0.47</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>5.1 ± 6.8</td>
<td>5.1 ± 7.6</td>
<td>1.00</td>
<td>3.04 ± 0.47</td>
</tr>
<tr>
<td>Stented length, mm</td>
<td>24.7 ± 16.4</td>
<td>22.5 ± 12.3</td>
<td>0.19</td>
<td>3.04 ± 0.47</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1.96 ± 1.23</td>
<td>1.94 ± 1.16</td>
<td>0.88</td>
<td>3.04 ± 0.47</td>
</tr>
<tr>
<td>At follow-up</td>
<td></td>
<td></td>
<td></td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.77 ± 0.92</td>
<td>1.82 ± 0.86</td>
<td>0.65</td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>43.3 ± 27.6</td>
<td>41.8 ± 24.7</td>
<td>0.63</td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>Restenosis rate, %</td>
<td>31.1 (23.6–38.5)</td>
<td>30.6 (23.0–38.1)</td>
<td>0.92</td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>2.77 ± 0.62</td>
<td>2.75 ± 0.61</td>
<td>0.78</td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>1.26 ± 0.85</td>
<td>1.21 ± 0.74</td>
<td>0.61</td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.47 ± 0.31</td>
<td>0.46 ± 0.31</td>
<td>0.94</td>
<td>1.77 ± 0.92</td>
</tr>
<tr>
<td>Net gain, mm</td>
<td>1.51 ± 0.94</td>
<td>1.54 ± 0.96</td>
<td>0.80</td>
<td>1.77 ± 0.92</td>
</tr>
</tbody>
</table>

Data are expressed as mean value ± SD or percentage (95% confidence interval).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Cumulative combined frequency of death, reinfarction and TLR during 30-day follow-up in the two treatment groups.
formation suggested an advantage of abciximab over the reference regimen, and binary angiographic restenosis rates were virtually identical in both groups. These findings correspond to similar rates of late (>30 days) TLR in both study groups.

Benefit of abciximab during the acute phase after stenting following AMI. Our study demonstrated an important contribution of abciximab to efficient interventional treatment of AMI. Although it lacked power to detect statistically significant differences between the individual components of the clinical end point, it suggests a consistent effect on each type of adverse cardiac events. Most notably, abciximab conferred conspicuous 2.5% absolute reduction in the rate of death. The advantageous effects of abciximab may be explained by improvement of both large-vessel patency and microcirculation. In a study comparing abciximab with conventional antithrombotic treatment after stenting following AMI, we recently showed improved recovery of coronary microvascular reperfusion with abciximab that was linked to better recovery of contraction in the area at risk (15). The underlying mechanisms for these effects may be diminished distal embolization of platelet aggregates as well as inhibition of direct interaction of platelets with the reperfused endothelium by abciximab (7,17–20).

We investigated the effect of abciximab in a cohort that comprised the entire spectrum of patients with AMI referred to a tertiary-care hospital within 48 h after onset pain. Apart from patients with Q-wave AMI within the first 12 h, our study included patients with non-Q-wave AMI, those with persistent angina for more than 12 h and those with failed thrombolysis. Abciximab, thus, improved the 30-day clinical outcome of stenting in a very broad spectrum of patients with AMI.

The 53% relative risk reduction by abciximab we found during the acute phase after stenting following AMI is similar to the 51% risk reduction reported for abciximab in plain PTCA following AMI on one hand (21) and to the 51% risk reduction reported for abciximab in stenting in the absence of AMI on the other hand (22). This consistent effect of abciximab supports the concept that the benefit from glycoprotein IIb/IIIa receptor blockade in interventional cardiology is not restricted to a certain device or coronary syndrome.

Lack of effect on angiographic and clinical restenosis. To our knowledge, the effect of abciximab on angiographic or clinical restenosis after stenting following AMI has not been investigated before. Thus, our study demonstrates for the first time that the thrombus-containing lesions of AMI do not constitute a subset in which abciximab inhibits neointima formation.

The concept that abciximab reduces angiographic restenosis rates in specific high-risk subgroups is suggested by the EPISTENT angiographic substudy. In EPISTENT, diabetics assigned to abciximab had a significantly lower target vessel revascularization at six months than did those assigned to placebo, an effect that was absent in nondiabetics (10,12). Based on published animal experiments (3,5,13), we hypothesized that thrombus-containing lesions such as those of AMI may constitute another subgroup in whom abciximab protects from angiographic or clinical restenosis.

Our findings confirm the concept that patients with AMI constitute a high-risk subgroup for in-stent restenosis. Comparing our study with contemporary angiographic studies on stenting we found a substantially increased neointima formation. In Evaluation of ReoPro and Stenting to Eliminate Restenosis, EPISTENT, and BENESTENT II (10,11,22,23), average late loss was 0.63 to 0.80 mm, while it was 1.24 mm in our current study. Nevertheless, we were unable to detect a beneficial effect of abciximab on angiographic in-stent restenosis. Our primary end point, late loss, did not show a reduction in neointima formation by abciximab. None of the other variables of neointima formation demonstrated superiority of abciximab over control treatment. Moreover, the angiographic results were corroborated by nearly identical rates of TLR in both groups from day 30 to one-year follow-up. Our inability to show an effect of abciximab on angiographic in-stent restenosis
cannot be attributed to limited statistical power because the observed insignificant treatment effect favors control.

**Study limitations.** The fact that physicians were not blinded to the treatment represents a limitation of our study. Angiographic evaluations, however, were performed by blinded operators. Thus, bias in the assessment of the primary end point can be excluded. By the use of a predefined clinical end point criteria and of strict indications for TLR, we also minimized bias in the assessment of clinical outcome.

In some eligible patients we could not obtain angiographic follow-up. This problem affected both study groups similarly. Previous analyses have shown that reliable estimates of restenosis rates can be obtained with angiography rates ≥80% as in our study (24).

In 14 patients of the usual-care group, operators administered abciximab to deter a detrimental outcome of the intervention. These crossovers may have attenuated somewhat the observed beneficial effect of abciximab.

**Implications.** The investigators of the ReoPro in Acute MI Primary PTCA Organization and Randomized Trial (RAPPORT) on glycoprotein Ib/IIa receptor blockade with PTCA following AMI concluded that “the use of (these) platelet inhibitors may be particularly valuable in patients who are not candidates for stenting” (21). Our study extends the findings of RAPPORT in demonstrating that the benefit from abciximab following AMI is as prominent with stenting as it is with plain PTCA. We found a 53% reduction in 30-day event rates, and although we did not detect an additional benefit from inhibition of angiographic or clinical restenosis, there was no appreciable attenuation of the initial beneficial effect either.

Our studies add weight to the concept that stenting and glycoprotein IIb/IIIa receptor blockade afford beneficial synergy (10) in AMI. As shown previously by the Zwolle group and the PAMI group, stents improve the six-month clinical outcome compared with PTCA by reducing TLR, but they have no beneficial effect on the risk of early complications and even deteriorate the rate of TIMI flow grade 3 (25,26). In contrast, our studies demonstrate that, compared with conventional treatment, abciximab enhances myocardial reperfusion (15) and improves 30-day outcome after stenting following AMI (this study). Combining the assets of stenting with those of GPIIb/IIIa receptor blockade may thus afford a highly efficient reperfusion strategy.

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