EXPEDITED REVIEW

A Randomized Trial of Coronary Stenting Versus Balloon Angioplasty as a Rescue Intervention After Failed Thrombolysis in Patients With Acute Myocardial Infarction

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OBJECTIVES
This study was conducted to assess whether coronary stenting produces better results compared with balloon angioplasty in patients with acute myocardial infarction (AMI) after failed thrombolysis.

BACKGROUND
Little evidence exists on the value of rescue mechanical reperfusion after failed thrombolysis.

METHODS
This open-label, randomized study enrolled 181 patients with AMI referred for failed thrombolysis performed within the previous 24 h. The patients had to have a Thrombolysis In Myocardial Infarction (TIMI) flow grade of ≤2 in coronary angiography. Patients were randomly assigned to coronary stenting (90 patients) or coronary balloon angioplasty (91 patients). Salvage index (proportion of initial perfusion defect salvaged by rescue intervention), which was obtained by paired scintigraphic studies performed 7 to 10 days apart, was the primary end point of the trial. One-year clinical follow-up was assessed.

RESULTS
Myocardial salvage index (median [25th, 75th percentiles]) was significantly greater in the stent group than in the angioplasty group (0.35 [0.24, 0.56] vs. 0.25 [0.04, 0.43]; p = 0.005). Major bleeding occurred in four patients (4%) in the stent group and four patients (4%) in the angioplasty group. One-year mortality was 8% (7 patients) in the stent group versus 12% (11 patients) in the angioplasty group (relative risk, 0.6; 95% confidence interval 0.2 to 1.6; p = 0.35).

CONCLUSIONS
Patients with AMI and failed thrombolysis benefit from rescue mechanical reperfusion in terms of myocardial salvage. Coronary stenting is associated with a greater myocardial salvage in this setting compared with coronary balloon angioplasty. (J Am Coll Cardiol 2004;44:2073–9) © 2004 by the American College of Cardiology Foundation

Thrombolytic therapy fails to restore full patency of the infarct–related arteries in up to 54% of the patients (1,2). The Thrombolysis In Myocardial Infarction (TIMI) investigators demonstrated that patients with angiographic occlusion of infarct–related arteries (TIMI flow grades 0 and 1) and those with suboptimal reperfusion (TIMI flow grade 2) have double the mortality of patients with an optimal (TIMI flow grade 3) reperfusion (3). Percutaneous transluminal coronary angioplasty has been used for the treatment of failed thrombolysis, but the results have been either contradictory or of marginal clinical benefit (4–15). The Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints (RESCUE) study showed a trend toward reduced 30-day mortality and severe heart failure in patients treated with rescue angioplasty versus those treated with conservative therapy (8). Other studies of rescue angioplasty have reported higher rates of bleeding complications or in-hospital repeat revascularizations but not a clear-cut benefit in survival (4,6,10,11). Furthermore, it is unanimously accepted that failed rescue angioplasty is associated with an excessively high mortality (13,14). For these reasons, there is a considerable variability in the use of rescue angioplasty in patients with acute myocardial infarction (AMI) after failed thrombolysis, and even the strategy of rescue angioplasty has been called into question (13).

The fact that failed thrombolysis is more likely associated with complex atherosclerotic plaques (16) and that post-thrombolytic state leads to a greater degree of platelet activation than that seen in the setting of AMI (17,18) may explain the less than optimal efficacy of rescue angioplasty in the setting of failed thrombolysis. Although coronary stenting may offer advantages over angioplasty in the acute phase of myocardial infarction (19), only limited research on small series of patients has been performed to date with regard to the efficacy of rescue stenting in the setting of failed thrombolysis (20–22). We conducted this randomized prospective study with a two-fold objective: we assessed whether patients with AMI and failed thrombolysis benefit from rescue mechanical reperfusion in terms of myocardial salvage. Coronary stenting is associated with a greater myocardial salvage in this setting compared with coronary balloon angioplasty.
from percutaneous coronary interventions (rescue stenting or balloon angioplasty) in terms of myocardial salvage, and we compared the reperfusion efficacy and clinical outcome achieved by coronary stenting versus balloon angioplasty in this setting.

**METHODS**

**Patients.** Eligible for this study were patients with AMI referred from other hospitals to the Deutsches Herzzentrum and 1. Medizinische Klinik rechts der Isar owing to the suspicion of failed thrombolysis (on the basis of clinical and electrocardiographic criteria) in the period from September 1998 through December 2002. Before randomization, all patients received intravenous aspirin (500 mg) and heparin up to a total dose of 5,000 U if activated clotting time was <200 s. After diagnostic coronary angiography showed TIMI flow grade of ≥2 in the infarct-related artery, the patients were then randomly assigned to either coronary stenting or balloon angioplasty according to the randomization code contained in sealed envelopes. Coronary placement of bare stents and balloon angioplasty were performed according to standard techniques. The protocol allowed but did not mandate the use of stents in patients assigned to balloon angioplasty in the presence of suboptimal results (large dissections or residual diameter stenosis visually estimated to be 30% or greater). Abciximab (ReoPro, Lilly Deutschland GmbH, Bad Homburg, Germany) was given as a bolus dose of 0.25 mg/kg of body weight followed by a continuous infusion of 0.125 μg/kg/min (up to a maximum of 10 μg/kg/min) for 12 h. Post-interventional antithrombotic therapy consisted of 200 mg of aspirin indefinitely and thienopyridines (ticlopidine or clopidogrel) for at least four weeks.

**Angiographic evaluation.** The initial and post-procedural flow in the infarct-related artery was graded according to the TIMI classification (1). Left ventricular (LV) ejection fraction was measured using LV angiograms. Digital coronary angiograms were analyzed offline in the angiographic core laboratory with an automated edge-detection system (CMS, Medis Medical Imaging Systems, Nuenen, the Netherlands). Grades of collateral filling were assessed according to Rentrop et al. (23).

**Technetium sestamibi myocardial scintigraphy.** Before initiation of the assigned therapy, patients received an intravenous injection of 27 mCi (1,000 MBq) of technetium 99mTc sestamibi. Single-photon emission computed tomography (SPECT) was performed within 6 to 8 h after injection of the radionuclide. A follow-up myocardial scintigraphy was scheduled 7 to 10 days after the primary coronary intervention and was done using the same protocol as in the initial study. The methods used for scintigraphic studies have been described in detail previously (24). All measurements were performed in the core laboratory by operators who were unaware of the assigned treatment. Paired scintigraphic data allowed the calculation of initial perfusion defect (perfusion defect at baseline scintigraphy), final infarct size (perfusion defect at follow-up scintigraphy), and salvage index, which represents the proportion of the initial perfusion defect that is salvaged (calculated as initial perfusion defect minus final infarct size divided by initial perfusion defect).

**Study definitions and follow-up.** The primary end point of the study was the salvage index in SPECT. We also monitored the occurrence of death, recurrent myocardial infarction, stroke, major bleeding complications, and target vessel revascularization. The diagnosis of recurrent myocardial infarction was based on the findings of typical chest pain accompanied by either new ST-segment changes or an increase in the creatine kinase activity of at least 50% above the trough level in at least two consecutive samples reaching a level of at least three times the upper limit of normal. A bleeding complication was defined as major if it was intracranial, or if clinically significant overt signs of hemorrhage were associated with a drop in hemoglobin of >5 g/dl or when hemoglobin was not available, an absolute drop in hematocrit of at least 15% (25). The diagnosis of stroke required confirmation by computed tomography or magnetic resonance imaging of the head.

The follow-up protocol after discharge consisted of a phone interview at 1 month after the procedure, a visit at 6 months, and a phone interview at 12 months. Patients were advised to present to the outpatient clinic or their referring physicians if they developed chest pain or other cardiac symptoms. In case of symptoms, at least one clinical, laboratory and electrocardiographic check-up was performed.

**Statistical analysis.** Based on our findings with stenting in patients with failed thrombolysis before the initiation of this trial, we assumed a salvage index of 0.40 for stenting and a
A 33% increase with respect to balloon angioplasty (assumed salvage index of 0.30). A sample size of 140 patients (70 patients in each group) was required to ensure the detection of this 30% difference between the groups with a two-sided alpha value of 0.05 and a power of 80%. A total of 181 patients were included in the study to allow for the possibility of incomplete SPECT examinations in some of the patients.

The analysis was done according to the intention-to-treat principle. Data are presented as median [25th, 75th percentiles], counts, or proportions (percentages). Continuous data were compared using the Wilcoxon rank-sum test. Categorical data were compared with chi-square test or Fisher exact test when expected cell values were <5. The Kaplan-Meier method was used to estimate cumulative adverse event rates. Differences in the cumulative adverse event rates were assessed by the log-rank test that also allowed the calculation of the relative risk (95% confidence intervals). A value of p < 0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics. Of the 181 patients enrolled in the study, 90 patients were assigned to the stent group and 91 patients to the angioplasty group. The groups were balanced in terms of baseline demographic and clinical characteristics (Table 1) as well as angiographic data (Table 2). The initial perfusion defect was also similar: 29.3% of the LV [16.0%, 44.5%] in the stent group versus 30.3% of the LV [19.3%, 58.0%] in the angioplasty group (p = 0.31).

Procedural characteristics. These characteristics are displayed in Table 3. As expected, diameter stenosis after intervention was smaller in the stent group. Periprocedural abciximab therapy was given to almost all patients in both groups. Although the TIMI flow grade in general did not differ significantly among the study groups, a trend was observed indicating that full restoration of anterograde flow was more frequent in the stent group (79 patients, 88%) than in the angioplasty group (72 patients, 79%; p = 0.11). Direct stenting (stenting without pre-dilatation) was performed in 14% of the patients in the stent group.

Scintigraphic results. Paired initial and follow-up SPECT examinations could be obtained in 75 patients (83%) assigned to the stent group and in 71 patients (78%) assigned to the angioplasty group (p = 0.36). Reasons for incomplete scintigraphic studies are shown in Table 3. The time interval from randomization to follow-up SPECT study was comparable: 9 days [7, 12 days] in the stent group versus 9 days [7, 10 days] in the angioplasty group (p = 0.91).

There was a trend toward a smaller final infarct size in the stent group, 18.6% of the LV [6.0%, 33.2%] versus 21.6% of the LV [10.0%, 41.7%] in the angioplasty group (p = 0.29). Salvage index was significantly greater in the stent group (0.35 [0.24, 0.56]) than in the angioplasty group (0.25 [0.04, 0.43]; p = 0.005) (Fig. 1). When the analysis was restricted to 125 patients with paired scintigraphic studies...
and no previous myocardial infarction, salvage index was also greater in the stent group than in the angioplasty group (0.36 [0.26, 0.60] vs. 0.25 [0.06, 0.45]; p = 0.006). When the patients were analyzed as treated, salvage index was 0.35 [0.15, 0.53] among patients who actually received stenting and 0.25 [0.10, 0.43] among patients who actually received plain balloon angioplasty (p = 0.08).

Clinical outcome. Five patients (6%) in the stent group and nine patients (10%) in the angioplasty group (p = 0.27) died during the first 30 days after randomization. There was also one non-fatal myocardial infarction in the angioplasty group. Major bleeding was encountered in 8 patients: in 5 of the 120 patients (4%) who had received fibrin-specific agents and in 3 of the 61 patients (5%) who had received streptokinase. This complication was observed in four patients (4%) in the stent group and four patients (4%) in the angioplasty group (p = 0.08).

DISCUSSION

Previous studies dedicated to the use of rescue angioplasty for failed thrombolysis included small numbers of patients (7,8), had non-optimal acute interventional results (4,10,11) or considerable selection bias with sicker patients having undergone rescue angioplasty and more stable patients

### Table 2. Angiographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stent Group (n = 90)</th>
<th>Angioplasty Group (n = 91)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of diseased vessels</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>1</td>
<td>35 (39)</td>
<td>34 (37)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27 (30)</td>
<td>31 (34)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28 (31)</td>
<td>26 (29)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>52.6 [41.0, 59.0]</td>
<td>52.5 [42.3, 60.1]</td>
<td>0.57</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>41 (46)</td>
<td>46 (51)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>8 (8)</td>
<td>11 (12)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>41 (46)</td>
<td>34 (37)</td>
<td></td>
</tr>
<tr>
<td>TIMI flow grade before intervention</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>0</td>
<td>36 (40)</td>
<td>29 (32)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30 (33)</td>
<td>42 (46)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24 (27)</td>
<td>20 (22)</td>
<td></td>
</tr>
<tr>
<td>Grades of collateral filling</td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>0</td>
<td>79 (88)</td>
<td>78 (86)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (8)</td>
<td>10 (11)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median [25th, 75th percentiles].

TIMI = Thrombolysis In Myocardial Infarction.

### Table 3. Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stent Group (n = 90)</th>
<th>Angioplasty Group (n = 91)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural abciximab therapy</td>
<td>87 (97)</td>
<td>89 (98)</td>
<td>0.64</td>
</tr>
<tr>
<td>Received the randomly assigned treatment</td>
<td>87 (97)</td>
<td>71 (78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>12 [12, 14]</td>
<td>12 [8, 12]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diameter stenosis after intervention, %</td>
<td>6.8 [2.1, 12.2]</td>
<td>15.8 [7.2, 29.4]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI flow grade after intervention</td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>0</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (8)</td>
<td>14 (15)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>79 (88)</td>
<td>72 (79)</td>
<td></td>
</tr>
<tr>
<td>Patients without paired scintigraphic studies</td>
<td>15 (17)</td>
<td>20 (22)</td>
<td>0.36</td>
</tr>
<tr>
<td>Reasons for incomplete scintigraphic studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Technical reasons</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median [25th, 75th percentiles].

TIMI = Thrombolysis In Myocardial Infarction.
having received conservative treatment (11), or have not specifically addressed rescue angioplasty (5). Furthermore, most studies of rescue angioplasty have been conducted without the adjunct use of newer antiplatelet drugs that seem to be beneficial in the setting of failed thrombolysis (26,27).

In this study, we used myocardial salvage as an efficacy index of the rescue intervention. Therefore, larger studies with hard end points such as mortality are needed in the future to validate our conclusions based on the assessment of myocardial salvage. We found that patients undergoing rescue percutaneous coronary interventions (coronary stenting or angioplasty) in the setting of failed thrombolysis benefit in terms of myocardial salvage. Thus, viable myocardium is still present at the time of rescue coronary intervention, and it could be saved by rescue stenting or angioplasty. One factor that may help explain the presence of viable myocardium after failed thrombolysis may be the presence of a certain amount of anterograde blood flow in the infarct-related artery at the time of coronary intervention. In 68% of the patients of this study, a poor anterograde blood flow (TIMI flow grades 1 and 2) was present at the time of coronary intervention. The sub-optimal blood flow may preserve muscle viability in the area of jeopardized myocardium; however, this factor may be important only if rescue coronary interventions are performed without delay. Angiographic studies have demonstrated that only a normal blood flow at the infarct-related artery is associated with reduced mortality (28), and a recent meta-analysis has shown no mortality benefit in patients with a TIMI flow grade 2 in comparison with patients with a TIMI flow grades 0 or 1 (29). For these reasons, we defined TIMI flow grade 2 as a marker of failed thrombolysis as we did for patients with lower TIMI flow grades of 0 or 1. Because initial SPECT was done after thrombolysis, the present study provides unique clues of the failed reperfusion: the perfusion defect after thrombolysis did not seem to differ from that recorded at baseline in patients with AMI before receiving reperfusion treatment (24,30,31). Optimally, the value of rescue interventions in patients with AMI and failed thrombolysis has to be investigated by including a control group with medical treatment. However, the fact that the present study was able to show a substantial degree of myocardial salvage indirectly supports the usefulness of rescue mechanical reperfusion. In addition, if we compare myocardial salvage achieved in this study with that reported for primary stenting and balloon angioplasty in AMI (24,30,31), the present findings suggest that the salvaging effects of the percutaneous coronary interventions are attenuated when performed after failed thrombolysis.

Most studies of rescue coronary stenting in the setting of failed thrombolysis have been designed as feasibility studies and performed in small series of patients (20–22). They uniformly have shown that rescue stenting for failed thrombolysis is feasible and safe and leads to favorable in-hospital and long-term results (20–22). One study found that rescue coronary stenting was associated with a low stent thrombosis rate and more favorable angiographic outcome (including residual stenosis) compared with a historic group of patients undergoing rescue angioplasty (21). With regard to bleeding complications after coronary stenting in the setting of failed thrombolysis, the reported evidence is contradictory (20,21).

A novel finding of this randomized study was that rescue stenting is associated with greater myocardial salvage and more favorable clinical outcome than rescue angioplasty. The proportion of initial perfusion defect that was salvaged was greater with rescue stenting than with rescue angioplasty. Although a high proportion of patients in both groups received abciximab as adjunct antithrombotic therapy, the rate of bleeding complications was low (4%) in both study groups. Because the risk of thrombotic formation after failed thrombolysis may be high as a result of predisposing lesion characteristics (16) and post-thrombolytic platelet activation (17,18), the findings of the present study may support the use of abciximab as adjunct antithrombotic therapy during rescue mechanical reperfusion.

Several factors may contribute to the more favorable results with rescue stenting compared with rescue angioplasty. First, angiographic results showed better acute results with stenting than with angioplasty. Thus, postinterventional diameter stenosis was smaller in the group with stenting than in the group with angioplasty. Furthermore, a trend toward a higher rate of post-interventional TIMI flow grade 3 was observed in the group assigned to rescue stenting compared with the group assigned to rescue angioplasty. As demonstrated previously, these factors influence the rate of vessel reclosure (6), myocardial salvage after reperfusion therapy (32), and clinical outcome (33). The achievement of better angiographic results in the group with rescue stenting may explain, at least in part, the improvement in the clinical outcome observed in this study. Second, postmortem examinations suggest that complex plaques are more likely to be associated with failed thrombolysis (16). Moreover, when plaque extension has contributed more than acute thrombosis to the vessel occlusion, thrombolysis is of limited value and the establishment of a TIMI flow grade 3 is less likely (34). It might be due to these local factors that a lower angiographic success and higher reocclusion rates are observed after rescue angio-

![Figure 1. Primary end point of the trial, salvage index (median and interquartile range), in the stent group and in the angioplasty group.](image-url)
plasty compared with primary angioplasty (35,36). These factors may also explain the 22% crossover rate in the angioplasty group of the present study that seems to be slightly higher than the 15% and 16% crossover rates reported in Stent Primary Angioplasty in Myocardial Infarction (Stent-PAMI [37]) and the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC [38]) trials, respectively. Finally, a major advantage of stenting is the sealing of intimal dissections that occur in response to balloon dilation (19,39).

In conclusion, patients with AMI and failed thrombolysis benefit from rescue mechanical reperfusion in terms of myocardial salvage. Coronary stenting is associated with a greater myocardial salvage in this setting as compared with coronary angioplasty.

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REFERENCES


**APPENDIX**