Early Administration of Reteplase Plus Abciximab vs Abciximab Alone in Patients With Acute Myocardial Infarction Referred for Percutaneous Coronary Intervention: A Randomized Controlled Trial

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IN HOSPITALS WITH CATHETERIZATION facilities, primary percutaneous coronary interventions (PCIs) are better than thrombolysis in patients with ST-segment elevation acute myocardial infarction (MI).1 Specifically designed randomized trials have also shown that patients with acute MI presenting at hospitals without catheterization facilities benefit more from PCI performed after transfer to centers with catheterization laboratories than from on-site thrombolysis.2-6

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Pharmacological strategies used as pre-treatment for bridging the delay between admission and performance of PCI in patients with acute MI are frequently observed as an integral part of the concept of “facilitated PCI.” Although several drugs or combinations of drugs may meet the requirements for effective facilitated PCI, comparative evidence regarding the optimal regimen is lacking. Abciximab is a glycoprotein IIb/IIIa inhibitor, with antiplatelet and anti-inflammatory actions that may be of particular benefit in patients with acute MI. Abciximab ameliorates microvascular flow in the jeopardized myocardial area and its early use may improve epicardial blood flow. Reteplase is a recombinant plasminogen activator that is widely used as a fibrinolytic drug because of its ease of administration in a bolus form. A regimen consisting of the combination of half-dose reteplase plus abciximab has been shown to better restore brisk blood flow in the infarct-related artery compared with therapy with full-dose reteplase.

The objective of this study was to assess whether early administration of reteplase plus abciximab produces better reduction of infarct size compared with abciximab alone in patients with acute MI referred for PCI.

METHODS

Patients

Eligible participants for this study were patients presenting less than 12 hours after the onset of symptoms with chest pain lasting at least 20 minutes and with at least 0.1 mV of ST-segment elevation in 2 or more limb leads or at least 0.2 mV in 2 or more contiguous precordial leads or left bundle-branch block of presumed new onset on surface electrocardiogram. We excluded patients with stroke within the last 3 months, active bleeding or bleeding diatheses, recent trauma or major surgery during the last month, suspected aortic dissection, noncompressible vascular punctures, oral anticoagulation therapy with coumadin derivatives, severe uncontrolled hypertension (systolic blood pressure >180 mm Hg, unresponsive to therapy), hemoglobin of less than 10 g/dL or hemocrit of less than 34% and platelet count of less than 100 × 10^9/L, malignancies, prolonged (>10 minutes) cardio-pulmonary resuscitation, cardiogenic shock, PCI in the 30 days preceding acute MI, older than 80 years or younger than 18 years, and known or suspected pregnancy, as well as those patients who did not provide written informed consent for participation. The study protocol was approved by the institutional ethics committees of each participating hospital.

Study Protocol

Patients fulfilling these criteria were randomly assigned to 1 of 2 treatment strategies: reteplase plus abciximab or abciximab alone. Randomization was performed according to a computer-generated random sequence enclosed in sealed envelopes in the coronary care units of the 5 centers with interventional facilities. The computer-generated random sequence was set in blocks of 50 for each of the 4 interventional centers. The size of the block was preselected and was unknown to the investigators and medical staff caring for the patients. No stratification was used. For patients admitted in hospitals without interventional facilities, the randomized assignment was designated by telephone, after calling the respective interventional center.

The assigned treatment was initiated at the emergency department or intensive care unit of the admitting hospital. Patients of both treatment groups received intravenous abciximab (ReoPro, Lilly Pharma Produktion GmbH & Co, Hamburg, Germany), administered as a bolus of 0.25 mg/kg of body weight followed with a continuous infusion of 0.125 μg/kg per minute (maximum dose, 10 μg/min) for 12 hours. Patients assigned to combination therapy, reteplase plus abciximab, received reteplase (Rapilysin, Hoffmann-La Roche AG, Grenzach-Wyhlen), administered in 2 intravenous bolus doses of 5 U (30 minutes apart). The first bolus of reteplase was administered immediately after the bolus of abciximab. All patients also received intravenous 500-mg aspirin and 60 U/kg body weight heparin (maximum dose, 5000 U).

Patients admitted at hospitals without interventional facilities were transferred to an interventional center by ambulance or helicopter after receiving study drugs. All patients were sent to the catheterization laboratory for coronary angiography and probable PCI. The decision to perform a coronary intervention was at the discretion of the operator. The recommended intervention was coronary stenting with bare stents. All patients were treated with clopidogrel, 75 mg/d, for at least 6 months and with 100-mg aspirin twice a day, indefinitely. No loading dose of clopidogrel was administered before the intervention. Other cardiac medications were administered at the discretion of the patient’s physician.

Radionuclide Studies

A single-photon emission computed tomography (SPECT) study was performed between 5 and 10 days after randomization using technetium Tc 99m sestamibi. The SPECT imaging was performed in 4 of 5 interventional centers that participated in the trial. Each center acquired data according to a standardized protocol requiring an activity of 800 to 1000 MBq, a time interval of more than 30 minutes between injection and acquisition, absence of attenuation correction, and filtered backprojection (Butterworth, 180°). Multithead camera systems with low-energy, high-resolution collimators were used to obtain images that were acquired in a 64 × 64 matrix with an acquisition time of 40 seconds per image. Acquired projection data were reconstructed into transaxial slices by using optimal camera specific corrections. All participating centers contributed 10 normal and 10 abnormal cases according to this protocol to achieve optimal performance. Creation of polar maps from transaxial image data was performed at the Scintigraphic Core Laboratory, Klinik und Poliklinik für Nuklearmedizin rechts der Isar, Munich, Germany. A volumetric sampling tool was applied to cre-
ate polar maps of relative activity
distribution throughout the entire left
ventricle. Each polar map was normal-
ized to its individual maximum. The in-
farction defect size was quantified by us-
ing a 50% threshold, which was derived
from phantom studies according to the
method of Gibbons et al17,18 and used as
an efficacy measure in previous reper-
fusion trials in patients with acute MI.19-21
Final infarct size was expressed in per-
centage of the left ventricle (FIGURE 1).

All measurements were performed in
the Scintigraphic Core Laboratory by op-
erators who were blinded to the as-
signed therapy. For image data ac-
quired by different camera systems, the
mean (SD) intraobserver and interob-
server variability of the left ventricle for
the measurement of the defect size in this
laboratory are both 2% (3%).22 In addi-
tion, we found an excellent correlation
between measurements of infarct size
(expressed in percentage of the left ven-
tricle) by using 2 different SPECT im-
ages obtained 5 and 30 days after reper-
fusion treatment in 13 patients with acute
MI (R=0.94; regression equation: in-
farct size [30 days]=0.99×infarct size
[5 days] – 2.1).

**Angiographic Evaluation**

All angiographic parameters were as-
se ssed in the Angiographic Core Labo-
ratory by operators blinded to treat-
ment assignment. Left ventriculograms
in the right anterior oblique projection
were used to measure the left ven-
tricular ejection fraction. Initial and
postprocedural, final blood flow in the
infarct-related artery was graded ac-
cording to the Thrombolysis In Myo-
cardial Infarction (TIMI) flow classifi-
cation (TIMI flow grade 0 indicates no
perfusion; 1, penetration of contrast ma-
terial but no perfusion; 2, slow perfu-
sion; and 3, complete perfusion).23 DIGi-
tal angiograms were analyzed off-line
with an automated edge detection sys-
tem CMS (Medis Medical Imaging Sys-
tems, Nuenen, the Netherlands).

**Study End Points and Definitions**

The primary end point was final infarct
size in the SPECT study. Two second-
ary end points were defined as a com-
posite of all-cause mortality, reinfarc-
tion, and hemorrhagic stroke; and the in-
hospital incidence of major bleeding.
Diagnosis of recurrent infarction was
based on the presence of at least 2 of the
following criteria: typical chest pain, new
ST-segment changes, and an increase in
creatine kinase and creatine kinase MB
of at least 50% more than the previous
trough level in at least 2 samples reach-
ing at least 3 times the upper limit of nor-

![Figure 1. Technetium Tc 99m Single-Photon Emission Computed Tomography Images Recorded in 2 Patients 1 Week After Acute Anterior Myocardial Infarction](image-url)
Keywords: acute MI, abciximab, reteplase, thrombolysis, primary angioplasty, stent, randomized controlled trial

Introduction

The diagnosis of hemorrhagic stroke required confirmation by computed tomography or magnetic resonance imaging of the head. A bleeding complication was defined as major if it was intracranial, or if clinically significant overt signs of hemorrhage were associated with a decrease in hemoglobin of more than 5 g/dL (or, when hemoglobin was not available, an absolute decrease in hematocrit of at least 15%).

During the hospital stay, electrocardiogram recordings and determination of creatine kinase, creatine kinase MB, hemoglobin content, and platelet count were performed before and 8, 16, and 24 hours after randomization as well as daily thereafter. Clinical status after discharge was assessed by a telephone interview at 30 days and follow-up visit at 6 months or whenever dictated by patient complaints. Six-month follow-up was complete in all but 2 patients: 1 patient in the reteplase plus abciximab group (last contact, 135 days after randomization) and 1 patient in the abciximab alone group (last contact, 47 days after randomization). All data were collected by research coordinators and forwarded to a data coordinating center. All data were verified against source documentation and all adverse clinical events were adjudicated by an events committee blinded to treatment assignment.

Time intervals were defined as follows: time from onset of symptoms to admission was the interval between onset of symptoms and emergency department admission at hospital (with or without interventional facilities); time of admission to randomization was the interval between emergency department admission and injection of the first bolus of the study drug; time of randomization to angiography was the interval between randomization and contrast angiographic visualization of the infarct-related coronary artery; and transport time was calculated for transported patients as the interval between leaving the emergency department of the admitting hospital without interventional facilities and arrival to the emergency department of the interventional center.

Statistical Analysis

Sample size calculation was performed on the basis of the primary end point of the trial. We prospectively assumed a mean (SD) scintigraphic final infarct size of 16% (12%) of left ventricle in the abciximab alone group. This assumption was based on the final infarct size measured by SPECT in the stent plus abciximab group of the Stent vs Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction study. We estimated that 110 patients would be required in each group for the trial to have 80% power to detect a 30% reduction in the infarct size (mean [SD], down to 11.2% [10%] of left ventricle) with combination therapy, reteplase plus abciximab, with a 2-sided \((a = .05\). We expected that not all patients would have a follow-up SPECT and therefore included a total of 253 patients.

All analyses were performed on the basis of the intention-to-treat principle using data from all patients as randomized. Depending on distribution, continuous data are presented as median (interquartile range) or as mean (SD). Categorical data are presented as counts or proportions (percentages). Differences between groups were assessed by using the \(\chi^2\) test or Fisher exact test for categorical data and the Wilcoxon rank sum test or \(t\) test for continuous data. Mean difference (95% confidence interval [CI]) in the primary end point of final infarct size between the study groups was also calculated after adjustment for important covariates, including prior MI, anterior infarct location, and time to start of study drug by using multivariable linear regression analysis. Survival analysis was made by applying the Kaplan-Meier method. Differences in survival parameters were assessed for significance and hazard ratios were calculated by means of the log-rank test (hazard ratios were changed to relative risks reported herein). The secondary composite end point was also reported in an information-preserving form. A 2-tailed \(P\) value of less than .05 was considered statistically significant.

RESULTS

Baseline Characteristics

From May 3, 2001, through June 2, 2003, 253 patients were enrolled and randomly assigned to receive either combination therapy of reteplase plus abciximab or abciximab alone (Figure 2). TABLE 1 shows baseline characteristics, which were comparable between the 2 treatment groups. TABLE 2 shows no major differences in time intervals between the 2 groups.

Transport

Of the 253 study patients, 186 (73.5%), equally distributed to the 2 study groups \((P = .80)\), were admitted and randomized in 1 of 13 community hospitals and thereafter transported to 1 of 5 intervention centers. The mean (SD) transfer distance was 39.4 (13.6) km in the reteplase plus abciximab group vs 38.5 (14.7) km in the abciximab group \((P = .69)\). There was also no significant difference in the transport time be-
between the 2 groups (median [interquartile range], 35 min [30-45 min] in the reteplase plus abciximab group vs 35 min [25-45 min] in the abciximab group; P = .90). During transport, 2 patients (1 in each group) developed ventricular fibrillation; both were successfully treated with external defibrillation. One patient in the abciximab group developed pulmonary edema and 1 patient in the reteplase plus abciximab group developed an atrioventricular block grade 3. No fatalities occurred during transport.

Catheterization Laboratory

Table 3 summarizes initial and final angiographic results as well as interventions. There were no significant differences in left ventricular ejection fraction and infarct-related artery between the 2 groups. The TIMI grade 3 flow was observed more frequently during initial angiography of the infarct-related artery with combination treatment. When the subset of patients in whom study treatment was initiated within 6 hours from symptom onset and initial angiography was performed more than 90 minutes after initiation of therapy was analyzed, TIMI grade 3 flow was found in 50.7% of the reteplase plus abciximab group and in 21.0% of the abciximab group (P = .90). During transport, 2 patients (1 in each group) developed ventricular fibrillation.

Final Infarct Size

The SPECT imaging was performed in 228 patients (90.1% of the entire study sample) after a median (interquartile range) of 6.2 days (5-8 days). Of 25 patients without SPECT imaging, 4 patients (2 in each group) had died before scheduled scintigraphy. The remaining patients did not return for planned imaging. The distribution of baseline characteristics among patients who had infarct size measured in the 2 groups reflected that observed for the whole population. The proportion of patients with anterior MI was 44.6% in the reteplase plus abciximab group and 37.9% in the abciximab group (P = .30); the left anterior descending coronary artery was the infarct-related vessel in 47.3% of patients with reteplase plus abciximab and 39.7% of patients with abciximab (P = .24); and 70.5% of patients with reteplase plus abciximab and 71.6% of patients with abciximab were randomized in hospitals without interventional facilities (P = .87).

The final infarct size of the left ventricle, the primary end point of the trial, was 13.0% (interquartile range, 3.0%-28.0%) in the reteplase plus abciximab group and 11.5% (interquartile range, 3.0%-26.3%) in the abciximab group (P = .81). The mean difference in final infarct size of the left ventricle between the reteplase plus abciximab group and the abciximab group was 1.3% (95% CI, –3.1% to 5.7%). After adjustment for prior MI, anterior infarct localization, and time to start of study drug, the difference in final infarct size of the left ventricle between the reteplase plus abciximab group and

Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Reteplase Plus Abciximab (n = 125)</th>
<th>Abciximab (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>63.1 (51.9-70.5)</td>
<td>62.3 (52.9-68.9)</td>
</tr>
<tr>
<td>Women</td>
<td>28 (22.4)</td>
<td>33 (25.8)</td>
</tr>
<tr>
<td>Arterial hypertension†</td>
<td>70 (56.0)</td>
<td>66 (51.6)</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>24 (19.2)</td>
<td>30 (23.4)</td>
</tr>
<tr>
<td>Current smoker†</td>
<td>53 (42.4)</td>
<td>52 (40.6)</td>
</tr>
<tr>
<td>Hypercholesterolemia†</td>
<td>79 (63.2)</td>
<td>85 (66.4)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>9 (7.2)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td>Prior aortocoronary bypass surgery</td>
<td>1 (0.8)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td><strong>Infarct Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>56 (44.8)</td>
<td>50 (39.1)</td>
</tr>
<tr>
<td>Inferior</td>
<td>53 (42.4)</td>
<td>67 (52.3)</td>
</tr>
<tr>
<td>Lateral</td>
<td>16 (12.8)</td>
<td>11 (8.6)</td>
</tr>
<tr>
<td>Killip class‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>93 (74.4)</td>
<td>97 (75.8)</td>
</tr>
<tr>
<td>II</td>
<td>29 (23.2)</td>
<td>29 (22.6)</td>
</tr>
<tr>
<td>III</td>
<td>3 (2.4)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Heart rate, median (IQR), beats/min</td>
<td>70 (62-82)</td>
<td>70 (63-84)</td>
</tr>
<tr>
<td>Blood pressure, median (IQR), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>135 (120-150)</td>
<td>130 (120-150)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 (70-90)</td>
<td>80 (70-90)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

*Data are presented as No. (%) unless otherwise specified.
†Arterial hypertension was defined as blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) at least on 2 separate occasions; diabetes mellitus, the presence of an active treatment with insulin or an oral antidiabetic agent; current smoker, regular smoking in the prior 6 months; hypercholesterolemia, documented total cholesterol value of at least 240 mg/dl (6.2 mmol/L).
‡Killip class I indicates the absence of rales over one half or less of the lung fields or the presence of a third heart sound; II, the presence of rales over one half of the lung fields and the absence of a third heart sound; III, the presence of rales over more than one half of the lung fields.

Table 2. Time Intervals From Symptom Onset to Angiography*

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Median (Interquartile Range), min</th>
<th>Reteplase Plus Abciximab (n = 125)</th>
<th>Abciximab (n = 128)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms to emergency department admission</td>
<td>130 (90-330)</td>
<td>140 (89-356)</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Emergency department admission to start of study drug</td>
<td>30 (15-45)</td>
<td>24 (13-40)</td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td>Start of study drug to angiography</td>
<td>125 (82-182)</td>
<td>120 (73-180)</td>
<td>.43</td>
<td></td>
</tr>
</tbody>
</table>

*See “Methods” section for definitions of time intervals.
the abciximab group was 0.7% (95% CI, –3.3% to 4.7%).

**Clinical Outcome**
During the first 30 days after randomization, 2 patients died in each group. There were also 2 patients in the reteplase plus abciximab group who had other adverse events: 1 with nonfatal recurrent MI and 1 with hemorrhagic stroke. No cases of ischemic stroke were observed. Four patients in the reteplase plus abciximab group and 1 patient in the abciximab group underwent transfusion of blood products.

Overall, the incidence of major bleeding was 5.6% (7 patients) in the reteplase plus abciximab group and 1.6% (2 patients) in the abciximab group (P = .16, Fisher exact test).

Within 6 months after randomization, 3 patients died in each group: 6-month mortality rates of 4.0% in the reteplase plus abciximab group and 3.9% in the abciximab group (P = .98). In addition, 2 patients in the reteplase plus abciximab group and 1 patient in the abciximab group experienced a nonfatal recurrent MI. **Figure 3** shows the cumulative incidence of the composite secondary end point, death, recurrent MI, or stroke in the reteplase plus abciximab group (6.4%) and in the abciximab group (4.7%) (relative risk, 1.4; 95% CI, 0.5-3.9; log-rank P = .56).

If the secondary composite end point is presented in an information-preserving form, the number of patients in each of the 4 categories (death, nonfatal recurrent MI, stroke, none of these events) was 5, 2, 1, 117, respectively, in the reteplase plus abciximab group and 5, 1, 0, 122, respectively, in the abciximab group.

**Table 3.** Initial Angiographic Characteristics, Procedures, and Final Angiographic Results

<table>
<thead>
<tr>
<th>Trait</th>
<th>Reteplase Plus Abciximab (n = 125)</th>
<th>Abciximab (n = 128)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial left ventricular ejection fraction, median (IQR), %†</td>
<td>51.6 (45.0-59.0)</td>
<td>52.0 (42.5-59.5)</td>
<td>.79</td>
</tr>
<tr>
<td>Infarct-related coronary artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>58 (46.4)</td>
<td>52 (40.7)</td>
<td>.35</td>
</tr>
<tr>
<td>LCx</td>
<td>17 (13.6)</td>
<td>16 (12.5)</td>
<td>.80</td>
</tr>
<tr>
<td>RCA</td>
<td>50 (40.0)</td>
<td>57 (44.5)</td>
<td>.47</td>
</tr>
<tr>
<td>Venous bypass graft</td>
<td>0</td>
<td>3 (2.3)</td>
<td>.26</td>
</tr>
<tr>
<td>Initial TIMI flow grade‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31 (24.8)</td>
<td>64 (50.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>10 (8.0)</td>
<td>13 (10.1)</td>
<td>.55</td>
</tr>
<tr>
<td>2</td>
<td>34 (27.2)</td>
<td>28 (21.9)</td>
<td>.32</td>
</tr>
<tr>
<td>3</td>
<td>50 (40.0)</td>
<td>23 (18.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Initial diameter stenosis, median (IQR), %†</td>
<td>72.6 (61.6-95.2)</td>
<td>100.0 (65.4-100.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent</td>
<td>113 (90.4)</td>
<td>119 (93.0)</td>
<td>.46</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>6 (4.8)</td>
<td>4 (3.1)</td>
<td>.72</td>
</tr>
<tr>
<td>Aortocoronary bypass surgery</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>.67</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>5 (4.0)</td>
<td>4 (3.1)</td>
<td>.97</td>
</tr>
<tr>
<td>Final TIMI flow grade‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (2.4)</td>
<td>4 (3.1)</td>
<td>.97</td>
</tr>
<tr>
<td>1</td>
<td>3 (2.4)</td>
<td>1 (0.8)</td>
<td>.60</td>
</tr>
<tr>
<td>2</td>
<td>10 (8.0)</td>
<td>12 (9.4)</td>
<td>.70</td>
</tr>
<tr>
<td>3</td>
<td>109 (87.2)</td>
<td>111 (86.7)</td>
<td>.91</td>
</tr>
<tr>
<td>Final diameter stenosis, median (IQR), %</td>
<td>7.1 (2.5-11.5)</td>
<td>6.0 (1.8-10.2)</td>
<td>.30</td>
</tr>
</tbody>
</table>

*Abbreviations: IQR, interquartile range; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction.
†Available in 244 of the 253 patients.
‡A TIMI flow grade of 0 indicates no perfusion; 1, penetration of contrast material but no perfusion; 2, slow perfusion; and 3, complete perfusion.

**Figure 3.** Kaplan-Meier Analysis of Cumulative Incidence of Death, Recurrent MI, or Stroke for Both Treatment Groups

*MI indicates myocardial infarction.*

**COMMENT**
We assessed whether early administration of reteplase combined with abciximab produces infarct-size reduction compared with abciximab alone in patients with acute MI referred for PCI. Based on this primary end point of the trial, both combination therapy with reteplase plus abciximab and single therapy with abciximab provide comparable results. The cumulative 6-month incidence of the composite end point (death, recurrent MI, or stroke) was also comparable between the 2 treatment groups, whereas there was a trend toward more major bleeding events with reteplase plus abciximab.

Two limitations must be acknowledged regarding interpretation of these results. First, the open-label nature of the study may introduce bias. This bias is unlikely to have occurred, because both
the assessment of the scintigraphic primary end point in the core laboratory and the adjudication of the clinical adverse events were performed by investigators blinded to the assigned treatment. Second, the limited number of patients does not provide sufficient power for comparison of clinical outcomes. The required sample size of 220 patients with measured infarct size was calculated based on the assumption of a 30% reduction in infarct size in the reteplase plus abciximab group, departing from a mean (SD) infarct size of 16% (12%) of left ventricle assumed for the abciximab group. Because of data skewness, the actual median value of 11.5% of left ventricle for the infarct size in the abciximab group corresponds with a mean (SD) of 16.9% (13.9%) of left ventricle. With infarct size measurements available in 228 patients, our study had a power of 81% to detect a 30% reduction in infarct size with the use of reteplase plus abciximab.

The term “facilitated PCI” was first used to describe early, planned PCI after pharmacological treatment intended to open the infarct-related artery. Percutaneous coronary intervention allows achievement of excellent restoration rates of anterograde flow in patients with acute MI. The benefit of pharmacologically advancing the opening of the epicardial artery in patients with acute MI who undergo immediate PCI is not yet proven as successful tissue reperfusion depends on more than just restoration of epicardial flow. Therefore, “facilitated PCI” should be considered in a broader and more appropriate context as a PCI performed after pretreatment with antithrombotic drugs able to reduce final infarct size and improve prognosis. We compared 2 antithrombotic regimens with the potential of achieving this goal and could not demonstrate that reteplase plus abciximab is better than abciximab alone. The lack of a study group without pretreatment does not allow to say whether there is a benefit at all by pretreating patients with acute MI who undergo PCI with either drug regimen used in this study.

Currently, the assessment of several adjunct antithrombotic regimens is of interest in patients with acute MI, including fibrinolytic agents alone, fibrinolytic agents combined with glycoprotein IIb/IIIa inhibitors, and glycoprotein IIb/IIIa inhibitors alone started either early in the emergency department or only in the catheterization laboratory. In our study, we compared the combination between a fibrinolytic agent and a glycoprotein IIb/IIIa inhibitor with a glycoprotein IIb/IIIa inhibitor alone started early, immediately after emergency department presentation. Our primary end point was a scintigraphic one. In the ongoing Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, 3 strategies are being evaluated: fibrinolysis (half-dose reteplase) plus glycoprotein IIb/IIIa inhibitors (abciximab), glycoprotein IIb/IIIa inhibitors alone administered early after admission, and glycoprotein IIb/IIIa inhibitors alone administered only after angiography is performed. In the upcoming Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-IV trial, 2 approaches will be compared: PCI with or without prior fibrinolysis (tenecteplase). Both FINESSE and ASSENT-4 trials have clinical primary end points, which assessment is enabled by a large sample of patients with acute MI who plan to be enrolled. Therefore, FINESSE, ASSENT-4, and our study may serve as complementary trials considering the treatment options and the primary end points that they evaluate.

In 73.5% of our patients, the study therapy was started in the admitting community hospital without interventional facilities and patients were then transported to the PCI center. Data from this subset of patients confirm the safety of transportation in this setting. Although postprocedural TIMI flow rates were similar in our 2 study groups, TIMI 3 flow rates during diagnostic angiography of the infarct-related coronary artery were much better with reteplase plus abciximab than with abciximab alone (40.0% vs 18.0%, respectively). This difference was accentuated when the analysis was confined to patients treated within 6 hours from symptom onset and the delay to coronary angiography was more than 90 minutes, with a TIMI grade 3 flow found in 50.7% of the patients in the reteplase plus abciximab group and in 21.0% of the patients in the abciximab group. In the Strategies for Patency Enhancement in the Emergency Department trial, a TIMI grade 3 flow was observed in 54% of the 100 patients who were assigned to half-dose reteplase plus abciximab in phase B of the trial. Reteplase plus abciximab was not associated in our study with a reduction of infarct size compared with abciximab alone despite the higher initial TIMI 3 flow rate. In fact, it is not the first time that regimens shown to achieve higher angiographic patency rates fail to improve clinical outcomes in subsequent pharmacological reperfusion trials. This apparent discrepancy between clinical outcome and TIMI flow may reflect the inability of epicardial flow to reliably reflect the quality of perfusion at the tissue level. Furthermore, in trials with PCI in patients with acute MI, there is an additional factor that may have a determinant impact on the outcome: final TIMI flow rates recorded after the intervention, which were similar in the 2 treatment groups of our study.

In conclusion, the findings of this trial show that early administration of reteplase plus abciximab does not lead to a reduction of infarct size compared with abciximab alone in patients with acute MI referred for PCI. In addition, clinical outcome was not improved by combination therapy. The latter finding, however, should be interpreted with caution in view of the limited number of patients and deserves confirmation from the larger ongoing FINESSE trial before promoting definitive implications for the clinical practice.

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