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

Adnan Kastrati, MD
Julinda Mehilli, MD
Klaus Schlotterbeck, MD
Franz Dotzer, MD
Josef Dirschinger, MD
Claus Schmitt, MD
Stephan G. Nekolla, PhD
Melchior Seyfarth, MD
Josef Dirschinger, MD
Christina Markwardt, MD
Günter Clermont, MD
Hans-Wilhelm Gerbig, MD
Johannes Leiss, MD
Markus Schwaiger, MD
Albert Schömig, MD
for the Bavarian Reperfusion Alternatives Evaluation (BRAVE) Study Investigators

Context The optimal pharmacological strategy for bridging the delay between admission and performance of percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (MI) is not known.

Objective To assess whether early administration of reteplase plus abciximab produces better results compared with abciximab alone in patients with acute MI referred for PCI.

Design, Setting, and Patients Open-label, randomized controlled study conducted from May 3, 2001, through June 2, 2003, of 253 patients who were admitted to 13 community hospitals without catheterization facilities (n=186) and to 5 hospitals with catheterization facilities (n=67), with the diagnosis of an ST-segment elevation acute MI within 12 hours from onset of symptoms.

Interventions Patients received intravenously either the combination of a half-dose reteplase (two 5-U boluses, 30 minutes apart) with a standard dose of abciximab (0.25 mg/kg bolus, 0.125 µg/kg per minute infusion [maximum 10 µg/min for 12 hours]) or the standard dose of abciximab alone; all patients were then transferred for PCI.

Main Outcome Measure Final infarct size according to a single-photon emission computed tomography study with technetium Tc 99m sestamibi performed between 5 and 10 days after randomization in 228 patients (90.1% of entire sample).

Results Of the 253 patients enrolled, 125 were assigned to reteplase plus abciximab and 128 to abciximab alone. The median (interquartile range) of the final infarct size of the left ventricle was 13.0% (3.0%-28.0%) in the reteplase plus abciximab group and 11.5% (3.0%-26.3%) in the abciximab-alone group (P=.81). The mean difference in final infarct size of left ventricle between the reteplase plus abciximab group and the abciximab group was 1.3% (95% confidence interval [CI], –3.1% to 5.7%). Within 6 months after randomization, the composite secondary end point of death, recurrent MI, or stroke occurred in 8 patients (6.4%) in the reteplase plus abciximab group and 6 patients (4.7%) in the abciximab group (relative risk, 1.4; 95% CI, 0.5-3.9; log-rank P=.56). Major bleeding complications were observed in 7 patients (5.6%) in the reteplase plus abciximab group and 2 patients (1.6%) in the abciximab group (P=.16).

Conclusion 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.

JAMA. 2004;291:947-954 www.jama.com

©2004 American Medical Association. All rights reserved.

For editorial comment see p 1000.
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.”17-18 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.11 Abciximab ameliorates microvascular flow in the jeopardized myocardial area12 and its early use may improve epicardial blood flow.13 Reteplase is a recombinant plasminogen activator that is widely used as a fibrinolytic drug because of its ease of administration in a bolus form.14 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.15

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, non-compressible vascular punctures, oral anticoagulation therapy with coumarin derivatives, severe uncontrolled hypertension (systolic blood pressure >180 mm Hg, unresponsive to therapy), hemoglobin of less than 10 g/dL or hematocrit 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 Rothe AG, Grenzach-Wyhlen), administered in 2 intravenous bolus doses of 5 U (30 minutes apart).15 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°). Multislice 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 normalized to its individual maximum. The infarction defect size was quantified by using a 50% threshold, which was derived from phantom studies according to the method of Gibbons et al and used as an efficacy measure in previous reperfusion trials in patients with acute MI. Final infarct size was expressed in percentage of the left ventricle (FIGURE 1).

All measurements were performed in the Scintigraphic Core Laboratory by operators who were blinded to the assigned therapy. For image data acquired by different camera systems, the mean (SD) intraobserver and interobserver variability of the left ventricle for the measurement of the defect size in this laboratory are both 2% (3%). In addition, we found an excellent correlation between measurements of infarct size (expressed in percentage of the left ventricle) by using 2 different SPECT images obtained 5 and 30 days after reperfusion treatment in 13 patients with acute MI (R=0.94; regression equation: infarct size [30 days] = 0.99 × infarct size [5 days] – 2.1).

Angiographic Evaluation

All angiographic parameters were assessed in the Angiographic Core Laboratory by operators blinded to treatment assignment. Left ventriculograms in the right anterior oblique projection were used to measure the left ventricular ejection fraction. Initial and postprocedural, final blood flow in the infarct-related artery was graded according to the Thrombolysis In Myocardial Infarction (TIMI) flow classification (TIMI flow grade 0 indicates no perfusion; 1, penetration of contrast material but no perfusion; 2, slow perfusion; and 3, complete perfusion). Digital angiograms were analyzed off-line with an automated edge detection system CMS (Medis Medical Imaging Systems, Nuenen, the Netherlands).

Study End Points and Definitions

The primary end point was final infarct size in the SPECT study. Two secondary end points were defined as a composite of all-cause mortality, reinfarction, 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 reaching at least 3 times the upper limit of normal.

White arrowheads in images from patient 1 indicate a large perfusion defect (38%) of the left ventricle (large myocardial infarction). Black arrowheads in images from patient 2 indicate a small perfusion defect (6%) of the left ventricle (small myocardial infarction).
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 hospital and arrival to 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 alpha of .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-square 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 symptom onset and initial angiography of the infarct-related vessel was 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...
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.

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 antegrade 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)-4 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.

Author Contributions: Dr Kastrati as principal investigator and Dr Schömig as chairman of the steering committee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kastrati, Schömig.

©2004 American Medical Association. All rights reserved.
Acquisition of data: Kastrati, Mehlli, Schlottbeck, Dotzer, Dischinger, Schmitt, Seyfarth, Martinhoff, Markwardt, Clermont, Gerbig, Leis, Schweiger, Schömg. Analysis and interpretation of data: Kastrati, Mehlli, Schlottbeck, Schömg. Drafting of the manuscript: Kastrati, Clermont, Schömg.

Critical revision of the manuscript for important intellectual content: Widimsky, Budesinsky, Vorac, Schmitt, Nekolla, Seyfarth, Martinhoff, Markwardt, Clermont, Gerbig, Leis, Schweiger, Schömg. Statistical expertise: Kastrati, Mehlli.

Obtained funding: Schömg. Administrative, technical, or material support: Kastrati, Mehlli, Schlottbeck, Dotzer, Dischinger, Schmitt, Nekolla, Seyfarth, Martinhoff, Markwardt, Clermont, Gerbig, Leis, Schweiger, Schömg.

Supervision: Mehlli, Dotzer, Dischinger, Schmitt, Seyfarth, Schweiger, Schömg.


Centers With PCI Facilities (the number in parentheses indicates the number of patients randomized in the center): Hospital zur Grossen Schmiede, Munich (9, 3) (principal investigator), M. Schwaiger, J. Dirschinger; Hospital Großhadern, Munich (7, 2) (principal investigator), M. Schwaiger, J. Dirschinger; Hospital Ludwig, Munich (2, 1) (principal investigator), M. Schwaiger, J. Dirschinger; Hospital St. Anna, Munich (2, 1) (principal investigator), M. Schwaiger, J. Dirschinger.

Acknowledgment: We appreciate the invaluable contribution of the medical and technical staffs operating in the coronary care units, nuclear medicine, and catheterization laboratories of the participating institutions.

REFERENCES


