Mechanical Reperfusion in Patients With Acute Myocardial Infarction Presenting More Than 12 Hours From Symptom Onset: A Randomized Controlled Trial

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IN PATIENTS WITH ACUTE ST-segment elevation myocardial infarction (STEMI), numerous studies have demonstrated that early reperfusion within 12 hours of symptom onset is associated with increased myocardial salvage, preservation of left ventricular function, and improved survival.1 Due to time-dependent attenuation of the efficacy of thrombolysis,2 the application of this reperfusion modality itself has been controversial.3

RESULTS The primary end point was final left ventricular infarct size according to single-photon emission computed tomography study with technetium Tc 99m sestamibi performed between 5 and 10 days after randomization in 347 patients (95.1%). Secondary end points included composite of death, recurrent MI, or stroke at 30 days.

Conclusion An invasive strategy based on coronary stenting with adjunctive use of abciximab reduces infarct size in patients with acute STEMI without persistent symptoms presenting 12 to 48 hours after symptom onset.

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ity after 12 hours from symptom onset of acute myocardial infarction (MI) offers no benefit and may be even harmful.1,3,4 Between 8.5% and 40% of patients with acute MI present late after symptom onset, no longer being eligible for thrombolysis.5-9 Despite efforts to reduce time to presentation, recent studies have demonstrated that time-to-arrival has not changed9 or has even increased.6 The lack of efficacy of thrombolysis in patients with acute MI presenting more than 12 hours after symptom onset may be a reason why current guidelines oppose reperfusion therapy in this setting.11 Several findings suggest, however, that reperfusion therapy may be beneficial even among patients with acute MI who present late after symptom onset. First, recent studies have shown that viable salvageable myocardium exists even after more than 12 hours of severe ischemia.12-14 Second, previous studies have not only demonstrated that percutaneous coronary intervention (PCI) is better than thrombolysis in patients with acute MI,13,15-17 but also that the time window of efficacy for PCI may be wider than that for thrombolysis.18-20 Third, observational studies suggest that PCI is effective even when performed after 12 hours from symptom onset in patients with acute MI.21,22 The goal of our trial was to assess whether an invasive strategy based on PCI with stenting is associated with reduction of infarct size in patients with acute STEMI presenting more than 12 hours after symptom onset compared with a conventional conservative treatment strategy.

**METHODS**

**Study Population**

Patients aged 18 to 80 years who had at least 1 chest pain episode lasting at least 20 minutes between 12 and 48 hours before presentation and unequivocal changes (≥0.1 mV of ST-segment elevation in ≥2 adjacent limb leads or ≥0.2 mV in ≥2 contiguous precordial leads or new pathological Q waves) on surface electrocardiogram on admission were eligible for the Beyond 12 hours Reperfusion AlternatiVe Evaluation (BRAVE-2) trial. Exclusion criteria included persistent anginal chest pain, cardiogenic shock (systolic blood pressure <80 mm Hg, unresponsive to fluids, or necessitating catecholamines), electrical instability, severe congestive heart failure and/or pulmonary edema, or previous stroke (within the last 3 months); prior thrombolysis for index infarction; active bleeding or bleeding diatheses; recent trauma or major surgery (during the last month); relevant hematologic deviations (hemoglobin <10 g/dL or hematocrit <34%, platelet cell count of <100 × 10^9/µL, white blood cell count <3 × 10^9/µL) or malignancies; recent PCI (within the last 30 days); known or suspected pregnancy; inability to comply with study procedures; and unwillingness or inability to provide written informed consent for participation. Written informed consent was obtained from all included patients. Institutional ethics committee approval was obtained in all participating centers.

**Randomization**

A computer-generated randomization sequence was used to assign patients to either an invasive or a conservative treatment group. The sequence was set in blocks of 10. Allocation concealment was implemented using sealed, sequentially numbered envelopes. The individual who created the randomization sequence and filled and labeled the study envelopes was not involved in any other study procedures or analyses.

**Procedures**

All patients received an initial dose of clopidogrel (300-600 mg) or ticlopidine (500 mg) and 500 mg of aspirin as well as an intravenous bolus of 70 U/kg of body weight of heparin (up to 5000 U). Patients assigned to the conservative group received an intravenous infusion of unfractionated heparin (12 U/kg per hour, maximum 1000 U/h) or subcutaneous low-molecular-weight heparin in the dose appropriate for the specific agent for at least 24 hours.

Patients assigned to the invasive group were taken to the catheterization laboratory immediately. The decision whether to perform a PCI procedure (with or without stenting) or to send the patient for aortocoronary graft surgery was made by the operator on the basis of flow status, lesion severity, and anatomy of the infarct-related artery. Multilink stents (Guidant Advanced Cardiovascular Systems Inc, Santa Clara, Calif) were used for coronary stenting and adjunctive abciximab (ReoPro, Lilly Pharma Produktion GmbH & Co, Hamburg, Germany) was administered during and after the procedure (as an intravenous bolus of 0.25 mg/kg of body weight followed by a 12-hour infusion of 0.125 µg/kg per minute up to a maximal dose of 10 µg/min). Abciximab therapy was started immediately after diagnostic angiography was performed and a decision to intervene was taken.

In the conservative group, asymptomatic limited exercise test was scheduled to be performed before discharge. Patients were sent for unplanned invasive evaluation and treatment if they developed recurrent severe angina, hemodynamic and electrical instability, severe congestive heart failure and/or pulmonary edema, mechanical complications, new relevant electrocardiographic changes (new or reelevation of ST-segments of 0.2 mV in 2 contiguous precordial leads or 0.1 mV in 2 adjacent limb electrocardiographic leads), reevaluation of creatine kinase or creatine kinase-MB by at least 50% above the trough level after documentation that the level was decreasing prior to this reelevation, or signs of induced ischemia during exercise testing.

Patients of both treatment groups were admitted to a monitored bed for at least 48 hours after enrollment. All patients received 75-mg/d clopidogrel or 500-mg/d ticlopidine for at least 4 weeks and 200 to 325 mg/d of aspirin, indefinitely. Recommended concomitant drugs included β-blockers, angiotensin-converting enzyme inhibitors, and statins.
Infarct Size Measurement
A resting single-photon emission computed tomography (SPECT) study was performed between 5 and 10 days after randomization using technetium Tc 99m sestamibi to measure infarct size as a percentage of the left ventricle. All studies were processed and measured in a Scintigraphic Core Laboratory by experienced operators who were unaware of assigned therapy. Methods of data acquisition and processing as well as infarct size measurement have previously been described in detail.23

Angiographic Evaluation
Angiographic parameters of patients assigned to the invasive treatment group were assessed off-line in the Angiographic Core Laboratory by personnel unaware of study allocation. Classification of anterograde coronary flow in the infarct-related artery was performed according to Thrombolysis in Myocardial Infarction (TIMI) classification.24 Collateral circulation was quantified according to criteria of Rentrop et al.25 Quantitative assessment was performed with the use of an automated edge detection system (CMS, Medis Medical Imaging Systems, Nuenen, the Netherlands).

Follow-up and End Points
In-hospital follow-up protocol consisted of electrocardiographic recordings, determination of creatine kinase, creatine kinase-MB, hemoglobin content, and platelet cell count before and 8, 16, and 24 hours after the randomization as well as daily thereafter. After discharge, trained personnel blinded to patient’s allocation performed detailed telephone interviews at 30 and 90 days after randomization. For each event reported, evidence was sought from hospital case records or the family physician. The local research coordinators collected the data and forwarded them to the data coordinating center. A high quality of data was ensured by checking source documentation. An event adjudication committee blinded to the randomization status of the patients adjudicated adverse clinical events.

The primary end point was final left ventricular infarct size determined by SPECT. The secondary end points were a composite of all-cause death, recurrent MI, or stroke within 30 days after randomization. Diagnosis of recurrent MI 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% above the previous trough level in at least 2 samples reaching at least 3 times the upper limit of normal. The diagnosis of stroke required confirmation by computed tomography or magnetic resonance imaging of the head in the presence of a new onset focal or global neurological deficit lasting more than 24 hours.

The incidence of major bleeding complications as well as severe thrombocytopenia was also monitored. Major bleeding was defined as an intracranial bleeding or clinically significant overt signs of hemorrhage associated with a decrease of more than 5 g/dL in hemoglobin or, when hemoglobin was not available, an absolute decrease of at least 15% in hematocrit.26 Severe thrombocytopenia was defined as true decrease of thrombocytes to less than 20 × 10^9/L.

Statistical Analysis
Sample size calculation was performed on the basis of the primary end point of the trial. In a previous series of patients with acute MI presenting more than 12 hours after symptom onset and treated conservatively in Deutsches Herzzentrum, Munich, Germany, the mean (SD) left ventricular infarct size was 20% (16%). In patients assigned to the invasive strategy, we expected to achieve at least 30% reduction of infarct size. Choosing a 2-sided α=0.05 and power of 90%, 150 patients in each group were needed. The overall number of patients enrolled was expanded to 365 to accommodate for possible missing scintigraphic studies.

All analyses were performed on the basis of the intention-to-treat principle by using data from all patients as randomized. Because most continuous data were not normally distributed, they are presented as median (interquartile range [IQR]). Categorical data are presented as counts or proportions. Differences between the groups were assessed using Fisher exact test for categorical data and the nonparametric Wilcoxon rank sum test for continuous data. Kaplan-Meier method was used to assess event-free survival with differences checked by means of the log-rank test. Multiple linear regression modeling was used to identify independent predictors of final infarct size. A 2-tailed P<.05 was considered statistically significant. S-PLUS version 4.5 (Insightful Corp, Seattle, Wash) was used for all statistical analyses.

RESULTS
Patient Characteristics
Between May 23, 2001, and December 15, 2004, a total of 365 patients were enrolled; 182 patients were randomly assigned to the invasive group and 183 patients to the conservative group (Figure 1). Baseline clinical and infarct characteristics of the patients are shown in Table 1. Angiographic and procedural characteristics of patients assigned to the invasive group are shown in Table 2.

In the invasive treatment group, 90 patients (49.5%) had an initial TIMI flow grade of 0. Of these patients, 50 (56%) had collateral grade 0, 25 (28%) grade 1, 11 (12%) grade 2, and 4 (4%) grade 3. The median time of randomization to angiography (defined as the time of angiographic visualization of the infarct-related artery) was 1.5 hours (IQR, 0.9-3.3 hours). Following diagnostic angiography, 159 patients (87.4%) underwent coronary stenting, 13 patients (7.2%) plain balloon angioplasty, 7 patients (3.8%) received aortocoronary bypass graft surgery, and 3 patients (1.6%) received no interventional treatment because of an open infarct-related artery without significant residual stenosis. The median time from randomization to first balloon inflation among patients who under-
MECHANICAL REPERFUSION AND ACUTE MYOCARDIAL INFARCTION

Figure 1. Flow of Study Participants

STEMI indicates ST-segment elevation myocardial infarction; SPECT, single-photon emission computed tomography.

Among the 173 patients who had SPECT imaging in the conservative group, 15 patients (8.7%) underwent unplanned PCI before performing the follow-up SPECT imaging, which was due to recurrent angina in 7 patients, congestive heart failure in 4 patients, malignant arrhythmia in 1 patient, patient’s preference in 1 patient, and attending physician’s decision in 2 patients.

The final left ventricular infarct size was significantly smaller in patients assigned to the invasive group (median, 8.0%; IQR, 2.0%-15.8%) vs those assigned to the conservative group (median, 13.0%; IQR, 3.0%-27.0%; \( P < .001 \)). If expressed as mean (SD), left ventricular infarct size was 11.6% (13.4%) in the invasive group and 18.4% (18.0%) in the conservative group. The mean difference in final left ventricular infarct size between the invasive and conservative groups was −6.8% (95% confidence interval [CI], −10.2% to −3.5%). When the analysis was confined to only those patients in the conservative group who did not undergo unplanned PCI before SPECT imaging, the final left ventricular infarct size was 12.0% (IQR, 3.0%-26.8%), which was significantly smaller than the final infarct size in the invasive group (\( P < .001 \)). When the analysis was confined to only patients without a history of MI, the final left ventricular infarct size was 7% (IQR, 2.0%-14.0%) in the invasive group vs 12.0% (IQR, 3.0%-26.7%) in the conservative group (\( P < .001 \)). Among patients presenting between 12 and 24 hours, the final left ventricular infarct size was 9.0% (IQR, 2.0%-14.0%) in the invasive group vs 10.5% (IQR, 3.0%-23.0%) in the conservative group (\( P = .06 \)). Among patients presenting between 24 and 48 hours, the final infarct size was 6.5% (IQR, 2.0%-20.5%) in the invasive group vs 15.0% (IQR, 7.0%-35.0%) in the conservative group (\( P < .001 \)).

We constructed 2 multiple linear regression models aimed at the identification of predictors of final infarct size in the invasive group. The variables included in the first model were initial TIMI flow grade, collateral grade, left anterior descending artery as an infarct-related artery, and time of onset of pain to angiography. The second model included final TIMI flow grade in addition to the variables included in the first model. The only independent predictor of final infarct size that emerged from both models was initial TIMI flow grade (\( P = .04 \)).

Clinical Outcome

No patients were lost to 30-day follow-up. During this interval, 3 patients (1.6%) in the invasive group and 7 patients (3.8%) in the conservative group died (\( P = .21 \)). Five patients (2.7%) in the invasive group and 8 patients (4.4%) in the conservative group experienced recurrent MI. The combined incidence of death or recurrent MI was 4.4% (n=8 patients) in the invasive group and 6.0% (n=11) in the conservative group (\( P = .49 \)). Only 1 patient in the conservative group incurred disabling ischemic stroke. The cumulative incidence of the secondary end points, the composite of death, recurrent MI, or stroke within 30 days, was 4.4% (n=8) in the invasive group and 6.6% (n=12) in the conservative group (relative risk, 0.67; 95% CI, 0.27-1.62; \( P = .37 \)). If the composite end point is presented in an information preserving form, the number of patients in each of the 4 categories (death, nonfatal recurrent MI, nonfatal stroke, or none of these events) was 3, 5, 0, 174, respectively, in the invasive group and 7, 4, 1, 171, respectively, in the conservative group. Two patients (1.1%) in the invasive group and 60 patients (32.8%) in the conservative group underwent unplanned PCI during the 30-day period.

Major bleeding complications were observed in 6 patients (3.3%) in the invasive group and 2 patients (1.1%) in the conservative group (\( P = .28 \)). Severe thrombocytopenia was observed in 2 patients (1.1%) in the invasive group and none (0%) in the conservative group (\( P = .50 \)).

The 90-day follow-up was completed in 350 (95.9%) of 365 patients, and the cumulative incidence of the composite of death, recurrent MI, or stroke was 4.9% (n=9) in the invasive group and 7.1% (n=13) in the conservative group (log-rank \( P = .39 \)).
risk patients among those treated with mechanical reperfusion vs those receiving conservative treatment might have influenced the gradient in clinical outcome.\cite{21,22} Isolated modification and potentiation of antithrombotic regimen cannot produce a measurable benefit in patients ineligible for thrombolysis who do not undergo PCI.\cite{34} Currently, we lack clear evidence that could help guide the treatment of patients with acute MI presenting more than 12 hours after symptom onset.

Our trial included 365 patients with acute STEMI, who according to current guidelines, were not eligible for reperfusion treatment. Half of the patients were randomly assigned to an invasive strategy consisting of immediate diagnostic angiography followed predominantly by percutaneous coronary recanalization and the other half to the conservative, medical treatment strategy. Being the first prospective study to our knowledge to address this issue, we provided unique information useful for the characterization of this population. Complementary information relative to infarct size and angiographic features of these patients was also obtained. Scintigraphic infarct size measured in the conservative group appears to be smaller than that measured in patients with acute MI presenting within 12 hours after symptom onset.\cite{16,17,35} Correspondingly, the proportion of patients with a TIMI flow grade of 0 or 1 in the invasive group seems to be lower than that observed in previous trials that included patients with acute MI presenting within 12 hours after symptom onset.\cite{16,36}

We found that an invasive strategy based predominantly on mechanical reperfusion with coronary stenting and adjunctive abciximab in patients with

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Invasive Group (n = 182)</th>
<th>Conservative Group (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>65.7 (57.7-73.6)</td>
<td>67.1 (55.1-73.7)</td>
</tr>
<tr>
<td>Women</td>
<td>48 (25.8)</td>
<td>47 (25.6)</td>
</tr>
<tr>
<td>Arterial hypertension†</td>
<td>102 (56.0)</td>
<td>92 (50.0)</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>43 (23.6)</td>
<td>44 (24.0)</td>
</tr>
<tr>
<td>Current smoker†</td>
<td>62 (34.1)</td>
<td>68 (37.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia†</td>
<td>99 (54.3)</td>
<td>94 (51.4)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>16 (8.8)</td>
<td>17 (9.3)</td>
</tr>
<tr>
<td>Prior aortocoronary bypass graft surgery</td>
<td>7 (3.8)</td>
<td>10 (5.5)</td>
</tr>
<tr>
<td>Body mass index, median (IQR);‡</td>
<td>26.9 (25.1-29.8)</td>
<td>27.0 (24.6-29.6)</td>
</tr>
<tr>
<td>Infarct localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>68 (37.4)</td>
<td>69 (37.7)</td>
</tr>
<tr>
<td>Inferior</td>
<td>65 (35.7)</td>
<td>71 (38.8)</td>
</tr>
<tr>
<td>Lateral</td>
<td>49 (26.9)</td>
<td>43 (23.5)</td>
</tr>
<tr>
<td>Killip class§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>148 (81.3)</td>
<td>150 (82.0)</td>
</tr>
<tr>
<td>II</td>
<td>34 (18.7)</td>
<td>33 (18.0)</td>
</tr>
<tr>
<td>Heart rate, median (IQR), beats/min</td>
<td>72 (61-85)</td>
<td>75 (62-89)</td>
</tr>
<tr>
<td>Blood pressure, median (IQR), mm Hg</td>
<td>140 (120-150)</td>
<td>135 (120-150)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 (70-85)</td>
<td>80 (70-85)</td>
</tr>
<tr>
<td>Pain onset to time interval, median (IQR), h</td>
<td>22.5 (14.5-39.4)</td>
<td>22.5 (14.3-36.3)</td>
</tr>
</tbody>
</table>

**Abbreviation:** IQR, interquartile range.

**Data are presented as No. (%) unless otherwise specified.**

†Arterial hypertension was defined as blood pressure (systolic $\geq$140 mm Hg and/or diastolic $\geq$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; and hypercholesterolemia, documented total cholesterol value of at least 240 mg/dL (6.2 mmol/L).

‡Calculated as weight in kilograms divided by the square of height in meters.

§Killip class I indicates the absence of rales over the lung fields and the absence of a third heart sound; class II, the presence of rales over one half or less of the lung fields or the presence of a third heart sound.
acute STEMI presenting after 12 hours from symptom onset is associated with a reduction of infarct size compared with the currently recommended conservative strategy. The trend observed toward a better clinical outcome in the invasive group should be interpreted with caution due to the limited number of patients and insufficient power for the assessment of clinical events. Scintigraphic infarct size, however, contains useful prognostic information and is recognized for its accuracy as a marker of reperfusion efficacy in trials of patients with acute MI. Therefore, our findings show that a significant reduction of infarct size is achievable if an invasive reperfusion strategy is also offered to patients presenting later than 12 hours, promptly upon arrival to hospital.

We do not know to what extent the systematic administration of abciximab influenced the results obtained in the invasive group. Glycoprotein IIb/IIIa inhibitors have shown a beneficial additive effect when used in conjunction with PCI in patients with acute MI presenting within 12 hours and may also enhance the effectiveness of mechanical recanalization performed more than 12 hours after symptom onset. Several mechanisms may explain our main finding. Experimental and clinical studies have demonstrated that viable myocardium can persist after 12 hours of coronary occlusion or symptom onset. Apart from stuttering course with intermittent occlusion and recanalization, other factors such as ischemic preconditioning, persistence of residual blood flow in the infarct-related artery, or recruitment of collaterals may prevent complete necrosis and preserve some degree of myocardial viability. The presence of anterograde and/or collateral flow before PCI in patients with evolving MI is associated with reduced infarct size. Furthermore, stunned and/or hibernating myocardium may exist within the area at risk with a delicate balance between survival and apoptosis. All these studies lend credit to the theory that viable myocardium can be found.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Invasive Group (n = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction, median (IQR), %†</td>
<td>50.0 (41.7-56.0)</td>
</tr>
<tr>
<td>Infarct-related coronary artery</td>
<td>69 (37.9)</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>53 (29.2)</td>
</tr>
<tr>
<td>Right</td>
<td>57 (31.3)</td>
</tr>
<tr>
<td>Venous bypass graft</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Initial TIMI flow grade‡</td>
<td>90 (49.5)</td>
</tr>
<tr>
<td>0</td>
<td>37 (20.3)</td>
</tr>
<tr>
<td>Initial diameter stenosis, median (IQR), %</td>
<td>100.0 (68.5-100.0)</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td>159 (87.4)</td>
</tr>
<tr>
<td>Coronary stents</td>
<td>13 (7.2)</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>Aortic-coronary bypass graft surgery</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>2.66 (2.38-3.08)</td>
</tr>
<tr>
<td>Collateral grade§</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>0</td>
<td>129 (71.0)</td>
</tr>
<tr>
<td>1</td>
<td>33 (18.1)</td>
</tr>
<tr>
<td>2</td>
<td>14 (7.7)</td>
</tr>
<tr>
<td>3</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Infarct-related vessel size, median (IQR), mm</td>
<td>100.0 (68.5-100.0)</td>
</tr>
<tr>
<td>Final TIMI flow grade‡</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>0</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Final diameter stenosis, median (IQR), %</td>
<td>159 (87.4)</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td>8.7 (5.0-13.1)</td>
</tr>
</tbody>
</table>
MECHANICAL REPERFUSION AND ACUTE MYOCARDIAL INFARCTION

late after symptom onset and that this mycardium may be salvaged if an effective reperfusion strategy is applied.

In conclusion, our randomized controlled trial demonstrates that an invasive strategy based on coronary stenting with adjunctive use of abciximab reduces infarct size in patients with acute STEMI without persistent symptoms presenting 12 to 48 hours after symptom onset. This finding increases the level of evidence in support of the invasive strategy and deserves consideration when current treatment guidelines for this category of patients will be reassessed.

Author Contributions: Dr Schömig had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study Concept and design: Schömig, Antoniucci, Schwaiger, Kastrati.

Acquisition of data: Schömig, Mehilli, Antoniucci, Markwardt, Di Pede, Nekolla, Schlottbeer, Schülen, Pache, Seyfarth, Martinoff, Benzer, Schmitt, Dirschinger, Schwaiger, Kastrati.

Analysis and interpretation of data: Schömig, Mehilli, Ndrepeka, Kastrati.

Drafting of the manuscript: Schömig, Mehilli, Ndrepeka, Kastrati.

Critical revision of the manuscript for important intellectual content: Antoniucci, Markwardt, Di Pede, Nekolla, Schlottbeer, Schülen, Pache, Seyfarth, Martinoff, Benzer, Schmitt, Dirschinger, Schwaiger, Kastrati.

Statistical analysis: Ndrepeka, Kastrati.

Obtained funding: Schömig, Kastrati.

Administrative, technical, or material support: Schömig, Mehilli, Antoniucci, Markwardt, Di Pede, Nekolla, Schlottbeer, Schülen, Pache, Seyfarth, Martinoff, Benzer, Schmitt, Dirschinger, Schwaiger, Kastrati.

Study supervision: Schömig, Mehilli, Antoniucci, Di Pede, Schlottbeer, Benzer, Schmitt, Dirschinger, Schwaiger, Kastrati.

Final approval of the manuscript: None reported.

Centers and Investigators of the BRAVE-2 Trial: Steering Committee: A. Schömig (chairman), A. Kastrati (principal investigator), D. Antoniucci, M. Schwaiger.

Data Coordinating Center: I. Mehilli, C. Markwardt, H. Holle, A. Barth, Scintigraphic Core Laboratory: S. Nekolla, J. Neveure, A. Claus, A. Funk, Klinik und Poliklinik für Nuklearmedizin rechts der Isar, Munich, Germany, Angiographic Core Laboratory: A. Diba, A. Redl, S. Piniek, S. Mayer, Deutsches Herzzentrum, Munich, Germany; Clinical Follow-Up Center: K. Hösl, F. Rodrigues; C. Peterle, Deutsches Herzzentrum, Munich, Germany; Landeskranken Klinik Feldkirch, Austria; Herzzentrum Cottbus, Germany; C. Kalina (principal investigator), U. Grele; Asklepios Stadtklinik Bad Tölz, Germany: H. W. Gerbig (principal investigator), W. Rothenerberg (principal investigator), H. Brückmayer (principal investigator), G. Biedermann, Städtisches Krankenhaus Bad Reichenhall, Germany: H. Tanzer (principal investigator), R. W. Hauck; Krankenhaus Virzentiunum Rupolding, Germany: H. Fischer (principal investigator), T. Koch; Krankenhausen Freilassing, Germany: F. C. Himmer (principal investigator); Krankenhaus Schongau, Germany: V. Mayer (principal investigator).

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