Therapy-Dependent Influence of Time-to-Treatment Interval on Myocardial Salvage in Patients With Acute Myocardial Infarction Treated With Coronary Artery Stenting or Thrombolysis

Albert Schömig, MD; Gjin Ndrepepa, MD; Julinda Mehilli, MD; Markus Schwaiger, MD; Helmut Schühlen, MD; Stephan Nekolla, PhD; Jürgen Pache, MD; Stefan Martinoff, MD; Hildegard Bollwein, MD; Adnan Kastrati, MD

Background—The relationship between myocardial salvage and time-to-treatment interval in patients with acute myocardial infarction (AMI) treated with coronary artery stenting or thrombolysis has not been studied.

Methods and Results—This study analyzed 264 patients with AMI randomized to coronary stenting (133 patients) or thrombolysis (131 patients) in the setting of 2 randomized trials. Patients were divided into the following 3 groups defined by tertiles of the time-to-treatment interval: lower tertile (<165 minutes), middle tertile (165 to 280 minutes), and upper tertile (>280 minutes). Paired scintigraphic examinations were performed to obtain salvage index, which was the primary end point of the study. In the group with thrombolysis, the salvage index (median [25th; 75th] percentile) was 0.45 (0.16; 0.83) in the lower, 0.29 (0.17; 0.48) in the middle, and 0.20 (0.04; 0.46) in the upper tertile (P=0.03). In the group with stenting, the salvage index was 0.56 (0.49; 0.75) in the lower, 0.57 (0.36; 0.73) in the middle, and 0.57 (0.32; 0.75) in the upper tertile (P=0.59). In patients treated with stenting, the salvage index was greater than in patients treated with thrombolysis in the lower (0.56 versus 0.45, P=0.09), middle (0.57 versus 0.29, P=0.0003), and upper (0.57 versus 0.20, P=0.0005) tertiles of the time-to-treatment interval.

Conclusions—The influence of the time-to-treatment interval on the myocardial salvage in patients with AMI depends on the type of reperfusion therapy. Coronary artery stenting was superior to thrombolysis independent of the time-to-treatment intervals, and the difference in benefit increased with more prolonged time from symptom onset. (Circulation. 2003;108:1084-1088.)

Key Words: myocardial infarction ■ stents ■ thrombolysis ■ scintigraphy

Reperfusion therapy initiated within 6 or 12 hours after symptom onset in patients with acute myocardial infarction (AMI) results in a significant reduction of mortality. Several studies have suggested a clinically important difference in the time dependence of the efficacy of various reperfusion therapies. Large studies have shown that therapeutic efficacy of thrombolysis correlates closely with the time-to-treatment interval. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for occluded Coronary Arteries (GUSTO-I) study, 30-day mortality increased from 5.5% if treatment was initiated ≤2 hours to 9% if treatment was initiated >4 hours. The Thrombolysis in Myocardial Infarction (TIMI) investigators reported a decrease in TIMI grade 3 flow from 45% if streptokinase was applied at 2 to 4 hours to 17% if streptokinase was applied >6 hours after the onset of symptoms. The time dependence of the efficacy of percutaneous coronary interventions in patients with AMI is still a matter of debate. It has recently been reported that in patients treated with primary angioplasty, the rate of major adverse cardiac events and relative risk of death remain relatively stable with the increase of time-to-treatment or time-to-presentation intervals.

Myocardial salvage is the principal mechanism by which patients with AMI benefit from various reperfusion therapies, and it can be reliably assessed by technetium(Tc)-99m sestamibi scintigraphy. Myocardial salvage may represent a sensitive index for the assessment of the time dependence of reperfusion efficacy. Thus, the purpose of this study was to assess the relation between time-to-treatment interval and the myocardial salvage in patients treated with coronary stenting versus thrombolysis.

Methods

Patients

Between December 1997 and February 2001, 302 patients with AMI (presented within the first 12 hours from the onset of chest pain) were randomized to receive either stenting or thrombolysis in the framework of the Stent versus Thrombolysis for Occluded Coronary...
Arteries in Patients with Acute Myocardial Infarction (STOPAMI) 1 and 2 trials.12,13 Criteria for the diagnosis of AMI were chest pain lasting at least 20 minutes and ST segment elevation of at least 0.1 mV in 2 or more extremity leads or at least 0.2 mV in 2 or more contiguous precordial leads on the surface ECG. Patients with stroke (within previous 3 months), active bleeding or bleeding diathesis, trauma or major surgery (within previous 1 month), suspected aortic dissection, oral anticoagulation with coumarin derivatives, or severe uncontrolled arterial hypertension (>180 mm Hg) unresponsive to therapy and those with noncompressible vascular puncture sites were not included in the study. All patients gave written informed consent before recruitment in the study. The study protocol was approved by the institutional ethics committee.

Study Protocol
Detailed information about the enrolled patients and randomly assigned treatment has been published previously.12,13 Before assignment, all patients received aspirin 300 mg and intravenous heparin (60 U/kg up to a maximal dose of 5000 U). Overall, 152 patients were assigned to treatment with stenting plus abciximab, and 150 were assigned to thrombolysis with alteplase (69 patients with alteplase only and 81 patients with alteplase plus abciximab). Coronary stent placement was performed according to the previously described technique.14 Alteplase (Actilyse, Boehringer Ingelheim Pharma KG) was used as a full-dose therapy (in 69 patients) and half-dose therapy plus abciximab (in 81 patients). Abciximab (ReoPro, Lilly Deutschland GmbH) was used as adjunct therapy in all patients treated by stenting and in 81 patients treated with thrombolysis (those who received alteplase at half dose).

In patients assigned to the stent group, coronary angiography was performed before and after stent implantation. Digital angiograms were analyzed offline in the angiographic core laboratory with an automated edge detection system (CMS, Medis Medical Imaging Systems).

Te-99m Sestamibi Scintigraphy
Before the initiation of the assigned therapy, patients received an intravenous injection of 27 mCi (1000 MBq) of technetium Te-99m sestamibi. Single photon emission computed tomography was performed within 6 to 8 hours after the injection of the radioactive agent. A follow-up scintigraphy was performed 7 to 14 days after the reperfusion therapy. The calculation of the defect size was performed according to the previously described methods.12,13 The following 3 parameters were calculated: initial perfusion defect and final infarct size (perfusion defects in the initial and follow-up scintigraphy, respectively), both expressed as percentage of the left ventricle, and salvage index, which represents the proportion of the initial defect that was salvaged (initial perfusion defect minus final infarct size divided by initial perfusion defect). All measurements were performed in the scintigraphic core laboratory by investigators unaware of the type of therapy received.

Paired scintigraphic examinations were needed to obtain salvage index, which was the primary end point of the study. In 19 patients in the stent group (12.5%) and in 19 patients (12.7%) in the thrombolysis group, paired scintigraphic examination could not be performed. Thirteen of these 38 patients (8 patients treated with thrombolysis and 5 patients treated with stenting) died before completing the scheduled scintigraphic examinations (range, 0 to 5 days after randomization). The remaining 25 patients survived the 18-month follow-up period. Thus, 264 patients (87.4% or 133 patients in the stent group and 131 patients in the thrombolysis group) with completed paired scintigraphic examinations were included in this study. There were no significant differences in the time-to-treatment intervals (expressed as median [25th; 75th percentiles]) between patients with paired scintigraphic data who were included in the study and those without paired scintigraphic data who were excluded from the study (210 minutes [140; 316] versus 185 minutes [127; 311], P=0.59).

Study Definitions and Follow-Up Protocol
Patients were divided into the following 3 groups defined by tertiles of the time-to-treatment interval: lower tertile (<165 minutes), middle tertile (165 to 280 minutes), and upper tertile (>280 minutes). In patients treated with stenting, time-to-treatment interval was calculated from the onset of symptoms to the first balloon inflation. In patients who received thrombolysis, time-to-treatment interval was calculated from the onset of symptoms to initiation of lytic therapy.

The follow-up protocol after discharge consisted of a telephone interview after 1 month, a visit at 6 months, and the telephone interviews at 6-month intervals after hospital discharge. Furthermore, patients were advised to contact our outpatient clinic or their referring physicians in case of chest pain or other cardiac symptoms.

Statistical Analysis
Data are presented as median (with 25th and 75th percentiles) or counts and proportions (percentages). Categorical data were compared with χ² test. Continuous data were compared with Kruskal-Wallis rank-sum test or Wilcoxon rank-sum test, when appropriate. The independence of the main relation of this study between time-to-treatment interval and salvage index was checked after adjustment for the influence of other factors by multiple linear regression analysis. Subjected to the model were tertiles of time-to-treatment interval, age, sex, diabetes, arterial hypertension, smoking, cholesterol level, previous MI, previous coronary bypass graft surgery, anterior infarction, Killip class, and initial perfusion defect. P<0.05 was considered to indicate statistical significance.

Results
Baseline Characteristics
Patients were divided into 3 groups according to the tertiles of the time-to-treatment interval. Baseline characteristics of the patients are shown in the Table. There were few differences between patients in the lower (<165 minutes), middle (165 to 280 minutes), and upper (>280 minutes) tertiles of the time-to-treatment interval. Thus, more patients with arterial hypertension (73.6%) were in the upper tertile compared with the proportion of the patients in the lower (57.8%) or middle (56.3%) tertile. Furthermore, heart rate of patients in the middle tertile was higher than in patients of the lower or upper tertile of the time-to-treatment interval. Finally, a greater proportion of the patients were treated with thrombolysis in the lower tertile (64.4%) compared with the middle (41.4%) or upper (42.5%) tertile. This difference in the thrombolysis rate can be explained by shorter time needed for the initiation of therapy (door-to-needle time, 35 minutes [25; 45]) compared with time needed for percutaneous coronary intervention (door-to-balloon time, 65 minutes [50; 85], P<0.001) in the postrandomization period. There were no significant differences in the initial perfusion defect in the group with thrombolysis compared with the group with stenting in the lower (26.0% [13.9; 44.6] versus 27.2% [14.6; 48.1], P=0.65), middle (28.7% [15.0; 50.1] versus 28.9% [16.0; 45.6], P=0.94), or upper (32.0 [17.0; 46.5] versus 27.0 [19.2; 37.8], P=0.59) tertile of the time-to-treatment interval.

Time-To-Treatment Interval and Reperfusion Efficacy
In patients treated with thrombolysis, the final infarct size (median [25th; 75th percentile]) was 13.6% [4.1; 26.8], 20.2% [9.6; 33.1], and 24.0% [12.0; 36.1] in the lower, middle, and upper tertiles of time-to-treatment interval, respectively, showing a significant increase with time (Figure

Schömig et al Time-to-Treatment Interval and Myocardial Salvage 1085

Downloaded from http://circ.ahajournals.org/ by guest on July 24, 2017
In patients treated with stenting, the final infarct size was 10.1% [5.3; 19.5], 9.4% [4.4; 22.2], and 11.1% [5.0; 23.9] in the lower, middle, and upper tertile of time-to-treatment interval, respectively, showing no decrease over time (Figure 1, \( P = 0.54 \)). The same time pattern was seen for myocardial salvage index (Figure 2). In patients treated with thrombolysis, it was 0.45 (0.16; 0.83), 0.29 (0.17; 0.48), and 0.20 (0.04; 0.46) in the lower, middle, and upper tertile of time-to-treatment interval, respectively (\( P = 0.03 \)); in patients treated with stenting, it was 0.56 [0.49; 0.75], 0.57 [0.36; 0.73], and 0.57 [0.32; 0.75] in the lower, middle, and upper tertiles of time-to-treatment interval, respectively (\( P = 0.59 \)).

In a second step, myocardial salvage index was compared between groups treated with thrombolysis or stenting in each of the tertiles of the time-to-treatment interval (Figure 2). The myocardial salvage index was higher in patients treated with stenting than in those treated with thrombolysis in each tertile of the time-to-treatment interval. Differences did not reach the statistical significance in the lower tertile (0.56 versus 0.45, \( P = 0.09 \)) but were significantly higher in the middle (0.58 versus 0.29, \( P = 0.0003 \)) and upper (0.57 versus 0.20, \( P = 0.0005 \)) tertiles of the time-to-treatment interval.

In an additional analysis performed according to tertiles of time-to-randomization interval (lower tertile 113 minutes, middle tertile 113 to 210 minutes, and upper tertile >210 minutes), salvage index was 0.58 (0.48; 0.79), 0.57 (0.40; 0.69), and 0.57 (0.27; 0.75), respectively, in the group with stenting (\( P = 0.61 \)) and 0.45 (0.17; 0.72), 0.23 (0.10; 0.45), and 0.25 (0.05; 0.47), respectively, in the group with thrombolysis (\( P = 0.05 \)).

After adjustment in the multivariate model, time-to-treatment interval remained an independent predictor of the salvage index only in patients treated with thrombolysis (\( P = 0.02 \)). In patients treated with stenting, time-to-treatment interval was not a significant predictor of salvage index (\( P = 0.59 \)). The analysis of the interaction between the type of

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Time-to-Treatment Interval, min</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90</td>
<td>165 to 280</td>
<td>0.54</td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (52; 69)</td>
<td>59 (50; 69)</td>
<td>0.31</td>
</tr>
<tr>
<td>Female</td>
<td>21 (23.3)</td>
<td>19 (21.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (22.2)</td>
<td>12 (13.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>52 (57.8)</td>
<td>49 (56.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current smoker</td>
<td>62 (69.0)</td>
<td>58 (67.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>194 (169; 237)</td>
<td>195 (169; 223)</td>
<td>0.86</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>37 (41.1)</td>
<td>39 (44.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>140 (117; 155)</td>
<td>140 (125; 160)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80 (70; 90)</td>
<td>80 (75; 90)</td>
<td>0.54</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70 (60; 81)</td>
<td>80 (66; 86)</td>
<td>0.003</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>1</td>
<td>66 (73.3)</td>
<td>62 (71.3)</td>
<td>65 (74.7)</td>
</tr>
<tr>
<td>2</td>
<td>20 (22.3)</td>
<td>21 (24.1)</td>
<td>20 (23.0)</td>
</tr>
<tr>
<td>3</td>
<td>3 (3.3)</td>
<td>3 (3.4)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>4</td>
<td>1 (1.1)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of MI</td>
<td>15 (16.7)</td>
<td>8 (9.2)</td>
<td>10 (11.5)</td>
</tr>
<tr>
<td>Previous coronary angioplasty</td>
<td>8 (8.9)</td>
<td>4 (4.6)</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Previous bypass surgery</td>
<td>4 (4.4)</td>
<td>4 (4.6)</td>
<td>4 (4.6)</td>
</tr>
<tr>
<td>Initial perfusion defect, % LV</td>
<td>27.0 (14.0; 46.9)</td>
<td>28.9 (16.0; 47.7)</td>
<td>28.0 (18.2; 43.9)</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery stenting</td>
<td>32 (35.6)</td>
<td>51 (58.6)</td>
<td>50 (57.5)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>58 (64.4)</td>
<td>36 (41.4)</td>
<td>37 (42.5)</td>
</tr>
<tr>
<td>Medications at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta )-blockers</td>
<td>85 (94.4)</td>
<td>80 (92.0)</td>
<td>85 (97.8)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>87 (96.7)</td>
<td>78 (89.7)</td>
<td>79 (90.8)</td>
</tr>
<tr>
<td>Statins</td>
<td>75 (83.3)</td>
<td>78 (89.7)</td>
<td>78 (89.7)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7 (7.8)</td>
<td>4 (4.6)</td>
<td>9 (10.3)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>2 (2.2)</td>
<td>4 (4.6)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Data are No. of patients (%) or median (25th; 75th percentiles). BP indicates blood pressure; LV, left ventricle; and MI, myocardial infarction.
treatment (stent or thrombolysis) and the tertiles of time-to-treatment interval for the prediction of myocardial salvage yielded a probability value of 0.06.

Clinical Outcome
Sixteen patients (6%) died during an 18-month follow-up. In patients who received thrombolysis, there were 5 deaths (8.6%) in the lower, 2 deaths (5.6%) in the middle, and 5 deaths (13.5%) in the upper tertiles of the time-to-treatment interval. In patients treated with stenting, there was 1 death (3.1%) in the lower, 1 death (2.0%) in the middle, and 2 deaths (4.0%) in the upper tertiles of the time-to-treatment interval. During this period, the combined incidence of death, reinfarction, or stroke in the 3 tertiles of time-to-treatment interval was 9.4%, 7.6%, and 8.0%, respectively, in the group with stenting and 19.0%, 13.9%, and 16.2%, respectively, in the group with thrombolysis.

Discussion
Stratification of efficacy of various reperfusion therapies according to time-to-treatment interval has clinical relevance. Differences in the time-dependence efficacy of various reperfusion regimens and the fact that a sizable number of patients with AMI present relatively late after symptom onset underscore the clinical importance of such stratification strategy. Experimental studies in dogs and clinical studies in patients with AMI have demonstrated the existence of residual blood flow to the infarcted area. In line with these findings, several studies have demonstrated the existence of viable myocardium in the infarcted area, even late in the course of ischemia, and suggested that the amount of viable tissue correlates with residual blood flow to the area at risk.

Several recent studies in patients with AMI treated with primary angioplasty have reported an independence of clinical outcome from the time-to-treatment interval. In a recent study including 2635 patients enrolled in 10 randomized trials of primary angioplasty versus thrombolytic therapy, Zijlstra et al concluded that with increasing time-to-presentation interval, major adverse cardiac event rates increased after thrombolysis but remained relatively stable after angioplasty. In a cohort of 27,080 consecutive patients with AMI who were treated with primary angioplasty, Cannon et al found no association between symptom onset-to-balloon time and relative risk of death. The authors suggested that the outcome in patients presenting to the hospital late (after 6 to 12 hours) might have been influenced by a survivor-cohort effect. Berger et al found no relationship between time from symptom onset to primary angioplasty and 30-day mortality after AMI.

Our study offers mechanistic explanations for the differences in the time dependence of efficacy observed with thrombolytic and mechanic reperfusion therapies after AMI. In the group of patients treated with stenting within 12 hours from the symptom onset, myocardial salvage assessed by scintigraphic parameters such as final infarct size and salvage index was stable over the different time-to-treatment intervals. Conversely, myocardial salvage achieved by thrombolysis declined markedly with increasing time-to-treatment interval. Our data show also that stenting was superior to thrombolysis in terms of myocardial salvage and the difference in benefit increased with time. These data may offer an explanation for previous findings of increased mortality with thrombolysis as a function of time-to-treatment interval, a finding that was not reported after mechanical reperfusion. Although early after symptom onset, thrombolysis was associated with substantial myocardial salvage, its efficacy declined considerably with longer time intervals. These data show that time interval from symptom onset may represent an important factor in guiding selection of most appropriate reperfusion therapy in patients with AMI.

The mechanisms underlying the differences in the time dependence of myocardial salvage in patients with AMI treated with thrombolysis or stenting with adjunct abciximab are not entirely clear. However, several factors might be helpful in explaining these differences. Advantages of primary angioplasty over thrombolysis in restoring the blood flow through the infarct-related artery might explain, at least in part, the superiority of stenting over thrombolysis with regard to the myocardial salvage found in our study. In a series of 1352 consecutive patients treated with primary angioplasty, Brodie et al reported restoration of TIMI grade 3 flow in 93% of patients, which was independent of ischemia duration. In contrast, thrombolytic trials have indicated that successful restoration of epicardial blood flow through the infarct-related artery after thrombolytic therapy is achieved in a smaller proportion of patients with increasing time-to-
treatment interval. In the GUSTO-I trial, a TIMI 3 flow rate on a 90-minute angiogram was 54% in patients treated with accelerated tissue plasminogen and 33% in patients treated with streptokinase plus intravenous heparin, and the patency rates correlated with 30-day mortality.23

Failure of fibrinolysis with increasing time-to-treatment interval may be explained by several mechanisms. Experimental studies have shown that older thrombi are more resistant to thrombolysis because of continuation of fibrin polymerization.24 Increased availability of plasminogen activator inhibitor type-1 released from platelets25 may also contribute to resistance of thrombolysis. Failure or delay in restoration of the blood flow through infarct-related artery results in continuation of ischemia with progression of myocardial damage through necrosis26 or apoptosis27 and microvascular injury.28

Limitations of the Study
We analyzed patients included in 2 randomized trials, each sufficiently powered to compare stenting with thrombolysis in AMI in terms of myocardial salvage. However, comparison of these reperfusion strategies in 3 groups defined by the tertiles of time-to-treatment interval in the present study may carry the limitation of reduced statistical power with respect to the original studies.12,13

Conclusions
Our study showed that the influence of time-to-treatment interval on the myocardial salvage in patients with AMI depends on the type of reperfusion therapy. In patients treated with stenting within 12 hours from the symptom onset, the myocardial salvage remained stable and independent of the time-to-treatment interval. Myocardial salvage achieved by thrombolysis declined markedly with increasing time-to-treatment interval. Stenting was superior to thrombolysis in terms of myocardial salvage, and the difference in benefit was increased with more prolonged time-to-treatment intervals.

References
Therapy-Dependent Influence of Time-to-Treatment Interval on Myocardial Salvage in Patients With Acute Myocardial Infarction Treated With Coronary Artery Stenting or Thrombolysis

Albert Schömig, Gjin Ndrepepa, Julinda Mehilli, Markus Schwaiger, Helmut Schühlen, Stephan Nekolla, Jürgen Pache, Stefan Martinoff, Hildegard Bollwein and Adnan Kastrati

_Circulation._ 2003;108:1084-1088; originally published online August 18, 2003; doi: 10.1161/01.CIR.0000086346.32856.9C

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/9/1084

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/