Proximal embolic protection and biomarkers of reperfusion in ST-segment elevation myocardial infarction
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Early ST-segment recovery after primary percutaneous coronary intervention accurately predicts long-term prognosis after acute myocardial infarction


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Abstract

Background
Several ancillary studies reported on the prognostic value of ST-segment recovery (STR) with measurement at 30-240 minutes after primary percutaneous coronary intervention (PCI). We determined the long-term prognostic value of early STR, assessed at the end of primary PCI, in unselected patients after ST-segment elevation myocardial infarction (STEMI).

Methods
We analyzed 12-lead electrocardiograms (ECGs), recorded in the catheterization laboratory prior to arterial puncture and at time of the end of PCI, from 2124 STEMI patients who underwent primary PCI at our institution between 2000 and 2007. STR was categorized as complete (≥70%), partial (30-70%), or absent (<30%). Median follow-up was 4.1 years.

Results
The estimated 5-year mortality was 8.3% in patients with complete STR, 14.4% in patients with partial STR, and 22.8% in patients with absent STR (p<0.001). Multivariable-adjusted hazard ratios for 1-year death of patients with partial and absent STR, as compared to patients with complete STR, were 2.1 (95% CI, 1.2-3.8; p=0.014) and 3.2 (95% CI, 1.8-5.8; p<0.001), respectively. In a landmark analysis restricted to 1-year survivors, early STR was significantly predictive for 5-year mortality, even after multivariable adjustment.

Conclusions
Early STR assessment has strong, long-term prognostic properties in all-comer STEMI patients. Moreover, the prognostic power of early STR is not restricted to the early recovery phase after STEMI, but identifies high-risk subgroups among 1-year survivors.
Early ST-segment recovery predicts long-term prognosis in STEMI

Introduction

Primary percutaneous coronary intervention (PCI) is the preferred treatment to restore flow through the infarct-related coronary artery in patients who present with ST-segment elevation myocardial infarction (STEMI). Primary PCI facilitates reperfusion of the ischemic myocardium by restoration of flow through the epicardial segment. Despite successful epicardial revascularization, microvascular dysfunction as measured by ST-segment recovery (STR) has been associated with adverse cardiac remodelling and a poor prognosis. Despite the ongoing development of sophisticated cardiac imaging technologies, the 12-lead electrocardiogram (ECG) remains an important, readily available instrument in the diagnostic pathway of patients with acute chest pain. Furthermore, the ECG has proven its ability to identify subgroups at high risk for adverse outcome after primary PCI for STEMI. Several large, ancillary studies established the power of STR, a reflection of the multifactorial process of microvascular dysfunction, to predict prognosis in selected STEMI patients. In these studies, STR was assessed after admission at the coronary or intensive care unit, 30 minutes to 4 hours after completion of the PCI procedure.

Ideally, STEMI patients undergoing primary PCI should be stratified into high- and lower-risk subgroups at the catheterization laboratory, before transfer to the nursing department or the referring hospital, but data on the predictive value of early STR is scarce. Therefore, we sought to investigate whether early STR, assessed at the end of primary PCI, has short- to long-term prognostic properties in a single-centre, all-comer STEMI population.

Methods

Source population

The data analyzed in our study were obtained from STEMI patients who underwent primary PCI at the Academic Medical Center – University of Amsterdam between November 1, 2000 and January 1, 2007. The institutional review board of the Academic Medical Center allowed the use of patient-specific data. All patients gave
informed consent. Generally, primary PCIs were performed according to current guidelines. Patients with an indication for primary PCI received aspirin (500 mg) and unfractionated heparin (5000 IU) during transportation to the catheterization laboratory. As per 2005, 300 mg or 600 mg of clopidogrel was added as pre-treatment prior to primary PCI. Glycoprotein IIb/IIIa inhibitors were not routinely used, but administered during the procedure at the discretion of the operator.

From the local electronic database at the catheterization laboratory, we abstracted baseline demographic variables, procedural and angiographic information that had been prospectively collected and entered by specialized nurses and interventional cardiologists concurrently with routine patient care. We obtained information on 1-year vital status from the institutional follow-up database of PCI patients. Patients are surveyed 1 year after PCI by means of a mailed, self-administered questionnaire. Follow-up information was synchronized with computerized, long-term mortality records from the National Death Index and local authorities, which were updated until October 2008. We reviewed outpatients’ files and contacted general practitioners by telephone in case of conflicting or missing data. Follow-up could be obtained in 2103 of 2124 patients (99%).

**ECG collection and analysis**

We retrospectively sought to collect 12-lead ECGs recorded immediately prior to arterial puncture at the catheterization laboratory for all STEMI patients at our institution. These pre-procedural ECGs were compared with 12-lead ECGs recorded at the end of primary PCI, but before patients were transferred to the coronary or intensive care unit.

ECGs of included patients were analyzed by 1 investigator (N.J.V.), unaware of the angiographic and outcome data. ST-segment deviation was measured with a handheld caliper and magnifying glass at 80 milliseconds after the J-point in all available leads. ST-segment deviation was measured to the nearest 0.05 mV with the TP segment as preferred iso-electric baseline. We defined STR as the percentage change of summed ST-segment deviations on the 12-lead ECG immediately post-PCI relative to the pre-procedural ECG and classified this change into complete (≥70%), partial (between 70% and 30%), or absent (<30%), according to Schröder et al..12
In case of missing leads or artifacts, patients were included if at least 50% of the corresponding, infarct-related leads were suitable for ST-segment analysis. Leads V₁ to V₆, I, and aVL were considered directly infarct-related in anterior myocardial infarction; II, III, aVF, V₇, and V₈ in non-anterior myocardial infarction.

**Study population**
All consecutive STEMI patients who underwent primary PCI at our institution according to our digital database and were alive at the end of the PCI procedure were eligible for inclusion. We excluded patients who underwent primary PCI of the left main coronary artery or a bypass graft because of the distinctive ECG pattern observed in such cases. Patients, from whom either a pre-procedural or a post-procedural ECG could not be retrieved, were excluded from this analysis. Furthermore, patients with ECG recordings containing a complete left bundle branch block, an accelerated idioventricular rhythm, a paced rhythm, or severe artifacts which prohibit accurate ST-segment evaluation were excluded. STEMI patients who were referred for primary PCI but in whom we observed normalization of ST-segment elevation on arrival at the catheterization laboratory, post-PCI STR analysis was not appropriate and therefore these patients were also excluded.

**Statistical analysis**
Mortality curves were generated by the Kaplan-Meier method and differences in mortality were compared using the log-rank statistic. The association between immediate STR and long-term, all-cause mortality was investigated with the use of Cox proportional-hazards regression in both crude models and multivariable-adjusted models. Candidate covariates were entered into the multivariable models when they were significantly associated (p<0.05) in the univariable analyses with differences between patients with complete, partial, and absent STR. All variables were entered en block and the results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Total ischemic time and peak CK-MB levels were not included in multivariable analyses because of a considerable amount of missing values. Unadjusted and adjusted landmark analyses focused on patients who survived the first year after primary PCI.
Normally distributed, continuous variables are expressed as means (±SD), while other continuous data are expressed as median with interquartile range (IQR). All categorical variables are depicted using relative frequency distributions. Characteristics of patients with complete, partial, or absent STR were compared using the χ² test to detect a trend for categorical variables, while the 1-way ANOVA or Kruskal-Wallis test was used for continuous variables. For all tests, differences were considered significant if the 2-sided p Value was less than 0.05. All analyses were performed using SPSS software package (Version 16.0; SPSS, Inc., Chicago, Illinois).

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all presented analyses, the drafting and editing of the paper and its final contents.

Results

Study cohort

A total of 3185 consecutive STEMI patients underwent primary PCI at our institution between November 1, 2000 and January 1, 2007. We excluded 67 patients who underwent primary PCI of the left main coronary artery or a bypass graft and 508 patients because of missing ECG recordings. In 2610 patients with a complete set of ECGs, electrocardiographic exclusion criteria were present in 132 patients and pre-procedural ST-segment normalization occurred in 354 patients. As a result, 2124 patients were available for this analysis (Figure 1).

Electrocardiography

On average 97% of the leads on each 12-lead ECG could be analyzed. The pre-procedural standard 12-lead ECG was recorded at a median time of 161 minutes (IQR 115; 234) after symptom onset and 11 minutes (IQR 5; 18) before restoration of flow through the infarct-related artery. The post-procedural ECG was recorded at the end of PCI at a median time of 33 minutes (IQR 24; 47) after first balloon inflation. Median summed ST-segment deviation on the pre-procedural ECG was 19 mm (IQR 11.5; 28) and early STR was 50% (IQR 21; 70).
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**Baseline characteristics**

A total of 549 patients (26%) showed complete STR, 901 patients (42%) showed partial STR, and 674 patients (32%) showed absent STR. Baseline and procedural characteristics of the patients by category of STR are depicted in Table 1. Patients with complete STR were younger and less frequently had risk factors for coronary artery disease. Furthermore, they presented less often with anterior myocardial
infarction, less often had multivessel disease, more often had normal TIMI-graded flow after the procedure, and less often needed cardiac support with intra-aortic balloon counter pulsation (IABP). Peak CK-MB levels were significantly lower in patients with complete STR compared to patients with partial or absent STR. Thus, patients with complete STR had a favorable risk profile compared to patients with partial or absent STR.

Table 1 Characteristics of included patients stratified by category of ST-segment recovery

<table>
<thead>
<tr>
<th></th>
<th>Complete (n=549)</th>
<th>Partial (n=901)</th>
<th>Absent (n=674)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y (SD)</td>
<td>59 (12)</td>
<td>61 (13)</td>
<td>62 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>72</td>
<td>73</td>
<td>71</td>
<td>0.79</td>
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<td>Current smoking</td>
<td>53</td>
<td>47</td>
<td>41</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>8</td>
<td>11</td>
<td>14</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, mean, kg/m² (SD)</td>
<td>26 (4)</td>
<td>27 (4)</td>
<td>27 (4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
<td>31</td>
<td>33</td>
<td>0.08</td>
</tr>
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<td>Hypercholesterolemia</td>
<td>22</td>
<td>23</td>
<td>20</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous MI</td>
<td>9</td>
<td>12</td>
<td>13</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>0.54</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>27</td>
<td>50</td>
<td>56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>27</td>
<td>31</td>
<td>33</td>
<td>0.02</td>
</tr>
<tr>
<td>Pre-PCI TIMI 3 flow</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td>0.07</td>
</tr>
<tr>
<td>Stent inserted</td>
<td>90</td>
<td>87</td>
<td>86</td>
<td>0.03</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor used</td>
<td>24</td>
<td>30</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-PCI TIMI 3 flow</td>
<td>95</td>
<td>91</td>
<td>83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-PCI TIMI 2-3 flow</td>
<td>99</td>
<td>99</td>
<td>95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IABP inserted</td>
<td>5</td>
<td>6</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total ischemic time, median, min. (IQR)</td>
<td>166 (125-232)</td>
<td>180 (135-252)</td>
<td>175 (130-262)</td>
<td>0.03</td>
</tr>
<tr>
<td>Door-to-balloon time, median, min. (IQR)</td>
<td>62 (46-83)</td>
<td>65 (48-88)</td>
<td>63 (48-90)</td>
<td>0.22</td>
</tr>
<tr>
<td>Peak CK-MB, median, µg/L (IQR)</td>
<td>200 (109-345)</td>
<td>274 (149-466)</td>
<td>267 (124-475)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as percentages unless otherwise stated. Data available in *1864 patients, †1897 patients, and ‡1272 patients. SD, standard deviation; BMI, body mass index; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; GP, glycoprotein; IABP, intra-aortic balloon pump; IQR, interquartile range; CK, creatine kinase.
Early ST-segment recovery predicts long-term prognosis in STEMI

Mortality by ST-segment recovery
At a median follow-up of 4.1 years (IQR, 2.7; 5), overall mortality was 13% (272 of 2103 patients died). The estimated 5-year cumulative mortality was 8.3% in patients with complete STR, 14.4% in patients with partial STR, and 22.8% in patients with absent STR (p<0.001 for overall comparison). Median STR was significantly lower among patients who died than among those who survived (33% [IQR 11; 55] vs. 53% [IQR 24; 72]; p<0.001). Furthermore, the associations did not substantially change when the outcome analysis was restricted to patients with post-procedural TIMI-3 flow (data not shown).

ST-segment recovery and 1-year mortality
A total of 145 patients (7%) died within 1 year. One-year Kaplan-Meier estimates of mortality according to the category of STR are presented in Figure 2A. In a Cox regression analysis with STR as a categorical variable, the unadjusted hazard ratios for death of patients with partial and absent STR, as compared to patients with complete STR, were 2.4 (95% CI, 1.4-4.4; p=0.003) and 4.6 (95% CI, 2.6-8.2; p<0.001), respectively. In a multivariable Cox regression model, the hazard ratio for death among patients with partial STR, as compared to patients with complete STR, was 2.1 (95% CI, 1.2-3.8; p=0.01) and that for patients with absent STR was 3.2 (95% CI, 1.8-5.8; p<0.001) (Figure 2B).

ST-segment recovery and late mortality in 1-year survivors
In a landmark analysis restricted to 1-year survivors, an additional 127 patients died. In a Cox regression analysis with 1958 1-year survivors, the unadjusted hazard ratios for death of patients with partial and absent STR, as compared to patients with complete STR, were 1.6 (95% CI, 0.9-2.8; p=0.08) and 2.3 (95% CI, 1.4-3.8; p=0.001), respectively (Figure 3A). After multivariable modeling, STR as a categorical variable remained independently predictive of death in 1-year survivors (p=0.04). The adjusted hazard ratio for death among 1-year survivors with partial STR, as compared to 1-year survivors with complete STR, was 1.4 (95% CI, 0.8-2.3; p=0.19) and that for 1-year survivors with absent STR was 1.9 (95% CI, 1.1-3.2; p=0.014) (Figure 3B). Early STR remained significantly associated with 5-year mortality when analyses were restricted to 30-day or 6-month survivors (data not shown).
Figure 2. One-year mortality estimates according to category of ST-segment recovery.
Both unadjusted estimates (Panel A) and adjusted estimates (Panel B) are shown. p-Values, calculated with the log-rank test for unadjusted estimates and the Cox proportional hazard method for adjusted estimates, are reported for the comparison among the 3 groups.
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**Figure 3** Five-year mortality estimates restricted to 1-year survivors.

Both unadjusted (Panel A) and adjusted (Panel B) 5-year survival estimates are shown for patients who survived the first year after primary PCI. Estimates are stratified according to the category of ST-segment recovery.
Discussion

In the present study, we established that there is a strong and lasting association between early STR and short- to long-term mortality in an unselected STEMI population undergoing primary PCI. Our data show that early STR is highly predictive for mortality until 5 years after the index event and enables risk prediction beyond the early post-STEMI episode in patients who survive the first year after primary PCI. Our results confirm and extend the data on the predictive value of early STR in the setting of primary PCI. Although the association of STR at 30 to 240 minutes after primary PCI with outcome has extensively been studied in numerous large ancillary studies, these reports showed associations of STR with outcomes at varying, static time points. In these first hours after reperfusion, when the electrocardiogram changes rapidly, the optimal time of measuring STR has remained unclear. Our findings suggest that already at the end of PCI, early STR is perfectly capable of predicting mortality up to 5 years of follow-up. Early STR may fit the PCI model of reperfusion better than assessment times such as 30, 60, or even 240 minutes after PCI. Early STR better reflects restoration of the myocardial tissue perfusion than TIMI-graded epicardial flow. Unsuccessful restoration of microvascular perfusion, in spite of optimal epicardial flow, may explain the strong association of early STR with mortality. Microvascular dysfunction after successful epicardial reperfusion, as measured by STR, is a complex process with several probable interrelating stimuli and factors, such as the inflammatory reaction in the ischemic myocardium, rapid changes in both pH and electrolyte levels after restoration of blood flow, and the presence of distal embolization. Also, STR in patients with STEMI could fail or be worsened by irreversible ischemic necrosis, edema with microvascular compression, reperfusion injury, or dyskinesia of infarct wall segments. Assessment of early STR has numerous advantages as compared to measurements at a time point between 30 and 240 minutes after the PCI procedure. Early STR assessment enables physicians at the catheterization laboratory to instantly identify high-risk patients, without the time delay associated with patient’s transportation to other departments of care. Moreover, with current data on the strong prognostic power of early STR presented in this paper, this instrument may be an important addition to other prognostic markers, like cardiac enzyme concentrations and left
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ventricular ejection fraction. These latter variables can only be reliably assessed at a later time point after the acute phase of STEMI. The 12-lead ECG, a simple and widely available tool for very early risk stratification, facilitates the identification of high-risk subgroups of patients which could be a target population for novel protective therapies. Absent STR occurred in 32% of the patients included in current study and was associated with an adjusted 3.2-fold risk of 1-year death as compared to patients with complete STR. Therefore a more aggressive approach, including intracoronary pharmacological agents such as glycoprotein IIb/IIIa inhibitors or streptokinase, or postconditioning might be beneficial to enhance microvascular reperfusion.

Data on the accuracy of STR to predict mortality beyond 1 year is limited. In most studies reporting on the predictive accuracy of STR, included patients were followed for a 30-day to 1-year period after primary PCI. Brodie et al. reported a significant association between STR and late mortality in 1005 patients at a median follow-up of 6.2 years. However, interpretation of these results is difficult because more than 50% of eligible patients were excluded from analysis and included patients were treated between 1984 and 2003, a time period when major changes in standard treatment of patients with STEMI occurred. Moreover, all post-procedural ECGs recorded within 4 hours following the PCI procedure were acceptable for evaluation, which may have resulted in considerable variation in the time points between revascularization and ECG recording. Despite the methodological limitations in this study of Brodie, the ability of STR to predict mortality beyond 1 year is in concordance with the data of our study. Importantly, our landmark analyses showed that early STR remained significantly predictive of mortality until 5 years after the index event when the analyses were restricted to 1-year survivors. Therefore, our data suggests that early STR is capable of identifying patients at high risk for both early and late mortality.

The current knowledge on the predictive value of STR has been largely derived from ancillary studies of randomized controlled trials. Large studies on the applicability of STR in unselected, consecutive STEMI populations are scarce. The largest study showed a significant association between STR at 3 hours after PCI and 1-year mortality in an unselected cohort of 1660 primary PCI patients. However, STR was assessed at the time the patient had left the catheterization laboratory, a time when nowadays patients frequently have already been transferred to the referring hospital. As noted by the authors, this delayed timing may have resulted in a considerable selection
towards low-risk patients who survived the first hours after primary PCI, which is reflected by a low 1-year mortality of 3.8% in this study. Our study, however, does not have abovementioned limitations due to early STR assessment.

Several limitations of this study are noteworthy. The most important limitation is the absence of an independent ECG core laboratory for analyses and adjudication of the data. ST-segment analyses for this study were conducted by 1 investigator, albeit blinded to patient and outcome data. Nevertheless, ST-segment analyses are straightforward and not susceptible to large variation between observers, which supports an application of this instrument in daily practice for early risk stratification of post-PCI STEMI patients. Furthermore, 16% of patients in this study had to be excluded because of missing data, which is comparable to other observational studies. We consider the retrospective collection of the ECGs as another limitation of this study. But, information on patient characteristics and mortality were prospectively collected in all patients. Observations in larger populations are necessary to further affirm the prognostic power of early STR in consecutive STEMI patients who are referred for primary PCI. Finally, because our analyses are limited to the data collected by the National Death Index and local authorities, we are unable to directly address whether reinfarction, ventricular arrhythmias, heart failure, or non-cardiovascular causes were driving mortality in the present STEMI cohort.

Conclusions

Early STR is an independent predictor of short- to long-term mortality in an all-comer STEMI population. In patients who survive the first year after primary PCI, early STR accurately identifies patients at risk of death at 5 years after the index event. These results, which affirm the impact of STR on long-term mortality in a real-world STEMI cohort, provide a persuading argument for implementation of early STR as a standard prognostic tool in STEMI patients undergoing primary PCI.

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Reference list


