Proximal embolic protection and biomarkers of reperfusion in ST-segment elevation myocardial infarction
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Prediction of one-year mortality with different measures of ST-segment recovery in all-comers after primary percutaneous coronary intervention for acute myocardial infarction


Circulation: cardiovascular quality and outcomes; accepted
Abstract

Background
Post-hoc analyses from several randomized controlled trials have established the prognostic importance of different measures of ST-segment recovery in highly selected patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI). In this single-center registry, we investigated whether various measures of ST-segment recovery can be applied to unselected STEMI patients undergoing primary PCI.

Methods
We analyzed 12-lead electrocardiograms (ECGs) from 2124 consecutive STEMI patients who underwent primary PCI at our institution between November 1, 2000 and January 1, 2007. ECGs were recorded at the catheterization laboratory immediately prior to arterial puncture and at the end of PCI. We examined measures assessing ST-segment recovery on the postprocedural ECG and measures comparing both ECGs and related these to one-year, all-cause mortality.

Results
Cumulative ST-segment recovery (∑ST-D resolution) at a 50% cut off had the highest unadjusted accuracy (C statistic 0.646, 95% CI 0.602 - 0.689; p<0.001) as compared to the other eight measures evaluated. Furthermore, ∑ST-D resolution was the strongest contributor to both the net reclassification and integrated discrimination improvement.

Conclusions
Although each measure of ST-segment recovery provided univariable prognostic information, the ∑ST-D resolution measure comparing summed ST-segment deviations on the pre- and postprocedural ECG was the best independent predictor of one-year mortality in all-comer STEMI patients after primary PCI.
Background

Despite successful epicardial recanalization, primary percutaneous coronary intervention may be limited by suboptimal myocardial reperfusion caused by microcirculatory dysfunction, which is associated with adverse outcome.\textsuperscript{1,2} Non-invasive, simple, readily available methods to assess the success of mechanical reperfusion therapy at the tissue level after primary PCI will become increasingly important. ST-segment recovery on the 12-lead electrocardiogram (ECG) can be measured in several different ways, reflecting successful microcirculatory reperfusion. Several post-hoc analyses from randomized controlled trials have established ST-segment recovery as a powerful predictor of prognosis in selected STEMI patients undergoing primary PCI.\textsuperscript{3-11} Buller et al. examined various, previously published measures of ST-segment recovery in the large cohort of 4866 STEMI patients, who underwent primary PCI as part of the APEX-AMI trial.\textsuperscript{11,12} Conclusions from this ancillary study were generated with data from a highly-selected population of patients with electrocardiographically large myocardial infarctions enrolled in a randomized trial. We investigated whether various measures of ST-segment recovery can be applied to an unselected primary PCI population with varying degrees of ST-segment elevation.

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. Patients with an indication for primary PCI received aspirin (500 mg) and unfractionated heparin (5000 IU) during transfer 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.
We obtained information on one-year vital status from the institutional follow-up database of PCI patients. Patients are surveyed one year after PCI by means of a mailed, self-administered questionnaire. Follow-up information was synchronized with computerized, one-year mortality records from the National Death Index and local authorities. We reviewed outpatients’ files and contacted general practitioners by telephone in case of conflicting or missing data.

Data sources
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. This information included the operator’s online assessment of antegrade flow using the Thrombolysis In Myocardial Infarction (TIMI) scale,\textsuperscript{13} the extent of coronary artery disease, and the timing of reestablishment of antegrade flow through the infarct-related artery (IRA).

ECG collection and analysis
We retrospectively sought to collect 12-lead ECGs recorded immediately prior to arterial puncture for all STEMI patients who underwent primary PCI at our institution. Pre- and postprocedural 12-lead ECGs were regularly recorded at our catheterization laboratory as part of standard care. All 12 radiolucent ECG leads were positioned at the start of the procedure and remained in place until transportation to the coronary care unit. The preprocedural ECGs were compared with 12-lead ECGs recorded at the end of PCI (postprocedural ECGs).

ECGs of included patients were analyzed by one investigator (N.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. Per-lead measurements were recorded in an electronic database for statistical analysis. The following measures of ST-segment recovery were calculated from the electronic dataset with per-lead measurements:

1. $\sum_{\text{ST-D}}$ resolution (percentage change in cumulative ST-segment deviation
Prediction of one-year mortality with different measures of ST-segment recovery

between preprocedural and immediately postprocedural ECG); (2) $\sum$ST-E resolution (percentage change in cumulative ST-segment elevation between preprocedural and immediately postprocedural ECG); (3) Single-lead ST-E resolution (percentage change in maximum-lead ST-segment elevation between preprocedural and immediately postprocedural ECG); (4) Worst-lead residual ST-E (absolute amount of ST-segment elevation in most affected lead on postprocedural ECG); and (5) $\sum$ residual ST-D (absolute amount of cumulative ST-segment deviation on the postprocedural ECG).

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, V5, and V6 in non-anterior myocardial infarction.

Study population
Consecutive STEMI patients who underwent primary PCI at our institution between November 1, 2000 and January 1, 2007 were eligible for inclusion. We excluded patients who underwent primary PCI of the left main coronary artery or a bypass graft. Patients whose preprocedural or postprocedural ECG could not be retrieved were excluded from this analysis. Furthermore, patients with a complete left bundle branch block, an accelerated idioventricular rhythm, a paced rhythm, or severe ECG artifacts which prohibited accurate ST-segment evaluation were excluded. STEMI patients accepted for primary PCI whose ST-segment elevation had resolved on arrival at the catheterization laboratory, were also excluded.

Statistical analyses
The relation between all-cause mortality at one year and different ST-segment recovery measures was investigated with the use of Cox proportional-hazards regression in two sets of models: crude models and models adjusted for baseline and procedural characteristics that showed an univariate association ($p<0.10$) with one-year mortality (sex, age, current smoking, the presence or absence of diabetes mellitus, hypercholesterolemia, a history of myocardial infarction or coronary artery bypass grafting, postprocedural TIMI flow, anterior STEMI, multivessel disease, use of GP IIb/IIIa inhibitors, and intra-aortic balloon counter pulsation).
Various measures of ST-segment recovery were subdivided in two categories with a cut-off at 50% or in three categories with cut-offs at 30% and 70%, as previously described in literature.14-16 Worst-lead residual ST-E measure was subdivided in three categories: <1, 1 to <2, ≥2 mm.4,17 Because previous validation of the worst-lead residual ST-E measure with abovementioned cut-off points was done at 30 to 240 minutes after the procedure,4,17 we investigated this measure of ST-segment recovery also with cut-off points at 2 and 4 mm. ∑ residual ST-D was investigated at a 9mm cut off (median). Hazard ratios (HR) with 95% confidence intervals (CI) for death were computed with patients showing ≥70% ST-segment recovery, <1 mm residual ST-segment elevation, or ≤9 mm ∑ residual ST-D as a reference. ∑ST-D resolution, single-lead ST-E resolution, worst-lead residual ST-E, and ∑ residual ST-D were also evaluated as continuous variables and HRs (95% CIs) were expressed for the per-unit (percentage or mm) increase of ST-segment recovery. These continuous variables were then concurrently forced into both crude and adjusted models to determine their independent strength to predict one-year mortality.

To estimate the discriminative value of predictive models, we calculated the C statistic (area under the receiver operating characteristic curve) for models based on prespecified baseline and procedural characteristics (referent model), on ST-segment recovery measures alone, and for combined models. Differences in C statistic after the addition of the different measures of ST-segment recovery to the referent model were estimated as described by DeLong et al.18 The discriminative power of the different measures of ST-segment recovery was further quantified with the method described by Pencina et al.19 We analyzed differences in patient’s individual estimated probability of death with different predictive models. After addition of a ST-segment recovery measure to the referent model, each probability increase in a patient who died and probability decrease in a patient who survived would imply improved prediction ability, whereas the opposite imply worse prediction ability. We combined the numbers of improved and worsened probabilities for patients who die within one year and patients who survive in the net reclassification improvement (NRI). We also calculated the integrated discrimination improvement (IDI), which directly compares the mean difference in probability between models with and without the ST-segment recovery measures.19
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 who did and did not die within one year were compared using the $X^2$ test to detect a trend for categorical variables, while the one-way ANOVA or Kruskal-Wallis test was used for continuous variables. For all tests, differences were considered significant if the two-sided $P$ value was less than 0.05. Analyses were performed using SPSS software package (Version 15.0; SPSS, Inc., Chicago, Illinois), Stata (Version 10; StatCorp LP, Texas) and R (R Foundation for Statistical Computing, Vienna, Austria).

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. There were 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 (Figure 1). Baseline and procedural characteristics of the remaining 2124 patients, stratified by outcome at one year, are depicted in Table 1.
3185 patients underwent primary PCI between November 2000 and January 2007

- 67 (2%) patients with primary PCI of left main coronary artery or bypass graft
- 508 (16%) patients with missing ECG recordings
- 132 (4%) patients with electrocardiographic exclusion criteria
- 354 (11%) patients with ST-segment normalization prior to primary PCI

2124 patients suitable for inclusion in current study

Figure 1 Flow chart of patient selection.
Table 1 Baseline and procedural characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=2124)</th>
<th>1-year survivors (n=1958)</th>
<th>Patients who died (n=145)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>61.0 (12.8)</td>
<td>60.4 (12.6)</td>
<td>69.3 (12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>72.1</td>
<td>72.9</td>
<td>62.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>46.3</td>
<td>47.7</td>
<td>28.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus, %</td>
<td>11.1</td>
<td>10.5</td>
<td>18.6</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>26.6 (4.0)</td>
<td>26.5 (4.0)</td>
<td>26.4 (4.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>31.0</td>
<td>31.1</td>
<td>29.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>21.9</td>
<td>22.5</td>
<td>13.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>11.2</td>
<td>10.9</td>
<td>11.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>0.7</td>
<td>0.6</td>
<td>2.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>6.9</td>
<td>6.9</td>
<td>4.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Anterior MI, %</td>
<td>45.7</td>
<td>45.0</td>
<td>54.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>30.6</td>
<td>29.2</td>
<td>47.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-PCI TIMI 3 flow, %</td>
<td>11.1</td>
<td>11.3</td>
<td>9.0</td>
<td>0.49</td>
</tr>
<tr>
<td>Stent inserted, %</td>
<td>87.5</td>
<td>87.5</td>
<td>86.9</td>
<td>0.80</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor used, %</td>
<td>30.5</td>
<td>30.4</td>
<td>31.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Post-PCI TIMI 3 flow, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IABP inserted, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total ischemic time, min. (25th, 75th percentile)</td>
<td>172 (130, 250)</td>
<td>174 (130, 250)</td>
<td>180 (142, 270)</td>
<td>0.18</td>
</tr>
<tr>
<td>Peak CK-MB, µg/L (25th, 75th percentile)</td>
<td>248 (131, 435)</td>
<td>240 (124, 422)</td>
<td>350 (201, 545)</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; CK, creatine kinase

Electrocardiography

The preprocedural 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 postprocedural ECG was recorded at the end of PCI at a median time of 33 minutes (IQR 24; 47) after flow restoration.

On average 97% of the leads on each 12-lead ECG could be analyzed. On the preprocedural ECG, the median ∑ST-segment deviation and elevation were 19 (IQR 11.5; 28) and 13 mm (IQR 8; 20.5), respectively. Maximum single-lead ST-E prior to
PCI was at median 4 mm (IQR 2.5; 6). The median ∑ST-D resolution was 50% (IQR 21%; 70%), ∑ST-E resolution was 52% (IQR 23%; 75%), single-lead ST-E resolution was 56% (IQR 29%; 80%), and worst-lead residual ST-E was 2 mm (IQR 1 mm; 3.5 mm).

Prognostic accuracy of different ST-segment recovery measures

One-year follow-up was complete in 2103 (99%) patients. A total of 145 (6.9%) patients died within one year. As shown in Table 2, all unadjusted hazard ratios for one-year mortality showed statistical significance, except for the 1 to 2 mm residual ST-segment elevation category within the worst-lead ST-E measure. The associations depicted in Table 2 did not substantially change when the analysis was restricted to patients with postprocedural TIMI-3 flow (data not shown).

As presented in the center panel of Table 2, ∑ST-D resolution with a 50% cut off showed the highest, unadjusted predictive accuracy (C statistic 0.646, 95% CI 0.602 - 0.689; p<0.001), while worst-lead residual ST-E showed the lowest accuracy to predict one-year mortality (C statistic 0.609, 95% CI 0.565 - 0.652; p<0.001). Predictive accuracy of worst-lead residual ST-E was substantially higher with cut-off points at 2 and 4 mm (C statistic 0.633, 95% CI 0.586 - 0.679). For all measures of ST-segment recovery, we observed a modest but statistically significant improvement in C statistic when the ST-segment recovery measures were individually added to the referent model containing patient and procedural predictors of one-year mortality (C statistic 0.779 in referent model to ≥0.789 in new models; all p<0.05) (Table 2, right panel). The multivariable-adjusted C statistic ranged from 0.789 with ∑ residual ST-D to 0.797 with ∑ST-D resolution (50% cut off).
Table 2 Result of unadjusted and adjusted one-year mortality analyses for different ST-segment recovery measures as categorical variables

<table>
<thead>
<tr>
<th>Measure</th>
<th>Outcome Unadjusted</th>
<th></th>
<th></th>
<th>Outcome Multivariable-adjusted*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Death,</td>
<td>HR</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td>C statistic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∑ST-D resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70%</td>
<td>543</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>0.641</td>
</tr>
<tr>
<td>30% - 70%</td>
<td>890</td>
<td>6.2</td>
<td>2.4</td>
<td>(1.4 - 4.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>&lt; 30%</td>
<td>670</td>
<td>11.3</td>
<td>4.6</td>
<td>(2.6 - 8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>1078</td>
<td>3.2</td>
<td>-</td>
<td>-</td>
<td>0.646</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>1025</td>
<td>10.7</td>
<td>3.5</td>
<td>(2.4 - 5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∑ST-E resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70%</td>
<td>631</td>
<td>3.2</td>
<td>-</td>
<td>-</td>
<td>0.628</td>
</tr>
<tr>
<td>30% - 70%</td>
<td>845</td>
<td>6.6</td>
<td>2.1</td>
<td>(1.3 - 3.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>&lt; 30%</td>
<td>627</td>
<td>11.0</td>
<td>3.6</td>
<td>(2.2 - 6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>1123</td>
<td>3.9</td>
<td>-</td>
<td>-</td>
<td>0.624</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>980</td>
<td>10.3</td>
<td>2.7</td>
<td>(1.9 - 3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single-lead ST-E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70%</td>
<td>729</td>
<td>3.8</td>
<td>-</td>
<td>-</td>
<td>0.626</td>
</tr>
<tr>
<td>30% - 70%</td>
<td>836</td>
<td>6.3</td>
<td>1.7</td>
<td>(1.1 - 2.6)</td>
<td>0.028</td>
</tr>
<tr>
<td>&lt; 30%</td>
<td>538</td>
<td>11.9</td>
<td>3.2</td>
<td>(2.1 - 5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>1289</td>
<td>4.3</td>
<td>-</td>
<td>-</td>
<td>0.625</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>814</td>
<td>11.1</td>
<td>2.7</td>
<td>(1.9 - 3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worst-lead residual ST-E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 mm</td>
<td>205</td>
<td>2.4</td>
<td>-</td>
<td>-</td>
<td>0.609</td>
</tr>
<tr>
<td>1 - &lt; 2 mm</td>
<td>683</td>
<td>4.1</td>
<td>1.7</td>
<td>(0.7 - 4.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>≥ 2 mm</td>
<td>1215</td>
<td>9.2</td>
<td>3.9</td>
<td>(1.6 - 9.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>&lt; 2 mm</td>
<td>888</td>
<td>3.7</td>
<td>-</td>
<td>-</td>
<td>0.633</td>
</tr>
<tr>
<td>2 - &lt; 4 mm</td>
<td>772</td>
<td>7.5</td>
<td>2.1</td>
<td>(1.3 - 3.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 4 mm</td>
<td>443</td>
<td>12.2</td>
<td>3.4</td>
<td>(2.2 - 5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∑ residual ST-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9 mm</td>
<td>1085</td>
<td>3.9</td>
<td>-</td>
<td>-</td>
<td>0.622</td>
</tr>
<tr>
<td>&gt; 9 mm</td>
<td>1018</td>
<td>10.1</td>
<td>2.7</td>
<td>(1.9 - 3.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* In each model, the following variables were entered en block: sex, age, current smoking, the presence or absence of diabetes mellitus, hypercholesterolemia, a history of myocardial infarction or coronary artery bypass grafting, post procedural TIMI flow, anterior STEMI, multivessel disease, use of GP IIb/IIIa inhibitors, and intra-aortic balloon counter pulsation (C statistic 0.779).

CI indicates confidence interval; HR, hazard ratio; ST-E, ST-segment elevation; and ST-D, ST-segment deviation.
When analyzed as continuous variables, ∑ST-D resolution and ∑ residual ST-D showed the highest unadjusted accuracy (C statistic 0.653 and 0.655, respectively) (Table 3, center panel). Each unit increase in ∑ST-D resolution and single-lead ST-E resolution was associated with a 1.7 and 1.5 percent relative risk reduction, respectively. With the worst-lead ST-E and ∑ residual ST-D measure, the relative risk of death increased with approximately 15% and 4%, respectively, with each mm increase. All four continuous measures remained predictive after multivariable modeling. When these continuous measures were concurrently forced into one model, ∑ST-D resolution was the strongest measure to predict one-year mortality (p=0.056) along with ∑ residual ST-D (p=0.064), while both single-lead ST-E resolution (p=0.19) and worst-lead residual ST-E were no longer predictive (P=0.52) (Table 3, lower panel). These differences in predictive power of the continuous measures did not substantially change after multivariable adjustment, except for ∑ residual ST-D.

As depicted in the upper panel of Table 4, all categorical ST-segment recovery measures significantly contributed to the net reclassification improvement (all p ≤ 0.003). All but the single-lead ST-E resolution and the ∑ residual ST-D measure significantly contributed to the integrated discrimination improvement. Moreover, ∑ST-D resolution with a cut off at 50% was the strongest contributor to both the net reclassification improvement (0.58; p<0.001) and the integrated discrimination improvement (0.0087; p=0.003). As depicted in the lower panel of Table 4, ∑ST-D resolution, single-lead ST-E resolution, and ∑ residual ST-D as continuous variables significantly contributed to the net reclassification improvement, whereas worst-lead residual ST-E did not (0.16; p=0.057). ∑ST-D resolution was the only measure that significantly contributed to the integrated discrimination improvement (0.0054; p=0.03). Thus, ∑ST-D resolution as a continuous variable was the only measure that significantly contributed to both the net reclassification improvement and the integrated discrimination improvement.
<table>
<thead>
<tr>
<th>No.</th>
<th>Measure</th>
<th>Unadjusted</th>
<th>Multivariable-adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1</td>
<td>∑ST-D resolution (%)</td>
<td>0.983</td>
<td>(0.977 - 0.988)</td>
</tr>
<tr>
<td>2</td>
<td>Single-lead ST-E resolution (%)</td>
<td>0.985</td>
<td>(0.980 - 0.991)</td>
</tr>
<tr>
<td>3</td>
<td>Worst-lead residual ST-E (mm)</td>
<td>1.148</td>
<td>(1.089 - 1.210)</td>
</tr>
<tr>
<td>4</td>
<td>∑ residual ST-D (mm)</td>
<td>1.039</td>
<td>(1.026 - 1.052)</td>
</tr>
<tr>
<td>5</td>
<td>∑ST-D resolution (%)</td>
<td>0.991</td>
<td>(0.982 - 1.000)</td>
</tr>
<tr>
<td></td>
<td>Single-lead ST-E resolution (%)</td>
<td>0.994</td>
<td>(0.986 - 1.003)</td>
</tr>
<tr>
<td></td>
<td>Worst-lead residual ST-E (mm)</td>
<td>0.960</td>
<td>(0.848 - 1.087)</td>
</tr>
<tr>
<td></td>
<td>∑ residual ST-D (mm)</td>
<td>1.028</td>
<td>(0.998 - 1.058)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; ST-E, ST-segment elevation; ST-D, ST-segment deviation
Table 4 Risk reclassification of 1-year death after addition of different measures of ST-segment recovery to the referent model*.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Patients who died (n=145)</th>
<th>1-year survivors (n=1958)</th>
<th>NRI†</th>
<th>P</th>
<th>IDI‡</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∑ST-D resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% and 70% cut-offs</td>
<td>0.60 (87)</td>
<td>0.53 (1038)</td>
<td>0.26</td>
<td>0.003</td>
<td>0.0075</td>
<td>0.003</td>
</tr>
<tr>
<td>50% cut-off</td>
<td>0.76 (110)</td>
<td>0.53 (1044)</td>
<td>0.58</td>
<td>&lt;0.001</td>
<td>0.0087</td>
<td>0.003</td>
</tr>
<tr>
<td>∑ST-E resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% and 70% cut-offs</td>
<td>0.60 (87)</td>
<td>0.54 (1055)</td>
<td>0.28</td>
<td>0.001</td>
<td>0.0064</td>
<td>0.018</td>
</tr>
<tr>
<td>50% cut-off</td>
<td>0.70 (101)</td>
<td>0.55 (1079)</td>
<td>0.50</td>
<td>&lt;0.001</td>
<td>0.0067</td>
<td>0.024</td>
</tr>
<tr>
<td>Single-lead ST-E resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% and 70% cut-offs</td>
<td>0.54 (78)</td>
<td>0.62 (1208)</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>0.0030</td>
<td>0.222</td>
</tr>
<tr>
<td>50% cut-off</td>
<td>0.62 (90)</td>
<td>0.63 (1234)</td>
<td>0.50</td>
<td>&lt;0.001</td>
<td>0.0040</td>
<td>0.167</td>
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<tr>
<td>Worst-lead residual ST-E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1- and 2-mm cut-offs</td>
<td>0.71 (103)</td>
<td>0.45 (881)</td>
<td>0.32</td>
<td>&lt;0.001</td>
<td>0.0043</td>
<td>0.028</td>
</tr>
<tr>
<td>2- and 4-mm cut-offs</td>
<td>0.63 (91)</td>
<td>0.59 (1147)</td>
<td>0.43</td>
<td>&lt;0.001</td>
<td>0.0045</td>
<td>0.076</td>
</tr>
<tr>
<td>∑ residual ST-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-mm cut-off</td>
<td>0.71 (103)</td>
<td>0.53 (1044)</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td>0.0034</td>
<td>0.110</td>
</tr>
<tr>
<td>Continuous measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∑ST-D resolution (%)</td>
<td>0.60 (87)</td>
<td>0.61 (1187)</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td>0.0054</td>
<td>0.031</td>
</tr>
<tr>
<td>Single-lead ST-E resolution (%)</td>
<td>0.61 (88)</td>
<td>0.60 (1175)</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td>0.0034</td>
<td>0.229</td>
</tr>
<tr>
<td>Worst-lead residual ST-E (mm)</td>
<td>0.45 (65)</td>
<td>0.63 (1241)</td>
<td>0.16</td>
<td>0.057</td>
<td>-0.0003</td>
<td>0.841</td>
</tr>
<tr>
<td>∑ residual ST-D</td>
<td>0.48 (70)</td>
<td>0.67 (1316)</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>-0.0007</td>
<td>0.697</td>
</tr>
</tbody>
</table>

Values are expressed as proportion (n). * The referent model contained the following baseline and procedural variables: sex, age, current smoking, the presence or absence of diabetes mellitus, hypercholesterolemia, a history of myocardial infarction or coronary artery bypass grafting, postprocedural TIMI flow, anterior STEMI, multivessel disease, use of GP IIb/IIIa inhibitors, and intra-aortic balloon counter pulsation.

†The NRI was defined as (A+B) - ((1-A) + (1-B)).

‡The IDI was defined as

NRI, net reclassification improvement; IDI, integrated discrimination improvement; ST-E, ST-segment elevation; ST-D, ST-segment deviation; p, probability.
Prediction of one-year mortality with different measures of ST-segment recovery

Discussion

Our study confirms the powerful predictive value of various measures of immediate ST-segment recovery for one-year mortality in an all-comer STEMI population undergoing primary PCI. Among various measures, $\Sigma ST-D$ resolution consistently yielded the best improvement in terms of C statistic, net reclassification improvement, and integrated discrimination improvement. This pattern was most prominent when $\Sigma ST-D$ resolution was applied as a categorical variable at a 50% cut off.

Several previous studies confirmed the prognostic value of ST-segment recovery in STEMI patients undergoing primary PCI. Although these studies were carried out in various settings and with different patient populations, all showed that ST-segment recovery is a useful prognostic instrument in addition to well-established patient and procedural predictors of outcome. In the largest study published until now, ST-segment recovery was strongly associated with 90-day death, congestive heart failure, and shock. Buller et al. showed no distinct differences in prognostic value between several different measures of ST-segment recovery.\textsuperscript{11} In agreement with previous smaller studies,\textsuperscript{4,20} they suggested that the worst-lead residual ST-E would be the measure of choice because of its easy bedside applicability. The discrepancy between these results and the results presented in this paper might be explained, in part, by three key differences.

First, ST-segment recovery in this study was assessed at the end of PCI, before the patient left the catheterization laboratory. In our daily practice, with STEMI patients transported to the catheterization laboratory by ambulance after field triage and subsequent transfer to local hospitals soon after completion of the procedure, early assessment of risk may be essential for further medical strategies and prognosis. We showed that $\Sigma ST-D$ resolution was the best measure to predict one-year mortality. Worst-lead residual ST-E in our study performed less well as compared to analyses with this measure at 30 minutes,\textsuperscript{11} (on average) 106 minutes,\textsuperscript{4} 180 minutes,\textsuperscript{70} and within four hours\textsuperscript{17} after the PCI procedure. By choosing different cut-off points, we showed that the predictive power of this measure may remain applicable when ST-segment recovery is assessed at the end of primary PCI. These dissimilarities in prognostic power may display the importance of ECG timing when using worst-lead residual
ST-E to predict outcome. With the increase in regional organization of primary PCI with so-called ‘hub-and-spoke’ centers and ‘drive-through’ PCI where patients are transferred to the catheterization laboratory by ambulances and returned to non-PCI capable hospitals in their own region, the 12-lead ECG recorded prior to and at the end of the PCI procedure will become an important prognostic indicator. In addition, such prognostic indicators may serve as an important performance measure to assess the quality of a primary PCI program.

Second, comprehensive comparisons between known measures of ST-segment recovery have predominantly been performed with data from randomized controlled trials. In the largest ancillary study, all 4866 included patients presented within six hours and had anterior myocardial infarction or extensive inferior myocardial infarction, defined as ≥ 2mm of ST-segment elevation in two inferior leads and ST-segment depression in two contiguous precordial leads for a total ST-segment deviation of ≥8 mm. As a result, 60 percent of the included patients had anterior STEMI, which raises the important question whether conclusions from this ancillary study can be applied to an every-day STEMI population. In our study, we included consecutive, all-comer STEMI patients undergoing primary PCI with varying degrees of ST-segment elevation and investigated whether different measures of ST-segment recovery would predict outcome. Other large studies on the prognostic properties of ST-segment recovery measures in all-comer STEMI populations are scarce. De Luca et al. showed a significant association between different ST-segment recovery measures and one-year mortality in an unselected cohort of 1286 primary PCI patients. However, paired ST-segment analysis was available in only 1072 patients and postprocedural ECGs were recorded at 180 minutes after PCI. Furthermore, only four measures were tested which makes a clear comparison with the current study difficult.

Third, previous studies mainly used the C statistic to determine the prognostic power of different ST-segment recovery measures. The C statistic (or area under the receiver operating characteristic (ROC) curve) has initially been developed to analyze a test’s accuracy to distinguish between persons with and without a disease of interest. Furthermore, improvement of the C statistic by adding a significant marker to a multivariable model is often modest and thereby has limited impact on the ROC
curve. In accordance with the analyses by Buller et al., we found only modest, non-intuitive differences in C statistic between the different multivariable-adjusted measures of ST-segment recovery. With the recently published net reclassification improvement and integrated discrimination improvement, we were able to further quantify the improvement of risk prediction offered by the different ST-segment recovery measures. With these additional methods, we could show that ∑ST-D resolution, when assessed at the end of the PCI procedure, is the most powerful measure for one-year risk prediction in patients undergoing primary PCI for STEMI. Worst-lead residual ST-E showed a slightly lower C statistic in our initial analyses but as a continuous variable did not significantly contribute to either net reclassification improvement or integrated discrimination improvement.

Another important result of our analysis is that ∑ST-D resolution with a cut off at 50% gave best improvement of risk prediction when assessed at the end of PCI. Along with our study, several previous studies showed that ∑ST-D resolution has prognostic power when assessed at various, static time points after primary PCI. Reports by Schröder et al. consistently stated that 30 and 70% cut offs would be preferable for a stepwise risk stratification. In our study, ∑ST-D resolution with cut offs at 30 and 70% also had good predictive power but was surpassed by ∑ST-D resolution at a 50% cut off. The discrepancy between previous studies and current study with regard to the optimal cut off might again be explained by the timing of ST-segment recovery assessment. At the end of primary PCI, the amount of patients with complete (i.e. ≥70%) ST-segment recovery is reasonably low, which implies that a lower cut off might better discriminate between patients at high and lower risk of one-year mortality. Use of the 50% cut off enabled us to identify a high-risk sub group of more than 1000 patients with nearly 11-percent mortality at one year and a multivariable-adjusted 2.6-fold increase in hazard as compared to the low-risk sub group.

The main limitation of our study is its retrospective design. From our source population, we excluded 16% of patients because of missing ECG recordings, which is similar to other, observational studies with unselected patient cohorts. Although we only included patients of whom a postprocedural ECG could be obtained, the timing of ECG recording at the end of PCI may have reduced selection bias. Second, ST-segment analyses were not performed by an established ECG core laboratory.
All measurements were conducted by one investigator. Nevertheless, other studies consistently showed a low variability between trained observers, which reflects the straightforwardness of ST-segment analysis. Furthermore, all ECG measurements were performed in a blinded fashion and importation, processing, and analysis of ECG data was all digital. Another possible limitation is the difficulty of capturing the peak ST-segment levels of the diagnostic ECG when using static ECGs. A recent publication by Terkelsen and colleagues showed that the timing of occurrence of peak ST-segment levels has a significant relationship with final infarct size, which in turn has been shown to be related to outcome. As such, there may be additional prognostic information using ST-segment recovery. However, the use of continuous ST-segment monitoring before, during and after PCI is not widely available and much more cumbersome in an acute clinical setting. Finally, information on left ventricular function and in-hospital cardiac events was not systematically collected as patients who undergo primary PCI at our institution are referred back to surrounding hospitals without undue delay. Moreover, 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.

In unselected STEMI patients undergoing primary PCI, $\sum_{ST-D}$ resolution, comparing summed pre- and postprocedural ST-segment deviation, is the best independent predictor of one-year, all-cause mortality when assessed at the end of PCI. The prognostic power of this ST-segment recovery measure is most explicit when a 50% cut off is used. Although worst-lead residual ST-E has obvious advantages over serial assessments and complex calculations in the clinical setting, this observational study provides robust information on prognostic properties in favor of immediate ST-segment recovery measures comparing pre- and postprocedural ECG.
Prediction of one-year mortality with different measures of ST-segment recovery

Reference list