Ischemic Electrocardiographic Abnormalities and Prognosis in Decompensated Heart Failure

Greig et al: Ischemic ECG Abnormalities and HF Prognosis

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Abstract

Background—Identification of coronary ischemia may enable targeted diagnostic and therapeutic strategies for acute heart failure (AHF). We determined the risk of 30-day mortality associated with ischemic ECG abnormalities in patients with AHF.

Methods and Results—Among 8772 patients (53.4% women, median 78 years [Q1,Q3 68,84]) presenting with AHF to 86 hospital emergency departments in Ontario, Canada, Q-waves, T-wave inversion, or ST-depression were present in 51.8% of subjects. However, presence of ST-depression was the only finding associated with 30-day mortality with adjusted odds ratio 1.24 (95%CI; 1.02-1.50). Using continuous net reclassification improvement, addition of ST-depression to the Emergency Heart failure Mortality Risk Grade (EHMRG) model reclassified 16.9% of patients overall, and 29.3% of those with a history of ischemic heart disease (both p<0.001). By adding ST-depression to the model, the EHMRG was extended to predict 30-day death with high discrimination (c-statistic 0.801), with mortality rate in the lowest risk decile of 0.57%. Adjusted odds ratios for 30-day mortality were 2.81 (95%CI; 1.48-5.31; p=0.002) in quintile 2, 7.41 (95%CI; 4.13-13.30; p<0.001) in quintile 3, and 14.47 (95%CI; 8.20-25.54; p<0.001) in quintile 4 compared to the lowest risk quintile. By subdividing into two equally-sized risk strata (deciles 9 and 10), the adjusted odds ratios for 30-day mortality were 27.20 (95%CI; 15.33-48.27; p<0.001) in decile 9 and 58.96 (95%CI; 33.54-103.65; p<0.001) in highest risk decile 10.

Conclusions—Presence of ST-depression on the ECG reclassified risk of 30-day mortality in patients with AHF, identifying both high- and low-risk subsets.

Key Words: heart failure, ECG, prognosis, mortality, outcome, prediction, risk stratification
Acute heart failure is characterized clinically by the development of new or worsening symptoms of heart failure that require urgent care. Heart failure is a major public health issue due to its high mortality, with one in every nine deaths including heart failure as a contributing cause.\(^1\) It is a leading cause of hospitalizations and readmissions, which contributes substantially to the high health care costs of this condition.\(^2\) Frequently, patients with AHF are evaluated in the emergency department (ED), where there are potential limitations or errors in intuitive clinical decisions made by physicians.\(^3\) Ideally, clinical decisions should be guided by prognostic information, however, safe and efficient instruments to aid decision-making in the ED are required.\(^3\)

Decision-making can be improved by the use of risk stratification methods, such as the Emergency Heart failure Mortality Risk Grade (EHMRG), which was designed for prediction of 7-day mortality in the broad group of AHF patients presenting to the emergency department.\(^4\) In the EHMRG risk stratification model and in other studies, the importance of even mild troponin elevation was underscored, suggesting the potential importance of cardiac injury or ischemia as a mechanism of adverse outcomes.\(^5,6\) In patients with acute coronary syndromes, the electrocardiogram (ECG) is a potentially useful tool in both diagnosis and prognosis. However, the prognostic importance of the ECG in AHF has not been well-defined.

In this study, we examined the prognostic importance of ECG abnormalities and the net reclassification improvement afforded by ischemic changes on 30-day mortality. Based upon our prior work, we hypothesized that the presence of ST-depression or T-wave inversion on the resting 12-lead ECG, would be associated with a significantly increased risk of mortality in a broad cohort of patients presenting to the emergency department with AHF.
Methods

**Cohort and sampling methods.** In this population-based retrospective cohort study, we studied the data of 8772 patients aged ≥18 years who were residents of Ontario, Canada, and visited an emergency department for AHF from April 1\textsuperscript{st}, 2004 to March 31\textsuperscript{th}, 2007. We examined those who were either discharged or hospitalized after the emergency department visit. In those with multiple visits during the study period, the first episode was selected as the index visit. The patients in the study were required to meet the Framingham criteria for heart failure and also have a final discharge diagnosis of heart failure using the International Classification of Diseases 10\textsuperscript{th} revision (ICD-10-CA) code I50 in the discharge abstract.\textsuperscript{7, 8} We examined the primary diagnoses in the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) for hospitalized and the National Ambulatory Care Reporting System (NACRS) database for non-hospitalized patients. All patients were required to have undergone a standard 12-lead ECG at 25 mm/sec performed upon presentation to ED. Research ethics approval was obtained from Sunnybrook Health Sciences Centre.

Patient information was obtained from the Emergency Heart failure Mortality Risk Grade (EHMRG) Study database for those patients who were discharged home, and the Enhanced Feedback for Effective Cardiac Treatment phase II study database (EFFECT) that contains the information on patients who were hospitalized for heart failure, which have been detailed previously.\textsuperscript{4, 9} Briefly, patients in both databases were randomly selected using stratified cluster sampling according to the type of hospital in the province (small, large and teaching hospital) and combined into one database for the purposes of this study. Patients with ST-elevation suggestive of transmural infarction were excluded because this acute ECG finding will directly
influence the care pathway. Those with complete bundle branch block or electronically paced rhythm were also excluded since these conditions preclude the evaluation of ST-segment and T-wave changes for evidence of myocardial ischemia. Finally, patients with do-not-resuscitate orders prior to emergency department arrival and those who were dialysis-dependent were excluded.

**Clinical data abstraction and ECG interpretation.** Clinical and ECG information were abstracted by highly trained nurses using validated methods described elsewhere. Nurse abstractors were required to demonstrate high reliability on standardized chart abstractions before field deployment. The ECG characteristics were analysed according to international standards criteria and definitions and ST-segment abnormalities indicative of ischemia were defined as flat or downsloping segment depression with ST-J depression of ≥1.0 mm in at least two adjacent leads. T-wave abnormalities indicative of ischemia were defined as any negative or biphasic T-wave in at least two contiguous leads, while significant Q-waves were ≥40 msec and more than 1/3 the height of the R wave. Ischemic ECG abnormalities included ST-segment depression, T-wave abnormalities, or Q-waves as described above. For descriptive purposes, ECG abnormalities were grouped according to location of the abnormality as anterior (leads V1-V4), anterolateral (leads V5-V6), lateral (leads I, aVL), or inferior (leads II, III, aVF).

**Outcomes and Definitions.** Mortality was determined by linking the clinical data abstracted from the EFFECT phase II and EHMRG studies to the Registered Persons Database (RPDB) for all deaths, using the patients’ unique, encrypted health card number. Unlike the EHMRG model (which focussed on 7-day mortality), the primary outcome was death within 30 days of the date of initial presentation to the emergency department with AHF. Patients were classified to be of ischemic etiology if there was a prior myocardial infarction, documented history of coronary
artery disease, or prior coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). All remaining patients were considered non-ischemic and were subclassified as hypertensive, valvular, or other, as described previously.\textsuperscript{11} 

**Statistical Analysis.** Continuous variables were expressed as medians (25\textsuperscript{th}, 75\textsuperscript{th} percentiles) and compared using the Wilcoxon-rank sum test. The distribution of categorical variables was compared between groups using the $\chi^2$ statistic. A random sample of 220 ECGs (2.5\%) was independently read by a cardiologist (DSL) and tested for inter-rater reliability using the kappa statistic.\textsuperscript{12} The odds of 30-day mortality was evaluated using univariate and multivariable logistic regression models adjusting for the variables contained in a validated clinical risk-model derived from a similar population and setting – the EHMRG risk score.\textsuperscript{4} The variables included were the following: age, presentation via emergency medical services, systolic blood pressure, heart rate, oxygen saturation, serum creatinine and potassium concentration, active cancer, use of metolazone at home, and troponin elevation exceeding the upper limit of normal.

We expanded the original EHMRG model that was initially designed for predicting 7-day mortality for use as our base model for predicting 30-day mortality (https://ehmrg.ices.on.ca).

We initially used two different methods to evaluate the incremental benefit of adding specific ECG abnormalities to the base model: (i) using a likelihood ratio test for comparing differences in the -2 log likelihood statistic due to the inclusion of ECG variables; (ii) examining the change in the area under the receiver operating characteristic (ROC) curve for 30-day mortality. We explored the impact of the ECG abnormalities and combinations of these abnormalities on 30-day death using univariate and multivariable logistic regression analysis. These ECG abnormalities included ST-depression, T-wave abnormality, or Q-wave in any anatomical wall location, and combinations of these abnormalities (i.e., ST-depression or T-wave abnormality,
ST-depression or Q-wave, T-wave abnormality or Q-wave, or presence of any of these abnormalities). To examine whether the ECG abnormalities prognosticated differently in those with known ischemic or non-ischemic etiology, we tested for interactions between ECG abnormalities and ischemic vs. non-ischemic etiology.

Net Reclassification Improvement (NRI). We examined the ability of prognostically significant ECG abnormalities to reclassify risk compared to the EHMRG risk model by examining net reclassification improvement (NRI). After calculating the predicted probability of 30-day death using the disaggregated EHMRG risk model covariates, we determined both categorical and continuous NRI as described by Pencina et al.\textsuperscript{13, 14} For categorical estimates, we subdivided the study sample into three risk groups by collapsing the lowest 2 risk quintiles into a low risk group, the middle 2 risk quintiles into an intermediate group, and the highest risk quintile as a standalone high risk group. Continuous NRI or NRI(>0), is equal to the sum of the differences in the probability of net upward reclassification for events (death) and probability of net downward reclassification for non-events (non-death). We defined a minimally important change in net reclassification of the predicted probability death to be 0.1% due to the severity of the outcome. All analyses were conducted using SAS, version 9.3 (SAS institute, Cary, NC) for UNIX environments.

Results

Description of the cohort. A total of 14,123 subjects were identified from the EFFECT II and the EHMRG cohorts who fulfilled the Framingham criteria, had an ECG performed in the emergency department, and did not have a do-not-resuscitate order prior to presentation. After applying exclusion criteria, the final cohort consisted of 8772 patients comprised of 4685
(53.4%) women (Figure 1). The median age of the study cohort was 78 years (Q1,Q3 69,84) and 4616 (52.6%) had heart failure deemed to be of ischemic etiology based on clinical criteria. Electrocardiographic manifestations of ischemic heart disease were present in 4545 (51.8%) patients. Kappa statistics were 0.915 for ST-depression, 0.800 for T-wave abnormality, and 0.817 for Q-waves, indicating excellent inter-rater reliability. Overall, 2352 (26.8%) patients were discharged home from the emergency department. The mortality rate at 30 days was 8.3% in the overall cohort.

Table 1 shows baseline characteristics of the patients according to presence or absence of ischemic ECG abnormalities. Patients with ischemic ECG abnormalities were predominantly men, and had higher prevalence of ischemic heart disease, smoking and diabetes mellitus. The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), β-adrenoreceptor antagonists, loop diuretics and aldosterone receptor antagonists was more frequent in patients with ischemic ECG abnormalities. Table 2 shows the clinical presentation and laboratory test results performed in the emergency department. Patients with ischemic ECG abnormalities presented with more severe clinical manifestations including lower systolic blood pressure. Although the majority of patients did not demonstrate troponin elevation, patients with ischemic ECG abnormalities more frequently exhibited values that exceeded the upper limit of normal. There were only minor differences in serum creatinine and glucose concentrations, and no differences in pulmonary congestion or other signs of volume overload. The baseline and clinical characteristics according to the presence or absence of ST-depression are presented in Appendix Tables A and B.

**ECG characteristics and predictors of mortality.** There were no differences in the prevalence of sinus rhythm (63.9% vs 63.4%, p=0.617) or atrial fibrillation/flutter (34.4% vs 34.7%, p=0.774)
between patients with ischemic ECG abnormalities present or absent, respectively. Among patients with ischemic ECG abnormalities, the most frequent finding was T-wave inversion, which was more evident in the lateral (34.1%) and anterolateral (30.6%) leads.

Figure 2 shows the unadjusted odds ratios of the ECG variables for prediction of 30-day mortality compared to those without ischemia-related abnormalities. Whether in isolation or in combination, all ECG features were associated with a significant increase in the unadjusted odds of 30-day mortality, with the exception of isolated Q-waves or T-wave abnormalities. However, after covariate adjustment, the only ECG finding associated with a significant increase in 30-day mortality was the presence of ST-segment depression with an adjusted odds ratio of 1.24 (95%CI; 1.02-1.50). The combination of ST-depression with either Q-waves or T-wave inversion was not significantly associated with 30-day mortality compared to those without the specified abnormality (Figure 3).

**Extension of the EHMRE AHF risk model to include ST-depression.** The multivariable model for 30-day mortality included the presence of ST-depression along with the covariates comprising the original EHMRE 7-day mortality model as shown in Table 3. As the presence of ST-depression was the only significant ECG abnormality in adjusted analyses, it was the sole electrocardiographic covariate entered into the 30-day mortality model. The EHMRE and ST-depression model for 30-day mortality (EHMRE30-ST) exhibited high discrimination with c-statistic 0.801 (95%CI; 0.785-0.817), with no lack of model fit (Hosmer-Lemeshow $\chi^2$ statistic = 12.1, $p=0.148$). In a subgroup of patients with continuous measurements of PR interval and QRS duration (n=2495), there was no significant association between these two covariates and 30-day mortality when these covariates were added to the EHMRE30-ST model. Adjusted odds ratios
for 30-day mortality were: 0.99 (95%CI; 0.95-1.04) per 10 msec increase in PR interval and 0.98 (95%CI; 0.89-1.07) per 10 msec increment in QRS duration.

The 30-day mortality rates and odds ratios for death based on the predicted probability risk quintiles and deciles from the EHRMG30-ST model are shown in Table 4. The 30-day mortality rate in the lowest quintile was 0.74%, whereas there was a very high risk in the highest quintile: 27-fold increase in risk in decile 9 and nearly 59-fold increase in risk in decile 10 (both p<0.001 vs quintile 1). When stratified into predicted risk deciles based on the EHRMG30-ST model, there was a gradient in predicted 30-day mortality that was similar to the observed mortality rates in the respective categories shown in Figure 4. The observed mortality rate was 0.57% (95%CI; 0.19-1.33) in the lowest and 30.56% (95%CI; 27.01-34.45) in the highest predicted risk decile based on the EHRMG30-ST model.

Net reclassification of risk and measures of model performance. The addition of ST-depression to the EHRMG model reclassified 16.9% of patients when using continuous NRI(>0). However, ST-depression did not significantly reclassify risk using categories (see Appendix Table), reclassifying only 0.6% of patients into low, intermediate, or high risk groups (p=0.396). The addition of ST-depression improved model fit, significantly reducing the -2 log likelihood statistic to 4160.4 from 4165.0 in the base EHRMG model (p=0.032). However, the c-statistic of the EHRMG30-ST model was not significantly different from that of the base EHRMG model alone, with c-statistics of 0.801 (95%CI; 0.785-0.817) in both models (p=0.694). As shown in the predictiveness curve (Figure 5), 25.7% of patients exhibited high predicted mortality risk ≥10%, 23.1% were low predicted risk (≤2% - equivalent to the average 7-day mortality rate), and 7.3% had a predicted probability of 30-day death less than 1%. Therefore, the middle 51.2% of
patients were not classified as high or low predicted 30-day mortality risk using the EHMRG30-ST model.

**Sub-group analyses.** There was a significant interaction between the presence of ST-depression alone and ischemic etiology in the unadjusted and adjusted analyses (both p-interaction <0.001). In patients with ischemic disease and ST-depression, the adjusted odds ratio for 30-day death was 1.63 (95%CI; 1.27-2.09), reclassifying 29.3% (p<0.001) of the patients when using NRI(>0). In patients with non-ischemic etiology, ST-depression was not associated with mortality, with adjusted odds ratio 0.86 (95%CI; 0.63-1.19).

**Discussion**

The 12-lead electrocardiogram is a simple, low-cost diagnostic test that is widely available; however, its usefulness in patients with primary AHF has not been delineated. In this study, we found that presence of ST-segment depression was a significant predictor of 30-day mortality, which improved net reclassification of risk beyond that of the EHMRG risk covariates. Other indicators of ischemia or infarction, specifically the presence of Q-waves or T-wave abnormalities, were not significantly associated with mortality in patients with AHF. Interestingly, nearly all of the 7-day mortality predictors comprising the EHMRG risk score (except metolazone use) were predictive of 30-day mortality when ST-depression was included in the multivariable model. Another important observation was that inclusion of ST-depression improved reclassification using continuous NRI(>0), suggesting that this ECG marker may assist in refining risk estimation beyond that of a validated mortality risk model.

Prior studies have examined the prognostic implications of the electrocardiogram in persons without cardiovascular disease, however few studies have examined its utility in those
with AHF. In NHANES III, which examined a healthy free-living population in the United States, the presence of combined nonspecific ST-segment and T-wave abnormalities was associated with an increased risk of overall mortality, using an ECG classification system similar to that used in our study. Furthermore, in both the Women’s Health Initiative and a cohort study of 46,950 healthy men, the presence of ST-segment depression, T-wave abnormalities, and minor Q-waves were associated with higher risk of death compared to those without electrocardiographic abnormalities. While there are many AHF risk prediction models, few have included electrocardiographic variables indicative of ischemia in the model, due in part to the complexity and wide range of potential features to consider. The time-insensitive predictive instrument did include flattened T-waves as a predictor of in-hospital mortality, but did not systemically evaluate multiple electrocardiographic indices of ischemia and did not examine reclassification of risk compared with validated predictors of death. A small, prospective cohort of 208 clinically stable ischemic heart failure patients with LVEF ≤40% and documented nonsustained ventricular tachycardia, reported that the presence of ST-segment depression in V5 or V6 without left ventricular hypertrophy was associated with greater than 2.8-fold mortality at three years. However, this study did not evaluate the presence of ST-segment depression in other leads or other concomitant ECG abnormalities.

Although the electrocardiogram has been widely available, the paucity of studies in the literature suggests that it has been a challenge to ascertain its prognostic value in the setting of AHF. The preponderance of studies examining the prognostic value of the electrocardiogram have focused on QRS width or bundle-branch block. In addition, previous registries reporting on the importance of the electrocardiogram in patients with AHF have focused on parameters other than ischemic ECG characteristics. Prior studies demonstrating that troponin
elevation is prognostically important in AHF have also not examined electrocardiographic features. The novelty of our findings are underscored by the demonstration that ST-depression was associated with 30-day mortality even after accounting for the presence of elevated troponin at presentation – a covariate in the EHRMG risk model.

The mechanisms by which ‘minor’ electrocardiographic alterations, such as ST-depression, confer increased risk of mortality remain poorly understood. In the Cardiovascular Health Study, the association between minor nonspecific ST-segment or T-wave abnormalities and cardiovascular mortality was attributed to an increased risk of arrhythmias. The mechanisms involved in the failing heart, however, are likely more complex. In a study of 11,327 patients with chronic heart failure, isolated electrocardiographic abnormalities, including ST-T abnormalities and presence of Q-waves, were not associated with major structural disease or significant left ventricular dysfunction. In the current study, we found that the mortality risk of patients with ST-depression was significant primarily among patients with ischemic heart failure, suggesting that the effect of this electrocardiographic feature is linked with but not fully explained by the presence of underlying coronary artery disease.

Our study has implications for both clinicians and researchers. From a clinical standpoint, the presence of ST-segment depression is prognostically important and adds incremental value to known predictors of early death in AHF. Inclusion of ST-segment depression in the EHRMG30-ST model resulted in additional stratification of risk for patients with the same predicted probability of 7-day death as shown in Figure 6. Our study lends further support to the hypothesis that improving outcomes of AHF may necessitate enhanced strategies for identification and early therapy of myocardial ischemia as a precipitant. This is a challenge in the context of AHF, where troponin elevation has demonstrated limitations as an indicator of
ischemic heart disease. Our study also demonstrated implications for the use of net reclassification improvement (NRI), which is a measure for assessing the clinical utility of a novel risk marker. The NRI allows clinicians to understand if the addition of a biomarker (e.g. ECG characteristic) to a previously defined risk model provides a ‘useful change’ of the risk category and which categories are reclassified predominantly. We found that continuous, but not categorical net reclassification improvement, was altered by the inclusion of ST-segment depression on the electrocardiogram. Furthermore, a statistically significant impact on continuous NRI was observed despite no significant change in the c-statistic. Future studies should consider examination of continuous NRI in cases where there are adverse outcomes with severe consequences, and small changes in predicted probabilities of events may be important.

Our research study was limited by the lack of repeat electrocardiograms performed in the emergency department. Potentially, the changes between a series of electrocardiograms could provide prognostically important information or greater sensitivity for the detection of myocardial ischemia occurring in the duration of the hospital stay. Our study did not consider left ventricular ejection fraction or brain natriuretic peptide, however the former is often not available in the emergency department and the latter, despite its prognostic significance, has not been shown to impact upon outcomes in the acute care setting.

Conclusions

In conclusion, we found that the presence of ST-depression on the 12-lead electrocardiogram performed at admission in the emergency department, independently predicted mortality at 30 days in patients with AHF. The combination of ST-depression on the electrocardiogram and the EHMGRG covariates extended the prediction of mortality to 30 days after AHF presentation. Greater awareness of the prognostic importance of electrocardiographic characteristics will assist
in the identification of patients who are at high risk of death and may benefit from more
intensive evaluation of ischemic heart disease.

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conflicts of interest to declare.
References


Figure Legends

Figure 1. Study flow diagram

Figure 2. Unadjusted odds ratios and 95% confidence intervals for 30-day mortality by different ECG characteristics

Figure 3. Adjusted odds ratios and 95% confidence intervals for 30-day mortality by different ECG characteristics

Figure 4. Predicted vs. observed 30-day mortality rates according to risk deciles of EHMRG30-ST model

Figure 5. Predictiveness curve for 30-day mortality based on EHMRG30-ST model

Figure 6. Scatterplot of predicted 7-day mortality using EHMRG and 30-day mortality using EHMRG30-ST model. Dashed vertical line shows range of predicted 30-day mortality for a fixed 20% probability of 7-day death.
Table 1. Baseline characteristics

<table>
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<tr>
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<th>Any Ischemic ECG Abnormality</th>
<th>No Ischemic ECG</th>
<th>p-value</th>
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<tbody>
<tr>
<td>N</td>
<td>4545</td>
<td>4227</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
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<td></td>
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<tr>
<td>Age (years), median (Q1,Q3)</td>
<td>78 (70.84)</td>
<td>78 (69.84)</td>
<td>0.473</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>2219 (48.8%)</td>
<td>1868 (44.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Etiology, n (%)</strong></td>
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<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>2830 (62.3%)</td>
<td>1786 (42.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1069 (23.5%)</td>
<td>1528 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>140 (3.1%)</td>
<td>154 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>506 (11.1%)</td>
<td>759 (18.0%)</td>
<td></td>
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<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>538 (14.1%)</td>
<td>435 (12.2%)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1826 (40.6%)</td>
<td>1515 (35.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2012 (45.5%)</td>
<td>1073 (25.9%)</td>
<td>&lt; 0.001</td>
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<tr>
<td>CABG / PCI</td>
<td>1053 (23.4%)</td>
<td>587 (13.9%)</td>
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<tr>
<td>Any valve disease</td>
<td>842 (19.0%)</td>
<td>664 (15.9%)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>856 (19.2%)</td>
<td>688 (16.4%)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>609 (13.7%)</td>
<td>447 (10.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Any cancer</td>
<td>512 (11.5%)</td>
<td>549 (13.0%)</td>
<td>0.023</td>
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<tr>
<td>COPD / Asthma</td>
<td>1284 (28.7%)</td>
<td>1260 (30.0%)</td>
<td>0.196</td>
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<td><strong>LV ejection fraction, n (%)</strong></td>
<td></td>
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<tr>
<td>&gt; 50%</td>
<td>917 (20.2%)</td>
<td>1115 (26.4%)</td>
<td>&lt; 0.001</td>
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<td>31-50%</td>
<td>864 (19.0%)</td>
<td>573 (13.6%)</td>
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<td>≤ 30%</td>
<td>572 (12.6%)</td>
<td>336 (7.9%)</td>
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<td><strong>Medications, n (%)</strong></td>
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<td>Aspirin</td>
<td>1955 (43.4%)</td>
<td>1497 (35.7%)</td>
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<td>ACE inhibitor or ARB</td>
<td>2620 (58.1%)</td>
<td>2253 (53.7%)</td>
<td>&lt; 0.001</td>
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<td>β-adrenoreceptor antagonist</td>
<td>2210 (49.0%)</td>
<td>1785 (42.5%)</td>
<td>&lt; 0.001</td>
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<td>Calcium antagonist</td>
<td>1456 (32.3%)</td>
<td>1403 (33.4%)</td>
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<td>Clopidogrel</td>
<td>528 (11.7%)</td>
<td>321 (7.6%)</td>
<td>&lt; 0.001</td>
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<td>Warfarin</td>
<td>1255 (27.8%)</td>
<td>1106 (26.4%)</td>
<td>0.117</td>
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<td>Digoxin</td>
<td>901 (20.0%)</td>
<td>591 (14.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Medication</td>
<td>Q1 (N=4681)</td>
<td>Q3 (N=10035)</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>2285 (50.7%)</td>
<td>1994 (47.5%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>449 (10.0%)</td>
<td>493 (11.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Aldosterone receptor antagonist</td>
<td>346 (7.7%)</td>
<td>251 (6.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Oral Nitrates</td>
<td>1120 (24.9%)</td>
<td>816 (19.4%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lipid-lowering Agent</td>
<td>2000 (44.4%)</td>
<td>1500 (35.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>304 (6.7%)</td>
<td>279 (6.6%)</td>
<td>0.856</td>
</tr>
</tbody>
</table>

Q1, Q3: 25th, 75th percentiles; CABG: Coronary artery bypass graft surgery; PCI: Percutaneous coronary intervention; COPD: Chronic obstructive pulmonary disease; ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blockers.
Table 2. Clinical characteristics of patients with ischemic and non-ischemic ECG

<table>
<thead>
<tr>
<th>Clinical presentation, median (Q1,Q3)*</th>
<th>Any Ischemic ECG Abnormality</th>
<th>No Ischemic ECG</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, (mmHg)</td>
<td>144 (126,167)</td>
<td>147 (129,170)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, (mmHg)</td>
<td>78 (67,91)</td>
<td>78 (67,90)</td>
<td>0.570</td>
</tr>
<tr>
<td>Heart rate, (beats/min)</td>
<td>89 (74,106)</td>
<td>88 (72,107)</td>
<td>0.443</td>
</tr>
<tr>
<td>Respiratory Rate, (breaths/min)</td>
<td>22 (20,28)</td>
<td>22 (20,28)</td>
<td>0.804</td>
</tr>
<tr>
<td>Rales &gt;50% of lung field, n(%)</td>
<td>569 (12.7%)</td>
<td>467 (11.2%)</td>
<td>0.078</td>
</tr>
<tr>
<td>Bilateral ankle edema, n(%)</td>
<td>2804 (63.3%)</td>
<td>2764 (66.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neck vein distension, n(%)</td>
<td>2311 (56.5%)</td>
<td>2119 (56.4%)</td>
<td>0.979</td>
</tr>
<tr>
<td>Hepatojugular reflux positive, n(%)</td>
<td>245 (6.0%)</td>
<td>209 (5.5%)</td>
<td>0.280</td>
</tr>
<tr>
<td>Third heart sound (S3), n(%)</td>
<td>191 (4.4%)</td>
<td>207 (5.1%)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Radiographic features

| Cardiomegaly, n(%)                     | 2263 (53.1%)                 | 1795 (45.8%)    | < 0.001 |
| Pleural effusion, n(%)                 | 2125 (49.4%)                 | 1811 (45.3%)    | < 0.001 |

Laboratory tests, median (Q1,Q3)*

| Hemoglobin, (g/dL)                     | 12.3 (10.9,13.7)             | 12.2 (10.9,13.6) | 0.703   |
| White blood cell, (x 10^9 /L)          | 8.8 (7.0,11.2)               | 8.6 (6.9,11.0)   | 0.031   |
| Serum sodium, (mmol/L)                 | 139 (136,141)                | 139 (136,142)    | 0.170   |
| Serum potassium, (mmol/L)              | 4.2 (3.8,4.6)                | 4.2 (3.8,4.6)    | 0.431   |
| Creatinine, (mg/dL)                    | 1.20 (0.95,1.62)             | 1.13 (0.89,1.50) | < 0.001 |
| Troponin >ULN, n(%)                    | 812 (17.9%)                  | 391 (9.3%)       | < 0.001 |
| Glucose, (mg/dL)                       | 132 (108,184)                | 124 (105,166)    | < 0.001 |

Q1,Q3: 25th, 75th percentiles; ULN: upper limit of normal

*Values are median (Q1,Q3) unless otherwise indicated

22
Table 3. ST-depression modified EHMRG model for 30-day mortality: EHMRG30-ST model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model β-Coefficient</th>
<th>Odds Ratio Units</th>
<th>Odds Ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.459</td>
<td>10 year increase</td>
<td>1.58 (1.45-1.72)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Transport by EMS</td>
<td>0.935</td>
<td></td>
<td>2.55 (2.12-3.06)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.518</td>
<td>20 mmHg increase*</td>
<td>0.60 (0.55-0.64)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.157</td>
<td>10 bpm increase†</td>
<td>1.17 (1.11-1.23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>-0.136</td>
<td>5% increase‡</td>
<td>0.87 (0.82-0.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.220</td>
<td>1 mg/dL increase‡</td>
<td>1.25 (1.17-1.32)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.470</td>
<td>≥4.6 mEq/L</td>
<td>1.60 (1.32-1.95)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>0.107</td>
<td>≤3.9 mEq/L</td>
<td>1.11 (0.90-1.37)</td>
<td>0.314</td>
</tr>
<tr>
<td>Troponin elevated§</td>
<td>0.645</td>
<td></td>
<td>1.91 (1.57-2.31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Active cancer</td>
<td>0.787</td>
<td></td>
<td>2.20 (1.74-2.77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Metolazone at home</td>
<td>0.375</td>
<td></td>
<td>1.45 (0.81-2.61)</td>
<td>0.210</td>
</tr>
<tr>
<td>ST-depression</td>
<td>0.212</td>
<td>Absent</td>
<td>Referent NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>1.24 (1.02-1.50)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

EMS=emergency medical services; NA=not applicable; BP=blood pressure; bpm=beats per minute
* Initial/triage SBP, maximum 160 mm Hg
† Initial/triage heart rate, minimum of 80 beats/min and maximum of 120 beats/min.
‡ Lowest initial/triage oxygen saturation, maximum of 92%
§ Greater than the upper limit of normal.
¥ 1 mg/dL = 88.4 μmol/L
Table 4. EHMRG30-ST risk quintiles and 30-day mortality

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Observed 30-day Mortality Rate (95%CI)</th>
<th>p-value*</th>
<th>Odds Ratio (95%CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1</td>
<td>0.74 (0.39, 1.27)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>2.05 (1.44, 2.84)</td>
<td>&lt; 0.001</td>
<td>2.81 (1.48, 5.31)</td>
<td>0.002</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>5.24 (4.23, 6.43)</td>
<td>&lt; 0.001</td>
<td>7.41 (4.13, 13.30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>9.75 (8.34, 11.32)</td>
<td>&lt; 0.001</td>
<td>14.47 (8.20, 25.54)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Decile 9</td>
<td>16.88 (14.27, 19.82)</td>
<td>&lt; 0.001</td>
<td>27.20 (15.33, 48.27)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Decile 10</td>
<td>30.56 (27.01, 34.44)</td>
<td>&lt; 0.001</td>
<td>58.96 (33.54, 103.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Overall</td>
<td>8.30 (7.71, 8.92)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* versus quintile 1
HF patients Presenting to Emergency Department  
N = 14,123

ST analysis not interpretable:  
Bundle branch block (n = 3339)  
Paced rhythm (n = 1138)  
Resting ST-elevation (n = 617)

Missing data (n = 245)  
Transferred into ED (n = 12)

Final analysis cohort  
N = 8772

Figure 1
ST depression or Q wave

ST depression or T inv

Q wave or T inv

Any criteria present

Unadjusted Odds Ratio

Figure 2
Figure 3

Adjusted Odds Ratio

- ST depression
- Q wave
- T inv
- ST depression or Q wave
- ST depression or T inv
- Q wave or T inv
- Any criteria present

P = 0.03
Figure 4

30-day Mortality, %

Risk Decile

- 30-day observed death
- 30-day predicted death
Figure 5
Figure 6

Probability of 30-day mortality vs. Probability of 7-day mortality.
Ischemic Electrocardiographic Abnormalities and Prognosis in Decompensated Heart Failure
Douglas Greig, Peter C. Austin, Limei Zhou, Jack V. Tu, Peter S. Pang, Heather J. Ross and Douglas S. Lee

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SUPPLEMENTAL MATERIAL
Appendix Table A. Baseline characteristics of patients with vs. without ST-segment depression

<table>
<thead>
<tr>
<th></th>
<th>ST-segment Depression</th>
<th>No ST-segment Depression</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1714</td>
<td>7058</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), median (Q1,Q3)</td>
<td>79 (72,85)</td>
<td>77 (69,84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>786 (45.9%)</td>
<td>3301 (46.8%)</td>
<td>0.497</td>
</tr>
<tr>
<td><strong>Etiology, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>1070 (62.4%)</td>
<td>3546 (50.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>398 (23.2%)</td>
<td>2199 (31.2%)</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>62 (3.6%)</td>
<td>232 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>184 (10.7%)</td>
<td>1081 (15.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>161 (11.1%)</td>
<td>812 (13.7%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>708 (41.9%)</td>
<td>2633 (37.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>719 (43.2%)</td>
<td>2366 (34.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG / PCI</td>
<td>347 (20.6%)</td>
<td>1293 (18.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Any valve disease</td>
<td>337 (20.2%)</td>
<td>1169 (16.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>346 (20.7%)</td>
<td>1198 (17.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>222 (13.3%)</td>
<td>834 (11.9%)</td>
<td>0.124</td>
</tr>
<tr>
<td>Any cancer</td>
<td>186 (11.1%)</td>
<td>875 (12.5%)</td>
<td>0.112</td>
</tr>
<tr>
<td>COPD / Asthma</td>
<td>520 (30.9%)</td>
<td>2024 (28.9%)</td>
<td>0.105</td>
</tr>
<tr>
<td><strong>LV ejection fraction, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>300 (17.5%)</td>
<td>1137 (16.1%)</td>
<td>0.005</td>
</tr>
<tr>
<td>31-50%</td>
<td>358 (20.9%)</td>
<td>1674 (23.7%)</td>
<td></td>
</tr>
<tr>
<td>≤ 30%</td>
<td>207 (12.1%)</td>
<td>701 (9.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Medications, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>750 (44.1%)</td>
<td>2702 (38.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>979 (57.6%)</td>
<td>3894 (55.6%)</td>
<td>0.138</td>
</tr>
<tr>
<td>β-adrenoreceptor antagonist</td>
<td>855 (50.3%)</td>
<td>3140 (44.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>600 (35.3%)</td>
<td>2259 (32.3%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>203 (11.9%)</td>
<td>646 (9.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin</td>
<td>524 (30.8%)</td>
<td>1837 (26.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>456 (26.8%)</td>
<td>1036 (14.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>922 (54.2%)</td>
<td>3357 (47.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug Category</td>
<td>Group 1</td>
<td>Group 2</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>147 (8.6%)</td>
<td>795 (11.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aldosterone receptor agonist</td>
<td>125 (7.4%)</td>
<td>472 (6.7%)</td>
<td>0.369</td>
</tr>
<tr>
<td>Oral Nitrates</td>
<td>465 (27.4%)</td>
<td>1471 (21.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering Agent</td>
<td>762 (44.8%)</td>
<td>2738 (39.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>117 (6.9%)</td>
<td>466 (6.7%)</td>
<td>0.735</td>
</tr>
</tbody>
</table>
Appendix Table B. Clinical characteristics of patients with vs. without ST-segment depression

<table>
<thead>
<tr>
<th>Clinical presentation, median (Q1,Q3)*</th>
<th>ST-segment Depression</th>
<th>No ST-segment Depression</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, (mmHg)</td>
<td>145 (126,167)</td>
<td>146 (127,169)</td>
<td>0.383</td>
</tr>
<tr>
<td>Diastolic blood pressure, (mmHg)</td>
<td>78 (66,91)</td>
<td>78 (67,90)</td>
<td>0.966</td>
</tr>
<tr>
<td>Heart rate, (beats/min)</td>
<td>92 (76,110)</td>
<td>88 (72,106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory Rate, (breaths/min)</td>
<td>24 (20,28)</td>
<td>22 (20,28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rales &gt;50% of lung field, n(%)</td>
<td>245 (14.5%)</td>
<td>791 (11.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilateral ankle edema, n(%)</td>
<td>1008 (60.6%)</td>
<td>4560 (66.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neck vein distension, n(%)</td>
<td>868 (56.4%)</td>
<td>3562 (56.5%)</td>
<td>0.931</td>
</tr>
<tr>
<td>Hepatojugular reflux positive, n(%)</td>
<td>74 (4.8%)</td>
<td>380 (6.0%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Third heart sound (S3), n(%)</td>
<td>63 (3.8%)</td>
<td>335 (5.0%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Radiographic features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomegaly, n(%)</td>
<td>859 (52.9%)</td>
<td>3199 (48.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pleural effusion, n(%)</td>
<td>787 (48.3%)</td>
<td>3149 (47.2%)</td>
<td>0.447</td>
</tr>
<tr>
<td>Laboratory tests, median (Q1,Q3)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, (g/dL)</td>
<td>12.1 (10.8,13.5)</td>
<td>12.3 (10.9,13.7)</td>
<td>0.036</td>
</tr>
<tr>
<td>White blood cell, (x 10⁹ /L)</td>
<td>9.2 (7.3,11.8)</td>
<td>8.6 (6.9,10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum sodium, (mmol/L)</td>
<td>139 (136,141)</td>
<td>139 (136,142)</td>
<td>0.231</td>
</tr>
<tr>
<td>Serum potassium, (mmol/L)</td>
<td>4.2 (3.8,4.6)</td>
<td>4.2 (3.9,4.6)</td>
<td>0.078</td>
</tr>
<tr>
<td>Creatinine, (mg/dL)</td>
<td>1.20 (0.95,1.64)</td>
<td>1.17 (0.92,1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin &gt;ULN, n(%)</td>
<td>424 (24.7%)</td>
<td>779 (11.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, (mg/dL)</td>
<td>140 (110,202)</td>
<td>126 (104,167)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Appendix Figure A. Kaplan-Meier curve comparing patients with and without ST-depression

Survival probability vs. Survival time (days)

- No ST-depression
- ST depression

p value < 0.001
Appendix Figure B. Adjusted survival curves comparing patients with and without ST-depression.