Does the discharge ECG provide additional prognostic insight(s) in non-ST elevation ACS patients from that acquired on admission?


University of Alberta, 2-51 Medical Science Building, Edmonton, Alberta, Canada T6G 2H7
Duke Clinical Research Institute, Durham, NC, USA
University Hospital Gasthuisberg, Leuven, Belgium

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Background Although the prognostic value of admission ST changes in patients with non-ST elevation acute coronary syndrome (ACS) is established, the utility of the discharge ECG is unknown. Accordingly, using the PARAGON-B Troponin substudy, we assessed the prevalence of ST depression on both admission and discharge ECG, the likelihood of developing new Q-waves at discharge and the additional prognostic value of these changes.

Methods and results Nine hundred and eighteen patients were studied; 542 patients (59%) had admission ST \( \geq 1 \) mm and 376 patients (41%) did not and their 6-month mortality was 4.4 vs 0.8%, \( P < 0.002 \), respectively. Of patients with ST \( \downarrow \) on admission, 320 (59%) normalized their ST segment at discharge. Of patients without ST \( \downarrow \) on admission, 35 (9.3%) developed new ST \( \downarrow \) at discharge. Patients with persistent ST \( \downarrow \) on discharge had a higher 6-month mortality (6.0 vs 0.9%), (re)MI (16.3 vs 7.4%), and death/(re)MI (20.0 vs 8.3%) than those who never had ST \( \downarrow \) (all \( P < 0.002 \)). Two hundred and fifty-six patients had Q-waves on admission whereas by discharge 320 had Q-waves. Patients with Q-waves on discharge vs those without had a higher mortality (4.8 vs 1.9%), (re)MI (13.8 vs 8.3%), and death/(re)MI (16.4 vs 9.6%) at 6 months (all \( P < 0.021 \)).

Conclusions This study highlights that the dynamic ECG changes which occur between admission and discharge in non-ST elevation ACS patients allows further risk stratification in determining the likelihood of 6-month death and/or (re)MI.

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KEYWORDS
Unstable angina; Non-Q wave MI; Electrocardiogram

Introduction

The electrocardiogram is a simple and non-invasive bedside diagnostic tool with a well-established role in the diagnosis of unstable angina and non-ST elevation MI (UA/NSTEMI). Many studies have found that the admission ECG provides immediate and independent prognostic information in these clinical situations. For instance, ST-segment depression on the admission ECG has been associated with poor early and long-term outcomes. A larger magnitude of ST depression (≥2 mm) at presentation identifies
a higher risk group who are often proved to have enzymatic changes indicative of myocardial necrosis,\textsuperscript{1–5} multivessel disease\textsuperscript{6} and a higher 1-year mortality.\textsuperscript{7} However, the admission ECG is limited to providing a single point assessment of patients presenting with acute coronary syndromes (ACS) and does not reflect the dynamic nature of myocardial ischaemia. Previous studies have shown that the presence of silent ST segment shift in patients with ACS is associated with an unfavourable 1 and 6 months prognosis.\textsuperscript{8,9} Moreover the presence of transient ischaemic episodes, detected as ST depression or elevation by ST-segment analysis, have been demonstrated to be independent predictors which are more sensitive than the admission ECG in identifying patients with multivessel disease, left main stenosis and unfavourable outcomes.\textsuperscript{10–12}

However, little is known about the prognostic significance of the discharge ECG, and/or the utility of combining this with the admission ECG in predicting short- and long-term outcomes in non-ST elevation ACS patients. Many studies have found that the absence of Q-waves after acute myocardial infarction (AMI) carries less in-hospital morbidity and mortality risk than patients with Q-waves.\textsuperscript{13–16} A more recent study in the era of widespread use of thrombolytic therapy in AMI has found that the absence of Q-waves after thrombolytic therapy is a marker of success implying better prognosis than those patients with Q-wave AMI.\textsuperscript{17} However the incidence of new Q-waves, their relationship to ST segment status and the prognostic implications of these findings are poorly understood. Accordingly, the objectives of our study were (1) to assess the prevalence of ST segment depression on the admission and the discharge ECGs of non-ST elevation ACS patients, (2) to assess the additional prognostic value of ST changes at discharge relative to those ST changes at admission on 6 month death and/or (re)MI, and (3) to assess the prevalence of Q-waves on both the admission and discharge ECG and their prognostic implications among non-ST elevation ACS patients.

**Methods**

**Patient population**

This study evaluated 1160 patients enrolled in PARAGON-B Troponin T substudy. This substudy was designed to examine the interaction of troponin T with the study drug and has been described elsewhere in detail.\textsuperscript{18} In brief, the PARAGON-B\textsuperscript{19} population comprised 5225 patients randomized either to lamifiban (platelet glycoprotein IIb/IIIa antagonist) or placebo and included patients ≥21 years of age with non-ST segment elevation ACS who presented within 12 h of symptom onset and who had symptoms lasting ≥10 min. Patients were required to have evidence of cardiac ischaemia, i.e. either electrocardiographic (ECG) changes or elevated creatine kinase (CK)-MB or troponin by local laboratory standards.

**ECG analysis**

ECGs were recorded in 12-lead format at a paper speed of 25 mm s\textsuperscript{−1} and calibrated correctly. All 12-lead ECG data were evaluated centrally using a manual caliper at the ECG core lab at the Canadian VIGOUR Centre by two readers who were blinded to the outcomes. ST depression was judged to be present if the J point was depressed by 1 mm or more and was followed by a horizontal or downward sloping ST segment for at least 0.08 s in two contiguous precordial leads or two limb leads.\textsuperscript{20} A Q-wave or Q-wave equivalent was determined at baseline and discharge using the Selvester QRS screening criteria.\textsuperscript{21} This was determined as a Q-wave of ≥30 ms in aVF (inferior), ≥40 ms in I and aVL (lateral), ≥40 ms in ≥two of V\textsubscript{4}, V\textsubscript{5}, V\textsubscript{6} (apical), or any Q-wave in V\textsubscript{2} (anterior). In addition, Q-wave equivalents were assessed as an R-wave of ≥40 ms in V\textsubscript{1} (posterior), or an R-wave ≤1 mm and ≤10 ms in V\textsubscript{2} (anterior). Patients who survived to hospital discharge free of confounding factors, which are left bundle branch block, right bundle branch block, paced ventricular rhythm, and left ventricular hypertrophy, were included in the analysis. Specifically, the distribution of these confounding factors (with 30-day mortality) was as follows: six patients had left bundle branch block (16.7%), three were paced (0%), 41 had right bundle branch block (2.4%) and 106 had left ventricular hypertrophy (2.9%). The definition of left ventricular hypertrophy used in this study was either the Sokolow–Lyon or Cornell Voltage criteria consisting of the following: Sokolow–Lyon: measure the amplitude of the S wave in V\textsubscript{1} and the amplitude of the R-wave in V\textsubscript{5} or V\textsubscript{6} (whichever lead has the greater amplitude). The sum of the amplitudes must be ≥35 mm or R-wave in lead V\textsubscript{5} or V\textsubscript{6} ≥26 mm; Cornell voltage: measure the amplitude of the S wave in V\textsubscript{1} and the amplitude of the R-wave in aVL. If the patient is a male, the sum of the amplitudes must be ≥28 mm. If the patient is female, the sum of the amplitude must be ≥20 mm.
Although there were 14% of our patients with ST $\downarrow \geq 2$ mm on the admission ECG, only 2.0% had this extent of ST $\downarrow$ on the discharge ECG: given this small sample, we used a cut off of $\pm 1$ mm ST $\downarrow$ or no ST $\downarrow$ to categorize both the admission and discharge ECG so as to make meaningful comparisons. The median day elapsed to the acquisition of discharge ECG (with 25th and 75th percentiles) is 8 (4,12). Patients were categorized into four groups based on ST status of the admission and discharge ECG: group 1: patients with no ST depression (No ST $\downarrow$) either on admission or discharge; group 2: patients with no ST $\downarrow$ on admission but who developed new ST $\downarrow$ at discharge; group 3: patients with ST $\downarrow$ on admission who had normalization of their ST $\downarrow$ by discharge; group 4: patients with ST $\downarrow$ on admission which persisted on discharge.

Outcomes

The relationship between ST depression and Q-wave status on the admission and the discharge ECG and their impact on 30 days and 6 months (re)MI and/or death was examined. In patients who did not undergo revascularization, (re)MI was defined as a CK-MB level at least twice the local upper limit of normal or as new significant Q-waves in two contiguous leads. After revascularization, (re)MI was defined as new, significant Q-waves in two contiguous leads or a CK-MB level at least three or at least five times the local upper limit of normal after PCI or bypass surgery, respectively. CK-MB was to be measured at baseline, at 8 and 16 h post-randomization, and at 8-h intervals for 24 h after episodes of ischaemic pain, and after PCI or bypass surgery. Troponin T was measured at baseline and another sample was obtained at 24 to 72 h after randomization. All cardiac troponin T measurements were performed with the third-generation troponin T STAT electrochemiluminescent immunoassay on the Elecsys 2010 system (Roche Diagnostics Corporation, Indianapolis). The minimum detectable concentration was 0.01 ng ml$^{-1}$, and precision was 6.2% at both 0.15 and 6 ng ml$^{-1}$ concentrations. Patients with cardiac troponin T levels greater than 0.1 ng m$^{-1}$ were categorized as cardiac troponin T-positive.

Statistical analysis

Descriptive statistics are summarized as median with 25th and 75th percentiles for continuous variables and the Kruskal–Wallis test was used for comparison of the four groups. Fisher’s exact test or chi-square test was used for categorical variables to assess group differences. Kaplan–Meier survival estimates and Cox proportional-hazards regression model were used to compare time to the first occurrence of the end point between the groups.

A univariate analysis was performed to identify important baseline characteristic associated with 6-months death and/or (re)MI. Variables examined included age, gender, family history of coronary artery disease, smoking, hypertension, diabetes, hyper-cholesterolemia, previous MI, previous angina, previous CHF, chronic obstructive pulmonary disease (COPD), Killip class, previous PCI and previous CABG. Multi-variate logistic and Cox proportional-hazard regression models were developed using a backward, stepwise variable selection procedure to assess the effect of the baseline characteristics and ECG variables on the outcomes. All tests were two-sided, with a 5% level of significance. All analyses were performed using SPSS (Version 10.07).

Results

Of the 1160 patients enrolled in the PARAGON-B Troponin substudy, 1097 had both baseline and discharge ECGs. Two hundred and forty-two patients (20.8%) were excluded because of confounding factors and or missing ECG. The study population comprised the remaining 918 patients who were analysed in the four groups based on ST status on both admission and discharge ECG (Fig. 1). There were 542 patients (59%) who had ST $\downarrow$ and 376 (41%) did not have ST $\downarrow$ on admission; by discharge 35 (9.3%) of those without ST $\downarrow$ on admission had developed new ST $\downarrow$ and 320 (59%) of those with ST $\downarrow$ on admission had normalized their ST segment. The median length of hospital stay (with 25th and 75th percentiles) for patients without ST $\downarrow$ with new ST $\downarrow$, with normalized ST $\downarrow$, and those with persistent ST $\downarrow$ are 7 (4, 11), 6 (5, 9), 9 (6, 15), and 9 (6, 14) days, respectively.

The baseline and ECG characteristics according to ST status of both admission and discharge ECG are listed in Table 1. Patients enrolled in this study were typical of those enrolled in trials of moderate- to high-risk acute coronary syndromes.$^{22-25}$ They were predominantly males in their mid-1960s with multiple risk factors for coronary artery disease. Patients without ST $\downarrow$ on either admission or discharge ECG were more likely to have a family history of coronary artery disease. Patients with new ST $\downarrow$ by hospital discharge were more likely to have had a history of previous MI and CHF and also higher rates of prior invasive cardiac...
procedures. Patients who had persistent ST \( \downarrow \) by hospital discharge were older and more likely to have been in Killip class >1 on admission and have a higher level of troponin T. The prevalence of Q-waves at discharge in this group was marginally higher as compared with other groups (\( P=0.082 \)).

In-hospital invasive cardiac procedures are depicted in Table 2. Patients without ST \( \downarrow \) on both admission and discharge had the highest rate of coronary angiography, 58.7% compared to the other three groups; however, there was no statistical difference in the rate of PTCA or CABG between the four groups.

Patients' clinical outcomes are depicted in Table 3. Patients with ST \( \downarrow \) on admission had higher rates of death at 6 months than those without such a change (4.4 vs 0.8%, \( P=0.002 \)) and tended to have higher rates of death/(re)MI at 6 months than those without such changes (13.8 vs 9.5%, \( P=0.056 \)). However, there was no significant difference in
the rate of (re)MI at 6 months between the two groups.

Patients with new ST\(\downarrow\) at discharge had higher rates of (re)MI and death/(re)MI at 6 months as compared to those who never had ST\(\downarrow\) (20.6 vs 7.4%, \(P=0.018\)) and (20.6 vs 8.3%, \(P=0.03\)), respectively. Patients with persistent ST\(\downarrow\) on discharge had higher rates of death, (re)MI or the composite of death and (re)MI at 6 months than those with no ST\(\downarrow\) on either admission or discharge (6 vs 0.9%, \(P=0.001\)) (16.3 vs 7.4%, \(P=0.002\)) (20 vs 8.3%, \(P=0.001\)), respectively. Even with the exclusion of 58 patients who had in-hospital (re)MI (Table 4), patients with persistent ST\(\downarrow\) on discharge still had higher rates of death, (re)MI or death/(re)MI at 6 months than those without such a change (6.2 vs 1.0%, \(P=0.002\)) (6.3 vs 2.6%, \(P=0.056\)) (10.4 vs 3.6%, \(P=0.004\)), respectively.

The group with new ST\(\downarrow\) by discharge had higher rate of (re)MI and death/(re)MI at 6 months than the group without such a change. However, because of the small sample size of this group and the fact that the inter-group difference in outcomes was driven by the higher rates of in-hospital (re)MI, we did not include them in the Kaplan–Meier curve analysis.

Figure 2 compares the survival pattern at 6 months between patients with no ST\(\downarrow\) on either admission or discharge, normalized ST\(\downarrow\), and persistent ST\(\downarrow\) at discharge. Survival in patients with no ST\(\downarrow\) on either admission or discharge differed significantly when compared with patients with persistent ST\(\downarrow\) \(P=0.001\) and those who normalized their ST\(\downarrow\) by discharge \(P=0.038\). The adjusted relative risk of death at 6 months among patients with normalized ST\(\downarrow\) vs those with no ST\(\downarrow\) was 3.38 (95% CI, 0.914 to 12.3, \(P=0.068\)); among patients with persistent ST\(\downarrow\) at discharge vs those with no ST\(\downarrow\), adjusted relative risk was 5.18 (95% CI, 1.45 to 18.5, \(P=0.011\)). Figure 3 depicts the
cumulative event-free survival at 6 months. Patients with persistent ST down had significantly higher rates of death/(re)MI when compared with patients with no ST down on both admission and discharge ECG and those with normalized ST down by discharge (all P ≤ 0.005). The adjusted relative risk of death/(re)MI at 6 months among patients with normalized ST down vs those with no ST down was 1.20 (95% CI, 0.72 to 2.14, P=0.44); among patients with persistent ST down at discharge vs those with no ST down, adjusted relative risk was 2.58 (95% CI, 1.56 to 4.27, P<0.001).

The prevalence of Q-waves on the baseline and discharge ECG according to whether the patient had unstable angina or non-ST elevation MI on admission is depicted in Fig. 4. There were no statistically significant differences in the prevalence of Q-waves on the baseline and discharge ECG within the unstable angina and non-ST elevation MI cohorts. Among patients without ST depression on both baseline and discharge ECGs, patients with non-ST elevation MI had a significantly higher prevalence of Q-waves at discharge than patients with unstable angina (P=0.006).

**Q- non Q-waves status on both the admission and discharge ECG**

Q-wave status on both admission and discharge ECG is depicted in Fig. 5. On admission, 662 (72%) did not have Q-waves and 256 (28%) had Q-waves. By discharge, 320 (35%) were found to have Q-waves and 53 (6%) had lost their Q-waves. Of the 249 patients with a history of prior MI, 136 (54.6%) did not have Q-waves on their admission ECG. Patients with Q-waves at discharge had higher rates of death, (re)MI and death/(re)MI at 6 months compared with patients without such a change at discharge (4.8 vs 1.9%, P=0.021), (13.8 vs 8.3%, P=0.011) (16.4 vs 9.6%, P=0.005), respectively (Table 5). Patients with Q-waves at discharge also had higher troponin T levels, 0.081 (0, 0.44) than

<table>
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<th>Patients</th>
<th>No ST down</th>
<th>New ST down</th>
<th>Normalized ST</th>
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<tr>
<td>MI at 30 days %</td>
<td>310 (98.8%)</td>
<td>28 (100%)</td>
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<td>193 (93.8%)</td>
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<td>Death at 6 months %</td>
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<td>0.7</td>
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<tr>
<td>Death/(re)MI at 6 months %</td>
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<td>3.1</td>
<td>6.2</td>
<td>0.006</td>
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</tbody>
</table>

Fig 2 Kaplan–Meier estimates of cumulative survival at 6 months based on ST status at both admission and discharge.
After adjusting for key baseline characteristics and status of ST depression in multivariate analysis, Q-waves at discharge were highly significant in predicting death and death/(re)MI at 6 months in comparison with the patients without such a change; 2.52 (95% CI, 1.14–5.56, \( P=0.021 \)) and 1.83 (95% CI, 1.22–2.75, \( P=0.003 \)), respectively.

**Discussion**

Given the increasing frequency of patients admitted to coronary care units with UA/NSTEMI coupled with the significant cardiac event rate in patients with this syndrome\(^{26-29}\) and limited health resources, it is crucial to identify patients with increased risk for cardiac events for further intervention. Both the admission and discharge ECG are simple and non-invasive tools to detect evolutionary changes in the ST segment from admission to discharge.

**The prognostic value of the admission and discharge ECG**

Our study has shown that ST segment depression on the admission ECG is associated with adverse short- and long-term outcomes. As is evident from the baseline characteristics of those with persistent ST depression on discharge, such patients were older, more likely diabetic with a greater frequency of prior myocardial infarction and heart failure: their Killip class on admission and greater elevation of cardiac troponin T all suggest a greater risk of future events. Whereas our study was drawn from a population enrolled in the PARAGON B study, the use of the glycoprotein IIb/IIIa inhibitor, lamifiban, was evenly balanced across the four ECG subsets and would therefore not be expected to materially affect our results. Although there was a greater frequency of double and triple vessel disease as well as involvement of the left anterior descending coronary artery, somewhat surprisingly, the frequency of angiography was lower in this population.
The unfavourable prognosis of these patients suggests but does not confirm that a more aggressive approach in evaluating potentially reversible ischaemic myocardial territories could be rewarded with enhanced outcome. This result is consistent with previous studies including our own that showed the importance of ST depression on admission ECG.6,10,30

The principal novel findings of our study are a new understanding of the evolutionary ST segment changes which occurred in 39% of our patient population from admission to discharge: the majority of these (90%) related to normalization of ST by discharge. We provide new information relating to the importance of the discharge ECG as it relates to the evaluation of long-term outcomes in patients with unstable angina and non-ST elevation MI. Schechtman and co-workers31 have previously shown that ST depression on discharge ECG in patients presenting with NSTEMI alone is a significant independent predictor of poor prognosis. The results in our study confirm and extend these observations to a broader, more comprehensive population and important differences between the two studies are worthy of note. These include a larger sample size in the current study, the broader inclusion criteria, i.e. patients within 12 h of admission including those who develop later Q as opposed to excluding such individuals and screening for up to 72 h after admission. The mechanism by which persistent ST increases in the rate of (re)MI and/or death is beyond the scope of this study. However, these findings could represent large residual areas of hypoperfused ischaemic myocardium subtended by a critically stenosed infarct-related artery, hibernating myocardium or continuing silent myocardial ischaemia, thereby predisposing to adverse outcomes.32–35

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The prognostic value of Q-waves on the discharge ECG

Kleiger et al.36 showed that patients with NSTEMI could develop Q-waves during hospitalization or at discharge, the majority (70%) of which developed within the first 3 days. Our study provides new information relating to the prognostic value of Q-waves on the discharge ECG in patient with non-ST elevation ACS. Even after excluding patients with in-hospital (re)MI, those with Q-waves on the
discharge ECG had significantly higher mortality at 6 months. We believe that this finding does not reflect a missed ST elevation MI or a temporal lag in the electrocardiogram since it was present at discharge as opposed to early post admission. The majority of our patients with prior MI, i.e. 54.6%, had no Q-waves on the admission ECG despite a prior history of myocardial infarction: this is consistent with the finding of Marcus et al. who reported that 42% of patients with a history of AMI which showed a total regression of Q-waves. The clinical significance of this finding remains controversial.

Conclusions

This study confirmed the prognostic value of ST segment depression ≥1 mm on the admission ECG and also demonstrates that the dynamic changes which occur between baseline and discharge ECG in patients with non-ST elevation ACS will allow further stratification of these patients. Furthermore this study provides new information relating to the prevalence of Q-waves on the discharge ECG in patients with non-ST elevation ACS and its association with poor long-term outcomes. Thus, the implication of adding a discharge ECG to the care plan of ACS patients will be useful to tailor appropriate follow-up management strategies.

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