Troponin T and Quantitative ST-Segment Depression Offer Complementary Prognostic Information in the Risk Stratification of Acute Coronary Syndrome Patients

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OBJECTIVES	Our primary objective was to examine the prognostic relationship between baseline quantitative ST-segment depression (ST↓) and cardiac troponin T (cTnT) elevation. The secondary objectives were to: 1) examine whether ST↓ provided additional insight into therapeutic efficacy of glycoprotein IIb/IIIa therapy similar to that demonstrated by cTnT; and 2) explore whether the time to evaluation impacted on each marker's relative prognostic utility.
BACKGROUND	The relationship between the baseline electrocardiogram (ECG) and cTnT measurements in risk-stratifying patients presenting with acute coronary syndromes (ACS) has not been evaluated comprehensively.
METHODS	The study population consisted of 959 patients enrolled in the cTnT substudy of the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON)-B trial. Patients were classified as having no ST↓ (n = 387), 1 mm ST↓ (n = 433), and ST↓ ≥ 2 mm (n = 139). Forty-percent (n = 381) were classified as cTnT-positive based on a definition of ≥ 0.1 ng/ml.
RESULTS	Six-month death/(re)myocardial infarction rates were 8.4% among cTnT-negative patients with no ST↓ and 26.8% among cTnT-positive patients with ST↓ ≥ 2 mm. On ECGs done after 6 h of symptom onset, ST↓ ≥ 2 mm was associated with higher risk compared to its presence on ECGs done earlier (odds ratio [OR] 7.3 vs. 2.1). In contrast, the presence of elevated cTnT within 6 h of symptom was associated with a higher risk of adverse events compared with elevations after 6 h (OR 2.4 vs. 1.5).
CONCLUSIONS	Quantitative ST↓ and cTnT status are complementary in assessing risk among ACS patients and both should be employed to determine prognosis and assist in medical decision making. (J Am Coll Cardiol 2003;41:371-80) © 2003 by the American College of Cardiology Foundation

The introduction of cardiac troponin measurements into routine clinical practice has been an important milestone in the continuing quest for more effective early risk stratification of patients presenting with acute coronary syndromes (ACS). Higher cardiac troponin levels are associated with worse outcomes in both ST-segment elevation myocardial infarction (MI) (1) and non-ST-segment elevation ACS patients (2,3). In addition to a prognostic role, elevated levels of this biomarker appear to effectively identify patients with an increased likelihood of intracoronary thrombi and complex coronary lesions (4-6) which are most likely to

benefit from either antithrombin or intravenous glycoprotein (GP) IIb/IIIa inhibitor therapy (7-13).

Another diagnostic tool, the presenting 12-lead electrocardiogram (ECG), provides the earliest available objective information for risk stratification of most ACS patients (14-17). Whereas the qualitative importance of ST-segment depression (ST↓) on the baseline ECG of ACS patients is recognized clinically, quantification of this phenomenon is rarely used in clinical practice. In a recent evaluation of patients from the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON)-A study, we documented the prognostic importance of quantitative ST↓ for one-year mortality among non-ST-segment elevation ACS patients (18). Patients with ST↓ of ≥ 2 mm in two contiguous leads were approximately six times (odds ratio [OR] 5.73; 95% confidence interval [CI]: 2.8, 11.6) more likely to die within one year than patients with no with ST↓.

Because cardiac troponin T (cTnT) takes a finite time to appear whereas the ECG is more immediately responsive to an acute ischemic event, their potential complementary role

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Abbreviations and Acronyms

ACS	= acute coronary syndromes
CI	= confidence interval
CV	= coefficient of variation
cTnT	= cardiac troponin T
ECG	= electrocardiogram
GP	= glycoprotein
IQR	= interquartile range
MI	= myocardial infarction
OR	= odds ratio
PARAGON	= Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network trial
ST ↓	= ST-segment depression

in risk-stratifying patients presenting with ACS is of interest. The relationship between these two fundamental diagnostic tests assessed quantitatively in a core laboratory has not been evaluated comprehensively and is the primary objective of the current study. The secondary objectives of the study were to: 1) examine whether quantitative ST ↓ provided additional insight into therapeutic efficacy of GP IIb/IIIa therapy similar to that demonstrated by cTnT; and 2) explore whether the time to evaluation (i.e., time between symptom onset and ECG or to when cTnT was drawn) had an impact on each marker's relative prognostic utility.

METHODS

Patient population. The study population consisted of patients enrolled in the troponin T substudy of the PARAGON-B trial. Both the overall PARAGON-B study and the troponin substudy have been described earlier (7,19). Briefly, the PARAGON-B study enrolled 5,225 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. All patients had evidence of cardiac ischemia, based on either ECG changes or elevated creatine kinase-MB or troponin T or I by local laboratory standards. Patients were randomized in a blinded fashion to either lamifiban or placebo therapy. The primary end point was the composite of death, MI, or severe, recurrent ischemia at 30 days. Six-month death and (re)MI were assessed as secondary end points. The institutional review board approved the substudy protocol at each site.

Cardiac troponin measurement. Of the 5,225 PARAGON-B patients, 1,160 patients were prospectively enrolled in the troponin T substudy. All cTnT measurements were performed with the third-generation troponin T STAT electrochemiluminescent immunoassay on the Elecsys 2010 system (Roche Diagnostics Corporation, Indianapolis, Indiana) at a Clinical Laboratory Improvement Act-accredited core lab at the Department of Pathology, University of Maryland School of Medicine. The minimum detectable concentration was 0.01 ng/ml, and the imprecision (coefficient of variation [CV]) observed at the core lab was 6.2% at both 0.15

and 6.0 ng/ml concentrations, consistent with the specifications of the manufacturer of a 6.0% CV at 5.07 ng/ml and 9.3% CV at 0.10 ng/ml for this U.S. Food and Drug Administration cleared assay. Imprecision (CV) at low troponin T concentrations was validated as 10% at a concentration of 0.03 ng/ml by the core lab. These data are consistent with the imprecision specified in the manufacturer's insert of 6% at 0.09 ng/ml, 7% at 0.06 ng/ml, 10% at 0.03 ng/ml, and 30% at 0.01 ng/ml. Patients with cTnT levels >0.1 ng/ml were categorized as cTnT-positive. Thirty-day and six-month end points were used as determined for the main PARAGON-B study (7). Baseline ECG data were available for 1,112 (96%) cTnT substudy patients.

ECG parameters. All ECG data were evaluated centrally at the ECG core laboratory at the University of Alberta. The ECGs were recorded in 12-lead format at a paper speed of 25 mm/s. The ST ↓ 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 one or more of the 12 leads except aVR.

For purposes of our analysis, ST ↓ was categorized into three mutually exclusive groups: no ST ↓, 1 mm ST ↓ in two contiguous leads, and ST ↓ ≥2 mm in two contiguous leads. Patients with potentially confounding factors affecting ECG interpretation, including left bundle branch block, right bundle branch block, left ventricular hypertrophy, ventricular pacemakers, or with incomplete ECG were excluded from the analysis.

Outcomes. The relationships between baseline ST-segment status and cTnT positivity and both short- and long-term outcomes, namely 30-day and 6-month (re)MI after admission and/or death, were examined. Six-month follow-up status was available for 97% of the patients enrolled in the PARAGON-B troponin T substudy.

Treatment effect. In the troponin T substudy, lamifiban was associated with a significant reduction in the 30-day primary end point among cTnT-positive patients (from 19.4% to 11.0%; $p = 0.01$) resulting in rates that were comparable to those among cTnT-negative patients (11.2% for placebo vs. 10.8% for lamifiban) (7). We examined whether the therapeutic response to treatment among patients with positive troponin persisted at six months. The relationship between the extent of ST ↓ and six-month death/(re)MI by treatment assignment was also examined to determine whether the marker provided additional insights into the therapeutic efficacy of GP IIb/IIIa therapy.

Time effect. We conducted exploratory analyses to determine whether the time from symptom onset to ECG and to when cTnT samples were drawn had an impact on the prognostic significance of the markers. Patients were classified according to whether the ECG and cTnT were done within 6 h of symptom onset or later. The relationship of ST ↓ and troponin positivity to six-month death/(re)MI outcomes were examined within each stratum. The 6-h window was selected for consistency with earlier studies (3) and because it has been suggested that cTnT drawn 6 to

Figure 1. Description of the patient population. ECG = electrocardiogram; ST-dep = ST-segment depression; TnT = troponin; T- = troponin negative; T+ = Troponin positive.

12 h after symptom onset is optimum in risk stratification (20).

Statistical analyses. Chi-square tests (for categorical variables) and the nonparametric Kruskal-Wallis tests (for continuous variables) were used to compare characteristics across groups of patients. Kaplan-Meier analysis was used to study the relationship between the magnitude of ST ↓ and cTnT positivity and six-month death/(re)MI rates. Survival curves were compared using the log-rank test statistic.

The univariate associations between ST ↓ categories and cTnT status and adverse outcomes were measured using both chi-squared tests and logistic regression analysis. Transformations of the continuous cTnT variable were considered to better examine its relationship with long-term outcomes.

A multivariable logistic regression model was developed to assess the combined prognostic value of positive cTnT and ST ↓ categories in predicting six-month death or (re)MI. Univariate analyses of baseline variables were followed by a backward stepwise variable selection procedure. The magnitude of ST ↓ (0, 1, and 2 mm) was included as a categorical variable. The cTnT variable was included as a continuous variable, a dichotomous variable (with values above 0.1 ng/ml being assigned a value of 1), as well as a categorical variable (using quartiles as cut points). The overall performance of the final model was assessed using the c-index. The 95% CI around the estimate (i.e., the interval within which we can say with 95% probability that the true c-index value is contained) was also calculated. The c-index is a measure of model discrimination: the extent to which the model predicts higher probabilities of outcome for patients who have the outcome and is equal to the area under the receiver operating characteristic curve (21).

RESULTS

Baseline ECG data were available for 1,112 (96%) of the 1,160 patients enrolled in the PARAGON-B troponin T substudy (Fig. 1). There were no differences in baseline characteristics or outcomes, other than a higher rate of previous MI (46% vs. 31%; $p = 0.04$) and prior coronary artery bypass graft (19% vs. 10%; $p = 0.05$), between the 48 patients with no ECG data and those with ECG data. Among the 1,112 patients with ECG data, 153 (14%) had ECG confounders and were excluded from the analyses. Patients with ECG confounders were significantly older and had higher frequency of risk factors such as prior heart failure, hypertension, and diabetes. Six-month mortality/(re)MI rate among patients with ECG confounders was 15% and 42% of these patients were classified as troponin positive.

After excluding patients with ECG confounding factors, the final study population consisted of 959 patients: 387 (40%) had no ST ↓; 433 (45%) had ST ↓ of 1 mm in two contiguous leads; and 139 (15%) had ST ↓ of ≥ 2 mm in two contiguous leads. Based on a definition of ≥ 0.1 ng/ml used in the cTnT substudy, 381 (40%) were classified as cTnT-positive.

Baseline characteristics of the patient population according to ST ↓ categories are presented in Table 1. Patients with ST ↓ ≥ 2 mm were older, more likely male, and less likely to have undergone prior percutaneous coronary intervention. These patients had significantly higher rates of hypertension, prior MI, prior angina, peripheral vascular disease, and history of congestive heart failure. Extent of ST ↓ and cTnT-positivity were positively correlated (Pearson correlation coefficient = 0.17, $p < 0.01$): patients with ST ↓ ≥ 2 mm had the highest median cTnT levels (0.15 ng/ml, interquartile range [IQR]: 0.02, 0.49) compared

Table 1. Baseline Characteristics of PARAGON-B Patients by ST ↓ Categories

Characteristics	No ST ↓	ST ↓ = 1 mm	ST ↓ ≥ 2 mm	p Value
Sample size	387	433	139	
Age*	61 (51, 68)	65 (55, 73)	69 (61, 74)	< 0.01
Female	35.1	42.0	28.8	0.01
Race (Caucasian)	89.1	95.4	95.7	< 0.01
Heart rate*	71 (61, 82)	76 (65, 87)	83 (74, 94)	< 0.01
Systolic BP*	135 (120, 152)	140 (124, 160)	140 (130, 165)	< 0.01
Diastolic BP*	80 (70, 90)	80 (76, 90)	85 (80, 92)	< 0.01
Family history of CHD	46.4	37.0	34.8	< 0.01
Prior heart failure	7.2	8.8	15.8	0.01
Hypertension	53.2	53.6	67.6	< 0.01
Hypercholesterolemia	44.2	45.4	46.8	0.86
Prior angina	65.4	66.5	79.9	< 0.01
Diabetes	17.6	20.8	23.0	0.30
Smoking				< 0.01
Never	35.4	42.5	40.3	
Past	29.7	31.6	38.1	
Current	34.4	25.9	21.6	
Stroke	3.9	3.2	4.3	0.80
TIA	1.6	3.5	2.9	0.22
Previous MI	26.4	27.5	41.7	< 0.01
Prior angio	30.5	25.6	20.9	0.07
Prior PTCA	14.2	10.9	6.5	0.04
Prior CABG	10.1	9.5	5.8	0.31
Severe COPD	4.9	4.4	4.3	0.93
Cancer	3.6	2.1	1.4	0.25
CRF	0.8	0.9	2.9	0.12
PVD	5.4	7.6	12.9	0.02
Arrhythmias	9.6	11.1	17.3	0.05
Enroll MI	30.2	32.6	38.8	0.10
Troponin				
Troponin+	32.3	40.2	59.0	< 0.01
Troponin measure*	0.03 (0.0, 0.21)	0.05 (0.0, 0.29)	0.15 (0.02, 0.49)	< 0.01

*Values presented are medians and interquartile range.

BP = blood pressure; CABG = coronary artery bypass surgery; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; MI = myocardial infarction; PARAGON = platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network trial; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; ST ↓ = ST-segment depression; TIA = transient ischemic attack.

with median values of 0.05 ng/ml (IQR: 0.0, 0.29) among patients with ST ↓ of 1 mm and 0.03 ng/ml (IQR: 0.0, 0.21) among patients with no ST ↓ ($p < 0.01$).

Prognostic significance of ST-segment depression on baseline ECG. Adverse outcomes by ST ↓ categories are presented in Table 2. At six months, the (re)MI rate among patients with ST ↓ ≥ 2 mm (16.7%) was almost twice that

of patients with no ST ↓ (8.6%). In addition, the mortality rate among patients with ST ↓ ≥ 2 mm was 10.1% compared with 1.8% among patients with no ST ↓. Figure 2A shows the Kaplan-Meier six-month death/(re)MI curves for the three ST ↓ subgroups. Survival free of (re)MI among patients with no ST ↓ was significantly higher compared with those with ST ↓ of 1 mm (log-rank statistic = 4.2; $p = 0.04$) and ST ↓ ≥ 2 mm (log-rank statistic = 14.2; $p < 0.01$). Similarly, the difference in survival between patients with 1 mm ST ↓ was significantly higher than that of patients with 2 mm ST ↓ (log-rank statistic = 4.6; $p = 0.03$).

Prognostic significance of troponin measures. The cTnT measurements ranged from 0.0 to 8.37 ng/ml in this population. In Table 3 and Figure 2B we present adverse outcomes by cTnT status using the PARAGON-B troponin T substudy definition of ≥ 0.1 ng/ml considered cTnT-positive. Six-month (re)MI-free survival among cTnT-positive patients was significantly lower than that of cTnT-negative patients (log-rank statistic = 10.24; $p < 0.01$).

We further explored the relationship between continuous

Table 2. Outcomes by ST ↓ category

Characteristics	No ST ↓	ST ↓ = 1 mm	ST ↓ ≥ 2 mm	p Value
Sample size	387	433	139	
Death 48 h	0.0	0.5	1.4	0.08
Death 30 day	0.8	3.2	5.0	< 0.01
Death 6 month	1.8	6.1	10.1	< 0.01
MI 48 h	2.1	2.8	4.3	0.37
MI 30 day	8.0	11.6	14.4	0.07
MI 6 month	8.6	11.8	16.7	0.03
Death/MI 48 h	2.1	3.2	5.8	0.10
Death/MI 30 day	8.3	12.9	17.3	0.01
Death/MI 6 month	9.8	14.5	22.3	0.01

Abbreviations as in Table 1.

Figure 2. Kaplan-Meier curves of six-month survival free of death/(re)myocardial infarction. **(A)** Categorized by ST-segment depression categories. *Log rank statistics (0 vs. 1 mm) = 4.2 ($p = 0.04$). #Log rank statistic (0 vs. 2 mm) = 14.2 ($p < 0.01$). **Log rank statistic (1 vs. 2 mm) = 4.6 ($p = 0.03$). **(B)** Categorized by troponin status. *Log rank statistics = 10.24 ($p < 0.01$).

cTnT values and long-term outcomes by considering several transformations. Figure 3 shows six-month rates of death/(re)MI by cTnT quartiles. The categorization of all patients with no troponin elevation (0.0 ng/ml) in the first quartile resulted in an unequal distribution of patients in the first and second quartile. Overall, 365 patients with a cTnT level of 0.0 ng/ml cTnT were categorized as the first quartile; patients with cTnT levels between 0.01 and 0.047 ng/ml were categorized as second ($n = 113$); from 0.048 to 0.277 as third ($n = 241$); and all cTnT levels >0.278 ng/ml were included in the fourth quartile ($n = 240$). Death/(re)MI rates ranged from 6.3% in the first cTnT quartile to 20.8% in the fourth quartile (chi-squared test for trend = 30.6; $p < 0.001$). The biggest increment in adverse event rate was seen between the first two quartiles (from 6.3% to 14.2%).

Prognostic significance of combining ECG and cTnT data. Figure 4 shows the six-month death/(re)MI rates by ST $\downarrow$ and cTnT status (positive ≥ 0.1 ng/ml). Rates ranged from 8.4% among patients with no ST $\downarrow$ and negative cTnT to 26.8% among patients with ST $\downarrow \geq 2$ mm and positive cTnT. Within each ST $\downarrow$ category positive cTnT was associated with higher risk; however, these differences

did not reach statistical significance. The difference was most pronounced among patients with ST $\downarrow \geq 2$ mm (15.8% among cTnT-negative vs. 26.8% among cTnT-positive, $p = 0.15$).

Table 4 shows the univariate and multivariable association between baseline variables and six-month death/(re)MI. Individually, both ST $\downarrow$ and cTnT (irrespective of categorization) were significant predictors of adverse outcomes (see univariate ORs column in Table 4). Odds ratios associated with a unit change in cTnT are difficult to interpret clinically and given our finding that quartiles were a more sensitive marker of risk compared with the dichotomous cTnT variable, cTnT quartiles were used in the multivariable analysis. After adjusting for other baseline factors, both ST $\downarrow$ and cTnT remained prognostically significant. Patients with ST $\downarrow \geq 2$ mm were twice as likely to experience an adverse outcome compared with patients with no ST $\downarrow$ (OR 1.91; 95% CI: 1.10 to 3.32) while patients with cTnT levels higher than 0.278 ng/ml had approximately four times the likelihood of death or (re)MI compared with patients with no cTnT elevation (OR 3.86; 95% CI: 2.24 to 6.66). Other significant predictors included prior percutaneous coronary intervention, peripheral vascular disease, and increasing age. The c-statistic for the model was 0.70 (95% CI: 0.65 to 0.75) indicating that the model had a moderately good ability to discriminate between patients who did and did not experience the outcome.

Treatment effect. Treatment effects according to ST $\downarrow$ and cTnT status are presented in Tables 5 and 6. In general, patients treated with lamifiban had lower adverse event rates compared to patients in the placebo arm across ST $\downarrow$ categories; however, these differences did not reach statistical significance. The significant reduction in (re)MI events among cTnT-positive patients treated with lamifiban ob-

Table 3. Outcomes by Troponin Status

Characteristics	Troponin–	Troponin+	p Value
Sample size	578	381	
Death 48 h	0.2	0.8	0.31
Death 30 day	1.7	3.7	0.09
Death 6 month	3.3	7.4	< 0.01
MI 48 h	1.6	4.5	< 0.01
MI 30 day	9.0	12.9	0.07
MI 6 month	9.7	13.6	0.07
Death/MI 48 h	1.7	5.2	< 0.01
Death/MI 30 day	9.5	15.0	0.01
Death/MI 6 month	10.9	18.1	< 0.01

Abbreviations as in Table 1.

Figure 3. Six-month death/(re)myocardial infarction (MI) rates by troponin quartiles.

Figure 4. Six-month death/(re)myocardial infarction (MI) rates by ST-segment depression categories and troponin status. Shaded square = troponin -; closed square = troponin +.

Table 4. Univariate and Multivariable Associations—Death/MI 6 Months

Variable	Univariate Associations			Multivariable Associations*		
	OR	Lower CI	Upper CI	OR	Lower CI	Upper CI
Age (10 yr increments)	1.25	1.16	1.36	1.15	1.05	1.26
Gender	0.92	0.63	1.35			
Diastolic blood pressure	1.00	0.99	1.01			
Systolic blood pressure	1.00	1.00	1.01			
Heart rate	1.00	0.99	1.01			
Hypertension	1.10	0.76	1.60			
Diabetes	1.64	1.08	2.50			
Hyperlipidemia	1.30	0.90	1.88			
Family history of CHD	1.11	0.77	1.62			
Previous MI	1.33	0.90	1.96			
Previous angina	1.42	0.94	2.15			
Prior PTCA	1.66	1.00	2.76	1.86	1.09	3.16
Prior CABG	1.21	0.66	2.21			
Severe COPD	2.19	1.08	4.44			
Cancer	1.20	0.41	3.55			
Peripheral vascular disease	2.66	1.53	4.62	2.32	1.29	4.17
Congestive heart failure	1.50	0.89	2.53			
Stroke/TIA	2.04	1.07	3.92			
Smoking						
Past	1.49	0.96	2.31			
Current	1.31	0.83	2.08			
ST-segment depression						
1 mm	1.56	1.02	2.40	1.34	0.86	2.09
2 mm	2.64	1.57	4.44	1.91	1.10	3.32
Troponin†‡						
0.01–0.047 ng/ml	2.45	1.25	4.82	2.43	1.22	4.85
0.048–0.277 ng/ml	3.23	1.89	5.16	3.18	1.83	5.53
0.278–8.37 ng/ml	3.91	2.32	6.61	3.86	2.24	6.66

*C-statistic = 0.70, 95% CI = 0.65 to 0.75; †cTnT as dichotomous value (≥ 0.1 ng/ml): univariate OR = 1.81, 95% CI = 1.25 to 2.62; multivariable OR = 1.57 (1.06 to 2.33); ‡cTnT as a continuous value: univariate OR = 1.31, 95% CI = 1.06 to 1.61; multivariable OR = 1.23 (0.99 to 1.54).

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

served at 30 days persisted at 6 months. However, as documented in the main PARAGON-B troponin substudy paper, there was no significant treatment difference in the six-month composite death/(re)MI rates (7). Overall, treatment with lamifiban did not have a significant impact on six-month death/(re)MI rates either in the univariate or in the multivariable context.

Time effect. Table 7 describes the impact of time to evaluation on the relationship between the markers and six-month death/(re)MI. The median time to ECG was 1.7 h (IQR: 0.2, 4.1) and the median time to cTnT was 6.8 h (IQR: 4.0, 10.2). The ECGs were done within 6 h of

symptom onset in 743 (78%) of patients enrolled in the study and after 6 h in 144 (15%) patients. The frequency of ST $\downarrow \geq 2$ mm was lower in the latter group (8% vs. 16%; $p = 0.02$); however, its presence was associated with a far greater risk of six-month death/(re)MI (OR of 7.3 compared to 2.1).

With respect to cTnT, a majority of the patients ($n = 532$, 56%) had their cTnT drawn after 6 h of symptom onset. However, the presence of elevated cTnT (≥ 0.1 ng/ml) within 6 h of symptom onset was associated with higher risk of adverse outcome than the presence of elevated cTnT after 6 h (OR 2.4; 95% CI: 1.4, 4.2 vs. OR 1.5; 95% CI: 0.92, 2.5).

Table 5. Treatment Effect by ST $\downarrow$ Status

Characteristics	No ST $\downarrow$		ST $\downarrow = 1$ mm		ST $\downarrow \geq 2$ mm	
	Rx	Placebo	Rx	Placebo	Rx	Placebo
Sample size	190	197	226	207	64	75
Death 30 day	0.0	1.5	3.1	3.4	4.7	5.3
Death 6 month	1.1	2.6	6.7	5.4	9.5	10.7
MI 30 day	6.3	9.6	9.8	13.6	14.1	14.7
MI 6 month	6.5	10.7	10.4	13.3	15.9	17.3
Death/MI 30 day	6.3	10.2	11.5	14.5	17.2	17.3
Death/MI 6 month	7.4	12.2	13.7	15.5	21.9	22.7

Abbreviations as in Table 1.

Table 6. Treatment Effect by Troponin Status

Characteristics	cTnT –		cTnT+	
	Rx	Placebo	Rx	Placebo
Sample size	290	288	190	191
Death 30 day	1.4	2.1	3.2	4.2
Death 6 month	2.8	3.8	8.0	6.9
MI 30 day	9.3	8.7	8.5	17.3*
MI 6 month	9.9	9.5	9.1	18.0*
Death/MI 30 day	9.7	9.4	11.1	18.8†
Death/MI 6 month	10.3	11.5	15.3	20.9

*Treatment groups are statistically significantly different at $p < 0.01$ level; †treatment group comparison $p = 0.04$.

Abbreviations as in Table 1.

DISCUSSION

Our study documents the complementary role of baseline quantitative ST $\downarrow$ and cTnT measurement in risk-stratifying non-ST-segment elevation ACS patients. In combination, the markers appear to provide an integrated and improved delineation of the spectrum of ACS risk: with the lowest rates of adverse outcomes being observed in cTnT-negative patients with no ST $\downarrow$ (8.4%) and the highest rates being observed in cTnT-positive patients with ST $\downarrow \geq 2$ mm (26.8%). In a multivariable logistic regression model, both markers were found to be independent predictors. Compared to patients with no ST $\downarrow$, there was a trend towards a higher six-month death/(re)MI rate among patients with 1 mm ST $\downarrow$ (OR 1.34; 95% CI: 0.86, 2.09); and a significant increase in the rate among patients with ST $\downarrow \geq 2$ mm (OR 1.91; 95% CI: 1.10, 3.32). Patients with cTnT levels higher than 0.278 ng/ml had approximately four times the likelihood of an adverse event compared with patients with no cTnT elevation (OR 3.86; 95% CI: 2.24, 6.66).

Our study has several interesting secondary findings. First, our results underscore the prognostic importance of lower levels of cTnT. The PARAGON-B troponin T substudy defined positivity as ≥ 0.1 ng/ml; however, in examining the relationship between continuous cTnT and six-month outcomes, we found this dichotomization may be less than optimal for risk stratification. Patients with cTnT levels in the range of 0.01 to 0.047 ng/ml had six-month death/(re)MI rates of 14.2% compared with 6.3% among patients with no detectable cTnT. Our results are consistent with those reported recently by Lindhal et al. (6). In the Fast Revascularization during Instability in Coronary artery disease (FRISC-II) substudy, any detectable elevation of cTnT was associated with higher risk of (re)MI or death at one year. One limitation of using lower cTnT cutoffs is the greater variability and loss in precision. Typical analytical performance of the cTnT assay used in the current study is characterized by a precision (CV) of about 20% at 0.01 ng/ml, the 99th percentile for a reference control population (95% CI: 0.006 to 0.014). The precision (CV) at 0.03 ng/ml achieves 10% (95% CI: 0.024 to 0.036); at cTnT concentrations > 0.05 ng/ml the precision (CV) is constant at 5% to 8% (data on file at Roche Diagnostics).

Second, the time from symptom onset to evaluation appears to have a significant impact on the prognostic value of the markers. Patients with ST $\downarrow \geq 2$ mm after 6 h of symptom onset had more than three times the risk of six-month death/(re)MI compared with patients with ST $\downarrow \geq 2$ mm on ECGs done within 6 h (OR 7.3 vs. 2.1). Worse outcomes with persistent ST $\downarrow$ may be indicative of worse myocardial ischemia and/or more extensive or severe coronary artery disease. Given the potential prognostic implications, further exploration of the temporal evolution of ST-segment changes is warranted.

In contrast, earlier elevations of cTnT appear to be markers of higher risk. A possible explanation is that early elevations of troponin are indicators of higher risk patients with active lesions and “stuttering” courses of intermittent occlusion and reperfusion preceding their ultimate presentation for medical attention. This hypothesis is supported, in part, by the higher frequency of cardiac symptoms among these patients in the two weeks prior to study enrollment (80% vs. 69%) (Table 7). Our results are consistent with those from the Thrombolysis In Myocardial Infarction (TIMI)-IIIb troponin I analysis in which patients enrolled within 6 h of symptom onset who had elevated troponin I levels had a 42-day mortality rate of 3.1% compared with 1.7% among patients without early troponin I elevations (3). In our study, the corresponding 30-day mortality rates were 3.9% among cTnT-positive and 1.4% among cTnT-negative patients. While the TIMI-IIIb result among patients presenting after 6 h of symptom onset appears inconsistent with our findings (42-day mortality risk ratio of 9.5 between troponin I positive and negative patients), this result is driven by the extremely low-risk of troponin I negative patients (0.4% mortality compared with 4.0% among troponin I positive patients). Among corresponding patients in our study, 30-day mortality rate in cTnT-positive patients was similar to those of the TIMI-IIIb cohort (3.6%) but was much higher among cTnT-negative patients (2.1%) resulting in a lower risk ratio.

Third, our study shows that cTnT is superior to ST $\downarrow$ in assisting treatment decisions, especially in the short-term. Among cTnT-positive patients, treatment with a GP IIb/IIIa inhibitor (lamifiban) significantly reduced the risk of both (re)MI (8.5 vs. 17.3, $p < 0.01$) and the composite outcome of death/(re)MI (11.1 vs. 18.8, $p = 0.04$) in the short term and of (re)MI alone at six months (9.1 vs. 18.0, $p < 0.01$). Although death/(re)MI rates were consistently lower among patients treated with lamifiban compared with placebo across all ST-depression categories, the differences did not reach statistical significance. Therefore, while the presence of ST-segment changes at baseline may have important prognostic information with respect to coronary revascularization (22,23), they may offer less guidance with respect to pharmacotherapy.

Two issues associated with the current study must be noted. First, an analysis examining the combined value of baseline ECG and troponins with respect to response to

Table 7. Examining the Impact of Time to ECG and Time to cTnT on Their Prognostic Significance

ST ↓	Time From Onset of Symptoms to ECG < 6 h	Time From Onset of Symptoms to ECG > 6 h
Number of patients	743	144
Distribution of ST ↓		
No ST ↓	281 (38%)	69 (48%)
1 mm ST ↓	344 (46%)	63 (44%)
ST ↓ ≥ 2 mm	118 (16%)	12 (8%)
Association with outcomes (OR for 6-Month death/MI)		
1 mm ST ↓	1.2 (0.8–2.0)	4.2 (1.1–15.9)
ST ↓ ≥ 2 mm	2.1 (1.2–3.7)	7.3 (1.3–42.0)
Duration of pain in min*	30 (20, 120)	210 (38, 618)
Troponin	Time From Onset of Symptoms to Troponin < 6 h	Time From Onset of Symptoms to Troponin > 6 h
Number of patients	421	532
Distribution of troponin values		
Negative	294 (70%)	280 (53%)
Positive	127 (30%)	252 (47%)
Continuous troponin*	0.02 (0, 0.14)	0.09 (0, 0.42)
Association with outcomes (OR for 6-month death/MI)		
Positive	2.4 (1.4, 4.2)	1.5 (0.92–2.5)
Symptoms of MI/UA in the last 2 weeks	80%	69%
Duration of pain in min*	30 (20, 64)	60 (25, 210)

*Values presented are medians and interquartile range.

cTnT = cardiac troponin T; UA = unstable angina; other abbreviations as in Table 1.

treatment would be of interest; however, the small sample sizes in some of the groups limit the utility of such an analysis. Second, the cTnT and ST ↓ measures used in our analysis were analyzed in core laboratories and, therefore, were not available to investigators. However, the investigators had access to the ECGs and may have had access to local cTnT data, which may have influenced decisions regarding revascularization therapy. This in turn may have had an impact on outcomes. A preliminary analysis revealed no relationship between increasing ST ↓ and procedure use; however, cTnT-positive patients had a higher frequency of revascularization. We believe that these issues are beyond the scope of the current investigation and deserve further exploration.

Comparison with previous studies. Earlier studies examining the relative contributions of ST ↓ and cTnT positivity have focussed on short-term prognosis. Holmvang *et al.* (24) examined the combined value of ECG and biochemical assessment for very early risk stratification among patients with unstable coronary artery disease as part of the Thrombin Inhibition in Myocardial Ischemia (TRIM) substudy. Among 470 patients with readable ECGs, 64 (14%) had ST ↓ of at least 1 mm in any lead. In univariate analyses, both ST ↓ and cTnT ≥ 0.1 ng/ml were highly predictive of death/(re)MI within 30 days. Although in the multivariable context, cTnT did not provide additional prognostic information over and above that of ST ↓, it was effective in further risk-stratifying patients with no ST ↓ (30-day

death/[re]MI rates of 6% and 3% among cTnT positive and negative patients, respectively).

As part of the Fast Assessment of Thoracic Pain (FAST) study, Jernberg *et al.* (25) examined the combination of a continuous 12-lead ECG and cTnT status in patient risk-stratification. As in our study, cTnT positivity was defined as >0.10 ng/ml, however, ST ↓ was categorized into ≥0.05 mV to <0.10 mV and ≥0.10 mV. In addition, ST episodes defined as a transient ST ↓ or elevations in any lead of at least 1 mm were identified. In a multivariable model, cTnT and ST episodes were independent predictors of 30-day death/(re)MI. Neither category of ST ↓ was found to be a statistically significant predictor of outcomes.

CONCLUSIONS

Our study documents that quantitative ST ↓ and cTnT status are complementary in assessing risk among ACS patients and that both should be employed to determine prognosis and assist in medical decision making. While both ST ↓ and cTnT are effective markers of risk, cTnT appears to be superior to ST ↓ in assisting decisions regarding the use of GP IIb/IIIa therapy. Furthermore, levels of cTnT lower than 0.1 ng/ml contain important prognostic information and should be incorporated into risk-assessment analysis. The relationship between cTnT and ST ↓ status and outcomes over a spectrum of times from symptom onset require further investigation.

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