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Prognostic Value of ST Segment Depression in Acute Coronary Syndromes: Insights From PARAGON-A Applied to GUSTO-IIb

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OBJECTIVES Our objectives were to develop a risk-stratification model addressing the importance of the magnitude and distribution of ST segment depression in predicting long-term outcomes and to validate the model in an analogous patient population.

BACKGROUND Although patients without ST segment elevation presenting with acute coronary syndromes represent an increasingly frequent population admitted to coronary care units, little attention has been paid to quantifying their ST segment abnormalities.

METHODS ST segment depression was categorized into three groups: 1) no ST segment depression; 2) 1-mm ST segment depression in two contiguous leads; and 3) ST segment depression ≥2 mm in two contiguous leads. A logistic regression model was developed using Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-A) data to assess the prognostic value of the extent and distribution of ST segment depression in predicting one-year mortality. The model was validated using the non-ST segment elevation population in Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO-IIb).

RESULTS ST segment depression was the strongest predictor of one-year mortality, accounting for 35% of the model's predictive power. Patients with ST segment depression ≥2 mm were ~6 times (odds ratio [OR] 5.73, 95% confidence interval [CI] 2.8 to 11.6) more likely to die within one year than patients with no ST segment depression. On validation, the model showed good discriminatory power (c-index = 0.75). Patients with ST segment depression ≥2 mm in more than one region were almost 10 times more likely to die within one year than patients with no ST segment depression.

CONCLUSIONS These data provide new evidence supporting the powerful prognostic value of the baseline electrocardiogram and, in particular, the magnitude and distribution of ST segment depression in predicting unfavorable events. (J Am Coll Cardiol 2001;38:64–71) © 2001 by the American College of Cardiology

Patients without ST segment elevation presenting with acute coronary syndromes represent an increasingly frequent population admitted to coronary care units. This group is a major socioeconomic burden on the health care system. In recent years, a large array of novel diagnostic and therapeutic options has become available for such patients. These developments have generated a high priority on establishing an early and accurate assessment of risk coupled with timely and prudent triage.

Previous studies have shown that ST segment depression on the hospital admission electrocardiogram (ECG) is associated with increased risk among such patients (1–4). A number of these investigations have been retrospective, observational and composed of modest sample sizes. Little comprehensively acquired data exist to address the importance of the magnitude of ST segment depression examined systematically in a core laboratory and its relationship to short- and longer term outcomes.

The Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-A) study provided us with an opportunity to examine the extent and distribution of ST segment depression and to evaluate its prognostic ability in predicting early and one-year outcomes (5). Employing these data, our objectives were to develop a risk-stratification model using baseline characteristics and to validate the model by testing it in an analogous patient group—namely, patients with non–ST-segment elevation who were enrolled in the Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO-IIb) study (6).

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Abbreviatons and Acronyms

CABG	=	coronary artery bypass graft surgery
CI	=	confidence interval
ECG	=	electrocardiogram or electrocardiographic
GUSTO-IIb	=	Global Use of Strategies To Open occluded arteries in acute coronary syndromes
MI	=	myocardial infarction
OR	=	odds ratio
PARAGON-A	=	Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network

METHODS

Patient population. This study consisted of two patient groups: the patients in PARAGON-A and those with non–ST segment elevation in GUSTO-IIb. The patient population enrolled in the PARAGON-A study has been described elsewhere (5). Briefly, 2,282 patients with chest discomfort within the previous 12 h, associated with transient or persistent ST segment depression ≥0.5 mm or T-wave inversion or transient ST segment elevation ≥0.5 mm, were included. The primary end point was death or nonfatal myocardial infarction (MI) at 30 days. One-year follow-up status was available for 91.5% of the patients enrolled in the study. All patients with baseline ECG data were included in the study. The clinical characteristics and outcomes of patients included in the study were compared with those excluded because of either incomplete or missing ECG data.

The GUSTO-IIb trial comparing recombinant hirudin and heparin therapy among patients presenting with unstable angina or acute MI enrolled 8,001 patients with non-ST segment elevation (6). Both treatment arms were combined for this analysis. As with PARAGON-A, the primary end point of the GUSTO-IIb study was a composite of death and MI in the first 30 days of follow-up. The end points of re-infarction and death were available at 6 months, and mortality data at 12 months. One-year status was known for 94% of this patient population. For the current study, patients with missing or incomplete baseline ECG data were excluded from this study.

Electrocardiographic variables. All ECG data, for both the PARAGON-A and GUSTO-IIb studies, were evaluated centrally at the ECG core laboratory at the Duke Clinical Research Institute. The 12-lead ECGs were recorded at a paper speed of 25 mm/s. ST segment depression was judged to be present if the J point was depressed by ≥1 mm and was followed by a horizontal or downsloping ST segment for at least 0.08 s in one or more of the 12 leads, except for the aVR lead.

Quantitative ST segment depression was measured at 1-mm intervals, with every fraction rounded to the nearest whole number. Therefore, ST segment depression of 0.5 mm was rounded to 1 mm, 1.5 mm to 2 mm, and so on. For purposes of our analysis, ST segment depression was categorized into three groups: 1) no ST segment depression; 2) 1-mm ST segment depression in two contiguous leads; and 3) ST segment depression ≥2 mm in two contiguous leads. For patients with potentially confounding factors affecting ECG interpretation—that is, left bundle branch block, right bundle branch block, left ventricular hypertrophy or ventricular pacemakers—ST segment depression was measured as described earlier, but this group was analyzed separately.

In addition to examining the impact of the magnitude of ST segment depression on long-term mortality, we investigated the role of the *distribution* of ST segment depression by identifying the number of ECG regions with ST segment depression. Four regions were examined: anteroseptal (leads V_1 to V_4), apical (leads V_4 to V_6), lateral (leads I and aVL) and inferior (leads II, III and aVF). A particular region was deemed to have ST segment depression if any two contiguous leads comprising the region had ST segment depression ≥2 mm.

Outcomes. The relationship between ST segment status on hospital admission and both short- and long-term outcomes—namely, 30-day and 6-month (repeat) MI after admission and/or death—was examined. A multivariable model to predict mortality at one year was developed and validated on an independent patient population.

Treatment effect. There were five treatment arms in the PARAGON-A study: 1 and 2) low-dose lamifiban with and without heparin; 3 and 4) high-dose lamifiban with and without heparin; and 5) placebo and heparin. The relationship between the extent of ST segment depression and one-year mortality was examined across treatment arms to identify differences in treatment effect.

Statistical analyses. The chi-square test for categorical variables and the nonparametric Kruskal-Wallis test 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 segment depression and one-year mortality. Survival curves were compared using the log-rank test statistic.

A logistic regression model was developed to assess the prognostic value of ST segment depression in predicting one-year mortality using PARAGON-A data (7). Univariate analyses of baseline variables (Table 1) were performed by using a backward stepwise variable selection procedure. The magnitude of ST segment depression (0, 1 and 2 mm) was included as a categorical variable. The logistic regression model developed from the PARAGON-A data base was validated on the non-ST segment elevation GUSTO-IIb patient population. A predicted probability of death for each GUSTO-IIb patient was calculated using the regression coefficients from the PARAGON-A model. The overall performance of the model was assessed using the c-index (8).

A second model incorporating the distribution of ST

Table 1. Baseline Characteristics by ST Segment Categories: PARAGON-A Study

Characteristics	No ST ↓ (n = 615)	ST ↓ 1 mm (n = 704)	ST ↓ ≥2 mm (n = 269)	p Value
Age (yrs)	62 (53, 70)	66 (58, 73)	67 (61, 74)	<0.001
Female (%)	34.8	38.2	23.4	<0.001
Heart rate (beats/min)	70 (60, 80)	72 (63, 80)	78 (68, 90)	0.003
Systolic BP (mm Hg)	130 (120, 145)	135 (120, 150)	140 (120, 150)	0.003
Diastolic BP (mm Hg)	80 (70, 86)	80 (70, 85)	80 (70, 90)	<0.001
Hypertension (%)	42.6	48.9	45.0	0.072
Diabetes (%)	15.1	18.2	18.2	0.284
Lipids (%)	41.1	44.2	40.9	0.459
Family history of CAD (%)	39.3	36.9	42.0	0.320
Previous MI (%)	33.0	33.7	39.0	0.196
Previous angina (%)	72.0	76.0	74.7	0.255
Previous CHF (%)	5.4	8.1	8.6	0.095
CVD (%)	4.1	4.7	5.9	0.473
Previous PTCA (%)	11.5	9.5	4.5	0.004
Previous CABG (%)	9.9	10.5	5.9	0.086
Smoking (%)				0.021
Never	35.1	40.1	36.4	
Past	38.9	35.9	45.4	
Current	26.0	24.0	18.2	
Severe COPD (%)	2.6	2.1	1.9	0.751
Cancer (%)	2.4	2.0	1.1	0.435
PVD (%)	4.6	8.5	11.9	<0.001
Enrollment with MI (%)	28.2	38.8	55.1	<0.001

Data are expressed as percentages, except for age, blood pressure and heart rate, which are expressed as median values (25th, 75th percentiles).

BP = blood pressure; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; ST ↓ = ST segment depression.

segment depression (number of regions) was developed using the PARAGON-A data. A new categorical variable corresponding to the following groups—no ST segment depression and 1 mm, 2 mm with one region and 2 mm with more than one region of ST segment depression—was created. As a final step, this model was extended to include patients with ECG confounders. An indicator variable for the presence of any confounder was incorporated into the model, and interactions between ST segment status and confounding factors were examined.

Ethics of protocol. The Institutional Review Boards of all participating institutions reviewed and approved the protocols for both the PARAGON-A and GUSTO-IIb studies. Written, informed consent was obtained from all patients enrolled in the two studies.

RESULTS

Of the 2,282 patients enrolled in the PARAGON-A study, interpretable baseline ECG data were available for 1,588 patients (70%); 396 patients (17%) had ECG confounders, and 298 (13%) had missing data. Among patients with missing data, 126 (42%) had no baseline ECG data and 172 had technically inadequate ECG data. There were no significant differences in age and gender between patients with interpretable ECGs and those with missing ECG data; however, a higher percentage of patients with missing ECG data had diabetes and hypertension. There were no significant differences in short- and long-term outcomes between the two groups.

Patients with ECG confounders had higher disease

Table 2. Outcomes by ST Segment Depression Categories: PARAGON-A and GUSTO-IIb Studies

	PARAGON-A			GUSTO-IIb		
Outcome	No ST ↓ (n = 615)	ST ↓ 1 mm (n = 704)	ST ↓ ≥2 mm (n = 269)	No ST ↓ (n = 3,158)	ST ↓ 1 mm (n = 1,961)	ST ↓ ≥2 mm (n = 1,182)
(Re) MI 30 days	6.8	11.2	14.1	4.9	6.0	8.5
(Re) MI 6 months	8.4	14.1	16.3	6.1	7.8	11.3
Death 30 days	0.7	2.8	6.3	2.0	2.7	8.3
Death 6 months	1.1	6.2	12.0	3.6	5.6	12.1
Death 1 year	2.0	7.8	13.4	4.4	6.9	14.1
Death/MI 30 days	7.2	12.1	17.1	6.5	7.8	14.6
Death/MI 6 months	9.2	16.7	23.9	8.9	11.7	19.9

Within each trial, all rates are statistically significantly different at $p < 0.001$. Data are presented as percentages.

MI = myocardial infarction; (Re) = repeat; ST ↓ = ST segment depression.

Table 3. Univariate and Multivariate Associations Between Baseline Variables and Mortality at One Year: PARAGON-A Study

	Univariate Associations				Multivariable Associations			
Variable	**OR**	**Lower CI**	**Upper CI**	**p Value**	**OR**	**Lower CI**	**Upper CI**	**p Value**
Age	1.08	1.05	1.10	<0.01	1.05	1.03	1.08	<0.01
Gender	0.98	0.64	1.50	0.93				
Diastolic BP	1.00	0.98	1.02	0.88				
Systolic BP	1.00	0.99	1.01	0.92				
Heart rate	1.02	1.00	1.03	<0.01				
Hypertension	1.13	0.75	1.68	0.56				
Diabetes	2.24	1.44	3.50	<0.01	1.86	1.15	3.01	0.01
Hyperlipidemia	0.75	0.49	1.13	0.17				
Family history of CHD	0.92	0.61	1.39	0.69				
Previous MI	2.33	1.56	3.48	<0.01	1.89	1.22	2.94	<0.01
Previous angina	2.52	1.39	4.55	<0.01				
CVD	3.37	1.79	6.37	<0.01	2.06	1.00	4.24	0.05
Previous PTCA	0.47	0.19	1.18	0.11	0.38	0.14	1.03	0.06
Previous CABG	0.68	0.31	1.49	0.33				
Severe COPD	6.03	2.83	12.89	<0.01	5.69	2.37	13.70	<0.01
Cancer	0.96	0.23	4.08	0.96				
PVD	3.84	2.30	6.43	<0.01	2.14	1.21	3.80	0.01
CHF	4.77	2.88	7.89	<0.01	2.16	1.20	3.86	0.01
Smoking				0.07				
Never	1.00	Ref.						
Past	0.77	0.50	1.20					
Current	0.50	0.28	0.90					
ST segment status				<0.01				<0.01
0	1.00	Ref.			1.00	Ref.		
1 mm	4.25	2.25	8.02		3.65	1.89	7.06	
2 mm	7.75	3.97	15.15		5.73	2.82	11.64	
Enrollment with MI	1.13	0.75	1.71	0.55				

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

severity, as indicated by their increased age, incidence of previous MI and previous coronary artery bypass graft surgery (CABG). These patients had significantly higher mortality compared with other patients in the study. At 30 days, the mortality rate among patients with ECG confounders was 6.1%, more than twice the mortality rate of patients with interpretable ECGs (2.6%). This difference in mortality widened to 6.1% by one year (6.5% for patients with ECG data and 12.6% for patients with ECG confounders).

In Table 1, baseline and clinical characteristics of PARAGON-A patients are presented according to ST segment depression status. Patients with ST segment depression ≥2 mm were older, more likely to be male and less likely to have undergone previous percutaneous transluminal coronary angioplasty or CABG. The risk of peripheral vascular disease increased with increasing ST segment depression, as did the likelihood of presenting with MI as the index event (28% for patients with no ST segment depression vs. 55% for patients with ST segment depression ≥2 mm).

Data on adverse outcomes are presented in Table 2. At six months, the (repeat) MI rate among PARAGON-A patients with ST segment depression was almost twice that of patients with no ST segment depression. Figure 1A shows the Kaplan-Meier one-year survival curves by magnitude of ST segment depression for this patient group. The risk of adverse events substantially increased with increasing ST segment depression, and all of the curves were statistically significantly different at $p < 0.05$.

Because the focus of the study was to examine the prognostic value of the ST segment depression, the five arms (four treatment arms and one placebo arm) in PARAGON-A were combined. An examination of one-year mortality by extent of ST segment depression across the PARAGON-A treatment groups revealed no statistically significant differences. However, this may be due to the small sample sizes resulting from the fragmented design of the trial.

Of 8,001 patients with non–ST segment elevation enrolled in GUSTO-IIb, 6,301 (79%) had interpretable baseline ECGs, 972 (12%) had ECG confounders and 728 (9%) had missing or incomplete baseline ECGs. As in PARAGON-A, patients in GUSTO-IIb with ST segment depression ≥2 mm were older and less likely to have undergone a percutaneous coronary intervention or CABG before the index hospital period; they also had higher rates of peripheral vascular disease and MI at enrollment (62% vs. 47% of patients with 1-mm ST segment depression and 37% of patients with no ST segment depression). In addition, patients with ≥2-mm ST segment depression had higher rates of cerebrovascular disease and severe chronic obstructive pulmonary disease.

Table 2 and Figure 1B present data on short- and

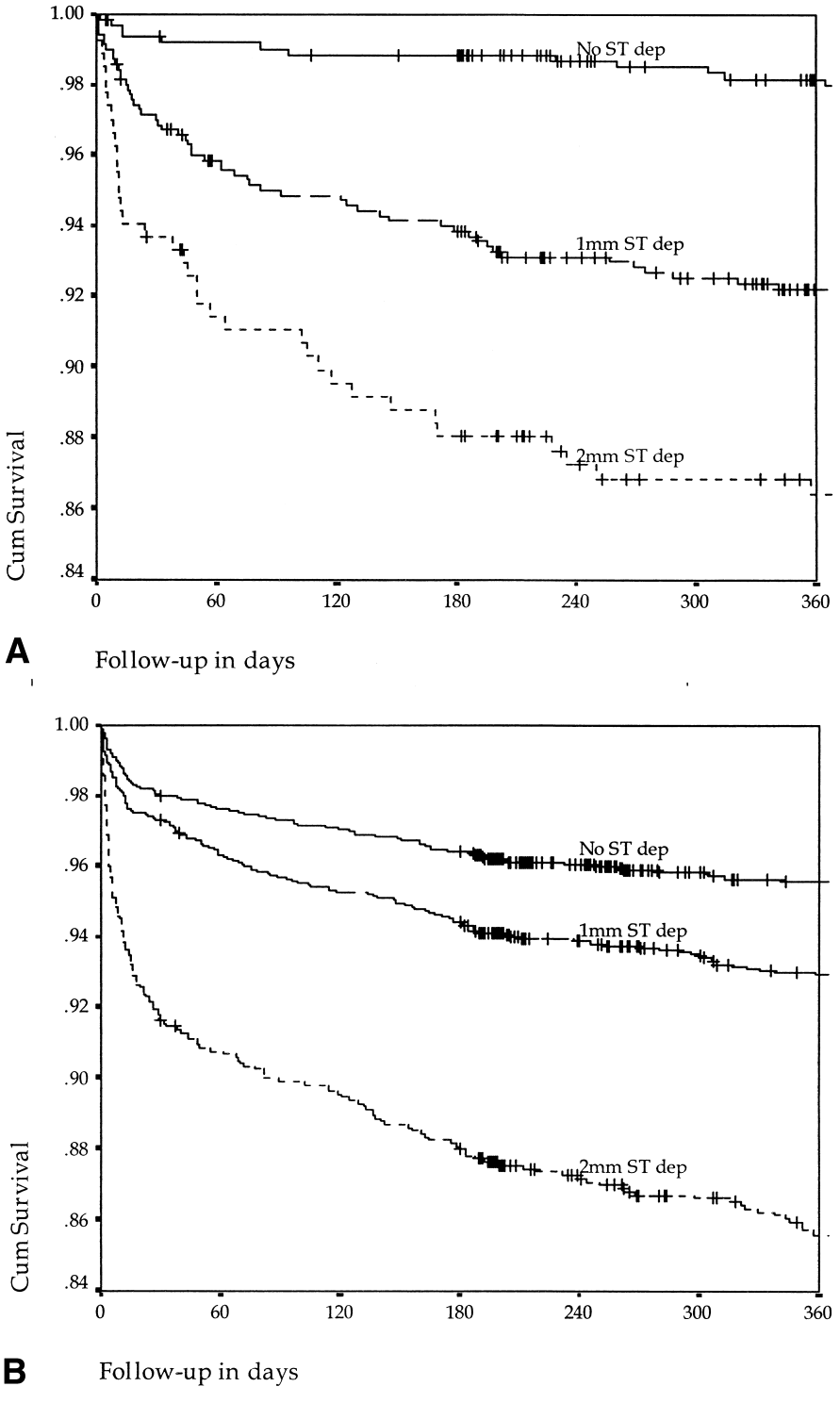

Figure 1. Survival curves corresponding to the categories of no ST segment depression (dep), 1-mm ST segment depression and ≥2-mm ST segment depression in the PARAGON-A study **(A)** and GUSTO-IIb **(B)** studies. Log-rank tests were used to compare the survival curves. All curves were statistically significantly different at $p < 0.05$.

long-term outcomes among GUSTO-IIb patients. Patients with ST segment depression ≥2 mm had the highest one-year mortality rate (14.1%) compared with patients with no ST segment depression (4.4%) and 1-mm ST segment depression (6.9%). All of the Kaplan-Meier survival curves were statistically significantly different at $p < 0.05$.

Table 3 shows the univariate and multivariable associations between baseline variables and one-year mortality among PARAGON-A patients. After controlling for other

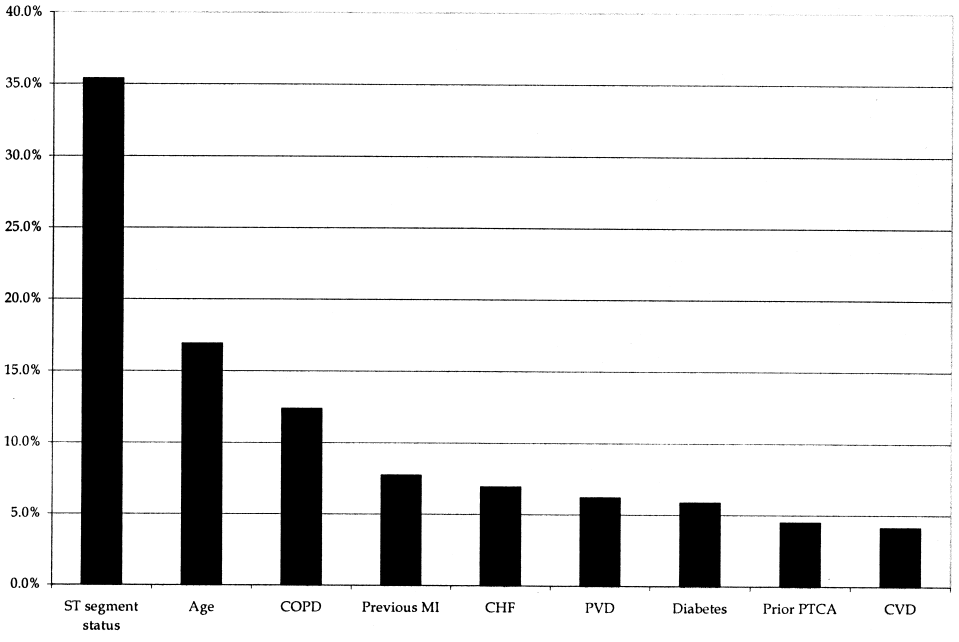

Figure 2. Relative contribution of baseline risk factors in predicting one-year mortality (PARAGON-A data). CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease.

baseline factors, the variable describing the extent of ST segment depression was the strongest predictor of one-year mortality. Patients with ST segment depression ≥2 mm were almost six times more likely to die by one year than patients with no ST segment depression (odds ratio [OR] 5.7, 95% confidence interval [CI] 2.8 to 11.6). Other significant predictors of one-year mortality, in decreasing order of importance, were age, severe chronic obstructive pulmonary disease, previous MI, congestive heart failure, peripheral vascular disease, diabetes, previous percutaneous transluminal coronary angioplasty and cerebrovascular disease. The relative contribution of the different baseline predictors is depicted in Figure 2. ST segment status accounted for 35% of the model's predictive power, followed by age, which accounted for 17%. The c-statistic for the model was 0.82, indicating that the model had a good discriminating ability.

A predicted risk of death was calculated for each patient in the GUSTO-IIb population by using regression coefficients from the model developed using PARAGON-A data. The c-index for the validation model was 0.75, indicating that the model had a reasonably good ability to discriminate one-year mortality in an independent patient population.

The one-year mortality rates for patients with ST segment depression ≥2 mm were 13.4% and 14.1% for the PARAGON-A and GUSTO-IIb populations, respectively (Table 3). Further stratification showed that patients with ST segment depression ≥2 mm in more than one region had significantly higher mortality than did patients with ST segment depression ≥2 mm in only one region. In PARAGON-A, 54 patients (3%) had ST segment depression ≥2 mm in multiple regions. The mortality rate among these patients was 21.2%, compared with 8.5% among patients with ST segment depression ≥2 mm in only one region. Similarly, in the GUSTO-IIb study, 252 patients (4%) with ST segment depression ≥2 mm in multiple regions had a mortality rate of 20.2%, compared with 12.5% among patients with ST segment depression ≥2 mm in one region. When including the number of regions into the PARAGON-A multivariable model, patients with ST segment depression ≥2mm in multiple regions were almost 10 times more likely (OR 9.2, 95% CI 4.1 to 20.5) to die than patients with no ST segment depression.

The event rates among PARAGON-A patients with ECG confounders, according to the extent of ST segment depression, are presented in Table 4. Among patients with

Table 4. Outcomes Among Patients With Electrocardiographic Confounders ST segment Depression Categories: PARAGON-A Data

Outcome	No ST ↓ (n = 90)	ST ↓ 1 mm (n = 175)	ST ↓ ≥2 mm (n = 131)
(Re) MI 30 days	4.4	8.0	20.6
(Re) MI 6 months	7.1	9.4	23.6
Death 30 days	3.3	2.9	12.2
Death 6 months	5.6	6.4	19.2
Death 1 year	6.7	8.0	22.9
Death/MI 30 days	6.7	9.1	22.1
Death/MI 6 months	11.8	14.1	29.1

All rates are statistically significantly different at $p < 0.001$. Data are presented as percentages.
Abbreviations as in Table 3.

no ST segment depression and 1-mm ST segment depression, the presence of confounders did not significantly change the rates of adverse events. However, the combination of ST segment depression ≥2 mm and ECG confounders was indicative of maximal risk (22.9% vs. 13.4% one-year mortality rate for patients with ST segment depression ≥2 mm and no ECG confounders). When extending the PARAGON-A model to include patients with confounders, we found that the extent and distribution of ST segment status dominated the presence of confounders in predicting one-year mortality. Therefore, patients with ST segment depression ≥2 mm in more than one region have the worst outcomes, irrespective of the presence of confounders.

DISCUSSION

To the best of our knowledge, our study is the first to develop and validate a model that examines the prognostic significance of the magnitude and extent of ST segment depression in predicting one-year mortality. Among PARAGON-A patients with baseline ECG data and no confounders, 704 patients (44%) had 1-mm ST segment depression and 269 patients (17%) had ST segment depression ≥2 mm in two contiguous leads. Although missing baseline ECG data on 298 patients (13%) is a possible limitation, these patients did not differ significantly from study patients in terms of baseline characteristics and outcomes.

Comparison with previous studies. Quantitative assessment of the extent of ST segment depression appears to be a more sensitive marker for adverse events than dichotomous assessment of the presence or absence of ST segment depression. In a study to prospectively validate the Braunwald classification for unstable angina, Calvin et al. (9) found the presence of ST segment depression at baseline to be an independent predictor of recurrent MI and death (OR 3.79, 95% CI 1.65 to 8.69) (10). In the PURSUIT study, Boersma et al. (11) found investigator-determined ST segment depression >0.5 mm to be associated with increased 30-day mortality (OR 1.8, 95% CI 1.4 to 2.3). In our logistic regression model to predict one-year mortality using PARAGON-A data, patients with 1-mm ST segment depression in two contiguous leads were associated with approximately four times the risk (OR 3.6, 95% CI 1.9 to 7.1), and patients with ST segment depression ≥2 mm were associated with approximately six times the risk (OR 5.7, 95% CI 2.8 to 11.6) of patients with no ST segment depression. The extent of ST segment depression accounted for more than one-third of the model's predictive power. The model was tested on an independent patient population enrolled in the GUSTO-IIb trial and showed good discriminating ability (c-index = 0.75).

Most recently, Antman et al. (12) published a risk score to stratify patients with unstable angina/non-ST segment elevation MI . In both univariate and multivariate analyses, ST segment deviation was associated with an increased risk (multivariate OR 1.4, 95% CI 1.06 to 1.85) of mortality, (repeat) MI or severe, recurrent ischemia prompting revascularization in the short term (14 days). No attempt was made to quantify the extent of ST segment deviation. Our findings show that ST segment depression ≥2 mm in two contiguous leads may be a more effective risk stratifier for short- and long-term mortality, as demonstrated by the better discriminatory power of our model (c-statistic = 0.82 vs. 0.74).

Savonitto et al. (13), using data from the GUSTO-IIb study, examined the prognostic value of the admission ECG in acute coronary syndromes. The 30-day rate of death/MI was the highest for patients with a combination of ST segment elevation and depression (12.4%, 95% CI 10.9 to 14.0), and next highest for patients with ST segment depression (10.5%, 95% CI 9.6 to 11.5). After adjusting for baseline factors, ECG category was a highly significant predictor of 30-day outcomes.

Our study differs from that of Savonitto et al. (13) in several aspects. First, our focus was the non-ST segment elevation population, and we examined one-year mortality as opposed to shorter term death/MI outcomes. Second, Savonitto et al. (13) classified ST segment depression as >0.5 mm, whereas we examined the quantitative extent of ST segment depression, and as the data show, patients with ST segment depression ≥2 mm fare far worse than patients with less extensive ST segment depression. A third distinction relates to the source of ECG data used to classify patients. Although our study used ECG data analyzed systematically at a central ECG core laboratory, the previous study used investigator-reported data, which has the potential for site-related biases.

Impact of regions and confounders. There is no documentation in the published data on the impact of the distribution of ST segment depression (i.e., the number of regions affected by it) on adverse events. Although our finding—that the extent of ST segment depression (0 to ≥2 mm) is positively correlated with long-term adverse events—is consistent with previous findings (2), we found that further stratification of the ST segment depression ≥2-mm group into those with more than one region was a better prognostic indicator of one-year mortality.

Previous studies have generally excluded patients with confounding factors. As shown in our study, patients with left ventricular hypertrophy, complete bundle branch block and cardiac pacing are a substantial part of the population (17% in PARAGON-A and 12% in GUSTO-IIb). We have shown that the higher risk associated with the presence of ECG confounders is further accentuated by the extent of ST segment depression. In a multivariable setting, the extent and distribution of ST segment depression was the most important predictor of one-year mortality, irrespective of the presence of confounders.

Conclusions. These data provide new evidence supporting the powerful prognostic value of the baseline ECG and, in

particular, the magnitude and distribution of ST segment depression in predicting unfavorable events in both the short and long term. The extent of ST segment depression is an independent and important modulator of the risk of short- and long-term death and should be incorporated into early evaluations. Most ominous of all is the ≥2-mm ST segment depression sign. The high morbidity and mortality among these patients highlights the need for new strategies aimed at enhanced early triage and more aggressive therapies in this population.

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REFERENCES

1. Lee HS, Cross SJ, Rawles JM, Jennings KP. Patients with suspected myocardial infarction who present with ST depression. Lancet 1993; 342:1204–7.
2. Hyde TA, French JK, Wong C-K, et al. Four-year survival of patients with acute coronary syndromes without ST segment elevation and prognostic significance of 0.5-mm ST segment depression. Am J Cardiol 1999;84:379–85.
3. Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q-wave myocardial infarction: results of the TIMI III Registry ECG ancillary study. J Am Coll Cardiol 1997;30:133–40.
4. Areskog INM, Areskog N-H, Swahn E, et al. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. J Intern Med 1993;234:293–301.
5. The PARAGON Investigators. International, randomized, controlled trial of Lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Circulation 1998;97:2386–95.
6. GUSTO-IIb Investigators. The Global Use of Strategies To Open occluded coronary arteries: a comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775–82.
7. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York, NY: Wiley, 1989.
8. Iezzoni LI. Risk Adjustment for Measuring Health Care Outcomes. Ann Arbor, MI: Health Administration Press, 1994.
9. Calvin JE, Klein LW, VandenBerg BJ, et al. Risk stratification in unstable angina: prospective validation of the Braunwald classification. JAMA 1995;273:136–41.
10. Braunwald E. Unstable angina: a classification. Circulation 1989;80: 410–4.
11. Boersma E, Pieper KS, Steyeberg EW, et al., for the PURSUIT Investigators. Predictors of outcomes in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9,461 patients. Circulation 2000;101:2557–67.
12. Antman EM, Cohen M, Bernink PJLM, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision-making. JAMA 2000;284:835–42.
13. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707–13.