Relationship of ST elevation in lead aVR with angiographic findings and outcome in non–ST elevation acute coronary syndromes

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Background Limited data suggest that ST elevation (ST↑) in aVR is associated with higher mortality and more extensive coronary artery disease in the setting of non-ST↑ acute coronary syndromes (ACS).

Methods In the prospective Global Registry of Acute Coronary Events (GRACE) electrocardiographic substudy, the admission electrocardiograms were analyzed by a blinded core laboratory. We performed multivariable analysis to determine (1) the independent prognostic significance of ST↑ in aVR and (2) its association with significant (≥50% stenosis) left main or 3-vessel disease (LM/3-vd).

Results Among 5064 patients with non-ST↑ ACS, 4696 had no ST↑ in aVR, 292 (5.8%) had minor (0.5-1 mm) ST↑ in aVR, and 76 (1.5%) had major (>1 mm) ST↑ in aVR; their in-hospital mortality rates were 4.2%, 6.2%, and 7.9%, respectively (*P* for trend =.03). At 6 months follow-up, the cumulative mortality rates were 7.6%, 12.7%, and 18.3%, respectively (log-rank *P* for trend <.001). However, minor and major ST↑ in aVR were not independent predictors of in-hospital or 6-month death after adjusting for other validated prognosticators in the GRACE risk model. Of the 2416 patients without prior coronary bypass surgery who underwent cardiac catheterization, the prevalence of LM/3-vd was 26.1%, 36.2%, and 55.9% for the groups with no, minor, and major ST↑ in aVR, respectively (*P* for trend <.001). After adjusting for other clinical characteristics, major ST↑ in aVR remained an independent predictor of LM/3-vd (adjusted odds ratio, 2.68; 95% confidence interval, 1.29-5.58; *P* = .008).

Conclusion ST↑ in aVR is less prevalent than reported in previous smaller studies. Although it is associated with higher unadjusted in-hospital and 6-month mortality, it does not provide incremental prognostic value beyond comprehensive risk stratification using the validated GRACE risk model. However, ST↑ greater than 1 mm in aVR may be useful in the early identification of LM/3-vd in ACS patients with ST depression. (Am Heart J 2007;154:71-8.)

Patients with non–ST elevation (non-ST↑) acute coronary syndromes (ACS) comprise a heterogeneous group with a variable prognosis.[1] The admission electrocardiogram (ECG) plays a pivotal role in early risk stratification,[1,2] which is a critical step in the effective management of these patients. Studies have consistently demonstrated that even minor ST depression (≥0.5 mm) on the admission ECG is a powerful adverse prognosticator that warrants aggressive medical therapies and early invasive management.[3-7] Accordingly, current practice guidelines recognize ST depression as an important high-risk feature.[1] Several validated risk scores, derived from both clinical trial and registry populations, have also incorporated ST depression as an independent predictor of adverse outcome.[8-10]

Because lead aVR is considered to provide reciprocal information from the left lateral leads on the ECG, it is often ignored in clinical practice.[11] Several single-center studies have shown that compared to ST depression in other leads, ST↑ in aVR is a better predictor of adverse events in patients with non-ST↑ ACS.[12,13] Furthermore, it has been suggested that ST↑ in aVR is a useful

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Table I. Baseline characteristics according to ST↑ in lead aVR

	No ST↑ in aVR (n = 4696)	0.5-1 mm ST↑ in aVR (n = 292)	>1 mm ST↑ in aVR (n = 76)	*P* value for trend
Demographic characteristics				
Age, y*	66 (56,75)	69 (60,77)	70 (65,79)	<.001
Men (% of patients)	63.8	54.9	56.6	.003
Medical history (% of patients)				
Cigarette smoking (past or current)	57.2	54.2	49.3	.10
Hypertension	60.0	70.1	66.7	.001
Hyperlipidemia	49.6	44.3	50.0	.25
Diabetes	24.2	33.0	31.6	<.001
Myocardial infarction	33.3	33.7	35.5	.71
Heart failure	10.5	13.2	6.6	.83
Percutaneous coronary intervention	18.9	15.3	9.2	.01
Coronary artery bypass graft surgery	13.7	12.1	14.5	.69
Stroke/transient ischemic attack	8.1	8.1	13.3	.26
Peripheral artery disease	9.5	13.5	9.2	.15
Presenting characteristics				
Heart rate (beats/min)*	75 (64,88)	84, (70,100)	90 (77,100)	<.001
Systolic blood pressure (mm Hg)*	140 (123,160)	150 (130,170)	150 (121,175)	<.001
Diastolic blood pressure (mm Hg)*	80 (70,90)	80 (70,96)	83 (69,99)	.01
Killip class (% of patients)				<.001
I	83.8	75.3	64.9	
II	13.3	17.8	21.6	
III	2.5	6.6	9.5	
IV	0.4	0.4	4.1	
Cardiac arrest (% of patients)	1.0	1.0	2.6	.29
ST depression in other leads (% of patients)	40.7	95.9	100	<.001
Abnormal cardiac biomarker (% of patients)	38.7	38.0	52.1	.13
Creatinine (mg/dL)*	1.0 (0.9,1.2)	1.0 (0.9,1.3)	1.1 (0.9,1.4)	.01
GRACE risk score*	128 (104,154)	145 (127,174)	150 (135,179)	<.001

*Data presented as median (interquartile range).

indicator of left main or 3-vessel disease (LM/3-vd), thereby guiding the appropriate choice of initial antithrombotic therapies and the triage of these high-risk patients who may require urgent surgical revascularization.[14-16] However, the generalizability of these findings to larger and less selected patient cohorts across the broad spectrum of ACS has not been confirmed.

The Global Registry of Acute Coronary Events (GRACE) is a prospective, multinational, observational study that examines the epidemiology, treatment practices, and outcome of patients with the entire spectrum of ACS.[17] Using data from this registry, we aimed to determine (1) the incremental prognostic value of ST↑ in aVR beyond comprehensive risk assessment with the validated GRACE risk score and (2) its independent association with LM/3-vd on coronary angiography among patients without previous coronary bypass surgery.

Methods

Study design

Details of the objectives and methodology of GRACE have been published.[17,18] In brief, GRACE is an ongoing prospective registry in 13 countries designed to study representative ACS patient populations, irrespective of geographic locations.

To be eligible for recruitment into this registry, patients had to be at least 18 years old, be admitted for a presumptive diagnosis of ACS, with at least one of the following: ECG changes consistent with ACS, abnormal cardiac biomarkers, and/or documentation of coronary artery disease. The qualifying ACS must not have been precipitated by a serious comorbidity. Data on patient demographics, clinical characteristics, laboratory results, treatment, and outcome in hospital were collected on standardized case report forms. To minimize selection bias, study investigators enrolled consecutive eligible patients starting on the first day of each month until the site-specific monthly enrollment target is attained. Where required, the local institutional review board approved the study protocol.

Electrocardiogram substudy

Between March 1999 and January 2004, 39 sites in 11 countries participated in the ECG substudy and enrolled a total of 8202 patients. All admission ECG data were evaluated centrally at the ECG core laboratory at the Canadian Heart Research Centre, with blinding to clinical data and outcome. Previous studies had validated the accuracy of ECG interpretation by this core laboratory.[19] The 12-lead ECGs were recorded at the standard paper speed of 25 mm/s and calibration of 10 mm/mV. ST deviation was measured to the nearest 0.5 mm at 0.08 seconds after the J point in all leads.[3-5,7,15] Left ventricular hypertrophy was

Table II. In-hospital management and outcome

Management and outcome	Overall (n = 5064)	No ST↑ in aVR (n = 4696)	0.5-1 mm ST↑ in aVR (n = 292)	>1 mm ST↑ in aVR (n = 76)	*P* value for trend
Cardiac catheterization	55.9	56.0	54.8	53.9	.59
Percutaneous coronary intervention	28.5	28.7	25.2	30.3	.51
Coronary artery bypass graft surgery	4.5	4.3	6.5	4.0	.28
Any revascularization	32.5	32.6	31.1	34.7	.90
Death	4.4	4.2	6.2	7.9	.03
Myocardial (re)infarction	9.2	9.0	10.7	13.2	.12
Death/myocardial (re)infarction	12.2	12.0	14.1	18.4	.049
Heart failure/pulmonary edema	12.2	11.5	18.3	30.3	<.001
Cardiac arrest/ventricular fibrillation	3.5	3.2	5.8	9.3	.001

Values are percentages.

diagnosed by the Cornell or Sokolow-Lyon criteria. Based on current guidelines,[2] ST↑ myocardial infarction was defined as ST-segment elevation 1 mm or greater in 2 contiguous leads, irrespective of lead location (precordial or limb leads). ST↑ in aVR was not used to define ST↑ myocardial infarction. ST depression was considered to be present if ST-segment depression was 0.5 mm or greater in any lead (except aVR), since this has been previously shown to predict worse outcome.[3-5,7] The present analysis excluded patients with poor quality ECGs (n = 174), ventricular or paced rhythm (n = 128), or ST↑ myocardial infarction or left bundle branch block (n = 2836). Thus, 5064 patients with non-ST↑ ACS formed the study cohort.

GRACE risk models

To assess the independent prognostic significance of ST↑ in aVR, we adjusted for other known prognosticators in the GRACE risk models. The GRACE risk model for in-hospital mortality is composed of the following predictor variables on presentation: age, heart rate, systolic blood pressure, cardiac arrest, Killip class, creatinine, ST-segment deviation, and biomarker status.[8] It was derived using data from 11,389 patients in GRACE and was designed to predict in-hospital mortality(c-statistic = 0.83). It has also demonstrated excellent discrimination for both in-hospital (c-statistic = 0.83) and 1-year mortality (c-statistic = 0.79) in an external validation cohort.[20,21] The GRACE risk model for predicting postdischarge death at 6 months also included prior myocardial infarction and heart failure.[22]

Clinical outcome and angiographic data

Outcome data were collected on the case report form according to standardized definitions. In-hospital death included all-cause mortality. At approximately 6 months after admission, patient follow-up was conducted via telephone interview to ascertain vital status and recurrent cardiovascular events. Cardiac catheterization during index hospitalization was performed at the discretion of the treating physicians. Significant stenosis was defined as ≥50% narrowing in reference to the diameter of the adjacent normal segment of the coronary artery. Three-vessel disease was present if there were significant stenoses involving all 3 epicardial coronary arteries (or their main branches), namely the left anterior descending, left circumflex, and right coronary arteries. For this analysis, we excluded patients with previous coronary bypass surgery. Angiographic data were interpreted at the local site and recorded on the case report form.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges and categorical variables as frequencies or percentages. To examine trends across groups, Spearman and Mantel-Haenszel χ^2 tests were used for continuous and categorical data, respectively. We stratified a priori the study population into 3 groups: (1) no ST↑ in aVR; (2) minor ST↑ in aVR (0.5-1 mm); and (3) major ST↑ in aVR (>1 mm). To evaluate the independent association of ST↑ in aVR and in-hospital mortality, we used multivariable logistic regression to adjust for all the predictor variables of the GRACE risk score. We constructed a separate multivariable logistic regression model to predict the presence of LM/3-vd on coronary angiography by backward stepwise elimination (for $P > .05$) of all associated baseline characteristics on bivariable analysis ($P < .25$). Because preexisting angina was associated with more severe coronary artery disease in a prior study, this variable was also entered into the model.[23] Model discrimination and calibration were assessed by the c-statistic and the Hosmer-Lemeshow goodness-of-fit test, respectively.

Six-month follow-up data were available for 88.2% of hospital survivors. Patients lost to follow-up were censored at the time of hospital discharge. These patients did not differ from the remaining cohort in their GRACE risk score and prevalence of ST↑ in aVR. Survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. We performed Cox proportional hazards regression to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for death across the categories of ST↑ in aVR. Because previous myocardial infarction and heart failure were associated with postdischarge death in GRACE,[24] these factors (in addition to the components of the GRACE risk model for in-hospital mortality) were also considered in multivariable analysis. We used backward stepwise elimination ($P > .10$ for removal) to arrive at the parsimonious model. To confirm the robustness of our results, we conducted a series of sensitivity analyses by excluding patients with left ventricular hypertrophy or in-hospital revascularization, by using the composite

Table III. Multivariable analysis: predictors of in-hospital mortality

Predictors	Adjusted OR	95% CI	*P*
Age (per decade increase)	2.06	1.76-2.40	<.001
Heart rate (per 10 beats/min increase)	1.12	1.05-1.19	<.001
Systolic blood pressure (per 10 mm Hg increase)	0.87	0.83-0.92	<.001
Killip class			
I	Referent		
II	2.57	1.81-3.65	<.001
III	2.95	1.66-5.25	<.001
IV	8.73	3.00-25.4	<.001
Cardiac arrest on presentation	8.00	3.83-16.7	<.001
Creatinine (per 1 mg/dL increase)	1.28	1.12-1.46	<.001
Abnormal initial cardiac biomarker	1.79	1.29-2.47	<.001
ST-segment depression	1.74	1.23-2.46	<.002
ST↑ in aVR			
None	Referent		
0.5-1 mm	1.07	0.62-1.86	.81
>1 mm	0.95	0.34-2.62	.92

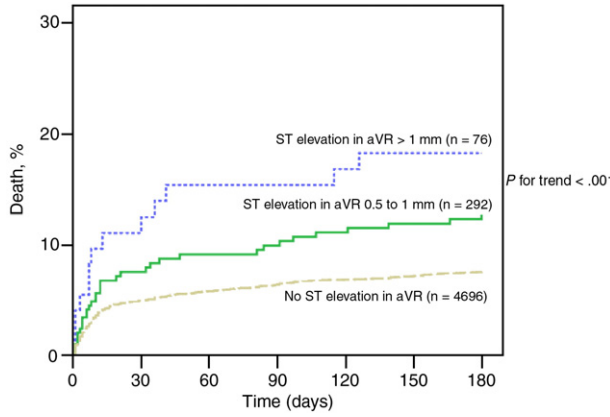
end point of death or myocardial (re)infarction, by considering the presence of any ST↑ in aVR (≥0.5 mm) as a dichotomous explanatory variable, and by categorizing ST↑ in aVR with different cutoffs (none vs 0.5 mm vs ≥1 mm). Data were processed and analyzed using SAS version 9.1 (SAS Institute, Cary, NC) and SPSS version 12.0 (SPSS Inc, Chicago, IL). Statistical significance was set at a 2-sided *P* value of less than .05.

Results

Of the 5064 patients with non-ST↑ ACS, 292 (5.8%) and 76 (1.5%) had 0.5 to 1 mm and greater than 1 mm of ST↑ in aVR, respectively. The baseline characteristics of the study population are presented in Table I. The presence of ST↑ in aVR was associated with advanced age, higher heart rate, worse Killip class, presence of ST depression in other leads, and higher GRACE risk score on presentation (all *P* for trend <.001).

Table II summarizes the in-hospital treatment and outcome of the study population. Overall, 223 patients (4.4%) died during index hospitalization. The in-hospital mortality rates were higher for patients with greater ST↑ in aVR (*P* for trend =.03). There was a higher rate of the composite end point of death or myocardial (re)infarction with increasing ST↑ in aVR (*P* for trend = .049). After adjusting for other prognosticators in the GRACE risk score, ST↑ in aVR was not an independent predictor of in-hospital mortality (Table III). The model c-statistic and Hosmer-Lemeshow *P* value were 0.85 and .99, respectively, indicating excellent model discrimination and calibration. Elimination of ST↑ in aVR from the multivariable model did not alter its discriminatory performance (c-statistic = 0.85). There was no significant interaction between ST↑ in aVR and ST depression in other leads (*P* = .99). The results were unchanged using the composite end point of in-hospital death or myocardial (re)infarction when any ST↑ in aVR 0.5 mm or greater was analyzed together as one group, or when patients with left ventricular hypertrophy (n = 189) were excluded.

Figure 1



Kaplan-Meier curves for mortality in relation to ST↑ in aVR.

At 6 months follow-up, the cumulative mortality rates were 7.6% for patients with no ST↑ in aVR, 12.7% for those with 0.5 to 1 mm ST↑ in aVR, and 18.3% for those with greater than 1 mm ST↑ in aVR (log-rank *P* for trend <.001). Figure 1 illustrates the Kaplan-Meier curves for death among these 3 patient groups. Compared with patients with no ST↑ in aVR, those with 0.5 to 1 mm ST↑ in aVR (HR, 1.71; 95% CI, 1.20-2.43; *P* = .003) and greater than 1 mm ST↑ in aVR (HR, 2.58; 95% CI, 1.48-4.48; *P* < .001) had a higher risk of death. Multivariable Cox regression analysis by stepwise backward elimination showed that all components of the GRACE risk score maintained an independent association with 6-month mortality (Table IV). In contrast, 0.5 to 1 mm and greater than 1 mm ST↑ in aVR were not independent predictors (*P* = .32 and 0.48, respectively) and were not retained in the final model (change in model −2 log likelihood = 1.50; *df* = 2; *P* = .47). The results were similar after excluding patients who underwent in-hospital revascularization, when patients with any ST↑ in aVR (≥0.5 mm) were combined into one group (*P* = .21) or when different cutoff points (none vs 0.5 mm vs ≥1 mm) were used.

During index hospitalization, 2416 (47.7%) patients without prior coronary bypass surgery underwent cardiac catheterization. The prevalence of LM/3-vd was

Table IV. Multivariable Cox regression: independent predictors of 6-month mortality*

Predictors	Adjusted HR	95% CI	*P*
Age (per decade increase)	1.84	1.65-2.05	<.001
Previous heart failure	1.41	1.07-1.85	.014
Heart rate (per 10 beats/min increase)	1.09	1.04-1.14	<.001
Systolic blood pressure (per 10 mm Hg increase)	0.90	0.87-0.94	<.001
Killip class			
I	Referent		
II	1.91	1.46-2.49	<.001
III	1.93	1.28-2.93	<.002
IV	6.38	3.20-12.7	<.001
Cardiac arrest on presentation	4.56	2.67-7.80	<.001
Creatinine (per 1 mg/dL increase)	1.26	1.17-1.36	<.001
Abnormal initial cardiac biomarker	1.59	1.27-2.00	<.001
ST-segment depression	1.64	1.30-2.29	<.001

*0.5-1 mm and >1 mm ST↑ in aVR were not independently associated with mortality (*P* = .32 and 0.48, respectively) and were removed from the final model by backward elimination.

Table V. Angiographic findings

% of patients*	Overall (N = 2416)	No ST↑ in aVR (n = 2252)	0.5-1 mm ST↑ in aVR (n = 130)	>1 mm ST↑ in aVR (n = 34)	*P* value for trend
LAD stenosis	59.6	59.2	66.2	61.8	.20
LCx stenosis	50.0	48.6	70.8	64.7	<.001
RCA stenosis	55.0	54.4	61.5	70.6	.02
LM coronary stenosis	5.4	5.1	9.2	14.7	.002
3-vd	24.0	23.3	32.3	44.1	<.001
LM/3-vd disease	27.0	26.1	36.2	55.9	<.001

LAD, Left anterior descending; *LCx*, left circumflex; *RCA*, right coronary artery.
*Not mutually exclusive.

significantly higher among patients with ST↑ in aVR (Table V). Table VI lists the independent predictors of LM/3-vd by multivariable analysis. The model demonstrates moderate discrimination for LM/3-vd (c-statistic= 0.669), which did not change substantially when ST↑ in aVR was not included in the model (c-statistic = 0.666). The Hosmer-Lemeshow *P* value was .31, suggesting adequate model fit with the data. When previous angina was entered into the model (*P* = .14), ST↑ greater than 1 mm in aVR remained an independent predictor of LM/3-vd (adjusted odds ratio [OR], 2.65; 95% CI, 1.28-5.50; *P* = .009).

Discussion

In this study of a wide spectrum of non-ST↑ ACS, ST↑ in aVR was associated with higher mortality during index hospitalization and at 6 months, but it did not confer incremental prognostic value beyond comprehensive risk assessment by the GRACE risk score. Nevertheless, the presence of major ST↑ in aVR (>1 mm) was an independent predictor of more extensive coronary artery disease.

Over the past decade, several risk scores have been developed to provide more objective and comprehensive risk assessment in ACS.[8-10] Although these risk scores were derived from diverse ACS patient populations, in keeping with prior ECG studies, ST depression has consistently emerged as a powerful independent predictor of unfavorable outcome. ST depression is also regarded as a high-risk feature in the management guidelines.[1] By comparison, lead aVR has frequently been neglected because it is believed to provide merely reciprocal information from the oppositely oriented left lateral leads.[11] However, more recent studies suggest that ST↑ in aVR may reflect transmural ischemia in the dominant basal septum, which results in a superior orientation of the ST-segment vector.[11,24,25]

Although an early invasive strategy has gained more widespread acceptance in the current management of non-ST↑ ACS, prompt identification of patients with LM/3-vd disease is still of clinical relevance. For instance, glycoprotein IIb/IIIa inhibitors may substitute for clopidogrel as the initial antiplatelet therapy in addition to aspirin, and coronary angiography may be expedited in anticipation of the potential need for surgical revascu-

Table V1. Multivariable analysis: predictors of left main or 3-vessel Disease

Predictors	Adjusted OR	95% CI	*P*
Age (per decade increase)	1.34	1.23-1.47	<.001
Male	1.71	1.37-2.13	<.001
Diabetes	1.37	1.10-1.72	.006
Previous myocardial infarction	1.55	1.25-1.93	<.001
Previous heart failure	1.63	1.08-2.44	.02
Peripheral artery disease	1.51	1.08-2.10	.016
Heart rate (per 10 beats/min increase)	1.06	1.01-1.11	.03
ST-segment depression	1.40	1.14-1.72	.001
ST ↑ in aVR			
None	Referent		
0.5-1 mm	1.22	0.81-1.84	.35
>1 mm	2.68	1.29-5.58	.008

larization in these patients. In an early study of 113 patients with rest angina, Gorgels et al[14] showed that ST ↑ in aVR in combination with ST depression in other leads was associated with LM/3-vd disease. In acute myocardial infarction, greater ST ↑ in aVR than in V1 may portend occlusion of the LM coronary artery.[23] Kosuge et al[15] studied 310 patients with non-ST ↑ ACS admitted to their coronary care unit and found that ST ↑ in aVR (≥0.5 mm) (present in 27% of their patients) and elevated troponin T were the only independent predictors of LM/3-vd. Nonetheless, patients with previous coronary artery bypass surgery were not excluded, which might have confounded the definition of true LM/3-vd. In another report by Kosuge et al,[13] ST ↑ in aVR (OR, 13.8; $P = .03$) and abnormal troponin T were the only independent predictors of death or myocardial infarction at 90 day. However, the small number of events (2 deaths and 11 myocardial infarctions) might have precluded full adjustment of other established prognosticators and limited the power of the study, as reflected by the wide CI of the corresponding OR (1.4-101). Finally, Barrabes et al[12] analyzed the initial ECG of 775 consecutive patients with non-ST ↑ acute myocardial infarction admitted to their institution over a 15-year period. The in-hospital mortality rates were 1.3%, 8.6%, and 19.4% for patients without ST ↑ in aVR (n = 525 68%), with 0.5 to 1 mm (n = 116, 15%), and with ≥1 mm or greater ST ↑ (n = 134, 17%) in aVR, respectively ($P < .001$). After adjusting for various baseline characteristics, ST ↑ in aVR (adjusted OR, 4.24 and 6.61 for 0.5-1 mm and ≥1 mm ST ↑ in aVR, respectively)—but not ST depression in other leads—was independently associated with in-hospital death. In addition, there was a higher prevalence of LM/3-vd among patients with ST ↑ in aVR. These investigators suggested future studies to confirm their results in larger patient populations.

The present study extends the previous work and offers new insights into the clinical use of lead aVR in the management of ACS. To the best of our knowledge, this is the largest study to date of unselected non-ST ↑ ACS patients that examined the prognostic importance of ST ↑ in aVR and its relationship to the extent of coronary artery disease. Adjustment of predictor variables in the GRACE risk model, which has been well validated in other patient cohorts,[8,26,27] allows more rigorous assessment of the independent prognostic value of ST ↑ in aVR. The use of a blinded core ECG laboratory should have minimized any ascertainment bias. Moreover, the inclusion of patients with a wide range of non-ST ↑ ACS from multiple centers in GRACE enhances the generalizability of our results. We found that ST ↑ in aVR was associated with other unfavorable clinical characteristics and higher unadjusted in-hospital and 6-month mortality. However, after adjusting for other validated prognosticators in the GRACE risk score, ST ↑ in aVR did not retain any independent association with adverse outcome. Although inadequate power could possibly account for this negative finding, the CIs are less consistent with the several-fold increase in mortality reported in previous smaller studies.[12,13] Furthermore, compared with ST ↑ in aVR, ST depression in other leads was an independent and stronger predictor of death. The excellent model discrimination and calibration lend further support to the validity of these findings.

In accordance with the results of previous studies,[5,6] we found that ST depression was associated with more extensive coronary artery disease. Mathew et al[21] reported that clinical risk stratification correlated with the angiographic extent of coronary artery disease in 795 patients with unstable angina, although the additive predictive value of various clinical factors alone or in combination was not formally assessed. The present study is the first to show that both ST depression and major ST ↑ in aVR (>1 mm) are independent predictors of LM/3-vd in a multivariable model adjusting for other associated clinical characteristics.[23,27] Thus, in addition to ST depression in other leads, greater than 1 mm ST ↑ in aVR may be a simple marker for severe coronary artery disease in patients with non-ST ↑ ACS.

Several study limitations are noteworthy. Although GRACE aimed to enroll consecutive and relatively unselected patients from multiple centers, selection bias could not be ruled out, and our results may also not be generalizable to patients who do not fulfill the registry inclusion criteria. Vital status at 6 months was not available for 11.3% of the study population. Although these patients did not differ from the remaining cohort in their GRACE risk score and prevalence of ST ↑ in aVR, we could not verify the assumption of noninformative censoring in our survival analysis. At the discretion of the treating physician, cardiac catheterization was not

performed in all study patients. However, the rates were similar irrespective of the presence of ST ↑ in aVR. Although unlikely, electrocardiographic findings might have influenced the site interpretation of angiographic data, which were not adjudicated in a blinded core laboratory. Because we only evaluated the admission ECGs, which might not have captured the dynamic ST-segment changes, the prognostic impact of ST ↑ in aVR could be underestimated. Finally, although we found that ST ↑ in aVR greater than 1 mm was a significant predictor of LM/3-vd in a multivariable model, it was a relatively uncommon (1.5%) finding. Its clinical use may be limited (with minimal improvement in model discrimination) and should be better defined in future prospective studies.

In conclusion, ST depression is an independent and stronger predictor of adverse outcome than ST ↑ in aVR across the broad spectrum of non-ST ↑ ACS. Because ST ↑ in aVR does not yield additional prognostic information beyond comprehensive risk assessment, its routine incorporation into the validated GRACE risk model does not appear warranted. However, the presence of severe ST ↑ in aVR may facilitate the early identification and triage of patients with LM/3-vd in the setting of ACS.

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Trimetazidine added to combined hemodynamic antianginal therapy in patients with type 2 diabetes: a randomized crossover trial

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Background In nondiabetic patients with stable angina, combined treatment with hemodynamic agents and trimetazidine is well-tolerated and effective in controlling ischemia. This study aims to evaluate the antiischemic and metabolic effects of trimetazidine in patients with type 2 diabetes mellitus, not eligible for revascularization, who remained symptomatic despite the use of at least 2 antianginal agents.

Methods A randomized, double-blind, crossover clinical trial was used. Ten patients were randomized to receive trimetazidine (20 mg, 3 times a day) or placebo for 6-week periods. At baseline and at the end of each 6-week intervention period, clinical and biochemical evaluations, exercise testing, 24-hour ambulatory blood pressure, and Holter monitoring were performed.

Results During trimetazidine therapy, patients had significant improvement on angina functional class ($P < .05$), with decrease in the number of weekly angina episodes (1.5 ± 0.8 vs 0.4 ± 0.7, $P < .01$), and in sublingual nitrate doses (1.4 ± 0.7 mg vs 0.1 ± 0.3 mg, $P < .001$). Time to 1-mm ST-segment depression during exercise test was increased after trimetazidine use (229 ± 126 seconds at baseline, 276 ± 101 seconds after placebo, and 348 ± 145 seconds after trimetazidine, $P < .001$). No differences were observed between treatment periods on mean 24-hour blood pressure, heart rate, and rate-pressure product evaluated concomitantly with ambulatory blood pressure and Holter monitoring. Glycemic and lipid profiles were similar after trimetazidine and placebo use.

Conclusions In patients with diabetes who remain symptomatic, the addition of trimetazidine improves symptoms and exercise responses without hemodynamic or metabolic changes. The present data suggest that trimetazidine may be an effective adjunct therapy for these patients, but further investigation is needed to confirm these findings. (Am Heart J 2007;154:78.e1-78.e7.)