Short- and Long-Term Prognostic Significance of ST-Segment Elevation in Lead aVR in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

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We sought to evaluate the prognostic significance of ST-segment elevation (STE) in lead aVR in unselected patients with non-STE acute coronary syndrome (NSTE-ACS). We enrolled 1,042 consecutive patients with NSTE-ACS. Patients were divided into 5 groups according to the following electrocardiographic (ECG) patterns on admission: (1) normal electrocardiogram or no significant ST-T changes, (2) inverted T waves, (3) isolated ST deviation (ST depression [STD] without STE in lead aVR or transient STE), (4) STD plus STE in lead aVR, and (5) ECG confounders (pacing, right or left bundle branch block). The main angiographic end point was left main coronary artery (LM) disease as the culprit artery. Clinical end points were in-hospital and 1-year cardiovascular death defined as the composite of cardiac death, fatal stroke, and fatal bleeding. Prevalence of STD plus STE in lead aVR was 13.4%. Rates of culprit LM disease and in-hospital cardiovascular death were 8.1% and 3.8%, respectively. On multivariable analysis, patients with STD plus STE in lead aVR (group 4) showed an increased risk of culprit LM disease (odds ratio 4.72, 95% confidence interval [CI] 2.31 to 9.64, p <0.001) and in-hospital cardiovascular mortality (odds ratio 5.58, 95% CI 2.35 to 13.24, p <0.001) compared to patients without any ST deviation (pooled groups 1, 2, and 5), whereas patients with isolated ST deviation (group 3) did not. At 1-year follow-up 127 patients (12.2%) died from cardiovascular causes. On multivariable analysis, STD plus STE in lead aVR was a stronger independent predictor of cardiovascular death (hazard ratio 2.29, 95% CI 1.44 to 3.64, p <0.001) than isolated ST deviation (hazard ratio 1.52, 95% CI 0.98 to 2.36, p = 0.06). In conclusion, STD plus STE in lead aVR is associated with high-risk coronary lesions and predicts in-hospital and 1-year cardiovascular deaths in patients with NSTE-ACS. Therefore, this promptly available ECG pattern could be useful to improve risk stratification and management of patients with NSTE-ACS. **(Am J Cardiol 2011;108:21–28)**

In recent years, it has been suggested that evaluation of lead aVR on standard electrocardiogram may improve risk stratification in patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) because STE in lead aVR has been associated with a higher rate of left main coronary artery (LM)/3-vessel disease[1,2] and worse prognosis.[3,4] However, these findings have been only partly confirmed in a recent large electrocardiographic (ECG) substudy of the Global Registry of Acute Coronary Events (GRACE).[5] Indeed, STE in lead aVR was a marker of LM/3-vessel disease (even if data on the culprit lesion were not reported), but it was not independently associated with in-hospital and 6-month mortality. However, the lower prevalence of STE in lead aVR compared to previous studies[3,4] (1.5% vs >10%, respectively) may have partly influenced the results of multivariable analysis. Moreover, data regarding longer follow-up have not yet been reported. This topic is relevant because it is well known that patients with NSTE-ACS carry a persistent risk of cardiovascular mortality after discharge. Thus, the role of lead aVR in patients with NSTE-ACS still appears uncertain. Accordingly, the main objectives of the present study were to investigate (1) the predictive value of STE in lead aVR associated with ST depression (STD) in other leads (STD plus STE in lead aVR) for identifying LM disease as the culprit lesion and (2) the role of this ECG pattern in predicting in-hospital and 1-year cardiovascular death.

Methods

Patients admitted to the emergency department and/or to the coronary care unit of St. Orsola/Malpighi Hospital, Bologna University from January 1, 2006 through May 31, 2008 and receiving the initial diagnosis of NSTE-ACS were screened. Inclusion criteria were chest pain within 24 hours plus 1 of the following: (1) STD ≥0.05 mV in any lead, (2) transient (<20 minutes) significant STE in 2 contiguous leads, (3) inverted T waves ≥0.1 mV, (4)

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positive cardiac biomarkers, and (5) documentation of coronary artery disease.

Of 1,372 screened patients, 75 (5%) had symptom onset >24 hours, 73 (5%) had persistent STE or new-onset left bundle branch block, 45 (3%) had atypical chest pain without signs of coronary artery disease, and 81 (6%) had increased troponin associated with other clinical conditions and without overt signs of myocardial ischemia[6] (35 patients had acute heart failure, 24 tachyarrhythmia, 8 stroke, 8 sepsis, 2 major bleeding, 2 pulmonary embolism, and 2 metastatic malignancy). Twenty-six patients (2%) had other miscellaneous diagnoses, and 30 patients (2%) lacked the qualifying electrocardiogram. Thus, the final cohort of this study included 1,042 patients.

Patients' files referring to the qualifying episode were carefully reviewed by expert investigators. Demographic data, clinical history, risk factors for coronary artery disease, physical examination and laboratory findings, medications, and cardiac procedures were collected. The following in-hospital adverse events were also recorded: overall mortality, cardiovascular death, recurrence of myocardial infarction (MI), stroke, and bleedings. Events were adjudicated independently by 2 physicians and disagreements were resolved by consensus.

Admission electrocardiogram was collected separately and assessed by investigators blinded to clinical data, angiographic features, and outcome. The 12-lead electrocardiogram was recorded at a standard paper speed of 25 mm/s and calibration of 10 mm/mV. Standard criteria were used for the diagnosis of right bundle branch block and left bundle branch block. ST deviation was measured to the nearest 0.05 mV at 80 and 20 ms after the J point for STD and STE, respectively. STD was considered present if it was ≥0.05 mV in any lead. STE was considered present if it was ≥0.1 mV in 2 contiguous leads. Inverted T waves were considered present if the T wave was biphasic or negative and ≥0.1 mV in 2 contiguous leads. STE in lead aVR ≥0.1 mV was considered significant. Lead aVR was not used to define STD or STE. In patients with ECG confounders (right bundle branch block, left bundle branch block, or ventricular paced rhythm), ST deviation was not measured.

Angiographic data were available for all patients who underwent in-hospital coronary catheterization. All angiograms were independently reviewed by 2 experienced investigators who were blinded to all data. Controversies were resolved by consensus. Number of diseased vessels, culprit lesion, Thrombolysis In Myocardial Infarction flow grade, presence of endoluminal thrombi, and signs of plaque rupture were assessed. Stenosis ≥50% in the lumen of the LM or ≥70% in ≥1 other major epicardial vessel or main branches was considered significant. Culprit artery was defined as the most severe stenosis, presence of Thrombolysis In Myocardial Infarction grade <3 flow, or angiographic signs of endoluminal thrombi and/or plaque rupture.

The main angiographic end point was LM disease as the culprit artery. The study also assessed the association between STE in lead aVR and overall LM or LM/3-vessel disease.

The clinical study end points were cardiovascular death (i.e., composite of cardiac death, fatal stroke, and fatal bleeding) during the index hospitalization and at 1-year follow up. Cardiac death was defined as death from cardiac cause, sudden death, or any death without another known cause. In-hospital recurrence of MI was defined as recurrence of typical clinical symptoms and new ECG changes with an increase of creatine kinase-MB ≥50% of the previous level. Stroke was defined as sudden onset of a focal neurologic deficit lasting >24 hours. Major bleedings were defined as bleeding requiring transfusion or surgery, decrease in hemoglobin of >5 g/dl, and intracranial hemorrhage. Minor bleedings were defined as local hematoma and any other clinically relevant bleeding that did not meet criteria for severity.

Out-of-hospital data concerning vital status of patients and cause of death were obtained by telephone interviews or independently from the Emilia-Romagna Regional Health Agency through analysis of hospital discharge records and municipal civil registries, thus relying on the treating physicians' diagnoses. One-year follow-up was available for 1,024 patients (98.3%).

Categorical data are expressed as proportions and continuous variables reported as medians and interquartile ranges (twenty-fifth to seventy-fifth percentiles). Patients were divided into 5 groups according to the following ECG patterns: (1) normal electrocardiogram or no significant ST-T change, (2) inverted T waves, (3) isolated ST deviation (i.e., STD without STE in lead aVR or transient STE), (4) STD plus STE in lead aVR, and (5) ECG confounders. For comparisons among groups, Kruskal–Wallis test was used for continuous variables and chi-square test for categorical variables. Multivariable logistic regression analysis was used to identify predictors of LM or LM/3-vessel disease and in-hospital cardiovascular death. The following variables were selected: age, gender, diabetes, smoking status, hypertension, previous stroke, previous MI, previous coronary bypass, previous percutaneous coronary intervention, peripheral artery disease, systolic blood pressure and heart rate on admission, Killip class, cardiac arrest, troponin level, atrial fibrillation on admission, creatinine, and ECG patterns. Three multivariable models were constructed including ECG variables as follows: model 1, any ST-segment deviation (pooled groups 3 and 4) versus no ST-segment deviation (pooled groups 1, 2, and 5); model 2, isolated ST deviation (group 3) or STD plus STE in lead aVR (group 4) versus no ST deviation (pooled groups 1, 2, and 5); model 3, isolated ST deviation (group 3) or STD plus STE in lead aVR (group 4) versus no ST deviation (pooled groups 1 and 2); patients belonging to the fifth group were excluded. The discriminative power of the models was assessed by the mean of the area under the receiver operating characteristic curve (c-statistic).

Kaplan–Meier method was used to analyze the occurrence of events during follow-up and ECG patterns were compared by log-rank Cox-Mantel test. Patients were censored at the time of the last contact.

Multivariable Cox regression analysis was performed to identify predictors of 1-year cardiovascular death. Proportional hazard assumption was checked by "log-minus-log" plotting. To adjust for possible confounding factors, all described variables plus bypass during the index hospitalization were included in multivariable models. A p value <0.05 in 2-tailed tests was considered statistically signifi-

Table 1
Baseline clinical and laboratory findings and in-hospital management

Variable	Normal Electrocardiogram or No Significant ST-T Changes (pattern 1) (n = 294)	Inverted T Waves (pattern 2) (n = 172)	Isolated ST Deviation (pattern 3) (n = 280)	STD + STE in Lead aVR (pattern 4) (n = 140)	ECG Confounders (pattern 5) (n = 156)	p Value
Age (years)	73 (63–79)	76 (66–82)	75 (65–81)	76 (70–84)	81 (74–85)	<0.001
Men	190 (65%)	106 (62%)	190 (68%)	87 (62%)	96 (62%)	0.58
Previous myocardial infarction	103 (35%)	56 (33%)	107 (38%)	45 (32%)	91 (58%)	<0.001
Previous percutaneous coronary intervention	78 (27%)	32 (19%)	67 (24%)	27 (19%)	41 (26%)	0.21
Previous coronary bypass	24 (8%)	12 (7%)	26 (9%)	18 (13%)	22 (14%)	0.12
Previous stroke	25 (9%)	16 (9%)	30 (11%)	17 (12%)	25 (16%)	0.15
Peripheral artery disease	52 (18%)	21 (12%)	55 (20%)	43 (31%)	39 (25%)	0.001
Diabetes mellitus	75 (26%)	29 (17%)	84 (30%)	30 (21%)	46 (30%)	0.02
Hypercholesterolemia*	182 (62%)	98 (57%)	154 (55%)	70 (50%)	87 (56%)	0.19
Hypertension†	222 (76%)	137 (80%)	223 (80%)	113 (81%)	136 (87%)	0.07
Smoker	145 (49%)	65 (38%)	132 (47%)	55 (39%)	56 (36%)	0.01
Presenting characteristics						
Systolic blood pressure (mm Hg)	144 (130–160)	140 (125–160)	140 (125–160)	140 (120–160)	140 (125–170)	0.07
Heart rate (beats/min)	77 (63–90)	77 (65–90)	81 (68–99)	90 (79–109)	87 (73–107)	<0.001
Cardiac arrest	2 (1%)	0	4 (1%)	3 (2%)	1 (1%)	0.31
Atrial fibrillation	25 (9%)	12 (7%)	28 (10%)	25 (18%)	23 (15%)	0.007
Killip class						<0.001
I	237 (81%)	121 (70%)	192 (69%)	82 (59%)	85 (55%)	
II	29 (10%)	31 (18%)	47 (17%)	24 (17%)	41 (26%)	
III	26 (9%)	19 (11%)	39 (14%)	29 (21%)	30 (19%)	
IV	2 (1%)	1 (1%)	2 (1%)	5 (4%)	0	
Laboratory findings						
Troponin T (ng/ml)	0.16 (0.06–0.36)	0.13 (0.05–0.34)	0.15 (0.06–0.51)	0.38 (0.14–1.19)	0.17 (0.07–0.48)	<0.001
Peak creatine kinase-MB (U/L)	15 (1–46)	1 (1–32)	21 (1–51)	42 (1–96)	22 (1–61)	<0.001
Creatinine (mg/dl)	1.2 (1.0–1.4)	1.2 (0.9–1.5)	1.2 (1.0–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.7)	<0.001
GRACE risk score (25th to 75th)	123 (98–146)	132 (109–158)	163 (141–191)	181 (159–210)	155 (135–175)	<0.001
Medical treatment within 24 hours						
Aspirin	269 (92%)	151 (88%)	255 (91%)	121 (86%)	138 (89%)	0.39
Thienopyridine						0.009
Clopidogrel	192 (65%)	106 (62%)	170 (61%)	74 (53%)	73 (47%)	
Ticlopidine	23 (8%)	14 (8%)	18 (6%)	13 (9%)	12 (8%)	
β Blockers	246 (84%)	147 (86%)	234 (84%)	113 (81%)	116 (74%)	0.06
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	219 (75%)	130 (76%)	204 (73%)	91 (65%)	113 (72%)	0.25
Unfractionated heparin/low-molecular-weight heparin	256 (87%)	149 (87%)	241 (86%)	117 (84%)	121 (78%)	0.075
Glycoprotein IIb/IIIa inhibitors	111 (38%)	54 (31%)	96 (34%)	50 (36%)	34 (22%)	0.013
Invasive management‡	221 (75%)	123 (72%)	192 (69%)	103 (74%)	87 (56%)	0.001
Coronary angiography	237 (81%)	129 (75%)	210 (75%)	104 (74%)	91 (58%)	<0.001
Percutaneous coronary intervention	156 (66%)	88 (68%)	153 (73%)	71 (68%)	59 (65%)	0.53
Coronary bypass	12 (5%)	6 (5%)	17 (8%)	19 (18%)	4 (4%)	<0.001

* Patients taking lifestyle-modification or drug therapy for treatment of known hypercholesterolemia or total cholesterol level ≥200 mg/dl or low-density lipoprotein level ≥130 mg/dl on admission.
† Patients taking lifestyle-modification or drug therapy for treatment of known hypertension.
‡ Patients undergoing diagnostic catheterization without additional risk-stratification procedures.

cant. All analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, Illinois).

Results

Baseline clinical and laboratory findings and in-hospital management are listed in Table 1. The median (interquartile range) age of the study population was 76 years (67 to 83), and 669 patients (64%) were men. Overall, 889 patients (85%) had NSTEMI and 153 (15%) unstable angina. Prevalences of study ECG patterns were (1) 28% for normal or no significant ST-T changes (normal electrocardiogram, n = 105; no significant ST-T changes, n = 189), (2) 17% for inverted T waves (n = 172), (3) 27% for isolated ST deviation (isolated STD, n = 248; transient STE, n = 38), (4) 13% for STD plus STE in lead aVR (n = 140), and (5) 15% for ECG confounders (right bundle branch block, n = 61; left bundle branch block, n = 73; pacing, n = 22). As presented in Table 1, patients with STD plus STE in lead aVR were more likely to have peripheral artery disease, atrial fibrillation, higher heart rate, more

Table 2
Rate of high-risk coronary lesions and distribution of culprit artery in patients undergoing coronary angiography*

Variable	Normal Electrocardiogram or No Significant ST-T Changes (pattern 1) (n = 220)	Inverted T Waves (pattern 2) (n = 123)	Isolated ST Deviation (pattern 3) (n = 188)	STD + STE in Lead aVR (pattern 4) (n = 92)	ECG Confounders (pattern 5) (n = 78)	p Value
Left main coronary artery disease	11 (5%)	5 (4%)	17 (9%)	27 (29%)	10 (13%)	<0.001
3-Vessel disease	27 (12%)	26 (21%)	45 (24%)	40 (44%)	16 (21%)	<0.001
Left main coronary artery/3-vessel disease	34 (16%)	27 (22%)	53 (28%)	52 (57%)	21 (27%)	<0.001
Culprit coronary artery						<0.001
0	42 (19%)	20 (16%)	21 (11%)	3 (3%)	10 (13%)	
Left anterior descending	63 (29%)	59 (48%)	66 (35%)	28 (30%)	28 (36%)	
Left circumflex	30 (14%)	5 (4%)	33 (18%)	9 (10%)	8 (10%)	
Right	41 (19%)	21 (17%)	28 (15%)	14 (15%)	12 (15%)	
Diagonal branches	16 (7%)	6 (5%)	9 (5%)	2 (2%)	7 (9%)	
Obtuse marginal branches	19 (9%)	8 (7%)	20 (11%)	12 (13%)	4 (5%)	
Left main	9 (4%)	4 (3%)	11 (6%)	24 (26%)	9 (12%)	

* Patients with previous coronary bypass excluded.

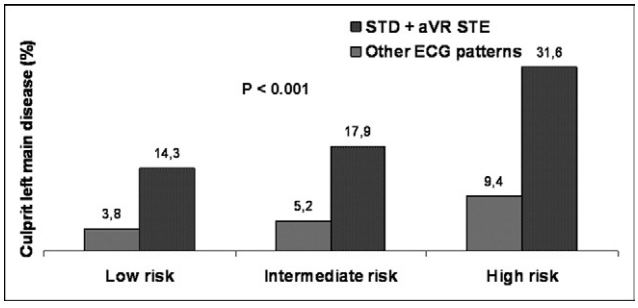

Figure 1. Rate of disease in culprit left main coronary artery in patients with low, intermediate, and high GRACE risk score according to presence/absence of ST elevation in lead aVR associated with ST depression.

advanced Killip class, positive cardiac biomarkers, and higher GRACE risk score[7] on admission than other groups. In contrast, patients with ECG confounders were older, more likely to have previous MI, but less likely to receive clopidogrel treatment and undergo coronary angiography compared to the remaining study population.

Overall, 771 patients (74%) underwent coronary angiography before discharge. Prevalences of LM disease, LM/3-vessel disease, and distribution of the culprit artery in the study groups are listed in Table 2. Patients with STD plus STE in lead aVR showed the highest rate of LM or LM/3-vessel disease and were treated more often with coronary bypass. As presented in Figure 1, for each GRACE risk score tertile, patients with STD plus STE in lead aVR had a higher rate of culprit LM disease compared to patients with no STD plus STE in lead aVR.

On multivariable analysis (Table 3), model 1 showed that patients with any ST deviation had an increased risk of culprit LM disease compared to patients without ST deviation. Models 2 and 3 showed that in patients with ST deviation, only those with STD plus STE in lead aVR had an increased risk of culprit LM disease, whereas those with isolated ST deviation did not. STD plus STE in lead aVR was also independently associated with an increased risk of overall LM disease (adjusted odds ratio [OR] 3.82, 95% confidence interval [CI] 2.04 to 7.17, p <0.001) and LM/3-vessel disease (adjusted OR 4.90, 95% CI 2.89 to 8.32, p <0.001).

During hospitalization, 45 patients (4.3%) died with 40 (3.8%) having a cardiovascular death (cardiac death, n = 37; fatal stroke, n = 1; fatal bleeding, n = 2). Of patients who underwent coronary angiography, in-hospital cardiovascular mortality rate was higher in subjects whose culprit vessel was the LM (14.0% vs 1.3%, p <0.001) or disclosed LM/3-vessel disease (6.3% vs 0.5%, p <0.001). As presented in Figure 2, patients with STD plus STE in lead aVR had a significantly higher rate of in-hospital cardiovascular death compared to patients with no STD plus STE in lead aVR in the intermediate and high GRACE risk score groups. On multivariable analysis (Table 4), patients with any ST deviation had an increased risk of in-hospital cardiovascular death compared to patients without ST deviation (model 1). However, in patients with ST deviation, only those with STD plus STE in lead aVR had an increased risk of cardiovascular death, whereas those with isolated ST deviation did not.

During 1-year follow-up 160 patients (15.4%) died with 127 (12.2%) having a cardiovascular death (cardiac death, n = 120; fatal stroke, n = 5; fatal bleeding, n = 2). As shown in Figure 3, patients with isolated ST deviation, STD plus STE in lead aVR, or ECG confounders had a higher risk of cardiovascular death at 1 year compared to patients who had normal electrocardiogram or no significant ST-T changes on admission. On multivariable analysis (Table 5), model 1 showed that patients with any ST deviation had an increased risk of 1-year cardiovascular death compared to patients without ST deviation. Model 2 showed that in patients with ST deviation, those with STD plus STE in lead aVR had an increased risk of cardiovascular death compared to patients without any ST deviation, whereas those with isolated ST deviation did not. When patients with ECG confounders were excluded (model 3), STD plus STE in lead aVR and isolated ST deviation were independently associated with the end point. STD plus STE in lead aVR was still associated with 1-year cardiovascular mortality even after adjustment for left ventricle ejection fraction

Table 3
Independent predictors of culprit left main coronary artery disease in multivariable logistic regression analysis*

Variable	Model 1		Model 2		Model 3†	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, each incremental year	1.04 (1.00–1.07)	0.027	1.03 (1.00–1.06)	0.041	1.03 (0.99–1.06)	0.14
Male gender	2.28 (1.15–4.53)	0.019	2.25 (1.11–4.58)	0.024	1.84 (0.86–3.93)	0.12
ST deviation	2.11 (1.17–3.80)	0.004	not included	—	not included	—
Electrocardiographic patterns	not included	—		<0.001		<0.001
No ST deviation	—	—	reference		reference	
Isolated ST deviation	—	—	1.11 (0.52–2.38)	0.79	1.46 (0.63–3.40)	0.37
ST depression + ST elevation in lead aVR	—	—	4.72 (2.31–9.64)	<0.001	5.94 (2.69–13.28)	<0.001
c-Statistic	0.760		0.787		0.792	

* Patients with previous coronary bypass excluded.
† Patients with electrocardiographic confounder excluded.

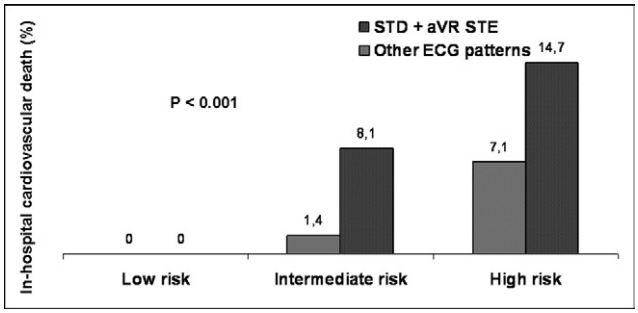

Figure 2. Rate of in-hospital cardiovascular death in patients with low, intermediate, and high GRACE risk score according to presence/absence of ST elevation in lead aVR associated with ST depression.

(available in 991 patients, hazard ratio 2.33, 95% CI 1.47 to 3.68, p = 0.001).

After adjustment for variables included in the in-hospital GRACE risk score,[7] the prognostic value of STD plus STE in lead aVR for prediction of in-hospital and 1-year mortalities, although attenuated, was maintained (OR 2.98, 95% CI 1.23 to 7.25, p = 0.016; hazard ratio 1.63, 95% CI 1.01 to 2.64, p = 0.046). However, we cannot exclude colinearity as an explanation for this finding given the correlation between ST deviation and STD plus STE in lead aVR (r = 0.50, p <0.001).

ECG confounder pattern was not independently associated with 1-year cardiovascular death (hazard ratio 1.48, 95% CI 0.78 to 2.82, p = 0.78).

Discussion

The present study shows that STD plus STE in lead aVR is independently associated with high-risk coronary lesions, in particular culprit LM disease, in patients with NSTE-ACS. Moreover, this ECG pattern predicts in-hospital and 1-year cardiovascular deaths. Therefore, the present findings suggest that evaluation of STE in lead aVR on admission electrocardiogram may be useful to improve risk stratification and management of patients with NSTE-ACS.

It is well known that electrocardiography plays an important role in prognostic stratification and management of patients with NSTE-ACS.[8,9] In particular, STD has been consistently associated with poorer outcome compared to normal electrocardiogram.[10–15] However, given the heterogeneity in pathophysiological mechanisms and amount of jeopardized myocardium, many efforts have been continuously conducted to improve risk stratification based on ECG findings. Thus far, the role of magnitude[16–21] and distribution[22] of STD is less established and contemporary risk scores derived from clinical trials[23] and population-based studies[7] have included STD as a dichotomous variable.

To date few studies with conflicting data have evaluated the prognostic role of lead aVR in patients with NSTE-ACS. Barrabés et al[3] investigated the role of lead aVR in 775 consecutive patients with a first episode of NSTEMI recruited during a 15-year period. Prevalences in the study population of minor (0.05 to 0.1 mV) and major (>0.1 mV) STEs in lead aVR were 15% and 17%, respectively. The investigators found that patients with minor or major STE in lead aVR showed a higher prevalence of LM/3-vessel disease and had an increased risk of in-hospital death (adjusted ORs 4.2 and 6.6, respectively) compared to patients without STE in lead aVR. More recently, Kosuge et al[2,4] showed that patients with STE (≥0.05 mV) in lead aVR (prevalence 27%) had an increased risk of LM/3-vessel disease and death or reinfarction at 90 days (adjusted OR 13.8, 95% CI 1.43 to 100.9, p = 0.03) in approximately 300 patients with NSTE-ACS. Conversely, Yan et al[5] showed that STE in lead aVR >1 mm independently predicted LM/3-vessel disease in 5,064 patients with NSTE-ACS included in an ECG substudy of GRACE. However, STE in lead aVR >1 mm was not an independent predictor of in-hospital and 6-month mortalities after adjustment by GRACE risk score.

Compared to previous studies, this study presents important distinctive features that further define the role of lead aVR in NSTE-ACS. (1) We enrolled a contemporary series of patients across the entire clinical and ECG spectra of NSTE-ACS because there were no exclusion criteria. Specifically, we included also patients at higher risk such as those with right or left bundle branch block.[17] (2) A considerable portion of patients was managed in keeping with current guidelines. (3) Blind analysis of angiographic findings included systematic research of the culprit lesion. (4) Patients were stratified based on the GRACE risk score. (5) We evaluated the prognostic value of STE in lead aVR at 1-year follow-up.

Table 4
Independent predictors of in-hospital cardiovascular death in multivariable logistic regression analysis

Variable	Model 1		Model 2		Model 3*	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, each incremental year	1.08 (1.03–1.13)	0.002	1.08 (1.03–1.13)	0.001	1.06 (1.01–1.12)	0.016
Systolic blood pressure (mm Hg)	0.98 (0.97–0.99)	0.005	0.98 (0.97–0.99)	0.013	0.98 (0.97–0.99)	0.008
Heart rate (beats/min)	1.02 (1.01–1.02)	0.019	1.02 (1.01–1.03)	0.036	1.01 (0.99–1.03)	0.22
Killip class		0.07		0.07		0.05
I	reference		reference		reference	
II	1.71 (0.66–4.40)	0.26	1.81 (0.69–4.68)	0.22	1.43 (0.47–4.29)	0.52
III and IV	2.85 (1.21–6.74)	0.019	2.74 (1.15–6.54)	0.023	3.05 (1.21–7.67)	0.018
Cardiac arrest	8.74 (1.69–45.25)	0.01	9.67 (1.90–48.91)	0.006	5.65 (0.94–34.06)	0.059
ST deviation	2.98 (1.40–6.32)	0.004	not included	—	not included	—
Electrocardiographic patterns	not included	—		<0.001		<0.002
No ST deviation	—	—	reference		reference	
Isolated ST deviation	—	—	1.93 (0.77–4.85)	0.16	2.10 (0.72–6.21)	0.16
ST depression + ST elevation in lead aVR	—	—	5.58 (2.35–13.24)	<0.001	5.99 (2.14–16.79)	0.001
c-Statistic	0.878		0.886		0.897	

* Patients with electrocardiographic confounder excluded.

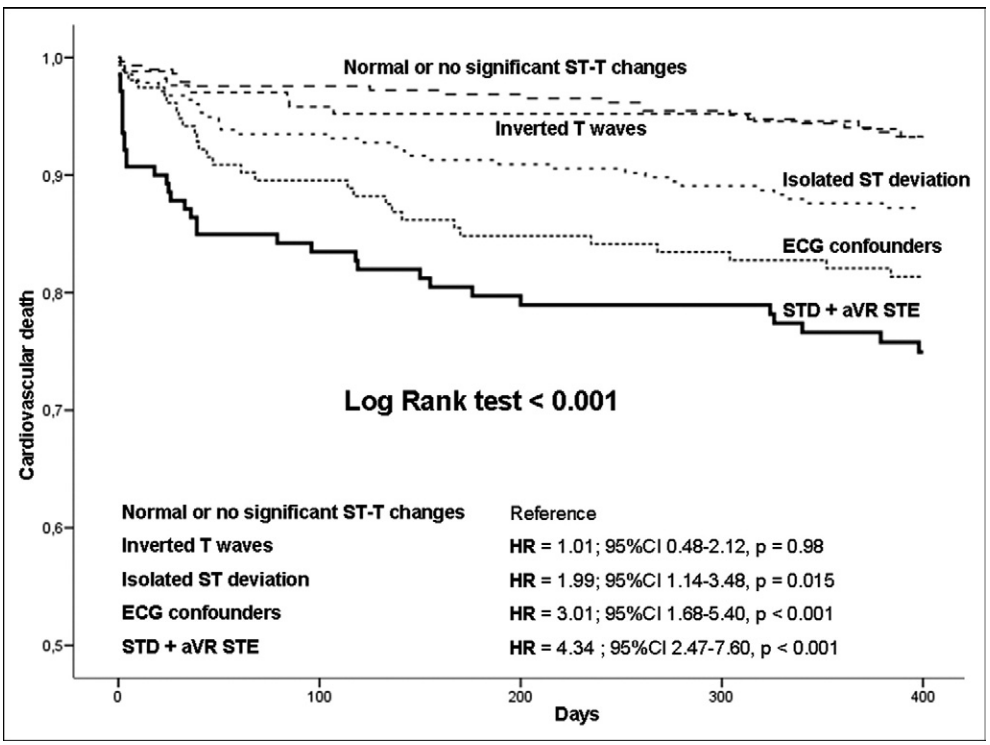

Figure 3. Kaplan–Meier estimates for rates of cardiovascular death at 1-year follow-up. HR = hazard ratio.

In our study, in-hospital overall mortality (4.3%) and type of in-hospital management were quite comparable to those observed in the large GRACE multicenter registry,[7,24] whereas the study by Kosuge et al,[4] which included only patients who underwent coronary angiography, showed a very low mortality rate (0.6% at 90 days). In the study by Barrabés et al,[3] it should be noted that only 52% of patients underwent coronary angiography before discharge and only 24% of patients underwent percutaneous coronary intervention or had surgical revascularization.

Prevalence of STE in lead aVR in our study was definitely higher compared to the GRACE ECG substudy[5] (13.4% vs 1.5%). A possible explanation of this finding could stem from the observation that patients with STE in lead aVR presenting with critical clinical conditions may have been excluded from registries whose data entry was voluntary and required informed written consent. Indeed, in our study median in-hospital GRACE risk score and rate of LM disease of patients with STE in lead aVR were higher compared to those observed in the homologous group of the GRACE ECG substudy (181% vs 150% and 29.3% vs 14.7%, respectively).

Similar to previous studies, we confirmed that STE in lead aVR is associated with more severe coronary lesions

Table 5
Independent predictors of one-year cardiovascular death in multivariable Cox regression analysis

Variable	Model 1		Model 2		Model 3*	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, each incremental year	1.07 (1.04–1.09)	<0.001	1.07 (1.04–1.09)	<0.001	1.06 (1.04–1.09)	<0.001
Previous stroke	1.69 (1.06–2.63)	0.021	1.70 (1.08–2.65)	0.02	1.76 (1.06–2.93)	0.03
Peripheral artery disease	1.46 (0.96–2.20)	0.08	1.42 (0.94–2.16)	0.09	1.71 (1.67–2.72)	0.023
Previous myocardial infarction	1.69 (1.13–2.54)	0.011	1.73 (1.16–2.60)	0.008	1.74 (1.09–2.77)	0.019
Previous percutaneous coronary intervention	0.50 (0.29–0.86)	0.012	0.50 (0.29–0.86)	0.013	0.37 (0.19–0.73)	0.004
Blood pressure (mm Hg)	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001	0.98 (0.98–0.99)	<0.001
Heart rate (beats/min)	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.02)	0.004	1.01 (1.00–1.02)	0.034
Killip class		0.001		0.001		0.009
I	reference		reference		reference	
II	1.75 (1.10–2.79)	0.019	1.76 (1.10–2.81)	0.018	1.40 (0.80–2.45)	0.24
III and IV	2.42 (1.52–3.86)	<0.001	2.41 (1.51–3.85)	<0.001	2.48 (1.34–3.78)	0.002
Creatinine (mg/dl)	1.29 (1.12–1.49)	<0.001	1.28 (1.11–1.47)	0.001	1.22 (1.02–1.45)	0.032
ST deviation	1.71 (1.18–2.48)	0.005	not included	—	not included	—
Electrocardiogram patterns	not included	—		<0.002		<0.001
No ST deviation	—	—	reference		reference	
Isolated ST deviation	—	—	1.52 (0.98–2.36)	0.06	1.95 (1.16–3.29)	0.012
ST depression + ST elevation in lead aVR	—	—	2.29 (1.44–3.64)	<0.001	2.88 (1.67–4.96)	<0.001

HR = hazard ratio.
* Patients with electrocardiographic confounder excluded.

(LM or 3-vessel disease). This finding is consistent with the concept that STE in lead aVR underlies transmural ischemia of the basal septum[25,26] or circumferential subendocardial ischemia of the left ventricle.[27] Of note, our study is the first to evaluate the role of STE in lead aVR in predicting the LM disease as the culprit artery. This is remarkable because patients with culprit LM disease had an approximately two-fold (14.0% vs 6.3%) higher risk of death than patients with LM/3-vessel disease.

Unlike the GRACE ECG substudy we found that STE in lead aVR was independently associated with short- and long-term mortality. However, in addition to a possible selection bias, colinearity between variables may have mitigated the prognostic value of STE in lead aVR in the GRACE ECG substudy[5] because ST deviation and STE in lead aVR were entered simultaneously in the multivariable model. Indeed, it should be noted that in this study all patients with STE in lead aVR >1 mm also had ST deviation.

To overcome this problem we chose for the first time to evaluate the prognostic value of a specific ECG pattern derived from the combined evaluation of STE in lead aVR and STD in other leads. In the present study, as expected, patients with any ST deviation had an increased risk of in-hospital mortality. However, when we assessed separately the predictive role of isolated ST deviation and STD plus STE in lead aVR, we found that only the latter ECG pattern emerged significantly and strongly linked to in-hospital mortality. Of interest, for each category of risk according to GRACE risk score, patients with STD plus STE in lead aVR had a higher incidence of in-hospital cardiovascular death. At 1-year follow-up our results confirmed that STD plus STE in lead aVR was strongly associated with cardiovascular death compared to isolated ST deviation. The long-term prognostic relevance of STD plus STE in lead aVR was maintained even after adjustment for a well-known prognosticator, left ventricle ejection fraction.[28] Taken together, the findings of the present study are remarkable because they suggest that STD plus STE in lead aVR, an easily and routinely detectable ECG pattern, may add incremental information to conventional clinical and ECG markers that so far appear suboptimal to identify patients who can benefit most from invasive strategies.[29]

This study is a retrospective analysis of a single-center registry and it is not immune to sources of bias. Although we corrected for many confounders, unmeasured selection bias may persist. In contrast, the prognostic significance of STE in lead aVR was confirmed even after adjustment for in-hospital GRACE risk score, thus further endorsing the validity of our findings.

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1. Gaitonde RS, Sharma N, Ali-Hasan S, Miller JM, Jayachandran JV, Kalaria VG. Prediction of significant left main coronary artery stenosis by the 12-lead electrocardiogram in patients with rest angina pectoris and the withholding of clopidogrel therapy. *Am J Cardiol* 2003;92: 846–848.
2. Kosuge M, Kimura K, Ishikawa T, Ebina T, Shimizu T, Hibi K, Toda N, Tahara Y, Tsukahara K, Kanna M, Okuda J, Nozawa N, Ozaki H, Yano H, Umemura S. Predictors of left main or three-vessel disease in patients who have acute coronary syndromes with non-ST-segment elevation. *Am J Cardiol* 2005;95:1366–1369.
3. Barrabés JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic value of lead aVR in patients with a first non–ST-segment elevation acute myocardial infarction. *Circulation* 2003;108:814–819.
4. Kosuge M, Kimura K, Ishikawa T, Ebina T, Hibi K, Tsukahara K, Kanna M, Iwahashi N, Okuda J, Nozawa N, Ozaki H, Yano H, Kusama I, Umemura S. Combined prognostic utility of ST segment in lead aVR and troponin T on admission in non-ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2006;97:334–339.

5. Yan AT, Yan RT, Kennelly BM, Anderson FA Jr, Budaj A, López-Sendón J, Brieger D, Allegrone J, Steg G, Goodman SG. Relationship of ST elevation in lead aVR with angiographic findings and outcome in non-ST elevation acute coronary syndromes. *Am Heart J* 2007;154: 71–78.
6. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation* 2007;116:2634–2653.
7. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med* 2003;163:2345–2353.
8. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50(suppl):e1–e157.
9. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28:1598–1660.
10. Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, Pearce DJ, Diver DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, Braunwald E. 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. Thrombolysis in Myocardial Ischemia. *J Am Coll Cardiol* 1997;30:133–140.
11. Savonitto S, Ardissino D, Granger CB, Morando G, Prando MD, Mafrici A, Cavallini C, Melandri G, Thompson TD, Vahanian A, Ohman EM, Califf RM, Van de Werf F, Topol EJ. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;281:707–713.
12. Holmvang L, Clemmensen P, Wagner G, Grande P. Admission standard electrocardiogram for early risk stratification in patients with unstable coronary artery disease not eligible for acute revascularization therapy: a TRIM substudy. ThRombin Inhibition in Myocardial Infarction. *Am Heart J* 1999;137:24–33.
13. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;101:2557–2567.
14. Mahon NG, Codd MB, McKenna CJ, O'Rorke C, McCann HA, Sugrue DD. Characteristics and outcomes in patients with acute myocardial infarction with ST-segment depression on initial electrocardiogram. *Am Heart J* 2000;139:311–319.
15. Diderholm E, Andrén B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, Lindahl B, Wallentin L II. ST depression in ECG at entry indicates severe coronary lesions and large benefits of an early invasive treatment strategy in unstable coronary artery disease; the FRISC II ECG substudy. The Fast Revascularisation during InStability in Coronary artery disease. *Eur Heart J* 2002;23:41–49.
16. Kaul P, Fu Y, Chang WC, Harrington RA, Wagner GS, Goodman SG, Granger CB, Moliterno DJ, Van de Werf F, Califf RM, Topol EJ, Armstrong PW. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. *J Am Coll Cardiol* 2001;38:64–71.
17. Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, Wallentin L, Grande P. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. *J Am Coll Cardiol* 2003;41:905–915.
18. Savonitto S, Cohen MG, Politi A, Hudson MP, Kong DF, Huang Y, Pieper KS, Mauri F, Wagner GS, Califf RM, Topol EJ, Granger CB. Extent of ST-segment depression and cardiac events in non–ST-segment elevation acute coronary syndromes. *Eur Heart J* 2005;26:2106–2113.
19. Westerhout CM, Fu Y, Lauer MS, James S, Armstrong PW, Al-Hattab E, Califf RM, Simoons ML, Wallentin L, Boersma E. Short- and long-term risk stratification in acute coronary syndromes: the added value of quantitative ST-segment depression and multiple biomarkers. *J Am Coll Cardiol* 2006;48:939–947.
20. Yan AT, Yan RT, Tan M, Chow CM, Fitchett DH, Georgescu AA, Hassan Q, Luchansky J, Langer A, Goodman SG. ST-segment depression in non-ST elevation acute coronary syndromes: quantitative analysis may not provide incremental prognostic value beyond comprehensive risk stratification. *Am Heart J* 2006;152:270–276.
21. Yan RT, Yan AT, Granger CB, Lopez-Sendon J, Brieger D, Kennelly B, Budaj A, Steg PG, Georgescu AA, Hassan Q, Goodman SG. Usefulness of quantitative versus qualitative ST-segment depression for risk stratification of non-ST elevation acute coronary syndromes in contemporary clinical practice. *Am J Cardiol* 2008;101:919–924.
22. Barrabés JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic significance of ST segment depression in lateral leads I, aVL, V5 and V6 on the admission electrocardiogram in patients with a first acute myocardial infarction without ST segment elevation. *J Am Coll Cardiol* 2000;35:1813–1819.
23. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–842.
24. Yan AT, Yan RT, Tan M, Eagle KA, Granger CB, Dabbous OH, Fitchett D, Grima E, Langer A, Goodman SG. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. *Am J Cardiol* 2005;96:913–916.
25. Engelen DJ, Gorgels AP, Cheriex EC, De Muinck ED, Ophuis AJ, Dassen WR, Vainer J, van Ommen VG, Wellens HJ. Value of the electrocardiogram in localizing the occlusion site in the left anterior descending coronary artery in acute anterior myocardial infarction. *J Am Coll Cardiol* 1999;34:389–395.
26. Yamaji H, Iwasaki K, Kusachi S, Murakami T, Hirami R, Hamamoto H, Hina K, Kita T, Sakakibara N, Tsuji T. Prediction of acute left main coronary artery obstruction by 12-lead electrocardiography. ST segment elevation in lead aVR with less ST segment elevation in lead v(1). *J Am Coll Cardiol* 2001;38:1348–1354.
27. Yu PN, Stewart JM. Subendocardial myocardial infarction with special reference to the electrocardiographic changes. *Am Heart J* 1950;39:862–880.
28. Bedetti G, Gargani L, Sicari R, Gianfaldoni ML, Molinaro S, Picano E. Comparison of prognostic value of echocardiographic risk score with the Thrombolysis In Myocardial Infarction (TIMI) and Global Registry in Acute Coronary Events (GRACE) risk scores in acute coronary syndrome. *Am J Cardiol* 2010;106:1709–1716.
29. Damman P, Hirsch A, Windhausen F, Tijssen JG, de Winter RJ. 5-Year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial a randomized comparison of an early invasive versus selective invasive management in patients with non–ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2010;55:858–864.