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Predictors of Left Main or Three-Vessel Disease in Patients Who Have Acute Coronary Syndromes With Non–ST-Segment Elevation

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To identify an early, simple, noninvasive predictor of left main (LM) or 3-vessel disease (3-VD), we retrospectively studied clinical variables on admission in 310 patients with acute coronary syndromes with non–ST-segment elevation. Univariate analysis indicated that many factors were related to LM/3-VD. Multivariate analysis showed that ST-segment elevation in lead aVR of ≥0.5 mm was the strongest predictor of LM/3-VD, followed by positive troponin T (odds ratio 19.7, $p < 0.001$, and odds ratio 3.08, $p = 0.048$, respectively). ST-segment elevation in lead aVR of ≥0.5 mm and positive troponin T identified LM/3-VD with sensitivities of 78% and 62%, specificities of 86% and 59%, positive predictive values of 57% and 26%, and negative predictive values of 95% and 87%, respectively ($p < 0.05$). Our findings suggest that in patients with non–ST-segment elevation acute coronary syndromes, ST-segment elevation in lead aVR of ≥0.5 mm and positive troponin T on admission (especially the former) are useful predictors of LM/3-VD.
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Among patients who present with acute coronary syndromes (ACSs) with non–ST-segment elevation (NSTE), those with left main (LM) disease or 3-vessel disease (3-VD) are more likely to undergo coronary artery bypass graft surgery (CABG). Because clopidogrel improves clinical outcome, regardless of the magnitude of risk in patients with NSTE-ACS,[1,2] the American College of Cardiology/American Heart Association guidelines recommend treatment with a combination of clopidogrel and aspirin on admission for patients with NSTE-ACS who are scheduled to undergo percutaneous coronary intervention or noninterventional treatment, considered a class I indication.[3] However, in some patients who require early CABG, this combination therapy may increase the risk of major bleeding. The administration of clopidogrel within 5 days before CABG has been associated with operative bleeding.[4,5] It is therefore preferable to withhold clopidogrel until assessment of the coronary anatomy, especially in patients who require early CABG. Early, accurate, noninvasive identification of patients likely to require CABG, such as those with LM/3-VD, is thus crucial for deciding whether treatment with clopidogrel should be

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TABLE 1 Clinical Characteristics of Subjects

	LM or 3VD		
	Yes (n = 60)	No (n = 250)	p Value
Age (yrs)	69 ± 11	66 ± 10	<0.05
Men	41 (68%)	172 (69%)	0.94
Systolic blood pressure on admission (mm Hg)	144 ± 27	152 ± 24	0.06
Heart rate on admission (beats/min)	80 ± 14	76 ± 17	0.08
Killip class ≥II	8 (13%)	7 (3%)	<0.01
Symptom onset ≤6 h	50 (83%)	201 (82%)	0.77
Previous myocardial infarction	21 (35%)	45 (18%)	<0.01
Previous percutaneous coronary intervention	13 (22%)	45 (18%)	0.51
Previous CABG	10 (17%)	8 (3%)	<0.01
Risk factors			
Smoker	22 (37%)	124 (50%)	0.07
Hypercholesterolemia*	28 (47%)	134 (54%)	0.33
Diabetes mellitus	25 (42%)	82 (33%)	0.20
Hypertension	40 (67%)	160 (64%)	0.70
High-sensitive C-reactive protein on admission (mg/dl)	0.898 ± 1.235	0.401 ± 0.919	0.02
Positive troponin T	37 (62%)	102 (41%)	<0.01
Cardiac procedures during hospitalization			
Percutaneous coronary intervention	23 (38%)	153 (61%)	<0.01
CABG	29 (48%)	17 (7%)	<0.01
Any revascularization (percutaneous coronary intervention or CABG)	50 (83%)	166 (66%)	0.01
30-d outcome			
Death	2 (3%)	0	<0.01
Myocardial (re)infarction	3 (5%)	7 (3%)	0.40
Death/myocardial (re)infarction	5 (8%)	7 (3%)	<0.05
Urgent percutaneous coronary intervention	5 (8%)	11 (4%)	0.22
Urgent CABG	21 (35%)	8 (3%)	<0.01
Urgent revascularization (percutaneous coronary intervention or CABG)	26 (43%)	19 (8%)	<0.01
Any of the above	27 (45%)	19 (8%)	<0.01

Data are presented as mean ± SD or number (percent) of patients.
*Hypercholesterolemia, defined as a previous total serum cholesterol level >220 mg/dl when known.

TABLE 2 Electrocardiographic Findings on Admission

	LM or 3-VD	
	Yes (n = 60)	No (n = 250)
ST-segment depression ≥1.0 mm	49 (82%)	120 (48%)*
Maximal ST-segment depression (mm)	2.0 ± 1.2	0.9 ± 1.0*
Sum of ST-segment depression (mm)	7.9 ± 5.3	2.7 ± 3.7*
No. of leads with ST-segment depression ≥1.0 mm	4.0 ± 2.5	1.4 ± 1.9*
Anterior ST-segment depression	22 (37%)	24 (10%)*
Lateral ST-segment depression	42 (70%)	64 (26%)*
Inferior ST-segment depression	14 (23%)	18 (7%)*
ST-segment elevation ≥0.5 mm in lead aVR	47 (78%)	36 (14%)*

Data are presented as number (percent) of patients.
*p <0.01.

initiated on admission. In the present study, we compared the clinical variables of patients with LM/3-VD on admission with those of patients without it to derive an early, simple predictor of LM/3-VD in patients with NSTE-ACS.

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We retrospectively studied 310 consecutive patients (213 men and 97 women; mean age 66 ± 10 years, range 38 to 89) who were admitted to our coronary care unit between March 2001 and March 2004 and fulfilled the following criteria: (1) typical chest discomfort attributed to cardiac ischemia, lasting ≥5 minutes and occurring within 24 hours before hospital admission and involving an unstable pattern of pain, consisting of new onset pain and pain at rest, severe or frequent angina, accelerating angina, or angina occurring within 21 days after an acute myocardial infarction;[6] (2) no conditions precluding the evaluation of ST-segment changes on the electrocardiogram (left or right bundle branch block, left ventricular hypertrophy defined as a sum of the R wave in leads V_5 or V_6 plus an S wave in lead V_1 ≥35 mm,[7] digitalis glycoside therapy, or ventricular pacing); (3) fully assessable electrocardiogram on admission; and (4) fully assessable angiographic data during hospitalization. Patients with nonischemic or atypical pain, transient or persistent new ST-segment elevation except on lead aVR, or a Q-wave myocardial infarction on presentation were excluded. A 12-lead electrocardiogram was recorded on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. ST-segment shifts were measured 80 ms after the J point for ST-segment depression and 20 ms after this point for ST-segment elevation using the preceding TP segment as a baseline[7] by 1 cardiologist who was blinded to all other clinical data. ST-segment depression was considered present if ≥1.0 mm in any lead and its magnitude and extent were measured. Anterior, inferior, and lateral ST-segment depressions were defined, respectively, as ST-segment depression of ≥1.0 mm in ≥2 leads oriented anteriorly (V_1 to V_4), inferiorly (II, III and aVF), or leftward, either laterally or apically (I, aVL, V_5 and V_6).[8] Because ST-segment elevation in lead aVR of only 0.5 mm has been related to poor outcomes in NSTE-ACS,[7] ST-segment elevation of ≥0.5 mm in lead aVR was defined as being clinically significant.

Blood samples for measuring plasma C-reactive protein levels were obtained on admission. C-reactive protein levels were measured by N Latex CRP Mono tests (Dade Behring Limited, Tokyo, Japan), performed on a Behring BN II Nephelometer (Dade Behring) using polystyrene microbeads coated with monoclonal mouse antibodies.[9] In addition, a qualitative assay for a cardiac-specific troponin T (Roche Diagnostics, Tokyo, Japan detection limit 0.1 ng/ml of cardiac-specific troponin T) was simultaneously performed. Troponin T ≥0.1 ng/ml

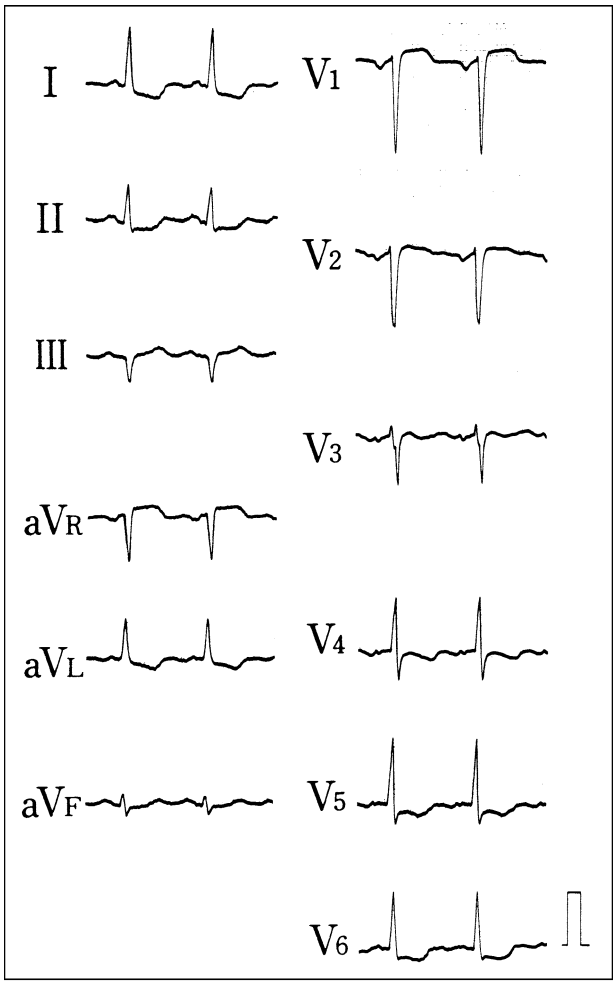

FIGURE 1. Representative electrocardiogram of patient (a 69-year-old woman) with LM/3-VD. Troponin T was positive on admission. ST-segment elevation in lead aVR was 1.5 mm on the admission electrocardiogram. Coronary angiography showed total occlusion at the right coronary artery (segment 3) and 75% stenosis at the LM trunk, left anterior descending coronary artery (segment 6), and left circumflex coronary artery (segment 11).

was defined as positive. The test was repeated at 8 to 12 hours in patients who were negative for troponin T within 6 hours after the onset of symptoms. Creatine kinase-MB levels were determined on admission, at 3-hour intervals during the first 24 hours, and in any patient with suspected reinfarction. All patients underwent cardiac catheterization a median of 3 days (range 0 to 9) after admission, excluding urgent cardiac catheterization. All coronary angiograms were evaluated by 1 cardiologist who was blinded to all other clinical data. Stenosis was considered clinically significant if the lumen diameter was narrowed by ≥75% in any projection. Demographic data, risk factors for coronary artery disease, and data from physical examination on admission were collected. Major adverse events such as death, myocardial (re)infarction, or urgent revascularization were also recorded in all patients. Myocardial (re)infarction was diagnosed on the basis of either cardiac enzyme or electrocardiographic evidence. Enzyme evidence of reinfarction was defined as a reelevation of creatine kinase-MB to higher than the upper limit of normal if the previous creatine kinase-MB level was in the normal range or 50% above the previous level if the previous level was above the normal range (i.e., a recurrent myocardial infarction in patients with evolving non–Q-wave myocardial infarction on admission). Patients were followed up for 30 days after admission to the hospital.

Continuous data are expressed as mean ± SD and categorical data as percentages. Analysis of variance was used for continuous variables. Chi-square analysis was used to compare categorical variables. Differences were considered statistically significant at $p < 0.05$. A multivariate logistic regression analysis was used to identify clinical predictors of LM/3-VD among the variables associated ($p \leq 0.2$) with this diagnosis on univariate analysis. Odds ratios and 95% confidence intervals were calculated. Data were analyzed using SPSS software (Release 10, SPSS Inc., Chicago, Illinois).

The prevalence of LM/3-VD was 19% (LM 4%), 2-vessel disease 21%, 1-vessel disease 47%, and 0-vessel disease 13%. Baseline characteristics of the subjects are listed in Table 1. Patients with LM/3-VD were older, had higher prevalences of previous myocardial infarction, previous CABG, a Killip class ≥2, and positive troponin T, and had a higher level of high-sensitive C-reactive protein than did patients without LM/3-VD. Systolic blood pressure was slightly lower and heart rate was slightly higher in patients with LM/3-VD than in those without it, but the differences did not reach statistical significance. There were no significant differences in gender, previous percutaneous coronary intervention, or coronary risk factors between patients with and without LM/3-VD. Aspirin, intravenous heparin, and nitrates were administered to most patients (98%, 98%, and 96%, respectively). All other treatment was left to the attending physicians' discretion. During hospitalization, revascularization procedures were more frequently performed in patients with LM/3-VD. The frequency of death, (re)infarction, or urgent revascularization within 30 days after admission was more frequent in patients with LM/3-VD, mainly because of the increased rate of urgent CABG in these patients (35%) than in patients without LM/3-VD (3%). Patients with LM/3-VD had a higher prevalence of ST-segment elevation in lead aVR and a higher prevalence and greater amount of ST-segment depression in leads other than lead aVR than did patients without LM/3-VD (Table 2). In the multivariate models, ST-segment elevation in lead aVR of ≥0.5 mm was the strongest predictor of LM/3-VD, followed by only positive troponin T (Figure 1 and Table 3). The other variables, which were associated with LM/3-VD ($p \leq 0.2$) on univariate analysis, were not significant predictors of LM/3-VD. ST-segment elevation in lead aVR of ≥0.5 mm identified LM/3-VD more accurately than positive troponin T (Table 4).

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In this study, we investigated factors related to LM/3-VD in 310 patients with NSTE-ACS. The term "so-called" NSTE-ACS could be used instead of

TABLE 3 Univariate and Multivariate Predictors of Left Main or Three-vessel Disease

	p Value (univariate)	p Value (multivariate)	Odds Ratio (95% CI)
Age	<0.05	0.386	
Systolic blood pressure on admission	0.06	0.713	
Heart rate on admission	0.08	0.538	
Killip class ≥II	<0.01	0.411	
Previous myocardial infarction	<0.01	0.137	
Previous CABG	<0.01	0.089	
Smoking	0.07	0.282	
Diabetes mellitus	0.20	0.109	
High sensitive C-reactive protein on admission	0.02	0.189	
Positive troponin T	<0.01	0.048	3.08 (1.01–9.38)
Maximal ST-segment depression	<0.01	0.075	
Sum of ST-segment depression	<0.01	0.130	
No. of leads with ST-segment depression ≥1.0 mm	<0.01	0.830	
Anterior ST-segment depression	<0.01	0.992	
Lateral ST-segment depression	<0.01	0.955	
Inferior ST-segment depression	<0.01	0.667	
ST-segment elevation ≥0.5 mm in lead aVR	<0.01	<0.001	19.7 (7.94–39.2)

CI = confidence interval.

TABLE 4 Comparison of ST-segment Elevation in Lead aVR Versus Positive Troponin T for Predicting Left Main or Three-vessel Disease

	ST-segment Elevation in Lead aVR ≥0.5 mm	Positive Troponin T
Sensitivity	78%	62%*
Specificity	86%	59%†
Positive predictive value	57%	26%†
Negative predictive value	95%	87%†
Predictive accuracy	84%	60%†

*p <0.05; †p <0.001.

NSTE-ACS in this study, because NSTE-ACS is usually defined without considering ST-segment deviation in lead aVR. Univariate analysis indicated that many factors were related to LM/3-VD. However, multivariate analysis revealed that only ST-segment elevation in lead aVR and positive troponin T were independently related to LM/3-VD. The former factor was especially useful in identifying patients with LM/3-VD.

Elevation of cardiac troponins has been associated with more extensive coronary artery disease, more complex and severe coronary lesions, and a greater burden of intracoronary thrombus on coronary angiography in patients with NSTE-ACS.[10–13] We found that positive troponin T was independently associated with LM/3-VD, consistent with the results of previous investigations.[14,15] However, in our study, the predictive accuracy of positive troponin T for LM/3-VD was relatively low.

Our study suggests that ST-segment elevation in lead aVR and positive troponin T on admission (especially the former) are useful for predicting the risk of LM/3-VD in patients with NSTE-ACS. Although lead aVR is often ignored, ST-segment deviation in this lead is useful for evaluating patients with NSTE-ACS.

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