An Early and Simple Predictor of Severe Left Main and/or Three-Vessel Disease in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

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Clopidogrel should be initiated as soon as possible in patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) except those who urgently require coronary artery bypass grafting (CABG). The present study assessed the ability to predict severe left main coronary artery and/or 3-vessel disease (LM/3VD) that would most likely require urgent CABG based on only clinical factors on admission in 572 patients with NSTE-ACS undergoing coronary angiography. Severe LM/3VD was defined as ≥75% stenosis of LM and/or 3VD with ≥90% stenosis in ≥2 proximal lesions of the left anterior descending coronary artery and other major epicardial arteries. Patients were divided into the 3 groups according to angiographic findings: no LM/3VD (n = 460), LM/3VD but not severe LM/3VD (n = 57), and severe LM/3VD (n = 55). Severe LM/3VD was associated with a higher rate of urgent CABG compared to no LM/3VD and LM/3VD but not severe LM/3VD (46%, 2%, and 2%, p <0.001). On multivariate analysis, degree of ST-segment elevation in lead aVR was the strongest predictor of severe LM/3VD (odds ratio 29.1, p <0.001), followed by positive troponin T level (odds ratio 1.27, p = 0.044). ST-segment elevation ≥1.0 mm in lead aVR best identified severe LM/3VD with 80% sensitivity, 93% specificity, 56% positive predictive value, and 98% negative predictive value. In conclusion, ST-segment elevation ≥1.0 mm in lead aVR on admission electrocardiogram is highly suggestive of severe LM/3VD in patients with NSTE-ACS. Selected patients with this finding might benefit from promptly undergoing angiography, withholding clopidogrel to allow early CABG. **(Am J Cardiol 2011;107: 495–500)**

Dual antiplatelet therapy with clopidogrel and aspirin should be initiated as soon as possible in patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS).[1,2] However, such combination therapy can increase perioperative bleeding in patients undergoing early coronary artery bypass grafting (CABG).[3–7] Therefore, one might consider with-holding clopidogrel until coronary angiography and definition of the coronary anatomy.[8] The proportion of patients with NSTE-ACS who undergo CABG during hospitalization is 9% to 21%.[4,5,8–12] CABG can often be deferred for several days, and few patients require urgent CABG. Ideally, clopidogrel should be withheld in the minority of patients who urgently require CABG and should be given to the remaining majority of patients. We previously examined clinical factors related to left main coronary artery and/or 3-vessel disease (LM/3VD) that would most likely lead to CABG in patients with NSTE-ACS but did not evaluate severity of coronary lesions in that study.[13] In the present study, we assessed the ability to predict "severe" LM/3VD, which would most likely to require urgent CABG, using only clinical factors on admission in patients with NSTE-ACS.

Methods

We studied 572 consecutive patients (mean age 67 ± 11 years, range 30 to 92, 397 men and 175 women) who were admitted to Yokohama City University Medical Center (Yokohama, Japan) coronary care unit and fulfilled the following criteria: (1) typical chest discomfort attributed to cardiac ischemia, lasting ≥5 minutes, occurring within 24 hours before hospital admission, and involving an unstable pattern of pain including pain at rest, new onset, severe or frequent angina, or accelerating angina[14]; (2) no conditions precluding evaluation ST-segment changes on electrocardiogram (ECG) such as left or right bundle branch block, left ventricular hypertrophy, or ventricular pacing; (3) fully assessable ECGs on admission; and (4) fully assessable angiographic data during hospitalization. We excluded patients with nonischemic or atypical pain, persistent new ST-segment elevation in leads other than lead aVR, recent (<6 months) percutaneous coronary intervention, or previous CABG. All patients gave informed consent. The study protocol was approved by the internal review board of Yokohama City University Medical Center.

Standard 12-lead ECGs were recorded on admission at a

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Table 1
Clinical characteristics

	No LM/3VD (n = 460)	LM/3VD		p Value
		Nonsevere (n = 57)	Severe (n = 55)	
Age (years)	66 ± 11	69 ± 10	68 ± 11	0.06
Men	322 (70%)	39 (68%)	36 (66%)	0.78
Systolic blood pressure on admission (mm Hg)	150 ± 25	150 ± 32	141 ± 26	0.07
Heart rate on admission (beats/min)	76 ± 17	81 ± 20	89 ± 23	<0.001
Killip class ≥II on admission	26 (6%)	9 (16%)	17 (31%)	<0.001
Symptom onset ≤6 hours	356 (78%)	43 (75%)	49 (89%)	0.13
Previous myocardial infarction	86 (19%)	18 (32%)	12 (22%)	0.07
Previous percutaneous coronary intervention	90 (20%)	15 (26%)	5 (9%)	0.06
Risk factors				
Hypertension	304 (66%)	42 (74%)	38 (69%)	0.49
Diabetes mellitus	136 (30%)	29 (51%)	30 (55%)	<0.001
Smoking	229 (50%)	22 (39%)	23 (42%)	0.18
Hyperlipidemia*	230 (50%)	25 (44%)	29 (53%)	0.61
Family history of coronary artery disease	120 (26%)	13 (23%)	16 (29%)	0.75
Hemoglobin on admission (g/dl)	14 ± 2	13 ± 2	13 ± 2	0.033
High-sensitivity C-reactive protein on admission (mg/dl)	0.131 (0.061–0.323)	0.180 (0.079–0.453)	0.253 (0.099–0.801)	0.005
Positive troponin T on admission	135 (29%)	28 (49%)	33 (60%)	<0.001
Creatine kinase-MB on admission (IU/L)	14 ± 16	18 ± 24	27 ± 36	<0.001
Estimated glomerular filtration rate on admission (ml/min/1.73 m^2)	68 ± 25	58 ± 28	58 ± 26	0.004
Brain natriuretic peptide on admission (pg/ml)†	67 (26–179) (n = 297)	187 (81–429) (n = 32)	230 (67–571) (n = 31)	<0.001
Cardiac procedures and outcomes at 30 days				
Death	1 (0.2%)	1 (2%)	2 (4%)	0.010
Myocardial (re)infarction	14 (3%)	3 (5%)	5 (9%)	0.23
Death/myocardial (re)infarction	15 (3%)	4 (7%)	7 (13%)	0.004
Urgent percutaneous coronary intervention	29 (6%)	7 (12%)	5 (9%)	0.22
Urgent coronary artery bypass surgery	7 (2%)	1 (2%)	25 (46%)	<0.001
Urgent revascularization (percutaneous coronary intervention or coronary artery bypass surgery)	36 (8%)	8 (14%)	30 (55%)	<0.001
Cardiac procedures				
Percutaneous coronary intervention	272 (59%)	36 (63%)	14 (25%)	<0.001
Coronary artery bypass surgery	27 (6%)	13 (23%)	40 (73%)	<0.001
Any revascularization (percutaneous coronary intervention or coronary artery bypass surgery)	291 (63%)	49 (86%)	54 (98%)	<0.001

Data are presented as mean ± SD, median (interquartile range), or number of patients (percentage).
* Fasting total cholesterol concentration ≥220 mg/dl, fasting triglyceride concentration ≥150 mg/dl, or use of antihyperlipidemic therapy.
† Available for 360 patients.

Table 2
Electrocardiographic findings

Variable	No LM/3VD (n = 460)	LM/3VD		p Value
		Nonsevere (n = 57)	Severe (n = 55)	
ST-segment depression ≥0.5 mm	288 (63%)	53 (93%)	55 (100%)	<0.001
Maximal ST-segment depression (mm)	0.8 ± 1.0	1.7 ± 1.1	2.6 ± 1.7	<0.001
Sum of ST-segment depressions (mm)	2.6 ± 3.6	6.7 ± 5.1	10.5 ± 7.3	<0.001
Number of leads with ST-segment depression ≥0.5 mm	2.5 ± 2.5	5.1 ± 2.6	6.1 ± 2.2	<0.001
ST-segment elevation ≥0.5 mm in lead aVR	68 (15%)	39 (68%)	50 (91%)	<0.001
ST-segment elevation in lead aVR (mm)	0.1 ± 0.3	0.6 ± 0.5	1.2 ± 0.7	<0.001

Data are presented as mean ± SD or number of patients (percentage).

paper speed of 25 mm/s and an amplification of 10 mm/mV. All ECGs were examined by a single investigator who was blinded to all other clinical data. 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.[15] ST-segment deviation was considered present if deviation was ≥0.5 mm in any lead.[14]

A qualitative assay for cardiac-specific troponin T (de-

tection limit 0.1 ng/ml of cardiac-specific troponin T; Roche Diagnostics, Tokyo, Japan) was performed on admission. Troponin T ≥0.1 ng/ml was defined as positive. Blood samples for measuring hemoglobin, plasma high-sensitivity C-reactive protein levels, and estimated glomerular filtration rate were also taken on admission. Japanese equations were used to calculate estimated glomerular filtration rate from serum creatinine level.[16] Brain natriuretic peptide was simultaneously measured in 360 patients. Creatine kinase-MB levels were measured 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 after admission. Urgent cardiac catheterization was performed in patients with unstable hemodynamics from ischemic attacks or with ischemic attacks that could not be controlled by intensive drug treatment. Type and timing of revascularization were left to the discretion of the treating physician. All coronary angiograms were evaluated by a single investigator who was blinded to all other clinical data. Stenosis ≥50% in the diameter of the LM or stenosis of ≥75% in ≥1 major epicardial vessel or its main branches was considered clinically significant. Severe LM/3VD was defined as (1) ≥75% stenosis of the LM, (2) 3VD with ≥90% stenosis of the proximal portion of the left anterior descending coronary artery and ≥90% stenosis of the right coronary artery and/or left circumflex coronary artery, and (3) definitions 1 and 2. Patients were categorize according to presence (n = 112) or absence (n = 460) of LM/3VD, and the former group was subdivided according to severity of coronary lesions: nonsevere LM/3VD (n = 57) and severe LM/3VD (n = 55).

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 for all patients. Myocardial infarction was diagnosed according to cardiac enzyme levels or electrocardiographic criteria. Enzymatic evidence of myocardial infarction was defined as an increase 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.[17] Electrocardiographic evidence of myocardial infarction was defined as new clinically significant Q waves in ≥2 contiguous leads distinct from the enrollment myocardial infarction.[17] Patients were followed for 30 days after admission.

Results are expressed as mean ± SD or as frequency (percentage), and high-sensitivity C-reactive protein and brain natriuretic peptide levels are expressed as median and interquartile range. Data were compared by 1-way analysis of variance, Kruskal-Wallis test, and chi-square analysis. Differences were considered statistically significant at p value <0.05. Multivariate logistic regression analysis was used to identify clinical predictors of severe LM/3VD among the variables associated (p <0.05) with this diagnosis on univariate analysis. Odds ratios and 95% confidence intervals were calculated. In addition, sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of predictors of severe LM/3VD identified on multivariate analysis were determined. SPSS statistical software (SPSS, Inc., Chicago, Illinois) was used for all analyses.

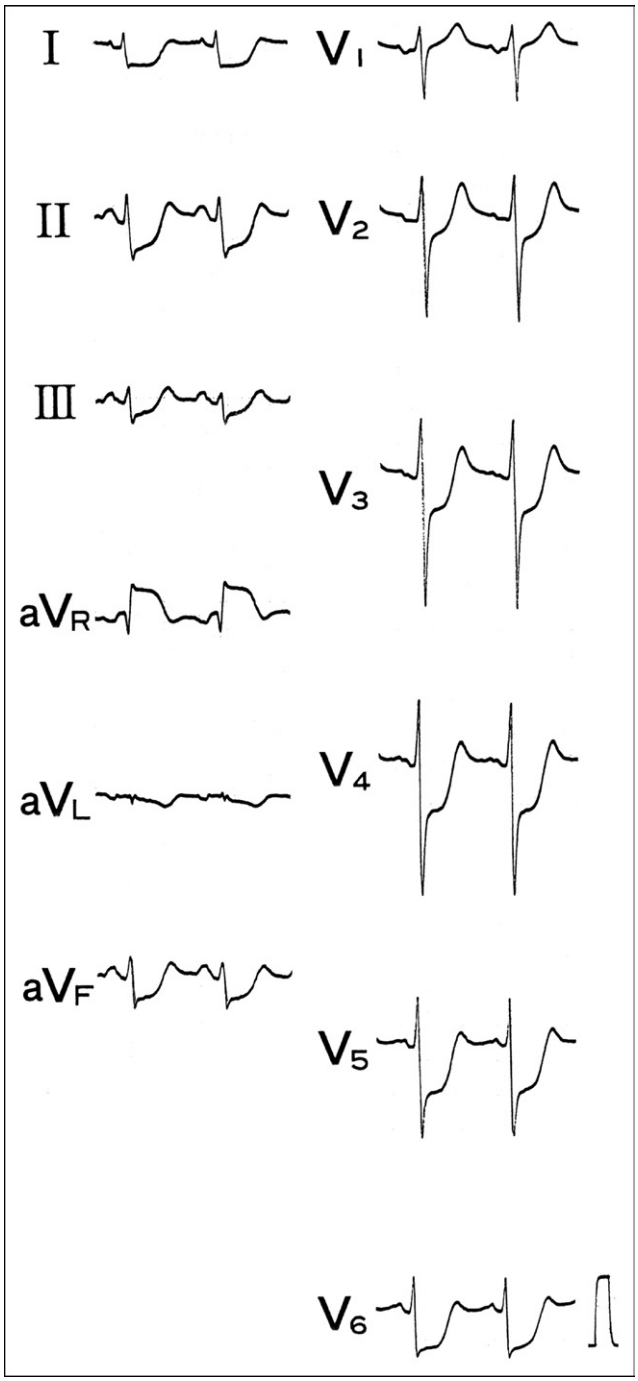

Figure 1. Representative electrocardiogram of a patient with severe left main coronary artery and/or 3-vessel disease. Troponin T was positive on admission. ST-segment elevation in lead aVR was 4.5 mm on admission electrocardiogram. Urgent coronary angiography showed 90% stenosis of the left main trunk.

Results

Baseline characteristics are listed in Table 1. Patients with LM/3VD, especially severe LM/3VD, had a more

Table 3
Univariate and multivariate predictors of severe left main coronary artery and/or three-vessel disease

Variable	Odds Ratio (95% CI)	p Value	
		Univariate	Multivariate
Systolic blood pressure		0.020	0.07
Heart rate		<0.001	0.29
Killip class ≥II		<0.001	0.29
Previous percutaneous coronary intervention		0.045	0.80
Diabetes mellitus		0.001	0.08
High-sensitivity C-reactive protein		<0.001	0.30
Positive troponin T	1.27 (1.10–2.78)	<0.001	0.044
Creatine kinase-MB		<0.001	0.33
Estimated glomerular filtration rate		<0.001	0.32
Maximal ST-segment depression		<0.001	0.053
Sum of ST-segment depressions		<0.001	0.055
Number of leads with ST-segment depression ≥0.5 mm		<0.001	0.24
Degree of ST-segment elevation in lead aVR	29.1 (9.54–49.8)	<0.001	<0.001

CI = confidence interval.

Table 4
Comparison of ST-segment elevation in lead aVR and positive troponin T for predicting severe left main coronary artery and/or three-vessel disease

	Sensitivity	Specificity	PPV	NPV	Predictive Accuracy
ST-segment elevation in lead aVR					
≥0.5 mm	91%	79%†	32%†	99%	80%†
≥1.0 mm	80%	93%	56%	98%	92%
≥1.5 mm	27%†	98%†	58%	93%†	91%
Positive troponin T	60%*	69%†	17%†	94%†	68%†

NPV = negative predictive value; PPV = positive predictive value.
* $p < 0.05$; † $p < 0.01$ versus ST-segment elevation ≥1.0 mm in lead aVR.

rapid heart rate, higher prevalences of Killip class ≥II, diabetes mellitus, positive troponin T, and higher levels of high-sensitivity C-reactive protein, creatine kinase-MB, and brain natriuretic peptide than did patients without LM/3VD. LM/3VD was associated with lower levels of hemoglobin and estimated glomerular filtration rate. There were no significant differences in other clinical variables among the 3 groups.

Urgent CABG was more frequently done in patients with severe LM/3VD (46%). In contrast, urgent CABG was done in only 2% of patients with LM/3VD but not severe LM/3VD.

Electrocardiographic findings are presented in Table 2. Compared to patients without LM/3VD, those with LM/3VD, especially severe LM/3VD, had a higher prevalence and a larger amount of ST-segment depression, a larger number of leads other than lead aVR with ST-segment depression, and a higher prevalence and greater magnitude of ST-segment elevation in lead aVR. Figure 1 shows a representative ECG of a patient with severe LM/3VD.

In multivariate models, degree of ST-segment elevation in lead aVR was the strongest predictor of severe LM/3VD, followed by positive troponin T (Table 3). Sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of ST-segment elevation in lead aVR and positive troponin T for severe LM/3VD are presented in Table 4. ST-segment elevation ≥1.0 mm in lead aVR best identified severe LM/3VD.

Discussion

Our study showed that ST-segment elevation ≥1.0 mm in lead aVR and positive troponin T on admission (especially the former) were highly suggestive of severe LM/3VD, and the converse was also true, i.e., absence of these findings was rarely associated with severe LM/3VD. To our knowledge, this is the first study to establish a reliable technique for early identification of patients with severe LM/3VD who are most likely to require urgent CABG in patients with NSTE-ACS. Our findings have important implications for identification of high-risk patients and selection of optimal treatment strategy in the setting of NSTE-ACS.

The standard 12-lead ECG, which is an inexpensive, noninvasive, and readily available clinical tool, has a central role in diagnosis and immediate triage for NSTE-ACS and provides important prognostic information. In particular, presence of ST-segment depression on admission ECG has been recognized to be a strong predictor of adverse outcomes in patients with NSTE-ACS.[14,17–20] The Global Utilization of Strategies to Open Occluded Arteries in Acute Coronary Syndrome IV (GUSTO-IV ACS) trial of 7,800 patients with NSTE-ACS has highlighted the striking prognostic value of ST-segment depression on admission compared to expanded biomarker profiles and traditional risk factors.[18] However, most previous studies assessing the clinical significance of admission ECG in patients with NSTE-ACS have focused on ST-segment deviation in leads other than lead aVR; i.e., clinicians have used an "11-lead" ECG, neglecting lead aVR.

Several studies have found that analysis of lead aVR is useful for evaluation of NSTE-ACS.[13,15,21,22] Gorgels et al[21] reported that ST-segment elevation in lead aVR accompanied by ST-segment depression in leads I, II, and V_4 to V_6 during episodes of angina strongly suggests LM/3VD in

patients with angina at rest. Barrabés et al[15] demonstrated that presence of ST-segment elevation in lead aVR predicts risk of in-hospital death in patients with a first non–ST-segment elevation acute myocardial infarction. In that study, ST-segment elevation in lead aVR was also related to LM/3VD; however, coronary angiography was performed in only 56% of subjects within 6 months after infarction. We previously demonstrated that presence of ST-segment elevation ≥0.5 mm in lead aVR on admission ECG strongly suggested LM/3VD and had a higher prognostic value than ST-segment depression in other leads in patients with NSTE-ACS who underwent coronary angiography in the acute phase.[13,22] However, previous studies, including ours, did not consider severity of LM/3VD, which has clinical implications for timing of CABG in relation to dual antiplatelet therapy. An increased risk of perioperative bleeding events due to early clopidogrel administration is clinically problematic in patients with LM/3VD who urgently require CABG. In such patients, postponing CABG for several days might seriously compromise outcomes. Timing of CABG depends on many factors including severity of coronary lesions, risk of ongoing ischemia, general condition of a patient, bleeding risk associated with upstream antithrombotic therapies, and local logistic factors such as collocation of cardiac surgical services and surgical waiting lists. The present study examined predictors of patients with severe LM/3VD likely to require urgent CABG, considering the coronary anatomy. We demonstrated that ST-segment elevation ≥1.0 mm in lead aVR was the most accurate predictor of severe LM/3VD. However, its positive predictive value was 56%, which was moderate. More importantly, the negative predictive value of ST-segment elevation ≥1.0 mm in lead aVR for detection of severe LM/3VD was 98%, which was very high. Absence of this finding was rarely associated with severe LM/3VD. If ST-segment elevation ≥1.0 mm in lead aVR is absent, treatment with upstream clopidogrel is strongly recommended. Lead aVR has a unique position because the positive pole is oriented toward the right upper side of the heart and looks into the left ventricular cavity from the right shoulder in the setting of NSTE-ACS.[23] Lead aVR is therefore referred to as a "cavity lead," and ST-segment elevation in this lead might reflect global subendocardial ischemia.[24] In patients with LM/3VD, severe extensive ischemia of the subendocardial layer leads to ST-segment elevation in lead aVR and extensive ST-segment depression in leads other than lead aVR. The magnitude of these changes is thought to reflect severity of LM/3VD. In the present study, LM/3VD, especially severe LM/3VD, was associated with a greater degree and extent of ST-segment depression and a greater degree of ST-segment elevation in lead aVR. A meta-analysis of 12,030 patients with stable coronary artery disease enrolled in 60 studies demonstrated that amount of ST-segment depression during exercise stress testing is strongly associated with critical coronary artery disease such as LM/3VD.[25] Furthermore, a greater degree and extent of ST-segment depression, not only its presence or absence, has been shown to correlate with an increased likelihood of LM/3VD and poor outcomes in patients with NSTE-ACS.[17,19,20] The present study demonstrated that the value of ST-segment elevation in lead aVR for detection of severe LM/3VD surpassed that of ST-segment depression in other leads in patients with NSTE-ACS.

Recently approved antiplatelet agents such as prasugrel and ticagrelor, a new reversible agent, have been shown to decrease ischemic events compared to clopidogrel, but the former increased the risk of perioperative bleeding[7] and the latter did not decrease the risk of perioperative bleeding.[26] Until an antiplatelet agent that decreases ischemic events and decreases perioperative bleeding compared to clopidogrel becomes available, some patients will be exposed to a risk of urgent CABG-related bleeding caused by upstream dual antiplatelet therapy.

This study was retrospective, performed at a single center, and included a small number of patients who underwent coronary angiography during hospitalization. However, the proportion of patients undergoing CABG during hospitalization in this study (14%) was similar to that in previous studies.[4,10,12] Moreover, because our subjects underwent cardiac catheterization a median of 3 days after admission, our data on clinical outcomes according to angiographic findings cannot be generalized to hospitals that provide early invasive strategies. Further studies in larger numbers of patients are needed to verify our results.

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