Table 1. Clinical profiles of patients

	Overall	ONCABG	OPCABG	P value
Age (years)	67.3 ± 9.3	65.7 ± 9.5	71.2 ± 7.9	0.0001
Gender (f/m)	42/157	33/107	9/50	
Unstable AP (%)	46 (22.6)	28 (21.2)	18 (30.5)	
Preop. IABP (%)	15 (7.5)	12 (6.8)	3 (5.1)	
LVEF (%)	56.2	54.2 ± 14.9	60.8 ± 13.3	0.0039

f, female; m, male; AP, angina pectoris; preop., preoperative; IABP, intra-aortic balloon pumping; LVEF, left ventricular ejection fraction; ONCABG, on-pump coronary bypass grafting; OPCABG, off-pump coronary artery bypass grafting.

Table 2. Number of diseased vessels in the two groups

	Overall (190/191)	ONCABG (131/132)	OPCABG (59/59)
SVD (%)	7 (3.7)	4 (3.0)	3 (5.1)
DVD (%)	84 (44.0)	51 (38.6)	33 (55.9)
TVD (%)	99 (51.8)	76 (57.6)	23 (38.9)

SVD, single-vessel disease; DVD, double-vessel disease; TVD, triple-vessel disease; ONCABG, on-pump coronary artery bypass grafting; OPCABG, off-pump coronary artery bypass grafting.

Results

Operative method

Sixty patients underwent OPCABG after the allocation process. One patient in this group was converted to ONCABG because of hemodynamic instability; therefore 141 patients underwent ONCABG (59 OPCABG and 140 ONCABG patients). Mean age at surgery was 65.7 ± 9.5 years in the ONCABG group, whereas that in the OPCABG group was 71.2 ± 7.9 years (p <0.0001). There were 107 men (74.2%) and 33 women (25.8%) in the ONCABG group, and 50 men (84.7%) and 9 women (15.3%) comprised the OPCABG group. Table 1 shows preoperative patient profiles.

The mean cross-clamp time for the ONCABG patients was 73.9 ± 26.7 min. Preoperative left ventricular ejection fraction (LVEF) in the ONCABG patients was worse than in the OPCABG patients (p <0.0039). The prevalence of diabetes mellitus, the history of previous cerebral infarction, and atherosclerotic disease in the ascending aorta were more frequent in the OPCABG than in the ONCABG group. Table 2 shows the analysis of the number of diseased vessels between the two groups. One ONCABG patient had pure left main disease. The difference in the number of diseased vessels between the groups did not reach statistical significance.

The total number of distal anastomoses was 3.2 ± 0.9 per patient. It was greater in the ONCABG group (3.4 ± 0.8 per patient) than in the OPCABG group (2.8 ± 0.8 per patient) (p <0.0001). Detailed information on the anastomoses is listed in Table 3. Total flow through the left ITA stem was 84.9 ± 35.9 ml/min: 88.6 ± 37.8 ml/min in the ONCABG group and 77.0 ± 30.3 ml/min in the OPCABG group (p <0.0401) (Table 3).

Major morbidity and mortality

There was no operative mortality. The ONCABG group contained 1 case of late cardiac tamponade, 1 of reexploration for bleeding, 1 of mediastinitis, 1 of acute cholecystitis, and 2 of long intubation (defined as intubation period > 48 hrs). None had neurologic disturbance immediately after surgery. However, 2 patients had postoperative cerebral infarction, presumably related to postoperative atrial fibrillation. Both patients were discharged with full neurological recovery. The OPCABG group contained 1 case of late tamponade and 1 of long intubation. No cerebral complications occurred immediately after surgery. One patient, however, had a minor cerebral infarction, possibly from postoperative atrial fibrillation, and recovered completely by the time of hospital discharge. There was no statistically significant difference in the incidence of major morbidity, and the duration of ICU stay was the same between the two groups.

Table 3. Operative data

	Overall	ONCABG	OPCABG	P value
No. of anastomoses	3.2 ± 0.9	3.4 ± 0.8	2.8 ± 0.8	<0.0001
No. of LITA anastomoses	1.4 ± 0.5	1.4 ± 0.5	1.2 ± 0.4	0.0027
No. of RITA anastomoses	1.8 ± 0.7	2.0 ± 0.8	1.6 ± 0.7	0.0005
ITA flow (ml/min)	84.9 ± 35.9	88.6 ± 37.8	77.0 ± 30.3	0.0401
ICU stay (days)	4.4 ± 6.6	4.3 ± 6.8	4.6 ± 6.3	0.7053

LITA, left internal thoracic artery; RITA, right internal thoracic artery; ITA, internal thoracic artery; ICU, intensive care unit; ONCABG, on-pump coronary artery bypass grafting; OPCABG, off-pump coronary artery bypass grafting.

Discussion

In 2000, we developed a new CABG program aimed at (1) avoiding the perioperative neurological complications associated with ascending aortic maneuvers and/or with the use of cardiopulmonary bypass; and (2) obtaining the best possible long-term patency and survival results. Therefore patients scheduled for CABG underwent screening chest CTs and neck and head MRAs to evaluate ascending aortic disease and occlusive neck and intracranial artery disease. If deemed necessary, a patient might also undergo preoperative brain-stress ^{133}Xe single-photon emission CT to evaluate intracranial perfusion status. All patients underwent AITACR procedure with either ONCABG or OPCABG after individual screening and allocation. The effect of OPCABG procedure on a patient's postoperative renal function and remote outcome has not been fully clarified. However, at the beginning of the present study we set the inclusion criteria for OPCABG as serum creatinine > 1.5 mg/dl, which still remains a matter of debate.

It is our belief that the surgical quality of coronary anastomosis in ONCABG is generally superior to that in beating-heart OPCABG anastomosis. The surgical quality in anastomosis is most likely to influence the long-term results. For these reasons, we believe that individualized allocation to the OPCABG technique should be performed instead of a compulsory OPCABG strategy for all revascularization candidates if the best possible long-term results may be expected.

Long-term patency of the graft is an important key factor determining the long-term success rate after CABG. In this sense there has been growing interest in completing CABG, using all arterial grafts.[4,7,8] The concept of complete arterial revascularization has been based on the assumption that all arterial grafts are associated with superior long-term patency rates. In the literature, grafts reported for use in complete arterial revascularization include the ITA, radial artery, gastroepiploic artery, and others.[9,10] However, recent results have suggested that all arterial grafts do not function postoperatively as favorably as the ITA graft.[11-13] Thus as an extreme approach to complete arterial revascularization, Tector and associates reported a CABG graft strategy that exclusively used ITAs with T- or I-shaped grafts in patients with triple-vessel disease.[4]

We have been interested in AITACR since 2000 and reported the success rate and most suitable graft design for AITACR from our experience in 2005.[14] In the present study, no patient experienced intraoperative cerebral complications. However, 3 patients (1 in the OPCABG group and 2 in the ONCABG group) experienced postoperative cerebral complications, possibly related to postoperative atrial fibrillation. This may illustrate the importance of prophylaxis against postoperative atrial fibrillation or transient anticoagulation.

There was a statistically significant difference in the patient profiles between the two groups. The OPCABG group had better LVEF than the ONCABG group. The reason for this difference could not be explained through this study. There were statistically more patients in the OPCABG group with a history of diabetes mellitus, old cerebral infarction, and disease in the ascending aorta than in the ONCABG group. This difference is related to our selection criteria for OPCABG.

One of the technical differences between the two groups was the total number of distal coronary anastomoses and the ITA stem flow. The total flow in the ONCABG group was greater than in the OPCABG group, and the OPCABG group had fewer distal anastomoses than the ONCABG group did. These differences could be a result of the difference in the number of diseased coronary vessels in the two groups (Table 3).

There were several limitations in this study. It was a

retrospective, nonrandomized study investigating perioperative cerebral complications in a small number of patients who underwent AITACR. The allocation to the type of revascularization procedures (on-pump or off-pump) was determined by our selection criteria. There may thus have been an unavoidable patient allocation bias.

In terms of overall mortality and morbidity in the present series, the incidence of neurological complications was comparable or better than those in other reports in the literature.[9] When patients were allocated by our criteria to either the on-pump or the off-pump group in the AITACR program, excellent results with acceptable morbidity were achieved. A large-scale randomized trial is indicated to investigate further the role of minimizing neurological complications in the individualized OPCABG AITACR approach and of obtaining better long-term results. In summary, we conclude that the individualized OPCABG approach in our AITACR program is reasonable and safe with excellent immediate neurological outcomes.

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Predictors of In-Hospital Outcome After Primary Percutaneous Coronary Intervention for Recurrent Myocardial Infarction

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Background Recurrent acute myocardial infarction (AMI) is a deteriorated condition with high in-hospital morbidity and mortality, but the predictors of in-hospital outcome after primary percutaneous coronary intervention (PCI) for repeat AMI remain unclear.

Methods and Results Using the AMI-Kyoto Multi-Center Risk Study database, clinical background, angiographic findings, results of primary PCI, and in-hospital prognosis were retrospectively compared between primary PCI-treated AMI patients with previous myocardial infarction (MI) (repeat-MI patients, n=235) and those without previous MI (first-MI patients, n=1,550). The repeat-MI patients had higher prevalence of Killip class ≥3 at admission, larger number of diseased vessels, and a significantly higher in-hospital mortality rate than the first-MI patients. On multivariate analysis, number of diseased vessels ≥2 or diseased left main trunk (LMT) on initial coronary angiography was the independent positive predictor of in-hospital mortality in the repeat-MI patients, not in the first-MI patients, whereas acquisition of Thrombolysis In Myocardial Infarction 3 flow in the infarct-related artery immediately after primary PCI and elapsed time <24 h were the negative predictors in the first-MI patients, not in the repeat-MI patients.

Conclusions Number of diseased vessels ≥2 or diseased LMT on initial coronary angiography is an independent risk factor of in-hospital death in recurrent-AMI patients undergoing primary PCI. (*Circ J* 2008; **72:** 1225–1229)

Key Words: Multivessel disease; Primary percutaneous coronary intervention; Prognosis; Recurrent myocardial infarction

Repeat acute myocardial infarction (AMI) is a deteriorated condition with high in-hospital morbidity and mortality, which can be attributed to the frequent coexistence of multivessel disease and shock. Previous accumulating evidence shows that primary percutaneous coronary intervention (PCI) can improve the prognosis of AMI complicated with cardiogenic shock[1–4] although a recent report indicated that previous myocardial infarction (MI), older age, and failed reperfusion were independent predictors of in-hospital death in AMI patients with cardiogenic shock[5] However, the clinical manifestations and the predictors of in-hospital prognosis of repeat AMI patients undergoing primary PCI remain to be elucidated. The AMI-Kyoto Multi-Center Risk Study, a large multicenter observational study in which 16 collaborating hospitals in Kyoto Prefecture have collected demographic, procedural, and outcome data on AMI patients, was established in 2000 in order to analyze these data and establish an emergency-hospital network for heart diseases in Kyoto[6–9] The purpose of the present study was to compare clinical background, in-hospital prognosis, and determinants of in-hospital outcome in recurrent AMI patients undergoing primary PCI with those of first AMI patients undergoing primary PCI, using data from the AMI-Kyoto Multi-Center Risk Study.

Methods

Patient Population

From January 2000 to December 2005, 2,230 consecutive patients with a diagnosis of AMI who were admitted to AMI-Kyoto Multi-Center Risk Study Group Hospitals within 1 week after the onset of AMI, were enrolled in the present study. Of these, 328 patients had previous MI, and 1,817 patients underwent primary PCI, of whom data on clinical background were available in 1,785. Previous MI was identified by medical history and echocardiographic findings. We retrospectively compared clinical background, coronary

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Table 1 Clinical Characteristics of the Study Patients

	Repeat MI (n=235)	First MI (n=1,550)	p value
Age (mean years ± SD)	67.9±13.1	67.8±12.2	0.898
Male (%)	191 (81.3)	1,123 (72.5)	0.004
Previous PCI (%)	111 (47.2)	37 (2.4)	<0.001
Previous CABG (%)	7 (3.0)	7 (0.5)	<0.001
Risk factors			
Smoking (%)	77 (32.8)	547 (35.3)	0.450
Hypercholesterolemia (%)	80 (34.0)	502 (32.4)	0.614
Hypertension (%)	99 (42.1)	718 (46.3)	0.229
Diabetes mellitus (%)	69 (29.4)	370 (23.9)	0.069
Elapsed time <24 h (%)	215 (91.5)	1,365 (88.1)	0.125
Killip 3/4 (%)	49 (20.9)	189 (12.2)	<0.001

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 2 Angiographic Findings of the Study Patients

	Repeat MI (n=235)	First MI (n=1,550)	p value
Culprit lesion			
RCA (%)	85 (36.2)	552 (35.6)	0.664
LAD (%)	104 (44.3)	720 (46.5)	
LCX (%)	34 (14.5)	223 (14.4)	
LMT (%)	5 (2.1)	23 (1.5)	
Multivessel (%)	7 (3.0)	31 (2.0)	
SVG	0 (0.0)	1 (0.1)	
No. of diseased vessels			
0 (%)	0 (0.0)	2 (0.1)	<0.001
1 (%)	111 (47.2)	913 (58.9)	
2 (%)	73 (31.1)	444 (28.6)	
3 (%)	46 (19.6)	166 (10.7)	
LMT (%)	5 (2.1)	25 (1.6)	

RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; SVG, saphenous vein graft.

risk factors, angiographic findings, acute results of primary PCI, and in-hospital prognosis between primary PCI-treated patients with previous MI (repeat MI group, n=235) and those without previous MI (first MI group, n=1,550). The diagnosis of AMI required the presence of 2 of the following 3 criteria: (1) characteristic clinical history, (2) serial changes on the ECG suggesting infarction (Q-waves) or injury (ST-segment elevations), and (3) transient increase in cardiac enzymes to more than 2-fold the normal laboratory value.

Data Collection

The patients' demographic information, cardiovascular history, and risk factors (ie, smoking, hypercholesterolemia, hypertension, and diabetes mellitus) were recorded. Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl or the use of cholesterol-lowering agents; hypertension was defined as systemic blood pressure ≥140/90 mmHg or the use of antihypertensive treatment; diabetes mellitus was defined as fasting blood sugar ≥126 mg/dl or the use of specific treatment. After informed consent to participate in the AMI-Kyoto Multi-Center Risk Study was confirmed by each patient, all in-hospital data were transmitted to the center located at the Department of Cardiology and Vascular Regenerative Medicine in Kyoto Prefectural University School of Medicine for analysis. The study protocol was approved by each hospital's ethics committee.

Table 3 Results of Coronary Intervention in the Study Patients

	Repeat MI (n=235)	First MI (n=1,550)	p value
Pre TIMI grade*			
0	120 (51.1)	802 (51.7)	0.300
1	28 (11.9)	221 (14.3)	
2	32 (13.6)	164 (10.6)	
3	37 (15.7)	197 (12.7)	
Post TIMI grade*			
0	5 (2.1)	36 (2.3)	0.840
1	3 (1.3)	12 (0.8)	
2	12 (5.1)	66 (4.3)	
3	197 (83.8)	1,270 (81.9)	
Stent (%)	173 (73.6)	1,221 (78.8)	0.075
IABP (%)	52 (22.1)	220 (14.2)	0.002
PCPS (%)	7 (3.0)	21 (1.4)	0.062
Pacing (%)	18 (7.7)	143 (9.2)	0.435
Urgent CABG (%)	1 (0.4)	3 (0.2)	0.483

TIMI, Thrombolysis In Myocardial Infarction; IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support. Other abbreviations see in Table 1.
**Data available for 217 of the repeat-MI group and 1,384 of the first-MI group.*

Emergency Coronary Angiography (CAG) and Reperfusion Therapy

Emergency CAG was performed using the standard technique. The coronary flow in the infarct-related artery was graded according to the classification used in the Thrombolysis In Myocardial Infarction (TIMI) trial. Significant coronary artery stenosis was defined as at least 75% reduction in the internal diameter of the right, left anterior descending, or left circumflex coronary arteries and their major branches, or 50% reduction in the internal diameter of the left main trunk (LMT). Non-significant stenosis was defined as coronary arterial narrowing less than a significant stenosis. Patients with either angiographically normal coronary arteries or non-significant stenosis were classified as having zero-vessel disease. Multivessel disease as the culprit lesion was defined as simultaneous thromboses of multiple coronary arteries on initial CAG. After the culprit lesions were ascertained by CAG, primary PCI was subsequently performed.

Statistical Analysis

Data are expressed as mean ± SD. The repeat MI and the first MI groups were compared using the chi-square test for discrete variables and unpaired Student's t-test for continuous variables according to standard statistical methods. The odds ratio and 95% confidence intervals assessing the risk of in-hospital death were estimated by multivariate logistic regression analysis. In the multivariate logistic regression analysis, TIMI flow grade was categorized into 2 groups: grade 3 and grade ≤2 or unknown. In all analyses, significance was accepted at $p<0.05$.

Results

Patient Characteristics and Risk Factors

The clinical characteristics and risk factors in the 2 groups are summarized in Table 1. The repeat-MI group had higher frequency of males, previous PCI, previous coronary artery bypass grafting (CABG), and Killip class ≥3 on admission, compared with the first-MI group. The prevalence of coronary risk factors did not differ between the 2 groups,

Table 4 In-Hospital Outcomes of the Study Patients

	Repeat MI (n=235)	First MI (n=1,550)	p value
Length of hospital stay (days)	23.0±18.3	22.8±18.6	0.855
Max. CK (IU/L)	2,559.6±3,585.8	2,749.5±2,827.2	0.362
Death (%)	36 (15.3)	145 (9.4)	0.005
Cardiac-related (%)	24 (10.2)	110 (7.1)	0.091
Shock	8	47	0.758
Heart failure	8	37	0.354
Rupture	4	14	0.253
Vf	4	12	0.160
Noncardiac-related (%)	12 (5.1)	35 (2.3)	0.011

CK, creatine kinase; Vf, ventricular fibrillation. Other abbreviation see in Table 1.
Data on Max. CK available only for 229 of the repeat MI group and for 1,506 of the first MI group.

Table 5 Predictors of In-Hospital Mortality in the Study Patients (Multivariate Logistic Regression Analysis)

	Repeat MI			First MI		
	OR	95%CI	p value	OR	95%CI	p value
Killip 3/4	6.884	2.824–16.784	<0.0001	13.440	8.847–20.417	<0.0001
Multivessel or LMT as culprit	1.638	0.379–7.082	0.5091	4.336	2.024–9.289	0.0002
No. of diseased vessels ≥2 or LMT	2.673	1.029–6.944	0.0435	1.367	0.896–2.086	0.1463
Age	1.052	1.009–1.098	0.0186	1.039	1.018–1.060	0.0002
TIMI 3 after PCI	0.563	0.174–1.825	0.3384	0.552	0.330–0.924	0.0238
Elapsed time <24 h	0.716	0.198–2.583	0.6095	0.539	0.316–0.920	0.0234
Hypertension	1.114	0.456–2.723	0.8127	1.413	0.908–2.199	0.1256
Diabetes mellitus	1.294	0.490–3.422	0.6027	0.931	0.570–1.520	0.7743

OR, odds ratio; CI, confidence intervals. Other abbreviations see in Tables 1–3.

although the repeat-MI group tended to have a higher frequency of diabetes mellitus, but not significantly.

Angiographic Data

Table 2 shows the emergency CAG data for the 2 groups. The repeat-MI group had a larger number of diseased vessels than the first-MI group, but the prevalence of culprit lesions did not vary between groups.

Results of Coronary Intervention

Table 3 shows the results of primary PCI in the 2 groups. Data on TIMI grade were available in 217 of the 235 repeat-MI patients and in 1,384 of the 1,550 first-MI patients. The distribution of TIMI grade before and after primary PCI did not differ significantly between the 2 groups. The repeat-MI group had a higher rate of intra-aortic balloon pumping (IABP) than the first-MI group.

In-Hospital Outcomes

Table 4 shows the in-hospital prognoses in the 2 groups. The repeat-MI group had a significantly higher in-hospital overall mortality rate than the first-MI group. The repeat-MI group had slightly, but not significantly higher prevalence of cardiac-related death, and a significantly higher incidence of noncardiac-related death, compared with the first-MI group. The length of hospital stay and the maximum creatine phosphokinase concentration did not differ between the 2 groups. In order to assess the contribution of clinical background, risk factors, angiographic findings, and results of primary PCI, multivariate logistic regression analysis using all available variables (age, gender, previous PCI, previous CABG, smoking, hypercholesterolemia, hypertension, diabetes mellitus, multivessel or LMT as culprit lesion, number of diseased vessels ≥2 or diseased LMT, stent usage, elapsed time <24 h, Killip class ≥3 at admission, TIMI 3 flow before/after primary PCI) was developed for overall death during hospitalization in the repeat-MI group as well as in the first-MI group (Table 5). Killip class ≥3 at admission and age were the independent positive predictors of in-hospital mortality in both groups. The presence of multivessel or LMT as culprit lesion was the independent positive predictor of in-hospital mortality in the first-MI group, but not in the repeat-MI group. Achieving of TIMI 3 flow just after primary PCI and elapsed time <24 h were the negative predictors in the first-MI group, but not in the repeat MI group. In contrast, the number of diseased vessels ≥2 or diseased LMT was an independent positive predictor of in-hospital mortality in the repeat-MI group, but not in the first-MI group.

Discussion

The major findings of the present multicenter study are as follows: in AMI patients undergoing primary PCI, the number of diseased vessels ≥2 or diseased LMT on initial CAG was an independent positive predictor of in-hospital mortality in repeat-MI patients, but not in first-MI patients; achieving of TIMI 3 flow immediately after primary PCI and elapsed time <24 h were independent negative predictors in first-MI patients, but not in repeat-MI patients.

This study is the first to investigate the clinical manifestations and determinants of in-hospital outcome in recurrent AMI patients undergoing primary PCI. In the present report, repeat-MI patients had higher prevalence of being male, prior percutaneous/surgical revascularizations, and Killip class ≥3 at admission, larger number of diseased vessels on initial CAG, higher frequency of IABP during primary PCI, and a significantly higher in-hospital mortality rate, compared with the first-MI patients, although TIMI flow grade in the infarct-related artery before/after primary PCI did not differ between the repeat-MI patients and the first-MI patients. Hemodynamic instability and residual myocardial

ischemia derived from their clinical backgrounds might be associated with the higher in-hospital mortality in the repeat-MI patients. In the present report, the repeat-MI patients had a slightly, but not significantly higher prevalence of cardiac-related death, but a significantly higher incidence of noncardiac-related death, compared with the first-MI patients. However, we cannot rule out the possibility that cardiac impairments might have influenced the clinical course of the noncardiac diseases in the repeat-MI patients. Thus, there is a possibility that revascularization therapy in the infarct-related artery alone might be an inadequate strategy for improving the in-hospital outcome in repeat-MI patients with multivessel disease.

The present report has demonstrated for the first time that the number of diseased vessels ≥2 or diseased LMT on initial CAG was an independent positive predictor of in-hospital mortality in the recurrent-MI patients undergoing primary PCI, but not in the first-MI patients. In contrast, acquisition of TIMI 3 flow in the infarct-related artery just after primary PCI was not an independent negative predictor in the repeat-MI patients, but was in the first-MI patients. These inconsistent data suggest that for the repeat-MI patients with multivessel disease, primary PCI in the infarct-related artery alone might be insufficient and additional IABP, multivessel PCI or early staged PCI should be considered in order to improve the in-hospital prognosis. However, according to the guidelines for PCI published by the American Heart Association, the American College of Cardiology, and the Society for Cardiovascular Angiography and Interventions in 2005, PCI should not be performed in a non-infarct-related coronary artery at the time of primary PCI of the infarct-related artery in AMI patients without hemodynamic compromise![10] Multivessel PCI might require larger amounts of contrast, leading to contrast-induced nephropathy. In addition, there is a possibility that acute closure, no or slow reflow, or vasospasm in a non-infarct-related coronary artery during primary PCI could result in a critical condition such as cardiogenic shock. Therefore, early staged PCI for the non-infarct-related coronary artery under sufficient medication, such as antiplatelet drugs, statins, and vasodilators, might be a more suitable therapy for recurrent AMI patients with multivessel disease, compared with multivessel PCI during primary PCI. On the other hand, based on our data, for first-MI patients, primary PCI for the infarct-related artery alone is an appropriate strategy.

Previous and recent reports have indicated that approximately 50% of patients presenting with AMI have multivessel coronary artery disease, and even in the primary PCI era, those patients have a higher risk of in-hospital death![9,11,12] However, the role of multivessel PCI or early staged PCI in AMI patients with multivessel disease during the index hospital stay remains controversial![13–15] A recent report from Corpus et al indicated that in AMI patients with multivessel disease, multivessel PCI was associated with higher frequency of re-infarction, revascularization, and major adverse cardiac events (MACE), compared with PCI restricted to the infarct-related artery alone, suggesting that in AMI patients with multivessel disease, PCI should be performed for the infarct-related artery alone during the index hospital stay![13] In contrast, another recent report has shown that in AMI patients with multivessel disease, multivessel PCI was not associated with additional death and MACE, compared with PCI in the infarct-related artery alone![14] and another recent study has also pointed out that incomplete revascularization was a significant and independent risk of death and MACE, particularly in AMI patients with lowered ejection fraction, impaired renal function, or diabetes mellitus![15] Our study has also demonstrated that the presence of multivessel disease or diseased LMT on initial CAG was an independent positive predictor of in-hospital death in the repeat-MI patients, a subgroup of high-risk patients with AMI, but not in the first-MI patients. Further prospective and long-term follow-up studies are necessary to ascertain the determinants of prognosis in patients with recurrent MI and to evaluate the safety and efficacy of multivessel PCI or early staged PCI in this population.

Study Limitations

First, this was a retrospective observational analysis of a relatively small number of patients. Second, data on clinical background and angiographic results of primary PCI were not available for all AMI patients undergoing primary PCI. Third, we have not accounted for left ventricular function and door-to-balloon time, which might be a predicting risk of in-hospital death. Fourth, "ST-elevation MI" was not discriminated from "non-ST-elevation MI".

Conclusion

The present study provides evidence that the number of diseased vessels ≥2 or diseased LMT on initial CAG is an independent risk factor of in-hospital death in recurrent-MI patients undergoing primary PCI. However, the relatively small sample size of our report is a major limitation and a larger study should be performed to confirm our findings.

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Appendix 1

The following institutions and principal investigators participated in the present study as the AMI-Kyoto Multi-Center Risk Study Group.
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Effects of Pretreatment With Statins on Infarct Size in Patients With Acute Myocardial Infarction Who Receive Fibrinolytic Therapy

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Background Experimental studies suggest that statins promote vascular fibrinolysis, so statin treatment before the onset of acute myocardial infarction (AMI) may result in a smaller infarct size.

Methods and Results The study group comprised 310 patients with AMI who received fibrinolysis within 12 h after symptom onset: 39 had received statin pretreatment (statin group) and 271 had not (non-statin group). Initial Thrombolysis In Myocardial Infarction (TIMI) flow grade did not differ between groups. Among 120 patients with initial TIMI flow grade 0/1, achievement of TIMI flow grade ≥2 after passing the guidewire through the culprit lesion was more frequent in the statin group (70% vs 35%, P=0.03). The final rate of TIMI flow grade 3 was higher in the statin group (95% vs 86%, P=0.11). Area under the curve (AUC) for creatine kinase (CK) was lower in the statin group (55,972±45,934 vs 84,195±84,276 IU·L^{-1}·h^{-1}, P=0.04). Multivariate analysis revealed statin pretreatment as an independent negative predictor of larger infarct size as defined by the upper tertile of AUC for CK (odds ratio 0.25, 95% confidence interval 0.07–0.91, P=0.035).

Conclusion Statin pretreatment may enhance fibrinolysis and reduce infarct size in patients with AMI. (*Circ J* 2009; **73:** 330–335)

Key Words: Acute myocardial infarction; Electrocardiogram; Fibrinolysis; Statins

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used clinically to decrease serum cholesterol levels.[1] Recent studies have focused on the pleiotropic effects of statins, which are independent of their lipid-lowering effects, such as stimulation of fibrinolysis by altering the levels and activities of tissue-plasminogen activator (t-PA) and plasminogen activator inhibitor-1.[2,3] Statins also reduce hemostasis by inhibiting platelet activation and the procoagulation cascade, and by augmenting the anticoagulation cascade.[4] Thus, statins appear to effectively enhance the fibrinolytic activity of t-PA. An experimental study in animals has shown that combination treatment with a statin and t-PA after stroke increases cerebral blood flow and reduces infarct volume as compared with fibrinolytic treatment alone;[5] however, data in humans are lacking. Prompt reperfusion of the occluded artery is crucial to limiting the size of an infarct. The present study was designed to test the hypothesis that statin treatment before the onset of acute myocardial infarction (AMI) contributes to prompt coronary artery reperfusion and smaller infarct size in patients with AMI who receive fibrinolytic therapy. We examined the relationship between statin pretreatment and the rate of coronary artery reperfusion assessed according to the Thrombolysis In Myocardial Infarction (TIMI)[6] flow grade and infarct size in patients with AMI who were given fibrinolytic therapy. The degree of myocardial damage before and after reperfusion therapy was also assessed on the basis of electrocardiographic (ECG) findings.

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Methods

Study Population

We enrolled 310 consecutive patients with ST-segment elevation AMI (mean age 60±11 years; 268 men, 42 women) who fulfilled the following criteria: (1) no history of myocardial infarction; (2) admission to Yokohama City University Medical Center within 12 h of symptom onset; (3) absence of conditions precluding the evaluation of ST-segment changes on ECG (left or right bundle-branch block, ventricular pacing); and (4) received fibrinolytic therapy. The diagnosis of AMI was based on typical chest pain lasting at least 30 min, ST-segment elevation of at least 1 mm in 2 contiguous leads, and a subsequent increase in the serum creatine kinase (CK) level to more than twice the upper limit of normal. Cardiac symptoms occurring within 48 h before the onset of AMI were defined as preinfarction angina.[7] In Yokohama City University Medical Center, in principle, patients without any contraindications for fibrinolysis were given 200 mg oral aspirin, 50 IU/kg intravenous heparin, and

800,000 units (approximately half the standard dose) intravenous monteplase, which is a mutant t-PA developed in Japan that can be given as a single-bolus intravenous injection. Glycoprotein IIb/IIIa inhibitors were not available in Japan at the time of the study. The final decision about fibrinolysis was left to the physician's discretion. In this study, we selected only patients who underwent fibrinolysis. All patients provided informed consent and the study protocol was approved by the hospital's Ethics Committee.

Definitions

We measured white blood cell and neutrophil counts, and triglycerides, total cholesterol, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol-concentrations in serum on admission, using standard methods. Hypercholesterolemia was considered present if it had been previously diagnosed or if the total cholesterol concentration on admission was higher than 220 mg/dl or the low-density lipoprotein-cholesterol concentration on admission was higher than 140 mg/dl. Whether statins had been administered before admission was determined from detailed interviews or medical records.

Coronary Angiography (CAG)

CAG was performed as soon as possible after admission. The perfusion status of the infarct-related artery was assessed according to the TIMI study classification. The grade of collateral filling in the infarct-related artery was evaluated as described by Rentrop et al[8] and a good collateral channel was defined as grade 2 or 3. We initially evaluated TIMI flow grade in the infarct-related artery 29 min after fibrinolysis on average. If TIMI flow grade at this time was 0, 1, or 2, percutaneous coronary intervention, including stent implantation, was immediately performed. As a rule, immediate percutaneous coronary intervention was not done in patients with TIMI flow grade 3. Reperfusion time was defined as the time from symptom onset to the time when TIMI flow grade ≥2 was confirmed angiographically. In patients who had an improvement in symptoms and a decrease in ST-segment elevation before cardiac catheterization in whom TIMI flow grade ≥2 was confirmed on the first angiogram, reperfusion time was defined as the time from symptom onset until the time of confirming such clinical findings.

ECG Analysis

A 12-lead ECG was recorded on admission and 1 h after the final angiogram, at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The isoelectric line was defined as the level of the preceding TP segment. ST-segment elevation was measured 80 ms after the J point by a single cardiologist who was unaware of all other clinical data. ST-segment elevation was calculated as the sum of ST-segment elevations in leads I, aV_L, and V_{1-6} for anterior AMI and leads II, III, aV_F, and V_{5-6} for non-anterior AMI? In addition to ST-segment measurement, we calculated the 32-point QRS score[10] which has been validated in patients with AMI and strongly correlates with infarct size[11]

Cardiac Enzyme Study

Blood samples were obtained on admission, at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge. Peak levels of CK and the areas under the curve (AUC) for CK were calculated by the linear-trapezoidal method[12]

Statistical Analysis

Data are expressed as mean values ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Analysis of variance was used to calculate P-values for continuous variables. Chi-square analysis or Fisher's exact test was used to compare categorical variables. Differences were considered statistically significant at $P<0.05$. Multivariate analysis was used to identify clinical predictors of larger infarct size, defined as the upper tertile of AUCs for CK among the variables associated ($P<0.10$) with this index on univariate analysis. Odds ratios and 95% confidence intervals were calculated. Data were analyzed with the SPSS statistical package (Release 10, SPSS Inc, Chicago, IL, USA).

Results

Among the 310 study patients, 39 had received statin treatment for at least 1 month before admission[13] (statin group: 17 [43.6%] pravastatin, 15 [38.5%] atrovastatin, 4 [10.3%] simvastatin, 2 [5.1%] fluvastatin, 1 [2.6%] pitavastatin), and 271 had not (non-statin group).

Patient Characteristics

The baseline characteristics of the patients in the 2 groups are summarized in **Table 1**. There were no significant differences between the 2 groups in age, smoking, preinfarction angina, heart rate, systolic blood pressure, Killip class, white blood cell count, lipid profiles on admission, time from onset to admission, time from admission to fibrinolysis, time from fibrinolysis to angiography, percutaneous coronary intervention, or stent implantation. Patients in the statin group were less likely to be male and to have anterior AMI, and were more likely to have coronary risk factors such as hypertension, hyperlipidemia, and diabetes mellitus and to have received long-term therapy with drugs such as aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blocker, and β-blockers before admission. There was a trend toward a lower neutrophil count on admission in the statin group, but the difference did not reach statistical significance.

ECG and CAG Findings

ECG and CAG findings are shown in **Table 2** and **Figs 1, 2**. Patients in the statin group had a smaller sum of ST-segment elevation and a lower QRS score, both on admission and 1 h later. When the analysis was limited to patients with anterior AMI, QRS scores were significantly lower in the statin group on admission and 1 h later. In addition, the sum of ST-segment elevation on admission was similar in the 2 groups, and there was a trend toward a lower ST-segment elevation 1 h later in the statin group, but the difference did not reach statistical significance.

There were no significant differences between the 2 groups in multivessel disease or collateral circulation. Initial TIMI flow grade did not differ between the 2 groups. Among the 120 patients with an initial TIMI flow grade 0 or 1, the achievement of TIMI flow grade ≥2 after passing the guidewire through the culprit lesion was more frequent in the statin group (**Fig 1**). The rate of final TIMI flow grade 3 was slightly, but not significantly, higher in the statin group.

Infarct Size and Predictors of Larger Infarct Size

Peak CK and AUC of CK were lower in the statin group (**Table 1**). When the analysis was limited to patients with an-

Table 1 Clinical Characteristics of the Patients

	Statin group (n=39)	Non-statin group (n=271)	P value
Age (years)	63±10	60±11	0.15
Men	25 (64%)	243 (90%)	<0.001
Hypertension	29 (74%)	144 (55%)	0.020
Diabetes	18 (47%)	69 (26%)	0.006
Hypercholesterolemia	39 (100%)	144 (55%)	<0.001
Current smoker	27 (71%)	203 (77%)	0.39
Preinfarction angina	12 (31%)	103 (38%)	0.38
Heart rate on admission (beats/min)	77±17	75±22	0.69
SBP on admission (mmHg)	135±31	141±33	0.29
Killip class on admission ≥2	1 (3%)	20 (8%)	0.27
WBC count on admission (/mm^3)	9,960±2,363	10,641±3,823	0.28
Neutrophil count (/mm^3)	5,977±2,199	7,036±3,687	0.08
Lipid profile on admission (mg/dl)			
Total cholesterol	205±52	212±44	0.41
LDL-cholesterol	127±44	138±39	0.11
HDL-cholesterol	49±13	44±11	0.54
Triglycerides	173±111	169±181	0.91
Anterior AMI	13 (33%)	142 (53%)	0.025
Time intervals to treatment			
Symptom onset to admission (min)	110±108	106±102	0.79
Symptom onset to recanalization (min)	147±117	158±105	0.55
Admission to fibrinolysis (min)	13±6	16±16	0.22
Fibrinolysis to first angiography (min)	32±16	29±12	0.10
Fibrinolysis to passing the guidewire* (min)	51±18	48±18	0.38
PCI	30 (79%)	190 (71%)	0.29
Stent implantation	21 (57%)	143 (53%)	0.67
Medications before admission			
Aspirin	9 (23%)	11 (4%)	<0.001
ACEI/ARB	16 (46%)	39 (15%)	<0.001
β-blocker	6 (17%)	14 (5%)	0.010
Medication in hospital			
Aspirin	39 (100%)	259 (99%)	0.70
ACEI/ARB	31 (80%)	229 (85%)	0.43
β-blocker	21 (54%)	129 (50%)	0.62
Peak CK (IU/L)	2,187±1,967	3,334±3,320	0.036
Peak CK for anterior AMI (IU/L)	2,758±2,910	4,136±3,924	0.22
AUC-CK (IU·L^{-1}·h^{-1})	55,972±45,934	84,195±84,276	0.042
AUC-CK for anterior AMI (IU·L^{-1}·h^{-1})	60,572±54,742	97,940±98,138	0.18

Data are means±SD or numbers (%) of patients.
SBP, systolic blood pressure; WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CK, creatine kinase; AUC, area under the curve.
**Passing the guidewire through the culprit lesion.*

Table 2 Electrocardiographic and Angiographic Findings

	Statin group (n=39)	Non-statin group (n=271)	P value
Sum of ST-segment elevation			
On admission (mm)	13±14	21±17	0.012
1 h later (mm)	4±6	8±8	0.004
On admission for anterior AMI (mm)	26±18	30±18	0.53
1 h later for anterior AMI (mm)	9±6	13±8	0.15
Multivessel disease	10 (26%)	72 (27%)	0.97
Initial TIMI flow grade			
0/1	16 (41%)	104 (38%)	0.66
2	10 (26%)	86 (32%)	0.44
3	13 (32%)	81 (30%)	0.99
Good collateral circulation* (%)#	5/16 (31%)	18/104 (17%)	0.19
Final TIMI flow grade			
0/1	1 (3%)	8 (3%)	0.91
2	1 (3%)	31 (11%)	0.09
3	37 (95%)	232 (86%)	0.11

Data are number (%) of patients.
**Grade 2 or 3 collateral flow to the infarct-related artery.*
#Only patients with initial TIMI flow grade 0 or 1.
TIMI, Thrombolysis In Myocardial Infarction. Other abbreviation see in Table 1.

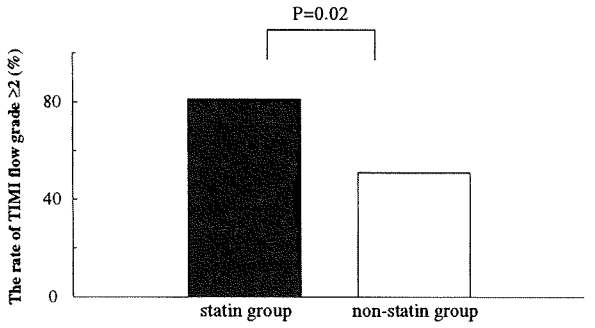

Fig 1. Comparison of the achievement of Thrombolysis In Myocardial Infarction (TIMI) flow grade ≥2 after passing the guidewire through the culprit lesion in the statin and non-statin groups. It was more frequent in patients who had initial TIMI flow grade 0 or 1 (statin group, n=16; non-statin group, n=104).

terior AMI, there were trends toward lower peak CK levels and smaller AUCs for CK in the statin group, but the differences did not reach statistical significance. In the multivariate analysis, statin pretreatment was a negative determinant, and Killip class ≥2 on admission, anterior AMI, and initial TIMI flow grade 0 or 1 were positive determinants of a larger infarct size as defined by the upper tertile of AUC for CK (**Table 3**). Other variables such as multivessel disease, final TIMI flow grade ≤2, and percutaneous coronary intervention, which were associated with a larger infarct size on univariate analysis (P<0.10), were not significant predictors of a larger infarct size.

Discussion

Our study showed that statin pretreatment reduced infarct size in patients with AMI who received fibrinolytic therapy. Although statin pretreatment was not associated with restoration of TIMI flow grade ≥2 at initial angiography, among patients with initial TIMI flow grade 0 or 1, the achievement TIMI flow grade ≥2 was more frequent in the statin group. At final angiography, the rate of TIMI flow grade 3 tended to be higher in the statin group. Moreover, statin pretreatment was associated with reduced myocardial damage during ischemia and reperfusion, as assessed by ECG findings.

Table 3 Multivariate Analysis of Factors Associated With Large Infarct Size as Defined by the Upper Tertile of AUC for CK

	OR (95%CI)	*P value*
Killip class on admission ≥2	*4.13 (1.52–11.23)*	*0.005*
Anterior AMI	*2.44 (1.35–4.41)*	*0.003*
Multivessel disease	*1.74 (0.93–3.28)*	*0.086*
PCI	*1.25 (0.63–2.46)*	*0.525*
Initial TIMI flow grade 0/1	*2.59 (1.45–4.62)*	*0.001*
Final TIMI flow grade ≤2	*2.02 (0.92–4.42)*	*0.078*
Statin pretreatment	*0.25 (0.07–0.91)*	*0.035*

Only univariate variables with a value of P<0.10 are shown.
OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

Statins and Fibrinolysis

An experimental study in animals has shown beneficial effects of combination treatment with a statin and t-PA on cerebrovascular patency after stroke[5] Following plaque disruption, statins promote vascular fibrinolysis by exerting various inhibitory actions on platelet deposition and aggregation, coagulation factors, and rheology[14,15] However, our study found no significant difference in the coronary artery reperfusion rate as assessed by initial TIMI flow grade after fibrinolytic therapy between patients with and without statin pretreatment. Susceptibility to coronary fibrinolytic treatment is influenced by a number of related factors, including the age of the thrombus, its composition, the characteristics of the surrounding plasma, and the temporal evolution of the occluding thrombosis[16,17] Perhaps the small dose of t-PA (approximately half the standard dose) used in our study was inadequate and the timing of initial coronary angiography (mean, 29 min from fibrinolysis) was too early to demonstrate an effect of statin pretreatment on coronary artery reperfusion after fibrinolytic therapy. When the analysis was limited to patients with an occluded infarct-related artery

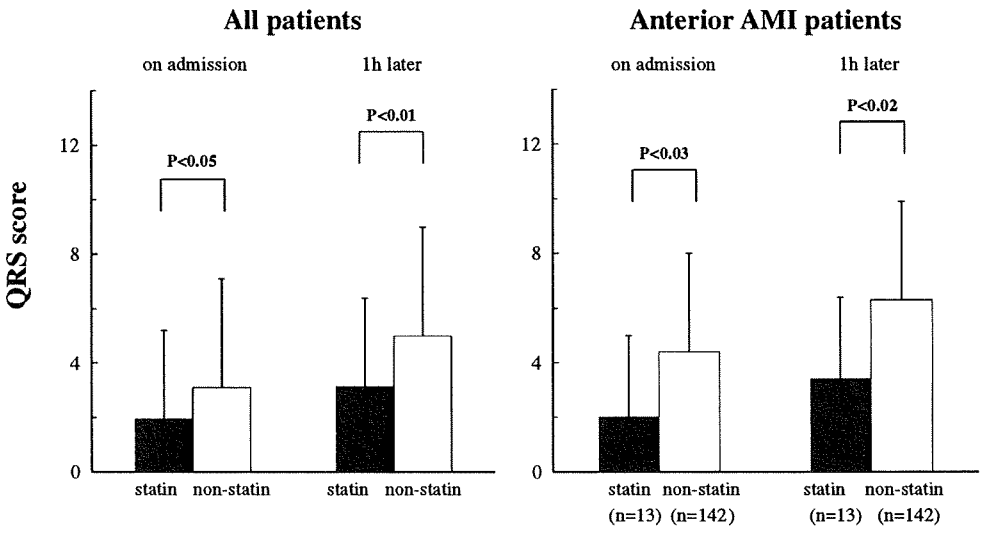

Fig 2. Comparisons of QRS scores on ECG at admission and 1 h later in the statin and non-statin groups. AMI, acute myocardial infarction.

on the initial angiogram, coronary artery reperfusion with TIMI flow grade ≥2 after passing the guidewire through the culprit lesion was more frequently associated with statin pretreatment, suggesting that the thrombus was more fragile. This finding may imply that statins partially enhance the efficacy of t-PA.

Statins and Myocardial Damage

In the early stages of AMI, the degree of ST-segment elevation and the evolution of abnormal Q waves may reflect the severity of myocardial damage[18–20] Greater ST-segment elevation implies ongoing severe myocardial injury, and higher QRS scores imply broader transmural myocardial damage. In our study, patients who received statin pretreatment had a smaller magnitude of ST-segment elevation and lower QRS scores on admission as well as after reperfusion. The ECG findings on admission are not affected by myocardial damage occurring after reperfusion therapy, such as reperfusion injury or distal embolization, which suggests that statin pretreatment was associated with less myocardial damage during ischemia and reperfusion, resulting in a smaller infarct size as assessed by peak CK levels and AUC for CK. Although the precise mechanisms underlying the protective effects of statins against ischemia–reperfusion injury are unclear, statins have shown vasculoprotective and cardioprotective effects in experimental studies. Statins may improve endothelial function by decreasing expression of endothelial adhesion molecules, increasing nitric oxide bioavailability, and attenuating the production of reactive oxygen species[2,21,22] In addition, statins are thought to stabilize plaque by decreasing lipid oxidation, inflammation, matrix metalloproteinase-2, and cell death and by increasing the content of tissue inhibitor of metalloproteinase-1 and collagen; these effects might reduce distal embolization[23] Furthermore, statins have been shown to open mitochondrial adenosine triphosphate-sensitive potassium channels, suggesting pharmacological ischemic preconditioning effects[24,25] These effects might contribute to reduced myocardial damage during ischemia–reperfusion. Several studies have demonstrated that statin pretreatment reduces microvascular and myocardial damage after coronary intervention in patients with AMI[13,26]

Study Limitations

First, this was a single-center retrospective study performed in a relatively small number of patients. Second, we could not precisely assess the effects of the pretreatment period or the dose of statins. Furthermore, we could not analyze the effects of differences in statin type because of the small number of patients. Third, patients with statin pretreatment were more likely to have received drugs such as aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blocker, and β-blockers before admission. Although these medications may affect clinical outcomes, they were not found to be associated with larger infarct size. In addition, patients with statin pretreatment were more likely to have hypertension, hyperlipidemia, and diabetes mellitus. Patients given statin pretreatment may thus have been more aggressively treated in terms of diet, exercise, or other lifestyle interventions.

Conclusions

The present study shows that statin pretreatment is associated with a smaller infarct size in patients with AMI who receive fibrinolytic therapy. Our results provide evidence that statins have cardioprotective effects and enhance the effectiveness of t-PA.

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Early, Accurate, Non-Invasive Predictors of Left Main or 3-Vessel Disease in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

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Background: In patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS), identification of left main and/or 3-vessel disease (LM/3VD) is crucial for deciding whether to initiate early treatment with clopidogrel, which can increase the risk of surgical bleeding.

Methods and Results: On admission, the clinical factors of 501 patients with NSTE-ACS, who underwent coronary angiography, were evaluated. ST-segment shifts and the widest QRS duration were measured on an admission 12-lead electrocardiogram. Ninety-six patients had LM/3VD. Univariate analysis indicated that many factors were related to LM/3VD. On multivariate analysis, QRS duration (odds ratio (OR) 9.04, P<0.01), the degree of ST-segment elevation in lead aVR (OR 7.10, P<0.01), and positive-troponin T (OR 1.52, P<0.05) were independent predictors of LM/3VD. A QRS duration of >90 ms and a ST-segment elevation in lead aVR of ≥0.5 mm best identified LM/3VD. A QRS duration of >90 ms, a ST-segment elevation in lead aVR of ≥0.5 mm, and a positive-troponin T identified LM/3VD with sensitivities of 88%, 76%, and 54% (P<0.01), and specificities of 88%, 86%, and 71% (P<0.01), respectively.

Conclusions: A prolonged QRS duration, ST-segment elevation in lead aVR, and a positive-troponin T on admission are useful predictors of LM/3VD in patients with NSTE-ACS. In particular, a maximal QRS duration of >90 ms was the most sensitive predictor of LM/3VD. (*Circ J* 2009; **73:** 1105–1110)

Key Words: Acute coronary syndrome; Diagnosis; Electrocardiography

An early identification of patients with left main and/or 3-vessel disease (LM/3VD) is an important factor in the prognosis and selection of the optimal treatment strategy in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). Because combined antiplatelet therapy with aspirin and clopidogrel improves outcomes in patients with NSTE-ACS[1,2] current international clinical guidelines for the management of NSTE-ACS recommended the early initiation of clopidogrel plus aspirin[3,4] However, such a combined therapy can increase the risk of perioperative bleeding events and the need for blood transfusions in patients undergoing early coronary artery bypass graft surgery (CABG).[5,6] Therefore, clinicians might withhold treatment with clopidogrel until visualization of the coronary anatomy because of concern about operative bleeding in patients likely to require CABG, that is, in such patients, the early initiation of clopidogrel plus aspirin can cause CABG to be postponed until these agents have been eliminated. However, delayed treatment with clopidogrel can increase the risk of cardiac events in patients who do not require CABG. Early (ie, before angiography), accurate, non-invasive identification of patients with LM/3VD in whom CABG is most likely to be indicated is thus a major clinical issue with important therapeutic implications. We have previously demonstrated that ST-segment elevation in lead aVR and positive-troponin T on admission (especially the former) are useful predictors of the risk of LM/3VD in patients with NSTE-ACS[7–9] however, QRS duration in previous studies was not considered. Although electrocardiographic assessment of myocardial ischemia is usually based on ST-segment deviation, QRS prolongation has been shown to be more sensitive than ST-segment changes for the detection of myocardial ischemia[10–12] Several studies have found that that exercise-induced QRS prolongation is related to the severity and extent of coronary artery disease[13,14] However, the relationship between QRS duration on the admission electrocardiogram (ECG) and the severity and extent of coronary artery disease has not been explored previously in patients with NSTE-ACS. In the present study, we investigated clinical factors related to LM/3VD on admission, including QRS duration, in patients with NSTE-ACS who underwent coronary angiography.

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Methods

Study Group

We studied 501 consecutive patients (mean age 66±11 years, range 30–92 years; 348 men and 153 women) who were admitted to our coronary care unit and fulfilled the following criteria: (1) typical chest discomfort attributed to

cardiac ischemia, lasting at least 5 min and occurring within 24 h before hospital admission and involving an unstable pattern of pain, including rest pain, new onset, severe, or frequent angina, or accelerating angina;[6] (2) no conditions precluding the evaluation of QRS duration or ST-segment changes on the ECG (left or right bundle branch block, left ventricular hypertrophy, ventricular pacing, ventricular pre-excitation, non-ischemic cardiomyopathy, or antiarrhythmic drugs); (3) fully assessable ECG on admission; and (4) fully assessable angiographic data during hospitalization. We excluded patients with non-ischemic or atypical pain, transient or persistent new ST-segment elevation in leads other than lead aVR, Q-wave acute myocardial infarction on presentation, recent (<6 months) percutaneous coronary intervention, or prior CABG.

In our hospital, we perform emergency cardiac catheterization and revascularization immediately upon admission in patients with unstable hemodynamics caused by ischemic attacks and in whom ischemic attacks cannot be controlled by intensive drug treatment (particularly, patients with decreased cardiac function). In other patients, drug treatment is given after admission to stabilize their condition, and cardiac catheterization is performed after their condition has stabilized. In patients with indications for revascularization, revascularization is performed later. Urgent cardiac catheterization and revascularization are performed in patients with repeated episodes of angina or hemodynamic instability despite intensive drug therapy.

Electrocardiographic Classification

Standard 12-lead ECGs were recorded on admission at a 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.[15,16] The widest QRS duration on each ECG was manually measured after magnification to 200% by a single investigator who was blinded to all other clinical data. The measurement of the QRS complex began at the left side of the line of junction of the baseline and the Q wave, and ended at the left side of the line of junction of the R or S wave.[17] If there were no Q waves, the measurement was done from the R wave. If there was an obscure S-wave ending, the patient was excluded. Intraobserver variability for the QRS prolongation was 0.8±1.3 ms.

Analysis of Biochemical Markers

A qualitative assay for cardiac-specific troponin T (Roche Diagnostics, detection limit, 0.1 ng/ml of cardiac-specific troponin T) was performed on admission. Troponin T ≥0.1 ng/ml was defined as positive. Blood samples for measuring plasma high-sensitivity C-reactive protein levels were also taken on admission. Brain natriuretic peptide was simultaneously measured in 304 patients by an immunoenzymometric assay using a commercial kit (Shionogi Co, Ltd, Osaka, Japan). Creatine kinase (CK)-MB levels were determined on admission, at 3-h intervals during the first 24 h, and in any patient with suspected reinfarction.

Angiographic Analysis

All patients underwent cardiac catheterization 3 days on average after admission. All coronary angiograms were evaluated by a single investigator who was blinded to all other clinical data. Stenosis of ≥50% in the diameter of the left main coronary artery or stenosis of ≥75% in 1 or more of the major epicardial vessels or their main branches was considered clinically significant.

Clinical Data

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 re-elevation of CK-MB to higher than the upper limit of normal if the previous CK-MB level was in the normal range, or 50% above the previous level if the previous level was above the normal range (ie, a recurrent myocardial infarction in patients with evolving non-Q-wave myocardial infarction on admission). The patients were followed up for 30 days after admission to the hospital.

Statistical Analysis

Continuous data are expressed as mean ± SD, and categorical data as percentages. Analysis of variance was used to assess continuous variables. Chi-squared 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/3VD among the variables associated ($P<0.05$) with this diagnosis on univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In addition, the sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of predictors of LM/3VD identified by multivariate analysis were determined. Data were analyzed using SPSS software (Release 10, SPSS Inc, Chicago, IL, USA).

Results

Patient Characteristics

The prevalence of LM/3VD was 19% (LMT 6%), 2-vessel disease 19%, 1-vessel disease 43%, and 0-vessel disease 19%. The baseline characteristics of the subjects are shown in **Table 1**. Patients with LM/3VD were older and had higher prevalences of a Killip class of ≥2, prior myocardial infarction, diabetes mellitus, and positive-troponin T; a lower prevalence of smoking; a higher heart rate; and higher levels of CK-MB and brain natriuretic peptide than patients without LM/3VD did. There were no significant differences in sex, systolic blood pressure, symptom onset ≤6 h, prior percutaneous coronary intervention, renal insufficiency (defined as serum creatinine ≥1.5 mg/dl on admission), hypercholesterolemia, or a family history of coronary artery disease between patients with and those without LM/3VD. There was a trend toward a higher rate of hypertension and a higher level of high-sensitivity C-reactive protein in patients with LM/3VD, but the differences did not reach statistical significance. During hospitalization, revascularization procedures, including CABG, were more frequently performed in patients with LM/3VD. Within 30 days after admission, the rate of death was higher in patients with LM/3VD. The rate of (re)infarction was slightly but not significantly higher in patients with LM/3VD. Urgent revascularization, especially urgent CABG, was more fre-

Table 1. Clinical Characteristics

	LM/3VD (n=96)	Non-LM/3VD (n=405)	P value
Age (years)	68±11	66±11	0.027
Men	63 (66%)	285 (70%)	0.36
Systolic blood pressure on admission (mmHg)	146±29	150±25	0.21
Heart rate on admission (beats/min)	83±20	76±17	0.001
Killip class ≥2 on admission	20 (21%)	20 (5%)	<0.001
Symptom onset ≤6 h	79 (82%)	313 (77%)	0.29
Prior myocardial infarction	26 (27%)	72 (18%)	0.039
Prior PCI	17 (18%)	77 (19%)	0.77
Renal insufficiency*	11 (12%)	32 (8%)	0.26
Risk factors			
Smoking	37 (39%)	206 (51%)	0.030
Hypercholesterolemia	48 (50%)	201 (50%)	0.95
Diabetes mellitus	47 (49%)	124 (31%)	0.001
Hypertension	69 (72%)	262 (65%)	0.18
Family history of coronary artery disease	25 (26%)	106 (26%)	0.98
High-sensitivity CRP on admission (mg/dl)	0.488±0.906	0.352±0.612	0.09
Positive Troponin T on admission	52 (54%)	116 (29%)	<0.001
CK-MB on admission (IU/L)	22±35	15±16	0.006
BNP on admission** (pg/ml)	284±312 (n=49)	162±281 (n=255)	0.007
Cardiac procedures during hospitalization			
PCI	38 (40%)	239 (59%)	0.001
CABG	48 (50%)	24 (6%)	<0.001
Any revascularization (PCI or CABG)	83 (87%)	255 (63%)	<0.001
30-day outcome			
Death	2 (2%)	1 (0.2%)	0.036
Myocardial (re)infarction	7 (7%)	14 (4%)	0.09
Death/myocardial (re)infarction	9 (9%)	15 (4%)	0.019
Urgent PCI	10 (11%)	23 (6%)	0.09
Urgent CABG	32 (33%)	9 (2%)	<0.001
Urgent revascularization (PCI or CABG)	42 (44%)	32 (8%)	<0.001
Any of the above	46 (48%)	41 (10%)	<0.001

Data are mean±standard deviation or numbers (%) of patients.
LM/3VD, left main and/or 3-vessel disease; PCI, percutaneous coronary intervention; CRP, C-reactive protein; CK, creatine kinase; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft surgery.
*Renal insufficiency was defined as serum creatinine ≥1.5 mg/dl on admission.
**Available for 304 patients.

Table 2. Electrocardiographic Findings on Admission

	LM/3VD (n=96)	Non-LM/3VD (n=405)	P value
ST-segment depression ≥0.5 mm	91 (95%)	254 (63%)	<0.001
Maximal ST-segment depression (mm)	1.9±1.2	0.8±1.0	<0.001
Sum of ST-segment depression (mm)	7.8±5.8	2.5±3.5	<0.001
Number of leads with ST-segment depression ≥0.5 mm	5.4±2.5	2.5±2.5	<0.001
ST-segment elevation ≥0.5 mm in lead aVR	73 (76%)	58 (14%)	<0.001
ST-segment elevation in lead aVR (mm)	0.7±0.6	0.1±0.3	<0.001
Maximal QRS duration (ms)	102±10	85±7	<0.001

Data are numbers (%) of patients.
Abbreviation see in Table 1.

Table 3. Univariate and Multivariate Predictors of LM/3VD on Admission

	Univariate P value	Multivariate P value	OR (95%CI)
Age	0.027	0.17	
Heart rate	0.001	0.40	
Killip class ≥2	<0.001	0.31	
Prior myocardial infarction	0.039	0.19	
Smoking	0.030	0.31	
Diabetes mellitus	0.001	0.56	
Positive-Troponin T	<0.001	0.049	1.52 (1.02–3.99)
CK-MB	0.006	0.48	
Maximal ST-segment depression	<0.001	0.09	
Sum of ST-segment depression	<0.001	0.06	
Number of leads with ST-segment depression ≥0.5 mm	<0.001	0.21	
Degree of ST-segment elevation in lead aVR	<0.001	<0.001	7.10 (4.91–76.2)
Maximal QRS duration (per 10 ms)	<0.001	<0.001	9.04 (4.88–16.7)

OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 1.

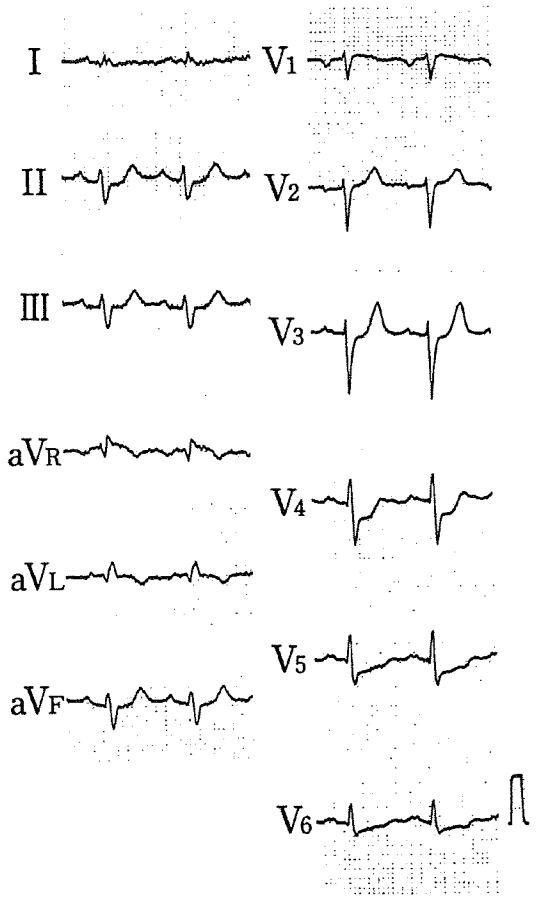

Figure. A representative electrocardiogram (ECG) of a patient (a 73-year-old man) with left main and/or 3-vessel disease (LM/3VD). Troponin T was positive on admission. The ST-segment elevation in lead aVR was 1.0 mm and the maximal QRS duration was 110 ms in lead V_4 on admission ECG. A coronary angiography showed total occlusion at the left anterior descending coronary artery (segment 6) and the left circumflex coronary artery (segment 13), and 90% stenosis at the right coronary artery (segment 1).

quently done in patients with LM/3VD.

Electrocardiographic Findings

Patients with LM/3VD had a higher prevalence and a greater amount of ST-segment depression, as well as a greater number of leads with ST-segment depression (excluding lead aVR) than patients without LM/3VD did. Patients with LM/3VD also had a higher prevalence and a greater magnitude of ST-segment elevation in lead aVR. Patients with LM/3VD had a longer QRS duration (**Table 2**).

Predictors of LM/3VD

In the multivariate models, maximal QRS duration was the strongest predictor of LM/3VD, followed by the degree of ST-segment elevation in lead aVR, and positive-troponin T (**Table 3**, **Figure**). The other variables that were associated with LM/3VD ($P<0.05$) on univariate analysis were not significant predictors of LM/3VD. The sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of a prolonged QRS duration, greater ST-segment elevation in lead aVR, and positive-troponin T for LM/3VD are shown in **Table 4**. For each successive 10-ms increase in the definition of prolonged QRS duration (from >80 to >100 ms), there was a stepwise increase in specificity from 38% to 99%, with a corresponding stepwise decrease in sensitivity from 99% to 46%. For each successive 0.5-mm increase in the definition of greater ST-segment elevation in lead aVR (from ≥0.5 to ≥1.5 mm), there was a stepwise increase in specificity from 86% to 99%, with a corresponding stepwise decrease in sensitivity from 76% to 18%. A maximal QRS duration of >90 ms and a ST-segment elevation in lead aVR of ≥0.5 mm were the 2 variables that best identified LM/3VD. Multivariate analysis also showed that maximal QRS duration of >90 ms was the strongest predictor of LM/3VD (OR 33.4, 95%CI 13.5–62.7, $P<0.001$), followed by ST-segment elevation in lead aVR of ≥0.5 mm (OR 8.18, 95%CI 2.64–25.3, $P<0.001$), and positive-troponin T (OR 1.72, 95%CI 1.10–4.12, $P<0.05$).

Discussion

Our study showed that prolonged QRS duration, ST-segment elevation in lead aVR, and positive-troponin T on admission were useful predictors of LM/3VD in patients with NSTE-ACS. In particular, a maximal QRS duration of >90 ms was the most sensitive predictor of LM/3VD. These inexpensive, non-invasive, and easily available markers facilitated the early identification of LM/3VD.

We have previously demonstrated that ST-segment elevation in lead aVR and a positive-troponin T on admission are useful for predicting the risk of LM/3VD in patients with NSTE-ACS[7–9] Troponin T on admission is a well-established marker of high risk in patients with NSTE-ACS;[18,19] whereas ST-segment elevation in lead aVR is more useful for identifying patients with LM/3VD. The results of the

Table 4. Comparison of QRS Duration, ST-Segment Elevation in Lead aVR, and Positive-Troponin T on Admission for Predicting LM/3VD

	Sensitivity	Specificity	PPV	NPV	Predictive accuracy
Maximal QRS duration					
>80 ms (%)	99**	38**	27**	99	49**
>90 ms (%)	88	88	63	97	88
>100 ms (%)	46**	99**	92**	89**	89
ST-segment elevation in lead aVR					
≥0.5 mm (%)	76*	86	56	94*	84
≥1.0 mm (%)	43**	96**	74	88**	86
≥1.5 mm (%)	18**	99**	85	84**	84
Positive-troponin T	54**	71**	31**	87**	68**

PPV, positive predictive value; NPV, negative predictive value. Other abbreviation see in Table 1.
*$P<0.05$, **$P<0.01$ vs maximal QRS duration >90 ms.

present study support these findings. Most previous studies assessing the clinical significance of changes on the admission ECG in patients with NSTE-ACS have focused on ST-segment depression in leads other than aVR[16,19–22] However, ST-segment elevation in lead aVR was more strongly associated with LM/3VD than ST-segment depression was in other leads in patients with NSTE-ACS, which is consistent with the results of previous studies[7–9,15,23]

In the present study, we included QRS duration in the electrocardiographic analysis, in addition to ST-segment deviation. QRS duration was strongly associated with LM/3VD; furthermore, maximal QRS duration of >90 ms was the most sensitive predictor of LM/3VD. Several mechanisms might account for these findings. First, QRS prolongation is most likely caused by extensive ischemia, as indicated by concomitant greater ST-segment deviation. Experimental studies have reported that myocardial ischemia results in slow conduction velocity in ischemic areas[24,25] Such decreased conduction velocity is apparently a consequence of regional hyperkalemia, caused by leakage of potassium from ischemic cells[24,25] This decreased conduction velocity associated with myocardial ischemia is manifested as QRS prolongation on the surface ECG. Cantor et al reported that QRS duration was more prolonged when the proximal and middle segments of major arteries were occluded than when the distal segments or smaller branches were occluded during percutaneous transluminal coronary angioplasty in humans[12] Other studies have reported that exercise-induced QRS prolongation without bundle-branch block is directly related to the number of diseased vessels or segmental contraction abnormalities[13,14] Several studies have demonstrated that the specificity of QRS prolongation for the detection of myocardial ischemia is similar to that of ST-segment changes, whereas the sensitivity of the former is higher[10–12] In the present study, QRS prolongation and ST-segment elevation in lead aVR had similar specificity, but the former was more sensitive, for predicting LM/3VD. The second possible reason for the strong association between QRS duration and LM/3VD is that QRS prolongation might correlate with heart failure. Murkofsky et al reported that a QRS duration of >100 ms on a standard resting 12-lead ECG was a marker of decreased left ventricular function[26] In the present study, a QRS duration of >100 ms was highly specific (99%), but insensitive (46%) for the prediction of LM/3VD. In addition, QRS prolongation was an independent predictor of LM/3VD after adjusting for heart failure, as evidenced by the worse Killip class. Third, QRS prolongation might reflect of a greater amount of infarction[27,28] However, the relationship of QRS prolongation to LM/3VD remained relevant even after adjustment for myocardial damage, as indicated by troponin T or CK-MB.

Study Limitations

Several limitations of the present study should be considered when evaluating the clinical implications of our findings. In routine clinical practice, the measurement of QRS duration on ECGs enlarged to 200% would be troublesome, and the use of computerized ECG techniques might help to standardize measurements of QRS duration. However, this study was retrospective, and ECGs were recorded at a paper speed of 25 mm/s by means of an electrocardiograph without a computer-based automatic analysis system. We therefore could not compare our manually measured values of QRS duration with those automatically measured by computer. This point should be addressed in future studies. Another limitation was that this study was performed at a single center and involved a small number of patients with NSTE-ACS who underwent coronary angiography. Furthermore, patients with known causes of a prolonged QRS duration were excluded.

Clinical Implications

In several previous studies, the prediction of high-risk patients with NSTE-ACS likely to undergo CABG was difficult solely on the basis of baseline clinical characteristics. However, these studies did not consider either ST-segment elevation in lead aVR or QRS duration on the admission ECG[29,30] A standard 12-lead ECG on admission is the initial and most widely used method for early risk stratification in patients with NSTE-ACS[31] Our study showed that QRS prolongation and ST-segment elevation in lead aVR on admission (especially the former) are useful for predicting LM/3VD and can thereby facilitate decision-making, that is, patients likely to have LM/3VD should promptly undergo an angiography and not receive clopidogrel therapy to allow early CABG. Our results emphasize the importance of analyzing QRS duration as well as ST-segment deviation on the admission ECG in the diagnostic workup of patients with NSTE-ACS.

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