Table 1 Clinical characteristics of the study subjects.

	DM	Non-DM	*p* value
N	178	151	
Age (year)	64.7 ± 9.2	65.8 ± 9.2	NS
Male (%)	143 (80)	120 (79)	NS
Hypertension (%)	116 (66)	111 (74)	NS
Dyslipidemia (%)	109 (62)	108 (72)	NS
Current smoker (%)	91 (54)	72 (49)	NS
Familial history (%)	40 (24)	33 (23)	NS
Fasting blood glucose (mg/dl)	159 ± 63	108 ± 24	<0.01
HbA1c (%)	7.1 ± 1.3	5.1 ± 0.4	<0.01
LDL-C (mg/dl)	115 ± 34	110 ± 41	NS
HDL-C (mg/dl)	47 ± 13	48 ± 13	NS
Triglyceride (mg/dl)	140 ± 77	143 ± 76	NS
Creatinine (mg/dl)	1.3 ± 1.7	1.2 ± 1.9	NS
C-reactive protein (mg/dl)	0.5 ± 1.5	0.3 ± 0.3	NS
History of MI (%)	38 (28)	31 (25)	NS
History of PCI (%)	4 (2)	0 (0)	NS
History of previous CABG (%)	8 (4)	0 (0)	NS
Diseased vessels			
LMT (%)	36 (20)	21 (14)	NS
3VD (%)	103 (58)	89 (59)	NS
1–2VD (%)	39 (22)	41 (27)	NS
Ejection fraction (%)	57.3 ± 15.2	59.1 ± 16.3	NS
Off-pump CABG (%)	174 (98)	151 (100)	NS

Data are presented as the mean value ± SD. DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary arterial bypass grafting; LMT, left main trunk; VD, vessel disease.

angiotensin II receptor blockers, and statins. In the DM group, 110 patients (61%) and 55 (31%) patients were treated with oral anti-diabetic agents and insulin, respectively.

Exercise tolerance and muscle strength

The exercise tolerance and muscle strength of the 2 groups are presented in Table 3. The levels of peak $\dot{V}O_2$ ($12.5 \pm 3.7\,ml\,kg^{-1}\,min^{-1}$ vs. $13.7 \pm 4.0\,ml\,kg^{-1}\,min^{-1}$; $p = 0.01$) and AT ($8.3 \pm 1.6\,ml\,kg^{-1}\,min^{-1}$ vs. $8.8 \pm 2.1\,ml\,kg^{-1}\,min^{-1}$, $p = 0.02$) were significantly lower in the DM group than in the non-DM group. Ext muscle strength was significantly lower in the DM group than in the non-DM group ($131 \pm 40\,Nm\,kg^{-1} \times 100$ vs. $146 \pm 45\,Nm\,kg^{-1} \times 100$, $p < 0.01$). No significant differences in HGP (27.7 ± 9.0 kg vs. 29.5 ± 9.0 kg, NS) were observed between the 2 groups. Peak $\dot{V}O_2$ values were correlated with Ext muscle strength of thigh ($r = 0.49$, $p < 0.005$) (Fig. 1A) and HGP ($r = 0.44$, $p < 0.005$) (Fig. 1B); MAMA values were correlated with Ext muscle strength of thigh ($r = 0.42$, $p < 0.005$) (Fig. 2A) and HGP ($r = 0.64$, $p < 0.005$) (Fig. 2B). The same trends were observed in the DM and non-DM patients (Figs. 1C–F, 2C–F).

Diabetes mellitus and MAMA

To assess the effects of insulin treatment, we divided DM patients into the following 2 groups: DM patients undergoing insulin therapy (insulin-treated DM group) and DM patients

Table 2 Comparison of anthropometric parameters between the DM and non-DM groups.

	DM	Non-DM	*p* value
Body mass index (kg/m^2)	23.3 ± 2.7	23.2 ± 2.7	NS
Lean body weight (kg)	49.2 ± 8.6	48.0 ± 4.1	NS
Waist circumference (cm)	84.8 ± 8.0	84.0 ± 8.0	NS
Thigh circumference (cm)	47.0 ± 6.7	48.1 ± 4.1	NS
Arm forced circumference (cm)	28.3 ± 2.7	28.7 ± 2.5	NS
Triceps skinford thickness (mm)	10.9 ± 6.0	10.7 ± 4.0	NS
Mid-upper arm muscle circumference (cm)	24.9 ± 2.6	25.4 ± 2.5	NS
MAMA (cm^2)	50.0 ± 10.0	52.0 ± 10.0	NS

Data are presented as the mean ± SD. DM, diabetes mellitus; MAMA, mid-upper arm muscle area.

Table 3 Comparison of exercise tolerance and muscle strength between the DM and non-DM groups.

	DM	Non-DM	*p* value
Baseline			
SBP (mmHg)	134 ± 23	128 ± 19	<0.01
HR (min^{-1})	87 ± 13	90 ± 13	0.04
PRP ($mmHg\,min^{-1}$)	11673 ± 2333	11634 ± 2280	NS
Anaerobic threshold			
Anaerobic threshold ($ml\,kg^{-1}\,min^{-1}$)	8.3 ± 1.6	8.8 ± 2.1	0.02
Workload (W)	32 ± 12	34 ± 16	NS
HR (min^{-1})	101 ± 13	105 ± 13	0.01
Peak exercise			
Peak VO_2 ($ml\,kg^{-1}\,min^{-1}$)	12.5 ± 3.7	13.7 ± 4.0	0.01
Workload (W)	73 ± 22	71 ± 27	NS
RER	1.06 ± 0.14	1.07 ± 0.14	NS
SBP (mmHg)	180 ± 31	181 ± 30	NS
HR (min^{-1})	117 ± 17	121 ± 17	0.02
PRP ($mmHg\,min^{-1}$)	21177 ± 5097	22088 ± 5427	NS
Peak HR–resting HR (min^{-1})	30 ± 13	32 ± 15	NS
$\Delta VO_2/\Delta WR$ ($ml\,min^{-1}\,W^{-1}$)	8.4 ± 2.6	8.6 ± 2.2	NS
Muscle strength			
Knee extension ($Nm\,kg^{-1} \times 100$)	131 ± 40	146 ± 45	<0.01
Knee flexion ($Nm\,kg^{-1} \times 100$)	73 ± 23	79 ± 28	NS
Hand grip power (kg)	27.7 ± 9.0	29.5 ± 9.0	NS

Data are presented as the mean value ± SD. DM, diabetes mellitus; SBP, systolic blood pressure; HR, heart rate; PRP, pressure rate product; RER, respiratory exchange ratio; WR, work rate.

without insulin therapy (non-insulin-treated DM group). No significant differences in risk factors, number of diseased vessels, prevalence of re-CABG, and ejection fraction were observed between the non-insulin-treated DM group and the insulin-treated DM group. The insulin-treated DM group had a significantly longer duration of DM history than the non-insulin-treated DM group (17.7 ± 9 years vs. 11.7 ± 10 years, $p < 0.01$). The prevalence of microvascular complications, including retinopathy, nephropathy, and neuropathy, tended to be higher in the insulin-treated DM group than in the non-insulin-treated DM group (86% vs. 67%, $p = 0.09$). MAMA levels were significantly lower in the insulin-treated DM group than in the non-insulin-treated DM group (45.9 ± 9.8 cm^2 vs. 51.9 ± 9.7 cm^2, $p < 0.01$). The insulin-treated DM group had a low thigh muscle strength (121.5 ± 29 $Nm\,kg^{-1} \times 100$ vs. 135.4 ± 42 $Nm\,kg^{-1} \times 100$, $p = 0.06$) and HGP (25.6 ± 8.0 kg vs. 28.9 ± 8.0 kg, $p = 0.05$). In addition, a significant inverse relationship was observed between fasting blood glucose and Ext muscle strength of thigh in the DM group ($r = -0.26$, $p < 0.005$) (Fig. 3). A weak but significant inverse relationship was also observed between HbA1c and Ext muscle strength of thigh ($r = -0.17$, $p < 0.05$).

Discussion

In the present study, we demonstrated that: (1) DM patients had a significantly lower exercise tolerance and muscle strength compared with non-DM patients; (2) exercise tolerance and muscle mass correlated with muscle strength; and (3) fasting glucose levels significantly and negatively correlated with muscle strength in patients who received CR after CABG. These data suggest that a high glucose level may affect these deteriorations in DM patients after CABG. A relationship between muscle strength and peak VO_2 has already been reported [12,13]. However, to the best of our knowledge, this is the first report demonstrating the impact of DM on muscle mass, muscle strength, and exercise tolerance in patients at the beginning of CR after CABG.

The reason why DM patients have low levels of exercise tolerance and muscle strength should be discussed. Tesfamariam et al. showed that the dysfunction of endothelium-dependent relaxation associated with exposure to elevated glucose levels is due to the increased production of vasoconstrictor prostanoids by the endothelium as a consequence of protein kinase C activation [14]. Previous studies have demonstrated that metabolisms of both glucose and fatty acids by skeletal muscle as well as the bioenergetic capacity of skeletal muscle mitochondria are impaired in DM patients [15]. These proposed mechanisms may explain the data in the present study because a significant inverse relationship was observed between fasting blood glucose levels and thigh muscle strength in the DM group (Fig. 3). Recently, Womack et al. showed that DM patients with microvascular complications have impaired capillary recruitment to contractile exercise [16]. In the present study, the prevalence of microvascular complications tended to be higher in the insulin-treated DM group than in the non-insulin-treated DM group. This may also be one of the mechanisms by which thigh muscle strength and HGP were significantly lower in the insulin-treated DM group than in the non-insulin-treated DM group. Low exercise tolerance in DM patients may be caused by sensorineural and autonomic dysfunction. An impaired heart rate response to exercise has been regarded as chronotropic incompetence and is seen in DM patients with impaired

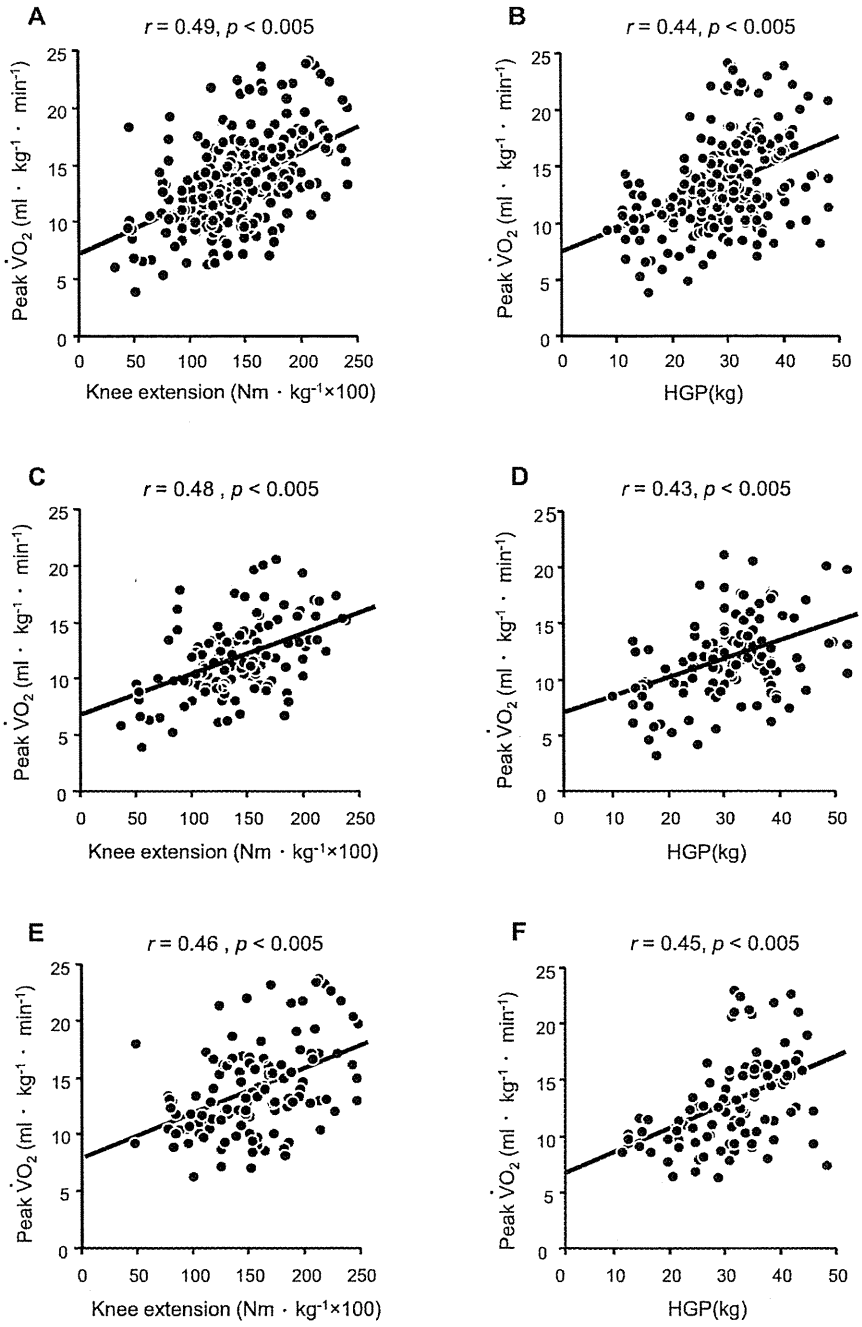

Figure 1 Correlations between exercise tolerance and muscle strength. Peak $\dot{V}O_2$ correlated with extensor muscle strength of thigh ($r = 0.49$, $p < 0.005$) (A), and HGP ($r = 0.44$, $p < 0.005$) in all patients (B) ($n = 259$). Peak $\dot{V}O_2$ correlated with extensor muscle strength of thigh ($r = 0.48$, $p < 0.005$) (C), and HGP ($r = 0.43$, $p < 0.005$) in the DM group (D) ($n = 128$). Peak $\dot{V}O_2$ correlated with extensor muscle strength of thigh ($r = 0.46$, $p < 0.005$) (E), and HGP ($r = 0.45$, $p < 0.005$) in the non-DM group (F) ($n = 131$). HGP, hand grip power; DM, diabetes mellitus.

exercise capacity. A previous study showed that low exercise capacity may be an impaired chronotropic response to exercise in DM patients with acute myocardial infarction [17]. In the present study, the heart rate values at peak $\dot{V}O_2$ and AT were significant lower in the DM group than in the non-DM group; however, the increased changes in heart rate were identical for the two groups (Table 3). Therefore, sensorineural and autonomic dysfunction may not have affected exercise intolerance in the DM group. The changes in sympathetic nervous activity (e.g. plasma catecholamine levels and R–R interval variability on an electrocardiogram) would be assessed in the subsequent step. Besides, a delta-$\dot{V}O_2$/delta-WR ($\Delta\dot{V}O_2/\Delta WR$) is determined by the rate of increase in cardiac output and the rate of

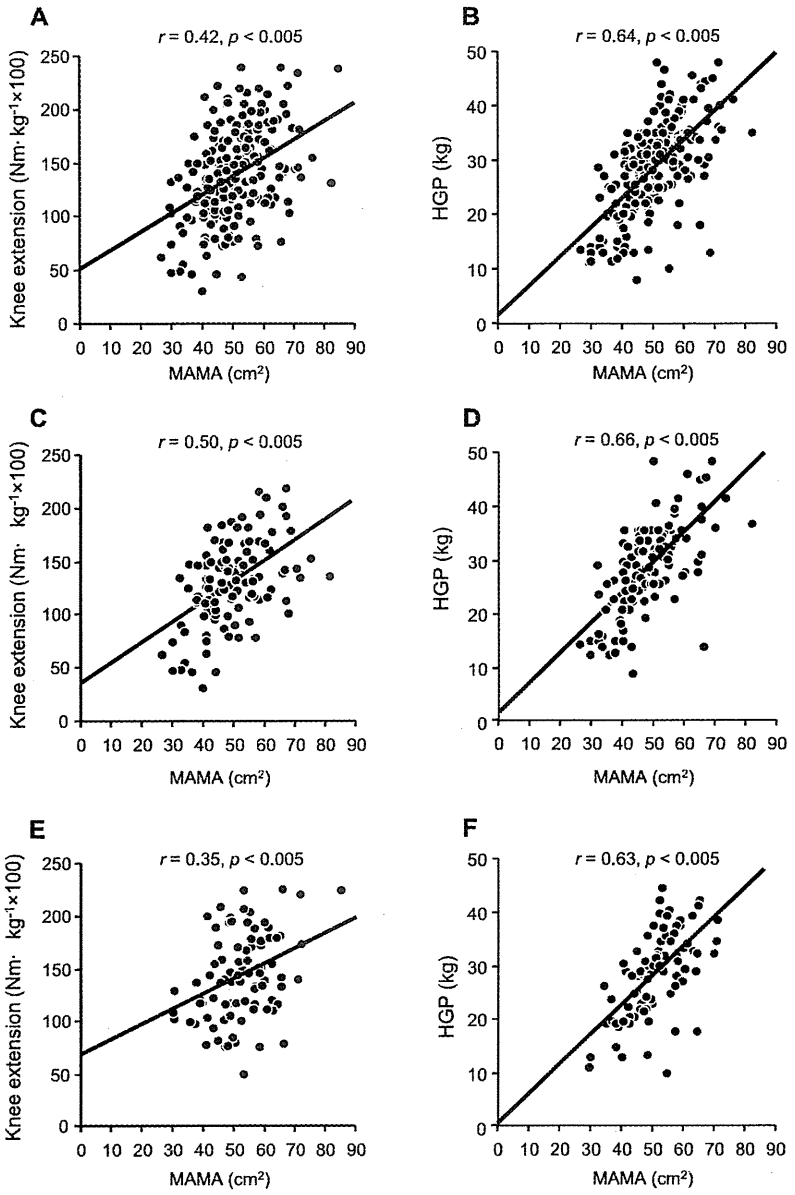

Figure 2 Correlations between muscle strength and muscle mass. MAMA correlated with extensor muscle strength of thigh ($r = 0.42$, $p < 0.005$) (A), and HGP ($r = 0.64$, $p < 0.005$) (B) in all patients ($n = 201$). MAMA correlated with extensor muscle strength of thigh ($r = 0.50$, $p < 0.005$) (C), and HGP ($r = 0.66$, $p < 0.005$) (D) in DM patients ($n = 108$). MAMA correlated with extensor muscle strength of thigh ($r = 0.35$, $p < 0.005$) (E), and HGP ($r = 0.63$, $p < 0.005$) (F) in non-DM patients ($n = 93$). MAMA, mid-upper arm muscle area; HGP, hand grip power; DM, diabetes mellitus.

difference in arterial mixed venous oxygen during incremental exercise [18]. Comparing with the non-DM group, $\Delta\dot{V}O_2/\Delta WR$ values were low but not significant in the DM group (Table 3).

The present study demonstrated that MAMA correlated with thigh muscle strength and HGP and MAMA levels were significantly lower in the insulin-treated DM group than the non-insulin-treated DM group. Chronic hyperglycemia leads to the production of amadori products through nonenzymatic glycation reactions between glucose and reactive amino groups of serum proteins [19]. These products undergo further irreversible reactions to form advanced glycation end products that promote insulin resistance as well as trigger inflammation and secretion of cytokines and growth factors, which leads to amplification or progression of various diseases including diabetic vascular complications (metabolic memory) [20]. In the present study, the insulin-treated DM group had a significantly longer duration of DM history than the non-insulin-treated DM group. The loss of muscle mass may be caused by chronic hyperglycemia, the so-called negative legacy effect, particularly in the insulin-treated DM group. A recent study demonstrated that a low

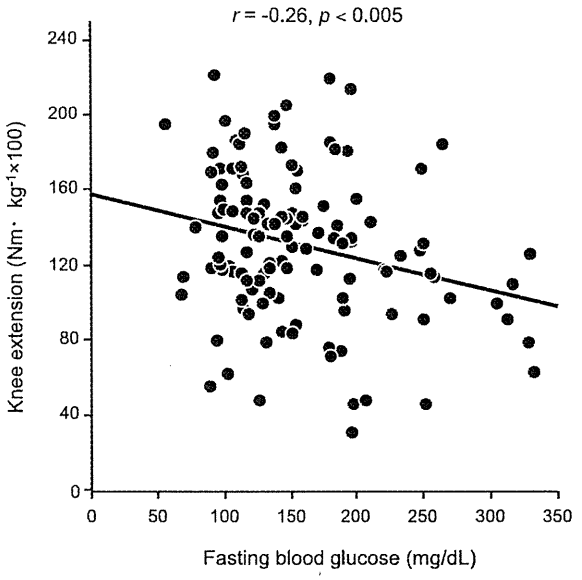

Figure 3 Correlation between fasting glucose levels and extensor muscle strength of thigh. A significant inverse relationship was observed between fasting blood glucose levels and extensor muscle strength of thigh in the diabetes mellitus group ($r = -0.26$, $p < 0.005$) ($n = 120$).

level of arm muscle area was an independent risk factor for the 2-year mortality in a cohort of community dwelling Japanese elderly [21]. We would like to further clarify whether the levels of arm muscle area before and after CR can predict morbidity and mortality in DM patients after CABG.

CR is class I recommendation in most contemporary cardiovascular clinical practice guidelines. Exercise tolerance has proven to be the strongest predictor of the risk of death among subjects with and without known cardiovascular disease [22]. Vergès et al. reported that the benefit of CR on exercise capacity is significantly lower in DM patients than non-DM patients and the response to CR was influenced by blood glucose levels [7]. A previous study demonstrated that exercise increases the activity of AMP-activated protein kinase in muscle, which in turn, promotes translocation of the glucose transporter-4 from the cytosol to the plasma membrane, increases insulin-independent glucose uptake by muscle, and improves muscle insulin resistance by a reduction of intramyocellular lipids [23]. Therefore, it is necessary to investigate the effects of CR on muscle mass, muscle strength, exercise capacity, and long-term outcome.

The present study has some limitations. First, this was a single-center study with a small sample size. Studies with larger sample sizes can confirm these results. Secondly, we performed a cardiopulmonary exercise test at the beginning of phase I CR (6–8 days after CABG). Therefore exercise tolerance and muscle strength might be attenuated by confounding factors. However, no significant differences in the clinical characteristics were observed between the DM group and the non-DM group. Thirdly, we enrolled patients who received CR after CABG. Therefore, the results of the present study may not be representative of all DM patients with CAD. Finally, this was a cross-sectional study. As discussed above, the clinical importance of muscle parameters and exercise tolerance prospectively as well as the effects of CR on muscle mass, muscle strength, exercise capacity, and future cardiovascular events in DM patients after CABG must be investigated.

Conclusions

DM patients had a lower muscle strength and exercise tolerance than non-DM patients at the beginning of CR after CABG. Moreover, a high glucose level may affect these deteriorations in DM patients after CABG. Further studies are required to assess whether CR would ameliorate these deteriorations and improve the clinical prognosis in DM patients after CABG.

Acknowledgement

This work was partially supported by High Technology Research Center Grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Clinical Investigations

Long-Term Effect of Metabolic Syndrome With and Without Diabetes Mellitus on Coronary Revascularization in Japanese Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: Metabolic syndrome (MS) plays a crucial role in the long-term prognosis and primary or secondary prevention of coronary artery disease, regardless of the presence or absence of diabetes mellitus (DM). We previously reported that after percutaneous coronary intervention (PCI), patients with MS had worse long-term outcome. However, there is no evidence indicating the importance of MS with and without DM on re-revascularization procedures in Japanese patients undergoing PCI.

Hypothesis: We hypothesized that MS patients without DM have an increased risk of re-revascularization following PCI.

Methods: We classified 748 consecutive Japanese patients who had undergone PCI into 4 groups as follows: neither DM nor MS, DM alone, MS alone, and both DM and MS. Post-hoc analyses were conducted using prospectively collected clinical data. Multivariate Cox regression was used to evaluate the risk within each group for subsequent revascularization (repeat PCI and bypass surgery), adjusting for baseline covariates.

Results: The progress of 321 (42.9%) patients without DM or MS, 109 (14.6%) patients with DM alone, 129 (17.2%) patients with MS alone, and 189 (25.3%) patients with both DM and MS was followed up for a mean duration of 12.0 ± 3.6 years. Patients with MS alone (hazard ratio: 1.38, 95% confidence interval: 1.01–1.89, $P = 0.04$) and those with both DM and MS (hazard ratio: 1.36, 95% confidence interval: 1.02–1.81, $P = 0.04$) had a significantly increased risk for revascularization.

Conclusions: The presence of MS significantly increased the risk for subsequent revascularization among Japanese patients who underwent PCI, regardless of the presence or absence of DM.

Introduction

The prevalence of metabolic syndrome (MS) is increasing, and MS has been associated with increased cardiovascular disease morbidity and mortality even in the Japanese population.[1–4] We previously reported that MS patients after coronary revascularization had worse outcomes than non-MS patients.[5–7] Diabetes mellitus (DM) is included in the definitions of MS, and DM has been well known to be strongly associated with a high restenosis rate and progression of coronary atherosclerosis.[8,9] There have been several studies indicating that MS itself is associated with a risk of coronary artery disease (CAD) progression or mortality, both in patients with and without preexisting CAD, regardless of the presence of DM.[6,10–13] However, it remains unclear whether there is a relationship between MS and increased restenosis or subsequent revascularization rate following coronary revascularization.[14–20] Furthermore, it was reported that MS without DM does not have an impact on increased restenosis and/or subsequent revascularization rate in patients following percutaneous coronary intervention (PCI).[15–18] However, most of those studies were conducted in a Western population, and the impact of MS regardless of the presence or absence of DM on the revascularization rate among Asians has not been investigated. Therefore, we examined whether MS affects the subsequent revascularization rate of Japanese patients with and without DM who had undergone PCI.

Methods

Subjects

This study is an additional analysis of data from a previous study using the same population investigating the impact

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 34, 10, 610–616 (2011)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20946

Received: April 28, 2011
Accepted with revision: June 29, 2011

of MS on long-term mortality and incidence of acute coronary syndrome (ACS) regardless of the presence or absence of DM.[13] In brief, we analyzed data from 748 consecutive Japanese patients who had undergone PCI at Juntendo University Hospital in Japan between January 1984 and December 1992. The indications for PCI included objective evidence of myocardial ischemia (positive stress test) or ischemic symptoms associated with significant angiographic stenosis. This study was performed according to the ethics policies of our institution.

Data Collection

Demographic data including age, gender, body mass index (BMI), and coronary risk factors including blood sampling data, medication use, and interventional procedures were prospectively collected in the database at our institution, as previously described.[13] Because intravascular ultrasound was not performed in all cases, the reference vessel diameter was estimated by the size of the balloon used for PCI and was also collected in the database. The degree of luminal narrowing was determined by the consensus opinion of 2 experienced interventional cardiologists.

Outcome Data

Subsequent revascularization data, including repeat PCI and coronary artery bypass grafting (CABG), were assessed from the medical records of patients who were followed up at our hospital until September 2002. In patients who were followed up elsewhere, whether they underwent subsequent revascularization or not and details of the subsequent revascularization were supplied by the institutions where they had been followed up, or where the subsequent revascularization was performed. The repeat PCI was further classified into 2 outcomes: (1) target vessel revascularization (TVR), if subsequent revascularization was performed in the same vessel as the target vessel of the baseline PCI; and (2) revascularization of a new lesion (NL), if subsequent revascularization was performed in vessels different from those targeted in the baseline PCI.

Definitions

Patients were classified based on the presence or absence of MS at baseline using a modified American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition.[21] In this definition, obesity was defined as BMI of $\geq 25\ kg/m^2$ based on the Japanese criteria for obesity[22] rather than waist circumference as in the AHA/NHLBI definition. The other MS criteria were the same as those in the AHA/NHLBI definition: triglycerides $\geq$150 mg/dL; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL for females; blood pressure (BP) $\geq$ 130/85 mm Hg or treatment with antihypertensive medications; and fasting blood glucose (FBG) $\geq$ 100 mg/dL or treatment with oral hypoglycemic drugs or insulin injection. Patients who had 3 of 5 criteria were regarded as having MS. Furthermore, patients in each group with and without MS were divided into 2 subgroups according to the presence or absence of DM, which was defined as a FBG level $\geq$ 126 mg/dL[23] or treatment with oral hypoglycemic drugs or insulin injection. The patients were separated into 4 groups: neither DM nor MS, DM alone, MS alone, and both DM and MS. Definitions for other variables were described previously.[13]

Statistical Analysis

Continuous variables are expressed as mean ± SD and were compared using one-way analysis of variance with Dunnett's test. Categorical data are tabulated as frequencies and ratios (%), and were compared using the χ^2 test. Cumulative revascularization-free rate was analyzed by Kaplan-Meier estimation with the log-rank test. Multivariate Cox proportional hazards regression analysis adjusted for age, gender, low-density lipoprotein cholesterol (LDL-C) level, hypertension, current smoker, history of CABG, ACS, left ventricular ejection fraction (LVEF), number of diseased vessels, reference vessel diameter, percentage of stenosis before PCI, and procedural success (defined as residual stenosis <50% after PCI) was used to determine the risk of subsequent revascularization in MS patients with or without DM. In addition, in patients without DM, risks of each MS component, as well as of the cumulative effect of having multiple MS components, for subsequent revascularization were also assessed using multivariate analyses including age, gender, LDL-C level, current smoker, history of CABG, ACS, LVEF, number of diseased vessels, reference vessel diameter, percentage of stenosis before PCI and procedural success. A P value of <0.05 was considered statistically significant. All data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL).

Results

Baseline and clinical event data were fully documented for all 748 enrolled patients during the follow-up period (mean follow-up, 12.0 ± 3.6 y). Most patients were middle-aged, nonobese males who were treated with nitrates and aspirin and had normal LVEF. Simple balloon angioplasty was applied because stents were not yet available at the time of the PCI procedures. Of the 748 patients, 298 (39.8%) had DM at the time of PCI. None of the patients who underwent PCI during the study period had type 1 DM.

Baseline Characteristics of 4 Groups

Overall, of the 748 patients, 321 (42.9%) had neither DM nor MS, 109 (14.6%) had DM alone, 129 (17.2%) had MS alone, and 189 (25.3%) had both MS and DM. The baseline characteristics, medication use, and angiographic and procedural data in these 4 groups are shown in Table 1, which have been previously published.[13] As compared with patients with neither DM nor MS, patients with DM alone were older, had a higher FBG level by definition, and were more frequently taking statins. Patients with MS alone had worse MS-related baseline profiles, except for FBG level, than those with neither DM nor MS. A greater percentage of patients with MS alone were on β-blockers and calcium channel blockers (CCBs) than those with neither DM nor MS. Patients with both DM and MS also had worse MS-related baseline profiles, including FBG level, than those

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DOI:10.1002/clc.20946

Table 1. Baseline Characteristics

	Neither DM Nor MS	DM Alone	MS Alone	Both DM and MS
No.	321	109	129	189
Age (y)[a]	58.2 ± 10.3	62.4 ± 8.8[b]	58.2 ± 10.5	60.0 ± 9.3
Male, n (%)	287 (89.4)	93 (85.3)	109 (84.5)	162 (85.7)
BMI (kg/m²)[a]	22.5 ± 2.5	22.3 ± 1.9	25.1 ± 2.4[b]	24.9 ± 2.7[b]
Hypertension, n (%)[a]	183 (57.0)	53 (48.6)	100 (77.5)[b]	149 (78.8)[b]
Systolic BP (mm Hg)[a]	128.0 ± 17.8	125.7 ± 16.0	133.4 ± 18.0[c]	137.8 ± 19.4[b]
Diastolic BP (mm Hg)[a]	74.3 ± 13.4	73.1 ± 12.0	77.6 ± 13.8[c]	78.7 ± 12.3[b]
Cholesterol				
LDL (mg/dL)	135.7 ± 38.7	128.8 ± 41.4	143.5 ± 42.2	137.3 ± 48.7
HDL (mg/dL)[a]	46.0 ± 13.2	48.0 ± 10.4	36.4 ± 9.7[b]	38.3 ± 11.6[b]
Triglycerides (mg/dL)[a]	123.5 ± 51.2	115.6 ± 52.9	203.8 ± 117.8[b]	189.7 ± 98.8[b]
FBG (mg/dL)[a]	88.3 ± 9.2	113.7 ± 37.5[b]	94.4 ± 11.7	120.2 ± 45.2[b]
Current smoker, n (%)	248 (77.3)	82 (75.2)	100 (77.5)	149 (78.8)
Family history of CAD, n (%)	103 (32.1)	43 (39.5)	46 (35.7)	67 (35.5)
Medications, n (%)				
Nitrates	286 (89.1)	104 (95.4)	116 (89.9)	166 (87.8)
Nicorandil	66 (20.6)	15 (13.8)	23 (17.8)	36 (19.1)
ACEI	19 (5.9)	6 (5.5)	13 (10.1)	20 (10.6)
β-Blockers	75 (23.4)	22 (20.2)	42 (32.6)[c]	47 (24.0)
CCB[a]	78 (24.3)	22 (20.2)	54 (41.9)[b]	67 (35.5)[b]
Aspirin	227 (70.7)	82 (75.2)	88 (68.2)	131 (73.2)
Warfarin	127 (38.8)	42 (38.5)	41 (31.8)	80 (42.3)
Statins	99 (30.8)	46 (42.2)[c]	36 (27.9)	62 (32.8)
Angiographic/procedural data				
Presentation of ACS, n (%)	94 (29.2)	36 (33.0)	36 (27.9)	50 (26.5)
Previous CABG, n (%)	54 (16.8)	26 (23.9)	27 (20.9)	28 (14.8)
No. of diseased vessels[a]	1.57 ± 0.74	1.76 ± 0.74	1.76 ± 0.74[c]	1.57 ± 0.75
Multivessel disease n (%)[a]	135 (42.1)	63 (57.8)[b]	71 (55.0)[c]	112 (59.3)[b]
Ref. vessel diameter (mm)	2.92 ± 0.43	2.87 ± 0.43	2.98 ± 0.44	2.99 ± 0.49
% of ≥ 2.50 mm (%)	305 (95.0)	12 (89.0)	7 (94.6)	13 (93.1)
% Stenosis before PCI (%)	92.0 ± 8.3	92.4 ± 7.0	91.5 ± 8.3	93.3 ± 7.7
% Stenosis after PCI (%)	37.9 ± 2.4	36.9 ± 2.3	40.3 ± 2.5	36.1 ± 2.2
Procedural success, n (%)	283 (88.2)	95 (87.2)	109 (84.5)	166 (87.8)
LVEF (%)	67.5 ± 10.1	65.7 ± 12.6	68.2 ± 11.3	65.5 ± 13.1

Abbreviations: ACE, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium channel blockers; DM, diabetes mellitus; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; Ref., reference; PCI, percutaneous coronary intervention. Data are presented as mean ± SD, unless otherwise indicated. [a]$P < 0.01$ across groups. [b]$P < 0.01$ compared with neither DM nor MS. [c]$P < 0.05$ compared with neither DM nor MS.

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DOI:10.1002/clc.20946

with neither DM nor MS. A greater percentage of patients with both DM and MS were on CCBs than those with neither DM nor MS. Interestingly, there was no significant difference in the LDL-C levels across the groups. As compared with patients with neither DM nor MS, those with DM alone, MS alone, and both DM and MS more frequently had multivessel disease. However, there were no significant differences in other angiographic and procedural data.

Subsequent Revascularization

Overall, subsequent revascularization was performed in 312 patients (41.7%); PCI was repeated in 255 patients (34.1%) and 57 patients (7.6%) underwent CABG during follow-up. Furthermore, of the patients who underwent repeated PCI, 192 (25.7%) underwent TVR and 63 (8.5%) underwent PCI for a NL. Revascularization-free rates of patients with MS alone and those with both MS and DM were significantly higher than those of patients with neither MS nor DM (Figure 1).

Multivariate analysis showed that patients with MS, regardless of the presence or absence of DM, have a significantly greater risk for subsequent revascularization compared with patients with neither MS nor DM (Table 2). In particular, patients with MS and DM have a significantly greater risk for repeat PCI than those with neither MS nor DM (Table 2). In terms of the target lesion in repeated PCI, only patients with both MS and DM had a significantly greater risk for TVR compared with patients with neither MS nor DM (Table 3).

In patients without DM (n = 450), a low HDL-C level was a significant risk factor for subsequent revascularization, in addition to the number of accumulated MS components (Table 4).

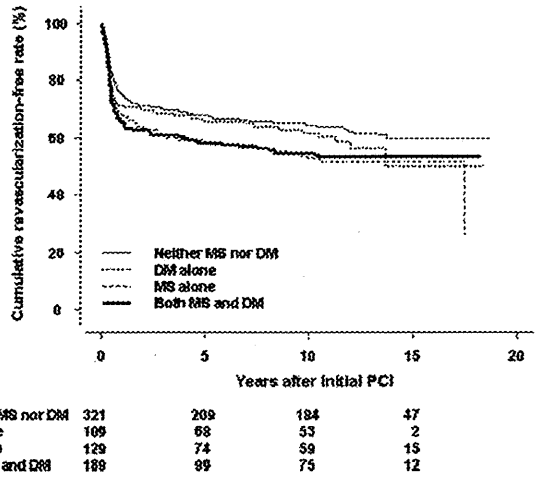

Figure 1. Cumulative revascularization-free rates. Revascularization-free rates between patients with MS alone and those without DM and MS differed significantly (log-rank test, $P = 0.03$). Patients with DM and MS and neither DM nor MS also differed significantly (log-rank test, $P = 0.04$). However, there was no significant difference between patients with DM alone and those with neither DM nor MS (log-rank test, $P = 0.37$). Abbreviations: DM, diabetes mellitus; MS, metabolic syndrome; PCI, percutaneous coronary intervention.

Table 2. Risk for Subsequent Revascularization in Patients With DM Alone, Those With MS Alone, and Those With Both DM and MS

	Incidence (%)	HR	95% CI	*P* Value
Revascularization				
Neither DM nor MS	121 (30.5)	1.00		
DM alone	45 (41.2)	1.12	0.79–1.59	0.51
MS alone	62 (48.0)	1.38	1.01–1.89	0.04
Both DM and MS	82 (43.4)	1.36	1.02–1.81	0.04
Repeat PCI				
Neither DM nor MS	98 (30.5)	1.00		
DM alone	36 (33.0)	1.09	0.74–1.60	0.68
MS alone	49 (38.0)	1.35	0.95–1.91	0.10
Both DM and MS	72 (38.1)	1.42	1.04–1.95	0.03
CABG				
Neither DM nor MS	24 (7.5)	1.00		
DM alone	11 (8.5)	1.21	0.56–2.66	0.94
MS alone	9 (8.3)	1.14	0.54–2.40	0.73
Both DM and MS	13 (6.9)	1.03	0.52–2.05	0.94

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; PCI, percutaneous coronary intervention. Hazard ratios and 95% CIs were adjusted for age, gender, LDL-C, current smoker, hypertension, history of CABG, ACS, LVEF, number of diseased vessels, reference vessel diameter, percentage of stenosis before PCI, and procedural success.

Discussion

This additional analysis of long-term follow-up ($\geq$ 10 y) data in patients who had undergone PCI revealed an association between MS and subsequent coronary revascularization, even in groups without DM at the baseline examination. To the best of our knowledge, this is the first study to evaluate the risk of MS regardless of the presence or absence of DM on coronary revascularization in an Asian population, with a long-term follow-up period.

In terms of the relationship between MS and restenosis/revascularization following PCI, Rana and colleagues showed that the presence of MS at baseline is not associated with TVR or the composite endpoint 12 months after PCI.[14] Their study differs from ours because it was conducted among a Western population and patients were followed up for only 12 months. Canibus et al also reported that MS was not associated with an increased restenosis rate 12 months after PCI using drug-eluting stents (DES).[19] More recently, Kim and colleagues reported that MS at baseline was not a significant independent predictor of increased restenosis or revascularization after PCI.[20] The patients in their study were Asians and were followed up for a longer period (36 mo) than in the study by Rana and colleagues[14]; however, the follow-up period was still shorter than that in our study and they did not separate DM from MS. According

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DOI:10.1002/clc.20946 © 2011 Wiley Periodicals, Inc.

Table 3. Risk of Repeat PCI in Patients With Neither DM nor DS, DM Alone, MS Alone, and Both DM and MS

	Incidence (%)	HR	95% CI	*P* Value
TVR				
Neither DM nor MS	72 (22.4)	1.00		
DM alone	35 (32.1)	1.01	0.63–1.60	0.98
MS alone	25 (19.4)	1.30	0.86–2.00	0.22
Both DM and MS	12 (6.3)	1.50	1.05–2.13	0.02
NL				
Neither DM nor MS	26 (8.1)	1.00		
DM alone	14 (12.8)	1.45	0.70–3.01	0.46
MS alone	11 (8.5)	1.45	0.82–2.53	0.22
Both DM and MS	12 (6.4)	1.20	0.56–2.26	0.75

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; NL, new lesion; PCI, percutaneous coronary intervention; TVR, target vessel revascularization. Hazard ratios and 95% CIs were adjusted for age, gender, LDL-C, current smoker, hypertension, history of CABG, ACS, LVEF, number of diseased vessels, reference vessel diameter, percentage of stenosis before PCI, and procedural success.

to the entire definition of MS, patients with DM simultaneously satisfied the high blood glucose criterion.[21,24,25] In other words, the MS groups included many patients with DM, and most of the diabetic patients were classified as having MS among the population in which type 2 DM resulted from obesity. Therefore, there may be significant overlap between DM and MS in the risk for subsequent revascularization. In this regard, Stellbrink et al reported that MS without DM did not result in an increase of TVR 6 months after DES implantation.[16] However, this negative finding might be associated with an insufficient number of TVR. Hoffmann and colleagues evaluated the risk of MS separate from DM, and they showed that MS without DM was not associated with increased restenosis and revascularization rates following PCI.[15] More recently, another study showed similar negative results[17]; however, their follow-up term was approximately 2 to 3.5 years, much shorter than in our study. Yatskar et al investigated the impact of MS on long-term outcome in nondiabetic patients with multivessel CAD who were undergoing coronary revascularization in the Bypass Angioplasty Revascularization Investigation (BARI) trial and registry.[18] They found that the 10-year risk of subsequent revascularization was not greater in nondiabetic patients with MS compared with patients with neither MS nor DM. Patients in their study were followed up for a time period that was similar to ours, but their study was conducted in a Western population. Therefore, the impact of MS without DM on the long-term restenosis and revascularization rates among Asian patients following PCI was still unclear.

Table 4. Risk of Subsequent Revascularization According to Each MS Component in Patients Without DM

	Incidence (%)	HR	95% CI	*P* Value
High BMI	50/111 (45.0)	1.25	0.88–1.78	0.21
High BP	121/285 (42.5)	0.94	0.61–1.44	0.76
High triglycerides	71/167 (42.5)	1.18	0.87–1.60	0.29
Low HDL-C	95/202 (47.0)	1.50	1.12–2.02	0.01
High FBG	35/83 (42.2)	1.12	0.77–1.64	0.54
No. of accumulated MS component (for each 1-component increase)		1.18	1.03–1.36	0.02

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; FBG, fasting blood glucose; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; PCI, percutaneous coronary intervention. Hazard ratios and 95% CIs were adjusted for age, gender, LDL-C, current smoker, hypertension, history of CABG, ACS, LVEF, number of diseased vessels, reference vessel diameter, percentage of stenosis before PCI, and procedural success.

Here, we examined the risk of restenosis and revascularization among Asian patients with MS alone, DM alone, and with both MS and DM following PCI. The results showed that patients with MS were at significantly increased risk for subsequent revascularization, regardless of the presence or absence of DM. In particular, patients with both MS and DM were at significantly increased risk for repeat PCI and TVR. Furthermore, we demonstrated that low HDL-C level may be a risk factor for subsequent revascularization in patients without DM, and that there was a dose-response relationship between the number of accumulated MS components and the subsequent rate of revascularization. These results indicate that MS is important to reduce subsequent revascularization rates and that aggressive and multifactorial intervention in MS is required for the secondary prevention of CAD.

The mechanism for an increased revascularization rate in MS patients without DM is likely related to impaired endothelial function, increased inflammation, and increased platelet function. However, we do not know why results of our study were different from those of other studies.[15–18] Clinical manifestations of MS in Asian patients may be different from MS in Western patients. For example, the BMI of MS patients in the previous Western studies are quite different from the BMI in the Asian studies. Therefore, obesity-related clinical features in Asians, specifically in Japanese, might be considerably different from those in others,[26–28] and these different clinical features may affect the outcome. The precise mechanism behind the adverse effect of MS without DM on subsequent revascularization remains uncertain and should be investigated further.

Study Limitations

We did not find a significant risk for revascularization among patients with DM alone. Although we cannot fully explain this, ethnic differences might influence the risk of MS and DM. Of course, the relatively small number of patients and

differences in patient characteristics between our study and previous studies that indicated the relationship between DM and increased revascularization rate[8,9] also might have contributed to this disparity. Patients with DM alone had the lowest BMI, were the least hypertensive, and smoked the least among the 4 groups, which may have led to the biased results.

The present study had several other limitations. First, because waist circumference was not measured, we used BMI to classify individuals as obese. Recent clinical studies have shown that most individuals identified as having MS based on BMI would also have been identified as obese had waist circumference cutoff points been applied.[29,30] Clinical trials conducted in Western populations used BMI ≥ 30 kg/m^2 as the cutoff point for obesity, which differs from the cutoff of BMI ≥ 25 kg/m^2 used in the present study. We selected BMI ≥ 25 kg/m^2 as the cutoff for obesity based on results from a study of the relationship between BMI, visceral fat area or waist circumference, and obesity in the Japanese population.[22]

Second, balloon angioplasty was the sole PCI used in all patients. The outcomes might have been quite different if stents and other supportive devices that are currently available had been applied. Indeed, most studies that did not find a significant relationship between MS without DM and increased restenosis and revascularization included patients who underwent PCI with bare-metal stents and DES.[15–17] In addition, because we analyzed patients who underwent PCI 20–25 years ago to assess long-term outcomes following PCI, patterns of medication use for these patients differed from those of present day and were not based on the evidence from the current randomized study.

Third, crossover among the 4 groups during follow-up was not considered. For example, data about new-onset DM, particularly among patients with MS alone, were not available. This may have introduced bias to our results. In addition, we did not take into account changes in the status and control level of other risk factors (ie, control of weight, BP, lipid levels, FBG, and smoking status), which may alter our results.

Conclusion

The presence of MS without DM at the time of PCI was associated with an increased incidence of subsequent revascularization during a follow-up period of >10 years. The association of MS with a greater risk for subsequent revascularization was significant regardless of the presence of DM in multivariate analysis. The present study showed the clinical importance of MS in the secondary prevention of CAD regardless of the presence of DM in an Asian population, and highlights the need for aggressive treatment for MS.

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Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20946

Journal of Cardiology (2011) xxx, xxx–xxx

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Clinical significance of the measurements of plasma N-terminal pro-B-type natriuretic peptide levels in patients with coronary artery disease who have undergone elective drug-eluting stent implantation

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Received 6 January 2011; received in revised form 23 January 2011; accepted 29 January 2011

KEYWORDS
Coronary artery disease;
N-terminal pro-B-type natriuretic peptide;
Drug-eluting stent;
Cardiovascular events

Summary
Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a diagnostic biomarker for patients with congestive heart failure (CHF). However, the clinical significance of measurements of NT-proBNP levels in patients with coronary artery disease (CAD) who have undergone drug-eluting stent (DES) implantation has not been fully elucidated.
Methods and results: We recruited 280 patients with documented CAD who were scheduled for elective coronary intervention and also age- and gender-matched 140 healthy subjects. Subjects with acute coronary syndrome, ongoing CHF, and stage IV or V chronic kidney disease were excluded. We measured the plasma NT-proBNP levels and followed the CAD patients who have undergone DES implantation for up to 62 months until occurrence of major adverse cardiovascular events (MACE). Plasma NT-proBNP levels were significantly higher in CAD patients compared to control subjects ($p < 0.0001$). In the CAD group, 25 patients developed MACE and the NT-proBNP levels in the MACE group were significantly higher compared to that in the non-MACE group ($p = 0.005$). After adjusting for the confounding factors, high NT-proBNP levels were observed to be independent factors for CAD ($p < 0.0001$) and MACE ($p = 0.021$).

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0914-5087/$ – see front matter
doi:10.1016/j.jjcc.2011.01.015

Please cite this article in press as: Masaki Y, et al. Clinical significance of the measurements of plasma N-terminal pro-B-type natriuretic peptide levels in patients with coronary artery disease who have undergone elective drug-eluting stent implantation. J Cardiol (2011), doi:10.1016/j.jjcc.2011.01.015

Conclusions: These results demonstrated that the measurements of NT-proBNP levels may be useful in identifying high-risk subjects among CAD patients who have undergone elective DES implantation.

Introduction

A high level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a useful marker in diagnosis of acute and chronic congestive heart failure (CHF) and also an important predictor for future cardiovascular events in those patients [1–6]. NT-proBNP levels increase in patients with chronic kidney disease (CKD) and are significantly correlated with estimated glomerular filtration rate (eGFR) in patients irrespective of CHF [7,8]. Several reports also demonstrated that NT-proBNP levels were significantly higher in patients with stable coronary artery disease (CAD) than in comparison to patients without CAD [9]. Also a high NT-proBNP level predicts cardiovascular morbidity and mortality independent of traditional risk factors in patients with stable CAD [7,10].

Currently, drug-eluting stents (DES) have become the standard of care for the treatment of CAD [11]. Recent advances in DES such as sirolimus eluting-stents (SES) have substantially reduced angiographic and clinical restenosis across broad lesion and patient subsets. However, there are no data available regarding the predictive value of NT-proBNP levels for future cardiovascular events in patients with stable CAD who have undergone elective DES implantation.

The purpose of this study is to assess the clinical significance of the measurements of NT-proBNP levels in stable CAD patients who have undergone elective DES implantation. We hence compared NT-proBNP levels between the stable CAD patients with CKD stages from I to III and who were scheduled for percutaneous coronary intervention (PCI), and age- and gender-matched apparently healthy subjects. We then followed the CAD patients for up to 62 months after DES implantation until occurrence of major adverse cardiovascular events (MACE).

Methods

Subjects

We recruited 280 consecutive stable CAD patients, who were scheduled to undergo PCI from September 2004 to December 2006 at Juntendo University Hospital. The documented CAD, defined as more than 75% stenosis in at least one major coronary artery, was diagnosed by coronary angiography at nearly 2 weeks prior to PCI procedure as a safety-check for dual antiplatelet therapy. Patients with acute coronary syndrome, ongoing CHF, and CKD stage IV or V were excluded. We also recruited 352 apparently healthy subjects who had undergone a medical check-up at a medical center in the urban area during December 2004 to January 2005. After computer-based random selection, 140 age- and gender-matched healthy subjects were enrolled as the control group. None of the control subjects had a history of cardiovascular disorders or systemic inflammatory diseases. All subjects gave written informed consent and the ethical committee approved this study.

Blood sampling and biochemical analysis

Following overnight fasting, whole blood samples were drawn from the subjects. Samples from the CAD group were collected immediately prior to PCI. Following centrifugation, plasma samples were aliquoted and stored at −80 °C until further use. The plasma NT-proBNP levels were measured using a commercially available immunoassay kit (Elecsys proBNP, Roche Diagnostics, Basel, Switzerland). The lower limit of detection was observed to be 5 pg/ml. The intraassay and interassay coefficients of variation at different concentrations of NT-proBNP were as follows: 2.7% and 3.2%, respectively, at 175calculated using the following /ml; 1.8% and 2.3%, respectively, at 4962 pg/ml. The eGFR was calculated using the following equation: $eGFR = 194 \times age^{-0.287} \times Cre^{-1.094} \times 0.739$ (if female), as described previously [12]. CKD was classified into five different stages, defined with $eGFR \geq 90$, $90 > eGFR \geq 60$, $60 > eGFR \geq 30$, $30 > eGFR \geq 15$, and $eGFR > 15\ ml/min/1.73\ m^2$ for stages I, II, III, IV, and V, respectively [12]. Levels of total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) were measured using the standard methods. The values of low-density lipoprotein cholesterol (LDL-C) were calculated using Friedewald's formula. HbA1c (JDS) (%) was measured by the previous Japanese standard substance and measurement methods and HbA1c method (National Glycohemoglobin Standardization Program-certified).

Angiographic analyses

Selective coronary angiography was performed at baseline. The number of stenotic vessels was recorded as 1-, 2-, 3-vessel disease or stenosis of the left main artery. Lumen narrowing by >75% of the prestenotic diameter was considered to be clinically significant for stenosis, except for the left main artery where a narrowing by >50% was considered significant. Quantitative coronary angiography (QCA) assessments were carried out in all patients. The PCI was performed by implantation of DES (Cypher®, Cordis, Johnson & Johnson, Miami Lakes, FL, USA). All procedural decisions, including device selection and adjunctive pharmacotherapy were made at the discretion of the individual PCI operator. Intravenous unfractionated heparin and intracoronary nitroglycerin were administered before the PCI. After stent implantation, angiographic optimization was performed by high-pressure dilatation to achieve an acceptable angiographic result. Intravascular ultrasound (IVUS) was carried

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out according to the operator's decision. Procedural success was defined as a residual stenosis <20% without major complications. Dual antiplatelet therapy (aspirin 100 mg and ticlopidine 200 mg or clopidgrel 75 mg) was prescribed for at least 2 weeks to all the patients treated with DES. In the CAD group, selective coronary angiography was performed after PCI to assess restenosis.

Follow-up

All the patients were implanted with DES. A total of 262 patients, who had undergone a follow-up coronary angiography, were followed for up to 62 months (median 46 months). The primary endpoint of the study was MACE. MACE was defined as all cause death, nonfatal myocardial infarction (MI), unstable angina, refractory angina requiring PCI or coronary artery bypass grafting (CABG), and admission for stroke.

Statistical analyses

Continuous variables are expressed as mean ± SD and categorical variables are reported in percentages. Statistical intergroup differences were analyzed by the chi-square test, one-way ANOVA, and the Student's t test. Correlation between the two parameters was determined by simple linear regression analysis. A value of $p < 0.05$ was considered to be significant. Chi-square tests for homogeneity across strata were applied for categorical variables. We selected log NT-proBNP levels, which were normally distributed, for analysis because the plasma NT-proBNP levels were not normally distributed. Logistic regression analysis was performed to identify independent factors for the CAD including the following variables: age, gender, body mass index, eGFR, LDL-C, HDL-C, prevalence of hypertension (HT), prevalence of diabetes mellitus (DM), and log NT-proBNP levels. Cox proportional hazard analysis was performed to identify independent predictors for the MACE including the following variables; age, gender, eGFR, multivessel disease, prevalence of DM, and log NT-proBNP levels. We examined the sensitivity and specificity of various cut-off values of independent predictive factors for predicting survival and created receiver operating characteristic (ROC) curves. We divided each group into two sub-groups based on their cut-off values (determined by the ROC curve analysis), examined the results of Kaplan–Meier survival analysis, and compared the difference in survival rates using the log-rank tests.

Results

Characteristics of the subjects

The characteristics of the subjects are shown in Table 1. No significant difference for age, gender, prevalence of smoking history, distribution of CKD stage, triglyceride, or blood glucose levels between the two groups were observed. The CAD group showed higher prevalence of HT ($p < 0.0001$), DM ($p < 0.0001$), and metabolic syndrome ($p = 0.01$), and also significantly higher levels of body mass index ($p = 0.009$), waist size ($p = 0.0003$), and HbA1c (JDS) ($p = 0.011$) compared to the control group. Levels of total cholesterol ($p = 0.009$), HDL-C ($p = 0.009$), and LDL-C ($p = 0.009$) in the CAD group were significantly lower compared to the control group ($p < 0.0001$, $p < 0.0001$, $p = 0.009$, respectively).

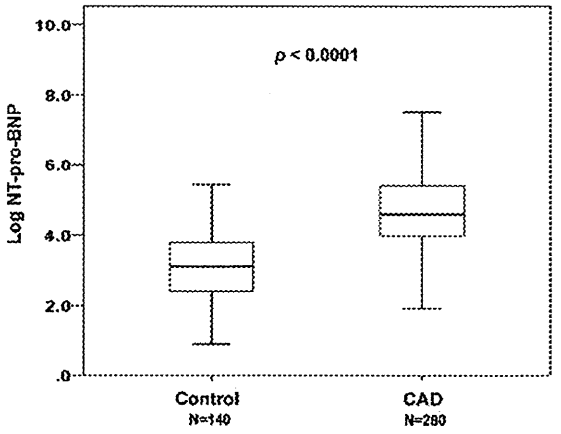

Figure 1 Comparison of logarithmically transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels between the control and the coronary artery disease (CAD) groups. Lines within boxes represent median values, with top and bottom lines of boxes representing the 75th and 25th percentiles.

Plasma NT-proBNP levels in the CAD group

Plasma levels of log NT-proBNP were significantly higher in the CAD group compared to the control group ($p < 0.0001$) (Fig. 1). Negative correlation between NT-proBNP levels and left ventricular ejection fraction has been previously reported [4]. We then divided the CAD group into the Previous Event (+), including previous history of MI, PCI, and CABG ($n = 133$) and Previous Event (−) ($n = 147$) groups. Plasma levels of log NT-proBNP were significantly higher in the Previous Event (+) group compared to the Previous Event (−) group ($p = 0.006$) (Fig. 2A). However, plasma levels of log NT-proBNP were also significantly higher in the Previous Event (−) group compared to the control group ($p < 0.0001$) (Fig. 2A). It has also been reported that NT-proBNP levels were increased in patients with left ventricular diastolic dysfunction [13]. To study this effect, we excluded the patients with HT and DM from the Previous Event (+) group. Plasma levels of log NT-proBNP were observed to be significantly higher even in the Previous Event (−) HT (−) DM (−) group ($n = 23$) compared to the control group ($p = 0.0003$) (Fig. 2B).

Follow-up

MACE was observed in 25 patients (death: 3 patients; nonfatal MI: 2 patients; unstable angina requiring PCI: 8 patients; CHF admission: 4 patients; CABG: 4 patients; and stroke: 4 patients). The characteristics of the MACE (−) and MACE (+) groups are shown in Table 2. There were no significant differences between the MACE (−) and MACE (+) groups except for prevalence of DM ($p = 0.004$) and HbA1c (JDS) levels ($p = 0.004$). There were also no

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Table 1 Comparison of clinical characteristics between the control and CAD groups.

	Control	CAD	*p* value
No. of patients	140	280	
Age (years)	58 ± 7	58 ± 6	NS
Male (%)	126 (90)	252 (90)	NS
Body mass index (kg/m^2)	24.0 ± 2.6	24.9 ± 3.1	0.009
Waist (cm)	85.1 ± 7.7	88.1 ± 8.2	0.0003
Hypertension (%)	31 (22)	193 (69)	<0.0001
Diabetes mellitus (%)	16 (11)	130 (46)	<0.0001
Current smoker (%)	47 (34)	95 (34)	NS
Metabolic syndrome (%)	47 (34)	131 (46)	0.010
Chronic kidney disease			NS
Stage I (%)	10 (7)	40 (14)	
Stage II (%)	98 (70)	181 (65)	
Stage III (%)	32 (23)	59 (21)	
Estimated GFR (ml/min/1.73m^2)	70 ± 13	72 ± 16	NS
Total cholesterol (mg/dl)	213 ± 34	185 ± 36	<0.0001
Triglyceride (mg/dl)	145 ± 85	150 ± 73	NS
HDL-cholesterol (mg/dl)	63 ± 18	43 ± 11	<0.0001
LDL-cholesterol (mg/dl)	122 ± 34	113 ± 31	0.009
Blood glucose (mg/dl)	108 ± 28	112 ± 37	NS
HbA1c (%)	5.8 ± 1.0	6.1 ± 1.4	0.011
Previous myocardial infarction (%)	(—)	98 (35)	
Previous CABG (%)	(—)	27 (10)	
Previous coronary revascularization (%)	(—)	51 (18)	
Ejection fraction (%)	(N.D.)	62 ± 13	
No. of diseased vessels			
One (%)	(—)	97 (34)	
Two (%)	(—)	95 (34)	
Three (%)	(—)	84 (31)	
LMT	(—)	4 (1)	

Values are mean ± SD. CAD, coronary artery disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; CABG, coronary artery bypass graft surgery; LMT, left main trunk.

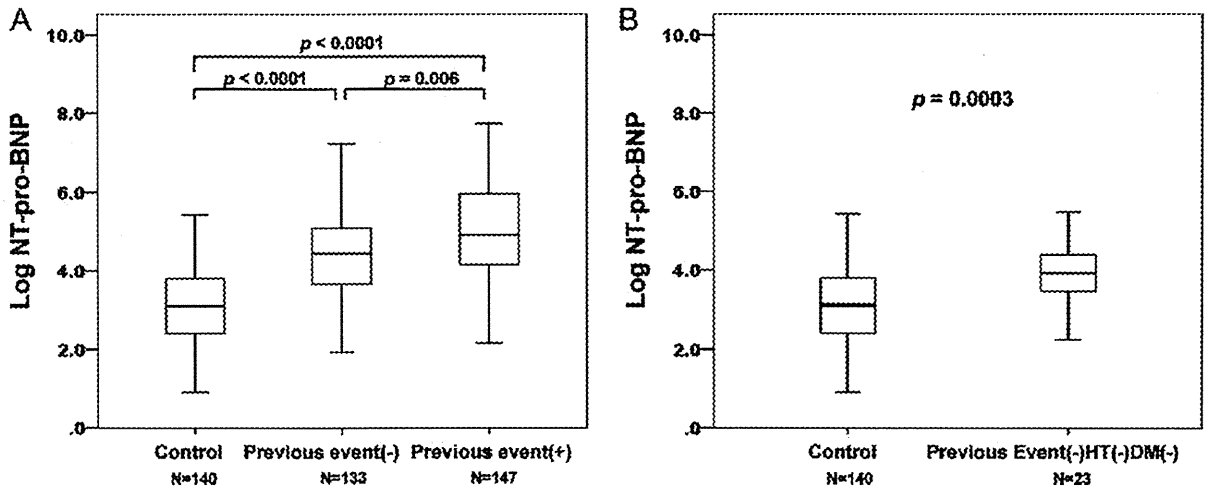

Figure 2 Comparison of logarithmically transformed N-terminal pro-B-type natriuretic peptide NT-proBNP levels (A) among the control, the Previous Event (—), and the Previous Event (+) groups and (B) between the control and the Previous Event (—) HT (—) DM (—) groups. Lines within boxes represent median values, with top and bottom lines of boxes representing the 75th and 25th percentiles HT, hypertension; DM, diabetes.

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Table 2 Comparison of clinical characteristics of MACE (−) and MACE (+).

	CAD MACE (−)	CAD MACE (+)	p value
No. of patients	237	25	
Age (years)	59 ± 6	59 ± 6	NS
Male (%)	215(91)	21 (85)	NS
Body mass index (kg/m^2)	24.8 ± 3.1	25.0 ± 3.5	NS
Waist (cm)	87.6 ± 7.3	90.1 ± 9.4	NS
Hypertension (%)	161 (68)	19 (76)	NS
Diabetes mellitus (%)	100 (42)	18(72)	0.004
Current smoker (%)	78 (33)	12 (48)	NS
Metabolic syndrome (%)	106 (45)	15 (60)	NS
Chronic kidney disease			NS
Stage I (%)	29 (12)	5 (20)	
Stage II (%)	157 (66)	14 (56)	
Stage III (%)	51 (22)	6 (24)	
Estimated GFR (ml/min/1.73 m^2)	72 ± 15	71 ± 17	NS
Total cholesterol (mg/dl)	186 ± 34	180 ± 40	NS
Triglyceride (mg/dl)	150 ± 72	150 ± 85	NS
HDL-cholesterol (mg/dl)	43 ± 11	44 ± 14	NS
LDL-cholesterol (mg/dl)	114 ± 31	106 ± 34	NS
Blood glucose (mg/dl)	109 ± 34	115 ± 38	NS
HbA1c (%)	6.0 ± 1.3	6.8 ± 1.8	0.004
Previous myocardial infarction (%)	82 (35)	10 (40)	NS
Previous CABG (%)	24 (10)	3 (12)	NS
Previous coronary revascularization (%)	44 (19)	7 (27)	NS
Ejection fraction (%)	63 ± 13	63 ± 14	NS
No. of diseased vessels			NS
One (%)	83 (35)	6 (24)	
Two (%)	82 (35)	7 (28)	
Three (%)	69 (29)	12 (48)	
LMT	3 (1)	0 (0)	
Lesion type			NS
A	7 (3)	0 (0)	
B1	37 (16)	5 (20)	
B2	68 (29)	5 (20)	
C	125 (53)	15 (60)	
Stent size (mm)	2.92 ± 0.39	2.86 ± 0.34	NS
Stent length (mm)	23.1 ± 5.6	23.6 ± 5.3	NS
MLD			
Pre-PCI (mm)	0.47 ± 0.32	0.42 ± 0.33	NS
Post-PCI (mm)	2.72 ± 0.46	2.66 ± 0.43	NS
Reference diameter			
Pre-PCI (mm)	2.74 ± 0.45	2.71 ± 0.46	NS

Values are ±SD. MACE, major adverse cardiac events; CAD, coronary artery disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; CABG, coronary artery bypass graft surgery; LMT, left main trunk; MLD, minimumal luminal diameter; PCI, percutaneous coronary intervention.

significant differences between the two groups regarding concomitant use of medications including antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nitrates, insulin use, and statins. Plasma levels of log NT-proBNP were significantly higher in the MACE (+) group compared to the MACE (−) group ($p = 0.0045$) (Fig. 3). The cut-off value of log NT-pro-BNP for MACE determined by ROC curve analysis was 4.93 (NT-proBNP level 139 pg/ml). Kaplan–Meier analysis demonstrated that the patients with high log NT-pro-BNP levels had a significantly higher prevalence of MACE during the entire follow-up period (log-rank test, $p = 0.0058$) (Fig. 4). The same trend was observed after dividing the CAD group into two groups using cut-off value of 125 pg/ml of NT-proBNP level (data not shown).

Multivariate analyses

Log NT-proBNP levels as well as body mass index, LDL-C, HDL-C, HT, and DM were observed to be independent for CAD by the multivariate analysis [odds ratio 3.79, 95% confidence interval (CI) 2.62–5.48, $p < 0.0001$] (Table 3A). In addition, multivariate Cox proportional hazard analysis showed that

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Table 3 Univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
A. Analysis for CAD						
Age	1.01	0.98–1.04	0.314			
Male	1.00	0.50–1.96	0.999			
BMI	1.10	1.02–1.18	0.001			
Estimated GFR	1.00	0.99–1.02	0.217			
LDL-C	0.99	0.98–0.99	0.010			
HDL-C	0.90	0.88–0.92	<0.0001	0.90	0.87–0.93	<0.0001
HT	7.80	4.86–12.51	<0.0001	4.45	2.23–8.88	<0.0001
DM	6.72	3.79–11.89	<0.0001	4.39	1.83–10.52	0.0009
Log NT-proBNP	3.59	2.74–4.69	<0.0001	3.79	2.62–5.48	<0.0001
	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
B. Analysis for MACE in patients with CAD						
Age	1.02	0.96–1.09	0.491			
Male	0.61	0.21–1.77	0.359			
Estimated GFR	0.99	0.97–1.02	0.824			
Multivessel disease	2.29	0.99–5.28	0.051	2.75	1.23–6.14	0.014
DM	3.52	1.42–8.76	0.007	2.64	1.09–6.43	0.032
Log NT-proBNP	1.61	1.15–2.26	0.006	1.48	1.06–2.07	0.021

CAD, coronary artery disease; MACE, major adverse cardiac events; OR, odds ratio; CI, confidence interval; HR, hazard ratio; BMI, body mass index; GFR, glomerular filtration rate; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HT, hypertension; DM, diabetes mellitus; NT-proBNP, N-terminal pro B-type natriuretic peptide.

the levels of log NT-proBNP were a significant and independent predictor of MACE. The adjusted hazard ratios for MACE were higher by 1.48 (95%CI 1.06–2.07, $p = 0.021$) times in the high log NT-proBNP group patients compared to the low log NT-proBNP group patients (Table 3B).

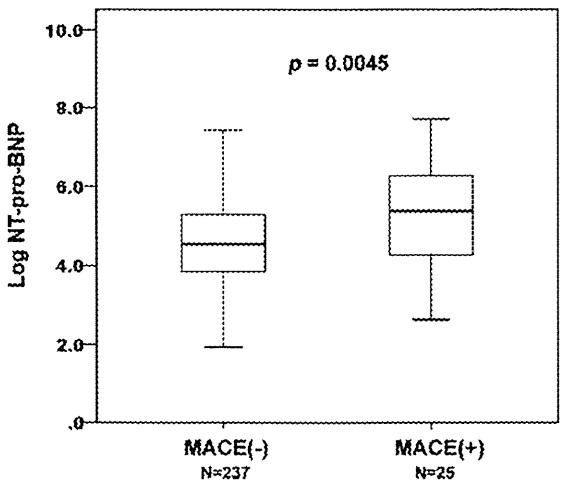

Figure 3 Comparison of logarithmically transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels between the MACE (−) and the MACE (+) groups. Lines within boxes represent median values, with top and bottom lines of boxes representing the 75th and 25th percentiles. MACE, major adverse cardiovascular event.

Discussion

This study demonstrated that the plasma NT-proBNP levels were significantly higher in CAD patients even without a history of HT, DM, CHF, MI, or coronary revascularization compared to the apparently healthy subjects. In addition, high NT-proBNP level was a significant and independent predictor of MACE in CAD patients after the elective DES implantation. To the best of our knowledge, this is the first report that demonstrates the significance of the

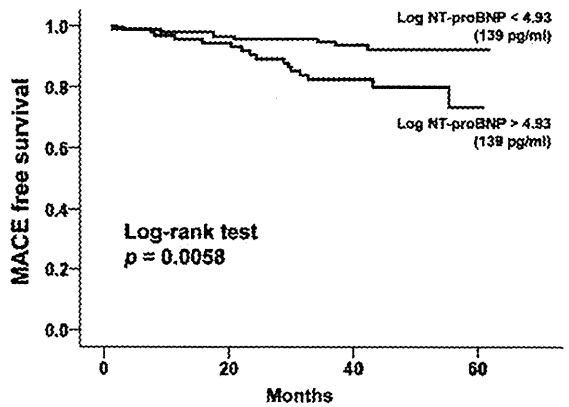

Figure 4 Kaplan–Meier curves for MACE-free survival in patients with coronary artery disease according to high and low N-terminal pro-B-type natriuretic peptide (NT-proBNP) groups. MACE, major adverse cardiovascular event.

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measurements of NT-proBNP levels in identifying the high-risk subjects in CAD patients who have undergone elective DES implantation.

Our findings are consistent with those of reported studies, which have demonstrated that the elevation of NT-proBNP level is associated with CAD [7,9,10]. BNP is synthesized as pre-proBNP$_{1-134}$ mainly in the ventricular myocardium by various stimuli such as mechanical stretch, myocardial injury, ischemic injury, endothelin-1, angiotensin II, interleukin-1β, and α-adrenergic agonists [14]. Pre-proBNP$_{1-134}$ undergoes rapid removal of a 26-amino acid signal peptide, which results in the formation of proBNP$_{1-108}$. Subsequently, proBNP$_{108}$ is enzymatically cleaved to biologically active BNP$_{1-32}$ (BNP) and biologically inactive NT-proBNP$_{1-76}$ (NT-proBNP) [14]. BNP and NT-proBNP have differential modes of clearance. BNP is cleared by receptor-mediated binding and removal by natriuretic peptide receptor-C as well as through the activity of neutral endopeptidases [15,16]. On the other hand, NT-proBNP lacks active clearance mechanisms and is cleared by organ beds with large degrees of blood flow such as kidneys [14]. Therefore, the NT-proBNP levels, rather than BNP, are thought to be associated with renal function as well as age and gender differences [17,18]. In the present study, prevalence of CKD stages from I to III was identical between the CAD patients and the age- and gender-matched controls. Moreover, higher NT-proBNP level may reflect subclinical levels of ventricular systolic or diastolic dysfunctions. However, NT-proBNP levels were significantly high even in CAD patients with no history of confounding factors for ventricular function such as HT, DM, CHF, MI, and coronary revascularization when compared to the apparently healthy subjects. Therefore, ventricular dysfunction and renal insufficiency may not sufficiently explain elevation of the NT-proBNP levels in CAD patients.

Previous studies have reported that NT-proBNP level predicts cardiovascular events, independent of traditional risk factors in patients with stable CAD [7,10]. The present study also demonstrated that the higher NT-proBNP level is an independent predictor of MACE even in CAD patients who have undergone elective DES implantation. After the adjustment of factors such as age and DM, higher NT-proBNP levels were still found to be significant for MACE. The reason why elevations of NT-proBNP levels predict future cardiovascular events may reflect subclinical levels of inducible ischemia [19]. Natriuretic peptides are secreted from the ventricle in response to ventricular stress from volume and pressure overload. Therefore, elevations of NT-proBNP level may reflect adverse hemodynamic alterations. This can probably explain the mechanism by which elevation of NT-proBNP level is associated with CAD, as discussed above. It has been reported that elevations of NT-proBNP level may also reflect vascular dysfunction, in which the natriuretic peptides produce the proliferation of vascular smooth muscle cells and change its contractility [10,20]. We did not study these vascular functions in the present study. Clinical studies to investigate the association between NT-proBNP level and vascular function (e.g. flow-mediated dilatation of brachial artery) are required in the future.

Different prognostic values have been reported between BNP and NT-proBNP [6,21]. Compared to BNP, higher NT-proBNP level is superior in predicting mortality and morbidity in patients with CHF [6] and in patients with stable CAD [21]. NT-proBNP is more stable than BNP in the blood stream due to lack of both biological activity and active clearance mechanisms. Indeed, BNP and NT-proBNP have different half-lives, which are 20 min and 120 min, respectively. In addition, NT-proBNP is stable for at least 72 h in whole blood at room temperature and requires no additives [17]. In this study, we could not elucidate the difference in clinical significances between BNP and NT-proBNP. Nevertheless, a single measurement of NT-proBNP level may prove to be a sensitive and an accurate marker to predict future cardiovascular risks in patients with stable CAD. However, further studies are needed to elucidate this probability.

The following are some limitations in our study. Firstly, it is a single center study with a small sample size. However, we prospectively enrolled consecutive CAD patients, who had undergone elective DES implantation and observed a significant association between NT-proBNP levels and MACE. Studies with larger sample size are needed to confirm this association. Secondly, we did not measure the plasma NT-proBNP levels during the follow-up period as we needed to clarify the meaning of reassessment. Thirdly, the plasma NT-proBNP level might have been affected by the treatments, including the use of antiplatelets, anti-hypertensive agents, and lipid-lowering drugs; however, the prevalence of medications at baseline was not significantly different between the patients with and without MACE. Fourthly, the detailed data of systolic and diastolic functions evaluated by echocardiography were not available for all subjects. The values of left ventricular ejection fraction were identical for the two groups. In addition, a higher NT-proBNP level was a still significant factor for MACE after the adjustment of risk factors, which may link to ventricular function such as age, HT, and DM.

Conclusions

These results demonstrated that the measurement of plasma NT-proBNP level may be useful in identifying high-risk subjects among CAD patients who have undergone elective DES implantation.

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