Journal of Cardiology (2011) 57, 303—310

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jjcc

Original article

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

Yoshiyuki Masaki (MD)[a], Kazunori Shimada (MD, FJCC)[a,*], Takahiko Kojima (MD)[a], Katsumi Miyauchi (MD, FJCC)[a], Kenji Inoue (MD)[a], Takashi Kiyanagi (MD)[a], Makoto Hiki (MD)[a], Kosuke Fukao (MD)[a], Kuniaki Hirose (MD)[a], Hiromichi Ohsaka (MD)[a], Atsumi Kume (MD)[a], Tetsuro Miyazaki (MD)[a], Hirotoshi Ohmura (MD)[a], Akimichi Ohsaka (MD)[b], Hiroyuki Daida (MD, FJCC)[a]

[a] *Department of Cardiovascular Medicine, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan*
[b] *Department of Transfusion Medicine and Stem Cell Regulation, Juntendo University School of Medicine, Tokyo, Japan*

Received 6 January 2011; received in revised form 23 January 2011; accepted 29 January 2011
Available online 8 March 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 ($p = 0.021$).

* Corresponding author. Tel.: +81 3 5802 1056; fax: +81 3 5689 0627.
E-mail address: shimakaz@juntendo.ac.jp (K. Shimada).

0914-5087/$ — see front matter
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

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).

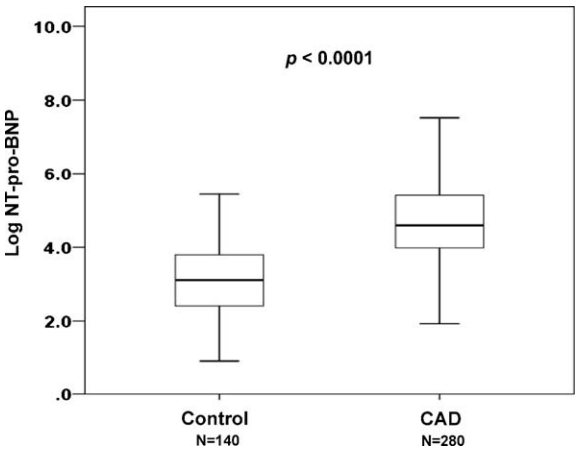

Figure 1 Comparison of logarithmically transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels between the control and the coronary artery disease (CAD) groups. Lines within boxes represent median values, with top and bottom lines of boxes representing the 75th and 25th percentiles.

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

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.

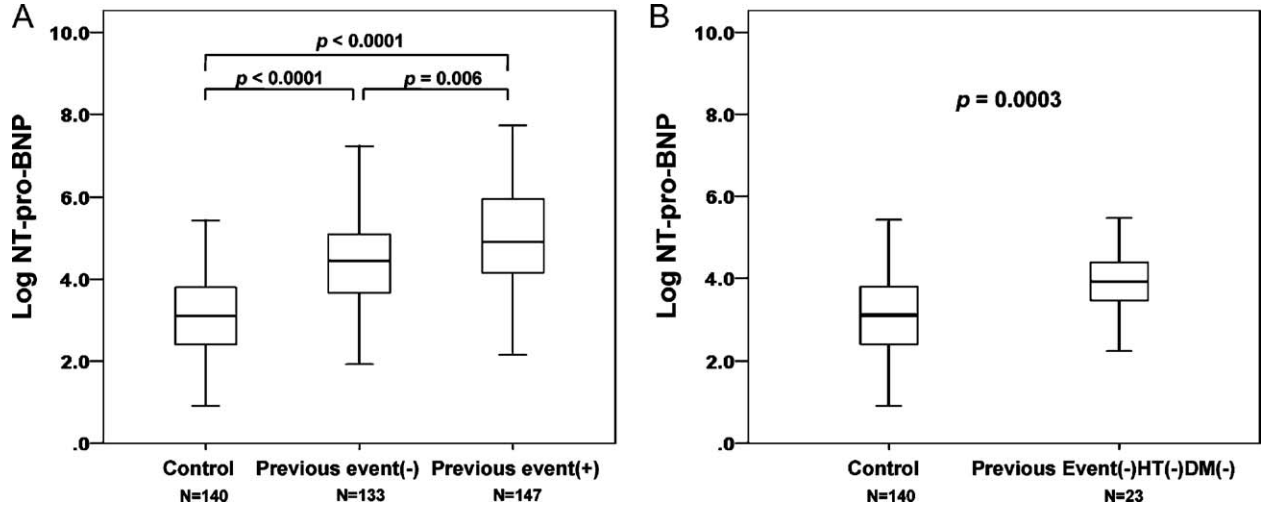

Figure 2 Comparison of logarithmically transformed N-terminal pro-B-type natriuretic peptide NT-proBNP levels (A) among the control, the Previous Event (−), and the Previous Event (+) groups and (B) between the control and the Previous Event (−) HT (−) DM (−) groups. Lines within boxes represent median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

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

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).

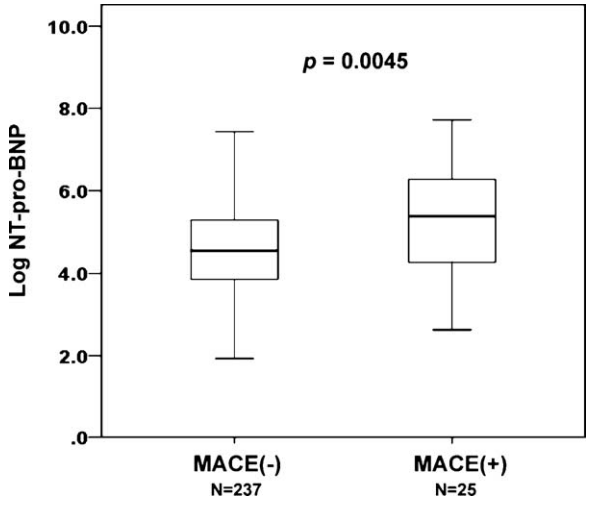

Figure 3 Comparison of logarithmically transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels between the MACE (—) and the MACE (+) groups. Lines within boxes represent median values, with top and bottom lines of boxes representing the 75th and 25th percentiles. MACE, major adverse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

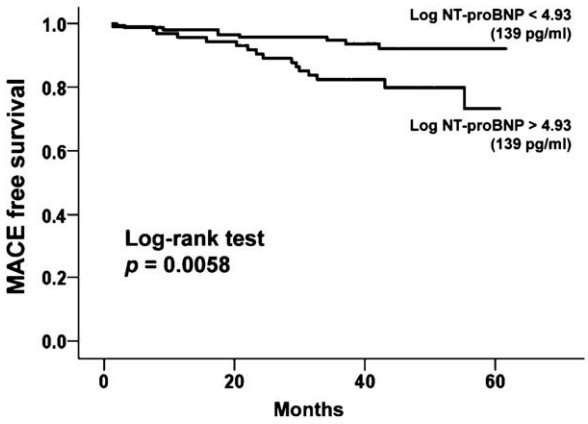

Figure 4 Kaplan—Meier curves for MACE-free survival in patients with coronary artery disease according to high and low N-terminal pro-B-type natriuretic peptide (NT-proBNP) groups. MACE, major adverse cardiovascular event.

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.

References

[1] Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, Storrow AB, Christenson RH, Apple FS, Ravkilde J, Wu AH, National Academy of Clinical Biochemistry Laboratory Medicine. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: clinical utilization of cardiac biomarker testing in heart failure. Circulation 2007;116:e99—109.

[2] Januzzi Jr JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948—54.

[3] Yamashita T, Seino Y, Ogawa A, Ogata K-i, Fukushima M, Tanaka K, Mizuno K. N-terminal pro-BNP is a novel biomarker for integrated cardio-renal burden and early risk stratifica-

tion in patients admitted for cardiac emergency. J Cardiol 2010;55:377—83.
[4] Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001;39:571—88.
[5] Hildebrandt P, Collinson PO. Amino-terminal pro-B-type natriuretic peptide testing to assist the diagnostic evaluation of heart failure in symptomatic primary care patients. Am J Cardiol 2008;101:25—8.
[6] Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, Missov ED, Clerico A, Tognoni G, Cohn JN, Val-HeFT Investigators. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. Clin Chem 2006;52:1528—38.
[7] Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med 2005;352:666—75.
[8] McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109:1004—9.
[9] Weber M, Dill T, Arnold R, Rau M, Ekinci O, Müller KD, Berkovitsch A, Mitrovic V, Hamm C. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. Am Heart J 2004;148:612—20.
[10] Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. JAMA 2007;297:169—76.
[11] Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315—23.
[12] Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, Ura N, Kiyohara Y, Moriyama T, Ando Y, Fujimoto S, Konta T, Yokoyama H, Makino H, Hishida A, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol 2009;13:621—30.
[13] Tschöpe C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J 2005;26: 2277—84.
[14] Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi Jr JL. Biology of the natriuretic peptides. Am J Cardiol 2008;101: 3—8.
[15] de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316—22.
[16] Burnett Jr JC. Novel therapeutic directions for the natriuretic peptides in cardiovascular diseases: what's on the horizon. J Cardiol 2006;48:235—41.
[17] Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006;92: 843—9.
[18] Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi Jr JL. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J Am Coll Cardiol 2006;47:91—7.
[19] Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. B-type natriuretic peptide and ischemia in patients with stable coronary disease: data from the Heart and Soul study. Circulation 2003;108:2987—92.
[20] Ahluwalia A, MacAllister RJ, Hobbs AJ. Vascular actions of natriuretic peptides Cyclic GMP-dependent and -independent mechanisms. Basic Res Cardiol 2004;99:83—9.
[21] Omland T, Sabatine MS, Jablonski KA, Rice MM, Hsia J, Wergeland R, Landaas S, Rouleau JL, Domanski MJ, Hall C, Pfeffer MA, Braunwald E, PEACE Investigators. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease: the PEACE Trial. J Am Coll Cardiol 2007;50: 205—14.