Proximal embolic protection and biomarkers of reperfusion in ST-segment elevation myocardial infarction

Haeck, J.D.E.

Publication date
2010

6

Comparison of usefulness of N-Terminal pro Brain Natriuretic Peptide as an independent predictor of cardiac function among admission cardiac serum biomarkers in patients with anterior wall versus non-anterior wall ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

Haeck JD, Verouden NJ, Kuijt WJ, Koch KT, van Straalen JP, Fischer J, Groenink M, Bilodeau L, Tijssen JG, Krucoff MW, and de Winter RJ

American Journal of Cardiology; 2010; 105(8): 1065-1069

Abstract

The purpose of this study was to determine the prognostic value of N-Terminal pro B-type Natriuretic Peptide (NT-pro-BNP) among other serum biomarkers on cardiac magnetic resonance (CMR) imaging parameters of cardiac function and infarct size in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). We measured NT-pro-BNP, cardiac troponin T, creatine kinase-MB fraction, high-sensitivity C-reactive protein, and creatinine on arrival at the catheterization laboratory in 206 STEMI patients. NT-pro-BNP levels were divided in quartiles and correlated with left ventricular (LV) function and infarct size measured by CMR at 4 to 6 months. Compared to the lower quartiles, patients with non-anterior wall myocardial infarction in the highest quartile of NT-pro-BNP (≥260 pg/mL) more often had a higher LV end-systolic volume (68 mL/m^2 vs. 39 mL/m^2, p<0.001), a lower LV ejection fraction (LVEF, 42% vs. 54%, p<0.001), a larger infarct size (9 g/m^2 vs. 4 g/m^2, p=0.002), and a larger number of transmural segments (11% of segments vs. 3% of segments, p<0.001). Multivariable analysis revealed that NT-pro-BNP ≥260 pg/mL was the strongest independent predictor of LVEF in patients with non-anterior wall myocardial infarction compared with the other serum biomarkers (β=-5.8; p=0.019). In conclusion, in non-anterior wall myocardial infarction patients undergoing primary PCI, admission NT-pro-BNP ≥260 pg/mL is a strong, independent predictor of LV function assessed by CMR at follow-up. Our findings suggest that NT-pro-BNP, a widely available biomarker, may be helpful in early risk stratification in patients with non-anterior wall myocardial infarction.

Introduction

Cardiovascular magnetic resonance (CMR) imaging nowadays is the gold standard to determine left ventricular (LV) function and infarct size (late gadolinium enhancement [LGE]) in patients with ST-segment elevation myocardial infarction (STEMI).[1,2] We sought to evaluate whether plasma levels of admission N-terminal fragment Brain natriuretic peptide (NT-pro-BNP) relates with LV function and infarct size measured by CMR during follow-up and we compared the results of NT-pro-BNP with other serum biomarkers markers associated with prognosis, cardiac troponin T, creatinine clearance rate, and C-reactive protein (CRP).

Methods

All patients included in this study were participants of the PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation (PREPARE) trial. In this two-centre, randomized, open trial patients with STEMI were randomized to primary percutaneous coronary intervention (PCI) with combined proximal embolic protection and thrombus aspiration (n=141) or primary PCI alone (n=143). Results from this randomized trial have been previously published.[3,4] Briefly, patients were eligible for inclusion in the PREPARE trial if they experienced onset of symptoms of myocardial infarction less than 6 hours before presentation and had electrocardiographic evidence of persistent ST-segment elevation of at least 200 μV in ≥2 contiguous leads and Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 1 on diagnostic angiography. Exclusion criteria were: age <18 years, any contraindications to the use of glycoprotein IIb/IIIa receptor antagonists, co-existent condition associated with a limited life expectancy, prior coronary artery bypass grafting or lytics, and recurrence of myocardial infarction in same myocardial area. Primary endpoint of the PREPARE study was ST-segment resolution at 60 minutes after last contrast injection by continuous ST Holter monitoring and analysed at independent core lab. Also all reported clinical end points have been previously defined.[3] Clinical end points included death, spontaneous or procedural myocardial infarction, stroke, and percutaneous or surgical target vessel revascularization.

The current analysis included patients with an admission blood sample and CMR parameters.

Blood was collected in 4.5-mL, gel/lithium-heparine-coated tubes through the arterial sheath at the start of the procedure, centrifuged without undue delay, and stored at -70 ˚C until further analysis. NT-pro-BNP was measured offline (Hitachi Modular E-170, Roche Diagnostics GmbH, Mannheim, Germany). The coefficient of variation was 125 pg/mL 2.7%, 177 pg/mL 1.8%, 355 pg/mL 2.4%, respectively. The functional detection limit was 50.0 pg/mL, linearity was up to 70,000 pg/mL. Serum cardiac troponin T was determined using a Hitachi modular E-170 analyzer (Roche Diagnostics GmbH, Mannheim Germany). Cardiac troponin T elevation was determined as ≥0.03 μg/L for detection of the presence of a myocardial infarction. The lower detection limit of this assay is ≤0.01 μg/L with a recommended diagnostic threshold of ≤0.03 μg/L. Creatine kinase-myocardial band (CK-MB) mass levels were measured at admission, after 5, 7, 10, 12, 18, and 24 hours for determination of the infarct size, using an immunoassay (Hitachi Modular E-170, Roche Diagnostics GmbH). The upper limit of normal of CK-MB mass was ≤7.0 μg/L. Creatinine and CRP were measured on the Hitachi Modular P-unit (Roche Diagnostics GmbH). Lower and upper limits of normal for creatinine were 65 and 95 μmol/L for women and 75 and 110 μmol/L for men. The upper limit of normal (ULN) for CRP was ≤3.0 mg/L. For values below the limit of detection of cardiac troponin T and CRP, the ULN was used for statistical analysis. The estimated creatinine clearance rate was calculated according the Cockcroft and Gault formula[5] and defined as abnormal if ≤90 mL/min, as reported earlier.[6] All testing was performed by personnel blinded to baseline characteristics and clinical outcomes.

As part of an ancillary study, patients underwent CMR at 4 to 6 months after index procedure. CMR imaging was performed with a 1.5T clinical scanner (Sonato/ Avanto, Siemens, Erlangen, Germany). Functional assessment was studied with a standard cine steady-state free precession sequence, and LGE images were acquired after administration of gadolinium-based contrast agent (0.2 mmol/kg, Magnevist, Schering AG, Berlin, Germany). All functional and LGE images were analyzed as described previously.[4] The CMR data were analyzed by a single experienced physician (J.D.E.H.) who was blinded to clinical data using the MASS software (version 5.1, MEDIS Medical Imaging Systems, Leiden, The Netherlands).

Patients were divided according to highest quartile (≥260 pg/mL) and lower quartiles (<260 pg/mL) of NT-pro-BNP levels. Continuous baseline variables are expressed as mean±SD or median (interquartile range) and compared with the unpaired Student's t Test or Mann-Whitney's U test whenever appropriate. Categorical baseline variables were compared by Fisher's Exact Test or chi-square statistic when appropriate. The association between admission NT-pro-BNP ≥260 pg/ml and LVEF (%) and infarct size (g/m^2) was investigated with the use of multivariable linear regression model adjusted for the other serum biomarkers in predicting LVEF or infarct size (admission CK-MB mass ≥7.0 μg/L, admission troponin T ≥0.03 μg/L, admission CRP ≥3 mg/L, and admission creatinine clearance rate ≤90 mL/min). All serum biomarkers were entered en block. Patients who were lost to clinical follow-up due to death received imputed values equal to the worst cardiac CMR parameters in our study population. Analysis of variance (ANOVA) was used to test the significance of the interaction between infarct location and the effect of admission NT-pro-BNP on LVEF. Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

Results

Two-hundred-and-six patients of the PREPARE study were included for the current analysis. The flow chart of patients is shown in Figure 1. As shown in Table 1, there were more patients with diabetes mellitus in patients with an admission NT-pro-BNP ≥260 pg/mL, but overall incidence of diabetes was low. In univariable analysis, an admission NT-pro-BNP ≥260 pg/mL was associated with higher admission levels of CK-MB mass, cardiac troponin T, and high-sensitivity CRP. Patients with an admission NT-pro-BNP ≥260 pg/mL more often had an anterior wall myocardial infarction compared to the patients with admission NT-pro-BNP <260 pg/mL.

Table 1 Patient Characteristics

Variable	NT-pro-BNP (pg/mL) ≥260 (n=52)		NT-pro-BNP (pg/mL) <260 (n=154)		p Value
NT-pro-BNP on admission (pg/ml)	688	(377 - 1550)	58	(14 - 108)	
Age (years)	62	± 11	58	± 11	0.65
Body surface area (m^2)	2.0	± 0.2	2.0	± 0.2	0.95
Men	42	(81%)	131	(85%)	0.47
History					
Diabetes mellitus	7	(14%)	8	(5%)	0.05
Hypertension*	12	(23%)	34	(22%)	0.88
Hypercholesterolemia*	6	(12%)	20	(13%)	0.79
Myocardial infarction	3	(6%)	6	(4%)	0.57
Percutaneous coronary intervention	1	(2%)	7	(5%)	0.40
Cerebrovascular disease	2	(4%)	4	(3%)	0.64
Cardiovascular disease in family	16	(31%)	63	(41%)	0.19
Current smokers	28	(54%)	98	(64%)	0.21
Symptom onset to balloon (min)	177	(131 - 270)	156	(127 - 211)	0.18
Systolic blood pressure (mm Hg)	137	± 32	132	± 26	0.59
Diastolic blood pressure (mm Hg)	79	± 20	78	± 16	0.52
Heart rate (bpm)	77	± 21	74	± 20	0.32
Infarct-related coronary artery					0.001
Left anterior descending	27	(52%)	33	(21%)	
Left circumflex	7	(14%)	16	(10%)	
Right	18	(35%)	105	(68%)	
Pre-procedural TIMI-graded flow					0.64
0	47	(90%)	144	(94%)	
1	4	(8%)	8	(5%)	
2	1	(2%)	2	(1%)	
Creatine kinase-myocardial band on admission (µg/L)	11.5	(5.6 - 20.5)	4.5	(3.3 - 6.8)	<0.001
Serum creatinine on admission (µmol/L)	81	(63 - 92)	74	(65 - 84)	0.17
Creatinine clearance rate (mL/min)	106	(77 - 133)	108	(87 - 137)	0.28
Troponin T on admission (µg/L)	0.12	(0.02 - 0.23)	0.02	(0.02 - 0.036)	<0.001
C-reactive protein on admission (mg/L)	3.7	(1.9 - 8.4)	2	(1.2 - 4.1)	0.001

Data are expressed as mean±SD, median (interquartile range), or number of patients (percent). Data for CK-MB mass on admission were available for 52 patients in the highest quartile of NT-pro-BNP and 153 in the lower quartiles of NT-pro-BNP, for CRP on admission 52 and 144, respectively, and for creatinine clearance rate 46 and 152. *Hypertension and hypercholesterolemia were defined as that requiring prescription medication.

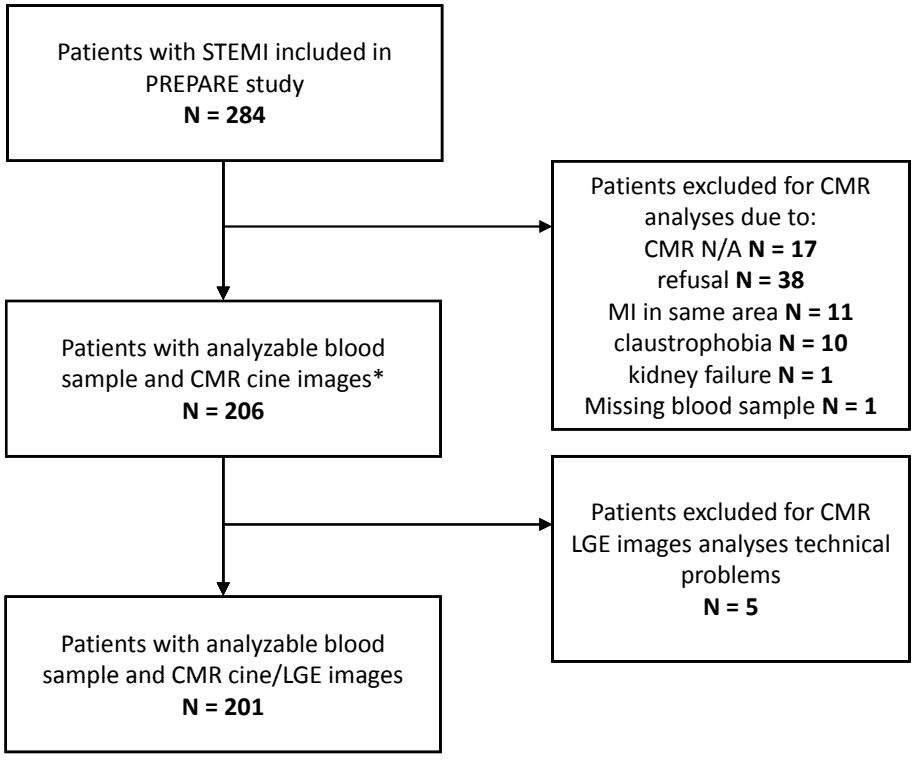

Figure 1 Flow chart of patients included in the analysis. *Including imputed values for the seven deaths. CMR = cardiovascular magnetic resonance; LGE = late gadolinium enhancement; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

The CMR outcome data by admission NT-pro-BNP levels are summarized in Table 2. Patients with an admission NT-pro-BNP ≥260 pg/mL more often had a higher LV end-diastolic volume, a higher LV end-systolic volume, a lower LVEF, a larger infarct size, and a larger number of transmural segments. Because the test for interaction between infarct location and the effect of admission NT-pro-BNP on LVEF was significant ($p<0.0001$), we separately analyzed the effect of an admission NT-pro-BNP ≥260 pg/mL on LVEF in patients with anterior and non-anterior wall myocardial infarction. Overall, anterior wall myocardial infarctions were larger with a larger number of transmural segments.

Table 2 Cardiovascular Magnetic Resonance Outcomes

	All patients			Anterior Wall Myocardial Infarction			Non-anterior Wall Myocardial Infarction		
Variable	NT-pro-BNP (pg/mL) ≥260	NT-pro-BNP (pg/mL) <260	p Value	NT-pro-BNP (pg/mL) ≥260	NT-pro-BNP (pg/mL) <260	p Value	NT-pro-BNP (pg/mL) ≥260	NT-pro-BNP (pg/mL) <260	p Value
	(n=52)	(n=154)		(n=27)	(n=33)		(n=25)	(n=121)	
NT-pro-BNP (pg/mL)	1406 ± 2413	71 ± 63	<0.001	1490 ± 1832	79 ± 71	<0.001	1316 ± 2954	68 ± 61	<0.001
Functional									
End-diastolic LV mass (g/m^2)	52 ± 13	45 ± 9	0.001	51 ± 12	47 ± 10	0.25	53 ± 14	45 ± 9	0.005
Left ventricular end-diastolic volume (mL/m^2)	110 ± 34	87 ± 21	<0.001	110 ± 29	96 ± 29	0.04	110 ± 40	85 ± 17	0.001
Left ventricular end-systolic volume (mL/m^2)	66 ± 35	42 ± 18	<0.001	65 ± 29	54 ± 23	0.11	68 ± 41	39 ± 15	<0.001
Left ventricular ejection fraction (%)	43 ± 13	52 ± 9	<0.001	43 ± 13	46 ± 8	0.32	42 ± 15	54 ± 9	<0.001
Late gadolinium enhancement	(n=50)	(n=151)		(n=27)	(n=33)		(n=23)	(n=118)	
Infarct size (g/m^2)	10 ± 8	5 ± 5	<0.001	10 ± 7	9 ± 6	0.71	9 ± 8	4 ± 5	0.001
Number of transmural segments (% of segments)	15 ± 14	6 ± 10	<0.001	18 ± 14	17 ± 13	0.75	11 ± 13	3 ± 6	0.005

Data are expressed as mean±SD.

There was no effect of an admission NT-pro-BNP ≥260 pg/mL on LVEF in patients with anterior wall myocardial infarction (absolute difference, -3%, 95% confidence interval (CI): -11% to 5%; p=0.32). However, in patients with a non-anterior wall myocardial infarction and an admission NT-pro-BNP ≥260 pg/mL, the LVEF was 12% lower compared with the patients with admission NT-pro-BNP <260 pg/mL (95% CI: -20% to -4%; p<0.001). As shown in Table 3, multivariable analysis revealed that admission NT-pro-BNP ≥260 pg/mL was the strongest independent predictor of a lower LVEF among the serum biomarkers in patients with non-anterior wall myocardial infarction.

Table 3 Univariable and Multivariable Linear Regression Analysis of Admission N-Terminal Pro Brain Natriuretic Peptide ≥ 260 pg/mL for the Prediction of Left Ventricular Ejection Fraction

	Left Ventricular Ejection Fraction (%)			
	Univariable		Multivariable	
Variable	β*	p Value	β†	p Value
In patients with anterior wall myocardial infarction				
Admission NT-pro-BNP ≥ 260 pg/mL	-3.0	0.27	-1.0	0.75
In patients with non-anterior wall myocardial infarction				
Admission NT-pro-BNP ≥ 260 pg/mL	-11.9	<0.0001	-5.8	0.019

Unadjusted absolute difference in left ventricular ejection fraction points (%). †Absolute difference in left ventricular ejection fraction points (%) adjusted for admission CK-MB ≥7.0 µg/L, admission troponin T ≥0.03 µg/L, admission CRP ≥3.0 mg/L*, and admission creatinine clearance rate ≤90 mL/min. The test for interaction between infarct location and the effect of admission NT-pro-BNP ≥260 pg/mL on left ventricular ejection fraction was significant (p<0.0001).

Also, multivariable analysis depicted admission troponin T ≥0.03 µg/L as independent predictor of a larger infarct size (β=3.2; p=0.001) and a larger number of transmural segments (β=6.5; p=0.002) compared with the other serum biomarkers.

A total of 7 patients died before follow-up CMR could be obtained. Two patients with anterior wall myocardial infarction died and 5 with non-anterior wall myocardial infarction. Of these patients, 6 patients had an admission NT-pro BNP in the highest quartile and one patient had a lower NT-pro BNP level (12% vs. 1%, p<0.001). Causes of death in the patients in the highest quartile were progression of heart failure (3),

malignancy (2), and stroke (1). One patient in the group in the lower quartiles (NT-pro-BNP of 240, third quartile) died from heart failure progression. In the patients that underwent CMR, there were no significant differences in the occurrence of spontaneous or procedure-related myocardial infarction (2% vs. 3%), stroke (2% vs. 0%), target vessel revascularization (6% vs. 4%), non-target vessel revascularization (4% vs. 10%), stent thrombosis (0% vs. 1%), and overall MACCE (6% vs. 8%) among patients with or without an admission NT-pro-BNP ≥260 pg/mL. Furthermore, limiting these analyses to the data without the imputed values for the 7 deaths did not appreciably weaken these relationships (data not shown).

Discussion

The current study shows that an admission level of NT-pro-BNP ≥260 pg/mL, measured in patients with a non-anterior wall myocardial infarction undergoing primary PCI, is a strong and independent predictor of LV function, assessed by CMR at follow-up. NT-pro-BNP was the strongest independent predictor of cardiac function among other serum biomarkers. Smaller previous studies have reported a strong relationship between NT-pro-BNP and LV remodelling.[7-10] This study affirms and extends these observations. To our knowledge, this report is the largest study conducted with contrast-enhanced CMR derived outcomes. Furthermore, this is the first study that shows that NT-pro-BNP is a strong predictor of cardiac function in STEMI patients independent of CK-MB, troponin T, CRP, and creatinine clearance rate before PCI. Because NT-pro-BNP was measured on admission, there was no interference of any therapeutic reperfusion modality, as reported in the other studies,[8, 11-13] which led to a strong association of NT-pro-BNP and cardiac function at long-term follow-up.
Although we did not find a significant difference in LV function in patients with an anterior wall myocardial infarction with or without a high NT-pro-BNP level, we did find a significantly impaired LV function among patients with a non-anterior wall myocardial infarction and an admission NT-pro-BNP ≥260 pg/mL compared with the patients with a non-anterior wall myocardial infarction and an admission NT-pro-BNP <260 pg/mL. We believe that this significant difference may be explained by the fact that patients who suffer from a non-anterior wall myocardial infarction have a

smaller amount of salvable LV myocardium at risk compared with patients with an anterior wall myocardial infarction. This result in a limited deterioration of LV function in patients with a non-anterior wall myocardial infarction and a lower NT-pro-BNP compared with patients with an anterior wall myocardial infarction. Apparently, there is a threshold of size of jeopardized myocardium beyond which a NT-pro-BNP in the highest quartile does not relate to adverse remodelling and transmurality of the final infarct. Noteworthy, as the result of the necessity of a "landing zone" for the Proxis system (St. Jude Medical, St. Paul, MN) in our study, patients with a myocardial infarction related to a very proximal lesion of the left anterior descending artery were not included. This resulted in more patients with a non-anterior wall myocardial infarction compared with a "typical" acute myocardial infarction population.

The CMR examinations were performed at 4 and 6 months after the primary PCI. Despite the timing of the CMR scan in the chronic phase of the myocardial infarction, a strong association of admission NT-pro-BNP with cardiac function in the non-anterior wall myocardial infarction patients remained. As such, more robust risk stratification utilizing elevated NT-pro-BNP levels might have clinical implications for choice of adjuvant therapies in patients presenting with acute myocardial infarction, such as intracoronary Abciximab.[14] Importantly, patients with non-anterior wall myocardial infarction and an admission NT-proBNP <260 pg/mL will have better preserved LV function and adjuvant therapies may have only a modest benefit.

Our study has several limitations. Patients included in this study were extracted from a randomized controlled trial, which has caused a selection of patients. Therefore, results from this study may only be applied to acute myocardial infarction patients who meet the criteria mentioned in the method section. Furthermore, patients who refused to undergo a CMR scan at follow-up were excluded, which may have caused an additional bias.

Acknownledgment

We gratefully acknowledge the technical and nursing staff (Heads Martin G.H. Meesterman, Ronald Schmeddes and Raschel D. Snoeks) of the Cardiac Catheterization Laboratory, Coronary Care Unit and Radiology, and Wim J. Rohling for the data acquisition and management

Reference List

1. Kim RJ, Albert TS, Wible JH, et al. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation* 2008;117(5):629-637.
2. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;100(19):1992-2002.
3. Haeck JD, Koch KT, Bilodeau L, et al. Randomized comparison of primary percutaneous coronary intervention with combined proximal embolic protection and thrombus aspiration versus primary percutaneous coronary intervention alone in ST-segment elevation myocardial infarction: the PREPARE (PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation) study. *JACC Cardiovasc Interv* 2009;2(10):934-943.
4. Haeck JD, Kuijt WJ, Koch KT, et al. Infarct size and left ventricular function in the Proximal Embolic Protection in Acute myocardial infarction and Resolution of ST-segment Elevation (PREPARE) trial: ancillary cardiovascular magnetic resonance study. *Heart* 2010; 96:190-95.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16(1):31-41.
6. Kim KE, Onesti G, Ramirez O, Brest AN, Swartz C. Creatinine clearance in renal disease. A reappraisal. *Br Med J* 1969;4(5674):11-14.
7. Cerisano G, Pucci PD, Sulla A, et al. Relation between plasma brain natriuretic peptide, serum indexes of collagen type I turnover, and left ventricular remodeling after reperfused acute myocardial infarction. *Am J Cardiol* 2007;99(5):651-656.
8. Garcia-Alvarez A, Sitges M, Delgado V, et al. Relation of plasma brain natriuretic peptide levels on admission for ST-elevation myocardial infarction to left ventricular end-diastolic volume six months later measured by both echocardiography and cardiac magnetic resonance. *Am J Cardiol* 2009;104(7):878-882.
9. Hirayama A, Kusuoka H, Yamamoto H, et al. Usefulness of plasma brain natriuretic peptide concentration for predicting subsequent left ventricular remodeling after coronary angioplasty in patients with acute myocardial infarction. *Am J Cardiol* 2006;98(4):453-457.
10. Paelinck BP, Vrints CJ, Bax JJ, Bosmans JM, De Hert SG, de RA, Lamb HJ. Relation of B-type natriuretic peptide early after acute myocardial infarction to left ventricular diastolic function and extent of myocardial damage determined by magnetic resonance imaging. *Am J Cardiol* 2006;97(8):1146-1150.
11. Cochet A, Zeller M, Cottin Y, et al. The extent of myocardial damage assessed by contrast-enhanced MRI is a major determinant of N-BNP concentration after myocardial infarction. *Eur J Heart Fail* 2004;6(5):555-560.
12. Nakagawa K, Umetani K, Fujioka D, et al. Correlation of plasma concentrations of B-type natriuretic peptide with infarct size quantified by tomographic thallium-201 myocardial scintigraphy in asymptomatic patients with previous myocardial infarction. *Circ J* 2004;68(10):923-927.
13. Panteghini M, Cuccia C, Bonetti G, Pagani F, Giubbini R, Bonini E. Rapid determination of brain natriuretic peptide in patients with acute myocardial infarction. *Clin Chem Lab Med* 2003;41(2):164-168.
14. Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. *Circulation* 2008;118(1):49-57.