Value of Increased B-type Natriuretic Peptide for Detection and Risk Reclassification of Obstructive Coronary Artery Disease on Computed Tomography Angiography

（冠動脈 CT における冠動脈狭窄の診断及びリスク分類における脳性ナトリウム利尿ペプチドの有用性）

２０１７

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博 士 （医 学） 学 位 論 文

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Key Words: B-type natriuretic peptide; coronary artery disease; computed tomography angiography

Abstract

Background*:* B-type natriuretic peptide (BNP) is well known to increase as a result of left ventricular systolic dysfunction and is a useful diagnostic marker for heart failure. The purpose of this study was to assess the incremental value of BNP for predicting obstructive coronary artery disease (CAD) on computed tomography angiography (CTA) in patients with suspected CAD.

Methods: This was an observational analysis of patients with stable CAD undergoing CTA in our institution between 2008 April and 2014 June. A consecutive 947 patients with suspected CAD underwent 64-slice CTA were enrolled. Obstructive CAD was defined as more than 50% luminal narrowing. We divided the patients into 2 groups according to median BNP value (20.3 pg/ml). Duke clinical score for obstructive CAD was calculated for each patient.

Results: Obstructive CAD was found in 273 (28.0%) patients. Median follow-up periods was 37 months (interquartile range 21 to 55 months). Kaplan-Meier curves showed BNP above median was significantly associated with major adverse cardiac events (P=0.001). In multivariable logistic analysis, patients with BNP above median were associated with the presence of obstructive CAD, as compared with BNP below median (Odds ratio, 2.55; 95% confidence interval [CI], 1.79–3.63; P<0.001).

Analyzing the incremental value of the Duke clinical score and BNP, the predictive value of the Duke clinical score (area under the curve [AUC], 0.714) could be increased by BNP (AUC 0.745 for the combined model; $P<0.001$). Addition of BNP to a model containing the Duke clinical score resulted in continuous net reclassification improvement of 0.39 (95% CI, 0.26–0.53; $P<0.001$).

Conclusions: BNP might provide an incremental improvement in the detection of obstructive CAD on CTA when combined with a conventional cardiovascular risk score.

Introduction

The early detection of coronary artery disease (CAD) is one of the most important tasks in medical practice. Contrast-enhanced computed tomography angiography (CTA) has been proposed as an emerging tool for stenosis detection and characterization and quantification of coronary atherosclerotic plaques [1–3]. Previous studies have demonstrated high diagnostic accuracy of CTA for the detection and assessment of the severity of CAD when compared with invasive coronary angiography [4,5] and the incremental prognostic value of CAD detected by CTA in patients with suspected CAD [6]. The presence of obstructive CAD on CTA is significantly associated with an increased risk of major cardiac events [6,7]. Conversely, patients with no CAD on CTA have a better prognosis [8,9].

B-type natriuretic peptide (BNP) is well known to increase as a result of left ventricular (LV) systolic dysfunction and is recommended by the European Society of Cardiology guidelines as a test to rule out heart failure [10]. However, some previous studies have shown that an increased BNP can identify inducible ischemia by standard noninvasive stress test independent of LV ejection fraction (LVEF) [11]. Recently, some studies have suggested an association between BNP levels and the extent of coronary atherosclerosis [11, 12]. N-terminal pro-BNP (NT pro-BNP) is also associated with

calcium score independent of conventional cardiovascular risk factors [12]. Although an increased BNP is associated with worse prognosis in patients with stable CAD, it is not clear whether BNP is a useful tool for the detection of CAD. The purpose of this study was to evaluate the association between plasma BNP level and the presence of obstructive CAD as assessed by CTA.

Materials and Methods

Study Population

The present study was a retrospective cohort study based on a consecutive 1269 patients with suspected CAD not previously treated with percutaneous coronary intervention or coronary artery bypass grafting and prior myocardial infarction who underwent CTA in our institution between April 2008 and June 2014. We excluded patients with poor CTA imaging due to motion artifact (n=39), atrial fibrillation (n=78), previous heart failure (n=26), acute myocardial infarction (n=13), lower LVEF (less than 50%) (n=77), hypertrophic cardiomyopathy or left ventricular hypertrophy (n=29), and missing BNP value (n=60). This study thus comprised 947 patients (Figure 1). The study was approved by an institutional review committee and the subjects gave informed consent. Patient demographic information, cardiovascular risk factors,

laboratory findings, and symptoms were recorded. The following cardiac risk factors were considered. Hypertension was defined as the presence of current treatment with antihypertensive drugs or otherwise as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg. We defined dyslipidemia if a patient met one or more of the following criteria: serum low density lipoprotein (LDL) cholesterol level ≥140 mg/dL, high density lipoprotein (HDL) cholesterol level 40 mg/dL, serum fasting triglyceride level ≥150 mg/dL, or taking medications to treat dyslipidemia [13]. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dl or treatment with oral hypoglycemic agents or insulin. The estimated glomerular filtration rate (eGFR) was calculated with the following equation: eGFR = 194 × (serum creatinine)(-1.094) × (age)(-0.287) (× 0.739 if female) [14].

From these data, the Duke clinical score for obstructive CAD was calculated for each patient [15,16]. Duke clinical score model was shown in appendix. A blood sample was withdrawn prior to CTA. BNP was measured using the ARCHITECT BNP assay (ABBOTT JAPAN Diagnostics, Tokyo, Japan). Measurement of BNP was routinely performed in all patients undergoing CTA at the examination. The detection limit was 5.8 pg/ml, and the upper measurement limit was 14510 pg/ml. However, BNP values were missing for 60 patients, who were censored from further statistical analysis (Figure

1). We divided the patients into two groups according to median BNP value. BNP below median was <20.3 pg/ml (n = 476); BNP above median was ≥20.3 pg/ml (n = 469). LVEF was measured by echocardiography.

CTA Protocol

Scanning was performed with a Philips Brilliance-64 scanner (Philips Medical Systems, Cleveland, Ohio) with 64×0.625-mm detector configuration. Scanning was performed in retrospective gating at 120 to 140 kV and 600 to 1050 mA, 0.2 pitch, and with ECG-based tube current modulation. The cardiac phase best demonstrating each artery (usually 75% of the RR interval) was analyzed using a dedicated computed tomography workstation (Philips CT Brilliance Workspace, Philips Medical Systems). In some cases, additional reconstructions were made at different time points of the RR interval. Nonionic contrast (iopamidol 370 mg/ml; Schering AG, Berlin, Germany) was injected intravenously at a rate of 4 to 5 m/l. Automated peak enhancement detection in the ascending aorta was used for timing of the bolus using a threshold of +100 Hounsfield units (HU). The data acquisition was performed during an inspiratory breath hold of approximately 10 s. Atenolol (25 mg) orally was administered 12 hour before the examination to decrease heart rate to less than 60 beats/min. When heart rate below

60 bpm could not be achieved using atenolol 25mg, heart rate control with a target of 60 bpm was achieved using 12.5–25mg landiolol, an ultra-short-acting beta-adrenergic blocking agent, injected before data acquisition [17]. All patients received sublingual nitroglycerin (0.3 mg) 5 min before the scan.

CTA Analysis

All CTA scans were analyzed by two experienced readers who were unaware of clinical presentation, patient characteristics, and biomarker analysis. Image display settings for lumen and plaque quantification were determined according to previously published data [18]. The coronary artery tree was segmented according to a American Heart Association classification [19]. The degree of lesion severity was graded into 3 groups: normal was defined as no coronary artery plaques and no obstruction of the coronary lumen, nonobstructive was defined as an estimated obstruction of coronary luminal diameter of ≤50%, and obstructive was defined as an estimated obstruction of coronary luminal diameter of >50%. The total coronary artery calcium burden was quantified using the Agatston scoring method [20]. Coronary plaque characteristics were classified as follows [21,22]. Noncalcified coronary plaque was defined as any discernible structure that could be assigned to the coronary artery wall, had a CT

number below that of the contrast-enhanced coronary lumen but above that of the surrounding connective tissue, and could be identified in at least two independent planes. Any structure with a density of more than 130 HU that could be visualized separately from the contrast-enhanced coronary lumen, assigned to coronary artery wall, and identified in at least two independent planes was defined as calcified plaque. Partially calcified plaque was defined as having both calcified and noncalcified elements within a single plaque. One coronary plaque was assigned per coronary segment.

Clinical outcomes

The follow-up information was gathered by either reviewing clinical visits or contacting general practitioners. Primary outcomes were examined included major adverse cardiovascular events (MACE) defined as any cause of death, acute coronary syndrome (ACS) and revascularization beyond 90 days after CTA. ACS was defined as a non-ST elevation and ST elevation myocardial infarction or unstable angina resulting in admission to the hospital. Patients undergoing coronary revascularization within 90 days were censored at the time of the intervention.

Statistical Analysis

Continuous variables are expressed as means ± standard deviation (SD) or median and interquartile range for non-normally distributed data, and categorical variables as frequencies and percentages. The two groups divided by median BNP were compared using the chi-square test for nominal variables, student *t* test or Mann-Whitney *U* test for continuous variables. Univariable and multivariable logistic regression analysis was used to assess the association between BNP and the presence of obstructive CAD. Variables, including multivariable regression model, were those that achieved statistical significance ($P<0.05$) or were close to significance ($P<0.10$) in the univariable analysis. Survival analysis was performed by applying the Kaplan-Meier method and log-rank test. To compare the accuracy of BNP and the Duke clinical score, receiver operating characteristics (ROC) curves were generated and the area under the curve (AUC) was calculated. The net reclassification improvement was determined by assessing net improvement in risk classification [23]. Reclassification tables were constructed as a further measure to assess any incremental value for BNP in improving the risk classification afforded by the Duke clinical score using the risk categories <15%, 15% to ≤30%, 30% to ≤45%, and >45%. Statistical significance was accepted for 2-sided probability values of <0.05. Statistical analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for

the R statistical analysis program (The R Foundation for Statistical Computing, version 2.13.0) [24] and statistical package R version 3.1.1.

Results

Baseline characteristics

The mean patient age was 64±11 years, and 402 patients (42.4%) were women. The presence of any plaques was detected in 568 patients (60.0%). Among these 568 patients with coronary plaques, calcified plaques were present in 463 (81.5%), noncalcified plaques in 283 (50.0%), and partially calcified plaques in 169 (29.8%) patients. Nonobstructive CAD was detected in 297 (31.4%) and normal arteries in 384 (40.6%) patients. Obstructive CAD was found in 265 (28.0%) patients. Mean BNP level in patients with obstructive CAD was significant higher than those without obstructive CAD (26.2 ± 30.2 pg/ml vs 51.7 ± 106.6 pg/ml; $P<0.001$). The Duke clinical score was low (<30%) in 242 patients (25.5%), intermediate (30–70%) in 345 patients (36.3%), and high (>70%) in 360 patients (38.0%). The median Agatston score was 5 (Interquartile range 0–118).

The baseline characteristics of the 947 patients according to median BNP are shown in Table 1. Patients with BNP above median were older, more often female, and more

often had a lower eGFR and LDL level. The prevalence of hypertension was significantly higher in patients with BNP above median, but that of history of smoking, family history of CAD, diabetes mellitus, and dyslipidemia were similar regardless of BNP level. Prevalence of undergoing revascularization within 90 days after CTA were significantly higher in patients with BNP above median than those with BNP below median (P<0.001).

CTA results and the Duke clinical score are shown in Table 2. The prevalence of obstructive CAD, one-vessel disease, two-vessel disease, and three-vessel or left main disease was significantly higher in patients with BNP above median than those with BNP below median. Numbers of total plaque, calcified plaque, noncalcified plaque, and partially calcified plaque were increased as BNP levels increased. The prevalence of high Duke clinical score was significantly higher in patients with BNP above median than those with BNP below median (P<0.001).

The distribution of BNP within CAD is shown in Figure 2. As the severity of CAD increased, there was a significant increase in BNP level (P<0.001). The mean BNP was 23.1 (SD 29.6) pg/ml in patients with normal arteries, 30.4 (SD 30.6) pg/ml in patients with nonobstructive CAD, and 51.7 (SD 106.5) pg/ml in patients with obstructive CAD.

Clinical outcomes

Median follow-up periods was 37 months (interquartile range 21 to 55 months). Coronary revascularization within 90 days after CTA was performed in 123 (13.0%) patients. Excluding patients undergoing coronary revascularization within 90 days after CTA, 42 (4.4%) patients experienced MACE, of which 11 patients died (1.2%), 9 patients experienced ACS (1.0%) and 22 (2.6%) patients undergoing late coronary revascularization due to ischemic-related CAD. Kaplan-Meier curves showed BNP above median was significantly associated with MACE (P=0.001) (Figure 3).

Multivariable logistic regression analysis for the prediction of obstructive CAD

Multivariable logistic regression analysis demonstrated that BNP above median (odds ratio [OR], 2.55; 95% confidence interval [CI], 1.79–3.63; P<0.001) was independent predictors of obstructive CAD as compared with BNP below median (Table 3).

Incremental value of BNP in addition to the Duke clinical score for the prediction of obstructive CAD

The AUCs for detecting obstructive CAD for BNP, Duke clinical score, and

composite of BNP and Duke clinical score were 0.673, 0.714, and 0.745, respectively (Figure 4). The AUC for the composite of BNP and Duke clinical score was significantly higher than the AUC for BNP alone and for Duke clinical score alone (P<0.001, for both). Reclassification of patients when predicting obstructive CAD based on BNP and Duke clinical score instead of Duke clinical score alone are summarized in Table 4. In patients with obstructive CAD, 42 patients (15.7%) correctly moved upward and 41 patients (15.4%) incorrectly moved downward in the classification. In patients without obstructive CAD, 39 patients (5.7%) incorrectly moved upward and 134 patients (19.6%) correctly moved downward in the classification. Continuous net reclassification improvement was calculated at 0.39 (95% CI, 0.26–0.53; P<0.001).

Discussion

In this study of patients with suspected CAD undergoing CTA, we scrutinized the diagnostic value of BNP. We report three major finding with the potential to improve the diagnosis of CAD: First, BNP levels were significantly higher in patients with obstructive CAD than in those without CAD. Second, the prediction of obstructive CAD with BNP was independent of conventional cardiovascular risk factors. Third, BNP added incremental improvement to conventional cardiovascular risk factors in

predicting obstructive CAD. Critical coronary stenosis is associated with worse cardiovascular outcomes depending on the location, functional significance, and extent of coronary atherosclerosis [25]. Patients with obstructive CAD on CTA have a worse long-term cardiovascular prognosis than those without obstructive CAD [26]. Therefore, the prediction of obstructive CAD on CTA is important in clinical practice. Although some previous studies have demonstrated that BNP is associated with CAD [11,12], a few reports have suggested that elevated BNP in patients with suspected CAD on CTA are associated with the presence of obstructive CAD. To our knowledge, this is the first study to elucidate the incremental value of BNP for the diagnosis of obstructive CAD on CTA.

BNP and NT-proBNP are widely used clinically as biomarkers for evaluating patients with heart failure [27]. However, few studies have investigated the association between obstructive CAD on CTA and BNP levels. In patients with stable CAD, myocardial ischemia, independent of LV dysfunction, might be a cause of elevated BNP [28,29]. NT-proBNP is increased in patients with CAD and correlates closely with disease severity [30,31]. These results might lead to the hypothesis that myocardial ischemia and CAD are major causes of the release of BNP. An increase in BNP as a response to myocardial ischemia can be explained by an increase in the LV filling

pressure, which occurs early in the ischemic cascade. However, because natriuretic peptides and their receptors are abundantly present in atherosclerotic plaques in human coronary arteries, atherosclerosis itself may be a cause of an elevated BNP level [32]. In the present study, the number of plaque was significantly higher in patients with a higher BNP level. This might explain the mechanism by which the higher BNP level is associated with coronary plaque burden.

The observed relation between BNP and obstructive CAD is in accordance with previous studies. Some studies have investigated the diagnostic performance of BNP and NT-proBNP in patients with suspected CAD. BNP in one study was not independently associated with CAD, but this study based the diagnosis of CAD on coronary catheterization findings [33]. Weber et al. [30] has demonstrated that NTproBNP was an independent predictor for obstructive CAD and closely linked to the number of diseased vessel as assessed by coronary angiography. In their study, AUC of NTproBNP for the predicting obstructive CAD was 0.72. Lee G et al. [34] has showed that combining BNP at rest and clinical judgment increased diagnostic accuracy regarding the presence of myocardial ischemia evaluated by rest/bicycle myocardial perfusion single-photon emission computed tomography. BNP at rest and clinical judgement achieved an AUC of 0.69 and 0.70 respectively. Clinical judgment added to

BNP improved the AUC to 0.75. Our data reveal that BNP is an independent predictor of the presence of obstructive CAD and added to cardiovascular risk factors have incremental value for the predicting obstructive CAD as assessed by CTA.

Cut off value of BNP for the predicting obstructive CAD in this study was quite low (25.4 pg/ml) when compared with contemporary thresholds used for the diagnosis of heart failure (100 pg/ml) [35], because we excluded patients with atrial fibrillation, left ventricular hypertrophy and previous myocardial infarction, which are known to be associated with cardiomyocyte damage and elevations in BNP regardless of the presence of coronary artery disease [36]. Our study suggests that BNP has the potential to become a serum biomarker that will improve identification of patients with obstructive CAD. We acknowledge that AUC of 0.745 for BNP plus Duke clinical score is suboptimal and there are remaining challenges to establish the role of non-invasive examination in the diagnosis of CAD.

Study Limitations

Patients with LV dysfunction, atrial fibrillation, and previous heart failure were excluded. Therefore, the value of BNP in diagnosing obstructive CAD in these subgroups is unknown, and the results of our study cannot necessarily be generalized to

those patients. This may have introduced bias due to referral characteristics. Some previous studies have demonstrated that high sensitive troponins correlated with angiographic atherosclerotic extent and burden [37]. However, high sensitive troponins were not available in this study, we could not compare BNP value with high sensitive troponins. Finally, we analyzed the data from a single institution. Therefore, careful attention should be paid when the results are generalized and extrapolated.

Conclusion

BNP might provide incremental improvement in the detection of obstructive CAD on CTA when combined with a conventional cardiovascular risk score.

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Figure legends

Figure 1. Study population.

BNP, B-type natriuretic peptide; CTA, computed tomography angiography; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

Figure 2. Distribution of plasma BNP levels according to the severity of CAD.

BNP, B-type natriuretic peptide; CAD, coronary artery disease.

Figure 3. Kaplan-Meier curves for MACE-free survival according to median of BNP.

BNP, B-type natriuretic peptide, MACE, major adverse cardiac events.

Figure 4. AUC for detecting obstructive CAD for BNP, Duke clinical score, and the composite of both.

AUC, area under curve; BNP, B-type natriuretic peptide; CAD, coronary artery disease; DCS, Duke clinical score.

Appendix.

Duke clinical score was calculated as

$$1/(1+e^{-x})$$

where e = base of natural logarithm

$$x = ay_1 + a_2y_2 + \ldots + a_ky_k + B$$

where $y_1, y_2, \ldots, y_k$ are the characteristics,

$a_1, a_2, \ldots, a_k$ are the corresponding logistic regression coefficients, and

B is the intercept term (in this case, −7.376).

The predictive characteristics are listed below with their coefficients:

Characteristics	Coefficient
Age	0.1126
Sex (0 = male, 1 = female)	−0.328
Age * Sex (interaction)	−0.0328
Typical angina (1 if present)	2.581
Atypical angina (1 if present)	0.976
History of MI (1 if present)	1.093
ECG Q waves (1 if present)	1.213
History of MI * Q waves (interaction)	0.741
Smoking (1 if present)	2.596
Hyperlipidemia (1 if present)	1.845
Diabetes (1 if present)	1.845
ECG ST-T wave changes (1 if present)	0.637
Age * Smoking (interaction)	−0.0404
Age * Hyperlipidemia (1 if present)	−0.0251
Sex * Smoking (interaction)	0.55

ECG, electrocardiogram; MI, myocardial infarction.

Table 1. Baseline patients characteristics by median BNP levels

	BNP below median (<20.3 pg/ml) n=476	BNP above median (≥20.3 pg/ml) n=469	*P* Value
Age, yrs	60.7 ± 10.8	67.7 ± 9.6	<0.001
Female	180 (37.8)	211 (45.0)	0.029
BMI, kg/m^2	24.6 ± 4.5	23.7 ± 4.4	0.023
Family history of CAD	149 (31.3)	147 (31.3)	1.000
LVEF, %	64.0 ± 7.4	64.6 ± 8.1	0.223
Smoker	217 (45.6)	195 (41.6)	0.238
Diabetes mellitus	94 (19.7)	116 (24.7)	0.071
Dyslipidemia	227 (47.7)	198 (42.2)	0.102
Hypertension	257 (54.0)	287 (61.2)	0.025
LDL, mg/dl	126.1 ± 32.9	119.0 ± 34.7	0.001
HDL, mg/dl	56.5 ± 16.0	59.2 ± 30.6	0.089
TG, mg/dl	163.4 ± 107.6	153.0 ± 148.8	0.221
CRP, mg/dl	0.21 ± 0.66	0.31 ± 1.18	0.106
eGFR, ml/min/1.73 m^2	63.4 ± 16.6	59.8 ± 16.9	0.001
Exertional chest pain	113 (23.7)	136 (29.0)	0.076
Atypical chest pain	213 (44.7)	183 (39.0)	0.075
Dyspnea	36 (7.6)	42 (9.0)	0.444
Revascularization within 90 days	42 (8.8)	79 (16.8)	<0.001

Data are expressed as mean value ± SD or number of patients (percentage).
BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; TG, triglyceride.

Table 2. Computed tomography angiography results and Duke clinical score

	BNP below median (<20.3 pg/ml) n = 476	BNP above median (≥20.3 pg/ml) n = 469	*P* Value
Obstructive CAD	82 (17.2)	182 (38.8)	<0.001
One-vessel	56 (11.8)	105 (22.4)	<0.001
Two-vessel	15 (3.2)	48 (10.2)	
Three-vessel or left main	11 (2.3)	29 (6.2)	
Non-obstructive CAD	142 (29.8)	155 (33.0)	0.294
Normal coronary arteries	252 (52.9)	132 (28.1)	<0.001
Total plaque	1.54 ± 2.25	2.98 ± 2.97	<0.001
Calcified plaque	1.07 ± 1.79	1.97 ± 2.37	<0.001
Non-calcified plaque	0.30 ± 0.72	0.63 ± 1.03	<0.001
Partially calcified plaque	0.16 ± 0.51	0.37 ± 0.79	<0.001
Calcium score*	0 [0, 52]	32 [0, 241]	<0.001
Duke clinical score, %	50.3 ± 28.2	60.7 ± 28.2	<0.001

Data are expressed as mean value ± SD or number of patients (percentage). *Median and interquartile range.
BNP, B-type natriuretic peptide; CAD, coronary artery disease.

Table 3. Univariable and multivariable logistic regression analysis for the presence of obstructive CAD

	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
BNP below median (<20.3 pg/ml)		reference			reference	
BNP above median (≥20.3 pg/ml)	3.05	2.25–4.12	<0.001	2.55	1.79–3.63	<0.001
Age, per yrs	1.05	1.03–1.06	<0.001	1.04	1.02–1.06	<0.001
CRP, per kg/m^2	1.15	0.99–1.33	0.058	1.10	0.93–1.30	0.244
Dyslipidemia	1.38	1.04–1.83	0.023	1.61	1.15–2.27	0.005
Hypertension	2.07	1.54–2.79	<0.001	1.62	1.14–2.31	0.007
Diabetes mellitus	2.14	1.56–2.94	<0.001	1.78	1.22–2.60	0.002
eGFR, per ml/min/1.73 m^2	0.96	0.95–0.97	<0.001	0.99	0.97–1.00	0.206
Female	0.36	0.26–0.49	<0.001	0.31	0.20–0.48	<0.001
Exertional chest pain	1.91	1.41–2.59	<0.001	1.93	1.29–2.89	0.001
Atypical chest pain	0.56	0.41–0.75	0.001	0.85	0.57–1.26	0.422
Dyspnea	1.27	0.80–2.00	0.311			
Family history	1.11	0.82–1.50	0.502			
BMI, per kg/m^2	1.00	0.97–1.03	0.897			
LVEF, per %	0.99	0.97–1.01	0.491			
Smoker	1.11	0.83–1.47	0.483			

CI, confidence interval. OR, odds ratio. See Table 1 for other abbreviations.

Table 4. Reclassification of study participants with or without obstructive CAD by BNP to a model containing the Duke clinical score

Patients with obstructive CAD (n=266)					
	Model with Duke clinical score plus BNP				
Model with Duke clinical score	<15% risk	15% to <30% risk	30% to 45% risk	>45% risk	Total
<15% risk	24	4	2	1	31
15% to <30% risk	1	36	7	1	45
30% to 45% risk	0	22	54	27	103
>45% risk	0	0	18	69	87
Total	25	62	81	98	266
Patients without obstructive CAD (n=681)					
	Model with Duke clinical score plus BNP				
Model with Duke clinical score	<15% risk	15% to <30% risk	30% to 45% risk	>45% risk	Total
<15% risk	224	11	2	1	238
15% to <30% risk	43	140	10	2	195
30% to 45% risk	0	44	97	13	154
>45% risk	0	0	47	47	94
Total	267	195	156	63	681

Continuous net reclassification improvement was calculated at 0.39 (95% CI, 0.26–0.53; *P*<0.001).
BNP, B-type natriuretic peptide; CAD, coronary artery disease; CI, confidence interval.

Figure 1.

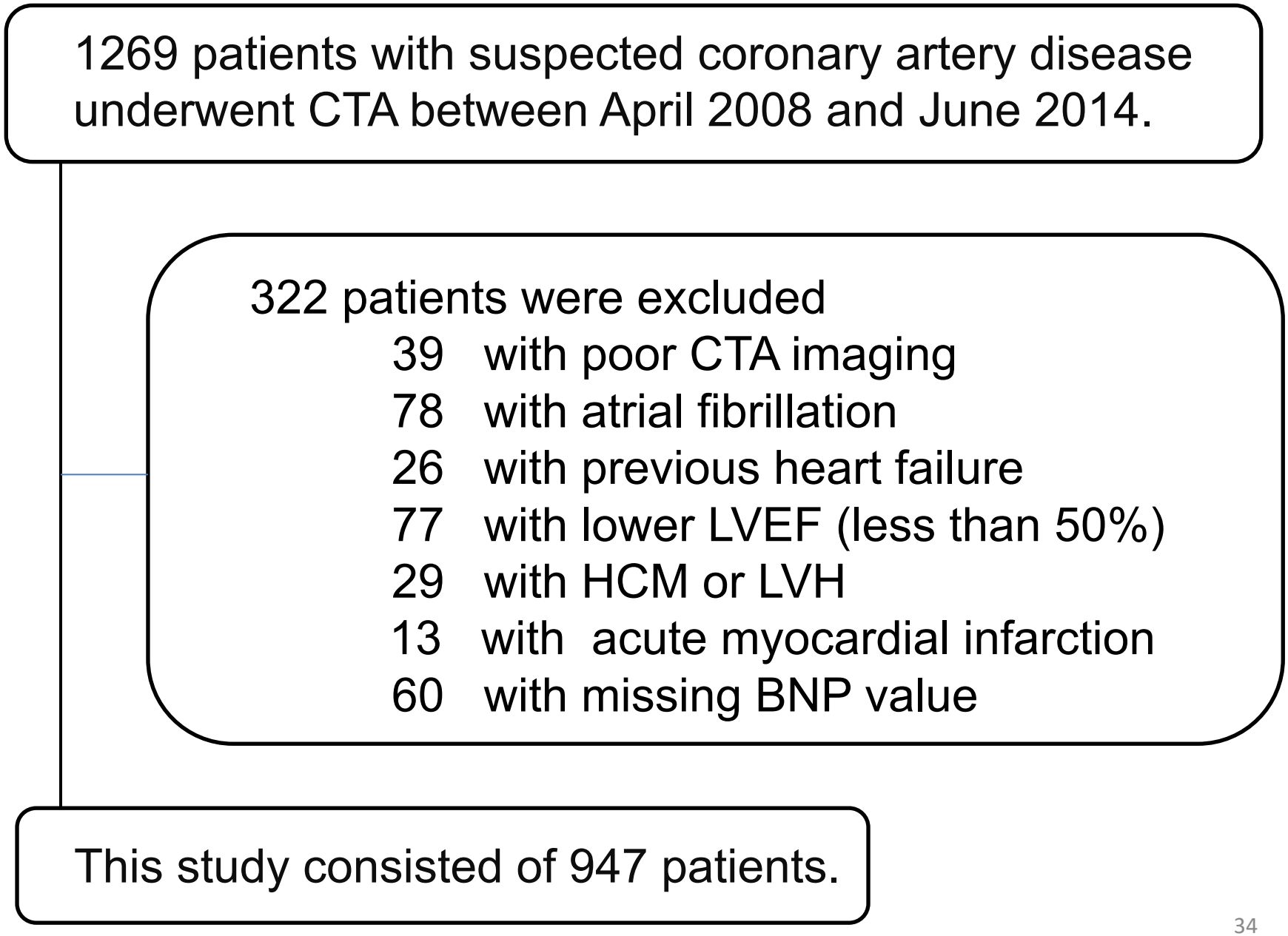

1269 patients with suspected coronary artery disease underwent CTA between April 2008 and June 2014.
322 patients were excluded
39 with poor CTA imaging
78 with atrial fibrillation
26 with previous heart failure
77 with lower LVEF (less than 50%)
29 with HCM or LVH
13 with acute myocardial infarction
60 with missing BNP value
This study consisted of 947 patients.

Figure 2.

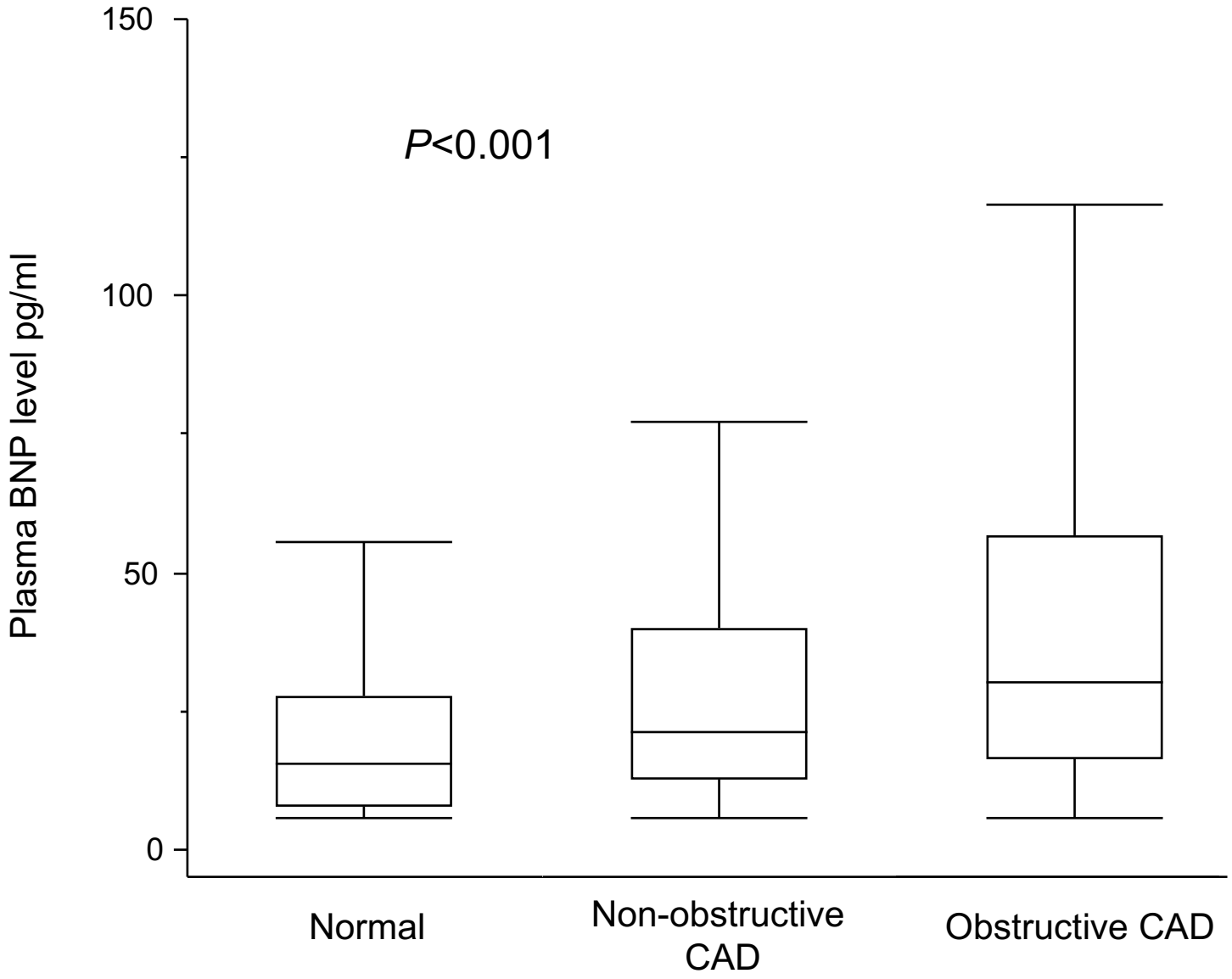

150
100
50
0
Plasma BNP level pg/ml
P<0.001
Normal
Non-obstructive CAD
Obstructive CAD

Figure 3.

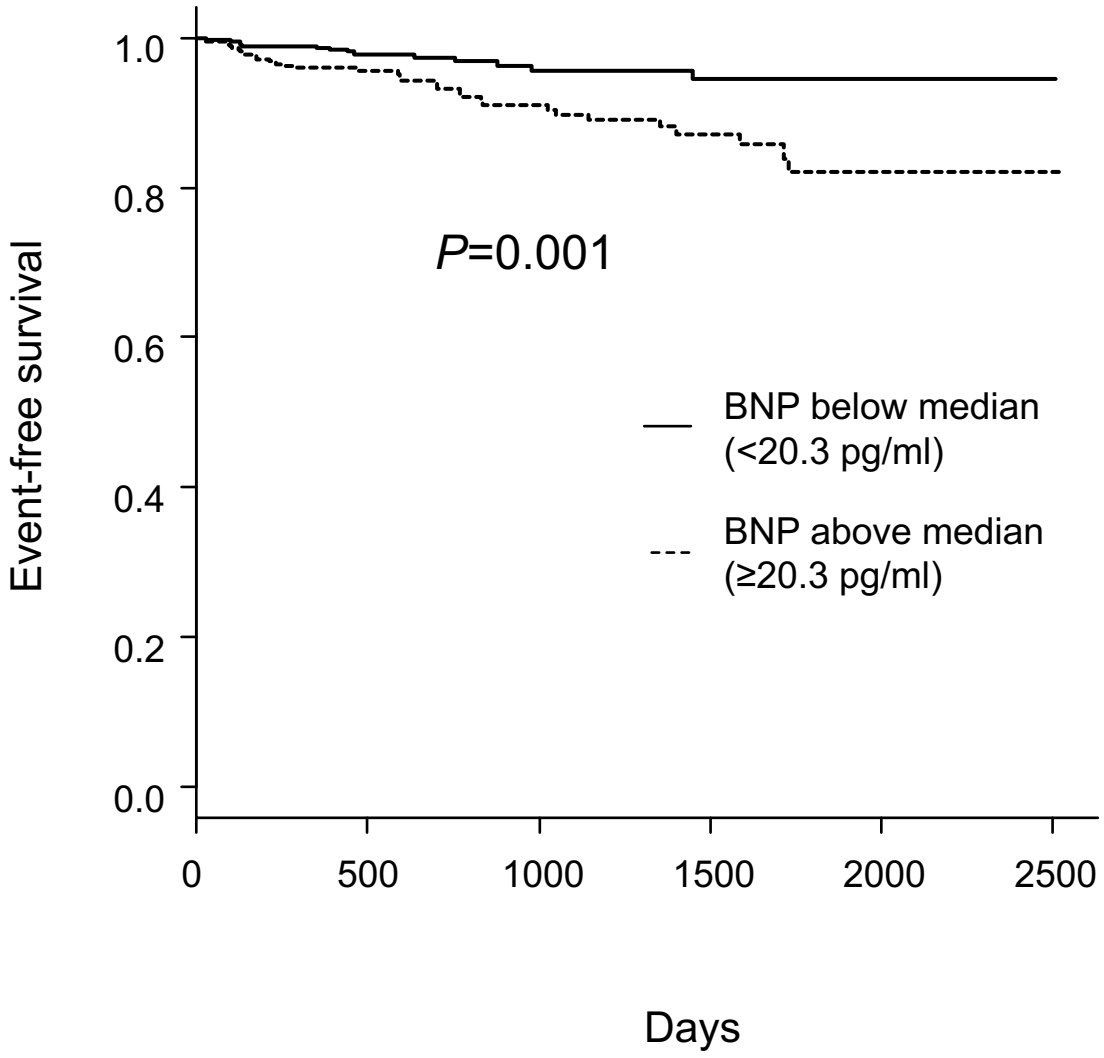
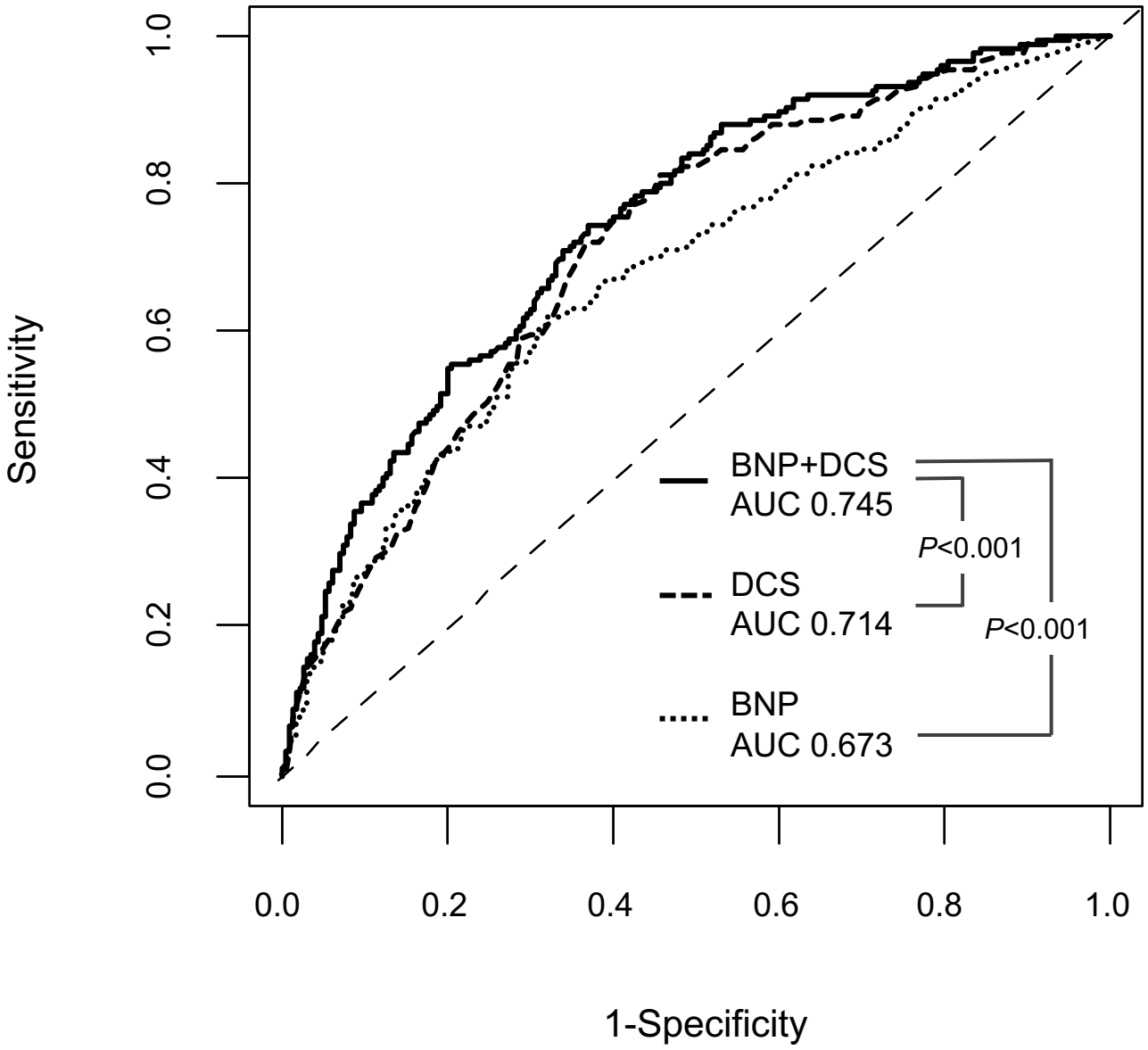

1.0
0.8
0.6
0.4
0.2
0.0
Event-free survival
P=0.001
BNP below median
(<20.3 pg/ml)
BNP above median
(≥20.3 pg/ml)
0
500
1000
1500
2000
2500
Days

Figure 4.


Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
BNP+DCS
AUC 0.745
DCS
AUC 0.714
BNP
AUC 0.673
P<0.001
P<0.001