Original Paper

Correlation between B-Type Natriuretic Peptide and N-Terminal pro-B-Type Natriuretic Peptide in a Large Japanese Population at Risk of Stage A Heart Failure

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Keywords

B-type natriuretic peptide · N-terminal pro-B-type natriuretic peptide · Stage A heart failure · High-risk population · Japanese population

Abstract

Background: The measurements of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are useful for ruling out heart failure and as prognostic markers in not only heart failure populations but also general populations. It is not clear whether these two biomarkers are elevated in parallel or associated with demographic characteristics in large populations at risk of stage A heart failure. Here we investigated the relationship between BNP and NT-proBNP and extended the evaluation of this association to known demographic disparities in stage A heart failure. **Methods:** Of 4,310 ambulatory patients, we analyzed the cases of the 3,643 (mean age 65 ± 11 years, 46% male, and 79% on antihypertensive medication) patients whose serum BNP and NT-proBNP levels were both measured and who had a history of and/or risk factors for cardiovascular disease from the Japan Morning Surge-Home Blood Pressure (J-HOP) Study dataset. **Results:** The median (25th–75th percentiles) BNP and NT-proBNP values were 18.7 (9.3–38.5) pg/mL and 50.3 (25.5–97.4) pg/mL. There was a significant association between log-transformed BNP and log-transformed NT-proBNP ($r = 0.818$, $p < 0.001$). A multiple linear regression analysis showed that log-transformed NT-proBNP was significantly associated with log-transformed BNP (beta coefficient = 0.774, $p < 0.001$). When stratified by demographic characteristics, these associations remained (all $p < 0.001$). **Conclusion:** In a large Japanese population at risk of stage A heart failure, there was a significant association between BNP and NT-proBNP after adjustment and stratification by demographics.

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Introduction

The measurements of the serum levels of an individual's natriuretic peptide hormones, in particular B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are established as useful biomarkers for ruling out heart failure [1, 2]. Both BNP and NT-proBNP have also been reported to be prognostic markers in not only heart failure populations but also general or hypertensive populations [3–5]. In some studies performing a head-to-head comparison of the diagnostic utility of BNP and NT-proBNP for the screening of left ventricular function and the prognostic power of cardiovascular prognosis, the utility of the two biomarkers was largely similar [6, 7]. However, BNP and NT-proBNP are released into the circulation with different biological activations, in which BNP has biological activity and NT-proBNP does not [8, 9]. Both BNP and NT-proBNP are influenced by demographic characteristics such as age, gender, obesity, and renal function [10–13]. Few studies have been performed to determine whether BNP is elevated in parallel or associated with NT-proBNP in accord with demographic characteristics.

The management of stage A heart failure patients – who, with their cardiovascular risk factors, are at high risk of developing advanced heart failure – is one of the challenging issues in the field of cardiovascular disease (CVD) [14]. Although the use of BNP and NT-proBNP as biomarkers may be useful for risk stratification in this population, there have been no data explaining whether the correlation between BNP and NT-proBNP would differ according to the presence or absence of demographic risk factors for stage A heart failure.

In the present study, using the data of a large clinical population of patients who had more than one cardiovascular risk factor, we investigated the relationship between BNP and NT-proBNP levels and extended the examination of this association to known demographic disparities in stage A heart failure.

Methods

Study Population

We used the baseline data of the Japan Morning Surge-Home Blood Pressure (J-HOP) Study. The protocol of the J-HOP study has been published [15]. Briefly, the J-HOP study is a prospective observational study (University Hospital Medical Information Network Clinical Trials Registry, UMIN000000894) evaluating the use of home blood pressure (BP) measurements to predict cardiovascular events between January 2005 and May 2012 in 4,310 Japanese ambulatory patients who had a history of and/or risk factors for CVD as follows: hypertension, hyperlipidemia, diabetes, glucose intolerance, metabolic syndrome, chronic kidney disease (CKD), history of CVD, atrial fibrillation, current smoking, chronic obstructive pulmonary disease, or sleep apnea syndrome. All participants provided written informed consent for their data to be used, and the Institutional Review Board of Jichi Medical School approved the study.

Of the 4,310 patients enrolled in the J-HOP study, we excluded 667 patients for whom there was no data of either BNP or NT-proBNP. A final total of 3,643 patients was thus included in the present analysis. The diagnostic criteria of diabetes were defined as a fasting glucose level of ≥ 126 mg/dL and/or a casual glucose level of ≥ 200 mg/dL or treated diabetes. Hyperlipidemia was defined as a total cholesterol level of ≥ 240 mg/dL or treated hyperlipidemia. CKD was defined as the presence of proteinuria or a value of < 60 mL/min/ 1.73 m² for the estimated glomerular filtration rate (eGFR).

A past history of CVD included diagnosed angina pectoris, myocardial infarction, and stroke. Three office BP values measured in a sitting position at two clinic visits were taken by a physician or nurse using an upper arm cuff oscillometric BP device (HEM-5001; Omron Healthcare, Kyoto, Japan), and these values were averaged in the present study.

Table 1. Patients' characteristics
(*n* = 3,643)

Age, years	65.0±10.6
Male, %	46.2
Body mass index	24.2±3.5
Smoking, %	12.1
Alcohol, %	27.8
Diabetes, %	24.6
Dyslipidemia, %	42.1
Antihypertensive treatment, %	79.1
Past history of CVD, %	12.9
Estimated GFR, mL/min/1.73 m ²	73.1±17.3
Clinic SBP, mmHg	141.4±16.4
Clinic DBP, mmHg	81.4±10.4
BNP, pg/mL	18.7 (9.3–38.5)
NT-proBNP, pg/mL	50.3 (25.5–97.4)

Data are mean ± SD or median (25–75% percentile). CVD, cardiovascular disease; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Natriuretic Peptides

Blood and spot urine samples were collected in the morning in a fasting state at study enrollment. The plasma level of BNP (MI02 Shionogi BNP; Shionogi, Osaka, Japan) was measured by using a chemiluminescent enzyme. NT-proBNP was measured by an automated Cobas analyzer using an electrochemiluminescent immunoassay (Roche Diagnostics, Japan).

Statistical Analysis

Data are expressed as the mean ± SD, median (25th–75th percentile), or percentage. Because the distribution of BNP and NT-proBNP values was highly skewed, it was log-transformed before the statistical analysis. The χ^2 test was used to compare proportions, and the unpaired *t* test was used to compare the means for the two groups. The univariate associations were assessed using the Pearson correlation. To develop a model that is useful for predicting the value of the BNP level for a given value of the NT-proBNP level, we applied a formula using a simple linear regression between the log BNP and log NT-proBNP values. We assessed the association between log NT-proBNP and log BNP by using a multiple linear regression analysis that included age, sex, body mass index (BMI), smoking status, alcohol, diabetes, dyslipidemia, history of CVD, antihypertensive therapy and CKD. To identify multicollinearity, we assessed the variance inflation factor. Using the thresholds of BNP and NT-proBNP for individuals suspected of having heart failure as provided by the Japanese guidelines [16], we also calculated Cohen kappa coefficients to investigate the concordance of those values of BNP and NT-proBNP [17]. All statistical analyses were performed with the SPSS program, ver. 19.0 (Chicago, IL, USA).

Results

Among the 3,643 patients, 1,683 (46.2%) were men and 1,960 (53.8%) were women. The mean ± SD values were as follows: age, 65.0 ± 10.6 years; BMI, 24.2 ± 3.5; clinic SBP/DBP 141.4 ± 16.4/81.4 ± 10.4 mm Hg; eGFR 73.1 ± 17.3 mL/min/1.73 m². The median (25th–75th percentiles) BNP and NT-proBNP values were 18.7 (9.3–38.5) and 50.3 (25.5–97.4) pg/mL (Table 1). As shown in Supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000485660), the included participants (*n* = 3,643) compared to the excluded subjects without BNP and NT-proBNP data (*n* = 667) had a significantly lower percentage of men (46.2 vs. 51.6%, *p* = 0.01), significantly higher dyslipidemia (42.1 vs. 32.8%, *p* < 0.001), and significantly lower eGFR values (73.1 vs. 75.4 mL/min/1.73 m²).

Fig. 1. Scatterplot of log-transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) and log-transformed B-type natriuretic peptide (BNP) values in 3,643 Japanese patients (65 ± 11 years old) from the J-HOP Study.

Figure 1 is the scatter plot illustrating the association between log-transformed values of BNP and NT-proBNP. There was a significant association between log-transformed BNP and log-transformed NT-proBNP ($r = 0.818$, $p < 0.001$). The regression formula was $y = -0.127 + 0.815x$, where -0.127 was the y-intercept and 0.815 was the slope. As an example, the predicted values of BNP (y) calculated using this formula and NT-proBNP (x) are shown in Table 2.

A multiple linear regression analysis showed that log-transformed NT-proBNP was significantly associated with log-transformed BNP (beta coefficient = 0.774 , $p < 0.001$). When we also stratified the patients according to demographics (<65 vs. ≥ 65 years, women or men, <25 vs. ≥ 25 in BMI, and absence vs. presence of smoking, alcohol, diabetes, dyslipidemia, and antihypertensive medication, past history of CVD, and CKD), the significant associations between log-transformed NT-proBNP and BNP remained (all $p < 0.001$) (Table 3).

The prevalence of the subjects with a BNP level >200 pg/mL and that of subjects with an NT-pro BNP level >900 pg/mL and thus suspected of having heart failure according to the 2010 Japanese Circulation Society (JCS) guidelines for the treatment of chronic heart failure were 1.8% ($n = 64$) and 1.6% ($n = 59$), respectively. The Cohen kappa coefficient calculated to investigate the concordance of these values was revealed to be 0.68 .

Discussion

Our findings showed that there was a significant correlation between BNP and NT-proBNP in a large Japanese population of individuals who had a history of and/or risk factors for CVD, which is a potential contributor to stage A heart failure. When the study population was stratified by individual risk factors, this association between BNP and NT-proBNP remained.

Several studies have indicated that BNP and NT-proBNP are both very useful markers for the diagnosis and prognosis of heart failure [1, 2]. In some guidelines, these two biomarkers

Table 2. Predicted value of BNP for a given value of NT-proBNP using the regression formula

NT-proBNP, pg/mL	BNP, pg/mL	NT-proBNP, pg/mL	BNP, pg/mL
10	5	190	54
20	9	200	56
30	12	300	78
40	15	400	99
50	18	500	118
55	20	600	137
60	21	700	156
70	24	800	173
80	27	900	191
90	29	1,000	208
100	32	1,500	289
110	34	2,000	366
120	37	2,500	439
125	38	3,000	509
130	39	3,500	577
140	42	4,000	644
150	44	4,500	709
160	47	5,000	772
170	49	5,500	834
180	51	6,000	896

NT-proBNP, N-terminal pro B-type natriuretic peptide; BNP, brain natriuretic peptide.

have an equal role in the diagnostic evaluation of heart failure, based on the results of several comparisons of the two biomarkers' utility for the diagnosis or exclusion of acute heart failure [14, 16, 18]. Both the BNP and NT-proBNP levels at less than a cutoff point for the diagnosis of heart failure have also provided prognostic power for cardiovascular outcomes in general and hypertensive populations [3–5].

These previous studies may indicate that stage A heart failure patients, who are at high risk of experiencing advanced heart failure and have cardiovascular risk factors but are without symptoms, would have poor cardiovascular prognoses. However, there have been few studies about the correlation between BNP and NT-proBNP levels in large populations of individuals with the risk factor of stage A heart failure. In the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure, the upper limits of normal in the nonacute setting of heart failure for the BNP and NT-proBNP levels are 35 and 125 pg/mL, respectively [18]. In the present study, the BNP and NT-proBNP values calculated from a simple regression formula were 38 and 125 pg/mL, respectively. Although there is a lack of evidence regarding the limits of the BNP and NT-proBNP levels for the diagnosis of heart failure in the Japanese population, the 2010 JCS guidelines for the treatment of chronic heart failure demonstrated that the thresholds of BNP and NT-proBNP values for patients suspected of having heart failure were 200 and 900 pg/mL, respectively [16]. In the present study, the BNP and NT-proBNP levels were 191 and 900 pg/mL, respectively. In addition, the Cohen kappa coefficient was 0.68, indicating substantial agreement [17]. Thus, our findings support the concordance of values between BNP and NT-proBNP for the threshold of heart failure status in both the ESC and JSC guidelines.

After the adjustment for demographic factors, our multiple linear regression analysis showed a significant association between BNP and NT-proBNP levels. When we stratified the population by demographic characteristics, these significant associations remained. Both

Table 3. Association of log-transformed NT-proBNP with log-transformed BNP

	<i>n</i>	Beta coefficient (95% CI)	<i>p</i>
All participants	3,643	0.774 (0.753–0.794)	<0.001
Age			
<65 years	1,695	0.796 (0.766–0.826)	<0.001
≥65 years	1,948	0.754 (0.726–0.782)	<0.001
Sex			
Women	1,960	0.759 (0.729–0.789)	<0.001
Men	1,683	0.783 (0.755–0.811)	<0.001
BMI			
<25	2,312	0.781 (0.756–0.806)	<0.001
≥25	1,331	0.761 (0.727–0.796)	<0.001
Smoking			
Absent	3,201	0.768 (0.746–0.790)	<0.001
Present	4,42	0.811 (0.755–0.868)	<0.001
Alcohol			
Absent	2,631	0.762 (0.738–0.786)	<0.001
Present	1,012	0.799 (0.761–0.837)	<0.001
Diabetes			
Absent	2,631	0.762 (0.738–0.786)	<0.001
Present	1,012	0.799 (0.761–0.837)	<0.001
Dyslipidemia			
Absent	2,109	0.774 (0.748–0.801)	<0.001
Present	1,534	0.772 (0.740–0.804)	<0.001
Antihypertensive medication			
Absent	781	0.713 (0.663–0.764)	<0.001
Present	2,882	0.786 (0.764–0.808)	<0.001
Past history of CVD			
Absent	3174	0.773 (0.750–0.795)	<0.001
Present	469	0.781 (0.733–0.829)	<0.001
Chronic kidney disease ^a			
Absent	761	0.797 (0.757–0.837)	<0.001
Present	2,882	0.766 (0.742–0.789)	<0.001

NT-proBNP, N-terminal pro B-type natriuretic peptide; BNP, brain natriuretic peptide; BMI, body mass index; CVD, cardiovascular disease. ^aChronic kidney disease was defined as <60 mL/min/1.73m² in estimated glomerular filtration rate. Beta coefficient was adjusted for age, sex, BMI, smoking, alcohol, diabetes, dyslipidemia, antihypertensive medication, past history of CVD and chronic kidney disease.

BNP and NT-proBNP have been reported to be influenced by age, gender, obesity, and renal dysfunction [10–13]. Renal dysfunction in particular has shown a significant effect on the BNP/NT-proBNP ratio because of the difference in clearance between two markers [19]. Our present findings suggest that the elevations of both BNP and NT-proBNP occur in parallel regardless of demographic characteristics.

The measurement of plasma levels of BNP is more complicated compared to that of NT-proBNP. When whole blood is used for assays, NT-proBNP is stable under a variety of storage conditions (including room temperature) for a prolonged period [20]. In the future, NT-proBNP rather than BNP might be more useful in clinical and research fields.

Our study population was predominantly men, with higher dyslipidemia and lower eGFR values compared to the excluded participants. These imbalances, or selection biases, might limit the external validity of the present findings to some extent.

In conclusion, in the dataset of a large Japanese population at risk of stage A heart failure, there was a significant association between BNP and NT-proBNP levels after adjustment and

stratification by demographics. NT-proBNP values were elevated in parallel with BNP values in this population. Both BNP and NT-proBNP may provide equal information for ruling out heart failure and may be used as prognostic markers regardless of demographic factors.

Disclosure Statement

K. Kario has received research funding from Teijin Pharma Limited, Omron Healthcare Co., Ltd., Fukuda Denshi, Bayer Yakuhin Ltd., A&D Co., Ltd., Daiichi Sankyo Company Limited, Mochida Pharmaceutical Co., Ltd., EA Pharma, Boehringer Ingelheim Japan Inc., Tanabe Mitsubishi Pharma Corporation, Shionogi & Co., Ltd., MSD K.K., Sanwa Kagaku Kenkyusho Co., Ltd., Bristol-Myers Squibb K.K., and honoraria from Takeda Pharmaceutical Company Limited and Omron Healthcare Co., Ltd.

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