Original Article

Does B-Type Natriuretic Peptide Predict the New Onset of Hypertension?

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Increased B-type natriuretic peptide (BNP) expression precedes the development of hypertension in spontaneously hypertensive rats. We therefore tested the hypothesis that elevated plasma BNP levels predict the onset of hypertension in normotensive subjects. Japanese normotensive participants who were at our hospital for a yearly physical check-up (mean age 52.7 years, 35.9% women, *n*=5,026) were enrolled in the study. Blood pressure and BNP were measured at baseline and subjects were followed up for 5 years (median 1,114 d), with the endpoint being the development of hypertension. We evaluated the relationship between plasma BNP levels at baseline and the incidence of hypertension during the follow-up period. Hypertension was defined as systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, or the use of antihypertensive medications. During the follow-up period, hypertension developed in 23.4% (77.0 per 1,000 person-years) and 14.9% (51.0 per 1,000 person-years) of male and female subjects, respectively. Cox proportional hazard regression analysis demonstrated that after adjustment for known risk factors, the risk of hypertension was increased from the first to fourth quartiles of baseline BNP levels. However, after additional adjustment for baseline blood pressure, BNP did not predict the new onset of hypertension. Baseline BNP levels are closely associated with the risk of hypertension in individuals with normal blood pressure, but the prediction of hypertension with BNP is largely dependent on baseline blood pressure. Measurements of BNP may serve as a complementary method for the prediction or confirmation of hypertension. (*Hypertens Res* 2008; 31: 1737–1744)

***Key Words*: blood pressure, B-type natriuretic peptide, hypertension, prediction**

Introduction

B-type natriuretic peptide (BNP) is secreted from ventricular myocytes in response to increased ventricular filling pressure or volume, and is hence a sensitive and significant marker of cardiac dysfunction (*1–4*). Indeed, circulating levels of the peptide are elevated in various cardiac disorders such as cardiomyopathy (*5*), previous myocardial infarction (*6*), and valvular diseases (*7*). BNP is also elevated in subjects with hypertension (*8–11*). Since BNP levels were independently associated with blood pressure after adjustment for left ventricular mass index in patients with hypertension (*11*), an increase in blood pressure *per se* may stimulate the secretion of BNP through an increase in left ventricular wall stress. On the other hand, secreted BNP counteracts increased blood pressure through its vasodilatory properties. This implies that BNP elevation may predate the overt onset of hypertension. Although this hypothesis has been proved in an animal model of hypertension (*12*), it remains unproved in human hypertension. In the Framingham Heart Study, which followed 1,801 subjects without hypertension for 4 years, an elevated BNP

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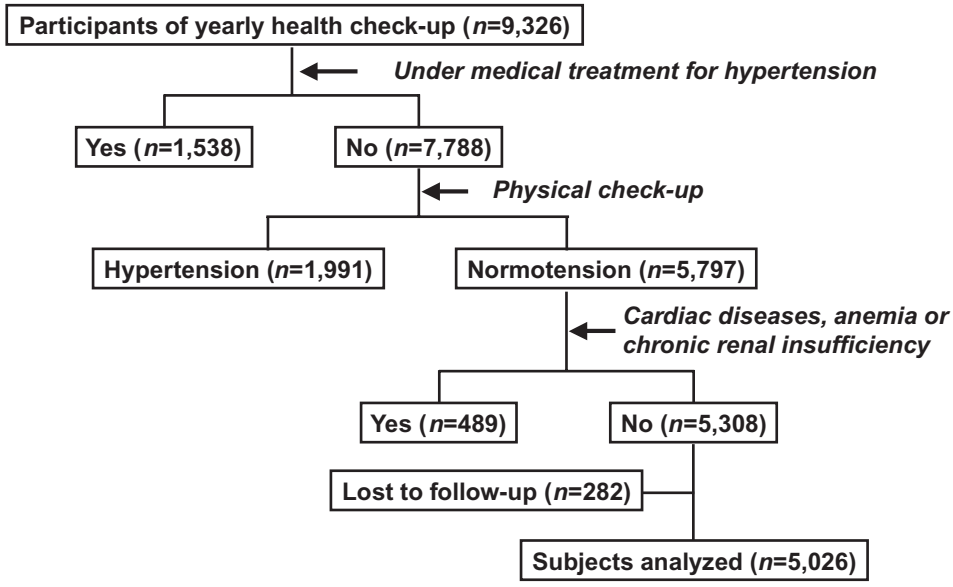

Fig. 1. *Flow diagram of the participants.*

level at baseline was associated with an increased risk of blood pressure progression in men, but not women, after adjustment for known risk factors (*13*). However, this study failed to prove a relationship between elevated baseline BNP levels and the risk of developing hypertension, indicating that additional investigation is necessary to confirm the association.

Hypertension is a major risk factor for the development of cardiovascular disease (*14–17*) and the ability to predict the onset of new hypertension is an attractive proposition (*18*). We hypothesized that normotensive individuals with higher plasma BNP levels have a higher probability of developing hypertension in the future. Thus, in the present observational study, we investigated the impact of baseline plasma BNP levels on the incidence of hypertension in normotensive subjects.

Methods

Study Design

This study was a prospective endpoint trial to assess the relation of BNP levels to the future development of hypertension in subjects with normal blood pressure. We undertook the study in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Enshu Hospital. All patients gave written informed consent to participate prior to the start of the study. Subjects were followed-up by investigators at Enshu Hospital, Hamamatsu, Japan.

Study Subjects and Procedures

Japanese participants who visited our hospital for a yearly physical check-up from January 2001 to June 2002 ($n=9,326$, 33.9% women, mean age 55.8±11.6 years, ranging from 20–94 years old) were screened for their eligibility for inclusion in the present study (Fig. 1). Participants under medical treatment for hypertension were excluded first. Among the remaining subjects, the check-up program (including a routine physical examination, chest X-ray, electrocardiography, and laboratory assessment of cardiovascular risk factors) revealed that 5,797 subjects were not hypertensive. Participants under medication and/or with a known history of cardiac diseases, such as coronary artery disease, arrhythmia and congestive heart failure, chronic renal insufficiency (creatinine levels in women ≥0.9 mg/dL, men ≥1.2 mg/dL) or anemia (hemoglobin levels in women <12.0 g/dL, men <13.0 g/dL) were also excluded from the study because cardiac disease (*3–7*), renal insufficiency (*19*, *20*), and anemia (*21*) affect BNP concentrations. Finally, 5,308 participants were enrolled in the present study. Blood was sampled for BNP measurement and the follow-up period was decided to be up to 5 years, with the endpoint being the development of hypertension. During the follow-up period, subjects' blood pressure was measured every year. Since data on blood pressure beyond the baseline measurements were not available for 282 subjects, data from the remaining 5,026 subjects (35.9% women, mean age of 52.7±11.6 years, ranging from 20 to 84 years) were analyzed.

Blood pressure was measured after subjects were seated in a chair for 5 min with their backs supported and their arms supported at heart level. The proper cuff size was determined

Table 1. Baseline Characteristics of Subjects

	Male (n=3,224)	Female (n=1,802)
Age (years old)	53.3±11.4	51.8±12.1*
Body height (cm)	166.2±6.5	154.1±5.8*
Body weight (kg)	62.7±9.2	52.1±7.5*
Body mass index (kg/m^2)	22.7±2.7	21.9±2.9*
Systolic blood pressure (mmHg)	119.8±11.9	118.0±12.8*
Diastolic blood pressure (mmHg)	74.1±8.3	71.5±8.6*
Heart rate (bpm)	61.4±9.3	66.3±9.5*
Serum creatinine (mg/dL)	0.79±0.11	0.60±0.09*
Estimated GFR (mL/min/1.73 m^2)	78.2±13.1	80.6±14.1*
Uric acid (mg/dL)	5.8±1.2	4.2±0.9*
Fasting plasma glucose (mg/dL)	101.8±20.5	94.3±14.5*
LDL-cholesterol (mg/dL)	122.8±30.0	124.8±32.6†
HDL-cholesterol (mg/dL)	58.9±15.0	67.6±15.2*
Triglyceride (mg/dL)	120.4±74.3	89.6±49.6*
Hemoglobin (g/dL)	15.3±1.0	13.5±0.8*
Current smoking status (n (%))	1,499 (46.5)	103 (5.7)*
Follow-up period (d)	1,118 [730–1,473]	1,112 [728–1,466]
BNP (ng/L)	7.5 [3.3–15.1]	13.0 [6.8–22.3]*
BNP Quartile 1	2.0 [2.0–2.4]	4.2 [2.5–5.5]
BNP Quartile 2	5.3 [4.2–6.3]	9.8 [8.3–11.2]
BNP Quartile 3	10.7 [9.0–12.6]	17.0 [14.9–19.1]
BNP Quartile 4	23.1 [18.5–32.0]	32.5 [26.7–42.6]

Data are expressed as the mean±SD, except for BNP and the follow-up period (median [interquartile range]). GFR, glomerular filtration rate (estimated using the MDRD formula); LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide. *$p<0.0001$, $^\dagger p<0.05$ *vs*. men by unpaired Student's *t*-test (except for BNP, follow-up period, and current smoking status), Mann-Whitney *U*-test (BNP and follow-up period), or Yates' corrected χ^2 test (current smoking status).

based on arm circumference. Systolic and diastolic blood pressure levels were recorded as the first and fifth Korotkoff phases, respectively, using a mercury sphygmomanometer. Three consecutive blood pressure measurements with 2 min between measurements were taken, and the mean of the second and third measurements was recorded as the blood pressure. Hypertension was defined as ≥140 mmHg systolic blood pressure, ≥90 mmHg diastolic blood pressure (*22*), or the use of antihypertensive medications. Pre-hypertension was defined as systolic blood pressure between 130 and 140 mmHg or diastolic blood pressure between 85 and 90 mmHg (*18*).

Measurement of Plasma BNP Concentration

For the measurement of BNP, a 3 mL sample of blood was transferred to plastic tubes containing 4.5 mg 2Na-ethylenediamine-tetraacetic acid. Plasma samples were prepared within 30 min by pre-cooled centrifuge, immediately frozen and stored at −70°C until analysis. The BNP level was measured by radioimmunoassay (Shionoria BNP kit, Shionogi, Osaka, Japan) (*4*). The intra- and inter-assay coefficients of variation of the BNP assay were 5.7%, and 8.2%, respectively. The minimal detectable quantity of BNP was 2.0 ng/L.

Statistical Analysis

All analyses were performed using StatView 5.0 (SAS Institute, Inc., Cary, USA). Data in the text and tables are expressed as the mean±SD except for BNP and the follow-up period, which are expressed as the median±median absolute deviation because they did not have normal distributions. Differences between the two means with normal distribution were compared by unpaired Student's *t*-test. The significance of any difference in medians was assessed by the Mann-Whitney *U*-test. The Yates' corrected χ^2 test was used for comparisons between categorical data.

Gender-specific quartiles of baseline BNP were used as predictor variables and Cox proportional hazard regression analysis was applied to calculate hazard ratios and their 95% confidence intervals (CIs) of hypertension for elevated BNP. Regression analysis was performed before (model A) and after adjustment for known risk factors (age, gender, smoking, impaired glucose tolerance [IGT], dyslipidemia, and body mass index [model B]; age, gender, smoking, IGT, dyslipidemia, body mass index, systolic blood pressure, and diastolic blood pressure at baseline [model C]). Impaired glucose tolerance was defined as fasting glucose ≥110 mg/dL or the use of anti-diabetic medications, and dyspilidemia was

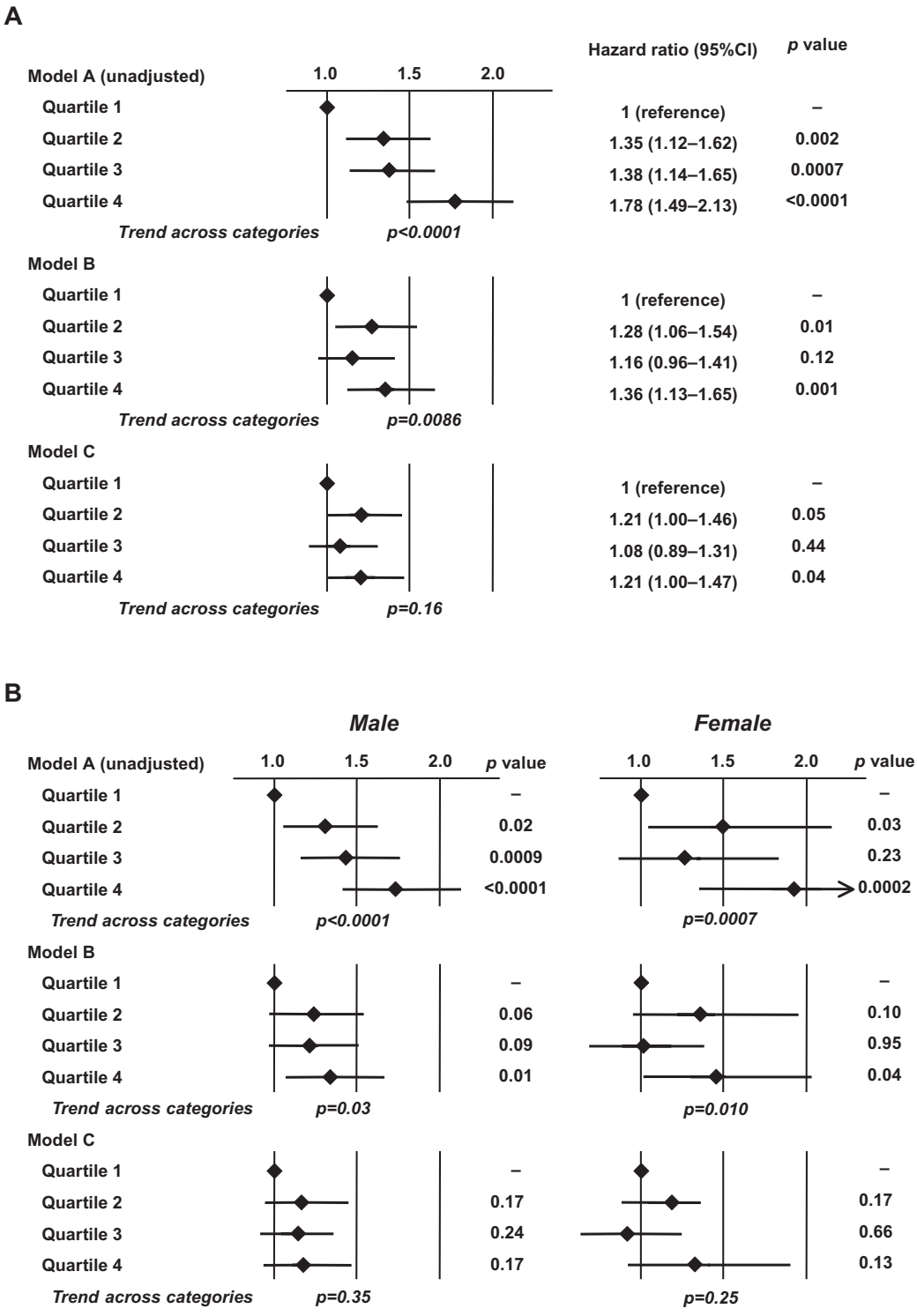

Fig. 2. *A: Hazard ratio and 95% confidence intervals (CI) for the development of hypertension in the quartiles of B-type natriuretic peptide. Model A: unadjusted model. Model B: adjusted for age, gender, smoking, impaired glucose tolerance, dyslipidemia, and body mass index. Model C: adjusted for age, gender, smoking, impaired glucose tolerance, dyslipidemia, body mass index, and systolic blood pressure. B: Hazard ratio and 95% CI for the development of hypertension in the quartiles of B-type natriuretic peptide: subanalysis in male and female subjects. Model A: unadjusted model. Model B: adjusted for age, gender, smoking, impaired glucose tolerance, dyslipidemia, and body mass index. Model C: adjusted for age, gender, smoking, impaired glucose tolerance, dyslipidemia, body mass index, and systolic blood pressure.*

Table 2. Multivariable Cox Proportional Hazard Regression Analysis

	Model I		Model II	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
BNP	1.26 (1.07–1.48)	0.006	1.11 (0.94–1.31)	0.21
Age	1.05 (1.04–1.06)	<0.0001	1.04 (1.03–1.05)	<0.0001
Gender; male	1.36 (1.16–1.59)	0.0002	1.29 (1.10–1.52)	0.0017
Smoking	0.98 (0.90–1.06)	0.58	1.07 (0.98–1.15)	0.12
IGT	1.48 (1.27–1.71)	<0.0001	1.26 (1.09–1.46)	0.002
Dyslipidemia	0.90 (0.79–1.02)	0.11	1.02 (0.89–1.15)	0.82
BMI	1.11 (1.09–1.14)	<0.0001	1.06 (1.04–1.09)	<0.0001
SBP			1.07 (1.07–1.08)	<0.0001

Cox proportional hazard regression analysis was performed using baseline BNP levels as continuous variables (Model I: adjusted for age, gender, smoking, IGT, dyslipidemia, and BMI; Model II: adjusted for age, gender, smoking, IGT, dyslipidemia, BMI, and SBP). Analyses were performed after logarithm conversion of BNP concentrations. CI, confidence interval; BNP, B-type natriuretic peptide; IGT, impaired glucose tolerance; BMI, body mass index; SBP, systolic blood pressure.

defined as low-density lipoprotein-cholesterol ≥140 mg/dL, high-density lipoprotein-cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or the use of anti-dyslipidemic medications. Probability values for trends were calculated by entering the median value of BNP into each quartile. Separate Cox proportional hazard regression analysis was performed using baseline BNP levels as continuous variables. A *p* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of normotensive subjects are shown in Table 1. In cross-sectional analysis at baseline, BNP levels were higher in subjects with pre-hypertension (10.5±6.7 ng/L) than in those with lower blood pressure (9.0±5.8 ng/L, $p<0.001$). The actual follow-up time was 15,055 person-years and the median follow-up period was 1,114 d. During the follow-up period, 1,022 subjects developed hypertension (20.3%, or 67.9 per 1,000 person-years), with the incidence being more frequent in male ($n=753$, 23.4%, or 77.0 per 1,000 person-years) than in female subjects ($n=269$, 14.9%, or 51.0 per 1,000 person-years, $p<0.0001$).

In the first to fourth quartiles of baseline BNP, the hypertension incidence rates were 50.3, 66.9, 68.1, and 88.2 hypertensions per 1,000 person-years, respectively. Cox proportional hazard regression analysis demonstrated that the unadjusted risk for hypertension was increased across the quartiles of baseline BNP levels (Fig. 2A, model A). This trend remained statistically significant after adjustment for known risk factors, including age, gender, smoking, IGT, dyslipidemia, and body mass index (Fig. 2A, model B). After additional adjustment for baseline systolic blood pressure, the hazard ratio of hypertension tended to increase across the quartiles, but this did not reach statistical significance ($p=0.16$, Fig. 2A, model C). Although similar results were obtained in the subanalysis, in which subjects were divided into male and female groups, the impact of BNP on the incidence of hypertension was somewhat smaller in female than in male subjects (Fig. 2B). We performed a separate analysis in which BNP was treated as a continuous variable in Cox proportional hazard regression models (Table 2). In this analysis, BNP was also a significant predictor for hypertension after adjustment for age, gender, smoking, IGT, dyslipidemia, and body mass index (model I), while BNP did not predict the incidence of hypertension independently of baseline systolic blood pressure (model II). Similar results were obtained in the male sub-group, but BNP was not closely related to the onset of hypertension in the female sub-group (Table 3).

Discussion

In a previous study that followed 1,801 subjects, an elevated BNP level at baseline was associated with an increased risk of blood pressure progression, but not of developing hypertension (*13*). These apparently obscure findings needed further investigation regarding a possible relationship between baseline BNP and the incidence of hypertension. Although the race studied was different between the previous and our present study, we may conclude that baseline BNP is not an independent predictor for new onset of hypertension. The prediction of hypertension by baseline BNP is largely dependent on baseline blood pressure.

In the present study, the incidence of new hypertension during follow-up increased across the quartiles of baseline BNP in normotensive subjects without cardiovascular disease, anemia, or renal insufficiency. BNP plays a significant role in regulation of the circulation through vasodilation and natriuresis (*1*, *8*). Taking into consideration the pharmacological property of the peptide, an increase in BNP does not promote an elevation of blood pressure. Thus, the increase in baseline BNP may have simply resulted from an increase in left ventricular wall stress in individuals who are in the process of developing hypertension. In such individuals, a mild increase in blood pressure (even within normal levels) may have stim-

Table 3. Multivariable Cox Proportional Hazard Regression Analysis: Subanalysis in Male and Female Subjects

	Model I		Model II	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Male subjects				
BNP	1.28 (1.07–1.54)	0.008	1.13 (0.93–1.36)	0.22
Age	1.04 (1.04–1.05)	<0.0001	1.03 (1.02–1.04)	<0.0001
Smoking	0.96 (0.88–1.04)	0.29	1.05 (0.96–1.14)	0.29
IGT	1.41 (1.20–1.67)	<0.0001	1.20 (1.02–1.42)	0.028
Dyslipidemia	0.97 (0.83–1.12)	0.64	1.07 (0.92–1.24)	0.39
BMI	1.12 (1.09–1.15)	<0.0001	1.07 (1.04–1.10)	<0.0001
SBP			1.08 (1.07–1.09)	<0.0001
Female subjects				
BNP	1.21 (0.86–1.70)	0.29	1.09 (0.77–1.54)	0.63
Age	1.07 (1.06–1.09)	<0.0001	1.06 (1.04–1.08)	<0.0001
Smoking	1.14 (0.87–1.50)	0.34	1.24 (0.95–1.64)	0.12
IGT	1.83 (1.31–2.56)	0.0004	1.60 (1.14–2.23)	0.006
Dyslipidemia	0.81 (0.63–1.06)	0.12	0.94 (0.73–1.22)	0.66
BMI	1.09 (1.04–1.13)	0.0001	1.05 (1.00–1.09)	0.034
SBP			1.07 (1.05–1.08)	<0.0001

Cox proportional hazard regression analysis was performed using baseline BNP levels as continuous variables (Model I: adjusted for age, gender, smoking, IGT, dyslipidemia, and BMI; Model II: adjusted for age, gender, smoking, IGT, dyslipidemia, BMI, and SBP). Analyses were performed after logarithm conversion of BNP concentrations. CI, confidence interval; BNP, B-type natriuretic peptide; IGT, impaired glucose tolerance; BMI, body mass index; SBP, systolic blood pressure.

ulated the secretion of BNP. However, secreted BNP may not have been enough to overcome increased blood pressure. This leads to the positive, continuous association between blood pressure and BNP. Thus, the prediction of the new onset of hypertension by an increase in baseline BNP depends on a mild increase in baseline blood pressure. This concept is also supported by Cox proportional hazard regression analysis in which BNP was treated as a continuous variable. Indeed, in the present study, BNP levels at baseline were slightly, but significantly, increased in subjects with pre-hypertension as compared to those with lower blood pressure. Most reports demonstrated that plasma BNP levels are increased in patients with hypertension as compared to normotensive subjects (*8–11*, *23*), although the circadian rhythm of blood pressure may affect BNP levels (*24*). These observations are also compatible with our interpretation. On the other hand, normotensive subjects with left ventricular hypertrophy or diastolic dysfunction are at increased risk from the future development of hypertension (*25*, *26*). Thus, the contribution of left ventricular hypertrophy or diastolic dysfunction to the mild increase in baseline BNP levels in subjects who developed hypertension during the follow-up is also possible, although we cannot verify the possibility because the participants did not undergo echocardiography at baseline. Alternatively, a combination of multiple biomarkers may have a stronger power for predicting the onset of overt hypertension.

The present results suggest a limitation of BNP as a candidate for a biochemical marker of hypertension, because BNP is not an independent predictor of hypertension. Also, it is quite difficult to define the (gender-specific) normal reference range of BNP for the prediction of hypertension. In the present study, only a mild increase in BNP levels within the normal reference range (used for the diagnosis and management of heart failure) had clinical significance in predicting hypertension. Moreover, circulating levels of the peptide are influenced by several factors, such as age, renal function, and hemoglobin levels (*19–21*, *27*, *28*). However, BNP measurement may still have clinical significance. Although increased blood pressure within the normal level is the strongest predictor of hypertension in the population at large (*29–31*), periodic measurement of blood pressure in individuals often cannot detect subjects in the process of developing hypertension. Blood pressure increases gradually with marked fluctuation in blood pressure measurements and the reproducibility of office blood pressure measurements is not satisfactory (*32–35*). Individuals at this stage of the disease may present with high BNP. Thus, measurements of BNP and blood pressure have complementary roles in the prediction and confirmation of hypertension, especially at its early stage. Indeed, BNP and blood pressure provide basically different information. However, it should be noted that in female subjects the impact of BNP on the onset of new hypertension might not be significant, as suggested by a previous study (*13*), although only 36% of our subjects were female and the statistical power may not be enough to draw a conclusion. Our study also demonstrated that age, male gender, impaired glucose tolerance, obesity, and increased blood pressure within the normal range are the independent predictors of the onset of hypertension,

confirming previous reports (*13*, *18*, *29*, *30*, *36*).

Interpretation of the data is limited because of the following conditions: 1) subjects were participants in a yearly physical checkup program of our hospital and thus there may have been some selection bias, 2) 282 subjects (5.3%) were lost to follow-up, which might affect the results obtained, and 3) blood pressure was measured at a yearly physical checkup (only once a year) and some participants were possibly misclassified into a wrong blood pressure category. These should be noted when interpreting the present data.

In conclusion, baseline BNP levels are closely associated with a risk of hypertension in individuals with normal blood pressure. Since adjustment for baseline blood pressure eliminates the correlation between baseline BNP and the risk of hypertension, prediction of the new onset of hypertension by BNP is largely dependent on baseline blood pressure.

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