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Prediction of Atrial Fibrillation by B-type Natriuretic Peptide

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Abstract

Background: Although several conditions have been proposed as risk factors contributing to the incidence of atrial fibrillation, many individuals without such 'risk factors' also suffer from atrial fibrillation. The present study tested the hypothesis that the risk of new-onset atrial fibrillation increases with increasing circulating levels of B-type natriuretic peptide in the general population.

Methods: Participants in our health checkup program without atrial fibrillation or a history of atrial fibrillation were enrolled (n=10,058, 54.3±11.3 years old). After baseline evaluation, subjects were followed up for the median of 1,791 days with the endpoint being the new onset of atrial fibrillation.

Results: Atrial fibrillation occurred in 53 subjects during the follow-up period (1.16 per 1,000 person-year). The risk of new-onset atrial fibrillation increased across the gender-specific quartiles of B-type natriuretic peptide levels at baseline. In multivariate Cox proportional hazard regression analysis where B-type natriuretic peptide concentrations were taken as a continuous variable, B-type natriuretic peptide was a significant predictor of new onset of atrial fibrillation after adjustment for possible factors (hazard ratio 5.65 [95% CI 2.63–12.41]).

Conclusions: The risk of new onset of atrial fibrillation increases with increasing B-type natriuretic peptide levels in the general population. Measurement of B-type natriuretic peptide may improve the prediction of incident atrial fibrillation.

Introduction

Atrial fibrillation (AF) is a common arrhythmia frequently observed both in clinical practice and in the general population.[1–3] This non-fatal arrhythmia often underlies serious complications including heart failure and stroke,[4–6] which are important causes of mortality [7–9] as well as diminished quality of life.[10] Identifying those individuals at increased risk for developing AF therefore has important public health implications. Several conditions, such as aging, hypertension, diabetes mellitus, chronic kidney disease, and heart disease, have been proposed as risk factors contributing to the initiation of AF.[11–16] On the other hand, many individuals without such conditions also suffer from AF, highlighting the limitation of identifying high-risk individuals for AF among the general population using only these classical 'risk factors'. In this regard, development of a biomarker that predicts AF is desirable. B-type natriuretic peptide (BNP) is secreted from ventricular myocytes in response to increased cardiac stress, and is a sensitive and significant marker of cardiac dysfunction.[17–20] Indeed, circulating levels of BNP are elevated in various organic cardiac disorders,[20–23] as well as in patients

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with AF,[18,24] both chronic and paroxysmal, even in the absence of heart failure. Since AF can be triggered by cardiac overload, an increase in BNP levels may, conversely, precede the onset of AF. Indeed, BNP was reported to predict incident AF in the Framingham cohort.[25,26] Interestingly, the prevalence of AF is more frequent in the United States than in Japan,[1–3,27] thus the predictive value of BNP for incident AF may differ depending on ethnicity.[28] The present study therefore sought to evaluate whether the risk of new-onset AF increases with increasing circulating BNP concentrations in the Japanese general population.

Methods

Study Design

This was an observational and follow-up study to assess the impact of BNP on the incidence of AF in subjects with normal sinus rhythm. The present study accorded with the principles of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Enshu Hospital. All participants gave written informed consent to participate prior to the start of the study.

Study Subjects and Procedures

Apparently healthy participants who visited our hospital for a yearly physical checkup from July 2001 to June 2009 were included. The health checkup program included a routine physical examination, chest X-ray, electrocardiogram (ECG), and laboratory assessment of cardiovascular risk factors including BNP concentration. The 12-lead ECGs were recorded after participants had

Table 1 Baseline Characteristics of Subjects

	Total (n=10,058)	Female (n=3,606)	Male (n =6,452)
Age (year-old)	54.3±11.3	54.2±10.4	54.3±11.8
Body height (cm)	161.7±8.7	153.7±5.8	166.1±6.6*
Body weight (kg)	59.9±10.6	52.8±7.9	63.8±9.8*
Body mass index (kg/m2)	22.8±3.0	22.4±3.1	23.1±2.9*
Systolic blood pressure (mmHg)	126.4±16.9	124.7±17.3	127.3±16.7*
Diastolic blood pressure (mmHg)	77.0±10.6	75.0±10.4	78.1±10.6*
Mean blood pressure (mmHg)	93.4±11.9	91.6±11.9	94.5±11.8*
Heart rate (bpm)	63.5±10.1	66.2±10.2	62.0±9.7*
Serum creatinine (mg/dl)	0.74±0.21	0.60±0.10	0.81±0.22*
eGFR (ml/min/1.73m2)	81.4±14.5	82.4±14.9	80.8±14.3*
Uric acid (mg/dl)	5.3±1.4	4.3±0.9	5.9±1.3*
Fasting plasma glucose (mg/dl)	100.3±19.8	96.4±16.2	102.5±21.2*
LDL-cholesterol (mg/dl)	125.0±31.1	128.3±31.9	123.1±30.5*
HDL-cholesterol (mg/dl)	61.2±15.4	66.3±14.8	58.3±15.0*
Triglyceride (mg/dl)	114.6±75.4	94.3±51.3	126.0±83.9*
Hemoglobin (g/dl)	14.5±1.5	13.2±1.2	15.2±1.1*
Current smoking n (%)	2,749 (27.3%)	164 (4.5%)	2,585 (40.1%)*
BNP (pg/ml)	10.1±6.3	13.6±7.4	8.4±5.5#
Follow-up period (days)	1,791±762	1,482±752	1,815±740#
Hypertension n (%)	2,779 (27.6%)	885 (24.5%)	1,894 (29.4%)*
Diabetes mellitus n (%)	698 (6.9%)	145 (4.0%)	553 (8.6%)*
Dyslipidemia n (%)	4,581 (45.5%)	1,552 (43.0%)	3,029 (46.9%)†
Heart disease n (%)	188 (1.9%)	44 (1.2%)	144 (2.2%)†

Data are mean±SD, median±median absolute deviation (BNP and follow-up period), or number of subjects (%), *p<0.0001, †p<0.001 vs. female by unpaired Student's t test or chi-square test. #p<0.0001 vs. female by Mann-Whitney U-test for BNP and follow-up period, eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide.

rested for 1 minute in the supine position in an air-conditioned room and the diagnosis of AF was based on AF or atrial flutter present on ECG, which was confirmed by cardiologists. Consecutive 10,127 participants were screened for eligibility for the present study. Subjects with AF, either chronic or paroxysmal, or a history of AF (n=69, 0.68% of the total participants) were excluded and the remaining participants were enrolled (n=10,058, male=6,452, aged 54.3±11.3 years). After the baseline medical checkup, participants were followed up for a median of 1,791 days with the endpoint being new onset of chronic or paroxysmal AF. ECGs were recorded once a year in annual health checkups at our hospital. Participants were instructed to bring their ECG records when they visited other hospitals or clinics during the follow-up period and underwent an ECG examination. The onset of AF was confirmed based on these ECG results.

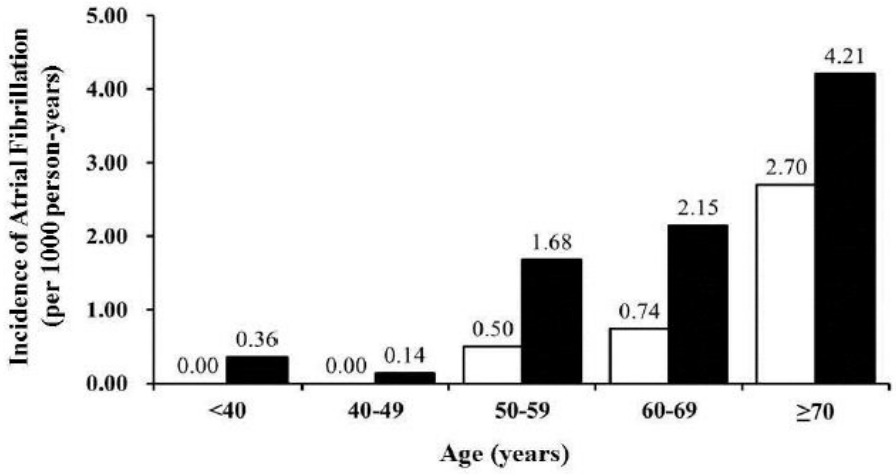
The relationship between baseline BNP concentration and the incidence of AF during the follow-up was analyzed using gender-specific quartiles of BNP and the BNP concentration as a continuous variable. Linear regression analysis was performed in each participant using BNP concentrations as a dependent variable and follow-up period (years) as an independent variable, with the slope of the regression line taken as the yearly increase in BNP. In participants who developed AF during the follow-up, the yearly increase in BNP was calculated using data collected prior to the onset of AF. The relationship between the new-onset AF and longitudinal changes in the BNP concentration during the follow-up period was also investigated.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications.[29] Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl or the use of anti-diabetic medications, and dyslipidemia was defined as low-density lipoprotein-cholesterol ≥140 mg/dl, high-density lipoprotein-cholesterol <40 mg/dl, triglyceride ≥150 mg/dl, or the use of anti-dyslipidemic medications. Ischemic heart disease, dilated or hypertrophic cardiomyopathy, and valvular heart disease were defined as heart disease.

Measurement of Plasma BNP Concentrations

For the measurement of BNP, a 3-ml sample of patient blood was transferred to plastic tubes containing 4.5 mg 2Na-ethylenediamine-tetraacetic acid. Plasma samples were prepared within 30 min by pre-cooled centrifuging, and were then immediately frozen and stored at –70°C until analysis. The BNP concentration was measured by radioimmunoassay (Shionoria BNP kit, Shionogi, Osaka, Japan).[20] The normal reference range of BNP concentrations in our hospital is <21.3 pg/ml, which equates to the median (9.3 pg/ml) plus two median

Figure 1: Bar Graphs Showing the Incidence of Atrial Fibrillation in Different Age Groups, and in Female and Male Subjects, Respectively. White Columns Indicate Females and Black Columns Indicate Males



absolute deviations (6.0 pg/ml) obtained from 300 consecutive normal subjects (women, 38%; age 57.0 years, range 22–81 years).[20] The intra- and interassay coefficients of variation of the BNP assay were 4.0% and 4.7%, respectively. The lower limit of detection of the assay was 2.0 pg/ml BNP.

Statistical Analysis

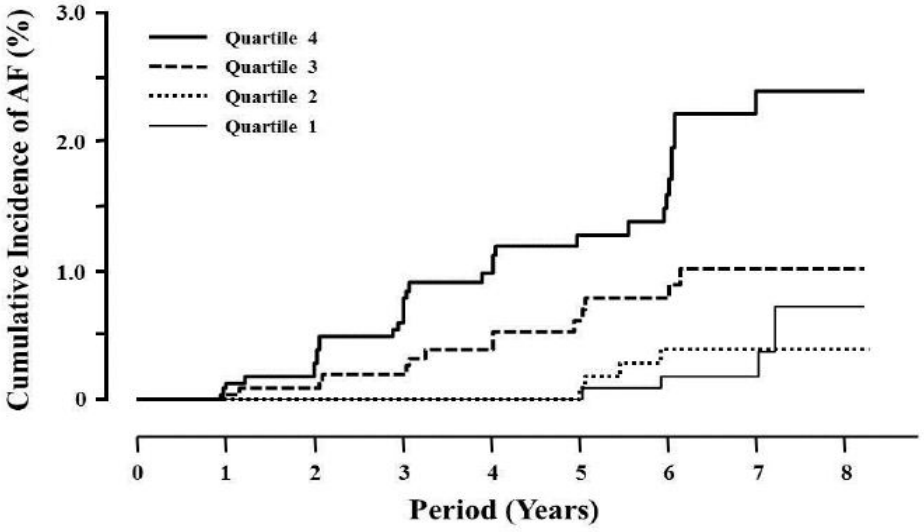
All analyses were performed using StatView 5.0 (SAS Institute, Inc, Cary, NC, USA). Data in the text and the tables are expressed as mean±standard deviation except for BNP concentrations and follow-up period, which were expressed as median±median absolute deviation. Differences between two means that had a 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 or Wilcoxon signed-rank test. Yates' corrected chi-squared (χ^2) test was used for comparisons between categorical data. Univariate and multivariate Cox proportional hazard regression models were applied to examine the relationships of the baseline BNP concentration or longitudinal changes in BNP concentrations with the new-onset AF. In a separate analysis, gender-specific quartiles of baseline BNP values were used as a predictor of incident AF. To analyze the endpoint throughout the observation period, the difference in Kaplan-Meier curves for the quartiles was tested by the log-rank test. The cutoff value of the BNP level, sensitivity, and specificity of the cutoff value was calculated using receiver operating characteristic (ROC) curve analysis. A p value less than 0.05 is considered statistically significant.

Results

Baseline characteristics of subjects are listed in Table 1. Some subjects were under medical treatment for hypertension (n=1,271, 12.6%), diabetes mellitus (n=405, 4.0%), dyslipidemia (n=478, 4.8%), or heart disease (n=188, 1.9%). The actual follow-up of this study was 45,526 person-years, during which AF occurred in 53 subjects (1.16 per 1,000 person-years). The incidence was higher in male than in female subjects (1.51 vs. 0.51 per 1,000 person-years) and increased with increasing age (Figure 1).

The impact of the BNP value on the development of AF was analyzed using the gender-specific quartiles of BNP concentrations at baseline.

Figure 2: Kaplan-Meier analysis for new onset of atrial fibrillation. Participants were divided into gender-specific quartiles according to their baseline BNP concentrations. The median±median absolute deviation of BNP [range] is 4.5±1.5 [2.0–7.3], 10.2±1.4 [7.4–13.5], 17.9±2.5 [13.6–23.7], and 34.0±7.5 [23.8–298.0] pg/ml for females and 2.0±0.0 [2.0–3.8], 5.9±1.1 [3.9–8.3], 11.7±2.0 [8.4–16.7], and 26.1±6.9 [16.8–546.0] pg/ml for males in the first, second, third, and fourth quartiles, respectively. p<0.0001 by log-rank test

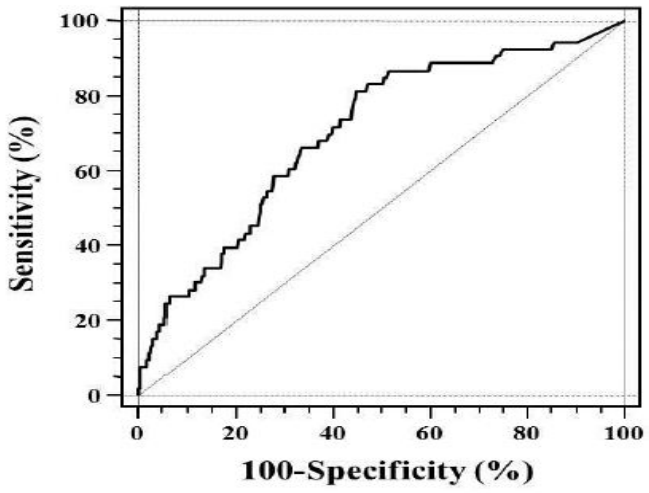


Kaplan-Meier curves clearly demonstrated that the incidence of AF increased across the quartiles of BNP values (0.34, 0.36, 1.23, and 2.79 per 1,000 person-years in the first, second, third, and fourth quartiles, respectively; Figure 2). The hazard ratio of incident AF (first quartile as reference) was 0.935 (95% CI 0.232–3.769), 2.876 (95% CI 0.920–8.996), and 5.229 (95% CI 1.716–15.931) in the second, third, and fourth quartiles, respectively, after adjustment for age, male gender, body mass index, systolic blood pressure, heart rate, serum creatinine, uric acid, fasting plasma glucose, hemoglobin, current smoking status, and the presence of dyslipidemia and heart disease at baseline. To confirm the predictive significance of the BNP value, univariate and multivariate Cox proportional hazard regression analyses were performed taking the BNP concentration as a continuous variable (Table 2). By univariate analysis, incident AF was correlated and with age, male gender, blood pressure, serum creatinine, eGFR, uric acid, BNP, and heart disease. BNP remained an independent predictor of new onset of AF in the multivariate analysis after adjustment for age, male gender, body mass index, systolic blood pressure, heart rate, serum creatinine, uric acid, fasting plasma glucose, presence of dyslipidemia and heart disease, hemoglobin, and current smoking status. BNP was also an independent predictor of new onset of AF in subanalyses performed in male and female subjects (data not shown). The risk of developing AF increased by approximately 5.7-fold for every 10 pg/ml increase in BNP concentration. Similar results were obtained in a subanalysis on subjects not taking medications for hypertension, diabetes mellitus, dyslipidemia, or heart disease; BNP was an independent predictor of the incident AF (n=8,138, hazard ratio 5.19 (95% CI 1.91–14.04)).

Another approach to elucidating the importance of circulating BNP concentration for the risk evaluation of developing AF was made by calculating yearly changes in the BNP value. The yearly increases in BNP were significantly higher in participants with incident AF than those without incident AF (6.32±13.32 vs. 0.94±8.99 pg/ml/year). The impact of longitudinal changes in BNP concentration on the new onset of AF was also assessed by multivariate Cox proportional hazard regression analysis. Longitudinal changes in BNP concentrations independently predicted the new onset of AF after adjustment for possible factors including BNP levels at baseline (Table 3). Similar results were obtained in participants not taking medications (Table 3).

The cutoff level of BNP, sensitivity and specific-

Figure 3: Receiver Operating Characteristic (ROC) Curve for BNP Levels in the Prediction for New Onset of Atrial Fibrillation



ity of the level determined by ROC-curve analysis were 11.4 pg/mL, 81.1%, and 55.2%, respectively (Figure 3). The area under the ROC curve for BNP was 0.703.

Discussion

To the best of our knowledge, the present study demonstrated for the first time that circulating BNP concentration independently predicts the new onset of AF in the Japanese general population. Although AF is not a fatal arrhythmia by nature, it is associated with an increase in cardiovascular mortality as well as morbidity, including stroke and heart failure. Identifying individuals with increased risk of AF is therefore an important step for the primary prevention of AF, which may be prevented or postponed in such individuals by medical intervention or lifestyle modification aimed at intensive overall risk reduction.

The prevalence of AF in our cohort at baseline (0.7%) was quite similar to that in previous reported in Japanese subjects,[3,9,27] suggesting that our cohort represented the Japanese general population. Although the incidence of AF during the follow-up in the present study (1.16 per 1,000 person-years) was slightly lower than that in previous studies from Japan,[30,31] the difference among the studies can largely be attributable to the difference in the prevalence of 'classical risk factors' such as hypertension, diabetes, and aging. Our study confirmed that the incident AF was less frequent in Asian populations than in Caucasian ,[14] suggesting that ethnic difference should be considered when discussing the nature, prevalence, etiology, and prevention of the arrhythmia.[28]

This study clearly indicated that an increase in BNP concentration translates to elevated risk of AF, and that such risk in the Japanese general population could be evaluated by measuring BNP. Strikingly, BNP concentrations in individuals in the first to third quartiles were within normal ref-

Table 2 Univariate and multivariate Cox Proportional Hazard Regression Analyses Demonstrating the Relationships Between Variables Obtained at Baseline and New-Onset AF

	Univariate Analysis		Multivariate Analysis	
Variables at Baseline	**Hazard Ratio (95%CI)**	**P**	**Hazard Ratio (95%CI)**	**P**
Age	1.10 (1.06–1.13)	<0.0001	1.07 (1.04–1.11)	<0.0001
Gender; Male	2.89 (1.36–6.13)	0.006	1.51 (0.57–4.00)	0.41
Body mass index	1.03 (0.94–1.13)	0.57	1.03 (0.93–1.15)	0.57
Systolic blood pressure	1.02 (1.01–1.04)	0.004	-	-
Diastolic blood pressure	1.04 (1.01–1.07)	0.003	-	-
Hypertension	2.51 (1.46–4.30)	0.001	1.24 (0.69–2.22)	0.48
Heart rate	0.98 (0.95–1.01)	0.17	1.00 (0.97–1.03)	0.87
Serum creatinine	1.66 (1.11–2.48)	0.01	1.17 (0.58–2.35)	0.68
eGFR	0.97 (0.95–0.99)	0.01	-	-
Uric acid	1.25 (1.04–1.51)	0.02	1.11 (0.89–1.38)	0.37
Fasting plasma glucose	1.01 (0.99–1.02)	0.55	-	-
Diabetes mellitus	1.49 (0.59–3.73)	0.40	1.02 (0.40–2.63)	0.97
LDL-cholesterol	1.00 (0.99–1.00)	0.25	-	-
HDL-cholesterol	1.00 (0.98–1.01)	0.69	-	-
Triglyceride	1.00 (0.99–1.00)	0.97	-	-
Dyslipidemia	1.06 (0.62–1.81)	0.84	1.07 (0.60–1.90)	0.82
Hemoglobin	1.21 (0.99–1.47)	0.05	1.26 (0.98–1.61)	0.07
Current smoking	1.37 (0.78–2.41)	0.27	1.70 (0.91–3.17)	0.10
Heart disease	6.40 (2.55-16.09)	<0.0001	2.33 (0.90–6.04)	0.08
BNP	7.13 (3.62–14.04)	<0.0001	5.25 (2.48–11.11)	<0.0001

eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide, Levels of BNP were log-transformed before statistical analysis

erence range, indicating that an increase in BNP concentration, even within the normal reference range, provides valuable information for the risk of incident AF. The predictive value of BNP was confirmed by regression analysis taking BNP as a continuous variable. Although several variables at baseline were significantly correlated with the new onset of AF by univariate analysis, most of them were not independent predictors by multivariate analysis, which identified only age and BNP remaining as significant independent predictors of AF risk. Indeed, small increases in baseline BNP (10 pg/ml) had a great impact on the incidence of AF (5.7-fold increase) after adjustment for classical risk factors. Changes in BNP concentration could also be important in predicting the new onset of AF, because longitudinal increases in BNP independently predicted the incidence of AF, even after adjustment for the baseline value of BNP. This finding reinforced the clinical significance of BNP for the prediction of incident AF and implicated mechanisms underlying the present observation. Although some medications may affect BNP concentrations, the effect of medications seemed minimal in the present study because similar results were obtained in sub-analysis performed in participants without medications.

Although the present result does not provide causal relationships, it does offer a possible explanation for the close relationship between BNP concentration and incident AF. An increase in cardiac load, either manifest or subclinical, associated with systolic dysfunction, ventricular hypertrophy, and cardiac fibrosis potentially provokes or mediates AF and increases the ventricular secretion of BNP. Thus, the small BNP increases observed in the present study may reflect an increase in cardiac load, although the clinical significance of an increase in the BNP value within normal range is not clear. Diastolic dysfunction also has a close association with the development of AF through an increase in atrial pressure and volume ,[31] and atrium is a source for BNP secretion even in the absence of ventricular dysfunction. [32,33] These interpretations could imply that intervention to reduce BNP levels could, at least in part, prevent the incident AF in individuals at high risk of AF via a reduction in cardiac load. Whether preventing an increase in or reducing BNP levels reduces the incidence of AF must be clarified by prospective follow-up studies. On the other hand, an increase in circulating BNP concentrations at baseline may have reflected the presence of clinically unidentified paroxysmal AF. Indeed, BNP is elevated in patients with paroxysmal as well as chronic AF without overt heart

Table 3 Multivariate Cox proportional Hazard Regression Analyses Demonstrating the Impact of Yearly Increases in the BNP Level on the Risk of Developing AF

	Total Study Participants (n=10,058)		Participants not Taking Medications (n=8,138)	
Variables at Baseline	**Hazard Ratio (95%CI)**	**p**	**Hazard Ratio (95%CI)**	**p**
Age	1.09 (1.05–1.14)	<0.0001	1.07 (1.03–1.12)	0.002
Gender; Male	1.16 (0.34–4.03)	0.81	1.39 (0.25–7.8)	0.71
Body mass index	0.97 (0.85–1.10)	0.64	0.93 (0.79–1.10)	0.40
Hypertension	1.22 (0.63–2.38)	0.56	0.88 (0.30–2.04)	0.62
Heart rate	0.99 (0.96–1.03)	0.67	0.96 (0.91–1.01)	0.09
Serum creatinine	0.50 (0.03–8.05)	0.63	1.47 (0.33–6.47)	0.61
Uric acid	1.17 (0.89–1.53)	0.27	1.22 (0.88–1.69)	0.22
Diabetes mellitus	0.77 (0.23–2.57)	0.67	0.91 (0.12–6.88)	0.93
Dyslipidemia	1.13 (0.58–2.17)	0.72	1.35 (0.60–3.02)	0.47
Hemoglobin	1.63 (1.22–2.17)	0.001	1.85 (1.28–2.66)	0.001
Current smoking	1.63 (0.80–3.31)	0.18	0.64 (0.26–1.60)	0.34
Heart disease	1.01 (0.24–4.36)	0.99	–	–
BNP	3.09 (1.30–7.33)	0.01	3.49 (1.17–10.44)	0.03
Yearly increase in BNP	1.03 (1.02–1.05)	<0.0001	1.04 (1.02–1.05)	<0.0001

BNP, B-type natriuretic peptide, Levels of BNP were log-transformed before statistical analysis

failure ,[18,20,24] although an acute decrease in BNP levels has been reported after sinus rhythm restoration without alterations in echocardiographic parameters.[33] Such findings should be taken into account when interpreting BNP values. Alternatively, integrating changes in numerous factors may contribute to the predictive value of BNP, because the BNP concentration reflects many factors such as age, gender, renal function, hemoglobin, and cardiac function.

We confirmed that classical risk factors are predictive of new onset of AF, although some of them were not independent factors. Furthermore, inflammation has also been associated with AF [34] and C-reactive protein (CRP) has been reported as a significant predictor of new onset.[25,35] Thus, evaluating combinations of these factors may improve the predictive value of each individual risk factor. In this context, measuring BNP is particularly valuable because it provides basically different information from other risk factors.

Interpretation of the data is limited due to the following considerations: (1) selection bias may have existed because the study subjects were participants in a yearly physical checkup program of our hospital; (2) we may have missed asymptomatic AF episodes and clinically undetected paroxysmal AF at baseline and during the follow-up; (3) ECG was recorded only once a year in most of the participants; (4) there may be ethnic difference in the prediction value of BNP; and (5) the use of single measurement of BNP and the reproducibility of BNP values may work as biases. Since the present study offers the significant concept that BNP level could predict the development of AF, further studies with a large number of subjects should be pursued.

Conclusions

BNP independently predicts the new onset of AF in the Japanese general population. Identifying individuals with increased risk of AF may be helpful for the primary prevention of AF.

Disclosures

No disclosures relevant to this article were made by the authors.

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