Serum N-terminal pro-B-type natriuretic peptide as a predictor for future development of atrial fibrillation in a general population: the Hisayama Study

永田, 拓也

International Journal of Cardiology 320 (2020) 90–96

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Serum N-terminal pro-B-type natriuretic peptide as a predictor for future development of atrial fibrillation in a general population: the Hisayama Study

Takuya Nagata [a,b], Jun Hata [a,c,d,*], Satoko Sakata [a,c,d], Emi Oishi [a,d], Takanori Honda [a], Yoshihiko Furuta [a,d], Tomoyuki Ohara [a], Daigo Yoshida [a], Yoichiro Hirakawa [a,d], Mao Shibata [a,c], Tomomi Ide [b], Takanari Kitazono [c,d], Hiroyuki Tsutsui [b], Toshiharu Ninomiya [a,c]

[a] Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[b] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[c] Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[d] Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

ARTICLE INFO

Article history:
Received 18 March 2020
Received in revised form 27 May 2020
Accepted 12 June 2020
Available online 24 June 2020

Keywords:
Atrial fibrillation
Natriuretic peptide
Biomarker
Prospective study

ABSTRACT

Background: Biomarkers for predicting future development of atrial fibrillation (AF) have not been fully established in general populations. The aim of this study was to assess the predictive ability of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) for the development of AF.
Methods and results: A total of 3126 community-dwelling Japanese subjects aged ≥ 40 years without a history of AF in 2002 were followed up for a median of 10.2 years. Serum NT-proBNP levels at baseline were divided into four categories (≤ 54, 55–124, 125–299, and ≥ 300 pg/mL) according to the current guidelines and prior reports. The hazard ratios for the development of AF were estimated using a Cox proportional hazards model. During the follow-up period, 153 subjects developed new-onset AF. The age- and sex-adjusted cumulative incidence of AF increased significantly with higher serum NT-proBNP levels ($p < 0.001$ for trend). The association remained significant after adjustment for known risk factors for AF and cardiovascular disease (hazard ratio [95% confidence interval]: ≤ 54 pg/mL: 1.00 [reference]; 55–124 pg/mL: 1.72 [1.00–2.97]; 125–299 pg/mL: 3.95 [2.23–6.98]; ≥ 300 pg/mL: 8.51 [4.48–16.17]; $p < 0.001$ for trend). Furthermore, incorporation of serum NT-proBNP levels into the model consisting of known risk factors for AF and cardiovascular disease significantly improved the predictive ability for developing AF (Harrell's c-statistics: 0.828 to 0.844, $p = 0.01$; continuous net reclassification improvement: 0.41, $p < 0.001$; integrated discrimination improvement: 0.031, $p < 0.001$).
Conclusions: Serum NT-proBNP levels can be a risk biomarker for predicting future development of AF in a general Japanese population.

1. Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmia and is known to be associated with increased risks of various cardiovascular diseases, including ischemic stroke, heart failure, coronary heart disease, and sudden cardiac death [1]. Due to the aging of populations, the incidence and prevalence of AF and mortality from AF-related complications are expected to grow in future decades worldwide [2]. It is considered that a large proportion of AF and its complications can be prevented by better management of risk factors for AF and a close follow-up for the early detection of AF for people at higher risk of AF [3–5]. The identification of risk factors and easily accessible biomarkers for AF is necessary to establish a risk stratification strategy for the prevention of new-onset AF in primary care practices [3].

Plasma B-type natriuretic peptide (BNP) and serum/plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) are widely used as diagnostic biomarkers for heart failure [6–8] and have been reported to be predictive biomarkers for future cardiovascular events in general populations [9–11]. A number of prospective studies have demonstrated that elevated plasma BNP levels or serum/plasma NT-proBNP levels were independently associated with an increased risk of future development of AF in general populations [9,12–21]. However, all of these investigations were performed in Western populations. To the best of our knowledge, no observational studies have examined this issue in general Asian populations that have different genetic and

* Corresponding author at: Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: junhata@eph.med.kyushu-u.ac.jp (J. Hata).

https://doi.org/10.1016/j.ijcard.2020.06.018
0167-5273/

environmental backgrounds from Western populations [22–24]. In addition, only a limited number of studies have assessed the improvement of the discrimination ability for the development of AF by adding plasma BNP or serum/plasma NT-proBNP levels to the models with known risk factors [17–21], and their conclusions have been inconsistent. The objective of the present study was to assess the association of serum NT-proBNP levels with the development of AF and its discrimination ability in a general Japanese population.

2. Methods

2.1. Study population

The Hisayama Study is a prospective population-based cohort study in the town of Hisayama, located in a suburb of the Fukuoka metropolitan area in Japan [25,26]. Full community surveys of the residents have been repeated since 1961. In 2002 and 2003, 3328 residents aged 40 years and older underwent a baseline screening examination (participation rate 77.6%). After the exclusion of 30 subjects who did not consent to participate in the study, 69 subjects who had AF or atrial flutter at baseline or in the past history, 1 subject without electrocardiogram (ECG) examination at baseline, and 4 subjects without available data of serum NT-proBNP, the remaining 3224 individuals were eligible for the follow-up survey. After the additional exclusion of 98 subjects for whom there was insufficient information to determine the presence or absence of AF during the follow-up, a total of 3126 individuals (1331 men and 1795 women) were enrolled in the study (follow-up rate 97.0%).

2.2. Follow-up survey

The participants were followed up prospectively from the date of the baseline screening examination to November 2012 (median 10.2 years, interquartile range 9.7–10.3 years). Information on new AF events has been primarily collected at the annual health examinations in the town via a standard 12-lead ECG and an interview by one of the study physicians. Mail or telephone follow-ups have been used to collect health information of subjects who did not undergo regular examinations or who had moved out of town, and we asked the participants whether they had experienced new cardiovascular events, including stroke, coronary heart diseases, arrhythmia, and other heart diseases. We also established a daily monitoring system among the study team, local physicians, and the members of the town's Health and Welfare Office. In this system, the study team's physicians visited clinics, hospitals, and the town's office regularly to collect the information of new cardiovascular events. When a new cardiovascular event was suspected or a subject died, all the available medical information, including standard 12-lead ECG, ambulatory monitoring ECG, physicians' diagnosis on medical records, and death certificates, was collected to confirm whether the participants had experienced new-onset AF. During the follow-up period, 471 subjects died from any cause.

2.3. Diagnosis of AF

The definition of AF included AF and atrial flutter (Minnesota code, 8–3–1 to 8–3–4). The primary outcome of this study was a newly diagnosed AF present at the annual health examinations, clinics, or hospitals. All events of AF were verified by ECG findings from the annual health examination and/or medical records of the clinic or hospital by the study team's cardiologists.

Since it was difficult to classify AF events using a standard classification (i.e., first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF [5]) in our study design, new-onset AF events were classified into two subtypes. (1) Subjects were defined as having "Definite permanent AF" if they had AF on all of the 12-lead ECGs at the subsequent annual health examinations during the follow-up. (2) Subjects were defined as having "Other or indefinite subtype of AF" if they experienced sinus rhythm on ECG at least once after the onset of AF during the follow-up, or if they did not undergo ECG examinations after the AF onset during the follow-up.

2.4. Measurement of NT-proBNP

At baseline, blood samples were collected from an antecubital vein, and a portion of the serum was stored at −80 °C until use for the measurement of serum NT-proBNP levels in 2009. Serum NT-proBNP levels were measured using an Elecsys proBNP Immunoassay (Roche Diagnostics, Risch, Switzerland). Serum NT-proBNP levels were divided into four categories: ≤ 54, 55–124, 125–299, and ≥ 300 pg/mL, according to the current guidelines and prior reports [6–8,11,27].

2.5. Risk factor measurements

At baseline, a self-administered questionnaire regarding smoking habits, alcohol intake, regular exercise, medical history, and treatment of hypertension and diabetes was checked by trained interviewers. Smoking habits and alcohol intake were classified as either current habitual use or not. Subjects engaging in sports or other exercise at least three times a week during their leisure time were defined as the regular exercise group. History of coronary heart disease, including myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery, was defined on the basis of all clinical data adjudicated by available medical records [25,26]. Cardiac murmur was defined as a systolic murmur of grade 3 or louder (on a 6-point scale) or any diastolic murmur [28]. Left ventricular hypertrophy was defined as Minnesota Code 3–1. Arrhythmia other than AF was defined as Minnesota Code 8–1, 8–2, 8–4, 8–5, 8–6, or 8–9. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated. Sitting blood pressure was measured 3 times at the right upper arm using an automated sphygmomanometer after 5 min of rest; an average of 3 measurements was used for the analysis. Plasma glucose levels were measured by the hexokinase method, and diabetes was defined as a fasting glucose level ≥ 7.0 mmol/L, 2-hour postload or postprandial glucose level ≥ 11.1 mmol/L, according to the 1998 World Health Organization criteria [29], and/or the use of oral hypoglycemic agents or insulin. Total and high-density lipoprotein (HDL) cholesterol levels were measured using an enzymatic method. Serum creatinine concentrations were measured enzymatically, and the estimated glomerular filtration rate (eGFR) was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation [30]. Serum high-sensitivity C-reactive protein (HS-CRP) concentrations at baseline were measured using the frozen serum portion by a modified version of the Behring Latex-Enhanced CRP assay on a Behring Nephelometer BN-100 (Behring Diagnostics, Westwood, MA) in 2004.

2.6. Statistical analysis

The trends in means and frequencies of risk factors across serum NT-proBNP levels were tested using linear regression analysis and logistic regression analysis, respectively. Serum NT-proBNP and serum HS-CRP concentrations were transformed into logarithms due to the skewed distribution. The crude incidence rate of AF was calculated using a person-years method. The age- and sex-adjusted cumulative incidence of AF across serum NT-proBNP levels was estimated on the basis of regression estimates from a Cox proportional hazards model including age and sex [31]. The hazard ratios (HRs) for the development of AF and their 95% confidence intervals (CIs) according to serum NT-proBNP levels were estimated using a Cox proportional hazards model. We evaluated 3 different models: model 1, adjusted for age and sex; model 2, adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol,

serum HDL cholesterol, BMI, eGFR, smoking habits, alcohol intake, regular exercise, and serum HS-CRP; and model 3, adjusted for the covariates included in model 2 plus history of coronary heart disease, cardiac murmur, left ventricular hypertrophy, and arrhythmia other than AF. In the Cox analyses, subjects without AF events were censored at the date of death, the date of the last follow-up survey, or November 30, 2012. The heterogeneity in the association between the subgroups stratified by eGFR levels was tested by adding the multiplicative interaction term to the relevant Cox model.

The accuracy of the risk assessment for development of AF was evaluated by Harrell's c-statistics [32] for three statistical models: (1) a known-risk-factor-based model (17 variables consisting of known risk factors of AF and cardiovascular disease: age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum HDL cholesterol, BMI, eGFR, smoking habits, alcohol intake, regular exercise, and serum HS-CRP, history of coronary heart disease, cardiac murmur, left ventricular hypertrophy, and arrhythmia other than AF), (2) a simple model (3 variables: age, sex, and serum NT-proBNP levels), and (3) a full model (18 variables: the variables from the known-risk-factor-based model plus serum NT-proBNP levels). The consistency in the Harrell's c-statistics among the models was estimated using an approach, as described by Newson [33]. We additionally evaluated continuous and categorized net reclassification improvement (NRI) [34,35] and integrated discrimination improvement (IDI) [35]. For these analyses, the predicted probabilities of incident AF for 10 years were calculated for each participant using relevant Cox models. The predicted probabilities of 10-year AF risk were classified into three categories of less than 5%, 5–10%, and above 10% for categorized NRI.

We also evaluated the predictive ability of serum NT-proBNP levels for the risk of developing AF using four risk scores of AF developed in East Asia (the C_2HEST score [36], the HATCH score [37], the Hamada's risk score [38], and the Suita risk score [39]) by Harrell's c-statistics, continuous NRI, and IDI. The optimal cut-off value of serum NT-proBNP for the discrimination of AF risk was determined as the serum NT-proBNP concentration that minimizes the value of $\sqrt{(1-\text{sensitivity})^2+(1-\text{specificity})^2}$ in the receiver operating characteristic analysis [40].

A two-sided value of $p < 0.05$ was considered to be statistically significant in all analyses. All statistical analyses were performed with the SAS statistical software program, version 9.4 (SAS Institute Inc., Cary, NC) and Stata version 14.0 (StataCorp, College Station, TX).

2.7. Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Board for Clinical Research. Written informed consent was obtained from all subjects.

3. Results

The age- and sex-adjusted baseline characteristics of the study population according to serum NT-proBNP levels are summarized in Table 1. Subjects with higher serum NT-proBNP levels were likely to be older and to be female. The mean values of systolic blood pressure, the geometric mean values of serum HS-CRP, and the frequencies of the use of antihypertensive agents, history of coronary heart disease, cardiac murmur, left ventricular hypertrophy, and arrhythmia other than AF increased significantly with elevating serum NT-proBNP levels. Conversely, the mean values of serum total cholesterol, BMI, and eGFR and the frequencies of regular exercise decreased significantly with higher serum NT-proBNP levels.

During the follow-up period, a total of 153 subjects (74 men and 79 women) developed new-onset AF: 38 events were first identified by ECG at the annual health examinations and 115 events were first diagnosed by ECG at clinics or hospitals. Among the latter 115 events, 27 AF events were detected again by ECG at the subsequent health examinations during the follow-up. Therefore, a total of 65 AF events were detected by ECG at the annual health examination.

The age- and sex-adjusted cumulative incidences of AF increased significantly with higher serum NT-proBNP levels (p for trend < 0.001) (Fig. 1). Table 2 shows the hazard ratios (HRs) for the development of AF according to the serum NT-proBNP levels. In model 1 with adjustment for age and sex, higher serum NT-proBNP levels were significantly associated with an increased risk of AF (p for trend < 0.001). The risk of AF was significantly higher among the subjects with serum NT-proBNP

Table 1
Age- and sex-adjusted characteristics of subjects according to serum NT-proBNP levels at baseline.

	Serum NT-proBNP levels (pg/mL)				p for trend
	≤ 54	55–124	125–299	≥ 300	
	(n = 1570)	(n = 935)	(n = 419)	(n = 202)	
Age, mean (SE), years[a]	56 (0.3)	64 (0.3)	72 (0.5)	79 (0.7)	< 0.001
Women, %[b]	48.8	65.9	68.0	62.5	< 0.001
Systolic BP, mean (SE), mmHg	130 (0.6)	133 (0.7)	137 (1.0)	137 (1.5)	< 0.001
Diastolic BP, mean (SE), mmHg	78 (0.3)	79 (0.4)	80 (0.6)	77 (0.9)	0.56
Use of antihypertensive agents, %	19.4	24.8	24.0	32.4	< 0.001
Diabetes mellitus, %	15.8	17.1	19.2	12.9	0.93
Serum total cholesterol, mean (SE), mmol/L	5.45 (0.02)	5.17 (0.03)	5.07 (0.05)	4.82 (0.07)	< 0.001
Serum HDL cholesterol, mean (SE), mmol/L	1.60 (0.01)	1.64 (0.01)	1.64 (0.02)	1.61 (0.03)	0.21
BMI, mean (SE), kg/m^2	23.5 (0.09)	23.0 (0.11)	22.3 (0.17)	21.4 (0.25)	< 0.001
eGFR, mean (SE), mL/min/1.73m^2	79 (0.3)	79 (0.3)	77 (0.5)	67 (0.8)	< 0.001
Current smoking, %	13.5	16.4	17.9	9.5	0.54
Current drinking, %	41.4	41.2	45.5	31.0	0.51
Regular exercise, %	12.1	10.5	8.4	5.4	0.002
Serum HS-CRP, geometric mean [95% CI], mg/L	0.52 [0.48–0.55]	0.47 [0.44–0.51]	0.63 [0.56–0.72]	0.89 [0.75–1.07]	< 0.001
History of coronary heart disease, %	0.6	1.4	1.9	5.1	< 0.001
Cardiac murmur, %	0.2	1.1	1.6	3.3	< 0.001
Left ventricular hypertrophy, %	7.3	10.2	17.0	21.8	< 0.001
Arrhythmia other than AF, %	5.1	6.8	11.1	9.5	< 0.001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimate glomerular filtration rate; HDL, high-density lipoprotein; HS-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SE, standard error.

[a] Age was sex-adjusted.

[b] Percentage of women was age-adjusted.

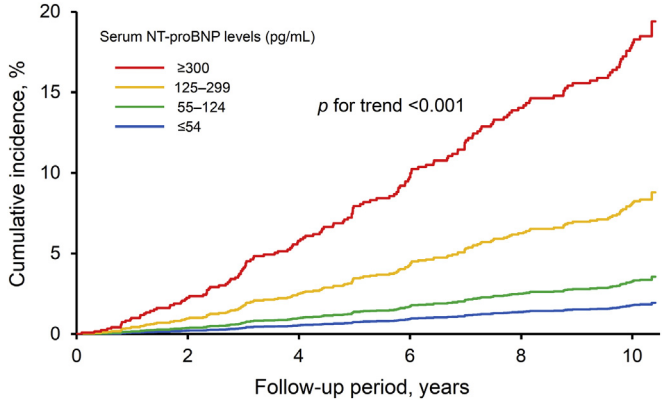

Fig. 1. Age- and sex-adjusted cumulative incidence of atrial fibrillation according to serum N-terminal pro-B-type natriuretic peptide levels.

levels of 55–124 pg/mL or greater compared to those with the lowest serum NT-proBNP level (≤ 54 pg/mL) in this model. This association remained significant after adjustment for known cardiovascular risk factors (model 2, p for trend < 0.001), and even after additional adjustment for history of coronary heart disease, cardiac murmur, left ventricular hypertrophy, and arrhythmia other than AF (model 3, p for trend < 0.001). With serum NT-proBNP levels as a continuous variable, every 1-SD increment in log-transformed serum NT-proBNP levels was associated with a 1.96-fold (95% CI = 1.60–2.41, $p < 0.001$) risk of incident AF in model 3. Among 153 events of new-onset AF, 51 events were defined as "definite permanent AF" and 102 events were defined as "other or indefinite subtype". Higher serum NT-proBNP levels were significantly associated with both subtypes of AF (Table S1).

Then, we examined the association of serum NT-proBNP levels with the risk of AF in the subgroups stratified by age. Higher serum NT-proBNP levels were associated with an increased risk of AF in all age groups from the middle-aged to the elderly (all p for trend < 0.001) (Table S2). In addition, we performed the subgroup analysis by eGFR levels. As a result, there was no evidence of heterogeneity in the association of serum NT-proBNP levels with the risk of incident AF between subgroups of eGFR levels (p for heterogeneity = 0.54) (Table S3).

We also performed five sets of sensitivity analyses for the association between serum NT-proBNP levels and the risk of developing AF: (1) a sensitivity analysis in which the serum NT-proBNP levels were grouped into five categories by quintiles, instead of guideline-based categories (Table S4); (2) a sensitivity analysis using only 65 AF events detected by ECG at the annual health examination as an outcome (Table S5); (3) a sensitivity analysis excluding 26 events of AF occurred during the first 2 years of follow-up (Table S6); (4) a sensitivity analysis excluding 564 subjects with cardiac disorders (i.e., a history of coronary heart disease, a history of self-reported heart diseases, cardiac murmur, or left ventricular hypertrophy on ECG at baseline) (Table S7); and (5) a sensitivity analysis excluding 59 subjects with serum NT-proBNP ≥ 900 pg/mL (Table S8). These sensitivity analyses did not change the study conclusions substantially.

We assessed the discrimination and reclassification ability of serum NT-proBNP levels for the development of AF (Table 3). The model that included NT-proBNP with age and sex achieved good discrimination (Harrell's c-statistics: 0.830) comparable to that by the known-risk-factor-based model that included 17 established risk factors for AF and cardiovascular diseases (Harrell's c-statistics: 0.828). Furthermore, when the serum NT-proBNP level was incorporated into the known-risk-factor-based model, Harrell's c-statistics increased significantly (Harrell's c-statistics: 0.844; $p = 0.01$ vs. the known-risk-factor-based model). The improvement in predictive ability by adding NT-proBNP was further confirmed (continuous NRI: 0.41 [$Z_{NRI} = 4.89$, $p < 0.001$]; categorized NRI: 0.09 [$Z_{NRI} = 2.40$, $p = 0.02$]; IDI: 0.031 [$Z_{IDI} = 4.51$, $p < 0.001$]) (Table 3 and Table S9). Furthermore, the addition of serum NT-proBNP levels into each of the four risk scores developed in East Asian populations [36–39] also improved the predictive ability for developing AF (Table S10).

Finally, we examined the cut-off value of serum NT-proBNP concentration that optimized the discriminating ability (i.e., sensitivity and specificity) for the risk of developing AF. The optimal cut-off values of serum NT-proBNP were 72 pg/mL in total, 60 pg/mL for men, and 82 pg/mL for women (Fig. S1).

4. Discussion

4.1. Findings/meaning

This prospective study clearly showed that the risks of developing AF increased significantly with elevating serum NT-proBNP levels in a community-dwelling Japanese population. In addition, incorporation of serum NT-proBNP values into the known-risk-factor-based model consisting of 17 variables significantly improved the predictive ability for the development of AF. Further, the simple model consisting of only 3 variables—namely, age, sex, and serum NT-proBNP levels—had a discrimination ability comparable to that of the known-risk-factor-based model. These findings highlight that the measurement of serum NT-proBNP in clinical practices may be effective for identifying populations at high-risk for the future development of AF.

4.2. Comparison with related studies

A number of prospective cohort studies have reported that elevated plasma BNP or serum/plasma NT-proBNP levels were independent risk factors for the development of AF in general Western populations

Table 2
Hazard ratio for the development of atrial fibrillation according to serum NT-proBNP levels, 2002 to 2012.

NT-proBNP (pg/mL)	No. of events /subjects	Crude incidence (per 10^3 person-years)	Hazard ratio (95% confidence interval)		
			Model 1[a]	Model 2[b]	Model 3[c]
≤ 54	24 / 1570	1.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	35 / 935	4.1	1.84 (1.07–3.16)	1.75 (1.02–3.02)	1.72 (1.00–2.97)
125–299	49 / 419	14.3	4.68 (2.70–8.11)	4.17 (2.37–7.35)	3.95 (2.23–6.98)
≥ 300	45 / 202	40.8	10.98 (6.08–19.84)	9.59 (5.10–18.03)	8.51 (4.48–16.17)
p for trend			< 0.001	< 0.001	< 0.001
Every 1-SD increment in log (serum NT-proBNP levels)			2.01 (1.72–2.34)	2.07 (1.69–2.53)	1.96 (1.60–2.41)

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.
The SD of log-transformed serum NT-proBNP levels (pg/mL) was 1.144.
[a] Model 1: adjusted for age and sex.
[b] Model 2: adjusted for age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, body mass index, estimated glomerular filtration rate, smoking habits, alcohol intake, regular exercise, and serum high-sensitivity C-reactive protein.
[c] Model 3: adjusted for the covariates in model 2 + history of coronary heart disease, cardiac murmur, left ventricular hypertrophy, and arrhythmia other than atrial fibrillation.

Table 3
Discrimination and reclassification ability of atrial fibrillation by serum NT-proBNP levels and potential risk factors, 2002 to 2012.

	Harrell's c-statistics	*p* value for the difference in Harrell's c-statistics	Continuous NRI[b]	*p* value for continuous NRI	IDI[b]	*p* value for IDI
Known-risk-factor-based model[a]	0.828		ref.		ref.	
Age + sex + NT-proBNP	0.830	0.79	0.05	0.56	0.005	0.63
Known-risk-factor-based model[a] + NT-proBNP	0.844	0.01	0.41	< 0.001	0.031	< 0.001

Abbreviations: CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a] The known-risk-factor-based model: age, sex, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, body mass index, estimated glomerular filtration rate, smoking habits, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein, history of coronary heart disease, cardiac murmur, left ventricular hypertrophy, and arrhythmia other than atrial fibrillation.
[b] Comparisons with the known-risk-factor-based model.

[9,12–21]. Although the Multiethnic Study of Atherosclerosis showed that the risk of incident AF increased with elevated serum NT-proBNP levels in Chinese Americans (American residents with Chinese ancestry) as well as in Americans of other ancestries [16], no observational studies have examined this issue in a general Asian population. In the present study, we clearly confirmed a positive association between serum NTproBNP levels and the risk of incident AF in a general Asian population with an environmental background distinct from that of Western populations [22–24].

Some prospective studies [17,20,21] have demonstrated that the discrimination ability for incident AF was improved by the addition of serum NT-proBNP levels or plasma BNP levels to a model consisting of potential risk factors for AF. Meanwhile, in the Copenhagen Holter Study [18] and the Heinz Nixdorf Recall Study [19], the inclusion of serum NT-proBNP levels or plasma BNP levels did not significantly improve the discrimination ability for the development of AF, probably due to the relatively small numbers of AF events and different follow-up methods. In the present study, we demonstrated that the discrimination ability for future onset of AF could be improved by adding serum NT-proBNP levels to the known risk factors for AF and other cardiovascular risk factors in a general Japanese population.

4.3. Possible mechanisms

The present study showed that the risk of AF was higher in subjects with serum NT-proBNP levels of 55–124 pg/mL (i.e., subjects unlikely to have heart failure) than in those with serum NT-proBNP levels of ≤ 54 pg/mL, indicating that serum NT-proBNP levels could be a risk factor for new-onset AF even in subjects without clinically apparent evidence of cardiac dysfunction. In support of this notion, a number of longitudinal studies have demonstrated that elevated serum NT-proBNP levels are associated with increased risks of stroke, ischemic heart disease, and heart failure, even among subjects whose NT-proBNP levels were within the normal range or not diagnostic of heart failure [9–11]. Therefore, these previous and our present findings suggest that the elevation of serum NT-proBNP levels, even at clinically normal level, reflects the accumulation of vascular risk factors [3,4,41] and subclinical impairment of ventricular diastolic and systolic function [5,42], which result in atrial remodeling, the elevation of atrial pressure, and subsequent AF.

4.4. Clinical implications and perspectives

In this study, the ability of a simple model including age, sex, and serum NT-proBNP levels to discriminate the future onset of AF was comparable to that by a known-risk-factor-based model that included many cardiovascular risk factors other than serum NT-proBNP levels. Therefore, the measurement of serum NT-proBNP levels at a health check-up or in a primary care setting may be useful to identify subjects at higher risk of incident AF without the need to gather more detailed clinical information [21,24]. Furthermore, adding serum NT-proBNP levels to the known-risk-factor-based model improved the accuracy of the risk assessment for the future onset of AF, likely suggesting that the combination of serum NT-proBNP with detailed clinical information would enable an even more accurate determination of the high-risk population for AF. The early management of established risk factors for AF, such as hypertension, may reduce the risk of developing AF for subjects with elevated serum NT-proBNP levels in particular [43]. In addition, the measurement of serum NT-proBNP may be useful for the early detection of AF, because a considerable proportion of patients with AF are undiagnosed [44] since AF can be minimally symptomatic or clinically silent [45]. A close follow-up or screening for AF using 12-lead ECG or ambulatory monitoring ECG for subjects with elevated serum NT-proBNP levels may allow earlier detection of AF [46,47] and may result in the prevention of AF-related complications such as cardioembolic stroke by optimal treatment including anticoagulation therapy [5]. Since we observed significant association between serum NT-proBNP levels and the risk of AF in all subgroups stratified by age, the measurement of serum NT-proBNP concentrations may be useful for identifying high-risk individuals even in the middle-aged population as well as in the elderly.

In the present study, the optimal cut-off values of serum NT-proBNP concentration were determined as 60 pg/mL for men and 82 pg/mL for women, suggesting that men should have lower cut-off values of serum NT-proBNP than women. However, it is unclear whether these statistically determined cut-off values would be reasonable in a clinical practice setting. Further investigations will be needed to elucidate a clinically useful and reasonable cut-off value of serum NT-proBNP for the risk assessment of AF in consideration of public health and cost effectiveness.

4.5. Strengths and limitations

The strengths of our study include its community-based prospective cohort study design, the high participation rate in the baseline examination, the high follow-up rate, and the accurate diagnosis of AF based on the medical records and ECG. However, several limitations should be noted. First, our findings were based on a single measurement of serum NT-proBNP levels at baseline. During the follow-up, the serum NT-proBNP levels and other risk factors may have changed. This could have weakened the association observed in this study, biasing the results toward the null hypothesis. Second, our follow-up survey was primarily dependent on a standard 12-lead ECG at the annual health examinations. The long-term ECG recordings, a more effective tool for the detection of AF, were performed only at clinics or hospitals as required. The observed associations might have been affected by detection bias, because participants with higher serum NT-proBNP levels at baseline were likely to have other cardiovascular risk factors or cardiovascular events during the follow-up period [48]. The subjects with higher serum NT-proBNP levels might visit clinics or hospitals more frequently and thus might have a greater chance of being diagnosed with AF by standard or long-term ECG examinations compared to the subjects with lower serum NT-proBNP levels. However, the association

between serum NT-proBNP levels and incident AF was substantially unchanged even in the sensitivity analysis using only AF events detected by ECG at the annual health examinations (Table S5), suggesting that such bias would not have substantially distorted our results. Third, although the subjects with a history of AF were excluded from the present study, we cannot deny the possibility of the presence of a history of paroxysmal AF, which would not have been detected by ECG at baseline. However, when we performed a sensitivity analysis excluding AF events occurred during the first 2 years of the follow-up period (Table S6), the findings were not substantially changed. Fourth, we did not have any data on morphological or functional cardiac information, such as echocardiography, at baseline. However, the sensitivity analysis after excluding subjects with a history of coronary heart disease, a history of self-reported heart diseases, cardiac murmur, or left ventricular hypertrophy on ECG did not change the study conclusion substantially (Table S7). Fifth, although the participation rate of the present study was very high (77.6% of the Hisayama residents aged ≥ 40 years), 22.4% of the residents did not participate in the baseline examination. The non-participants were likely to be less healthy and to have poorer sociodemographic profiles than the participants. However, it is generally recognized that an acceptable participation rate in a population-based study (i.e., a rate that practically eliminates the threat of selection bias attributable to non-participants) is > 70% of the target population [49,50]. Therefore, we considered that the impact of selection bias was modest. Finally, residual confounding factors (e.g., undiagnosed cardiovascular risk factors, sleep apnea) might exist on the association of serum NT-proBNP levels with the risk of AF. For example, the subjects with higher serum NT-proBNP levels were likely to have more undiagnosed cardiovascular risk factors than those with normal levels [48]. However, a sensitivity analysis excluding the subjects with serum NT-proBNP ≥ 900 pg/mL did not change the study conclusion substantially (Table S8).

5. Conclusions

The present study revealed a significant association between increased serum NT-proBNP levels and the development of AF in a general Japanese population. In addition, the risk discrimination of AF was significantly improved by the addition of serum NT-proBNP levels to the model consisting of known risk factors for AF and cardiovascular disease. These findings suggest that serum NT-proBNP is a novel biomarker for risk stratification to estimate a future risk of developing AF in a primary care setting. Further studies are needed to clarify the efficacy and effectiveness of risk stratifications using serum NT-proBNP levels for the prevention of incident AF and AF-related complications.

Funding source

This study was supported in part by Grants-in-Aid for Scientific Research (A) (JP16H02692), (B) (JP16H05850, JP17H04126, and JP18H02737), and (C) (JP17K09114, JP17K09113, JP17K01853, JP18K07565, JP18K09412,and JP19K07890), and Grants-in-Aid for Early-Career Scientists (JP18K17925 and JP18K17382) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; by Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare of Japan (H29-Junkankitou-Ippan-003 and H30-Shokuhin-[Sitei]-005); and by the Japan Agency for Medical Research and Development (JP19dk0207025, JP19ek0210082, JP19ek0210083, JP19km0405202, JP19ek0210080, and JP19fk0108075).

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

The authors thank the residents of the town of Hisayama for their participation in the survey and the staff of the Division of Health and Welfare of Hisayama for their cooperation with this study. The statistical analyses were carried out using the computer resource offered under the category of General Projects by Research Institute for Information Technology, Kyushu University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.06.018.

References

[1] A. Odutayo, C.X. Wong, A.J. Hsiao, S. Hopewell, D.G. Altman, C.A. Emdin, Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis, BMJ 354 (2016) i4482, https://doi.org/10.1136/bmj.i4482.
[2] S.S. Chugh, R. Havmoeller, K. Narayanan, et al., Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study, Circulation 129 (2014) 837–847, https://doi.org/10.1161/CIRCULATIONAHA.113.005119.
[3] X. Du, J. Dong, C. Ma, Is atrial fibrillation a preventable disease? J. Am. Coll. Cardiol. 69 (2017) 1968–1982, https://doi.org/10.1016/j.jacc.2017.02.020.
[4] R.R. Huxley, F.L. Lopez, A.R. Folsom, S.K. Agarwal, L.R. Loehr, E.Z. Soliman, R. Maclehose, S. Konety, A. Alonso, Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, Circulation 123 (2011) 1501–1508, https://doi.org/10.1161/CIRCULATIONAHA.110.009035.
[5] P. Kirchhof, S. Benussi, D. Kotecha, et al., 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962, https://doi.org/10.1093/eurheartj/ehw210.
[6] P. Ponikowski, A.A. Voors, S.D. Anker, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (2016) 2129–2200, https://doi.org/10.1093/eurheartj/ehw128.
[7] S.L. Chow, A.S. Maisel, I. Anand, et al., Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association, Circulation 135 (2017) e1054–e1091, https://doi.org/10.1161/CIR.0000000000000490.
[8] H. Tsutsui, M. Isobe, H. Ito, et al., JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure- digest version, Circ. J. 83 (2019) 2084–2184, https://doi.org/10.1253/circj.CJ-19-0342.
[9] T.J. Wang, M.G. Larson, D. Levy, et al., Plasma natriuretic peptide levels and the risk of cardiovascular events and death, N. Engl. J. Med. 350 (2004) 655–663, https://doi.org/10.1056/NEJMoa031994.
[10] P. Willeit, S. Kaptoge, P. Welsh, et al., Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis, Lancet Diabetes Endocrinol. 4 (2016) 840–849, https://doi.org/10.1016/S2213-8587(16)30196-6.
[11] Y. Doi, T. Ninomiya, J. Hata, et al., N-terminal pro-brain natriuretic peptide and risk of cardiovascular events in a Japanese community: the Hisayama Study, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 2997–3003, https://doi.org/10.1161/ATVBAHA.111.223669.
[12] F.W. Asselbergs, M.P. van den Berg, S.J. Bakker, et al., N-terminal pro B-type natriuretic peptide levels predict newly detected atrial fibrillation in a population-based cohort, Neth. Hear. J. 16 (2008) 73–78, https://doi.org/10.1007/bf03086122.
[13] K.K. Patton, P.T. Ellinor, S.R. Heckbert, et al., N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study, Circulation 120 (2009) 1768–1774, https://doi.org/10.1161/CIRCULATIONAHA.109.873265.
[14] S. Kurl, M. Ala-Kopsala, H. Ruskoaho, et al., Plasma N-terminal fragments of natriuretic peptides predict the risk of stroke and atrial fibrillation in men, Heart 95 (2009) 1067–1071, https://doi.org/10.1136/hrt.2008.150342.
[15] J.G. Smith, C. Newton-Cheh, P. Almgren, et al., Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation, J. Am. Coll. Cardiol. 56 (2010) 1712–1719, https://doi.org/10.1016/j.jacc.2010.05.049.
[16] K.K. Patton, S.R. Heckbert, A. Alonso, et al., N-terminal pro-B-type natriuretic peptide as a predictor of incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis: the effects of age, sex and ethnicity, Heart 99 (2013) 1832–1836, https://doi.org/10.1136/heartjnl-2013-304724.
[17] E. Svennberg, B. Lindahl, L. Berglund, et al., NT-proBNP is a powerful predictor for incident atrial fibrillation: validation of a multimarker approach, Int. J. Cardiol. 223 (2016) 74–81, https://doi.org/10.1016/j.ijcard.2016.08.001.
[18] P. Kumarathurai, M.R. Mouridsen, N. Mattsson, et al., Atrial ectopy and N-terminal pro-B-type natriuretic peptide as predictors of atrial fibrillation: a population-based cohort study, Europace 19 (2017) 364–370, https://doi.org/10.1093/europace/euw017.

[19] K. Kara, M.H. Geisel, S. Mohlenkamp, et al., B-type natriuretic peptide for incident atrial fibrillation: the Heinz Nixdorf Recall Study, J. Cardiol. 65 (2015) 453–458, https://doi.org/10.1016/j.jjcc.2014.08.003.
[20] R.B. Schnabel, M.G. Larson, J.F. Yamamoto, et al., Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community, Circulation 121 (2010) 200–207, https://doi.org/10.1161/CIRCULATIONAHA.109.882241.
[21] M.F. Sinner, K.A. Stepas, C.B. Moser, et al., B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies, Europace 16 (2014) 1426–1433, https://doi.org/10.1093/europace/euu175.
[22] Y. Li, D. Pastori, Y. Guo, Y. Wang, G.Y.H. Lip, Risk factors for new-onset atrial fibrillation: a focus on Asian populations, Int. J. Cardiol. 261 (2018) 92–98, https://doi.org/10.1016/j.ijcard.2018.02.051.
[23] T. Ohira, H. Iso, Cardiovascular disease epidemiology in Asia: an overview, Circ. J. 77 (2013) 1646–1652, https://doi.org/10.1253/circj.cj-13-0702.
[24] Y. Kokubo, M. Watanabe, A. Higashiyama, Y.M. Nakao, K. Kusano, Y. Miyamoto, Development of a basic risk score for incident atrial fibrillation in a Japanese general population: the Suita Study, Circ. J. 81 (2017) 1580–1588, https://doi.org/10.1253/circj.CJ-17-0277.
[25] T. Ninomiya, Japanese legacy cohort studies: the Hisayama Study, J. Epidemiol. 28 (2018) 444–451, https://doi.org/10.2188/jea.JE20180150.
[26] J. Hata, T. Ninomiya, Y. Hirakawa, et al., Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961–2009), Circulation 128 (2013) 1198–1205, https://doi.org/10.1161/CIRCULATIONAHA.113.002424.
[27] T. Nagata, T. Ohara, J. Hata, et al., NT-proBNP and risk of dementia in a general Japanese elderly population: the Hisayama Study, J. Am. Heart Assoc. 8 (2019), e011652. https://doi.org/10.1161/JAHA.118.011652.
[28] R.B. Schnabel, X. Yin, P. Gona, et al., 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study, Lancet 386 (2015) 154–162, https://doi.org/10.1016/S0140-6736(14)61774-8.
[29] K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, Diabet. Med. 15 (1998) 539–553, https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S.
[30] M. Horio, E. Imai, Y. Yasuda, T. Watanabe, S. Matsuo, Modification of the CKD Epidemiology Collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates, Am. J. Kidney Dis. 56 (2010) 32–38, https://doi.org/10.1053/j.ajkd.2010.02.344.
[31] SAS/STAT 14.3 User ' s Guide CTPP. , SAS Institute Inc, Cary, NC, 2017 7139–7145 , Available at https://support.sas.com/documentation/onlinedoc/stat/143/phreg.pdf (Accessed October 9, 2019).
[32] M.J. Pencina, R.B.S. D'Agostino, L. Song, Quantifying discrimination of Framingham risk functions with different survival C statistics, Stat. Med. 31 (2012) 1543–1553, https://doi.org/10.1002/sim.4508.
[33] R.B. Newson, Comparing the predictive powers of survival models using Harrell's C or Somers, D, Stata J. 10 (2010) 339–358.
[34] M.J. Pencina, R.B.S. D'Agostino, R.B.J. D'Agostino, R.S. Vasan, Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond, Stat. Med. 27 (2008) 112–157, https://doi.org/10.1002/sim.2929.
[35] M.J. Pencina, R.B.S. D'Agostino, E.W. Steyerberg, Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers, Stat. Med. 30 (2011) 11–21, https://doi.org/10.1002/sim.4085.
[36] Y.G. Li, D. Pastori, A. Farcomeni, et al., A simple clinical risk score (C_2HEST) for predicting incident atrial fibrillation in Asian subjects: derivation in 471,446 Chinese subjects, with internal validation and external application in 451,199 Korean subjects, Chest 155 (2019) 510–518, https://doi.org/10.1016/j.chest.2018.09.011.
[37] K. Suenari, T.F. Chao, C.J. Liu, Y. Kihara, T.J. Chen, S.A. Chen, Usefulness of HATCH score in the prediction of new-onset atrial fibrillation for Asians, Medicine 96 (2017), e5597. https://doi.org/10.1097/MD.0000000000005597.
[38] R. Hamada, S. Muto, Simple risk model and score for predicting of incident atrial fibrillation in Japanese, J. Cardiol. 73 (2019) 65–72, https://doi.org/10.1016/j.jjcc.2018.06.005.
[39] Y. Kokubo, M. Watanabe, A. Higashiyama, Y.M. Nakao, K. Kusano, Y. Miyamoto, Development of a basic risk score for incident atrial fibrillation in a Japanese general population: the Suita Study, Circ. J. 81 (2017) 1580–1588, https://doi.org/10.1253/circj.CJ-17-0277.
[40] N.J. Perkins, E.F. Schisterman, The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve, Am. J. Epidemiol. 163 (2006) 670–675, https://doi.org/10.1093/aje/kwj063.
[41] U. Mutlu, M.A. Ikram, A. Hofman, P.T. de Jong, C.C. Klaver, M.K. Ikram, N-terminal pro-b-type natriuretic peptide is related to retinal microvascular damage: the Rotterdam Study, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 1698–1702, https://doi.org/10.1161/ATVBAHA.116.307545.
[42] C. Luers, R. Wachter, S. Kleta, et al., Natriuretic peptides in the detection of preclinical diastolic or systolic dysfunction, Clin. Res. Cardiol. 99 (2010) 217–226, https://doi.org/10.1007/s00392-009-0108-z.
[43] P.M. Okin, D.A. Hille, A.C. Larstorp, et al., Effect of lower on-treatment systolic blood pressure on the risk of atrial fibrillation in hypertensive patients, Hypertension 66 (2015) 368–373, https://doi.org/10.1161/HYPERTENSIONAHA.115.05728.
[44] J. Engdahl, E. Svennberg, L. Friberg, et al., Stepwise mass screening for atrial fibrillation using N-terminal pro b-type natriuretic peptide: the STROKESTOP II study design, Europace 19 (2017) 297–302, https://doi.org/10.1093/europace/euw319.
[45] M.P. Turakhia, J. Shafrin, K. Bognar, et al., Estimated prevalence of undiagnosed atrial fibrillation in the United States, PLoS One 13 (2018), e0195088. https://doi.org/10.1371/journal.pone.0195088.
[46] T. Sanna, H.C. Diener, R.S. Passman, et al., Cryptogenic stroke and underlying atrial fibrillation, N. Engl. J. Med. 370 (2014) 2478–2486, https://doi.org/10.1056/NEJMoa1313600.
[47] K. Kemp Gudmundsdottir, T. Fredriksson, E. Svennberg, et al., Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II Study, Europace 22 (2020) 24–32, https://doi.org/10.1093/europace/euz255.
[48] F. Al-Khalili, K. Kemp-Gudmundsdottir, E. Svennberg, et al., Clinical and echocardiographic characteristics of individuals aged 75/76 years old with screening-detected elevated NT-proBNP levels, Open Heart 7 (2020), e001200. https://doi.org/10.1136/openhrt-2019-001200.
[49] R.M. Groves, Survey Errors and Survey Costs, Wiley, New York, 1989.
[50] J.D. Kasper, S. Shapiro, J.M. Guralnik, K.J. Bandeen-Roche, L.P. Fried, Designing a community study of moderately to severely disabled older women: the Women's Health and Aging Study, Ann. Epidemiol. 9 (1999) 498–507, https://doi.org/10.1016/s1047-2797(99)00026-5.