Prognostic Value of Serum N-Terminal Pro-Brain Natriuretic Peptide Level over Heart Failure for Stroke Events and Deaths in Patients with Atrial Fibrillation

A SAKURA AF Registry Sub-Study

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Summary
Atrial fibrillation (AF) and heart failure (HF) often coexist. The aims of this study were to explore the factors associated with the serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), and the association between prognosis and a history of HF or the serum NT-proBNP level in Japanese patients with AF.

The present sub-study was based on the SAKURA AF Registry, a Japanese multicenter observational registry that included 3267 AF patients (median follow-up period: 39 months). All the patients were receiving warfarin or any of four direct oral anticoagulants. Serum NT-proBNP levels were available for 2417 patients, and the median value was 508 (interquartile range 202-1095) pg/mL at the time of enrollment. Log NT-proBNP was associated with non-paroxysmal AF, creatinine clearance > 60 mL/minute, history of HF and ischemic heart disease, antiarrhythmic drug use, anemia, being elderly female, and history of AF ablation. The relative risk of adverse clinical events, except major bleeding, was significantly higher in the highest NT-proBNP quartile as compared to the lowest quartile (adjusted hazard ratios: 2.87 for death, 2.39 for stroke), but a history of HF was associated only with a higher incidence of all-cause death.

Concomitant HF was associated with a higher mortality, but the high NT-proBNP was associated with higher mortality and stroke events. In Japanese AF patients receiving anticoagulant treatment, high serum NT-proBNP levels predict the risk for both stroke events and deaths, and intensive follow-up is needed in such patients.

Key words: Adverse clinical events, Japanese

Atrial fibrillation (AF) and heart failure (HF) are common cardiac conditions that often coexist and predispose to each other, and both are associated with the risk of adverse clinical events, such as stroke, cardiovascular events, and death. Since 2007, Japan has been a super-aging society, and accordingly, the incidences of both AF and HF are increasing. The number of patients with AF in Japan is expected to reach over 1 million,15 and that with HF to reach over 1.3 million by the year 2030.15 In the Framingham Heart Study, 20% of patients with new-onset AF had prevalent or concurrent HF, and 45% of patients with new-onset HF had prevalent or
concurrent AF. For the AF patients who were not receiving anticoagulation therapy, HF is widely known as a risk factor for stroke, and is a major component of the CHADS: score. The B-type brain natriuretic peptide (BNP) and the N-terminal pro-BNP (NT-proBNP) are neurohormonal peptides secreted from the myocytes of both the atria and ventricles, and their secretion is increased under a variety of conditions, such as advanced age and presence of renal dysfunction, AF, and/or HF. The levels of these peptides are widely measured for clinical management and risk stratification of patients with HF. Hijazi, et al. suggested that measurement of the serum NT-proBNP levels is useful to estimate the risk of adverse clinical events in patients with AF receiving anticoagulant treatment. In regard to studies based on the Japanese registry alone, Hayashi, et al. reported the usefulness of measuring serum BNP levels for stratification of patients for the risk of stroke and death in a total of 1013 AF patients, but 127 (12.5%) patients had not received anticoagulants. The aim of this study was as follows: to investigate adverse clinical events in Japanese patients with AF and/or HF receiving anticoagulant treatment, to identify factors associated with the serum levels of NT-proBNP in Japanese patients with AF, and to clarify the associations between the serum NT-proBNP levels and adverse clinical events in Japanese patients with AF.

**Methods**

Our investigation was conducted as a sub-study of the SAKURA AF Registry (UMIN000014420), which was set up to support multicenter, prospective, observational research by tracking clinical events in patients with AF for at least 2 years and up to 4 years after their enrollment in the registry. A total of 3267 patients were enrolled from 63 institutions (2 cardiovascular centers, 20 affiliated hospitals or community hospitals, and 41 private clinics) in the Tokyo area between September 2013 and December 2015. Patients were eligible for inclusion if they were ≥ 20 years old, had been diagnosed as having nonvalvular AF, and were being initiated/had already been initiated on oral anticoagulant therapy for stroke prevention. All the patients provided written informed consent for inclusion in the Registry. Patient data for the registry were collected by means of a website and web-based registration system created for the Registry, through which relevant clinical data, such as the body height, body weight, blood pressure, presence/absence of comorbidities, including a history of HF, medication history, and laboratory test results, including serum BNP and NT-proBNP levels, were collected. Paroxysmal AF was defined as AF lasting for up to 7 days. History of HF was defined as a diagnosis of HF prior to enrollment of the patient in the Registry. Creatinine clearance (CrCl) was estimated by the Cockcroft-Gault formula: CrCl [mL/minute] = [140 – age (years)] × [weight (kg)] / [72 × SCr (mg/dL)] × 0.85 (if female), where SCr is the serum creatinine level. All BNP data were converted to NT-proBNP using the following formula: NT-proBNP = BNP1.341 − 15.10. We also determined the incidences of death from any cause, stroke (ischemic stroke, hemorrhagic stroke, or transient ischemic attack/systemic embolism (SE), and major bleeding. A death was classified as vascular, nonvascular, or of unknown cause. Vascular death included sudden cardiac death, HF, myocardial infarction, stroke/SE, and extracranial bleeding. Nonvascular death included malignancies, respiratory infections, other infections, and all other causes of death. Major bleeding was defined as a reduction of the blood hemoglobin concentration by at least 2 g/dL, need for at least two units of blood transfusion, and/or symptomatic bleeding in any critical area or organ. Net clinical events included death, stroke/SE, and major bleeding. Analysis of the data from the Registry was conducted with the approval of the Nihon University School of Medicine Itabashi Hospital institutional review board and the review boards of the hospitals at which the patients were receiving treatment.

**Statistical analysis:** Continuous variables are shown in median values (25th, 75th percentiles), and categorical variables are shown in numbers and percentages. Differences in the categorical variables among groups were analyzed by the chi-squared test, while those in the continuous variables were analyzed by Mann-Whitney’s U or Kruskal-Wallis test, as appropriate. Kaplan-Meier curves were drawn for the time-to-events, which were compared by the log-rank test. Multivariable regression analysis was performed to identify the main factors associated with the log NT-proBNP; as the NT-proBNP data were not normally distributed, log NT-proBNP was used for the multivariable regression analysis. To examine the associations between the serum NT-proBNP levels and the development of adverse clinical events, we divided the subjects into four quartiles of the serum NT-proBNP levels. A Cox proportional hazards model was used to assess the associations of the serum NT-proBNP levels with the risk of adverse clinical events, and the results are shown as hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable regression analysis was performed using components of the CHADS2-VASc score (congestive HF, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and sex category), and factors that were identified as being associated with the serum NT-proBNP in the univariable analyses (P < 0.05). These factors were also used in the multivariable Cox regression analysis. In addition, to assess the best cutoff value of the serum NT-proBNP for predicting each adverse clinical event, receiver-operating characteristic (ROC) curves were drawn and the areas under the curve (AUCs) were calculated. All statistical analyses were performed with the JMP 14.1.0 (SAS Institute Inc., Cary, NC, USA) or EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided P-value of < 0.05 was considered as being indicative of statistical significance.

**Results**

Of the 3267 patients enrolled in the SAKURA AF Registry, 30 were lost to follow-up, all of whom were re-
significantly associated with the CHA2DS2-VASC score, and NT-proBNP quartiles are shown in Table II. Univariate statistics of the overall subject population and of each of the 508.2 [IQR 202.0-1094.8] pg/mL. The baseline character-

median serum NT-proBNP level in these patients was

been recorded for 2417 of the total of 3267 enrollees. The baseline character-

istics of the overall subject population and of each of the patients with and without a history of HF.

significant differences in the all-cause death rate (P = 0.721), there were significant differences in the all-cause death rate (P < 0.0001) and net clinical event rate (P < 0.0001) between the patients with and without a history of HF.

The baseline characteristics of the subjects according to the presence/absence of a history of HF are shown in Table I. The median follow-up period was 39.3 (inter-

quartile range [IQR] 28.5-43.6) months. The Kaplan-

Meier curves for all-cause death, stroke/SE, major bleeding, and net clinical events for the patients with and without a history of HF are shown in Figure 1. Although there was no significant difference in the incidence of stroke/SE (P = 0.693) or major bleeding (P = 0.721), there were significant differences in the all-cause death rate (P < 0.0001) and net clinical event rate (P < 0.0001) between the patients with and without a history of HF.

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Figure 1. Kaplan-Meier curves for all-cause death, stroke/systemic embolism (SE), major bleeding, and net clinical events in patients classified according to the presence/absence of a history of heart failure. Net clinical events included: death, stroke/SE, major bleeding.

29.4-43.9) months, and the total person-years of this cohort was 7265. During the follow-up period, 155 patients (2.1 per 100 person-years) died; stroke/SE occurred in 107 patients (1.5 per 100 person-years), major bleeding in 93 patients (1.3 per 100 person-years), and net clinical events in 285 patients (3.9 per 100 person-years). Of the total 155 deaths, 60 were classified as a vascular death, 72 as a nonvascular death, and 23 as an unknown death. Of the 60 vascular deaths, 24 were due to HF. Kaplan-Meier curves for these adverse clinical events were drawn for each of the NT-proBNP quartiles and are shown in Figure 2. Patients with elevated serum NT-proBNP levels at the time of enrollment (baseline) showed a low event-free survival rate, including all adverse clinical events except for major bleeding (P = 0.7; Figure 2). The number of adverse clinical events in each NT-proBNP quartile, and the results of the Cox proportional hazard analysis are shown in Table IV. The risk of death was shown to be significantly high in patients in the highest NT-proBNP quartile as compared to that in patients in the lowest NT-proBNP quartile (adjusted HR 2.87, 95% CI 1.52-5.43; P = 0.0011); similar observations were made for the risk of stroke/SE (adjusted HR 2.39, 95% CI 1.51-4.95; P = 0.0193) and net clinical events (adjusted HR 2.22, 95% CI 1.43-3.46; P = 0.0004). In contrast, there were no differences in the risk of major bleeding among the NT-proBNP quartiles (Table IV). The adjusted HR of patients with paroxysmal AF compared to those with nonparoxysmal AF was not significantly different in each adverse clinical event (adjusted HR 1.27 [95% CI 0.83-1.93; P = 0.2935] for death; adjusted HR 1.22 [95% CI 0.73-2.03; P = 0.4399] for stroke/SE; adjusted HR 0.91 [95% CI 0.52-1.57; P = 0.7242] for major bleeding; and adjusted HR 1.16 [95% CI 0.85-1.58; P = 0.3487] for net clinical events).

Comparison of the diagnostic performance between serum NT-proBNP and the CHADS2 or CHA2DS2-VASC score for death and stroke/SE: By means of ROC analy-
### Patients Characteristics According to NT-proBNP Quartiles

| Number of patients | NT-proBNP (pg/mL) |
|--------------------|-------------------|
| Overall            | <202 pg/mL | 202-508/mL | 509-1095 mL | >1095 pg/mL | P-value |
| N                  | 2417        | 604        | 605         | 604         | 604    |
| Age (years)        |             |            |             |             |        |
| Overall            | 72.0 [66.0, 79.0] | 69.0 [62.0, 75.0] | 72.0 [66.0, 78.0] | 73.0 [67.0, 79.0] | 76.0 [70.0, 82.0] | < 0.001 |
| Age ≥ 75 years     | 983 (40.7) | 157 (26.0) | 240 (39.7) | 251 (41.6) | 335 (55.5) | < 0.001 |
| Female sex         | 640 (26.5) | 132 (21.9) | 148 (24.5) | 156 (25.8) | 204 (33.8) | < 0.001 |
| Body height (cm)   | 164.0 [156.0, 169.5] | 165.0 [158.0, 171.0] | 165.0 [157.0, 170.0] | 164.0 [157.0, 169.0] | 162.0 [152.0, 167.5] | < 0.001 |
| Body weight (kg)   | 63.5 [55.2, 71.6] | 65.4 [57.1, 73.0] | 64.5 [57.0, 73.0] | 64.0 [56.5, 71.0] | 60.0 [50.0, 68.0] | < 0.001 |
| BMI (kg/m²)        | 23.8 [21.8, 26.0] | 24.0 [22.0, 26.0] | 24.1 [22.0, 26.4] | 23.9 [22.0, 26.0] | 23.2 [21.1, 25.5] | < 0.001 |
| Systolic BP (mmHg) | 126.0 [118.0, 137.0] | 129.0 [120.0, 138.0] | 126.0 [117.0, 138.0] | 126.0 [116.0, 136.0] | 125.0 [115.8, 136.0] | 0.005 |
| Diastolic BP (mmHg)| 74.0 [68.0, 82.0] | 74.0 [69.0, 82.0] | 74.0 [68.0, 81.0] | 74.0 [68.0, 82.0] | 70.5 [66.0, 80.0] | 0.003 |
| Heart rate (beats/minute) | 72.0 [65.0, 83.0] | 70.0 [62.8, 78.0] | 72.0 [64.0, 82.0] | 76.0 [68.0, 86.0] | 75.0 [67.8, 85.0] | < 0.001 |
| Paroxysmal AF      | 886 (36.7) | 479 (76.0) | 216 (35.7) | 113 (18.7) | 98 (16.2) | < 0.001 |
| CHADS₂ score       | 2.0 [1.0, 3.0] | 1.0 [1.0, 2.0] | 2.0 [1.0, 3.0] | 2.0 [1.0, 3.0] | 2.0 [1.0, 3.0] | < 0.001 |
| CHA₂DS₂-VASc score | 3.0 [2.0, 4.0] | 2.0 [1.0, 3.0] | 3.0 [2.0, 4.0] | 3.0 [2.0, 4.0] | 4.0 [3.0, 4.0] | < 0.001 |

**Medical History**

- **Hypertension**: 1747 (72.3) | 424 (70.2) | 343 (72.6) | 451 (74.7) | 433 (71.7) | 0.368
- **Dyslipidemia**: 975 (40.3) | 262 (43.4) | 260 (43.0) | 249 (41.2) | 204 (33.8) | 0.002
- **Diabetes**: 568 (23.5) | 120 (19.9) | 146 (24.1) | 161 (26.7) | 141 (23.3) | 0.048
- **Current smoker**: 301 (12.5) | 70 (11.6) | 75 (12.4) | 80 (13.2) | 76 (12.6) | 0.856
- **Heart failure**: 625 (25.9) | 64 (10.6) | 139 (23.0) | 163 (27.0) | 259 (42.9) | < 0.001
- **Stroke/TIA**: 275 (11.4) | 54 (8.9) | 71 (11.7) | 75 (12.4) | 75 (12.4) | 0.177
- **Ischemic heart disease**: 243 (10.1) | 46 (7.6) | 57 (9.4) | 70 (11.6) | 70 (11.6) | 0.061
- **AF ablation**: 221 (9.1) | 124 (20.5) | 38 (6.3) | 31 (5.1) | 28 (4.6) | < 0.001
- **Antiplatelet use**: 392 (16.2) | 83 (13.7) | 102 (16.9) | 104 (17.2) | 103 (17.1) | 0.3
- **DOAC use**: 1221 (50.5) | 349 (57.8) | 279 (46.1) | 279 (46.2) | 314 (52.0) | < 0.001
- **Warfarin use**: 1196 (49.5) | 255 (42.2) | 326 (53.9) | 325 (53.8) | 290 (48.0) | < 0.001
- **New OAC use (OAC therapy duration < 3 months)**: 474 (19.6) | 137 (22.7) | 106 (17.5) | 107 (17.7) | 124 (20.5) | 0.072
- **Antiarrhythmic drug class I**: 274 (11.3) | 148 (24.5) | 69 (11.4) | 34 (5.6) | 23 (3.8) | < 0.001
- **β-blocker use**: 1165 (48.2) | 202 (33.4) | 278 (46.0) | 316 (52.3) | 369 (61.1) | < 0.001
- **Amiodarone use**: 28 (1.2) | 7 (1.2) | 6 (1.0) | 4 (0.7) | 11 (1.8) | 0.288
- **Bepridil use**: 250 (10.3) | 121 (20.0) | 67 (11.1) | 34 (5.6) | 28 (4.6) | < 0.001
- **Hemoglobin (mg/dL)**: 138 [126.0, 149.0] | 140 [129.0, 150.0] | 140 [126.0, 151.0] | 139 [129.0, 150.0] | 133 [120.0, 145.0] | < 0.001
- **CCR (mL/minute)**: 64.7 [50.1, 82.1] | 74.8 [60.2, 93.0] | 67.1 [53.5, 84.0] | 65.1 [51.6, 81.8] | 50.9 [38.0, 66.0] | < 0.001
- **NT-proBNP (pg/mL)**: 508.2 [202.0, 1094.8] | 88.0 [49.9, 137.9] | 344.6 [273.4, 423.5] | 744.2 [619.9, 895.6] | 1701.0 [1351.2, 2538.8] | < 0.001

**Abbreviations as in Table I.**
sis, the best cutoff value of the serum NT-proBNP (and AUC) for predicting all-cause death was 1069 pg/mL (AUC = 0.68 [95% CI 0.63-0.72]); the cutoff value of the CHADS2 score was 2 (AUC = 0.61 [95% CI 0.56-0.65]), and that of the CHA2DS2-VASc score was 4 (AUC = 0.63 [95% CI 0.58-0.67]). For predicting all-cause death, the AUC of serum NT-proBNP was significantly larger than that of the CHADS2 score (P = 0.0142) and larger than that of the CHA2DS2-VASc score (P = 0.0599; Figure 3). For predicting stroke/SE, comparison of the AUCs for serum NT-proBNP and the CHADS2 score, and for serum NT-proBNP and the CHADS2-VASc score showed no significant differences (P = 0.49 and P = 0.424, respectively; Figure 4).

**Discussion**

There were three major findings of this study: 1) patients with a history of HF had a higher rate of mortality events, while those with high serum NT-proBNP had a higher rate of mortality as well as stroke events. Neither of these factors was associated with the risk of major bleeding; 2) elevated log NT-proBNP was associated with non-paroxysmal AF, CrCl < 60 mL/minute, history of HF and ischemic heart disease, female sex, and amiodarone use. It has been reported that the serum NT-proBNP value is associated with the AF burden, and that the serum NT-proBNP decreases after successful AF ablation. Therefore, the positive correlation with non-paroxysmal AF and the negative correlation with AF ablation of the serum NT-proBNP are easy to understand. The negative association between class I antiarrhythmic drug use and the log NT-proBNP may be a result of the drug being used more often in patients with paroxysmal AF. In this study, the serum NT-proBNP was strongly affected by renal dysfunction (CrCl < 60 mL/minute). In general, renal function in AF patients deteriorates rather quickly as compared to the general population. In the patients enrolled in the SAKURA AF Registry, the estimated glomerular filtration rate declined by 1.07 mL/minute/1.73 m² annually, and this decline was especially obvious in patients with initially preserved renal function. Therefore, renal function should be managed more carefully in patients with AF. In addition, beta-blocker and amiodarone use were positively associated with the log NT-proBNP. The Japanese Circulation Society guideline recommends beta-blocker therapy for heart rate control in AF patients, and a half of all the patients in this registry were receiving beta-blockers. Although we indicated that beta-blocker and amiodarone use were positively correlated with the log NT-proBNP, this might be explained by patients requiring these agents having high NT-proBNP values at the baseline.

**Association among history of HF, NT-proBNP levels, and clinical adverse events:** HF is a widely known risk

| Variables                  | β-value | SE   | P-value |
|----------------------------|---------|------|---------|
| Female                     | 0.041*  | 0.0110* | 0.0190* |
| Age ≥ 75 years             | 0.089*  | 0.0111* | < 0.0001* |
| BMI < 18.5 kg/m²           | 0.024   | 0.0235 | 0.1569  |
| Non-paroxysmal AF (versus paroxysmal) | 0.384*  | 0.0112* | < 0.0001* |
| Hypertension               | 0.002   | 0.0106 | 0.8878  |
| Diabetes                   | -0.009  | 0.0112 | 0.5903  |
| History of heart failure   | 0.088*  | 0.0114* | < 0.0001* |
| History of stroke/TIA      | -0.004  | 0.0149 | 0.8132  |
| History of ischemic heart disease | 0.052*  | 0.0177* | 0.0063* |
| History of AF ablation     | -0.060* | 0.0176* | 0.0010* |
| DOAC use (versus warfarin) | 0.000   | 0.0094 | 0.9925  |
| Antiplatelet drug use       | -0.016  | 0.0146 | 0.4017  |
| Antiarrhythmic drug class I use | -0.053*  | 0.0160* | 0.0035* |
| β-blocker use              | 0.141*  | 0.0097* | < 0.0001* |
| Amiodarone use             | 0.039*  | 0.0434* | 0.0188* |
| Bepridil use               | -0.029  | 0.0165 | 0.1005  |
| Hb < 12 g/dL               | 0.069*  | 0.0138* | < 0.0001* |
| CrCl < 60 mL/minute        | 0.193*  | 0.0113* | < 0.0001* |

*Statistically significant results (P < 0.05). Abbreviations as in Table I.

**Table III.** Multivariable Regression Analysis for Log NT-ProBNP.
factor for stroke/thromboembolism, and is a major component of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. These risk scores were derived from the data of AF patients in Western countries who were not under anticoagulant therapy, and had a high incidence of ischemic stroke (4.4 per 100 person-years). Nonetheless, we did not find any association between a history of HF and stroke/SE events. This lack of association between a history of HF and stroke/SE events in our study is possibly due to the different incidences of stroke events between Western countries and Japan. In fact, in a Japanese study conducted in AF patients not under anticoagulant therapy (pooled analysis of J-RHYTHM registry, Fushimi registry, and Shinken Database), a low incidence of ischemic stroke was shown (1.3 per 100 person-years), and HF was not identified as an independent risk factor for ischemic stroke by Cox regression analysis (HR 0.86, 95% CI 0.45-1.65).

These differences in the incidence rate and risk factors may be derived from differences in the healthcare system or racial differences. Another factor that could influence the results is whether the study subjects are under anticoagulant therapy or not. In the SAKURA AF Registry, all patients were under anticoagulant therapy. In this study, a history of HF was associated with all-cause death, but not with the risk of stroke or major bleeding. These findings are consistent with the results of a sub-analysis of the ROCKET trial.

While we found no association between a history of HF and stroke/SE events in this study, the serum NT-proBNP level was associated with the risk of stroke/SE. Our finding of a significant difference in the risk for stroke/SE and death between the lowest (< 202 pg/mL) and highest (> 1095 pg/mL) NT-proBNP quartiles was consistent with the results of two large trials conducted in

Figure 2. Kaplan-Meier curves for all-cause death, stroke/systemic embolism (SE), major bleeding, and net clinical events in each N-terminal pro-brain natriuretic peptide quartile. Net clinical events included: death, stroke/SE, major bleeding.
The Cox model was adjusted for sex, age (≥75 years), BMI (<18.5 kg/m²), AF type, hypertension, diabetes, history of heart failure, history of stroke/TIA, history of ischemic heart disease, history of AF ablation, DOAC use, antiplatelet use, antiarrhythmic drug use, anemia (hemoglobin <12 g/dL), and impaired renal function (CrCl <60 mL/minute). *Mean P<0.05. Abbreviations as in Table I.

AF patients receiving anticoagulant treatment, namely the RE-LY⁷ and ARISTOTLE trials.⁸ Similarly, in the Hokuriku-plus AF registry,⁹ a high BNP level (≥170 pg/mL) was significantly associated with a risk of thromboembolism (adjusted HR 3.11). In the present study, although a strong positive correlation was found between log NT-proBNP values and the AF type (non-paroxysmal AF versus paroxysmal AF), the risk of all adverse clinical events did not differ between the AF types. The prognostic performance of serum NT-proBNP for stroke/SE events was comparable to that of the CHADS₃ or CHA₂DS₂-VASC scores, although it was weak for all the three factors (AUC = 0.57 for NT-proBNP, AUC = 0.59 for CHADS₃, and AUC = 0.60 for CHA₂DS₂-VASC). Moreover, the AUC of NT-proBNP for predicting all-cause death was larger than that for predicting stroke/SE (AUC = 0.68 for death, AUC = 0.57 for stroke/SE). Importantly, the cutoff value of NT-proBNP for predicting death was >1069 pg/mL and the NT-proBNP level in the highest quartile was >1095 pg/mL. Therefore, the findings of this
Figure 4. Receiver-operating characteristic curve analysis for the risk of stroke/SE. Comparison between N-terminal pro-brain natriuretic peptide (NT-proBNP) and the CHADS\textsubscript{5} score (A) and between NT-proBNP and the CHA\textsubscript{2}DS\textsubscript{2}-VASc score (B).

study suggest that measurement of serum NT-proBNP is more useful to estimate the risk of death than to estimate the risk of stroke events, although serum NT-proBNP levels of more than 1000 pg/mL would serve as a surrogate marker for predicting a high risk of death and stroke in AF patients under anticoagulant therapy.

**Limitations:** Our study results should be interpreted in light of the study limitations. First, the study was conducted as a retrospective analysis of prospectively collected data; therefore, we were not able to obtain the serum BNP or NT-proBNP data for all patients enrolled in this study. Second, for analysis of the serum NT-proBNP, data on the BNP were obtained for almost half the patients and the data were converted to NT-proBNP values using the formula mentioned above. However, we obtained the same results even when we excluded patients in whom the BNP data were converted to NT-proBNP data. For example, the median NT-proBNP was 552.0 (IQR 221.8-1070.0) pg/mL, and a significant difference in the risk of net adverse clinical events was observed between the lowest and highest NT-proBNP quartiles (adjusted HR 2.00). Therefore, we believe that our findings suggest that measurement of serum NT-proBNP could contribute to clinical management of AF patients receiving anticoagulant treatment. Third, HF was defined differently between the conventional CHADS\textsubscript{2} score\textsuperscript{4) and large trials of DOAC\textsuperscript{22,23)) i.e., recent exacerbation of HF in CHADS\textsubscript{2} score,\textsuperscript{4) HF or a left ventricular ejection fraction (LVEF) of 35% or less in the ROCKET trial,\textsuperscript{22) and symptomatic HF within the previous 3 months or a LVEF of 40% or less in the ARISTOTLE trial.\textsuperscript{23) Unfortunately, we did not have data on the LVEF, symptoms, New York Heart Association functional class, or the medical therapy for HF in our study. We defined a history of HF as a diagnosis of HF prior to enrollment; however, this definition may not fully reflect the association between HF and stroke, and the correlation between HF and NT-proBNP. Finally, only selected institutions within a limited geographical area in Japan participated in the SAKURA AF Registry, and it would be difficult to assume that our findings can be generalized to the entire population of AF patients in Japan. It should be noted, however, that patient selection and regional enrollment biases are limitations of all prospective observational studies.

**Conclusion**

The major factors associated with elevated serum NT-proBNP levels were non-paroxysmal AF, impaired renal function, and beta-blocker use. Patients with a history of HF had a high mortality risk, while patients with elevated serum NT-proBNP levels showed a high risk for both mortality and stroke. Measurement of the serum NT-proBNP value is useful for stratifying the risk for stroke/mortality of Japanese patients with AF receiving anticoagulant treatment. Patients with elevated serum NT-proBNP values should be carefully monitored, and additional interventions, including AF ablation, should be considered in these patients to prevent adverse clinical events.

**Disclosure**

**Conflicts of interest:** Dr. Okumura has accepted remuneration from Daiichi-Sankyo; Dr. Hirayama has received research funding from Bayer Healthcare, Daiichi-Sankyo, Otsuka Pharmaceutical, Astellas Pharma, Eisai, Sumitomo Dainippon Pharma, MSD, Nihon Medi-Physics, Bristol-Meyers Squibb, Boehringer Ingelheim, Pfizer, Boston Scientific Corporation, Hokushin Medical, and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, Eisai, Bristol-Meyers Squibb, Astellas Pharma, Sanofi, and Takeda Pharmaceutical; Dr. Matsumoto has received research funding from Daiichi-Sankyo, Otsuka Pharmaceutical, and Sumitomo Dainippon Pharma, and has accepted remuneration from Nihon Medi-Physics, FUJIFILM RI
Pharma, and Biosensors Interventional Technologies Japan.

Appendix

The key personnel and institutions participating in this registry are as follows: Chief investigator: Hirayama A (Division of Cardiology, Department of Medicine, Nihon University School of Medicine) Vice-chief investigator: Okumura Y (Division of Cardiology, Department of Medicine, Nihon University School of Medicine) Steering Committee: Kunimoto S, Okumura Y, Kato M (Division of Cardiology, Department of Medicine, Nihon University School of Medicine) Statistical analysis: Udagawa S (Department of Mathematics, Nihon University School of Medicine) Participating institutions: Division of Cardiology, Department of Medicine, Nihon University School of Medicine (Hirayama A, Okumura Y, Watanabe I, Hiro T, Takayama T, Kunimoto S, Nakai T, Kato M); Department of Cardiology, Nihon University Hospital (Yokoyama K, Matsumoto N); Kawaguchi Municipal Medical Center (Tachibana E, Kuronuma K); Yokohama Chuo Hospital (Otsuka K); Sekishindo Hospital (Okajima J); Asakadai Central General Hospital (Hanada S); Tokyo Rinkai Hospital (Nomoto K); Kasukabe Municipal Hospital (Arima K); Yasuda Hospital (Takahashi F) Itou Cardiovascular Clinic (Itoh T); Makita General Hospital (Kotani T); Itabashi Medical Association Hospital (Ikeya Y); Kondo Clinic (Kondo K); Ukima Central Hospital (Fukushima S); Keiai Hospital (Chiku M); Ohno Medical Clinic (Ohno Y); Onikura Clinic (Onikura M); Kobari General Clinic (Kobari C); Chikuma Central Hospital (Tokai K); Kondo Clinic (Kondo K); Yamada Clinic (Omisaki Y); Higashi Saitama General Hospital (Fukuda Y, Nakahara S); Zengyo-odanchi Ishikawa Clinic (Ishikawa N); Tokutake Clinic (Tokutake E); Sugino Clinic (Sugino K); Yokohama Sotetsu Bldg. Clinic (Mori H); Suzuki Clinic (Suzuki Y); Fujita Clinic (Fujita M); Yamukima Clinic (Yamukima S); Keiai Hospital (Ando H); Sekimachi Medical Clinic (Shin I); Tokiwadai Surgical Hospital (Mochizuki R); Hikari-aoka Clinic (Tokuyasu Y); Osuga Clinic (Osuga E); Nakai Clinic (Nakai K); Kurumatani Clinic (Kurumatani H); Horinaka Hospital (Sato C); Nasu Red Cross Hospital (Akabane M); Sato Clinic (Sato K); Kofu Clinic (Kofu T); Ikekuburo Okubo Clinic (Yamane A); Minami Machida Hospital (Hori H); Ishii Clinic (Ishii N); Akabane Central Hospital (Ominato M); Hirose Clinic (Hirose S); Sekimoto Memorial Hospital (Sekimoto M); Matsumura Clinic (Matsumura K); Tanaka Clinic (Tanaka M); Nakadai Clinic (Ogawa T); Naruse Clinic (Naruse K); Narumine Clinic (Kato A); Miyata Clinic (Miyata H); Aoyama Clinic (Aoyama H); Harada Clinic (Harada K); Yano Clinic (Yano F); Sekino Hospital (Sekino H); Kurokawa Clinic (Kurokawa H); Ishii Clinic (Ishii T); Abe Clinic (Abe Y); Kikuchi Clinic (Kikuchi T); Imamato Clinic (Imamato S); Nireno Clinic (Nagai C); Kachidoki View Tower Clinic (Sugino K).

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