Comparison of the CHADS2, CHA2DS2-VASc and R2CHADS2 Scores in Japanese Patients with Non-valvular Paroxysmal Atrial Fibrillation Not Receiving Anticoagulation Therapy

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Abstract:
Objective It remains unclear whether the CHADS2, CHA2DS2-VASc, or R2CHADS2 score is the most useful for the risk stratification of ischemic stroke/systemic thromboembolism (IS/SE) in Japanese patients with paroxysmal non-valvular atrial fibrillation (PNAVAF).
Methods We investigated the incidence of IS/SE on the basis of the CHADS2, CHA2DS2-VASc, and R2CHADS2 scores in 332 consecutive PNAVAF patients (224 men, mean age: 65±13 years) who had not been administered anticoagulation therapy but who were administered antiarrhythmic drug therapy to maintain sinus rhythm between August 1995 and July 2008 before the 2008 Japanese Circulation Society guideline was issued (mean follow-up period: 53±35 months).
Results The annual rates of IS/SE without underlying antiarrhythmic drug therapy are shown in the table included in this article. Higher CHADS2, CHA2DS2-VASc, and R2CHADS2 scores were associated with greater annual rates of IS/SE (p<0.001). In a multivariate logistic regression analysis adjusted for potentially confounding variables, the CHADS2 scores [odds ratio (OR): 4.74, 95% confidence interval (CI): 2.80-8.00, p<0.001], CHA2DS2-VASc scores (OR: 4.15, 95% CI: 2.57-6.71, p<0.001), and R2CHADS2 scores (OR: 1.94, 95% CI: 1.48-2.53, p<0.001) were significant independent predictors of IS/SE. The area under the receiver-operator characteristic curve for predicting IS/SE was 0.89 for CHA2DS2-VASc scores, 0.87 for CHADS2 scores, and 0.85 for R2CHADS2 scores (all, p<0.001), with no significant difference among the three scores.
Conclusion In Japanese patients with PNAVAF, the CHADS2, CHA2DS2-VASc, and R2CHADS2 scores are all useful for the risk stratification of IS/SE cases.

Key words: CHADS2 score, CHA2DS2-VASc score, R2CHADS2 score, Japanese patients, non-valvular paroxysmal atrial fibrillation

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Introduction

According to recent epidemiological studies in Europe and the United States, the prevalence of atrial fibrillation (AF) is about 4% in individuals in their 70s and about 10% in those over 80 years of age, showing a significant increase with age. In Japan, where the elderly population is increasing rapidly, the prevalence of AF in the elderly population is also high, occurring in about 2-3% of those in their 70s, and is expected to reach 1,000 per 100,000 population in 2010-2030 (1), with further increases in the future. AF is thus considered an important condition that will significantly affect the healthcare system in Japan.

AF is the most common sustained clinical arrhythmia in humans and not only impairs the quality of life but also causes serious complications, such as embolism and hemodynamic dysfunction. It also generates arrhythmia that wors-
ens the cardiovascular prognosis in cases of left ventricular dysfunction (2).

The \text{R}_{CHADS}_2 score has been newly proposed for stratifying patients with non-valvular atrial fibrillation (NVAF) according to the risk of stroke (3). We previously demonstrated that the \text{CHADS}_2 and \text{CHA2DS2-VASc} scores were useful for risk stratification of cardiovascular events in Japanese patients with paroxysmal AF (4, 5). However, it remains unclear whether the \text{CHADS}_2, \text{CHA2DS2-VASc}, or \text{R}_{CHADS}_2 score is the most useful for the risk stratification of ischemic stroke/systemic thrombembolism (IS/SE) in Japanese patients with paroxysmal non-valvular atrial fibrillation (PNVAF).

We therefore investigated the incidence of IS/SE on the basis of the \text{CHADS}_2, \text{CHA2DS2-VASc}, and \text{R}_{CHADS}_2 scores in patients with PNVAF who did not receive anticoagulation therapy before the Japanese Circulation Society (JCS) guidelines were issued in 2008.

\section*{Materials and Methods}

A total of 548 patients had paroxysmal AF confirmed based on symptoms and 12-lead surface electrocardiograms (ECG) and/or ambulatory 24-hour monitoring findings at Iwate Medical University School of Medicine between August 1995 and July 2008 before the publication of the Japan Circulation Society (JCS) guidelines in 2008. Our database, which was established in August 1995, contains data on all new patients admitted to Iwate Medical University School of Medicine in Morioka, Japan. The principle aim for establishing this hospital-based database is to monitor the prevalence and prognosis of cardiovascular diseases in a local area of Japan. The registry started in August 1995, and patients have been continually registered in the database annually. The study sample was drawn from this group and comprised 332 patients (224 men and 108 women; mean age: 65±13 years) who were not receiving anticoagulation therapy and in whom transthoracic echocardiography (TTE) had ruled out cardiac valvular disease. Valvular AF was defined as AF with mitral stenosis and/or a history of valvular surgery (both biological and mechanical valve). All subjects were treated on an outpatient basis every two to four weeks, underwent rhythm control therapy using antiarrhythmic drugs, and were followed for at least one year. All patients were screened for diabetes mellitus using fasting glucose and hemoglobin A1c levels. All patients also underwent a medical interview, chest X-ray, exercise tolerance test, and TTE or other appropriate noninvasive examinations for underlying cardiopulmonary diseases, and the investigators performed a pulmonary function test, chest computed tomography (CT), and cardiac catheterization whenever necessary.

Patients with congestive heart failure; serious bradyarrhythmia (e.g. sick sinus syndrome, atrioventricular block, bi-fascicular block or more); thyroid, hepatic, or renal dysfunction; child-bearing potential during the study period; a history of drug allergy; and receiving warfarin anticoagulation therapy were excluded from the study. In this study, the mean observation period was 53±35 months (range: 12 to 127 months).

\section*{Definition}

Paroxysmal AF was defined as AF terminating spontaneously within seven days of onset (6). Permanent (chronic) AF was defined as AF refractory to antiarrhythmic drug therapy or electrical cardioversion and where a sinus rhythm could not be maintained for more than 12 months, as assessed by ECG. Ischemic stroke was confirmed based on typical neurological symptoms and the presence of a ≥3 mm infarct area, as obtained by brain CT or magnetic resonance imaging (MRI), which was performed in all patients. The diagnosis of hypertension followed the 2009 Japanese Society of Hypertension (JSH) guidelines (7). Dyslipidemia was defined as fasting serum cholesterol of ≥220 mg/dL and triglycerides of ≥150 mg/dL (8). AF was divided into three types depending on the time of onset: diurnal type (7:00 to 17:00), nocturnal type (17:00 to 7:00), and mixed type (any time) (9). Chronic obstructive pulmonary disease was defined as a forced expiratory volume in one second of <70%, as measured by a pulmonary function test. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging or surgery.

\text{CHADS}_2 and \text{CHA2DS2-VASc} scores were defined according to 2006 the American Heart Association (AHA) guidelines (10) and 2010 the European Society of Cardiology (ESC) guidelines (11), respectively. The \text{R}_{CHADS}_2 score (3) awards one point each for the presence of congestive heart failure, hypertension, age ≥75 years old, and diabetes mellitus and two points for prior stroke or transient ischemic attack and renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/m$^2$).

\section*{Protocol for antiarrhythmic drug therapy}

In patients in whom TTE revealed a left ventricular ejection fraction ≥40% after spontaneous or pharmacological/electrical cardioversion, Class I or III antiarrhythmic drugs were administered based on the judgment of the outpatient attending physician. When TTE by contrast showed a left ventricular ejection fraction <40% after spontaneous or pharmacological/electrical cardioversion, aprindine, bepridil, or amiodarone was administered based on the judgment of the outpatient attending physician.

To confirm recurrence of AF, we performed a subjective assessment through history taking. We also obtained recordings from a standard 12-lead ECG and a portable monitor at the time of the medical examination after 2-4 weeks of administration or a change in antiarrhythmic drugs. Furthermore, ambulatory 24-hour ECG monitoring was performed every 3 months to detect recurrence of AF if considered necessary by the outpatient attending physician.

If AF became permanent despite antiarrhythmic therapy, β-blockers, Ca antagonists, or digitalis was administered
The obtained values were expressed as the mean and standard deviation. The patient characteristics were compared between subgroups with the Mann-Whitney U test, and patient percentages were compared with the chi-squared test. The percentage of patients without IS/SE was evaluated using the Kaplan-Meier method, and differences between subgroups were tested for significance using the log-rank test. A multivariate logistic analysis was used to identify predictive factors for ischemic stroke and systemic embolism, and the Hosmer-Lemeshow goodness-of-fit test was used to validate the model. All statistical analyses were performed using the SPSS 13.0 statistical software package. A p value <0.05 was considered statistically significant.

Ethical issues

The ethical committee at Iwate Medical University School of Medicine granted approval for this study, and all of the patients gave their informed consent.

Results

Patient characteristics

All patient characteristics are shown in Tables 1-3.

Distribution of CHADS$_2$, CHA$_2$DS$_{2}$-VASc, and R:CHADS$_2$ scores in patients with PNVAF

The CHADS$_2$, CHA$_2$DS$_{2}$-VASc, and R:CHADS$_2$ score distributions are shown in Fig. 1. The mean CHADS$_2$ score was $1.2 \pm 1.2$ points, the mean CHA$_2$DS$_{2}$-VASc score was $2.0 \pm 1.6$ points, and the mean R:CHADS$_2$ score was $1.6 \pm 1.6$
The survival rate free from IS/SE among the CHADS₂, CHA₂DS₂-VASc, and R₂CHADS₂ score groups

The respective survival rates free from IS/SE on the basis of the CHADS₂ score at 12, 36, 60, 90, and 120 months of follow-up were as follows: score value 0: 100%, 100%, 100%, 99%, and 99%; score value 1: 100%, 100%, 99%, 99%, and 99%; score value 2: 98%, 94%, 89%, 87%, and 85%; score value 3: 93%, 77%, 60%, 50%, and 47%; and score value ≥ 4: 90%, 80%, 65%, 60%, and 50% (Fig. 2). There was a significant difference in the survival rate during the follow-up period among the 5 groups (p<0.001).

The respective survival rates free from IS/SE on the basis of the CHA₂DS₂-VASc score at 12, 36, 60, 90, and 120 months of follow-up were as follows: score value 0: 100%, 100%, 100%, 100%, and 100%; score value 1: 100%, 100%, 98%, 98%, and 97%; score value 2 group: 99%, 99%, 97%, 97%, and 97%; score value 3: 99%, 94%, 91%, 91%, and 90%; score value 4: 96%, 93%, 89%, 79%, and 75%; score value 5: 96%, 78%, 70%, 52%, and 48%; and score value ≥ 6: 86%, 71%, 57%, 43%, and 43% (Fig. 3). Here as well, there was a significant difference in the survival rate during the follow-up period among the 7 groups (p<0.001).

The respective survival rates free from IS/SE on the basis of the R₂CHADS₂ score at 12, 36, 60, 90, and 120 months of follow-up were as follows: score value 0: 100%, 100%, 100%, 99%, and 99%; score value 1: 100%, 100%, 98%, 98%, and 98%; score value 2: 98%, 92%, 87%, 85%, and 83%; score value 3: 98%, 91%, 79%, 77%, and 77%; score value 4: 91%, 91%, 83%, 70%, and 70%; and score value ≥ 5: 95%, 75%, 70%, 60%, and 55% (Fig. 4). Here as well, there was a significant difference in the survival rate during the follow-up period among the 6 groups (p<0.001).

Annual incidence of IS/SE on the basis of the CHADS₂, CHA₂DS₂-VASc, and R₂CHADS₂ scores

Table 4 shows the annual rates of IS/SE by CHADS₂, CHA₂DS₂-VASc, and R₂CHADS₂ score. In each category, the higher value groups had higher annual rates of IS/SE. In total patients, the annual rates of IS/SE in the no anticoagulant therapy group and in the aspirin group were 2.6%/year and 3.1%/year, respectively.

Predictors of IS/SE in patients with PNVAF

In a multivariate logistic regression analysis adjusted for other potentially confounding variables, the CHADS₂ score [odds ratio (OR): 4.735, 95% confidence interval (CI): 2.803-7.998, p<0.001], CHA₂DS₂-VASc score (OR: 4.152, 95% CI: 2.570-6.709, p<0.001), R₂CHADS₂ score (OR: 1.937, 95% CI: 1.481-2.533, p<0.001), and mixed type onset (OR: 3.380, 95% CI: 1.133-10.08, p=0.003 in Table 5A; OR: 3.120, 95% CI: 1.018-9.565, p=0.046 in Table 5B; and OR: 2.782, 95% CI: 1.021-7.584, p=0.045 in Table 5C) were significant independent predictors of IS/SE.

Predictability of IS/SE by CHADS₂, CHA₂DS₂-VASc, and R₂CHADS₂ score using a receiver operating characteristic (ROC) curve

When the predictability of IS/SE was compared based on the area under the ROC curve, the CHADS₂ score was 0.865
FIGURE 2. Survival curve free from ischemic stroke/systemic embolism on the basis of the CHADS² score.

FIGURE 3. Survival curve free from ischemic stroke/systemic embolism on the basis of the CHA²DS–VASc score.

(p<0.001), the CHA²DS–VASc score was 0.899 (p<0.001), and the R²CHADS₂ score was 0.851 (p<0.001). All of the parameters were useful for predicting the occurrence of IS/SE. The area under the ROC curve for the CHA²DS–VASc score was higher than that for the CHADS₂ and R²CHADS₂ scores, but not to a significant degree (Fig. 5).

Discussion

Major findings of the present study

During antiarrhythmic drug therapy to maintain sinus rhythm in patients with PNVAF, higher CHADS₂, CHA²DS–VASc, and R²CHADS₂ scores were associated with higher annual rates of IS/SE in patients with PNVAF not receiving anticoagulant therapy. All three parameters were independent predictors for IS/SE. In addition, the discriminative ability
Figure 4. Survival curve free from ischemic stroke/systemic embolism on the basis of the R2CHADS2 score.

Table 4. Incidences and Annual Rates of Ischemic Stroke/Systemic Embolism on the Basis of the CHADS2, CHA2DS2-VASc, and R2CHADS2 Scores.

| Score | Number | Follow up period (months) | Annual rate (%/year; 95%CI) |
|-------|--------|--------------------------|----------------------------|
| Score 0 | (n=115) | 46±32 | 0.21 (0.10-0.33) |
| Score 1 | (n=114) | 51±35 | 0.93 (0.79-1.07) |
| Score 2 | (n=53) | 65±39 | 2.78 (2.61-2.96) |
| Score 3 | (n=30) | 68±39 | 9.41 (8.98-9.85) |
| Score 4 ≤ | (n=20) | 55±30 | 10.90 (10.18-11.67) |

| CHA2DS2-VASc score | Number | Follow up period (months) | Annual rate (%/year; 95%CI) |
|--------------------|--------|--------------------------|----------------------------|
| Score 0 | (n=76) | 45±33 | 0 |
| Score 1 | (n=60) | 42±31 | 0.60 (0.45-0.76) |
| Score 2 | (n=69) | 58±34 | 0.95 (0.73-1.18) |
| Score 3 | (n=69) | 62±39 | 1.96 (1.65-2.28) |
| Score 4 | (n=28) | 55±32 | 5.45 (5.06-5.85) |
| Score 5 | (n=23) | 69±33 | 9.06 (8.41-9.72) |
| Score 6c | (n=7) | 50±29 | 13.70 (11.79-15.62) |

| R2CHADS2 score | Number | Follow up period (months) | Annual rate (%/year; 95%CI) |
|----------------|--------|--------------------------|----------------------------|
| Score 0 | (n=110) | 47±33 | 0.23 (0.12-0.35) |
| Score 1 | (n=89) | 49±35 | 0.56 (0.36-0.77) |
| Score 2 | (n=47) | 62±39 | 3.29 (3.00-3.58) |
| Score 3 | (n=43) | 56±32 | 4.98 (4.57-5.40) |
| Score 4 | (n=23) | 53±37 | 5.80 (5.13-6.47) |
| Score 5 ≤ | (n=20) | 70±32 | 7.71 (5.81-9.61) |

Non-valvular paroxysmal AF (n=332, mean age 65±13 years, mean follow-up 53±35 months)

for the incidence of IS/SE in patients with PNVAF was compared by ROC. No significant differences were observed among the parameters, indicating that all score schemes were useful for risk stratification.

A comparison of the CHADS2, CHA2DS2-VASc, and R2CHADS2 scores in NVAF patients

NVAF is a risk factor for IS/SE. The annual rate of ischemic stroke among patients with NVAF (approximately 5%) has been shown to be 2- to 7-fold higher than in sub-
objects without AF (13-15). In general, the CHADS score is recommended for the risk stratification of IS/SE or determining whether or not to introduce anticoagulant therapy in patients with NVAF (16-18). The CHADS score was estimated as the sum of points obtained after assigning one point each for age ≥75 years, hypertension, diabetes mellitus, and heart failure and two points for previous IS/SE.

The CHADS-VASc score was established in the 2010 ESC guidelines and incorporated other risk factors in addition to those mentioned in the CHADS score, such as cardiomyopathy, age 65 to 74 years, a history of myocardial infarction, aortic plaque, vascular disease, and gender (female). The CHA2DS-VASc score was estimated as the sum of points obtained after assigning one point each for age 65 to 74 years, hypertension, diabetes mellitus, heart failure, vascular disease, and gender (female) and two points each for previous IS/SE and age ≥75 years (19).

The R.CHADS score, which accounts for renal dysfunction (Crr <60 ml/min/m²), has also been proposed for the risk stratification of IS/SE (3). Piccini et al. found that the R.CHADS score enhanced the stroke risk assessment on the basis of the net reclassification index by 8.2% compared with the CHADS score and by 6.2% compared with the CHA2DS-VASc score (3).

To our knowledge, there have been no studies comparing the CHADS, CHA2DS-VASc and R.CHADS scores in Japanese patients with PNVAF not receiving anticoagulation therapy. However, our study showed that the CHADS, CHA2DS-VASc, and R.CHADS scores were all useful for the risk stratification of IS/SE in Japanese patients with PNVAF with no significant differences among the three scores. These results may reflect ethnic differences in stroke risk assessment in patients with NVAF.

**Table 5A. Predictors of Ischemic Stroke/Systemic Embolism in Patients with PNVAF Not Receiving Antithrombotic Therapy.**

| Variables         | Odds ratio (95%CI) | p value |
|-------------------|------------------|---------|
| CHADS; score      | 4.735 (2.803 - 7.998) | <0.001  |
| Mixed type (time of AF onset) | 3.380 (1.133 - 10.08) | 0.003  |
| Statins           | 3.185 (0.978 - 13.72) | 0.068  |
| Age (years)       | 0.956 (0.908 - 1.007) | 0.091  |
| RAAS inhibitors   | 2.106 (0.667 - 6.648) | 0.145  |
| Chronic AF        | 1.420 (0.490 - 4.116) | 0.204  |
| Underlying heart disease | 1.662 (0.244 - 11.30) | 0.518  |
| Underlying pulmonary disease | 0.801 (0.231 - 2.771) | 0.604  |
| AF recurrence     | 0.984 (0.899 - 1.077) | 0.726  |
| LVDD (mm)         | 1.005 (0.974 - 1.038) | 0.726  |
| AF history (months) | 0.988 (0.908 - 1.074) | 0.739  |
| LAD (mm)          | 1.007 (0.960 - 1.056) | 0.770  |
| LVEF (%)          | 0.998 (0.980 - 1.017) | 0.788  |
| Male              | 1.150 (0.394 - 3.357) | 0.799  |

* - A multivariate logistic regression analysis -
AF: atrial fibrillation, RAAS: renin-angiotensin-aldosterone system, LVDD: left ventricular end-diastolic dimension, LAD: left atrial dimension, LVEF: left ventricular ejection fraction

**Table 5B. Predictors of Ischemic Stroke/Systemic Embolism in Patients with PNVAF Not Receiving Antithrombotic Therapy.**

| Variables         | Odds ratio (95%CI) | p value |
|-------------------|------------------|---------|
| CHADS2; VASC score| 4.152 (2.570 - 6.709) | <0.001  |
| Mixed type (time of AF onset) | 3.120 (1.018 - 9.565) | 0.046  |
| Male              | 2.907 (0.991 - 8.530) | 0.052  |
| Age (years)       | 0.965 (0.901 - 1.012) | 0.098  |
| Statins           | 2.743 (0.892 - 5.972) | 0.290  |
| RAAS inhibitors   | 2.095 (0.752 - 5.837) | 0.357  |
| Chronic AF        | 1.871 (0.586 - 5.972) | 0.290  |
| Underlying pulmonary disease | 0.957 (0.279 - 1.161) | 0.537  |
| AF history (months) | 1.003 (0.989 - 1.016) | 0.702  |
| AF recurrence     | 1.256 (0.379 - 4.161) | 0.709  |
| LAD (mm)          | 0.985 (0.904 - 1.075) | 0.739  |
| LVEF (%)          | 0.993 (0.949 - 1.039) | 0.765  |
| LVDD (mm)         | 0.988 (0.903 - 1.083) | 0.795  |
| Underlying heart disease | 1.119 (0.388 - 3.225) | 0.835  |

* - A multivariate logistic regression analysis -
AF: atrial fibrillation, RAAS: renin-angiotensin-aldosterone system, LAD: left atrial dimension, LVEF: left ventricular ejection fraction, LVDD: left ventricular end-diastolic dimension

**Table 5C. Predictors of Ischemic Stroke/Systemic Embolism in Patients with PNVAF Not Receiving Antithrombotic Therapy.**

| Variables                  | Odds ratio (95%CI) | p value |
|---------------------------|-------------------|---------|
| R:CHADS2; score           | 1.937 (1.481 - 2.533) | <0.001  |
| Mixed type (time of AF onset) | 2.782 (1.021 - 7.584) | 0.045  |
| Statins                   | 2.920 (0.992 - 9.246) | 0.068  |
| Chronic AF                | 1.778 (0.643 - 4.918) | 0.268  |
| RAAS inhibitors           | 1.610 (0.659 - 3.933) | 0.296  |
| LAD (mm)                  | 1.031 (0.962 - 1.015) | 0.385  |
| Symptomatic AF            | 0.634 (0.225 - 1.738) | 0.388  |
| AF history (months)       | 1.003 (0.991 - 1.015) | 0.651  |
| Male                      | 1.199 (0.471 - 3.051) | 0.704  |
| Underlying pulmonary disease | 1.336 (0.252 - 7.081) | 0.734  |
| LVDD (mm)                 | 1.011 (0.934 - 1.094) | 0.789  |
| LVEF (%)                  | 0.934 (0.957 - 1.037) | 0.846  |
| Underlying heart disease  | 1.015 (0.406 - 2.539) | 0.974  |
| AF recurrence             | 1.005 (0.335 - 3.019) | 0.993  |

* - A multivariate logistic regression analysis -
AF: atrial fibrillation, RAAS: renin-angiotensin-aldosterone system, LAD: left atrial dimension, LVDD: left ventricular end-diastolic dimension, LVEF: left ventricular ejection fraction

**Chronic renal failure and cardiovascular complications**

Chronic kidney disease (CKD) is usually considered a risk factor for cardiovascular complications. In patients with chronic renal failure, arteriosclerosis is enhanced (20, 21) by vascular inflammation and protein catabolism as well as by poor nutrition. In addition, patients with chronic renal fail-
ure have high oxidative stress. It has been reported that oxidative stress can activate several complements, increase vascular endothelial adhesion molecules, deteriorate endothelial NO production via reactive oxygen species, and induce the development of vascular endothelial dysfunction (22, 23). Serum concentrations of asymmetric dimethylarginine [asymmetric dimethyl arginine (ADMA)], an endogenous NOS inhibitor of the release of NO from arginine, have been shown to be increased in patients with not only renal dysfunction but also cerebral infarction (24-26). However, the structure of the brain blood vessels is similar to that of the renal ones from an anatomical perspective (27), which may help analyze the mechanisms underlying the onset of stroke in patients with renal dysfunction. We therefore investigated the relationship between the R2CHADS2 score and IS/SE in patients with NVAF, as the above findings suggest that the R2CHADS2 score, which accounts for renal dysfunction, may be more useful than the CHADS2 score for the risk stratification of IS/SE in patients with NVAF.

### Association of chronic renal failure with AF

The 2013 Japanese guideline of chronic renal failure recommend renal dysfunction be considered a risk factor for cardiovascular disease, and a number of previous reports have described the close relationship between AF and chronic renal failure (28-32). Soliman et al. reported that the incidence of AF increased in patients ≥70 years of age with moderate renal dysfunction (average eGFR 43.6 mL/min/m²) when their eGFR was ≤45 mL/min/m² (33). Furthermore, Watanabe et al. reported that the incidence of AF was newly found in 2,947 of 235,818 patients with chronic renal failure during 4.5 years of follow-up. They further found that the hazard ratio of patients with eGFR <30 mL/min/m² was 1.52 (95% CI: 0.89-2.77) (34). However, the Atherosclerosis Risk in Communities (ARIC) study, which compared the cardiovascular prognosis between patients with and without a history of AF during 10.1 years of follow-up, found that an impaired renal function was not an independent predictor in patients with AF (35), and Roldán et al. reported that the addition of renal dysfunction to the CHADS2 and CHA2DS2-VASc score as a risk factor of cardiovascular events did not improve the predictive probability in patients with AF (36). In the present study, no significant difference was observed among the CHADS2, CHA2DS2-VASc, and R2CHADS2 scores for discriminative ability of IS/SE in Japanese patients with PNVAF, and our results were consistent with those of previous studies.

However, it constitutes the R2 CHADS 2 score is moderate to severe renal dysfunction, so further examination is particularly important in patients with mild renal dysfunction.

### Study limitations

Several limitations associated with the present study warrant mention. First, the patient background likely did not conform to the current AF status because the follow-up period in this study was from August 1995 to July 2008. According to a large-scale epidemiological study conducted from 2000 to 2010, the incidence of AF in the Japanese population increased by 1.4, and it is suspected that the incidence of female AF patients may be rapidly increasing in Japan (1). Second, the present study was conducted only in patients with paroxysmal AF, and it is unclear whether or not the same findings would be obtained in patients with persistent and permanent AF. Third, there are a number of methodological limitations hindering physicians from deter-

### Table 1

| Receiver-operator characteristic (ROC) curve | Area (95% CI) | p value |
|---------------------------------------------|--------------|--------|
| CHA2DS2-VASc score                          | 0.894 (0.846-0.951) | p<0.001 |
| CHADS2 score                               | 0.866 (0.807-0.925) | p<0.001 |
| R2CHADS2 score                             | 0.851 (0.794-0.908) | N.S.    |

**Figure 5.** Predictive ability of the CHADS2, CHA2DS2-VASc, and R2CHADS2 scores for ischemic stroke/systemic emboli based on the receiver operating characteristic curve.

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mining when AF actually recurred, and none of the currently available monitoring methods can make a correct evaluation, except for dedicated devices. Finally, the number of patients was relatively small. A large-scale multicenter study should be performed in Japanese patients with NVAF to further evaluate the utility of the CHADS2, CHA2DS2-VASc, and R-CHADS2 scores in risk stratification.

Conclusion

In Japanese patients with PNVAF, the CHADS2, CHA2DS2-VASc, and R-CHADS2 scores were all found to be useful for risk stratification of IS/SE.

The authors state that they have no Conflict of Interest (COI).

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