Comparison Between CHADS₂ and CHA₂DS₂-VASc Score for Risk Stratification of Ischemic Stroke in Japanese Patients With Non-Valvular Paroxysmal Atrial Fibrillation Not Receiving Anticoagulant Therapy

Takashi KOMATSU,¹ MD, Yoshihiro SATO,¹ MD, Mahito OZAWA,¹ MD, Fusanori KUNUGITA,¹ MD, Reisuke YOSHIZAWA,¹ MD, Yoshihiro MORINO,¹ MD, and Motoyuki NAKAMURA,¹ MD

SUMMARY

It remains unclear if the CHADS₂ score or CHA₂DS₂-VASc score is more useful for the risk stratification of ischemic stroke/systemic thromboembolism in Japanese patients with non-valvular paroxysmal atrial fibrillation (NVPF).

We retrospectively investigated the incidence of ischemic stroke on the basis of CHADS₂ and CHA₂DS₂-VASc scores in 332 NVPF patients (224 men, mean age, 65 ± 13 years) who were not administered anticoagulation therapy before publication of the 2008 JCS guideline (mean follow-up period, 53 ± 35 months). Annual rates of ischemic stroke/systemic thromboembolism underlying antiarrhythmic drug therapy were 0.2%/year for the 0-point group; 0.9%/year for the 1-point group; 2.8%/year for the 2-point group; 9.4%/year for the 3-point group; and 10.9%/year for the ≥ 4-point group on the basis of the CHADS₂ scores, and 0%/year for the 0-point group; 0.6%/year for the 1-point group; 1.0%/year for the 2-point group; 2.0%/year for the 3-point group; 5.5%/year for the 4-point group; 9.1%/year for the 5-point group; and 13.7%/year for the ≥ 6-point group on the basis of the CHA₂DS₂-VASc scores. Both higher CHADS₂ and CHA₂DS₂-VASc scores were associated with greater annual rates of ischemic stroke/systemic thromboembolism ($P < 0.001$). In multivariate logistic regression analysis, the CHADS₂ (odds ratio [OR]:4.74, 95% confidence interval [CI]:2.80-8.00, $P < 0.001$) and CHA₂DS₂-VASc scores (OR: 4.15, 95% CI:2.57-6.71, $P < 0.001$) were significant independent predictors for ischemic stroke/systemic thromboembolism. Area under the receiver-operator characteristic curves for predicting ischemic stroke/systemic thromboembolism were 0.89 in the CHA₂DS₂-VASc scores ($P < 0.001$) and 0.87 in the CHADS₂ scores ($P < 0.001$).

In Japanese patients with NVPF, both the CHADS₂ and CHA₂DS₂-VASc scores are useful parameters for the risk stratification of ischemic stroke/systemic thromboembolism. (Int Heart J 2014; 55: 119-125)

Key words: Thromboembolism, Prognosis

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, showing a significant increase with aging.¹⁾ In Japan, whose population is rapidly aging, the prevalence of AF is about 1% in the 60s cohort and about 2-3% in the 70s cohort, which represent increases as seen in Europe and the United States. It is predicted that the prevalence of AF in Japan in 2020 will be 1000 per 100,000 of population.²⁾ It is expected that this rate will increase further in the future. AF is therefore regarded as an important cardiovascular disease in terms of public health.

Atrial fibrillation is frequently encountered in daily medical practice. In addition to causing cardiovascular complications such as thromboembolism and cardiac failure,³⁾ it also generates arrhythmia⁴⁾ that worsens the cardiovascular prognosis

in cases of left ventricular dysfunction. AF is recognized as a disease that must be treated and managed vigorously. American Heart Association (AHA) guidelines published in 2006 recommend that an antithrombotic regimen be put in place depending on risk⁵⁾ in order to prevent ischemic stroke as this is a severe complication of non-valvular AF, and that cases be stratified according to the CHADS₂ score. In 2010 the European Society of Cardiology (ESC) guidelines established the CHA₂DS₂-VASc score for stratification of ischemic stroke risk in non-valvular AF patients with lower risk.⁶⁾ However, it remains unknown which of these two indices is more useful for ischemic stroke risk stratification in Japanese patients with non-valvular paroxysmal AF.

In this study, we retrospectively examined the incidence of ischemic stroke/systemic embolism according to the CHADS₂ and CHA₂DS₂-VASc scores in patients with non-val-

From the ¹ Division of Cardioangiopathy, Nephrology and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan.

Address for correspondence: Takashi Komatsu, MD, Division of Cardioangiopathy, Nephrology and Endocrinology, Department of Internal Medicine, Iwate Medical University, 19-1 Uchimarui, Morioka 020-8505, Japan. E-mail: sym.koma@iwate-med.ac.jp

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vular atrial paroxysmal AF that was not treated with anticoagulant therapy (warfarin) prior to publication of the Guidelines for Pharmacotherapy of Atrial Fibrillation published by the Japanese Circulation Society (JCS) in 2008.

METHODS

Subjects: Before publication of the JCS guidelines in 2008, of the 505 patients in whom paroxysmal AF had been confirmed based on symptoms and 12-lead and ambulatory 24-hour monitoring electrocardiography (ECG), 332 consecutive cases (male: 224 cases, female 108 cases, average age: 65 ± 13) who were not receiving anticoagulant therapy without cardiac valvular disease estimated by transthoracic echocardiography (TTE) were enrolled as subjects. 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. Fasting blood glucose and hemoglobin A_{1c} were measured in all patients to screen for diabetes mellitus. To detect underlying cardiopulmonary diseases, noninvasive tests, including history taking, chest X-rays, exercise testing, and transesophageal echocardiography were performed. The attending physicians ordered pulmonary function tests, chest computed tomography (CT), and cardiac catheterization if considered necessary.

The study excluded patients with the following conditions: severe bradyarrhythmia (sick sinus syndrome, atrioventricular block, or intraventricular conduction defect); hepatorenal dysfunction; women in whom pregnancy was likely; or patients receiving warfarin anticoagulation therapy.

Definitions: Paroxysmal AF was defined as AF terminating spontaneously within 7 days of onset.⁷⁾ Permanent (chronic) AF was defined as AF refractory to antiarrhythmic drug therapy or electrical cardioversion in which sinus rhythms could not be maintained for more than 6 months, as assessed by ECG. Cerebral thromboembolism was confirmed based on clinical symptoms and the presence of a ≥ 3 -mm infarct area, as obtained by brain CT examination or magnetic resonance imaging (MRI). Diagnoses of hypertension followed the 2009 JSH guidelines.⁸⁾ Dyslipidemia was defined as fasting serum cholesterol of ≥ 220 mg/dL and triglycerides of ≥ 150 mg/dL.⁹⁾ AF was divided into 3 types as follows, depending on the time of onset: diurnal type (7:00 a.m.-5:00 p.m.); nocturnal type (5:00 p.m.-7:00 a.m.); and mixed type (any time).¹⁰⁾ Cardiovascular events were defined as any of the following: sudden death, cardiac failure, ischemic stroke, or systemic embolism. Chronic obstructive pulmonary disease was defined as forced expiratory volume in one second of $< 70\%$, as measured by a lung function test.

Antiarrhythmic drug therapy protocol: In patients in whom TTE revealed a left ventricular ejection fraction $\geq 40\%$ after spontaneous or pharmacological/electrical cardioversion, Class I or III antiarrhythmic drugs were administered depending on the judgment of the outpatient attending physician.

In contrast, where TTE showed left ventricular ejection fraction $< 40\%$ after spontaneous or pharmacological/electrical cardioversion, aprindine, bepridil, or amiodarone were administered according to the judgment of the outpatient attending physician.

In order to confirm recurrence of AF, we performed a

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

In patients whose AF became permanent despite antiarrhythmic therapy, digitalis, β -blockers, or Ca antagonists were administered orally to control the ventricular rate.

Antithrombotic regimen protocol: Before publication of the Japanese Circulation Society guidelines¹¹⁾ in November 2001, attending physicians administered antithrombotic therapy at their own discretion. After November 2001, antithrombotic therapy was generally performed according to the guidelines, but the decision to administer antithrombotic therapy was left to the physician. Doses of aspirin were 81 to 100 mg/day.

The subjects of the present study had not received anticoagulation therapy or had received only aspirin. We retrospectively examined patient distributions in relation to the CHADS₂ and CHA₂DS₂-VASc scores, patient background factors, ischemic stroke, and cardiovascular events in patients with non-valvular paroxysmal AF in whom anticoagulant therapy was not administered before the JCS guideline issued in 2008. The observation period for the present study was from June 1995 to August 2008. Mean follow-up period was 53 ± 35 months (range, 12-127 months).

Statistical analysis: Numerical values are expressed as the mean $\pm$ standard deviation. When comparing background factors among patient groups, we used the Mann-Whitney *U* test for statistical analysis and the χ^2 test for comparing ratios. The Kaplan-Meier method was used to analyze the survival rate without ischemic stroke. We applied the log-rank method for significance analysis among groups; multivariate logistic analysis to predict ischemic stroke and cardiovascular events; and the Hosmer-Lemeshow goodness-of-fit test for model verification. We used the SPSS 13.0 statistical package for statistical analyses, with the level of significance set to $P < 0.05$.

RESULTS

Patient characteristics: Patient characteristics are shown in Tables IA, IB, and IC. The mean CHADS₂ score was 1.2 ± 1.2 points and the mean CHA₂DS₂-VASc score was 2.0 ± 1.6 points. (Table IA, IB and IC)

Distribution of CHADS₂ and CHA₂DS₂-VASc scores in patients with non-valvular paroxysmal AF: The CHADS₂ and CHA₂DS₂-VASc score distributions are shown in Figures 1A and 1B.

Survival rate free from ischemic stroke/systemic thromboembolism among CHADS₂ and CHA₂DS₂-VASc score groups: Survival rates free from ischemic stroke/systemic thromboembolism on the basis of the CHADS₂ score at 12, 36, 60, 90 and 120 months of follow-up were as follows; score value 0 group: 100%, 100%, 100%, 99%, 99%, score value 1 group: 100%, 100%, 99%, 99%, 99%, score value 2 group: 98%, 94%, 89%, 87%, 85%, score value 3 group: 93%, 77%, 60%, 50%, 47%, and score value ≤ 4 group: 90%, 80%, 65%, 60%, 50% (Figure 2). On the other hand, survival rates free from ischemic stroke/systemic thromboembolism on the basis of the CHA₂DS₂-

Table I. Patient Characteristics

A			
Number	332		
Follow-up period (months)	53 ± 35	LVDd (mm)	46 ± 5
Age (years)	65 ± 13	LAD (mm)	34 ± 6
Male : female	224 : 108	LVEF (%)	69 ± 10
Hypertension	142 (43%)	RAAS inhibitors	80 (24%)
Diabetes Mellitus	42 (13%)	Statins	45 (14%)
Dyslipidemia	44 (13%)	Antithrombotic therapy ;	
Smoking habits	89 (27%)	None	223 (67%)
Alcohol habits	134 (40%)	Aspirin	109 (33%)
Hyperuricemia	19 (6%)	Warfarin	0 (0%)
Underlying heart disease	65 (20%)	ANP during SNR (pg/mL)	38 ± 37
Underlying pulmonary disease	18 (5%)	Onset of AF	
AF history (months)	18 ± 32	diurnal : nocturnal : mixed	65 : 129 : 138

B

Underlying heart disease	Number (%)	
OMI	15 (19%)	Ischemic heart disease (57%, n = 37)
Angina pectoris	20 (25%)	
Syndrome X	2 (3%)	
DCM	5 (6%)	
HCM	13 (16%)	Non-ischemic heart disease (43%, n = 28)
Myocarditis	1 (1%)	
ASD	2 (3%)	
SSS	7 (9%)	

C

Antiarrhythmic drug	Number (%)	
Disopyramide	80 (24%)	Class-I AAD (95%, n = 314)
Aprindine	51 (15%)	
Cibenzoline	101 (30%)	
Pilsicainide	40 (12%)	
Flecainide	25 (8%)	
Propafenone	6 (2%)	
Pirmenol	11 (3%)	Class-III AAD (5%, n = 15)
Bepridil	14 (4%)	
Amiodarone	1 (0.3%)	
Verapamil	2 (0.7%)	
β-blockers	1 (0.3%)	

Continuous values are the mean ± SD. Values in parentheses are %. AF indicates atrial fibrillation; LVDd, left ventricular end-diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin-al-dosterone system; ANP, atrial natriuretic peptide; OMI, old myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ASD, atrial septal defect; and SSS, sick sinus syndrome.

Figure 1. Distribution of CHADS₂ and CHA₂DS₂-VASC scores in patients with non-valvular paroxysmal atrial fibrillation.

VASc score at 12, 36, 60, 90 and 120 months of follow-up were as follows; score value 0 group: 100%, 100%, 100%, 100%, 100%, score value 1 group: 100%, 100%, 98%, 98%, 97%, score value 2 group: 99%, 99%, 97%, 97%, 97%, score value 3 group: 99%, 94%, 91%, 91%, 90%, score value 4 group: 96%, 93%, 89%, 79%, 75%, score value 5 group: 96%, 78%, 70%, 52%, 48%, and score value 6 ≤ group: 86%, 71%, 57%, 43%, 43% (Figure 3).

Annual incidence of ischemic stroke/systemic thromboembolism on the basis of CHADS₂ and CHA₂DS₂-VASC scores: Table II shows the annual rates of ischemic stroke/systemic thromboembolism among the CHADS₂ and CHA₂DS₂-VASC score groups. In each category, the higher value groups had higher annual rates of ischemic stroke/systemic thromboembolism. Annual rates of ischemic stroke/systemic thromboembolism in the no anticoagulant therapy group and in the aspirin group

Figure 2. Survival curve free from ischemic stroke/systemic thromboembolism on the basis of CHADS₂ score.

were 2.1%/year and 3.1%/year, respectively.

Predictors of ischemic stroke/systemic thromboembolism in patients with non-valvular paroxysmal AF: In a multivariate logistic regression analysis adjusted for other potentially confounding variables, the CHADS₂ score (odds ratio: 4.735, 95% confidence interval: 2.803-7.998, $P < 0.001$), CHA₂DS₂-VASC score (odds ratio: 4.152, 95% confidence interval: 2.570-6.709, $P < 0.001$), and mixed type onset (odds ratio: 3.380, 95% con-

fidence interval: 1.133-10.08, $P = 0.003$ in Table IIIA and odds ratio: 3.120, 95% confidence interval: 1.018-9.565, $P = 0.046$ in Table IIIB) were significant independent predictors for ischemic stroke/systemic thromboembolism.

Predictability of ischemic stroke/systemic thromboembolism among CHADS₂ and CHA₂DS₂-VASc score groups observed from receiver operating characteristic (ROC) curve: When the predictability of ischemic stroke/systemic thromboembolism was compared by the receiver operating characteristic (ROC) and area under the ROC curve, the CHADS₂ score was 0.865 ($P < 0.001$) and the CHA₂DS₂-VASc score was 0.899 ($P < 0.001$). Both parameters were useful for predicting the occurrence of ischemic stroke/systemic thromboembolism. The CHA₂DS₂-VASc score was higher than the CHADS₂ score with regard to area under the ROC curve, but there was no significant difference between the two areas (Figure 4).

Figure 3. Survival curve free from ischemic stroke/systemic thromboembolism on the basis of CHA₂DS₂-VASc score.

Table II. Annual Incidence of Ischemic Stroke/Systemic Thromboembolism on the Basis of CHADS₂ and CHA₂DS₂-VASc Scores

CHADS ₂ score	Number (%)	Observed periods (months)	Annual rates (95% CI; %/year)
Score 0	115 (35)	46 ± 32	0.21 (0.10-0.33)
Score 1	114 (34)	51 ± 35	0.93 (0.79-1.07)
Score 2	53 (16)	65 ± 39	2.78 (2.61-2.96)
Score 3	30 (10)	68 ± 39	9.41 (8.98-9.85)
Score 4 ≤	20 (5)	55 ± 30	10.92 (10.18-11.67)

CHA ₂ DS ₂ -VASc score	Number (%)	Observed periods (months)	Annual rates (95% CI; %/year)
Score 0	76 (23)	45 ± 33	0%
Score 1	60 (18)	42 ± 31	0.60 (0.45-0.76)
Score 2	69 (21)	58 ± 34	0.95 (0.73-1.18)
Score 3	69 (21)	62 ± 39	1.96 (1.65-2.28)
Score 4	28 (8)	55 ± 32	5.45 (5.06-5.85)
Score 5	23 (7)	69 ± 33	9.06 (8.41-9.72)
Score 6 ≤	7 (2)	50 ± 29	13.70 (11.79-15.62)

($n = 332$, mean age 65 ± 13 y.o., follow-up; 53 ± 35 months)
CI indicates confidence interval.

DISCUSSION

Major findings of this study: During antiarrhythmic drug therapy, the higher CHADS₂ and CHA₂DS₂-VASc score groups had higher annual rates of ischemic stroke/systemic thromboembolism in patients with non-valvular paroxysmal AF without anticoagulant therapy. Both parameters were independent predictors for ischemic stroke/systemic thromboembolism. In addition, the discriminative ability for the incidence of ischemic stroke/systemic thromboembolism in patients with non-valvular paroxysmal AF was compared by ROC. No significant difference was observed between the two parameters. This result indicated that both score schemes were useful parameters for risk stratification.

Ischemic stroke/systemic thromboembolism in patients with non-valvular AF in Japan: According to a large-scale controlled study in Europe and the United States, the annual rate of ischemic stroke in patients with non-valvular AF was 3-6.3%,¹²⁻¹⁵⁾ whereas clinical studies in Japan revealed an annual rate of 2.8-4.5%.^{16,17)} The annual incidence in Japan thus appears to be similar to that in Europe and the United States. The CHADS₂ score in particular is an independent predictor

Receiver-operating characteristic (ROC) curve	AUC (95% CI)	P
CHA ₂ DS ₂ -VASc score	0.899 (0.846-0.951)	0.001
CHADS ₂ score	0.866 (0.807-0.925)	0.001

N.S.

Figure 4. Predictive ability for ischemic stroke/systemic thromboembolism by CHADS₂ and CHA₂DS₂-VASc scores observed from receiver operating characteristic curve (ROC).

Table III. Predictors of Ischemic Stroke/Systemic Thromboembolism in Patients With Non-Valvular Paroxysmal Atrial Fibrillation

A			B		
Variables	Odds ratio (95%CI)	P	Variables	Odds ratio (95%CI)	P
CHADS ₂ score	4.735 (2.803 – 7.998)	0.001	CHA ₂ DS ₂ -VASC score	4.152 (2.570 – 6.709)	0.001
Mixed type (onset of AF)	3.380 (1.133 – 10.08)	0.003	Mixed type (onset of AF)	3.120 (1.018 – 9.565)	0.046
Statins	3.985 (0.924 – 13.72)	0.062	Female	2.907 (0.991 – 8.530)	0.052
Age	0.956 (0.908 – 1.007)	0.091	Age	0.965 (0.901 – 1.012)	0.098
RAAS Inhibitors	2.106 (0.667 – 6.648)	0.145	Statins	2.743 (0.892 – 11.41)	0.113
Conversion to chronic AF	1.420 (0.490 – 4.116)	0.204	RAAS Inhibitors	2.095 (0.752 – 5.837)	0.157
Underlying heart disease	1.662 (0.244 – 11.30)	0.518	Conversion to chronic AF	1.871 (0.586 – 5.972)	0.290
Underlying pulmonary disease	0.801 (0.231 – 2.771)	0.604	Underlying pulmonary disease	0.537 (0.279 – 1.161)	0.537
AF recurrence	0.984 (0.899 – 1.077)	0.726	AF history (months)	1.003 (0.989 – 1.016)	0.702
LVDd (mm)	1.005 (0.974 – 1.038)	0.726	AF recurrence	1.256 (0.379 – 4.161)	0.709
AF history (months)	0.988 (0.908 – 1.074)	0.739	LAD (mm)	0.985 (0.904 – 1.075)	0.739
LAD (mm)	1.007 (0.960 – 1.056)	0.770	LVEF (%)	0.993 (0.949 – 1.039)	0.765
LVEF (%)	0.988 (0.908 – 1.074)	0.788	LVDd (mm)	0.988 (0.903 – 1.082)	0.795
Female	1.150 (0.394 – 3.357)	0.799	Underlying heart disease	1.119 (0.388 – 3.225)	0.835

(n = 332, mean age 65 ± 13 y.o, follow-up; 53 ± 35 months)

(n = 332, mean age 65 ± 13 y.o, follow-up; 53 ± 35 months)

AF indicates atrial fibrillation; LVDd, left ventricular end-diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; and RAAS, renin-angiotensin-aldosterone system.

not only for ischemic stroke but also for conversion to chronic AF in patients with paroxysmal AF during antiarrhythmic drug therapy. It is reported that cases with higher CHADS₂ scores involve a clinical course refractory to antiarrhythmic drug therapy.¹⁸⁾ It has also been demonstrated that conversion to chronic AF refractory to antiarrhythmic drug therapy is an independent predictor for cardiovascular events, including ischemic stroke.¹⁹⁾ According to a recent study, rhythm control therapy improves cardiovascular prognosis in patients with paroxysmal atrial fibrillation to a greater extent than rate control therapy.²⁰⁾

According to the guidelines for pharmacotherapy of AF published by JCS in 2008,²¹⁾ only anticoagulant therapy (warfarin) as an antithrombotic regimen is recommended for patients with non-valvular AF. Based on the results of a large-scale controlled study in Japan, Europe, and the United States,^{17,22)} antiplatelet therapy recommended in the previous JCS guidelines was deleted. Furthermore, warfarin therapy for prevention of ischemic stroke/systemic thromboembolism in patients with non-valvular AF is expected to be about more than 60% in Europe and the United States,²³⁾ and Japan,²⁴⁾ although its efficacy is influenced by the quality of anticoagulant control that it provides (management of PT-INR).^{25,26)} According to a report from the J-RHYTHM registry, anticoagulant therapy is administered in more than 80% of patients with non-valvular AF.²⁷⁾ Therefore, it appears to be impossible to discuss the natural incidence of ischemic stroke/systemic embolism in Japanese patients with AF based on current clinical practice. In this study, the subjects were limited to non-valvular AF cases not receiving anticoagulant therapy. We performed a retrospective study within the follow-up period from June 1995 to August 2008 prior to the 2008 JCS guideline being issued. As a result, the higher CHADS₂²⁸⁾ and CHA₂DS₂-VASC²⁹⁾ score groups had higher annual rates of ischemic stroke/systemic thromboembolism in our patients with non-valvular paroxysmal AF not receiving anticoagulant therapy. Furthermore, in a multivariate logistic regression analysis adjusted for other potentially confounding variables, both the CHADS₂ and CHA₂DS₂-VASC scores were independent predictors of ischemic stroke/systemic thromboembolism.

Comparison of CHADS₂ and CHA₂DS₂-VASC scores in patients with non-valvular paroxysmal AF:

According to the 2010 ESC guidelines, parameters such as “age from 65-74,”³⁰⁾ “vascular disease,”³¹⁾ and “female”³²⁾ were added to the risk factors for ischemic stroke. The CHA₂DS₂-VASC score has recently been established as a scheme for risk stratification in patients with non-valvular AF. A large-scale epidemiological study in Europe demonstrated the intimate relationship between high CHA₂DS₂-VASC scores and annual incidence of ischemic stroke.³³⁾ The 2012 ESC guidelines recommended anticoagulant therapy only for cases with a CHA₂DS₂-VASC score of 1 or more without contraindication.⁶⁾ In other words, by adding a new risk factor for ischemic stroke into the 2012 ESC guidelines, an improved discriminative ability compared to conventional CHADS₂ scores of 0-1 (low-middle risk group) was achieved, and the CHA₂DS₂-VASC score can adequately evaluate the appropriateness of an antithrombotic regimen. Additionally, there are differences of degree among risk factors corresponding to one point of CHA₂DS₂-VASC score. It has been reported that “age from 65-74” is a high-degree risk factor that is especially regarded as an important factor among the CHA₂DS₂-VASC score.³⁴⁾ However, it has remained unclear which index is most useful for ischemic stroke risk stratification in Japanese patients with non-valvular AF. In the present study, the predictive ability for ischemic stroke/systemic thromboembolism was assessed by comparing the area under the ROC curve. Our findings showed that as a risk stratification index the CHA₂DS₂-VASC score had a higher true positive rate and a lower false negative rate than the CHADS₂ score. However, there was no significant difference in predictive ability for ischemic stroke/systemic thromboembolism between the CHADS₂ and CHA₂DS₂-VASC scores. Both risk schemes may be useful indices for risk stratification. On the other hand, the 65-74 age range is a risk factor which corresponds to one CHA₂DS₂-VASC score point and may affect the difference in area under the ROC curve between two scores examined in this study. A more detailed assessment will therefore be required in the future.

Study limitations: First, this study was retrospective and ob-

servational in design. The follow-up period was from June 1995 to August 2008. It is conceivable that the patient backgrounds did not conform to current AF status. According to a large-scale epidemiological study conducted over a decade from 2000 to 2010, the incidence of atrial fibrillation in the Japanese population increased by 1.4 times, and it is estimated that the incidence of female AF patients may rapidly increase in Japan.²⁾ Second, rhythm control therapy was attempted in all patients in order to maintain sinus rhythm. We were therefore unable to identify its therapeutic efficacy in patients with persistent or permanent AF on the basis of rate control therapy. However, the SPAF and ACTIVE-W studies reported no significant differences in annual rates of ischemic stroke between cases of paroxysmal and permanent AF.^{22,32)} Third, since the attending physicians administered antithrombotic therapy at their own discretion during the follow-up period, it may reflect biases in the patient backgrounds in the present study. Lastly, the number of patients was relatively small. In future, we should compare CHADS₂ and CHA₂DS₂-VASc scores as an index of risk stratification in patients with non-valvular AF through a large-scale multicenter study.

Conclusion: Both the CHADS₂ score and CHA₂DS₂-VASc score are useful risk stratification indices for ischemic stroke/systemic thromboembolism in Japanese patients with non-valvular paroxysmal atrial fibrillation.

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