Relationship Between CHADS₂ Score and Efficacy of Antiarrhythmic Drug Therapy in Patients With Paroxysmal Atrial Fibrillation

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Background: The Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled] (CHADS₂) score is a useful scheme for risk stratification of thromboembolism patients, but there is little information about its usefulness for the evaluation of antiarrhythmic drug (AAD) therapy.

Methods and Results: This study included 459 paroxysmal atrial fibrillation (AF) patients (309 men, mean age 66±12 years, mean follow-up 50±35 months) and prophylactic efficacy was analyzed on the basis of CHADS₂ score. (1) Survival rates free from AF recurrence at 1, 6, 12 and 24 months were, respectively, 89%, 74%, 63% and 47% in score-0 group (n=152); 92%, 68%, 59% and 48% in score-1 group (n=158); 86%, 64%, 56% and 46% in score-2 group (n=84); 81%, 65%, 51% and 35% in score-3 group (n=43); and 68%, 50%, 36% and 18% in ≥score-4 group (n=22) (P<0.05; score-0, score-1 or score-2 vs. ≥score-4 group). (2) Survival rates free from progression to chronic AF at 12, 36, 60 and 90 months were, respectively, 95%, 93%, 91% and 89% in score-0 group; 97%, 91%, 89% and 88% in score-1 group; 96%, 93%, 88% and 83% in score-2 group; 91%, 74%, 67% and 60% in score-3 group; and 91%, 82%, 68% and 55% in ≥score-4 group (P<0.01; score-0, score-1 or score-2 vs. ≥score-4 group). (3) In multivariate logistic regression analysis adjusted for potentially confounding variables, CHADS₂ score was associated with AF recurrence (odds ratio [OR] 1.45, 95% confidence interval [CI] 1.16–1.81, P<0.001), and progression to chronic AF during AAD therapy (OR 1.64, 95% CI 1.04–2.69, P<0.001).

Conclusions: When using a rhythm control strategy, the CHADS₂ score is a useful scheme for predicting the outcome of AAD treatment of patients with paroxysmal AF. (*Circ J* 2013; **77**: 639–645)

Key Words: Antiarrhythmic drugs; Atrial fibrillation; CHADS₂ score; Prevention; Prognosis

Epidemiological studies in Europe and the United States indicate that the prevalence of atrial fibrillation (AF) increases substantially with age to approximately 4% in people in their 70s and approximately 10% in people in their 80s.¹ In Japan, where the elderly population is increasing rapidly, the prevalence of AF is also high, at approximately 1% among people in their 60s and 2–3% among those in their 70s, and it is expected that the prevalence of AF will reach 1,000 per 100,000 population in 2010–2030,² and further increase in the future. AF is thus considered an important condition that will significantly affect the healthcare system in Japan and other developed countries.

Because AF often causes cardiovascular complications such as thromboembolism and heart failure³ and deteriorates prognosis, especially in patients with left ventricular (LV) dysfunction,⁴ patients with AF should be properly treated and man-

aged. The prognosis of patients with cardiogenic ischemic stroke is poorer than those with atherosclerotic cerebral infarction, and it is reported that cardiogenic stroke recurs within 1 year in approximately 40% of patients who do not receive appropriate anticoagulation therapy.⁵ In the Guidelines for the Management of Patients with Atrial Fibrillation proposed by the American College of Cardiology, the American Heart Association and the European Society of Cardiology in 2006, stroke risk in patients with nonvalvular AF is stratified according to the Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled] (CHADS₂) score, and antithrombotic therapy for patient with AF is recommended for each risk category.⁶ However, few studies have investigated the relationship between the long-term preventive efficacy of recurrent AF by antiarrhythmic drugs (AAD) used to maintain sinus rhythm in patients with paroxysmal AF and the CHADS₂ score.

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Methods

Study Participants

A total of 459 consecutive patients (309 males, 150 females) with symptomatic paroxysmal AF detected using the standard 12-lead ECG and ambulatory 24-h ECG participated in the study. The mean age was 66 ± 12 years, and the mean CHADS₂ score was 1.2 ± 1.1 . Participants had to visit the clinic every 2–4 weeks, undergo rhythm control therapy using AAD, and be under observation for more than 1 year. All patients were screened for diabetes mellitus using fasting glucose and hemoglobin A_{1c} levels. All patients also underwent medical interview, chest X-ray, exercise tolerance test and echocardiography or other appropriate noninvasive examination for underlying cardiopulmonary diseases, and the investigators performed pulmonary function test, chest CT and cardiac catheterization whenever necessary.

Patients with congestive heart failure; serious bradyarrhythmia (eg, sick sinus syndrome, atrioventricular block, bifascicular block or more); thyroid, hepatic or renal dysfunction; or a history of drug allergy and women of child-bearing potential during the study period were excluded. The study was conducted between June 1997 and October 2010, and the mean observation period was 50 ± 35 months (range 12–127 months).

Definitions

Paroxysmal AF was defined as episodes that terminate spontaneously within 7 days.⁷ Permanent (chronic) AF was defined as long-standing AF in which pharmacologic agents and/or electrical cardioversion had failed to maintain sinus rhythm for at least 6 months. Cerebral thromboembolism was diagnosed from the occurrence of typical clinical signs/symptoms and the presence of infarction ≥ 3 mm in diameter detected by CT or MRI. Hypertension was defined according to the guidelines proposed by the Japanese Society of Hypertension in 2009,⁸ and hyperlipidemia was defined as a fasting serum cholesterol ≥ 220 mg/dl and triglycerides ≥ 150 mg/dl.⁹ Chronic obstructive pulmonary disease was defined as a forced expiratory volume in 1 s percent (FEV_{1.0}) $\leq 70\%$. AF was classified by time of onset into diurnal type (episodes occurring during the day, from 7:00 to 17:00 hours), nocturnal type (episodes occurring at night, from 17:00 to 7:00 hours), and mixed type (within 24 hours in both day and night).¹⁰ Recurrence of AF was defined as the first ECG-documented AF episode during treatment with antiarrhythmic treatment.

Protocol for AAD Therapy

All patients received rhythm control therapy to maintain sinus rhythm. For AF patients who had $\geq 40\%$ LV ejection fraction (LVEF) revealed by transthoracic echocardiography, Class I AAD were administered at the discretion of outpatient physicians after spontaneous or electrical cardioversion to sinus rhythm. When AF recurred during treatment with more than 1 Class I AAD, patients who provided informed consent for more aggressive treatment received amiodarone at a dose of 200 mg/day. For patients who did not give consent to receive amiodarone, their physicians prescribed Class I AAD other than those previously used.

Patients with LVEF $< 40\%$ were treated with aprindine 60 mg/day or bepridil 150 mg/day as a first- or second-line therapy after spontaneous or electric cardioversion. Patients in whom AF recurred during treatment with either of these 2 drugs received amiodarone 200 mg/day as third-line therapy.

At 2–4 weeks after the initiation or modification of AAD treatment, the patients were interviewed for subjective symptoms of AF and underwent standard 12-lead ECG and simple ambulatory ECG monitoring. When considered necessary by the attending physicians, patients underwent 24-h ambulatory ECG monitoring every 3 months to evaluate for recurrent AF.

Patients with chronic AF despite full AAD therapy were treated orally with β -blockers, calcium-channel blockers or digoxin to control the ventricular heart rate.

Protocol of Antithrombotic Therapy

Before the guidelines for drug treatment of arrhythmia were published by the Japanese Circulation Society (JCS) in November 2001,¹¹ physicians determined whether antithrombotic therapy was indicated and, if indicated, which type of treatment should be given. In November 2001 and thereafter, patients received antithrombotic therapy according to the JCS guidelines, and were treated with antithrombotic drugs when the physicians considered them necessary. During antithrombotic treatment, patients received aspirin at a dose of 81–100 mg/day or warfarin according to the guidelines to achieve an INR of 1.6–3.0.

The CHADS₂ score was calculated for each patient to evaluate the distribution of patients, patient characteristics and the efficacy of AAD treatment in preventing recurrent AF and chronic AF on the basis of CHADS₂ score. The patients were also stratified by the efficacy of AAD therapy to specify predictive factors for recurrent and chronic AF.

Table 1. Patients' Characteristics and First-Line Therapy on the Basis of CHADS₂ Score

	CHADS ₂ score					P value
	0	1	2	3	4≤	
A. Patients' characteristics						
n	152	158	84	43	22	
Observation period (months)	45±33	49±36	56±40	58±33	54±30	NS
Age (years)	58±12	67±10	72±9	72±9	78±7	<0.001
Sex (M/F)	110/42	100/58	53/31	30/13	16/6	NS
Hypertension	0 (0%)	105 (66%)	57 (68%)	26 (60%)	16 (73%)	<0.001
Diabetes mellitus	0 (0%)	16 (10%)	25 (30%)	14 (33%)	5 (23%)	<0.001
Dyslipidemia	20 (13%)	21 (13%)	12 (14%)	5 (12%)	2 (9%)	NS
Smoking	47 (31%)	31 (20%)	21 (25%)	13 (30%)	2 (9%)	NS
Alcohol	79 (52%)	55 (35%)	26 (31%)	16 (37%)	6 (27%)	NS
Hyperuricemia	6 (4%)	12 (8%)	7 (8%)	2 (5%)	2 (9%)	NS
Underlying heart disease	34 (22%)	45 (28%)	35 (42%)	10 (23%)	6 (27%)	NS
Underlying pulmonary disease	6 (4%)	6 (4%)	3 (4%)	4 (9%)	1 (5%)	NS
Asymptomatic AF	9 (6%)	18 (11%)	9 (11%)	9 (21%)	4 (18%)	NS
B. Patients' characteristics						
n	152	158	84	43	22	
AF history (months)	17±31	20±52	19±32	19±44	14±17	NS
LVDd (mm)	45.4±5.4	45.9±5.5	46.3±6.2	45.6±5.6	47.1±3.9	NS
LAd (mm)	33.9±7.0	36.5±6.9	36.8±7.7	36.1±6.27	37.2±5.4	<0.001
LVEF (%)	68.9±10.1	67.0±10.9	66.6±12.0	69.0±10.9	63.6±11.6	NS
RAAS inhibitors	14 (9%)	59 (37%)	40 (48%)	15 (35%)	8 (36%)	NS
Statin	20 (13%)	22 (14%)	13 (15%)	5 (12%)	2 (9%)	NS
Antithrombotic therapy						
None	83 (55%)	75 (47%)	30 (36%)	17 (40%)	10 (45%)	NS
Aspirin	28 (18%)	49 (31%)	22 (26%)	13 (30%)	2 (10%)	NS
Warfarin	41 (27%)	34 (22%)	32 (38%)	13 (30%)	10 (45%)	NS
At registration						
ANP during SR (pg/ml)	34.5±38.1	46.6±48.9	50.0±48.2	40.4±27.6	38.5±27.8	NS
Onset of AF						
Diurnal: nocturnal: mixed	19:67:66	35:52:71	17:18:49	8:07:28	3:05:14	NS
C. Patients' characteristics						
OMI	5 (15%)	6 (13%)	7 (20%)	4 (40%)	1 (17%)	NS
Angina pectoris	6 (18%)	12 (27%)	7 (20%)	0 (0%)	1 (17%)	NS
DCM	4 (12%)	5 (11%)	5 (14%)	1 (10%)	1 (17%)	NS
HCM	5 (15%)	5 (16%)	4 (11%)	2 (20%)	1 (17%)	NS
Valvular disease	8 (24%)	9 (20%)	10 (29%)	1 (10%)	2 (32%)	NS
Myocarditis	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NS
Syndrome X	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NS
ASD	2 (6%)	3 (7%)	1 (3%)	0 (0%)	0 (0%)	NS
Tetralogy of Fallot	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	NS
SSS	2 (6%)	2 (4%)	1 (3%)	2 (20%)	0 (0%)	NS
D. First-line therapy						
Disopyramide	32 (21%)	35 (22%)	18 (21%)	7 (16%)	7 (32%)	NS
Aprindine	21 (14%)	18 (11%)	18 (21%)	8 (19%)	3 (14%)	NS
Cibenzoline	46 (30%)	50 (32%)	24 (29%)	8 (19%)	5 (23%)	NS
Pilsicainide	19 (13%)	22 (14%)	9 (11%)	9 (21%)	4 (18%)	NS
Flecainide	12 (8%)	8 (5%)	4 (5%)	4 (9%)	1 (5%)	NS
Propafenone	3 (2%)	1 (1%)	1 (1%)	2 (5%)	0 (0%)	NS
Pirmenol	7 (5%)	6 (4%)	0 (0%)	1 (2%)	0 (0%)	NS
Bepridil	6 (4%)	11 (7%)	4 (5%)	2 (5%)	2 (9%)	NS
Amiodarone	5 (3%)	6 (4%)	3 (4%)	2 (5%)	0 (0%)	NS
Verapamil	1 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	NS
β-blockers	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	NS

AF, atrial fibrillation; ANP, atrial natriuretic peptide; ASD, atrial septal defect; CHADS₂, Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled] score; HCM, hypertrophic cardiomyopathy; LAd, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; OMI, old myocardial infarction; RAAS, renin-angiotensin-aldosterone system; SR, sinus rhythm; SSS, sick sinus syndrome.

Figure 2. Survival curve free from atrial fibrillation recurrence on the basis of CHADS₂ score.

Table 2. Predictors of Recurrent AF During Antiarrhythmic Drug Therapy*

	OR (95% CI)	P value
Mixed type (onset of AF)	6.081 (3.857–9.586)	0.001
CHADS ₂ score	1.766 (1.140–2.737)	0.011
Statins	1.845 (0.966–3.525)	0.063
Hypertension	0.612 (0.341–1.099)	0.100
AF history (months)	1.005 (0.999–1.011)	0.119
Diabetes mellitus	0.586 (0.268–1.283)	0.182
Non-ischemic heart disease	0.621 (0.300–1.287)	0.200
Sex (male)	1.367 (0.845–2.211)	0.203
RAAS inhibitors	0.716 (0.422–1.213)	0.214
LVDd (mm)	0.974 (0.934–1.016)	0.219
Valvular heart disease	1.857 (0.616–5.601)	0.272
Age (years)	0.994 (0.973–1.015)	0.567
Cardiac failure	1.366 (0.448–4.168)	0.583
Ischemic heart disease	0.870 (0.420–1.801)	0.707
LVEF (%)	1.003 (0.981–1.026)	0.763
LAd (mm)	0.995 (0.964–1.027)	0.774
Past history of cerebral infarction	0.881 (0.300–2.586)	0.881

*Multivariate logistic regression analysis.

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Statistical Analysis

The obtained values were expressed as mean and standard deviation. Patient characteristics were compared between subgroups by use of the Mann-Whitney U test, and patient percentages were compared with the chi-square test. The percentage of patients without ischemic stroke was evaluated using the Kaplan-Meier method, and differences between subgroups

were tested for significance using the log-rank test. Multivariate logistic analysis was used to identify predictive factors for ischemic stroke and cardiovascular accidents, 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 package (Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

Results

Distribution of CHADS₂ Score in Patients With Paroxysmal AF

In the 459 patients evaluated in the study, the CHADS₂ score was 0 in 152 patients (33%), 1 in 158 patients (34%), 2 in 84 patients (19%), 3 in 43 patients (9%) and ≥4 in 22 patients (5%) (Figure 1).

Comparison of Patient Characteristics on the Basis of CHADS₂ Score (Table 1)

Although significant differences in age and the prevalence of hypertension and diabetes and left atrial diameter (LAd) were observed among subgroups stratified by CHADS₂ score (P<0.01), no differences on the basis of CHADS₂ score were observed in other factors evaluated.

Survival Curve Free From AF Recurrence on the Basis of CHADS₂ Score

The percentages of patients without recurrent AF (AF recurrence-free rate) at months 1, 6, 12 and 24 of follow-up were, respectively, 89%, 74%, 63% and 47% in the patients with a CHADS₂ score of 0 (n=152); 92%, 68%, 59% and 48% in the patients with a CHADS₂ score of 1 (n=158); 86%, 64%, 56% and 46% in the patients with a CHADS₂ score of 2 (n=84); 81%, 65%, 51% and 35% in the patients with a CHADS₂ score of 3 (n=43); and 68%, 50%, 36%, and 18% in the patients with

Figure 3. Survival curve free from progression to chronic atrial fibrillation on the basis of CHADS₂ score.

a CHADS₂ score ≥ 4 ($n=22$). The survival rate free from AF recurrence at month 24 of follow-up was significantly higher in patients with a CHADS₂ score of 0, 1 or 2 than in those with score ≥ 4 ($P<0.05$) (Figure 2).

Predictors for Recurrent AF During AAD Therapy

Multivariate analysis adjusted for potentially confounding variables evaluated in the study revealed that mixed type AF [odds ratio (OR) 6.20, 95% confidence interval (CI) 3.96–9.70, $P=0.001$] and CHADS₂ score (OR 1.45, 95% CI 1.18–1.87; $P=0.002$) were independent predictors for recurrent AF during AAD therapy (Table 2).

Survival Curve Free From Progression to Chronic AF on the Basis of CHADS₂ Score

The percentages of patients without chronic AF (chronic AF-free rate) at months 12, 36, 60, 90 and 120 of follow-up were, respectively, 95%, 93%, 91%, 91% and 89% in the patients with CHADS₂ score 0; 97%, 91%, 89%, 88% and 87% in the patients with CHADS₂ score 1; 96%, 93%, 88%, 83% and 82% in the patients with CHADS₂ score 2; 91%, 74%, 67%, 60%, and 58% in the patients with CHADS₂ score 3; and 91%, 82%, 68%, 55% and 50% in the patients with CHADS₂ score 4 or 5. The survival rate free from progression to chronic AF at month 120 of follow-up was significantly higher in the patients with CHADS₂ score 0, 1 or 2 than in those with CHADS₂ score 4 or 5 ($P<0.01$) (Figure 3).

Predictors for Progression to Chronic AF During AAD Therapy

Multivariate analysis adjusted for potentially confounding variables evaluated in the study revealed that mixed type AF [OR 16.43, 95% CI 1.02–263.8, $P=0.001$], CHADS₂ score (OR 1.64, 95% CI 1.01–2.69; $P=0.001$), AF history (OR 1.01, 95% CI 1.00–1.13; $P=0.002$) and LAd (OR 1.053; 95% CI 1.00–

Table 3. Predictors of Progression to Chronic AF During Antiarrhythmic Drug Therapy*

	OR (95% CI)	P value
Mixed type (onset of AF)	18.57 (7.394–46.66)	0.001
AF history (months)	1.012 (1.004–1.020)	0.004
LAd (mm)	1.067 (1.019–1.116)	0.005
CHADS ₂ score	2.198 (1.246–3.880)	0.007
Hypertension	0.469 (0.215–1.023)	0.057
RAAS inhibitors	0.202 (0.037–1.099)	0.064
Ischemic heart disease	0.513 (0.246–1.070)	0.075
Cardiac failure	2.356 (0.800–6.933)	0.120
LVDd (mm)	1.041 (0.982–1.104)	0.177
LVEF (%)	1.032 (0.963–1.061)	0.399
Valvular heart disease	1.541 (0.550–4.316)	0.410
Statins	0.459 (0.204–1.998)	0.452
Age (years)	1.013 (0.978–1.048)	0.476
Sex (male)	1.252 (0.619–2.532)	0.531
Past history of cerebral infarction	0.698 (0.201–2.429)	0.572
Non-ischemic heart disease	1.232 (0.480–3.160)	0.664
Diabetes mellitus	0.926 (0.357–2.401)	0.874

*Multivariate logistic regression analysis.
Abbreviations as in Tables 1,2.

1.03; $P=0.019$) were independent predictors for chronic AF during AAD therapy (Table 3).

Discussion

Main Results of the Study

In the present study, CHADS₂, which is a risk stratification

score for thromboembolism, was identified as an independent predictor for recurrent and progression to chronic AF in patients with paroxysmal AF during AAD therapy to maintain sinus rhythm.

Significance of CHADS₂ Score in Patients With AF

It has been reported that prior ischemic stroke, age, hypertension, diabetes and heart failure are independently associated with increased risk of cardiogenic cerebral embolism in patients with nonvalvular AF.¹² The CHADS₂ score was developed on the basis of these findings. In an epidemiological study of 1,733 patients aged 65–95 years with nonvalvular AF who were discharged from hospital without anticoagulation therapy, high CHADS₂ scores were associated with increased age-adjusted incidence of stroke.¹³ The CHADS₂ score has been reported as a useful tool in risk stratification for ischemic stroke in patients with nonvalvular paroxysmal AF in Japan,¹⁴ but as far as we know, there have been no studies of the relationship between CHADS₂ score and efficacy of AAD therapy. Because most of the patients in the present study had normal or slightly impaired LVEF (Table 1B), Class I AAD were selected as the first-line therapy in approximately 90% of all patients with paroxysmal AF. However, it should be noted that aimless long-term treatment with Class I AAD may endanger the cardiovascular prognosis in patients with LV dysfunction,¹⁵ even if it is ideal for the maintenance of sinus rhythm. A previous report demonstrated the progressive nature of paroxysmal AF during long-term observation.¹⁶ In particular, the survival rate free from progression to chronic AF at months 60 and 90 of follow-up in the patients with CHADS₂ score 3 or ≥4 in the present study seems to be similar to that in the previous report. However, in the present study, a higher CHADS₂ score was associated with poor efficacy of antiarrhythmic therapy in preventing AF. In the multivariate analysis adjusted for potentially confounding variables evaluated, CHADS₂ score was an independent predictor for the efficacy of AAD therapy in preventing recurrent and chronic AF.

It has been pointed out that duration of AF episodes,^{17,18} medical history,¹⁹ increased LAD,¹⁸ underlying heart disease,^{18,19} heart failure,¹⁸ age,^{20,21} and diabetes mellitus²² among others predict the efficacy of AAD therapy in patients with paroxysmal AF. The CHADS₂ score includes age, heart failure and diabetes, which have been reported to affect the efficacy of AAD in preventing AF. The age-related increase in the prevalence of AF has been reported in epidemiological studies,^{1,2} and explained as being caused by the formation of an electrophysiological propensity to AF because of the increased incidence of age-related supraventricular extrasystole,²³ as well as fibrosis or degeneration of atrial muscles.²⁴ The Framingham Heart Study,²⁵ a large-scale epidemiological survey in the United States, revealed that the risk of AF increases by a factor of 4.5–5.9 in patients with heart failure as compared with those without it, and it has been reported that AF develops in 10–30% of patients with decreased LV function, represented by LVEF ≤40%, and the incidence increases as the severity of heart failure increases.²⁶ It also has been pointed out that volume and pressure overload related to heart failure activates the renin-angiotensin-aldosterone system (RAAS), hypertrophy and fibrosis of atrial muscles, and that calcium overload typical of heart failure may increase the dispersion of the atrial refractory period and cause supraventricular extrasystole. Patients with diabetes mellitus often have diffuse fibrosis of the cardiac interstitium and typical findings of myocardial degeneration with wall thickening and luminal narrowing because of the deposition of mucopolysaccharides in the intramyocar-

dial coronary vessels.²⁷ Also, prolonged hyperglycemia may activate the polyol pathway and decrease the activity of scavenging active oxygen species and hydrogen peroxide, which may eventually decrease the nerve conduction velocity.²⁸ Because many AAD act on particular membrane channels and receptors on the atrial myocytes, it is readily expected that the progression of deterioration and fibrosis of atrial muscles associated with diabetes may cause attenuation of the pharmacological effect of AAD on their targets. In the present study, mixed type AF, irrespective of circadian variation, was also a significant predictor for recurrent and progression to chronic AF during AAD therapy. The initiation of paroxysmal AF and clinical course refractory to AAD therapy may occur in mixed type AF that derives from fibrosis or degeneration of atrial muscles rather than from involvement of the autonomic nervous system.

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study, a large-scale multinational study that compared 2 long-term treatment strategies for AF, sinus rhythm and anticoagulation therapy were independent predictors for cardiovascular prognosis in patients with AF.²⁹ If the sinus rhythm maintenance rate is actually lower in patients with paroxysmal AF with cardiovascular risks and high CHADS₂ score, as suggested in the present study, the cardiovascular prognosis of such patients is expected to be poor. In a study investigating long-term cardiovascular prognosis in Japanese patients with paroxysmal AF receiving AAD therapy using a composite outcome measure including sudden death, heart failure and thromboembolism,³⁰ progression to chronic AF was specified as an independent predictor for cardiovascular events. These findings suggest that maintaining sinus rhythm is most important in patients with higher CHADS₂ scores.

The results of the present study suggest that the CHADS₂ score is not only beneficial in selecting an appropriate anticoagulation strategy to prevent ischemic stroke,^{31,32} but also useful in predicting the efficacy of AAD in preventing recurrent or chronic AF and thus ensuring optimal rhythm management.

Study Limitations

First, the present study was a retrospective observational study and there were some biases in the patient characteristics of the subgroups. Second, all participants underwent rhythm control therapy to maintain sinus rhythm, and the physicians selected AAD and upstream treatment using RAAS inhibitors and statins at their discretion. Although no significant difference in patients' characteristics were observed among the subgroups, we cannot rule out the possibility that some characteristics may affect the efficacy of AAD.^{33,34} Third, the study only involved patient with paroxysmal AF, and it is unclear whether the same findings would be obtained for patients with persistent AF. Finally, recurrent AF was diagnosed as ECG-documented AF. It has been reported that even patients with symptomatic paroxysmal AF are unaware of more than half of the episodes of tachycardia recorded during ambulatory 24-h ECG.³⁵ In a study using the portable ECG monitoring device, Cardio-Phone, 30–70% of the episodes noticed as palpitation by patients with symptomatic AF were associated with sinus tachycardia or atrial extrasystole.³⁶ There are a number of methodological limitations hindering physicians' ability to know when AF actually recurs, and none of the currently available monitoring methods, other than device systems, can make a correct evaluation. Prospective multicenter comparative studies will be necessary to reevaluate the efficacy of AAD therapy in Japanese patients with paroxysmal AF.

Conclusions

The CHADS₂ score is a useful scheme for predicting the efficacy of AAD in preventing recurrent or chronic AF in Japanese patients with paroxysmal AF. The preventive efficacy of AAD therapy was lower in paroxysmal AF patients with higher CHADS₂ scores.

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