Effectiveness of Risk Stratification According to CHADS2 Score in Japanese Patients With Nonvalvular Atrial Fibrillation

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SUMMARY

Cerebrovascular events increase with additional risk factors in patients with nonvalvular atrial fibrillation (NVAf). The relative risk proportional to the number of risk factors in Japanese patients has not been reported.

The prevalence of risk factors was investigated for over 2 years in a prospective cohort study of 265 patients with NVAf. The CHADS2 score is a widely used risk stratification scheme that includes age, hypertension, diabetes mellitus, previous stroke, and heart failure.

Cerebral infarction occurred in 23 patients. This group was significantly older and had a significantly higher prevalence of hypertension. The ratio of a CHADS2 score of 0 - 2 was 77% among patients without stroke, but 44% in the cerebral infarction group. Univariate logistic regression analysis showed that the predictive factors of cerebral infarction were: age (odds ratio (OR) 1.087 (confidence interval (CI) 1.032 - 1.145, $P = 0.002$), hypertension (OR 3.288 (CI 1.086 - 9.962, $P = 0.03$) and CHADS2 score (OR 1.762 (CI 1.222 - 2.543, $P = 0.002$). Furthermore, a CHADS2 score of 3 - 6 was associated with a greater risk of cerebral infarction (OR 4.420 (CI 1.838 - 10.631, $P < 0.001$).

The CHADS2 score was a useful marker of stroke risk in this Japanese population. An increased CHADS2 score was associated with an approximate 1.8-fold increase in risk. (Int Heart J 2009; 50: 323-329)

Key words: Atrial fibrillation, Stroke

THE rate of cerebral infarction increases with additional risk factors in patients with nonvalvular atrial fibrillation (NVAf). The CHADS2 score is a popular

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method of evaluating accumulated risk¹⁻³⁾ and to determine the choice of anticoagulation therapy.⁴⁾ However, the effectiveness of the scheme in Japanese patients has not been fully determined.

METHODS

We prospectively observed 306 patients with atrial fibrillation between December 2005 and December 2007 at the outpatient clinic of Kameda Medical Center, Kamogawa, Japan. The exclusion criterion was severe valvular disease requiring valve replacement surgery. Patients who could be not examined before the end of the observation period were also excluded from the analysis.

The endpoint was cerebral infarction caused by thromboembolism or atherosclerosis. Transient ischemic attack (TIA) was included when hospitalization was considered necessary.

The physicians in charge determined the administration of warfarin for each patient. Cerebrovascular risk was assessed based upon the following definitions. Hypertension was identified as blood pressure above 160/95 mmHg or preceeding medication. Diabetes mellitus and hyperlipidemia were defined as a fasting plasma glucose ≥ 126 mg/dL or use of insulin or oral hypoglycemic agents, and total cholesterol ≥ 220 mg/dL or medication, respectively. Paroxysmal atrial fibrillation was recognized by conversion to sinus rhythm in electrocardiograms. Left ventricular diameters in systolic and diastolic phase were derived from baseline M-mode echocardiography. Ejection fraction of the left ventricle was calculated by either M-mode or 2-dimensional (2D) echocardiography.

The CHADS2 score is a risk stratification system for NVAF patients.²⁾ Scores of 0 to 6 points are determined based on the following factors: congestive heart failure (1 point); hypertension (1 point); age over 75 years (1 point); diabetes mellitus (1 point); and previous stroke or TIA (2 points). In the risk scheme, scores of 0, 1 to 2, and 3 to 6 reflect low risk, intermediate risk, and high risk, respectively.

All data were statistically analyzed using Stat View version 5.0 (Abacus USA). All values are expressed as the mean $\pm$ standard deviation. Scales among 3 groups were compared using Student's *t* test. For nominal parameters, either the Chi square test or Fisher exact test was selected. The occurrence of cerebral infarction was examined using univariate logistic regression analysis. A value of $P < 0.05$ was considered significant for all results.

RESULTS

Patients: We enrolled 293 patients because 13 patients were lost during the observation. Among the 293 patients, 19 had already undergone valve replacement surgery and 9 required new valve surgery. Risk of cerebral infarction was finally assessed in the 265 patients. The average of the duration to reach the endpoint was 703 ± 88 days.

Cerebrovascular events: Table I compares the baseline characteristics of patients with and without cerebral infarction. Cerebral infarction occurred in 23 patients (8.7%), and none developed TIA. The mean age was significantly older and hypertension was more frequent among patients with cerebral infarction. The rates of previous cerebral infarction and cardiovascular disease did not differ between the two groups. Warfarin was prescribed for 182 patients (67%) and another 15 started using warfarin during the observation period. Three patients started using

Table I. Patient Characteristics

Parameter	All patients (n = 265)	Cerebral infarction (+) (n = 23)	Cerebral infarction (-) (n = 242)	P value
Age, years	72 $\pm$ 11	80 $\pm$ 8	72 $\pm$ 11	0.001
Male	172 (65%)	12 (52%)	160 (66%)	0.210
BMI, kg/m ²	23 $\pm$ 3.4	23 $\pm$ 4.3	23 $\pm$ 3.3	0.620
Hypertension	162 (61%)	19 (83%)	143 (59%)	0.027
Hyperlipidemia	80 (30%)	8 (35%)	72 (30%)	0.616
Diabetes mellitus	71 (27%)	9 (39%)	62 (26%)	0.162
Smoking	75 (30%)	7 (30%)	75 (30%)	0.973
CHADS2 score				0.003
0	39 (15%)	1 (4%)	38 (16%)	
1-2	158 (60%)	9 (39%)	149 (62%)	
3-4	65 (25%)	12 (52%)	53 (22%)	
5-6	3 (1%)	1 (4%)	2 (1%)	
Paroxysmal atrial fibrillation	10 (4%)	1 (4%)	9 (4%)	0.880
Cerebral infarction	31 (12%)	3 (13%)	28 (12%)	0.834
Heart failure	35 (13%)	4 (17%)	31 (13%)	0.535
Myocardial infarction	17 (6%)	3 (13%)	14 (6%)	0.175
CABG	6 (2%)	0	6 (2%)	0.445
PCI	16 (6%)	3 (13%)	13 (5%)	0.140
Pacemaker	16 (6%)	1 (4%)	15 (6%)	0.722
Medications				
Aspirin	141 (53%)	14 (61%)	127 (52%)	0.441
Warfarin*	182 (67%)	13 (57%)	169 (70%)	0.188
Discontinuation	3 (1%)	1 (4%)*	2 (1%)	0.239
Initiation	15 (6%)	4 (17%)#	11 (5%)	0.031
Ticlopidine hydrochloride	6 (2%)	0	6 (2%)	0.445

Data are number (%) or mean $\pm$ standard deviation. CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; *, Warfarin group includes patients who discontinued warfarin during the observation period; **, A patient stopped warfarin after cerebral infarction and #, One and three patients started warfarin before and after cerebral infarction occurred, respectively.

warfarin after cerebral infarction. The average of PT-INR was 1.89 ± 0.31 .

Left ventricular diastolic diameter tended to be smaller in the cerebral infarction group (Table II). However, left atrial diameter and left ventricular ejection fraction did not differ between the groups.

Other events: Six deaths (Table III) occurred, including 3 cardiac deaths (2 myocardial infarctions and 1 acute heart failure) and 3 deaths from other causes (1 colon cancer and 2 sudden deaths of unknown etiology).

None of the patients died from cerebral infarction or intracranial hemorrhage. One major hemorrhagic event occurred in a patient on warfarin, who had intracranial hemorrhage associated with trauma. Minor hemorrhagic events occurred in 4 patients, including gastrointestinal hemorrhage in a patient who did not take warfarin. Subcutaneous hemorrhage developed in 3 patients on warfarin.

Table II. Echocardiographic Measurements

	All patients (<i>n</i> = 265)	Cerebral infarction (+) (<i>n</i> = 23)	Cerebral infarction (-) (<i>n</i> = 242)	<i>P</i> value
LVDd (mm)*	49 ± 7	47 ± 6	49 ± 7	0.068
LVDs (mm)**	32 ± 8	30 ± 7	33 ± 8	0.203
LAD (mm)*	49 ± 8	50 ± 7	49 ± 8	0.442
LVEF (%)#	62 ± 12	59 ± 15	62 ± 12	0.259

LVDd indicates left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; #, Four patients each with cerebral infarction (+) and (-) were lost and **, Eight patients with cerebral infarction (-) were lost. All data are shown as the mean ± standard deviation. Two patients with cerebral infarction (-) were lost.

Table III. Follow-up Events

	All patients (<i>n</i> = 265)	Warfarin (+) (<i>n</i> = 182)	Warfarin (-) (<i>n</i> = 83)	<i>P</i> value
All deaths	6 (2%)	2 (1%)	4 (5%)	0.059
Cardiac death	3 (1%)	1 (0.5%)	2 (2%)	0.184
Noncardiac death*	3 (1%)	1 (0.5%)	2 (2%)	0.184
Cerebral infarction	23 (9%)	13 (7%)	10 (12%)	0.188
Major bleeding**	1 (0.4%)	1 (0.5%)	0	0.499
Minor bleeding#	4 (1%)	3 (2%)	1 (1%)	0.784
Heart failure	18 (7%)	9 (5%)	9 (11%)	0.077
Myocardial infarction	8 (3%)	5 (3%)	3 (4%)	0.702
CABG	3 (1%)	2 (1%)	1 (1%)	0.940
PCI	7 (3%)	6 (3%)	1 (1%)	0.325
Pacemaker	3 (1%)	3 (2%)	0	0.240

*indicates Noncardiac death includes sudden death of unknown cause; **, Major bleeding defined as extracranial fatal bleeding or hemorrhagic shock needing blood transfusion or surgery, and intracranial hemorrhage including hemorrhagic stroke; #, Minor bleeding is any hemorrhage other than major bleeding; CABG, coronary artery bypass grafting and PCI, percutaneous coronary intervention.

Risk analysis: Low and intermediate risk patients comprised 78% in the group without events (Table I) and high-risk patients with CHADS2 scores of 3 - 6 comprised 56% of the cerebral infarction group. The incidence rate of stroke proportionally increased with the score (Figure). Among the patients who were not on warfarin, the event rates (number of stroke patients/all patients) of CHADS2 scores of 0, 1 - 2, 3 - 4, and 5 - 6 were 0 (0/7), 7.7% (4/48), 21.7% (5/18), and 100% (1/1), respectively. Among the patients who were on warfarin, these values were 3.1% (1/32), 4.7% (5/106), 16.7% (7/42), and 0 (0/2), respectively.

Univariate logistic analysis demonstrated that significant prognostic factors for cerebral infarction were age, hypertension, and CHADS2 score (Table IV). CHADS2 scores of 3 - 6 were associated with a greater risk of cerebral infarction. The relative risk was about 4.4. The CHADS2 scores were not assessed by multivariate analysis because the scheme takes age and hypertension into account.

The types of predictive factors were unchanged by warfarin therapy. The risk factors of patients with warfarin therapy were age (OR 1.082 (CI 1.005 - 1.166, $P = 0.04$) and CHADS2 score (OR 1.575 (CI 0.997 - 2.489, $P = 0.05$), while those of patients without warfarin were age (OR 1.097 (CI 0.999 - 1.203, $P = 0.05$) and CHADS2 score (OR 2.145 (CI 1.118 - 4.118, $P = 0.02$). Hyper-

Figure. Incidence of stroke over 2 years.

Table IV. Univariate Logistic Regression Analysis

	OR	CI	P value
Age*	1.087	1.032-1.145	0.002
Hypertension	3.288	1.086-9.962	0.034
Diabetes mellitus	1.866	0.770-4.525	0.167
Cerebral infarction	1.147	0.320-4.098	0.834
Heart failure	1.433	0.457-4.484	0.537
Warfarin	0.561	0.236-1.339	0.193
CHADS2 score*	1.762	1.222-2.543	0.002
CHADS2 ≥ 3	4.420	1.838-10.631	< 0.001

* indicates by unit increase; OR, odds ratio and CI, confidence interval.

tension was not statistically significant in the subgroup analysis. In addition, the severity of risk determined by CHADS2 score did not affect the effectiveness of warfarin therapy (low and intermediate risk; OR 1.600 (CI 0.516 - 6.012, $P = 0.37$), (high risk; OR 1.600 (CI 0.434 - 5.893, $P = 0.48$).

DISCUSSION

The CHADS2 score was an independent prognostic factor for cerebral infarction in NVAf patients as reported.⁵⁾ We proved that risk increased approximately 1.8-fold according to the CHADS2 score. Our results demonstrated that this scoring system has predictive power regardless of warfarin administration. A previous study showed that the significance of the CHADS2 score was inferior for Japanese patients on antiplatelet therapy and that the score became partially dissociated with the incidence of stroke in patients on warfarin.⁶⁾ However, high-risk patients defined by the CHADS2 scheme had a high rate of stroke despite receiving warfarin.

The overall event rate of 8.7% for 2 years in the present study was slightly higher than that in a previous article.⁷⁾ However, the mean age of our patients was about 5 years older than theirs. Age is one of the most important risk factors for stroke, because the prevalence of other risk factors generally increases with age.⁸⁾ Other guidelines have simply categorized patients under 65 years old with no other risk factors as being of low risk.⁹⁻¹¹⁾ Two strokes occurred in the subgroup of 63 patients who were younger than 65 years. The predictive value of the CHADS2 score might have been clearer in the more elderly population in our study.

Chamber size and left ventricular function had relatively little influence on stroke as reported in a guideline.³⁾ Left ventricular diastolic diameter was paradoxically smaller in stroke patients. Left atrial diameter tended to be larger in patients on warfarin therapy (50 ± 8 versus 48 ± 8 mm, $P = 0.096$). The size of the left atrium on transthoracic echocardiograms is less associated with the

prevalence of thromboembolism under appropriate anticoagulation.³⁾ On the other hand, our study also suggested that warfarin alone cannot prevent cerebral infarction in the elderly. To evaluate the effectiveness of anticoagulation, further investigation of warfarin control in individual patients is warranted.

This study has several limitations. Firstly, we had a small patient cohort. Secondly, we did not distinguish cardiac thromboembolism from other causes of stroke. Thirdly, warfarin therapy was not randomized for evaluation as a prognostic factor. The interpretation of warfarin effectiveness was limited because a control was not assessed in this study and a few patients started or discontinued warfarin during the observation period.

In conclusion, the CHADS2 score was useful in Japanese population. Individual risk factors should be managed and anticoagulation therapy should be applied to patients at high risk according to CHADS2 scores.

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