ORIGINAL ARTICLE

CHADS₂ and CHA₂DS₂-VASc scores as bleeding risk indices for patients with atrial fibrillation: the Bleeding with Antithrombotic Therapy Study

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The CHADS₂ and CHA₂DS₂-VASc scores, that is, ischemic stroke risk indices for patients having atrial fibrillation (AF), may also be useful as bleeding risk indices. Japanese patients with AF, who routinely took oral antithrombotic agents were enrolled from a prospective, multicenter study. The CHADS₂ and CHA₂DS₂-VASc scores were assessed based on information at entry. Scores of 0, 1 and ≥ 2 were defined as the low, intermediate and high ischemic risk categories, respectively, for each index. Of 1221 patients, 873 took warfarin, 114 took antiplatelet agents and 234 took both. The annual incidence of ischemic stroke was 0.76% in the low-risk category, 1.46% in the intermediate-risk category and 2.90% in the high-risk category by CHADS₂ scores, and 1.44, 0.42 and 2.50%, respectively, by CHA₂DS₂-VASc scores. The annual incidence of major bleeding in each category was 1.52, 2.19 and 2.25% by CHADS₂, and 1.44, 1.69 and 2.24% by CHA₂DS₂-VASc. After multivariate adjustment, the CHADS₂ was associated with ischemia (odds ratio 1.76, 95% confidence interval 1.03–3.38 per 1 –category increase) and the CHA₂DS₂-VASc tended to be associated with ischemia (2.18, 0.89–8.43). On the other hand, associations of the indices with bleeding were weak. In conclusion, bleeding risk increased gradually as the CHADS₂ and CHA₂DS₂-VASc scores increased in Japanese antithrombotic users, although the statistical impact was rather weak compared with their predictive power for ischemic stroke.

Hypertension Research (2014) 37, 463–466; doi:10.1038/hr.2013.150; published online 7 November 2013

Keywords: anticoagulation; atrial fibrillation; intracerebral hemorrhage; stroke; warfarin

INTRODUCTION

Decision-making for thromboprophylaxis needs to balance the risk of ischemic stroke against the risk of major bleeding.¹ Known bleeding risk scores such as HEMORR₂HAGES and HAS-BLED include hypertension, advanced age and history of stroke as their components,^{2,3} which are also known risk factors for ischemic stroke and compose the stroke risk scores for patients having atrial fibrillation (AF), such as the CHADS₂ and CHA₂DS₂-VASc scores.^{4,5} Thus, the CHADS₂ and CHA₂DS₂-VASc scores may also be useful as bleeding risk indices.

To determine the incidence and severity of bleeding complications in patients with cardiovascular diseases and stroke treated with oral antithrombotic therapy in Japan, a prospective, multicenter, observational study (the Bleeding with Antithrombotic Therapy (BAT

Study) was conducted. In its initial report of the overall results, adding antiplatelet agents to warfarin or single antiplatelet therapy doubled the risk of life-threatening or major bleeding events.⁶ In the second report, an increase in blood pressure levels during antithrombotic medication was positively associated with the development of intracerebral hemorrhage.⁷ The series of the findings from the BAT register indicate that patients who require pharmacotherapeutic prevention from ischemic events are also high-risk subjects for bleeding events. Thus, it is important to ascertain the power of known ischemia-risk indices for prediction of bleeding events.

The associations between the CHADS₂/CHA₂DS₂-VASc scores of AF patients and the development of bleeding events, as well as ischemic stroke, were examined in the present study.

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Received 8 May 2013; revised 2 July 2013; accepted 31 July 2013; published online 7 November 2013

METHODS

A total of 4009 patients (2728 men, 69 ± 10 years old) who were taking oral antiplatelet agents or warfarin for cardiovascular or cerebrovascular diseases were enrolled in the BAT Study from 19 stroke and cardiovascular centers in Japan (see Appendix) and were observed for 2–30 months between October 2003 and March 2006. The study protocol, inclusion/exclusion criteria and general results were published previously.^{6,7} The medical ethics review boards of the participating institutes approved the study protocol, and all patients provided their written informed consent.

In the present sub-study, AF patients were enrolled from the BAT register. AF was defined by a diagnosis at entry based on a confirmed history or identification on ECG. Baseline data included components of the CHADS₂ and CHA₂DS₂-VASc scores, as well as of neoplasm, liver cirrhosis, hypercholesterolemia, current smoking, alcohol consumption, systolic and diastolic blood pressure levels and antithrombotic medication at entry. Definitions of these comorbidities and cardiovascular risk factors were the same as those in the previous study.⁶ Scores of 0, 1 and ≥2 were defined as the low, intermediate and high ischemic risk categories, respectively, for each index.^{5,8}

The outcomes included ischemic stroke and bleeding events during the observation period. Bleeding events were defined as life-threatening or major bleeding events according to the definition by the Management of

AThrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke study.⁹ Briefly, life-threatening bleeding was defined as any fatal bleeding event, a drop in hemoglobin of ≥50 g l⁻¹, hemorrhagic shock, symptomatic intracranial hemorrhage or transfusion of ≥4 units of red blood cells. Major bleeding was defined as significantly disabling, severe intraocular bleeding or transfusion of ≤3 units of red blood cells. Secondary hemorrhagic transformation of an ischemic stroke was not regarded as a bleeding event.

Statistics

All analyses were performed using the JMP 8 statistical software (SAS Institute, Cary, NC, USA). To compare baseline clinical characteristics among the three ischemic risk categories according to the CHADS₂ and CHA₂DS₂-VASc scores, one-way factorial analysis of variance with *post-hoc* comparison by Dunnett's test (with the high-risk category as control) was used for continuous variables and the χ^2 -test was used for categorical variables. Multivariate logistic regression analysis was performed using a forced entry method of baseline clinical characteristics to examine the associations of the CHADS₂ and CHA₂DS₂-VASc scores with risks of ischemic stroke and bleeding events, as well as to examine those of the components of the CHA₂DS₂-VASc score. A *P*-value <0.05 was considered significant.

Table 1 Baseline clinical characteristics

	Total	CHADS ₂			CHA ₂ DS ₂ -VASc		
		Low	Intermediate	High	Low	Intermediate	High
Number	1221	186 (15.2%)	283 (23.2%)	752 (61.6%)	53 (4.3%)	163 (13.4%)	1005 (82.3%)
Observation period, months	19.4 (13.8–23.3)	17.4 (13.3–23.0)	18.6 (13.1–23.2)	20.9 (14.2–23.6) [†]	17.2 (10.6–22.8)	17.9 (13.6–23.0)	20.2 (13.8–23.4)*
Age, years	70 ± 10	63 ± 9	69 ± 10	72 ± 8 [†]	55 ± 8	62 ± 9	72 ± 8 [†]
Female	376 (30.8%)	67 (36.1%)	76 (26.9%)	233 (31.0%)	0	39 (23.9%) [†]	337 (33.5%) [†]
<i>Components of the CHADS₂ score</i>							
Congestive heart failure	101 (8.3%)	0	20 (7.1%)	81 (10.8%) [†]	0	7 (4.3%)	94 (9.4%) [†]
Hypertension	634 (51.9%)	0	146 (51.6%)	488 (64.9%) [†]	0	46 (28.2%)	588 (58.5%) [†]
65–4 Years old	443 (36.3%)	94 (50.5%)	102 (36.0%)	247 (32.9%) [†]	0	63 (38.7%)	380 (37.8%) [†]
75 Years old or older	438 (35.9%)	0	87 (30.7%)	351 (46.9%) [†]	0	0	438 (43.6%) [†]
Diabetes mellitus	264 (21.6%)	0	30 (10.6%)	234 (31.1%) [†]	0	8 (4.9%)	256 (25.5%) [†]
Prior cerebral ischemia	541 (44.3%)	0	0	541 (71.9%) [†]	0	0	541 (53.8%) [†]
Prior thromboembolism	11 (0.9%)	0	1 (0.4%)	10 (1.3%)	0	0	11 (1.1%)
Vascular disease	64 (5.2%)	5 (2.7%)	21 (7.4%)	38 (5.1%)	0	0	64 (6.4%)
<i>Comorbidities</i>							
Neoplasm	96 (7.9%)	13 (7.0%)	22 (7.8%)	61 (8.1%)	2 (3.8%)	10 (6.1%)	84 (8.4%)
Liver cirrhosis	40 (3.3%)	9 (4.8%)	6 (2.1%)	25 (3.3%)	2 (3.8%)	5 (3.1%)	33 (3.3%)
<i>Risk factors</i>							
Hypercholesterolemia	375 (30.7%)	41 (22.0%)	83 (29.3%)	251 (33.4%) [†]	12 (22.6%)	36 (22.1%)	327 (32.5%)*
Current smoking	156 (12.8%)	27 (14.5%)	38 (13.4%)	91 (12.1%)	11 (20.8%)	30 (18.4%)	115 (11.4%) [†]
Alcohol consumption	53 (4.3%)	5 (2.7%)	13 (4.6%)	35 (4.7%)	3 (5.7%)	6 (3.7%)	44 (4.4%)
Systolic blood pressure, mmHg	129 ± 18	123 ± 16	130 ± 18	131 ± 19 [†]	120 ± 15	126 ± 18	130 ± 18 [†]
Diastolic blood pressure, mmHg	75 ± 11	72 ± 12	76 ± 12	75 ± 11 [†]	72 ± 16	74 ± 11	75 ± 11
Antithrombotic medication				[†]			*
Warfarin alone	873 (71.5%)	141 (75.8%)	191 (67.5%)	541 (71.9%)	38 (71.7%)	120 (73.6%)	715 (71.1%)
Antiplatelets alone	114 (9.3%)	24 (12.9%)	35 (12.4%)	55 (7.3%)	8 (15.1%)	22 (13.5%)	84 (8.4%)
Both	234 (19.2%)	21 (11.3%)	57 (20.1%)	156 (20.7%)	7 (13.2%)	21 (12.9%)	206 (20.5%)

Data are medians (interquartile range) for the observation period, means ± s.d. for age and blood pressure, and percent of patients for others.

**P* < 0.05, [†]*P* < 0.01 among three groups.

CHADS₂ scores in high-risk category group; 2: 289 patients, 3: 248 patients, 4: 164 patients, 5: 48 patients, 6: 3 patients.

CHA₂DS₂-VASc scores in high-risk category group; 2: 240 patients, 3: 260 patients, 4: 231 patients, 5: 165 patients, 6: 89 patients, 7: 18 patients, 8: 2 patients.

RESULTS

A total of 1221 patients (376 women, 70 ± 10 years old (mean ± s.d.)) were studied. Their baseline characteristics are listed in Table 1. In total, 101 patients (8.3%) had congestive heart failure, 634 (51.9%) had hypertension, 443 (36.3%) were between 65 and 74 years old, 438 (35.9%) were 75 years old or older, 264 (21.6%) had diabetes, 545 (44.6%) had either prior ischemic stroke/transient ischemic attack or prior thromboembolism and 64 (5.2%) had vascular diseases. Overall, 186 patients belonged to the low-risk category, 283 to the intermediate-risk category and 752 to the high-risk category by CHADS₂ scores, and 53, 163 and 1005 patients, respectively, by the CHA₂DS₂-VASc scores. As antithrombotic medications, 873 patients (71.5%) took warfarin, 114 (9.3%) took antiplatelet agents (including 14 patients taking dual antiplatelet agents) and 234 (19.2%) took both (including 19 patients taking warfarin plus dual antiplatelet agents). The median international normalized ratio at entry was 1.95 (interquartile range 1.67–2.30) for warfarin users.

During the median observation period of 19.4 months, 40 ischemic stroke and 39 bleeding events occurred. The annual incidence of both events gradually increased as the CHADS₂ risk category became higher, and that of bleeding increased gradually as the CHA₂DS₂-VASc risk category became higher (Figure 1). After adjustment for

antithrombotic medication (model 1), the CHADS₂ score was associated (odds ratio 1.76, 95% confidence interval 1.04–3.38 per 1-category increase; 1.35, 1.05–1.74 per 1-point increase) and the CHA₂DS₂-VASc score tended to be associated (2.20, 0.91–8.46 per 1-category increase; 1.23, 1.01–1.51 per 1-point increase) with ischemia (Table 2). After further adjustment for neoplasm, liver cirrhosis, hypercholesterolemia, current smoking and alcohol consumption (model 2), the CHADS₂ score was associated (odds ratio 1.76, 95% confidence interval 1.03–3.38 per 1-category increase; 1.33, 1.03–1.73 per 1-point increase) and the CHA₂DS₂-VASc tended to be associated (2.18, 0.89–8.43 per 1-category increase; 1.21, 0.99–1.49 per 1-point increase) with ischemia. On the other hand, there were no significant associations of the indices with bleeding after multivariate adjustment.

Finally, associations of components of the CHA₂DS₂-VASc score with risks of ischemic stroke and bleeding events were also determined (Table 3). Among the components, 'stroke and thromboembolism' tended to be associated with ischemic stroke (odds ratio 1.81, 95% confidence interval 0.93–3.66, *P* = 0.073) and '75 years or older' tended to be associated with bleeding events (2.31, 0.96–6.45, *P* = 0.064).

DISCUSSION

The major finding of the present observational study was that bleeding risk increased gradually as the CHADS₂ and CHA₂DS₂-VASc scores increased, although the statistical impact was rather

Figure 1 Annual incidence of ischemic stroke and bleeding events by CHADS₂ and CHA₂DS₂-VASc scores. Low, score of 0; IM (intermediate), score of 1; high, score of ≥2.

Table 3 Associations of the components of the CHA₂DS₂-VASc score with risks of ischemic stroke and bleeding events

	Ischemic stroke		Bleeding	
	HR	95% CI	HR	95% CI
Heart failure	0.98	0.23–2.84	1.17	0.34–3.02
Hypertension	1.03	0.54–1.98	0.80	0.42–1.52
65–74 Years old	1.02	0.44–2.53	1.68	0.67–4.78
75 Years old or older	1.60	0.72–3.80	2.31	0.96–6.45*
Diabetes mellitus	1.28	0.62–2.52	1.25	0.57–2.54
Stroke and thromboembolism	1.81	0.93–3.66*	0.98	0.51–1.88
Vascular disease	0.82	0.13–2.89	1.68	0.54–4.33
Women	0.75	0.34–1.55	0.86	0.39–1.76

Abbreviations: CI, confidence interval; HR, hazard ratio.

*0.05 < *P* < 0.1 (L 0.073, R 0.064).

Adjusted for antithrombotic medication, neoplasm, liver cirrhosis, hypercholesterolemia, current smoking and alcohol consumption.

Table 2 Associations of CHADS₂ and CHA₂DS₂-VASc scores with risks of ischemic stroke and bleeding events

	Ischemic stroke: model 1			Ischemic stroke: model 2			Bleeding: model 1			Bleeding: model 2		
	HR	95% CI	P-values	HR	95% CI	P-values	HR	95% CI	P-values	HR	95% CI	P-values
CHADS ₂												
Per 1-category increase	1.76	1.04–3.38	0.033	1.76	1.03–3.38	0.037	1.10	0.71–1.80	0.679	1.12	0.72–1.84	0.623
Per 1-point increase	1.35	1.05–1.74	0.019	1.33	1.03–1.73	0.025	1.04	0.81–1.32	0.776	1.05	0.82–1.34	0.717
CHA ₂ DS ₂ -VASc												
Per 1-category increase	2.20	0.91–8.46	0.087	2.18	0.89–8.43	0.096	1.20	0.63–2.85	0.622	1.17	0.61–2.82	0.668
Per 1-point increase	1.23	1.01–1.51	0.043	1.21	0.99–1.49	0.059	1.10	0.90–1.34	0.362	1.11	0.90–1.36	0.328

Abbreviations: CI, confidence interval; HR, hazard ratio.

Model 1: adjusted for antithrombotic medication.

Model 2: adjusted for antithrombotic medication, neoplasm, liver cirrhosis, hypercholesterolemia, current smoking and alcohol consumption.

weak as compared with their predictive power for ischemic stroke.

The association of bleeding risk with the CHADS₂ score for antiplatelet users and anticoagulant users was determined using the cohort of ACTIVE-W,¹⁰ where patients with a score of 0 did not develop major bleeding and those with a score of 1 had a lower incidence of bleeding than those with higher scores. The incidence for intracranial hemorrhage increased as the CHADS₂ and CHA₂DS₂-VAsC scores increased in patients treated with either warfarin, dabigatran, rivaroxaban or apixaban.¹¹ In the present study, a similar tendency was seen in Japanese antithrombotic users with AF. A different finding from that of ACTIVE-W was that the annual incidence of major bleeding in patients with the CHADS₂/CHA₂DS₂-VAsC scores of 0 exceeded 1% per year; it suggests more careful consideration for antithrombotic use in Japanese patients, a known race for high incidence of intracerebral hemorrhage,¹² with the low ischemic risk category than Western patients.

A history of ischemic stroke is a known risk factor for intracerebral hemorrhage.^{6,13} Hypertension does not only trigger arteriosclerosis and cause ischemic stroke but also triggers arterial damage and cause bleeding.¹⁴ Aging is another risk factor for both ischemia and bleeding. Thus, ischemic events and bleeding events seem to share many risk factors. To prevent bleeding complications for antithrombotic users, it is essential to choose appropriate numbers and dosages of antithrombotic agents, as well as to avoid elevation of blood pressure and lower it adequately.⁷

The strengths of the study include the multicenter, prospective study design with about 2000 patient-years of follow-up. The limitations of the study include the lack of data about bleeding history and genetic factors in the database to calculate HEMOR-R₂HAGES and HAS-BLED. In addition, the small number of patients in the low ischemic risk category, as well as the relatively low incidences of ischemic stroke and bleeding events, might affect the statistical results. Another potential limitation is heterogeneity of the subjects registered in the BAT study. In particular, patients with different antithrombotic medication seemed to have different clinical backgrounds. However, it was statistically inappropriate to analyze patients separately according to the antithrombotic medication due to small sample size. Finally, the INR levels when the events occurred were not fully collectable.

In conclusion, in Japanese antithrombotic users, bleeding risk increased gradually as the CHADS₂ and CHA₂DS₂-VAsC scores increased, although the statistical impact was relatively weak. The annual incidence of major bleeding in Japanese antithrombotic users with the CHADS₂/CHA₂DS₂-VAsC scores of 0 exceeded 1% per year.

APPENDIX

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ACKNOWLEDGEMENTS

This study was supported in part by a Research Grant for Cardiovascular Diseases (15C-1) and Grants-in-Aid (H23-Junkanki-Ippan-010, H24-Junkanki-Ippan-011) from the Ministry of Health, Labour and Welfare of Japan, and a Grant-in-Aid for Scientific Research (C, 23591288) from the Japan Society for the Promotion of Science.

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