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ORIGINAL ARTICLE

$CHADS_2$ and CHA_2DS_2-VASc scores as bleeding risk indices for patients with atrial fibrillation: the Bleeding with Antithrombotic Therapy Study

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The $CHADS_2$ and CHA_2DS_2-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 $CHADS_2$ and CHA_2DS_2-VASc scores were assessed based on information at entry. Scores of 0, 1 and $\geqslant 2$ 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 $CHADS_2$ scores, and 1.44, 0.42 and 2.50%, respectively, by CHA_2DS_2-VASc scores. The annual incidence of major bleeding in each category was 1.52, 2.19 and 2.25% by $CHADS_2$, and 1.44, 1.69 and 2.24% by CHA_2DS_2-VASc. After multivariate adjustment, the $CHADS_2$ was associated with ischemia (odds ratio 1.76, 95% confidence interval 1.03–3.38 per 1 −category increase) and the CHA_2DS_2-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 $CHADS_2$ and CHA_2DS_2-VASc scores increased in Japanese antithrombotic users, although the statistical impact was rather weak compared with their predictive power for ischemic stroke.
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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 $HEMORR_2HAGES$ 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 $CHADS_2$ and CHA_2DS_2-VASc scores.[4,5] Thus, the $CHADS_2$ and CHA_2DS_2-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 $CHADS_2$/CHA_2DS_2-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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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 $CHADS_2$ and CHA_2DS_2-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 ATherothrombosis 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 $\geqslant 50\,g\,l^{-1}$, 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 $CHADS_2$ and CHA_2DS_2-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 $CHADS_2$ and CHA_2DS_2-VASc scores with risks of ischemic stroke and bleeding events, as well as to examine those of the components of the CHA_2DS_2-VASc score. A P-value <0.05 was considered significant.

Table 1 Baseline clinical characteristics

		$CHADS_2$			*CHA_2DS_2-VASc*		
	Total	*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%)†
Components of the $CHADS_2$ score							
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%)
Comorbidities							
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%)
Risk factors							
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, mm Hg	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.
$CHADS_2$ scores in high-risk category group; 2: 289 patients, 3: 248 patients, 4: 164 patients, 5: 48 patients, 6: 3 patients.
CHA_2DS_2-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 $CHADS_2$ scores, and 53, 163 and 1005 patients, respectively, by the CHA_2DS_2-VAS 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 $CHADS_2$ risk category became higher, and that of bleeding increased gradually as the CHA_2DS_2-VASc risk category became higher (Figure 1). After adjustment for antithrombotic medication (model 1), the $CHADS_2$ 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 CHA_2DS_2-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 $CHADS_2$ 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 CHA_2DS_2-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 CHA_2DS_2-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, $P = 0.064$).

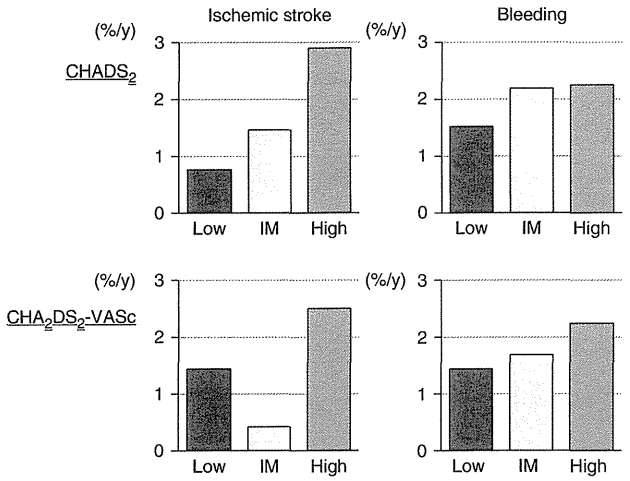

Figure 1 Annual incidence of ischemic stroke and bleeding events by $CHADS_2$ and CHA_2DS_2-VASc scores. Low, score of 0; IM (intermediate), score of 1; high, score of ⩾2.

DISCUSSION

The major finding of the present observational study was that bleeding risk increased gradually as the $CHADS_2$ and CHA_2DS_2-VASc scores increased, although the statistical impact was rather

Table 3 Associations of the components of the CHA_2DS_2-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 $CHADS_2$ and CHA_2DS_2-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_2DS_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 CHADS$_2$ 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 CHADS$_2$ and CHA$_2$DS$_2$-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 CHADS$_2$/CHA$_2$DS$_2$-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 HEMORR$_2$HAGES 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 CHADS$_2$ and CHA$_2$DS$_2$-VASc scores increased, although the statistical impact was relatively weak. The annual incidence of major bleeding in Japanese antithrombotic users with the CHADS$_2$/CHA$_2$DS$_2$-VASc scores of 0 exceeded 1% per year.

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APPENDIX

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Anticoagulant medication for secondary prevention of stroke/TIA in Japanese NVAF patients in the NOAC era: an interim report of the SAMURAI-NVAF study

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Objective: In Japan, three NOACs were recently approved for clinical use in NVAF patients; dabigatran in January 2011, rivaroxaban in January 2012, and apixaban in December 2012. We determined choice of anticoagulant medication at acute hospital discharge in Japanese acute stroke/TIA patients with NVAF and clarified background patients' characteristics associated with the choice.
Methods: 658 acute ischemic stroke/TIA survivors with NVAF (295 women, 77±10 years old) between September 2011 and May 2013 were studied from a multicenter prospective registry (the SAMURAI-NVAF study including 18 Japanese stroke centers, NCT01581502). Anticoagulant choice at hospital discharge (median 23 days) was assessed. Observation period was divided into three 7-month parts.
Results: Warfarin was chosen for 419 patients (64%), dabigatran for 143 (22%), rivaroxaban for 64 (10%), and anticoagulant was not chosen for the remaining 32 (5%). Of 204 prestroke warfarin users, 159 (78%) continued to take warfarin, 27 changed to dabigatran, and 16 changed to rivaroxaban. Among three stages, warfarin users decreased (70%, 69%, 50%), dabigatran users unchanged (24%, 21%, 20%), and rivaroxaban users increased (0.5%, 7%, 24%). Warfarin users had higher scores of $CHADS_2$ (median W 4, D 4, R 3), CHA_2DS_2-VASc (6, 5, 5), admission NIHSS (10, 3, 6), 7-day NIHSS (5, 1, 1) and discharge mRS (3, 1, 2). Of components of CHA_2DS_2VASc, congestive heart failure (W 27%, D 12%, R 12.7%), stroke history (30%, 16%, 18%), and women (48%, 34%, 42%) were more common in warfarin users than the others. Age (W 79±10, D 73±9, R 74±10 years old) and admission creatinine clearance (52±26, 72±23, 66±24 ml/min) were also different.
Conclusion: In the initial two years after approval of NOACs, warfarin use at discharge was still common, although the percentage gradually decreased. Index stroke was milder and ischemia-risk indices were lower in NOAC users than warfarin users.

Key words: atrial fibrillation, anticoagulation, stroke prevention

Early anticoagulant therapy for secondary stroke prevention in Japanese NVAF patients with TIA/minor stroke: an interim report of the SAMURAI-NVAF study

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Objective: Although urgent anticoagulation is not recommended for treatment of patients with acute ischemic stroke in AHA and ESO guidelines, it is commonly used in Japan. We aimed to clarify the usefulness and safety of urgent anticoagulant therapy in patients with cardioembolic TIA/minor stroke.

Methods: In a Japanese multicenter prospective registry (the SAMURAI-NVAF study NCT01581502), 722 acute ischemic stroke/TIA survivors with NVAF were registered between September 2011 and May 2013. 206 patients (134 men, 74.3±9.8 years old) with TIA or minor stroke (NIHSS score≦3 on admission) were assessed for the anticoagulant therapy during the hospital stay and the occurrence of ischemic or major hemorrhagic events within 30 days after the onset.

Results: Anticoagulant therapy was initiated during hospital stay (median 15 days) in all patients.

Intravenous unfractionated heparin (UFH) was administrated for 152 patients (74%) and was initiated on median 0 day (IQR 0-1day) after the onset. As oral anticoagulants, warfarin was started from median 2 (IQR 1-4) days for 116 patients (56.3%), dabigatran from median 3 (2-5) days for 78 (38%), and rivaroxaban from median 3 (2-5) days for 22 (11%). Ischemic events were developed in 6 patients (2.9%, 3 patients treated with UFH, 1 with warfarin, 1 with dabigatran, 1 with UFH and warfarin), and major hemorrhage in only 2 patients (1.0%) during warfarin mono therapy.

Conclusion: In our cohort, initiation of anticoagulant therapy is relatively early after the onset of cardiogenic TIA/minor stroke as compared to that from the European statements. Incidence of ischemic events and major hemorrhage seems to be low.

Key words: atrial fibrillation, anticoagulation, TIA and minor stroke

参考 : Within 30 days after the initial stroke, 395 patients (4.9%) developed a recurrent stroke. Recurrence most frequently occurred in atherothrombotic patients (6.6%), followed by cardioembolic patients (6.2%). Overall, hypertension (OR 1.348, 95% CI 1.071-1.696) and atrial fibrillation (OR 1.503, 95% CI 1.177-1.918), but not diabetes mellitus, were independently predictive of early recurrence. In atherothrombotic patients, diabetes mellitus (OR 1.485, 95% CI 1.058-2.085) and atrial fibrillation (OR 1.998, 95% CI 1.231-3.244) were independently related to early recurrence. (Toyoda et al. Cerebrovasc Dis. 2007;24(2-3):289-95.)

Choice of warfarin and novel oral anticoagulants for secondary prevention of stroke/TIA in Japanese NVAF patients: the SAMURAI-NVAF study

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Purpose: We aimed to determine choice of oral anticoagulants (OACs) at acute hospital discharge in stroke patients with NVAF and clarify their underlying characteristics potentially influencing the choice from a multicenter prospective registry (the SAMURAI-NVAF, NCT01581502).

Methods: 668 acute ischemic stroke/TIA survivors with NVAF (298 women, 77±10 years old) between Sep '11 and Jun '13 were studied; dabigatran (Jan '11), rivaroxaban (Jan '12), and apixaban (Dec '12) were approved for clinical use in NVAF patients in Japan just before or during the periods. OAC choice at hospital discharge (median 23 days) was assessed.

Results: Warfarin was chosen for 420 patients (63%), dabigatran for 143 (21%), rivaroxaban for 72 (11%), and OACs were not chosen for 33 (5%). Of 204 prestroke warfarin users, 160 (78%) continued to take warfarin, 27 changed to dabigatran, and 17 to rivaroxaban. Among three 7-month parts of observation period, warfarin users decreased (70%, 69%, 48%), dabigatran users unchanged (23%, 21%, 19%), and rivaroxaban users increased (0.5%, 7%, 26%). Warfarin users had higher scores of $CHADS_2$ (median 4 in warfarin, 4 in dabigatran, 3 in rivaroxaban, same orders in the following parentheses, $p<0.001$) and CHA_2DS_2-VASc (6, 5, 5, $p<0.001$). Of components for CHA_2DS_2VASc, congestive heart failure (27%, 12%, 13%, $p<0.001$), stroke history (29%, 15%, 15%, $p=0.001$), vascular disease (18%, 11%, 7%, $p=0.019$), and women (47%, 34%, 40%, $p=0.020$) were more common in warfarin users than the others. Age (79±10, 73±9, 74±10 years old, $p<0.001$), body weight (54±12, 62±11, 59±12 kg, $p<0.001$), admission creatinine clearance (52±26, 72±23, 67±25 ml/min, $p<0.001$), and concomitant antiplatelet use (12%, 10%, 1%, $p=0.020$) were also different. As features of index stroke, infarcts >33% in size of the culprit arterial territory were more common (29%, 8%, 13%) and scores of admission NIHSS (median 10, 3, 6), 7-day NIHSS (5, 1, 1) and discharge mRS (3.5, 1, 2, $p<0.001$ for all) were higher in warfarin users.

Conclusion: In the initial two years after approval of novel OACs (NOACs), warfarin use at acute hospital discharge was still common, although NOAC users gradually increased. Index stroke was milder and ischemia-risk indices were lower in NOAC users than warfarin users.

Key words: 1 anticoagulation, 2 atrial fibrillation, 3 embolism, 4 prevention, 5 acute stroke care

Length of stay and hospital charges in Japanese NVAF inpatients with acute stroke/TIA: the SAMURAI-NVAF study

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Purpose: Warfarin needs several days to reach the steady anticoagulative state, however novel oral anticoagulants (NOACs) does not. It may cause differences in acute hospital stay for stroke and hospital charges between NVAF patients taking warfarin and those taking NOACs. We aimed to determine the association of OAC choice after stroke with length of hospital stay and hospital charges from a multicenter prospective registry (the SAMURAI-NVAF, NCT01581502) involving 18 hospitals.

Methods: 634 acute ischemic stroke/TIA survivors with NVAF (277 women, 77±10 years old) who was taking OACs at discharge between Sep 2011 and Jun 2013 were studied; three NOACs were approved for clinical use in NVAF patients in Japan just before or during the periods (dabigatran in Jan 2011, rivaroxaban in Jan 2012, apixaban in Dec 2012). Hospital charges were analyzed using 217 patients in the first author's hospital where the Diagnosis Procedure Combination, a Japanese diagnosis-dominant case-mix system was used for charges.

Results: Warfarin was chosen for 420 patients (66%), dabigatran for 143 (23%), and rivaroxaban for 71 (11%) at hospital discharge. Warfarin users were older (warfarin 79±10, dabigatran 73±9, rivaroxaban 74±10 years old, $p<0.001$) and more female (47%, 34%, 41%, $p=0.021$), and had higher scores of admission NIHSS (median 10, 3, 6, $p<0.001$) and discharge mRS (3.5, 1, 2, $p<0.001$) than the others. Median hospital stay was longer in warfarin users (28 [IQR 18-36] days) than dabigatran users (15 [12-22] days) and rivaroxaban users (18 [13-26] days, $p<0.001$). As compared to NOAC use, warfarin use was independently associated with longer stay both after adjustment for sex, age, and initial NIHSS score ($p<0.001$) and after adjustment for sex, age, and discharge mRS ($p<0.001$). Median hospital charges were $1,645*10^3$ [IQR 987-2136] JPY for warfarin users (n=139), $967*10^3$ [IQR 716-1240] JPY for dabigatran users (n=43), and $1,354*10^3$ [IQR 944-2063] JPY for rivaroxaban users (n=137, $p<0.001$). There was no independent association of OAC choice with hospital charges after multivariate adjustment.

Conclusion: Use of NOACs for secondary prevention shortened acute hospital stay after stroke/TIA independently from stroke severity.

Key words: acute stroke, anticoagulation, atrial fibrillation, cardioembolism, stroke prevention, health care cost

Atrial fibrillation unidentified prior to stroke/TIA: background features, stroke severity and outcome - the SAMURAI-NVAF study

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Purpose: Atrial fibrillation (AF) is often detected after embolic events occur, and it is an obstacle to effective preventive anticoagulation. We aimed to determine a percentage of patients with nonvalvular AF (NVAF) unidentified prior to stroke in the overall stroke patients with NVAF, as well as background features, stroke severity and outcome of such occult NVAF patients.

Methods: A total of 743 acute ischemic stroke/TIA patients with NVAF (344 women, 78±10 years old) were enrolled between Sep 2011 and Jun 2013 from a multicenter prospective registry (the SAMURAI-NVAF study, NCT01581502). Patients were divided into two groups; those with identified AF before stroke/TIA (Group I) and those with unidentified AF that was documented at emergent visit or later (Group U). Favorable outcome was defined as mRS 0-2 at hospital discharge (for 710 patients, median 23 days) and at 3 months (for 565 patients).

Results: 285 patients belonged to the Group U (38%; 138 women, 78±11 years old). Although both median $CHADS_2$ (2 vs. 2, $p<0.001$) and CHA_2DS_2-VASc (3 vs. 4, $p<0.001$) were lower in the Group U than the Group I, patients with the high ischemic risk category (≥ 2 in each score) accounted for 68% according to $CHADS_2$ and 91% according to CHA_2DS_2-VASc in the Group U. After multivariate adjustment, paroxysmal AF (OR 1.91, 95% CI 1.24-2.75) was more common and congestive heart failure (0.63, 0.40-0.99) and premorbid use of oral anticoagulants (0.08, 0.04-0.13) were less common in the Group U than the Group I. The median initial NIHSS was higher in the Group U (11 [IQR 4-19]) than in the Group I (6 [2-17], $p<0.001$). Favorable outcome was less common in the Group U than the Group I both at discharge (41% vs. 51%, $p=0.011$) and at 3 months (46% vs. 56%, $p=0.036$). Unidentified AF was independently associated with mRS 3-6 after adjustment for sex and age both at discharge (OR 1.57, 95% CI 1.13–2.18) and at 3 months (1.60, 1.10-2.32), but was no longer associated with mRS 3-6 after further adjustement for the initial NIHSS.

Conclusion: Two fifth of the stroke/TIA patients with NVAF were not diagnosed as having AF prior to the attack, though their ischemia-risk indices were generally high. Patients with such occult NVAF had severer stroke and worse outcome than those with identified AF.

Key words: atrial fibrillation, stroke, anticoagulation

Early anticoagulant therapy for the initial treatment of acute stroke/TIA in Japanese NVAF patients: an interim report of the SAMURAI-NVAF study

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Objective: Early anticoagulant therapy is commonly used for acute cardioembolic stroke in Japan, although its usefulness remains undetected. The purpose of this study was to estimate the efficacy and safety of early anticoagulation for the treatment of acute stroke/TIA patients with nonvalvular atrial fibrillation (NVAF).

Methods: From September 2011 through June 2013, 697 acute ischemic stroke/TIA patients with NVAF were registered from a multicenter prospective registry (the SAMURAI-NVAF study including 18 Japanese stroke centers, NCT01581502). Of those, the patients who started anticoagulant therapy within 48 hours after the onset were assessed for the incidence of ischemic and hemorrhagic events during the first 30 days.

Results: A total of 438 patients (62.8%; 247 men, 77.4±9.8 years old) was evaluated. Of these, 292 patients (66.7%) started anticoagulation with intravenous unfractionated heparin (UFH) mono-therapy, 87patients (19.9%) with UFH and warfarin, and 2 patients (0.5%) with UFH switched to novel oral anticoagulants (NOACs). As oral anticoagulants mono-therapy, 34 patients (7.8%) started with warfarin, and 23(5.3%) with NOAC. Ischemic events were developed in 11 patients (2.5%: 11 recurrent ischemic strokes), and hemorrhagic events in 11 patients (2.5%: 6 symptomatic intracranial hemorrhages during the first 7days and 5 extracranial hemorrhages). Patients with major artery occlusion had higher incidence of hemorrhagic events than those without (4.0% versus 0.6%, p=0.02), whereas ischemic events were similar in both groups (2.4% versus 2.7%, p=0.82). In multivariable analysis, major artery occlusion was independently associated with higher rate of major hemorrhagic events (OR 6.19; 95% CI 1.01-119.75) adjusted for age, sex, BMI, HAS-BLED score before index TIA/stroke, and NIHSS on admission.

Conclusion: In our cohort, early initiation of anticoagulant therapy is often performed in patients with acute stroke/TIA with NVAF patient, and the frequency of ischemic and hemorrhage events seems to be low compared with previous reports. Early anticoagulant therapy can be safe for patients without major artery occlusion.

Anticoagulation intensity of low-dose rivaroxaban for Japanese patients with nonvalvular atrial fibrillation

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Objective: In Japan, low-dose rivaroxaban [15 mg o.d. and 10 mg o.d. only for CCr 30-49 mL/min] was approved for clinical use to NVAF patients, because of its unique pharmacokinetics in Japanese subjects showing higher rivaroxaban concentration than Caucasian subjects when using the same dosage and the results of the J-ROCKET AF trial (Hori M, et al: Circ J 2012). We aimed to determine the anticoagulation intensity of rivaroxaban and its determinant factors in Japanese NVAF patients, especially in those taking crushed tablets.
Methods: Consecutive stroke patients with NVAF admitted between July 2012 and July 2013 were studied. Prothrombin time (PT, Recombiplastin/HemosIL®), activated partial thromboplastin time (aPTT, Actin/Sysmex®), and anti-Xa chromogenic assay (Stago®) were measured just before and 4h and 9 h after the administration at the steady state of rivaroxaban (mean 6th day). We calibrated its plasma concentration based on anti-Xa assay.
Results: Of 104 patients (32 women, 74±9 y.o., BW 59±11 kg) involving 36 with CCr <50 ml/min (Cockcroft-Gault), 57 took 15 mg o.d. of rivaroxaban and 46 took 10 mg o.d. Median PT, aPTT, and concentration were 12.8s, 31s, and 13.5 ng/ml just before administration, 19.3s, 42s, and 170.5 ng/ml at 4h, and 15.8s, 37s, and 63.0 ng/ml at 9h. Both PT and aPTT were positively correlated with concentration (r=0.88, 0.74, respectively). Age, BW, CCr, and rivaroxaban dosage were not associated with concentrations at 4h and 9h, though they were associated with concentration just before administration. In 10 patients taking crushed tablets, including 5 patients via a nasogastric tube, median PT (15.8s vs. 19.7s, p<0.001), aPTT (33s vs. 42s, p=0.012) and concentration (53 ng/ml vs. 186 ng/ml, p<0.001) at 4h were lower than the remaining 94 patients. Crushed tablets were independently associated with lower anticoagulant intensity.
Conclusion: Nearly peak concentration of rivaroxaban was similar or a little lower than that in the ROCKET AF and J-ROCKET AF trials (Kaneko M, et al: Drug Metab

Pharmacokinet 2013). Tablet crushing may decrease anticoagulation intensity.

1903 characters, 337 words

Key word: Rivaroxaban, nonvalvular atrial fibrillation, anticoagulation marker, anti-Xa chromogenic assay, nasogastric tube, cardioembolism, acute stroke, anticoagulant

日本人脳血管障害患者におけるリバーロキサバン導入後の抗凝固能の強度の実態について

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Successful resolution of the cardiac thrombus using novel oral anticoagulants

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Objective:

We aimed to determine therapeutic effects of novel oral anticoagulants (NOACs) on cardiac thrombi in acute stroke.

Methods:

We studied consecutive acute ischemic stroke/TIA patients with non-valvular atrial fibrillation who started to take rivaroxaban or dabigatran and was diagnosed as having cardiac thrombi on transesophageal echocardiography (TEE) within 10 days after the admission between July 2012 and July 2013. All continued to take NOACs without additional antithrombotic agents. Plasma concentrations for rivaroxaban were calibrated based on anti-Xa chromogenic assay for rivaroxaban (Stago®) and thrombin clotting time assay for dabigatran (Hemoclot®) just before (trough) and 4h after medication (peak) at steady state.

Results:

Eight patients (7 men, 52-83 years old) were studied. Their BW ranged 41.0-88.8 kg, $CHADS_2$ ranged 2-5, and NIHSS ranged 2-18. NOACs were initiated at median 3 days and TEE was performed at median 3 days after admission. As a NOAC, one patient took 15 mg o. d. of rivaroxaban, 5 took 10 mg o.d. of rivaroxaban (officially approved dose in Japan) and the other 2 took 110 mg b.i.d. of dabigatran. For all the patients, the thrombus was identified in the left atrial appendage with median size of 14.7 mm; two of them were hyperechoic, being judged as already-organized. In follow-up TEE examinations median 19 days after admission , 5 thrombi disappeared (rivaroxaban in 3, dabigatran in 2), 1 diminished in size (rivaroxaban), and the other 2, all being initially hyperechoic, did not change (rivaroxaban for both). For 6 patients with absolute/partial dissolution of the thrombi, median peak/trough concentrations of rivaroxaban were 69 (19-255)/10 (range10-20) ng/ml, and those of dabigatran were 100 (40-160)/40 (20-60) ng/ml, median peak/trough aPTT was 42/34.5 s in rivaroxaban users and 45/37 s in

dabigatran users, and median peak/trough PT was 20.2/12.9 s and 15.3/13.3 s, respectively.

Conclusion:

Rivaroxaban and dabigatran have potential to resolve non-organized cardiac thrombi. Monotherapy using NOACs may be enough for early prevention of recurrent stroke in patients with cardioembolic stroke/TIA.

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