Table 1 Underlying characteristics and stroke features of patients according to anticoagulant choice at discharge

	Total* (*n* = 1192)	Warfarin (*n* = 650)	Dabigatran (*n* = 203)	Rivaroxaban (*n* = 238)	Apixaban (*n* = 25)	None (*n* = 49)	Any NOAC (*n* = 466)	*P* (W vs. NOAC)
Women	527 (44·2)	313 (48·2)	67 (33·0)	92 (38·7)	8 (32·0)	27 (55·1)	167 (35·8)	<0·001
Age, years	77·7 ± 9·9	79·1 ± 9·7	73·1 ± 8·8	75·8 ± 9·0	74·0 ± 12·0	85·0 ± 10·7	74·5 ± 9·2	<0·001
CHADS2†	4 [3–4]	4 [3–5]	3 [3–4]	4 [3–4]	4 [3–4]	4 [3–4]	4 [3–4]	<0·001
CHA2DS2-VASc†	5 [4–6]	6 [5–6]	5 [4–6]	5 [4–6]	5 [4–6]	6 [5–6·5]	5 [4–6]	<0·001
HAS-BLED†	3 [3–4]	3 [3–4]	3 [3–4]	3 [2–4]	3 [3–4]	3 [3–4]	3 [3–4]	0·002
Body weight, kg	56·3 ± 12·3	54·3 ± 12·1	61·4 ± 11·2	58·3 ± 11·5	58·5 ± 15·3	51·9 ± 11·8	59·7 ± 11·7	<0·001
Creatinine clearance, ml/min	56·6 ± 26·3	51·2 ± 25·7	71·7 ± 22·4	61·9 ± 21·8	60·8 ± 33·5	38·4 ± 22·0	66·1 ± 23·3	<0·001
Atrial fibrillation								
Unidentified‡	466 (39·1)	227 (34·9)	88 (43·4)	105 (44·1)	7 (28·0)	24 (49·0)	200 (42·9)	0·007
Paroxysmal	434 (36·4)	210 (32·3)	87 (42·9)	99 (41·6)	10 (40·0)	18 (36·7)	196 (42·1)	<0·001
Premorbid oral anticoagulants								<0·001
Warfarin	341 (28·6)	241 (37·1)	37 (18·2)	49 (20·6)	6 (24·0)	4 (8·2)	92 (19·7)	
Dabigatran	23 (1·9)	15 (2·3)	3 (1·5)	4 (1·7)	0	1 (2·0)	7 (1·5)	
Rivaroxaban	15 (1·3)	7 (1·1)	2 (1·0)	6 (2·5)	0	0	8 (1·7)	
Stroke features								
TIA	51 (4·3)	23 (3·5)	11 (5·4)	15 (6·3)	1 (4·0)	1 (2·0)	27 (5·8)	0·073
Infarct size§								<0·001
Small	263 (23·7)	133 (21·6)	58 (31·2)	57 (26·8)	8 (34·8)	4 (8·7)	123 (29·1)	
Medium	534 (48·1)	277 (44·9)	110 (59·1)	116 (54·5)	14 (60·9)	14 (30·4)	240 (56·9)	
Large	314 (28·3)	207 (33·5)	18 (9·7)	40 (18·8)	1 (4·3)	28 (60·9)	59 (14·0)	
Admission NIHSS score	8 [2–18]	11 [4–20]	4 [1–8]	5 [2–14]	7 [1–14]	18 [9–24]	4 [1–12]	<0·001
NIHSS score at day 7	3 [0–12·75]	6 [1–17]	1 [0–2]	1 [0–4]	2 [0–5]	20 [5·5–27]	1 [0–3]	<0·001
Discharge mRS score	3 [1–4]	4 [1–5]	1 [0–2]	2 [1–3·25]	2 [1–3]	5 [4–5]	1 [0–3]	<0·001

Data are presented as means ± SD, medians (interquartile range), or numbers (%).
*Including 27 patients with acute hospital death.
†After onset of index stroke/transient ischemic attack (TIA).
‡Unidentified prior to index stroke/TIA.
§TIA patients and those with incomplete data are excluded.
mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; NOAC, nonvitamin K antagonist oral anticoagulant.

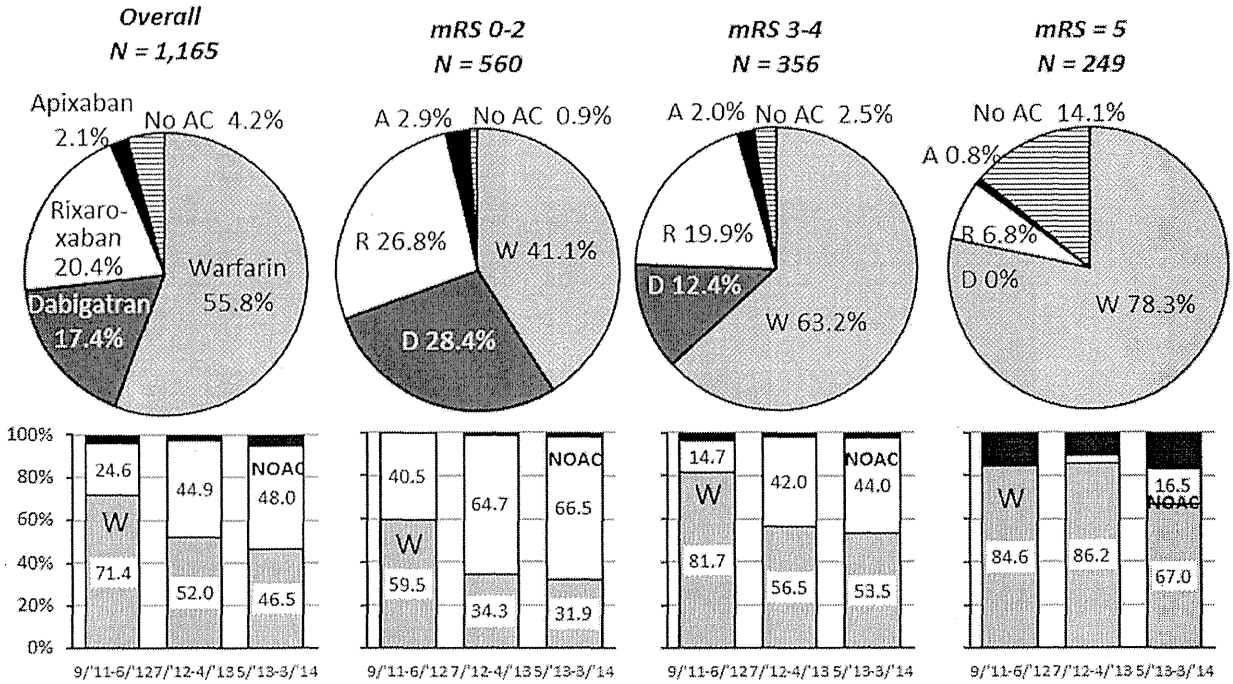

Fig. 1 Choice of oral anticoagulants at acute hospital discharge in overall patients and in patients with different discharge mRS scores. Upper panels: percentage of oral anticoagulant use. Bottom panels: Change in percentage of warfarin and nonvitamin K antagonist oral anticoagulant (NOAC) use over the three periods. $P < 0{\cdot}001$ in all. W, warfarin; D, dabigatran; R, rivaroxaban; A, apixaban; No AC, no anticoagulation.

scores changed from: 2 (95% CI 1–3) to 4 (3–4, $P < 0{\cdot}001$) for $CHADS_2$; from 4 (3–5) to 5 (4–6, $P < 0{\cdot}001$) for CHA_2DS_2-VASc; and from 2 (2–3) to 3 (3–4, $P < 0{\cdot}001$) for HAS-BLED.

Of the 1192 patients, 27 died during acute hospitalization; 20 died directly from stroke. In the remaining 1165 patients, warfarin was chosen as the OAC at discharge for 650 patients (55·8%), dabigatran for 203 (17·4%), rivaroxaban for 238 (20·4%), apixaban for 25 (2·1%), and OACs were not chosen for 49 (4·2%, Fig. 1). Over the three 10-month observation periods, patients taking warfarin decreased from 71·4% to 52·0%, and finally to 46·4%; and patients taking NOACs increased from 24·6% to 44·9%, and finally to 48·1% ($P < 0{\cdot}001$). Patients' characteristics for those on warfarin and those on NOACs were compared (Table 1). NOAC users included more men, were younger, and had lower poststroke scores ($CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED), lower weights, and higher creatinine clearance than warfarin users. NVAF was less commonly identified prior to index stroke/TIA and was more commonly paroxysmal, and premorbid warfarin medication was less common in NOAC users. As stroke features, NOAC users more commonly had small infarcts and had lower NIHSS scores (both on admission and at seven-days) and discharge mRS scores than warfarin users. When only the patients in the third period (May 2013 to March 2014) were assessed, ischemia- and hemorrhage-risk indices were still lower, and the index stroke was still milder in NOAC users than in warfarin users (Supporting Information Table S1). In NOAC users, the creatinine clearance decreased gradually over the three periods (71·6 ± 24·2, 69·0 ± 23·4, 60·9 ± 21·7 ml/min, $P < 0{\cdot}0001$).

The percentages of OAC choice differed greatly among patients with different discharge mRS scores (Fig. 1). In patients with mRS score 0–2, NOACs were more common than warfarin (58·1% vs. 41·1%). In the third period, NOAC use was more than twice as common as warfarin use (66·5% vs. 31·9%). In patients with mRS score 5, warfarin users accounted for 91·1% of any OAC users (195/214).

Of the 1165 patients, 790 (67·8%) did not receive any OAC prior to the index stroke/TIA (Fig. 2a). Of these, 387 (49·0%) chose warfarin, and 359 (45·4%) chose NOACs at hospital discharge. Over the three periods, patients taking NOACs increased from 29·8% to 50·7%, and finally to 52·8% ($P < 0{\cdot}001$). Of the remaining 375 OAC-experienced patients, 337 were warfarin users (Fig. 2b); the median international normalized ratio (INR) of prothrombin time on admission was 1·34 (IQR 1·14–1·66). Of these, 241 (71·5%) with median admission INR of 1·39 (1·14–1·75) resumed warfarin, and 92 (27·3%) with median INR of 1·30 (1·12–1·50) were changed to NOAC.

Warfarin was chosen for 456 (62·8%) of 726 patients with poststroke $CHADS_2 \geq 4$, and 242 (60·0%) of 403 patients with poststroke HASBLED ≥ 4; the percentage of warfarin users decreased gradually, and that of NOAC users increased gradually over the three periods in both groups ($P < 0{\cdot}001$ for both, Fig. 2c,d).

Figure 3a shows the days until starting OAC medication. The median days of initiation after stroke/TIA onset were three-days for warfarin and dabigatran, four-days for rivaroxaban, and 2·5 days for apixaban; the median was four-days (IQR two to six-days) for any NOAC. The median days of initiating NOACs were two-days in TIA patients, three-days in small-size stroke patients, four-days in medium-size stroke patients, and six-days in large-size stroke patients (Fig. 3b, $P < 0{\cdot}01$); they were three-days in

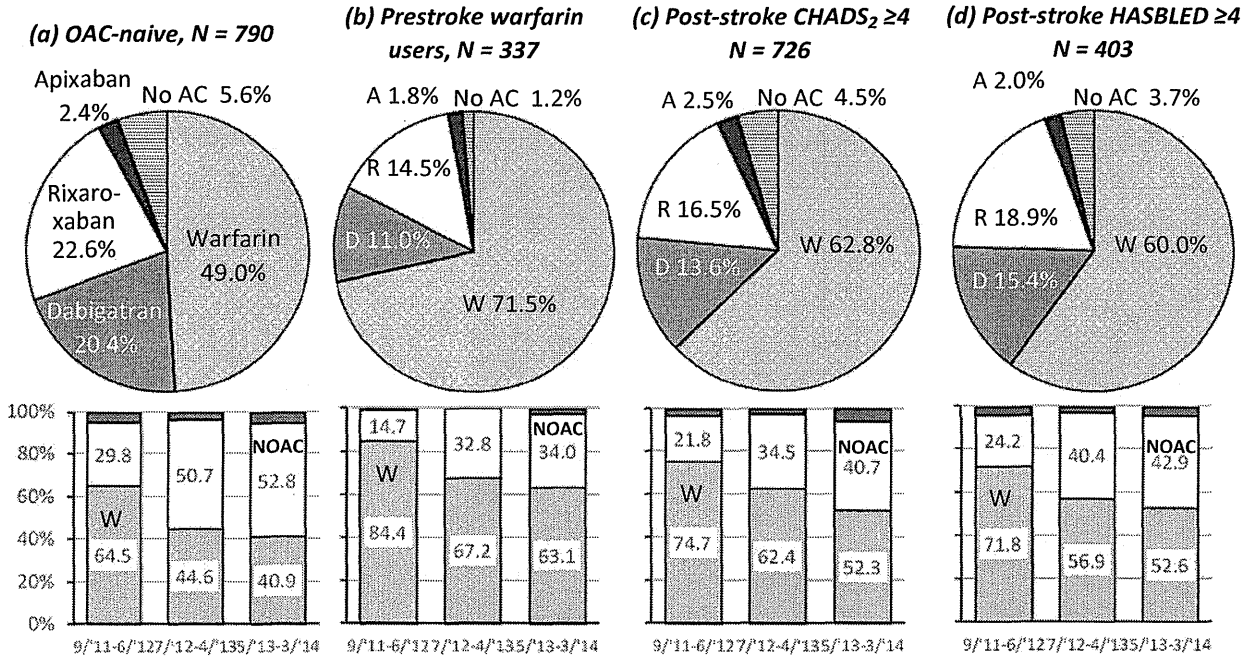

Fig. 2 Choice of oral anticoagulants (OACs) at acute hospital discharge in prestroke OAC nonusers (a), prestroke warfarin users (b), patients with poststroke CHADS2 ≥4 (c), and those with poststroke HASBLED ≥4 (d). Upper panels: percentage of oral anticoagulant use. Bottom panels: change in percentage of warfarin and nonvitamin K antagonist oral anticoagulant (NOAC) use over the three periods. $P < 0{\cdot}001$ in all. W, warfarin; D, dabigatran; R, rivaroxaban; A, apixaban; No AC, no anticoagulation.

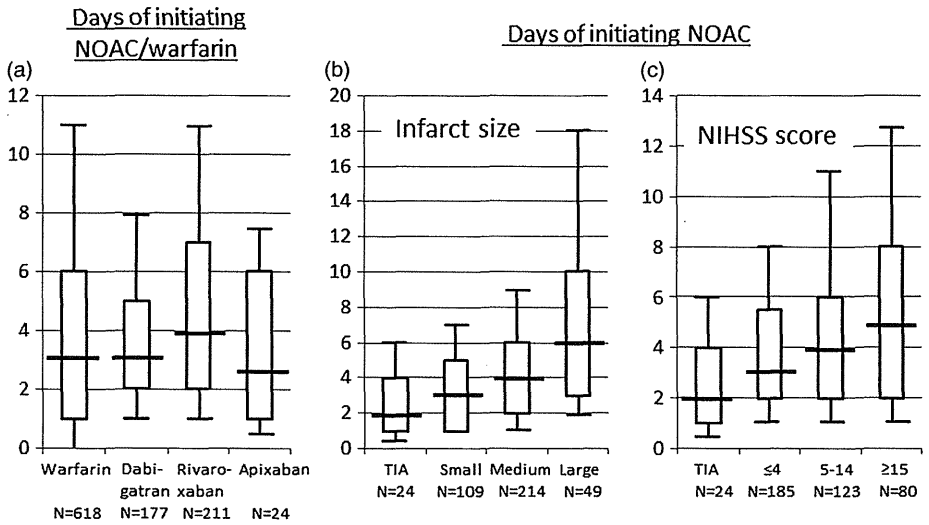

Fig. 3 Days prior to initiating oral anticoagulants (OACs). (a) Days of initiating OACs after onset of index stroke/TIA. Eighty-six patients who changed OACs during acute hospitalization were excluded. (b) Days of initiating nonvitamin K antagonist OACs (NOACs) according to infarct size. (c) Days of initiating NOACs according to initial neurological severity. Boxes represent interquartile range. Lines across box indicate median values. Whiskers represent 10 percentile and 90 percentile values. NIHSS, National Institutes of Health stroke scale; TIA, transient ischemic attack.

patients with admission NIHSS score ≤4, four-days in those with a score of 5 to 14, and five-days in those with a score ≥15 (Fig. 3c, $P < 0{\cdot}01$). As compared with patients starting NOACs at ≥four-days, NVAF was more commonly identified prior to index stroke/TIA and less commonly paroxysmal, infarcts were smaller, and scores of NIHSS (both on admission and at seven-days) and of discharge mRS were lower in patients starting NOACs within three-days (Supporting Information Table S2). One patient who started rivaroxaban two-days after stroke onset developed gastrointestinal bleeding seven-days later. None of the NOAC users developed ICH prior to discharge.

The median duration of acute hospital stay (or 30 days after onset, whichever occurred first) was 27 days in warfarin users, 16 days in dabigatran users, 18·5 days in rivaroxaban users, and 20 days in apixaban users; it was 17 days (IQR 12–26 days) for any NOAC users. After adjustment for gender, age, and initial NIHSS

Table 2 Multivariate-adjusted association of anticoagulant choice with hospital stay within 20 days

	OR	95% CI	*P*
Model 1			
Women (vs. men)	0·73	0·55–0·97	0·031
Age, per 10 years	1·16	1·00–1·34	0·052
Initial NIHSS score, per 1 point	0·91	0·89–0·92	<0·001
NOAC (vs. warfarin)	2·46	1·87–3·24	<0·001
Model 2			
Women (vs. men)	0·79	0·59–1·06	0·112
Age, per 10 years	1·44	1·23–1·69	<0·001
Discharge mRS score, per 1 point	0·53	0·48–0·58	<0·001
NOAC (vs. warfarin)	1·92	1·44–2·56	<0·001

NIHSS, National Institutes of Health stroke scale; NOAC, nonvitamin K antagonist oral anticoagulant; mRS, modified Rankin Scale.

score, NOAC use was independently associated with acute hospital stay within 20 days (OR 2·44, 95% CI 1·86–3·22, Table 2). After adjustment for gender, age, and discharge mRS score, NOAC use was also independently associated with acute hospital stay within 20 days (OR 1·92, 95% CI 1·44–2·56).

Discussion

In this prospective observational study, several major findings related to the trends of OAC choice for NVAF patients with acute ischemic stroke/TIA over 31 months during which three NOACs were approved for clinical use in Japan were identified. The first finding was that warfarin use at acute hospital discharge was still common in patients overall, although NOAC users increased gradually and exceeded warfarin users in the last 11 months. Second, the index stroke was milder and the ischemia-risk indices were lower in patients taking NOACs than in those taking warfarin at discharge. In particular, NOACs were prevalent for independent patients, corresponding to discharge mRS scores 0–2, and warfarin was overwhelmingly more common for patients with mRS score 5. Third, prior OAC nonusers relatively often chose NOACs at discharge as compared with prior warfarin users. In contrast, 72% of prior warfarin users resumed anticoagulation with warfarin, although the stroke/TIA had not been prevented using this agent. Fourth, NOAC therapy was initiated at a median four-days after stroke/TIA onset, with small infarct and mild neurological symptoms being associated with early initiation of NOACs. NOAC users did not develop ICH during acute hospitalization. Finally, NOAC use was independently associated with acute hospital stay after adjustment for initial NIHSS scores or discharge mRS scores.

The European Society of Cardiology guidelines advocate that, when an OAC is recommended for NVAF patients, one of the NOACs should be considered instead of adjusted-dose warfarin (14). The Japanese guidelines also referred to the advantages of NOAC use in patients with $CHADS_2 \geq 2$ (15). On the other hand, in the AHA/ACC/HRS guidelines, the levels of evidence were higher for warfarin than for NOACs (16). As described above, dabigatran was approved in clinical use several months before study initiation, and rivaroxaban and apixaban were approved during the study period in Japan. As it is not allowed to prescribe new drugs for more than 14 days at outpatient clinics within a year after approval in Japan, it usually takes time for the new drug use to increase. This might be a reason that NOAC use was relatively infrequent, and apixaban users were especially infrequent in this study.

Based on the results of a meta-analysis of the trials, NOACs offer better efficacy than warfarin for elderly (≥75 years old) and high $CHADS_2$ score (3–6) patients (17). However, the present NOAC users were younger, had lower $CHADS_2$ scores, and had obviously milder strokes than warfarin users. NOAC use accounted for around three-fifths of patients with discharge mRS scores 0–2, whereas warfarin use accounted for more than nine-tenths of anticoagulant users with discharge mRS score 5. There are a few possible reasons for the uncommon NOAC use for more severe stroke patients. The first reason might be economic issues. In nursing homes and chronic hospitals, it is often difficult to offer expensive drugs due to financial or insurance limitations; thus, NOACs might not be chosen in acute hospitals for patients who are less likely to be directly discharged home. Severe stroke patients might lose their job or become financially disadvantaged and stay away from expensive NOACs. The second possible reason is dysphagia. Dabigatran cannot be crushed and is not suitable for dysphagic patients. Although tablets of rivaroxaban and apixaban may be effective after crushing, the method has not been in wide use as for warfarin (18). In addition, severe stroke patients often have advanced renal insufficiency (19). Because the NOAC with low renal excretion was approved in the later periods, the mean creatinine clearance of NOAC users gradually decreased over the three periods.

Physicians relatively often chose NOACs for OAC-naïves. However, three-fourths of prior warfarin users were put back on warfarin after its failure to prevent stroke/TIA. As most of prior warfarin users showed subtherapeutic INR on admission, many physicians might prefer to continue warfarin with optimal dose adjustment rather than change to NOACs. Nevertheless, it may be difficult to maintain the optimal INR range for patients whose warfarin intensity was once underpowered, because the intensity depends on many factors other than the efforts of physicians.

The optimal timing for initiation of oral anticoagulation has not been established. In the AHA/ASA guidelines, it is regarded as reasonable to initiate OACs within 14 days after onset (20). The European Heart Rhythm Association Practical Guide introduces personalized recommendation using the 1–3–6–12 day rule depending on stroke severity (21). In the present cohort, even severe patients with an initial NIHSS score ≥15 started NOACs at a median five-days after onset. ICH did not occur in NOAC users during acute hospitalization. Thus, early NOAC initiation may be safe. In a study of 41 patients starting NOACs at a median of two-days after onset, symptomatic ICH was not identified (22).

In Japan, hospital stays for acute stroke are usually longer than in other countries partly because of the differences in the medical insurance systems and partly because recovery rehabilitation therapy is also performed in some acute hospitals. Patients taking NOACs had median stays that were 10 days shorter than warfarin

users, and NOAC use was related to shorter stay, independently of initial neurological severity or independence at discharge. The main cause appears to be the difference in the duration for reaching pharmacologically steady state between warfarin and NOACs.

This study has some limitations. First, it was an observational study and the choice of OACs was determined by each investigator. Thus, the underlying characteristics of the OAC users differed greatly. Second, the findings regarding OAC choice and length of hospitalization may not be generalizable to countries where hospital stays are much shorter and warfarin dosing is often stabilized on an outpatient basis. Third, this study did not assess the occurrence of ischemic and hemorrhagic events after registration. This theme will be discussed elsewhere when the observations are completed.

In conclusion, the choice of OAC for stroke/TIA patients with NVAF during the initial years of NOACs in Japan was evaluated. NOAC use increased gradually during the study period, but NOACs were mainly taken by younger patients with milder strokes. The present results might not be innovative but depict the cautious clinical approach of neurologist to the novel pharmacotherapy. A unique feature of this cohort was the relatively high ischemia- and hemorrhage-risk indices after the index stroke/TIA. Using this cohort, we are continuing to explore event occurrence and related characteristics.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Changes in $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores between before and after onset of index stroke or transient ischemic attack.

Table S1. Underlying characteristics and stroke features of patients in the third period (May 2013–March 2014) according to anticoagulant choice at discharge.

Table S2. Underlying characteristics and stroke features of patients starting nonvitamin K antagonist oral anticoagulants (NOACs) within three-days after onset and those initiating NOACs at four-days or later.

Appendix S1. Participating sites and investigators.

Hypertension Research (2014) 37, 463–466

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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$_2$DS$_2$-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 ⩾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$_2$DS$_2$-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$_2$DS$_2$-VASc scores with risks of ischemic stroke and bleeding events, as well as to examine those of the components of the CHA$_2$DS$_2$-VASc score. A P-value <0.05 was considered significant.

Table 1 Baseline clinical characteristics

		CHADS$_2$			*CHA$_2$DS$_2$-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$_2$DS$_2$-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, $P = 0.064$).

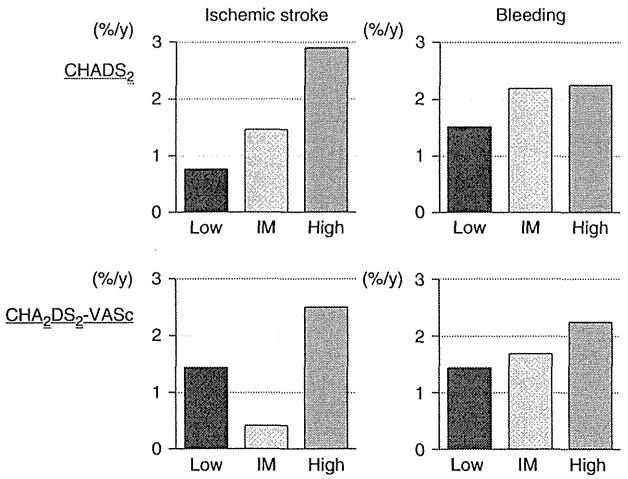

Figure 1 Annual incidence of ischemic stroke and bleeding events by $CHADS_2$ and CHA_2DS_2-VASc scores. Low, score of 0; IM (intermediate), score of 1; high, score of ⩾2.

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 HEMOR-R$_2$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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RESEARCH ARTICLE

Anticoagulation Intensity of Rivaroxaban for Stroke Patients at a Special Low Dosage in Japan

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Competing Interests: KT, TM, KN, and KM report speakers' honoraria from Bayer. Kazunori Toyoda and Toshiyuki Miyata are PLOS ONE Editorial Board members. This, in addition to the previously declared competing interests, does not alter the authors' adherence to PLOS ONE Editorial policies and criteria.

Abstract

Objectives: In Japan, low-dose rivaroxaban [15 mg QD/10 mg QD for creatinine clearance of 30–49 mL/min] was approved for clinical use in NVAF patients partly because of its unique pharmacokinetics in Japanese subjects. The aim of the study was to determine the anticoagulation intensity of rivaroxaban and its determinant factors in Japanese stroke patients.

Methods: Consecutive stroke patients with NVAF admitted between July 2012 and December 2013 were studied. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and estimated plasma concentration of rivaroxaban (C_{riv}) based on an anti-factor Xa chromogenic assay were measured just before and 4 and 9 h after administration at the steady state level of rivaroxaban. Determinant factors for C_{riv} were explored using a linear mixed-model approach.

Results: Of 110 patients (37 women, 75±9 years old), 59 took 15 mg QD of rivaroxaban and 51 took 10 mg QD. C_{riv} at 4 h was 186 ng/mL for patients taking 15 mg QD and 147 ng/mL for those taking 10 mg QD. Both PT and aPTT were positively correlated with C_{riv}. C_{riv} was 72% lower at 4 h in 15 patients receiving crushed tablets than in the other patients, and tablet crushing was significantly associated with lower C_{riv} (adjusted estimate −0.43, 95% CI −0.60 to −0.26) after multivariate-adjustment.

Conclusion: The anticoagulation effects of rivaroxaban in the acute stroke setting for Japanese NVAF patients were relatively low as compared with those in the ROCKET-AF and J-ROCKET AF trials. Tablet crushing, common in dysphagic patients, decreased C_{riv}.

Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke and thromboembolism, and effective antithrombotic therapy significantly reduces this risk [1]. Oral anticoagulant therapy with vitamin K antagonists (VKAs) has been established as the standard for stroke prevention in patients with AF [2]. Recently, novel oral anticoagulants (NOACs) have emerged as an alternative to VKAs for thromboembolic prevention in patients with nonvalvular AF (NVAF). Among these, rivaroxaban (Bayer Schering Pharma AG, Wuppertal, Germany) is an oral direct activated coagulation factor X (FXa) inhibitor that binds directly to the catalytic site of the serine protease FXa independently of antithrombin and inhibits both free and prothrombinase-bound FXa [3].

To reduce the risk of stroke and systemic embolism in patients with NVAF, special low dosages of rivaroxaban are recommended in Japan; i.e. 15 mg quaque die (QD) for patients with creatinine clearance (CrCl) $\geq$50 mL/min, and 10 mg QD for those with CrCl of 15–49 mL/min, as compared to globally approved dosages of 20 mg QD and 15 mg QD, respectively. This recommendation was based on the unique pharmacokinetics in Japanese subjects showing higher rivaroxaban exposure than Caucasian subjects when using the same dosage [4], and the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET AF) proved the safety and efficacy of this low-dose rivaroxaban medication in Japanese NVAF patients [5]. However, the anticoagulation effect of rivaroxaban, especially with the low dosage, has been understudied in the acute stroke setting because acute stroke patients were excluded in the above pharmacokinetics study and trial. For example, the ROCKET-AF, J-ROCKET AF, RELY, and ENGAGE AF-TIMI 48 excluded acute stroke patients within 14 days after onset [5, 6, 7, 8], and the ARISTOTLE excluded those within 7 days from enrollment [9]. Thus, these major trials did not prove the efficacy and safety of NOACs for acute stroke patients at all. Various clinical conditions associated with stroke, such as highly advanced age, differences in drug administration, and potential damage to the kidney and other organs by acute stroke effects, might affect anticoagulation intensity. To examine the issue of the anticoagulation effect of rivaroxaban in clinical practice, the aim was to determine the anticoagulation intensity of rivaroxaban and its determinant factors in Japanese patients with stroke.

Methods

Ethic Statement

The study conformed to the guiding principles of the Declaration of Helsinki and was approved by the local ethics committee of National Cerebral and Cardiovascular Center. All patients or their next of kin gave their written informed consent to participate.

Patients and demographic data

Among patients admitted to our cerebrovascular unit due to stroke and transient ischemic attack (TIA) from July 2012 through December 2013 (recruitment interrupted from August 2013 to November 2013 due to technical problems), data of patients who had NVAF and started to take rivaroxaban for the prevention of stroke and systemic embolism were collected prospectively.

The baseline characteristics of patients, including components of the $CHADS_2$ and CHA_2DS_2-VASc scores, weight, National Institutes of Health Stroke Scale (NIHSS) score, renal function, and other medications on the day of blood collection, as well as whether the rivaroxaban tablet was crushed, were recorded. Renal function was expressed as CrCl using the Cockcroft and Gault equation.

Blood Collection and Measurements of Coagulation Assays

All patients took rivaroxaban after breakfast. Blood sampling was performed at least 2 days after rivaroxaban was started, when its concentration was considered to have reached steady state. Two venous blood samples were collected each time in citrate-containing tubes just before (0 h) and 4 h and 9 h after drug administration. The sampling point at 4 h was meant to capture the maximum concentration of rivaroxaban because the maximum concentration has been reported to occur 1 to 3 h after tablet intake and to be delayed by 2 h with food [10]. The sampling point at 9 h was meant to reflect the half-life of rivaroxaban, which has been reported to be 11 to 13 h in the elderly, partly due to renal dysfunction [11]. For 1 of the 2 tubes, following double centrifugation at 2,500 g for 15 min, platelet-poor plasma was collected, quick-frozen, and stored at −80℃ until the analysis for anti-FXa activity was performed. Blood samples were drawn into a citrate-containing tube using a 21-gauge needle. The prothrombin time (PT, Recombiplastin [Instrumentation Laboratory, Bedford, MA, USA] and activated partial thromboplastin time (aPTT, Actin [Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA]) were measured immediately, and the calibrated plasma rivaroxaban concentration (C_{riv}) was analyzed based on the anti-FXa activity (anti-factor Xa chromogenic assay, STA-Liquid Anti-Xa [Diagnostica Stago, Asnières, France]) of the stored samples. Anti-factor Xa chromogenic assays have previously been shown to have acceptable accuracy and precision [12], and they have been recommended for quantitative measurements of rivaroxaban exposure, using rivaroxaban calibrators with results expressed as ng/mL of rivaroxaban. The minimum detectable sensitivity of estimated rivaroxaban concentration based on the anti-factor Xa chromogenic assay was 10 ng/mL. If the estimated rivaroxaban concentration was below the limit of detection, it was treated as 5 ng/mL for convenience. These assays were all measured on a STA-R coagulometer (Diagnostica Stago, Asnières, France).

Statistical analysis

Data are presented as values and percentages, means ± SD, or medians (interquartile range). Rivaroxaban concentrations were log-transformed due to right skewness of the original distributions (log C_{riv}). The baseline characteristics and laboratory profiles were compared by rivaroxaban dosage subgroup using the Wilcoxon signed-rank test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

In order to identify variables affecting rivaroxaban concentrations at the three fixed time points, a linear mixed-effects (LME) model approach was adopted. LME models are statistical models that are used in the analysis of clustered or longitudinal data. LME models estimate the relationship between the dependent variable and the predictors included in the model, accounting for both the fixed effects and the random effects of the independent variables. Compared with linear regression models without considering clustering or temporal effects, LME models are able to more accurately estimate the fixed effects by estimating the covariance structure through the inclusion of individual-specific random effects [13]. First, for the purpose of selecting the variables to be included in the model, the effects of various baseline characteristics on rivaroxaban concentrations were evaluated, using a LME model with fixed effects for each variable and time points of blood sampling and a random effect for patients. Second, variables with $P<0.20$ and time points of blood sampling were included as fixed effects in the LME model performed with rivaroxaban concentrations, whereas patients were treated as a random effect. The level of significance was set at 95% ($P=0.05$). Statistical analysis was performed using JMP, version 10.0.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' Characteristics

A total of 126 patients started to take rivaroxaban. Of these, seven patients who did not consent to participate, one with off-label dosage (7.5 mg QD), and eight who took rivaroxaban with the evening meal were excluded. Thus, 110 patients (37 women, 75±9 years old) were studied. All patients had breakfast or tube feeding in the morning on the day of blood collection. Fifty-nine patients (54%) took 15 mg QD of rivaroxaban, and the other 51 took 10 mg QD. Thirty-seven patients (34%) taking 10 mg QD had renal function of CrCl 30–49 mL/min. In addition, six patients with prior intracerebral hemorrhage, one with prior muscular hemorrhage, and seven very elderly patients took 10 mg QD based on the judgment of the physician in charge even though their CrCl values were 50 mL/min or greater. Eighty-four patients (76%) were hospitalized due to acute ischemic stroke, and rivaroxaban was initiated at a median of 5 days after symptom onset. Eight patients were hospitalized due to acute TIA (initiation of rivaroxaban at a median of 2.5 days), and seven were hospitalized due to acute intracerebral hemorrhage (at a median of 11 days). The other 11 patients were

Table 1. Baseline clinical characteristics of patients.

	Overall (n=110)	15 mg QD (n=59)	10 mg QD (n=51)	P value
Women	37(34)	13(22)	24(47)	0.008
Age, y	74.6±9.4	68.8±7.4	81.4±6.6	<0.001
Congestive heart failure	13(12)	3(5)	10(20)	0.035
Hypertension	70(64)	36(61)	34(67)	0.558
Diabetes mellitus	29(26)	15(25)	14(27)	0.831
Index cerebrovascular events				0.949
Acute ischemic stroke	84(76)	46(78)	38(74)	
Acute TIA	8(7)	5(9)	3(6)	
Acute intracerebral hemorrhage	7(6)	2(3)	5(10)	
Chronic ischemic stroke	11(10)	6(10)	5(10)	
Prior vascular disease	11(10)	5(9)	6(12)	0.752
$CHADS_2$	2(1–3)	1(1–2)	2(2–3)	0.001
CHA_2DS_2-VASc	3(2–4)	2(1–4)	4(3–5)	0.001
Weight	59.1±11.0	64.0±9.4	53.4±10.0	<0.001
NIHSS score on admission	4(2–14)	4(2–13)	5(1–15)	0.727
Concomitant use of antiplatelet agent	8(7)	4(7)	4(8)	0.831
Creatinine clearance (mL/min)	61.6±20.0	74.0±16.7	47.2±12.4	<0.001
30–49 mL/min	37(34)	0(0)	37(73)	<0.001
Liver dysfunction				
Child-Pugh grade B or C	0(0)	0(0)	0(0)	0.999
Tablet crushing	15(14)	5(9)	10(20)	0.103
Time from initiation of rivaroxaban to blood sampling, day	6(5–7)	6(5–7)	6(5–8)	0.625
Time from stroke/TIA onset to blood sampling, day*	12(8–15)(n=99)	12(8–13)(n=53)	12(9–15)(n=46)	0.212

Data are numbers (%), means±SD, or medians (interquartile range). *Patients with chronic ischemic stroke are excluded. TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

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hospitalized due to chronic ischemic stroke. The baseline characteristics of the patients are shown in Table 1. Fifteen patients received crushed rivaroxaban tablets due to dysphagia (five orally and ten via a nasogastric (NG) tube of which tip placement in the stomach was confirmed by chest X-ray).

Coagulation markers and estimated rivaroxaban concentration

The distribution of plasma coagulation markers is shown in Table 2. Among the three sampling points, 99 patients (90%) reached the highest estimated concentration of rivaroxaban at 4 h, while the other 11 (10%) reached it at 9 h. The baseline characteristics of these 11 patients did not differ from those of the remaining 99 patients.

Coagulation markers and C_{riv} at 0 h, 4 h, and 9 h after administration of two different dosages are shown in Figure 1. Between the two dosage groups, there were no significant differences in aPTT and PT at all sampling points. The 15 mg QD group demonstrated higher rivaroxaban concentrations at 0 h and 9 h than

Table 2. Coagulation markers and estimated rivaroxaban concentration.

	0 h	4 h	9 h
aPTT, sec	32(29–34)	43(37–48)	37(34–41)
PT, sec	12.8(12.1–13.7)	19.4(16.7–22.3)	16.3(14.5–18.2)
PT-INR	1.04(0.98–1.11)	1.56(1.34–1.80)	1.32(1.17–1.47)
Rivaroxaban concentration, ng/mL	11(5–22)	168(109–243)	65(44–103)

aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio.

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the 10 mg QD group [Figure 1], and the median C_{riv} was 27% higher at 4 h (186 ng/mL vs. 147 ng/mL) and 24% higher at 9 h (73 ng/mL vs. 59 ng/mL).

Both PT and aPTT values were prolonged in a concentration-dependent manner, and they showed positive correlations with C_{riv} at 0 h, 4 h, and 9 h (Figure 2). The linearity of the relationship seen between PT and C_{riv} had a higher R^2 value than that between aPTT and C_{riv}.

In comparison to the 95 patients receiving regular tablets, the other 15 patients receiving crushed tablets showed lower rivaroxaban concentrations at all three time points [Figure 3]; the median C_{riv} was 72% lower at 4 h (54 ng/mL vs. 193 ng/mL, $P<0.001$) and 70% lower at 9 h (21 ng/mL vs. 71 ng/mL, $P<0.001$). C_{riv} did not differ between the ten patients receiving crushed tablets via an NG tube (median 46 ng/mL at 4 h) and the five patients receiving oral administration (median 69 ng/mL, $P=0.624$). After exclusion of these 15 patients, the median C_{riv} at 4 h of the 95 patients receiving regular tablets was 193 ng/mL (206 ng/mL for 54 patients on 15 mg QD and 168 ng/mL for 41 patients on 10 mg QD). The median PT (15.8 sec vs. 20.0 sec at 4 h, $P<0.001$) and aPTT values (14.5 sec vs. 16.7 sec t 4 h, $P<0.001$) were also shorter in patients receiving crushed tablets than in the other patients.

In addition to tablet crushing ($P<0.001$), congestive heart failure ($P=0.073$), diabetes mellitus ($P=0.005$), NIHSS score on admission ($P=0.022$), rivaroxaban

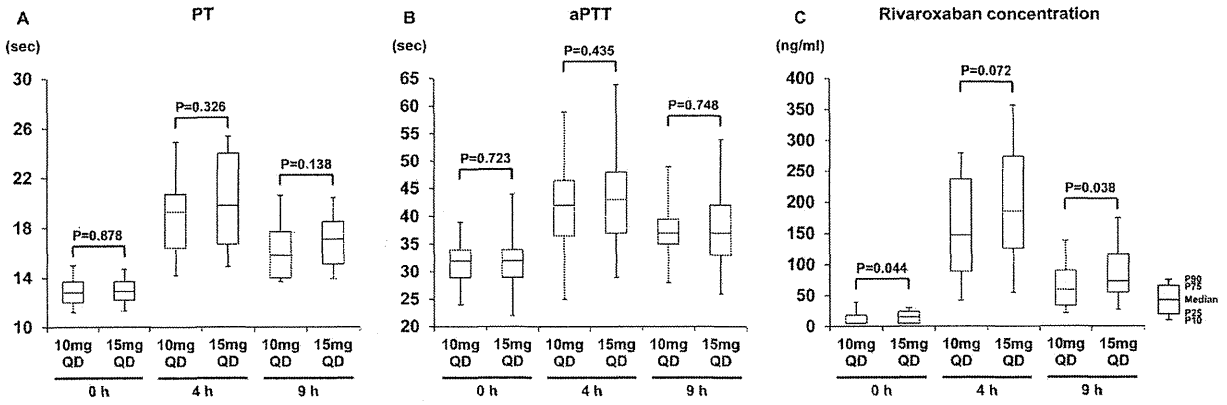

Figure 1. PT (A), aPTT (B), and rivaroxaban concentration (C_{riv}) at 0 h, 4 h, and 9 h after administration.

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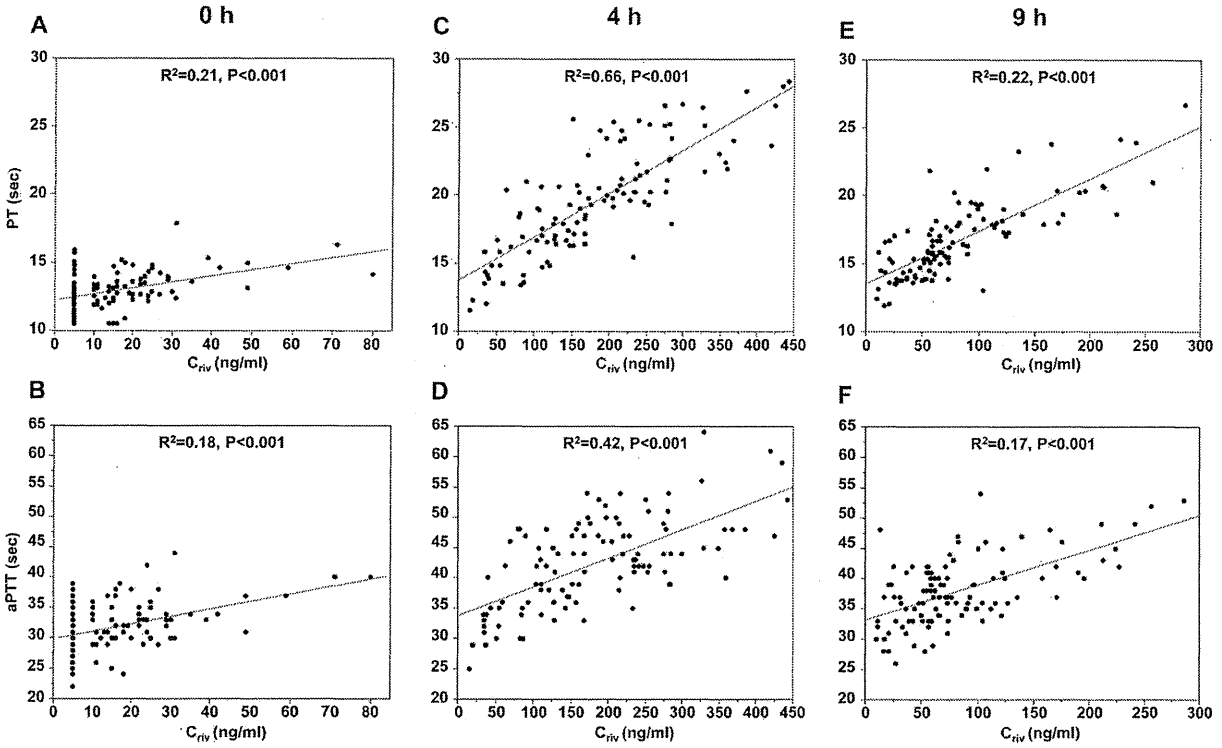

Figure 2. Correlations of estimated rivaroxaban concentration (C_{riv}) with PT (sec) and aPTT (sec) at 0 h (A, B), 4 h (C, D), and 9 h (E, F).

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dosage (P=0.029), and time from stroke/TIA onset to blood sampling (P=0.010) were identified as variables with P<0.20 by the preceding analysis for the linear mixed-effect model. Table 3 provides the adjusted estimates and 95% confidence intervals for the linear mixed-effect model. The results showed that diabetes mellitus (P=0.029), time from stroke/TIA onset to blood sampling (P=0.047), and tablet crushing (P<0.001) were significantly associated with C_{riv}.

Discussion

In the present study, the outcomes of conventional clotting tests and anti-factor Xa chromogenic assays in Japanese stroke patients taking rivaroxaban were evaluated to assess the anticoagulation intensity of rivaroxaban and explore its determinant factors. The anti-factor Xa chromogenic assay has showed acceptable accuracy and precision for quantitative measurements of rivaroxaban exposure, using rivaroxaban calibrators. The first major finding of this study was that C_{riv} at 4 h, indicating nearly peak concentration, was relatively low as compared with the maximum C_{riv} values in the ROCKET AF and J-ROCKET AF trials. The second major finding was that tablet crushing decreased anticoagulation intensity.

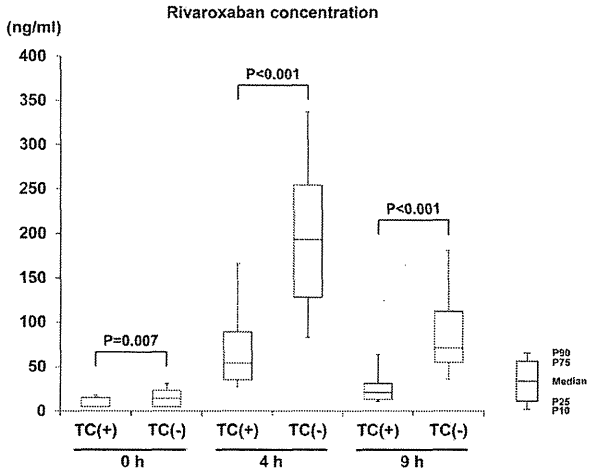

Figure 3. Comparison of rivaroxaban concentrations between groups with tablet crushing [TC (+)] and those without [TC (−)]. TC indicates tablet crushing.

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Since stroke patients are often aged and often have renal dysfunction [14, 15], lower dosages of NOACs tend to be chosen for such patients. In particular, special low dosages of rivaroxaban are recommended in Japan. Thus, we had a concern that C_{riv} in Japanese stroke patients was much lower than C_{riv} from global data. On the other hand, by transiently worsened renal function in the acute stroke setting, there was also a concern about accidental elevation of C_{riv}. According to exposure simulations performed in patients included in the ROCKET AF and

Table 3. Linear mixed-effect model to determine variables that influence rivaroxaban concentration.

Variable		Adjusted Estimate (95%CI)	P value
Congestive heart failure	No	Reference	0.482
	Yes	0.07 (−0.11 to 0.23)	
Diabetes mellitus	No	Reference	0.029
	Yes	0.13 (0.01 to 0.25)	
NIHSS score, per 1 point		−0.01(−0.02 to 0.01)	0.346
Rivaroxaban dosage	15 mg QD	Reference	0.146
	10 mg QD	−0.08 (−0.19 to 0.03)	
Tablet crushing	No	Reference	<0.001
	Yes	−0.43 (−0.60 to −0.26)	
Time from stroke/TIA onset to blood sampling, per day		−0.02 (−0.03 to 0.01)	0.047
Time points of blood sampling	0 h	Reference	
	4 h	1.13 (1.06 to 1.20)	<0.001
	9 h	0.29 (0.22 to 0.37)	<0.001

NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

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J-ROCKET AF trials, the maximum C_{riv} in Japanese patients with 15 mg QD (mean 249 ng/mL, J-ROCKET AF) was identical with that in non-Japanese patients with 20 mg QD (mean 249 ng/mL, ROCKET AF), and the maximum C_{riv} in Japanese with 10 mg QD (mean 168 ng/mL) was lower than that in non-Japanese with 15 mg QD (mean 229 ng/mL) [4]. These levels were still higher than the mean C_{riv} at 4 h in the present patients (197 ng/mL for 15 mg QD, 163 ng/mL for 10 mg QD). A reason for the large difference in C_{riv} was inclusion of patients receiving crushed tablets in the present study, since the mean C_{riv} at 4 h only in the patients receiving uncrushed tablets showed smaller differences from previous data (207 ng/mL for 15 mg QD, 188 ng/mL for 10 mg QD).

Previous studies demonstrated an 18% decrease in maximum C_{riv} for the crushed tablets suspended in water and administered via an NG tube followed by a liquid meal, compared to that after the whole tablet [10, 16], and a 29% decrease in AUC and a 56% decrease in maximum C_{riv} when the granulate was directly released into the proximal small intestine immediately followed by food. Thus, absorption of rivaroxaban seems to be dependent on the site of drug release in the gastrointestinal tract [10]. Indeed, the manufacturer recommends avoiding administration of rivaroxaban directly into the proximal small intestine (e.g., feeding tube) and illustrates the administration of crushed tablets via an NG tube or gastric feeding tube as a special option if patients are unable to swallow whole tablets. However, the present differences in C_{riv} between patients receiving crushed tablets and those receiving whole tablets were more divergent (72% at 4 h) than the above-mentioned results. Since rivaroxaban tablets are small, practically insoluble in water, and need to be crushed and suspended in water instead of a simple suspension method when administered via an NG tube [10], drug loss in the grinding, sifting, and packaging processes or drug remaining in the syringe and NG tube may occur.

Another possible reason for the low C_{riv} in the present patients was that the data were based on fixed time-point measurements, not on consecutive measurements to identify the peak level. The timing of blood sampling at 4 h in the present study was determined based on the previous finding noted in the Methods [10]. However, 10% of the present patients showed higher C_{riv} at 9 h than at 4 h, suggesting that the peak concentration time could be delayed in the clinical setting of acute stroke care, probably because the patients are old and often have renal dysfunction. Additionally, a previous phase-1 study displayed minor double peaks in rivaroxaban concentration after receiving crushed tablets via NG tubes; the first peak occurring around 45 minutes, and the second one between 4 and 6 h [16]. Our sampling timing at 4 h may be the nadir of biphasic peaks.

Although reduced CrCl is the only criterion for selecting a low dosage of rivaroxaban (10 mg QD) in Japan, 14 patients without a reduced CrCl were also given a low dosage based on the judgments of the physicians in charge because they had a history of bleeding or were very old. Such judgments appeared to contribute to the present low C_{riv} values. In addition, some patients might show higher serum creatinine levels in the acute stage of stroke than usual due to

hypovolemia and potential damage by acute stroke. CrCl in such patients might return to higher levels within several days; that might be another cause of the present low C_{riv} values.

The present study showed a linear relationship between PT and C_{riv}, as was also shown in the J-ROCKET AF and ROCKET AF trials [4, 17]. The present study also showed a linear relationship between aPTT and C_{riv}, although the R^2 level was lower than that of PT, and most earlier publications showed that aPTT is less sensitive than PT for rivaroxaban exposure assessment [18, 19]. However, the aPTT and PT results should be carefully interpreted because their sensitivities depend on the reagents.

The unique point of the present study was that most of the studied patients were enrolled into the study soon after onset of stroke or TIA; such acute patients were excluded from the major clinical trials [5, 6, 7, 8, 9] and have been infrequently studied after the approval of clinical use of NOACs. Although the optimal timing for initiation of NOACs has not been established, none of 412 patients who began to take NOACs in acute stage of ischemic stroke/TIA did not develop intracranial hemorrhage during acute hospitalization in our ongoing multicenter observational SAMURAI-NVAF study (Toyoda K, et al: unpublished data). The limitations of the present study included a relatively small sample size and the poor estimation accuracy of the anti-Xa chromogenic assay for C_{riv} when the concentration is low, as well as the fixed-point measurement of anticoagulation intensity.

In conclusion, this is the first study of Japanese stroke patients examining the anticoagulation intensity of rivaroxaban. The impressive finding was that tablet crushing, required for dysphagic patients, who are common in stroke medicine, decreased rivaroxaban concentration. Thus, tablet crushing should be carefully considered. At the least, patients with CrCl $\geq$50 mL/min should not be given a lower dosage (10 mg QD) when they need tablet crushing.

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Author Contributions

Conceived and designed the experiments: TO. Performed the experiments: TO. Analyzed the data: TO. Contributed reagents/materials/analysis tools: TO AO TM. Wrote the paper: TO KT. Provided study supervision: KN KM.

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