Intracranial Hemorrhage Caused by Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

– Multicenter Retrospective Cohort Study in Japan –

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Background: We conducted a multicenter retrospective cohort study to elucidate the characteristics of intracranial hemorrhage (ICH) in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants (NOACs).

Methods and Results: We sent a questionnaire to the directors of 241 stroke centers in Japan to establish the clinical characteristics of NOAC-associated cerebral hemorrhage (CH), including hematoma size, hematoma enlargement (HE) and in-hospital mortality of patients treated in their institutions. We undertook a literature review to establish the clinical characteristics of warfarin-associated CH and compared these with our data. We received 174 responses (72.2%), of which 67 (38.5%) gave anonymous details of 130 eligible patients (male, 67.7%; mean age, 77.3±8.3 years, in-hospital mortality rate, 11.5%). We judged that 87 of the 130 patients had presented with CH: one-fifth had taken antiplatelet drugs. We found that the incidences of HE and mortality in the 87 patients presenting with NOAC-associated CH were lower than would have been expected in those with warfarin-associated CH (17% vs. 26%, and 16% vs. 35%, respectively).

Conclusions: More than half the stroke center directors who responded to our questionnaire had not experienced cases of NOAC-associated ICH. Compared with warfarin, NOACs appear to present a lower risk of HE and death in patients with atrial fibrillation who develop CH. (*Circ J* 2015; **79**: 1018–1023)

Key Words: Atrial fibrillation; Cerebral hemorrhage; Intracranial hemorrhage; Non-vitamin K antagonist oral anticoagulants

Patients with atrial fibrillation (AF) should be administered anticoagulant therapy to prevent thromboembolic events such as ischemic stroke.^{1–5} Treatment, however, may be complicated by anticoagulant-associated intracranial hemorrhage (ICH); there is a well-recognized risk of cerebral hemorrhage (CH), resulting in poor outcome or death, in patients treated with warfarin.^{3,6–11} Hematoma enlargement (HE) further increases the risk in patients who have developed CH.^{12,13}

ICH in Asians have not yet been established.

The aim of this study was to use a nationwide questionnaire survey in Japan to elucidate the characteristics of AF patients taking NOACs who developed CH, and to establish the extent of the relationship between treatment with NOACs and adverse clinical outcomes such as HE and death.

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Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly in widespread use, and are frequently used as substitutes for warfarin because of their more favorable safety and efficacy profiles.^{3,6–10} There have been many reports that NOACs carry a lower risk of ICH than warfarin.^{3,8–11,14,15} Asians have a higher risk of warfarin-associated ICH than non-Asians;^{16,17} however, the characteristics of NOAC-associated

Methods

Study Design

We conducted a nationwide, multicenter, retrospective cohort questionnaire survey in May 2014. The questionnaire was sent by post to the directors of 241 stroke centers in Japan that met 2 criteria: (1) providing acute stroke management as defined by the Japanese Neurosurgical Society and/or the Societas Neurologica Japonica, and (2) equipped as a stroke unit and/or a specialized stroke care unit with or without intensive care unit provision. Participating hospitals were selected from 7

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districts according to juridical regions defined by the Ministry of Health, Labor and Welfare, Japan, depending on the population residing in each district: Hokkaido (18 hospitals); Tohoku (17 hospitals); Kanto (76 hospitals); Chubu (35 hospitals); Kinki (36 hospitals), Chugoku-Shikoku (26 hospitals), and Kyushu (33 hospitals). Details of the questionnaire and response rates are provided in [Supplementary File 1](#). A covering letter accompanying the survey informed recipients that: (1) any neurologist or neurosurgeon at the director's institution who had experienced at least 1 case of ICH among patients with AF during NOAC therapy between March 2011 and April 2014 was eligible to complete the survey; (2) that participation was voluntary; and (3) that responses should comprise anonymized patient data and be approved by the center director. Responses not approved by the stroke center director were excluded. Data were collected from returned questionnaires by research assistants and a neurologist (N.S.). The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Kawasaki Medical School Hospital. The study was registered with the UMIN Clinical Trials Registry (UMIN000014230).

Questionnaire

We categorized ICH into the 3 types: CH, subarachnoid hemorrhage (SAH) and subdural hematoma (SDH). The characteristics of the hematoma such as location and volume (calculated using the ABC/2 formula,^{12,13} [Appendix S1](#)) were recorded. Hematoma expansion was defined as >33% enlargement in hematoma volume on subsequent images compared with the baseline hematoma volume on admission.¹³ Treatment with a NOAC was defined as any use of dabigatran, rivaroxaban or apixaban. The questionnaire also required the inclusion of: (1) demographic data such as age, sex and CHADS₂ score²; (2) risk factors; (3) medical history; (4) medications on admission (antiplatelet drugs, warfarin, NOACs, or dual therapy defined as use of both a NOAC and an antiplatelet drug); (5) the results of laboratory investigations; (6) brain imaging findings; (7) National Institutes of Health Stroke Scale (NIHSS) score on admission; (8) details of treatment after admission; (9) clinical outcomes such as modified Rankin scale (mRS) scores at discharge, discharge destination and death in hospital.

Literature Search and Data Extraction

We undertook a literature review to establish the clinical characteristics of warfarin-associated CH and compared these with our data. Relevant literature was identified by searches of Medline using the search terms "NOAC" or "non-vitamin K antagonist oral anticoagulants", "warfarin" or "oral anticoagulants", and "ICH" or "CH" in the date range January 2001 to September 2014. Only papers in English were reviewed. We manually reviewed all papers, selected relevant references and extracted the data.

Statistical Analysis

Continuous, ordinal and categorical variables are expressed as mean $\pm$ standard deviation, median and interquartile range, and frequencies and proportions (percentages), and were compared using the unpaired Student's t-test, Wilcoxon rank-sum test, and χ^2 test, respectively. We assessed the relationships between the characteristics of the patients who developed ICH, in particular those who developed CH, and therapy with a NOAC, HE and in-hospital death. We compared the incident rates of HE and death between patients treated with a NOAC and those with warfarin, using data obtained from the literature review. We identified the mean incident rates of HE and death in the warfarin group using the published data available, but did not undertake formal analyses as we did not have access to raw data. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). All comparisons were 2-tailed and $P < 0.05$ was considered statistically significant. All data were analyzed using the JMP 11.2 software package (SAS Institute Inc, Cary, NC, USA).

Results

Patients

Of 241 stroke center directors, 174 returned the questionnaire ([Figure S1](#)). Those who participated are listed in [Appendix S2](#). More than half (95 of 174 respondents, 54.6%) had not experienced a case of a patient with AF treated by a NOAC and complicated by ICH, but 67 responded with details of 130 eligible patients ([Figure A](#)). The diagnoses of ICH were as follows: CH (n=87, 67.0%), SDH (n=30, 23.0%), SAH (n=6,

Table 1. Characteristics of Patients in Atrial Fibrillation Presenting With ICH During Treatment With NOAC

	ICH	Classification of ICH				P value
		CH	SDH	SAH	Other	
Demographics						
n (%)	130 (100)	87 (67.0)	30 (23.0)	6 (4.6)	7 (5.4)	
Age, years	77.3±8.3	76.2±8.1	80.0±8.4	81.2±9.7	76.7±6.7	0.127
Male sex, n (%)	88 (67.7)	62 (71.3)	21 (70.0)	3 (50.0)	2 (28.6)	0.096
Physical status						
SBP, mmHg	158 (136–179)	164 (140–185)	140 (129–165)	164 (128–179)	158 (141–185)	0.017
DBP, mmHg	85 (74–100)	87 (76–103)	74 (65–88)	88 (75–100)	94 (79–109)	0.009
NIHSS score	12 (3–20)	14 (4–21)	5 (2–11)	2 (0–28)	9 (2–12)	0.141
CHADS ₂ score	3 (1–4)	3 (2–4)	3 (2–4)	4 (2–4)	4 (3–5)	0.092
Risk factors						
Hypertension, n (%)	103 (79.2)	69 (79.3)	24 (80.0)	5 (83.3)	5 (71.4)	0.331
Diabetes mellitus, n (%)	34 (26.2)	20 (23.0)	9 (30.0)	2 (33.3)	3 (42.9)	0.604
CKD, n (%)	103 (79.2)	67 (77.0)	25 (92.6)	6 (100)	5 (71.4)	0.350
Laboratory data						
Serum creatinine, mg/dl	0.8 (0.62–0.91)	0.81 (0.67–0.98)	0.80 (0.64–0.91)	0.66 (0.58–0.86)	0.60 (0.52–0.7)	0.059
eGFR	39.6 (29.3–49.4)	38.4 (30.7–50.4)	39.9 (24.3–45.7)	37.5 (32.4–46.9)	55.5 (33.9–66.3)	0.233
Premorbid medication						
APs, n (%)	28 (21.5)	18 (20.7)	5 (16.7)	2 (33.3)	3 (42.9)	0.418
NOACs						0.004
Dabigatran, n (%)	42 (32.3)	22 (25.3)	16 (53.3)	3 (50.0)	1 (14.3)	
Rivaroxaban, n (%)	82 (63.1)	62 (71.3)	13 (43.3)	3 (50.0)	4 (57.1)	
Apixaban, n (%)	6 (4.6)	3 (3.5)	1 (3.3)	0 (0)	2 (28.6)	
Premorbid antihypertensive drug, n (%)	95 (73.1)	60 (69.0)	24 (80.0)	5 (83.3)	6 (85.7)	0.500
Treatment						
Antihypertensive therapy after onset of ICH, n (%)	102 (78.5)	76 (87.4)	17 (56.7)	5 (83.3)	4 (57.1)	0.002
Vitamin K, n (%)	3 (2.3)	2 (2.3)	0 (0)	1 (16.7)	0 (0)	0.095
PCC, n (%)	13 (10.0)	9 (10.3)	3 (10.0)	1 (16.7)	0 (0)	0.781
Surgery, n (%)	35 (26.9)	11 (12.6)	21 (70.0)	3 (50.0)	0 (0)	<0.001
Discharge						
In-hospital death, n (%)	15 (11.5)	14 (16.1)	0 (0)	1 (16.7)	0 (0)	0.013
mRS 0–2 at discharge	48 (36.9)	20 (23.0)	22 (73.3)	2 (33.3)	4 (57.1)	<0.001

Data are presented as mean±standard deviation, median (interquartile range), or number (%). AP, antiplatelet drug; CH, cerebral hemorrhage; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HE, hematoma enlargement; ICH, intracranial hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; PCC, prothrombin complex concentrate; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SDH, subdural hematoma.

4.6%) and other (n=7, 5.4%). Of the 130 cases reported, the median CHADS₂ score was 3, 103 had chronic kidney disease (CKD), 28 had been receiving dual anticoagulant therapy, 13 were treated with prothrombin complex concentrate (PCC) and 15 (11.5%) died during their hospitalization (Table 1). The complete data are shown in Table S1.

NOAC-Associated CH

The characteristics of the 87 patients who developed CH were as follows: the median CHADS₂ score was 3, 67 had CKD, 18 had been receiving dual therapy, 12 (13.8%) developed HE and 14 (16.1%) died during hospitalization (Table 1). A representative case is shown in Figure S2. The anticoagulation strategy that had been adopted in these patients was as follows (Figure B): low-dose rivaroxaban (10 mg/day, n=33), high-dose rivaroxaban (15 mg/day, n=29), low-dose dabigatran (≤220 mg/day, n=17), high-dose dabigatran (300 mg/day, n=5), and apixaban (10 mg/day, n=3).

Rivaroxaban vs. Dabigatran

Among the patients who developed ICH, patients taking rivaroxaban were at significantly higher risk of CH (76.8% vs. 52.4%, respectively; P=0.008) and HE (19.4% vs. 0%, respectively; P=0.031, Table 2) than those taking dabigatran, but at significantly lower risk of SDH than those taking dabigatran (14.6% vs. 38.1%, respectively; P=0.006).

NOACs vs. Warfarin

We obtained data of warfarin-associated CH from our literature review.^{12,13,18–26} The initial size of the hematoma was at least equal to or smaller in patients treated with NOACs compared with a control group of patients treated with warfarin whose outcomes were published in previous studies (Table 3). The incidence of HE and death in those taking NOACs described by our respondents was lower than in the warfarin control group (14% vs. 26%, and 17% vs. 35%, respectively; Table 3), although lack of raw data from the warfarin studies

Table 2. Comparison of Patients Presenting With CH During Therapy With Dabigatran or Rivaroxaban

	Dabigatran	Rivaroxaban	P value
n	22	62	
Age, years	77.9±7.8	75.8±8.3	0.153*
Male sex, n (%)	13 (59.1)	46 (74.2)	0.183‡
Premorbid mRS 0–2, n (%)	6 (27.3)	9 (14.5)	0.204‡
NIHSS score	12 (3–21)	17 (7–24)	0.379†
CHADS ₂ score	3 (2–3)	3 (2–4)	0.895†
Hematoma volume on admission, cm ³	14.4 (4.5–48.5)	15.8 (6–34)	0.734†
HE, n (%)	0 (0)	12 (19.4)	0.031‡
In-hospital death, n (%)	2 (9.1)	11 (17.7)	0.498‡

*Unpaired Student's t-test; †Wilcoxon rank-sum test; ‡ χ^2 test. Abbreviations as in Table 1.

Table 3. Summary of Present Findings in the Context of Previous Studies of Patients With Atrial Fibrillation Who Developed CH During Antithrombotic Therapy

Reference no.	No. of patients	Anticoagulant	Hematoma, cm ³	HE, n (%)	Mortality, n (%)
Warfarin					
Witt et al ¹⁸	259	Warfarin	NA	NA	99 (27)
Dowlashahi et al ¹⁹	71*	Warfarin	16 (32)	15/33 (46)	30 (42)
Alonso et al ²⁰	723	Warfarin	NA	NA	244 (34)
Chen et al ²¹	94	Warfarin	41±39	NA	36 (38) ^d
Horstmann et al ²²	51	Warfarin	20 (8–49)	4/32 (13)	23 (45) ^c
Kuwashiro et al ¹²	41	Warfarin	34±55	15 (39)	24 (59) ^a
Toyoda et al ¹³	67	Warfarin	23±31	16 (37)	11 (16) ^b
Toyoda et al ¹³	21	Warfarin+AP	29±41	5 (45)	9 (43) ^b
Liotta et al ²³	56	Warfarin	20 (8–76)	NA	21 (37)
Hagii et al ²⁴	56	Warfarin	11 (7–34)	10/48 (21)	10 (18) ^a
Total	1,440	Warfarin	NA [‡]	65/250 (26)	507 (35)
NOAC					
Komori et al ²⁵	2†	Dabigatran	1 and 5	0 (0)	0 (0) ^a
Simonsen et al ²⁶	1	Dabigatran	15	1 (100)	1 (100) ^b
Present study	87	NOAC	15 (6–38)	12/74 (14)	14 (17) ^a
Total	90	NOAC	15 (5–34)	13/77 (17)	15 (16)

^aIn-hospital death; ^bdeath at 3 weeks; ^cdeath at 3 months; ^ddeath at 1 month. *Patients treated with prothrombin complex concentrates for anticoagulant-associated ICH were analyzed. †Among 8 patients who developed ICH, the data of 2 patients who developed CH were extracted. ‡Hematoma size was not averaged because data were not presented consistently, with either mean or median values reported by other investigators. NA, not applicable. Other abbreviations as in Table 1.

meant that these differences were not subject to formal statistical analysis.

In-Hospital Death

Patients presenting with ICH who died during their hospitalization were significantly more likely to have sustained CH, have elevated serum creatinine concentration on admission and were less likely to have been taking an antihypertensive drug before admission (Table S2). Patients presenting with CH who died during their hospitalization had significantly larger hematomas on admission and more elevated admission serum creatinine concentration and were more likely to have been taking antiplatelet drugs (Table S3).

Discussion

We used a nationwide anonymous questionnaire survey to establish the clinical outcomes of Japanese patients who developed NOAC-associated CH. We found that more than half of the

241 stroke centers in Japan that participated had not treated 1 or more patients with NOAC-associated ICH, suggesting that the incidence is low. Those with clinical experience of NOAC-associated CH reported the initial size of the hematoma as smaller, and lower incident rates of both HE and death than would have been expected if their patients had been anticoagulated with warfarin.

Numerous studies have reported the characteristics of NOAC-associated ICH.^{9,24–27} Furthermore, a recent meta-analysis showed that NOACs significantly reduced the risk of ICH compared with warfarin (OR 0.49, 95% CI 0.36–0.65).²⁸ The main difference regarding the anticoagulant mechanism of action of NOACs is that they do not affect the plasma concentration of factor VII or VIIa, but warfarin suppresses factor VII production;^{25,28} both factors are essential in the coagulation cascade. When patients with ischemic stroke undergo thrombolysis, NOACs could also be neuroprotective by inhibiting the activation of matrix metalloproteinase-9 and preventing disruption of astrocytes and pericytes, thereby reducing the further risk

of ICH.²⁹ These differences may explain why treatment with NOACs appears to be associated with lower risks of HE and death in patients with ICH.

Treatment with PCC or other hemostatic agents has been proposed as a means of preventing HE in patients with NOAC-associated ICH;^{16,25} however, it is still unclear whether acute reversal is necessary to improve outcome.²⁶ In our cohort, 12 of the 13 patients treated with PCC survived, although the data were not statistically significant and may have been influenced by selection bias. For example, patients who developed very large hematomas presenting with severe neurological deficit may have been managed conservatively or given palliative care rather than PCC or surgery. This issue will need to be addressed in future studies.

There has been a great deal of interest in establishing whether there are therapeutic differences between the NOACs, and differences in the incidence of adverse events. In our study, the incidence of HE was lower in patients taking dabigatran compared with those taking rivaroxaban, but this finding may have been influenced by our relatively small sample size and non-significant trends suggesting more favorable pre-morbid mRS (0–2) and lower initial NIHSS scores in patients who had been taking dabigatran. However, even when taking these factors into consideration, the findings of other studies suggest that there may be differences between the groups. For example, there is reportedly a substantially lower risk of ICH with dabigatran than warfarin (hazard ratio 0.32, 95% CI 0.20–0.50),¹⁴ but the risk with rivaroxaban is broadly comparable to that with warfarin (hazard ratio 1.17, 95% CI 0.66–2.05).³⁰ Furthermore, bleeding event rates in patients aged ≥75 years taking rivaroxaban are reportedly higher than in those taking warfarin.³¹ Although NOACs consistently reduce the incidence of ICH regardless of the site of the bleed within or outside the brain parenchyma,²⁸ we found significant differences between the rate of CH and SDH in the dabigatran and rivaroxaban groups. Our study was not designed to offer an explanation for the differences in clinical outcomes that we found, but it is possible that the different mechanisms of action of the drugs may be an explanation: rivaroxaban selectively inhibits factor Xa whereas dabigatran inhibits thrombin.^{17,28}

Study Limitations and Strengths

We were unable to adjust for variables that may influence HE and death because of the retrospective design of the study, and we did not conduct a meta-analysis. Despite the high response rate to our survey, selection bias may have occurred. We did not ask our respondents for details of warfarin-induced CH, as we judged that these data would be substantially more onerous for respondents to collect, which might adversely influence the response rate. Furthermore, we did not seek denominator data of NOAC use in the populations served by the stroke centers, which would have allowed us to calculate the incidence of NOAC-induced CH. The HAS-BLED score^{3,32} was not assessed. The increasing global popularity of NOACs means that there are still some safety issues that need to be urgently addressed, and their use substantially increases prescribing costs. It will be important to establish whether the increased costs compared with warfarin are counterbalanced by reductions in the costs of treating stroke, its consequences,³³ or the other complications of anticoagulation. Nonetheless, our study had some notable strengths. We obtained a large sample of patients with NOAC-associated ICH, in particular NOAC-associated CH, allowing us to make some comparisons of dabigatran and rivaroxaban in addition to comparisons of warfarin and NOACs. Although such comparisons of dabigatran and rivaroxaban

have not yet been undertaken, our data could be used to inform the design of larger controlled trials.

Conclusions

The incidence of NOACs-associated CH in Japanese patients with AF appears to be low. Patients who developed NOAC-associated CH had lower incident rates of both HE and mortality than would have been expected had they been treated with warfarin. Comparisons of the incidence and risk of CH among the NOACs, and between NOACs and warfarin, should be investigated in future studies.

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Supplementary Files

Supplementary File 1

Methods

Figure S1. Study flow chart.

Figure S2. Representative case from among those reported by respondents to the questionnaire.

Table S1. Full demographic and clinical characteristics of patients in atrial fibrillation presenting with ICH during treatment with NOAC

Table S2. Characteristics of patients presenting with ICH during NOAC treatment, comparing those who survived with those who died

Table S3. Characteristics of patients presenting with CH during NOAC treatment, comparing those who survived with those who died

Appendix S1. The ABC/2 Method

Appendix S2. Personnel

Please find supplementary file(s);
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