Characteristics of Acute Spontaneous Intracerebral Hemorrhage in Patients Receiving Oral Anticoagulants

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Objective: We investigated the precise clinical and radiologic characteristics of intracerebral hemorrhage associated with direct oral anticoagulant use. *Methods:* Patients with acute spontaneous intracerebral hemorrhage admitted to our department from September 2014 to November 2017 were retrospectively analyzed. Clinical and neuroradiological characteristics of patients with direct oral anticoagulant-related intracerebral hemorrhage, and effects of prior treatment on the severity at admission and on outcome at discharge were assessed. *Results:* Of the 301 enrolled patients (103 women; median age 68 years), 261 received no oral anticoagulants (86.8%), 20 received warfarin (6.6%), and 20 received direct oral anticoagulants (DOACs) (6.6%). Median initial National Institutes of Health Stroke Scale scores differed significantly among the groups ($P = .0283$). Systolic blood pressure ($P = .0031$) and estimated glomerular filtration rate ($P = .0019$) were significantly lower in the oral anticoagulant-related intracerebral hemorrhage group than in other groups. Total small vessel disease scores were significantly higher in the oral anticoagulant-related intracerebral hemorrhage group than in the warfarin group ($P = .0413$). Multivariate analysis revealed that prior oral anticoagulant treatment (odds ratio: 0.21, 95% confidence interval: 0.05-0.96, $P = .0445$) was independently negatively associated with moderate-to-severe neurological severity (stroke scale score $\geq$10) after adjusting for intracerebral hemorrhage location and various risk factors. There were significant differences in hematoma volume in the basal ganglia ($P = .0366$). *Conclusions:* DOAC-related intracerebral hemorrhage may occur particularly in patients with a high risk of bleeding; however, they had a milder initial neurological severity than those with warfarin-related intracerebral hemorrhage, possibly due to relatively smaller hematoma volume, especially in the basal ganglia.

Key Words: Intracerebral hemorrhage—direct oral anticoagulants—warfarin—small vessel disease

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Introduction

Intracerebral hemorrhage (ICH) is among the most severe subtypes of stroke, and has a higher tendency to result in sequelae than cardiac events. Thus, the long-term rehabilitation and care required for patients with ICH are associated with a significant socio-economic burden. Furthermore, oral anticoagulant (OAC) therapy with warfarin aggravates hematoma expansion, in turn leading to poor outcomes.[1] Among those treated with warfarin, the incidence of ICH is higher in Asian patients than in nonAsian patients.[2] Recent evidence indicates that direct oral anticoagulants (DOACs) can be used in the treatment of nonvalvular atrial fibrillation (NVAF) or deep vein thrombosis (DVT). Phase III clinical trials have demonstrated that the incidence of ICH is nearly 50% lower in patients taking DOACs than in those taking warfarin, even among the Asian population.[3,4] Because DOACs are theoretically more suitable for patients with NVAF or DVT, they are used liberally in clinical practice.[5] Recently, we have experienced an increasing number of DOAC-related cases of ICH.

Total small vessel disease (SVD) score has been reported to help predict the recurrence of ICH or hematoma expansion.[6-8] Neuroimaging markers of SVD severity may be good candidates to provide insights regarding the indication for OAC therapy. However, information regarding SVD severity and hematoma volume based on site of involvement in patients with ICH occurring during DOAC treatment is limited. In the present study, we evaluated ICH incidence, hematoma volume, neurological severity, and neuroimaging characteristics in order to clarify the characteristics of DOAC-related ICH.

Methods

Patients and Evaluation

This study retrospectively enrolled 301 consecutive patients with acute ICH who were admitted to the stroke center at Nippon Medical School Hospital between September 2014 and December 2017. The study was approved by the ethics committee of Nippon Medical School and conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients or their relatives. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission. Initial ICH severity was defined as mild (NIHSS score: 0-10), moderate (NIHSS score 11-20), or severe (21 < NIHSS score). Functional outcomes were assessed using the modified Rankin Scale (mRS) score at the time of discharge. A good discharge outcome was defined as a mRS score of 0-2, while a poor outcome was defined as a mRS score of 3-5 or death (mRS score of 6).

Clinical Information

Clinical background characteristics including sex, age, vascular risk factors, pre-mRS, blood glucose level, estimated glomerular filtration rate (eGFR), and coagulation test results (prothrombin time international normalized ratio [PT-INR]) were recorded on admission. Prior stroke was defined as a previous diagnosis of and treatment for stroke. Prior ischemic heart disease was defined as a previous diagnosis of and treatment for myocardial infarction and/or angina.

Neuroimaging Acquisition and Analysis

The hemorrhage volume on computed tomography images was estimated via the ABC/2 method at the time of admission.[9] Hematoma expansion was defined as a 33% or more increase in hematoma volume on the computed tomography scan 24-hour after the admission (baseline).[10] When hemorrhage volume was high and the hemorrhage had spread to more than 2 areas, the location of ICH was defined based on the area that included the main hemorrhage.

To evaluate small vessel disease (SVD) scores in patients taking OACs, magnetic resonance imaging (MRI) was performed in 32 of 40 patients during hospitalization, as 2 patients had died during the acute phase and 6 exhibited contraindications. MRI scanning was performed using a 1.5-Tesla scanner (Echelon Oval, Hitachi Medical Systems, Tokyo, Japan) and included axial T2-weighted imaging, fluid-attenuated inversion recovery imaging, diffusion-weighted imaging, time-of-flight MR-angiography, and gradient-recalled echo (GRE) T2-weighted sequences (slice thickness: 5 mm; repetition time/echo time: 480 ms/18 ms). All GRE T2-weighted images were systematically assessed for evidence of cerebral microbleeds (CMBs, defined as parenchymal hemorrhages ≤10 mm in diameter), as previously described.[11,12] An ordinal scale representing the total burden of SVD was then created as previously described.[13] Briefly, total SVD scores (range: 0-4) were determined by assessing the presence of each of the 4 MRI markers for SVD (white matter hyperintensities [WMH], lacunes, CMBs, and perivascular spaces). WMH were assessed according to the Fazekas scale.[14] The presence of WMH was defined as a periventricular WMH Fazekas score of 3 and/or deep WMH Fazekas score of 2 or 3. Lacunes and CMBs were assessed according to the international consensus definitions, and 1 point was added to the total SVD score if at least 1 lacune or CMB was present.[13,15] Imaging analyses were performed by observers (S.S. and T.S.) who were blinded to the clinical data and patient information.

Statistical Analysis

We initially compared clinical characteristics among patients taking no OACs, warfarin, and DOACs. Next, we compared the clinical characteristics of all patients based on initial neurological severity and discharge outcomes. Age, sex, and variables with P values less than .10 in the univariate analysis were entered into a multivariate

logistic regression model to identify variables independently associated with moderate-to-severe ICH (initial NIHSS score ≥ 11) and poor discharge outcome (mRS ≥ 3). Lastly, MRI characteristics including WMH, lacunes, CMBs, and perivascular spaces were compared between the warfarin and DOAC groups. Intergroup differences were assessed using the chi-square test or the Wilcoxon rank-sum test, as appropriate. All analyses were performed using JMP 13 statistical software (SAS Institute Inc., Cary, NC). The level of statistical significance was set at P less than .05.

Results

A total of 301 consecutive patients with ICH (female: 103; median age: 68 [IQR: 59-78] years; NIHSS score: 9 [IQR: 3-17]) were enrolled in the present study. On admission, 40 patients (13.2%) were prescribed oral anticoagulants, 20 of whom were prescribed DOACs (6.6%). The reason for prior DOAC therapy was atrial fibrillation (AF) in 17 patients (85%) and deep venous thrombosis in 3 patients (15%). The reason for prior warfarin therapy was AF in 15 patients (75%), mechanical heart valve surgery in 4 patients (20%), and no clear reason in 1 patient (5%). There were no patients treated with any specific neutralization therapy such as prothrombin complex concentrates and idarucizumab.

The baseline characteristics of the patients are shown in Table 1. There were significant differences in age (P = .0233), CHA_2DS_2 score (P = .0120), CHA_2DS_2-VASc score (P = .0126), HAS-BLED score (P = .0072), systolic blood pressure (P = .0031), PT-INR (P < .0001), activated partial thromboplastin time (aPTT) (P < .0001), and eGFR (P = .0019) among the 3 groups. Median initial NIHSS scores (no-OAC group: 10, warfarin group: 13, DOAC group: 4; P = .0283), discharge NIHSS scores (no-OAC group: 4, warfarin group: 9, DOAC group: 1; P = .0140), discharge mRS scores (no-OAC group: 4, warfarin group: 4, DOAC group: 3; P = .0205), rates of poor functional outcomes (no-OAC group: 10%, warfarin group: 13%, DOAC group: 40%; P = .0346), and mortality rates (no-OAC group: 1.2%, warfarin group: 10%, DOAC group: 0%, P = .0097) significantly differed among the 3 groups. The locations of ICH were similar among the groups, such as basal ganglia (P = .3095) and lobar (P = .2194). Although there was no significant difference in median hematoma volume (no-OAC group: 8.4 mL, warfarin group: 11.9 mL, DOAC group: 6.4 mL; P = .1306) among the groups, there were significant differences in median hematoma volume in the basal ganglia (no-OAC group: 15.0 mL, warfarin group: 28.5 mL, DOAC group: 4.8 mL; P = .0366).

Table 2 shows the associations between baseline characteristics and initial neurological severity. Patients in the moderate-severe group exhibited higher systolic and diastolic blood pressure (P = .0189 and P = .0105, respectively), had a lower frequency of hypertension (P = .0135), and higher frequency of basal ganglia hemorrhage (P = .0486) than those in the mild group. Fig 1A shows the distribution of initial severity, according to OAC status. Multivariate logistic regression analysis revealed that a lack of treatment with OACs (odds ratio [OR]: 0.29, 95% CI: 0.10-0.82, P = .0196, Table 3) and prior treatment with DOACs were independently negatively associated with moderate-to-severe ICH when compared with outcomes following warfarin treatment (OR: 0.21, 95% CI: 0.05-0.96, P = .0445, Table 3).

Table 4 shows the associations between baseline characteristics and functional outcomes at discharge. Patients in the poor outcome group had a lower frequency of alcohol use (P = .0093), higher blood glucose level, higher NIHSS scores at admission (P < .0001), and larger hematoma volume (P < .0001) than those in the mild group. Fig 1B shows the distribution of discharge mRS scores according to OAC status. Although there was a significant difference in prior OAC status between good and poor outcomes, multivariate logistic regression analysis revealed that DOAC-related ICH was not independently associated with poor outcomes when compared with outcomes associated with warfarin treatment (OR: 0.17, 95% CI: 0.02-1.94, P = .1549, Table 5).

Table 6 shows the comparison of MRI characteristics between patients taking warfarin and those taking DOACs. Most importantly, total SVD scores were significantly higher in patients of the DOAC group than in those of the warfarin group (3 versus 2, P = .0413).

Discussion

In the present study, 13.2% of patients with acute spontaneous ICH received prior anticoagulant therapy, half of whom experienced DOAC-related ICH. Furthermore, after adjusting for the effects of ICH location, various risk factors, and comorbidities, prior treatment with DOACs was independently associated with milder initial neurological severity (relative to treatment with warfarin). There were no significant differences in ICH location based on prior OAC status, although SVD scores seemed to be higher among those with DOAC-related ICH than among those with warfarin-related ICH.

The relationship between DOAC administration and the ICH characteristics has not been confirmed. Some retrospective studies have reported that DOAC-related ICH is associated with lower hematoma volume and better clinical outcomes than warfarin-related ICH.[16,17] However, these previous studies did not evaluate the difference between DOAC and warfarin using a multivariate analysis that included various baseline characteristics. Recently, a nationwide study using the Diagnosis Procedure Combination (DPC) database in Japan revealed that DOAC-treated patients experienced less severe ICH and lower mortality rates than warfarin-treated patients.[18] Conversely, another prospective observational study

Table 1. *Comparison of clinical background characteristics of the included patients according to the prior OAC status*

Variable	Total (n = 301)	No-OAC (n = 261)	Warfarin (n = 20)	DOAC (n = 20)	*P*
Age, years, median (IQR)	68 (59-78)	67 (57-78)	73 (65-84)	73 (64-82)	.0223
Sex, n (%)	103 (34.2)	90 (34.5)	6 (30.0)	7 (35.0)	.9178
Risk factor					
Smoking, n (%)	88 (29.2)	78 (29.9)	4 (20.0)	6 (30.0)	.6429
Alcohol, n (%)	157 (52.2)	136 (52.1)	9 (45.0)	12 (60.0)	.6363
Hypertension, n (%)	203 (67.4)	167 (64.0)	18 (90.0)	18 (90.0)	.0048
Diabetes, n (%)	61 (20.3)	48 (18.4)	7 (35.0)	6 (30.0)	.1093
Dyslipidemia, n (%)	63 (20.9)	50 (19.2)	8 (40.0)	5 (25.0)	.0784
Ischemic heart disease, n (%)	15 (5.0)	10 (3.8)	3 (15.0)	2 (10.0)	.0490
Prior ischemic stroke, n (%)	29 (9.6)	15 (5.8)	5 (25.0)	9 (45.0)	<.0001
Prior ICH, n (%)	27 (9.0)	23 (8.9)	2 (10.0)	2 (10.0)	.9705
Antiplatelet use, n (%)	42 (14.0)	36 (14.2)	1 (5.0)	5 (25.0)	.1851
Systolic blood pressure, mmHg, median (IQR)	184 (162-206)	186 (168-207)	172 (147-197)	156 (144-189)	.0031
Diastolic blood pressure, mmHg, median (IQR)	101 (88-117)	102 (89-117)	98 (80-110)	92 (80-123)	.1818
Biochemistry sign at admission, median (IQR)					
PT-INR	1.05 (0.98-1.16)	1.02 (0.97-1.11)	1.86 (1.35-2.19)	1.16 (1.06-1.27)	<.0001
Blood glucose, mg/dl	121 (105-148)	120 (104-144)	139 (118-162)	124 (100-147)	.1168
eGFR, ml/min/1.73m^2	70 (54-84)	72 (57-86)	69 (46-76)	54 (43-66)	.0019
Preadmission mRS, median (IQR)	0 (0-0)	0 (0-0)	0 (0-3)	0 (0-1)	.1658
NIHSS score at admission, median (IQR)	9 (3-17)	10 (4-17)	13 (4-17)	4 (0-12)	.0283
ICH location					
Lobar hemorrhage, n (%)	54 (17.9)	43 (16.5)	5 (25.0)	6 (30.0)	.2194
Basal ganglia, n (%)	115 (38.2)	104 (39.9)	6 (30.0)	5 (25.0)	.3095
Hematoma volume, ml, median (IQR)	8.0 (3.0-22.0)	8.4 (3.0-22.0)	11.9 (5.0-51.5)	6.4 (1.2-18.0)	.1306
Lobar hemorrhage volume, ml, median (IQR)	24.0 (9.3-70.0)	21.5 (8.6-75.4)	52 (26-128.5)	19.5 (7.6-53.5)	.3446
Basal ganglia hemorrhage volume, ml, median (IQR)	15 (6.6-36.5)	15 (6.8-37.8)	28.5 (7.0-57.0)	4.8 (2-8.1)	.0336
Hematoma expansion, n (%)	32 (10.6)	25 (9.6)	4 (20.0)	3 (15.0)	.2789
Onset to arrival, h, median (IQR)	2.6 (1.0-12.6)	2.3 (1.0-11.2)	6.8 (1.9-29.8)	3.9 (0.9-21.5)	.1320
Surgical treatment, n (%)	40 (13.3)	36 (13.8)	1 (5.0)	3 (15.0)	.5218
Length of hospital stay, days, median (IQR)	15 (9-24)	15 (9-24)	24 (14-33)	12 (6-15)	.0086
NIHSS score at discharge, median (IQR)	4 (1-12)	4 (1-11)	9 (4-14)	1 (0-10)	.0140
mRS at discharge, median (IQR)	4 (2-5)	4 (2-5)	4 (4-5)	3 (1-5)	.0205
Poor functional prognosis, n (%)	183 (60.8)	159 (60.9)	16 (80.0)	8 (40.0)	.0346
Mortality, n (%)	5 (1.7)	3 (1.2)	2 (10.0)	0 (0)	.0097

Abbreviations: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; OAC, oral anticoagulation; PT-INR, prothrombin time-international normalized ratio.

Table 2. *Factors related to initial neurological severity in acute intracerebral hemorrhage patients*

Variable	Total (n = 301)	mild ICH (n = 163)	moderate-severe ICH (n = 138)	*P*
Age, years, median (IQR)	68 (59-78)	70 (60-79)	67 (58-78)	.2107
Sex, n (%)	103 (34.2)	54 (33.1)	49 (35.5)	.7283
Risk factor				
Smoking, n (%)	88 (29.2)	50 (30.7)	38 (27.5)	.5778
Alcohol, n (%)	157 (52.2)	93 (57.1)	64 (46.4)	.0646
Hypertension, n (%)	203 (64.1)	119 (73.0)	84 (60.9)	.0252
Diabetes, n (%)	61 (20.3)	34 (20.9)	27 (19.6)	.7809
Dyslipidemia, n (%)	63 (20.9)	34 (20.9)	29 (21.0)	.9736
Ischemic heart desease, n (%)	15 (5.0)	7 (4.3)	8 (5.8)	.5505
Prior ischemic stroke, n (%)	29 (9.6)	17 (10.4)	12 (8.7)	.6115
Prior ICH, n (%)	27 (9.0)	15 (9.2)	12 (8.7)	.8781
Antiplatelet use, n (%)	42 (14.0)	23 (14.1)	19 (13.8)	.9319
Anticoagulant use, n (%)	40 (13.3)	16 (13.6)	24 (13.1)	.9117
Warfarin use, n (%)	20 (6.6)	4 (3.4)	16 (8.7)	.0469
DOAC use, n (%)	20 (6.6)	12 (10.2)	8 (4.4)	.0486
Systolic blood pressure, mmHg, median (IQR)	184 (162-206)	180 (156-200)	188 (169-210)	.0189
Diastolic blood pressure, mmHg, median (IQR)	101 (88-117)	100 (84-114)	108 (90-120)	.0105
Biochemistry sign at admission, median (IQR)				
PT-INR	1.05 (0.98-1.16)	1.06 (0.98-1.17)	1.02 (0.98-1.13)	.2582
Blood glucose, mg/dL	121 (105-148)	121 (102-147)	122 (106-148)	.4617
eGFR, mL/min/1.73 m^2	70 (54-84)	67 (53-81)	75 (57-87)	.0557
Preadmission mRS, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	.8166
NIHSS score at admission, median (IQR)	9 (3-17)	4 (2-7)	18 (14-22)	<.0001
ICH location				
Lobar hemorrhage, n (%)	54 (17.9)	33 (29.6)	22 (15.9)	.4058
Basal ganglia, n (%)	115 (38.2)	46 (28.2)	69 (50.0)	.0001

Abbreviation: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; OAC, oral anticoagulation; PT-INR, prothrombin time-international normalized ratio.

reported that DOAC-related ICH is associated with a high mortality and an unfavorable outcome, and hematoma expansion is frequent.[19] In the present study, DOAC-related ICH was independently associated with milder initial neurological severity than warfarin-related ICH, possibly due to relatively smaller hematoma volume, especially in the basal ganglia. Moreover, median PT-INR (1.86) and initial hematoma volume (11.9 mL) were lower in the warfarin group of the present study than in those of previous studies.[16-18] While our univariate analysis revealed a significant difference in prior OAC status between good and poor outcomes, the results of the multivariate analysis were not statistically significant. However, as the sample size of the present study was relatively small, larger-scale studies are required.

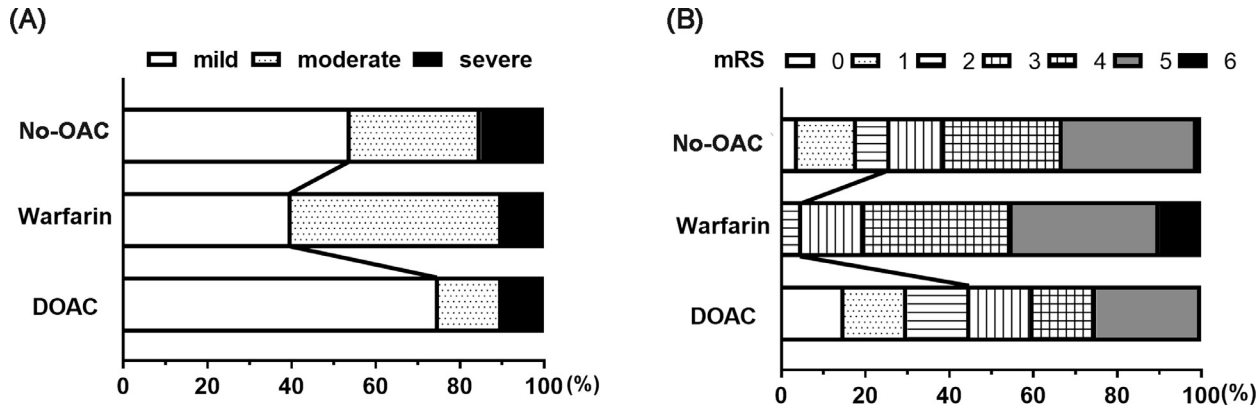

Figure 1. *(A) Distribution of initial ICH severity according to oral anticoagulant (OAC) status. Neurological severity was defined as mild (NIHSS score 0-10), moderate (NIHSS score 11-20), or severe (21 < NIHSS score) (B) Distribution of modified Rankin Scale (mRS) scores upon discharge according to OAC status. ICH: intracerebral hemorrhage; NIHSS: National Institutes of Health Stroke Scale*

Table 3. *Multiple logistic regression analysis of predictors of moderate-severe ICH (initial NIHSS score ≥11)*

Variables	OR	95% CI	*P* value
Age (per 10 years)	0.84	0.64-1.08	.1740
Female sex	0.99	0.52-1.91	.9818
Alchol	0.67	0.35-1.27	.2184
Hypertension	0.34	0.18-0.64	.0008
Diastolic blood pressure (per 10 mmHg)	1.33	1.13-1.56	.3072
eGFR (per 10 mL/min/1.73m^2)	0.90	0.80-1.02	.0798
Basal ganglia hemorrhage	2.64	1.45-4.81	.0016
Anticoagulant status prior to the ICH			
Warfarin	1	Ref.	
No-OAC	0.29	0.10-0.82	.0196
DOAC	0.21	0.05-0.96	.0445

Abbreviation: CI, confidence interval; DOAC, direct oral anticoagulant; eGFR, estimate glomerular filtration rate; OR, odds ratio; OAC, oral anticoagulation.

Several fundamental studies have explored the possible protective mechanisms of DOACs in ICH. First, DOACs not only have a shorter half-life than warfarin but also selectively inhibit thrombin or factor Xa, and thus have no effect on factor VII (FVII), which forms a complex with the cell surface cofactor tissue factor (TF). TF appears after vascular injury, and the FVII and TF complex initiates the coagulation cascade.[20] Second, ICH causes blood-brain

Table 4. *Factors related to discharge outcome in acute intracerebral hemorrhage patients*

Variable	Total (n = 301)	Good outcome (n = 77)	Poor outcome (n = 224)	*P*
Age, years, median (IQR)	68 (59-78)	66 (55-75)	69 (60-79)	.0662
Sex, n (%)	103 (34.2)	21 (27.3)	81 (36.2)	.1552
Smoking, n (%)	88 (29.2)	20 (26.0)	68 (30.4)	.4657
Alcohol, n (%)	157 (52.2)	50 (64.9)	107 (47.8)	.0093
Hypertension, n (%)	193 (64.1)	57 (74.0)	146 (65.2)	.1529
Diabetes, n (%)	61 (20.3)	10 (13.0)	51 (22.8)	.0655
Dyslipidemia, n (%)	63 (20.9)	17 (22.1)	46 (20.5)	.7741
Ischemic heart disease, n (%)	15 (5.0)	1 (21.3)	14 (6.3)	.0850
Prior stroke, n (%)	54 (17.6)	11 (14.3)	43 (19.2)	.3326
Antiplatelet use, n (%)	42 (14.0)	7 (9.1)	35 (15.6)	.1534
Anticoagulant use, n (%)				.0149
No-OAC use, n (%)	261 (86.8)	67 (87.0)	194 (86.6)	
Warfarin use, n (%)	20 (6.6)	1 (1.3)	19 (8.5)	.0469
DOAC use, n (%)	20 (6.6)	9 (11.7)	11 (4.9)	.0486
Systolic blood pressure (mmHg)	184 (162-206)	180 (155-200)	185 (165-210)	.0681
Diastolic blood pressure (mmHg)	101 (88-117)	100 (85-117)	101 (89-117)	.5264
Biochemistry sign at admission, median (IQR)				
PT-INR	1.05 (0.98-1.16)	1.03 (0.97-1.15)	1.06 (0.98-1.16)	.2542
Blood glucose, mg/dL	121 (105-148)	117 (100-139)	123 (106-152)	.0599
eGFR, mL/min/1.73 m^2	70 (54-84)	69 (53-83)	70 (55-84)	.6280
Preadmission mRS, median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	.0033
NIHSS score at admission, median (IQR)	9 (3-17)	2 (1-4)	13 (6-19)	<.0001
ICH location				
Lobar hemorrhage, n (%)	54 (17.9)	15 (19.5)	39 (17.4)	.6830
Basal ganglia, n (%)	115 (38.2)	29 (37.7)	86 (38.4)	.9094
Hematoma volume (mL), median (IQR)	8.0 (3.0-22.0)	3.3 (1.5-9.9)	10.5 (4.6-31.5)	<.0001
Hematoma expansion, n (%)	32 (10.6)	4 (5.2)	28 (12.5)	.0728
Surgical treatment, n (%)	39 (13.0)	2 (2.6)	37 (16.5)	.0017
Length of hospital stay, days, median (IQR)	15 (9-24)	12 (9-18)	16 (9-27)	.0153
NIHSS score at discharge, median (IQR)	4 (1-12)	2 (1-4)	13 (6-19)	<.0001

Abbreviation: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; OAC, oral anticoagulation; PT-INR, prothrombin time-international normalized ratio.

Table 5. *Multiple logistic regression analysis of predictors of poor discharge outcome (mRS ≥3)*

Variables	OR	95% CI	*P* value
Age (per 10 years)	1.41	1.07-1.88	.0149
Female sex	0.99	0.52-1.91	.6793
Alcohol	0.47	0.24-0.92	.0587
Systolic blood pressure (per 10 mmHg)	1.08	0.97-1.21	.1573
Blood glucose (per 10mg/dL)	1.06	0.97-1.18	.1763
Hematoma volume (per 1mL)	1.06	1.03-1.10	.0025
Anticoagulant status prior to the ICH			
Warfarin	1	Ref.	
No-OAC	0.17	0.02-1.94	.1549
DOAC	0.24	0.03-2.06	.1931

Abbreviation: CI confidence interval; DOAC, direct oral anticoagulant; OAC, oral anticoagulation; OR, odds ratio; mRS, modified Rankin Scale.

barrier disruption via upregulation of matrix metalloproteinase (MMP)-9 and protease-activated receptor (PAR).[21,22] Previous studies have demonstrated that DOAC inhibits hemorrhagic transformation by downregulating MMP-9/PAR-1 and PAR-2 in a tissue-type plasminogen activator-induced model of hemorrhagic stroke.[23,24] In large phase 3 trials, the frequency of ICH was nearly 50% lower in patients taking DOACs than in those taking warfarin, despite their similar efficacy. Furthermore, a recent prospective, longitudinal study demonstrated that DOAC use did not increase CMBs in patients with AF at 1 year.[17] These results may explain milder initial symptoms and lower hemorrhage volume in patients taking DOACs, relative to those observed in patients taking warfarin.

Although we observed no significant differences in hemorrhage location, SVD scores were higher in the DOAC group than in the warfarin group. A previous retrospective observational study revealed that DOAC-associated ICH aptly occurs in patients with multiple CMBs.[25] Most recently, a prospective observational study reported that patients with DOAC-related ICH are more likely to exhibit more extensive white matter lesions and a greater number of CMBs than patients treated with DOACs who experience an ischemic stroke.[26] Interestingly, in the present study, systolic blood pressure and eGFR on admission were significantly lower in those with DOAC-related ICH than in those with warfarin-related ICH. Taken together, these findings suggest that DOAC use may trigger ICH in patients who are at particular risk for ICH. However, we had no data about prior blood pressure control levels and adherence to OAC therapy. Furthermore, there were several differences in the background characteristics between patients treated with DOAC and those treated with warfarin. Further large-scale studies that investigate prior blood pressure control levels and adherence to OAC therapy are needed in order to clarify the characteristics of ICH in patients receiving OACs.

Several limitations should be considered in the interpretation of our study.

First, the present study was a single-center retrospective analysis with a small sample size. Therefore, our findings should be interpreted with caution. In contrast with our findings, a recent observational study reported that DOAC-related ICH is associated with an increased risk of both hematoma expansion and unfavorable clinical outcomes.[19] Second, mRS score at the time of hospital discharge did not necessarily reflect long-term prognoses. Furthermore, the median length of hospital stay in the DOAC group was significantly shorter than that in the warfarin group. This may have led to the underestimation or overestimation of the protective effects of DOAC on outcomes.

Table 6. *Comparison of MRI characteristics between warfarin and DOAC*

Variable	Total (n = 32)	Warfarin (n = 15)	DOAC (n = 17)	*P*
MRI feature				
Lacunes, n (%)	10 (31.3)	4 (26.7)	6 (35.3)	.5983
WMH grading, median (IQR)	1 (1-2)	1 (1-2)	2 (1-2)	.5433
DSWMH grading, median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	.0961
CMBs, median (IQR)	3 (0-8)	3 (0-9)	3 (0-8)	.8478
EPVS grading (basal ganglia), median (IQR)	2 (1-2)	2 (1-3)	2 (1-2)	.9015
EPVS grading (semiovale), median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	.1336
Total SVD score, median (IQR)	3 (1-3)	2 (1-3)	3 (1-3)	.0413

Abbreviation: CMBs, cerebral microbleeds; DOAC, direct oral anticoagulant; DSWMH, deep and subcortical white matter hyperintensity; EPVS, enlarged perivascular spaces; IQR, interquartile range; SVD, small vessel disease; WMH, white matter hyperintensity.

Third, more patients showed hematoma expansion in the warfarin group, but there was a lower proportion of surgical treatment in patients with warfarin-related ICH than in those with no-OAC and DOAC. However, the differences were not statistically significant. We think that possible reasons for this discrepancy are 1) the sample size of the present study was small, and 2) there were patients who did not undergo surgery based on a decision of the family. Fourth, the incidence of mortality in the present study was 3%, which is low compared to that shown in previous studies. ICH patients accompanied with severe loss of consciousness may be transferred to the emergency and critical care medical center in our hospital. A low proportion of mortality in our study may have been related to the initial NIHSS score of 9 (IQR, 3-17), which is lower than that in previous studies.[2,17]

In conclusion, our results suggest that DOAC-related ICH was associated with milder initial neurological severity than warfarin-related ICH, even after adjusting for risk factors and comorbidities. Our findings further suggested that, relative to those taking warfarin, patients with DOAC-related ICH were more likely to have an increased risk of bleeding as reflected by high SVD scores, low eGFR, and low blood pressure. Larger-scale prospective studies are required to verify our findings.

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