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The dose of direct oral anticoagulants and outcomes of intracerebral hemorrhage: Preliminary findings

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ABSTRACT

Objectives: The effect of a direct-acting oral anticoagulant (DOAC) dose on intracerebral hemorrhage (ICH) severity and outcome remains unclear. The aim of this study is to clarify the frequency of off-label dosing of DOAC treatments in ICH patients and compare clinical characteristics.

Patients and methods: We studied 43 patients with ICH who were treated with DOAC for nonvalvular atrial fibrillation before the onset of ICH. DOAC treatments were categorized into three groups based on the following doses: optimal dose, under-dose, and overdose.

Results: Overall, 31 patients were optimally dosed, 10 were under-dosed, and 2 were overdosed. $CHADS_2$ and CHA_2DS_2-VASc scores were the highest in the overdose group (median, 4, 6, respectively) and the lowest in the optimal dose group (median, 2, 4, respectively) ($p = 0.006$, $p = 0.005$, respectively). ICH severity measured using the National Institutes of Health Stroke Scale scores was the highest in the overdose group (median, 26.5) and the lowest in the under-dose group (median, 6.5) ($p = 0.244$). Larger initial hematoma volume was observed in the overdose group. The ratio of good outcome (modified Rankin Scale score ≤ 2) was higher in the under-dose group (40%) than the other groups, but this difference was not significant.

Conclusion: Our study shows only a few patients received overdosing of a DOAC before the onset of ICH, and they were associated with poorer functional outcomes. Conversely, under-dosing was associated with better functional outcomes than the other groups.

1. Introduction

Direct-acting oral anticoagulants (DOAC) are increasingly used as substitutes for warfarin because of their more favorable safety and efficacy profiles [1,2]. In randomized, clinical trials, patients taking a DOAC showed almost half the frequency of intracerebral hemorrhage (ICH) compared with warfarin [2]. Moreover, recent studies have shown that even if ICH occurs, DOAC-related ICH results in smaller ICH volumes and better clinical outcomes than warfarin-related ICH [3–6]. This may be because of the different mechanisms in the coagulation pathway targeted by warfarin and DOAC; the effects of DOAC can be readily overcome by tissue factor-mediated activation of blood coagulation compared with warfarin [7].

The effect of DOAC dosing on ICH severity and outcome has not been elucidated, although under-dosing or overdosing of DOAC prescriptions are common in general practice [8–10]. Patients overdosed with a DOAC may develop larger ICH volumes or experience poorer outcomes than those under-dosed with a DOAC.

The aim of this study is to clarify the frequency of off-label dosing of DOAC treatments in ICH patients and compare clinical characteristics, stroke severity, ICH volume and clinical outcomes, with each dose of a DOAC (optimal dose, under-dose and overdose).

2. Material and methods

This study included 43 consecutive Japanese patients with nonvalvular atrial fibrillation who were treated with a DOAC before the onset of ICH and then admitted to our hospital for ICH between March 2014 and February 2018. For the purpose of the study, DOAC treatments were categorized into three groups as follows: (1) the optimal dose group, (2) the under-dose group, and (3) the overdose group. The DOAC dose was evaluated based on the manufacturer's labeling

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Table 1
Dosing information for patients with non-valvular atrial fibrillation according to the Japanese summary of product characteristics.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Release date	March 2011	April 2012	February 2013	September 2014
Standard dose	300 mg/day	15 mg/day	10 mg/day	60 mg/day
Reduced dose	220 mg/day	10 mg/day	5 mg/day	30 mg/day
Dose adjustment	No definite dose reduction criteria 220 mg/day recommended if: ● Age ≥70 years ● CrCl 30–50 mL/min ● History of major bleeding ● Use of p-glycoprotein inhibitors	10 mg/day if: ● CrCl 15–50 mL/min	5 mg/day if two of: ● Body weight ≤60 kg ● Serum Cr levels ≥1.5 mg/dL ● Age ≥80 years	30 mg/day if: ● Body weight ≤60 kg ● CrCl 15–50 mL/min ● Use of p-glycoprotein inhibitors

CrCl: Creatinine clearance, Cr: Creatinine.

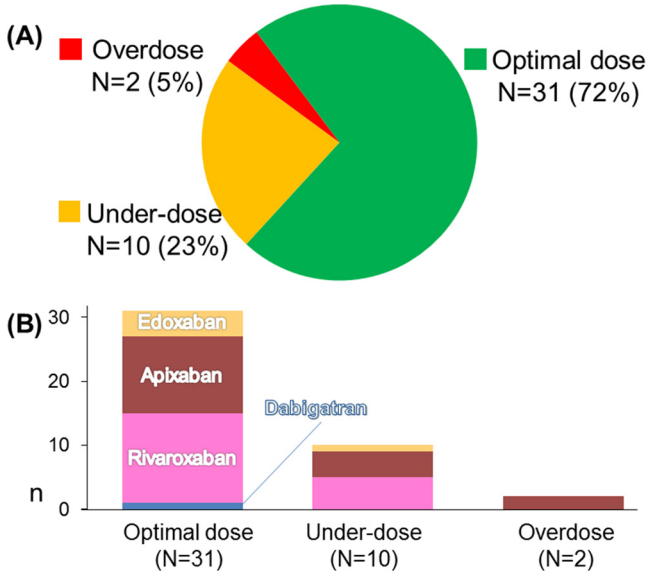

Fig. 1. (A) Direct-acting oral anticoagulants (DOAC) dosing before the onset of intracerebral hemorrhage (ICH). (B) Number of DOAC prescriptions before the onset of ICH. As shown, the number of patients administered DOAC overdoses is very small.

recommendations for Japan (Table 1). Patients who were prescribed a lower drug dose, but did not meet the criteria for dose reduction, were grouped in (2). Patients who were prescribed a standard drug dose, but met the criteria for dose reduction, were grouped in (3).

Electronic medical charts and summaries were retrospectively reviewed to obtain the following variables: demographic information (age and sex), body weight, body mass index, pre-admission modified Rankin Scale (mRS) score [11], DOAC prescriber (from a university hospital, regional hospital, specialist clinic [cardiology, neurology, or neurosurgery], or general clinic), and past medical history. Cardiovascular risk factors were defined as follows: (i) hypertension, a history of using antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg before or ≥2 weeks after onset of stroke; (ii) diabetes mellitus, use of hypoglycemic agents, random glucose levels ≥200 mg/dL, or glycosylated hemoglobin ≥6.5% on admission; (iii) dyslipidemia, use of antihyperlipidemic agents, or serum low-density lipoprotein cholesterol levels ≥140 mg/dL; (iv) current smoking; (v) alcohol intake, consumption of more than 10 g alcohol/day ; (vi) prior stroke; (vii) coronary artery disease, angina, or prior myocardial infarction; and (viii) heart failure, a history of congestive heart failure, or an ejection fraction < 40%. The pre-stroke $CHADS_2$ score, CHA_2DS_2-VASc score, or HAS-BLED score was calculated for each patient based on the published literature [12–14].Serum creatinine and creatinine clearance (Cockcroft–Gault equation [15]), prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time (APTT) upon admission were also evaluated.

Stroke severity was assessed by the Glasgow Coma Scale (GCS) score and the National Institutes of Health Stroke Scale (NIHSS) score. ICH location, initial hematoma volume and expansion during follow-up were assessed based on computed tomography. The ICH volume was calculated using the ABC/2 method from the initial axial computed tomography images [16].The diameters of A and B were measured by the screen ruler, and C (slice thickness) was 5 mm. Hematoma expansion was defined as an increase of more than 33% or 6 ml from the initial ICH volume within 72 h [17]. Surgical or conservative therapy, clinical outcome using the mRS score at discharge, duration of hospital stay, and discharge destinations (home, rehabilitation hospital, or nursing home) were also evaluated. The mRS score of 0–2 was defined as a good outcome. All aspects of this study were approved by the institutional ethics committee (approval #18-015).

Data are expressed as the median (interquartile range) or n (%). One-way analysis of variance followed by Bonferroni post-hoc tests for continuous variables, or the Pearson χ^2 test for categorical variables were used to compare differences between the three groups. Statistical analysis was performed using PASW Statistics software (version 20; SPSS Inc., Chicago, IL). All p values are 2-sided, with $p < 0.05$ considered statistically significant.

3. Results

Among 1039 patients with ICH, 43 (4.1%) were taking a DOAC. There were 16 women and 27 men, with a mean age of 73 ± 9 years. Thirty-one patients (72%) were treated with an optimal dose, 10 patients (23%) were under-dosed, and 2 patients (5%) were treated with an overdose before the onset of ICH (Fig. 1A). Dabigatran was prescribed in only one case in our study (Fig. 1B).

The patient profiles of each group are shown in Table 2. The mean age and sex distributions were similar in all groups. Body weight in the overdose group was smaller than the other groups, though this difference was not statistically significant. The pre-admission mRS score was good in all of the groups. BMI and creatinine clearance were the largest in the optimal dose group and the smallest in the overdosed group, though this difference was not statistically significant. The overdoses of DOAC were all prescribed from the general clinic.

The risk factors for each group were not significantly different except for a higher prevalence of diabetes in the overdose group and a higher prevalence of prior ICH in the under-dose group. $CHADS_2$ and CHA_2DS_2-VASc scores were the highest in the overdose group and the

Table 2
Background characteristics of patients with intracranial hemorrhage.

Characteristics	(1) Optimal dose (n = 31)	(2) Under-dose (n = 10)	(3) Overdose (n = 2)	*p* value
Age, years	72.9 ± 9.2	73.5 ± 7.4	75.0 ± 14.0	0.969
Female sex, n (%)	11 (35)	4 (40)	1 (50)	0.899
Body weight (kg)	61.0 ± 16.8	61.5 ± 13.6	57.5 ± 3.5	0.955
BMI (kg/m^2)	27.9 ± 24.5	23.5 ± 4.3	22.4 ± 2.4	0.919
Pre-admission mRS score	0 (0-0)	0 (0-0)	0.5 (0.25-0.75)	0.269
DOAC prescriber, n (%)				0.650
University hospital	3 (10)	0 (0)	0 (0)	
Regional hospital	8 (26)	4 (40)	0 (0)	
Specialist clinic	6 (19)	1 (10)	0 (0)	
General clinic	14 (45)	5 (50)	2 (100)	
Risk factors				
Hypertension, n (%)	27 (87)	8 (80)	2 (100)	0.720
Diabetes mellitus, n (%)	5 (16)	6 (60)	2 (100)	**0.003**
Dyslipidemia, n (%)	11 (35)	3 (30)	1 (50)	0.856
Current smoking, n (%)	2 (6)	1 (10)	0 (0)	0.859
Alcohol intake, n (%)	7 (23)	3 (30)	0 (0)	0.648
Prior stroke				
Ischemic stroke, n (%)	12 (39)	4 (40)	1 (50)	0.951
Hemorrhagic stroke, n (%)	0 (0)	4 (40)	0 (0)	**0.001**
CAD, n (%)	1 (3)	1 (10)	1 (50)	0.222
Heart failure, n (%)	5 (16)	4 (40)	1 (50)	0.196
$CHADS_2$ score	2 (2-3)	3 (3-4)	4 (3.5-4.5)	**0.006***
CHA_2DS_2-VASc score	4 (3-4)	5 (4-5)	6 (6-6)	**0.005**†
HAS-BLED score	2 (2-3)	2 (2-3)	2.5 (2.3-2.8)	0.794
Antiplatelet drugs, n (%)	2 (6.5)	0 (0)	0 (0)	0.666
Laboratory data on admission				
Creatinine, mg/dL	0.80 ± 0.23	0.93 ± 0.25	1.12 ± 0.86	0.371
Creatinine clearance, mL/min	75 ± 33	61 ± 20	55 ± 30	0.578
PT-INR	1.35 ± 0.41	1.43 ± 0.61	1.22 ± 0.12	0.989
APTT	34.3 ± 6.8	40.4 ± 20.3	30.6 ± 5.3	0.559

Date are presented as the median (interquartile range) or number (%).
Abbreviations: BMI, body mass index; DOAC, direct oral anticoagulant; CAD, coronary artery disease; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time.
*Bonferroni correction showed that the under-dose group had significantly higher scores than the optimal dose group (p = 0.015).
†Bonferroni correction showed that the optimal dose group had significantly lower scores than the under-dose group (p = 0.031) and the overdose group (p = 0.048).

lowest in the optimal dose group (p = 0.006, p = 0.005, respectively). HAS-BLED scores were not different among the groups. PT-INR and APTT were similar in all groups.

The stroke characteristics in each group are shown in Table 3. The overdose group had worse GCS scores upon admission. The NIHSS score was the highest in the overdose group (median, 26.5) and the lowest in the under-dose group (median, 6.5), though this difference was not statistically significant (Fig. 2A). The under-dose group developed cerebellar ICH more often than other groups. We observed a trend toward a larger initial hematoma volume in patients receiving an overdose of a DOAC (Fig. 2B). The ratio of good outcomes was higher in the under-dose group (40%) than the other groups, although this difference was not statistically significant (Fig. 3). In-hospital death was seen in 4 cases of optimal dose group. Three cases died of cerebral herniation due to hematoma within 2 days after admission. One died of recurrent aspiration pneumonia on the 47th hospital day.

4. Discussion

In our study, 28% of patients received an inappropriate dose of a DOAC; this observation is compatible with previous atrial fibrillation registry studies [9,10] and an ischemic stroke case series study [11]. The relationship between the DOAC and the incidence of ICH still remains unclear.

Although a previous study showed an association between advanced age and inappropriate doses of DOAC [9], we did not find any age trends among the three groups. A higher prevalence of diabetes in the overdose group was likely due to a small number of patients (n = 2). Conversely, a higher prevalence of prior ICH in the under-dose group was considered as the reason for the off-label use. In our study, the background of patients in the off-label use groups appeared to be at higher risk than the optimal dose group in terms of the $CHADS_2$ and the CHA_2DS_2-VASc scores. This finding is consistent with the ORBIT-AF II registry [8]. Physicians, especially in general clinics, may be tailoring the doses of these medications specifically to a patient's underlying risk.

As expected, we found that the overdose group had more severe symptoms, larger ICH volumes, and poorer functional outcomes. It is reported that overdosing with a DOAC, particularly in the setting of impaired renal failure, is associated with more severe bleeding events [8,18].

The under-dose group had smaller ICH volumes and better functional outcomes despite having more risk factors than the optimal dose group, which could be attributed to a reduced anticoagulant effect in this group. Data from the ENGAGE AF-TIMI 48 trial also found that under-dosing was associated with decreased ICH severity. In the low-dose group (30/15 mg edoxaban, not an approved dose), ischemic stroke rates were higher than in the high-dose group (60/30 mg edoxaban, an approved dose), but a reduction of fetal ICH decreased the

Table 3
Stroke characteristics of patients with intracranial hemorrhage.

Characteristics	(1) Optimal dose (n = 31)	(2) Under-dose (n = 10)	(3) Overdose (n = 2)	*p* value
GCS score on admission	13.0 (5-15)	13.5 (11-15)	9.5 (8-11)	0.421
NIHSS score	11 (4-30)	6.5 (3.3-12.8)	26.5 (23.8-29.3)	0.244
ICH location, n (%)				0.742
Lobar area	9	2	1	
Supratentorial deep area	13	4	1	
Brainstem	4	0	0	
Cerebellum	5	4	0	
Ventricle	1	0	0	
Initial hematoma volume, mL	29 ± 32	16 ± 10	38 ± 11	0.349
Hematoma expansion, n (%)	0 (0)	1 (10)	0 (0)	0.185
Acute neurosurgery, n (%)	8	0	1	0.128
Outcomes at discharge				
mRS score 0-2, n (%)	6 (19)	4 (40)	0 (0)	0.295
Mortality, n (%)	4 (13)	0 (0)	0 (0)	0.426
Duration of hospital stay, days	27 ± 27	22 ± 12	81 ± 64	0.163
Discharge destination, n (%)				0.726
Home	4 (13)	2 (20)	0 (0)	
Rehabilitation hospital	18 (58)	7 (70)	1 (10)	
Nursing home	5 (16)	1 (10)	1 (10)	

Date are presented as median (interquartile range), mean ± SD or number (%). Abbreviations: GCS, Glasgow Coma Scale score; NIHSS, National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale.

overall mortality to the same level as that seen in the high-dose group [19,20]. In the present study, there were 4 cases with clinical manifestation of hemorrhagic lacunar stroke. Three cases were in the optimal dose group, and one was in the under-dose group. As previously reported [21], these patients showed good outcome.

In our study, only one patient (2%) received dabigatran before the onset of ICH. This ratio is quite different from the ratio of dabigatran administered in the ischemic stroke case series at the same facility (42%) [11].Dabigatran markedly reduced ICH when compared with warfarin (hazard ratio 0.32) [22]. Among DOAC, direct thrombin inhibitors and factor Xa inhibitors act differently on the coagulation system, which may help explain the differences in ICH occurrence among DOAC [23].

Our study has some limitations. First, our study was a single-center, retrospective study, and therefore, generalization of our results may be limited. Second, there was a small number of study patients, with a risk of statistical misinterpretation. Such a small sample size might be related to the low incidence of ICH during DOAC treatment. Previous study revealed that oldest old patients (85 years or older) have worse outcome [24], but we could not confirm this in the present study. This is again because of the small sample size. Third, we did not investigate the duration or adherence to DOAC treatment. Fourth, we were not able to identify the reasons for off-label dosing of DOAC. Nevertheless, our data indicate that DOAC doses may influence the severity of ICH once it occurs.

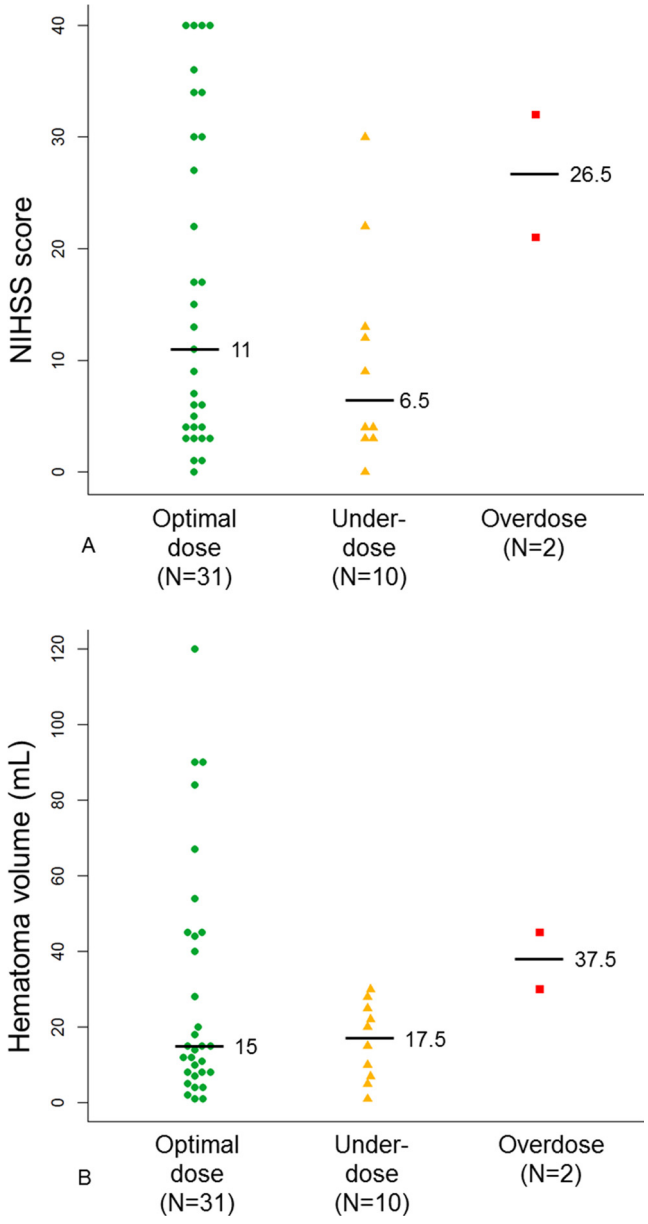

Fig. 2. (A) Comparison of the National Institutes of Health Stroke Scale score upon admission. The black line and number indicate the median value of each group. (B) Comparison of the initial hematoma volume upon admission. The black line and number indicate the median value of each group.

5. Conclusion

Our study shows only a few patients received overdosing of a DOAC before the onset of ICH, and these patients were associated with poorer functional outcomes. Conversely, under-dosing was associated with better functional outcomes than the optimal dose and over-dose groups. Further large-scale studies are required to validate our results, as this study is one with a small sample size. The results of ongoing ELDER-CARE-AF study may provide information about efficacy and safety of under-dosed DOAC [25].

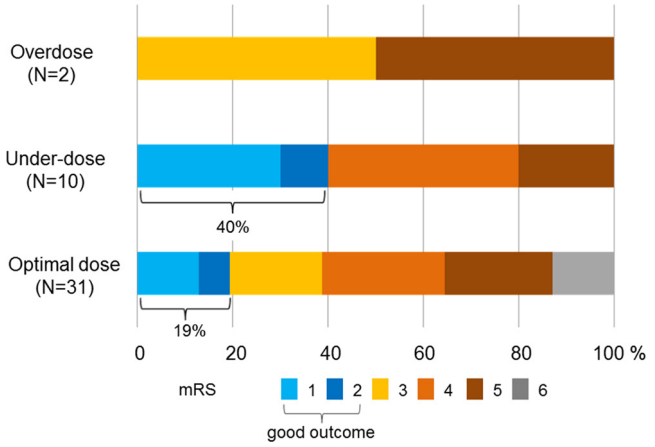

Fig. 3. Modified Rankin Scale score at discharge and the drug dose. The overdose group was associated with poor outcomes.

Conflict of interest

There is no conflict of interest.

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