

Resumption of Direct Oral Anticoagulants in Patients with Acute Spontaneous Intracerebral Hemorrhage

Yuji Kato, MD, PhD,* Takeshi Hayashi, MD, PhD,* Kaima Suzuki, MD, PhD,†
Hajime Maruyama, MD, PhD,* Yuichiro Kikkawa, MD, PhD,†
Hiroki Kurita, MD, PhD,† and Masaki Takao, MD, PhD*

Background: Decisions regarding whether and when to resume direct oral anticoagulants (DOAC) after acute intracerebral hemorrhage (ICH) are challenging. We examined the timing of DOAC resumption and factors that influence decision-making in DOAC resumption. *Methods:* We retrospectively analyzed 43 patients with ICH who were treated with DOAC for nonvalvular atrial fibrillation before ICH onset. All patients were divided into 2 groups (resumption of DOAC and no resumption of DOAC) during hospitalization. Clinical backgrounds, laboratory data, and stroke severity were compared between the groups. *Results:* DOAC were resumed in 19 of 39 (49%) acute ICH survivors and were not resumed in 24 patients, including 4 deceased patients. The National Institutes of Health Stroke Scale score at admission tended to be higher in the no resumption group (median, 17) than in the resumption group (median, 6) ($P = .119$). The modified Rankin Scale score was slightly poorer in the no resumption group (median, 4) than in the resumption group (median, 3) ($P = .070$). In the resumption group, DOAC were resumed at a median of 11 days (interquartile range, 5-21 days) after ICH onset. The modified Rankin Scale score at discharge was positively correlated with the days of DOAC resumption ($R^2 = .31, P = .013$). *Conclusions:* In half of patients, DOAC were resumed relatively early after ICH onset. Early resumption of DOAC for ICH in patients with nonvalvular atrial fibrillation is considered to be safe. The functional outcome was associated with not only resumption of DOAC but also the timing of resumption.

Key Words: Atrial fibrillation—direct oral anticoagulants—safety—hematoma volume
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Introduction

Decisions regarding whether and when to resume direct oral anticoagulants (DOAC) following acute intracerebral hemorrhage (ICH) are challenging and require an assessment of associated risks and benefits. Clinical data, imaging, and risk factors for both ischemic and hemorrhagic complications may aid in decision-making.

In fact, no guideline for DOAC therapy after acute ICH in patients with atrial fibrillation (AF) who were treated with DOAC has yet been established.^{1,2} To the best of our knowledge, no studies to date have evaluated the safety or effectiveness of resumption of DOAC in patients with acute ICH. The present study was performed to reveal the timing of DOAC resumption and factors that influence decision-making in DOAC resumption.

From the *Department of Neurology and Cerebrovascular Medicine, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; and †Department of Cerebrovascular Surgery, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan.

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Address correspondence to Yuji Kato, MD, PhD, Department of Neurology and Cerebrovascular Medicine, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan. E-mail: yujik@saitama-med.ac.jp.

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Methods

This study included 43 consecutive Japanese patients with nonvalvular AF who were treated with DOAC before the onset of ICH and then admitted to our hospital for ICH from March 2014 to February 2018. All patients were divided into those who resumed DOAC (resumption group) and those who did not resume DOAC (no resumption group) during hospitalization. The indication for and timing of DOAC resumption were determined at the attending physicians' discretion. The patients' electronic medical charts and summaries were retrospectively reviewed to obtain the following variables: demographic information (age and sex), body weight, body mass index, preadmission modified Rankin Scale (mRS) score,³ and medical history. Cardiovascular risk factors were defined as follows: (1) hypertension, a history of using antihypertensive agents, systolic blood pressure of greater than or equal to 140 mmHg, or diastolic blood pressure of greater than or equal to 90 mmHg before or greater than or equal to 2 weeks after onset of stroke; (2) diabetes mellitus, use of hypoglycemic agents, randomly measured glucose concentration of greater than or equal to 200 mg/dL, or glycosylated hemoglobin concentration of greater than or equal to 6.5% on admission; (3) dyslipidemia, use of anti-hyperlipidemic agents, or serum low-density lipoprotein cholesterol concentration of greater than or equal to 140 mg/dL; (4) current smoking; (5) alcohol intake and consumption of greater than 10 g/day of alcohol; (6) prior stroke; (7) coronary artery disease, angina, or prior myocardial infarction; and (8) heart failure, a history of congestive heart failure, or an ejection fraction of less than 40%. The prestroke CHADS₂ score, CHA₂DS₂-VASc score, or HAS-BLED score was calculated for each patient based on the published literature.⁴⁻⁶ The serum creatinine concentration and creatinine clearance (Cockcroft-Gault equation),⁷ prothrombin time-international normalized ratio, and activated partial thromboplastin time upon admission were also evaluated.

Stroke severity was assessed by the Glasgow Coma Scale score and the National Institutes of Health Stroke Scale score. The ICH location was classified as follows: lobar (located in cortical or cortical-subcortical areas), supratentorial deep (located in the basal ganglia or thalamus), brain stem, cerebellum, and ventricle (intraventricular). The 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.⁸ 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 greater than 33% or greater than 6 mL from the initial ICH volume within 72 hours.⁹ Magnetic resonance imaging, including T2*-gradient echo imaging, was performed during admission, and the presence of cerebral

microbleeds (CMBs) was assessed. Surgical or conservative therapy, the number of days from ICH onset to resumption of DOAC therapy, the clinical outcome according to the mRS score at discharge, the duration of hospital stay, and discharge destinations (home, rehabilitation hospital, or nursing home) were also evaluated. All aspects of this study were approved by the institutional ethics committee of Saitama Medical University International Medical Center (approval#18-015).

Data are expressed as mean \pm standard deviation, median (interquartile range), or number and percentage. One-way analysis of variance for continuous variables and Pearson's χ^2 test for categorical variables were used to compare differences between the 2 groups. Statistical analysis was performed using IBM SPSS Statistics software, version 20 (IBM Corp., Armonk, NY). All *P* values are 2-sided, with *P* less than .05 considered statistically significant.

Results

The patient profiles of each group are shown in [Table 1](#). The mean age, sex distributions, and body weight were similar between the 2 groups. The median preadmission mRS score was 0 in both groups. The risk factors were not significantly different between the 2 groups. The CHADS₂ score was higher in the no resumption group (median, 3) than in the resumption group (median, 2), although the difference was not statistically significant (*P* = .298). Laboratory data (renal function and coagulation system) were similar between the 2 groups.

The stroke characteristics in each group are shown in [Table 2](#). The Glasgow Coma Scale score and National Institutes of Health Stroke Scale score on admission were worse in the no resumption group (median, 10.5 and 17, respectively) than in the resumption group (median, 14 and 6, respectively) (*P* = .041 and *P* = .119, respectively). With respect to hemorrhagic regions, DOAC were not resumed in most patients with ICH in the brain stem or cerebellum ([Table 2](#)). Based on the mRS, DOAC were not resumed in most patients with poor functional outcomes (*P* = .070). T2*-gradient echo imaging was performed in 25 (58%) patients during hospitalization, and CMBs were detected in 17 (68%) patients. There was no significant difference in the frequency of CMBs between the 2 groups.

In the resumption group, DOAC were resumed at a median of 11 days (interquartile range, 5-21 days) after ICH onset. A worse mRS score at discharge was associated with later DOAC resumption ($R^2 = .31$, *P* = .013) ([Fig 1](#)). During the hospital stay, 1 patient developed hematoma expansion immediately after DOAC resumption and 1 patient developed cerebral embolism during the DOAC discontinuation period.

Discussion

The present study showed that DOAC were resumed in 49% of acute ICH survivors shortly after onset (median of

Table 1. Background characteristics of patients with intracranial hemorrhage

| Characteristics | Resumption group (n = 19) | No resumption group (n = 24) | P value |
|--|---------------------------|------------------------------|---------|
| Age, y | 74.1 y | 72.4 y | .412 |
| Female sex | 9 (47) | 7 (29) | .220 |
| Body weight, kg | 62.4 weight | 60.7 weight | .922 |
| BMI, kg/m ² | 24.0 weight | 22.8 weight | .413 |
| Preadmission mRS score | 0 [0-0] | 0 [0-0] | .542 |
| Risk factors | | | |
| Hypertension | 18 (95) | 19 (79) | .143 |
| Diabetes mellitus | 5 (26) | 8 (33) | .619 |
| Dyslipidemia | 8 (42) | 7 (29) | .377 |
| Current smoking | 1 (5) | 2 (8) | .695 |
| Alcohol intake | 5 (26) | 5 (9) | .673 |
| Prior stroke | | | |
| Ischemic stroke | 6 (32) | 11 (46) | .342 |
| Hemorrhagic stroke | 1 (5) | 3 (13) | .417 |
| CAD | 1 (5) | 2 (8) | .695 |
| Heart failure | 6 (32) | 4 (17) | .250 |
| CHADS ₂ score | 2 [2-3] | 3 [2-3.25] | .298 |
| CHA ₂ DS ₂ -VASc score | 4 [3-5] | 4 [3-5] | .754 |
| HAS-BLED score | 2 [2-3] | 2 [2-3] | .660 |
| Antiplatelet drugs | 1 (5) | 1 (4) | .865 |
| Laboratory data on admission | | | |
| Creatinine, mg/dL | .83 inine | .86 inine | .990 |
| Creatinine clearance, mL/min | 71.6 inine | 70.0 inine | .912 |
| PT-INR | 1.25 Rnine | 1.45 Rnine | .221 |
| APTT, s | 35.3 Rnine | 35.7 Rnine | .448 |

Abbreviations: APTT, activated partial thromboplastin time; BMI, body mass index; CAD, coronary artery disease; mRS, modified Rankin scale; PT-INR, prothrombin time-international normalized ratio.

Data are shown as mean \pm standard deviation, n (%), or median (interquartile range).

Table 2. Stroke characteristics of patients with intracranial hemorrhage

| Characteristics | Resumption group (n = 19) | No resumption group (n = 24) | P value |
|------------------------------|---------------------------|------------------------------|---------|
| GCS score on admission | 14 [11.5-15] | 10.5 [4-14.25] | .041 |
| NIHSS score | 6 [3.5-14] | 17 [4.75-30.5] | .119 |
| ICH location | | | .080 |
| Lobar area | 5 (26) | 7 (28) | |
| Supratentorial deep area | 11 (58) | 7 (28) | |
| Brain stem | 0 (0) | 4 (16) | |
| Cerebellum | 2 (11) | 7 (28) | |
| Ventricle | 1 (5) | 0 (0) | |
| Initial hematoma volume, mL | 23.3 mL | 28.9 mL | .723 |
| Hematoma expansion | 1 (5) | 0 (0) | .255 |
| Presence of microbleeds* | 6 (55) | 11 (79) | .389 |
| Acute neurosurgery | 4 (21) | 5 (21) | .986 |
| mRS score at discharge | 3 [2-4] | 4 [3-5] | .070 |
| Mortality | 0 (0) | 4 (17) | .062 |
| Duration of hospital stay, d | 31 \pm 23 | 32 \pm 31 | .625 |
| Discharge destination | | | .113 |
| Home | 4 (21) | 2 (10) | |
| Rehabilitation hospital | 14 (74) | 12 (60) | |
| Nursing home | 1 (5) | 6 (30) | |

Abbreviations: GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Data are given as median (interquartile range), n (%), or mean \pm standard deviation.

25 patients (11 in resumption group and 14 in no resumption group) underwent T2 imaging.

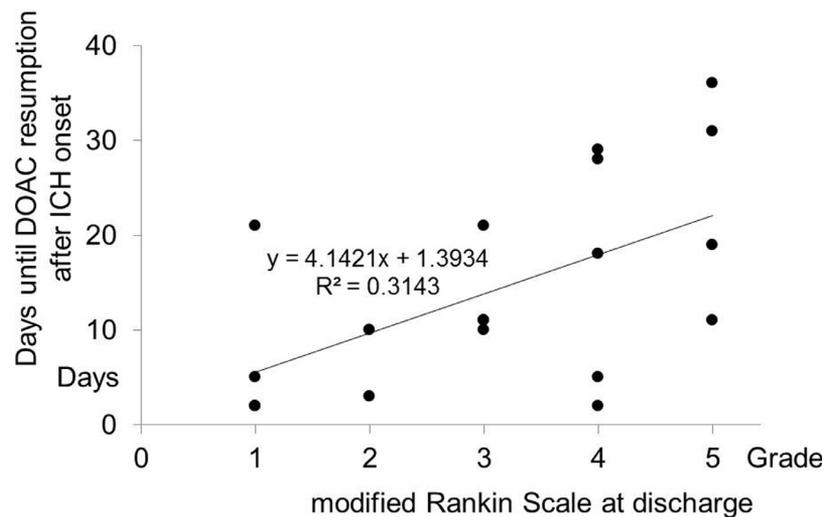


Figure 1. Comparison of modified Rankin Scale score at discharge and days until DOAC resumption after the onset of intracerebral hemorrhage. A worse modified Rankin Scale score at discharge was associated with later resumption of direct oral anticoagulants.

11 days from ICH onset). This rate seems relatively higher than that in previous reports, in which the proportion of patients restarting anticoagulant therapy (mainly warfarin) after ICH ranged from 6.3% to 48.0%.¹⁰ Moreover, there was little excess risk of hematoma expansion or hemorrhagic complications after resumption of DOAC.

Of the remaining 24 patients who did not receive DOAC, the most common reason for no resumption of DOAC was the development of severe neurological conditions (not older age or a larger hematoma volume). Because this was a retrospective analysis, we could not identify the specific reason for avoidance of DOAC prescription in patients with poor functional outcomes. We speculate that physicians avoid resumption of DOAC if they predict during hospitalization that the final outcome of patients with ICH will be poor. Indeed, many neurosurgeons consider that a poor functional status (mRS score of 4 or 5) is a contraindication for restarting anticoagulation in patients with ICH.¹¹

Clinicians deciding whether and when to resume DOAC following ICH face a considerable dilemma. Early resumption of DOAC may lead to enlargement of hematomas. Conversely, withholding DOAC may result in thromboembolic complications, although early DOAC resumption does not improve outcomes, especially in patients with AF. A large-scale study of ICH in patients with AF suggested that restarting warfarin at 7 to 8 weeks after ICH provided the greatest benefit without an increased risk of major bleeding.¹² In another study, anticoagulation was safely restarted within 1 week after ICH onset.¹³

Although not statistically significant, the presence of CMBs in the no resumption group (79%) was larger than that in the resumption group (55%). How this finding affects decision-making regarding resumption of DOAC is unclear because the decision should be made on a case-by-case basis. Physicians might avoid resumption of DOAC in patients with

CMBs. In a prospective study of survivors of ICH, the total number of microbleeds at baseline predicted the risk of future symptomatic ICH (3-year cumulative risk of 14%-51% for patients with 1-6 foci of microbleeds).¹⁴ Intriguingly, microbleeds have also been associated with an increased risk of ischemic stroke, further complicating the decisions regarding appropriate therapy in this subset of patients.¹⁵ A large retrospective study showed that antithrombotic medication is not associated with the development of CMBs if adequate antihypertensive therapy is provided.¹⁶

This study has several limitations. First, it was a single-center, retrospective study. Second, a small number of patients were followed-up only during the hospital stay. In some patients, functional recovery after discharge might lead to resumption of DOAC.

In conclusion, resumption of DOAC was performed in 49% of acute ICH survivors at a median of 11 days after ICH onset. In particular, physicians might avoid the use of DOAC in patients who are expected to have a poor functional outcome. Early resumption of DOAC for ICH in patients with nonvalvular AF is considered to be safe because hematoma expansion and excessive bleeding events were rarely observed. A further rigorous analysis may warrant the adequate indications for and timing of DOAC resumption in patients with ICH.

Conflicts of Interest: None.

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