Timing of Treatment Initiation With Oral Anticoagulants for Acute Ischemic Stroke in Patients With Nonvalvular Atrial Fibrillation

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Background: Only a few studies have addressed the optimal start time for oral anticoagulants (OACs) after acute ischemic stroke in patients with nonvalvular atrial fibrillation (NVAF). The aim of this retrospective study was to analyze the time of OAC administration after stroke onset.

Methods and Results: This study included 300 patients with NVAF who had acute ischemic stroke and were treated with OACs between April 2012 and March 2016. We investigated the time at which OACs were started by anticoagulant type and the relationship between the time of OAC administration and stroke severity (the National Institutes of Health Stroke Scale [NIHSS] score on admission). Of the 300 patients, 114 and 186 patients received warfarin and direct-acting OACs (DOACs), respectively. Patients in the DOAC group had OAC initiated therapy significantly sooner (3 days) than in the warfarin group (7 days; P<0.001). With regard to stroke severity (NIHSS score <8, mild; 8–16, moderate; >16, severe), the median time for starting therapy was 2, 7, and 11 days for mild, moderate, and severe stroke, respectively. Hemorrhagic events occurred in 3 patients in the warfarin group; however, no hemorrhagic events occurred in the DOAC group.

Conclusions: Our study revealed that neurologists began OACs earlier in patients with mild acute cerebral infarction. Even in patients with severe stroke, OACs were started earlier than expected.

Key Words: Acute ischemic stroke; Nonvalvular atrial fibrillation; Oral anticoagulants

Patients with nonvalvular atrial fibrillation (NVAF) have an ischemic stroke risk almost 5-fold that of those with normal sinus rhythm.1 In particular, they tend to develop cardiogenic embolic stroke and thus may have a poor prognosis. In addition, patients with cardiogenic embolic stroke have a higher risk of stroke recurrence in the early clinical phase, and therefore anticoagulants should be started or resumed as early as possible.2 The American Heart Association and the American Stroke Association recommend that oral anticoagulant (OAC) therapy needs to be started within 14 days after ischemic stroke in patients with NVAF.3 Similarly, the European Heart Rhythm Association (EHRA) has proposed the “1–3–6–12 day rule”. According to this recommendation, the start time of anticoagulation therapy may be decided based on the stroke severity,4 although the recommendation is not based on rigorous evidence. In fact, there are reports in which anticoagulant therapy has been started much earlier, even in the acute phase of cerebral infarction.5 In this study, we assessed the timing of OAC therapy after the onset of ischemic stroke, with a hypothesis that OAC therapy is administered to patients with relatively mild acute ischemic stroke, which is less likely to cause hemorrhagic stroke, earlier than recommended by the EHRA.

Methods

This study included 300 patients with NVAF who were admitted to hospital within 24 h of the onset of acute ischemic stroke and then treated with OACs between April 2012 and March 2016. Before April 2012, warfarin was approved for long-term treatment; however, direct-acting OACs (DOACs) were not. Therefore, we focused on the patients who were admitted to hospital after April 2012. Patients who were dependent in their activities of daily living before hospitalization were excluded from this study based on family information or patient’s recollection. The National Institutes of Health Stroke Scale (NIHSS) score at the time of hospital admission of such patients may be affected by the level of dependency before their stroke onset. Echocardiography was performed in all patients to evaluate the presence of valvular disease. NVAF was
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Creatinine clearance (CCr; Cockcroft-Gault equation), CHADS2 and CHA2DS2-Vasc scores before stroke onset, and NIHSS score on admission. Previous use of anticoagulant type drugs before the onset of cerebral infarction, acute recanalization therapy, intravenous heparin therapy before OACs, the days before starting heparin therapy, duration of hospital stay (days) and number of days until the start of OACs were also analyzed. In particular, NIHSS scores were classified into 3 categories based on the EHRA guidelines (<8, mild; 8–16, moderate; and >16, severe) to evaluate the start time of OACs relative to stroke severity.

### Statistical Analysis

Data were analyzed using SPSS software (version 20; IBM, Armonk, NY, USA). Age, BW, Cr, and CCr were compared between groups using Student’s t-test. The CHADS2 score, CHA2DS2-VASc score, NIHSS score on admission, the days before starting heparin and duration of hospital stay and the number of days until the start of OACs were compared using the Wilcoxon rank-sum test, and ratios were compared using Fisher’s exact test (two-sided).

In addition, we established a logistic regression model using warfarin or DOACs as an objective variable and using variables with a significant difference on univariate analysis as explanatory variables. We selected patients treated with DOACs and matched patients treated with warfarin based on propensity scores. Then, we analyzed the time to the initiation of OAC therapy. P values <0.05 were considered significant.

### The Institutional Review Board of Saitama Medical University International Medical Center approved this study protocol (No. 16-104).

| Table. Clinical Characteristics of the Warfarin and DOAC Groups of NVAF Patients With Ischemic Stroke |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Total (n=300)  | Warfarin (n=114) | DOACs (n=186) | P value (W vs. DOACs) | After propensity-matching |
| Age, years                     | 76.7±8.8      | 79.7±8.4        | 74.8±8.5      | <0.001        | 78.4±8.4        | 78.6±8.3        | 0.895           |
| ≥75 years                      | 177 (59)      | 84 (73.7)       | 93 (50)       | <0.001        | 35 (70)         | 35 (70)         | 1.000           |
| Female sex                     | 131 (43.7)    | 66 (57.9)       | 65 (36.9)     | <0.001        | 28 (56)         | 29 (58)         | 1.000           |
| Body weight, kg                | 56.2±12.5     | 52.5±11.1       | 58.6±12.9     | <0.001        | 53.8±11.3       | 51.6±10.0       | 0.390           |
| Creatinine, mg/dL              | 0.94±0.74     | 1.14±1.13       | 0.81±0.20     | 0.002         | 0.83±0.31       | 0.82±0.22       | 0.913           |
| Creatinine clearance, mL/min   | 58.8±24.7     | 47.5±21.6       | 66.1±23.9     | <0.001        | 55.2±21.2       | 52.5±15.6       | 0.346           |
| CHADS2 score                   | 2 (1–2)       | 2 (1–3)         | 2 (1–2)       | 0.001         | 2 (1–3)         | 2 (1–2.5)       | 0.903           |
| CHA2DS2-Vasc score             | 3 (2–4)       | 4 (3–4.25)      | 3 (2–4)       | <0.001        | 4 (3–4.25)      | 4 (3–4.5)       | 0.877           |

### Treatment with antithrombotic drugs on admission

|                                | Warfarin (n=50) | DOACs (n=50) | P value (W vs. DOACs) |
| Antithrombotic drugs admission | 50 (16.7)       | 18 (15.8)    | 32 (17.2)             | 0.873           |
| Anticoagulant                  | 95 (31.7)       | 44 (38.6)    | 51 (27.4)             | 0.055           |
| NIHSS score on admission       | 7 (2–12.25)     | 9.5 (4.25–15.75) | 4 (2–10)              | <0.001         |
| Recanalization therapy         | 52 (17.3)       | 14 (12.3)    | 38 (20.4)             | 0.115           |
| Intravenous heparin therapy before OACs | 41 (13.7) | 27 (23.7) | 14 (7.5) | <0.001 |
| No. of days before starting heparin therapy | 1 (1–2) | 1 (1–5) | 1 (1–1.75) | 0.109 |
| Duration of hospital stay, days | 24 (13–40.25)  | 37 (21–49.75) | 18.5 (13–31.75) | <0.001         |

Data are given as mean±SD, median (interquartile range), or number (%). DOACs, direct oral anticoagulants; NIHSS, National Institute of Health Stroke Scale; NVAF, nonvalvular atrial fibrillation; W, warfarin; OACs, oral anticoagulants.

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defined as the presence of AF without rheumatic mitral valve disease (mitral valve stenosis) or artificial valve replacement. AF was confirmed based on medical records such as ECGs, bedside ECG monitoring and 24-h Holter monitoring.

We retrospectively compared the following variables between the patients who received warfarin (warfarin group) and the patients who received DOACs (DOAC group). The variables analyzed include patient attributes (age and sex), body weight (BW), creatinine levels (Cr), creatinine clearance (CCr; Cockcroft-Gault equation), CHADS2 and CHA2DS2-Vasc scores before stroke onset, and NIHSS score on admission. Previous use of anticoagulant type drugs before the onset of cerebral infarction, acute recanalization therapy, intravenous heparin therapy before OACs, the days before starting heparin therapy, duration of hospital stay (days) and number of days until the start of OAC therapy were also analyzed. In particular, NIHSS scores were classified into 3 categories based on the EHRA guidelines (<8, mild; 8–16, moderate; and >16, severe) to evaluate the start time of OACs relative to stroke severity.

Figure 1. Percentage of warfarin vs. DOACs given to each age group of patients with NVAF and ischemic stroke. The average age of patients receiving DOACs was lower than that in the warfarin group. DOACs, direct oral anticoagulants; NVAF, nonvalvular atrial fibrillation.
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The number of days before starting therapy in the warfarin group was 7 days (interquartile range; IQR 2–12.75 days) compared with 3 days (IQR 1–7 days) for the DOAC group (P<0.001; Figure 2). When the time to the initiation of warfarin or DOAC therapy was compared after resampling based on propensity-score matching (Table), no significant difference was observed between the warfarin group (6 days [IQR 2−12 days]) and the DOAC group (5 days [IQR 2−11.75 days]; P=0.539).

The start day for each DOAC was 1.5 days (IQR 1–4.75 days) for dabigatran, 4 days (IQR 1–7 days) for rivaroxaban, 4 days (IQR 1–7 days) for apixaban and 4 days (IQR 3–11 days) for edoxaban. The NIHSS score (median) was 2, 4, 6 and 7 for dabigatran, rivaroxaban, apixaban and edoxaban, respectively. Dabigatran treatment began sooner than any other DOAC (Figure 3). With regard to

Table shows the clinical characteristics of the warfarin and DOAC groups. Of the 300 patients, 114 (38%) received warfarin, and 186 (62%) were treated with DOACs (dabigatran: 24; rivaroxaban: 108; apixaban: 45; edoxaban: 9). Reduced-dose DOAC therapy was administered to 82 patients (44.1%) based on dose reduction criteria. The average age of the DOAC group was lower than that of the warfarin group. In particular, the rate of DOAC administration gradually decreased with age (Figure 1). The DOAC group showed significantly higher BW and CCr values. In contrast, the warfarin group had more females and higher Cr, CHADS2 score, CHA2DS2-Vasc score, NIHSS scores on admission, and intravenous heparin therapy before OAC. In addition, the duration of hospital stay was significantly shorter in the DOAC group than in the warfarin group (Table).

![Figure 2](image-url) **Figure 2.** Number of days before starting oral anticoagulation (OAC) therapy in the warfarin and DOAC groups: 7 days (interquartile range; IQR 2–12.75 days) in the warfarin group compared with 3 days (IQR 1–7 days) for the DOAC group. Boxes represent IQR. Lines across boxes indicate median values. DOACs, direct oral anticoagulants.

![Figure 3](image-url) **Figure 3.** Number of days before starting treatment, by type of DOAC: dabigatran, 1.5 days (IQR 1–4.75 days); rivaroxaban, 4 days (IQR 1–7 days); apixaban, 4 days (IQR 1–7 days); edoxaban, 4 days (IQR 3–11 days). Boxes represent interquartile range (IQR). Lines across boxes indicate median values. DOACs, direct oral anticoagulants; NIHSS, National Institute of Health Stroke Scale.

![Figure 4](image-url) **Figure 4.** (A) Days before starting OAC therapy, according to neurological severity: the mild group began OAC treatment after 2 days (interquartile range; IQR 1–6 days); the moderate group after 7 days (IQR 3–12.25 days); and the severe group after 11 days (IQR 8–15 days). (B) Days before treatment with DOACs, according to neurological severity: the mild stroke group began DOAC therapy after 3 days (IQR 1–6 days); the moderate group started after 4 days (IQR 2–9.5 days), and the severe group began after 9 days (IQR 6–13 days). Boxes represent IQR. Lines across boxes indicate median values. Abbreviations as in Figures 2,3.
stroke severity, the mild group began OAC treatment (warfarin and DOACs) after 2 days (IQR 1–6 days); the moderate groups after 7 days (IQR 3–12.25 days); and the severe group after 11 days (IQR 8–15 days; Figure 4A). In particular, in the DOAC group, the mild stroke group began therapy after 3 days (IQR 1–6 days), the moderate group started after 4 days (IQR 2–9.5 days), and severe group began after 9 days (IQR 6–13 days; Figure 4B).

Bleeding events leading to withdrawal of anticoagulants did not occur in patients who took DOACs, but they did occur in 3 patients who took warfarin (gastrointestinal bleeding in 1 patient [age 80] and hemorrhagic infarction in 2 patients [age 81 and 84]). However, these bleeding events did not fit the criteria of the International Society on Thrombosis and Hemostasis (ISTH).18

Discussion

In this hospital study, DOAC treatment was started earlier than warfarin for secondary prevention in individuals with NVAF who had an ischemic stroke. This difference may be associated with patient characteristics, such as age and stroke severity. The DOAC group included many patients with mild disease for whom an early start with anticoagulant therapy was considered to be safe. Therefore, a comparison of patients matched for severity, age, and other background characteristics showed no difference in the time to initiation of OAC therapy (DOAC vs. warfarin). In the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-NVAF Registry, a multicenter prospective study targeting patients with acute-phase cerebral infarction accompanied by NVAF in Japan,5 that DOAC group included younger patients and had a higher proportion of mild cases with a smaller infarct area than the warfarin group. The patient characteristics in the DOAC group of that registry study were representative of those of the present patients.

In the DOAC group, we found that patients treated with dabigatran had treatment started earlier than those treated with other DOACs. Dabigatran, a direct thrombin inhibitor, is approved as a capsule for oral use. Decapsulation of the product affects the area under the blood concentration time curve (personal communication; Boehringer Ingelheim, Germany) and may result in unsteadiness of the anticoagulation effect. In the present study, patients treated with dabigatran had lower NIHSS scores on admission compared with other DOAC patients, suggesting that dabigatran was chosen for patients with milder disease states who were capable of taking capsules. However, some of the DOACs examined in this study had not been approved during the first part of the study period, and the number of treated patients differed greatly among the DOACs examined. Thus, additional accumulation and analysis of cases may be necessary for further comparison of the DOACs.

In our study, the timing of the start of anticoagulant therapy, when assessed by stroke severity, was comparable to or earlier than the 1–3–6–12 day rule that is recommended by the EHRA.4 In particular, DOACs were found to have been administered earlier, even in moderate and severe cases. In the SAMURAI-NVAF Registry,4 administration of DOACs was initiated early in both moderate and severe cases, as in our study (moderate [median], present vs. SAMURAI, 3 days vs. 4 days, severe [median], present vs. SAMURAI, 9 days vs. 5 days), although the definition of a severe case slightly differed between the 2 studies (SAMURAI-NVAF Registry, NIHSS score <5, mild; 5–14, moderate; and >14, severe). When comparing the warfarin and DOAC groups within each severity category, the time to treatment initiation was shorter in the DOAC group. A delayed initiation of warfarin therapy may have been attributable to significantly increased use of intravenous heparin in the warfarin group.

Regarding safety, bleeding events did not occur in patients taking DOACs, but did occur in 3 patients taking warfarin. However, none of the 3 bleeding events, for which drug withdrawal was necessary at the discretion of the attending physician, was symptomatic intracranial bleeding associated with the deterioration of neurological findings. Gastrointestinal hemorrhage was not serious enough to decrease hemoglobin levels or to require blood transfusion, as described in the criteria of the ISTH.18 In the SAMURAI-NVAF study,8 1 patient developed gastrointestinal bleeding, and none of the patients taking DOACs in that study developed intracranial hemorrhage. Therefore, OAC administration may be safe for secondary prevention of ischemic stroke in patients with NVAF. However, additional data and statistical validation are needed to comprehensively determine the safety of OACs, because the safety assessment results in this study were based on a small number of events and short-term outcomes.

A limitation of this study is that it included only one university hospital. Although we discussed the selection of medication for each patient in conference, the final selection was left to each neurologist in charge. Therefore, there may be some bias in the selection of warfarin and DOAC treatments.

Although the results were obtained from a retrospective analysis in a single center, the timing of OAC administration was slightly earlier than the general recommendation, without serious adverse events. Because there is still no strong evidence for the appropriate timing of initiation of anticoagulant therapy for acute ischemic stroke in patients with NVAF, even in the recent European Society of Cardiology guidelines,18 a prospective study is required, taking all influential factors into consideration.

Conclusions

The results of this study revealed the following: (1) DOACs were more likely to be administered to younger patients as compared with warfarin; (2) acute cerebral infarction patients received DOAC therapy sooner than warfarin therapy; (3) OAC therapy was initiated in patients with early-stage mild ischemic stroke; DOAC therapy was also initiated earlier than under the 1–3–6–12 day rule, even in patients with severe ischemic stroke; and (4) OAC therapy was safe, even in the acute ischemic stroke setting.

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Conflict of Interest Statement

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References


