Early Administration of Non-Vitamin K Antagonist Oral Anticoagulants for Acute Ischemic Stroke Patients With Atrial Fibrillation in Comparison With Warfarin Mostly Combined With Heparin

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Background: This study evaluated the rates of new lesions on diffusion-weighted images (DWIs) of magnetic resonance imaging (MRI) and hemorrhagic transformation (HT) during 2 weeks after acute ischemic stroke (AIS) in patients with atrial fibrillation (Af) who were given one of the non-vitamin K antagonist oral anticoagulants (NOACs); this was then compared with those who were given warfarin.

Methods and Results: Consecutive AIS patients with Af were enrolled between January 2008 and June 2013, and those selected were patients who had a MRI that included DWIs both on admission and after 2 weeks, and those given only warfarin (warfarin group) or only one of the NOACs (NOAC group) within 2 weeks of admission. Of all 257 enrolled patients, 50 patients were selected for the NOAC group (median age of 80.0 years) and 125 patients for the warfarin group (median age of 80.0 years). Both NOAC and warfarin were started at a median of the second day after admission. There was no significant difference in the rates of new lesions on DWIs (26.0% vs. 28.0%, P=0.7888) and HT (30.0% vs. 39.2%, P=0.2536) between the NOAC and warfarin groups. The NOAC group had a lower rate of concomitant use of heparin (44.0% vs. 92.8%, P<0.0001) than the warfarin group.

Conclusions: This study suggests that NOACs are suitable for AIS patients with Af, perhaps even better than warfarin, given their simplicity. (Circ J 2015; 79: 862–866)

Key Words: Acute ischemic stroke; Atrial fibrillation; Diffusion-weighted image; Non-vitamin K antagonist oral anticoagulants; Warfarin

Cardioembolic stroke is the most severe type of acute ischemic stroke (AIS).1,2 Compared with other types of stroke, patients with cardioembolic stroke are prone to early (1–10%)1,2 and long-term stroke recurrence (2–15% in the first year).3 It has been reported that atrial fibrillation (Af) is a leading risk factor and accounts for approximately three-quarters of cardioembolic stroke.1,2 An oral anticoagulation drug, warfarin, can reduce the recurrence of cardioembolic stroke due to Af by 66%,3 as well as a 64% reduction in primary prevention.4 Although recurrence after cardioembolic stroke frequently occurs during the acute stage,1,2 the efficacy of intravenous anticoagulant therapy like heparin has not been proven,5,7 and the timing of starting warfarin for those patients is still unclear.

Furthermore, recent studies demonstrated that diffusion-weighted images (DWIs) of magnetic resonance imaging (MRI) detected more than a few new lesions at the acute or subacute stage of AIS,8–10 and this was also suggested to be a surrogate marker for subsequent recurrence of stroke.8 In cases of AIS with Af, it was reported that the rate of recurrent new lesions on DWIs was 47%.8,9 We also reported the frequency of new lesions on DWIs at 2 weeks from admission to be 28.5% under early warfarinization, with a median starting day of the second day, and found that achieving the targeted prothrombin time-international normalized ratio (PT-INR) at 2 weeks was associated with a lower frequency of new lesions.11

Recently, some non-vitamin K antagonist oral anticoagulants (NOACs) were developed and have been reported to have equivalent or more power than warfarin to reduce stroke recurrence...
in Af patients; as an additional advantage, they are also associated with fewer hemorrhagic complications than warfarin.\textsuperscript{12,13} Furthermore, even if intracranial hemorrhage occurs, hematoma reportedly seems to remain small to moderate, having difficulty expanding.\textsuperscript{14} Although there is little evidence about the mode of administering NOACs to AIS patients,\textsuperscript{15} NOACs may be superior to warfarin to prevent recurrence from the acute stage owing to their rapid action, simplicity, and safety.

The purposes of this study are thus to investigate the clinical characteristics and neuroradiological outcomes (the rates of recurrent new lesions on DWIs and hemorrhagic transformation (HT) during 2 weeks) in AIS patients with Af who were given NOACs at the acute stage and to compare them with those who were given warfarin.

**Methods**

For cardioembolic stroke patients who cannot receive revascularization therapy, one of the goals is to prevent recurrence (including worsening of symptoms) during the acute stage, avoiding HT. For this purpose, Suiseikai Kajikawa Hospital established a regimen of early anticoagulation therapy for AIS patients with Af in 2008, as described below.

Early anticoagulation therapy for AIS patients with Af who cannot receive revascularization therapy can be performed if the patient is not comatose, does not have any bleeding complications, and meets at least one of the following head computed tomography (CT) criteria: (1) no hemorrhagic lesion is shown on a head CT scan both at admission and on the next day; (2) the patient is admitted after 24h from onset and an initial CT shows no hemorrhagic lesion; and (3) the patient’s National Institutes of Health Stroke Scale (NIHSS) score on admission is less than 5 and the initial head CT shows no hemorrhagic lesion. In Japan, only warfarin had been used as an oral anticoagulation drug until one of the NOACs, dabigatran, became available for patients with Af in March 2011; rivaroxaban then became available in April 2012. According to our regimen, if warfarin is used, it is recommended to start it as early as possible, and the concomitant use of unfractionated heparin (10,000 units a day intravenously) is recommended in order to prevent a presumed pro-thrombotic state during the initiation of warfarin\textsuperscript{16,17} until the targeted PT-INR is achieved (recommended in Japan as 2.0–3.0 for patients <70 years or 1.6–2.6 for those ≥70 years).\textsuperscript{18} The checking of PT-INR should be carried out on the third, fifth, seventh, and 10th days when possible, as well as at admission and on the 14th (±1) day, to titrate warfarin. If one of the NOACs is used, it is also recommended to start it as early as possible, and the use of unfractionated heparin (10,000 units a day intravenously) is recommended until the NOAC is initiated. Regardless of the kind of oral anticoagulation drug, a head CT on the second day and head MRI assessment including DWIs on the 14th (±2) day are usually scheduled to confirm recurrence and HT. When the patient is eligible for early anticoagulation therapy, the timing of the initiation and the selection of an anticoagulation drug are at the discretion of the physician in charge. If any hemorrhagic complication occurs during the anticoagulant therapy, discontinuation and resumption are also at the discretion of the physician in charge. Because this regimen was within the medical treatment covered by health insurance in Japan during this study period, our hospital approved its use, but required informed consent needs to be obtained from the patient or a relative on admission. Under these circumstances, we enrolled consecutive AIS patients with Af between January 2008 and June 2013. We selected the patients who met all of the following conditions: (1) patients were admitted within 72h of onset; (2) clinical assessment and MRI including DWIs both on admission and at 2 weeks were accomplished; (3) patients were given warfarin or NOACs within 2 weeks of admission, irrespective of heparin use; (4) patients did not have severe renal dysfunction on admission, which is defined as creatinine clearance (CrCl) <15 ml/min and calculated using the Cockcroft-Gault equation;\textsuperscript{19} and (5) more than 2 types of anticoagulant drug were not given within 2 weeks. Then, we divided the selected patients into the NOAC group and the warfarin group.

Any new lesion on a DWI at 2 weeks from admission was defined as a recurrent lesion because it was sometimes difficult

![Figure. Details of exclusion from consecutively enrolled acute stroke patients with atrial fibrillation to extract the patients. Af, atrial fibrillation; AIS, acute ischemic stroke; CrCl, creatinine clearance; MRI, magnetic resonance imaging; NOAC, non-vitamin K antagonist oral anticoagulants.](image-url)
ratio statistic can be computed for each effect in the model. The data were analyzed with JMP 7.0.1 (SAS Institute Inc, Cary, NC, USA), with P-values <0.05 considered significant.

Results

Of all the 257 enrolled patients, 50 patients were extracted for the NOAC group and 125 patients for the warfarin group (Figure). In terms of the breakdown of NOACs, the dabigatran consisted of 34 patients (26 patients given 220 mg/day and 8 patients given 300 mg/day) and the rivaroxaban consisted of 16 patients (11 patients given 10 mg/day and 5 patients given 15 mg/day).

Table 1 provides a comparison of the clinical characteristics, which showed no significant difference between the NOAC and warfarin groups, except for a difference in median NIHSS on admission (4.0 [2.0–8.0] vs. 7.0 [2.0–16.5], P=0.0318). Comparisons of therapies and outcomes are shown in Table 2. The NOAC group had a lower rate of concomitant use of heparin (44.0% vs. 92.8%, P<0.0001) than the warfarin group. In patients treated with heparin, the median number of days of heparin administration was significantly fewer in the NOAC group than in the warfarin group (3.5 [1.8–5.0] vs. 9.0 [6.0–10.8], P<0.0001). The rates of recurrent lesions on DWIs were similar between the NOAC and warfarin groups, but the rate of symptomatic recurrence appeared to be higher in the NOAC group than in the warfarin group (10.0% vs. 6.4%, P=0.4120). However, the rate of symptom-
atic recurrence after any anticoagulant therapy was identical in the 2 groups (4.0% vs. 4.0%, P=1.0000). There was no significant difference in the rate of HT between the NOAC and warfarin groups (30.0% vs. 39.2%, P=0.2536).

Multivariate logistic regression analysis was carried out to compute the likelihood-ratio statistic of the use of NOACs over warfarin for the occurrence of recurrent lesions on DWIs or HT, adjusting the confounding factors. NIHSS on admission, past history of dyslipidemia, CrCl value, PT-INR value on admission, and starting day of oral anticoagulant drug were included in the model to investigate the association with the occurrence of recurrent lesions on DWIs. For the whole model, the likelihood-ratio statistic and the lack-of-fit test showed P values of 0.0006 and 0.2206, respectively. The result of the likelihood-ratio test for each effect is shown in Table 3A. Only a higher NIHSS on admission (P=0.0003), but not the use of NOACs over warfarin (P=0.7392), was independently associated with the occurrence of recurrent lesions on DWIs, with statistical significance. Age, NIHSS on admission, past history of stroke, CrCl value, PT-INR value on admission, and starting day of oral anticoagulant drug were included in the model to investigate the association with the occurrence of HT. For the whole model, the likelihood-ratio statistic and the lack-of-fit test showed P values of <0.0001 and 0.0703, respectively. The result of the likelihood-ratio test for each effect is shown in Table 3B. Younger age (P=0.0026), higher NIHSS on admission (P=0.0012), and later starting day of oral anticoagulant drug (P=0.0475), but not use of NOACs over warfarin (P=0.8732), were independently associated with the occurrence of HT, with statistical significance.

Discussion

In the present study, there was no significant difference in the rates of new lesions on DWIs and HT between the NOAC group and the warfarin group in AIS patients with Af during the first 2 weeks. Multivariate logistic regression analysis with adjusting the confounders did not change the results. The use of NOACs was significantly associated with lower concomitant use of heparin, shortening its period if used, and lower NIHSS on admission compared with the use of warfarin.

It has been reported that the rate of early symptomatic embolic recurrence in cardioembolic stroke with Af is not as high as expected. Large, well-designed studies have included their frequency to be 5–8% within the first 14 days in groups without anticoagulation therapy. However, recent studies using MRI found that recurrent lesions were detected on DWIs in 26–34% of AIS patients within 1–2 weeks, indicating an older age, a higher frequency of Af, and a higher frequency of ipsilateral carotid stenosis, and higher NIHSS on admission in patients with a recurrent lesion on DWIs than in those without. Once a stroke occurs, it is sometimes difficult to diagnose recurrence by only neurological examination because pre-existing severe deficits may obscure it. Additionally, it was reported that silent ischemic lesions on MRI might be a surrogate marker of clinical recurrence. Therefore, it should be meaningful to investigate whether any therapy like anticoagulant therapy can reduce the recurrence on DWIs.

Warfarin has been used to prevent recurrent ischemic stroke in stroke patients with Af at the non-acute stage based on evidence from a clinical trial. Recently, meta-analysis of several large-scale trials demonstrated that NOACs had non-inferiority to warfarin for preventing non-hemorrhagic stroke and significantly reduced intracranial bleeding. In addition, in Japan, non-inferiority of rivaroxaban to warfarin for combined stroke and systemic embolism was confirmed using a Japan-specific dose of rivaroxaban. When it comes to AIS, the use of any oral or intravenous anticoagulant drug is not recommended;

one of the reasons for this is that increased hemorrhagic events counterbalance the efficacy of reducing recurrent cardioembolic stroke. In particular, it is sometimes difficult to use warfarin appropriately at the acute stage owing to its slow action with the induction of an initial prothrombic state and interaction with other drugs. Bridging heparin with warfarin is performed in daily clinical practice, although its efficacy was not demonstrated in a previous symptom-oriented study. Recently, we reported that achieving a target PT-INR at 2 weeks in AIS patients with Af was significantly associated with a lower frequency of new lesions on DWI; however, only 42.3% of all patients could achieve a target PT-INR at 2 weeks. NOACs are promising alternatives given their rapid action, safety, and stable pharmacological effect. Recently, Shibazaki et al reported a satisfactory outcome (no symptomatic intracerebral hemorrhage and no recurrent stroke or TIA within 3 months) in 41 patients with AIS and Af for whom a NOAC (dabigatran or rivaroxaban) was given at a median interval of 2 days from onset. In the present study, the NOAC group showed similar rates of recurrent new lesions on DWIs and HT compared with the warfarin group, with a quartile of PT-INR of 1.5–2.5 at 2 weeks, which was considered to be moderately controlled for patients with median age of 80.0 years. Additionally, rapid action of NOACs could obviate the need for concomitant use of heparin or shorten the period of heparin administration, which might make the acute therapy for AIS patients with Af simple and help shorten their hospital stay. In the present study, NOACs were prescribed to milder cases of stroke than in the warfarin group. This was probably because dabigatran could not be given via a gastric tube. The NOAC group had more, albeit not significantly more, symptomatic recurrence despite a similar rate of recurrent new lesions on DWIs at 2 weeks. However, the rate became identical, except for recurrence before any anticoagulant therapy. Because it was reported that early recurrence was associated with poor outcome in cardioembolic stroke, we believe that oral anticoagulant drugs, and

| Table 3. Multivariate Logistic Regression Analysis of the Use of NOACs Over Warfarin, and Confounders Associated With the Occurrence of New Lesions on (A) DWIs or (B) HT |
|-----------------|-----------------|-----------------|
| **(A) DWIs**    | **Odds ratio**  | **P value**     |
| Use of NOACs over warfarin | 1.15 | 0.74 |
| NIHSS score on admission | 1.10 | <0.01 |
| Past history of dyslipidemia | 0.51 | 0.16 |
| CrCl | 0.99 | 0.44 |
| PT-INR on admission | 2.74 | 0.17 |
| Starting day of oral anticoagulant drug | 0.97 | 0.63 |
| **(B) HT**      | **Odds ratio**  | **P value**     |
| Use of NOACs over warfarin | 0.94 | 0.87 |
| Age | 0.93 | <0.01 |
| NIHSS score on admission | 1.09 | <0.01 |
| Past history of stroke | 0.75 | 0.49 |
| CrCl | 0.99 | 0.27 |
| PT-INR on admission | 0.19 | 0.06 |
| Starting day of oral anticoagulant drug | 1.15 | <0.05 |

Abbreviations as in Tables 1, 2.
if possible one of the NOACs, should be initiated as early as possible, weighing the prevention of recurrent ischemic stroke against the risk of HT or its enlargement. The present study has some limitations. The use and choice of oral anticoagulant drugs were at the discretion of the physician in charge. To compare the NOAC group with the warfarin group, most of the patients in the warfarin group were selected from the period before we could use NOACs, which may have affected the comparison of outcomes. We performed early anticoagulant therapy for a limited group of AIS patients with AF using our cautious criteria to prevent hemorrhagic complications, which resulted in the accumulation of patients with relatively mild ischemic stroke. Our study is not appropriate to resolve whether any oral anticoagulant therapy should be performed for every AIS patient with AF. A rigorous cohort study and a randomized controlled study are needed to investigate the best mode of oral anticoagulant therapy for AIS patients with AF.

Conclusions
Our study suggests that NOACs are suitable for AIS patients with AF, or even better than warfarin, given their simplicity.

Disclosures
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