Can Early Effective Anticoagulation Prevent New Lesions on Magnetic Resonance Imaging in Acute Cardioembolic Stroke?

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Background: The timing of warfarin administration for acute ischemic stroke (AIS) patients with atrial fibrillation (Af) has not been established. We hypothesized that achieving targeted prothrombin time and international normalized ratio (PT-INR) at 2 weeks could prevent AIS patients with Af from developing a new lesion on diffusion-weighted magnetic resonance imaging (DW-MRI). *Methods:* Of consecutively enrolled AIS patients with Af between 2008 and 2011, we selected the patients who were given warfarin within 2 weeks of admission and had DW-MRI and blood test for PT-INR both on admission and at 2 weeks. Warfarin was started as early as possible and heparin was administered until the targeted PT-INR (2.0-3.0 for patients aged <70 years or 1.6-2.6 for those aged ≥70 years) was achieved. *Results:* One hundred and twenty-three patients were selected, consisting of 88 patients without a new lesion and 35 patients with a new lesion. Patients with a new lesion had a significantly higher median score on National Institutes of Health Stroke Scale (11.0 vs. 5.5, $P = .0053$), a lower rate of achieving targeted PT-INR at 2 weeks (25.7% vs. 48.9%, $P = .0190$), and a lower median dosage of warfarin at 2 weeks (2.0 mg vs. 2.5 mg, $P = .0209$) than patients without a new lesion. Multivariate logistic regression analysis showed that failure to achieve targeted PT-INR ($P = .0298$) was significantly associated with the occurrence of a new lesion. *Conclusions:* Our findings suggest that achieving targeted PT-INR at 2 weeks by using warfarin prevents new lesions in AIS patients with Af. **Key Words:** Acute ischemic stroke—atrial fibrillation—diffusion-weighted magnetic resonance imaging—prothrombin time and international normalized ratio—warfarin.

Cardioembolic stroke is the most severe ischemic stroke subtype. Atrial fibrillation (Af) is the most common cause, accounting for three quarters of cardioembolic stroke.[1] Heparin, low-molecular-weight heparin (LMWH), and heparinoid have been expected to be effective for acute ischemic stroke (AIS) patients with Af; however, their use is not recommended because the effect of reducing recurrence is offset by an increase of hemorrhagic complications.[2-4] Warfarin can reduce the risk of recurrence of ischemic stroke with Af by 66%,[5] which encourages us to administer warfarin as soon as possible for secondary prevention. However, it takes several days for warfarin to achieve the targeted prothrombin time and international normalized ratio (PT-INR). In addition, there is concern about a presumed prothrombotic state during the initiation of warfarin, until an anticoagulant effect is achieved.[6] Bridging heparin with warfarin is performed in clinical practice to prevent a prothrombotic state, although its efficacy has not been demonstrated.[7] It has

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also never been shown whether achieving the targeted PT-INR at the acute stage can improve stroke recurrence, which may be helpful to determine the timing and method of starting or resuming warfarin in AIS patients with Af. Recently, new oral anticoagulants (NOACs) have been gradually replacing warfarin for stroke prevention in patients with Af without severe renal dysfunction.[8] Although giving NOACs early for AIS patients with Af may have a promising future because of their rapid action, simplicity and safety compared with warfarin, little evidence for this has been shown.[9]

Apart from symptomatic recurrence, recent studies have reported a high frequency of recurrent lesions on diffusion-weighted magnetic resonance imaging (DW-MRI) within a few weeks of AIS.[10-12] Kang et al[10] reported that this could be a predictor for subsequent clinical vascular events, even if the lesion is asymptomatic. Having an Af is associated with a significantly higher risk of developing a new lesion on DW-MRI.[11,12] However, it is not clear whether early anticoagulation therapy can prevent recurrent lesions on MRI.

In the present study, we hypothesized that achieving targeted PT-INR with warfarin at the acute stage could prevent AIS patients with Af from developing new lesions on DW-MRI.

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 hemorrhagic transformation. For this purpose, our hospital established a regimen of early anticoagulation therapy for AIS patients with Af in 2008, as described in the following.

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 head CT scan both on admission and the next day; (2) the patient is admitted after 24 hours from onset, and 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 initial head CT shows no hemorrhagic lesion. 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 to prevent a presumed prothrombotic state during the initiation of warfarin until the targeted PT-INR (recommended in Japan as 2.0-3.0 for patients <70 years or 1.6-2.6 for those ≥70 years[13]) is achieved. Checking of PT-INR should be carried out on the third, fifth, seventh, and 10th days when possible, as well as on admission and the 14th (±1) day, to titrate warfarin. To confirm recurrence and hemorrhagic transformation, head CT on the 2nd day and head MRI assessment including DW-MRI on the 14th (±2) day are usually scheduled. Even if the patient is eligible for early anticoagulation therapy, timing of the initiation is 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 between 2008 and 2011, our hospital approved its use, but required informed consent to be obtained from the patient or relative on admission.

Under these circumstances, we enrolled consecutive AIS patients with Af treated with this regimen between 2008 and 2011. For the present study, we selected the patients who met all the following conditions: (1) patients were admitted within 72 hours of onset; (2) clinical assessment, DW-MRI, and blood test including PT-INR both on admission and at 2 weeks were accomplished; and (3) patients were given warfarin within 2 weeks of admission, irrespective of heparin use. We had patients who were given dabigatran instead of warfarin, which became available for patients with Af from March 2011 in Japan, but they were excluded from the present study. In the present study, any new lesion on DW-MRI at 2 weeks from admission was defined as a recurrent lesion because it was sometimes difficult to discriminate enlargement of the initial lesion from a recurrent one. Symptomatic recurrence was defined as having both worsening of NIHSS score from that on admission and a recurrent lesion on DW-MRI. Hemorrhagic transformation was diagnosed by CT or MRI. Two doctors (the physician in charge and E.N.) independently diagnosed recurrent lesion on DW-MRI and hemorrhagic transformation. Discordance was resolved by discussion. We classified the patients into 2 groups: patients with a new lesion on DW-MRI and those without one. Comparisons of demographics (age and gender), risk factors for stroke (hypertension, diabetes, dyslipidemia, past history of stroke, and past history of ischemic heart disease), treatment details, the rate of achieving targeted PT-INR at 2 weeks, and the rate of any hemorrhagic transformation within 2 weeks were carried out between the 2 groups. Multivariate logistic regression analysis was performed to adjust confounding variables. Hypertension, diabetes, dyslipidemia, past history of stroke, and past history of ischemic heart disease were defined if the patient had a past history or was under medical treatment.

In addition, we performed subanalysis for the patients without severe renal dysfunction, who would have been candidates for one of the NOACs being prescribed. Severe renal dysfunction was defined as creatinine clearance (CrCl) < 30 mL/minute calculated with the Cockcroft–Gault equation because clinical trials of NOACs adopted the Cockcroft–Gault equation to estimate renal function and excluded patients with CrCl < 25-30 mL/minute.[8,14]