Timing of Anticoagulation Therapy in Patients With Acute Cardioembolic Stroke

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The rate of recurrent ischemic stroke in patients with acute cardioembolic stroke (within 7–14 days) ranges from 1% to 10%.¹ This indicates the need to start anticoagulation therapy as early as possible for secondary prevention. Anticoagulation therapy with unfractionated heparin or low-molecular-weight heparin, however, does not significantly reduce recurrent ischemic stroke and significantly increases hemorrhagic stroke compared with placebo or aspirin in patients with acute cardioembolic stroke (Figure 1).¹ Based on this evidence, anticoagulation therapy is not highly recommended for acute ischemic stroke.²

(TIA) associated with atrial fibrillation (AF), anticoagulation therapy within 14 days after onset is an option,³ but the appropriate timing remains unclear. Furthermore, production of protein C and protein S, which have anticoagulant activity, is blocked for several days after treatment with warfarin, which results in hypercoagulability and a probable increased risk for ischemic stroke.⁴

Non-vitamin K antagonist oral anticoagulants (NOAC) have a more rapid effect and less hemorrhagic complications compared with warfarin, and are likely to provide effective anticoagulation therapy for acute cardioembolic stroke. Particularly, NOAC can strongly reduce the incidence of intracranial bleeding in Asian patients with non-valvular AF (NVA) when compared with warfarin.⁵ Clinical trials of NOAC and warfarin in patients with NVA, however, have excluded

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In patients with ischemic stroke/transient ischemic attack

Figure 1. All stroke, recurrent ischemic stroke, and symptomatic intracranial bleeding within 14 days in trials comparing anticoagulants with placebo or aspirin for the initial treatment of acute cardioembolic stroke. (Constructed from Paciaroni M, et al.¹)

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patients with ischemic stroke in the early stage.^{6–10} In the ARISTOTLE trial, 44 patients were randomly assigned to receive apixaban or warfarin within 7–14 days of previous stroke, and there was no stroke or systemic embolism in these patients and only 1 major bleed in the warfarin group.⁷ Despite these results, the utility and safety of NOAC for acute cardioembolic stroke within 7 days after onset remain unclear.

In Japan, warfarin treatment concomitant with unfractionated heparin is common in the acute cardioembolic stroke patients with low hemorrhagic risk; low-molecular-weight heparin is not officially approved for stroke patients. In this issue of the Journal, Nomura et al reported the starting of anticoagulation therapy in patients with acute cardioembolic stroke without intracerebral hemorrhage on computed tomography (CT) within 14 days after onset (median, 2 days after hospitalization).¹¹ No differences in the incidence of new ischemic lesions or in hemorrhagic transformation on magnetic resonance imaging were found between patients treated with warfarin and those with NOAC. Concomitant heparin was used in 93% of patients treated with warfarin and in 44% of those who received NOAC. Despite anticoagulation therapy in the acute stage, the rate of recurrent symptomatic ischemic stroke within 2 weeks was 4%, which is similar to that in patients treated with placebo or aspirin.¹ The incidence of symptomatic intracranial hemorrhage was not described. Therefore, treatment with NOAC for cardioembolic stroke in the early stage is similarly effective to treatment with warfarin concomitant with heparin bridging, but the net clinical benefit is still unclear.

A European practical guide proposed the 1-3-6-12 rule to determine the timing of NOAC based on the severity of stroke or TIA.¹² In the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-NVAF

registry, which was a Japanese study in patients with acute ischemic stroke/TIA associated with NVAF within 7 days after onset, the median time to initiation of oral anticoagulants was 3 days after onset in the warfarin group and 4 days after onset in the NOAC group (Figure 2A).¹³ The median time to initiation of NOAC was 2 days in TIA patients, 3 days in patients with small infarct, 4 days in those with medium-sized infarct, and 6 days in those with large infarct (Figure 2B; $P < 0.01$). Of the NOAC patients, only 1 developed gastrointestinal bleeding and none developed intracranial hemorrhage during acute hospitalization.

Whiteley et al tried to identify a subgroup of patients with ischemic stroke for whom anticoagulation therapy in the early stage would be effective, but no net benefit of heparin was shown despite stratification of the risks for embolism and hemorrhage.¹⁴ Risk factors for intracranial hemorrhage during anticoagulation therapy include hemorrhage detected on CT, platelet count and blood pressure, but information on these factors has not been included in previous randomized trials of the efficacy of heparin in patients with acute ischemic stroke. Large-scale registered studies and comparative trials considering these factors are required to determine the appropriate timing of treatment with anticoagulants, including NOAC, in acute cardioembolic stroke.

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