Timing of Anticoagulant Therapy After Acute Ischemic Stroke

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Anticoagulation is an effective means of preventing recurrent stroke in patients with ischemic stroke caused by nonvalvular atrial fibrillation (NVAF).¹ Oral anticoagulants (OACs) reduce the risk of cerebrovascular accident and systemic embolism, despite the increased risk of bleeding. The use of OACs is strongly recommended for secondary prevention in patients with NVAF. Nevertheless, it is still unclear whether early initiation of OAC therapy is beneficial after acute ischemic stroke caused by NVAF.

The risk of stroke recurrence is high in the early stage of acute ischemic stroke. In patients with cardioembolic stroke, the rate of early recurrence of ischemic stroke, defined as a new event within 2 weeks of onset, is reportedly 1–10%.² A meta-analysis showed that early initiation of low-molecular weight heparin (LMWH), unfractionated heparin (UFH) or heparinoid within 48 h of cardioembolic stroke was not associated with a reduced risk of recurrent ischemic stroke, death or disability, but did increase the risk of intracranial hemorrhage (ICH).³ The increased incidence of ICH negated any benefit of early treatment with anticoagulants for the prevention of recurrent ischemic events.⁴ Currently, OACs are generally initiated within 1–2 weeks of stroke onset, but the evidence informing this practice is limited.⁵ Current expert consensus is that earlier anticoagulation could be considered for patients at low risk of bleeding (e.g., those with a small infarct or without evidence of hemorrhagic transformation on brain imaging).⁶

Recent analysis of the Virtual International Stroke Trials Archive (VISTA) found that early introduction of anticoagulants 2–3 days after stroke was associated with substantially fewer recurrent strokes over the following weeks without excess risk of symptomatic ICH.⁷ Additionally, the Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) study showed that initiation of anticoagulation treatment between 4 and 14 days after acute ischemic stroke was safe and effective compared with starting treatment before or afterwards.⁸ Those results suggested that early initiation of anticoagulation therapy is beneficial in patients with acute ischemic stroke caused by NVAF. The most recent consensus recommendation on the timing of initiation of anticoagulation is that OACs can be initiated at 1, 3, 6 or 12 days after onset, guided by stroke severity and considering the risk of hemorrhagic transformation.⁹

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As well as the timing of initiation, the choice of OAC is also critical. Vitamin K antagonists (VKAs) require a longer time to sufficiently inhibit coagulation than intravenous heparin. Therefore UFH, or preferably LMWH, is often used as secondary prevention during the acute stage of cardioembolic stroke. The newer direct OACs (DOACs) have a more rapid onset of action than VKAs, and full anticoagulation can be achieved within hours of the first dose. Furthermore, DOACs cause fewer hemorrhagic complications than VKAs. Even though the incidence of ICH is higher in Asians, DOACs are reported to substantially decrease the incidence of ICH in Asian patients with NVAF compared with VKAs.¹⁰ Thus, DOACs may be useful as prophylactic anticoagulation in the early stages after ischemic stroke caused by NVAF.²

Seiffge et al¹¹ recently assessed the starting time of DOACs for secondary prevention of stroke and the rate of

Figure. Number of days before initiating a direct oral anticoagulant according to infarct size (A) and initial stroke severity assessed by NIHSS (B) in the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI-NVAF) registry. Boxes represent interquartile ranges, whiskers represent the 10th and 90th percentiles. NIHSS, National Institute of Health Stroke Scale; TIA, transient ischemic attack. (Reproduced with permission from Toyoda K, et al.¹³)

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received December 14, 2016; accepted December 14, 2016; released online December 28, 2016

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ICH or recurrent ischemic events in 204 patients with acute ischemic stroke or transient ischemic attack and NVAF. They found that DOACs were started within 7 days in 65% of patients, but early initiation did not significantly influence the rate of recurrent stroke or ICH. Nomura et al¹² evaluated the rates of new lesions and hemorrhagic transformation on diffusion-weighted magnetic resonance brain images in the first 2 weeks after acute ischemic stroke in patients with NVAF. They found no significant difference in the rates of new lesions (26.0% vs. 28.0%) or hemorrhagic transformation (30.0% vs. 39.2%) between 50 patients treated with DOACs and 125 patients treated with warfarin. In a multicenter prospective cohort study in Japan (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI-NVAF] registry), DOACs were administered a median of 4 days after onset in patients with acute ischemic stroke and NVAF. The median time from onset to initiation of DOACs differed according to infarct size (transient ischemic attack, 2 days; small infarct, 3 days; medium infarct, 4 days; large infarct, 6 days) and the initial stroke severity (National Institute of Health Stroke Scale, NIHSS score ≤ 4 , 3 days; NIHSS score 5–14, 4 days; NIHSS score ≥ 15 , 5 days, **Figure**).¹³ There was no incidence of ICH in the patients taking DOACs. These results suggested that the risk of ICH was low even if DOACs were started soon after stroke onset.

In this issue of the Journal, Deguchi et al¹⁴ report a retrospective analysis of the timing of OAC therapy in Japanese patients with acute ischemic stroke and NVAF. They found that the characteristics of the patients treated with DOACs differed from those treated with VKAs. Patients treated with DOACs were younger and had less severe strokes than those with VKAs. Furthermore, DOACs were started earlier than VKAs, even earlier than under the “1–3–6–12” rule. Also, no bleeding events were detected in the patients on DOACs, suggesting that early administration of a DOAC is safe in patients with ischemic stroke and NVAF. More data are needed to confirm the safety of DOACs administered in the hyper-acute stage of ischemic stroke.

Whether early administration of OACs is safe and effective is still unclear. To avoid a variety of potential biases underlying any observational study, further large-scale randomized controlled studies are needed in patients with acute ischemic stroke caused by NVAF. These should seek to establish the optimum initiation time for OACs to balance the prevention of recurrent stroke against the risk of ICH, and whether DOACs are safer and more effective than other anticoagulants.

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