New Era of Oral Anticoagulation for Japanese Non-Valvular Atrial Fibrillation Patients

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Warfarin, once the only drug used orally to prevent thromboembolic events in patients with non-valvular atrial fibrillation (NVAF), has now been replaced, more rapidly than expected, by new-generation drugs called “novel” or “non-vitamin K antagonist” oral anticoagulants (NOACs).¹ The NOACs target specific coagulation enzymes, either thrombin or factor Xa, whereas warfarin lowers the levels of multiple coagulation factors (II, VII, IX and X) by inhibiting vitamin K supply. Though the target differs between the direct thrombin inhibitor, dabigatran, and Xa inhibitors such as rivaroxaban, apixaban, and edoxaban, a low incidence of major bleeding and intracranial hemorrhage (ICH) compared

with warfarin is a notable common feature of both classes of drugs as demonstrated by large clinical trials such as RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF TIMI48.²⁻⁵ Of the 4 NOACs, dabigatran was the first to be commercially available, since 2011 in Japan, and thus began the new era of anticoagulation therapy.

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In this issue of the Journal, Komori et al⁶ describe 9 ICHs that occurred in 8 patients treated with dabigatran. The purpose of their survey was to elucidate the clinical characteristics of

Figure 1. Coagulation cascade and the target sites blocked either directly or indirectly by oral anticoagulants.

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ICH during dabigatran treatment. Their key messages are: the extent of the ICH is small to moderate, does not readily expand, and the outcome is good. Although this survey had the inevitable selection bias related to its retrospective and hospital-based nature, the number of ICHs was low among the participating high-volume stroke centers in Kyushu, Japan. Lacking information on how many patients in their region received this drug, an estimate of ICH incidence would be of most interest, though that was not the purpose of the survey.

During the first 6-month period from March 2011, dabigatran was estimated to be used in approximately 70,000 patients with NVAF in Japan. Post-marketing surveillance in the 6 months⁷ disclosed 29 cases of severe ICH, including 8 patients with cerebral (parenchymal) hemorrhage, 5 with hemorrhagic infarction, and 1 each of intraventricular hemorrhage, ICH, cerebellar hemorrhage, hemorrhagic stroke, and pituitary bleeding. The remaining patients suffered from subdural hematoma in 8 cases and subarachnoid hemorrhage in 3. Among them, dabigatran was used as secondary prevention in 14, and 6 patients were administered the drug within 14 days of a previous stroke. Fatal outcome was reported for 3 patients, 1 each from parenchymal hemorrhage, subdural hematoma and subarachnoid hemorrhage. In contrast, despite strict intensity control of prothrombin time, the incidence of major hemorrhage with warfarin remains high even in recent studies (eg, 1.5–4.1%).⁸ These data obtained from real-world experience are in accord with global experience² and the Japanese subanalysis⁹ of RE-LY. The low incidence of ICH even in high-age groups¹⁰ is the most striking feature of the new-generation anticoagulants, that is, the NOACs' era.

One point to be emphasized about the present study is that only 2 parenchymal hemorrhages were observed. The authors relate this phenomenon to the preservation of factor VIIa, which initiates the coagulation cascade by complexing with tissue factor (Figure 1). The brain is one of the organs that have an abundance of tissue factor. Thus, microbleeds from minor in-

jury of the brain vasculature could be stopped by the complex of tissue factor and factor VIIa.¹¹ Such a mechanism is not activated during warfarin treatment because of the shortage of factor VIIa, and thus results in enlargement of hematoma.¹² NOACs' short half-life with a blood concentration of the peak-and-trough pattern also contribute to its favorable clinical features. Should these be the main characteristics of not only with dabigatran, but also other factor Xa inhibitors, their use would reduce the incidence of anticoagulation-related parenchymal hemorrhage.

Another possibility of the low ICH incidence reported by Komori et al is preservation of thrombin activatable fibrinolysis inhibitor (TAFI) and subsequent inhibition of fibrinolysis by TAFIa (Figure 2).¹³ In addition, the neuroprotective potential of another direct thrombin inhibitor, argatroban, has been observed in animal models.¹⁴ If these factors relate to the prevention of major bleeding and subsequent neurological deficit, the feature might be specific for direct thrombin inhibitors, including dabigatran.

The presented data are important as this is the first presentation of details of dabigatran-related ICH. At the same time, however, this study is also hypothesis generating. We need to elucidate the exact incidence of ICH, especially parenchymal hemorrhage, in real-world clinics by population-based studies.¹⁵ Is this low rate of parenchymal hemorrhage generalizable to all NOACs, or restricted to the direct thrombin inhibitor? With twice-daily, but not once-daily NOACs? We definitely need more experience and clinical studies.

Disclosures

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