Innovative Edoxaban Overcomes Undesirable Characteristics of Warfarin in East Asian Patients

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Issues Associated With Warfarin Treatment in East Asia and Asia

Non-valvular atrial fibrillation (NVAF) has become a big issue not only in Western countries, but also Asia and East Asia.1–5 This pathology contributes to a significant burden of mortality and morbidity from stroke and systemic embolic events. Effective stroke prevention requires oral anticoagulation, and until recently our options were limited to administration of the vitamin K antagonist, warfarin. Although the efficacy of warfarin is well established and several guidelines for preventing stroke in patients with NVAF recommend administration of warfarin, this pharmacotherapy is inconvenient because it requires regular monitoring at least once a month to keep the prothrombin time-international normalized ratio (PT-INR) within a narrow therapeutic range, and both efficacy and safety depend on treatment adherence and high-quality control of anticoagulant therapy as reflected by time in the therapeutic range (TTR).6–8 In East Asian and Asian patients, warfarin presents additional issues as compared with other populations, because East Asian and Asian patients on warfarin carry higher risks for stroke, major bleeding, and intracranial hemorrhage, as well as difficulties in maintaining a high TTR.3–5

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Edoxaban vs. Warfarin in East Asia

In this issue of the Journal, Yamashita et al compare the efficacy and safety of edoxaban in patients from East Asia and outside East Asia using data from the multinational, double-blinded, double-dummy ENGAGE AF-TIMEx phase III study.9 They found that the annualized rate of stroke and systemic embolic events for the higher-dose regimen of edoxaban was 1.34%, compared with 2.62% for warfarin (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.31–0.90; P=0.02) and 2.52% for the lower-dose regimen of edoxaban (HR, 0.98; 95% CI, 0.63–1.54; P=0.93), and that compared with warfarin (4.80%), the risk of major bleeding was significantly reduced for both higher-dose (2.86%; HR, 0.61; 95% CI, 0.41–0.89; P=0.011) and lower-dose regimens (1.59%; HR, 0.34; 95% CI, 0.21–0.54; P<0.001). Annual incidences of intracranial hemorrhage were also significantly lower for the higher-dose (0.60%; HR, 0.31; 95% CI, 0.15–0.66; P=0.002) and lower-dose regimens (0.46%; HR, 0.24; 95% CI, 0.11–0.56; P<0.001) in comparison with warfarin (1.92%). They then concluded that once-daily edoxaban under both higher- and lower-dose regimens provided comparable efficacy to warfarin, while reducing the risk of major bleeding in the East Asian population.

The higher-dose regimen is permitted in Japan and many other countries around the world; patients receive higher-dose 60mg of edoxaban while patients with creatinine clearance of 30–50 ml/min, weighing ≤60 kg, or receiving strong p-glycoprotein inhibitors receive 30 mg of edoxaban. When comparing data for the primary endpoint of stroke and systemic embolic events, major bleeding, and intracranial hemorrhage between the higher-dose regimen of edoxaban and the warfarin group, the reduction in the incidences of these events on the higher-dose regimen of edoxaban was much greater in the East Asian population than in non-East Asians, helping to minimize the undesirable East Asian characteristics of higher risks for stroke, major hemorrhage, and intracranial bleeding on warfarin treatment (Figure). The reason why these deleterious characteristics of warfarin are so prominent among East Asian patients remains unknown.

Pharmacological Considerations Supporting Innovation With Once-Daily Edoxaban

Edoxaban shows a peak and a trough in the concentration curve when administered once daily.10 In the peak phase, coagulation is directly and strongly suppressed by inhibition of factor Xa. However, the coagulation cascade may not be inhibited in the trough phase, as the activity of edoxaban is low in this phase because of its short half-life of half a day. Another mechanism is therefore suggested to be involved in the anti-coagulation effects of edoxaban. One potential explanation for the lack of thrombus formation during the trough phase is the presence of physiological coagulation inhibitors, such as tissue factor pathway inhibitor, antithrombin, protein C, protein S and the fibrinolytic system, which suppress thrombus formation if activity of thrombin increases during the trough phase. Continuous activation of thrombin may reduce the activity of physiological coagulation inhibitors and the fibrinolytic system, by exhausting these components in a strongly activated reaction of the coagulation pathway. However, on once-daily intermittent anticoagulation with edoxaban, thrombin activity is strongly suppressed in the peak phase, so physiological coagulation inhibitors can recover. Once-daily edoxaban treatment would thus repeatedly prevent thrombus formation in the cardiovascular system in both peak and trough phases through so-called “hybrid anticoagulation”, achieving anticoagulation...
through the combination of a direct oral anticoagulant (DOAC) and physiological coagulation inhibitors. DOACs are well known to not affect plasma concentrations of factor VII and the complexes of tissue factor and factor VIIa that are essential for the first reaction in the coagulation cascade, whereas warfarin suppresses factor VII production even within the therapeutic range of the INR, resulting in higher rates of major bleeding and intracranial hemorrhage. This may be one explanation for the marked difference in annual rates of major bleeding and intracranial hemorrhage between

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**Figure.** Annual rates of stroke and systemic embolic events (A), major bleeding (B), and intracranial hemorrhage (C) for warfarin and higher-dose edoxaban in East Asian and non-East Asian populations. The analysis was conducted in a modified intention-to-treat population. CI, confidence interval; RR, relative risk. (Figure drawn from Yamashita T, et al by the author.)
the higher-dose regimen of edoxaban and warfarin treatment within the PT-INR range of 2.0–3.0 among East Asian patients.

Although edoxaban is administered once daily, contributing to higher and lower concentrations in the peak and trough phases, respectively, when compared to twice-daily regimens, the current study by Yamashita et al demonstrated comparable efficacy to warfarin while reducing risks of both major bleeding and intracranial bleeding in the East Asian population. The reason why major bleeding was reduced in edoxaban therapy with higher and lower concentrations in the peak and trough phases, respectively, may be that major bleeding with edoxaban treatment was associated with the concentration in the trough phase more strongly than that in the peak phase. The lower concentration in the longer trough phase with once-daily edoxaban treatment compared with a twice-daily regimen may contribute to the recovery of injured tissues, resulting in a lower bleeding rate.

I hope that this innovative edoxaban, a once-daily factor Xa inhibitor, to overcome the undesirable characteristics of warfarin therapy in East Asian populations, such as the higher risk of stroke, major bleeding and intracranial hemorrhage, will contribute to the prevention of stroke in patients with NVAF in East Asia.

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