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EDITORIAL

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Editorial to the Postmarketing surveillance on the clinical use of edoxaban in patients with nonvalvular atrial fibrillation (ETNA-AF Japan): One-year safety and effectiveness analyses

The prevalence of atrial fibrillation (AF) has exploded, particularly in the elderly, which increases their all-cause mortality. With the growing clinical evidence for AF-related stroke prevention, direct oral anticoagulants (DOACs) have been widely used in Japan. Large randomized controlled trials (RCTs) on the current four DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) have shown the superiority or at least noninferiority of their effectiveness and safety in the comparison with conventional vitamin-K antagonists.[1] One major concern, however, would be the inapplicability of the RCT results to specific patients, that is, patients at low risk or aged patients with a low body weight, renal impairment, or frailty, who are common in the super-aged society of Japan. In addition, both stroke/ systemic embolic (SE) (1.2%–1.8%/year) and major bleeding (0.5%–1.2%/year) events are known to be less frequent in the Japanese population than in the RCT results, which mostly consisted came from Western countries.[2] For bridging the gap between the RCT-based evidence and "real-world evidence" accounting for the Japanese features, large-scale observational studies would be warranted. The Japanese postmarketing survey-based studies have shown the effectiveness and safety of the former three DOACs: 1.3%/year of strokes/ transient ischemic attacks (TIAs)/ SEs and 1.1%/year of major bleeding with dabigatran in patients (n = 6443) aged 70.9 ± 9.9 years with a $CHADS_2$ score of 1.8 ± 1.3[3]; 1.6%/year and 1.8%/year for rivaroxaban in patients (n = 9578) aged 73.2 ± 9.8 years with a $CHADS_2$ score of 2.2 ± 1.3[4]; and 1.0%/year and 2.4%/year for apixaban in patients (n = 6306) aged 74.5 ± 10.1 years with a $CHADS_2$ score of 2.0 ± 1.4.[5]

The present issue by Yamashita et al[6] shows the 1-year effectiveness and safety of edoxaban in Japanese patients with non-valvular AF in the real-world clinical setting. In that study, 11 569 Japanese outpatients (aged 74 ± 10 years; male, 59%) with a CHA_2DS_2-VASc score of 3.5 ± 1.6 ($CHADS_2$ score 2.2 ± 1.3) have been followed up. These results from the postmarket surveillance of edoxaban characterized the Japanese patients in clinical practice. As compared to the results from the surveillance of other DOACs, the patients were relatively older and at a higher stroke risk. The study design would be reasonable and well applicable to the Japanese clinical practice because 61% of the patients received 30 mg (low-dose) of edoxaban due to a body weight ≤60 kg, CLCr ≤ 50 mL/min, or the concomitant use of P-glycoprotein inhibitors, and 11% of the patients received 30 mg as a non-recommended under-dose, which reflected the real-world features of the Japanese population described above. When considering the patient characteristics such as being older and higher risk patients, the incidence of ischemic strokes/ SEs (excluding TIAs) of 1.10% (1.05% in standard-dose and 1.12% in low-dose) and major bleeding of 1.08% (0.72% with a standard-dose and 1.22% with a low-dose) appeared to be similar to or rather lower than those events reported by the other DOAC surveillances. Interestingly, the incidence of strokes and bleeding was similar between a standard-dose and a low-dose, despite a higher age and risk in the low-dosed patients. This suggests that a low-dosed edoxaban regimen may fit specific patients, balancing the stroke prevention and bleeding risk of edoxaban. Edoxaban has several clinical advantages including a once-daily regimen and orally disintegrating tablets, which would help to improve the adherence of the elder patients. Given these results, edoxaban seems to be a reasonable option for the Japanese population. However, this observational study had a couple of limitations that should be carefully interpreted. First, the present issue was based on the interim analyses, which included a non-negligible quantity of follow-up loss, leaving open the possibility of underestimating the adverse events. We should wait for the final analyses to conform this study. Second, this study was a single-armed analysis. The results cannot be applicable to the comparison of edoxaban with the vitamin K antagonists or three other DOACs. Despite those unresolved issues, this study was the largest observational study of edoxaban in the world, and convincingly showed the effectiveness and safety of edoxaban, in particular, in Japanese patients. These results of the postmarket surveillance will give physicians the confidence in prescribing edoxaban for an AF management especially in specific patients such as those with an old age, low body weight, and renal impairment in whom the physicians often encounter in Japan.

CONFLICT OF INTEREST

The following authors have potential conflicts of interest: YO has received research funding from Bayer Healthcare, Daiichi-Sankyo, Bristol-Meyers Squibb, Nippon Boehringer Ingelheim, Pfizer Japan,

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