Has the Safety of Edoxaban 60 mg Among East Asian Atrial Fibrillation Patients Been Truly Proven by the ENGAGE AF-TIMI 48 Subanalysis? – Reply –

On behalf of all the authors I thank the Editor for providing an opportunity to respond to Dr Yasumasu's comments on our study design and the analyses performed.

The ENGAGE AF-TIMI 48 trial enrolled 1,943 patients from East Asia.¹ The objective of the East Asian subanalysis of the trial was to evaluate the efficacy and safety of edoxaban in patients from East Asia based on the treatment groups to which patients were randomized at baseline: higher-dose edoxaban (60 mg once daily) or lower-dose edoxaban (30 mg once daily) (Tables 2, 4, respectively).² Here, 646 patients were randomized to the higher-dose edoxaban group, including 296 (45.8%) patients who received a dose reduction at baseline (edoxaban 30 mg), and 653 patients randomized to the lower-dose edoxaban group, of whom 315 (48.2%) received a dose reduction at baseline (edoxaban 15 mg). The analysis of the higher-dose edoxaban group included patients randomized to edoxaban 60 mg as well as patients within this group eligible for a dose reduction at baseline who received edoxaban 30 mg. Likewise, the analysis of the lower-dose edoxaban group included patients randomized to receive edoxaban 30 mg as well as patients within this group eligible for a dose reduction at baseline who received edoxaban 15 mg.

All safety analyses were conducted on the modified intent-to-treat set, defined as all patients who underwent randomization and received ≥ 1 dose of study drug, not on the randomized treatment group, as stated by Dr Yasumasu. The on-treatment safety data is presented in Table 4 of our report. Safety outcomes for the 250 patients who received only edoxaban 60 mg were not presented. As mentioned above, data were presented for all East Asian patients in the higher-dose edoxaban group, which included those who received the full 60-mg dose and those who were dose-reduced to 30 mg. This is consistent with other published phase 3 NOAC studies.^{3–6}

In addition to assessment of the full analysis set, a subanalysis of patients who received a dose reduction at randomization was performed on the 296 patients in the higher-dose regimen who received a dose reduction of edoxaban at randomization and the 316 patients in the lower-dose regimen who received a dose reduction of edoxaban at randomization. The statement that 611 patients discontinued their first edoxaban dosage prematurely is incorrect; this is clearly illustrated in figure 1, which shows that of the 1,943 East Asian patients who were randomized, 49 patients in the warfarin group, 33 patients in the higher-dose edoxaban group, and 40 patients in the lower-dose

edoxaban group did not complete the study. Our Table 3 presents the efficacy data from this subanalysis of patients randomized to receive a dose reduction at baseline. Likewise, Table 5 shows the safety data from this subanalysis. Because the statistical power was too low to be meaningful, no formal statistical analyses were planned of the components of the efficacy or safety endpoints in the cohort of East Asian patients who received a dose reduction.

Based on these analyses, we concluded that among East Asian patients who met the criteria for dose reduction at randomization, bleeding rates of those randomized to edoxaban were lower relative to warfarin. In both the dose-reduced and full-treatment cohorts in the East Asian and non-East Asian populations, we demonstrated a greater reduction in bleeding rates relative to warfarin with no apparent differences in the rate of stroke and SEE.

Finally, regarding the number of patients who experienced hemorrhagic and ischemic stroke presented in Table 2, 1 patient in the warfarin group and 1 patient in the edoxaban higher-dose group each had a hemorrhagic stroke and an ischemic stroke on different days during the treatment period.

We hope these responses are helpful in providing additional clarity and alleviating concerns regarding the safety of edoxaban.

Disclosures

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