To the Editor:

I read the study by Yamashita et al.1 and the related editorial by Yasaka2 with great interest. Among the double-blinded clinical trials conducted to evaluate the efficacy and safety of direct oral anticoagulants (DOACs), the 1,010 Japanese patients of the 1,943 East Asians subanalyzed among the total 21,105 patients in the ENGAGE AF-TIMI 48 trial represent the second-largest Japanese entry after the 1,280 Japanese patients of the J-ROCKET AF study.3 The incidence of intracranial bleeding is known to be markedly higher in Japan and other East Asian countries than in countries outside East Asia, and DOACs have a much lower risk of intracranial bleeding than warfarin in Asian people.4 However, in both the ROCKET AF5 and the ARISTOTLE trials,6 East Asian people with atrial fibrillation (AF) had lower body weights (by nearly 16.1 kg and 17 kg, on average, in the ROCKET AF and the ARISTOTLE trial, respectively) and lower creatinine clearance (CrCL), but higher rates of prior stroke/TIA compared with patients outside East Asia. Therefore, is it truly safe for us to prescribe the same dosage of DOACs to East Asian AF patients with these characteristics as for patients outside East Asia, considering we have adjusted the warfarin dosage to prevent ischemic stroke/embolism and bleeding?

In the ENGAGE AF-TIMI 48 trial, the higher-dosed edoxaban group received 60 mg, and the lower-dosed group received 30 mg. For patients in either group, the dose was halved if any of the following characteristics were present at randomization or during the study: estimated CrCL of 30–50 ml/min, body weight ≤60 kg, or concomitant use of verapamil or quinidine (potent p-glycoprotein inhibitors). In this study,4 compared with patients outside East Asia, the East Asian patients weighed nearly 18.6 kg less on average, there was a larger proportion of people whose CrCL was <50 ml/min, and who used verapamil or quinidine (Table 1), and the East Asian population was twice as likely to require dose reduction at randomization. In addition, among 646 patients initially randomized to the edoxaban higher-dose regimen, 296 patients (45.8%) received edoxaban 60 mg during the study while the remaining 350 (54.2%) received edoxaban 30 mg. Similarly, among 653 patients initially randomized to the edoxaban lower-dose regimen, 315 patients (48.2%) received edoxaban 15 mg during the study, and the remaining 338 (51.8%) received edoxaban 30 mg. However, safety analyses were conducted on randomized treatment instead of on-treatment even though overall, 611 (31.4%) discontinued their first edoxaban dosage prematurely before the study endpoint: 296 (45.8%) of the higher-dosed group and 315 (48.2%) of the lower-dosed group. Because these treatment flows were not described, we easily mistake the higher- and lower-dosed edoxaban groups for the 60 mg and 30 mg groups, respectively. The safety outcomes of 350 patients who received only edoxaban 60 mg were not shown at any point. On-treatment analyses concentrate on compliant patients so that the biological effects of the treatment can be studied.7 The safety outcomes should be re-analyzed on-treatment, and the data, including rates of intracranial bleeding and gastrointestinal bleeding of patients who received a dose reduction, should be disclosed in Table 5. Furthermore, in Table 3, describing the efficacy in patients who received a dose reduction, details of stroke (those who experienced ischemic or hemorrhagic stroke) should be also disclosed. I hope the study is re-evaluated and the new safety outcomes are found to be nearly the same because an edoxaban dose of 60 mg once daily has been approved for treatment of AF patients in East Asia, and the issue of necessity for DOACs dosage adjustment in East Asia will arise.

Lastly, Table 2 showed that in the East Asian population, among the warfarin group, the number of patients who experienced hemorrhagic stroke was 18 and the number who experienced ischemic stroke was 19, but the total was 36. Why is this? A similar anomaly is shown among the edoxaban higher-dosed group. Is it right for us to conclude that in each case, 1 patient suffered from hemorrhagic infarct (ischemic stroke complicated with hemorrhage) among the warfarin and edoxaban higher-dosed group in the East Asian population, respectively?

References


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