Asian populations, particularly East Asians including Japanese, Chinese and Korean, are genetically quite similar and different from Caucasians. Therefore, comparisons between East Asian and non-East Asian populations for the efficacy and safety of oral anticoagulants in patients with non-valvular atrial fibrillation are meaningful when focused on ethnic differences. However, levels of risk factor management, intake of food and drinks, and lifestyle vary considerably even among East Asian populations. Therefore, comparison of the efficacy and safety of oral anticoagulants between Japanese and other East Asian populations is also an important issue when focusing on regional differences, although this has been little studied to date.

In this issue of the Journal, Shimada et al. compare the efficacy and safety of edoxaban and warfarin in ENGAGE AF TIMI 48 between Japan and the rest of East Asia (EA). They observed greater relative efficacy and safety with higher-dose edoxaban (60/30mg) in EA compared with Japan. Patients randomized to higher-dose edoxaban had a significantly lower rate of stroke or systemic embolism as compared with warfarin in EA (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.14–0.68, P=0.004) but not in Japan (HR 0.95, 95% CI 0.44–2.09, P=0.91). Patients allocated to higher-dose edoxaban had fewer major bleeding episodes as compared with warfarin in EA (HR 0.39, 95% CI 0.21–0.71, P=0.002) but not in Japan (HR 0.84, 95% CI 0.51–1.40, P=0.51). Do these results mean that higher-dose edoxaban is more efficacious and safer in EA than in Japan? The answer is no.

The relative efficacy and safety of NOACs in comparison with warfarin largely depend on the results in the corresponding warfarin group. If the rates of stroke or systemic embolism and major bleeding in the warfarin group are higher than in the NOAC group, the apparent efficacy and safety in NOACs will be overestimated. In reality, the rate of stroke or systemic embolism was much higher in the warfarin group (4.07%/year) than in the higher-dose edoxaban group (1.17%/year) among EA patients, and was comparable between the warfarin group (1.56%/year) and the higher-dose edoxaban group (1.47%/year) among Japanese patients. The rate of major bleeding showed a similar trend. It was much higher in the
warfarin group (5.85%/year) than in the higher-dose edoxaban group (2.23%/year) among EA patients, but was comparable between the warfarin group (4.03%/year) and the higher-dose edoxaban group (3.38%/year) among Japanese patients. As in the authors’ discussion, higher rates of stroke or systemic embolism and major bleeding in the warfarin group might be attributable to more common warfarin-naïve patients and lower time in the therapeutic range (TTR) in EA than in Japan. In addition to the authors’ discussion, common use of Chinese herbs may also contribute to lower TTR in EA. The relatively better efficacy and safety of higher-dose edoxaban as compared with warfarin in EA might be explained by higher rates of stroke or systemic embolism and major bleeding in the EA warfarin group.

The absolute rates of stroke or systemic embolism (1.17% vs. 1.47%) and major bleeding (2.23% vs. 3.38%) were slightly higher in Japan than in EA among patients receiving higher-dose edoxaban. This numerically higher rate of stroke or systemic embolism in Japan might be explained by significantly higher rate of dose reduction from 60 mg to 30 mg (51% vs. 40%) because of higher rates of creatinine clearance ≤50 ml/min (33% vs. 28%), body weight ≤60 kg (34% vs. 26%), and use of verapamil or quinidine (11% vs. 2.3%), and the numerically higher rate of major bleeding in Japan might be explained by significantly higher HAS-BLED scores (2.2±1.1 vs. 1.8±1.0) among patients received higher-dose edoxaban.

The results of this study clearly demonstrate that regional difference is not consistent with ethnic difference, because regional difference may be influenced not only by genetic factors but also by many environmental factors such as lifestyle, foods and drinks, levels of medical management, socioeconomic background, and geographic conditions. In reality, regional differences are quite large between Asian countries. It has already been reported that rates of thromboembolism and major bleeding are different not only between Asians and non-Asians, but also between non-Japanese Asians and Japanese (Figures 1, 2). Even among East Asian countries, the difference is large in many regional aspects despite genetic similarity, as shown in the case of the warfarin groups in this study. Therefore, interpretation of regional subgroup analyses between Asian or East-Asian and non-Asian or non-East-Asian patients should be very cautious in order to not mislead, because such regional subgroup analyses will show only an average difference across the region and may conceal important differences between countries in the region.

This study also suggests that the relative efficacy and safety of NOACs as compared with warfarin do not represent the true efficacy and safety of NOACs when the results in the warfarin group as the comparator considerably vary between the subgroups. This problem may also exist in the interpretation of indirect comparison of the relative efficacy and safety between different NOACs as compared with warfarin.

References