To the Editor:

We read with great interest the report of PRASFIT-ACS, in which low-dose prasugrel (20/3.75 mg) vs. standard-dose clopidogrel (300/75 mg) reduced the incidence of ischemic events (9.4% vs. 11.8%; risk reduction 23%) with a similar risk of major bleeding (1.9% vs. 2.2%) in Japanese ACS patients undergoing PCI. We believe these results provide strong evidence against the current concept of “One-Guideline-Fits-All-Races”. There are growing concerns about a potentially higher incidence of hemorrhagic stroke and serious bleeding among East Asians on anti-thrombotic therapy compared with Westerners. Intriguingly, some investigators have suggested that the optimal INR may differ between races, with 1.6–2.6 being more appropriate for East Asians with higher-risk bleeding.

During dual antiplatelet therapy with aspirin and P2Y12 receptor inhibitor, patients having high on-treatment platelet reactivity (HPR) are at increased risk of ischemic events, whereas those with low on-treatment platelet reactivity have a higher risk of serious bleeding. Therefore, personalized antiplatelet therapy based on the concept of a therapeutic window of platelet reactivity has been proposed to balance clinical efficacy and safety in patients with coronary stents. However, hypercoagulable factors and fibrinolytic activity (so-called, “thrombogenicity”) is dependent on the clinical situation and population characteristics. Consequently, the influence of platelet reactivity on clinical outcome may depend on the cohort studied, and each cohort may possess its own therapeutic window. Compared with Western populations, East Asians appear less influenced by HPR and have a higher propensity for bleeding (a shift of the therapeutic window to higher levels). This “East Asian Paradox” phenomenon may be substantially associated with a lower level of thrombogenicity in East Asians vs. Westerners.

In PRASFIT-ACS, greater clinical efficacy of low-dose prasugrel vs. standard-dose clopidogrel was not observed in STEMI patients (hazard ratio [HR], 1.02; HR: 0.73 in unstable angina, respectively). However, the pharmacokinetic profile of prasugrel in East Asians is markedly different from that in Western populations, with a 30% lower exposure during 5 mg/day prasugrel in East Asians compared with Caucasians. This pharmacokinetic characteristic in East Asians vs. Caucasians corresponds with the pharmacodynamic profile. In a healthy volunteer study, the level of platelet inhibition during 5 mg/day prasugrel in East Asians was similar to that during 10 mg/day prasugrel in Caucasians (68.9% vs. 70.1% at 4 h last-dose). In PCI-treated Japanese, 2.5 mg/day prasugrel and 75 mg/day clopidogrel achieved similar antiplatelet effects (Caucasians: 4.5 mg/day prasugrel = 75 mg/day clopidogrel).

Taken together, the unique characteristics of East Asians in thrombogenicity and pharmacokinetic/pharmacodynamic profile of P2Y12 inhibitors may have influenced the results of PRASFIT-ACS. Although the size of East Asia is the greatest in the world (>1.5 billion people), few East Asians have been included in the major randomized clinical trials assessing the benefit of newer P2Y12 inhibitors. Simple adoption of Western guidelines and recommendations, mostly based on clinical data derived from Western populations, may not be appropriate for East Asians. Excessive inhibition of platelet function by new P2Y12 inhibitors in East Asians may markedly increase the risk of serious bleeding without further protection against thrombotic events. Therefore, dedicated studies for East Asians are required before we can readily apply established novel anti-thrombotic regimens used for Western populations. In this line, PRASFIT-ACS is a big step toward the concept of “race-based anti-thrombotic therapy”.

References