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Letters

Effect of Low-Dose Versus Standard-Dose Ticagrelor and Clopidogrel on Platelet Inhibition in Acute Coronary Syndromes

Because of different risk profiles and genetic backgrounds, East Asian populations are regarded as more susceptible to bleeding events but relatively resistant to atherothrombosis compared with Western populations (the so-called "East Asian paradox") (1). Thus, we sought to determine whether the relative safety and efficacy margin with the more potent $P2Y_{12}$ antagonist (i.e., ticagrelor or prasugrel) is identical between Asian and Western patients with acute coronary syndrome (ACS). To explore the potential applicability of a reduced dose of ticagrelor in East Asian patients with ACS, we compared the effect of low-dose ticagrelor (120-mg loading dose, 60 mg twice daily) versus standard-dose ticagrelor (180-mg loading dose, 90 mg twice daily) and clopidogrel (600-mg loading dose, 75 mg once daily) on platelet inhibition.

The OPTIMA (Optimal anti-Platelet Therapy In Management of Asian patients with acute coronary syndromes) trial was a prospective, single-center, randomized, parallel-group study involving patients >18 years of age with ACS (either unstable angina or acute myocardial infarction [MI]) who were $P2Y_{12}$ antagonist-naïve within the past 6 months (NCT02319941). Patients were randomly assigned (1:1:1) to low-dose ticagrelor, standard-dose ticagrelor, or standard-dose clopidogrel added on aspirin. Study drugs were loaded at the time of coronary angiography and were maintained at least 30 days after randomization. Platelet reactivity was assessed by the VerifyNow $P2Y_{12}$ function assay (Accumetrics, San Diego, California) at pre-dose and at 0.5, 1, 2, 4, 8, and 24 h and 30 days post-dose. Measurements at 24 h and 30 days were done 2 h post-last study-drug dose. Pharmacokinetic parameters of ticagrelor and its active metabolite AR-C124910XX were assessed at pre-dose and at 0.5, 1, 2, 4, 8, 10, and 24 h post-dose.

The primary outcome was the $P2Y_{12}$ reaction unit (PRU) value at 8 h after the loading dose and at 30 days during the maintenance dose. The mixed-effect model was used to compare pharmacodynamic assessments at each time point with the baseline PRU, body mass index, and presence of diabetes mellitus as covariates. To detect an absolute mean difference of 60 ± 65 PRU 8 h after loading and at 30 days during maintenance of low-dose ticagrelor versus clopidogrel, which was assumed based on prior research (2,3), we estimated that 60 patients in total (20 in each group) were required to reach statistical significance with a power of 80%, a 2-sided α value of 0.05, and an attrition rate of 5%.

Between January 2016 and February 2017, 65 patients with ACS (72% unstable angina, 28% acute MI) were randomized. Baseline characteristics did not significantly differ among groups. As a primary endpoint, both ticagrelor therapies showed significantly lower mean PRU values than clopidogrel therapy at 8 h after loading (94 ± 81 PRU vs. 71 ± 55 PRU vs. 251 ± 71 PRU for low-dose ticagrelor vs. standard-dose ticagrelor vs. clopidogrel, respectively; $p < 0.001$) and at 30 days (77 ± 41 PRU vs. 59 ± 38 PRU vs. 234 ± 71 PRU, respectively; $p < 0.001$) (**Figure 1**). There was no statistical difference in PRU values between low- and standard-dose ticagrelor at any time point. At 8 h after loading, the incidence of high on-treatment platelet reactivity (>208 PRU) was rare with low-dose ticagrelor (n = 2; 9.1%) and absent with standard-dose ticagrelor, but was significantly higher with clopidogrel (n = 17; 80.9%). At 30 days, no patient in both ticagrelor groups but only 14 patients (66.7%) in the clopidogrel group had high on-treatment platelet reactivity. The maximal plasma concentrations and the area under the curve from time zero to the last measurable time point of ticagrelor and AR-C124910XX were ~1.5-fold higher with standard-dose versus low-dose ticagrelor, suggesting linear dose-exposure relationship.

The OPTIMA trial suggests that 60 mg or even a lower dose of ticagrelor may be a potential therapeutic option for East Asian patients with ACS. The overall pharmacodynamic and pharmacokinetic findings of our trial are similar to those of a substudy of

the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial (4). Along with the findings in the large PEGASUS-TIMI 54 clinical trial that a 60-mg dose of ticagrelor might offer a more attractive risk-benefit profile than a 90-mg dose (5), the key findings of the OPTIMA trial assume that ticagrelor 60 mg might provide better safety and tolerability than ticagrelor 90 mg with similar efficacy in East Asian patients with ACS. However, a larger, adequately powered trial is required to definitively assess the efficacy and safety of this approach.

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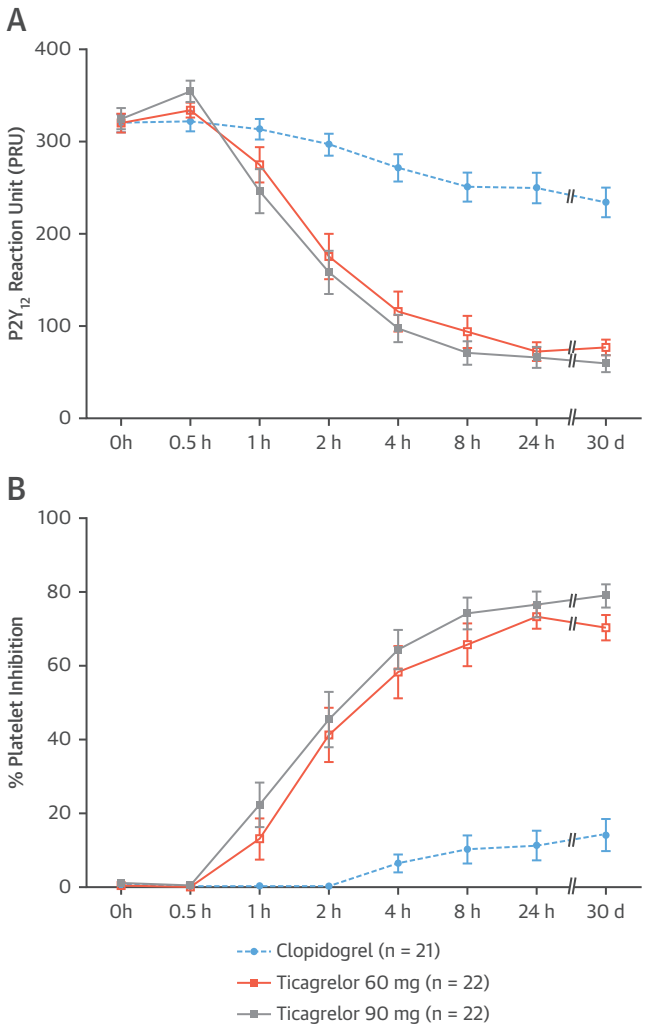
FIGURE 1 Platelet Reactivity by the VerifyNow $P2Y_{12}$ Assay



(A) $P2Y_{12}$ reaction unit (PRU) values and **(B)** percent platelet inhibition. Data are expressed as mean ± SEM.

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