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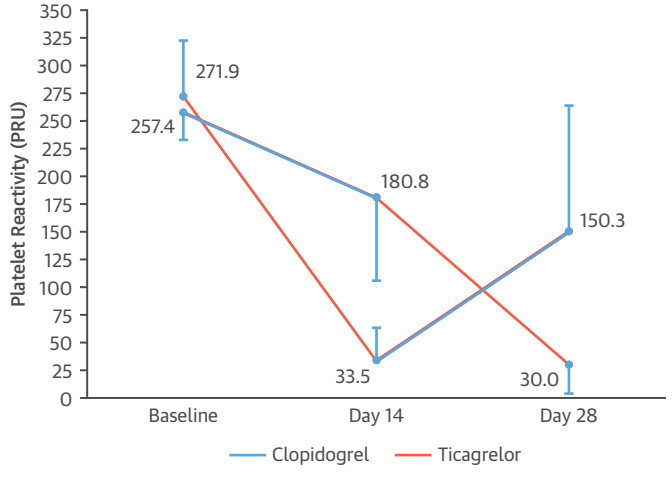
Letters

Low-Dose Ticagrelor Versus Clopidogrel in Patients With Prior Myocardial Infarction

In patients with prior myocardial infarction (MI), long-term treatment with clopidogrel or prasugrel reduced ischemic events, with an increase in moderate or severe bleeding (1,2). In the PEGASUS-TIMI 54 (Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, both ticagrelor doses reduced the ischemic events over placebo; the 60-mg dose demonstrated a more attractive benefit-to-risk profile (3). Physicians may consider extending treatment beyond 1 year or reinitiating treatment with a $P2Y_{12}$-receptor antagonist in patients with prior MI and features of high ischemic and low bleeding risks (4). In patients with PEGASUS-TIMI 54 characteristics, we therefore aimed to compare ticagrelor 60 mg twice a day (b.i.d.) with clopidogrel 75 mg.

FIGURE 1 Platelet Reactivity (Nadir) by Treatment Sequence



Dots and error bars represent means with SD. PRU = $P2Y_{12}$ reaction units.

The ALTIC (A Randomized, Pharmacodynamic Comparison of Low Dose Ticagrelor to Clopidogrel) study was a prospective, single-center, randomized, crossover study involving patients >50 years of age, with an MI 1 to 3 years earlier, who were receiving aspirin 100 mg and who had at least 1 high-risk feature: age >65 years, diabetes mellitus, second MI, multivessel disease, or renal dysfunction. The local ethics committee approved the study (NCT02663713). All patients gave informed consent. After a 14-day washout period if previously receiving a $P2Y_{12}$-receptor antagonist, patients were randomized to either ticagrelor 60 mg b.i.d. or clopidogrel 75 mg for 14 days, with a crossover directly to the alternate treatment for another 14 days. Platelet reactivity (PR) was assessed (VerifyNow $P2Y_{12}$ reaction assay, Accriva Diagnostics, San Diego, California) at baseline (day 0), pre-crossover (day 14), and post-crossover (day 28). Device-calculated percentage of inhibition was considered for all assessments and was calculated as follows: $(1 - \text{PRU/BASE}) \times 100$, where PRU represented $P2Y_{12}$ reaction units. All measurements were done 2 h post last study-drug dose.

The primary endpoint of PR, in PRU, at the end of the 2 treatment periods was analyzed by a mixed linear model, adjusting for period, sequence (carryover effect), and treatment as fixed factors, patient indicator as a random intercept, and baseline PR as a covariate. Platelet inhibition (%) and high PR rate were analyzed with the Mann-Whitney *U* test and the Prescott test, respectively. We hypothesized that ticagrelor would result in lower PR compared with clopidogrel (60 and 140 PRU, respectively), on the assumption that the within-patient SD of the response variable is 60 (5). With 95% power and a 2-sided alpha level of 0.05, ≥20 patients in total were required to reach statistical significance on the basis of the previous assumptions.

Among 20 randomized patients (mean age 58.5 ± 10.2 years, all men, 40% ≥65 years of age, 70% diabetic, 35% smokers, with well-balanced baseline characteristics), ticagrelor resulted in significantly lower PR compared with clopidogrel: estimate of fixed effects of −133.8 (95% confidence interval: −174.9 to −92.7); $p < 0.001$). No period or

carryover effect was observed (p = 0.40 for both). PR at baseline was 264.7 ± 39.4 PRU, and at the end of the treatment periods it was 31.8 ± 27.4 PRU and 165.6 ± 94.6 PRU for ticagrelor and clopidogrel, respectively; platelet inhibition was 92.0% (75.8% to 97.0%) versus 18.0% (12.8% to 53.5%) (p < 0.001), and the high PR rate (PRU >208) was 0% versus 45.0% (p = 0.005) in ticagrelor versus clopidogrel-treated patients, respectively. PR values by treatment sequence are depicted in **Figure 1**. There were no dropouts; 3 patients had mild dyspnea while receiving ticagrelor. No patient exhibited a major adverse cardiovascular or bleeding event. A Bleeding Academic Research Consortium type 1 event was observed in 3 patients, all while receiving ticagrelor.

This study compared ticagrelor 60 mg b.i.d. with clopidogrel 75 mg. Clopidogrel remains the most widely used $P2Y_{12}$-receptor antagonist; it is available in a generic form and carries a lower bleeding potential. However, it is less potent than ticagrelor 60 mg b.i.d. and has a variable response. Levels of platelet inhibition achieved by ticagrelor 60 mg b.i.d. in ALTIC confirmed PEGASUS-TIMI 54 platelet substudy results (5). ALTIC was a pharmacodynamic study with small sample size and no clues for clinical outcome differences. However, direct clinical comparisons among the different $P2Y_{12}$-receptor antagonists for the long-term treatment of post-MI patients would require thousands of patients (4).

In a PEGASUS-TIMI 54–like population, we demonstrated that ticagrelor 60 mg b.i.d. provides greater platelet inhibition than clopidogrel 75 mg. With the foregoing limitations, this dedicated pharmacodynamic study could be informative for the practicing clinician.

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Prediction of Mid-Term Outcomes in Adult Obstructive Hypertrophic Cardiomyopathy After Surgical Ventricular Septum Myectomy

Several earlier studies attempted to predict cardiovascular events in patients with obstructive hypertrophic cardiomyopathy (HCM) who underwent surgical myectomy; however, conclusions were inconsistent (1,2). We sought to ascertain the prognostic predictors in these patients. We recruited and followed 472 consecutive patients with drug-refractory adult obstructive HCM who had undergone surgical myectomy and pre-operative cardiovascular magnetic resonance (CMR) examinations at Fuwai Hospital in Beijing, China from June 2011 to April 2016. The extent of late gadolinium enhancement (LGE) was assessed semiquantitatively using a 17-segment model of the left ventricle (0 = absent, 1 = point-shaped or focal, 2 = limited to 2 left ventricular segments, 3 = involving >2 segments [extensive LGE]) by 2 independent observers blinded to the clinical characteristics and outcomes. Maximum left atrial volume (LAV) was calculated using the biplane area-length method. The primary endpoint was cardiovascular death, including sudden cardiac death (SCD), resuscitation from SCD, congestive heart failure–related death, and stroke-related death. The secondary endpoint (nonfatal cardiovascular event) included stroke, embolism, onset of congestive heart failure requiring hospitalization, and subsequent cardiac surgical procedure. The composite endpoint included both the primary and secondary endpoints.