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CME

Recovery of Platelet Function After Discontinuation of Prasugrel or Clopidogrel Maintenance Dosing in Aspirin-Treated Patients With Stable Coronary Disease

The Recovery Trial

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JACC JOURNAL CME

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to assess the ofset of the antiplatelet effects of prasugrel and clopidogrel.

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The Recovery Trial

Objectives The goal of this study was to assess the offset of the antiplatelet effects of prasugrel and clopidogrel.

Background Guidelines recommend discontinuing clopidogrel at least 5 days and prasugrel at least 7 days before surgery. The pharmacodynamic basis for these recommendations is limited.

Methods Aspirin-treated patients with coronary artery disease were randomly assigned to either prasugrel 10 mg or clopidogrel 75 mg daily for 7 days. Platelet reactivity was measured before study drug administration and for up to 12 days during washout. The primary endpoint was the cumulative proportion of patients returning to baseline reactivity after study drug discontinuation.

Results A total of 56 patients were randomized; 54 were eligible for analysis. Platelet reactivity was lower 24 h after the last dose of prasugrel compared with clopidogrel. After prasugrel, ≥75% of patients returned to baseline reactivity by washout day 7 compared with day 5 after clopidogrel. Recovery time was dependent on the level of platelet reactivity before study drug exposure and the initial degree of platelet inhibition after study drug discontinuation but not on treatment assignment.

Conclusions Recovery time after thienopyridine discontinuation depends on the magnitude of on-treatment platelet inhibition, resulting, on average, in a more delayed recovery with prasugrel compared with clopidogrel. The offset of prasugrel was consistent with current guidelines regarding the recommended waiting period for surgery after discontinuation. (Prasugrel/Clopidogrel Maintenance Dose Washout Study; NCT01014624) (J Am Coll Cardiol 2012;59:2338–43) © 2012 by the American College of Cardiology Foundation

Thienopyridines are prodrugs that require biotransformation into an active metabolite that irreversibly antagonizes the $P2Y_{12}$ receptor for the platelet's lifespan. A prasugrel 60-mg loading dose and 10-mg daily maintenance dose (MD) provide greater and more consistent levels of platelet inhibition than clopidogrel due to more efficient active metabolite generation (1,2). Clopidogrel use before cardiac surgery increases bleeding (3,4). In the 437 patients who underwent coronary artery bypass graft (CABG) in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, more bleeding occurred with prasugrel compared with clopidogrel up to 1 week after discontinuation (5). Based on these clinical observations, the American College of Cardiology/American Heart Association guidelines recommend empirical discontinuation of clopidogrel for at least 5 days and prasugrel for at least 7 days before planned CABG, unless the net benefit of the thienopyridine outweighs the potential risks of excess bleeding (6). However, the dynamics of platelet functional recovery after prasugrel cessation have not been specifically assessed. Therefore, we performed this study to examine the relationship between the timing of drug discontinuation and the recovery of platelet function after prasugrel compared with clopidogrel therapy.

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Methods

Study design. This trial was a randomized, double-blinded study conducted at 4 sites in the United States. The study was approved by the institutional review boards at all sites and was conducted in accord with the provisions of the Declaration of Helsinki. All subjects provided written informed consent.

Study population. Subjects were eligible to be enrolled if they were <75 years of age, had stable coronary artery disease (CAD), and were receiving aspirin. Detailed inclusion and exclusion criteria and participating sites are listed in the Online Appendix.

Study procedures. Patients were randomly assigned 1:1 to prasugrel 10 mg or clopidogrel 75 mg daily for 7 days. Patients returned over the course of the washout period for platelet function assessment (Fig. 1). Randomization and visit details are provided in the Online Appendix. Patients were considered to have completed the study when platelet function returned to baseline according to the primary and