Defining a Role for Prasugrel in Patients With Stable Coronary Artery Disease Undergoing Ad Hoc Percutaneous Coronary Intervention*

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In patients undergoing percutaneous coronary intervention (PCI), pre-treatment with a P2Y₁₂ receptor inhibitor has been for years advocated as a strategy to protect from periprocedural thrombotic events (1). However, most recently, the need for pre-treatment before diagnostic angiography has been largely debated, particularly in patients with stable coronary artery disease (CAD) (1,2). Accordingly, although practice guidelines have traditionally advocated the importance of early initiation of P2Y₁₂-inhibiting therapies in patients undergoing PCI, most recent guidelines provide less emphasis on timing of initiation of treatment (1). Nevertheless, effective levels of P2Y₁₂ receptor blockade reduce ischemic events in the vulnerable peri-PCI period (3). However, systematic upstream administration of a P2Y₁₂ receptor inhibitor in all patients going to the catheterization laboratory inevitably leads to unnecessary treatment of those who do not require PCI; moreover, this can also increase the risk of hemorrhagic complications and prolong hospitalization in patients requiring surgical revascularization (1).

Clopidogrel is still the most widely used P2Y₁₂ receptor inhibitor and is the only agent of this class approved for patients with stable CAD undergoing PCI (4). However, it is well-established that the pharmacodynamic (PD) response profiles of clopidogrel are delayed and subject to variability. Most importantly, patients with high on-treatment platelet reactivity (HPR) have an increased risk of ischemic events, in particular stent thrombosis (5). The shorter time frames from clinical presentation to the catheterization laboratory, the development of antiplatelet therapies with more prompt and potent effects, and the fact that most elective PCIs are performed on an ad hoc basis (immediately after diagnostic coronary angiography) have further questioned the need for pre-treatment with P2Y₁₂ receptor inhibitors (1). However, there is limited experience with the new-generation oral P2Y₁₂ receptor inhibitors (i.e., prasugrel and ticagrelor) in non-acute coronary syndrome (ACS) settings. Although it may also be argued that peri-PCI thrombotic events are less likely to occur in non-ACS patients, clinical investigations with the potent intravenous P2Y₁₂ receptor antagonist cangrelor showed a significant reduction in early thrombotic events after PCI, including in patients with stable CAD, highlighting the clinical benefits of peri-interventional reduction of platelet reactivity (3). Importantly, peri-PCI thrombotic events are known to be related to long-term adverse ischemic outcomes, including mortality (6).

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In this issue of JACC: Cardiovascular Interventions, Hochholzer et al. (7) report the results of a study investigating the PD effects of prasugrel loading.
dose (LD) in patients with stabilized CAD undergoing elective PCI not pre-treated with a P2Y$_{12}$ receptor inhibitor. Patients (n = 300) were randomly assigned to receive a LD of either prasugrel 60 mg, prasugrel 30 mg, or clopidogrel 600 mg immediately before PCI, after defining coronary anatomy. A cohort of pre-treated patients (n = 100) was included in a registry. ADP-induced platelet aggregation was measured at baseline and 30, 60, 90, 120 min and 24 h after LD using the Multiplate Analyzer (Roche Diagnostics, Mannheim, Germany). The authors found that at 60 min following LD, prasugrel (Roche Diagnostics, Mannheim, Germany). The authors found that at 60 min following LD, prasugrel 30 mg led to a significant reduction in HPR (>468 arbitrary aggregation units × min) rates compared with clopidogrel 600 mg (33% vs. 55%; p < 0.001; primary endpoint). The reduction in HPR rates with prasugrel 60 mg was already evident at 30 min and maintained up to 2 h. Prasugrel 30 mg exerted intermediate effects, with lower incidence of HPR than clopidogrel only at 30 and 60 min following LD. Overall, platelet inhibition achieved by prasugrel 60 mg at 1 h post-LD was achieved by clopidogrel 600 mg only 2 h post-LD. Differences between treatments were no longer evident at 24 h. Of note, HPR rates and levels of platelet reactivity achieved by prasugrel 60 mg at 2 h post-LD were lower than those of the cohort of patients pre-treated with clopidogrel included in the registry. In an exploratory analysis, clinical outcomes at 30 days, including bleeding and ischemic events, were low and similar between groups, although a numerical increase in minor bleeding was noted in the prasugrel 30-mg group (7).

The major strength of this study is that this is the first to prospectively assess the effects of prasugrel LD, administered after coronary angiography, in patients with stable CAD undergoing ad hoc PCI, showing a remarkable reduction in HPR rates and platelet reactivity. These results are overall anticipated because of the known pharmacological profile of prasugrel (4), and are in line with another study of CAD patients in stable condition, but who were pre-treated with either prasugrel 60 mg or clopidogrel 600 mg (8). The results of this investigation are also in line with a recent study comparing the PD effects of ticagrelor versus clopidogrel in low-risk troponin-negative ACS patients undergoing ad hoc PCI (9). Although the current investigation was not designed to assess the clinical impact of this approach, the authors provide informative PD data (i.e., HPR rates) that in larger investigations have shown to be associated with thrombotic events (5). In line with the observations made above, in this study, less than one-half of patients undergoing coronary angiography ultimately underwent PCI. This observation further underscores how in real-world clinical practice routine pre-treatment with a P2Y$_{12}$ receptor inhibitor among patients going to the catheterization laboratory exposes a high number of patients to unnecessary treatment, which can potentially be a bleeding hazard. This issue is noteworthy considering the low “threshold” to send patients to the catheterization laboratory, particularly in the United States, where 20% to 40% of patients undergoing elective angiography were found to have angiographically normal coronary arteries, ~50% with obstructive disease, and only 25% receiving PCI (10).

Several considerations need to be made in order to correctly interpret the findings of this study. First, the authors used only 1 platelet function assay. Indeed, the use of other assays would have been useful to confirm the consistency of study results. Second, the authors did not include a group of patients randomized to pre-treatment with clopidogrel before coronary angiography. This would have allowed defining whether in-laboratory use of prasugrel provides greater peri-PCI platelet inhibition than clopidogrel pre-treatment. Although this might be assumed from the data of patients included in the registry of this study, these patients had significantly different baseline characteristics than those who were randomized, which makes it difficult to make any meaningful comparisons. Third, the study was not powered for clinical endpoints. Therefore, no ascertainments on the safety and efficacy of this approach can be made, and the absence of increased bleeding with prasugrel needs to be interpreted with caution. Accordingly, whether the use of a lower LD of prasugrel (i.e., 30 mg) may represent a favorable strategy to balance thrombotic and bleeding risk is unknown. Finally, the authors did not explore the PD effects of switching from prasugrel to clopidogrel. In fact, understanding optimal timing and dosing of clopidogrel administration when switching from the new-generation oral P2Y$_{12}$ receptor antagonists remains an important conundrum in clinical practice (11).

Defining the best antiplatelet approach in P2Y$_{12}$ receptor antagonist naive patients undergoing ad hoc PCI is a topic of debate. The study by Hochholzer et al. (7) provides important PD data showing that a LD of prasugrel achieves prompt, potent, and predictable antiplatelet effects in the peri-PCI period among CAD patients in stable condition. However, the clinical impact of this strategy needs to be defined in studies adequately powered for safety and efficacy. Moreover, how such strategy of using in-lab treatment
with a new generation oral P2Y₁₂ inhibitor in non-ACS settings compares with cangrelor is currently unknown. Indeed, the greater practicality and lower costs associated with an oral agent would make this an attractive treatment option, but would warrant dedicated clinical investigation.

**REFERENCES**


**KEY WORDS** coronary artery disease, percutaneous coronary intervention, platelet reactivity, prasugrel