The Conundrum of Platelet P2Y<sub>12</sub> Inhibition in ST-Segment Elevation Myocardial Infarction

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Prasugrel and ticagrelor are 2 new-generation P2Y<sub>12</sub> receptor inhibitors which, compared with clopidogrel, provide more prompt and potent antiplatelet effect with less response variability. This more favorable pharmacological profile translates into a greater reduction in the number of atherothrombotic events in ACS patients, albeit at the expense of an increased risk of bleeding. Importantly, the clinical benefits of prasugrel and ticagrelor have been shown to be consistent across several subgroups, including in patients with STEMI undergoing PCI.

Accordingly, in the past years there has been a significant growth in the use of these agents in primary PCI (PPCI), which are now considered the first choice for P2Y<sub>12</sub> inhibition in this setting. However, pharmacodynamic (PD) studies have shown that in patients undergoing PPCI, prasugrel and ticagrelor are characterized by suboptimal platelet inhibition in the early phase after loading dose (LD) administration, with more than 2 h required to exert full antiplatelet effects. The mechanism of the delayed onset of the pharmacological effects of orally administered drugs in STEMI might be multifactorial, including enhanced prothrombotic status, hemodynamic instability, adrenergic activation, systemic vasoconstriction, pharmacotherapy (eg, morphine administration), abnormal muscular activity of the gastrointestinal tract, nausea and vomiting, and therapeutic hypothermia. In particular, recent studies have shown that this delayed onset and attenuated antiplatelet effect of P2Y<sub>12</sub> receptor inhibitors is mainly attributed to impaired drug absorption in the early hours after LD.

In this issue of the Journal, Ichikawa and colleagues report their results of a study investigating the PD comparison of prasugrel and clopidogrel in STEMI patients. In this study, 78 Japanese patients undergoing PPCI were randomly assigned to receive approved doses of either prasugrel (20 mg LD followed by 3.75 mg/day maintenance dose) or clopidogrel (300 mg LD followed by 75 mg/day maintenance dose). Platelet reactivity was measured by VerifyNow-P2Y<sub>12</sub> at 5 time points: baseline, 1, 3 and 24 h after the LD and after 14 days of maintenance treatment. The authors found that prasugrel was associated with significantly lower platelet reactivity compared with clopidogrel as early as 3 h post-LD, with an effect that was sustained at 14 days. At 1 h after the LD, platelet reactivity was higher than at baseline, with no difference between groups. This could have been related to the exclusive use of heparin as anticoagulant, which is known to increase platelet reactivity. Interestingly, however, this was evident up to 24 h in patients treated with clopidogrel, perhaps because of the high number of patients with CYP2C19 loss-of-function alleles. The rates of HPR, defined as PRU >262 based on studies performed in Japanese populations, were numerically lower with prasugrel compared with clopidogrel at all time points, although the difference reached statistical significance only at 24 h. Of note, 3 h post-LD, 36 patients treated with prasugrel still had HPR, which is in line with studies conducted in Western countries.

Although the results of this study were overall anticipated because of the known pharmacological profiles of prasugrel and clopidogrel, the authors should be commended for their work as they have, for the first time, investigated this topic in Japanese patients, where different dosing regimens of P2Y<sub>12</sub> receptor inhibitors are used. Importantly, this study confirms that, although prasugrel provides more potent platelet inhibition than clopidogrel in PPCI patients, there is still room for improvement in this setting. Several considerations need to be made in order to correctly interpret the findings of this study. First, the authors used only one platelet function assay. Indeed, the use of other assays would have been useful to confirm the consistency of study results. Second, the authors used reduced ticagrelor and clopidogrel doses and a different cut-off to define HPR than used in other studies. Therefore, whether the results of this study would be reproducible in different populations is still an open question.
unknown. However, in the PRASFIT-ACS trial low-dose prasugrel was shown to be associated with a benefit over clopidogrel, which was similar to that of standard-dose prasugrel in the TRITON-TIMI 38 trial. Moreover, these results are in line with those of a similar study conducted in Europe. Third, the authors did not assess platelet reactivity between 3 and 24 h. Thus, this study does not allow to define the exact time needed to reach maximal antiplatelet effect with these dosing regimens of prasugrel and clopidogrel in STEMI patients. Finally, the study was not powered for clinical endpoints. Therefore, no conclusions on the clinical benefit of prasugrel vs. clopidogrel in reducing peri-PPCI thrombotic events can be drawn.

Defining the best antiplatelet approach during PPCI is pivotal because of the enhanced prothrombotic milieu of these patients, and several strategies to overcome impaired P2Y₁₂ inhibition have been tested. Although the use of higher LD regimens seems a natural strategy to increase drug bioavailability, in PD studies this led only to marginal or absent improvement of antiplatelet effects. Investigations conducted in healthy volunteers showed that P2Y₁₂ receptor inhibitors can be safely crushed and administered, achieving faster and greater bioavailability than an equal dose taken orally as whole tablets. Recently, PD studies testing this strategy in patients undergoing PPCI showed that the administration of a crushed LD of prasugrel or ticagrelor was associated with faster drug absorption and more prompt platelet inhibition compared with whole tablets (Figure). However, whether these strategies would apply to Japanese patients and to different dosing regimens is unknown and would require specific investigations. Moreover, the clinical benefit of crushing prasugrel and ticagrelor tablets should be tested in larger trials powered for efficacy and safety.

The use of intravenous agents has the potential to provide immediate platelet inhibition until the full antiplatelet effect of oral P2Y₁₂ inhibitors is achieved. In a PD study, the use of a bolus of the glycoprotein IIb/IIIa inhibitor tirofiban led to nearly complete platelet inhibition in STEMI patients receiving a 60-mg LD of prasugrel, but the clinical profile of this strategy is unknown. The intravenous P2Y₁₂ receptor antagonist can-grelor has shown better clinical outcomes compared with clopidogrel in a broad spectrum of patients undergoing PCI, including STEMI. However, its efficacy and safety when administered to patients receiving prasugrel or ticagrelor have not been tested yet.

References

P2Y12 Inhibitors in STEMI


