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EDITORIAL COMMENT

Drug-Drug Interactions When Switching Between Intravenous and Oral $P2Y_{12}$ Receptor Inhibitors

How Real Is It?*

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Switching between 2 platelet $P2Y_{12}$ receptor inhibitors commonly occurs in clinical practice (1). Multiple factors, including a patient's bleeding or thrombotic risk, occurrence of an adverse event, socioeconomic issues, results of platelet function or genetic tests, or physician or patient preference, among other reasons, may lead to switching of therapy. Indeed, the potential for drug-drug interactions (DDIs) represents a concern when switching between platelet $P2Y_{12}$ receptor inhibitors. In particular, the different pharmacological profiles of these agents have raised unease as to whether switching may lead to enhanced (increasing the risk for bleeding) or mitigated (increasing the risk for thrombosis) $P2Y_{12}$ inhibitory effects (1,2). Cangrelor, a recently approved potent intravenous $P2Y_{12}$ receptor inhibitor, is characterized by a rapid onset and offset of action (2,3). During the clinical development of cangrelor, a pharmacodynamic (PD) investigation identified a DDI when clopidogrel was concomitantly administrated with cangrelor (4). The high receptor occupancy that occurs with cangrelor infusion prevents binding of the active metabolite of clopidogrel to the $P2Y_{12}$ receptor. Given the short plasma half-life of the active metabolite of thienopyridines, it gets rapidly (within a few hours) eliminated from the systemic circulation if no binding occurs, translating into no platelet inhibitory effect (1–3). This DDI can be prevented by administering clopidogrel at the end of the cangrelor infusion, which allows a washout of cangrelor while clopidogrel is being absorbed, undergoes hepatic metabolism, and for its active metabolite to bind with the $P2Y_{12}$ receptor. On this background, in 3 large-scale clinical trials with 24,910 patients testing the safety and efficacy of cangrelor in patients undergoing percutaneous coronary intervention (PCI), clopidogrel was judiciously administered at the end of the cangrelor infusion (5). Accordingly, with the approval of cangrelor for clinical use, drug-regulating agencies specify the importance of clopidogrel loading dose (LD) administration at the end of cangrelor infusion to avoid a DDI (1).

Although there are robust clinical and PD data to support the optimal transitioning strategy from cangrelor to clopidogrel, there are very limited data on switching from cangrelor to the more potent oral $P2Y_{12}$ receptor antagonists prasugrel and ticagrelor (1). This knowledge gap is noteworthy given the ever increasing use of these latter agents, particularly for the treatment of high-risk patients undergoing PCI, among whom cangrelor is also more likely to be used. The results of these PD studies suggest that the transition from cangrelor to prasugrel (which like clopidogrel is a thienopyridine with an unstable active metabolite) should occur at the end of cangrelor infusion to avoid a DDI and ideally 30 min prior to the

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end of the infusion to allow the smoothest transition (6,7). Ticagrelor, on the contrary, because of its longer systemic half-life (including that of its major metabolite), can be given at any time (before, during, or after cangrelor infusion) without resulting in a DDI (8). The findings of these PD studies have been taken into consideration by drug-regulating agencies when providing recommendations on how to transition from cangrelor to prasugrel and to ticagrelor (1). However, the fact that these were very small PD studies and not conducted in patients undergoing PCI underscores the need for further investigations on transitioning from cangrelor to prasugrel and ticagrelor.

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In this issue of *JACC: Cardiovascular Interventions*, Hochholzer et al. (9) report the results of the ExcelsiorLOAD2 study, in which the investigators examined the transition between cangrelor and oral $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, and ticagrelor) in a total of 110 patients (20 patients with clopidogrel, 45 patients with prasugrel and with ticagrelor) undergoing PCI (9). Cangrelor bolus and infusion were initiated immediately before the PCI procedure and continued for at least 2 h or for the duration of the procedure, whichever was longer. Patients were then randomly assigned to receive 1 of the 3 oral agents. Those who were randomized to prasugrel and ticagrelor received the LD at the same time of the cangrelor bolus, while the clopidogrel group received the LD at the end of cangrelor infusion. Platelet reactivity was assessed using the Multiplate Analyzer at 7 time points, and high on-treatment platelet reactivity (HPR) was defined as >468 arbitrary units per min. The primary endpoint was the comparison of rates of patients without HPR (prasugrel vs. clopidogrel) 1 h after discontinuation of the cangrelor infusion. Ischemic and bleeding outcomes were assessed at 30 days post-PCI. Considered from the other perspective, the rates of HPR 1 h after cangrelor infusion were 35%, 6.7%, and 4.4% with clopidogrel, prasugrel, and ticagrelor, respectively. The investigators conclude that a prasugrel LD given at the same time as the cangrelor bolus can provide sufficient platelet inhibition following cangrelor discontinuation (9).

The investigators should be commended for this investigation, which provides important and novel insights on switching from cangrelor to oral $P2Y_{12}$ receptor inhibitors. Importantly, for the first time, all 3 oral $P2Y_{12}$ receptor antagonists were investigated in a randomized fashion. At difference from most prior PD studies, this investigation enrolled patients undergoing PCI, making the findings more applicable to real-world practice. Moreover, this is a rather large PD investigation, with platelet reactivity being assessed at 7 time points in 110 PCI patients. Most important, the investigators challenged a dogma with regard to the timing of prasugrel administration when cangrelor is being used. Specifically, they showed that administering prasugrel at the time of cangrelor bolus was not associated with a DDI. The rationale for this observation is that although prasugrel's active metabolite is unstable, its half-life is longer than that of clopidogrel (10). Therefore, this would provide sufficient time for prasugrel's active metabolite to bind with the $P2Y_{12}$ receptor after discontinuation of cangrelor infusion. Accordingly, although not powered for clinical outcomes, no safety concerns emerged from this analysis. These findings indeed represent a paradigm shift and have important implications for clinical practice. In fact, the notion that prasugrel needs to be given at the end of the cangrelor infusion to avoid a DDI, while ticagrelor can be given at any time without incurring in this complication, inevitably disadvantages the use of prasugrel. The results of this study thus provide new insights and importantly give more options to physicians on when to administer prasugrel, including in the catheterization laboratory, when cangrelor is being used.

There are some other aspects that need to be taken into account when interpreting the results of the ExcelsiorLOAD2 study. First, the choice of absence of HPR at 1 h after discontinuation of cangrelor infusion as the primary endpoint may be debated. In fact, although HPR is a well-recognized marker of thrombotic complications, differences in absolute values of platelet reactivity could have represented a more sensitive endpoint to discern the presence of a DDI. Moreover, given the presence of some PD variability, it cannot be ruled out that at 1 h after discontinuation of cangrelor infusion there could have been some residual effect (3). Thus, a later time point (e.g., 2 h) would have diminished the chances of this potential confounder.

Second, the well-established superior PD potency of prasugrel makes the choice of a comparison with clopidogrel somewhat less attractive than a study that would have been specifically designed to consider ticagrelor as the primary comparator. Although the study does provide some encouraging insights on this comparison, this remains an exploratory observation, as the study was not powered for this assessment.

Third, study arms comprising administration of prasugrel and ticagrelor also during and at the end of the cangrelor infusion would have provided further important information. Fourth, the use of additional

platelet function assays would have allowed to corroborate the study conclusions.

Overall, these considerations should represent a stimulus for further investigation to better elucidate some residual knowledge gaps in this field and define the optimal approach to switch between $P2Y_{12}$-inhibiting therapies. This would indeed allow to better characterize potential DDIs of which clinicians need to be aware. Most importantly, this would give the opportunity to clinicians to choose and switch among available agents, on the basis of individual needs or preference in the safest possible way for our patients.

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