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EDITORIAL COMMENT

De-Escalation of Platelet $P2Y_{12}$ Receptor Inhibiting Therapy After Percutaneous Coronary Intervention

Does One Size Fit All?*

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Oral platelet $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, ticagrelor), used in adjunct to aspirin, are key in reducing ischemic events among patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (1). Prasugrel and ticagrelor have more prompt and potent antiplatelet effects than clopidogrel, which translates into lower rates of ischemic events, at the expense of increased bleeding, in patients with ACS undergoing PCI (1). The first month following an ACS is the most critical for atherothrombotic recurrences. Thereafter, ischemic event rates decline, whereas the risk of bleeding continues to accrue over time (2). This has prompted clinicians to consider limiting the use of the more potent $P2Y_{12}$ inhibitors to the high-thrombotic-risk phase early after an ACS and then switching to clopidogrel, a strategy known as "de-escalation," as an approach to reduce long-term bleeding events (2).

The TOPIC (Timing Of Platelet Inhibition after acute Coronary Syndrome) trial was the first randomized study to test this strategy. One month after PCI, patients with ACS treated with prasugrel or ticagrelor per standard of care were assigned to either remain on the same treatment or de-escalate to clopidogrel. De-escalation led to a reduction in the primary endpoint (a composite of cardiovascular death, urgent revascularization, stroke, and bleeding defined by the Bleeding Academic Research Consortium classification ≥2) at 1 year post-ACS, largely driven by a reduction in bleeding (2). A number of critiques have been made to the TOPIC trial, including sample size, the risk profile of the study population, and study endpoints. Another key concern with the TOPIC trial is whether there are patient cohorts who could benefit the most from a de-escalation strategy (or alternatively where this approach can be harmful). This is also in light of registry findings showing that nonguided de-escalation is associated with harm (3). In fact, oral $P2Y_{12}$ receptor inhibitors are characterized by variability in their response profiles, including high on-treatment platelet reactivity (HPR) and low on-treatment platelet reactivity (LPR). Although the pharmacodynamic effects of these agents have been more extensively studied with clopidogrel, variability in response profiles also occurs with prasugrel and ticagrelor (4). Importantly, in patients undergoing stent implantation, HPR and LPR are independent predictors of thrombotic and hemorrhagic events, respectively (1). These findings make results of platelet function testing (PFT) an attractive tool to personalize the selection of $P2Y_{12}$ inhibiting therapies. However, with the exception of the TROPICAL-ACS (Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial, all other randomized trials considering the use of PFT to guide the choice of antiplatelet therapy have failed to meet their primary endpoint (5,6).

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In this issue of *JACC: Cardiovascular Interventions*, Deharo et al. (7) report the results of a post hoc pharmacodynamic analysis of the TOPIC trial, exploring the

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role of LPR to stratify patients. At the time of randomization (1 month post-ACS), patients (n = 646) underwent a 1-time PFT by vasodilator-stimulated phosphoprotein (VASP) and were classified as LPR (platelet reactivity index [PRI] ≤20%), normal responder (20% < PRI ≤50%), or HPR (PRI >50%). Given the low HPR rate (~10%), patients were then pooled into 2 groups: LPR (47%) and no-LPR (53%). PFT was not repeated during follow-up. The authors found that in patients not undergoing de-escalation, LPR was associated with a higher incidence of the primary endpoint compared with no LPR (33.1% vs. 20.1%; p = 0.01), including a significant increase in both bleeding and ischemic events. On the other hand, in patients de-escalating $P2Y_{12}$ inhibiting therapy, baseline LPR status did not affect the primary endpoint. The study also showed that de-escalation was superior on prevention of bleeding regardless of LPR status, without an increase in ischemic complications. However, the benefit of this strategy seemed to be increased in LPR patients. In particular, in LPR patients de-escalation resulted in a significant reduction in the primary endpoint compared with standard treatment (11.9% vs. 33.1%; p < 0.01), driven by a significant reduction in both bleeding and ischemic events. In no-LPR patients, the primary endpoint was not significantly different in patients switching compared with those not switching therapy (14.6% vs. 20.1%; p = 0.39). The risk of bleeding was significantly lower in patients de-escalating therapy also in this subgroup (2.9% vs. 11.8%; p < 0.01), but this occurred at the expense of a numerical increase in ischemic events (11.7% vs. 8.3%; p = 0.17) (7).

The authors need to be congratulated for their study as they provided a very large dataset of PFT in patients treated with prasugrel or ticagrelor post-ACS. They confirmed that HPR status is infrequent in patients receiving these agents, whereas the rate of LPR is high, occurring in almost one-half of treated patients, and is more frequent with ticagrelor than with prasugrel. Importantly, LPR on prasugrel or ticagrelor was significantly associated with increased long-term major bleeding events in patients who did not de-escalate. Moreover, the present analysis provides insights on patients potentially benefiting from de-escalation. In particular, switching to clopidogrel provided an 81% improvement in net clinical outcomes in LPR patients, with a reduction in both bleeding and ischemic events, whereas no significant benefit was shown in patients with no LPR. However, the results of this study need to be interpreted in light of some limitations.

Although the proportion of LPR patients was similar between groups, the randomization was not stratified by LPR status. Therefore, the present analysis cannot be considered as a positive trial of PFT-guided antiplatelet therapy. The authors measured platelet reactivity only with the VASP assay. Although this PFT is considered the most reliable to assess the $P2Y_{12}$ signaling pathway, it is not user friendly because it requires expert laboratory personnel (5). Therefore, a strategy using VASP to stratify patients before de-escalation would probably not be feasible in clinical practice. The study showed an important reduction in bleeding events, which can easily be explained by the use of less potent antithrombotic therapy. However, it was underpowered to detect differences in ischemic endpoints. Although the increase in ischemic events in LPR patients not de-escalating therapy could be explained by dual antiplatelet therapy switch or disruption following a bleeding event, play of chance due to the low number of events cannot be ruled out. On the other hand, the numerical increase in ischemic events seen in no-LPR patients switched to clopidogrel could have potentially been significant in an adequately powered study. Finally, PFT was not reassessed after randomization, therefore clopidogrel responsiveness after switching is not known. Recent findings from the TROPICAL-ACS trial, a study investigating the safety and efficacy of early PFT-guided de-escalation of antiplatelet treatment from prasugrel to clopidogrel in ACS patients undergoing PCI, showed that 39% of patients switching to clopidogrel experienced HPR and had to be escalated back to prasugrel (6). The TROPICAL-ACS trial, showing noninferiority of PFT-guided de-escalation compared with standard treatment with prasugrel, demonstrated the feasibility of this strategy, which can be helpful to optimize resources and for those patients that are not candidate for long-term treatment with prasugrel or ticagrelor due to clinical or socioeconomic factors. However, in the TROPICAL-ACS trial no action was taken on LPR patients. A strategy of treatment adjustments with de-escalation and escalation of antithrombotic therapies in patients with LPR and HPR, respectively, may be the best approach to optimize safety and efficacy.

In conclusion, although the TOPIC trial suggests de-escalating $P2Y_{12}$ inhibiting therapy following the acute phase in ACS patients undergoing PCI to be safe, this should not be routinely recommended. Indeed, the use of PFTs to guide the choice of antiplatelet agents and personalize switching approaches is an attractive strategy to optimize bleeding risk and resources without a trade-off in ischemic protection. However, the lack of broad availability of PFTs, the variability in their results, and the inconvenience of multiple follow-up visits to monitor response to therapy after

switching represent major limitations of applying such an approach in real-world practice. Alternative strategies integrating results of genetic testing are currently under investigation and may represent a future approach to optimize the safety and efficacy of antithrombotic treatment in PCI patients (8).

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