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Letters to the Editor

$P2Y_{12}$-Based Platelet Function Assays Should be Complemented With Cyclooxygenase-Dependent Testing in Framing the Therapeutic Windows for Dual Antiplatelet Therapy

We read with interest the paper by Cuisset et al. (1) on the subject of very low on-treatment platelet reactivity (VLTPR) as a measure of hyper-response to thienopyridines. The efficacy of platelet inhibition as evaluated by vasodilator-stimulated phosphoprotein (VASP) phosphorylation flow cytometry assay was used as a predictor of non–access site–related bleeding events. The absence of information regarding the periprocedural use of aspirin and the related cyclooxygenase-dependent platelet inhibitory response is a major drawback of the present study (1). Dual antiplatelet therapy, capitalizing on different pathways of platelet inhibition, has been paramount in improving outcomes in patients with acute coronary syndromes within both the low- and high-risk strata (2). It is unclear from the study by Cuisset et al. (1) whether their utilization of different thienopyridine protocols had any impact on aspirin administration or dosing. We believe that this omission compromises the robustness of the presented data. By disregarding the variability in the individual responsiveness to aspirin, the authors have assumed that all patients had a similar level of platelet inhibition before exposure to thienopyridines. By adhering to this assumption, the authors have negated the independent contribution of aspirin response as a confounding variable in their clinical outcomes trial. The acknowledged widespread variability in aspirin-induced platelet inhibition may have influenced both the incidence of ischemic and bleeding events (3,4). The cumulative effect of dual antiplatelet therapy is achieved by compounding 2 different mechanisms of anti-aggregation. It stands to reason, therefore, that strategies designed to delineate the therapeutic window of antiplatelet therapy need to be more comprehensive than the one presented in the current study, which focused solely on $P2Y_{12}$ platelet receptor activity. They would need to incorporate platelet function testing exploring all drug-specific pathways of platelet inhibition implemented in an individual patient. This point is underscored by the very low sensitivity of the VLTRP dichotomization threshold of the platelet reactivity index VASP. The proposed marker performs sufficiently in isolating patients who are unlikely to suffer a bleeding event. Conversely, its sensitivity of 17% is clearly inadequate in identifying patients who are prone to bleeding. The authors demonstrated that patients with VLTRP did not have a lower thrombotic adverse event rate compared with those remaining within the targeted therapeutic window. This information coupled with the high negative predictive value of the platelet reactivity index VASP threshold is interesting and warrants further validation. Another issue worth looking into stems from the authors' decision to exclude patients with a known bleeding diathesis (1). Although the rationale for selecting a homogenous patient population is clear, in doing so the authors have excluded high-risk patients who are likely to gain the greatest benefit from individualized antiplatelet therapy management. The aforementioned caveats notwithstanding, the authors are to be congratulated on highlighting the importance of documenting interpatient variability in response to antiplatelet therapy, which is the foundation of subsequent individual tailoring of platelet inhibition.

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Reply

Reply: $P2Y_{12}$-Based Platelet Function Assays Should be Complemented With Cyclooxygenase-Dependent Testing in Framing the Therapeutic Windows for Dual Antiplatelet Therapy

We thank Drs. Gasparovic and Petricevic for their interest in our study (1) and their comments. They strongly suggest that $P2Y_{12}$-based platelet function assays should be complemented with cyclooxygenase-dependent testing in framing the therapeutic windows for dual antiplatelet therapy. We think that this statement is highly speculative and not supported by the available evidence. Indeed, aspirin resistance has been extensively discussed as a real entity by itself and its association with clinical outcomes. First, response to aspirin assessed by cyclooxygenase-dependent testing has probably been overestimated due to a problem of compliance, and a previous study by our group showed that noncompliance was the main explanation for aspirin resistance, being a rare entity in compliant patients (2). For ischemic risk, some studies suggest the potential impact of aspirin resistance on ischemic events (3), but a recent study assessing the benefit of tailored therapy based on platelet testing of aspirin response failed to show any significant benefit (4). Therefore, testing aspirin response for ischemic prognosis and increasing aspirin dose on the basis of the test results is not supported by available evidence. For bleeding risk, as assessed in our study, to our knowledge, no study has ever linked the variability of aspirin response and bleeding complications in patients undergoing percutaneous coronary intervention after acute coronary syndrome. Therefore, the proposal in their letter is not in line with current data available on platelet monitoring. Also, the major risk of assessing aspirin response could be to use a higher dose in some patients, whereas recent evidence clearly showed that a high dose of aspirin does not provide any ischemic benefit, only a constant increase in bleeding and gastrointestinal events (5).

Accordingly, we performed an additional analysis to confirm previous assumptions. In the present study, aspirin response was assessed by arachidonic acid–induced platelet aggregation (AA-Ag). The rate of aspirin resistance was very low, with only 60 patients (4%) with aspirin resistance defined as AA-Ag above the 30% threshold previously proposed. We did not observe any relationship between AA-Ag and the occurrence of bleeding complications in our population, as suggested by Gasparovic et al. This could also be explained by the biological profile of aspirin response in 1,082 patients (70%) of patients with AA-Ag = 0%. Indeed, to identify a predictor of bleeding with platelet monitoring, we need to define *hyperresponse*, which is probably impossible with a drug providing 0% in more than two thirds of the patients with the present test.

We appreciate the suggestions of Drs. Gasparovic and Petricevic; however, this statement is supported neither by available evidence nor by the new analysis provided in this letter. Therefore, it was not an omission, and we believe that does not compromise the robustness of the presented data. Following the proposal to integrate the aspirin effect into bleeding risk assessment, the next step might be to use the new $P2Y_{12}$ blockers as long-term monotherapy without aspirin as currently tested in the GLOBAL LEADERS study (NCT01813435).

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Looking for the Native Annulus After Transcatheter Aortic Valve Replacement?

I read with great interest the recently published paper by Binder et al. (1) that described the impact of post-implantation SAPIEN XT (Edwards Lifesciences Inc., Irvine, California) geometry and positioning on clinical outcome after transcatheter aortic valve replacement (TAVR).