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EDITORIAL COMMENT

Aspirin Treatment and Outcomes in Patients Undergoing Percutaneous Coronary Intervention

Is There a Role for Pharmacodynamic Testing?*

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Aspirin is an irreversible inhibitor of the platelet cyclooxygenase (COX)-1 enzyme, which in adjunct to a $P2Y_{12}$ receptor antagonist, represents the cornerstone of treatment for patients undergoing percutaneous coronary interventions (PCI) (1). Despite the clinical benefits, ischemic events may continue to occur, which may be attributed in part to variability in pharmacodynamic (PD) response to antiplatelet therapy (2). Investigations assessing the PD effects of the $P2Y_{12}$ receptor inhibitor clopidogrel in the setting of PCI have consistently shown an association between high on-treatment platelet reactivity and risk of ischemic recurrences, including stent thrombosis (3). However, PD studies evaluating aspirin effects have been subject to critique, and the clinical impact of these PD findings also have resulted in conflicting data (4–6). Overall, these results have hampered the level of enthusiasm toward studies assessing the clinical implications of the PD effects of aspirin.

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In this issue of the *Journal*, Mayer et al. (7) report the results of a large-scale observational registry assessing the PD effects of aspirin, the ISAR-ASPI (Intracoronary Stenting and Antithrombotic Regimen—Aspirin and Platelet Inhibition) study (7). Patients (n = 7,090) pretreated with a 500 mg intravenous (IV) dose of aspirin underwent PD testing prior to PCI by means of the Multiplate analyzer (Roche Diagnostics, Basel, Switzerland). Patients in the upper quintile distribution of arachidonic acid-induced platelet aggregation (n = 1,414), corresponding to a cut-off value of 203 aggregation units (AU) × min, were defined as having high on-aspirin treatment platelet reactivity (HAPR). At 1 year, the primary composite endpoint of death from any cause or stent thrombosis (definite or probable) was nearly 2-fold higher in HAPR patients than in non-HAPR patients. HAPR was confirmed to be an independent predictor of the primary outcome in a multivariate analysis, and the results also were supported by propensity score matching assessment. Ultimately, statistical modeling using different metrics showed that the presence of HAPR allowed further risk stratification of the patients. The investigators are to be commended for the conduct of this study. Major strengths include the very large cohort of patients, the long-term follow-up with a clinically relevant primary endpoint, the detailed statistical approach, and the homogeneous conditions under which the PD assessments were performed. However, several considerations need to be addressed.

A full PD effect of aspirin and complete COX-1-mediated inhibition of platelet thromboxane production can be achieved with low-dose therapy (8). In fact, the prevalence of "aspirin resistance" is approximately close to null when assays specifically measuring COX-1 activity are used, challenging the concept of "aspirin resistance" (2,9). Many available

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assays are not specific for measuring platelet COX-1 activity, which may explain the broad prevalence of "aspirin resistance" in published reports and the inconsistent association with clinical correlates (2,4-6,9). These observations highlight some methodological considerations of the ISAR-ASPI study. Only 1 PD assay was used to identify HAPR, which also was arbitrarily defined (7). A receiver operating characteristic curve analysis to define the optimal HAPR cut-off value in this large study cohort would have been of interest. In addition, PD assessments were conducted at a single time point prior to PCI in patients treated with an IV aspirin formulation. PD findings may vary according to the aspirin formulation and dosing regimen, and they also can change over time (2,4,8). Thus, the prognostic implications of a more commonly used oral maintenance regimen remain elusive. Differences in $P2Y_{12}$ receptor antagonist usage and levels of adenosine diphosphate-induced platelet aggregation also may have represented potential confounders.

These observations may contribute to why, in another large-scale study (n = 8,665), the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stent) trial, which considered a pre-defined cut-off value using a different assay (VerifyNow; Accumetrics, San Diego, California) assessed the day after PCI, showed a different prevalence rate (5.6%) of HAPR (6). Importantly, HAPR was not associated with any ischemic endpoint but was inversely related to bleeding. Interestingly, in the ISAR-ASPI study, patients with HAPR paradoxically had numerically more in-hospital bleeding than non-HAPR patients, which was significant in the propensity score matching analysis. Indeed, knowing the impact of HAPR on long-term bleeding complications would have been of interest. It cannot thus be excluded that the increased bleeding potential could have contributed to the differences in mortality observed.

Although the results of the ISAR-ASPI study do not argue against the prognostic value of HAPR as assessed in this study cohort, the main challenge remains focused on what to do with this adjunctive information. Studies assessing the clinical implications of modifying treatment in patients with inadequate PD response to antiplatelet therapy have been disappointing to date (10,11). Potential treatment options in the acute phase for HAPR patients undergoing PCI include the use of IV aspirin and glycoprotein IIb/IIIa inhibitors (GPI). However, the use of IV aspirin among HAPR patients pretreated with an oral aspirin regimen has not shown to be associated with any clinical benefit (12). Moreover, despite its acute benefits, the use of the GPI tirofiban did not translate into long-term benefits among poor responders to aspirin (13). In the maintenance phase of therapy, strategies to increase aspirin-induced effects include high-maintenance and twice-daily aspirin dosing regimens (9,14). However, the safety and efficacy of these strategies tailored to HAPR patients have yet to be tested. The potential impact of ADP-mediated signaling on HAPR also has led to suggest the potential role of $P2Y_{12}$-inhibiting strategies in these patients (15). However, adjunctive clopidogrel therapy did not reduce cardiovascular events among aspirin-treated patients with incomplete inhibition of thromboxane biosynthesis (16). Moreover, in a prospective, randomized study, switching HAPR patients to clopidogrel did not affect clinical outcomes (17). Ultimately, the impact of tailored use of the novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor, which have been suggested to exert some degree of modulating effects on thromboxane generation (18), remains unknown.

In summary, HAPR, as measured in the ISAR-ASPI study, is a biomarker associated with an increased risk of worse outcomes and allows better risk stratification of patients undergoing PCI. However, investigations corroborating these findings are warranted, particularly in light of the controversial findings of the prognostic value of PD measures of aspirin-induced antiplatelet effects. Ultimately, defining the treatment strategies tailored to these high-risk patients that can improve outcomes, which thus far has yielded unsatisfactory results, remains the ultimate objective that would enable this biomarker to be incorporated into routine clinical practice.

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