When Less Becomes More: Insights on the Pharmacodynamic Effects of Aspirin Withdrawal in Patients With Potent Platelet P2Y\textsubscript{12} Inhibition Induced by Ticagrelor

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Dual-antiplatelet therapy (DAPT) with aspirin and a P2Y\textsubscript{12} inhibitor is recommended by guidelines to reduce the risk of thrombotic complications and ischemic events in patients experiencing an acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention. This strategy was developed in light of the synergism in antithrombotic effects achieved with blockade of both the cyclooxygenase 1 enzyme induced by aspirin and the P2Y\textsubscript{12} signaling pathway by selective inhibitors (ie, clopidogrel, prasugrel, and ticagrelor). In this context, clopidogrel has been the most studied P2Y\textsubscript{12} inhibitor in pharmacodynamic investigations. The potent P2Y\textsubscript{12} inhibitors prasugrel and ticagrelor followed the footsteps of investigations using clopidogrel, and were developed for patients with ACS in adjunct to aspirin as an unmovable backbone therapy. Although improvements in the design of coronary stents and intravascular techniques have made the duration of DAPT for preventing stent thrombosis a less critical issue than in the past, it is also known that extended DAPT duration in high-risk subjects exerts a protective effect not only on stented coronary segments, but on the coronary vasculature as a whole. The emphasis on a mandatory and possibly extended period of DAPT comes despite the known and unavoidable risk of bleeding complications. Twenty years of DAPT trials have established this approach as a reference standard, and therefore trials investigating emerging strategies to reduce bleeding typically use guideline-recommended DAPT as a control. Such strategies include modulating DAPT intensity (eg, by deescalating P2Y\textsubscript{12} inhibitor type or dose) and reducing the duration of DAPT. An abbreviated duration of DAPT approach has traditionally consisted of withdrawing the P2Y\textsubscript{12} inhibitor at some point after percutaneous coronary intervention and maintaining the patient on aspirin monotherapy. In recent years, a mirrored approach has emerged, which instead consists of withdrawing aspirin and maintaining P2Y\textsubscript{12} inhibitor monotherapy. The rationale to withdrawal of aspirin to reduce bleeding relies on basic pharmacologic concepts. On one hand, although aspirin is effective in achieving complete cyclooxygenase 1 blockade, it is associated with gastrointestinal toxicity, a key driver of bleeding complications. On the other hand, pharmacodynamic...
investigations have suggested that, in the presence of potent P2Y12 blockade, such as that achieved by prasugrel or ticagrelor, aspirin provides limited additional antithrombotic effects. More important, potent P2Y12 inhibition impacts not only platelet activation but also amplification processes key in arterial thrombus formation. Collectively, on the basis of these observations, the use of P2Y12 inhibitor monotherapy has been proposed as a strategy to reduce the risk of bleeding complications without compromising efficacy (ie, thrombotic complications). A strategy of P2Y12 inhibitor monotherapy is now supported by several recent randomized clinical trials. Studies of short aspirin (eg, 1–3 months) or even aspirin-free strategies have been conducted with clopidogrel, ticagrelor, and prasugrel. Understanding the pharmacodynamic effects of P2Y12 monotherapy is critical for implementation of this strategy in clinical practice. In fact, most pharmacodynamic investigations of P2Y12 inhibitors have been conducted on a background of aspirin therapy. Thus, dedicated pharmacodynamic studies of short aspirin duration may be insightful and add new understandings of platelet function when the P2Y12 is the only targeted receptor.

In this issue of the Journal of the American Heart Association (JAHA), Johnson and colleagues present the result of the TEMPLATE (Ticagrelor Monotherapy and Platelet Reactivity) trial, a pharmacodynamic comparison of ticagrelor monotherapy versus the combination of aspirin and ticagrelor conducted in 110 patients with an ACS who underwent percutaneous coronary intervention and terminated a 12-month period of DAPT without a bleeding episode. Patients were randomized in an open-label manner to ticagrelor monotherapy (180-mg loading dose, followed by 90 mg twice daily) or DAPT (the same ticagrelor regimen plus aspirin, 75 mg once daily) for 4 weeks. Subsequently, all patients were switched to aspirin monotherapy for an additional 4 weeks. The panel of pharmacodynamic tests conducted at baseline, 4 weeks, and 8 weeks included light transmission aggregometry with stimuli by various doses of thrombin receptor activation peptide-6, collagen-related peptide, thromboxane A2 receptor agonist (U46619), arachidonic acid, and ADP. The primary outcome (maximal amplitude of platelet activation after stimulus with 10 μmol/L of thrombin receptor activation peptide-6) was similar between the study groups at 4 weeks (absolute difference with ticagrelor monotherapy versus DAPT with ticagrelor and aspirin: 4.29; 95% CI, 0.87 to 9.46; P=0.103). Conversely, aggregation was higher in the ticagrelor monotherapy group after stimuli with collagen-related peptide (1 and 0.5 mg/mL) and arachidonic acid (1 mmol/L), whereas all other agonists resulted in similar degrees of platelet aggregation between the 2 groups. At 8 weeks, all tests were similar between groups, consistent with the notion that all patients were receiving the same drug regimen (ie, aspirin monotherapy).

The authors should be commended for a comprehensive characterization of the pharmacodynamic effects of ticagrelor monotherapy, which provides important insights on an emerging area of clinical interest. New European guidelines for non-ST-segment-elevation ACSs now recommend a P2Y12 inhibitor monotherapy strategy with a class IIa, level of evidence A. To better appreciate the results of the TEMPLATE trial, one has to consider the different platelet signaling pathways elicited by the agonists used. At 4 weeks, the ADP-dependent pathway was inhibited to a similar extent in both groups by the effects of ticagrelor on the P2Y12 receptor. Conversely and as expected, the response to arachidonic acid was reduced only in the DAPT group by the effects of aspirin. Platelet response to thrombin receptor activation peptide-6 and U46619, which block the thrombin and thromboxane A2 receptors, respectively, was similar, indicating that potent P2Y12 inhibition may modulate pathways other than P2Y12 and irrespective of the presence of aspirin. By contrast, increased aggregation following collagen-related peptide stimuli with ticagrelor monotherapy supports the role of aspirin in inhibiting platelet response to collagen. Notably, collagen acts on the platelet glycoprotein VI receptor, an essential component of normal hemostasis.

Taken together, these pharmacodynamic findings suggest that the reduced rates of bleeding complications demonstrated in clinical trials of P2Y12 inhibitor monotherapy may be in part explained by residual activation of the collagen-mediated platelet pathway. The pharmacodynamic observations from this study, in addition to the direct toxicity induced by aspirin on the gastrointestinal mucosa, can explain why a strategy of P2Y12 inhibitor monotherapy (without aspirin) can markedly reduce the risk of bleeding but still provide adequate antithrombotic protection. However, these antithrombotic efficacy considerations occur with reliable and potent P2Y12 inhibitor blockade, such as that induced by ticagrelor. In fact, in the presence of modest levels of P2Y12 inhibitory effects, such as those achieved by clopidogrel, aspirin withdrawal is not only associated with an increase in markers sensitive to cyclooxygenase 1 enzyme activity, but also an increase in markers of P2Y12 reactivity. Overall, observations from both in vitro and ex vivo investigations of aspirin-free strategies, including the present one, suggest that the synergism between the cyclooxygenase 1 and P2Y12 pathways may be less relevant in the presence of more potent P2Y12 inhibition. These findings from Johnson et al must be considered in view of several limitations, including the open-label nature of the trial, the enrollment at a single center, and the relatively small number of patients...
imparing the investigation of meaningful subsets (eg, diabetes mellitus). Moreover, the patients were enrolled at a time point (ie, 12 months post-ACS) that does not reflect the typical time when ticagrelor monotherapy is initiated after an ACS (eg, 3 months), as now also recommended by guidelines.\textsuperscript{17} Strategies to reduce bleeding in patients requiring prolonged antiplatelet treatment (>1 year) are also warranted. To this extent, a reduced ticagrelor monotherapy dosing regimen (eg, 60 mg) remains a potential avenue of investigation. These limitations do not overly undermine this elegant investigation, which provides timely pharmacodynamic insights into the beneficial effects of ticagrelor monotherapy, as shown by several contemporary trials supporting its implementation in clinical practice.

ARTICLE INFORMATION

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Disclosures
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