A
tiplatelet therapy is one of the central pillars of treatment for patients with coronary artery disease. Aspirin and clopidogrel, the most widely used adenosine 5'-diphosphate (ADP)-receptor antagonist, have each been shown to incrementally reduce the risk of recurrent adverse cardiovascular events by \( \approx 20\% \).\(^1\)\(^,\)\(^2\) These agents inhibit distinct but interrelated signaling pathways that mediate and potentiate platelet aggregation at sites of vascular injury. Exposure to subintimal collagen, von Willebrand factor, and strong agonists such as thrombin stimulate platelets to generate thromboxane \( A_2 \) (TXA\(_2\)) through cyclooxygenase-1 (COX-1)–mediated metabolism of arachidonic acid and to release of ADP stored in dense granules. TXA\(_2\) and ADP not only promote sustained activation of the platelet in which they are formed, but both are also released and amplify the thrombotic stimulus by activating adjacent quiescent platelets via binding to specific membrane receptors. Aspirin and clopidogrel synergistically suppress platelet activation and thrombosis by irreversibly binding to and inhibiting the COX-1 enzyme and the P2Y12 ADP receptor, respectively. In the last decade, it has become clear that many patients taking aspirin and clopidogrel do not realize the full biological effects of these agents and remain at increased risk for cardiovascular events. This apparent nonresponsiveness or resistance has been revealed by a host of studies, using a wide array of different types of platelet function and biochemical assays, indicating that high degrees of platelet reactivity can persist despite use of these agents.\(^3\)\(^,\)\(^4\) The term high on-treatment platelet reactivity (HTPR) is now frequently used to describe this phenomenon. Complicating the picture is the fact that TXA\(_2\) and ADP are just 2 of a number of signaling pathways that mediate platelet activation, and many platelet function assays do not specifically measure their effects in isolation (reviewed by Gurbel et al\(^5\)). Thus, not all instances of HTPR are necessarily attributable to aspirin or clopidogrel resistance. Strictly defined, resistance is the failure of an agent to inhibit its biological target. Studies using assays that specifically measure COX-1 activity, such as arachidonic acid platelet aggregometry or serum thromboxane \( B_2 \) formation, reveal that true aspirin resistance in compliant subjects is uncommon, with a prevalence of \(<1\%\) to \(5\%\) in several large studies.\(^6\)\(^–\)\(^8\) In contrast, aspirin HTPR detected by assays measuring more global platelet function, such as the Platelet Function Analyzer-100 (PFA-100; Siemens HealthCare Diagnostics, Newark, DE) using the collagen/epinephrine agonist cartridge, is significantly more common (prevalence \(20\%–40\%\)) and heavily influenced by the degree of underlying platelet reactivity and level of von Willebrand factor in addition to platelet COX-1 activity.\(^6\)\(^–\)\(^10\)

HTPR also frequently observed after clopidogrel administration, with a prevalence of \(10\%\) to \(45\%\) depending on the assay used and patient population studied.\(^4\)\(^–\)\(^11\) Unlike aspirin, a more substantial portion of this residual platelet reactivity is readily attributable to clopidogrel resistance owing to the inefficiency and interindividual genetic variability in its bioactivation.\(^3\) Clopidogrel effect is best detected by assays that specifically measure P2Y12 ADP receptor activation, such as vasodilator-stimulated phosphoprotein phosphorylation and, to a lesser extent, the VerifyNow P2Y12 test (Accumetrics, San Diego, CA) and ADP platelet aggregometry.\(^5\)\(^,\)\(^12\) Aspirin and clopidogrel HTPR frequently coexist in the same patient.\(^13\) This observation, along with studies correlating pre- and posttreatment platelet function studies, testifies to the importance of pretreatment platelet hyperreactivity as a modifier of antiplatelet drug effect.\(^14\)

Whether attributable to drug resistance, underlying platelet hyperreactivity, or both, HTPR has been linked to increased risk of recurrent cardiovascular events. This has most convincingly been demonstrated in patients taking clopidogrel after recent acute coronary syndrome and/or percutaneous coronary intervention with stent placement. A meta-analysis of 20 studies comprising 9187 percutaneous coronary intervention patients observed clopidogrel HTPR to be present in a third of patients and associated with 3- to 4-fold increases in the risk of myocardial infarction, stent thrombosis, and death.\(^15\) In a recent analysis of the landmark Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) trial, clopidogrel HTPR defined as \(\geq 208\) P2Y12 reaction units occurred in half of all subjects and was associated with a \(>5\)-fold increased risk of cardiovascular death, myocardial infarction, and stent thrombosis at 60 days.\(^16\) Though less widely studied, aspirin HTPR has similarly been linked to increased cardiovascular
risk. In a meta-analysis of 20 studies involving nearly 3000 subjects, aspirin nonresponsiveness by a variety of assays occurred in 28% and was associated with nearly a 4-fold increased risk of adverse cardiovascular events.9

One open question has been whether measuring HTPR in patients with chronic stable coronary disease would have the same prognostic value as it does in a more acute patient population. There are several reasons to think that it may not. For one, a newly placed stent or ruptured plaque is inherently more thrombogenic than a fully endothelialized stent or a healed/quiescent plaque. Additionally, underlying platelet reactivity and the prevalence of aspirin and clopidogrel HTPR have both been observed to be greater during the acute phase of a cardiovascular illness than during the chronic phase.7,17,18 Two recent studies begin to examine this question.

In this issue of Circulation, Reny and colleagues19 report the findings of the Antiplatelet Drug Resistance and Ischemic Events (ADRIE) study. In the ADRIE study, 771 subjects with stable coronary artery disease chronically treated with aspirin, clopidogrel, or both were subjected to a battery of platelet function studies detecting the presence of aspirin or clopidogrel HTPR. The subjects were followed for 3 years with the primary outcome being the occurrence of a composite end point of acute coronary syndrome, revascularization, stroke/transient ischemic attack, acute limb ischemia, or cardiovascular death. Laudable characteristics of the multicenter study design were the exclusion of subjects who were within 1 month of an acute ischemic event or revascularization procedure and the serial assessment of HTPR using assays that were specific for platelet COX-1 activity (arachidonic acid platelet aggregometry and serum TXA2 formation) and P2Y12 ADP receptor activity (vasodilator-stimulated phosphoprotein phosphorylation) in addition to tests of more global platelet function (collagen and ADP platelet aggregometry, PFA-100 using the collagen/epinephrine agonist cartridge). The presence of HTPR was defined for each assay based on values obtained from the literature. The composite end point occurred in 16% of subjects and by multivariate analysis was associated with the traditional risk factors of hypertension, smoking, and advanced age, and elevated low-density lipoprotein. There was neither an association between outcome and presence of HTPR, as determined by any of the platelet function assays, nor did inclusion of assay data in the multivariate modeling modify that risk.

In summary, ADRIE and ASCET are 2 relatively large studies investigating the utility of performing platelet function testing in patients with chronic stable coronary artery disease for the purpose of risk stratification. Although each had limitations, their collective message suggests that this utility is likely to be low, especially in an unselected patient population. Although this should be somewhat reassuring to clinicians, a more definitive answer awaits further investigation. More pressing, however, is the need for answers to unresolved questions surrounding platelet function testing in acute patient populations. Although relatively more is known about the relationship between the presence of HTPR and adverse outcome in the acute setting, ambiguity still exists regarding what assay or assays best identify risk and, more importantly, what treatment or treatments will effectively modify that risk.

Disclosures

Dr Rade is party to a licensing agreement between Siemens Health-care Diagnostics, manufacturer of the PFA-100, and Johns Hopkins University.

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Platelet Function Testing in Patients With Coronary Artery Disease: Is the Who and the When Any Clearer Than the What and the What Then?

Jeffrey J. Rade

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