The Brave New World of Antiplatelet Therapy: Seeking Clarity in a World of Increasing Choice and Complexity

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The substantial reductions in ischemic events provided by the combination of aspirin and a $P2Y_{12}$ receptor antagonist compared with aspirin alone in patients presenting with acute coronary syndromes (ACS) and in those treated with coronary stents are well documented,[1-5] and dual antiplatelet therapy (DAPT) has therefore become the cornerstone of therapy in these patients. Despite these clinical benefits, nearly a decade ago investigators first observed substantial variability among individuals in the pharmacodynamic response to clopidogrel (ie, its effect on platelet function).[6,7] A large body of data has accumulated since that time supporting the concept that this variability is not just an intriguing laboratory phenomenon, but an important determinant of recurrent thrombotic events in patients treated with DAPT.[8-14] Furthermore, novel $P2Y_{12}$ antagonists that provide greater ischemic reductions have been successfully identified by using ex vivo platelet function studies to compare their antiplatelet effects with clopidogrel, validating the clinical relevance of platelet function in patients receiving DAPT.[15-18] Clinical (rather than research) use of platelet function tests is now possible with the development of user-friendly assays that do not require substantial technical training,[19] and the prognostic value of point-of-care testing in patients with ACS and those

receiving coronary stents has been demonstrated in several prospective registries and trials involving several thousand patients.[12,20-28] The results of small trials have shown the benefit of individualized antiplatelet therapy according to platelet function testing.[29,30] Although uniform treatment with double-dose clopidogrel based on a single platelet reactivity test after percutaneous coronary intervention (PCI) did not improve outcomes in a predominantly elective population,[31] patients who achieved lower levels of platelet reactivity over the course of that trial had superior ischemic outcomes, suggesting that a more intensive antiplatelet intervention may be a better strategy in patients with high reactivity.[28]

The clinician must also now choose among a burgeoning number of approved antiplatelet agents. Prasugrel and ticagrelor both provide more intense inhibition and reduce ischemic events compared with clopidogrel at the expense of greater noncoronary artery bypass graft-related bleeding.[17,18,32] Current society guidelines do not specify a preference of a particular agent, including clopidogrel, over another,[33] although they do note that platelet function testing may be considered if the results of testing may alter management.[33] The upcoming loss of patent protection for clopidogrel in the United States, in combination with exploding health care costs, will strongly interject economic considerations into these treatment decisions.

The goal of this supplement is to provide the clinician a practical summary of the current state of platelet function testing as we are faced with this increasingly complex environment. Drs. Tantry and Gurbel, who were involved in the initial descriptions of antiplatelet response variability, describe today's antiplatelet therapy landscape, including agents now in phase III studies; furthermore, they summarize the data supporting their benefits, their limitations, and remaining unmet clinical needs for patients who require DAPT. Drs. Fileti, Campo, and Valgimigli, who performed a seminal trial of "individualized" antiplatelet therapy in PCI, the Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) Study,[30] review the clinical data linking platelet function with clinical outcomes in patients with ACS and those undergoing PCI. Potential ways to apply these data are described by Drs. Lassar, Simon, and Croce, as they set forth clinical pathways used at their respective hospitals that integrate platelet function testing into practice. Drs. Mahmud and Ang present case studies from their own experiences to illustrate the application of platelet function testing to risk stratify PCI patients and to diagnose medication noncompliance. Finally, Drs. Brizzio and Zapolanski provide the oft-overlooked perspective of the cardiac surgeon with regard to antiplatelet therapy and bleeding.

The world of antiplatelet therapy for cardiovascular disease has entered an exciting, and at times bewildering, new phase, with the recognition of response variability and its impact on thrombotic risk, the introduction of new and more potent agents, a greater understanding of the morbidity associated with bleeding, the necessity for long-term DAPT in the setting of drug-eluting stents, and increasing pressure to reduce health care costs. In the midst of this uncertainty, I hope this supplement will provide the reader with a unique and useful perspective of novel therapeutic strategies to optimize the care of our patients. ■

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