Should Platelet Function Testing Guide Antiplatelet Therapy for Patients with Coronary Artery Stenting or Acute Coronary Syndromes?

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Inhibition of platelet activation ("antiplatelet therapy") with platelet P2Y12 (ADP) receptor antagonists (i.e., thienopyridines such as clopidogrel and prasugrel) reduces platelet-rich thrombi that cause coronary artery stent thrombosis and recurrent acute coronary syndrome (ACS) (i.e., unstable angina pectoris and myocardial infarction). However, several reports suggest that there are large interindividual variations in platelet inhibition by clopidogrel, with up to one-third of patients having apparently "high platelet reactivity" while on therapy; these patients may be at increased risk for stent thrombosis and recurrent ACS (1). Consequently, platelet function testing may identify patients in whom adjustment of thienopyridine therapy is warranted to minimize the risk of both ischemic and bleeding complications. The introduction of point-of-care devices has made it possible to consider the routine evaluation of on-treatment platelet reactivity in patients undergoing coronary stenting and in ACS patients.

Platelet Function Testing on Thienopyridine Therapy: Historical Studies and Recent Clinical Trials

Platelet function testing has been used in the research setting to individualize dosing of thienopyridine therapy in patients undergoing percutaneous intervention (PCI) with or without stent placement and in ACS patients (1). Several platelet function assays are available, including light transmission aggregometry (LTA), vasodilator-stimulated phosphoprotein (VASP) phosphorylation, and the point-of-care VerifyNow P2Y12 assay (Accumetrics). Both LTA and VASP phosphorylation analyses require substantial sample processing and specialized training, and diagnostic cutoff points for these two methods are uncertain, rendering these methods impractical for clinical care.

The VerifyNow P2Y12 is a whole-blood, turbidimetric assay that measures platelet agglutination to fibrinogen-coated polystyrene beads in response to ADP. Initial studies suggested that this assay could identify patients at increased risk for thrombotic events after PCI while on clopidogrel therapy (1). However, two recent studies have called this hypothesis into question. In the Gauging Responsiveness with a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) study, high platelet reactivity by the VerifyNow P2Y12 assay was ineffective in guiding antiplatelet therapy in patients undergoing implantation of a coronary drug-eluting stent. In this study, patients with high on-treatment platelet reactivity within 12–24 h after stent implantation were randomized to high- vs standard-dose clopidogrel (2). At 6 months of follow-up, the study endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis) was 2.3% in both groups. The Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation versus Continuation One Year after Stenting (ARCTIC) study randomly assigned 2440 patients undergoing coronary artery stenting to VerifyNow P2Y12 platelet function monitoring and thienopyridine dose adjustment vs conventional thienopyridine therapy with no monitoring or dose adjustment (3). At 12 months of follow-up, the study end-point rates (death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization) did not differ significantly in the monitored and dose-adjusted group (34.6%) compared to the conventional therapy group (31.1%).

Similar results were found in a recent trial of ACS patients. The TRILOGY-ACS study enrolled 9326 ACS patients treated medically with aspirin and either clopidogrel or prasugrel (4). Among a subset of 2500 participants undergoing serial VerifyNow P2Y12 testing,
platelet reactivity was significantly lower in the prasugrel group compared to the clopidogrel group. However, the primary efficacy endpoint rates (cardiovascular death, myocardial infarction, or stroke) at 30 months of follow-up did not differ significantly between the prasugrel (17.2%) and clopidogrel (18.9%) arms. Moreover, there was no association between platelet reactivity and ischemic outcomes.

Clinical Practice Guidelines

A 2010 US Food and Drug Administration (FDA) “boxed warning” on the potential for reduced clopidogrel efficacy due to impaired drug metabolism of the active form among carriers of the cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19) loss-of-function allele prompted the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) to issue a clopidogrel clinical alert summarizing the issues surrounding clopidogrel and the routine use of platelet function testing (5). The ACCF/AHA clinical alert concluded that the current evidence was insufficient to recommend routine platelet function testing. The FDA subsequently concluded in a label revision that testing for the CYP2C19 genotypes or overall platelet function was not mandated. The ACCF/AHA recommendations have been reaffirmed recently with completion of the GRAVITAS, ARTIC and TRILOGY-ACS (A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects) clinical trials demonstrating VerifyNow P2Y12 platelet function testing to be ineffective for thienopyridine management among coronary stent and/or ACS patients.

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References