Platelet Function Testing for Individualized Care?

An assessment of utility in therapy and future directions.

BY DAVID J. SCHNEIDER, MD

The development of a strategy to determine optimal antithrombotic treatment for patients who have had a myocardial infarction and/or coronary intervention would be useful for clinicians. The availability of multiple therapeutic agents to inhibit platelet function has added emphasis to the potential utility of such a strategy. In this article, we explore the use of platelet function testing, potential mechanisms responsible for its lack of utility in guiding therapy, and future directions.

PLATELET REACTIVITY AND SUBSEQUENT RISK OF CARDIOVASCULAR EVENTS

Many studies have consistently demonstrated that evidence of increased platelet reactivity at the time of percutaneous coronary intervention (PCI) identifies patients who are at increased risk of subsequent cardiovascular events. Breet et al reported results from a study in which 1,069 patients undergoing PCI had platelet function testing using multiple tests.[1] This study was notable because of its size and comparison of multiple methods to test platelet function. In this study, greater platelet reactivity demonstrated by light transmission aggregometry (LTA) and the VerifyNow P2Y12 point of care instrument (Accriva Diagnostics, representing ITC and Accumetrics) were significantly associated with a greater risk of subsequent cardiovascular events. Despite highly significant correlations, the negative predictive value (> 90%) was substantially greater than the positive predictive value (< 15%; Figure 1). Accordingly, demonstrating an absence of increased platelet reactivity has far greater prognostic implications than demonstrating evidence of increased platelet reactivity.

PLATELET FUNCTION TESTING TO GUIDE ANTIPLATELET THERAPY

The GRAVITAS trial enrolled 2,214 patients with high platelet reactivity.[2] The use of high-dose clopidogrel (150 mg daily) compared with standard-dose clopidogrel (75 mg daily) did not reduce the incidence of death from cardiovascular causes, nonfatal myocardial infarction, nor stent thrombosis. This trial did not support the use of high platelet reactivity to guide antiplatelet therapy (Figure 2). Factors that may have contributed to the apparent lack of efficacy included (1) the threshold for defining high platelet reactivity may have been too high, (2) the pharmacodynamics efficacy of high-dose clopidogrel was not tested and may not have effectively reduced high platelet reactivity, and (3) a low incidence of clinical events limited the power of the study.

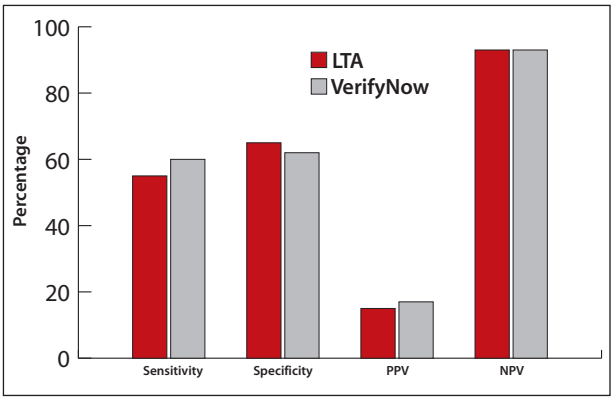

Figure 1. Predictive value of the LTA (20 µM adenosine diphosphate) and VerifyNow P2Y12 assays of platelet function. Breet et al characterized platelet function in 1,069 patients who underwent PCI.[1] They found that the LTA and VerifyNow results were significantly associated with the subsequent risk of cardiovascular events. Despite the highly significant association, there was modest sensitivity and specificity shown in the graph on the left. Due to a low incidence of cardiovascular events, a correspondingly low positive predictive value (PPV) and high negative predictive value (NPV) are shown in the graph on the right.

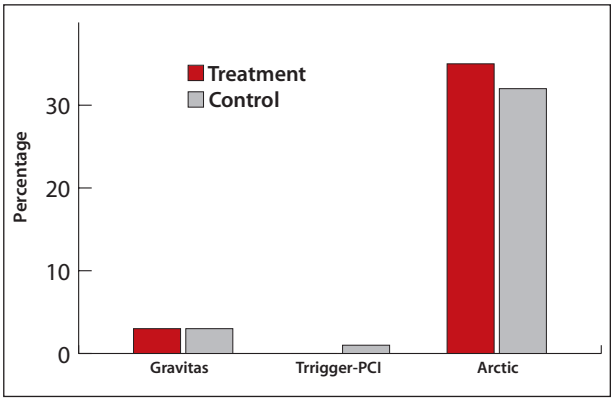

Figure 2. Cardiovascular event rates in trials designed to test the value of adjusting antiplatelet therapy based on results of platelet function testing with the VerifyNow P2Y12 assay. The event rates were not significantly different in the control and treatment arms of any of these studies.

The TRIGGER-PCI study addressed two of these concerns.[3] This study identified high platelet reactivity with the use of a lower threshold (208 platelet reactivity units). Patients with high platelet reactivity were randomized to prasugrel or standard-dose clopidogrel (75 mg daily). Pharmacodynamic assessment demonstrated effective suppression of high platelet reactivity among patients randomized to prasugrel. This study was prematurely closed because of a very low and similar event rate in both groups of patients (Figure 2).

The ARCTIC study evaluated a strategy that involved sequential platelet function testing that was used to adjust treatment in patients with evidence of high platelet reactivity in response to aspirin, thienopyridine (clopidogrel or prasugrel), or both.[4] Therapy in the control group was not guided by platelet function testing. A similar incidence of cardiovascular events was seen in both groups (Figure 2).

Results from the TRILOGY ACS trial suggest that patients who were treated with prasugrel compared with clopidogrel had lower platelet reactivity.[5] Despite this greater pharmacodynamic effect, those in the prasugrel group did not have a lower incidence of cardiovascular events. Furthermore, risk-adjusted analysis did not demonstrate a significant association between platelet reactivity and cardiovascular events. These results suggest that the prognostic implications of high platelet reactivity are greater after coronary stenting than after medical therapy alone.

CONCLUSIONS AND FUTURE DIRECTIONS

Prospective studies have shown that high platelet reactivity identified with the use of LTA and the VerifyNow P2Y12 assays are significantly associated with a greater risk of subsequent cardiovascular events after PCI. The prognostic implications have not been extended to patients treated with medical therapy in the absence of PCI. Despite the significant association, the sensitivity and specificity for the prediction of subsequent ischemic events are modest (in the range of 60% ± 10%). The positive predictive value of high platelet reactivity is low (~11%), whereas the negative predictive value of low platelet reactivity is high (> 90%). These tests are not useful to identify patients at increased risk of bleeding complications. Accordingly, platelet function testing should not be used to guide therapy due to the lack of benefit seen in randomized clinical trials that used this strategy (see the *Platelet Function Testing* sidebar).

Despite the lack of efficacy of platelet function testing to guide individualized treatment with antiplatelet agents, such testing remains useful to assess the pharmacodynamic effects of therapy and guide clinical trial design. In addition, the value of platelet function testing in patients who are at higher risk of cardiovascular events, such as those with acute coronary syndromes treated with coronary stenting, merits additional evaluation in randomized clinical trials. Because platelet function exhibits substantial intraindividual variability over time, novel assays that identify patients with consistently increased platelet reactivity may have greater prognostic implications and the ability to effectively guide individualized antiplatelet therapy. ■

PLATELET FUNCTION TESTING

- Evidence does not support its use in clinical practice to guide antiplatelet therapy
- Remains useful for pharmacodynamic assessment to guide clinical trial development
- Merits further development to identify measures that are less sensitive to day-to-day variation and more reflective of long-term platelet reactivity

David J. Schneider, MD, is Professor of Medicine, Director of Cardiovascular Services, Director Cardiovascular Research Institute, University of Vermont Health Network in Burlington, Vermont. He has stated that he has no financial interests related to this article. Dr. Schneider may be reached at (802) 656-8955; david.schneider@uvm.edu.

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