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EDITORIAL COMMENT

On-Clopidogrel Platelet Reactivity

A Target in Sight?*

Stephen D. Wiviott, MD,†
Willibald Hochholzer, MD†‡

Boston, Massachusetts; and Bad Krozingen, Germany

Clopidogrel blocks the $P2Y_{12}$ adenosine diphosphate receptor on platelets and, when given in addition to aspirin, has been shown to reduce cardiovascular events in patients with acute coronary syndromes (ACS) (1,2). Current guidelines recommend the use of clopidogrel 75 mg daily for up to 1 year after ACS (3) and between 1 and 6 months after elective percutaneous coronary intervention (PCI), depending on stent type, with an option of at least 12 months for patients who are not at high risk of bleeding (4).

The efficacy of such treatment is influenced by the large interindividual variability in the pharmacodynamic response to clopidogrel (5,6). Several clinical studies have demonstrated the impact of this variability on clinical outcomes (7). Patients with high residual platelet reactivity on clopidogrel are at increased risk for stent thrombosis and other major cardiac complications (7).

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The use of platelet function testing in risk stratification has limitations: most data on variability in response to clopidogrel and clinical outcome are single-center experiences, making the generalizability of the findings uncertain. Some of the assays used in studies are not widely available, are not standardized, or need qualified laboratory staff to implement. These issues have been barriers to widespread adoption of testing.

In this issue of the *Journal*, Brar et al. (8) present a meta-analysis of the association of platelet function to clinical outcome. This study adds to the current literature beyond simple confirmation. Each of the studies used the same automated bedside assay and therefore allows pooling of data, providing power for key outcomes assessments. Second, the threshold of platelet reactivity in relation to outcomes is consistent between cohorts and previous data, providing evidence for a reasonable clinical cut-point (230 platelet reaction units). As with other good meta-analyses, the increased sample size allows for analysis of patient subgroups demonstrating consistency across presenting syndromes.

There are some limitations as well. There may be publication bias with studies failing to show such a correlation either not being submitted or not published. That could have substantial implications given the modest sample size of even the meta-analysis. In addition, most of the data relates to only half of the clinical question of association with outcomes—limited information is provided about the relationship of platelet function and bleeding risk.

This analysis further establishes that on-treatment platelet reactivity is a marker of risk among clopidogrel-treated patients. The widespread adoption of platelet function testing as part of clinical practice would certainly be hastened by demonstrating that therapies cannot only alter this factor but also improve clinical outcome. That has proved elusive. Several trials have examined this question or are currently doing so. Most have the same significant limitations—inadequate sample size or modest therapeutic intervention to high on-treatment reactivity. The largest trial reported to date, the GRAVITAS (Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety) trial suffered from both of these limitations (9). In the GRAVITAS trial, high-dose clopidogrel did not reduce the incidence of ischemic events, although event rates were low in both arms, and the separation in platelet reactivity between the standard and the experimental arms was small. The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial randomly assigned subjects with a high platelet reactivity on clopidogrel after successful implantation of drug-eluting stents to either standard dose prasugrel or clopidogrel. This trial likely would have resulted in a greater separation of platelet function results in the experimental arms than the GRAVITAS trial, but was terminated for low event rates and, therefore, inadequate sample size. In both of these studies, randomization occurred after PCI—after the time of greatest thrombotic risk had passed. These results, therefore, do not negate the importance of high on-clopidogrel platelet reactivity, but suggest that to adequately test this concept, it would require more, higher-risk subjects, and creative design that allows for differentiation of therapies at the time they are most likely to be effective.

Three trials of more intensive inhibition of the $P2Y_{12}$ receptor—the CURRENT–OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal

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From the †TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the ‡Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany. Dr. Wiviott has received research funding from Eli Lilly, Daiichi Sankyo, Pfizer, and Merck; consulting income from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Ortho-McNeil, and Medco; and independent Continuing Medical Education speaking with grants from Eli Lilly, Schering-Plough, Medtronic, and Daiichi Sankyo. Dr. Hochholzer receives consulting income from Sanofi-Aventis.

Antiplatelet Strategy for Interventions) study, TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction), and the PLATO (Study of Platelet Inhibition and Patient Outcomes)—all generally support that greater inhibition of platelet aggregation reduces cardiovascular ischemic events and increases bleeding compared to standard clopidogrel treatment (10–12). That provides further circumstantial evidence that treating to lower levels of platelet inhibition could improve ischemic outcomes.

Nearly every paper about the relationship between platelet function testing and clinical outcomes—and every editorial written about such papers—concludes with a remark that the gap needs to be bridged between treatments that inhibit $P2Y_{12}$ receptors (the therapy) and platelet function tests (the risk marker) and clinical outcomes. If one draws a parallel to another risk marker (low-density lipoprotein [LDL] cholesterol) and therapy (HMG-CoA reductase inhibitors, or statins) an inconsistency emerges. Several studies—PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22), TNT (Treating to New Targets), A to Z (Aggrastat to Zocor), SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine), IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering), and others (13)—also generally show that treating with a higher intensity HMG-CoA reductase inhibitor improves clinical outcomes compared to treating with similar drugs with less intensity. Strictly speaking, PROVE IT–TIMI 22 (for example) demonstrated that the use of atorvastatin 80 mg after acute coronary syndromes improved ischemic outcomes compared to pravastatin 40 mg; it did not demonstrate that achieving LDL <70 mg/dl improves outcomes (14). In fact, in clinical practice—and in guidelines—the interpretation of these studies has not been that one should use a specific dose of a specific statin on the basis of a specific trial; rather, that we should treat to particular targets of a surrogate measure (LDL) of statin effect (15,16). Therefore, if we can treat to 70 mg/dl with a generic statin, clinicians generally feel satisfied that they have met guideline-based targets and also saved the health care system or patient money.

Why, then, the difference in interpretation of largely similar data sets between LDL cholesterol and platelet function testing? First, perhaps because LDL is a better-established risk marker from epidemiologic studies that clinicians can rapidly and consistently measure and are comfortable with the meaning and ranges of the results. This understanding has been accelerated by meta-analyses correlating LDL changes with clinical benefit (17,18). The data from the Brar et al. (8) meta-analysis and the growing platelet literature begin to similarly address this issue for on-treatment platelet reactivity. Secondly, there are several effective statins that have long-term safety experience. There is less comfort and clinical experience with high-dose clopidogrel, prasugrel, or ticagrelor. Importantly, severe bleeding events (the major side effect of intensive antiplatelet therapy) occur at a higher frequency than do severe side effects of statins such as liver failure or rhabdomyolysis. Therefore, targeting more intense platelet inhibition requires a greater consideration of the risk/benefit ratio. Clinical research should continue to address the relationship between on-treatment reactivity and bleeding risk, not just ischemic risk.

As similar economic pressures arise when clopidogrel becomes generic compared to newer branded therapies, will we be pushed by payers, or choose in balancing cost, to perform a similar leap of faith? As evidence-based practitioners, we select therapies on the basis of major clinical trial results. We would like to see studies funded and performed that adequately address the gap between achieved platelet function and clinical outcomes. Although additional trials are ongoing, we do not anticipate that the desired evidence will be available soon. We believe that future economic pressures may force an increase in the use of platelet function testing without the highest level of direct evidence. We are fortunate that we have data such as the analysis by Brar et al. (8) in this issue of the *Journal* to better understand the meaning of the results of these tests.

Reprint requests and correspondence: Dr. Stephen D. Wiviott, TIMI Study Group, 350 Longwood Avenue, 1st Floor, Boston, Massachusetts 02115. E-mail: swiviott@partners.org.

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