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EDITORIAL COMMENT

Resisting the Temptation to Oversimplify Antiplatelet Resistance*

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The variable response of platelets to different antiplatelet medications, often referred to as antiplatelet resistance, has generated immense interest among both clinicians and investigators. In several studies, variability in antiplatelet response has been associated with adverse cardiac outcomes.

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In patients undergoing elective percutaneous coronary intervention (PCI) who had not received glycoprotein (GP) IIb/IIIa inhibitors or clopidogrel pre-treatment, aspirin nonresponsiveness predicted periprocedural myocardial infarction (MI) (1,2). Similarly, clopidogrel nonresponsiveness has been associated with adverse outcomes, including periprocedural myonecrosis, stent thrombosis, MI, and even death (3–5). More recently, therapeutic strategies have been assigned on the basis of platelet responsiveness and seem to improve surrogate markers of clinical outcome (6). Not all studies, however, have been consistent in finding the aforementioned associations (7,8). Conflicting results have caused a great degree of confusion in the field about whether to test, how to test, in whom to test, and what to do with the information obtained from a test.

In this issue of *JACC: Cardiovascular Interventions*, 2 important reports examine critical issues surrounding variability in antiplatelet response. In patients who have received an intravenous GP IIb/IIIa inhibitor, the study by Saw et al. (9) demonstrates that neither aspirin nor clopidogrel nonresponsiveness affects periprocedural myonecrosis. The study by Cuisset et al. (10) finds that in patients who are clopidogrel nonresponders, those randomized to receive a GP IIb/IIIa inhibitor had a significantly lower rate of cardiovascular events, consisting primarily of periprocedural MI as defined by troponin elevation.

The results of these 2 well-done studies might seem contradictory at first glance, but closer examination shows that this is not the case. One study seems to find no prognostic value in point-of-care measurement of aspirin or clopidogrel response, whereas the other seems to find immense value in measuring clopidogrel response, along with therapeutic implications. It is important to realize that both studies essentially examined the short-term surrogate outcome of periprocedural myonecrosis. In the presence of the intravenous GP IIb/IIIa inhibitor eptifibatide, Saw et al. (9) did not find that aspirin or clopidogrel nonresponsiveness influenced myonecrosis in a low- to moderate-risk population. Perhaps, had active thrombus been present, the findings might have been quite different. It is also possible, if the study had followed a larger number of patients for a longer duration of follow-up, that a deleterious effect of aspirin and clopidogrel resistance might have been evident on end points such as spontaneous MI and stent thrombosis.

The study by Cuisset et al. (10) showed that the GP IIb/IIIa inhibitor abciximab decreased periprocedural MI in clopidogrel nonresponders as assessed by light transmittance aggregometry—these were patients who essentially still had activated platelets prone to aggregate. A reduction in troponin-defined post-procedural myonecrosis is probably a reasonable surrogate of more clinically important outcomes (11). Although the overall sample size was not large, it was encouraging that this strategy was not associated with any excess in major bleeding, although it might have been instructive to examine more minor degrees of bleeding as well.

An interesting finding in the Saw et al. (9) study is that low clopidogrel response was significantly associated with elevated body mass index. Other studies have also shown a similar relationship between weight and clopidogrel effect (12). Whereas the impaired platelet response seen in obese patients in this study did not seem to translate into adverse clinical outcomes, future studies will need to explore in greater depth the relationship between obesity and apparent antiplatelet resistance.

Novel agents in development might be particularly useful in patients with antiplatelet hyporesponsiveness (13). The more potent oral thienopyridine prasugrel was recently evaluated in acute coronary syndrome patients undergoing

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PCI in TRITON–TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction-38) and found to be superior to clopidogrel although with a significant accompanying risk of major bleeding (14–16). Diabetic patients are a group very likely to benefit from intensification of their antiplatelet regimen. This phenomenon of heightened treatment effect in diabetic patients has been observed with prasugrel versus clopidogrel, with high-dose versus low-dose clopidogrel, with clopidogrel versus aspirin, and with GP IIb/IIIa inhibitors versus placebo (17–20). Therefore, diabetic patients might benefit from more complete platelet blockade, regardless of what tests of platelet reactivity show.

The CURRENT–OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Antiplatelet Strategy for Interventions-7) trial is randomizing acute coronary syndrome patients to standard or high-dose clopidogrel, irrespective of clopidogrel responsiveness (21). Cangrelor is a potent intravenous adenosine diphosphate receptor antagonist that is being evaluated in the ongoing CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials (22,23). If more potent platelet inhibition with cangrelor proves superior to clopidogrel across the range of patients studied, the issue of measuring clopidogrel responsiveness might be moot, at least with respect to modifying periprocedural outcomes. The GRAVITAS (Gauging Responsiveness with a VerifyNow Assay–Impact on Thrombosis and Safety) trial is randomizing patients who are deemed nonresponsive to clopidogrel on point-of-care testing to receive higher dosing of clopidogrel (24). Of course, it might just be a matter of degree—that is, perhaps all patients benefit from more antiplatelet effect than provided by standard dosing of clopidogrel, but whether bleeding risk or cost justify the use of novel agents in all types of patients remains to be seen. These and other ongoing trials should help clarify whether antiplatelet testing is really necessary to optimize patient outcomes.

The studies by Saw et al. (9) and Cuisset et al. (10) bring great clarity to the field of antiplatelet response. These reports help reconcile several different studies that have reached apparently contradictory findings. Different tests of platelet responsiveness, different study populations, and different antiplatelet agents might interact in ways that will take years to unravel. Relationships between hypercholesterolemia and appropriate intensity of cholesterol reduction therapy continue to be debated despite years of data accumulation, so it should not be surprising that there is much more to learn about the appropriate role of measurement of platelet reactivity. Collectively, these 2 papers illustrate that the field of antiplatelet resistance is complex and we should resist the temptation to oversimplify.

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