Unraveling Questions Surrounding Clopidogrel Resistance and Stent Thrombosis
One Less Snag*

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Patients with symptomatic coronary atherosclerosis tend to have recurrent ischemic events despite treatment with evidenced-based therapies, including aspirin and clopidogrel. Recently, it has become appealing to speculate that some patients do not receive the anticipated benefit from antiplatelet agents because they are nonresponsive or resistant. Several trials have identified patients with relatively high platelet activity despite their being treated with aspirin, clopidogrel, or both. In some of these trials, a failure to inhibit ex vivo platelet function to a particular extent has been associated with an increased risk of subsequent ischemic events (1,2).

There is a considerable range in the reported prevalence of antiplatelet resistance, undoubtedly due to variability in patient populations, comparator groups, treatment regimens, detection methods, and definition cut points. In fact, a recent meta-analysis of 42 studies found the prevalence of aspirin resistance to vary between 0% and 57%, with a mean of 24% (95% confidence interval 20% to 28%) (3). The most recent American College of Cardiology/American Heart Association guidelines for percutaneous coronary intervention (PCI) (4) recommend platelet function testing in specific settings and that the clopidogrel maintenance dose be doubled when antiplatelet resistance is suspected—albeit without randomized study data to support the recommendation. The lack of prospective clinical trial evidence has caused some to question whether antiplatelet resistance is dichotomous or whether it exists at all.

In this issue of the Journal, Buonamici et al. (5) provide observations from a large reasonably designed study that suggest PCI patients with inadequate postprocedural platelet inhibition are at increased risk for subsequent ischemic events. The study enrolled patients receiving drug-eluting stents for ischemic heart disease presentations ranging from chronic stable angina to ST-segment elevation myocardial infarction. Lesion complexity ranged widely and included real-world cases of the left main coronary artery, complex bifurcation lesions, relatively long lesions, and chronic total occlusions.

The authors treated all patients with aspirin (325 mg) and a high loading dose (600 mg) of clopidogrel. Platelet function testing via light transmittance aggregometry was performed 12 to 18 h after clopidogrel loading unless a glycoprotein (GP) IIb/IIIa inhibitor was given during clopidogrel loading. In these situations, light transmittance aggregometry was performed 6 days later. Patients were considered nonresponsive to clopidogrel if they had residual platelet aggregation in response to 10 μmol/l adenosine diphosphate ≥90th percentile of a healthy control group.

The primary end point of the study was definite or probable stent thrombosis during 6-month follow-up. The secondary end point was a composite of cardiac death and definite or probable stent thrombosis. Definite stent thrombosis was angiographically or pathology proven, whereas probable stent thrombosis was defined as unexplained death or a myocardial infarction in the territory supplied by the stented vessel.

The study enrolled 804 patients, 13% of whom were classified as being nonresponsive to clopidogrel. The nonresponders appeared to be older and more likely to present with severe coronary artery disease, unstable angina, and diabetes as well as other features previously associated with stent thrombosis. In particular, they were more likely to have multivessel disease, long lesions, chronic occlusions, and reduced left ventricular ejection fraction. The responders were slightly younger and more likely to be current smokers, present with a thrombotic lesion (acute infarction), and receive a GP IIb/IIIa inhibitor.

Overall, stent thrombosis was infrequent, occurring in 25 of 804 patients. Most of these events were probable rather than definite. When only definite stent thrombosis was considered, the number of events decreased to 11 (1.4%). The average time to the primary end point was 54 days (range 4 to 180 days). Importantly, clopidogrel nonresponders were more likely than responders to have stent thrombosis (8.6% vs. 2.3%; p < 0.001), but in both groups patients with multiple risk factors for stent thrombosis, i.e., multivessel disease, complex lesions, and acute presentation, were at the highest risk. Nonresponders also were more likely to die (8.6% vs. 1.4%; p < 0.001) or reach the secondary composite end point of death or stent thrombosis.
function will be helpful mechanistically because variability as well as aggregation assessments. Serial analyses of platelet for stent thrombosis based on clinical and angiographic as it may be best to focus enrollment on patients at high risk mechanism of the association. To increase trial event rates, and cangrelor, an intravenous, rapid-acting, and rapidly diphosphate-receptor antagonists that are more potent and administration of clopidogrel at a higher dose or frequency (9), have excess residual platelet activity. Candidate add-ons apies for patients treated with aspirin and clopidogrel who antiplatelet therapy is warranted.

Next, high residual platelet aggregability was detected in a sizeable proportion of patients (13%), although most in this subgroup did not experience an adverse event. Again, these results are consistent with those from previous studies (7,8). As a diagnostic test for stent thrombosis, the methodology in the current study had low sensitivity (36%) but moderately high specificity (88%). Unfortunately, if these results are used to assign patients to more aggressive antiplatelet therapy as recommended by the guidelines (4), some patients not destined to experience stent thrombosis will need to be overly treated whereas many who will later develop stent thrombosis will be missed. In fact, more cases of stent thrombosis may be missed than treated, and any trade-off for increased bleeding is unknown. As such, a randomized trial of more aggressive antiplatelet therapy for patients considered nonresponders to current dual antiplatelet therapy is warranted.

There are currently no evidence-based supplemental therapis for patients treated with aspirin and clopidogrel who have excess residual platelet activity. Candidate add-ons include periprocedural GP IIb/IIIa inhibitors (7), the administration of clopidogrel at a higher dose or frequency (9), and cilostazol (10). On the horizon are platelet adenosine diphosphate-receptor antagonists that are more potent and faster acting than the current dose of clopidogrel. These include prasugrel, an oral, rapid-acting, irreversible inhibitor; AZD6140 an oral, rapid-acting, reversible inhibitor; and cangrelor, an intravenous, rapid-acting, and rapidly reversible agent.

A future antiplatelet resistance-stent thrombosis trial should be large and designed to provide insight into the mechanism of the association. To increase trial event rates, it may be best to focus enrollment on patients at high risk for stent thrombosis based on clinical and angiographic as well as aggregation assessments. Serial analyses of platelet function will be helpful mechanistically because variability in baseline platelet function affects variability after clopidogrel therapy (11). Additionally, given the fact that mechanical revascularization activates platelets (7), the determination of platelet function in the postprocedural period and serially during follow-up may help separate peri-procedural activation and events from those that are a result of ongoing vascular disease. The study by Buonamici et al. (5) further elevates the association of antiplatelet nonresponsiveness and stent thrombosis from a clinical curiosity to a strong hypothesis worth evaluating in a prospective trial of selective aggressive antiplatelet therapy.