EDITORIAL COMMENT

Resistance to Antiplatelet Resistance*

Is it Justified?

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It is unusual for a month to go by without a new antiplatelet “resistance” or “non-responder” article appearing in the cardiology literature. Considering the fact that antiplatelet therapies, primarily aspirin, have been around for more than a century and variability in response to some degree has been recognized for nearly 40 years (1), why is there now so much press interest? First, and most importantly, it is because atherosclerotic vascular disease remains the leading killer in the industrialized world today and antiplatelet therapy is still one of the most effective therapies for its treatment. For example, in the setting of an ST-segment elevation myocardial infarction, the 23% relative reduction in short-term mortality provided by an aspirin tablet (2) rivals the 27% mortality reduction achieved with primary angioplasty over fibrinolytic therapy (3).

Second, an acceptable alternative to aspirin, clopidogrel, recently has become widely available. Before this, the only alternatives to aspirin for chronic antithrombotic therapy were warfarin and ticlopidine, and there are several reasons that made each an inferior alternative. Therefore, for the first time we have a long-term antiplatelet treatment option that could make measuring a response to aspirin clinically worthwhile. Third, the medical relevance of antiplatelet responsiveness has tremendous implications because of the sheer number of people that are affected. It is estimated that in the U.S. alone roughly 30 million individuals take an aspirin daily for cardioprotection. Even as a newcomer, clopidogrel already has been prescribed to more than 20 million patients worldwide.

A final reason antiplatelet responsiveness has so much recent interest is because of our improved understanding of platelet biology and newfound appreciation that there are multiple genetic and environmental influences on platelet responsiveness. These multiple influences, not only on the platelet itself, but also on the absorption and metabolism of antiplatelet agents, render the assumption that one dose of an antiplatelet medication would yield the maximal clinical benefit in all patients about as tenable as assuming that one dose of hydrochlorothiazide would yield the same benefit in all hypertensive patients.

With the heightened interest and study of antiplatelet responsiveness, one would hope there has been clear headway in addressing several key issues. For instance, what percentage of cardiac patients “inadequately” responds to aspirin? Unfortunately, there is no certain answer. On the basis of trials that have correlated some change in platelet function among aspirin-treated patients with clinical outcomes, the reported prevalence ranges from 5% to 75% (4,5), a range too wide to be useful. Along these lines, it also remains unknown whether response to antiplatelet therapy is more binary or continuous. That is, can an individual really have an all-or-none response? Like other biologic processes under polygenetic and environmental control, it seems more plausible that platelet responsiveness is continuous. Indeed, a normally distributed platelet response to clopidogrel was reported among 544 individuals (6). The natural question therefore is what level of response to antiplatelet therapy along this continuum places a patient at increased risk for thrombosis or for bleeding events?

An underappreciated unknown—especially considering the many studies using different methods for measuring platelet response to therapy—is whether there is a single best way to measure platelet function and to define the lack of adequate suppression by antiplatelet therapies. Light transmittance platelet aggregometry generally is considered the gold standard for determining platelet function, but the artificial nature of the test makes its relevance to in vivo platelet function questionable, and the technical demands of the method make it somewhat impractical. In addition, aggregation is but one of several important platelet functions. Nonetheless, one clinical study has correlated light transmittance aggregometry results in patients treated with aspirin with clinical outcomes (5). Urinary thromboxane metabolite levels also have been found to be associated with clinical outcomes (4); however, other factors aside from aspirin influence thromboxane metabolite levels, including the degree of atherosclerosis (7) and inflammatory diseases (8). Multiple point-of-care devices have been developed and may be the key to widespread clinical use of platelet function testing. Some assays have been shown to provide predictive value (i.e., correlate with clinical outcomes) (9), whereas others have not (10).

Even more fundamental, however, a limitation to nearly all studies attempting to correlate aspirin “responsiveness” and clinical outcomes is that they have not truly measured the independent effects of aspirin. Rather, platelet function has been most commonly measured among patients already

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taking aspirin. Therefore, what is really being measured is the patient’s responsiveness to aspirin in conjunction with the underlying or basal platelet function, which is itself highly variable and correlated with clinical outcomes. Adequately powered clinical trials, with platelet function measured before and after the initiation of antiplatelet therapy, are still needed because the correlations between the differences in platelet response and clinical outcomes are what will permit bona fide inferences about the effects of aspirin. It will then be crucial to understand whether an alternate antiplatelet therapy (e.g., high-dose aspirin, clopidogrel, or combination therapy) improves platelet suppression and clinical outcome among those who are otherwise “nonresponders.” At present, there is no quantitative measure of the effect of aspirin that can reliably predict the drug’s ability to prevent ischemic vascular events.

What insights can be gleaned from the two studies (11,12) in this issue of the Journal? Both studies were relatively small (82 and 49 subjects) and focused on patients known to be acutely dependent on adequate antiplatelet protection: patients undergoing coronary stent placement. Each study retrospectively identified patients with stent thrombosis and determined their platelet responsiveness either to shear or to chemical agonists. Similar to previous studies, both reported differences in platelet responsiveness among patients who had experienced stent thrombosis as compared with a matched historical control group. Unfortunately, but clinically appropriate, neither study determined platelet function in patients free of all antiplatelet therapy. In the study by Ajzenberg et al. (11), the difference in platelet response between the groups is likely partially explained by the close proximity (mean, 4.6 days) of platelet testing after the index thrombotic event. As such, the increase in shear-induced platelet aggregation detected could represent an effect of the stent thrombosis rather than a cause. In the study by Wenaweser et al. (12), greater adenosine diphosphate-induced platelet aggregation was observed among patients treated with aspirin who had experienced stent thrombosis compared with control subjects, but no significant difference was found when patients were given aspirin and clopidogrel. Although the authors concluded that impaired responsiveness to aspirin may be associated with stent thrombosis, it is more likely that adenosine diphosphate-induced aggregation in the patients treated with aspirin is more a measure of intrinsic platelet function and less a measure of the effects of aspirin.

Where do these data leave us? Considering Figure 2 in the paper by Wenaweser et al. (12), one can see the sensitivity and specificity of aspirin resistance for predicting stent thrombosis in this study to be 48% and 68%, respectively. This result might seem a reasonable start, but if we assume that the incidence of stent thrombosis is 0.5% to 2%, the corresponding positive predictive value (between 0.7% and 3.0%) is dismal, signaling the need for better diagnostics. Likewise, a challenge inherent to these and nearly all retrospective studies is both the uncertainty of the true disease incidence and the inability to assess all identified affected individuals. This arena is strikingly reminiscent of previous studies and views of heparin-induced thrombocytopenia. Despite these many limitations and caveats and regardless of where we now stand, as a next step forward, we need to stop resisting the concept of aspirin and clopidogrel resistance and systematically move forward—next month’s papers will soon be here.

**REFERENCES**