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EDITORIAL COMMENT

Platelet Function Testing and Clinical Outcomes

Connecting the Dots*

David J. Schneider, MD

Although platelet function testing can demonstrate the pharmacodynamic effects of antiplatelet agents, it has not been shown to be an effective tool to guide individualized therapy. Increased platelet reactivity has been consistently associated with a greater risk of cardiovascular events (1). By contrast, randomized trials that used platelet function testing to guide individualized therapy failed to demonstrate improved outcomes (2,3).

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In this issue of *JACC: Basic to Translational Science*, Franchi et al. (4) sought to elucidate pharmacodynamic mechanisms by which vorapaxar reduced recurrent thrombotic events when added to treatment with aspirin plus clopidogrel in high-risk patients including those with prior myocardial infarction, peripheral arterial disease, and diabetes. Because the reduction in thrombotic events was associated with an increase in bleeding events, the authors assessed the pharmacodynamic effects of aspirin withdrawal.

The investigators used a series of assays to assess pharmacodynamic effects that included measures of both platelet function and coagulation. Their findings demonstrated that vorapaxar inhibited the effects of thrombin receptor agonist peptide on platelet aggregation without an effect on clot kinetics. The withdrawal of aspirin was associated with increased platelet aggregation in response to agonists (collagen and arachidonic acid) that are sensitive to the effects of aspirin. Accordingly, their results are consistent with the primary mechanisms by which aspirin, clopidogrel, and vorapaxar inhibit platelets, and they did not demonstrate effects on measures of coagulation nor did they show interplay between platelet activation pathways.

This is a well-designed study performed by an experienced group of investigators. The results are clearly presented and elucidate the pharmacodynamic effect of the selected combinations. The authors deserve credit for bringing this study to completion. Despite the loss of committed financial support, the investigators completed the study with the use of institutional research funds.

These results underscore the challenges associated with the translation of pharmacodynamic effects to the clinical care of patients. The investigators appropriately chose to use agonists that would reflect the mechanisms by which aspirin, clopidogrel, and vorapaxar influence platelet activation. Studies assessing the prognostic implications of platelet reactivity have predominantly used adenosine diphosphate (1). Accordingly, the prognostic implications of other agonists, alone or in combination, are limited. Additional potentially confounding aspects of platelet function testing include the method of preparation (phlebotomy technique and anticoagulant used) as well as the concentration of agonist (5). Intraindividual variability in platelet reactivity appears to be a major contributor to the failure of platelet function tests to guide individualized therapy. Pharmacodynamic assessment has not been

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From the Cardiology Unit, Department of Medicine, Cardiovascular Research Institute, University of Vermont, Burlington, Vermont. Dr. Schneider has reported that he has no relationships relevant to the contents of this paper to disclose.

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effective in identifying patients at greater risk of bleeding complications. In aggregate, these issues limit our ability to project the clinical implications of the pharmacodynamic effects observed.

In summary, the authors found that the addition of vorapaxar to treatment with aspirin plus clopidogrel would be expected to attenuate thrombin-induced activation of platelets, and the withdrawal of aspirin was associated with an increase in arachidonic acid and collagen-induced aggregation. Although it is plausible that the recovery of collagen-induced aggregation might reduce the incidence of bleeding, this must be proven in clinical trials. Clinical trials with vorapaxar have demonstrated that attenuation of thrombin-induced platelet activation reduces the risk of thrombotic events; however, clinical trials are necessary to determine whether this benefit will be preserved in the absence of aspirin.

ADDRESS FOR CORRESPONDENCE: Dr. David J. Schneider, Cardiology Unit, Department of Medicine, Cardiovascular Research Institute, University of Vermont, 360 South Park Drive, Colchester, Vermont 05446. E-mail: david.schneider@med.uvm.edu.

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