EDITORIAL COMMENT

The Pursuit of Clinically Relevant Measures of Platelet Function After Antiplatelet Drug Therapy*

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Although there is a marked reduction of cardiovascular (CV) events when clopidogrel is added to aspirin for patients with a range of clinical presentations of vascular disease and undergoing a variety of procedures, substantial rates of CV events persist among treated patients (1,2). The occurrence of CV events in some treated patients and not in others often is explained by their demographics and by temporal variation in the activity of their underlying vascular diseases. However, an important potentially modifiable cause of treatment failure is a poor response to clopidogrel or clopidogrel resistance, defined as failure of the drug to achieve the expected suppression of platelet function as measured by various laboratory tests specific to its mechanism of platelet inhibition (2,3).

If a test of platelet function could reliably identify patients with poor responsiveness to clopidogrel and therefore a relatively higher rate of CV events, it would have great potential clinical value. Among the many available tests of platelet function, measures of platelet aggregation using light transmission aggregometry (LTA) and measures of intraplatelet signaling using the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay have been fairly extensively studied. Both methods are predictive of subsequent cardiovascular events (4–8) and are reasonably well correlated (8–10). Although the VASP assay is specific for inhibition by clopidogrel of the P2Y$_{12}$ receptor pathway and sample preparation is simpler than for LTA (9–11), it is uncertain which test offers the best prediction of CV events (4).

Wallentin et al. (12) have previously reported a study in which they randomized 110 aspirin-treated patients with stable coronary artery disease to receive in a double-blind fashion either prasugrel (60-mg load, 10-mg/day maintenance) or clopidogrel (600-mg load, 75-mg/day maintenance) for 28 days. They assessed platelet aggregation at several key time points in relation to load and maintenance by LTA (reported as maximal platelet aggregation [MPA]) and P2Y$_{12}$ function by VASP assay (reported as platelet reactivity index [PRI]). They also measured the active metabolites of clopidogrel and prasugrel at these time points. They found that mean MPA and mean PRI were both significantly and substantially less with prasugrel than with clopidogrel at 2 h after the loading dose (LD). During maintenance dosing (MD) on days 14 and 28, the MPA and PRI values for prasugrel remained significantly less than those for clopidogrel. Mean area under the time-concentration curve (AUC) of the respective active metabolite was higher with prasugrel than with clopidogrel. The addition of the clopidogrel active metabolite to the blood samples reduced the PRI in all patients whose platelets were not already maximally inhibited. The investigators concluded that the faster onset and greater inhibition of P2Y$_{12}$ receptor-mediated platelet aggregation with prasugrel was accounted for by greater and more rapid generation of the active metabolite.

In this issue of the Journal, further analyses on the same 110 patients are reported (13). Patients were categorized as normal or poor responders to prasugrel and clopidogrel using 4 definitions that have been associated with worse clinical outcomes in studies of clopidogrel therapy (ΔMPA <10%, MPA >50%, and residual platelet aggregation [RPA] >14% using LTA and PRI >50% using the VASP assay). After the LD, in the prasugrel group, the proportion of patients with poor responsiveness varied from 0% to 16.4%, depending on the definition and the time after LD, whereas in the clopidogrel group the proportion varied from 9.6% to 92.5%. During the MD, the proportion of poor responders in the prasugrel group varied from 2% to 28% and in the clopidogrel group from 15% to 72%. The proportion of patients with poor responsiveness was less in the prasugrel than in the clopidogrel group for all tested definitions, both after LD and during MD.

The patients on clopidogrel who were classified as poor responders by each of the 4 definitions had significantly lower concentrations of the active metabolite by AUC at 2 h after the LD and on the Day 29 MD. The numbers of poor responders were so low in the prasugrel group (except when using the RPA >14% definition) that no formal comparison of AUCs between the poor- and normal-responder groups was made. Before clopidogrel administration (baseline), the PRI did not differ significantly between patients eventually.
found to be poor responders and those found to be normal responders. At 2 h post-LD and Day 29 MD, the PRI had decreased to low values in the normal responders but was relatively high in the poor responders. When the PRIs were again measured after the addition of the active clopidogrel metabolite, they were found to be very low and similar in all samples from both the poor- and normal-responder groups.

Although there was no prior hypothesis in regard to patients with diabetes mellitus (DM), the investigators observed an excess of DM in the poor-responder groups and carried out several exploratory analyses. There were 10 patients in the prasugrel group and 9 in the clopidogrel group who had previously been diagnosed with DM. The fraction of patients with DM was consistently higher in the poor responsiveness groups at all time points and using all 4 definitions. The concentrations of the active metabolite of both clopidogrel and prasugrel were nonsignificantly less at both 2 h post-LD and Day 29 MD in diabetic compared with nondiabetic patients. The addition of the clopidogrel active metabolite to the samples resulted in low levels of PRI. The investigators concluded that the mechanism of incomplete platelet inhibition in the clopidogrel poor-responder groups and in diabetic patients is lower levels of the active metabolite and not differences in P2Y$_{12}$ receptor function.

New in this report is the approach of dichotomizing the patients as poor responders or normal responders based on their platelet responsiveness in relation to cutoff values for 3 different expressions of platelet responsiveness using LTA, and 1 using the VASP assay, each of which has previously been reported to correlate with subsequent cardiovascular events. They show that the proportion of nonresponsive patients varies with the different tests, but is consistently less with prasugrel than with clopidogrel. They also show that the levels of active metabolite are lower in the patients categorized as poor responders, and that almost complete platelet suppression can be achieved by the addition of the metabolite to the samples.

This exercise moves us closer to the possibility of a laboratory test that might predict poor clinical responses and prompt changes in therapy in those patients found to be poor responders. However, LTA and the VASP assay are currently research tests with inherent challenges of quality control, high cost, and long turnaround times. Furthermore, although the mean levels of platelet responsiveness in the poor responders group are higher than in the normal subjects, there is extensive overlap, so that appropriate clinical interventions would be unclear unless the groups could be more sharply distinguished, as is possible, for instance, with use of the international normalized ratio in monitoring warfarin therapy. The proportion of patients identified as poor responders was highest when defined as RPA $>14\%$ and progressively lower when defined as PRI $>50\%$, MPA $>50\%$, and $\Delta$MPA $<10\%$. It is likely that the sensitivity for prediction of a patient with a future cardiovascular event is highest in the first group, but that the positive predictive rate will be low, as was determined by Frere et al. (4). Calculation of the receiver-operator characteristic curves of each test would be necessary to establish clinically useful cutoff values (4,14). If these issues can be successfully addressed, clinical trials of various management strategies incorporating assessments of platelet inhibition will be required to sort out the options for patients found to have clopidogrel resistance (e.g., GRAVITAS [Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety] [15]). Complex, expensive, and time-consuming assessments of platelet reactivity or of levels of the clopidogrel active metabolite may be obviated by newer therapies with less response variability than clopidogrel. Prasugrel seems to have a much more favorable pharmacokinetic profile than clopidogrel, with fewer nonresponsive patients (12,16), and new agents such as AZD6140 and cangrelor directly target the P2Y$_{12}$ receptor and are reversible (17). However, the challenges to optimizing the benefits (fewer CV events) and risks (more bleeding) of more potent platelet inhibition should not be minimized.

It is already known that diabetic patients have higher rates of vascular events and are less responsive to aspirin and clopidogrel than nondiabetic patients (18). Erlinge et al. (13) suggest that the poor responsiveness to clopidogrel may at least in part be the result of relatively less generation of the active metabolite in diabetic than in nondiabetic patients, perhaps as a result of increased esterase activity, reduced gastric motility, or alterations at the megakaryocyte level. However, their observations in diabetic patients must be regarded with caution because there was no prior hypothesis that there would be an excess of poor responders among diabetic patients or that they would have lower levels of the active metabolite. The numbers of diabetic patients were small, and these preliminary findings require confirmation.

The study by Erlinge et al. (13) contributes useful insights into the mechanisms and laboratory diagnosis of clopidogrel resistance, but many important issues remain unresolved. The complexity of the issues reinforces the recommendation in current guidelines that platelet function assessments be confined to research studies (1,19), while highlighting the promise of new antiplatelet therapies that may circumvent some of the therapeutic limitations of clopidogrel.

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