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EDITORIAL COMMENT

Acceptance of High Platelet Reactivity as a Risk Factor

Now, What Do We Do About It?*

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A lot of ground has been covered since the demonstration of clopidogrel response variability that initially questioned the rationale of a "one-size-fits-all" antiplatelet strategy to treat percutaneous coronary intervention (PCI)/acute coronary syndrome patients (1). Experiments modulating cytochrome P450 enzyme activity demonstrated the important relation of the latter to the pharmacodynamic effect of clopidogrel (2). Likewise, single nucleotide polymorphisms of a cytochrome P450 (CYP) gene encoding a key enzyme in the metabolic activation of clopidogrel have been associated with pharmacokinetic and pharmacodynamic responses to clopidogrel (3,4). High clopidogrel loading doses or repetitive loads have been effective in enhancing the pharmacodynamic response (5,6). Recently, the aforementioned findings have gained interest after their clinical relevance was exposed by the explosion of data demonstrating the link between ex vivo measurements of platelet reactivity to adenosine diphosphate (ADP) and post-PCI ischemic event occurrence (7). Intriguingly, it seems that risk grows significantly after a threshold of platelet reactivity (high on-treatment platelet reactivity [HPR] to ADP) is exceeded. Indeed, HPR is now achieving status as a major risk factor for the PCI patient (8). The threshold idea has big implications for personalized antiplatelet therapy and is used in the study by Barker et al. (9) in this issue of *JACC: Cardiovascular Interventions*; the VerifyNow assay is employed to measure platelet reactivity, and the cut point is based on a previous investigation (10). The therapeutic goal is to get platelet reactivity below the threshold to minimize ischemic risk but, to avoid bleeding, not drive it too low (7).

See page 1001

Importantly, the antiplatelet effect of clopidogrel is beholden to multiple influences. The primary explanation for response variability and HPR is variable and limited clopidogrel active metabolite generation by hepatic CYP enzymes, respectively. Active metabolite formation is influenced by interactions with proton pump inhibitors, statins, calcium channel blockers, smoking, St. John's wort, and r-warfarin and single nucleotide polymorphisms of the genes encoding the CYP isoenzymes. In addition, diabetes, body mass index, and disease acuity influence platelet reactivity (11). The unpredictable antiplatelet effect of clopidogrel and the HPR-ischemic risk link have provided a solid foundation for 2 important developments: 1) new $P2Y_{12}$ receptor blockers that have more rapid, potent, and predictable pharmacodynamic effects; and 2) personalized antiplatelet therapy based on ex vivo assays.

Recently, the Food and Drug Administration issued a "boxed warning" highlighting the relation of the *CYP2C19* pathway to clopidogrel active metabolite generation. The relation between poor clopidogrel metabolizers defined by genetic testing (loss-of-function [LOF] homozygotes) and increased risk was highlighted (12). The warning implied that poor metabolizers should be identified and treated with "alternative treatment or treatment strategies." Thus, the work of Barker et al. is timely. Although it is believed that the LOF allele confers its clinical risk by affecting the pharmacodynamic response to clopidogrel, no study has demonstrated a conclusive link between the presence of an LOF allele, suboptimal clopidogrel active metabolite generation (pharmacokinetic measurement), decreased clopidogrel responsiveness (pharmacodynamic measurement), and adverse clinical outcomes (Fig. 1). In line with the Food and Drug Administration warning, some have urged immediate and widespread implementation of genotyping alone to personalize antiplatelet therapy, whereas others have urged a more cautious approach, because the safety and efficacy of altering therapy in response to genetic testing is entirely unknown as recognized in an American College of Cardiology Foundation/American Heart Association Clinical Alert (11,13,14).

The work of Barker et al. (9) is relevant to 2 major questions of the interventional cardiologist: 1) When should platelet function testing and/or genotyping be performed? 2) How well does 150 mg/day clopidogrel overcome HPR? They treated 41 coronary artery disease patients with HPR on 75 mg/day clopidogrel with 150 mg/day for 7 days. It is unclear how patients were recruited and how many were screened. Patients were genotyped for *CYP2C19* LOF and gain-of-function alleles. "One-half" describes the pharmacodynamic and genetic messages of this study: 1) one-half had at least 1 LOF allele; 2) one-half had HPR overcome by high-dose clopidogrel; and 3) one-half carrying an LOF

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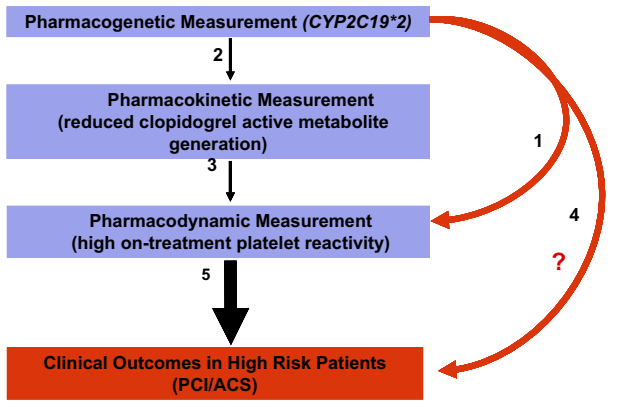

Figure 1. Relation of Pharmacogenetic, Pharmacokinetic, and Pharmacodynamic Measurements and Clinical Outcomes in Patients Treated With Clopidogrel

Studies have independently correlated: 1) pharmacogenetic measurements (PG) to pharmacodynamic measurements (PD); 2) PG to pharmacokinetic measurements (PK); 3) PK to PD; 4) PG to clinical outcomes; and 5) PD to clinical outcomes. A definitive link between PG, PK, and PD and clinical outcomes has never been examined in a single large-scale prospective study. The '?' addresses whether there could be other effects of loss-of-function allele on outcomes independent of effects of clopidogrel metabolism. ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

allele had HPR overcome by high-dose clopidogrel. These data are consistent with previous observations where the sensitivity of *2 carrier status in predicting HPR was approximately 50% (15,16). Interestingly, in the current study 15% were ultra-rapid metabolizers and, on the basis of genotyping, would not be expected to have HPR. Although the authors conclude that LOF carriage does not have a major influence on dose effect, the number of patients studied makes their conclusion tenuous.

On the basis of the current study, LOF carrier state is neither a robust surrogate for HPR nor a marker to predict the pharmacodynamic response to double-dose clopidogrel maintenance therapy in patients with HPR (9). If one chose to personalize antiplatelet therapy on the basis of genotype, many patients with HPR would be missed. Except for perhaps *2 homozygotes, genotype cannot predict response to high-dose clopidogrel. On the basis of Barker's data, the answer to question number 1 would be that genotyping plays a limited role diagnostically in choosing therapy for patients already receiving clopidogrel. Its role in clopidogrel-naive patients remains unexplored.

Regarding question number 2: in addition to strategies involving high-dose clopidogrel, new $P2Y_{12}$ inhibitors (prasugrel, ticagrelor, and elinogrel) overcome HPR. High-loading-dose clopidogrel is a better strategy to inhibit platelets than standard dose (5). However, in a recent study of coronary artery disease patients, approximately 35% exhibited HPR on the basis of the VerifyNow threshold despite a high loading dose (17). These data and the current study data indicate that high loading or maintenance doses might not be an effective strategy to overcome HPR in many patients. However, another study reported that repeated 600-mg loading (up to 2,400 mg) can overcome HPR in 86% of patients and lower 1-month post-PCI ischemic risk (6). In addition, treating HPR patients undergoing PCI with a glycoprotein IIb/IIIa inhibitor has been associated with lower periprocedural ischemic risk (18). Also, the addition of cilostazol enhanced platelet inhibition (19). Finally, the direct-acting $P2Y_{12}$ inhibitors ticagrelor and elinogrel seem very effective in overcoming HPR, irrespective of genotype (approximately 100% of patients with HPR receiving standard clopidogrel therapy are below the threshold after switching to ticagrelor) (17,20). Thus, in the era of the new $P2Y_{12}$ inhibitors, genotyping to predict response to clopidogrel might become less relevant.

On the basis of the pilot work of Barker et al. (9) and others (21), it does not seem that genotype correlates well enough with phenotype to adequately predict clopidogrel responsiveness in the HPR patient; nor does it seem that high-maintenance-dose clopidogrel is the optimal remedy for HPR. However, the clinical efficacy of high-maintenance-dose clopidogrel in the HPR patient will be examined prospectively in the GRAVITAS (Gauging Responsiveness with A VerifyNow assay–Impact on Thrombosis and Safety) trial. The entire interventional community anxiously awaits the results of this important trial that will provide the best answer thus far to the second question.

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Key Words: clopidogrel ■ high platelet reactivity ■ loss-of-function allele.