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EDITORIAL COMMENT

Diabetes Mellitus and Clopidogrel Response Variability*

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Platelet $P2Y_{12}$-receptor antagonists reduce major adverse cardiovascular events after percutaneous coronary intervention (PCI) and in acute coronary syndrome (ACS) (1–4). Together with aspirin, they are the cornerstones of adjunctive medical therapy in these clinical settings. Current American College of Cardiology Foundation/American Heart Association guidelines provide a class I recommendation for all 3 oral $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, and ticagrelor) in patients with ACS treated with PCI, but without preference for a particular agent (5). It is well established that clopidogrel's antiplatelet effect varies considerably among individuals (6,7) and that patients with higher levels of on-treatment reactivity (OTR) are at higher risk of thrombotic events after PCI (8–10). It remains controversial whether high OTR is itself a modifiable risk factor (11–13). However, elucidation of the mechanisms of clopidogrel response variability is clinically relevant as it may provide insight into the reasons for treatment failure and inform selection of 1 of the 3 available oral $P2Y_{12}$ receptor antagonists in ACS patients.

Clopidogrel is a prodrug requiring hepatic conversion into an active metabolite (AM) to exert its antiplatelet effect (**Figure 1**). Approximately 85% of absorbed clopidogrel is hydrolyzed by carboxylesterase-1 to an inactive metabolite; therefore, only a fraction of the absorbed prodrug is available for biotransformation into the AM. This is thought to occur through a 2-step process mediated by the cytochrome P-450 (CYP) system. Clopidogrel is first oxidized to 2-oxo-clopidogrel, which is then hydrolyzed to a highly labile AM that forms a disulfide bond with the $P2Y_{12}$ receptor as platelets pass through the liver (14). The CYP2C19 isoenzyme of CYP450 is important for both steps. Common genetic polymorphisms that reduce CYP2C19 catalytic activity decrease circulating AM levels, reduce platelet inhibition, and increase the risk of ischemic events in clopidogrel-treated patients with ACS undergoing PCI (15). The pronounced effect of *CYP2C19* loss-of-function (LOF) allele carriage on AM levels and clinical outcomes in ACS has led the U.S. Food and Drug Administration to include this information within a boxed warning. Similarly, the U.S. Food and Drug Administration recommends avoiding concomitant use of the proton pump inhibitors omeprazole and esomeprazole because pharmacokinetic and pharmacodynamic studies have demonstrated that they influence CYP2C19 activity, reducing circulating clopidogrel AM levels and diminishing its antiplatelet effect (16,17). However, the etiology of clopidogrel response variability is multifactorial, as *CYP2C19* LOF allele carriage accounts for only 5% to 12% of the overall variability (18–20).

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Diabetes is another major risk factor for diminished clopidogrel response, independent of the *CYP2C19* genotype (18,19). To date, the etiology of this phenomenon has largely been attributed to systemic inflammation and insulin resistance, the latter leading to platelet $P2Y_{12}$ receptor signaling abnormalities (21). In this issue of the *Journal*, Angiolillo et al. (22) attempt to clarify the mechanism of clopidogrel response variability in the setting of diabetes in a small, yet elegant study of 60 diabetic and nondiabetic subjects with stable coronary disease. They use a battery of platelet function tests to

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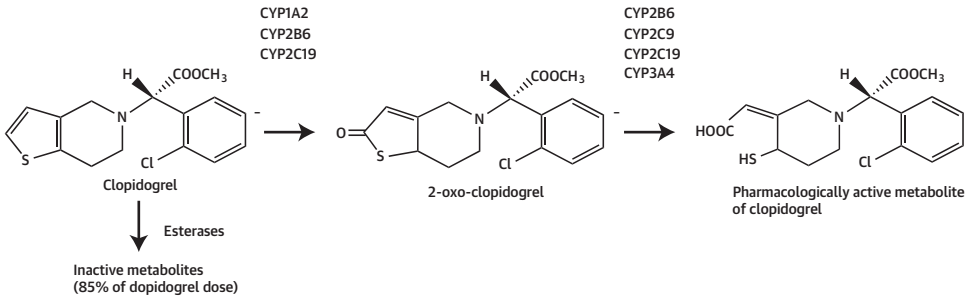

FIGURE 1 Biotransformation of Clopidogrel Into Its AM

Clopidogrel is a prodrug that requires conversion into an active metabolite (AM) to inhibit the platelet $P2Y_{12}$ receptor. According to a widely accepted model, clopidogrel is converted in a 2-step process mediated by cytochrome (CYP) P-450, with the CYP2C19 isoenzyme involved in both steps. A substantial portion of absorbed clopidogrel is shunted into a dead-end pathway by human carboxylesterase-1. Adapted with permission from Giusti and Abbate (29).

confirm that, after a 600-mg loading dose of clopidogrel, diabetic subjects have higher OTR levels than nondiabetic subjects, consistent with previous studies (18,19). After clopidogrel loading, the peak AM concentration in diabetics was roughly half that of nondiabetic subjects. Similarly, the area under the concentration-time curve (AUC), representing the average AM concentration over the time period measured, was ~60% lower in the diabetic group. To put this in perspective, *CYP2C19* LOF allele carriage has been associated with an approximate 30% reduction in the clopidogrel AM AUC in healthy volunteers (23), and coadministration of clopidogrel and omeprazole results in roughly a 40% reduction (24). Ex vivo platelet inhibition induced by escalating clopidogrel AM doses did not appear to differ greatly between the diabetic and nondiabetic patients, implying that differences in $P2Y_{12}$ receptor signaling was not a major driver of the diminished antiplatelet effect of clopidogrel loading observed in the diabetic subjects. Observations from subjects with stable coronary artery disease must be cautiously applied to ACS patients, and *CYP2C19* genotyping of the study population was not performed. Furthermore, the reason why circulating clopidogrel AM levels appear reduced in diabetic patients remains unknown. These shortcomings, however, do not undermine the key finding of this study: the impaired antiplatelet effect of clopidogrel among diabetics is mostly due to the lack of active drug rather than an inherent problem with their platelets.

This take-away message has substantial implications for the care of diabetic patients with unstable coronary artery disease, whom are at particularly high risk of recurrent cardiovascular events after ACS and stent thrombosis after PCI. Although the efficacy of point-of-care platelet reactivity or genetic testing to guide antiplatelet therapy has not yet been demonstrated (13), and there are no data linking specific clopidogrel AM levels with clinical outcomes, pharmacokinetic studies form the basis for identifying important drug-drug interactions that enable prescribers to avoid concomitant drugs that may increase adverse effects (by increasing AM levels) or diminish the desired effect (by decreasing AM levels). Angiolillo et al. have defined a similar "drug-patient" interaction between clopidogrel and diabetes, and their findings should similarly inform medical decision making. Ticagrelor is a direct-acting agent that does not require biotransformation into an AM to exert its antiplatelet effect (25), and diabetic status had no significant influence on prasugrel AM levels according to a pharmacokinetic study of >1,100 ACS patients (26). In TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38), prasugrel tended to provide a greater reduction in ischemic events than clopidogrel in diabetic patients compared with nondiabetic patients with ACS undergoing PCI (27). In PLATO (PLATelet inhibition and patient Outcomes), irrespective of diabetic status, there was a consistent benefit with ticagrelor over clopidogrel, including reduced mortality (28). Although these studies were not designed or powered to demonstrate the efficacy of ticagrelor or prasugrel in the diabetic subgroup alone, the drug-patient interaction observed by Angiolillo et al.