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EDITORIAL COMMENT

Optimizing Platelet Inhibition in Clopidogrel Poor Metabolizers

Therapeutic Options and Practical Considerations*

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Dual antiplatelet therapy with aspirin and clopidogrel represents the standard of care for the prevention of recurrent ischemic events in patients undergoing percutaneous coronary intervention with stent placement. However, some patients have impaired clopidogrel response and thus persist with high on-treatment platelet reactivity (HOPR), resulting in an increased risk of atherothrombotic events (1). This can be attributed to several factors, such as genetic polymorphisms regulating the activity of the cytochrome P450 (CYP) 2C19 enzyme, which is key in metabolizing clopidogrel into its active metabolite (2,3).

See pages 381, 392, and 403

The boxed warning recently added to the clopidogrel label underscoring the potential risk of adverse cardiovascular outcomes among patients with a "poor metabolizer" genotype (defined as subjects with 2 loss-of-function [LOF] alleles) and advocating the use of other antiplatelet medications or alternative dosing strategies for these subjects (4), has led to investigations of treatment options associated with more optimal platelet inhibition. These include increasing clopidogrel dosing, adding a third antiplatelet agent (e.g., cilostazol), and switching to a novel generation $P2Y_{12}$ inhibitor (e.g., prasugrel, ticagrelor, cangrelor) (Fig. 1). In this issue of *JACC: Cardiovascular Interventions*, the results of 3 independent investigations assessing these strategies among patients more prone to poorly metabolize clopidogrel based on the presence of *CYP2C19* LOF alleles are reported and provide important insights on this ever-rising clinical quandary (5–7).

The ability of clopidogrel loading-dose (LD) regimens to overcome "genetic resistance" was investigated by Collet et al. (5), who assessed in a prospective, crossover, randomized fashion, pharmacokinetic and pharmacodynamic (PD) responses to a standard (300-mg) versus a high (900-mg) LD of clopidogrel according to the carrier status of the *CYP2C19*2* LOF allele. The results of this study corroborate that carriers of *CYP2C19*2* have a reduced response to a standard LD with a gene-dose effect (wild-type [wt] homozygous > wt/*2 heterozygous > *2/*2 homozygous) and demonstrate that the use of a high LD regimen can overcome genetic resistance among heterozygous but not homozygous carriers of LOF alleles. The comprehensive pharmacokinetic assessments in this study correlate well with the PD findings and provide confirmatory data to support the inability of "poor metabolizers" to efficiently generate active metabolite despite high dosing of clopidogrel. Although these results provide insights into a treatment alternative to optimize platelet inhibition among heterozygous subjects, and clearly argue against a high LD strategy for homozygous LOF allele carriers, perplexity remains on the use of this treatment option. In fact, in addition to the lack of efficacy data, concerns emerge over the safety (liver toxicity) and practicality (long-term high LD regimens) of this strategy to overcome a fixed trait represented by our genetic patrimony for the treatment of a chronic illness process such as coronary artery disease. This emphasizes the need to define the ideal "maintenance" treatment regimen to optimize platelet inhibition among poor metabolizers.

Studies using a high (150-mg) maintenance dose (MD) of clopidogrel have been disappointing. In fact, investigations have shown that rates of HOPR remain elevated among *CYP2C19* LOF allele carriers, particularly homozygous patients, even with a high MD regimen (8,9). These findings have also been corroborated by the investigations from Kim et al. (6) and Alexopoulos et al. (7) reported in this issue of *JACC: Cardiovascular Interventions*. Further, these pharmacogenetic studies are in line with prior PD studies showing that high MD is associated with only modest antiplatelet effects (10,11). This may have also contributed to why high MD failed to improve outcomes in the GRAVITAS (Gauging Responsiveness With A VerifyNow Assay–Impact On Thrombosis And Safety) trial (11). Overall, the aforementioned findings from PD, pharmacogenetic, and clinical outcome studies argue against increasing clopidogrel dosing among poor metabolizers or patients with HOPR as a strategy to optimize platelet inhibition, and further emphasizes the need for alternative approaches.

Cilostazol is a phosphodiesterase-III inhibitor approved by the U.S. Food and Drug Administration for relief of

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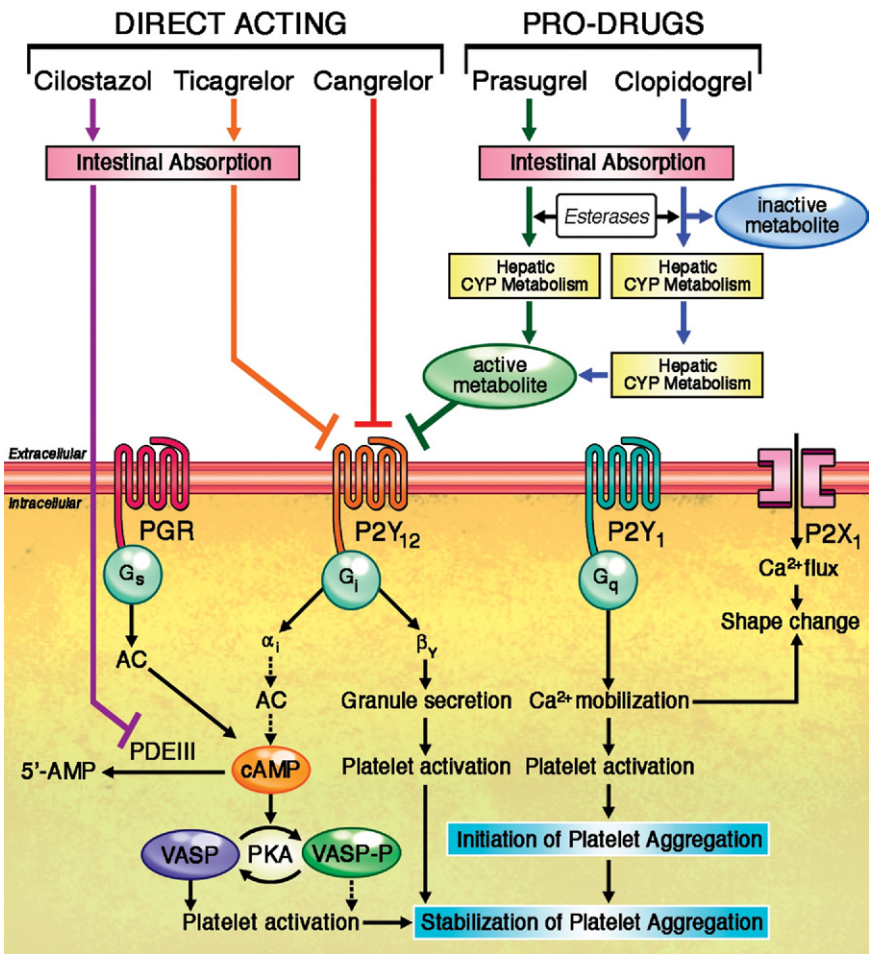

Figure 1. Therapeutic Options for Optimizing Platelet Inhibition in Clopidogrel Poor Metabolizers

Clopidogrel is a prodrug, which, after intestinal absorption, undergoes 2-step hepatic oxidation by cytochrome P450 (CYP) 2C19 enzymes (CYP3A, CYP2C9, CYP1A2 are involved in 1 step; CYP2B6, CYP2C19 are involved in both steps) to generate an active metabolite that inhibits platelet activation and aggregation processes through irreversible blockade of the $P2Y_{12}$ receptor. Approximately 85% of clopidogrel is hydrolyzed pre-hepatically by esterases into an inactive compound, thus, only 15% is available for hepatic metabolism. Genetic polymorphisms encoding for proteins/enzymes at various levels modulating clopidogrel metabolism can affect platelet inhibitory effects, intestinal absorption, P-glycoprotein (encoded by *ABCB1* gene), hepatic metabolism, CYP enzymes (particularly *CYP2C19* loss-of function alleles), and platelet membrane receptors (e.g., P2 receptors). Increasing the clopidogrel dose is not consistently associated with enhanced platelet inhibition in poor metabolizers, which may be achieved by other strategies. Prasugrel, like clopidogrel, is also an oral prodrug with a similar intestinal absorption process. However, in contrast to clopidogrel, esterases are part of prasugrel's activation pathway, and prasugrel is oxidized more efficiently to its active metabolite via a single CYP-dependent step. Direct-acting antiplatelet agents (cangrelor, ticagrelor, and cilostazol) have reversible effects and do not require hepatic metabolism for pharmacodynamic activity. Ticagrelor and cilostazol are administered orally and, after intestinal absorption, inhibit platelet activation by direct blockade of the $P2Y_{12}$ receptor and PDE-III, respectively. Cangrelor is administered intravenously, and directly inhibits the $P2Y_{12}$ receptor, bypassing intestinal absorption. Genetic polymorphisms of target proteins/enzymes (intestine, liver, and platelet membrane) modulating clopidogrel-mediated platelet inhibition do not affect the pharmacodynamic activity of prasugrel, cilostazol, ticagrelor, and cangrelor, which ultimately inhibit platelet activation and aggregation processes by modulating intraplatelet levels of cAMP and VASP-P. **Solid black arrows** indicate activation. **Dotted black arrows** indicate inhibition.
AC = adenylyl cyclase; ADP = adenosine diphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PDE-III = phosphodiesterase III (PDEIII); PGE_1 = prostaglandin E1; PKA = protein kinases; VASP-P = phosphorylation of vasodilator-stimulated phosphoprotein.

peripheral vascular disease symptoms. Cilostazol has pleiotropic effects; it exerts its mechanism of action, not only on platelets, but also on smooth muscle and endothelial cells (12). Numerous studies have shown that adjunctive cilostazol therapy, referred to as "triple antiplatelet therapy," enhances platelet inhibition and reduces rates of HOPR compared with dual antiplatelet therapy, even when high clopidogrel MD is used (13–15). Overall, these findings may explain why triple antiplatelet therapy has been associated with better clinical outcomes compared with dual antiplatelet therapy, particularly in high-risk settings, although this has not been confirmed in more recent investigations (16). Kim et al. (6) expand our understanding on the PD effects of adjunctive cilostazol

therapy according to the carrier status of LOF alleles of *CYP2C19* in patients undergoing primary percutaneous coronary intervention. In particular, triple antiplatelet therapy was associated with significant changes in PD measures as well as rates of HOPR compared with high clopidogrel MD among LOF allele carriers. However, changes in PD measures as well as rates of HOPR were not statistically different among noncarriers of LOF alleles. Overall, these findings are in line with recently reported results (17) and suggest that triple antiplatelet therapy may be a better option compared with high MD clopidogrel to achieve greater platelet inhibitory effects and reduce rates of HOPR only among carriers of LOF alleles of the *CYP2C19* gene. Unlike other investigations in this study, pre-discharge values of platelet reactivity were similar between noncarriers and carriers of LOF alleles, which might be explained by the small sample size or variability in PD measures associated with genetic testing. Although no patient discontinued cilostazol therapy in the present study, cilostazol is associated with a high rate of nonbleeding side effects (e.g., headache, tachycardia, palpitations, gastrointestinal disturbances), which is known to be associated with elevated (15% to 20%) rates of treatment discontinuation (13). Further, it should be kept in mind that the increase in heart rate associated with cilostazol therapy, and its contraindications in the presence of a low ejection fraction, limit the use of this drug among patients with an acute coronary syndrome or congestive heart failure.

Novel $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, are characterized by more potent antiplatelet effects and reduce recurrent ischemic event rates compared with clopidogrel among acute coronary syndrome patients (18). Notably, the effects of these agents are not attenuated by factors interfering with *CYP2C19* activity such as genetic polymorphisms or other drugs (e.g., omeprazole) (19). Therefore, these may be attractive alternatives for patients with "resistance" defined by genetic or platelet function testing. In their prospective, randomized, crossover investigation, Alexopoulos et al. (7) assessed the PD effects of prasugrel (10 mg/day) versus high-MD clopidogrel (150 mg/day) in patients with HOPR. These patients were also stratified according to *CYP2C19*2* carrier status. The study showed prasugrel to be more effective compared with high clopidogrel MD in reducing platelet reactivity and rates of HOPR, irrespective of genetic background, although this was more pronounced among LOF allele carriers. These data are consistent with that reported in a case series showing that only prasugrel, and not escalating doses of clopidogrel, was able to enhance platelet inhibition in patients with "clinical resistance" to clopidogrel presenting as stent thrombosis (20). Although switching to prasugrel therapy does not raise any concerns on PD interactions (21), and thus remains an attractive solution to treat patients with HOPR or poor clopidogrel metabolizers, it should be pointed out that novel $P2Y_{12}$ receptor antagonists are associated with an increased risk of spontaneous bleeding (18). Importantly, bleeding has emerged as an important predictor of poor long-term outcomes, including increased mortality, and therefore the potential benefits associated in terms of reduction of ischemic events need to be kept in perspective with known bleeding complications (22). In contrast to the novel $P2Y_{12}$ receptor antagonists, studies with cilostazol have not shown an increase in bleeding. This is likely attributable to the specific pharmacological properties of cilostazol (12), and making it an option for patients in whom greater platelet inhibition is required, particularly if bleeding is a concern or if novel $P2Y_{12}$ inhibitors are contraindicated.

Ultimately, it is important to highlight that the boxed warning on *CYP2C19* genotypes allude to subjects who have 2 LOF alleles ("poor metabolizers"), which occurs in 2% to 14% of the population, depending on racial background (4). The prevalence of LOF alleles is higher in Asian populations. Accordingly, 61% of patients in the study from Kim et al. (6) were carriers of LOF alleles, and 15% were poor clopidogrel metabolizers. However, analyses were only performed according to carrier status of LOF alleles, mostly represented by heterozygous or "intermediate metabolizers," and therefore, the impact of cilostazol on poor metabolizers in this study population remains elusive. On the contrary, Alexopoulos et al. (7) did not find any patient in their study with a poor metabolizer genotype. Therefore, the impact of prasugrel from this study cohort cannot be extrapolated, although prior investigations have shown that prasugrel can enhance platelet inhibition in these patients whereas high LD clopidogrel cannot (5,20). It is important to appreciate that although the prevalence of only 1 LOF allele ("intermediate metabolizers") is more common (30% to 60%, depending on racial background) and has also been independently associated with atherothrombotic events (23), this genotype is associated with a broad spectrum of response profiles to clopidogrel. As a result, PD measures among intermediate metabolizers overlap considerably with those of other genotypes (ultra, extensive, and poor metabolizers) (24). This is in line with the fact that *CYP2C19* genotypes contribute only in part to the PD effects of clopidogrel, and numerous other genetic, clinical, and cellular factors are determinants of platelet reactivity (Fig. 1) (2). Because of this, it is questionable whether individualizing antiplatelet therapy should be based on genetic testing, platelet function testing, or both (25). Indeed, the seminal investigations reported in this issue represent a step forward in answering some important questions. However, the results of ongoing large-scale outcome studies, which are evaluating the safety and efficacy of individualizing antiplatelet treatment strategies, are needed before its routine application can make its way into clinical practice (1,4).

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