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EDITORIAL COMMENT

Pharmacogenomic Testing to Select Antiplatelet Therapy*

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Clopidogrel, in combination with aspirin, reduces major adverse cardiovascular events (MACE) in patients with acute coronary syndromes (ACS) managed medically or with percutaneous coronary intervention (PCI) (1). Despite this, clopidogrel possesses several pharmacodynamic characteristics that may limit the clinical benefit that it can provide: its onset of action, even with a loading dose, is relatively slow; the extent of its antiplatelet effect varies substantially among individuals; and, on average, the magnitude of its antiplatelet effect is modest (2). These pharmacodynamic limitations are likely responsible in large part for the superiority of prasugrel over clopidogrel in preventing MACE in patients with ACS undergoing PCI (3) and of ticagrelor over clopidogrel in reducing MACE in patients with ACS treated with revascularization or medical therapy (4). In addition, in the latter case, off-target effects through ticagrelor-induced inhibition of equilibrative nucleoside transporter 1 may also be responsible for the observed benefits, including a reduction in cardiovascular mortality (5). The clinical advantages of prasugrel and ticagrelor, however, do not come without a cost. Both ticagrelor and prasugrel increase the rate of major bleeding at 1 year by approximately 0.5% (albeit, without an increase in fatal bleeding with ticagrelor); prasugrel has several relative and absolute contraindications; ticagrelor is associated with drug-related adverse effects, including dyspnea and bradycardia; and ticagrelor is costly to patients and health care systems compared with clopidogrel or prasugrel, which are both available in generic formulations. Therefore, it might be of value to identify patients who would have good outcomes with clopidogrel while having only limited benefit, or even net harm, with more intensive $P2Y_{12}$ inhibition.

Platelet function testing (PFT) to guide antiplatelet selection has been proposed as one such alternative to the indiscriminate use of the more potent $P2Y_{12}$ antagonists (6,7). High platelet reactivity (HPR) on clopidogrel (i.e., a diminished antiplatelet effect) is associated with a higher risk of MACE post-PCI, whereas very low levels of on-clopidogrel platelet reactivity seem to be associated with bleeding events (8,9). However, results of randomized clinical trials of PFT-guided therapy to reduce ischemic events have been mostly negative to date, possibly due to the low-risk populations studied (10,11), suboptimal antiplatelet strategies among patients with HPR (10,12), or simply because HPR is not a modifiable risk factor for post-PCI cardiovascular events (13). TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet for Acute Coronary Syndromes) showed that a strategy of guided de-escalation of antiplatelet treatment was

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noninferior to standard treatment with prasugrel at 1 year with respect to clinical benefit, although a large number of patients required resumption of prasugrel because of HPR after de-escalation (14).

Genetic polymorphisms are a major driver of an attenuated antiplatelet effect with clopidogrel, and pharmacogenomic guidance therefore represents another possible strategy to optimize antiplatelet therapy in patients with ACS (6). A loss-of-function (LOF) allele of the cytochrome P450 enzyme *CYP2C19* (denoted "*CYP2C19*2*"), which results in diminished production of the clopidogrel active metabolite, has been consistently identified as the primary genetic polymorphism influencing clopidogrel responsiveness, explaining approximately 10% to 12% of the observed variability in on-treatment reactivity (15). The antiplatelet effect and clinical outcomes of prasugrel and ticagrelor are not affected by this LOF allele (16,17). Other polymorphisms that may influence clopidogrel response and clinical outcomes include the "gain-of-function" allele, *CYP2C19*17*, which may result in an enhanced clopidogrel effect and an increased risk of bleeding, and polymorphisms of the *ABCB1* gene, which encodes the P-glycoprotein efflux transporter believed to mediate intestinal absorption of clopidogrel. However, data regarding the effect of *ABCB1* and *CYP2C19*17* on clopidogrel pharmacodynamics are inconsistent and have not been confirmed in studies that perform the appropriate statistical corrections for multiple comparisons across different genetic loci (15).

Pharmacogenomic testing is attractive because treatment decisions can be made before antiplatelet administration, unlike with PFT, and genotype does not change over time, unlike the phenotype of platelet reactivity (18). However, there are several disadvantages to this approach. First, clopidogrel response is also influenced by clinical characteristics, such as diabetes, body mass index, and renal function, as well as drug-drug interactions. Second, genotype does not necessarily dictate phenotype because patients who are heterozygous for the *CYP2C19*2* LOF allele may still display an adequate response to clopidogrel. Third, the turnaround time for result reporting must be rapid enough so that treatment decisions can be made as early as possible after presentation and preferably by the time of PCI, when most MACE events occur. Advances in genotyping technology have overcome this hurdle and should be considered a critical part of any pharmacogenomic approach in the acute setting.

In this issue of the *Journal,* Notarangelo et al. (19) present the results of PHARMCLO (Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes), a randomized trial of the safety and efficacy of an antiplatelet strategy that incorporated rapid pharmacogenomic testing compared with "standard-of-care" in patients with ACS. Patients randomly assigned to the intervention arm underwent rapid testing of several loci: the *CYP2C19*2* LOF allele; the *CYP219*17* gain-of-function allele; and the *ABCB1* genotype. $P2Y_{12}$ therapy (i.e., clopidogrel or prasugrel/ticagrelor) was then suggested based on the combination of alleles that were present, but the actual therapy that was given was at the discretion of the physician. Patients randomly assigned to the control arm were treated according to operator discretion alone. The primary endpoint was a composite of ischemic and bleeding events. The investigators planned to enroll a total of 3,612 patients, but prematurely halted the study after enrolling only 888 patients due to regulatory issues with the rapid genotyping platform in Italy. Most patients underwent angiography, and PCI was performed in 63% and surgical revascularization in 10%. Slightly more than one-half of the patients in the standard-of-care arm (50.7%) were treated with clopidogrel, compared with 43% of the pharmacogenomic arm; in contradistinction, fewer patients received ticagrelor in the standard-of-care arm compared with the pharmacogenomic arm (32.7% vs. 42.6%). At 12-month follow-up, the rate of the primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and Bleeding Academic Research Consortium type 3 to 5 bleeding) was significantly lower in the pharmacogenomic arm (15.9% vs. 25.9%; $p < 0.001$), driven primarily by a reduction in ischemic events. Stent thrombosis was exceedingly rare in either arm. The authors concluded that a personalized approach to the selection of antiplatelet therapy may lead to a clinically meaningful reduction in ischemic and bleeding outcomes.

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Importantly, the PHARMCLO study, in this issue of the *Journal*, shows that rapid genotyping can be successfully incorporated into the acute care of patients with ACS (19). Beyond this finding, however, the study raises more questions than answers. First, the standard-of-care arm was significantly undertreated according to current practice guidelines, even when considering the higher risk cohort studied. Second, the event rates in the standard-of-care arm were extraordinarily high. Third, the mechanistic basis of the findings is unclear. The pharmacogenomic decision-making scheme included polymorphisms whose relationships to clopidogrel-associated outcomes are ambiguous. Furthermore,