

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 P2Y₁₂ inhibition.

Platelet function testing (PFT) to guide antiplatelet selection has been proposed as one such alternative to the indiscriminate use of the more potent P2Y₁₂ 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

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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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. P2Y₁₂ 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 contrast, 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,

there was a risk reduction consistent with that of the overall study among the patients not treated with clopidogrel in the pharmacogenomic arm compared with similarly treated patients in the standard-of-care arm, a finding which cannot be readily explained. Finally, and foremost, the study was discontinued prematurely after only one-quarter of the planned study population was enrolled, and therefore the study is largely underpowered. Interrupted trials, particularly when small, often demonstrate large overestimates of effect size. These issues raise the specter of a type I error and hamper enthusiasm toward applying these findings to clinical practice.

So, what does the future hold for personalized antiplatelet therapy in ACS based on genotype or platelet reactivity testing? The challenge is to prove its worth in a world with ticagrelor and newer-generation drug-eluting stents. Ticagrelor is superior to clopidogrel, with reductions in cardiovascular mortality, with no increase in fatal bleeding. The treatment effect of ticagrelor compared with clopidogrel for ischemia or bleeding is consistent irrespective of *CYP2C19* or *ABCB1* genotype, albeit with a smaller absolute difference in ischemic outcomes in patients who are not carriers of a *CYP2C19* LOF allele (16). Whether a strategy of platelet function or pharmacogenomic testing to guide intensification of antiplatelet therapy from clopidogrel to ticagrelor would be noninferior to routine ticagrelor is a reasonable question. Indeed,

a recent study showed that post-PCI MACE rates were similar among clopidogrel-treated patients without a *CYP2C19* LOF allele and prasugrel- or ticagrelor-treated patients with a *CYP2C19* LOF allele (18). Unfortunately, the sample size that is required to conduct an adequately powered trial with an appropriate noninferiority margin is unreasonable.

For the foreseeable future, we will be left wanting for robust evidence to routinely add platelet function or pharmacogenomic testing to our ACS decision-making process at the time of clinical presentation beyond an evaluation of ischemic and bleeding risk. This situation does not mean, however, that pharmacogenomic testing and PFT are without utility. They can and should have an important role in risk stratification in specific clinical scenarios, including but not limited to antiplatelet de-escalation in the subacute or chronic phase in patients at higher risk for bleeding (14), timing of surgery after P2Y₁₂ inhibitor discontinuation (20), and in circumstances in which clopidogrel therapy in the acute setting is strongly preferred but not mandatory (18). For now, we will need to be precise in our application of precision medicine.

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REFERENCES

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
2. Price MJ, Coleman JL, Steinhilber SR, Wong GB, Cannon CP, Teirstein PS. Onset and offset of platelet inhibition after high-dose clopidogrel loading and standard daily therapy measured by a point-of-care assay in healthy volunteers. *Am J Cardiol* 2006;98:681-4.
3. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.
4. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
5. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol* 2014;63:2503-9.
6. Angiolillo DJ, Ferreiro JL, Price MJ, Kirtane AJ, Stone GW. Platelet function and genetic testing. *J Am Coll Cardiol* 2013;62:S21-31.
7. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y₁₂ receptor-inhibiting therapies. *Circulation* 2017;136:1955-75.
8. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2013;62:2261-73.
9. Price MJ, Angiolillo DJ, Teirstein PS, et al. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the gauging responsiveness with a VerifyNow P2Y₁₂ Assay: impact on Thrombosis and Safety (GRAVITAS) trial. *Circulation* 2011;124:1132-7.
10. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;305:1097-105.
11. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol* 2012;59:2159-64.
12. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100-9.
13. Stone GW, Witzensbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614-23.
14. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome

undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;390:1747-57.

15. Price MJ, Murray SS, Angiolillo DJ, et al. Influence of genetic polymorphisms on the effect of high- and standard-dose clopidogrel after percutaneous coronary intervention: the GIFT (Genotype Information and Functional Testing) study. *J Am Coll Cardiol* 2012;59:1928-37.

16. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary

syndromes: a genetic substudy of the PLATO trial. *Lancet* 2010;376:1320-8.

17. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* 2009;119:2553-60.

18. Cavallari LH, Lee CR, Beitelshes AL, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol Interv* 2018;11:181-91.

19. Notarangelo FM, Maglietta G, Bevilacqua P, et al. Pharmacogenomic approach to selecting

antiplatelet therapy in patients with acute coronary syndromes: PHARMCLO trial. *J Am Coll Cardiol* 2018;71:1869-77.

20. Price MJ, Baker BA, Jakubowski JA, Li W, Heiselman DE, Angiolillo DJ. Detecting a thienopyridine effect by platelet reactivity assessment and its implications for risk stratification. *J Thromb Haemost* 2014;12:560-3.

KEY WORDS acute coronary syndrome, antiplatelet therapy, clopidogrel, pharmacogenomics, platelet function testing, platelet reactivity, prasugrel, thienopyridine, ticagrelor