EDITORIAL

CYP2C19 Genotyping to Guide Antiplatelet Therapy After Percutaneous Coronary Interventions

One Size Rarely Fits All

David J. Moliterno, MD; Susan S. Smyth, MD, PhD; Ahmed Abdel-Latif, MD, PhD

Following percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) with aspirin and an inhibitor of the platelet adenosine diphosphate P2Y12 receptor (P2Y12) is standard care to reduce the occurrence of stent thrombosis and ischemic events. For many years, clopidogrel has been the most commonly used P2Y12 inhibitor for patients with an acute coronary syndrome (ACS) and those undergoing PCI. However, platelet function studies have revealed variability in the response to clopidogrel, with 20% to 40% of patients having persistent, high on-treatment platelet reactivity.[1] This attenuated pharmacodynamic response in some patients is partly explained by genetic variants of *CYP2C19*, the gene that encodes the CYP2C19 liver enzyme responsible for metabolizing clopidogrel (a prodrug) to its active form. Variants in the *CYP2C19* gene that reduce its activity (loss-of-function [LOF] variants) result in diminished activation of clopidogrel and reduced antiplatelet efficacy.

Related article page 761

Newer P2Y12 inhibitors, such as prasugrel and ticagrelor, do not require metabolic conversion and therefore are not influenced by *CYP2C19* variants. These newer drugs provide faster, more potent, and more consistent platelet inhibition, and several clinical studies have demonstrated that prasugrel[2] and ticagrelor[3] are more effective than clopidogrel in reducing ischemic events among patients with ACS undergoing PCI.[4] At the same time, these studies have revealed higher bleeding risks with prasugrel and ticagrelor, compared with clopidogrel.

The most functionally relevant LOF variant within *CYP2C19* is the **2* allele, which can be heterozygous, causing a reduction in clopidogrel metabolism, or homozygous, causing virtually complete absence of clopidogrel enzymatic conversion. Another variant allele, **3*, also contributes to a higher risk of clinical ischemic events with clopidogrel therapy, although present at a much lower frequency in the population than **2*. Gain-of-function alleles, such as **17*, and variants affecting intestinal absorption of clopidogrel (*ABCB1*) have also been shown to alter the platelet inhibition associated with clopidogrel. Clinical studies have shown the detrimental effects associated with these variants, including increased risk of coronary ischemic events among patients with LOF alleles and increased bleeding risk among those with gain-of-function alleles.[5,6]

Considering these genetic and biologic differences among patients, several genotype- and phenotype-guided approaches to optimize clopidogrel antiplatelet therapy have been tested using various laboratory and point-of-care assays. Observational studies and randomized trials in patients with ACS who underwent PCI have used genotype information to escalate antiplatelet therapy among poor clopidogrel metabolizers (carriers of LOF alleles) but with inconsistent reductions in ischemic events compared with standard practice.[7,8] Most recently, the POPular Genetics Trial[9] tested a genotype-guided approach among patients with ST-segment elevation myocardial infarction undergoing primary PCI. The experimental group assigned clopidogrel to those without a *CYP2C19* LOF allele and prasugrel or ticagrelor to LOF allele carriers. Genotype-guided treatment was comparable with standard treatment (all receiving prasugrel or ticagrelor) for ischemic events yet accomplished this with fewer bleeding events. On the basis of these studies, expert consensus statements acknowledged the utility of genotype-guided approaches in certain clinical scenarios but stopped short of endorsing their routine use.[1]

In this issue of *JAMA*, Pereira et al[10] report results from TAILOR-PCI, the largest randomized study to date to examine a clinical decision strategy that relies on *CYP2C19* genotyping (Spartan Rx, Spartan Bioscience) to guide antiplatelet drug assignment. The study included 5302 patients who underwent PCI, 2650 of whom were randomized to a conventional therapy group and received clopidogrel without initial genetic testing and 2652 of whom were randomized to a genotype-guided therapy group that received clopidogrel vs ticagrelor (or prasugrel) according to the absence or presence of a *CYP2C19* LOF allele, respectively. After 12 months, patients in the conventional therapy group had genotyping performed. Overall, the study found 1849 patients (35%) to carry a LOF allele, and these patients formed the final study cohort: 903 in the genotype-guided therapy group and 946 in the conventional therapy group. The primary end point (composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe myocardial ischemia at 12 months) was not statistically different between the genotype-guided therapy and conventional therapy groups (4.0% vs 5.9%, respectively; hazard ratio [HR], 0.66 [95% CI, 0.43-1.02]; $P = .06$), and there was no difference in the primary safety end point of major or minor bleeding (1.9% vs 1.6%, respectively; HR, 1.22 [95% CI, 0.60-2.51]; $P = .58$).

Does the neutral result from the TAILOR-PCI trial[10] portend the end of DAPT precision medicine and tailoring antiplatelet therapy according to *CYP2C19* variants? Despite

not achieving a statistically significant difference for the primary end point, this study provides many encouraging, hypothesis-generating findings. To begin, there was a 34% lower occurrence of major cardiovascular events with genotype-guided therapy. Moreover, a prespecified analysis that allowed inclusion of multiple end points per patient was statistically significant in favor of the genotype-based approach (HR, 0.60 [95% CI, 0.41-0.89]; *P* = .01). The consistency and durability of an effect of genotype guidance can be considered by reviewing the event curves for the treatment groups (Figure 2 in the report by Pereira et al[10]), which diverged very early after randomization and remained parallel for the remainder of the study. Post hoc analysis of the primary composite end point demonstrated a nearly 80% reduction with genotype guidance during the first 3 months (HR, 0.21 [95% CI, 0.08-0.54]; *P* = .001), but this effect was statistically lost during longer follow-up. This last observation is consistent with other studies that have suggested that shorter duration of DAPT could be optimal and that the majority of benefit with optimized antithrombotic drugs is realized in the first several months after PCI.[11]

Another important consideration is that this study was designed in 2012, before the widespread use of ticagrelor for patients with ACS, who comprised approximately 80% of the study population. This may be part of the reason why 15% of *CYP2C19* LOF carriers in the genotype-guided therapy group still received clopidogrel instead of ticagrelor. The subsequent years have also seen dynamic advances; coronary stents and stent delivery techniques have steadily improved, favorably reducing ischemic events. The TAILOR-PCI[10] results should be considered in the context of the large randomized trials[2,3] that established the benefit of prasugrel and ticagrelor compared with clopidogrel; how much of the observed benefit in these trials was exclusively derived from the *CYP2C19* LOF population is not certain but merits consideration.

The TAILOR-PCI trial[10] follows several similar studies that examined a genotype-based approach for selecting the optimal patient-specific antiplatelet agent after ACS or PCI. However, like prior studies, observed reduction in ischemic events appeared clinically meaningful, yet not statistically significant, and the number needed to treat for benefit remains relatively high. Accordingly, the important question is why has such a muted benefit been recurrently observed despite such a scientifically logical approach? It seems intuitive that escalating to more potent P2Y12 therapy for patients who are poor clopidogrel metabolizers and deescalating to clopidogrel for patients who are efficient metabolizers should optimize the effectiveness and safety of DAPT beyond a one-size-fits-all approach.

To consider the question, it is important to have a comprehensive view of current clinical practice. First, carrying the LOF alleles does not necessarily indicate inadequate platelet inhibition for a particular individual. The risk-benefit ratio of antithrombotic therapy depends on the intensity and duration of the therapy as well as the intensity and duration of the clinical condition. Second, advances in medical therapy, stent technology, and procedural techniques may have diminished the need for more intensive antithrombotic therapy, particularly beyond the first 3 months after PCI, when the rates of ischemic events are declining.[12] Third, while clopidogrel metabolism plays an undeniable part in the response to therapy and subsequently the rate of clinical events, other important epigenetic and patient-related factors have a larger role. Factors such as drug absorption, adherence to therapy, patient comorbidities, and coronary anatomical and interventional procedural factors account for the majority of ischemic events.

The utility of a personalized medicine approach as attempted by genotyping for drug response should not be abandoned in modern practice. Studies have shown that prasugrel and ticagrelor are associated with higher bleeding risk and are more expensive, prompting physicians to consider deescalation of antithrombotic therapy early after PCI.[13] In such patients, as well as those at higher risk of bleeding and those receiving triple antithrombotic therapy (ie, DAPT plus an oral anticoagulant, such as warfarin), a deescalation strategy could benefit from genotyping or platelet function testing to determine the optimal antiplatelet regimen. The broader question is how much the health care system should invest in integrating these strategies into daily practice and if the return on such an investment is clinically and financially rewarding. Clinicians and patients would argue that the clinical and financial cost of genotype testing would pale in comparison with the cost of an admission for stent thrombosis or a major bleeding complication.

The future is clearly pointing toward a personalized strategy for therapeutic interventions, and genotype-guided approaches should be part of this strategy—the question is how much. However, the clinical evidence at this critical moment of revamping the health care system does not support the routine use of personalized genotype-based selection of antiplatelet therapy for patients with coronary artery disease.

ARTICLE INFORMATION

Author Affiliations: Gill Heart Institute, Division of Cardiovascular Medicine, University of Kentucky, Lexington (Moliterno, Smyth, Abdel-Latif); Lexington VA Medical Center, Lexington, Kentucky (Moliterno, Smyth, Abdel-Latif).

Corresponding Author: David J. Moliterno, MD, Department of Internal Medicine, University of Kentucky, 900 S Limestone Ave, 329 Wethington Building, Lexington, KY 40536-0200 (Moliterno@uky.edu).

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2019;12(16):1521-1537. doi:10.1016/j.jcin.2019.03.034

2. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015. doi:10.1056/NEJMoa0706482

3. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327

4. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082-1115. doi:10.1016/j.jacc.2016.03.513

5. Price MJ, Berger PB, Teirstein PS, et al; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial [published correction appears in *JAMA*. 2011;305(21):2174]. *JAMA*. 2011;305(11):1097-1105. doi:10.1001/jama.2011.290

6. Simon T, Verstuyft C, Mary-Krause M, et al; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360(4):363-375. doi:10.1056/NEJMoa0808227

7. Cavallari LH, Lee CR, Beitelshees AL, et al; IGNITE Network. Multisite investigation of outcomes with implementation of *CYP2C19* genotype-guided antiplatelet therapy after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2018;11(2):181-191. doi:10.1016/j.jcin.2017.07.022

8. Collet JP, Hulot JS, Cuisset T, et al; ARCTIC Investigators. Genetic and platelet function testing of antiplatelet therapy for percutaneous coronary intervention: the ARCTIC-GENE study. *Eur J Clin Pharmacol*. 2015;71(11):1315-1324. doi:10.1007/s00228-015-1917-9

9. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. *N Engl J Med*. 2019;381(17):1621-1631. doi:10.1056/NEJMoa1907096

10. Pereira N, Farkou M, and Rihal C. Effect of genotype-guided oral $P2Y_{12}$ inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA*. Published August 25, 2020. doi:10.1001/jama.2020.12443

11. Ziada KM, Abdel-Latif AK, Charnigo R, Moliterno DJ. Safety of an abbreviated duration of dual antiplatelet therapy (≤6 months) following second-generation drug-eluting stents for coronary artery disease: a systematic review and meta-analysis of randomized trials. *Catheter Cardiovasc Interv*. 2016;87(4):722-732. doi:10.1002/ccd.26110

12. Moon JY, Franchi F, Rollini F, Angiolillo DJ. Evolution of coronary stent technology and implications for duration of dual antiplatelet therapy. *Prog Cardiovasc Dis*. 2018;60(4-5):478-490. doi:10.1016/j.pcad.2017.12.004

13. Sibbing D, Aradi D, Jacobshagen C, et al; TROPICAL-ACS Investigators. 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(10104):1747-1757. doi:10.1016/S0140-6736(17)32155-4

Serosurveillance and the COVID-19 Epidemic in the US
Undetected, Uncertain, and Out of Control

Tyler S. Brown, MD; Rochelle P. Walensky, MD, MPH

The true extent of the coronavirus disease 2019 (COVID-19) epidemic in the US is unknown. The 3.4 million confirmed cases reported (as of July 15, 2020) likely represent only a fraction of all the infections that have occurred in the US thus far. Limited laboratory capacity and restrictive testing guidelines early in the epidemic resulted in large numbers of undetected incident infections. Approximately 40% of all SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infections are thought to be asymptomatic,[1] and active surveillance for infections without symptoms is limited even now, nearly 5 months after the first COVID-19 cases were reported in Seattle[2] and Chicago.[3] The true cumulative incidence of infection—a basic but critically important measurement—remains uncertain at a time when communities nationwide are struggling to navigate an ongoing, unprecedented public health emergency, and while apprehensions about the near-term and long-term trajectories of the epidemic loom large.

Related article at jamainternalmedicine.com

The study by Havers et al,[4] published in *JAMA Internal Medicine*, reports the first multisite state- and city-level serosurveillance data on SARS-CoV-2 infection in the US; regions spanned from New York to Washington State and from Minnesota to Utah. In a cross-sectional study that tested residual sera from clinical blood samples that had been obtained for routine testing from March 23 through May 12, 2020, from 16 025 persons from 10 different sites across the country, the authors report estimates for the proportion of individuals with prior SARS-CoV-2 infection (adjusted for performance characteristics of serological testing) ranging between 1.0% in San Francisco and 6.9% in New York City. The estimated total number of infections (extrapolated from the measured proportion of individuals with positive SARS-CoV-2 serologies) was between 6- and 24-fold higher than the number of confirmed COVID-19 cases reported in each location prior to the study.

Responding to the urgent need for data tracking the extent of the COVID-19 epidemic, epidemiologists, medical researchers, and public health officials have in recent months advanced an array of research efforts seeking to measure the cumulative incidence of COVID-19 via serologic evidence of prior infection. These serosurveillance efforts, many implemented as rapid pilot studies using unstructured or convenience sampling strategies, have nonetheless yielded some important, early, and actionable findings.[5]

However, these studies are also challenging to interpret because of the limited reliability of some commercially available SARS-CoV-2 serology testing platforms[6] and the limitations inherent to convenience sampling.[7] Convenience sampling, although expedient and logistically less difficult than structured sampling, has numerous inherent biases, limiting generalizability. Virtually all of the early serologic studies have been narrow in scope, focused on specific geographic catchment areas[5] or local cohorts captured via unrestricted, "walk-up" enrollment.[8]

Havers et al[4] provide a substantial step forward in this rapidly changing landscape and an important reference point for contextualizing the profusion of SARS-CoV-2 serosurveillance studies anticipated in coming months. The authors comprehensively describe their data sources, including detailed maps on the geographic distribution of samples obtained in each study location and timelines comparing when sample collection occurred with respect to the epidemic trajectory in each location. This transparent approach provides important