Clopidogrel and the Reduced-Function CYP2C19 Genetic Variant: A Limited Piece of the Overall Therapeutic Puzzle

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http://jama.ama-assn.org/cgi/content/full/304/16/1839

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Effective platelet inhibition has become a cornerstone in the management of patients with acute coronary syndrome (ACS). The addition of clopidogrel to aspirin has provided significant reductions in major cardiovascular events in patients with ACS in general, and particularly among those treated invasively by percutaneous coronary intervention (PCI).1 Yet studies have demonstrated that the therapeutic response of clopidogrel is variable among patients,2 and low or incomplete platelet inhibition has been associated with increased risk for major adverse cardiovascular events.3

Multiple mechanisms have been proposed for the variable response to clopidogrel, including reduced drug bioavailability, patient nonadherence, drug-drug interactions (eg, proton pump inhibitors), ventricular dysfunction, dyslipidemia, and diabetes. More recently, genetic polymorphisms have been discovered in the hepatic cytochrome 2C19 enzyme (CYP2C19) that is partially responsible for the bioactivation of clopidogrel (a prodrug).4 Initial studies have determined that carriers of the allelic variant (CYP2C19*2) have significantly lower levels of the active clopidogrel metabolite, diminished platelet inhibition, and higher rates of cardiovascular events, including stent thrombosis, compared with noncarriers.5 Since these initial discoveries, multiple cohort studies have further linked the CYP2C19*2 and other loss-of-function allelic variants of this gene to major adverse cardiovascular events in patients taking clopidogrel.6-8

In March 2010, the US Food and Drug Administration approved a new label for clopidogrel with a “boxed warning” describing the diminished effectiveness of the standard drug dosing in individuals with impaired metabolic function (so-called poor metabolizers) based on their CYP2C19 genotype.6-8 The warning also notes that tests are available to identify patients with genetic polymorphisms and that alternative treatment strategies, either higher clopidogrel dosing regimen or the use of other antiplatelet agents, should be considered in those patients. The decision to perform CYP2C19 genetic testing and to adopt a therapeutic strategy is left to the clinician, leaving uncertainty on how such a warning should translate into clinical practice. Based on the most recent information, 4 critical issues require careful attention.

First, CYP219*2 and CYP2C19*3 are reduced-function alleles and account for the majority of the reduced function in poor metabolizers. The boxed warning distinguishes 2 groups of patients, those with impaired CYP2C19 function or poor metabolizers (homozygous *2/*2, *3/*3 or heterozygous *2/*3) and those with normal CYP2C19 function, but does not address patients with intermediate CYP2C19 function (eg, heterozygous *1/*2).6 In line with this 3-variant model (poor, intermediate, and normal metabolizers), in this issue of JAMA, Mega and colleagues3 address the relative clinical importance of the “genetic load” of this hazard allele. By retrospectively analyzing 9685 patients with ACS or undergoing PCI through a collaborative meta-analysis of individual data from 9 clopidogrel pharmacogenetic studies, they found a significantly increased risk of the composite end point of cardiovascular death, myocardial infarction, or stroke in both carriers of 1 and 2 reduced-function alleles (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.11-1.97; P = .01 and HR, 1.76; 95% CI, 1.24-2.50; P = .002), respectively. Given that approximately 30% of the study populations were carriers of at least 1 loss-of-function allele (2.2% had 2 loss-of-function alleles [homozygous, impaired-function group]) and 26.3% had 1 reduced-function allele (heterozygous, intermediate-function group), this study confirms that the prevalence of reduced-function alleles might not be as insignificant as previously thought.

Second, to date, the strongest association found between the carrier status of CYP2C19 genotype and adverse cardiovascular outcomes appears to be reserved for those patients with ACS undergoing PCI with stenting and within the first month postprocedure. In the TRITON-TIMI 38 trial, 13 608 patients with moderate- to high-risk acute coronary syndromes undergoing PCI were randomly assigned to receive prasugrel or clopidogrel and almost half (47%) received at least 1 drug-eluting stent.12 The recently published pharmacogenetic analysis of TRITON-TIMI 38 showed that among the group, when both CYP2C19 and ABCB1 (gene encoding P-glycoprotein...
tein) allelic variants were taken into account, approximately half (47%) of the population carried a genotype associated with increased risk of major cardiovascular events while taking clopidogrel.\textsuperscript{13} The effect of the loss-of-function allele on the clinical event outcome in patients treated with clopidogrel was 1.7 times greater than the risk among carriers vs non-carriers, with the greatest effect being stent thrombosis (2.6% vs 0.8%; HR, 3.09; \(P = .02\)), which largely occurred in the first week after starting clopidogrel treatment following the stent procedure.\textsuperscript{5} Similarly, the genetic substudy of the PLATO trial investigating clopidogrel vs ticagrelor in ACS involving a 61% PCI rate, showed in the clopidogrel-treated group, higher 30-day event rates, particularly stent thrombosis, among patients with any loss-of-function allele compared with those having no loss-of-function allele.\textsuperscript{14} The hazard of carrying the CYP2C19\textsuperscript{*2} allele among patients undergoing PCI for ACS, particularly stent thrombosis, is further supported in the current meta-analysis reported by Mega et al.\textsuperscript{11}

In contrast to these findings, however, the recently published large-scale analysis of 2 randomized trials, CURE in ACS and ACTIVE A in Atrial Fibrillation, indicated that the primary outcome was similar in carriers of the CYP2C19\textsuperscript{*2} loss-of-function alleles, as was seen in noncarriers.\textsuperscript{14,15} A reasonable explanation for this finding is the lower use of PCI with stenting in the CURE trial (14.5%) and the relatively lower-risk population enrolled in the ACTIVE A study (non-ACS and non-PCI/stenting). However, because a large proportion of patients in the meta-analysis of Mega et al\textsuperscript{11} underwent PCI with stenting in ACS, it remains to be determined whether the risks of CYP2C19\textsuperscript{*2} genetic testing can be generalized to non-ACS, or nonstented patients with chronic disease.

Third, it is uncertain whether these new findings in high-risk patients actually support the use of CYP2C19\textsuperscript{*2} genetic testing. Based on previous published studies, the positive predictive value of CYP2C19 reduced-function genetic testing is low, estimated to be between 12% and 20% in ACS patients undergoing PCI.\textsuperscript{16} These prior results are consistent with those reported in the meta-analysis by Mega et al.\textsuperscript{11} A large proportion of CYP2C19\textsuperscript{*2} carriers will not develop a future cardiovascular event and, therefore, the value of such genetic information is relative because multiple mechanisms beyond the CYP2C19\textsuperscript{*2} allelic variant will influence platelet reactivity. To date, as many as 25 polymorphic variants of the CYP2C19 gene have been identified, as well as other genes such as ABCB1 and CYP3A4, and can affect platelet response to clopidogrel in addition to multiple nongenetic factors noted previously.

Fourth, other therapeutic options, such as alternative clopidogrel dosing regimens or new platelet P2Y\textsubscript{12} ADP receptor blockers such as prasugrel and ticagrelor (respectively less dependent and independent of the CYP2C19 enzyme), have been developed in recent years, and have the potential to optimize platelet inhibition in these “poor metabolizer” patients. Additionally, data supporting the strategy of platelet reactivity testing as a way to identify patients who may be at risk for recurrent cardiovascular events, as well as guiding anti-platelet therapy after PCI, is limited but is the subject of ongoing large-scale clinical trials (GRAVITAS and ARCTIC).

In conclusion, in patients treated with clopidogrel, the best genome-guided strategy remains to be determined. The information obtained by CYP2C19 genetic testing may be particularly useful in patients at risk of poor outcomes, either because they have already had an adverse event (eg, stent thrombosis) or other at-risk characteristics such as diabetes mellitus, chronic renal failure, or angiographic high-risk features. Three ongoing studies (Genotyping Infarct patients to Adjust and Normalize Thienopyridine treatment [GIANT]; ClinicalTrials.gov identifier, NCT01134380), Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study (NCT00995514), and Thrombocyte Activity Reassessment and Genotyping for PCI (TARGET-PCI [NCT01177592]) are currently under way to find the best genome-guided strategy for these higher-risk patients. In the meantime, clopidogrel and CYP2C19 genetic testing appear to be only a limited piece of the overall therapeutic puzzle of clopidogrel therapy and personalized medicine.

Financial Disclosures: None reported.

REFERENCES


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