

## PERSONALIZED MEDICINE CORNER

## Pharmacogenetic Testing for Clopidogrel: Is There a Benefit?

Clopidogrel blocks the platelet P2Y<sub>12</sub> receptor to inhibit platelet activation and aggregation and is commonly prescribed after percutaneous coronary intervention (PCI) to prevent adverse cardiovascular (CV) events. This prodrug is converted to its active form via a two-step bioactivation process mediated in large part by the cytochrome P450 (CYP) 2C19 enzyme. Approximately 30% to 40% of individuals are heterozygotes or homozygotes for loss-of-function alleles in the *CYP2C19* gene, which leads to reduced or absent CYP2C19 activity. These patients may not attain sufficient levels of the active clopidogrel metabolite to inhibit platelet aggregation.<sup>1</sup>

Multiple studies have shown a higher rate of CV events among clopidogrel-treated patients with a *CYP2C19* loss-of-function genotype compared with similarly-treated patients without this genotype.<sup>2</sup> The data are strongest with clopidogrel use after acute coronary syndrome (ACS) and PCI.<sup>3</sup> The FDA-approved clopidogrel label contains a boxed warning about decreased drug effectiveness in individuals with the loss-of-function genotype and recommends considering alternative treatment in these patients. Although prasugrel and ticagrelor are more expensive than clopidogrel, these alternatives are not affected by *CYP2C19* genotype.<sup>4,5</sup> Clinical Pharmacogenetic Implementation Consortium guidelines strongly recommend considering prasugrel or ticagrelor after an ACS and PCI for individuals with a loss-of-function variant in the absence of contraindications (e.g., history of transient ischemic attack or stroke).<sup>6</sup>

These data have led to *CYP2C19* genotyping in clinical practice at some institutions to assist with choosing antiplatelet therapy after PCI. Investigators at the University of Florida presented data at the 2015 American Heart Association Scientific Sessions which suggested improved outcomes with clinical implementation of *CYP2C19* genotype-guided clopidogrel therapy.<sup>7</sup> Over 400 patients, most of whom had ACS, were genotyped after PCI. Approximately 30% of patients had a loss-of-function genotype, and 54% of these were switched to an alternative (prasugrel or ticagrelor). The risk for major adverse CV events, defined as a composite of cardiovascular death, myocardial infarction, cerebral vascular accident or stent thrombosis, was significantly lower among patients with a loss-of-function genotype switched to an alternative antiplatelet compared to those with a loss-of-function genotype who remained on clopidogrel (HR 0.09, 95% CI 0.01–0.84,  $p=0.034$ ).

Contact the UF Health Personalized Medicine Program ([PMP-HELP@ctsi.ufl.edu](mailto:PMP-HELP@ctsi.ufl.edu)) for more information about these findings or for assistance with interpreting CYP2C19 pharmacogenetic test results clinically.

## References:

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