CHARACTERISTICS

Clopidogrel is the most commonly used thienopyridine antiplatelet agent. By reducing platelet activity, clopidogrel helps prevent recurrence of coronary thrombus in patients with recent acute coronary syndrome (ACS) or who undergo percutaneous coronary intervention (PCI). Research has shown there is variable response in patients with the use of clopidogrel based, in part, on gene variants in the *CYP2C19* gene. Carriers of one or two copies of loss-of-function *CYP2C19* variants convert less clopidogrel into its active metabolite, resulting in diminished antiplatelet response and higher cardiovascular event rates[1]. Up to one-third of the US population carries a loss-of-function variant. A patient's *CYP2C19* genotype, determined through genetic testing, can be used to predict the degree of reduced platelet activity that will be achieved with clopidogrel treatment. The genetic test results should be considered when selecting an antiplatelet agent in the setting of ACS or PCI[2]. In accordance with these findings, the FDA added a boxed warning to the clopidogrel label 1) warning about reduced effectiveness in patients who are poor clopidogrel metabolizers; 2) informing healthcare professionals that tests are available to identify genetic differences in CYP2C19 function; and 3) advising healthcare professionals to consider use of other antiplatelet medications or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers.

INDICATIONS FOR *CYP2C19* TESTING

These guidelines apply to patients undergoing PCI, particularly patients with ACS undergoing PCI[2]. Studies evaluating the impact of CYP2C19 on clopidogrel-treatment outcomes for other indications with lower clinical risk (e.g., atrial fibrillation, stroke, and patients not undergoing PCI with stenting) have not reproducibly demonstrated an association between *CYP2C19* variants and clopidogrel-treatment outcomes [3,4]. Similarly, meta-analyses that include large proportions of patients who have not undergone PCI do not find support for a major role for CYP2C19 in clopidogrel dose response variability [5,6] Although there are limited data regarding the potential role of *CYP2C19* testing for elective PCI cases treated with clopidogrel, these guidelines may also be considered for these patients. However, the lack of an FDA-approved indication for alternative thienopyridines (prasugrel and ticagrelor) for treatment of elective PCI must be balanced with the boxed warning on the clopidogrel label recommending consideration of alternative antiplatelet therapy in poor metabolizers with ACS *or* PCI[2].

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ASSIGNMENT OF CYP2C19 PHENOTYPE BASED ON GENOTYPE

Phenotype	Genotype	Diplotypes
Normal Metabolizer	*1/*1†	*1/*1†
Intermediate Metabolizer	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2-*8) or one loss-of-function allele (*2-*8) plus one increased activity allele (*17)	*1/*2, *1/*3, *1/*4, *1/*6, *1/*8 *2/*17††, *3/*17††, *4/*17††, *6/*17††, *8/*17††
Poor Metabolizer	Individual carrying 2 loss-of-function alleles (*2-*8)	*2/*2, *2/*3, *2/*4, *2/*6, *2/*8, *3/*3, *3/*4, *3/*6, *3/*8, *4/*4, *4/*6, *4/*8, *6/*6, *6/*8, *8/*8
Rapid and Ultra-rapid Metabolizer	An individual carrying one functional allele (*1) plus one increased activity allele (*17) or two increased activity alleles (*17)	*1/*17, *17/*17

† *1 status is designated if no other alleles tested for are identified.
†† Predicted Intermediate Metabolizer-Provisional classification as of 2013 CPIC update[2]

TREATMENT RECOMMENDATIONS

Genotype	Treatment Recommendations
Normal Metabolizers	
*1/*1	• Clopidogrel (PLAVIX) 75 mg daily
Intermediate Metabolizers	
*1/*2	
*1/*3	
*1/*4	
*1/*6	
*1/*8	
*2/*17	
*3/*17	
*4/*17	
*6/*17	
*8/*17	
Poor Metabolizers	
*2/*2	
*2/*3	
*2/*4	
*2/*6	
*2/*8	
*3/*3	
*3/*4	
*3/*6	
*3/*8	
*4/*4	
*4/*6	
*4/*8	
*6/*6	
*6/*8	
*8/*8	
Rapid and Ultra-Rapid Metabolizers††	
*1/*17	
*17/*17	

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† The increased dose has efficacy on platelet reactivity/pharmacokinetics in Intermediate Metabolizers similar to 75 mg daily in normal metabolizers, but patient outcome data are not available. While not supported by the 2013 CPIC guidelines, this dosage is approved as a second-line therapy (when prasugrel or ticagrelor are not appropriate) by the P&T Committee's Pharmacogenomics Subcommittee based upon PK/PD data[4,5,7-15].

†† Rapid and Ultra-Rapid Metabolizers may be at increased risk of bleeding complications.

PHARMACOGENETIC COUNSELING

When an order for CYP2C19 genotype is placed, pharmacogenetic counseling will also be offered. The pharmacogenetic counseling service will consist of members from the following clinical services: pharmacy, medicine, and genetics. The counseling service will provide a progress note with patient-specific recommendations for each genotyped patient. The counseling service will also ensure that genetic testing results and treatment recommendations are sent to the patient's referring physician.

ADDITIONAL CONSIDERATIONS

These guidelines do not focus on demographic and other clinical variables, such as adherence to therapy, age, diabetes mellitus, obesity, smoking, and concomitant use of other drugs that may influence clopidogrel efficacy and clinical decision-making.

Given that genotype does not change over a person's lifetime, results (including which alleles were tested) should be accessible in the electronic health record so they can be accessed in the future or provided to the patient's health care team outside UMMC when applicable. It is important to note that the interpretation of the genotype could change as new *CYP2C19* alleles are discovered and the genotype assay evolves. Therefore attention to which alleles were tested is an important component of interpreting the genotype-phenotype relationship.

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