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Clopidogrel Therapy and *CYP2C19* Genotype

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Clopidogrel is an antiplatelet agent and it belongs to the drug class of thienopyridines. It is used in the secondary prevention of atherosclerotic events in patients who have recently had a myocardial infarction, stroke, or have established peripheral arterial disease. It is also used in patients presenting with acute coronary syndrome, including patients with unstable angina who are to be managed medically or managed with coronary revascularization, such as the placement of an intracoronary stent.

CYP2C19 is one of the main enzymes involved in the activation of clopidogrel. The recommended doses of clopidogrel are less effective in patients with loss of function mutations in *CYP2C19*. About 3% of Caucasians and 15 to 20% of Asians are homozygous for loss of function mutations and possess little or no CYP2C19 activity and are known as "poor metabolizers" (1).

The FDA advises that genetic testing to identify a patient's *CYP2C19* genotype can be used as an aid in determining therapeutic strategies in patients who require antiplatelet therapy. For example, alternative treatment should be considered in patients identified as poor metabolizers (1). The Clinical Pharmacokinetics Implementation Consortium (CPIC) has made therapeutic recommendations based on *CYP2C19* genotype for patients who are starting antiplatelet therapy because they have acute coronary syndrome or are undergoing percutaneous coronary intervention (see Table 1) (2).

Table 1. CYP2C19 phenotypes and the therapeutic recommendations for ACS/PCI patients starting antiplatelet therapy

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic recommendations for clopidogrel in ACS/PCI
Ultrarapid metabolizer	Normal or increased enzyme activity. Found in ~5–30% of patients.	**1/*17* **17/*17*	Dose recommended by drugs label
Extensive metabolizer	Normal enzyme activity (homozygous wild-type). Found in ~35-50% of patients.	**1/*1*	Dose recommended by drugs label
Intermediate metabolizer	Intermediate enzyme activity. Found in ~18-45% of patients.	**1/*2* **1/*3*	Alternative therapy recommended e.g., prasugrel, if no contraindication

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Table 1. continued from previous page.

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic recommendations for clopidogrel in ACS/PCI
Poor metabolizer	Low or absent enzyme activity. Found in ~2-15% of patients.	**2/*2* **2/*3* **3/*3*	Alternative therapy recommended e.g., prasugrel, if no contraindication

The strength of therapeutic recommendations is "moderate" for intermediate metabolizers, and "strong" for all other metabolizers.
ACS, acute coronary syndrome
PCI, percutaneous coronary intervention
Table is adapted from Scott S.A., Sangkuhl K., Gardner E.E., Stein C.M. et al. *Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy.*Clinical pharmacology and therapeutics. 2011;90(2):328–32 (2).

Drug: Clopidogrel

Clopidogrel inhibits ADP-mediated platelet activation and aggregation. It irreversibly binds to the platelet purinergic receptor, P2RY12. Once inhibited, the platelets are affected for their entire lifespan (7-10 days).

Clopidogrel is a prodrug. The effectiveness of clopidogrel as an antiplatelet agent depends upon its metabolism to an active metabolite in the liver. Activation takes place in two sequential oxidative steps, and involves the CYP2C19 enzyme along with other enzymes. Only about 15% of the drug is activated, the other 85% is hydrolyzed to inactive forms and excreted.

Patients who have coronary disease and carry loss of function *CYP2C19* alleles are at an increased risk of cardiovascular events when treated with clopidogrel, compared to patients without these alleles (3, 4).

Gene: *CYP2C19*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes and form the major system for metabolizing drugs. The CYP genes are often polymorphic and can result in either reduced or absent drug metabolism, or conversely, increased drug metabolism.

CYP2C19 is one of the main enzymes involved in the activation of clopidogrel and is highly polymorphic—more than 25 variants are known. *CYP2C19*1* is the wild-type allele and is associated with normal enzyme activity (5).

The most common loss-of-function variant is *CYP2C19*2* (681G>A) which has allele frequencies of ~15% in Caucasians and Africans, and 29–35% in Asians (2). It is inherited as an autosomal co-dominant trait.

Less common variants associated with reduced or absent function include *CYP2C19*3* (636G>A), which has allele frequencies of 2-9% in Asian populations, and *CYP2C19* variants **4-*8*, which have allele frequencies of <1% (2).

In contrast, the *CYP2C19*17* allele (-806C>T) is associated with increased enzyme activity. Allele frequencies range from 3 to 21% (2, 6).

The responsiveness of platelets to clopidogrel depends partly upon an individual's genotype. For example, the predicted response of an individual who has one functional allele (**1*) and one loss-of-function allele (**2-*8*) lies somewhere between a **1/*1* individual and a **2/*2* individual (2). Based on *CYP2C19* genotypes, four phenotypes have been identified: ultrarapid metabolizers, extensive metabolizers (normal), intermediate metabolizers, and poor metabolizers. See Table 1 for the corresponding therapeutic recommendations.

Genetic Testing

Genetic testing is available for several *CYP2C19* variant alleles, however only the relationship between the **2* allele on treatment response has been adequately studied. In addition, although clopidogrel is used for a variety of conditions, gene testing is only recommended in patients with coronary disease, e.g., those with acute coronary syndrome, or those who are undergoing percutaneous coronary intervention (2).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Please review the complete therapeutic recommendations that are located here: (1).

Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): Standard dosing of clopidogrel, as recommended in the product insert, is warranted among patients with a CYP2C19 extensive metabolizer or ultrarapid metabolizer phenotype (i.e., **1/*1*, **1/*17*, and **17/*17*). If clinical genotyping identifies a patient as a CYP2C19 poor metabolizer (i.e., **2/*2*), current literature supports the use of an alternative agent (e.g., prasugrel, ticagrelor), provided it is not contraindicated clinically.

The most challenging patient population to address is the CYP2C19 intermediate metabolizer phenotype (e.g., **1/*2*). Intermediate metabolizers have higher on-treatment residual platelet activity on average as compared to extensive metabolizers, and CYP2C19*2 heterozygous patients with ACSs who receive treatment with clopidogrel have higher risks for adverse cardiovascular outcomes including stent thrombosis. These data support switching to an alternative antiplatelet agent for intermediate metabolizers if there is no contraindication. Given the wide interindividual variability in residual platelet activity observed among intermediate metabolizers receiving clopidogrel, and taking into account other factors that may place intermediate metabolizer patients at increased risk of a cardiovascular (or adverse bleeding) event, clinical judgment should be exercised to determine the most effective individualized therapy.

Please review the complete therapeutic recommendations that are located here: (2).

The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*17*	-806C>T	NM_000769.1:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Acknowledgments

The Pharmacogenomics Knowledgebase: http://www.pharmgkb.org

The Clinical Pharmacogenetics Implementation Consortium: http://www.pharmgkb.org/page/cpic

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