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NLM Citation: Dean L. Clopidogrel Therapy and *CYP2C19* Genotype. 2012 Mar 8. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Clopidogrel Therapy and *CYP2C19* Genotype

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Created: March 8, 2012.

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).

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 (2, 3).

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 (4).

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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 (5). 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% (5).

In contrast, the *CYP2C19*17* allele (-806C>T) is associated with increased enzyme activity. Allele frequencies range from 3 to 21% (5, 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 (5). 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.

Table 1. Predicted 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
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 (5).

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 (5).

Therapeutic Recommendations

FDA Statement: Alternative treatment to clopidogrel should be considered in patients who have been identified as CYP2C19 poor metabolizers. Although an increased dose regimen of clopidogrel may increase antiplatelet response in poor metabolizers, a dose regimen has not been established in trials (1).

CPIC Statement: An alternative antiplatelet agent, such as Prasugrel (if there are no contraindications) is recommended for patents who are poor metabolizers (Table 1) (5). Alternative treatment may also be considered in patients who are intermediate metabolizers (7).

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
*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/rec.html

Acknowledgments

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

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

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