Clopidogrel Therapy and *CYP2C19* Genotype

Laura Dean, MD[1]

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Introduction

Clopidogrel is an antiplatelet agent used to reduce the risk of myocardial infarction (MI) and stroke among high-risk patients. It is also approved for secondary prevention of atherosclerotic events for patients who have recently had an MI or a stroke and those with established peripheral arterial disease, and administered with aspirin as dual antiplatelet therapy (DAPT) for patients with acute coronary syndrome (ACS) caused by an MI or unstable angina.

CYP2C19 is one of the principal enzymes involved in the hepatic bioactivation of clopidogrel. Of note, the recommended doses of clopidogrel are less effective in patients with loss-of-function variant alleles in the *CYP2C19* gene. Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese carry two loss-of-function variant alleles and are classified as "poor metabolizers" due to having little or no CYP2C19 enzyme activity (1).

The FDA-approved drug label for clopidogrel contains a boxed warning, stating that clopidogrel has diminished effectiveness among *CYP2C19* poor metabolizers. It advises that tests are available to identify a patient's *CYP2C19* genotype, they can be used as an aid in determining therapeutic strategy, and that alternative treatment strategies should be considered in patients identified as *CYP2C19* poor metabolizers.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has made antiplatelet therapy recommendations based on *CYP2C19* genotype for patients with ACS who are undergoing percutaneous coronary interventions (PCI), such as the placement of a stent. Given the reduced efficacy reported for both *CYP2C19* intermediate and poor metabolizers, CPIC recommends using an alternative antiplatelet agent (e.g., prasugrel or ticagrelor) when not contraindicated (Table 1) (2).

1 NCBI; Email: dean@ncbi.nlm.nih.gov.

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Table 1. Antiplatelet therapy recommendations based on *CYP2C19* status when considering clopidogrel for ACS/PCI patients

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* **2/*17*	Alternative antiplatelet therapy recommended if no contraindication, e.g., prasugrel, ticagrelor
Poor metabolizer	Low or absent enzyme activity. Found in ~2-15% of patients.	**2/*2* **2/*3* **3/*3*	Alternative antiplatelet therapy recommended if no contraindication, e.g., prasugrel, ticagrelor

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., Stein C.M., Hulot J.S., et al. *Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update.* Clinical pharmacology and therapeutics. 2013;94(3):317–23 (2)

Drug: Clopidogrel

Clopidogrel is a second-generation thienopyridine antiplatelet agent, which binds irreversibly to the P2RY12 receptor and inhibits ADP-mediated platelet activation and aggregation. Other currently approved antiplatelet agents include prasugrel and ticagrelor.

As an antiplatelet agent, clopidogrel is used to inhibit the formation of blood clots in the coronary, peripheral, and cerebrovascular arteries. It is typically given in addition to daily aspirin and other standard treatments, and is used in patients with ACS, and in patients who have either had a recent MI or stroke, or have established peripheral arterial disease (1).

ACS reflects a decreased blood flow in the coronary arteries, and comprises the entities' unstable angina, "STEMI" and "NSTEMI". Unstable angina, in contrast to stable angina, occurs suddenly, often at rest or with minimal exertion. It may be new in onset, or it may occur with less exertion than previously. An MI may be classified in two types, depending on what is shown on the EKG. If the EKG findings include an elevation of the ST-segment, this is known as an "ST segment elevation MI" (STEMI), and if there is no elevation but

an increase in myocardial biomarkers such as troponin I or T, this is known as a "non-ST segment elevation MI" (NSTEMI).

In patients who have ACS caused by STEMI, clopidogrel has been found to reduce the rate of death from any cause (3). In patients who have ACS caused by NSTEMI or unstable angina, clopidogrel has been found to decrease the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia (4).

In patients with atherosclerotic vascular disease, as indicated by a recent MI, a recent ischemic stroke, or symptomatic peripheral arterial disease, the long-term administration of clopidogrel reduces the combined risk of a new ischemic stroke or MI, and other vascular death (5).

Clopidogrel is a potent antithrombotic drug that inhibits ADP-induced platelet aggregation by selectively binding to the platelet purinergic receptor, P2RY12 (6). Because clopidogrel is a pro-drug, it first requires conversion into an active metabolite before it can act as an antiplatelet agent.

Clopidogrel activation takes place via two sequential oxidation reactions that are catalyzed by the cytochrome P450 (CYP450) system: the first involving CYP1A2, CYP2B6, and CYP2C19, and the second involving CYP2B6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5. Less than 15% of the clopidogrel pro-drug is activated, the remaining 85% is hydrolyzed by esterases to inactive forms and excreted (6-9). Of note, one small study suggested that a non P450 (CYP) enzyme, paraoxonase 1 (PON1), may also be involved in clopidogrel activation (10); however, this finding has not been replicated in dedicated studies (11-13) or in meta-analysis (14)

The active clopidogrel metabolite contains a reactive thiol group, which forms a disulfide bridge with a free cysteine residue on the P2RY12 receptor. Once bound, the receptor is unable to bind ADP, and platelet activation via this pathway is prevented for the rest of its lifespan (~10 days) (6).

Despite the general efficacy of clopidogrel to inhibit platelet aggregation, a substantial variability in response to clopidogrel is frequently observed—resistance and treatment failure can occur in some patients. It has been estimated that between 16-50% of patients treated with clopidogrel have "high on-treatment platelet reactivity" (HTPR), which indicates that a major portion of P2RY12 receptors are not blocked, despite treatment with clopidogrel (15).

An individual's response to clopidogrel can be influenced by many factors, such as age, comorbidities, and drug-drug interactions. In addition, genetic susceptibility to clopidogrel response has been reported, including variant alleles in the *ABCB1* gene, which influence the absorption of clopidogrel from the gut (16, 17), and variant alleles in the *CYP2C19* gene, which influence the generation of the active clopidogrel metabolite (18, 19).

CYP2C19 is the principal hepatic enzyme involved in converting clopidogrel to its active metabolite, and *CYP2C19* loss-of-function alleles result in reduced active clopidogrel metabolites and HTPR, as well as an increased risk for both major adverse cardiovascular events (MACE) and stent thrombosis compared to *CYP2C19* wild-type patients with ACS/PCI (20-22).

Gene: *CYP2C19*

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

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as antidepressants, benzodiazepines, some proton pump inhibitors, and the antiplatelet agent clopidogrel.

The variability of clopidogrel metabolism and treatment outcomes between individuals is partly determined by variant alleles of the *CYP2C19* gene. *CYP2C19* is highly polymorphic, as more than 25 variant star (*) alleles are currently catalogued at the Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se/cyp2c19.htm). The *CYP2C19*1* wild-type allele and is associated with normal enzyme activity and the "extensive metabolizer" phenotype.

The *CYP2C19*17* allele is associated with increased enzyme activity due to increased gene transcription and has allele frequencies range from 3 to 21% across different populations (2). Individuals with one or two copies of the *17 allele are typically classified as "ultrarapid metabolizers".

Individuals who carry one and two reduced-activity or non-functioning *CYP2C19* alleles are "intermediate" and "poor metabolizers", respectively. Given that the efficacy of clopidogrel is, in part, dependent upon it being metabolized by CYP2C19 to an active metabolite, intermediate and poor metabolizers can have reduced antiplatelet responses when treated with clopidogrel. However, only 6 to 12% of the observed variability in antiplatelet effect of clopidogrel is thought to be attributed to carriage of *CYP2C19*2* allele(s) (23). Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are *CYP2C19* poor metabolizers (1).

The most common loss-of-function variant is *CYP2C19*2*, which contains a c.681G>A variant in exon 5 that results in an aberrant splice site. This leads to the production of a truncated and non-functioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (2).

Another commonly tested loss-of-function variant is *CYP2C19*3*, which contains a c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2-9% in Asian populations, but rare in other racial groups. Other loss-of-

function variants occur in less than 1% of the general population, and include *CYP2C19*4-*8* (2).

As noted above, ACS/PCI patients that are *CYP2C19* intermediate or poor metabolizers and who are treated with clopidogrel have increased risks for major cardiovascular events including stent thrombosis (1) (17, 21).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles, and a list of test providers is available at the Genetic Testing Registry (GTR) of the National Institutes of Health: http://www.ncbi.nlm.nih.gov/gtr/tests/?term=1557[geneid].

Usually a patient's result is reported as a diplotype, such as *CYP2C19 *1/*1*, and may also include an interpretation of the patient's predicted metabolizer phenotype (ultrarapid, extensive, intermediate, or poor). Table 1 summarizes common CYP2C19 phenotypes with antiplatelet therapy recommendations developed by CPIC.

The association between *CYP2C19*2* and **3* and clopidogrel response has been extensively studied; however, the less common loss-of-function alleles (e.g., *CYP2C19*4-*8*) also likely influence clopidogrel response similar to **2* and **3*. Therefore, when other loss-of-function alleles are identified in patients with ACS/PCI, these alleles should be considered to reduce the effectiveness of clopidogrel therapy in a similar manner to the more common *CYP2C19**2 allele (2, 24).

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): WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS. 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

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

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 ACS/PCI patients with a predicted *CYP2C19* extensive metabolizer or ultrarapid metabolizer phenotype (i.e., **1/*1*, **1/*17*, and **17/*17*). If genotyping from a Clinical Laboratory Improvement Amendments–certified laboratory identifies a patient as a *CYP2C19* PM (i.e., **2/*2*), current literature supports the use of an alternative antiplatelet agent (e.g., prasugrel or ticagrelor) when not contraindicated clinically.

The most challenging patient population to address is the *CYP2C19* IM phenotype (e.g., **1/*2*, **1/*3*, and **2/*17*). IMs have higher on-treatment residual platelet activity on average as compared with extensive metabolizers, and ACS/PCI *CYP2C19*2* heterozygotes treated with clopidogrel have increased risks for serious adverse CV outcomes, including stent thrombosis. Consequently, these data support switching to an alternative antiplatelet agent for IMs when not contraindicated. However, given the wide interindividual variability in residual platelet activity observed among clopidogrel-treated IMs, clinical judgment also taking into account other factors that may place an IM at increased risk of a CV event (or adverse bleeding event) must be considered to most effectively individualize therapy.
Please review the complete therapeutic recommendations that are located here: (2).

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): There is an increased risk for a reduced response to clopidogrel in *CYP2C19* intermediate and poor metabolizers. Consider using an alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated with an increased bleeding risk compared to clopidogrel (Table 2).

Please review the complete therapeutic recommendations that are located here: (25).

Table 2. *CYP2C19* phenotypes and the therapeutic recommendations for clopidogrel therapy

Phenotype	Genotype	Therapeutic (dose) recommendation for clopidogrel
Ultrarapid metabolizer	More than two copies of functional alleles	No
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or	Increased risk for reduced response to clopidogrel. Consider alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated

The strength of the clopidogrel therapeutic recommendations scored a maximum of 4/4 (the highest quality of evidence) for poor and intermediate metabolizers, and a score of 3/4 for ultrarapid metabolizers. Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. *Pharmacogenetics: from bench to byte - an update of guidelines*. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (25).

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Phenotype	Genotype	Therapeutic (dose) recommendation for clopidogrel
	one decreased activity allele and one inactive allele	
Poor metabolizer	Two inactive alleles	Increased risk for reduced response to clopidogrel. Consider alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated with an increased bleeding risk compared to clopidogrel

The strength of the clopidogrel therapeutic recommendations scored a maximum of 4/4 (the highest quality of evidence) for poor and intermediate metabolizers, and a score of 3/4 for ultrarapid metabolizers. Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. *Pharmacogenetics: from bench to byte - an update of guidelines*. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (25).

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/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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Related Summaries by Gene

Amitriptyline Therapy and *CYP2D6* and *CYP2C19* Genotype

Carisoprodol Therapy and *CYP2C19* Genotype

Diazepam Therapy and *CYP2C19* Genotype

Esomeprazole Therapy and *CYP2C19* Genotype

Imipramine Therapy and *CYP2D6* and *CYP2C19* Genotype

Omeprazole Therapy and *CYP2C19* Genotype

Prasugrel Therapy and *CYP* Genotype

Related Summaries by Drug Class

Prasugrel Therapy and *CYP* Genotype

Tests in GTR by Condition

Clopidogrel response

Tests in GTR by Gene

CYP2C19 gene