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NLM Citation: Dean L, Kane M. Clopidogrel Therapy and *CYP2C19* Genotype. 2012 Mar 8 [Updated 2022 Dec 1]. 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; Updated: December 1, 2022.

Introduction

Clopidogrel (brand name Plavix) is an antiplatelet medicine that reduces the risk of myocardial infarction (MI) and stroke in individuals with acute coronary syndrome (ACS), and in individuals with atherosclerotic vascular disease (indicated by a recent MI or stroke, or established peripheral arterial disease) (1). Clopidogrel is also indicated in combination with aspirin for individuals undergoing percutaneous coronary interventions (PCI), including stent placement.

The effectiveness of clopidogrel depends on its conversion to an active metabolite, which is accomplished by the cytochrome P450 2C19 (CYP2C19) enzyme. Individuals who have 2 loss-of-function copies of the *CYP2C19* gene are classified as CYP2C19 poor metabolizers (PM). Individuals with a CYP2C19 PM phenotype have significantly reduced enzyme activity and cannot activate clopidogrel via CYP2C19, which means the drug will have a reduced antiplatelet effect. Approximately 2% of Caucasians, 4% of African Americans, 14% of Chinese, and 57% of Oceanians are CYP2C19 PMs (2). The effectiveness of clopidogrel is also reduced in individuals who are CYP2C19 intermediate metabolizers (IM). These individuals have one loss-of-function copy of *CYP2C19*, with either one normal function copy or one increased function copy. The frequency of the IM phenotype is more than 45% in individuals of East Asian descent, more than 40% in individuals of Central or South Asian descent, 36% in the Oceanian population, approximately 30% in individuals of African descent, 20–26% in individuals of American, European, or Near Eastern descent, and just under 20% in individuals of Latino descent (2).

The 2022 FDA-approved drug label for clopidogrel includes a boxed warning on the diminished antiplatelet effect of clopidogrel in CYP2C19 PMs (Table 1). The warning states that tests are available to identify individuals who are CYP2C19 PMs, and to consider the use of another platelet $P2Y_{12}$ (purinergic receptor P2Y, G-protein coupled 12) inhibitor in individuals identified as CYP2C19 PMs.

The 2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for clopidogrel recommends that for individuals with ACS or non-ACS indications who are undergoing PCI, being treated for peripheral arterial disease (PAD), or stable coronary artery disease following MI, an alternative antiplatelet therapy (for example, prasugrel or ticagrelor) should be considered for CYP2C19 PMs if there is no contraindication (Table 2) (3). Similarly, CPIC strongly recommends that CYP2C19 IMs should avoid clopidogrel for ACS or PCI but makes no recommendations for other cardiovascular indications (Table 2). For neurovascular indications, CPIC

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recommends avoidance of clopidogrel for CYP2C19 PMs and consideration of alternative medications for both IMs and PMs if not contraindicated (Table 3) (3).

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) have also made antiplatelet therapy recommendations based on *CYP2C19* genotype. For individuals with ACS who undergo PCI, they recommend an alternative antiplatelet agent in PMs, and for IMs they recommend choosing an alternative antiplatelet agent or doubling the dose of clopidogrel to 150 mg daily dose, 600 mg loading dose (Table 4) (4).

Table 1. The FDA (2022) Drug Label for Clopidogrel. Warning: Diminished Antiplatelet Effect in Individuals with 2 Loss-of-Function Alleles of the *CYP2C19* Gene.

Phenotype	Recommendations
CYP2C19 poor metabolizer	Clopidogrel bisulfate at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in individuals who are homozygous for no-function alleles of the *CYP2C19* gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify individuals who are CYP2C19 poor metabolizers. Consider use of another platelet P2Y12 inhibitor in individuals identified as CYP2C19 poor metabolizers

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. This table is adapted from (1).

Table 2. The CPIC (2022) Antiplatelet Therapy Recommendations based on CYP2C19 Phenotype when considering Clopidogrel for Cardiovascular Indications.

Phenotype	Examples of diplotypes	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendation-ACS, or PCI[a], or both	Classification of recommendation, non-ACS, non-PCI cardiovascular indications[b]
Ultrarapid metabolizer (UM)	**17/*17*	Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
Rapid metabolizer (RM)	**1/*17*	Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk			
Normal metabolizer (NM)	**1/*1* **1/*13*	Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	Strong
Likely intermediate metabolizer	**1/*9* **1/*16* **1/*10*	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard-dose clopidogrel (75 mg/day) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[c]	No recommendation[c]

Table 2. continued from previous page.

Phenotype	Examples of diplotypes	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendation-ACS, or PCI[a], or both	Classification of recommendation, non-ACS, non-PCI cardiovascular indications[b]
Intermediate metabolizer (IM)	**1/*2* **1/*3* **2/*17*	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard-dose (75 mg/day) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	No recommendation
Likely poor metabolizer	**2/*9* **3/*19* **4/*10*	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[c]	Moderate[c]
Poor metabolizer (PM)	**2/*2* **2/*3* **3/*3*	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	Moderate

[a] ACS or PCI, or both includes individuals undergoing PCI for an ACS or non-ACS (elective) indication.
[b] Non-ACS, non-PCI cardiovascular indications include peripheral arterial disease and stable coronary artery disease following a recent myocardial infarction outside the setting of PCI.
[c] The strength of the recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes; "likely" indicates the uncertainty in phenotype assignment due to limited data for reduced-function alleles.
ACS - acute coronary syndrome; PCI - percutaneous coronary intervention; CPIC - Clinical Pharmacogenetics Implementation Consortium
Please see Therapeutic Recommendations based on Genotype for more information from CPIC. This table is adapted from (3).

Table 3. The CPIC (2022) Antiplatelet Therapy Recommendations Based on CYP2C19 Phenotype when Considering Clopidogrel for Neurovascular[a] Indications

CYP2C19 phenotype	Implications for clopidogrel	Therapeutic recommendation	Classification of recommendation[b]
Ultrarapid metabolizer (UM)	Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity; no association with higher bleeding risk	No recommendation	No recommendation
Rapid metabolizer (RM)	Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk		
Normal metabolizer (NM)	Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity	If considering clopidogrel, use at standard dose (75 mg/day)	Strong
Likely and confirmed intermediate metabolizer (IM)	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Consider an alternative[c] P2Y12 inhibitor at standard dose if clinically indicated and no contraindication	Moderate
Likely and confirmed poor metabolizer (PM)	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Consider an alternative[c] P2Y12 inhibitor at standard dose if clinically indicated and no contraindication	Moderate

[a] Neurovascular disease includes acute ischemic stroke or transient ischemic attack (TIA), secondary prevention of stroke, or prevention of thromboembolic events following neurointerventional procedures, such as carotid artery stenting and stent-assisted coiling of intracranial aneurysms.
[b] The strength of the recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes; "likely" indicates the uncertainty in phenotype assignment due to limited data for reduced function alleles.
[c] Alternative P2Y12 inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in individuals with a history of stroke or TIA. Given limited outcomes data for genotype-guided antiplatelet therapy for neurovascular indications, selection of therapy should depend on the individual's treatment goals and risks for adverse events. Please see Therapeutic Recommendations based on Genotype for more information from CPIC. This table is adapted from (3). CPIC - Clinical Pharmacogenetics Implementation Consortium

Table 4. The DPWG (2019) Recommendations for Clopidogrel and *CYP2C19* Phenotype.

Phenotype	Recommendation
Ultrarapid metabolizer	NO action is required for this gene-drug interaction
Intermediate metabolizer	Percutaneous coronary intervention, stroke, or TIA: 1 choose an alternative or double the dose to 150 mg/day (600 mg loading dose) Prasugrel, ticagrelor, and acetylsalicylic acid/dipyridamole are not metabolized by CYP2C19 (or to a lesser extent) Other indications: 1 no action required

Table 4. continued from previous page.

Phenotype	Recommendation
Poor metabolizer	Percutaneous coronary intervention, stroke, or TIA: 1 Avoid clopidogrel Prasugrel, ticagrelor, and acetylsalicylic acid/dipyridamole are not metabolized by CYP2C19 (or to a lesser extent) Other indications: 1. determine the level of inhibition of platelet aggregation by clopidogrel 2. consider an alternative in poor responders Prasugrel and ticagrelor are not metabolized by CYP2C19 (or to a lesser extent)

TIA - Transient ischemic attack; DPWG – Dutch Pharmacogenetics Working Group
Please see Therapeutic Recommendations based on Genotype for more information from DPWG. This table is adapted from (4).

Drug: Clopidogrel

Clopidogrel is an antiplatelet medicine used in the treatment of individuals with ACS, managed medically or with PCI. Clopidogrel is also used in the treatment of individuals with atherosclerotic vascular disease, as indicated by a recent MI, a recent ischemic stroke, or symptomatic peripheral arterial disease. Clopidogrel has been shown to reduce the rate of subsequent MI and stroke in these individuals (1, 5, 6).

Clopidogrel is a $P2Y_{12}$ inhibitor, and acts by irreversibly binding to the platelet $P2Y_{12}$ receptor and blocking adenosine diphosphate (ADP)-mediated platelet activation and aggregation. Clopidogrel belongs to the second generation of thienopyridine antiplatelet agents.

Clopidogrel is given to treat or to prevent further occurrences of arterial thrombosis, which occurs when a blood clot (thrombus) forms inside an artery. Arterial thrombosis is often triggered in response to the rupturing of the atherosclerotic plaque lining the arterial wall. If the thrombus occludes the arterial lumen, the blood flow is reduced or stopped, resulting in ischemia. In the brain, thrombosis in the cerebral arteries can cause a transient ischemic attack (TIA) or ischemic stroke. In the peripheral vessels, thrombosis can cause peripheral artery disease, and in the heart, a thrombosis in the coronary arteries is a common cause of ACS. Platelet inhibitors such as clopidogrel interrupt the formation of the thrombus, which involves the rapid recruitment and activation of platelets.

Acute coronary syndrome reflects a decreased blood flow in the coronary arteries and comprises unstable angina and MI. Unstable angina occurs suddenly, often at rest or with minimal exertion, and may be new in onset or may occur with less exertion than previously.

Among individuals with ACS, the addition of 75 mg daily clopidogrel to aspirin and other standard treatments reduces the risk of MI, stroke, and death, compared with the addition of placebo (7, 8, 9). However, despite the general efficacy of clopidogrel, resistance is common. Resistance to an antiplatelet drug occurs when there is no significant reduction in platelet function after therapy, compared with baseline platelet function. Clopidogrel treatment failure occurs when there is a thrombotic or ischemic event (for example, stent thrombosis or recurrent ACS) during clopidogrel therapy in individuals with "High on-Treatment Platelet Reactivity" (HTPR). High on-Treatment Platelet Reactivity occurs when the platelet $P2Y_{12}$ receptors are still responsive despite clopidogrel therapy. It is tested for by adding an ADP agonist to a plasma sample and measuring aggregation or intracellular markers of platelet activation. It has been estimated that between 16–50% of individuals treated with clopidogrel have HTPR (10).

Platelet function assays are used to assess platelet response by measuring 'Platelet Reactivity Units' (PRU). The PRU cut-off values vary, but the therapeutic window for clopidogrel is approximately 95–208 PRU. A PRU value

higher than 208 indicates clopidogrel resistance, and a value below 95 is associated with a higher risk for major bleeding (11, 12). Many studies have reported an association between clopidogrel resistance (HTPR or high PRU) and an increased risk of thrombotic/ischemic event following PCI, such as stent thrombosis (13). Similarly, HTPR is associated with poor outcomes in stroke or TIA in the context of standard antiplatelet therapies, including clopidogrel (14).

A poor response to clopidogrel is due, in part, to genetic variants in the *CYP2C19* gene. Other genes that may influence clopidogrel response include *ABCB1*, *P2Y12*, *CES1*, *GPIIIA*, *B4GALT2,* and *PON1* (15, 16, 17, 18, 19, 20, 21, 22, 23). Clopidogrel is a prodrug, and CYP2C19 is the major enzyme involved in the conversion of clopidogrel into an active metabolite. Alternative antiplatelet drugs to clopidogrel, such as prasugrel (a third generation thienopyridine) and ticagrelor (a cyclopentyltriazolopyrimidine), are not dependent upon CYP2C19 for activation. Although both clopidogrel and prasugrel form active metabolites with similar potency, prasugrel is a more potent antiplatelet agent than clopidogrel due to the more efficient formation of the active metabolite from the prodrug (24).

The TRITON-TIMI 38 trial compared prasugrel with clopidogrel in 13,608 individuals with ACS who were undergoing PCI. Prasugrel was found to provide more potent platelet inhibition than clopidogrel; and after 15 months, individuals treated with prasugrel had a lower incidence of the combined endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke as compared with individuals treated with clopidogrel (9.9% versus 12.1%) (25, 26). However, prasugrel was associated with a higher risk of bleeding, leading to the FDA warning that the use of prasugrel is contraindicated in individuals with active pathological bleeding, or a history of stroke or TIA (27, 28). In addition, prasugrel has an FDA box warning for individuals with a high probability of undergoing coronary artery bypass grafting (prasugrel should not be started, or when possible, discontinue prasugrel at least 7 days before any surgery) (29).

In an analysis from the PLATelet inhibition and patient Outcomes (PLATO) trial, ticagrelor was found to be superior to clopidogrel in a subgroup of individuals with ACS who were treated with PCI. Consistent with the overall results of the trial, ticagrelor was found to have superior efficacy and similar safety compared with clopidogrel (30, 31, 32). Other studies have similarly observed a better response to ticagrelor for antiplatelet activities but noted an increased risk of bleeding when compared with clopidogrel for various indications (stroke, unstable angina, chronic coronary syndromes after PCI and other coronary artery diseases), which may be of particular concern in elderly individuals (33, 34, 35, 36).

In addition, the latest guideline from the American College of Cardiology/American Heart Association includes a preference for alternative therapy (prasugrel or ticagrelor) over clopidogrel in individuals with ACS/PCI. This is a class IIa recommendation based on moderate quality, from the 2016 focused update on dual antiplatelet therapy (37). In full, this recommendation states in individuals with ACS who are "treated with dual antiplatelet therapy after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y12 inhibitor therapy." These recommendations also state that "it is reasonable to use ticagrelor in preference to clopidogrel for maintenance of P2Y12 inhibitor therapy." (37)

Although prasugrel and ticagrelor are often reported to be more effective than standard-dose clopidogrel, dual antiplatelet therapy with clopidogrel and aspirin remains the standard of care at many institutions for individuals with ACS undergoing PCI (31, 38, 39, 40, 41). This may be because clopidogrel has a lower bleeding risk and is less expensive (42). However, the availability of *CYP2C19* genetic testing can facilitate personalized antiplatelet therapy by pursuing alternative antiplatelet agents specifically for individuals with impaired CYP2C19 activity (39, 43, 44, 45, 46).

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, voriconazole (47), 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. The *CYP2C19* gene is highly polymorphic with over 35 variant star (*) alleles catalogued by the Pharmacogene Variation (PharmVar) Consortium. The *CYP2C19*1* is considered the wild type allele when no variants are detected and is categorized as normal enzyme activity and the "normal metabolizer" phenotype. It should be noted that the *CYP2C19*1* haplotype has been determined to have a single nucleotide polymorphism in the coding region; however, the frequency of the variant nucleotide (G) is nearly 94% globally and this missense variant does not alter protein function (48, 49, 50).

The *CYP2C19*17* allele is associated with increased enzyme activity and, depending on the number of alleles present, is associated with the "rapid" (one **17* allele) and "ultrarapid" (2 **17* alleles) metabolizer phenotypes. Non-functional alleles include *CYP2C19*2* and **3*. The *CYP2C19* IMs have one copy of an allele that encodes a non-functional enzyme (for example, **1/*2*), whereas "PMs" have 2 non-functional alleles (for example, **2/*2*, **2/*3*) (Table 5).

Table 5. Activity Status of Selected *CYP2C19* Alleles

Allele type	Alleles
Increased function	*CYP2C19*17*
Normal function	*CYP2C19*1* *CYP2C19*13*
Decreased function^	*CYP2C19*9* *CYP2C19*10* *CYP2C19*16* *CYP2C19*19*
No function	*CYP2C19*2* *CYP2C19*3* *CY P2C19*4*
Uncertain function	*CYP2C19*12* *CYP2C19*23*

This table is adapted from (51).
^ Note: the evidence supporting the activity status of decreased function alleles is limited.

Approximately 2% of Caucasians, 4% of African Americans, 14% of Chinese, and 57% of Oceanians are CYP2C19 PM; and up to 45% of individuals are CYP2C19 IM (1, 2).

The most common no function variant is *CYP2C19*2*, which contains the NM_000769.1:c.681G>A variant in exon 5 that results in an aberrant splice site and produces a truncated and non-functioning protein. The *CYP2C19*2* allele frequencies are between 12–18% in individuals of European, American, or African ancestry, between 25–35% in Asians, Native Hawaiians, and Pacific Islanders, and up to 60% in Oceanian populations (2, 52). Approximately 6–12% of the observed variability in antiplatelet effect of clopidogrel is thought to be attributed to *CYP2C19* variants (53).

For *CYP2C19*, another commonly tested no functional 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 ancestral populations (52). Other non-functional variants occur in less than 1% of the general population and include *CYP2C19*4–*8* (54).

The frequency of the *CYP2C19*17* allele is approximately 22% in individuals of European ancestry, 8% for individuals from the Americas, 0.5–5.7% in Asian, Native Hawaiian, and Pacific Islander populations, 17% in African populations, and 20% in African American and Afro-Caribbean populations (2, 52).

The *CYP2C19*2, *3,* and **17* alleles are the 'Tier 1' alleles recommended by the Association for Molecular Pathology (AMP) to be included in *CYP2C19* clinical genotyping assays (55). The AMP further recommends testing laboratories consider **4A, *4B, *5, *6, *7, *8, *9, *10,* and **35* alleles as optional 'Tier 2' alleles that have all been shown to have decreased or no function but have either a low minor allele frequency, limited data characterizing the impact on enzyme function, or lack reference materials. Among the 'Tier 2' alleles, the *CYP2C19*35* allele is most common, and has a frequency of 9% in African populations (55).

Phenoconversion due to CYP2C19 Inhibitors and Inducers

Many medicines are metabolized by the CYP2C19 enzyme, and the activity level of the enzyme can be altered by administration of medications or supplements. Significant alterations in the effective enzyme activity level due to co-medication or other non-genetic factors is called phenoconversion. Increased enzymatic activity can be caused by induction of CYP2C19, such an effect can occur with medications like rifampin; this can lead to an increased bleeding risk due to increased activation of clopidogrel (1). St. John's wort and smoking may also increase CYP enzyme activity and increase the platelet inhibitory effect of clopidogrel (56). Inhibitors of CYP2C19 activity can cause reduced clopidogrel metabolism and thus trigger a blunted response to the medication. The FDA-approved drug label cautions that co-medication with proton pump inhibitors (PPIs) omeprazole or esomeprazole can decrease the antiplatelet effects of clopidogrel (1). One study found that co-medication with other CYP2C19 substrate medications was a significant risk factor for adverse drug reactions during clopidogrel treatment (57).

Linking *CYP2C19* Genetic Variation with Treatment Response

Several studies have reported an increase in adverse cardiovascular events in individuals who have one or 2 no function *CYP2C19* alleles (namely, IM or PM), compared with individuals with 2 normal copies of the *CYP2C19* gene (normal metabolizer). These studies focused on individuals with ACS undergoing PCI, with individuals who had no function alleles also being at a higher risk of stent thrombosis or major adverse cardiovascular and cerebrovascular events (58, 59, 60, 61, 62). These individuals may require much higher doses of clopidogrel (2- to 4-fold higher) or an alternative drug (63, 64, 65). A meta-analysis of 7 randomized control trials and 4 non-randomized control trials found a significant association between *CYP2C19* loss-of-function allele carriers and poorer outcomes when treated with clopidogrel as compared with an alternative $P2Y_{12}$ inhibitor (9). This analysis was limited to studies of individuals with ACS with at least 50% of participants undergoing PCI, where *CYP2C19* genotype was assessed and included in the outcomes, and clopidogrel was compared with an alternative medication. Some clinical studies did not find a significant association between *CYP2C19* and clinical outcome in individuals with ACS; however, these often included data from lower risk non-PCI individuals (66, 67, 68).

Several studies of individuals with TIA have reported that CYP2C19 status influences the risk of having an ischemic stroke or adverse clinical outcomes following a stroke when treated with clopidogrel (69, 70, 71, 72). One trial (CHANCE – Clopidogrel in High-risk Individuals with Acute Nondisabling Cerebrovascular Events; study size of 5,170 individuals) found that the use of clopidogrel plus aspirin compared with aspirin alone reduced the risk of a new stroke only in the subgroup of individuals who did not have the *CYP2C19* no function

alleles (73). The CHANCE-2 trial (study size 6,412 individuals) examined the superiority of ticagrelor to clopidogrel for *CYP2C19* loss-of-function allele carriers following TIA or minor ischemic stroke and found a modest but significant improvement in the rate of strokes in the first 90 days with no significant differences in risk of severe or moderate bleeding with either $P2Y_{12}$ inhibitor (74). Additional trials examining various antiplatelet regimens following stroke or TIA have been recently reviewed, which supports the role of *CYP2C19* genotype in contributing to potential risks with clopidogrel therapy for stroke or TIA (72). At least one study of *CYP2C19* variation and clopidogrel effectiveness in neurovascular conditions found an opposite effect of *CYP2C19* loss-of-function variants on poor treatment response. The authors of this study concluded more research was needed to fully understand the impact of these variants in the context of intracranial atherosclerotic disease; however, caution should be taken when considering these findings as the study only included 188 individuals (75).

Recent studies have found that *CYP2C19*-genotype-guided antiplatelet therapy results in a higher likelihood of achieving a therapeutic level of on-treatment platelet reactivity (11, 76, 77, 78). Genotype-guided therapy may also be cost effective among ACS individuals undergoing PCI (39, 79, 80, 81). However, many authors, including the American Heart Association, find more data are needed to determine whether routine genotyping and platelet function tests could help reduce future cardiovascular events in ACS individuals or for secondary stroke prevention (37, 82, 83, 84, 85).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides examples of genetic tests that are available for clopidogrel response, CYP2C19-related poor drug metabolism, and the *CYP2C19* gene.

Usually, an individual's result is reported as a diplotype, such as *CYP2C19 *1/*1*, and may also include an interpretation of the individual's predicted metabolizer phenotype (ultrarapid, rapid, normal, intermediate, or poor). When a test report does not provide a predicted metabolizer phenotype, resources such as PharmVar and PharmCAT are available to assist with predicting the functional impact of identified variants.

The association between *CYP2C19*2* and **3* and clopidogrel response has been extensively studied; however, the less common no function alleles (for example, *CYP2C19*4–*8*) also likely influence clopidogrel response similar to **2* and **3,* but the body of evidence is not as extensive. Therefore, these alleles should be considered to reduce the effectiveness of clopidogrel therapy in a similar manner to the more common *CYP2C19*2* allele (54, 86). Guidance regarding inclusion of specific alleles for clinical testing is available from AMP (55). The current recommendations from CPIC advise management of likely PMs and likely IMs as if these individuals were definitively in the predicted phenotype group (3).

The *CYP2C19* Gene Interactions with Medications Used for Additional Indications

The CYP2C19 enzyme metabolizes many medications and may have impacts on other conditions. Other medications affected by *CYP2C19* genetic variation may be used to treat:

- Gastrointestinal ulcers, gastroesophageal reflux, erosive esophagitis, and *Helicobacter pylori* infection—PPIs like omeprazole, esomeprazole, and others may have reduced metabolism in CYP2C19 IMs and PMs and thus these individuals have higher exposure to these medications, which imparts risk of adverse events. Conversely, *CYP2C19*17* confers increased activity and thus a more rapid clearance of PPIs and potential for treatment failure in ultrarapid metabolizers (UMs).

- Antifungal treatment—voriconazole is metabolized by CYP2C19 and UMs may have delayed target blood concentrations due to rapid clearance; PMs may experience high exposure and have a risk of adverse events.
- Depression, anxiety disorders, obsessive-compulsive disorder, or migraine prophylaxis—both selective serotonin reuptake inhibitors (SSRIs, such as citalopram, escitalopram, and sertraline) and tricyclic antidepressants (TCAs, such as the tertiary amines amitriptyline, clomipramine, doxepin, imipramine, and trimipramine) can be metabolized by CYP2C19. When administering SSRIs, UMs may experience treatment failure due to high clearance while PMs may require dose reduction. For the tertiary amine TCAs, UMs may experience altered responses or side effects due to rapid conversion to secondary amines while PMs are at risk of suboptimal responses and may require a lower dose. Diazepam is also partially metabolized by CYP2C19 and altered enzyme function may contribute to altered clearance of this medication.
- Epilepsy or seizures—brivaracetam, used for partial-onset (focal) epilepsy, is partially metabolized by CYP2C19 and PMs may require lower doses to avoid adverse effects due to reduced clearance of this medication. Clobazam is used to manage seizures in a variety of conditions and CYP2C19 PMs may experience higher exposure to norclobazam, putting them at higher risk for adverse effects. Lacosamide is also metabolized by CYP2C19, though there is no indication that PMs require altered dosing or management.
- Musculoskeletal pain—carisoprodol, a centrally acting muscle relaxant, is metabolized by CYP2C19 and PMs may be at a higher risk of carisoprodol toxicity.
- Hypoactive sexual desire disorder—flibanserin is metabolized, in part, by CYP2C19 and PMs have a higher exposure to this medication, resulting in an elevated risk of hypotension, syncope, and CNS depression.

Additional information on gene-drug interactions for *CYP2C19* are available from PharmGKB, CPIC and the FDA (search for "CYP2C19").

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.

2022 Statement from the US Food and Drug Administration (FDA)

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of clopidogrel bisulfate results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 … Clopidogrel bisulfate at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers … Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

[…]

[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. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 … The metabolism of clopidogrel can also be impaired by drugs that inhibit CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of clopidogrel bisulfate with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel bisulfate.

[…]

Rifampin strongly induces CYP2C19 resulting to both an increase level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, avoid concomitant use of strong CYP2C19 inducers. […]

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition… Avoid concomitant use of clopidogrel bisulfate with omeprazole or esomeprazole.

[…]

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxoclopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. Patients who are homozygous for nonfunctional alleles of the CYP2C19 gene are termed "CYP2C19 poor metabolizers." Approximately 2% of White and 4% of Black patients are poor metabolizers; the prevalence of poor metabolism is higher in Asian patients (e.g., 14% of Chinese). Tests are available to identify patients who are CYP2C19 poor metabolizers.

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

2022 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

In patients with ACS and/or undergoing PCI…avoid clopidogrel in CYP2C19 Ims and PMs and use an alternative antiplatelet agent, such as prasugrel or ticagrelor, if no contraindications.

[…]

If considering clopidogrel and the patient is a CYP2C19 NM, the standard dose (75 mg/day) is recommended. Although clopidogrel-treated CYP2C19 RMs and Ums may experience lower on-treatment platelet reactivity compared with NMs, clinical data also support the use of clopidogrel at standard doses in CYP2C19 RMs and Ums due to the lack of evidence demonstrating significant differences in risk of bleeding or ischemic events compared with NMs in patients undergoing PCI.

[…]

There remain limited data regarding the potential benefit of CYP2C19-guided antiplatelet therapy on outcomes exclusively in patients undergoing PCI for a non-ACS indication. Patients undergoing elective PCI have a lower risk of cardiovascular events compared with patients with ACS, but were included in multiple studies evaluating outcomes of genotype-guided antiplatelet therapy, including the IGNITE and TAILOR-PCI studies (Table S2). Therefore, the therapeutic recommendations for patients with ACS and/or undergoing PCI may also be considered for patients undergoing elective PCI.

[…]

In patients with a cardiovascular indication for clopidogrel outside the setting of an ACS or PCI, including the treatment of patients with peripheral arterial disease or stable coronary artery disease following a recent MI, the standard dose (75 mg/day) is recommended if the patient is a CYP2C19 NM. However, there are insufficient data to make a clinical recommendation for CYP2C19 Ums, RMs, and Ims. If the patient is a CYP2C19 PM, it is recommended to avoid clopidogrel and use prasugrel or ticagrelor at standard doses if no contraindication.

[…]

If considering clopidogrel for patients with neurovascular disease, including the treatment of acute ischemic stroke or TIA, the secondary prevention of stroke, or the prevention of thromboembolic events following neurointerventional procedures, such as carotid artery stenting and endarterectomy and stent-assisted coiling of intracranial aneurysms, the standard dose (75 mg/day) is recommended in CYP2C19 NMs (Table 3). In CYP2C19 Ims and PMs, there is a "moderate" recommendation to avoid clopidogrel if possible and consider an alternative P2Y12 inhibitor at standard doses if clinically indicated and no contraindication. Alternative P2Y12 inhibitors not impacted by *CYP2C19* genetic variants with indications for patients with stroke include ticagrelor and ticlopidine. However, ticlopidine has serious hematological adverse effects that also need to be considered. Prasugrel is contraindicated in patients with a history of stroke or TIA.

Please review the complete therapeutic recommendations that are located here: (3)

2019 Summary of Recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2C19 PM: CLOPIDOGREL

The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, because the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been proved in other patients.

- PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:
  - avoid clopidogrel
  - Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).
- OTHER INDICATIONS:
  - determine the level of inhibition of platelet aggregation by clopidogrel
  - consider an alternative in poor responders
  - Prasugrel and ticagrelor are not metabolised by CYP2C19 (or to a lesser extent).

CYP2C19 IM: clopidogrel

The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, as the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been observed in other patients.

- PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:
  - choose an alternative or double the dose to 150 mg/day (600 mg loading dose); Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).
- OTHER INDICATIONS:
  - no action required

CYP2C19 UM: clopidogrel

NO action is required for this gene-drug interaction.

The genetic variation results in increased conversion of clopidogrel to the active metabolite. However, this can result in both positive effects (reduction in the risk of serious cardiovascular and cerebrovascular events) and negative effects (increase in the risk of bleeding).

Please review the complete therapeutic recommendations that are located here: (4).

Nomenclature of Selected *CYP2C19* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	12662A>G	NM_000769.4:c.332-23A>G	(Splicing defect)	rs12769205
	19154G>A	NM_000769.4:c.681G>A	NP_000760.1:p. Pro227 =	rs4244285
*CYP2C19*3*	17948G>A	NM_000769.4:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*4*	1A>G	NM_000769.4:c.1A>G	NP_000760.1:p.Met1Val	rs28399504
*CYP2C19*9*	12784G>A	NM_000769.4:c.431G>A	NP_000760.1:p.Arg144His	rs17884712
*CYP2C19*10*	19153C>T	NM_000769.4:c.680C>T	NP_000760.1:p.Pro227Leu	rs6413438
*CYP2C19*12*	90209A>C	NM_000769.4:c.1473A>C	NP_000760.1:p.Ter491Cys	rs55640102
*CYP2C19*13*	87290C>T	NM_000769.4:c.1228C>T	NP_000760.1:p.Arg410Cys	rs17879685
*CYP2C19*16* [a]	90060C>T	NM_000769.4:c.1324C>T	NP_000760.1:p.Arg442Cys	rs192154563
*CYP2C19*17*	-806C>T	NM_000769.4:c.-806C>T	(Variant alters mRNA expression)	rs12248560
*CYP2C19*19*	151A>G	NM_000769.4:c.151A>G	NP_000760.1:p.Ser51Gly	rs1564657013
*CYP2C19*23*	12455G>C	NM_000769.4:c.271G>C	NP_000760.1:p.Gly91Arg	rs118203756

Note: the normal "wild type" allele is *CYP2C19*1* and is reported when no variant is detected. The wild type allele is characterized by the common A>G variant at rs3758581 (NM_000769.4:c.991A>G; *CYP2C19* p.Ile331Val), which is benign and is found in many *CYP2C19* haplotypes.
[a] This allele does not have the A>G variant at rs3758581.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (87).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

Acknowledgments

The authors would like to acknowledge Amber Beitelshees, PharmD, MPH, FAHA, FCCP, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA, and John McDermott, MRes, BSc, MBChB, NIHR Doctoral Research Fellow, University of Manchester, Clinical Genetics Registrar, Manchester University NHS Foundation Trust, Manchester, UK for reviewing this summary.

Third edition:

The author would like to thank Larisa H. Cavallari, PharmD, Associate Professor, Department of Pharmacotherapy and Translational Research & Director, Center for Pharmacogenomics, University of Florida, FLA, USA; Inge Holsappel, Pharmacist, Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), The Hague, The Netherlands; and Gerasimos Siasos, MD, PhD, FCCP, FACC, Associate Professor, Department of Cardiology, 'Hippokration' General Hospital,

School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, and Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical, Boston, MA, USA, for reviewing this summary.

Second edition:

The author would like to thank Stuart A. Scott, Assistant Professor of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; and Dietmar Trenk, Head of Clinical Pharmacology at the University Heart Center, Bad Krozingen and Professor at the Albert Ludwig University of Freiburg, Freiburg, Germany, for reviewing this summary.

Version History

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To view the 2012 version of this summary (Created: March 8, 2012) please click here.

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