

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (*CYP2C19*) Genotype and Clopidogrel Therapy

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CYP2C19 is one of the principal enzymes involved in the bioactivation of the antiplatelet prodrug clopidogrel. A common loss-of-function allele, *CYP2C19**2 (c.681G>A; rs4244285), is associated with increased risk for serious adverse cardiovascular events in both heterozygous and homozygous patients (~25–50% of the population) with acute coronary syndromes (ACSs) who are receiving clopidogrel, particularly among those undergoing percutaneous coronary intervention (PCI). We provide evidence from published literature and guidelines for *CYP2C19* genotype-directed antiplatelet therapy (periodically updated at <http://www.pharmgkb.org>).

The purpose of these guidelines is to provide information regarding the clinical use of *CYP2C19* genotype test results in patients requiring antiplatelet therapy. Detailed guidelines for use of other laboratory tests, such as platelet function monitoring, as well as a discussion of cost effectiveness, are beyond the scope of this article. The article does 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. The Clinical Pharmacogenetics Implementation Consortium of the National Institutes of Health's Pharmacogenomics Research Network develops peer-reviewed gene/drug guidelines that are published and updated

periodically at <http://www.pharmgkb.org> on the basis of new developments in the field.¹

FOCUSED LITERATURE REVIEW

A systematic literature review was conducted on *CYP2C19* genotype and clopidogrel (see **Supplementary Data** online). Guidelines for antiplatelet therapy were developed based on interpretation of the literature by authors and experts in the field.

Gene: *CYP2C19*

Background. The hepatic *CYP2C19* enzyme contributes to the metabolism of many clinically relevant drugs such as antidepressants, benzodiazepines, mephenytoin, some proton pump inhibitors, and clopidogrel. Like many other *CYP450* superfamily members, the *CYP2C19* gene is highly polymorphic, having more than 25 known variant alleles (<http://www.cypalleles.ki.se/cyp2c19.htm>). The *CYP2C19**1 allele is associated with functional *CYP2C19*-mediated metabolism. The most common *CYP2C19* loss-of-function allele is *2 (c.681G>A; rs4244285), with allele frequencies of ~15% in Caucasians and Africans, and 29–35% in Asians (**Supplementary Tables S3 and S4** online). Other *CYP2C19* variant alleles with reduced or absent enzymatic activity have been identified (e.g., *3–*8); however, their allele frequencies are typically <1%, with the exception of *CYP2C19**3

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Table 1 Assigning likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Ultrarapid metabolizer: normal or increased activity (~5–30% of patients)	An individual carrying two increased-activity alleles (*17), or one functional allele (*1) plus one increased-activity allele (*17)	*1/*17, *17/*17
Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)	An individual carrying two functional (*1) alleles	*1/*1
Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8)	*1/*2, *1/*3
Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)	An individual carrying two loss-of-function alleles (*2–*8)	*2/*2, *2/*3, *3/*3

For some rare genotype combinations metabolic phenotypes are difficult to predict; see **Supplementary Table S3** online.

(c.636G>A; rs4986893) in Asians (2–9%; **Supplementary Data** online).

*CYP2C19**2 is inherited as an autosomal co-dominant trait; platelet responsiveness to clopidogrel in heterozygotes (*1/*2) lies somewhere between the responsiveness in individuals with the *1/*1 genotype and that in those with the *2/*2 genotype.^{2–7} Therefore, based on identified *CYP2C19* genotypes, individuals can be categorized as extensive metabolizers (e.g., *1/*1), intermediate metabolizers (e.g., *1/*2), or poor metabolizers (e.g., *2/*2). The frequencies of *CYP2C19* poor metabolizers are ~2–5% among Caucasians and Africans and ~15% in Asians (**Supplementary Data** online).

In contrast, the *CYP2C19**17 allele (c.-806C>T; rs12248560) results in increased activity as a consequence of enhanced transcription, with average multi-ethnic allele frequencies of ~3–21% (**Supplementary Tables S3** and **S4** online). Individuals who carry this allele may be categorized as ultrarapid metabolizers (e.g., *17/*17). Some studies indicate that this allele results in enhanced platelet inhibition and clopidogrel response,^{6,8–10} and possibly an increased risk of bleeding complications.¹¹ However, other studies have not identified an effect of *CYP2C19**17 (refs. 7,12,13), and adequate evidence for an independent effect of this allele on clinical outcomes is lacking.

Genetic test interpretation. Clinical genotyping tests are available that interrogate variant *CYP2C19* alleles and predict an individual's *CYP2C19* metabolizer phenotype (**Supplementary Data** online). Each named star (*) allele is defined by the genotype at one or more specific single-nucleotide polymorphisms (**Supplementary Table S1** online) and is associated with a level of enzyme activity (**Supplementary Table S2** online). **Table 1** and **Supplementary Table S5** online summarize the assignment of the likely *CYP2C19* phenotype based on common star allele diplotypes, and these assignments are used to link genotypes with personalized antiplatelet therapy.

Available genetic test options. A number of academic and commercial clinical laboratories offer genetic testing for *CYP2C19**2 and other *CYP2C19* variant alleles (**Supplementary Data** online). However, at the time of this writing, only the *CYP2C19**2 allele has been adequately studied with respect to clinical outcomes on clopidogrel; other variants are too rare, have not been studied, or have resulted in inconclusive findings.

Incidental findings. There are no diseases or conditions that have been convincingly linked to variations in the *CYP2C19* gene independent of drug metabolism and response.

Other considerations. *CYP2C19* loss-of-function alleles do not account for all of the variability in clopidogrel response. Some studies have implicated variants in other genes associated with clopidogrel response (**Supplementary Data** online); however, these have not been consistently replicated.

Drug: clopidogrel

Background. Clopidogrel is a thienopyridine prodrug that requires hepatic biotransformation to form an active metabolite that selectively and irreversibly inhibits the purinergic P2RY₁₂ receptor, and thereby platelet aggregation, for the platelet's life span (~10 days). Only 15% of the prodrug is available for transformation to the active agent; the other 85% is hydrolyzed by esterases to inactive forms. Conversion of clopidogrel to its active metabolite requires two sequential oxidative steps involving several CYP450 enzymes (e.g., CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5; **Supplementary Figure S1** online). A recent study suggested that paraoxonase 1 (*PON1*) may also be involved in clopidogrel activation.¹⁴

Linking genetic variability to variability in drug-related phenotypes. Clopidogrel is commonly prescribed for ACSs and/or following PCI. However, responses to clopidogrel vary widely, with inhibition of adenosine diphosphate-induced platelet aggregation being normally distributed across a broad range.⁷ Many studies have shown that *CYP2C19**2 carriers have lower levels of active clopidogrel metabolites and higher on-treatment platelet aggregation as compared to noncarriers.^{2–4,6,7,15} Moreover, substantial evidence exists linking *CYP2C19* genotype with clinical response among clopidogrel-treated ACS patients,^{2,5–7,13,16,17} probably as a result of decreased formation of the active clopidogrel metabolite. For example, large meta-analyses (**Supplementary Table S7** online) have shown that *CYP2C19**2 carriers treated with clopidogrel have a higher risk for major adverse cardiovascular events as compared to noncarriers (hazard ratio (HR) 1.55, 95% confidence interval (CI) 1.11–2.17 for heterozygotes; HR 1.76, 95% CI 1.24–2.50 for homozygotes), and higher risks of stent thrombosis (HR 2.67, 95% CI 1.69–4.22 for heterozygotes; HR 3.97, 95% CI 1.75–9.02 for homozygotes).¹⁸

Table 2 Clopidogrel therapy based on CYP2C19 phenotype for ACS/PCI patients initiating antiplatelet therapy

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations ^a
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation ^b	Clopidogrel label-recommended dosage and administration	Strong
Intermediate metabolizer (IM) (*1/*2)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Prasugrel or other alternative therapy (if no contraindication)	Moderate
Poor metabolizer (PM) (*2/*2)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Prasugrel or other alternative therapy (if no contraindication)	Strong

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

^aSee **Supplementary Data** online, Strength of Therapeutic Recommendations. ^bThe CYP2C19*17 allele may be associated with increased risk of bleeding.¹¹

The growing body of literature implicating CYP2C19*2 (and perhaps other loss-of-function alleles) in adverse clopidogrel responses prompted the US Food and Drug Administration to implement a boxed warning on the clopidogrel label describing the relationship between CYP2C19 pharmacogenetics and drug response, particularly noting the drug's diminished effectiveness in poor metabolizers. However, because the agency's warning is not accompanied by a requirement for compulsory genetic testing before initiating clopidogrel therapy, if a patient's genotype is not known, the decision to perform CYP2C19 testing is up to the individual clinician and patient.

Studies linking CYP2C19 genotype with variability in clopidogrel response are summarized in **Supplementary Tables S6** and **S7** online; it is this body of evidence, rather than randomized clinical trials involving pharmacogenetic testing that provides the basis for the therapeutic guidelines in **Table 2**. Importantly, the most definitive studies showing a relationship between CYP2C19 genotype and clopidogrel response have been conducted in patients with ACSs, most of whom underwent PCIs. As such, these findings may not apply to all indications for clopidogrel, including atrial fibrillation, stroke, peripheral artery disease, and chronic stable angina.^{19,20} The guidelines set forth here, therefore, apply largely to patients taking clopidogrel in whom invasive PCIs have been performed with drug-eluting or bare-metal stents.

CYP2C19 genetic test interpretation and suggested clinical actions

Who should be genotyped for CYP2C19? Recently, the American College of Cardiology Foundation/American Heart Association outlined possible actions by clinicians in response to the Food and Drug Administration's boxed warning.²¹ The article fell short of recommending CYP2C19 genetic testing, citing the absence of prospective randomized clinical outcomes trials of genotype-directed antiplatelet therapy. However, such a clinical trial will take several years to perform; given the substantial body of evidence from the current literature (reviewed above) and potentially more efficacious antiplatelet therapy alternatives (see below), some physicians may choose to modify therapy based on genotype.

One option is to genotype all patients who undergo PCI and thereafter require antiplatelet therapy. Given the excellent

clinical course generally observed among the majority of PCI patients treated with clopidogrel, another approach is to target patients who are considered to be at moderate or high clinical risk for poor outcomes in the setting of suboptimal antiplatelet therapy. This includes, for example, patients undergoing high-risk multi-vessel PCI procedures, those who have already had an adverse outcome (e.g., stent thrombosis), and/or those with other high-risk clinical (e.g., ACS, diabetes mellitus, and chronic kidney failure) or angiographic features.

How should CYP2C19 genotype results be acted upon? Optimal individualized antiplatelet treatment should maximize benefit by reducing risk of recurrent cardiovascular events while minimizing adverse effects such as bleeding. Prasugrel is a new antiplatelet agent that does not depend on CYP2C19 for activation and that was found to be superior to clopidogrel with respect to cardiovascular events (HR for prasugrel vs. clopidogrel 0.81, 95% CI 0.73–0.90, $P < 0.001$).²² However, it may not represent a substitute for clopidogrel in all patients because of (i) a higher associated risk of bleeding (HR 1.32, 95% CI 1.03–1.68, $P = 0.03$), including fatal bleeding (prasugrel 0.4% vs. clopidogrel 0.1%, $P = 0.002$);²² (ii) the fact that its use at full dose is not recommended, and lower doses of prasugrel have not been adequately studied; (iii) the larger number of conditions for which clopidogrel is approved; and (iv) the lower expense of clopidogrel as it progressively comes off patent worldwide. In addition to prasugrel, ticagrelor²³ has been approved in Europe, and other antiplatelet alternatives are being developed. Older alternatives to clopidogrel include ticlopidine and cilostazol.

Table 2 and **Figure 1** summarize the therapeutic guidelines for clopidogrel based on CYP2C19 phenotype. 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).²⁴ 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.^{6,22,25–28}

The most challenging patient population to address is the CYP2C19 intermediate metabolizer phenotype (e.g., *1/*2).

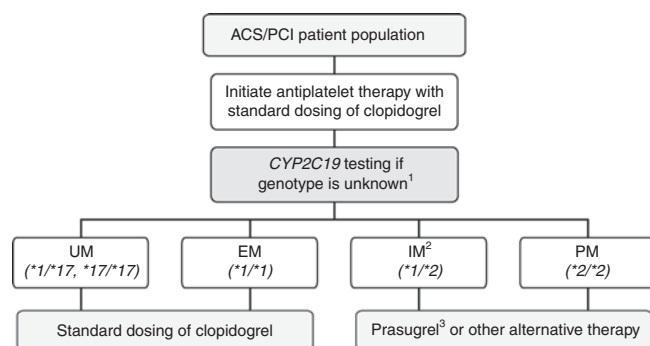


Figure 1 Algorithm for suggested clinical actions based on *CYP2C19* genotype in patients with acute coronary syndromes initiating antiplatelet therapy. ACS, acute coronary syndrome; EM, extensive metabolizer; IM, intermediate metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; UM, ultrarapid metabolizer. ¹Other rare *CYP2C19* genotypes exist apart from those illustrated (see **Supplementary Data** online for other genotypes and frequencies). ²Higher-dose clopidogrel has not been adequately studied at the time of this writing but may improve platelet function in a subset of IMs and PMs (**Supplementary Table S8** online). ³Note that prasugrel is recommended only when its use is not clinically contraindicated.

Intermediate metabolizers have higher on-treatment residual platelet activity on average as compared to extensive metabolizers,^{2–4,6,7} and *CYP2C19**2 heterozygous patients with ACSs who receive treatment with clopidogrel have higher risks for adverse cardiovascular outcomes including stent thrombosis¹⁸ (see **Supplementary Data** online). 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.

In recent pilot studies, increasing the clopidogrel maintenance dose from 75 to 150 mg/day increased platelet inhibition in some, but not all, patients who were *CYP2C19**2 heterozygotes (ref. 29 and **Supplementary Table S8** online). However, given that dose escalation was recently reported to produce no benefit among post-PCI patients with high on-treatment platelet reactivity,³⁰ it is currently premature to support a recommendation for an increased maintenance dose of 150 mg/day in *CYP2C19* intermediate metabolizers. Equally controversial is the use of platelet function testing alone (e.g., GRAVITAS and TRIGGER-PCI trial results) or in combination with *CYP2C19* genotype information. Future versions of these guidelines (updated at <http://www.pharmgkb.org>) will incorporate results from ongoing clinical trials that are designed to address these and other emerging issues.

Other considerations. Diabetes mellitus, increased age, and higher body mass index are associated with high on-treatment residual platelet aggregation, and the use of certain proton pump inhibitors may also affect clopidogrel response. In addition,

although these guidelines have been limited to the *CYP2C19**2 allele, many clinical genotyping platforms include other variant alleles (*3–*8, *17) that may alter the interpretation of a patient's predicted metabolizer phenotype (**Supplementary Table S3** online). There are reports that variants in other genes such as *ABCB1*, *P2YR₁₂*, and *PON1* may affect clopidogrel metabolism and/or efficacy, but the body of evidence does not support genotyping for these variants at the present time.

Potential benefits and risks for the patient. The potential benefits of *CYP2C19* testing are that patients with genotypes associated with a higher risk of adverse cardiovascular events during clopidogrel therapy can be identified, and an alternative antiplatelet strategy can be instituted. Although there is mounting evidence associating deficient *CYP2C19* with increased risks of adverse cardiovascular outcomes in patients on clopidogrel therapy, there are potential risks in making changes in a patient's therapy on the basis of *CYP2C19* genotype in the absence of randomized clinical trial evidence. *CYP2C19* genotyping is straightforward and reliable when performed in qualified laboratories. However, as with any laboratory test, an additional possible risk to the patient is an error in genotyping. Because genotype test results are applied life-long, any such error could have adverse health implications throughout the lifetime of the patient.

Caveats: appropriate use and/or potential misuse of genetic tests. One of the challenges for clinical pharmacogenetic testing is the need for rapid turnaround time and quick reporting of results. When a decision is made to pursue *CYP2C19* testing, it would be advantageous to have the results prior to initiating antiplatelet therapy because most potentially preventable recurrent events occur early; however, in the acute PCI setting, this is not easily achievable. Therefore, if *CYP2C19* genotype is not already known from prior testing, every effort should be made to initiate *CYP2C19* testing as early as possible and to emphasize the need for expedited results. These recommendations apply only to patients with coronary disease; e.g., those with ACSs or undergoing PCI, especially those with stent placements. Current data do not support the use of *CYP2C19* genotyping in other patient populations receiving clopidogrel.^{19,20}

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/cpt>

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CONFLICT OF INTEREST

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