# Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

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**ABSTRACT**

CYP2C19 catalyzes the bioactivation of the antiplatelet prodrug clopidogrel, and *CYP2C19* genotype impacts clopidogrel active metabolite formation. CYP2C19 intermediate and poor metabolizers who receive clopidogrel experience reduced platelet inhibition and increased risk for major adverse cardiovascular and cerebrovascular events. This guideline is an update to the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of clopidogrel based on *CYP2C19* genotype and includes expanded indications for *CYP2C19* genotype-guided antiplatelet therapy, increased strength of recommendation for CYP2C19 intermediate metabolizers, updated *CYP2C19* genotype to phenotype translation, and evidence from an expanded literature review (updates at www.cpicpgx.org).

**INTRODUCTION**

This document is an update to the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC®) guideline on the clinical use of *CYP2C19* genotype test results for patients requiring antiplatelet therapy (1). Since the previous update, results from prospective randomized clinical trials, multicenter pragmatic studies, and meta-analyses on *CYP2C19* genotype-guided antiplatelet therapy with clinical outcomes data have demonstrated the utility of this approach (2-6). The purpose of this guideline is to provide clinicians with information that facilitates the interpretation of clinical *CYP2C19* genotype test results to guide clopidogrel prescribing. As in

the previous guideline, recommendations for use of other laboratory tests, such as platelet function monitoring, as well as cost effectiveness analyses, are beyond the scope of this document. The guideline 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. CPIC guidelines are periodically updated at www.cpicpgx.org/guidelines/.

**FOCUSED LITERATURE REVIEW**

A systematic literature review focused on *CYP2C19* genotype and clopidogrel response was conducted (see **Supplemental Material** for more details). Evidence is summarized in **Tables S1-S4**.

**GENE: *CYP2C19***
**Background**

The *CYP2C19* gene is highly polymorphic; the Pharmacogene Variation Consortium (PharmVar) has currently defined over 35 star (*) allele haplotypes (7), including rare gene deletions (https://www.pharmvar.org/gene/CYP2C19; see ***CYP2C19* Allele Definition Table** online (8, 9)). The frequencies of these star (*) alleles significantly differ across ancestrally diverse populations (see ***CYP2C19* Allele Frequency Table** online (8, 9)). Alleles are categorized into functional groups as follows: normal function (e.g., *CYP2C19*1*), decreased function (e.g., *CYP2C19*9*), no function (e.g., *CYP2C19*2* and *3*), and increased function (e.g., *CYP2C19*17*). Clinical allele function, as described in the ***CYP2C19* Allele Functionality Table**, was determined based on reported *in vitro* and/or *in vivo* data when available (8, 9).

**Genetic Test Interpretation**

The combination of inherited alleles determines a person's diplotype (also referred to as genotype). **Table 1** defines each predicted phenotype based on allele function combinations and provides example diplotypes. CYP2C19 normal metabolizers (NMs) are characterized by the presence of two normal function alleles (e.g., *CYP2C19*1/*1*). CYP2C19 intermediate metabolizers (IMs) are characterized by the presence of one normal function allele and one no function allele (e.g., *CYP2C19*1/*2*). Limited data suggest that the increased function allele

*CYP2C19\*17* may not compensate for no function alleles such as *CYP2C19\*2,* and thus diplotypes containing one no function allele and one increased function allele (e.g., *CYP2C19\*2/\*17*) are also defined as IMs (10). CYP2C19 poor metabolizers (PMs) are characterized by the presence of two no function alleles (e.g., *CYP2C19 \*2/\*3*). Diplotypes characterized by one normal function allele and one increased function allele (i.e., *CYP2C19\*1/\*17)* are classified as rapid metabolizers (RMs), and diplotypes characterized by two increased function alleles (i.e., *CYP2C19\*17/\*17*) are classified as ultrarapid metabolizers (UMs). There are limited data available for decreased function alleles (e.g., *CYP2C19\*9* and *\*10*); therefore, individuals who have one normal function and one decreased function allele (i.e., *CYP2C19\*1/\*9*), or one increased function and one decreased function allele (i.e., *CYP2C19\*9/\*17*), or two decreased function alleles (i.e., *CYP2C19\*9/\*10*), are currently classified as "likely IM." Individuals with one no function and one decreased function allele are currently classified as "likely PM." The "indeterminate" phenotype is assigned when the individual carries one or two uncertain function alleles. See the **CYP2C19 Diplotype-Phenotype Table** online for a complete list of possible diplotypes and the corresponding predicted metabolizer phenotype assignments (8, 9). CPIC's standard operating procedures for assigning allele clinical function, translating diplotypes to phenotypes, and designating phenotypes as "likely" or "indeterminate" is available on the CPIC website (https://cpicpgx.org/resources/).

Most clinical laboratories report *CYP2C19* genotype results using star (\*) allele nomenclature. The star (\*) allele nomenclature for *CYP2C19* is found at the PharmVar website (https://www.pharmvar.org/gene/CYP2C19). Tables on the CPIC website contain a list of *CYP2C19* alleles, the combinations of variants that define each allele, allele function, and reported allele frequencies across major ancestral populations (8).

**Available Genetic Test Options**

See the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

**Incidental Findings**

No inherited diseases or conditions have been consistently or strongly linked to germline genetic variants in *CYP2C19* independent of drug metabolism and response.

## Other Considerations

*CYP2C19* genetic variation does not account for all of the variability in clopidogrel response. Some studies have implicated variants in other genes associated with clopidogrel response (e.g., *ABCB1*, *B4GALT2*, *CES1*, *CYP2B6*, *CYP2C9*, *P2RY12*, and *PON1*); however, these have not been consistently replicated, and *CYP2C19* is the most validated genetic determinant of clopidogrel response (11-13). Consequently, this guideline on genotype-guided antiplatelet therapy is limited to *CYP2C19* variant alleles.

## DRUG: CLOPIDOGREL

### Background

Clopidogrel is commonly prescribed to reduce the risk of myocardial infarction (MI) and stroke in patients with acute coronary syndromes (ACS) and/or following percutaneous coronary intervention (PCI). Despite the availability of newer and more potent agents (i.e., prasugrel and ticagrelor), clopidogrel remains the most commonly prescribed antiplatelet drug in North America for ACS and PCI (14-16). Clopidogrel is also indicated for patients with a recent MI, recent stroke, or established peripheral arterial disease. Clopidogrel is a thienopyridine prodrug that requires hepatic biotransformation to form an active metabolite that selectively and irreversibly inhibits the purinergic $P2Y_{12}$ receptor and thus platelet aggregation for the platelet's lifespan (~10 days). Only 15% of the prodrug is available for transformation to the active agent; the remaining 85% is hydrolyzed by carboxylesterase-1 (CES1) 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; **Figure S1**). However, in both steps CYP2C19 has the greatest contribution of all of these enzymes (17).

### Linking Genetic Variability to Variability in Drug-Related Phenotypes

Patient responses to clopidogrel vary widely, which is evidenced by the inhibition of adenosine diphosphate-induced platelet aggregation being normally distributed across a broad range (18). Many studies have shown that CYP2C19 IMs and PMs have reduced active clopidogrel metabolite concentrations and higher on-treatment platelet reactivity compared to CYP2C19 NMs (1). Moreover, substantial evidence exists linking *CYP2C19* no function alleles

with poorer clinical outcomes among clopidogrel-treated ACS patients, particularly those undergoing PCI, likely as a result of decreased clopidogrel active metabolite formation. Carriers of the increased function *CYP2C19\*17* allele exhibit modestly higher clopidogrel active metabolite formation, inhibition of platelet reactivity, and bleeding risk compared to non-carriers in some studies; however, because *\*17* does not occur on the *\*2* haplotype, these associations could be due in part to absence of the no function *\*2* allele (10, 12, 19, 20). Therefore, when accounting for the presence of *CYP2C19* no function alleles and assigning predicted CYP2C19 phenotype (**Table 1**), the magnitude of pharmacokinetic and pharmacodynamic differences in CYP2C19 RMs (i.e., *CYP2C19\*1/\*17)* and UMs (i.e., *CYP2C19\*17/\*17)* compared to NMs (i.e., *CYP2C19\*1/\*1)* are diminished, and associations of *\*17* with bleeding and ischemic outcomes after PCI in clopidogrel-treated patients have not been observed (12, 21).

Studies linking *CYP2C19* genotype with variability in clopidogrel response are summarized in **Tables S1-S4.** It is this body of evidence that provides the basis for genotype-informed therapeutic recommendations when considering treatment with clopidogrel (**Tables 2 and 3**). Importantly, the most definitive studies showing a relationship between *CYP2C19* genotype and clopidogrel response have predominantly been conducted in patients with ACS, almost all of whom underwent PCI. However, there are accumulating data showing a similar relationship between *CYP2C19* no function alleles and clopidogrel response when it is used for other indications, including treatment of acute ischemic stroke or transient ischemic attack (TIA) (22). These data, in combination with strong pharmacokinetic and pharmacodynamic data, support the use of *CYP2C19* genotype-guided antiplatelet therapy when considering clopidogrel for neurovascular indications (**Table 3**).

Large meta-analyses (**Table S4**) have shown that clopidogrel-treated patients undergoing PCI who are CYP2C19 IMs (e.g., *\*1/\*2, \*1/\*3*) or PMs (e.g., *\*2/\*2, \*2/\*3*) have an increased risk for major adverse cardiovascular events (MACE) and stent thrombosis compared to CYP2C19 NMs (i.e., *\*1/\*1*). Similar magnitudes of increased risk for MACE and stent thrombosis in clopidogrel-treated IMs and PMs have been shown in prior meta-analyses of predominantly European ancestry populations (23), and more recent meta-analyses in East Asian populations (MACE: odds ratio [OR] 1.92, 95% CI 1.34-2.76 for IMs and OR 3.08, 95% CI 1.85-5.13 for PMs; stent thrombosis: OR 4.77, 95% CI 2.84-8.01 for IMs and PMs combined) (24).

Patients treated with clopidogrel for ischemic stroke or TIA and who were genotyped as *CYP2C19\*2, \*3,* or *\*8* heterozygotes (IMs) or homozygotes (PMs) had an increased risk for composite vascular events (stroke, MI, or vascular death) compared to patients without those alleles (risk ratio [RR] 1.51, 95% CI 1.10-2.06), and increased risk of stroke (RR 1.92, 95% CI 1.57-2.35) (22). However, meta-analyses have also reported a lack of effect of *CYP2C19* no function alleles on adverse cardiovascular outcomes among patients receiving clopidogrel for non-PCI cardiovascular indications, possibly due to lower clinical benefit from treatment with clopidogrel in these patient populations (25). The growing body of literature implicating *CYP2C19* no function alleles in adverse clopidogrel responses prompted the U.S. Food and Drug Administration (FDA) to update the boxed warning on the clopidogrel label in 2016, noting the diminished effectiveness in CYP2C19 PMs to include all patients taking clopidogrel instead of just those with ACS who undergo PCI.

**Therapeutic Recommendations**

Optimal individualized antiplatelet treatment should maximize benefit by reducing risk of cardiovascular and cerebrovascular events while minimizing adverse effects such as bleeding. Prasugrel and ticagrelor are alternative $P2Y_{12}$ receptor inhibitors that exhibit more potent and consistent antiplatelet effects, and superior efficacy in ACS patients not subset by genotype, compared to clopidogrel in randomized clinical trials (26, 27). In contrast to clopidogrel, *CYP2C19* genotype did not influence the pharmacokinetics, antiplatelet effects, or clinical effectiveness of prasugrel or ticagrelor (28, 29). However, prasugrel and ticagrelor also had higher bleeding risk and cost compared to clopidogrel that, in addition to ticagrelor-associated dyspnea and requirement for twice daily dosing, have been associated with higher discontinuation rates (16, 30).

A comparison of guideline and label recommendations for *CYP2C19* and clopidogrel is summarized in **Table S5**. Despite several clinical guidelines recommending prasugrel or ticagrelor over clopidogrel in ACS patients (31, 32), clopidogrel continues to be a widely prescribed medication for ACS and non-ACS patients undergoing PCI as well as for patients with other cardiovascular and neurovascular indications or at increased risk for bleeding. As the FDA boxed warning does not require genetic testing to initiate clopidogrel therapy, if a patient's genotype is not known, the decision to perform *CYP2C19* testing is at the discretion of the

treating clinician. Although clinical guidelines from the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology recommend against routine *CYP2C19* testing, these groups have noted that use of *CYP2C19* testing to guide selection of prasugrel or ticagrelor in CYP2C19 IMs and PMs may be considered in select PCI and ACS patients at high risk for poor outcomes (e.g., urgent PCI for an ACS event, elective PCI for unprotected left main disease or last patent coronary artery) (31-33). Recent meta-analyses have demonstrated that *CYP2C19* genotype-guided therapy could identify PCI patients who benefit most from alternative antiplatelet therapy (5, 6).

With the growing ease and availability of genetic testing and other sequencing programs, an increasing number of patients in the near future may already know their *CYP2C19* genotype status at the time of treatment, and this document provides guidance on clinical management for those in whom genotype is available or for whom the clinician chooses to order a *CYP2C19* genotyping test. CPIC guidelines are designed to help clinicians understand how available genetic test results can be used to optimize drug therapy, rather than to recommend in whom pharmacogenetic testing should be conducted. **Table 2** and **Table 3** summarize the therapeutic recommendations for antiplatelet therapy based on *CYP2C19* status for cardiovascular and neurovascular indications, respectively, when considering treatment with clopidogrel. Selection of therapy will depend on individual patient treatment goals and risks for adverse events.

In patients with ACS and/or undergoing PCI, the clinical recommendations remain unchanged from the previous guideline – avoid clopidogrel in CYP2C19 IMs and PMs and use an alternative antiplatelet agent, such as prasugrel or ticagrelor, if no contraindications (**Table 2**). Of note, the strength of recommendation for CYP2C19 IMs in this guideline update has changed from "moderate" to "strong" based on the preponderance of clinical outcomes evidence among IMs. The reported literature indicates that both CYP2C19 IMs and PMs exhibit reduced clopidogrel active metabolite formation, increased on-treatment platelet reactivity, and higher rates of MACE compared to CYP2C19 NMs, RMs, and UMs (**Tables S1-S2**). A recent meta-analysis that included 15,949 patients (77% PCI, 98% ACS) of seven randomized controlled trials of genotype-guided antiplatelet therapy reported that treatment with prasugrel or ticagrelor reduced major ischemic events compared to clopidogrel in CYP2C19 IMs and PMs (RR 0.70, 95% CI 0.59-0.83), whereas no difference was observed in patients who were non-carriers of no function alleles (RR 1.0, 95% CI 0.80-1.25) (5). A significant genotype-treatment interaction

was reported (p=0.013), suggesting that the benefit of prasugrel or ticagrelor over clopidogrel is greatest in *CYP2C19* no function allele carriers (5). 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 to 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 to NMs in PCI patients (21, 34).

The therapeutic recommendations for patients with ACS and/or undergoing PCI were informed by a series of non-randomized prospective studies and randomized trials demonstrating that a *CYP2C19* genotype-guided antiplatelet therapy strategy (defined as use of prasugrel or ticagrelor in CYP2C19 IMs and PMs and standard-dose clopidogrel in NMs) lowers the risk of MACE compared to conventional treatment strategies (**Table S2**). We highlight three key studies. First, a multisite, pragmatic investigation by seven early adopter U.S. institutions in the Implementing Genomics in Practice (IGNITE) Network examined clinical outcomes in 1,815 patients undergoing *CYP2C19* genotype-guided antiplatelet therapy after PCI for either an ACS or non-ACS indication (2). CYP2C19 IMs and PMs treated with clopidogrel experienced a significantly higher risk of MACE over 12 months after PCI compared to IMs and PMs who received alternative therapy (adjusted HR 2.26; 95% CI 1.18–4.32; p=0.013).

Second, the POPular Genetics trial was a randomized, open-label, noninferiority trial that compared a *CYP2C19* genotype-guided de-escalation strategy (defined as use of standard-dose clopidogrel in NMs and prasugrel or ticagrelor in CYP2C19 IMs and PMs) against universal ticagrelor or prasugrel in 2,488 ST segment elevation MI patients undergoing primary PCI (3). The genotype-guided strategy was noninferior to ticagrelor or prasugrel in occurrence of the primary outcome of death, MI, stent thrombosis, stroke, or major bleeding (5.1% vs 5.9%, respectively; absolute difference -0.7%; 95% CI -2.0–0.7; p-value for non-inferiority <0.001). The strategy of genotype-guided de-escalation to clopidogrel in NMs significantly reduced major or minor bleeding (9.8 vs 12.5%, respectively; HR 0.78; 95% CI 0.61–0.98; p=0.04) and did not result in an overall increase in major ischemic events (2.7% vs 3.3%, respectively; HR 0.83; 95% CI 0.53–1.31), compared to universal ticagrelor or prasugrel. The difference in bleeding rates was driven by a reduction in minor bleeding since no difference in major bleeding was observed.

Third, the TAILOR-PCI trial was a randomized, open-label, superiority trial that compared a *CYP2C19* genotype-guided escalation strategy (defined as use of ticagrelor in CYP2C19 IMs and PMs and standard-dose clopidogrel in NMs) to universal clopidogrel in 5,302 patients undergoing PCI for either an ACS or non-ACS indication (4). In the primary analysis, ticagrelor-treated CYP2C19 IMs and PMs in the genotype-guided arm experienced a numerically lower rate of MACE at 12 months compared to clopidogrel-treated IMs and PMs in the conventional arm (4.0% vs 5.9%, respectively; HR 0.66, 95% CI 0.43–1.02; p=0.06); however, the overall event rate was lower than anticipated leading to wide confidence intervals and the difference was not statistically significant. In a post-hoc analysis, a reduction in cardiovascular events at 90 days was observed in the genotype-guided group versus control (HR 0.21; 95% CI 0.08–0.54; p=0.001). The rates of major or minor bleeding events were not significantly different across groups (HR 1.22; 95% CI 0.60–2.51; p=0.58).

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. Elective PCI patients have lower risk of cardiovascular events compared to ACS patients, 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 elective PCI patients (**Table 2**). In the setting of elective PCI, where clopidogrel is the preferred $P2Y_{12}$ inhibitor recommended by clinical practice guidelines and widely prescribed, the FDA label boxed warning recommends alternative antiplatelet therapy for CYP2C19 PMs. However, neither prasugrel nor ticagrelor are FDA-approved for elective PCI, and the consideration of clopidogrel must be weighed against the off-label use of prasugrel or ticagrelor (35).

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 myocardial infarction, 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. Although this recommendation is supported by limited clinical data, there are strong pharmacokinetic data that may be extrapolated to these clinical scenarios. Furthermore,

this recommendation is consistent with the FDA boxed warning on the clopidogrel drug label for alternative therapy in CYP2C19 PMs regardless of indication.

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 $P2Y_{12}$ inhibitor at standard doses if clinically indicated and no contraindication. Alternative $P2Y_{12}$ inhibitors not impacted by *CYP2C19* genetic variants with indications for stroke patients 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. Thus, selection of therapy will depend on individual patient treatment goals and risks for adverse events.

These therapeutic recommendations are supported by clinical data from the CHANCE-2 trial, which was a randomized, double-blind, superiority trial in 6,412 patients with acute ischemic stroke or TIA (36). The trial exclusively enrolled CYP2C19 IMs and PMs following rapid genotyping, and compared the effects of ticagrelor plus aspirin to standard-dose clopidogrel (75 mg/day) plus aspirin over 90 days. Compared to clopidogrel, ticagrelor-treated IMs and PMs experienced significantly lower rates of stroke (7.6% vs. 6.0%, respectively; HR 0.77, 95% CI 0.64-0.94; p=0.008) and major vascular events (9.2% vs 7.2%, respectively; HR 0.77, 95% CI 0.65-0.92). Similar reductions in stroke risk were observed in IMs and PMs. No significant differences in moderate or severe bleeding was observed (HR 0.82, 95% CI 0.34-1.98); however, ticagrelor was associated with higher rates of mild bleeding (HR 2.41, 95% CI 1.81-3.20). In addition, there are strong pharmacokinetic data that may be extrapolated to these clinical scenarios, and the recommendation for PMs is consistent with the FDA boxed warning on the clopidogrel drug label for alternative therapy in CYP2C19 PMs regardless of indication. There are insufficient data on ischemic outcomes and bleeding in the setting of neurovascular disease to make a clinical recommendation for CYP2C19 UMs and RMs.

### *Clopidogrel Dose Escalation*

Studies have reported that increasing clopidogrel loading and/or maintenance dose is an alternative strategy to improve inhibition of platelet reactivity among CYP2C19 IMs, and to a lesser degree in PMs (see **Table S2**). However, early dose escalation studies typically only doubled the clopidogrel maintenance dose to 150 mg/day in *CYP2C19* no function allele carriers, which has proven to be inadequate based on more rigorous recent studies demonstrating that even higher doses (225 mg/day) are required to achieve platelet inhibition among CYP2C19 IMs at a level comparable to standard dose clopidogrel (75 mg/day) in NMs (37, 38). However, a dose of 300 mg/day may be required in CYP2C19 IMs with diabetes, and doses as high as 300 mg/day in CYP2C19 PMs do not appear to result in a comparable degree of platelet inhibition (37-39). A meta-analysis showed significantly increased risk of MACE in CYP2C19 IMs and PMs treated with higher doses of clopidogrel compared to non-carriers of no function alleles treated with standard doses of clopidogrel (RR 1.68, 95% CI 1.19- 2.37) (40). Therefore, the current evidence does not support a clopidogrel dose escalation strategy based on *CYP2C19* genotype. If clopidogrel cannot be avoided, clopidogrel 225 mg/day could be considered as an alternative treatment option to prasugrel or ticagrelor in CYP2C19 IMs. In CYP2C19 PMs, it is recommended to avoid clopidogrel, as dose-escalation is not likely to produce adequate platelet inhibition.

### *Pediatrics*

Clopidogrel is not commonly used in the pediatric patient population. The clinical data on which this guideline is based were obtained from studies in adults. Given the well-characterized pharmacokinetic basis for this gene-drug interaction and the presence of fully mature CYP2C19 enzyme activity after 2-3 months of age, it is reasonable to extrapolate the recommendations presented in this guideline to pediatric patients if needed.

### Recommendations for Incidental Findings
Not applicable

### Other Considerations
Advanced age, body mass index, chronic kidney disease, and diabetes mellitus are associated with high on-treatment residual platelet aggregation (41). In addition, use of certain

proton pump inhibitors that inhibit CYP2C19 enzyme activity may also affect clopidogrel response. The impact of these effects in combination with *CYP2C19* genotype warrants further investigation.

### *Implementation of this Guideline*

The guideline supplement and CPIC website (https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/) contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* in the **Supplemental Material**).

## POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using *CYP2C19* genotype data to guide antiplatelet therapy for cardiovascular and neurovascular indications is the avoidance of standard dose clopidogrel in CYP2C19 IMs and PMs who are genetically predisposed to therapeutic failure, thereby reducing the risk of major adverse cardiovascular and cerebrovascular events. Randomized clinical trial and real-world implementation data in the setting of ACS and PCI support use of a genotype-guided strategy to reduce ischemic events without significantly increasing major bleeding; however, the effectiveness and safety of a genotype-guided approach remains less clear in the setting of neurovascular disease and cardiovascular indications outside the setting of ACS or PCI. As with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, which could have long-term adverse health implications for patients.

## CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

There are some important limitations to *CYP2C19* genetic tests. Targeted genotyping tests focus on interrogating previously described star (*) alleles and therefore are not designed to detect novel variants. Furthermore, rare allelic *CYP2C19* variants may not be included in the genotype test used, and patients with these rare variants may be assigned a NM phenotype (*CYP2C19*1/*1*) by default. As such, an assigned *CYP2C19*1* allele could potentially harbor an undetected genetic variant (e.g., rare no function alleles such as *4-*8*) that results in altered

metabolism and drug exposure. In addition, rare alleles with gene deletions at the *CYP2C19* locus have recently been reported (*36* and *37*) (42); however, most clinical laboratories do not currently test for *CYP2C19* deletions or any other structural variants. Therefore, it is important that clinical providers appreciate the limitations of targeted genotyping tests and understand which *CYP2C19* variant alleles were genotyped when interpreting results. The Association for Molecular Pathology has published recommendations for a minimum set of variants that should be included in clinical genotyping assays for *CYP2C19* (43). As with any diagnostic test, *CYP2C19* genotype is just one factor that clinicians should consider when prescribing clopidogrel.

## DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

## ACKNOWLEDGEMENTS

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**Table 1.** Assignment of Predicted CYP2C19 Phenotype Based on Genotype

| Predicted phenotype | Genotype | Examples of CYP2C19 diplotypes[a] |
|---|---|---|
| CYP2C19 ultrarapid metabolizer | An individual carrying two increased function alleles | *17/*17 |
| CYP2C19 rapid metabolizer | An individual carrying one normal function allele and one increased function allele | *1/*17 |
| CYP2C19 normal metabolizer | An individual carrying two normal function alleles | *1/*1 |
| CYP2C19 likely intermediate metabolizer[b] | An individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles | *1/*9, *9/*17, *9/*9 |
| CYP2C19 intermediate metabolizer | An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele | *1/*2, *1/*3, *2/*17, *3/*17 |
| CYP2C19 likely poor metabolizer[b] | An individual carrying one decreased function allele and one no function allele | *2/*9, *3/*9 |
| CYP2C19 poor metabolizer | An individual carrying two no function alleles | *2/*2, *3/*3, *2/*3 |
| Indeterminate | An individual carrying one or | *1/*12, *2/*12, *12/*14 |

| | two uncertain function alleles | |
| --- | --- | --- |

[a]Please refer to the **CYP2C19 Diplotype-Phenotype Table** online for a complete list. For allele functions and population-specific allele and phenotype frequencies, please refer to the **CYP2C19 Allele Functionality Table** and the **CYP2C19 Allele Frequency Table** online (8, 9).

[b]There are limited data to characterize the function of decreased function alleles.

**Table 2.** Antiplatelet therapy recommendations based on CYP2C19 phenotype when considering clopidogrel for cardiovascular indications

| CYP2C19 phenotype[a] | Implications for phenotypic measures | Therapeutic recommendation | Classification of recommendation[b] - ACS and/or PCI[c] | Classification of recommendation[b] - non-ACS, non-PCI cardiovascular indications[d] |
|---|---|---|---|---|
| CYP2C19 ultrarapid metabolizer | 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 |
| CYP2C19 rapid metabolizer | Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk | If considering clopidogrel, use at standard dose (75 mg/day) | Strong | No recommendation |
| CYP2C19 normal metabolizer | Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity | If considering clopidogrel, use at standard dose (75 mg/day) | Strong | Strong |

| CYP2C19 likely intermediate metabolizer | Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication. | Strong[e] | No recommendation[e] |
|---|---|---|---|---|
| CYP2C19 intermediate metabolizer | Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication. | Strong | No recommendation |
| CYP2C19 likely poor metabolizer | 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[e] | Moderate[e] |
| CYP2C19 poor metabolizer | Significantly reduced clopidogrel active metabolite formation; increased on- | Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard | Strong | Moderate |

| | treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | dose if no contraindication. | | |
|---|---|---|---|---|

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention

[a]The online **CYP2C19 Allele Frequency Table** provides phenotype frequencies for major race/ethnic groups, and the online **CYP2C19 Diplotype-Phenotype Table** provides a complete list of possible diplotypes and phenotype assignments (8, 9).

[b]Rating scheme described in the **Supplemental Material** online.

[c]ACS and/or PCI includes patients undergoing PCI for an ACS or non-ACS (elective) indication.

[d]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.

[e]The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

**Table 3.** Antiplatelet therapy recommendations based on CYP2C19 phenotype when considering clopidogrel for neurovascular indications[a]

| CYP2C19 phenotype[b] | Implications for phenotypic measures | Therapeutic recommendation | Classification of recommendation[c] | Other Considerations |
|---|---|---|---|---|
| CYP2C19 ultrarapid metabolizer | Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity | No recommendation | No recommendation | |
| CYP2C19 rapid metabolizer | Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity | No recommendation | No recommendation | |
| CYP2C19 normal metabolizer | Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity | If considering clopidogrel, use at standard dose (75 mg/day) | Strong | |
| CYP2C19 likely | Reduced clopidogrel active metabolite | Consider an alternative $P2Y_{12}$ inhibitor at standard dose if | Moderate[d] | Alternative $P2Y_{12}$ inhibitors not impacted by CYP2C19 genetic variants |

| intermediate metabolizer | formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | clinically indicated and no contraindication. | | include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA.[e] |
|---|---|---|---|---|
| CYP2C19 intermediate metabolizer | Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Consider an alternative P2Y$_{12}$ inhibitor at standard dose if clinically indicated and no contraindication. | Moderate | Alternative P2Y$_{12}$ inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA.[e] |
| CYP2C19 likely poor metabolizer | 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 P2Y$_{12}$ inhibitor at standard dose if clinically indicated and no contraindication. | Moderate[d] | Alternative P2Y$_{12}$ inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA.[e] |

| CYP2C19 poor metabolizer | 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 P2Y$_{12}$ inhibitor at standard dose if clinically indicated and no contraindication. | Moderate | Alternative P2Y$_{12}$ inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA. [e] |
|---|---|---|---|---|

[a]Neurovascular disease includes acute ischemic stroke or transient ischemic attack, 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 online **CYP2C19 Allele Frequency Table** provides phenotype frequencies for major race/ethnic groups, and the online **CYP2C19 Diplotype-Phenotype Table** provides a complete list of possible diplotypes and phenotype assignments (8, 9).

[c]Rating scheme described in the **Supplemental Material** online.

[d]The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

[e]Given limited outcomes data for genotype-guided anti-platelet therapy for neurovascular indications, selection of therapy should depend on individual patient treatment goals and risks for adverse events.