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

Craig R. Lee[1], Jasmine A. Luzum[2], Katrin Sangkuhl[3], Roseann S. Gammal[4,5], Marc S. Sabatine[6], Charles Michael Stein[7], David F. Kisor[8], Nita A. Limdi[9], Yee Ming Lee[10], Stuart A. Scott[11,12], Jean-Sébastien Hulot[13], Dan M. Roden[14], Andrea Gaedigk[15], Kelly E. Caudle[5], Teri E. Klein[3], Julie A. Johnson[16] and Alan R. Shuldiner[17,*]

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).

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 **Supplementary 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

[1]Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, North Carolina, USA; [2]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA; [3]Department of Biomedical Data Science, Stanford University, Stanford, California, USA; [4]Department of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, USA; [5]Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [6]Thrombolysis in Myocardial Infarction Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [7]Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [8]Department of Pharmaceutical Sciences, Manchester University, Fort Wayne, Indiana, USA; [9]Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama, USA; [10]Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado, USA; [11]Department of Pathology, Stanford University, Stanford, California, USA; [12]Clinical Genomics Laboratory, Stanford Health Care, Palo Alto, California, USA; [13]Université de Paris, CIC1418 and DMU CARTE, AP-HP, Hôpital Européen Georges-Pompidou, Paris, France; [14]Departments of Medicine and Pharmacology, Office of Personalized Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [15]Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Children's Mercy Kansas City and University of Missouri Kansas City School of Medicine, Kansas City, Missouri, USA; [16]Department of Pharmacotherapy and Translational Research, Center for Pharmacogenomics and Precision Medicine, College of Pharmacy, University of Florida, Gainesville, Florida, USA; [17]Department of Medicine, and Program for Genomic and Personalized Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA. *Correspondence: Alan R. Shuldiner (ashuldin@som.umaryland.edu; contact@cpicpgx.org)

Received September 20, 2021; accepted December 22, 2021. doi:10.1002/cpt.2526

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 IMs." Individuals with one no function and one decreased function allele are currently classified as "likely PMs." 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.

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 metabolizer	An individual carrying one or two uncertain function alleles	**1/*12*, **2/*12*, **12/*14*

[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.

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 patients with clopidogrel-treated ACS, 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 (**Table ,2 Table 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* and **1/*3*) or PMs (e.g., **2/*2* and **2/*3*) have an increased risk for major adverse cardiovascular events (MACEs) and stent thrombosis compared with 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% confidence interval (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 with 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 US 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 patients with ACS not subset by genotype, compared with 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 patients with ACS,[31,32] clopidogrel continues to be a widely prescribed medication for ACS and non-ACS patients

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-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

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 **Supplementary 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.

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 patients undergoing PCI and with ACS 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 patients undergoing PCI 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 with CYP2C19 NMs, RMs, and UMs (**Tables S1–S2**). A recent meta-analysis that included 15,949 patients (77% undergoing PCI and 98% with ACS) of 7 randomized controlled trials of genotype-guided antiplatelet therapy reported that treatment with prasugrel or ticagrelor reduced major ischemic events compared with 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 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.[21,34]

The therapeutic recommendations for patients with ACS and/or undergoing PCI were informed by a series of nonrandomized 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 with conventional treatment strategies (**Table S2**). We highlight three key studies. First, a multisite, pragmatic investigation by seven early adopter US 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 with 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 patients with ST segment elevation MI 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 noninferiority < 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 with universal ticagrelor or prasugrel. The difference in bleeding rates was driven by a reduction in minor bleeding because 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) with 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 with 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 CIs 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 vs. 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, $P = 0.58$).

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 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[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 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 **Supplementary 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.

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 (**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 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. 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 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. 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 with 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 were 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 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 **Supplementary 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 an 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

The 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 variations 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. The 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.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors acknowledge the critical input of Dr. Mary Relling and members of the Clinical Pharmacogenetics Implementation Consortium (CPIC), funded by the National Institutes of Health. CPIC members are listed here: https://cpicpgx.org/members/.

FUNDING

This work was funded by the National Institutes of Health (NIH) for CPIC (R24GM115264 and U24HG010135), PharmGKB (U24HG010615), and PharmVar (R24 GM123930). Additional grant funding includes R01HL149752 (C.R.L.), K08HL146990 (J.A.L.), UL1TR003098 (A.R.S.), R35GM131770 (C.M.S), and R01HL092173 and K24HL133373 (N.A.L.).

CONFLICTS OF INTEREST

In addition to his part-time faculty appointment at the University of Maryland School of Medicine, A.R.S. is an employee of Regeneron Pharmaceuticals, Inc and receives stock options and restricted stock units as part of his compensation. S.A.S. is a paid consultant of Sema4. J.S.H. has received speaker, advisory board or consultancy fees from Amgen, Astra Zeneca, Bayer, Bioserenity, Bristol-Myers Squibb, MSD, Novartis, Vifor, all unrelated to the present guidelines. M.S.S. reports grants and personal fees from Amgen, Anthos Therapeutics, AstraZeneca, Intarcia, Medicines Company, MedImmune, and Merck; personal fees from Althera, Bristol-Myers Squibb, CVS Caremark, DalCor, Dr. Reddy's Laboratories, Dyrnamix, Fibrogen, IFM Therapeutics, and Novo Nordisk; and grants from Bayer, Daiichi-Sankyo, Eisai, IONIS, Novartis, Pfizer and Quark Pharmaceuticals, and is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from: Abbott, Regeneron, Roche, and Zora Biosciences. All other authors declared no competing interests for this work.

1. Scott, S.A. *et al*. Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin. Pharmacol. Ther.* **94**, 317–323 (2013).
2. Cavallari, L.H. *et al*. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *JACC Cardiovasc. Interv.* **11**, 181–191 (2018).
3. Claassens, D.M.F. *et al*. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N. Engl. J. Med.* **381**, 1621–1631 (2019).
4. Pereira, N.L. *et al*. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA* **324**, 761–771 (2020).
5. Pereira, N.L. *et al*. Effect of CYP2C19 genotype on ischemic outcomes during oral P2Y12 inhibitor therapy: a meta-analysis. *JACC Cardiovasc. Interv.* **14**, 739–750 (2021).
6. Galli, M. *et al*. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet* **397**, 1470–1483 (2021).
7. Botton, M.R. *et al*. PharmVar GeneFocus: CYP2C19. *Clin. Pharmacol. Ther.* **109**, 352–366 (2021).

8. CPIC. CPIC® Guideline for Clopidogrel and CYP2C19 <https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/> (2021). Accessed March 30, 2021.
9. PharmGKB. Gene-specific Information Tables for CYP2C19 <https://www.pharmgkb.org/page/cyp2c19RefMaterials> (2021). Accessed March 30, 2021.
10. Sibbing, D. *et al*. Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy. *J. Thromb. Haemost.* **8**, 1685–1693 (2010).
11. Verma, S.S. *et al*. Genomewide association study of platelet reactivity and cardiovascular response in patients treated with clopidogrel: a study by the international clopidogrel pharmacogenomics consortium. *Clin. Pharmacol. Ther.* **108**, 1067–1077 (2020).
12. Lewis, J.P. *et al*. Pharmacogenomic polygenic response score predicts ischaemic events and cardiovascular mortality in clopidogrel-treated patients. *Eur. Heart J. Cardiovasc. Pharmacother.* **6**, 203–210 (2020).
13. Scott, S.A. *et al*. Exome sequencing of extreme clopidogrel response phenotypes identifies B4GALT2 as a determinant of on-treatment platelet reactivity. *Clin. Pharmacol. Ther.* **100**, 287–294 (2016).
14. Karve, A.M. *et al*. Contemporary use of ticagrelor in interventional practice (from Blue Cross Blue Shield of Michigan Cardiovascular Consortium). *Am. J. Cardiol.* **115**, 1502–1506 (2015).
15. Gandhi, S. *et al*. Increased uptake of guideline-recommended oral antiplatelet therapy: insights from the Canadian acute coronary syndrome reflective. *Can. J. Cardiol.* **30**, 1725–1731 (2014).
16. Dayoub, E.J. *et al*. Trends in platelet adenosine diphosphate P2Y12 receptor inhibitor use and adherence among antiplatelet-naive patients after percutaneous coronary intervention, 2008–2016. *JAMA Intern. Med.* **178**, 943–950 (2018).
17. Kazui, M. *et al*. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab. Dispos.* **38**, 92–99 (2010).
18. Shuldiner, A.R. *et al*. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* **302**, 849–857 (2009).
19. Lewis, J.P. *et al*. The CYP2C19*17 variant is not independently associated with clopidogrel response. *J. Thromb. Haemost.* **11**, 1640–1646 (2013).
20. Sibbing, D. *et al*. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation* **121**, 512–518 (2010).
21. Lee, C.R. *et al*. Impact of the CYP2C19*17 allele on outcomes in patients receiving genotype-guided antiplatelet therapy after percutaneous coronary intervention. *Clin. Pharmacol. Ther.* **109**, 705–715 (2021).
22. Pan, Y. *et al*. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Circulation* **135**, 21–33 (2017).
23. Mega, J.L. *et al*. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* **304**, 1821–1830 (2010).
24. Xi, Z., Fang, F., Wang, J., AlHelal, J., Zhou, Y. & Liu, W. CYP2C19 genotype and adverse cardiovascular outcomes after stent implantation in clopidogrel-treated Asian populations: A systematic review and meta-analysis. *Platelets* **30**, 229–240 (2019).
25. Sorich, M.J., Rowland, A., McKinnon, R.A. & Wiese, M.D. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. *Circ. Cardiovasc. Genet.* **7**, 895–902 (2014).
26. Wiviott, S.D. *et al*. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* **357**, 2001–2015 (2007).
27. Wallentin, L. *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* **361**, 1045–1057 (2009).
28. Mega, J.L. *et al*. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* **119**, 2553–2560 (2009).
29. Wallentin, L. *et al*. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* **376**, 1320–1328 (2010).
30. Gimbel, M. *et al*. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet* **395**, 1374–1381 (2020).
31. Amsterdam, E.A. *et al*. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **130**, e344–e426 (2014).
32. Collet, J.P. *et al*. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* **42**, 1289–1367 (2021).
33. Levine, G.N. *et al*. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines and the society for cardiovascular angiography and interventions. *Circulation* **124**, e574–e651 (2011).
34. Claassens, D.M.F. *et al*. Clopidogrel versus ticagrelor or prasugrel after primary percutaneous coronary intervention according to CYP2C19 genotype: A POPular genetics subanalysis. *Circ. Cardiovasc. Interv.* **14**, e009434 (2021).
35. Dayoub, E.J. *et al*. Use of prasugrel and ticagrelor in stable ischemic heart disease after percutaneous coronary intervention, 2009–2016. *Circ. Cardiovasc. Interv.* **12**, e007434 (2019).
36. Wang, Y. *et al*. Ticagrelor versus Clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. *N. Engl. J. Med.* **385**, 2520-2530 (2021).
37. Mega, J.L. *et al*. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA* **306**, 2221–2228 (2011).
38. Horenstein, R.B. *et al*. Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers. *J. Clin. Pharmacol.* **54**, 865–873 (2014).
39. Carreras, E.T. *et al*. Diabetes mellitus, CYP2C19 genotype, and response to escalating doses of clopidogrel. Insights from the ELEVATE-TIMI 56 Trial. *Thromb. Haemost.* **116**, 69–77 (2016).
40. Zhang, L. *et al*. Effect of high-dose clopidogrel according to CYP2C19*2 genotype in patients undergoing percutaneous coronary intervention- a systematic review and meta-analysis. *Thromb. Res.* **135**, 449–458 (2015).
41. Angiolillo, D.J. *et al*. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. *JACC Cardiovasc. Interv.* **13**, 606–617 (2020).
42. Botton, M.R. *et al*. Structural variation at the CYP2C locus: characterization of deletion and duplication alleles. *Hum. Mutat.* **40**, e37–e51 (2019).
43. Pratt, V.M. *et al*. Recommendations for clinical CYP2C19 genotyping allele selection: a report of the association for molecular pathology. *J. Mol. Diagn.* **20**, 269–276 (2018).