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AHA SCIENTIFIC STATEMENT

CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association

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ABSTRACT: There is significant variability in the efficacy and safety of oral P2Y12 inhibitors, which are used to prevent ischemic outcomes in common diseases such as coronary and peripheral arterial disease and stroke. Clopidogrel, a prodrug, is the most used oral P2Y12 inhibitor and is activated primarily after being metabolized by a highly polymorphic hepatic cytochrome CYP2C219 enzyme. Loss-of-function genetic variants in *CYP2C219* are common, can result in decreased active metabolite levels and increased on-treatment platelet aggregation, and are associated with increased ischemic events on clopidogrel therapy. Such patients can be identified by *CYP2C19* genetic testing and can be treated with alternative therapy. Conversely, universal use of potent oral P2Y12 inhibitors such as ticagrelor or prasugrel, which are not dependent on CYP2C19 for activation, has been recommended but can result in increased bleeding. Recent clinical trials and meta-analyses have demonstrated that a precision medicine approach in which loss-of-function carriers are prescribed ticagrelor or prasugrel and noncarriers are prescribed clopidogrel results in reducing ischemic events without increasing bleeding risk. The evidence to date supports *CYP2C19* genetic testing before oral P2Y12 inhibitors are prescribed in patients with acute coronary syndromes or percutaneous coronary intervention. Clinical implementation of such genetic testing will depend on among multiple factors: rapid availability of results or adoption of the concept of performing preemptive genetic testing, provision of easy-to-understand results with therapeutic recommendations, and seamless integration in the electronic health record.

Key Words: AHA Scientific Statements ■ genetic testing ■ platelet inhibitors

Pharmacogenomics is the study of how genetic variation affects an individual's response to drug therapy. The overarching clinical goal of pharmacogenomics is to enable prescription of the right drug to the right patient to maximize efficacy and minimize toxicity. There have been significant advances in the field from discovery and implementation to progress in genotyping and sequencing technology to easier access and lower costs. In general, pharmacogenes are typically related to the pharmacokinetics (absorption, distribution, metabolism, excretion) of a drug or pharmacodynamics (genes that influence the response at the drug target level).[1–3] As an example, 30% to 35% of the variability in warfarin response has been attributed to genetic variation in pharmacokinetic (*CYP2C9*,[4] *CYP4F2*) and pharmacodynamic (*VKORC1*)[5] pathways. In fact, the drug labeling information for warfarin includes recommended dosing based on *CYP2C9* and *VKORC1* genotypes.[6]

However, multiple factors pose a challenge to clinical implementation of pharmacogenetic information. These include physician and patient perceptions, insurance coverage, seamless integration of genetic data in electronic health records (EHRs), immediate availability of the data at the time of drug prescription, easy interpretation of genetic data, availability and turnaround time of genetic testing, and demonstration of clinical utility,[7] often in

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the form of randomized clinical trials (RCTs) or meta-analyses. Perhaps the cardiovascular drug-gene pair that has the most comprehensive pharmacokinetic, pharmacodynamic, observational, meta-analysis, and clinical trial data is clopidogrel-*CYP2C19*. This has led to a boxed warning in the drug labeling information for clopidogrel, an oral P2Y12 inhibitor, that states that *CYP2C19* poor metabolizers are at a higher risk for ischemic events when treated with clopidogrel, that these individuals can be identified by performing *CYP2C19* genetic testing, and that they should be treated with an alternative therapy.[8] Considering that newer information is available from recent clinical trials and meta-analyses, the purpose of this scientific statement is to provide clinicians guidance on the clinical use of *CYP2C19* genetic testing when prescribing oral P2Y12 inhibitor therapy. These drugs are among the most commonly used antiplatelet drugs, especially clopidogrel, which is approved for use in patients with acute coronary syndromes (ACSs), stroke, and peripheral arterial disease.

PHARMACOLOGY OF ORAL P2Y12 INHIBITORS

The platelet P2Y12 receptor is a Gi protein–coupled receptor that inhibits adenyl cyclase and activates phosphatidylinositol 3-kinase, leading to glycoprotein IIb/IIIa receptor activation and platelet aggregation.[9] The oral P2Y12 inhibitors block platelet aggregation by preventing the binding of ADP to the P2Y12 receptor on platelets (Supplemental Figure 1).[10–12] Differences in pharmacological properties among oral P2Y12 inhibitors are summarized in Supplemental Table 1.[8,13,14] The 2 most important pharmacological differences, which are unique to clopidogrel, are as follows: First, clopidogrel is a prodrug (ie, it requires metabolic activation in vivo to exert its antiplatelet effect). Second, clopidogrel is activated primarily by the metabolic enzyme cytochrome P450 2C19 (CYP2C19) (Supplemental Figure 2).[10,15] *CYP2C19* is highly polymorphic, meaning there are many different alleles in the gene that encodes CYP2C19 in the human population. These multiple variants in the gene confer wide variability in the metabolic activity of the enzyme across individuals. Therefore, there is wide variability in the activation of clopidogrel across individuals compared with the alternative agents prasugrel and ticagrelor.

PHARMACOKINETIC PROFILES FOR ORAL P2Y12 INHIBITORS

Genetic Factors

Pharmacokinetic studies in healthy subjects and patients with coronary disease receiving clopidogrel have shown that carriers of *CYP2C19* loss-of-function (LOF) alleles have significantly reduced area under the curve of the active clopidogrel thiol metabolite H4 (Table 1).[18,22–29,35,38]

For the purposes of this document, the term carrier indicates subjects who are homozygous or heterozygous for the allele that is being referenced. The most common LOF alleles include *CYP2C19**2 (rs4244285, c.681G>A) and *CYP2C19**3 (rs4986893, c.636G>A), which result in degraded or metabolically inactive protein.[49] Less common LOF alleles include *CYP2C19* *4, *5, *6, *7, and *8.[50] In addition, hundreds of rarer missense variants have been reported to the Genome Aggregation Database, but their functional significance is undefined, although recent high-throughput approaches may change this situation.[51] *CYP2C19**17 (rs12248560, c.-806 C>T) is considered a gain-of-function allele that increases transcription and enzyme expression.[52] However, because the *17 allele is in strong linkage disequilibrium with the *2 allele, its impact on clopidogrel pharmacokinetics and pharmacodynamic is minor once we account for the *2 allele.[32] Although additional enzymes and transporters have been found to contribute to clopidogrel metabolism and disposition, variation in these genes has yielded inconsistent results on clopidogrel pharmacokinetics (Table 1).[16–24,33] Combinations of *CYP2C19* alleles define the predicted phenotype or metabolizer status and serve as the basis of therapeutic recommendations (Table 2).[50]

In contrast, prasugrel pharmacokinetics have not been shown to be influenced by genetic polymorphisms (Table 1).[13,18,23–25,27,33,36,37] On the basis of a genome-wide association analysis, a few single nucleotide polymorphisms (SNPs) in *SLCO1B1*, *CYP3A4*, and *UGT2B7* have been significantly associated with ticagrelor and ticagrelor metabolite levels.[34] However, none of these SNPs were associated with major adverse cardiac events (MACEs). In a separate study, ticagrelor area under the curve levels were found to be significantly higher in *CYP3A4**22 variant carriers than in noncarriers.[33]

Nongenetic Factors

Demographic factors, including age, sex, and body weight, are minimally associated with clopidogrel active metabolite levels.[19,35] Active metabolite concentrations of prasugrel are elevated in older patients and those with a lower body weight.[36,39] Therefore, a lower (5-mg) dose is recommended in those weighing <60 kg, and prasugrel use in those ≥75 years of age is generally not recommended, as outlined in a black box warning. Demographic factors minimally affected ticagrelor pharmacokinetics, and no dose adjustment is warranted on the basis of these factors.[37] The drug interaction profiles of the 3 drugs differ as a result of the metabolism pathways involved. Omeprazole and esomeprazole, which inhibit the CY2C19 pathway, diminish the bioactivation of clopidogrel and result in lower levels of its active metabolite.[20,40,41] Ticagrelor is

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Table 1. Genetic and Nongenetic Factors Affecting Pharmacokinetic Response to Oral P2Y12 Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Pharmacogenetics			
ABCB1	Decreased active metabolite levels in 3435T allele carriers[16,17] No association[18–21]	No association[18]	…
CYP1A2	No association[21–23]	No association[23,24]	…
CYP2B6	Lower active metabolite levels in reduced function carriers[22] No association[23]	No association[23,24]	…
CYP2C9	Lower active metabolite levels in reduced function carriers[24] No association[22,23]	No association[23,24]	…
CYP2C19	Active metabolite levels lower in reduced function carriers[17,18,22–31] Increased function variant (*17) not independently associated with active metabolite levels once *2 was accounted for[32]	No association[18,23–25,27,29,30]	…
CYP3A4	No association[21,23,33]	No association[23,24,33]	Ticagrelor and active metabolite levels associated with 2 SNPs (rs62471956, rs56324128)[34] Active metabolite higher in *22 carriers[33]
CYP3A5	No association[19,22,23]	No association[23,24]	…
PON1	No association[19,22,23]	No association[18]	…
SLCO1B1	…	…	Ticagrelor and active metabolite levels associated with SNP rs113681054, which is in linkage with functional variant rs4149056[34]
UGT2B7	…	…	Active metabolite levels associated with rs61361928[34]
Demographics			
Age	Minimal[19,35]	Higher active metabolite levels in patients >75 y of age[36]	Minimal[37]
BMI	Lower active metabolite levels in patients with higher body weight[38]	Higher active metabolite levels in patients with lower body weight[36,39]	Minimal[37]
Sex	Similar active metabolite levels between men and women[19]	Similar between men and women[39]	Minimal[37]
Drug interactions			
Proton pump inhibitors	Lower clopidogrel active metabolite levels with omeprazole or esomeprazole; avoid concomitant use[40,41] Lansoprazole, dexlansoprazole, rabeprazole, and pantoprazole have minimal effect on the antiplatelet activity of clopidogrel.[40,42,43]	…	…
CYP3A inhibitors/ inducers	Minimal interaction with statins[21,44]	Minimal[13]	Strong CYP3A inhibitors (eg, ketoconazole, itraconazole) increased ticagrelor exposure; avoid concomitant use Strong CYP3A inducers (eg, rifampin, phenytoin) reduced ticagrelor exposure Ticagrelor increased exposure to simvastatin and lovastatin; avoid simvastatin/lovastatin doses >40 mg Ticagrelor FDA label[14]
P-glycoprotein	…	…	Ticagrelor inhibits P-glycoprotein; monitor digoxin levels when initiating[45]

(*Continued*)

Table 1. Continued

	Clopidogrel	Prasugrel	Ticagrelor
Comorbidities			
Diabetes	Lower active metabolite levels in patients with diabetes[46]	Lower active metabolite levels in patients with diabetes[46]	No impact[47]
Renal dysfunction	May inhibit conversion to active metabolite[17]	Minimal impact[48]	No impact[17]

BMI indicates body mass index; …, contributing factor was not assessed for the oral P2Y12 inhibitor in the referenced study or studies; FDA, US Food and Drug Administration; and SNP, single nucleotide polymorphism.

affected primarily by interactions of the CYP3A pathway, and strong inhibitors/inducers of this pathway should be avoided with ticagrelor therapy[14] (Table 1).

GENETIC AND NONGENETIC DETERMINANTS OF PHARMACODYNAMIC VARIATION OF ORAL P2Y12 INHIBITORS

In addition to variability in genes in the pharmacokinetic pathway described earlier, pharmacodynamic or drug target variability for oral P2Y12 inhibitors may also result in variability in inhibition of platelet aggregation, which can be measured in either whole blood or platelet-rich plasma with various established assays.[9] Although several studies suggest various pharmacodynamic response determinants, clinically significant interactions are not well established for most of them. The genetic and nongenetic determinants of the pharmacodynamic response of oral P2Y12 inhibitors are summarized in Supplemental Table 2.[9,19,53–62]

Genetic Determinants of Pharmacodynamic Variation of Oral P2Y12 Inhibitors

P2Y12 receptor genetic variants may affect the pharmacodynamic response of oral P2Y12 receptor inhibitors.[9,53–55] The presence of a haplotype defined as the cluster of 3 SNPs in *P2RY12* (P2Y12 receptor gene) and 1 nucleotide insertion was associated with greater ADP-induced platelet aggregation compared with the wild-type haplotype.[53,63] In contrast, 2 other haplotypes in the *P2RY12* locus were significantly associated with lower ADP-induced platelet aggregation in patients with coronary artery disease (CAD).[54] A separate haplotype defined by 4 SNPs in coding and regulatory regions of the *P2RY12* locus was significantly associated with reduced incidence of high on-treatment platelet reactivity compared with the reference haplotype H0 even after adjustment for *CYP2C19* LOF alleles.[55] Among patients receiving prasugrel, *P2RY12* SNPs were also associated with reduced platelet reactivity.[56] In contrast, no significant effect of *P2RY12* variation on platelet aggregation has been described in patients receiving ticagrelor.[64] Despite a number of such studies testing for associations with variation in *P2RY12* and oral P2Y12 inhibitor response, no consistent associations have been reported that rise to the level of consideration for use in the clinical setting.

Nongenetic Determinants of Pharmacodynamic Variation of Oral P2Y12 Inhibitors

Apart from these genetic factors, there are also nongenetic determinants responsible for pharmacodynamic variability (Supplemental Table 2).[19,57,65] These include age, sex, race, body mass index, diabetes, renal insufficiency, and smoking, all of which may contribute to the pharmacodynamic variability of clopidogrel (Supplemental Table 2).[19,57–61,65] For example, renal dysfunction can blunt the beneficial effect of genetic-guided oral P2Y12 inhibitor therapy in reducing MACEs.[66,67] In contrast, prasugrel and ticagrelor seem to remain pharmacodynamically unaffected by patients' demographics and by comorbidities such as diabetes or chronic kidney disease.[62,68–71]

In conclusion, among oral P2Y12 receptor inhibitors, clopidogrel is more susceptible to pharmacodynamic variability, leading to variable on-treatment platelet reactivity as measured by different assays, whereas prasugrel

Table 2. *CYP2C19* Genotype, Phenotype, and Impact on Clopidogrel Response

CYP2C19 genotype	Phenotype	Impact on clopidogrel response
2 increased-function alleles (*17/*17)	Ultrarapid metabolizer	Increased active metabolite levels
1 normal-function and 1 increased-function allele (*1/*17)	Rapid metabolizer	Normal or increased active metabolite levels
2 normal-function alleles	Normal metabolizer	Normal active metabolite levels
1 no-function and 1 normal-function allele (*1/*2) or no-function and 1 increased-function allele (*2/*17)	Intermediate metabolizer	Reduced active metabolite formation
2 no-function alleles (*2/*2)	Poor metabolizer	Significantly reduced active metabolite levels

Adapted from Lee et al[50] with permission of John Wiley and Sons.

and ticagrelor have a more consistent and predictable pharmacodynamic profile.

CYP2C19 GENETIC VARIATION AND CLINICAL OUTCOMES IN CAD AND STROKE

Multiple observational studies and post hoc analysis of RCT data have demonstrated an association with a higher risk for MACEs, including stent thrombosis, after percutaneous coronary intervention (PCI) among clopidogrel-treated patients with at least 1 LOF allele compared with those without an LOF allele.[22,50,72] The data are strongest for patients presenting with ACS. The gain-of-function *CYP2C19*17* allele has been associated with increased formation of the active clopidogrel metabolite. At least 2 studies that accounted for the linkage disequilibrium between the *17 and *2 alleles suggested that the *CYP2C19*17* allele does not independently influence clinical outcomes with clopidogrel treatment, but other studies have observed an association with increased adverse outcomes, particularly in Black *CYP2C19*17* allele carriers.[32,72,73] There is no association between *CYP2C19* genotype and clinical outcomes with either prasugrel or ticagrelor.[74,75] A study of 3391 patients receiving clopidogrel suggested that a polygenic score combining multiple variants predicted cardiovascular events better than any single variants; the greatest single effect was seen with *CYP2C19*2* (P=8.8×10^{-54}).[76]

A number of meta-analyses of RCT and observational study data have further examined the association between *CYP2C19* genotype and clinical outcomes with clopidogrel (Table 3).[50,77–88] They consistently demonstrate an increased risk for stent thrombosis among *CYP2C19* LOF allele carriers, which is the closest phenotype to P2Y12 inhibition. The data for the outcome of MACEs are more variable. However, meta-analyses that included predominantly studies in which the majority of patients had ACS and PCI consistently demonstrate an increased risk for MACEs among those with LOF alleles.

Several reviews have summarized studies on the effects of *CYP2C19* variants on outcomes in patients with ischemic strokes and transient ischemic attacks.[50,89,90] In general, similar to CAD, and especially in East Asian populations (in whom LOF alleles are more common than in subjects of European or African ancestry), *CYP2C19* LOF carriers have worse ischemic or vascular outcomes when treated with clopidogrel for ischemic stroke[91–93] or vertebral or carotid artery stenting.[94,95] These observations have also been extended to populations outside of East Asia,[96–99] but not all studies have demonstrated an association of *CYP2C19* LOF genotype and adverse cerebrovascular outcomes with treatment with clopidogrel.[100,101] However, these retrospective studies may have been underpowered (given lower LOF allele frequencies) to find a difference in outcomes. A meta-analysis of 15 studies, of which 11 were from China and 1 was from Korea, suggested that patients with at least 1 LOF allele were at increased risk of stroke and at significantly increased risk for a composite end point of stroke, myocardial infarction, and vascular death.[102] The increased risk of stroke remained significant for patients of European ancestry.

ANCESTRAL DIFFERENCES IN *CYP2C19* GENETIC VARIATION AND ORAL P2Y12 INHIBITORS

Significantly different frequencies of the LOF *CYP2C19* *2 and the reported gain-of-function *CYP2C19* *17 variants have been reported in distinct ancestral populations (Supplemental Table 3).[72,103–107] For example, the *CYP2C19* *2 LOF variant frequency can range from ≈15% in White individuals[108] to 40% to 50% in Asian populations,[109] and the *3 LOF variant, which is rare in White individuals, is much more common in East Asian subjects. However, although the wide range of allele frequencies in different populations has long been recognized, the paucity of data from diverse populations in large clinical trials of P2Y12 inhibitors is profound (Figure 1).[72,109,110] For example, in early trials such as CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events)[111] and TRITON-TIMI (Therapeutic Outcomes by Optimizing Platelet Inhibition by Prasugrel–Thrombolysis in Myocardial Infarction)[22] and in a meta-analysis among patients predominantly undergoing PCI treated with clopidogrel reported by Mega et al,[78] there were 0.2%, 0.7%, and <5% people of color, respectively. Although recent studies have attempted to enroll more diverse populations, a significant underrepresentation of people of color remains; the Popular Genetics trial (Patient Outcome After Primary PCI) had <6% people of color enrolled,[112] and although TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention) had 22.5% East Asian individuals, it had only 2.4% Black or African American individuals, 4.5% South Asian individuals, and 2.8% Hispanic or Latino individuals enrolled.[113] The lack of adequate representation of certain races and ethnicities in these studies does not necessarily imply that these individuals from these racial or ethnic backgrounds with *CYP2C19* LOF alleles will have different pharmacokinetic or pharmacodynamics profiles compared with White individuals. When *CYP2C19* genetic testing results are available to clinicians, oral P2Y12 inhibitor prescribing rates do not significantly differ between Black patients and White patients.[114] However more evidence is required on the clinical utility of prospectively performing *CYP2C19* genetic testing in these populations.

Table 3. Meta-Analyses Examining the Association Between *CYP2C19* Genotype and Clinical Outcomes With Clopidogrel In Patients With a Cardiac-Related Indication

Reference	Studies included (n)	Participants included (n)	Description of participants included	Risk for MACEs in LOF allele carriers vs noncarriers	Risk for stent thrombosis
Hulot et al,[77] 2010	10	11 959	Patients with ACS or stable CHD managed medically or with PCI	Event rate, 9.7% vs 7.8%; OR, 1.29 (1.12–1.49)	Event rate, 2.9% vs 0.9%; OR, 3.45 (2.14–5.57)
Mega et al,[78] 2010	9	9685	Patients with ACS or stable CHD; majority had ACS and underwent PCI	IM or PM: event rate,* 10.2% vs 8.4%; HR, 1.57 (1.13–2.16) IMs: event rate,* 10.1% vs 8.4%; HR, 1.55 (1.11–2.17) PMs: event rate,* 12.7% vs 9.1%; HR, 1.76 (1.24–2.50)	IM or PM: event rate,* 2.6% vs 0.9%; HR, 2.81 (1.81–4.37) IMs: event rate,* 2.4% vs 0.9%; HR, 2.67 (1.69–4.22) PMs: event rate,* 5.7% vs 1.0%; HR, 3.97 (1.75–9.02)
Holmes et al,[79] 2011	32	42 016	Patients with ACS or stable CHD managed medically or with PCI, patients with CHD or risk factors for CHD, and patients with atrial fibrillation and ≥1 additional risk factors for stroke	Event rate, NR; RR, 1.18 (1.09–1.28) when all data considered; RR, 0.97 (0.86–1.09) when studies with ≥200 cardiovascular events considered	Event rate,* 5.4% vs 2.8%; RR, 1.75 (1.50–2.03)
Jin et al,[80] 2011	8	8280	Patients who underwent PCI for ACS or stable CHD	Event rate,* 9.6% vs 8.1%; OR, 1.46 (1.01–2.13)	Event rate,* 2.5% vs 0.7%; OR, 3.81 (2.27–6.40)
Sofi et al,[81] 2011	7	8043	Patients with ACS or stable CHD; most underwent PCI	Event rate, NR; RR, 1.96 (1.14–3.37)	Event rate, NR; RR, 3.82 (2.23–6.54)
Zabalza et al,[82] 2012	11	16 360	Patients with ACS or stable CHD managed medically or with PCI	Event rate, NR; HR, 1.23 (0.97–1.55)	Event rate, NR; HR, 2.24 (1.52–3.30)
Bauer et al,[83] 2011	15	18 529	Patients with ACS or stable CHD managed medically or with PCI	Event rate,* 9.4% vs 8.9%; OR, 1.11 (0.89–1.39)	Event rate,* 2.7% vs 1.7%; OR, 1.77 (1.31–2.40)
Jang et al,[84] 2012	16	20 785	Patients with ACS or stable CHD managed medically or with PCI	Event rate, NR; OR, 1.42 (1.13–1.78)	Event rate, NR; OR, 2.41 (1.76–3.30)
Singh et al,[85] 2012	14	19 601	Patients with CHD mainly undergoing PCI	Event rate, 9.7% vs 8.4%; RR, 1.28 (1.06–1.54)	Event rate, 2.7% vs 1.1%; RR, 2.41 (1.69–3.41)
Sorich et al,[86] 2014	24	36 076	Patients with ACS or stable CHD managed medically or with PCI, patients with CHD or risk factors for CHD, and patients with atrial fibrillation and ≥1 additional risk factors for stroke	Overall population: event rate,* 9.3% vs 8.3%; RR, 1.27 (1.18–1.36) White patients with PCI: event rate,* 11.2% vs 9.4%; RR, 1.20 (1.10–1.31) Patients without PCI: event rate,* 9.4% vs 9.7%: RR, 0.99 (0.84–1.17)	Event rate: RR, 2.03 (1.74–2.36)
Biswas and Kali,[87] 2021	21	16 194	Patients with stable CHD who underwent PCI	IM or PM: event rate,* 9.7% vs 6.7%; OR, 1.71 (1.51–1.94) IM: event rate,* 7.8% vs 5.3%; OR, 1.65 (1.30–2.09) PM: event rate,* 8.9% vs 5.3%; OR, 2.08 (1.47–2.95)	Event rate,* 2.2% vs 0.5%; OR, 4.08 (2.52–6.61)
Biswas et al,[88] 2022	22	24 512	Patients with ACS who underwent PCI	Event rate, NR; RR, 1.53 (1.39–1.69)	Event rate, NR; RR, 1.90 (1.27–2.84)

Data are presented as RR, OR, or HR (95% CI).

ACS indicates acute coronary syndrome; CHD, coronary heart disease; HR, hazard ratio; IM, intermediate metabolizer; LOF, loss-of-function; MACE, major adverse cardiac event; NR, not reported; OR, odds ratio; PCI, percutaneous coronary intervention; PM, poor metabolizer; and RR, relative risk.

*Event rate was not reported but calculated from the reported number of cases/total number of patients.

INDIVIDUALIZING ORAL P2Y12 INHIBITION WITH *CYP2C19* GENETIC TESTING: IMPACT ON PLATELET AGGREGATION

Summary of Observational Studies, RCTs, and Meta-Analyses

Data to date evaluating platelet function testing during oral P2Y12 inhibition strategies based on *CYP2C19* genetic testing include 20 RCTs, 7 observational studies, and 1 meta-analysis, presented in Supplemental Table 4.[18,23–25,27,115–137] These studies have compared the pharmacodynamics profiles of standard-dose clopidogrel (75 mg daily) with that of high-dose clopidogrel (600/900 mg loading dose or 150 mg/d maintenance), cilostazol, prasugrel, or ticagrelor in *CYP2C19* LOF carriers. Only 1 RCT has directly compared the effect of prasugrel and ticagrelor on platelet aggregation.[115] Although varied

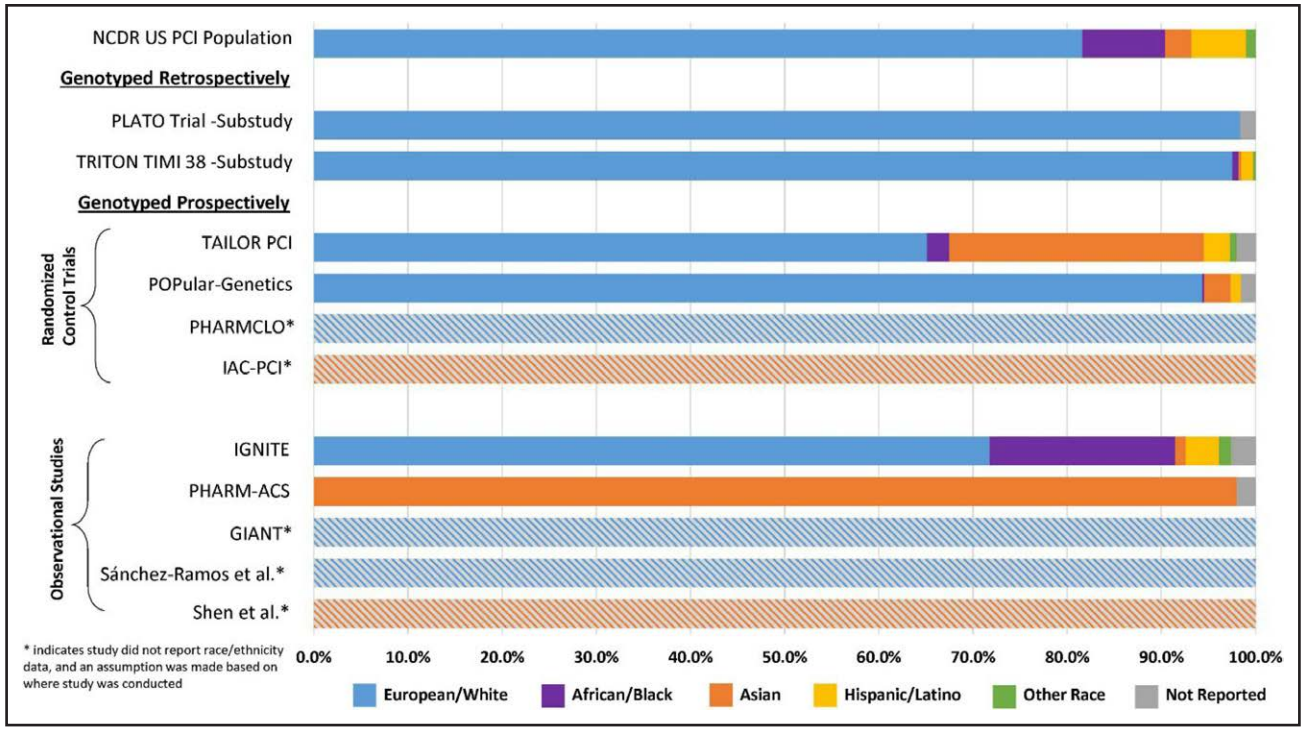

Figure 1. Reported race and ethnicity data from selected major clinical outcome trials using clopidogrel and in which *CYP2C19* status was reported.

This figure compares the relative percent distribution of reported race and ethnicity from study participants included in major retrospective and prospective clinical outcome studies of *CYP2C19* genotype-guided antiplatelet therapy. For reference, the demographic characteristics of each study were compared with data obtained from the NCDR (National Cardiovascular Data Registry). The race and ethnicity distribution of patients who underwent percutaneous coronary intervention (PCI) in the United States was as follows: 86.5% White or European, 8.8% Black or African American, 2.8% Asian, 0.7% Native American, 0.3% Pacific Islander, and 5.8% Hispanic or Latino ethnicity.[110] GIANT indicates Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment; IAC-PCI, Individual Applications of Clopidogrel After Percutaneous Coronary Intervention; IGNITE, Implementing Genomics in Practice; PHARMCLO, Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes; PHARM-ACS, Registry Study on Drug Therapy and Clinical Outcomes in Patients With Acute Coronary Syndrome; PLATO, Platelet Inhibition and Patient Outcomes; TAILOR-PCI, Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention; and TRITON-TIMI 38, Therapeutic Outcomes by Optimizing Platelet Inhibition by Prasugrel–Thrombolysis in Myocardial Infarction 38. Reprinted from Nguyen et al.[109]

in design, end points, and drug regimens, these studies allow several conclusions. It is evident that although high-dose clopidogrel reduces platelet reactivity more than standard-dose clopidogrel,[116–124,138] prasugrel and ticagrelor are more potent platelet inhibitors than high-dose clopidogrel.[18,23–25,27,128–137] However, there may be a tradeoff between efficacy and bleeding with these more potent agents.[139] The only study directly comparing prasugrel with ticagrelor in *CYP2C19* LOF carriers showed no difference in the degree of platelet inhibition achieved between these 2 drugs.[115]

Comparison of Genetic-Guided Therapy With Individualizing Oral P2Y12 Inhibition Based on Platelet Function Tests

To date, there are no direct comparisons between genetic testing and platelet function testing as assays to individualize the selection of oral P2Y12 inhibitors. However, each of these assays has advantages and disadvantages.[140] Platelet function testing has the key advantage of directly defining the intermediate phenotype of interest (ie, levels of on-treatment platelet reactivity) for which studies have shown an association with clinical outcomes (ie, increased thrombotic and bleeding risks with high and low platelet reactivity, respectively).[141] Nevertheless, its clinical implementation has been challenging given the need for multiple repeated assessments due to potential of variability of results over time and the need for a patient to be on treatment for a certain length of time with a given antiplatelet agent (eg, for at least 1–2 weeks with clopidogrel) to be able to assess antiplatelet effects and define responsiveness adequately. This may be problematic in patients with ACS treated with prasugrel and ticagrelor who would require a switch to clopidogrel and potentially switch back to prasugrel or

ticagrelor if found to have high platelet reactivity while on clopidogrel. In contrast, genetic testing can determine the phenotype of clopidogrel resistance, as measured by platelet functional assays, before therapy, and treating such *CYP2C19* LOF carriers once identified with an alternative therapy such as ticagrelor or prasugrel can result in improvement in platelet inhibition. The disadvantage of relying solely on genetic testing is that the *CYP2C19* genotype represents only one of the factors contributing to antiplatelet drug response, and not all *CYP2C19* LOF carriers or noncarriers have reduced platelet inhibition.[23] To this extent, integrating genetic data with clinical variables such as in the ABCD-GENE (age, body mass index, chronic kidney disease, diabetes, and genotyping) score may enhance the accuracy of identifying patients with impaired clopidogrel response.[142,143]

INDIVIDUALIZING ORAL P2Y12 INHIBITION WITH *CYP2C19* GENETIC TESTING: IMPACT ON CLINICAL OUTCOMES IN CAD AND STROKE

Observational Studies

Multiple prospective observational studies have evaluated the clinical utility of *CYP2C19* genetic testing, asking the question of whether altering oral P2Y12 inhibitor therapy according to the results of *CYP2C19* genetic testing changes clinical outcomes compared with standard of care. Some of these studies have been limited by being nonrandomized or having a small sample size.[144–148] However, 2 pragmatic prospective observational studies[149,150] that either recommended genetic testing or performed genetic testing and provided results to clinicians in patients who underwent PCI demonstrated that LOF carriers treated with clopidogrel had a significantly higher risk of MACEs compared with those who were treated with prasugrel or ticagrelor (hazard ratio [HR], 2.87–4.65). One of these studies expanded its study population by adding patients from additional sites, demonstrating a 44% significant reduction in ischemic events in LOF carriers when treated with alternative P2Y12 inhibitors compared with clopidogrel but without a discernible difference in outcomes in noncarriers.[151] A similar decreased risk of death, myocardial infarction, and stent thrombosis was observed in a randomized multicenter observational study when LOF carriers after primary PCI for ST-segment–elevation myocardial infarction were treated with alternative oral P2Y12 inhibitor therapy instead of clopidogrel (3.3% versus 15.6% at 1 year).[152] All of these studies simulated real-world clinical practice in academic or community-based medical centers, wherein laboratory-based or less frequently point-of-care *CYP2C19* genotyping information was either made available to the clinician in the EHR or provided to investigators.

Randomized Clinical Trials

The significant challenge in demonstrating the clinical utility of pharmacogenetic testing lies in the sample size required and the design and cost of conducting pharmacogenomic-based clinical trials.[153] To compare genetic-guided strategies with standard of therapy, RCTs need to be powered according to the prevalence and effect size of the relevant genotype that influences drug action.[154] The RCTs that have specifically evaluated the clinical impact of genetic-guided compared with standard or conventional oral P2Y12 inhibitor therapy are outlined in Table 4. The PHARMCLO open-label trial (Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes) showed a reduction in events with a genetic (*CYP2C19* and *ABCB1*) plus clinical variable–guided approach as opposed to standard clinician-determined oral P2Y12 inhibitor treatment (HR, 0.58 [95% CI, 0.43–0.78]).[144] Unfortunately, this trial was stopped prematurely with only 25% of the targeted enrollment because of the lack of certification for the genotyping platform used in the study; therefore, results need to be viewed with caution.[159] The IAC-PCI trial (Individual Applications of Clopidogrel After Percutaneous Coronary Intervention) also demonstrated a statistically significant reduction in cumulative ischemic events with genetic-guided therapy in which LOF carriers received high-dose clopidogrel plus or minus cilostazol compared with standard therapy with clopidogrel (2.66% versus 9.03%; $P<0.01$).[157,158] Genetic-guided therapy in the TAILOR-PCI study resulted in no statistically significant difference in ischemic outcomes among *CYP2C19* LOF carriers, who made up 35% of the total trial participants (HR, 0.66 [95% CI, 0.43–1.02]), according to the prespecified analysis plan and the treatment effect (minimum detectable HR, 0.50) that the study was powered to detect at 12 months. The secondary end point of major or minor bleeding was not significant between the 2 randomized groups (HR, 1.22 [95% CI, 0.60–2.51]). Among all 5302 randomized patients, ischemic events occurred in 4.4% of the genotype-guided group and 5.3% in those receiving clopidogrel therapy (HR, 0.84 [95% CI, 0.65–1.07]). A Bayesian analysis of TAILOR-PCI using informative priors demonstrated that the probability of benefit in reducing ischemic outcomes with a genotype-guided strategy was 99%.[156] Furthermore, a prespecified analysis of TAILOR-PCI evaluating the occurrence of cumulative events favored the use of genetic-guided oral P2Y12 inhibitors compared with conventional clopidogrel therapy with a 40% risk reduction using a genetic-guided approach in *CYP2C19* LOF carriers (95% CI, 0.41–0.89; $P=0.01$).[160] The Popular Genetics study demonstrated that genetic-guided oral P2Y12 inhibitor therapy (noncarriers receive clopidogrel, LOF carriers receive ticagrelor or prasugrel) is noninferior to standard treatment with ticagrelor or prasugrel in reducing the incidence of the primary combined outcome of ischemic plus bleeding events (95% CI, −2.0 to 0.7) in

Table 4. Randomized Clinical Trials That Have Specifically Evaluated the Clinical Impact of Genetic-Guided vs Standard or Conventional Oral P2Y12 Inhibitor Therapy

Trials	Target	Type of trial	Patients (n)	Gene	Intervention groups	Outcome	Outcome
POPular Genetics[155]	Primary PCI for STEMI	Open-label, non-inferiority RCT	2488	*CYP2C19*2* and **3*	GG group: *CYP2C19* LOF carriers receive ticagrelor or prasugrel and noncarriers receive clopidogrel ST group: ticagrelor or prasugrel	Outcome 1: composite of death resulting from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to PLATO criteria	Outcome 1: GG 5.1% vs ST 5.9%; absolute difference, −0.7% (95% CI, −2.0 to 0.7); *P*<0.001 for noninferiority
						Outcome 2: PLATO major or minor bleeding	Outcome 2: GG 9.8% vs ST 12.5%; HR, 0.78 (95% CI, 0.61–0.98); *P*=0.04
TAILOR-PCI[156]	PCI for ACS or stable CAD	Open-label, superiority RCT	5302	*CYP2C19*2* and **3*	GG group: *CYP2C19* LOF carriers receive ticagrelor and noncarriers receive clopidogrel ST group: clopidogrel	Outcome 1: composite of death resulting from cardiovascular cause, myocardial infarction, stent thrombosis, or severe recurrent ischemia at 12 mo in *CYP2C19* LOF carriers Outcome 2: major or minor bleeding by TIMI criteria at 12 mo in *CYP2C19* LOF carriers	Outcome 1: In LOF carriers: GG 4% vs ST 5.9%; HR, 0.66 (95% CI, 0.43–1.02); *P*=0.06 Outcome 2: in LOF carriers: GG 1.9% vs ST 1.6%; HR, 1.22 (95% CI, 0.60–2.51); *P*=0.58
PHARMCLO[157]	ACS	Open-label, superiority RCT	888	*ABCB1* c.3435C>T *CYP2C19*2* *CYP2C19*17*	GG group: clopidogrel, ticagrelor, or prasugrel based on algorithm including genetic testing and clinical characteristics ST group: clopidogrel, ticagrelor, or prasugrel based on clinician preference and clinical characteristics	Outcome: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and major bleeding as per Bleeding Academic Research Consortium type 3–5 criteria at 12 mo	Outcome: GG 15.9% vs ST 25.9%; HR, 0.58 (95% CI, 0.43–0.78); *P*<0.001
IAC-PCI[158]	PCI for CAD	Open-label RCT	623	*CYP2C19*2* and **3*	GG group: *CYP2C19* LOF noncarriers receive clopidogrel 75 mg daily; *CYP2C19* LOF heterozygote carriers receive clopidogrel 150 mg daily; *CYP2C19* LOF homozygote carriers receive cilostazol 100 mg twice daily with clopidogrel 150 mg daily ST group: clopidogrel 75 mg daily	Outcome: composite of death resulting from any cause, myocardial infarction, stroke, and ischemia-driven target-vessel revascularization at 6 mo	Outcome: GG 2.66% vs ST 9.03%; *P*<0.01

Data are presented as HR (95% CI).

ACS indicates acute coronary syndrome; CAD, coronary artery disease; GG, genetic-guided; HR, hazard ratio; IAC-PCI, Individual Applications of Clopidogrel After Percutaneous Coronary Intervention; LOF, loss of function; PCI, percutaneous coronary intervention; PHARMCLO, Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes; PLATO, Platelet Inhibition and Patient Outcomes; POPular Genetics, Patient Outcome After Primary Percutaneous Coronary Intervention Genetics Substudy; RCT, randomized clinical trial; ST, standard therapy; STEMI, ST-segment–elevation myocardial infarction; TAILOR-PCI, Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention; and TIMI, Thrombolysis in Myocardial Infarction.

patients with ST-segment–elevation myocardial infarction undergoing primary PCI.[155] The study had prespecified a noninferiority threshold for the absolute difference between the 2 groups in the incidence of the primary combined outcome at 2 percentage points, and an absolute difference of −0.7 percentage points was observed that was statistically highly significant (*P*<0.001 for noninferiority). Genetic-guided therapy also significantly reduced the primary bleeding outcome compared with ticagrelor/prasugrel (HR, 0.78 [95% CI, 0.61–0.98]). A single RCT, CHANCE-2 (Ticagrelor or Clopidogrel With Aspirin in High-Risk Patients With Acute Nondisabling Cerebrovascular Events II), has prospectively compared ticagrelor and clopidogrel in patients with stroke and transient ischemic attack with LOF alleles. The trial demonstrated that in Chinese LOF carriers with minor stroke or transient ischemic attack, ticagrelor and aspirin were superior to clopidogrel and aspirin for preventing stroke at 90 days (6.0% versus 7.6%; HR, 0.77 [95% CI, 0.64–0.94]), thus demonstrating the clinical utility of prospectively identifying such patients by genetic testing in this population.[161]

Meta-Analyses

Four meta-analyses[139,162–164] have been published to date that have evaluated the role of genetic-guided

oral P2Y12 inhibitor therapy in patients with CAD. A study that included 7 RCTs and ≈16 000 patients, most of whom had ACS and underwent predominantly PCI, demonstrated that there was a 30% reduction (95% CI, 0.59–0.83) in ischemic events in LOF carriers when treated with ticagrelor/prasugrel compared with clopidogrel; however, no difference (relative risk [RR], 1.00 [95% CI, 0.80–1.25]) was observed in noncarriers. This meta-analysis clearly demonstrates that *CYP2C19* genotype status affects the beneficial effect of ticagrelor/prasugrel compared with clopidogrel ($P_{interaction}$<0.001), further supporting the use of genetic testing to identify these patients.[162] This finding also provides an explanation for the noninferiority result of the Popular Genetics study. A meta-analysis that included 11 RCTs comprising 11 740 patients with CAD or those undergoing PCI demonstrated that genetic-guided therapy compared with standard therapy with clopidogrel (predominant group) or choice of antiplatelet therapy that was left to the discretion of the physician (that included prasugrel or ticagrelor use) demonstrated a significant 40% reduction (95% CI, 0.44–0.82) in major adverse cardiovascular events, a result that needs to be interpreted with caution given the significant heterogeneity observed. A significant reduction in individual outcomes of cardiovascular death, myocardial infarction, stroke, and stent thrombosis was also observed.[164] This study also demonstrated no significant increase in bleeding events with genetic-guided therapy compared with standard therapy. In another meta-analysis that included 20 743 patients from 11 randomized controlled trials and 3 observational studies of patients undergoing PCI, guided antiplatelet therapy that included both platelet function and genetic testing was associated with a significant reduction (RR, 0.78 [95% CI, 0.63–0.95]) in major adverse cardiovascular events and a nonsignificant reduction in any bleeding (RR, 0.88 [95% CI, 0.77–1.01]; *P*=0.069) compared with standard antiplatelet therapy.[163] There were no differences between subgroups according to the type of test used to guide selection of therapy (platelet function testing versus genetic testing) or strategy (de-escalation versus escalation). In a network meta-analysis comprising 61 898 patients from 15 RCTs of patients with ACS, neither prasugrel for all nor ticagrelor for all was found to decrease the risk of ischemic events compared with clopidogrel for all (incidence rate ratio [IRR], 0.89 [95% CI, 0.77–1.03] and 1.00 [95% CI, 0.86–1.18], respectively]. In an examination of direct comparisons, guided therapy (with only LOF carriers receiving prasugrel or ticagrelor) significantly reduced ischemic events (IRR, 0.70 [95% CI, 0.52–0.94]) compared with clopidogrel for all, whereas prasugrel for all (IRR, 0.90 [95% CI, 0.74–1.10]) and ticagrelor for all (IRR, 1.04 [95% CI, 0.84–1.29]) did not. When guided therapy was directly compared with ticagrelor for all or prasugrel for all, the IRRs were close to 1 with wide 95% CIs (0.97 [95% CI, 0.60–1.55] and 0.92 [95% CI, 0.62–1.35], respectively). When data from indirect comparisons were included, guided therapy significantly reduced ischemic events (IRR, 0.80 [95% CI, 0.65–0.98]) compared with clopidogrel for all and was associated with a reduction in ischemic events compared with ticagrelor for all (IRR, 0.79 [95% CI, 0.63–1.00]) but not with prasugrel for all (IRR, 0.89 [95% CI, 0.77–1.03]).[139]

In summary, these prospective studies and meta-analyses demonstrate that (1) continuing clopidogrel in LOF carriers results in increased ischemic events; (2) *CYP2C19* LOF carriers have significantly reduced ischemic events when treated with ticagrelor or prasugrel compared with clopidogrel; (3) the beneficial effect observed on ischemic events with ticagrelor/prasugrel is significantly determined by *CYP2C19* genotype; (4) genetic-guided therapy compared with universal clopidogrel use favors a lower risk of ischemic events without significantly increasing bleeding; and (5) *CYP2C19* genetic-guided therapy is noninferior to universal ticagrelor or prasugrel use with respect to MACEs plus bleeding and results in significantly reduced bleeding.

CYP2C19 GENETIC TESTING: CLINICAL CONSIDERATIONS

Assays

Clinical assays for *CYP2C19* genetic testing have demonstrated excellent accuracy compared with each other and the gold standard, Sanger sequencing, and are available at all major national reference laboratories, including those at large academic medical centers.[131,165–169] Point-of-care assays provide metabolizer status at the time of prescribing antiplatelet therapy and have been assessed in multiple studies. The Spartan RX *CYP2C19* test (Spartan Bioscience Inc) was used in TAILOR-PCI,[113] the Popular Genetics trial,[170] and the Bedside Testing of *CYP2C19* Gene for Treatment of Patients With PCI With Antiplatelet Therapy Trial.[171] It showed excellent accuracy (97%–100%), sensitivity (100% [95% CI, 92.3%–100%]), specificity (99.3% [95% CI, 96.3%–100%), and reproducibility[131,167–169] and is approved by the US Food and Drug Administration. There are several other US Food and Drug Administration–approved commercial assays, as well as laboratory-developed tests and those that are intended for research only (Supplemental Table 5).[172] A recent analysis has assessed whether there is cross-validation between some of these tests to help inform clinical genetic testing.[165]

The Association for Molecular Pathology has recommended a minimum set of *CYP2C19* alleles that should be included in *CYP2C19* genotyping panels and has designated these alleles as tier 1.[172] They define tier 1 alleles as those having (1) well-characterized alteration of CYP2C19 activity that has been shown to have an

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effect on drug response and for which the functional variant is known, (2) appreciable minor allele frequency in a patient population, and (3) available reference material and include *CYP2C19* *2, *3, and *17 alleles. Tier 2 *CYP2C19* alleles are those that meet at least 1 of the tier 1 criteria and are considered (by the Association for Molecular Pathology) optional for inclusion on clinical assay panels. It is important to note that, as a result of the optional inclusion criteria, current commercially available assay panels differ with respect to which tier 2 alleles they include.

Some investigators and institutions have advocated a preemptive approach in which pharmacogenetic information for variants important to drug response is deposited in a patient's EHR before drug exposure.[2,173] This appeals to a future genomic medicine vision, but issues such as implementation and reimbursement remain barriers. As discussed later, integration of such testing results in the EHR with provision of clinician alerts will be essential to clinical adoption.[174]

Insurance Reimbursement and Cost Considerations

As of June 2021, Medicare considers genetic testing for *CYP2C19* medically necessary in specific situations (eg, in a patient with ACS who is undergoing PCI and is initiating or reinitiating clopidogrel therapy). To be covered, "the test must be ordered by a physician (or qualified non-physician practitioner) who is treating a beneficiary for a specific medical problem and who uses the results in the management of that problem."[175,176] Although reimbursement rates may still vary by location and health insurance providers, recent analyses have observed similar reimbursement rates between commercial payers and Medicare.[177]

Cost-Effectiveness

Numerous decision-analytic models, using contemporaneous clinical event rates and medical costs, have found that *CYP2C19* genotyping to guide antiplatelet therapy in patients with ACS undergoing PCI is highly cost-effective in the United States[178–182] and other countries,[175,183–186] especially compared with the universal use of ticagrelor or prasugrel.[187] These studies used models in which the *CYP2C19* genotype was known preemptively. The most recent analysis is perhaps the most relevant because these authors based their cost analysis on 2020 Veterans Affairs data and costs, including 2020 costs for generic clopidogrel and prasugrel, and used a model in which 74% of patients were started on clopidogrel after PCI (5% on prasugrel, 21% on ticagrelor).[180] De-escalation (a switch from the more potent P2Y12 inhibitor ticagrelor or prasugrel to clopidogrel) in conjunction with escalation (a switch from clopidogrel to more potent P2Y12 inhibitors ticagrelor or prasugrel) was incorporated into the model and was required for *CYP2C19* testing to be cost-effective.[180] but the authors' overall conclusion was that "*CYP2C19* testing (compared with no testing) was dominant in 97% of simulations, making it cost-effective and high value."[180] The cost-effectiveness of *CYP2C19* genotyping to guide antiplatelet therapy for acute strokes and high-risk transient ischemic attacks has also been demonstrated in several studies.[188–190]

CLINICAL IMPLEMENTATION

Challenges in Clinical Implementation

The implementation of genetic testing for individualizing oral P2Y12 inhibitor therapy depends on multiple factors involving clinicians, health care and professional organizations, insurance companies, and patients. Although many clinicians have positive perceptions about pharmacogenetic testing and its clinical implications, <10% adopt pharmacogenetic testing in their routine clinical practice, primarily because of a lack of clinical guidelines and pharmacogenetic education.[191] Prospective observational studies have demonstrated that the uptake of genetic testing when prompted by a clinical algorithm at 1 institution was 72.8%,[150] and when provided with LOF carrier status, clinicians prescribed alternative oral P2Y12 inhibitors in 60.5%[149] of patients undergoing PCI. Another single-institution study of 2676 patients found that changes in antiplatelet therapy occurred in 57.6% of poor metabolizers and 33.2% of intermediate metabolizers.[192] In a randomized controlled single-center trial, physicians were significantly more likely to prescribe alternative dual antiplatelet therapy (DAPT; prasugrel or ticagrelor) for patients for whom they received *CYP2C19* LOF carrier status results compared with patients receiving usual care (odds ratio, 1.6). However, despite the identification of LOF carrier status, 47% of patients continued to be prescribed clopidogrel, likely because of a reluctance in prescribing more potent oral P2Y12 inhibitor alternatives in stable patients with CAD.[193] However, in another prospective multicenter RCT, when clinicians were provided LOF carrier status, there was an escalation in oral P2Y12 inhibitor therapy in 85% of patients. Conversely, when noncarrier status was presented to clinicians, de-escalation of therapy occurred in 92% of patients.[194]

Advances in PCI have also led to overall low annual ischemic event rates of <6%.[113,155] Therefore, the cost-effectiveness of a genetic testing strategy will play an important role. Moreover, it will be critical for clinicians to have easy access to genetic testing with rapid availability of results. Rapid point-of-care assays that have been adopted in clinical trials and are easy to perform by nonlaboratory personnel could potentially increase the adoption of *CYP2C19* genetic testing.[195] Moreover, with

the increasing use of de-escalation strategies after PCI, there is adequate time to obtain genetic testing results with laboratory-based techniques while a patient is on DAPT with prasugrel or ticagrelor before making the decision to de-escalate to clopidogrel. Results should be easily interpretable with treatment recommendations. *CYP2C19* genetic testing for antiplatelet therapy has been demonstrated to have the highest quality-adjusted life-years and the lower overall cost, especially compared with ticagrelor or prasugrel.[112,185,196–198]

Historically, the participation in genetic testing by families to identify individuals at high risk for diseases is variable and can be low.[199] However, with a significant projected compounded annual growth rate of 16.4% anticipated in direct-to-consumer genetic testing, patients appear to be increasingly amenable to the concept of the role of genetic testing in improving their overall health.[200] Patients also appear to be more receptive to pharmacogenetic testing compared with genetic testing to identify disease risk.[201] Although genetic data such as that from whole-exome or -genome sequencing may be viewed as privacy threats[202,203] because information that is unrelated to the current medical treatment (eg, predisposition to other diseases, cultural/ancestry, and paternity) may be obtained, focused pharmacogenetic testing does not pose such dilemmas. Patients express interest in pharmacogenetic testing and are comfortable with their clinicians using results from such testing to manage their care.[204]

The availability of direct-to-consumer genetic testing by which patients may present their genetic test results to their physician and the practice with consent of large health care organizations in preemptively sequencing patients and making that data available in the EHR may increase the adoption of pharmacogenetic testing.[2,173] Seamless integration of such testing results in the EHR with provision of clinician alerts with treatment recommendations will be essential.[174] Although genetic counselors play a critical role in educating patients and providing guidance in interpretation of results, the engagement of trained pharmacists both before a pharmacogenetic test is ordered and when test results are available may be desirable because these individuals have familiarity with testing technical procedures, interpreting pharmacogenetic results, and providing counseling to address patients' concerns. However, this may not be realistic or possible in the setting of emergency PCI or in the absence of these resources. Alternatives include follow-up or referral after point-of-care testing in the cardiac catheterization laboratory or consideration of preemptive pharmacogenetic testing. Preemptive testing enables genetic results to be available in the medical record before an intervention, thus allowing treatment decisions to be made when needed. The disadvantages are cost, uncertainty about reimbursement, and a need to periodically update the results as new knowledge is accrued.[205]

Clinical Guidelines

The ineffectiveness of clopidogrel in poor metabolizers is clearly outlined in a boxed warning in the drug labeling information for clopidogrel and has been extended to intermediate metabolizers in a more recent statement of pharmacogenetic associations provided by the US Food and Drug Administration.[206] Identification of such patients and prescription of alternative therapies are suggested.

The 2016 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Intervention guideline on DAPT in CAD does not recommend the routine use of genetic testing.[207] The 2017 European Society of Cardiology focused update on DAPT in CAD does not recommend genetic testing except in specific situations such as for patients with recurrent adverse events if the results of testing may change therapy.[208] An updated international expert consensus document, although not advocating for routine use of genetic testing, recommends its selective use particularly in scenarios when bleeding risk exceeds thrombotic risk for DAPT de-escalation after PCI for ACS or when thrombotic risk exceeds bleeding risk for DAPT escalation after elective PCI.[140] The 2020 European Society of Cardiology guidelines for the management of ACS in patients presenting without persistent ST-segment elevation similarly recommend an approach of DAPT de-escalation guided by *CYP2C19* genotyping in select patients with non–ST-segment–elevation ACS.[209] Although the 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Intervention guidelines for coronary artery revascularization and the 2023 American College of Cardiology/American Heart Association guidelines for the management of patients with chronic coronary disease[210] have been published, specific recommendations for genetic testing for guiding P2Y12 inhibitor therapy were not made.[211] These guidelines have not directly addressed recent results of the clinical trials such as Popular Genetics and meta-analyses demonstrating noninferiority and superiority of a genetic testing approach, respectively. The 2022 Clinical Pharmacogenetics Implementation Consortium guidelines recommend using prasugrel or ticagrelor at standard dose if no contraindications exist in CYP2C19 intermediate and poor metabolizers.[50] The classification of this recommendation in patients with ACS or PCI was strong because of the high-quality data that were available.

Oral P2Y12 Inhibitor Treatment Based on *CYP2C19* Genetic Testing Results

The totality of pharmacokinetic, pharmacodynamic, clinical outcomes, and meta-analyses data support performing *CYP2C19* genetic testing in patients with ACS or PCI before clopidogrel therapy is instituted to decrease

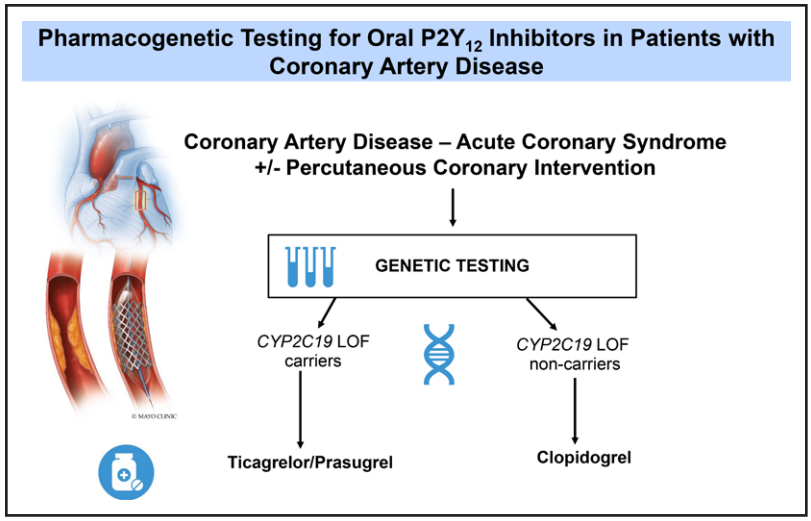

Figure 2. A proposed algorithm using *CYP2C19* pharmacogenetic testing to individualize oral $P2Y_{12}$ inhibitor therapy in patients with coronary artery disease on the basis of meta-analysis results.
LOF indicates loss of function. Modified from Pereira et al[162] with permission from Elsevier. Copyright © 2021.

ischemic outcomes and note that it is reasonable to do so before the use of ticagrelor/prasugrel to decrease bleeding complications (Figure 2).[162] Patients without LOF alleles could be treated with clopidogrel, but for those identified to be *CYP2C19* LOF carriers, alternative oral P2Y12 inhibitors such as ticagrelor or prasugrel could be prescribed. In addition, according primarily to the CHANCE-2 trial, genetic testing, especially in populations such as East Asian individuals with minor ischemic stroke or transient ischemic attack, to identify patients with *CYP2C19* LOF alleles for consideration of treatment with ticagrelor and aspirin instead of clopidogrel and aspirin for 90 days may be beneficial. If P2Y12 inhibitors need to be switched on the basis of genetic testing results, an international expert consensus statement has provided guidance to clinicians[212] on carrying out such a change in therapy.

CONCLUSIONS

Oral P2Y12 inhibitors are widely used in CAD, stroke, and peripheral arterial disease. The most commonly used oral P2Y12 inhibitor is clopidogrel, a prodrug that is metabolized primarily by the hepatic cytochrome P450 2C19 enzyme into an active metabolite that is responsible for its drug action. *CYP2C19* LOF alleles are present in up to 50% of patients (prevalence is variable according to ancestry) who are less able to metabolize and activate clopidogrel compared with noncarriers. An extensive number of studies have demonstrated that these patients have a significant decrease in active drug metabolite level, lack inhibition of platelet aggregation, and are at an increased risk of ischemic events when treated with clopidogrel. Treating *CYP2C19* LOF carriers with an alternative oral P2Y12 inhibitor such as ticagrelor or prasugrel (drugs that are not dependent on CYP2C19 for activation) results in improving high on-treatment platelet reactivity and decreasing ischemic events. However, these more potent oral P2Y12 inhibitors compared with clopidogrel can result in increased bleeding complications when used universally. A precision medicine approach based on *CYP2C19* genetic testing results in which LOF carriers are prescribed ticagrelor or prasugrel and noncarriers are prescribed clopidogrel decreases the risk of ischemic events compared with universal clopidogrel and decreases the risk of bleeding compared with universal ticagrelor or prasugrel and thus may offer a more balanced therapeutic approach. Given the totality of pharmacokinetic, pharmacodynamic, and recent clinical trial data with recent meta-analyses findings, *CYP2C19* genetic testing before prescription of clopidogrel or ticagrelor/prasugrel in patients with ACS or PCI can be beneficial. The implementation of *CYP2C19* genetic testing for individualizing oral P2Y12 inhibitor therapy depends on clinician and patient perceptions, recommendations provided by clinical guidelines that incorporate recently published clinical evidence, adoption by health care organizations by providing seamless integration in the EHR with supportive tools to understand results, reimbursement by insurance companies, and easy and timely availability of genetic testing.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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