

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 Update

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Cytochrome P450 (*CYP*)2C19 catalyzes the bioactivation of the antiplatelet prodrug clopidogrel, and *CYP2C19* loss-of-function alleles impair formation of active metabolites, resulting in reduced platelet inhibition. In addition, *CYP2C19* loss-of-function alleles confer increased risks for serious adverse cardiovascular (CV) events among clopidogrel-treated patients with acute coronary syndromes (ACSs) undergoing percutaneous coronary intervention (PCI). Guideline updates include emphasis on appropriate indication for *CYP2C19* genotype-directed antiplatelet therapy, refined recommendations for specific *CYP2C19* alleles, and additional evidence from an expanded literature review (updates at <http://www.pharmgkb.org>).

This document is an update to the 2011 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline on the clinical use of *CYP2C19* genotype test results for patients requiring antiplatelet therapy.¹ As of April 2013, a prospective randomized controlled trial on *CYP2C19* genotype-directed antiplatelet therapy with clinical outcomes has yet to be reported. Consequently, these recommendations are based on evaluation of the currently available evidence. Specifically, the updated therapeutic recommendations are more focused on patients with acute coronary syndromes (ACSs) undergoing percutaneous coronary intervention (PCI) than the original guideline, with additional updates involving refined recommendations for variant and novel *CYP2C19* alleles beyond *2 and

further evidence from an expanded literature review. As in the 2011 guideline, recommendations for the use of other laboratory tests, such as platelet function monitoring, and cost-effectiveness assessments are beyond the scope of this document. This document does not focus on demographic or other clinical variables such as adherence to therapy, age, diabetes mellitus, obesity, smoking, and concomitant use of other drugs that may influence clopidogrel efficacy and clinical decision making. The CPIC of the National Institutes of Health's Pharmacogenomics Research Network and PharmGKB develops peer-reviewed gene/drug guidelines that are published and updated on www.pharmgkb.org every 2 years or as needed based on significant developments in the field.²

FOCUSED LITERATURE REVIEW

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

DRUG: CLOPIDOGREL

Background

Clopidogrel is a thienopyridine prodrug that requires hepatic biotransformation to form an active metabolite that selectively and irreversibly inhibits the purinergic P2RY₁₂ receptor and thus platelet aggregation for the platelet's life span (~10 days).

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Only 15% of the prodrug is available for transformation to the active agent; the remaining 85% is hydrolyzed by esterases to inactive forms. Conversion of clopidogrel to its active metabolite requires two sequential oxidative steps involving several CYP enzymes (e.g., CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5; **Supplementary Figure S1** online). One small association study suggested that paraoxonase 1 (PON1) may also be involved in clopidogrel activation;³ however, this finding and the reported association between *PON1* variant alleles and clopidogrel response variability was not replicated in multiple recent publications (for review, see ref. 4).

GENE: CYP2C19

Background

A gene summary on *CYP2C19* has recently been published⁵ and is available online at PharmGKB: <http://www.pharmgkb.org/gene/PA124#tabview=tab3&subtab=31>. The hepatic CYP2C19 enzyme contributes to the metabolism of a large number of clinically relevant drugs such as antidepressants, benzodiazepines, mephenytoin, some proton pump inhibitors, and clopidogrel. Like many other *CYP450* superfamily members, the *CYP2C19* gene is highly polymorphic, with >25 known variant alleles (<http://www.cypalleles.ki.se/cyp2c19.htm>) (**Supplementary Tables S1** and **S2** online).⁵ The wild-type *CYP2C19**1 allele is associated with functional CYP2C19-mediated metabolism. The most common *CYP2C19* loss-of-function allele is *2 (c.681G>A; rs4244285), with allele frequencies of ~15% in Caucasians and Africans, and 29–35% in Asians (**Supplementary Tables S3** and **S4** online). Other *CYP2C19* variant alleles with reduced or absent enzymatic activity have been identified (e.g., *3–*8); however, their frequencies are typically below 1%, with the exception of *CYP2C19**3 (c.636G>A; rs4986893) in Asians (with an allele frequency of 2–9%; **Supplementary Tables S3** and **S4** online).

With respect to clopidogrel pharmacodynamics, *CYP2C19* loss-of-function alleles are inherited as autosomal codominant traits because heterozygotes (e.g., *1/*2 and *1/*3) have platelet responsiveness to clopidogrel that lies between homozygous wild-type (i.e., *1/*1) and loss-of-function allele homozygotes or compound heterozygotes (e.g., *2/*2 and *2/*3).^{6–11} Therefore, on the basis of identified *CYP2C19* genotypes, individuals typically are categorized as extensive metabolizers (EMs; *1/*1), intermediate metabolizers (IMs; e.g., *1/*2 and *1/*3),

or poor metabolizers (PMs; e.g., *2/*2 and *2/*3) **Table 1**. The frequencies of *CYP2C19* PMs are ~2–5% among Caucasians and Africans and ~15% in Asians (**Supplementary Materials and Methods** online).

By contrast, the common *CYP2C19**17 allele (c.-806C>T; rs12248560) results in increased activity as a consequence of enhanced transcription, with average multiethnic allele frequencies of ~3–21% (**Supplementary Tables S3** and **S4** online). Therefore, individuals who carry this allele may be categorized as ultrarapid metabolizers (e.g., *17/*17) **Table 1**. Some studies indicate that this allele results in enhanced platelet inhibition and clopidogrel response^{10,12–14} and perhaps an increased risk of bleeding complications.^{15,16} However, other studies have not identified an effect of *CYP2C19**17.^{11,17–20} Discordant results in the literature may be due in part to the linkage disequilibrium that exists between *17 and *2. Specifically, the gain-of-function “T” allele of *17 always occurs on a haplotype that also harbors the wild-type “G” allele of *2, so the observed effect of the gain-of-function *17 allele may actually be due, in part, to the absence of the loss-of-function “A” allele of *2. As such, adequate evidence for an independent effect of this allele on clinical outcomes is lacking. Moreover, given that *17 is unable to completely compensate for the *2 loss-of-function allele,¹³ *2/*17 compound heterozygotes should be classified as IMs (see **Supplementary Table S5** online).

Linking genetic variability to variability in drug-related phenotypes

Clopidogrel is commonly prescribed for ACSs and/or following PCI. However, responses to clopidogrel vary widely, with inhibition of adenosine diphosphate (ADP)-induced platelet aggregation being normally distributed across a broad range.¹¹ Many studies have shown that *CYP2C19**2 heterozygotes and homozygotes have reduced active clopidogrel metabolites and higher on-treatment platelet aggregation as compared with *1 homozygotes.^{6–8,10,11,21} Moreover, substantial evidence exists linking *CYP2C19* genotype with clinical outcomes among clopidogrel-treated ACS patients, particularly those undergoing PCI,^{9–11,18,22–24} probably as a result of decreased formation of the active clopidogrel metabolite. Studies linking *CYP2C19* genotype with variability in clopidogrel response are summarized in **Supplementary Tables S6** and **S7** online, and it is this

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

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

Some rare genotype combinations have unclear predicted metabolic phenotypes; see **Supplementary Table S5** online.

body of evidence, rather than randomized clinical trials, that provides the basis for genotype-informed therapeutic recommendations when considering treatment with clopidogrel (Table 2). Of note, the most definitive studies showing a relationship between *CYP2C19* genotype and clopidogrel response have predominantly been conducted in ACS patients, almost all of whom underwent PCI. Therefore, these recommendations do not apply to other situations in which clinicians may consider using clopidogrel, such as medical management of ACS, stroke, and peripheral artery disease.^{25,26}

Large meta-analyses (Supplementary Table S7 online) have shown that clopidogrel-treated ACS patients undergoing PCI who are *CYP2C19**2 heterozygotes or homozygotes have an increased risk for major adverse CV events as compared with *1 homozygotes (hazard ratio (HR) = 1.55, 95% confidence interval (CI) = 1.11–2.17 for heterozygotes; HR = 1.76, 95% CI = 1.24–2.50 for homozygotes) and increased risks of stent thrombosis (HR = 2.67, 95% CI = 1.69–4.22 for heterozygotes; HR = 3.97, 95% CI = 1.75–9.02 for homozygotes).²⁷ Additional meta-analyses have replicated the association between *CYP2C19* genotype and stent thrombosis, with reported odds ratios ranging from 1.75 to 3.82 among *2 heterozygotes and homozygotes (Supplementary Table S7 online).

As described above, a lack of effect of *CYP2C19* loss-of-function alleles on adverse CV outcomes has been reported among clopidogrel-treated patients with lower clinical risks (e.g., in clinical trials with fewer coronary patients undergoing PCI with stenting and in patients receiving clopidogrel for atrial fibrillation and stroke).²⁵ Consistent with these findings, meta-analyses that include studies with low frequencies of PCI, patients without coronary disease, follow-up periods beyond the duration of clopidogrel therapy, or non-CV outcomes have not supported a major role for *CYP2C19* in clopidogrel response variability in these patient populations²⁶ (Supplementary Table S7 online). Consequently, widespread adoption of *CYP2C19*-guided antiplatelet therapy for all patients is not recommended. Rather, this guideline is an example of indication-specific clinical pharmacogenetics whereby *CYP2C19* genotype-directed antiplatelet therapy is limited predominantly to ACS patients managed with PCI (ACS/PCI).²⁸ Although there are limited data regarding the potential role of *CYP2C19* for elective PCI cases treated with

clopidogrel, these guidelines may also be considered for these patients. However, the lack of indication for other US Food and Drug Administration–approved antiplatelet agents (e.g., prasugrel and ticagrelor) for treatment of elective PCI must be balanced with the boxed warning on the clopidogrel label recommending consideration of alternative antiplatelet therapy in *CYP2C19* PMs with ACS or PCI.

The growing body of literature implicating *CYP2C19**2 (and probably other loss-of-function alleles) in adverse clopidogrel responses prompted the Food and Drug Administration to implement a boxed warning on the clopidogrel label describing the relationship between *CYP2C19* pharmacogenetics and drug response among ACS/PCI patients, particularly noting the diminished effectiveness in PMs. Because the Food and Drug Administration warning does not require genetic testing to initiate clopidogrel therapy, if a patient's genotype is unknown, the decision to perform *CYP2C19* testing is up to the individual clinician.

Genetic test interpretation

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

Available genetic test options

A number of Clinical Laboratory Improvement Amendments–certified laboratories offer targeted genetic testing for *CYP2C19**2, *3, and other variant alleles (see Supplementary Materials and Methods online). A voluntary listing of testing providers and related genetic test information is publicly available through the Genetic Testing Registry of the National Institutes of Health: <http://www.ncbi.nlm.nih.gov/gtr/>. At the time of this writing, only the *CYP2C19**2 and *3 alleles have

Table 2 Antiplatelet therapy recommendations based on *CYP2C19* status when considering clopidogrel for ACS/PCI patients

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations ^a
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation ^b	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

^aSee Supplementary Materials and Methods (Strength of Therapeutic Recommendations) online. ^bThe *CYP2C19**17 allele may be associated with increased bleeding risks (ref. 15). ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

been adequately studied with respect to clinical outcomes on clopidogrel, although other known loss-of-function alleles with lower frequencies (e.g., *4–*8) also likely influence clopidogrel response (see **Supplementary Materials and Methods** online).

CYP2C19 sequencing and novel variants

In addition to targeted genotyping, clinical laboratories may test *CYP2C19* by direct sequencing, and clinical whole-exome and whole-genome sequencing programs are increasingly being deployed across academic medical centers and commercial laboratories. Sequencing-based tests capture the common *CYP2C19* variants (e.g., *2 and *3) but will also identify both rare (e.g., *4–*8) and novel *CYP2C19* variant alleles that have untested clinical significance with respect to clopidogrel response (**Supplementary Materials and Methods** online). Available evidence suggests that *CYP2C19* and other drug metabolism genes are highly polymorphic. Although it is challenging to infer any association with clopidogrel response in the context of a novel *CYP2C19* sequence variant, reported variants that are “pathogenic” or “likely pathogenic” (based on the American College of Medical Genetics and Genomics consensus nomenclature) may act in a manner biologically consistent with other common loss-of-function alleles (e.g., *2–*8) because these are sequence alterations that typically result in an upstream polypeptide frameshift, premature or mutated stop codon, or canonical splice-site mutation. Novel *CYP2C19* variants classified as having “unknown significance” (e.g., missense alterations, in-frame insertions/deletions, and nonconserved nucleotide substitutions) or “likely benign” should not be assumed to mimic the biological consequences of known *CYP2C19* loss-of-function alleles and their established roles in clopidogrel response variability.

Incidental findings

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

Other considerations

CYP2C19 loss-of-function alleles do not account for all the variability in clopidogrel response. Some studies have implicated variants in other genes associated with clopidogrel response (e.g., *ABCB1*, *CES1*, *CYP2B6*, *CYP2C9*, *P2RY12*, and *PON1*; see **Supplementary Materials and Methods** online for review); however, these have not been consistently replicated.

THERAPEUTIC RECOMMENDATIONS

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. 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. With respect to other professional statements, the 2012 American College of Cardiology Foundation/American Heart Association ACS guidelines noted that genetic testing for *CYP2C19* loss-of-function alleles may be considered on a case-by-case basis, especially for patients who experience recurrent ACS events despite ongoing therapy with clopidogrel.²⁹ In addition, the committee recommended that genotyping might be considered if results of testing may alter management, which they suggest until better clinical evidence exists to provide a more scientifically derived recommendation.²⁹

Optimal individualized antiplatelet treatment should maximize benefit by reducing risk of recurrent CV events while minimizing adverse effects such as bleeding. Prasugrel is an approved antiplatelet agent that was superior to clopidogrel in a large-scale randomized trial of ACS patients with planned PCI, with an HR for CV death, myocardial infarction, or stroke for prasugrel vs. clopidogrel of 0.81 (95% CI = 0.73–0.90, $P < 0.001$), as well as a 42% reduction in stent thrombosis.³⁰ However, it may not represent a substitute for clopidogrel in all patients due to an increased risk of non-coronary artery bypass grafting TIMI major bleeding (HR = 1.32, 95% CI = 1.03–1.68; $P = 0.03$), including fatal bleeding (prasugrel = 0.4% vs. clopidogrel = 0.1%; $P = 0.002$);³⁰ its contraindication in some patients (e.g., history of transient ischemic attack, stroke, or intracranial bleeding); and the lower expense of generic clopidogrel following the recent expiration of its patent. Of note, the benefit of prasugrel over clopidogrel was found to be greater in patients with a *CYP2C19* loss-of-function allele,³¹ with no significant difference estimated in composite outcome risk between the two antiplatelet agents among *CYP2C19* extensive metabolizers (i.e., *1/*1 patients).³²

In addition to prasugrel, ticagrelor is a recently approved antiplatelet agent that also was superior to clopidogrel in a large-scale randomized trial of ACS patients with an HR for CV death, myocardial infarction, or stroke for ticagrelor vs. clopidogrel of 0.84 (95% CI = 0.77–0.92; $P < 0.001$),³³ including a 26% reduction in stent thrombosis and 18% reduction in all-cause mortality. In the genetic substudy, as compared with clopidogrel, ticagrelor reduced the primary end point by 23% among patients carrying any *CYP2C19* loss-of-function allele (8.6 vs. 11.2%; HR = 0.77, 95% CI = 0.60–0.99; $P = 0.0380$) and 14% among patients without any *CYP2C19* loss-of-function allele (8.8 vs. 10.0%; HR = 0.86, 95% CI = 0.74–1.01), although this reduction did not reach statistical significance ($P = 0.0608$). However, formal interaction testing that evaluated if the effect of ticagrelor vs. clopidogrel varied by genotype was also not significant. Of note, the benefit of ticagrelor as compared with clopidogrel was subsequently shown to appear to be most pronounced among the subset of patients with *CYP2C19* loss-of-function alleles who were undergoing PCI (carriers: 7.7 vs. 10.6%, HR = 0.71; noncarriers: 7.4 vs. 8.2%, HR = 0.90).³⁴ In addition, it is not known to what extent twice-daily dosing may affect the efficacy of ticagrelor relative to clopidogrel in a real-world setting.

Despite the improvements in overall efficacy reported for prasugrel and ticagrelor as compared with clopidogrel, it is

anticipated that clopidogrel will continue to be a widely prescribed medication for ACS/PCI patients. Genotype-directed therapy could identify patients who benefit most from alternative antiplatelet therapy. For clinicians considering treatment with clopidogrel, **Table 2** and **Figure 1** summarize the therapeutic recommendations for antiplatelet therapy based on *CYP2C19* status. Standard dosing of clopidogrel, as recommended in the product insert, is warranted among ACS/PCI patients with a predicted *CYP2C19* extensive metabolizer or ultrarapid metabolizer phenotype (i.e., $*1/*1$, $*1/*17$, and $*17/*17$).³² If genotyping from a Clinical Laboratory Improvement Amendments–certified laboratory identifies a patient as a *CYP2C19* PM (i.e., $*2/*2$), current literature supports the use of an alternative antiplatelet agent (e.g., prasugrel or ticagrelor) when not contraindicated clinically.^{10,30,31,35–37}

The most challenging patient population to address is the *CYP2C19* IM phenotype (e.g., $*1/*2$, $*1/*3$, and $*2/*17$). IMs have higher on-treatment residual platelet activity on average as compared with extensive metabolizers.^{6–8,10,11} and ACS/PCI *CYP2C19**2 heterozygotes treated with clopidogrel have increased risks for serious adverse CV outcomes, including stent thrombosis²⁷ (see **Supplementary Materials and Methods** online). Consequently, these data support switching to an alternative antiplatelet agent for IMs when not contraindicated. However, given the wide interindividual variability in residual platelet activity observed among clopidogrel-treated IMs, clinical judgment also taking into account other factors that may place an IM at increased risk of a CV event (or adverse bleeding event) must be considered to most effectively individualize therapy.

In addition, although these guidelines have been focused on *CYP2C19**2 and *3, many clinical genotyping platforms include other variant alleles (e.g., $*4$ – $*8$ and $*17$) that can alter a patient's predicted metabolizer phenotype interpretation (**Supplementary Table S5** online). As mentioned above, the $*4$ – $*8$ alleles have strong *in vitro* evidence for complete loss of function of the *CYP2C19* enzyme (see **Supplementary Materials and Methods** online for references). Consequently, when these alleles are identified among ACS/PCI patients

treated with clopidogrel, they should be considered as influencing clopidogrel metabolism and clinical outcomes consistent with the *2 loss-of-function allele.

CLOPIDOGREL DOSE ESCALATION

Recent studies that have evaluated a significantly increased clopidogrel loading and/or maintenance dosing strategy in both healthy subjects and ACS patients have reported improved platelet inhibition among *CYP2C19**2 heterozygotes (IMs) based on *ex vivo* platelet aggregation but only nominal improvement among homozygotes (PMs) (see **Supplementary Table S8** online). Large clinical trials that evaluated higher-dose clopidogrel in ACS/PCI patients with high on-treatment platelet reactivity have concluded that adjusting clopidogrel dose on the basis of platelet function monitoring alone does not reduce the incidence of death from CV causes, nonfatal myocardial infarction, or stent thrombosis.^{38,39} However, typically these trials only doubled the clopidogrel maintenance dose, which may not be adequate on the basis of recent studies that suggest that even higher doses may be required to achieve adequate platelet inhibition among *CYP2C19**2 heterozygotes (see **Supplementary Table S8** online). Given these data and the lack of clinical outcome studies for clopidogrel dose adjustment on the basis of *CYP2C19* status alone, it is currently premature to support an increased dosing strategy based on *CYP2C19* genotype. Future versions of these guidelines (updated on www.pharmgkb.org) will continue to incorporate results from ongoing clinical trials designed to address these and other emerging issues, including the potential role for platelet function monitoring.

OTHER CONSIDERATIONS

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

Potential benefits and risks for the patient

The potential benefits of *CYP2C19* testing are that when considering treatment with clopidogrel in ACS/PCI patients, genotypes that confer a higher risk of a CV event on clopidogrel can be identified, and an alternative antiplatelet strategy can be instituted. Although there is mounting evidence associating deficient *CYP2C19* with increased risks of adverse CV outcomes in clopidogrel-treated ACS/PCI patients, the absence of randomized clinical trial evidence that *CYP2C19* genotyping improves outcomes must be acknowledged. Furthermore, although *CYP2C19* genotyping is straightforward and reliable when performed in qualified laboratories, as with any laboratory test, an additional possible risk to the patient is an error in genotyping. Because genotypes are lifelong test results, any such error could have adverse health implications for the life of the patient.

Caveats: appropriate use and/or potential misuse of genetic tests

If pursuing *CYP2C19* genotyping, one of the challenges is the need for rapid turnaround time of results. It would be

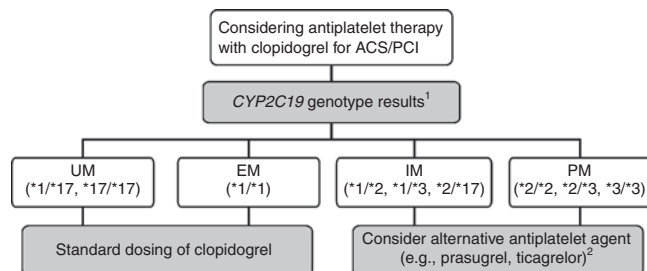


Figure 1 Algorithm for suggested clinical actions based on *CYP2C19* genotype when considering treatment with clopidogrel for ACS patients undergoing PCI (ACS/PCI). ¹Other rare *CYP2C19* genotypes exist beyond those illustrated (see **Supplementary Materials and Methods** online for other genotypes and frequencies). ²Note that prasugrel and ticagrelor are recommended only when not contraindicated clinically. ACS, acute coronary syndrome; EM, extensive metabolizer; IM, intermediate metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; UM, ultrarapid metabolizer.

advantageous to have the results before initiating antiplatelet therapy because the largest number of potentially preventable recurrent events occur early in treatment. For example, among other clinical and genetic factors, *CYP2C19*2* has recently been associated with definite early stent thrombosis in a case-control study.²² Therefore, if *CYP2C19* genotype is not already known from prior testing, early testing and expedited reporting would be advantageous. To address this issue, point-of-care genetic testing systems have been developed (see **Supplementary Materials and Methods** online), and some academic medical centers have deployed preemptive genotyping programs for selected patient populations.

Of note, as described above, these recommendations apply predominantly to ACS patients undergoing PCI. Current data do not support the use of *CYP2C19* genotype data to guide treatment in other scenarios.^{25,26,40} In addition, at the time of this writing, there are no data available on the possible role of *CYP2C19* in clopidogrel response in pediatric patient populations; however, there is no reason to suspect that *CYP2C19* variant alleles would affect clopidogrel metabolism differently in children as compared with adults.

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

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CONFLICT OF INTEREST

S.A.S. receives support from NIH for antiplatelet pharmacogenomics research, is a consultant to USDS, and is an assistant director of a clinical laboratory that performs *CYP2C19* testing. J.-S.H. has received research grant support from Biotronik and Medco Research Institute and consulting fees from Biotronik and Medco Health Solutions. J.L.M. receives research grant support through Brigham and Women's Hospital from Bayer Healthcare, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Johnson & Johnson, Sanofi-Aventis, Accumetrics, and Nanosphere, and is a consultant to Boehringer Ingelheim, Janssen, and American Genomics. D.M.R. receives support from the NIH for pharmacogenomics research and is a consultant to Merck, Novartis, Dai-ichi, Sanofi, and Astellas. M.S.S. receives research grant support through Brigham and Women's Hospital from AstraZeneca,

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