HHS Public Access

Author manuscript

Interv Cardiol Clin. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Interv Cardiol Clin. 2017 January ; 6(1): 141–149. doi:10.1016/j.iccl.2016.08.010.

Genetic determinants of P2Y12 inhibitors and clinical implications

Larisa H. Cavallari, Pharm.D. [Associate Professor] and

Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, Gainesville, FL; 1333 Center Drive, PO Box 100486, Gainesville, FL 32610; Fax: (352) 273-6485; Tel: (352) 273-8245

Aniwaa Owusu Obeng, Pharm.D.

The Charles Bronfman Institute for Personalized Medicine and Division of General Internal Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, and the Department of Pharmacy, The Mount Sinai Hospital, New York, NY; Tel: (212) 241-7371

Larisa H. Cavallari: lcavallari@cop.ufl.edu; Aniwaa Owusu Obeng: aniwaa.owusu-obeng@mssm.edu

Synopsis

There is significant inter-patient variability in clopidogrel effectiveness, which is due in part to cytochrome P450 (CYP) 2C19 genotype. Approximately 30% of individuals carry *CYP2C19* loss-of-function (LOF) alleles, which have been consistently shown to reduce clopidogrel effectiveness after an acute coronary syndrome and percutaneous coronary intervention (PCI). Guidelines recommend consideration of prasugrel or ticagrelor in these patients. A clinical trial examining outcomes with *CYP2C19*-genotype guided antiplatelet therapy in ongoing. In the meantime, based on the evidence available to date, several institutions have started clinically implementing *CYP2C19* genotyping to assist with antiplatelet selection after PCI.

Keywords

clopidogrel; prasugrel; ticagrelor; genotype; CYP2C19; pharmacogenomics

Introduction

Clopidogrel is commonly prescribed in combination with aspirin for the prevention of ischemic events in patients with an ACS, whether managed medically or with percutaneous coronary intervention (PCI).[1, 2] However, there is substantial interpatient response variability with clopidogrel. Contributions to this variability have been well studied and include both clinical factors and genotype.[3-5] Prasugrel and ticagrelor are alternative agents shown to be

Correspondence to: Larisa H. Cavallari, lcavallari@cop.ufl.edu.

Disclosure statement: The authors have nothing to disclose.

superior to clopidogrel in clinical trials, but are associated with increased bleeding risk.[6, 7] This review describes genetic contributions to variable response to platelet $P2Y_{12}$ inhibitors, guidelines for selecting antiplatelet therapy based on genotype, and examples of clinical implementation of genotype-guided antiplatelet therapy after PCI.

Pharmacology of ADP Antagonists / $P2Y_{12}$ Receptor Inhibitors

Clopidogrel and prasugrel are thienopyridines that irreversibly bind to platelet $P2Y_{12}$ receptors thereby inhibiting ADP-mediated platelet activation and aggregation. Both are administered as prodrugs that require hepatic bioactivation to their active moieties.[8] As shown in Figure 1, a number of cytochrome P450 (CYP) enzymes are involved in the two-step biotransformation of clopidogrel to its active compound (R1309641).[8, 9] Notably, only 15% of ingested clopidogrel is converted into the active compound, and the remainder is inactivated by carboxyl esterases.[8, 10]

A lack of uniformity in platelet inhibition after clopidogrel treatment has been observed, and patients with high pre-treatment platelet reactivity tend to respond poorly to the drug, with an increased risk for major adverse cardiovascular events (MACE), including stent thrombosis.[11-14] Clopidogrel response variability has been attributed to factors such as age, body mass index, co-medications, diabetes, renal failure, cardiac failure and most importantly loss-of-function (LOF) polymorphisms in the *CYP2C19* gene.[3-5]

Prasugrel also undergoes hepatic bioactivation mediated by multiple enzymes, as shown in Figure 2.[8] It has a more rapid onset of action and exhibits greater platelet inhibition than clopidogrel, with much less variability in response.[15] However, prasugrel is associated with an increased risk of major bleeding compared to clopidogrel, which has led to reduced dose (5mg per day) recommendations for patients weighing 60 kg or less and those 75 years of age or older, who have excess formation of active metabolites.[15, 16] Like clopidogrel, high on treatment platelet reactivity has been reported with prasugrel, which confers a higher risk of MACE after PCI.[17] Prasugrel is contraindicated in patients with pathological bleeding or a history of transient ischemic attack or stroke.

Ticagrelor is a non-thienopyridine that reversibly binds the $P2Y_{12}$ receptor and does not require bioactivation. It has a quicker onset and offset of antiplatelet activity compared to clopidogrel and this results in greater efficacy in terms of reduction in the risk for MACE in ACS patients.[7, 18] While risk for major bleeding is similar between ticagrelor and clopidogrel, ticagrelor is associated with an increased risk of non-coronary artery bypass graft related bleeding. Other adverse events with ticagrelor include dyspnea, bradyarrhythmia and minor spikes in serum creatinine and serum uric acid levels.[7, 19, 20] Ticagrelor is contraindicated in patients a history of intracranial hemorrhage, active bleeding, moderate to severe hepatic impairment and any hypersensitivity reactions to ticagrelor.[20]

Genetic Determinants of Clopidogrel Response

CYP2C19 Genotype

Polymorphisms in the *CYP2C19* gene (specifically loss-of-function variants) have been consistently implicated in clopidogrel response heterogeneity in both candidate gene and genome-wide association studies (GWAS).[21-26] *CYP2C19* or cytochrome P450, family 2, subfamily C, polypeptide 19, is located on chromosome 10 among a cluster of CYP genes including *CYP2C18, CYP2C9*, and *CYP2C8*.[27] Like many other cytochrome P450 genes, *CYP2C19* possesses genetic polymorphisms that lead to variable hepatic expression, which in turn alters the function of the resultant protein (i.e. CYP2C19 enzyme).

Over 30 *CYP2C19* alleles have been identified.(http://www.cypalleles.ki.se/). The *CYP2C19*1* allele represents a fully functional or normal activity allele. The most common loss-of-function (LOF) allele is the **2* allele (c.681 G>A; rs4244285), which occurs secondary to an aberrant splice site in exon 5 leading to a truncated protein.[27] The less common *CYP2C19*3* (c.636G>A; rs4986893) variation results in loss of enzyme activity secondary to premature termination of the amino acid sequence. *CYP2C19*4* through **8* are LOF alleles observed in less than 1% of the general population.[27, 28] Approximately 60% to 70% of East Asians carry a LOF allele, while the rate is lower (about 30%) in an ethnically and racially diverse population.[28, 29] The *CYP2C19*17* allele (c. -806C>T) occurs in the gene promoter region and results in enhanced enzymatic activity and is thus called a gain-of-function allele. While several groups have observed greater clopidogrel-induced platelet inhibition and high bleeding risk in patients with a **17* allele compared to noncarriers, data are inconsistent.[22, 30-32]

As shown in Table 1, *CYP2C19* genotype confers 5 phenotypes:

- Normal (or extensive) metabolizers (NMs)
- Poor metabolizers (PMs)
- Intermediate metabolizers (IMs)
- Rapid metabolizers (RMs)
- Ultra-rapid metabolizers (UMs)

The prevalence of CYP2C19 phenotypes by race is shown in Table 2. Consistent with having a higher frequency of LOF alleles, Asians have the highest prevalence of the PM and IM phenotypes.

CYP2C19 genotype and clopidogrel pharmacokinetics and pharmacodynamics

Carriers of a *CYP2C19* LOF allele (i.e. PMs and IMs) have diminished capacity to bioactive clopidogrel. A relative reduction of 32% in plasma concentrations of the active metabolite was reported in LOF carriers following clopidogrel exposure.[33] Consistent with this, LOF genotype is associated with high on-treatment platelet reactivity (HTPR) after PCI, which is an independent risk factor for MACE.[34] Therefore, it would follow that clopidogrel-treated LOF allele carriers may be at greater risk for MACE after PCI compared to non-carriers.

CYP2C19 genotype and clinical outcomes with clopidogrel

In an early study of nearly 800 PCI patients, a 3-fold increase in the incidence of death and myocardial infarction at one year was observed in *CYP2C19*2* allele carriers compared to the non-carriers.[21] This association was replicated in a number of subsequent studies.[22-25] In a meta-analysis including 9 studies and over 9600 patients (54% with ACS and 91% with PCI), carriers of a LOF allele had an increased risk for MACE compared to noncarriers (hazard ratio, 1.57; 95% confidence interval, 1.13-2.16).[35] The risk for stent thrombosis was even more marked, with a hazard ratio of 2.67 (95% CI, 1.69-4.22) in IMs and 3.97 (95% CI, 1.75-9.02) in PMs compared to non-LOF allele carriers.

The association between *CYP2C19* genotype and adverse outcomes has not been demonstrated with all indications of clopidogrel. Specifically, among lower risk patients, such as those receiving clopidogrel for stable coronary disease, atrial fibrillation, or with ACS managed medically, no difference in clinical outcomes has been reported by genotype.[32, 36] Similarly, a meta-analysis including studies of lower risk patients found only a modest association between genotype and clinical outcomes, which was abrogated when smaller studies were excluded.[37]

A more recent meta-analysis specifically aimed to assess outcomes among patients with and without PCI.[38] In non-PCI patients, no increased risk of cardiovascular events was apparent (relative risk 0.99, 95% CI 0.84-1.17). However, among those who underwent PCI, there were significantly more events among LOF allele carriers compared to noncarriers (relative risk 1.20, 95% CI 1.10-1.31). Overall, the data strongly and consistently support reduced clopidogrel effectiveness in carriers of a *CYP2C19* LOF allele after ACS and PCI, but not in those at lower risk for adverse cardiovascular events.

Other genes associated with clopidogrel response

Other genes involved in the metabolic and pharmacodynamics pathways of clopidogrel have also been examined for their association with clopidogrel effectiveness. These include the *ABCB1, CES1, CYP2B6, CYP2C9, CYP3A4*, *PON1,* and *P2Y12* genes.[22, 39-43] However, none of these have been consistently shown to contribute to clopidogrel response heterogeneity. In a GWAS conducted in healthy Amish volunteers given clopidogrel, only a cluster of polymorphisms on chromosome 10q24 in linkage disequilibrium with *CYP2C19*2* reached genome wide significance for its association with platelet aggregation, suggesting that no other gene has major contributions to clopidogrel response.[23]

Therapeutic approaches based on *CYP2C19* genotype

Clopidogrel dose escalation

Clopidogrel dose escalation as a means of compensating for reduced clopidogrel activation in the presence of a *CYP2C19* LOF allele has been the subject of several studies. In healthy volunteers, a clopidogrel maintenance dose of 150 mg in IMs and 300 mg in PMs resulted in similar inhibition of ADP-induced platelet aggregation as a 75 mg dose in NMs.[44] However, among patients with coronary heart disease, a 300 mg dose failed to reduce platelet reactivity in PMs to a level achieved with a 75 mg dose in NMs.[45] In IMs, a dose of 225 mg

in non-diabetics and 300 mg in diabetics resulted in desired on-treatment platelet reactivity. Taken together, these data suggest that while adequate antiplatelet activity may be attained with tripling or quadrupling the dose in IMs, such an approach may not be effective in PMs. Use of alternative agents whose effects are not influenced by *CYP2C19* genotype is a more viable option in IMs and PMs.

Alternative antiplatelet therapy

Unlike clopidogrel, *CYP2C19* genotype does not affect prasugrel pharmacokinetics or pharmacodynamics despite being involved in prasugrel bioactivation.[22] This is likely because CYP2C19 has a minor role in the bioactivation of prasugrel compared to other enzymes involved.[46] Since ticagrelor does not require bioactivation, CYP450 enzymes do not influence the amount of drug initially entering the body.

Genetic sub-studies of large randomized controlled trials that compared the efficacy of clopidogrel to prasugrel or ticagrelor have been conducted.[47, 48] In carriers of a *CYP2C19* LOF allele, both prasugrel and ticagrelor were shown to significantly reduce ischemic events compared to clopidogrel. However, prasugrel and clopidogrel were similarly effective in patients without a LOF allele.[48] Ticagrelor tended to remain superior to clopidogrel in the absence of the LOF genotype (p=0.06).[47] The test for interaction between genotype and treatment group was not significant, leading the authors to conclude that ticagrelor is superior in reducing ischemic events compared to clopidogrel regardless of genotype.

Guidelines for *CYP2C19* genotyping with clopidogrel

In March, 2010, the FDA approved a revision to the clopidogrel labeling to add a boxed warning stating that:[49]

- The efficacy of clopidogrel is reduced in PMs with ACS or undergoing PCI;
- Tests are available to determine genotype for clinical purposes; and
- Alternative treatment strategies should be considered for PMs.

This followed two previous revisions to the label, the first of which added initial information about reduced clopidogrel response in PMs, and the second of which advised avoidance of clopidogrel in patients with decreased CYP2C19 enzyme activity secondary to LOF genotype or concomitant use of CYP2C19 inhibitors.

Following the clopidogrel label revision, the American College of Cardiology Foundation and the American Heart Association issued guidance on the use of genetic testing to guide antiplatelet selection after PCI.[49] They state that the evidence base is insufficient to recommend routine genetic testing, citing a lack of data that routine testing improves outcomes. However, genetic testing may be considered before starting clopidogrel in patients at moderate to high risk for poor outcomes, such as those undergoing high-risk PCI procedures. For patients found to be PMs, then alternative therapy is recommended in the absence of contraindications.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) also provides guidelines for clopidogrel use based on *CYP2C19* genotype.[29] The guidelines do not provide recommendations on whether or not to order a genetic test, but rather on how to interpret genetic test results and use them to optimize drug therapy. The clopidogrel guidelines were the second of 17 CPIC gene-drug pair guidelines available as of mid-2016, indicating the high level of evidence supporting *CYP2C19*-guided clopidogrel use relevant to genotype-guided therapy for other drugs. The recommendations are outlined in Figure 3, with prasugrel or ticagrelor recommended after ACS and PCI in patients with a loss-of-function allele.[29] The recommendations are graded as strong for PMs, meaning that the desirable effects clearly outweigh the undesirable effects, and moderate for IMs, meaning that there is close or uncertain balance between desirable and undesirable effects.

Clinical implementation of *CYP2C19* genotyping

Examples of clinical implementation

A number of institutions have established a process for providing *CYP2C19* genotyping to help direct antiplatelet prescribing for patients undergoing PCI. Approaches vary from preemptive genetic testing in advance of patients needing dual antiplatelet therapy to reactive testing at the time of PCI when dual antiplatelet therapy is deemed necessary. For example, Vanderbilt University and University of Maryland implemented *CYP2C19* testing for patients scheduled to undergo left heart catheterization so that results would be available in the event that the patient proceeded to PCI.[50, 51] At the University of Florida, the approach is more reactive, with the genotype test order defaulted on the post-PCI order set so that patients are automatically genotyped unless the physician chooses to unselect the order.[52]

Patient selection for genotyping also varies by site, with some sites broadly genotyping all patients undergoing left heart catheterization or PCI, such as described above. Other sites focus on high risk patients. This is the approach at the University of North Carolina where testing is recommended in PCI patients with high-risk anatomic findings.[53] Rather than being a defaulted order, genetic testing is actively ordered after angiography-guided risk stratification by the interventional cardiologist.

In the U.S., genotyping must be performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory for results to be entered into the electronic health record and used for clinical purposes. Recommendations for alternative antiplatelet therapy for patients with LOF genotype may be provided to physicians via electronic decision support tools or through other forms of communication (e.g. telephone call, secure email). [50-52] For example, at the University of Florida, an alert will pop up in the EHR in response to an order for clopidogrel for a patient with a loss-of-function genotype, warning the clinician of potential reduced clopidogrel effectiveness and advising consideration of prasugrel or ticagrelor. Dosing information and contraindications for alternative agents are included in the alert to assist with prescribing decisions, and the physician may place the order for alternative therapy directly from the alert. Ultimately, the choice of antiplatelet therapy is left to the discretion of the physician. Recent preliminary data suggest that patients with a LOF allele who are switched to alternative therapy have a significant

reduction in risk for major adverse cardiovascular events compared to loss-of-function allele carriers continued on clopidogrel.[54]

Barriers to clinical implementation

Implementation of *CYP2C19* testing requires overcoming a number of barriers. These include establishing a process for genetic testing and the need to obtain genotype results prior to or soon after PCI. Ideally, a point-of-care platform would be available in the cardiac catheterization laboratory to rapidly provide genotype results. While such a platform is available, placing it in the cardiac catheterization laboratory is inconsistent with quality standard in the U.S., which requires that testing be done in a CLIA-licensed laboratory. Thus, a process must be established to transport samples efficiently to a CLIA-licensed laboratory for testing and efficient return of genotype results.

Another major barrier is the lack of data from large randomized clinical trials showing improved outcomes with genotype-guided clopidogrel use. Obviously, many sites feel that the available data linking *CYP2C19* genotype to poor outcomes with clopidogrel are sufficient to support clinical implementation. However, others argue that implementation is premature in the absence of prospective clinical trial data. While a clinical trial is currently underway, it is not expected to be completed until 2019.(clinical trials.gov identifier: NCT01742117) In the meantime, it is anticipated that clinical outcome data will emerge from sites implementing genetic testing, which may influence the landscape of clopidogrel pharmacogenetics.

The need for clinician preparedness to utilize genetic testing results is an additional barrier. Equipping clinicians with tools to translate genetic results into prescribing decisions at the time of care may be addressed through electronic decision support, as described above at the University of Florida, consultation with pharmacogenetic experts, or other means. Recognizing the knowledge and awareness barrier for pharmacogenetic testing, the National Institutes of Health and other stakeholders have also taken steps to better educate the clinician workforce on genomic medicine.(Genetics/Genomics Competency Center http://g-2-c-2.org//)

Pharmacogenetics of prasugrel and ticagrelor

Several investigators have examined associations between CYP450 genotypes and prasugrel response. One study reported overrepresentation of the *CYP2C9*2* variant among individuals with a lower level of platelet inhibition with prasugrel,[55] whereas others have found no significant effect of *CYP2C9*, *CYP2C19*, *CYP2B6*, *CYP3A4*, or *CYP1A2* genotypes on either prasugrel metabolite concentrations or antiplatelet effects.[22, 41]

A GWAS was conducted to identify associations with ticagrelor pharmacokinetics and clinical response.[56] A variant in the *CYP3A4* gene was found to be associated with ticagrelor concentrations. Two additional polymorphisms, one in the *SLCO1B1* gene, encoding for the organic anion transporter polypeptide, and another in *UGT2B7*, encoding for UDP-glucuronosyltransferase 2B7, were associated with concentrations of the major active metabolite of ticagrelor. However, effects were modest, and none of the

polymorphisms were associated with reductions in ischemic events or risk for bleeding or dyspnea with ticagrelor.

Summary and future projections for antiplatelet pharmacogenomics

Data clearly and consistently demonstrate reduced clopidogrel effectiveness in preventing ischemic events in patients with a *CYP2C19* LOF allele. Given the high prevalence of the LOF genotype, a substantial portion of the population is at risk for inadequate anti-platelet response to clopidogrel. The data have accumulated to the extent that an increasing number of institutions are beginning to offer *CYP2C19* genotyping for patients undergoing PCI to assist with antiplatelet selection. Randomized controlled trial data, considered the gold standard evidence needed to broadly influence practice patterns, are forthcoming on the efficacy of genotype-guided antiplatelet therapy. In the meantime, efforts to implement *CYP2C19* testing into practice to predict clopidogrel response will help to establish procedures for overcoming implementation barriers and may also provide useful “real world” data on outcomes with pharmacogenetics testing to complement clinical trial findings.

Acknowledgments

Funding Sources: Work by LHC is supported by NIH/NHGRI (U01 HG 007269). AOO is supported in part by NIH/NHGRI (U01HG006380). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH, Braunwald E. Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction I. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA. 2005; 294:1224–1232. [PubMed: 16143698]
2. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Clopidogrel in Unstable angina to prevent Recurrent Events trial I. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001; 358:527–533. [PubMed: 11520521]
3. Khalil BM, Shahin MH, Solayman M, Langaee T, Schaalan MF, Gong Y, Hammad LN, Al-Mesallamy HO, Hamdy NM, El-Hammady WA, Johnson JA. Genetic and Nongenetic Factors Affecting Clopidogrel Response in the Egyptian Population. Clin Transl Sci. 2016; 9:23–28. [PubMed: 26757134]
4. Cuisset T, Quilici J, Grosdidier C, Fourcade L, Gaborit B, Pankert M, Molines L, Morange PE, Bonnet JL, Alessi MC. Comparison of platelet reactivity and clopidogrel response in patients </= 75 Years Versus > 75 years undergoing percutaneous coronary intervention for non-ST-segment elevation acute coronary syndrome. Am J Cardiol. 2011; 108:1411–1416. [PubMed: 21872198]
5. Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Buttner HJ, Neumann FJ. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol. 2010; 55:2427–2434. [PubMed: 20510210]
6. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM.

Investigators T-T. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357:2001–2015. [PubMed: 17982182]

7. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361:1045–1057. [PubMed: 19717846]
8. Laine M, Paganelli F, Bonello L. P2Y12-ADP receptor antagonists: Days of future and past. World J Cardiol. 2016; 8:327–332. [PubMed: 27231519]
9. Kazui M, Nishiya Y, Ishizuka T, Hagihara K, Farid NA, Okazaki O, Ikeda T, Kurihara A. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos. 2010; 38:92–99. [PubMed: 19812348]
10. Karazniewicz-Lada M, Danielak D, Burchardt P, Kruszyna L, Komosa A, Lesiak M, Glowka F. Clinical pharmacokinetics of clopidogrel and its metabolites in patients with cardiovascular diseases. Clin Pharmacokinet. 2014; 53:155–164. [PubMed: 24127209]
11. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003; 107:2908–2913. [PubMed: 12796140]
12. Jaremo P, Lindahl TL, Fransson SG, Richter A. Individual variations of platelet inhibition after loading doses of clopidogrel. J Intern Med. 2002; 252:233–238. [PubMed: 12270003]
13. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD. Investigators AD. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet. 2013; 382:614–623. [PubMed: 23890998]
14. Angiolillo DJ, Bernardo E, Sabate M, Jimenez-Quevedo P, Costa MA, Palazuelos J, Hernandez-Antolin R, Moreno R, Escaned J, Alfonso F, Banuelos C, Guzman LA, Bass TA, Macaya C, Fernandez-Ortiz A. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol. 2007; 50:1541–1547. [PubMed: 17936152]
15. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, Angiolillo DJ, Hod H, Montalescot G, Miller DL, Jakubowski JA, Cairns R, Murphy SA, McCabe CH, Antman EM, Braunwald E. Investigators P-T. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation. 2007; 116:2923–2932. [PubMed: 18056526]
16. Roe MT, Goodman SG, Ohman EM, Stevens SR, Hochman JS, Gottlieb S, Martinez F, Dalby AJ, Boden WE, White HD, Prabhakaran D, Winters KJ, Aylward PE, Bassand JP, McGuire DK, Ardissino D, Fox KA, Armstrong PW. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. Circulation. 2013; 128:823–833. [PubMed: 23852610]
17. Bonello L, Pansieri M, Mancini J, Bonello R, Maillard L, Barnay P, Rossi P, Ait-Mokhtar O, Jouve B, Collet F, Peyre JP, Wittenberg O, de Labriolle A, Camilleri E, Cheneau E, Cabassome E, Dignat-George F, Camoin-Jau L, Paganelli F. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. J Am Coll Cardiol. 2011; 58:467–473. [PubMed: 21777742]
18. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009; 120:2577–2585. [PubMed: 19923168]
19. Yousuf O, Bhatt DL. The evolution of antiplatelet therapy in cardiovascular disease. Nat Rev Cardiol. 2011; 8:547–559. [PubMed: 21750497]

20. Htun WW, Steinhubl SR. Ticagrelor: the first novel reversible P2Y(12) inhibitor. Expert Opin Pharmacother. 2013; 14:237–245. [PubMed: 23268703]
21. Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Buttner HJ, Neumann FJ. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol. 2008; 51:1925–1934. [PubMed: 18482659]
22. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias WL, Braunwald E, Sabatine MS. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation. 2009; 119:2553–2560. [PubMed: 19414633]
23. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA. 2009; 302:849–857. [PubMed: 19706858]
24. Sibbing D, Stegherr J, Latz W, Koch W, Mehilli J, Dorrler K, Morath T, Schomig A, Kastrati A, von Beckerath N. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J. 2009; 30:916–922. [PubMed: 19193675]
25. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, Cayla G, Beygui F, Bensimon G, Funck-Brentano C, Montalescot G. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009; 373:309–317. [PubMed: 19108880]
26. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, Aiach M, Lechat P, Gaussem P. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood. 2006; 108:2244–2247. [PubMed: 16772608]
27. Scott SA, Sangkuhl K, Shuldiner AR, Hulot JS, Thorn CF, Altman RB, Klein TE. PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19. Pharmacogenet Genomics. 2012; 22:159–165. [PubMed: 22027650]
28. Jeong YH, Bliden KP, Park Y, Tantry US, Gurbel PA. Pharmacogenetic guidance for antiplatelet treatment. Lancet. 2012; 380:725. author reply 725-726.
29. Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation C. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013; 94:317–323. [PubMed: 23698643]
30. Sibbing D, Gebhard D, Koch W, Braun S, Stegherr J, Morath T, Von Beckerath N, Mehilli J, Schomig A, Schuster T, Kastrati A. Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy. J Thromb Haemost. 2010; 8:1685–1693. [PubMed: 20492469]
31. Tiroch KA, Sibbing D, Koch W, Roosen-Runge T, Mehilli J, Schomig A, Kastrati A. Protective effect of the CYP2C19 *17 polymorphism with increased activation of clopidogrel on cardiovascular events. Am Heart J. 2010; 160:506–512. [PubMed: 20826260]
32. Pare G, Mehta SR, Yusuf S, Anand SS, Connolly SJ, Hirsh J, Simonsen K, Bhatt DL, Fox KA, Eikelboom JW. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med. 2010; 363:1704–1714. [PubMed: 20979470]
33. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009; 360:354–362. [PubMed: 19106084]
34. Palmerini T, Calabro P, Piscione F, De Servi S, Cattaneo M, Maffeo D, Toso A, Bartorelli A, Palmieri C, De Carlo M, Capodanno D, Barozzi C, Tomasi L, Della Riva D, Mariani A, Taglieri N, Reggiani LB, Bianchi R, De Rosa R, Mariani M, Podda G, Genereux P, Stone GW, Angiolillo DJ. Impact of gene polymorphisms, platelet reactivity, and the SYNTAX score on 1-year clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention: the GEPRESS study. JACC Cardiovasc Interv. 2014; 7:1117–1127. [PubMed: 25240538]

35. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot JS, Kastrati A, Montalescot G, Neumann FJ, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010; 304:1821–1830. [PubMed: 20978260]

36. Doll JA, Neely ML, Roe MT, Armstrong PW, White HD, Prabhakaran D, Winters KJ, Duvvuru S, Sundseth SS, Jakubowski JA, Gurbel PA, Bhatt DL, Ohman EM, Fox KA. Investigators TA. Impact of CYP2C19 Metabolizer Status on Patients With ACS Treated With Prasugrel Versus Clopidogrel. J Am Coll Cardiol. 2016; 67:936–947. [PubMed: 26916483]

37. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA. 2011; 306:2704–2714. [PubMed: 22203539]

38. Sorich MJ, Rowland A, McKinnon RA, Wiese MD. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. Circ Cardiovasc Genet. 2014; 7:895–902. [PubMed: 25258374]

39. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, Antman EM, Braunwald E, Sabatine MS. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet. 2010; 376:1312–1319. [PubMed: 20801494]

40. Lewis JP, Horenstein RB, Ryan K, O'Connell JR, Gibson Q, Mitchell BD, Tanner K, Chai S, Bliden KP, Tantry US, Peer CJ, Figg WD, Spencer SD, Pacanowski MA, Gurbel PA, Shuldiner AR. The functional G143E variant of carboxylesterase 1 is associated with increased clopidogrel active metabolite levels and greater clopidogrel response. Pharmacogenet Genomics. 2013; 23:1–8. [PubMed: 23111421]

41. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, Lachno DR, Salazar D, Winters KJ. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost. 2007; 5:2429–2436. [PubMed: 17900275]

42. Harmsze A, van Werkum JW, Bouman HJ, Ruven HJ, Breet NJ, Ten Berg JM, Hackeng CM, Tjoeng MM, Klungel OH, de Boer A, Deneer VH. Besides CYP2C19*2, the variant allele CYP2C9*3 is associated with higher on-clopidogrel platelet reactivity in patients on dual antiplatelet therapy undergoing elective coronary stent implantation. Pharmacogenet Genomics. 2010; 20:18–25. [PubMed: 19934793]

43. Malek LA, Kisiel B, Spiewak M, Grabowski M, Filipiak KJ, Kostrzewa G, Huczek Z, Ploski R, Opolski G. Coexisting polymorphisms of P2Y12 and CYP2C19 genes as a risk factor for persistent platelet activation with clopidogrel. Circ J. 2008; 72:1165–1169. [PubMed: 18577829]

44. Horenstein RB, Madabushi R, Zineh I, Yerges-Armstrong LM, Peer CJ, Schuck RN, Figg WD, Shuldiner AR, Pacanowski MA. Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers. J Clin Pharmacol. 2014; 54:865–873. [PubMed: 24710841]

45. Mega JL, Hochholzer W, Frelinger AL 3rd, Kluk MJ, Angiolillo DJ, Kereiakes DJ, Isserman S, Rogers WJ, Ruff CT, Contant C, Pencina MJ, Scirica BM, Longtine JA, Michelson AD, Sabatine MS. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. JAMA. 2011; 306:2221–2228. [PubMed: 22088980]

46. Rehmel JL, Eckstein JA, Farid NA, Heim JB, Kasper SC, Kurihara A, Wrighton SA, Ring BJ. Interactions of two major metabolites of prasugrel, a thienopyridine antiplatelet agent, with the cytochromes P450. Drug Metab Dispos. 2006; 34:600–607. [PubMed: 16415119]

47. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, Becker RC. investigators P. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet. 2010; 376:1320–1328. [PubMed: 20801498]

48. Sorich MJ, Vitry A, Ward MB, Horowitz JD, McKinnon RA. Prasugrel vs. clopidogrel for cytochrome P450 2C19-genotyped subgroups: integration of the TRITON-TIMI 38 trial data. J Thromb Haemost. 2010; 8:1678–1684. [PubMed: 20492467]

49. Holmes DR Jr, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. Society for Cardiovascular A, Interventions, Society of Thoracic S, Writing Committee M. ACCF/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation. 2010; 122:537–557. [PubMed: 20585015]

50. Peterson JF, Field JR, Unertl K, Schildcrout JS, Johnson DC, Shi Y, Danciu I, Cleator JH, Pulley JM, McPherson JA, Denny JC, Laposata M, Roden DM, Johnson KB. Physician response to implementation of genotype-tailored antiplatelet therapy. Clin Pharmacol Ther. 2015

51. Shuldiner AR, Palmer K, Pakyz RE, Alestock TD, Maloney KA, O'Neill C, Bhatty S, Schub J, Overby CL, Horenstein RB, Pollin TI, Kelemen MD, Beitelshees AL, Robinson SW, Blitzer MG, McArdle PF, Brown L, Jeng LJ, Zhao RY, Ambulos N, Vesely MR. Implementation of pharmacogenetics: the University of Maryland Personalized Anti-platelet Pharmacogenetics Program. Am J Med Genet C Semin Med Genet. 2014; 166C:76–84. [PubMed: 24616408]

52. Weitzel KW, Elsey AR, Langaee TY, Burkley B, Nessl DR, Obeng AO, Staley BJ, Dong HJ, Allan RW, Liu JF, Cooper-Dehoff RM, Anderson RD, Conlon M, Clare-Salzler MJ, Nelson DR, Johnson JA. Clinical pharmacogenetics implementation: approaches, successes, and challenges. Am J Med Genet C Semin Med Genet. 2014; 166C:56–67. [PubMed: 24616371]

53. Lee JA, Lee CR, Reed BN, Plitt DC, Polasek MJ, Howell LA, Cicci JD, Tasca KE, Weck KE, Rossi JS, Stouffer GA. Implementation and evaluation of a CYP2C19 genotype-guided antiplatelet therapy algorithm in high-risk coronary artery disease patients. Pharmacogenomics. 2015; 16:303–313. [PubMed: 25823779]

54. Cavallari LH, Magvanjav O, Anderson RD, Gong Y, Owusu-Obeng A, Kong B, Vo T, Ashton JN, Staley BJ, Elsey AR, Allan RW, Starostik P, Cooper-DeHoff RM, Weitzel KW, Clare-Salzler MJ, Nelson DR, Johnson JA. Clinical implementation of CYP2C19 genotype guided antiplatelet therapy reduces cardiovascular events after PCI. Circulation. 2015; 132:A11802.

55. Franken CC, Kaiser AF, Kruger JC, Overbeck K, Mugge A, Neubauer H. Cytochrome P450 2B6 and 2C9 genotype polymorphism--a possible cause of prasugrel low responsiveness. Thromb Haemost. 2013; 110:131–140. [PubMed: 23615745]

56. Varenhorst C, Eriksson N, Johansson A, Barratt BJ, Hagstrom E, Akerblom A, Syvanen AC, Becker RC, James SK, Katus HA, Husted S, Steg PG, Siegbahn A, Voora D, Teng R, Storey RF, Wallentin L. Investigators P. Effect of genetic variations on ticagrelor plasma levels and clinical outcomes. Eur Heart J. 2015; 36:1901–1912. [PubMed: 25935875]

Key Points

- There is significant inter-patient variability in clopidogrel effectiveness in patients with an acute coronary syndrome and percutaneous coronary intervention (PCI).
- Clopidogrel is a prodrug that requires bioactivation, and cytochrome P450 (CYP) 2C19 is involved in both steps of the bioactivation process.
- Data consistently demonstrate reduced clopidgrel effectiveness after PCI in patients with the CYPC19 loss-of-function genotype.
- Neither prasugrel nor ticagrelor are affected by CYP2C19 genotype, and guidelines recommend consideration of one of these agents for PCI patients with the CYP2C19 loss-of-function genotype.
- A number of institutions have implemented CYP2C19 genotyping for patients undergoing PCI to assist with antiplatelet selection.

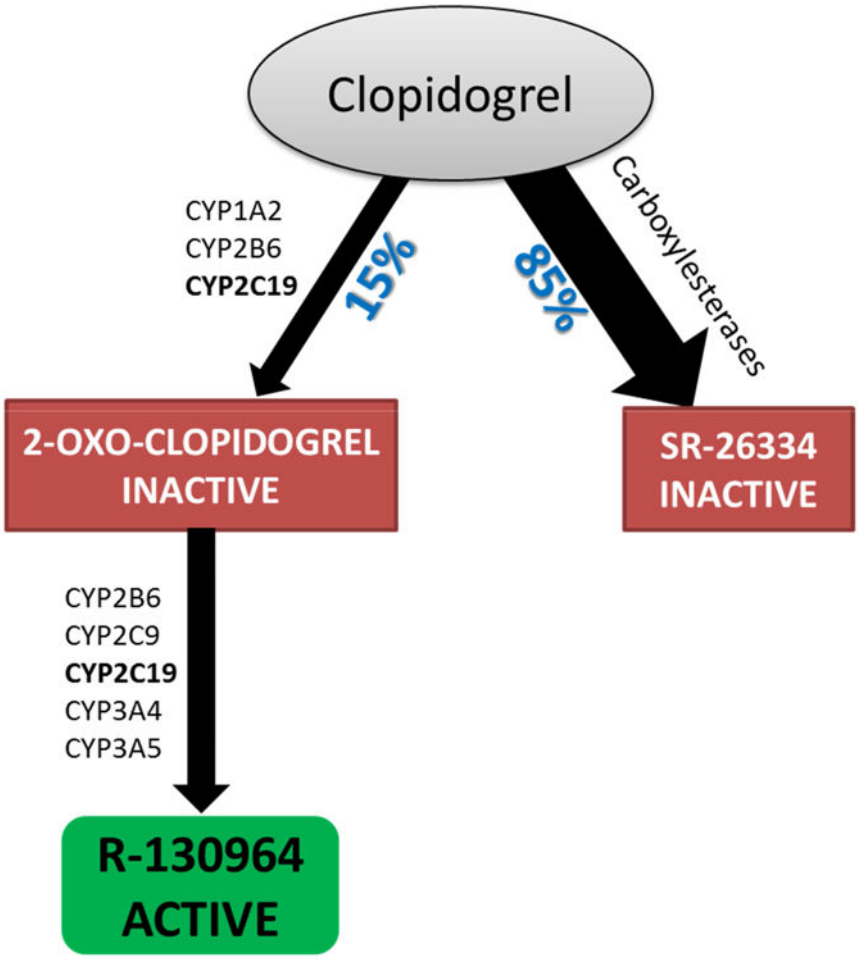

Figure 1. Depiction of clopidogrel metabolic pathway

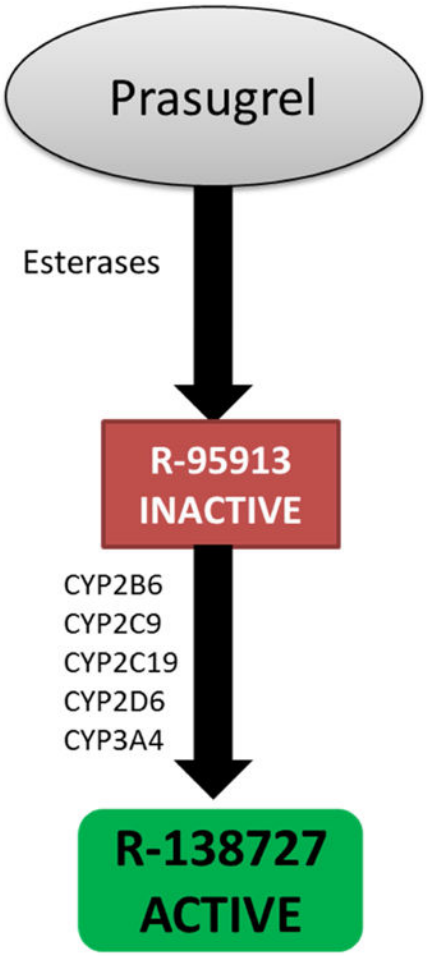

Figure 2.
Depiction of prasugrel metabolic pathway

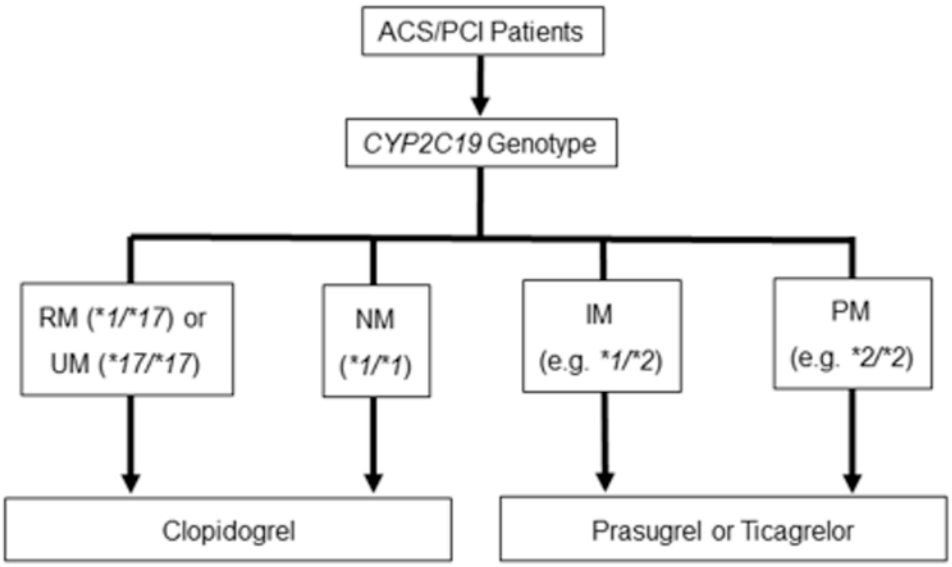

Figure 3.

Recommendations by the Clinical Pharmacogenetics Implementation Consortium (CPIC) for *CYP2C19*-guided antiplatelet therapy; ACS, acute coronary syndrome; IM, intermediate metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; RM, rapid metabolizer; UM, ultra-rapid metabolizer

Table 1
CYP2C19 phenotypes derived from *CYP2C19* genotype

Genotype	Phenotype
**1/*1*	Normal metabolizer (NM)
**2/*2, *2/*3*, or other combination of two loss-of-function alleles	Poor metabolizer (PM)
**1/*2, *1/*3*, *2/*17[†] or other genotypes with a single loss-of-function allele	Intermediate metabolizer (IM)
**1/*17*	Rapid metabolizer (RM)
**17/*17*	Ultra-rapid metabolizer (UM)

[†]The IM phenotype assignment for genotypes with one loss-of-function and one gain-of-function allele (e.g. **2/*17*) is based on evidence of increased platelet aggregation among clopidogrel treated patients with this genotype compared to the **1/*1* genotype, indicating that that the **17* allele is unable to completely compensate for reduced activity with the **2* allele.[29] However, the data are not completely consistent, and thus the IM phenotype assignment is considered provisional.

Table 2
Prevalence of CYP2C19 phenotypes by race

Race	Phenotype		
	PMs	IMs	RMs or UMs
White	2%	25%	40%
Black	4%	30%	45%
Asian	14%	50%	<5%

PMs, Poor metabolizers; IMs, intermediate metabolizers; RMs, rapid metabolizers; UMs, ultra-rapid metabolizers