

Genetic Causes of Clopidogrel Nonresponsiveness: Which Ones Really Count?

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Clopidogrel decreases the morbidity and mortality associated with several cardiovascular diseases. However, clopidogrel is a prodrug that needs to be metabolized to the active thiol metabolite by the cytochrome P450 (CYP) system. This activation is a source of significant interindividual variability in clopidogrel responsiveness. Drug interactions with and genetic variation in CYP3A4, CYP3A5, and CYP2C19 enzymes have been implicated in decreasing active metabolite production. In addition, polymorphisms in the genes encoding P-glycoprotein (an efflux transporter) and purinergic receptor P2Y₁₂ (the active site for clopidogrel) have been studied for their role in clopidogrel responsiveness. Several large studies have recently assessed the role of genetic variation in clopidogrel responsiveness as characterized by clinical outcomes. In this review, we summarize the genetic causes of clopidogrel nonresponsiveness, with a focus on larger outcomes-based studies. A MEDLINE search of the English-language literature (1990–2008) was conducted to identify studies that examined these relationships; additional citations were obtained from the articles retrieved from the literature search. Polymorphisms in *CYP2C19* and, to a lesser extent, the adenosine 5'-triphosphate-binding cassette gene, *ABCB1*, contribute to variability in clopidogrel responsiveness. Specifically, patients possessing at least one variant *CYP2C19* allele (*CYP2C19**2, *3) have impaired clopidogrel responsiveness due to decreased formation of the active metabolite. In addition, one study found that considering *ABCB1* genotype in addition to *CYP2C19* allowed better prediction of clopidogrel nonresponsiveness. However, routine genotyping for *CYP2C19* or *ABCB1* polymorphisms in order to predict clopidogrel responsiveness cannot be recommended at this time because of logistic and cost considerations.

Key Words: clopidogrel, pharmacogenetics, cytochrome P450, *CYP2C19*, *ABCB1*.

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Clopidogrel decreases the morbidity and mortality associated with several cardiovascular diseases. The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial demonstrated that clopidogrel improves outcomes in patients with a history of recent ischemic stroke, myocardial infarction, or symptomatic peripheral artery disease.¹ Subsequently, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated that the addition of clopidogrel improved outcomes in patients with non-ST-segment elevation acute coronary syndromes

(ACS).² The Clopidogrel for Reduction of Events During Observation (CREDO) trial found similar results in patients undergoing percutaneous coronary intervention (PCI).³ These trials resulted in the American College of Cardiology–American Heart Association guideline recommendations that clopidogrel be used in combination with aspirin for ACS and PCI.^{4, 5} Comprehensive recommendations for clopidogrel use in this setting have been published previously.⁶

Despite the well-documented benefits of clopidogrel, there is significant interindividual variability in clopidogrel responsiveness. This variability leads to some patients having decreased inhibition of platelet aggregation with clopidogrel, or nonresponsiveness, and this has been associated with increased risk for cardiovascular events.^{7, 8} Some studies have used *ex vivo* platelet aggregation testing whereas others have used increased rates of adverse cardiovascular events to characterize variability in response to clopidogrel.

The primary source of the variability in clopidogrel responsiveness lies in the pharmacokinetics of clopidogrel. Clopidogrel is a prodrug that needs to be metabolized to the active thiol metabolite by the cytochrome P450 (CYP) system (Figure 1). This metabolite then irreversibly inhibits the purinergic receptor P2Y₁₂.⁹ In recent years, significant interindividual variability in clopidogrel responsiveness has been noted. Drug interactions with and genetic variation in CYP3A4, CYP3A5, and CYP2C19 enzymes have been implicated in decreased active metabolite production. This has resulted in a recent change in the clopidogrel prescribing information, which now includes information on CYP2C19 genotyping and concomitant use of CYP2C19 inhibitors.¹⁰

A number of ongoing studies are using different dosing strategies to overcome some of

the interindividual variability associated with clopidogrel CYP drug interactions and genetic variability. In the meantime, it is important that clinicians understand the mechanisms of clopidogrel interindividual variability. In this review, we summarize the genetic causes of clopidogrel nonresponsiveness, with a focus on larger clinical outcome–based studies. A MEDLINE search of the English-language literature (1990–2008) was conducted to identify studies that examined these relationships; additional citations were obtained from the articles retrieved from the literature search.

Genetic Causes of Clopidogrel Nonresponsiveness

CYP2C19

Several studies have assessed the role of the CYP2C19 genotype in clopidogrel responsiveness. The CYP2C19*2 allele, along with the *3, *4, and *5 alleles, have been associated with decreased metabolic activity and have thus been termed loss-of-function alleles (Table 1). The CYP2C19*2 allele is the most frequently occurring variant allele in Caucasian, African-American, and Asian populations. However, the allele frequency differs by racial group (Figure 2).^{11, 12} The CYP2C19*2 allele frequency in Asian populations (~30%) is significantly higher than that seen in Caucasians (~13%) and African-Americans (~18%). The CYP2C19*3 allele occurs more frequently in Asian populations (~10%) compared with other racial groups (< 1%).

Several studies have demonstrated that CYP2C19 genotype affects the pharmacokinetics and pharmacodynamics of clopidogrel.^{13–15} Findings in smaller pharmacokinetic and pharmacodynamic studies have now been confirmed in large cohort studies (Table 2).^{15–21}

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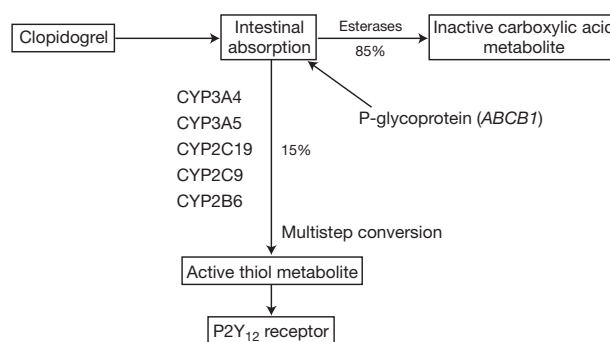


Figure 1. Metabolism of clopidogrel. CYP = cytochrome P450.

Table 1. Genes That Encode the Proteins Involved in Clopidogrel Pharmacokinetics and Pharmacodynamics

Gene	Protein Encoded	SNPs	Relative Change in Protein Function
<i>CYP2C19</i>	CYP2C19	*1	Wild-type
		*2	Decreased activity
		*3	Decreased activity
		*4	Decreased activity
		*5	Decreased activity
<i>CYP3A4</i>	CYP3A4	*1B	Wild-type
		23171T>C	Unknown activity
		IVS7+258A>G	Unknown activity
		IVS7+894C>T	Unknown activity
		IVS10+12G>A	Unknown activity
<i>CYP3A5</i>	CYP3A5	*1	Wild-type
		*3	Decreased activity
<i>ABCB1</i>	P-glycoprotein	3435C>T	Unknown activity
		2677G>T	Unknown activity
		136C>T	Unknown activity
<i>P2RY12</i>	P2Y ₁₂	744T>C	Unknown activity

SNP = single nucleotide polymorphism; CYP = cytochrome P450; IVS = intervening sequence; ABC = adenosine 5'-triphosphate-binding cassette; P2Y₁₂ = purinergic receptor.

The association between *CYP2C19* genotype and a composite end point of cardiovascular death, nonfatal myocardial infarction, and urgent revascularization was studied in a prospective cohort study that consisted of 259 young patients who survived a first myocardial infarction, received clopidogrel 75 mg/day, and were enrolled in a multicenter registry 3 months after the acute coronary event.¹⁸ Patients possessing the *CYP2C19**2 allele (28%), compared with *CYP2C19* wild-type homozygotes (72%), had a significant increase in the risk for the primary end

point at 1 year. This increased risk was demonstrated early after clopidogrel initiation and persisted throughout the study period. An increased risk for stent thrombosis was also found in *CYP2C19**2 allele carriers. A multivariable analysis suggested that *CYP2C19* genotype was the only significant predictor of the primary outcome in this population. Of note, this study population was fairly heterogeneous, and patients were not randomized to a specific treatment strategy. However, these results suggest that possession of at least one variant *CYP2C19**2 allele is associated with increased risk.

Another study assessed a cohort of 2208 patients from the prospective, observational French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) registry who had received clopidogrel and contributed a DNA sample.¹⁹ All patients had documented myocardial infarction, were admitted to the intensive care unit, and underwent genotyping for polymorphisms in the following genes: *CYP2C19*; *CYP3A5*; the adenosine 5'-triphosphate-binding cassette gene, *ABCB1*; the P2Y₁₂ gene, *P2RY12*; and the integrin β_3 gene, *ITGB3* (IIb-IIIa receptor). Unlike the above-mentioned study,¹⁸ in this study genotyping for *CYP2C19**2, *3, *4, and *5 alleles was performed. This study also used a composite primary outcome, which included death from any cause, nonfatal stroke, or myocardial infarction. Many demographic and clinical characteristics differed between those patients

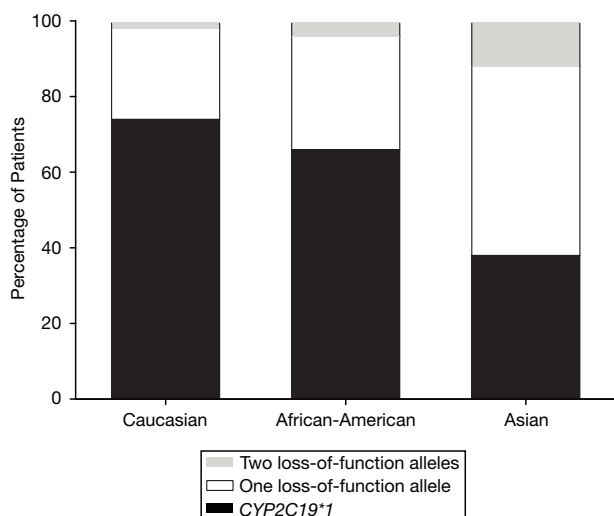


Figure 2. Distribution of *CYP2C19* genotype frequencies by race.^{11, 12}

Table 2. Clopidogrel-CYP2C19 Pharmacogenomic Studies That Evaluated Clinical Outcomes

Population	Gene and Alleles	Outcome Variable Studied
Patients undergoing elective coronary stent placement and received a routine clopidogrel 600-mg loading dose (n=797) ¹⁶	CYP2C19*1, *2	On-treatment platelet reactivity and association of platelet reactivity with risk of death or myocardial infarction
Patients with STEMI undergoing fibrinolysis with scheduled angiography and a clopidogrel 300-mg loading dose (n=465) ¹⁷	CYP2C19*1, *2, CYP1A2, CYP2C9, CYP3A4, CYP3A5	Occluded infarct-related artery, death, or recurrent myocardial infarction before angiography
Patients aged 18–45 yrs who survived their first myocardial infarction and received clopidogrel 75 mg/day for at least 1 mo with an average duration of clopidogrel exposure of 1.07 yrs (n=259) ¹⁸	CYP2C19*1, *2	Composite end point of death, nonfatal myocardial infarction, and urgent revascularization
Patients admitted to the intensive care unit after a myocardial infarction (n=2208) ¹⁹	CYP2C19*1, *2, *3, *4, *5, CYP3A5, ABCB1, P2RY12, ITGB3	Composite end point of death from any cause, nonfatal stroke, or myocardial infarction during 1 yr of follow-up
Patients undergoing primary PCI and received a routine clopidogrel 600-mg loading dose (n=2485) ²⁰	CYP2C19*1, *2	Definite stent thrombosis within the first 30 days after PCI
Patients with ACS and planned PCI from TRITON-TIMI 38, and received a clopidogrel 300-mg loading dose (n=1477) ¹⁵	CYP2C19*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *17, CYP2C9, CYP2B6, CYP3A5, CYP3A4, CYP1A2	Composite end point of death from cardiovascular causes, myocardial infarction, or stroke 15 mo after randomization
Patients receiving drug-eluting stents and received a routine clopidogrel 600-mg loading dose (n=772) ²¹	CYP2C19*1, *2	Definite or probable stent thrombosis within 6 mo of PCI

CYP = cytochrome P450; HR = hazard ratio; CI confidence interval; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; TRITON-TIMI = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction; OR = odds ratio.

who had the primary outcome and those who did not. Specifically, those who had the primary outcome (294 patients [13%]) were older, had more comorbidities, were more likely to be receiving drugs for secondary prevention (including clopidogrel) before their myocardial infarction, were less likely to receive primary PCI or intravenous fibrinolysis during the inclusion event, and were less likely to have received statins, β -blockers, angiotensin-converting enzyme inhibitors, glycoprotein IIb/IIIa inhibitors, or heparin during the event. No single nucleotide polymorphisms in CYP3A5, P2RY12, or ITGB3 were associated with the primary outcome. Patients possessing two variant CYP2C19 alleles were more likely to experience a primary outcome event compared with noncarriers. Similarly, those possessing two

ABCB1 3435T alleles had an increased risk for a primary outcome event compared with noncarriers. Those patients who possessed two CYP2C19 loss-of-function alleles and at least one ABCB1 variant allele were at the highest risk for a primary outcome event (hazard ratio [HR] 5.31, 95% confidence interval [CI] 2.13–13.20) compared with patients who were both CYP2C19 and ABCB1 wild-type homozygotes. When the analysis was limited to the 1535 patients who underwent PCI, the association with CYP2C19 genotype persisted, whereas the ABCB1 genotype was no longer significantly associated with risk of the primary outcome. This study was not randomized and is confounded by the fact that patients who had an event were more likely to be receiving clopidogrel at baseline. Thus, a group of clopidogrel nonresponders may have been

Table 2. (continued)

Results
Patients with at least one <i>CYP2C19</i> *2 allele had increased platelet reactivity
Increased platelet reactivity was associated with an increased risk of death or myocardial infarction (HR 3.0, 95% CI 1.4–6.8)
<i>CYP2C19</i> genotype was not associated with risk of death or myocardial infarction
No significant interactions between evaluated genotypes and composite end point ($p > 0.3$)
Patients with at least one <i>CYP2C19</i> *2 allele had an increased risk for the composite end point (HR 3.69, 95% CI 1.69–8.05)
Patients with two <i>CYP2C19</i> *2, *3, *4, or *5 alleles and those with two variant <i>ABCB1</i> 3435T alleles had increased risk for the composite outcome (HR 1.98, 95% CI 1.10–3.58 and HR 1.72, 95% CI 1.20–2.47, respectively)
Patients with at least one <i>CYP2C19</i> *2 allele had an increased risk for stent thrombosis (HR 3.81, 95% CI 1.45–10.02)
Patients with at least one <i>CYP2C19</i> loss-of-function allele had an increased risk for the composite end point (HR 1.53, 95% CI 1.19–8.0)
Patients with at least one <i>CYP2C19</i> *2 allele had an increased risk for stent thrombosis (OR 2.59, 95% CI 1.15–5.88)

preselected and overrepresented in this study. This study, in contrast to the previously mentioned study,¹⁸ does not clearly define the role of heterozygous genotypes for *ABCB1* or *CYP2C19* in this patient population.

Another large cohort study assessed 2485 consecutive patients undergoing PCI who were uniformly pretreated with a clopidogrel 600-mg loading dose.²⁰ In this study, genotyping was performed only for the *CYP2C19**1 and *2 alleles. The primary aim of the study was to determine whether *CYP2C19* genotype was associated with risk of stent thrombosis in the 30 days after PCI, defined as the occurrence of ACS with either angiographic or pathologic confirmation of thrombosis. Stent thrombosis occurred in 0.7% (17 patients). The *CYP2C19**2 allele carriers (680 patients [27%]) had a higher risk for stent thrombosis than did wild-type homozygotes (1.5% vs 0.4%). On multivariable analysis, *CYP2C19* genotype was the only

independent predictor of stent thrombosis risk. Although this study was not randomized, all patients were treated uniformly with PCI and standard clopidogrel doses. It does suggest that patients undergoing PCI who possess at least one *CYP2C19**2 allele are at increased risk for stent thrombosis.

The role of the *CYP2C19* genotype in clopidogrel responsiveness was also assessed in the Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis (RECLOSE) trial.²¹ The study included 772 consecutive patients receiving drug-eluting stents and dual antiplatelet therapy with aspirin and clopidogrel. All subjects received a clopidogrel 600-mg loading dose and a 75-mg/day maintenance dose. Genotyping for *CYP2C19**1 and *2 alleles was performed. The primary end point was definite or probable stent thrombosis during 6 months of follow-up. Patients carrying at least one variant *CYP2C19**2 allele were more likely to experience stent thrombosis. In addition, *CYP2C19* genotype was found to be an independent predictor of stent thrombosis risk after inclusion of several clinical risk factors in a multivariable logistic regression model. Similar to the above-mentioned study,²⁰ this would suggest that patients with at least one *CYP2C19* variant allele are at increased risk for stent thrombosis.

All of the studies assessing *CYP2C19* genotype and clopidogrel responsiveness discussed thus far have been cohort studies. One group of investigators addressed this question by using data from a randomized controlled trial.¹⁵ This was a genetic substudy of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial in which patients with ACS with planned PCI were randomly assigned to receive a clopidogrel 300-mg loading dose followed by 75 mg/day for up to 15 months or prasugrel (a new thienopyridine). In the 1477 patients assigned to clopidogrel and who provided a genetic sample, genotyping was performed for polymorphisms in the genes encoding *CYP2C19*, *CYP2C9*, *CYP2B6*, *CYP3A5*, *CYP3A4*, and *CYP1A2* enzymes. The rate of adverse cardiovascular outcomes, which consisted of death from cardiovascular causes, myocardial infarction, or stroke, was compared among genotype groups. Risk of stent thrombosis and safety outcomes (TIMI major and minor bleeding not related to coronary artery bypass grafting) were also assessed. Those possessing at least one *CYP2C19* reduced-

function allele (395 patients) had an increased risk for the primary outcome compared with wild-type homozygotes. Patients possessing at least one reduced-function *CYP2C19* allele also had 3 times the risk for stent thrombosis compared with noncarriers. Genetic variation in the other CYP enzymes studied was not associated with the primary outcome, and no association was seen between bleeding risk and CYP genotype. This study was not designed to assess whether possession of two reduced-function *CYP2C19* alleles is associated with risk of the primary outcome; therefore, we do not know whether carriers and homozygotes had different event rates. This study further confirms that patients carrying at least one variant *CYP2C19* allele have an increased risk for adverse cardiovascular events after PCI.

However, reports from substudies of the Impact of the Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate (EXCELSIOR) and Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY-TIMI 28) trials did not find an association between *CYP2C19* genotype and clopidogrel responsiveness.^{16, 17} A genetic substudy of EXCELSIOR was the first large cohort study to evaluate the role of *CYP2C19* genotype in clopidogrel responsiveness.¹⁶ The primary aim was to assess whether the loss-of-function *CYP2C19**2 polymorphism was associated with elevated platelet reactivity in patients receiving clopidogrel therapy. The association between this measure of elevated platelet reactivity and 1-year occurrence of death or myocardial infarction was also assessed. Seven hundred ninety-seven patients underwent elective coronary stent placement and received a 600-mg loading dose of clopidogrel and aspirin therapy. Platelet aggregation was assessed by ex vivo optical aggregation induced by adenosine 5'-diphosphate immediately after the loading dose of clopidogrel and before discharge 2–4 hours after the first clopidogrel maintenance dose. Patients carrying a variant *CYP2C19**2 allele were more likely to have elevated platelet aggregation, after both the loading and maintenance doses of clopidogrel, compared with wild-type homozygotes (before discharge 41.3% vs 22.5%, $p < 0.001$), but the study did not find an association between *CYP2C19* genotype and death or myocardial infarction. However, patients with elevated platelet aggregation before discharge had a 3-fold

increase in the 1-year occurrence of death or myocardial infarction.

A genetic substudy of CLARITY-TIMI 28 had similar results.¹⁷ In CLARITY-TIMI 28, a total of 3941 patients received fibrinolytic therapy for ST-segment elevation myocardial infarction and were randomly assigned to receive a clopidogrel 300-mg loading dose followed by 75 mg once/day or placebo. Patients were then scheduled to undergo angiography 48–192 hours after study entry and were followed for 30 days. Four hundred sixty-five patients participated in a substudy in which genotyping was performed for polymorphisms in the genes encoding *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP3A4*, and *CYP3A5* enzymes. The primary end point assessed was a composite of an occluded infarct-related artery at angiography, death before angiography could be performed, or recurrent myocardial infarction before angiography. None of the genotypes studied were associated with the primary composite end point.

CYP3A4 and *CYP3A5*

The *CYP3A4* and *CYP3A5* enzymes also play a role in the conversion of clopidogrel to its active metabolite. The *CYP3A* family is the most prolifically expressed CYP enzyme family in human hepatocytes. However, *CYP3A4* and *CYP3A5* levels differ by race, with Caucasians expressing primarily *CYP3A4* and African-Americans expressing *CYP3A5*. There is a significant amount of overlap in *CYP3A4* and *CYP3A5* substrates, and they are responsible for the metabolism of approximately half of the drugs used today. Although polymorphisms in *CYP3A4* have been extensively studied, no relatively common variants have been linked conclusively to a change in gene expression or drug metabolism (Table 1).²² There are, however, variants of functional consequence in *CYP3A5*. The *CYP3A5**3 variant allele has been associated with decreased functional *CYP3A* activity, and patients who possess two *CYP3A5**3 alleles have approximately 50% less *CYP3A* activity compared with *CYP3A5**1 (wild-type) homozygotes. The allele frequency for *CYP3A5**3 is 85% among Caucasians, 55% among African-Americans, and 65% among Chinese.^{22, 23}

Because of the number of variants in both *CYP3A4* and *CYP3A5* and their role in clopidogrel activation, polymorphisms in both genes have also been studied for their role in clopidogrel responsiveness. Several studies have

assessed changes in clopidogrel pharmacokinetics and pharmacodynamics associated with *CYP3A4* genotype. However, only one study found a positive association between *CYP3A4* genotype and the effect of clopidogrel on platelet aggregation, not clinical outcomes.²⁴ This study, however, assessed only the role of the *CYP3A4* genotype in clopidogrel responsiveness; polymorphisms in *CYP2C19* were not assessed. Most studies have found no association between *CYP3A4* genotype and clopidogrel responsiveness.^{14, 17, 25–27} In fact, when *CYP3A4* genotype was assessed in the large, outcomes-based study of TRITON-TIMI 38, in conjunction with *CYP2C19*, *2C9*, *2B6*, *3A5*, and *1A2*, no association was found.¹⁵

The results for the better characterized *CYP3A5* polymorphisms have been slightly different. One group of investigators found that patients who possess the *CYP3A5*3* (nonexpressor) allele had similar platelet aggregation with clopidogrel compared with those possessing the *CYP3A5*1/*1* genotype.²⁸ However, subjects with the *CYP3A5*3* allele had significantly decreased response to clopidogrel when it was combined with itraconazole, a *CYP3A* inhibitor, compared with *CYP3A5*1* homozygotes. In addition, they found that possession of the *CYP3A5*3* allele and increased number of coadministered *CYP3A* substrates and inhibitors were associated with an increased risk of atherothrombotic events. However, other studies have demonstrated that the association between *CYP3A* genotype and clopidogrel response does not appear to be as strong as that found with *CYP2C19* genotype.^{14, 25, 26, 29} In fact, most studies assessing *CYP3A4* or *CYP3A5* and *CYP2C19* genotypes have found an association only with *CYP2C19* genotype and clopidogrel responsiveness.

ABCB1

P-glycoprotein (P-gp) is an efflux transport protein located in many tissues in the body.³⁰ These tissues include the surface of the small and large intestine, the renal proximal tubules, and the blood-brain barrier. In the small and large intestines, P-gp pumps drugs back into the intestinal lumen, thus limiting bioavailability. The P-gp is just one of several ABCB superfamily transporters. Genetic variation in the gene encoding P-gp (*ABCB1*) has been well studied; however, the functional consequence of polymorphisms in *ABCB1* is unclear (Table 1). Some studies have found an association between protein expression and drug transport with

ABCB1 polymorphisms, but these associations have not been demonstrated consistently.

The P-gp is involved in clopidogrel absorption, and the role of *ABCB1* polymorphisms in clopidogrel responsiveness has been well studied. Three *ABCB1* single nucleotide polymorphisms (C3435T, G2677T, and C136T) have been evaluated for their role in clopidogrel pharmacokinetics.³¹ Lower clopidogrel concentrations (both maximum concentration and area under the concentration-time curve) after a single dose of 300 or 600 mg were noted in patients who were homozygous for the variant *ABCB1* 3435T allele. Of interest, a larger loading dose of 900 mg overcame this difference. In addition, results from the FAST-MI study suggest that subjects with two variant *ABCB1* 3435T alleles are at increased risk for clinically documented clopidogrel resistance, in the form of death, nonfatal stroke, or myocardial infarction (Table 2).¹⁹ Of note, in this study, consideration of *ABCB1* genotype combined with *CYP2C19* genotype improved prediction of clopidogrel nonresponsiveness. Unfortunately, none of the other large cohort studies assessed the role of *ABCB1* genotyping in addition to *CYP2C19*.

P2RY12

Studies have also assessed genetic variation in the gene encoding the P2Y₁₂ receptor (the active site for clopidogrel), *P2RY12*. Polymorphisms in *P2RY12* have not been consistently associated with clopidogrel response as measured by either platelet aggregation or clinical events (Table 1).^{32–34} The *P2RY12* genotype was also assessed in the FAST-MI study, and no association was found with clopidogrel responsiveness.¹⁹

The pharmacogenetic literature further supports the importance of the role of *CYP2C19* in the metabolism of clopidogrel, initially suggested by the drug interaction literature.³⁵ These data would also suggest that polymorphisms in *ABCB1* may be associated with a decrease in clopidogrel responsiveness.

Clinical Relevance

Patients at Risk for Decreased Response to Clopidogrel

Approximately 2–3% of Caucasian and African-American patients and 10–15% of Asian patients possessing two variant *CYP2C19* alleles will have impaired clopidogrel responsiveness. The data would also suggest that patients possessing only

one *CYP2C19* loss-of-function allele may be at increased risk. Approximately 25% of Caucasians, 30% of African-Americans, and 50% of Asians possess at least one variant allele. Also, patients possessing two variant *ABCB1* 3435T alleles may be more likely to have decreased clopidogrel responsiveness. In fact, patients possessing both a variant *CYP2C19* allele and two variant *ABCB1* 3435T alleles may be at the highest risk for clopidogrel nonresponsiveness.

Routine Genotyping for *CYP2C19* Variant Alleles to Predict Clopidogrel Responsiveness: Logistic and Cost Considerations

The updated clopidogrel label now includes information on the role of *CYP2C19* genotype in clopidogrel responsiveness.¹⁰ Specifically, the label states "...*CYP2C19* poor metabolizer status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolizers has yet to be determined."¹⁰ Although *CYP2C19* genotyping is currently available, this test often requires the use of a specialty laboratory and generally is sent out with a turnaround time of 6–10 days. Genotyping for *CYP2C19* is also quite expensive, with a list price of \$395–500 and is not being covered by insurance companies. Currently, *ABCB1* genotyping is not available. There are also logistic issues associated with genotyping an ACS population. Clopidogrel therapy is often started immediately upon presentation of the patient to the emergency department, so there is little time for genetic testing before initiation of therapy. If genotyping were to be done in this setting, a rapid and clinically useful platform would be necessary.

In addition, all of the variability in clopidogrel responsiveness is clearly not captured by genotyping only for *CYP2C19* loss-of-function alleles. This is partly because genetic variability in *ABCB1* and *CYP3A4* are not being assessed. Few *CYP3A4* polymorphisms have been shown to have functional effects. Therefore, there is no good way through genotyping to characterize the variability in *CYP3A4* metabolic activity. In addition, whereas the *ABCB1* genotype may contribute to prediction of clopidogrel nonresponsiveness, *ABCB1* genotyping is not available. It is also likely that drug interactions through the CYP system (such as those discussed in the drug interaction literature³⁵) serve as an additional source of variability in clopidogrel responsiveness. The amount of interindividual variability

in clopidogrel responsiveness remaining after *CYP2C19* genotyping may limit the utility of genotyping.

An alternative P2Y₁₂ receptor inhibitor is available, and others may be available soon. Prasugrel was recently approved by the United States Food and Drug Administration for use in combination with aspirin in patients with ACS who will be managed with PCI. Prasugrel is also a prodrug, and its active metabolite has similar affinity for the P2Y₁₂ receptor as does the active metabolite of clopidogrel.³⁶ However, whereas clopidogrel undergoes two activation steps through the CYP system, prasugrel requires only one. This drug appears to have little propensity for drug interactions or susceptibility to CYP genetic variation, so it may be an attractive treatment option in patients for whom clopidogrel therapy is indicated. This may be even more true when clopidogrel nonresponsiveness is predicted or measured by platelet aggregation testing.³⁶ There are several point-of-care tests available that measure *ex vivo* platelet aggregation, and they may be used clinically. The utility of these tests has been reviewed previously.^{7, 8, 37, 38}

Compared with clopidogrel, prasugrel is associated with an increased risk of bleeding.³⁹ In addition, prasugrel is contraindicated in patients with a previous transient ischemic attack or stroke, but careful consideration should be given to patients aged 75 years or older and weighing less than 60 kg. The retrospective data from the TRITON-TIMI 38 study suggest that patients aged 75 years or older with a history of diabetes mellitus or myocardial infarction can be treated with prasugrel 10 mg/day, and a daily dose of 5 mg for those weighing less than 60 kg can be beneficial, but this has not been tested prospectively.³⁹ However, the true excess bleeding risk with prasugrel is difficult to determine because approximately 30% of patients receiving clopidogrel are nonresponsive and therefore have no bleeding risk, creating an unequal reference population. In addition, we found no study that evaluated whether switching patients to prasugrel when they have been classified as clopidogrel nonresponsive leads to improved outcomes. It is therefore unclear how much advantage prasugrel therapy provides, which is particularly important given the increased risk of bleeding.

In the future, *CYP2C19* genotype or platelet aggregation test results could be used to predict a subset of patients most likely to respond to clopidogrel. This may ultimately become the

most cost-effective strategy for society, given that clopidogrel will become generic in 2012.

Conclusion

There is a considerable amount of interindividual variability in clopidogrel responsiveness. The literature suggests that *CYP2C19* polymorphisms and, to a lesser extent, *ABCB1* polymorphisms contribute to this variability. Specifically, patients possessing at least one variant *CYP2C19* allele (*CYP2C19**2, *3) have impaired clopidogrel responsiveness due to decreased formation of the active metabolite. In addition, one study found that considering the *ABCB1* genotype in addition to *CYP2C19* allowed better prediction of clopidogrel nonresponsiveness. However, routine genotyping for *CYP2C19* or *ABCB1* polymorphisms in order to predict clopidogrel response cannot be recommended because of logistic and cost considerations.

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