Impact of *CYP2C19* Genetic Testing on Provider Prescribing Patterns for Antiplatelet Therapy After Acute Coronary Syndromes and Percutaneous Coronary Intervention

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Background—Patients treated with clopidogrel who have ≥1 loss of function alleles for *CYP2C19* have an increased risk for adverse cardiovascular events. In 2010, the US Food and Drug Administration issued a boxed warning cautioning against the use of clopidogrel in such patients. We sought to assess the impact of *CYP2C19* genetic testing on prescribing patterns for antiplatelet therapy among patients with acute coronary syndrome or percutaneous coronary intervention.

Methods and Results—Patients with recent acute coronary syndrome or percutaneous coronary intervention prescribed clopidogrel were offered *CYP2C19* testing. Genotype and phenotype results were provided to patients and their physicians, but no specific treatment recommendations were suggested. Patients were categorized based on their genotype (carriers versus noncarriers) and phenotype (extensive, intermediate, and poor metabolizers). The primary outcome was intensification in antiplatelet therapy defined as either dose escalation of clopidogrel or replacement of clopidogrel with prasugrel. Between July 2010 and April 2012, 6032 patients were identified, and 499 (8.3%) underwent *CYP2C19* genotyping, of whom 146 (30%) were found to have ≥1 reduced function allele, including 15 (3%) with 2 reduced function alleles. Although reduced function allele carriers were significantly more likely than noncarriers to have an intensification of their antiplatelet therapy, only 20% of poor metabolizers of clopidogrel had their antiplatelet therapy intensified.

Conclusions—Providers were significantly more likely to intensify antiplatelet therapy in *CYP2C19* allele carriers, but only 20% of poor metabolizers of clopidogrel had an escalation in the dose of clopidogrel or were switched to prasugrel. These prescribing patterns likely reflect the unclear impact and evolving evidence for clopidogrel pharmacogenomics. **(*Circ Cardiovasc Qual Outcomes*. 2013;6:694-699.)**

Key Words: antiplatelet agents ■ pharmacogenetics ■ quality of health care

Clopidogrel, an irreversible ADP-receptor blocker, has been shown to reduce the risk of major adverse cardiovascular events in patients with an acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI).[1–5] However, there is significant interindividual variability in the response to clopidogrel, and patients with higher levels of platelet reactivity after receiving standard doses of clopidogrel are at significantly increased risk for recurrent adverse cardiovascular events.[6] Clopidogrel is a prodrug that requires bioactivation mediated by the cytochrome P450 enzyme system, and reduced function alleles in *CYP2C19* may help explain the observed variability in platelet reactivity. Patients who are both heterozygous and homozygous for reduced function *CYP2C19* alleles have reduced levels of the active metabolite of clopidogrel, diminished levels of platelet inhibition, and 55% to 76% relative increase in the risk of cardiovascular death, myocardial infarction, or stroke, as well as a 2.6- to 4.0-fold increase in the risk for stent thrombosis.[7] However, several pharmacogenetic analyses of clopidogrel have not found a significant association between *CYP2C19* genotype and clinical outcomes.[8,9]

However, the US Food and Drug Administration (FDA) advised avoiding the use of clopidogrel in patients with impaired *CYP2C19* function because of known genetic polymorphisms.[10] More recently, the FDA modified this boxed warning for clopidogrel and advised healthcare professionals to consider the use of other antiplatelet medications or alternative dosing strategies for [clopidogrel] in patients with particular *CYP2C19* genotypes.[10] Potential therapeutic options for patients with a *CYP2C19* loss of function allele

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WHAT IS KNOWN

- Clopidogrel is a prodrug that requires bioactivation mediated by the cytochrome P450 enzyme system.
- Carriers of reduced function *CYP2C19* alleles have reduced levels of the active metabolite of clopidogrel, diminished levels of platelet inhibition, and an increased risk of major adverse cardiovascular events, including stent thrombosis.
- The US Food and Drug Administration issued a boxed warning for clopidogrel advising providers to avoid its use in patients who carry certain *CYP2C19* alleles and are poor metabolizers.

WHAT THE STUDY ADDS

- Among clinically eligible patients, providers declined *CYP2C19* genetic testing in ≈25% of cases, whereas <10% of patients who were offered genetic testing for *CYP2C19* declined the test.
- In our real-world analysis of a clopidogrel-*CYP2C19* genotyping program among patients with acute coronary syndrome or undergoing percutaneous coronary intervention, we found that only 1 in 5 patients who are poor metabolizers of clopidogrel and subject to the US Food and Drug Administration boxed warning had their antiplatelet therapy changed.

include the dose escalation of clopidogrel, which has been shown to achieve comparable levels of platelet inhibition in heterozygotes as seen among wild-type patients[11] but has not been tested in a randomized trial, or switching to a newer generation $P2Y_{12}$ receptor blocker, such as prasugrel or ticagrelor, which offers more potent, consistent, and rapid platelet inhibition.[12,13]

Although the role of genetic testing to guide antiplatelet prescribing is currently debated,[14] it is important to understand whether and how *CYP2C19* testing influences physician prescribing patterns for secondary preventive antiplatelet therapy and, more generally, how willing physicians are to order this type of testing.

A genetic test benefit manager, Generation Health, and pharmacy benefit manager, CVS Caremark, developed a program offering elective *CYP2C19* genotype and phenotype testing for patients prescribed clopidogrel after ACS or PCI. This program provided the opportunity to longitudinally monitor prescribing behavior, specifically examining changes in antiplatelet therapy based on testing results.

Methods

A novel program administered between July 2010 and April 2012 by a genetic test benefit manager, Generation Health, offered physicians and patients an opportunity to identify the *CYP2C19* metabolizer status via a patient self-administered buccal swab sample collection kit. To be eligible for the program, patients must have their prescription drug benefits administered by CVS Caremark (CVSC), and their plan sponsor (ie, employer or health insurance plan) must have elected to offer the genetic testing benefit. The institutional review board of Brigham and Women's Hospital approved the conduct of this study and analysis.

Testing Procedures

Potentially eligible patients were those who had been prescribed clopidogrel in the prior 12 months as determined using filled prescription drug claims data. Each patient's prescribing physician was contacted to confirm that the patient had experienced an ACS or underwent PCI in the prior 12 months and, if so, to obtain consent for *CYP2C19* testing.

Patients whose physicians had agreed to testing were then contacted by a pharmacist to explain and obtain verbal consent for the test. Patients were then sent a sample collection kit that contained a buccal swab, instructions on how to administer the test, a written consent form, responses to frequently asked questions, and a prepaid return envelope. The expense of this program was fully covered by the patient's pharmacy benefit, and as a result, patients were offered testing free of charge.

CYP2C19 Testing

Samples (buccal) were evaluated by amplifying selected exons of the *CYP2C19* gene via a process of multiplex polymerase chain reaction, single-nucleotide primer extension, and subsequent detection of fluorescent extension products on an automated DNA sequencing platform. After an average of 3 to 5 days, test results were faxed directly to the prescribing physician. After test results, a more detailed summary report was sent to the physician with information on the patient's clopidogrel metabolizer status and the FDA boxed warning for clopidogrel[15] (see the online-only Data Supplement). On March 1, 2012, clinical pharmacists also began telephone outreach to physicians 30 days after results were faxed to provide test result interpretation support.

Based on genotype, patients were categorized into clopidogrel metabolizer phenotypes as presented in Table 1.

Changes in Antiplatelet Prescribing

Changes in antiplatelet prescribing were monitored for ≤120 days after reporting of *CYP2C19* genotype and phenotype results using prescription claims data. The primary outcome for the current study was intensification of antiplatelet therapy defined as either a dose escalation of clopidogrel or replacement of clopidogrel by prasugrel. When assessing changes to antiplatelet therapy, we excluded patients with an undefined phenotype (ie, carriers of 1 reduced function *CYP2C19* allele and 1 ultrarapid *CYP2C19* allele). Any changes to a patient's course of treatment after testing were solely at the discretion of the prescribing physician, and test results were not used for any medication coverage decisions.

Statistical Analysis

Baseline demographic, clopidogrel prescription, and insurance coverage characteristics were compared using χ^2 testing for categorical

Table 1. *CYP2C19* Genotype and Clopidogrel Metabolism Phenotype

Phenotype	Genotype
Extensive metabolizer	*1/*1, *1/*17
Intermediate metabolizer	*1/*2, *1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *1/*8, *1/*9, *1/*12
Poor metabolizer	*2/*2, *2/*3, *2/*4, *2/*5, *2/*6, *2/*7, *2/*8, *2/*9, *2/*12, *3/*3, *3/*4, *3/*5, *3/*6, *3/*7, *3/*8, *3/*9, *3/*12, *4/*4, *4/*5, *4/*6, *4/*7, *4/*8, *4/*9, *4/*12, *5/*5, *5/*6, *5/*7, *5/*8, *5/*9, *5/*12, *6/*6, *6/*7, *6/*8, *6/*9, *6/*12, *7/*7, *7/*8, *7/*9, *7/*12, *8/*8, *8/*9, *8/*12, *9/*9, *9/*12, *12/*12
Ultra metabolizer	*17/*17
Unknown	*17/*2, *17/*3, *17/*4, *17/*5, *17/*6, *17/*7, *17/*8, *17/*9, *17/*12

variables and Mann–Whitney test for continuous variables. Changes in prescribing patterns for antiplatelet therapy were evaluated using χ^2 or Fisher exact test if there were <5 observations. *P* values <0.05 were considered significant.

Results

Program Adoption and Cohort Characteristics

During the study period, 6032 potentially eligible individuals filled a prescription for clopidogrel. The prescribing physicians of 2692 provided relevant clinical eligibility information, of whom 1291 patients underwent a PCI or were hospitalized for an ACS within the prior 12 months. Consent for testing was provided by 945 physicians, and 678 patients were successfully contacted and offered testing. Of these, 623 consented and 499 completed testing (Figure 1).

The baseline demographic characteristics, duration of insurance coverage and clopidogrel therapy, coprescribed medications, and specialty of ordering provider for all identified patients (n=6032) and the patients who ultimately underwent testing (n=499) are presented in Table 2. The median age was 61 years, 70% were men, the median duration of clopidogrel treatment before identification for study enrollment was 40 days, and patients were receiving a median of 7.0 additional medications. There were no significant differences between groups except for prescriber practice setting. Cardiology, internal medicine, and family practice represented the specialties of the majority of treating providers.

CYP2C19 Genotype and Clopidogrel Metabolism Phenotype

The *CYP2C19* genotypes and phenotypes for the 499 subjects successfully undergoing genetic testing are shown in Figure 2. The majority of subjects (n=344; 69%) were noncarriers of reduced function alleles; 155 (31%) were carriers of ≥1 reduced function allele. In terms of clopidogrel metabolism phenotype, 16 (3.2%) were ultrarapid metabolizers, 328 (65.7%) were extensive metabolizers, 131 (26.3%) were intermediate metabolizers, 15 (3.0%) were poor metabolizers, and 9 (1.8%) were unknown given the presence of 1 reduced function allele and 1 ultrarapid allele. Baseline patient and provider characteristics by reduced function allele carrier status are shown in Table 2 and were well balanced across groups.

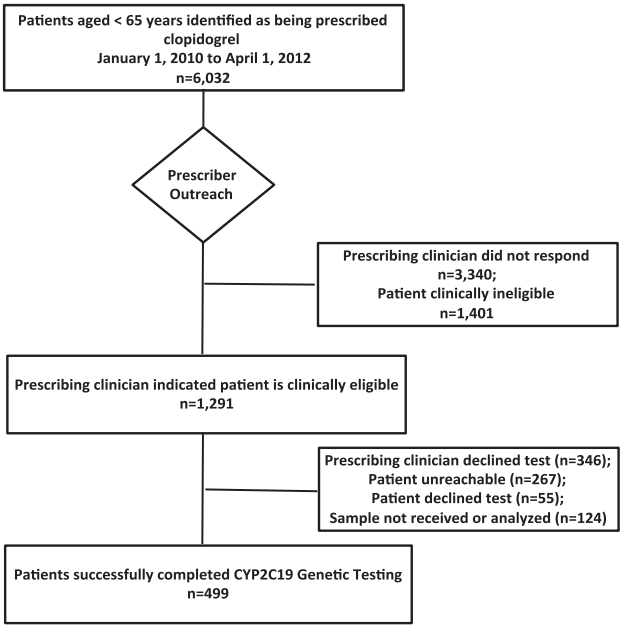

Figure 1. Patient flow.

Clinical Action by Testing and *CYP2C19* Genotype and Clopidogrel Metabolism Phenotype

Patients who underwent genetic testing were significantly more likely to have their antiplatelet regimen change and to continue clopidogrel as compared with patients not undergoing testing (*P*<0.001). Among patients identified as eligible for testing but who did not complete genetic testing, 51 (0.9%) had their antiplatelet agent changed from clopidogrel to prasugrel compared with 33 (6.6%) patients who were genotyped; of those not undergoing testing, 984 (17.8%) discontinued antiplatelet therapy compared with 46 (9.2%) patients who underwent testing.

The clinical action that occurred ≤120 days after the reporting of test results to providers and patients stratified by allele carrier status is shown in Figure 3. The primary outcome, intensification of antiplatelet therapy, occurred significantly more often in carriers of *CYP2C19* reduced function alleles as compared with noncarriers (20.5% versus 1.7%; *P*<0.001). As compared with noncarriers of reduced function *CYP2C19* alleles, carriers of ≥1 reduced function allele were significantly more likely to have their antiplatelet therapy changed from clopidogrel to prasugrel (17.8% versus 1.7%; *P*<0.001). Carriers of ≥1 reduced function allele were also significantly more likely to have an increase in their dose of clopidogrel when compared with noncarriers (2.7% versus 0%; *P*=0.008).

Figure 3 also shows the impact of genetic testing on provider prescribing patterns for antiplatelet therapy by the predicted phenotype of clopidogrel metabolism. The primary outcome occurred in 20.6% and 20% of intermediate and poor metabolizers, respectively, as compared with 1.7% of extensive and ultrarapid metabolizers (*P*<0.001 for each comparison versus extensive and ultrarapid metabolizers). As compared with ultrarapid and extensive metabolizers where 1.7% of patients had replaced clopidogrel with prasugrel, there was a step-wise increase in the percentage of patients with an escalation from clopidogrel to prasugrel in intermediate metabolizers (17.6%) and poor metabolizers (20%; *P*<0.001 for both groups compared with ultrarapid and extensive metabolizers). One of the 9 (11%) subjects with undefined phenotype had an escalation in their antiplatelet regimen from clopidogrel to prasugrel (data not shown).

Discussion

Our analysis of a commercial clopidogrel-*CYP2C19* genotyping program demonstrates that about one third of patients are carriers of reduced function alleles. Although the carriers (intermediate and poor metabolizers of clopidogrel) were more likely to have an intensification of their antiplatelet therapy, only 20% of the highest risk patients had an intensification of their antiplatelet therapy. In addition, we found that a small proportion of extensive and ultrarapid metabolizers were changed to prasugrel.

Table 2. Baseline Demographic, Clopidogrel Therapy, and Provider Characteristics by Testing Status and *CYP2C19* Allele Carrier Status

Characteristic	Identified But Untested Cases (n=5533)	Tested (n=499)	*CYP2C19* Allele Carriers (n=146)	*CYP2C19* Allele Noncarriers (n=344)
Patient age, y, median (IQR)	61.0 (54.9–66.4)	61.1 (55.9–66.0)	60.7 (55.8–64.7)	60.1 (54.7–64.7)
Men, n (%)	3761 (68)	355 (71)	100 (69)	248 (72)
Coprescribed medications, median (IQR)	7.0 (4.0–10.0)	7.0 (4.0–10.0)	6.5 (4.0–10.0)	6.0 (4.0–9.0)
Duration of clopidogrel therapy before identification for enrollment, d, median (IQR)	34 (0–433)	76 (0–314)	106 (0–327)	74 (0–297)
Prescriber practice specialty*, %				
Cardiovascular	2339 (43)	276 (55)	71 (49)	198 (58)
Internal medicine	876 (16)	65 (13)	18 (12)	47 (14)
Family practice	775 (14)	76 (15)	27 (18)	47 (14)
Other	1543 (27)	82 (17)	32 (21)	52 (14)

*$P<0.05$ for subjects identified but untested vs those undergoing testing and *CYP2C19* reduced function allele carriers vs allele noncarriers

To the best of our knowledge, our study is the first real-world analysis of a clopidogrel-*CYP2C19* genotyping program among patients with ACS or PCI and provides insight into how other genetic testing programs for other drugs may function. Notably, in ≈50% of cases, providers failed to respond to initial outreach, despite being contacted numerous times by mail and phone. Even among clinically eligible patients, providers declined testing in ≈25% of cases. Provider discomfort at how best to integrate FDA boxed warnings and genotype information to their selection of the appropriate antiplatelet regimen may underlie our findings. In contrast, <10% of patients offered genetic testing for *CYP2C19* declined the test, highlighting a potential gap between providers and patients in their desire for genetic testing, especially once the physicians had already approved the test. We also observed that the rate of discontinuation of clopidogrel was significantly lower among patients who underwent testing as compared with those who were eligible but did not undergo testing. However, in the current analysis, we are unable to further evaluate the impact of *CYP2C19* genetic testing on medication adherence.

Our observation that 1 in 3 patients are carriers of reduced function alleles and ≈3% are homozygotes for reduced function *CYP2C19* alleles is consistent with prior literature.[16] Genetic epidemiology studies have demonstrated that common polymorphisms in the *CYP2C19* gene are present in ≈30% of whites, 40% of blacks, and >50% of Asians.[17] In an analysis from the TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) 38 trial, 27% of the study population was found to be carriers of ≥1 reduced function *CYP2C19* allele.[16] Still further, in the randomized ELEVATE-TIMI (Escalating Clopidogrel by Involving a Genetic Strategy-Thrombolysis in Myocardial Infarction) 56 trial, 26% of enrolled subjects were carriers of ≥1 reduced function *CYP2C19* allele, with 2% of subjects being homozygous for reduced function alleles.[11] In a proof-of-concept study using point-of-care genetic testing for *CYP2C19* in 200 patients undergoing PCI for ACS or stable CAD, 24.5% were noted to be carriers of reduced function alleles.[18]

Our analysis uniquely offers the ability to observe provider prescribing patterns for antiplatelet therapy in response to genetic testing. We observed that carriers of reduced function alleles overall, and intermediate and poor metabolizers of clopidogrel specifically, were significantly more likely to have their antiplatelet therapy changed from clopidogrel to prasugrel or have their dose of clopidogrel increased—a clinical action that is consistent with FDA guidance. However, only 1 in 5 patients with 2 reduced function alleles, poor metabolizers of clopidogrel who would be expected to be at the highest risk for adverse events, had an intensification of

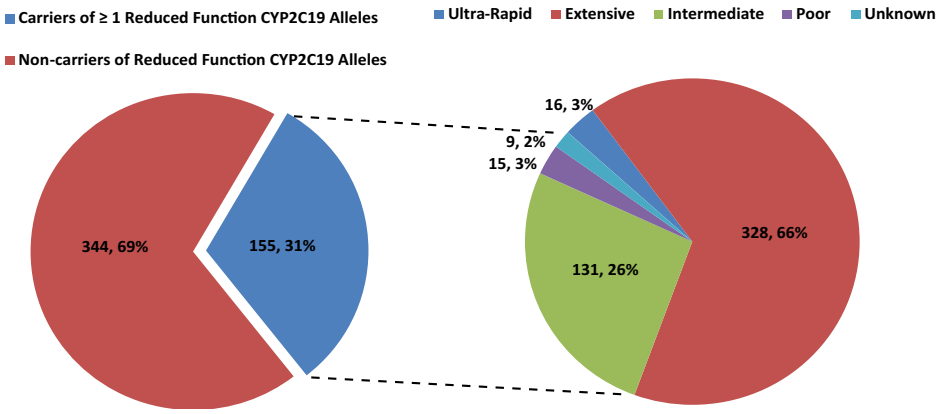

Figure 2. *CYP2C19* genotype and clopidogrel metabolism phenotype.

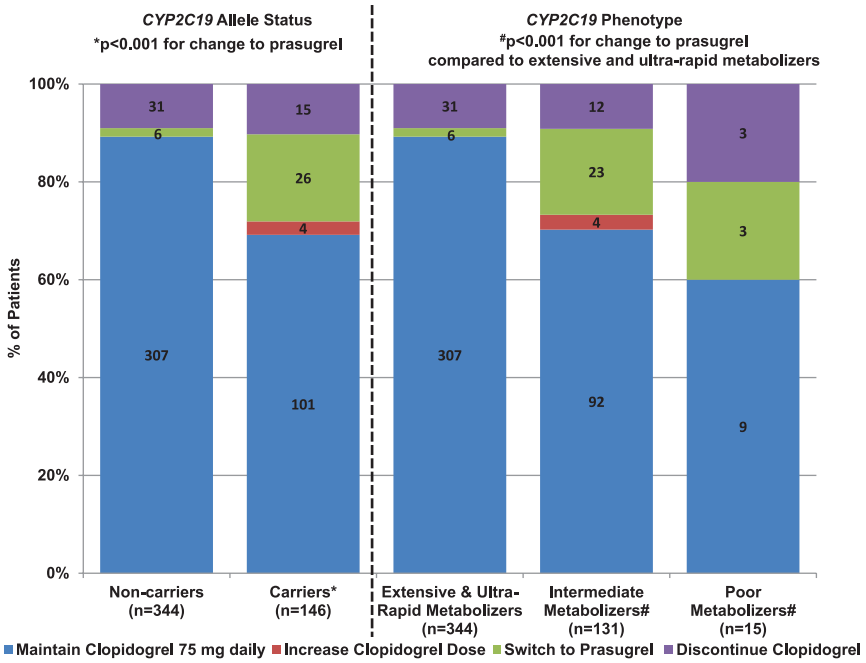

Figure 3. Provider response to *CYP2C19* testing results by allele carrier status and clopidogrel metabolism phenotype.

their antiplatelet therapy. These findings may have resulted from the providers' lack of understanding about how to interpret genetic test results or a belief that genetic testing has not been definitively established as a reliable approach to tailoring antiplatelet therapy. In addition, providers may have been reluctant to switch to one of the novel antiplatelet agents because of their relative lack of clinical experience with them. For instance, despite the FDA boxed warning, the American College of Cardiology/American Heart Association maintain that insufficient evidence remains for this warning.[10] In addition, multiple studies have failed to demonstrate a benefit to platelet function testing–guided therapy.[19–21] Although these studies focused on platelet function testing rather than genotyping, the inability to show the superiority of personalized therapy for clopidogrel may have dampened enthusiasm for *CYP2C19* genotype-guided antiplatelet therapy.

It is important to note that our analysis used pharmacy claims data and included many patients who were established users of clopidogrel. The median duration of clopidogrel use before their identification for allele carriers was 106 days. Providers and patients may have been less willing to alter therapy in patients who had been clinically stable on standard dose clopidogrel therapy after ACS/PCI. Given that the risk of recurrent adverse cardiovascular events and stent-related complications is highest in the first 30 days after ACS or PCI,[22,23] our findings likely underestimate the response to *CYP2C19* genetic testing when it is used for patients with more acute coronary artery disease. Patient factors such as the higher cost of branded antiplatelet agents and the increased risk of bleeding complications with alternative antiplatelet therapy may have also contributed to our findings.

There are several important limitations to our study. First, our study included a relatively small number of patients for whom we had comprehensive pharmacy claims data but limited clinical information or provider-level characteristics. However, given that this was a real-world analysis, it offers important insights into clinical practice patterns that could not be gained with the use of a controlled study design. Second, during our analysis period, ticagrelor was not an FDA-approved therapy, so we cannot make any conclusions about the medication providers would have selected if they chose to intensify therapy for a particular patient if ticagrelor were available. Third, the results of genetic testing were reported to the providers and patients but were not coupled with an active intervention highlighting the salient test results and potential therapeutic alternatives. Rather, this was a passive transmission of results to the physician with minimal integration of educational information and decision support as the American Heart Association/American College of Cardiology do not offer any specific recommendations on managing patients with ≥1 loss of function *CYP2C19* alleles. Although the test results are certainly less likely to influence provider prescribing behavior, they do offer important, unique insights into provider decision making that would be lost if a more directive intervention was used. Finally, we are unable to capture whether providers responded to the genotype results by referring patients for additional testing, including platelet function studies, and then based their prescribing decision on a more integrated assessment of platelet activity.

In conclusion, clopidogrel has been shown to reduce the rate of major adverse cardiovascular events among patients with ACS or undergoing PCI. Its efficacy has been shown in some studies to be attenuated in patients carrying reduced function *CYP2C19* alleles, a critical enzyme involved in the bioactivation of the drug. Regulatory agencies, including the FDA and European Medicines Agency, have reacted to these data, and the FDA has issued a boxed warning cautioning against the use of clopidogrel in patients carrying certain *CYP2C19* alleles. Although providers were significantly more likely to alter the antiplatelet regimen in *CYP2C19* allele carriers, ultimately only 20% of those at highest risk after ACS or PCI were switched to prasugrel or had an increase in the

dose of clopidogrel. These prescribing patterns likely reflect the unclear impact and physician uncertainty with the rapidly evolving evidence for clopidogrel pharmacogenomics.

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Disclosures

None.

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