

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 Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

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CLINICAL ALERT

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

Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

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TABLE OF CONTENTS

Preamble	321
1. Review of FDA Boxed Warning— What Did the FDA Say?	322
1.1. Background and Significance of Boxed Warnings and How These Relate to the Clopidogrel Warning	323
2. Evidence on Variability to Clopidogrel Response	323
2.1. Genetic Variability and Clopidogrel Response	323
2.1.1. CYP2C19 Variants	323
2.1.2. Other Genetic Polymorphisms	326
2.1.2.1. ABCB1	326
2.1.2.2. OTHER CYP ISOENZYMES	326
2.1.2.3. P2Y ₁₂ RECEPTOR	326
3. Current Status of CYP2C19 Genotyping Assays	326
4. Alternative Dosing Regimens for Clopidogrel	327
5. Review of Ongoing Trials	329

6. Conclusions	332
6.1. Issues for Consideration	332
6.2. Recommendations for Practice	334
References	335
Appendix 1. Author Disclosures	337
Appendix 2. Peer Reviewer Disclosures	338
Appendix 3. FDA Drug Safety Communication	340

Preamble

The recent U.S. Food and Drug Administration (FDA) “boxed warning” on clopidogrel raises important questions for practitioners and patients. The warning addresses the need for pharmacogenomic testing to identify patients’ altered clopidogrel metabolism and thus their risk for a suboptimal clinical response to clopidogrel. Although there is an expanding database on genetic polymorphisms that may affect clopidogrel metabolism and thus clinical outcomes, there are no evidence-based data upon which to

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develop specific recommendations on the role of genetic testing in routine care nor strategies proven to improve the safety/efficacy of specific pharmacologic approaches.

To provide guidance on this issue, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) convened a writing committee. The ACCF and AHA adhere to a rigorous policy regarding relationships with industry and other entities (RWI) of authors and peer reviewers for clinical document development (see <http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx>). This policy requires that a majority of writing committee members have no *relevant* relationships with industry to this topic, a standard that has been achieved for this document as indicated in [Appendix 1](#). In the spirit of full disclosure, *comprehensive* RWI (RWI not relevant to this document) for all authors is available online for public view. RWI restrictions are not applicable for participation in the external peer review process for clinical documents in order to ensure that a variety of constituencies/views inform the final document; however, all *relevant* reviewer RWI is published in [Appendix 2](#) for the purpose of full transparency. In addition, reviewer affiliation for this document is recorded in [Appendix 2](#), indicating participation of the following societies in the review process: the American Academy of Family Physicians, the American College of Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. The ACCF and AHA believe this document will be helpful during a time when information on this topic is incomplete and continually changing. For some of the clinical issues in this document, final published data may not be available, in which case we have clearly identified this concern in the text. In addition to this document, an expert consensus document on the interaction of clopidogrel and proton pump inhibitors is in progress by the ACCF, American College of Gastroenterology, and AHA. Our organizations remain committed to providing guidance on key clinical issues to promote optimal patient care.

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1. Review of FDA Boxed Warning— What Did the FDA Say?

On March 12, 2010, the FDA approved a new label for clopidogrel with a “boxed warning” ([Appendix 3](#)) about the diminished effectiveness of the drug in patients with impaired ability to convert the drug into its active form (1). This warning was the third FDA label change related to this issue in the last year. The boxed warning is based on the concern that the antiplatelet effect of clopidogrel depends

primarily on its activation by the cytochrome P450 (CYP) system. Patients with decreased CYP2C19 function because of genetic polymorphisms metabolize clopidogrel poorly and have higher rates of cardiovascular events after acute coronary syndrome (ACS) and percutaneous coronary interventions (PCIs) than patients with normal CYP2C19 function. The warning also notes that tests are available to identify patients with genetic polymorphisms, and that alternative treatment strategies should be considered in poor metabolizers of the drug.

The new label emphasizes a single study of 40 healthy subjects (10 each with different degrees of CYP2C19 function—poor, intermediate, extensive, and ultrarapid) in a crossover design. Each group was randomized to a 300-mg loading dose (LD) followed by a 75-mg per day maintenance dose (MD), or a 600-mg LD followed by 150-mg per day MD, each for a total of 5 days ([Appendix 3](#)). After a washout period, subjects were crossed over to the alternate treatment. The chief findings were decreased active metabolite exposure and increased platelet aggregation in the poor metabolizers compared with the other groups. When poor metabolizers received the 600-mg LD followed by 150 mg daily MD, active metabolite exposure and antiplatelet response were greater than with the 300-mg LD and 75 mg per day MD regimen, but remained quantitatively less than the response in the extensive metabolizers when they received the 300 mg and 75 mg regimen. Two different assays for platelet function were used—platelet aggregation stimulated by 5 micromolar adenosine diphosphate (ADP) and the vasodilator-stimulated phosphoprotein phosphorylation assay. Improvement in platelet inhibitory responses with higher-dose clopidogrel in poor metabolizers was apparent only with the former assay. There was no comment about statistical significance in the labeling material. Analysis of the final as yet unpublished data set of this study, which played a prominent role in the boxed warning, will be essential to a more complete understanding of the issues.

To fully understand the new label, it is necessary to consider the other background information upon which the label was developed. There are 3 major CYP2C19 genetic polymorphisms. CYP2C19*1 corresponds to normal function. CYP2C19*2 and CYP2C19*3 are loss-of-function alleles and explain most of the reduced function in those who are “poor metabolizers.” CYP2C19*2 and *3 account for 85% and 99% of the nonfunctional alleles in whites and Asians, respectively ([Appendix 3](#)). Poor metabolizers have 2 loss-of-function alleles. Intermediate metabolizers have 1 copy of a loss-of-function allele and may also have decreased active metabolite levels and reduced antiplatelet effects when treated with clopidogrel, but the boxed warning only refers to poor metabolizers. The new label alludes to multiple retrospective, prospective randomized, and cohort clopidogrel studies that document increased major adverse cardiac event (MACE) rates in populations with genetic polymorphisms. Several cohort studies cited in prior FDA versions of the label and referred to in the most recent label have also shown variations in event rates that

depend on CYP2C19 genotype (2–4). As the new label notes, tests are now available to determine CYP2C19 genotypes for clinical purposes.

Conversely, it is also important to note what the label does not say. When the first of the label revisions was being developed in early 2009, the FDA proposed a recommendation for genotyping to identify patients with impaired CYP2C19 function and a comment stating that higher doses may be considered in these patients. After discussion with the manufacturer, however, no recommendation for genotyping was included in the label at that time. Instead, the initial 2009 revision (dated May 5, 2009) simply noted that “poor metabolizer status is associated with diminished response to clopidogrel” and that “the optimal dose for poor metabolizers has yet to be determined” (5). The second revision in 2009 advised avoiding the use of clopidogrel “in patients with impaired CYP2C19 function due to known genetic polymorphisms or due to drugs that inhibit CYP2C19 activity” and added additional information about the interaction of clopidogrel and omeprazole (6). The most recent revision, in March 2010, no longer specifically advises avoidance of clopidogrel in patients with known genetic polymorphisms of CYP2C19 but rather states that physicians should “consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers” (1). In addition, it should be noted that although it is assumed that it is the influence of the genotype on the phenotype of platelet reactivity that causes the increased rate of adverse clinical events, it remains possible that there may be other independent adverse effects of the genotype.

In the current warning, the moderate position of the FDA does not appear merely to be a reluctance to make strong recommendations about genetic testing, but rather to reflect an attempt to weigh the evidence and to give the prescriber more information. The FDA has made recommendations of different strengths related to genetic variations on multiple occasions (7) in recent years with some boxed warnings like those for carbamazepine and abacavir that explicitly recommend genetic testing and advise against generally treating patients with certain genotypes with these drugs (8,9). In contrast, the FDA-approved label for warfarin mentions information about allelic variants that alter patient responsiveness to it, but does not include a “boxed warning” about this (10).

1.1. Background and Significance of Boxed Warnings and How These Relate to the Clopidogrel Warning

It is important to understand when the FDA requires such a warning. The Code of Federal Regulations (10a) requires that “labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. Special problems, particularly those that may lead to death or serious injury, may be required by the [FDA] to be

placed in a prominently displayed box. The ‘boxed warning’ ordinarily shall be based on clinical data” (11).

The FDA leaves decisions about what to do with the information in boxed warnings up to individual clinicians (11). It does not necessarily recommend a particular plan for how to deal with the information. It has been emphasized that the intent of information that the FDA puts into such a warning is to share the data with prescribers so they can be informed and make decisions based on patient-specific factors. The decision to perform CYP2C19 genetic testing is best made by the prescriber of the medication and the informed patient.

In brief, the clopidogrel boxed warning leaves the issue of whether to perform CYP2C19 testing up to the individual physician. It does not specifically require genetic testing or other changes in evaluation or treatment and does not imply that there are solid evidence-based reasons for such actions. Rather, it serves to make clinicians aware of the imperfect, but significant, knowledge that we have about genetic variations in response to clopidogrel and to emphasize that clinicians should use this knowledge to make decisions about how to treat individual patients.

2. Evidence on Variability to Clopidogrel Response

Clopidogrel, a thienopyridine P2Y₁₂ ADP receptor antagonist, requires bioactivation to its active metabolite (R130964) to inhibit platelet aggregation. There is substantial individual variability in response to clopidogrel, with inhibition of ADP-induced platelet aggregation ranging from less than 10% to almost complete inhibition of platelet aggregation with a wide distribution across this range, such that there is no dichotomous separation into “responders” and “nonresponders” (12). Nevertheless, a meta-analysis and other data suggest that residual platelet reactivity in patients receiving clopidogrel is associated with an increased risk of cardiac, cerebrovascular, and peripheral arterial events (12–14). This variability may be due to pharmacokinetic (PK) or pharmacodynamic (PD) factors (i.e., differences respectively in either kinetics/concentration of the active metabolite or in the response of platelets). The variability in clopidogrel PK and PD is due to several factors: demographic variables such as increased age and body mass index, comorbidities such as diabetes and dyslipidemia, and other factors that remain to be identified (15). Although genetic variability also plays an important role in ADP-stimulated platelet aggregation in response to clopidogrel, known genetic and nongenetic factors explain only a portion of the majority of variation (15).

2.1. Genetic Variability and Clopidogrel Response

2.1.1. CYP2C19 Variants

CYP2C19 plays an important role in the bioactivation of clopidogrel, a prodrug. Once absorbed, only approximately 15% of clopidogrel is bioactivated in the liver in a 2-step

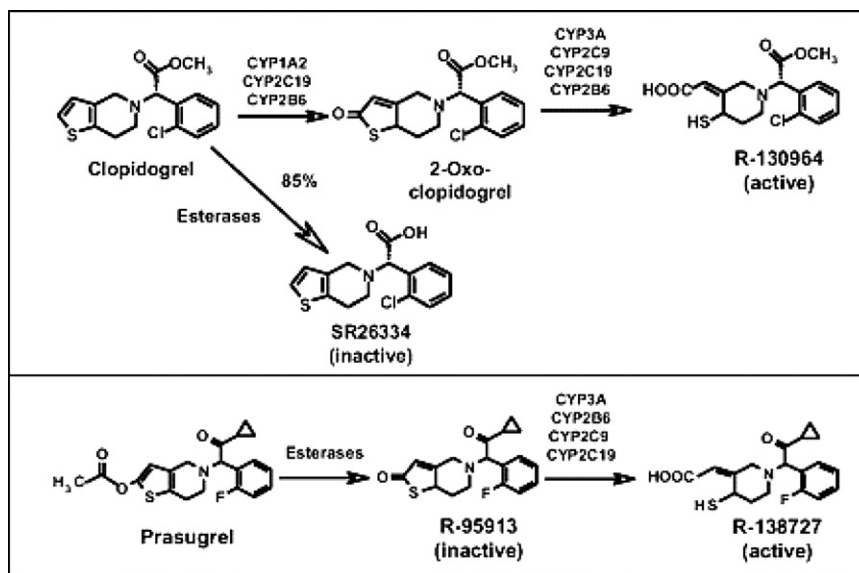


Figure 1. Schematic Representation of the Metabolism of Clopidogrel and Prasugrel

Reprinted with permission from Mega et al. (16).

process that is mediated by several CYP450 isoenzymes (Figure 1) (16). Of these, CYP2C19 is responsible for approximately 45% of the first step (the formation of 2-oxo-clopidogrel) and approximately 20% of the final step—the generation of the pharmacologically active thiol metabolite. There are genetic polymorphisms in several CYP450 enzymes involved in the metabolism of clopidogrel, but variants in CYP2C19, particularly CYP2C19*2, are reproducibly associated with variability in clopidogrel active metabolite bioavailability, antiplatelet effects, and clinical outcomes (2,15,17). The CYP2C19*2 variant encodes a nonfunctional protein. There are ethnic differences in its distribution; approximately 50% of Chinese, 34% of African Americans, 25% of Whites, and 19% of Mexican Americans carry at least 1 copy of the reduced function CYP2C19*2 allele (18,19). Other genetic polymorphisms associated with impaired CYP2C19 activity and possibly adverse clinical events (CYP2C19*3, *4, *5, *8) are much less common in Whites, African Americans, and Hispanics (18). In the randomized control TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38), comparing clopidogrel with prasugrel in patients with ACS, CYP2C19*2 accounted for 95% of the subjects classified as carriers of a reduced CYP2C19 function allele (17). The number of reduced function alleles is important: individuals with 1 variant allele (intermediate metabolizers) had 26% to 31% lower exposure to the active metabolite of clopidogrel, and those with 2 genetic polymorphisms (poor metabolizers) had 46% to 55% lower exposure compared with those with no CYP2C19 polymorphisms (17).

The effect of variant CYP2C19 alleles on clinical outcome in response to clopidogrel has been reported in

multiple studies (Table 1) (20,21). All of these were cohort studies, with 1 being a genetic substudy derived from TRITON-TIMI 38. A significant association between the CYP2C19*2 polymorphism and an increased risk of major adverse cardiovascular events was reported in 5 of 7 studies. The risk ranged from a 53% relative increase in TRITON-TIMI 38 (17) to an approximately 5-fold increase in a cohort study of young patients treated with clopidogrel after acute myocardial infarction (MI) (2). In the latter study, after multivariable analysis, CYP2C19*2 was the only factor independently associated with new cardiovascular events (hazard ratio [HR] 4.04 [95% confidence interval (CI) 1.81 to 9.02]; $p=0.0006$) (2). However, because none of the studies were randomized, the possibility of bias and confounding variables cannot be excluded. For example, patients who had an event were more likely to be receiving clopidogrel at baseline in some studies. Thus, a group of clopidogrel nonresponders may have been preselected and overrepresented in some studies. In addition, the scope of the genetic problem is not isolated to patients with 2 deficient alleles (homozygotes). This has important implications because of the higher prevalence of heterozygotes in the population. The data on positive and predictive risk in specific patient populations are incomplete (22). Thus, caution must be observed in drawing definitive conclusions from these observational studies.

These clinical efficacy data mirror the effect of genetic polymorphisms on platelet function in both heterozygotes as well as homozygotes. Carriers of a CYP2C19*2 allele have been found to have an absolute reduction in platelet aggregation in response to clopidogrel that was 9 percentage points less than that of noncarriers (17). Other studies (23) have noted that carriers of at least 1 reduced function CYP2C19 allele have less response to clopidogrel reflected

Table 1. CYP2C19*2 Polymorphisms and Cardiovascular Outcomes

Source, Year (Region)	Patients, n (Age, Years)	Disease	Clopidogrel Dosage	Duration of Follow-Up (Months)	Outcome (n)	Frequency of Genotype, n (%)			RR (95% CI)	Adjustment
						*1/*1	*1/*2	*2/*2		
Trenk et al., 2008 (Germany) (21)	797 (mean: 66.4)	CAD	LD 600 mg MD 75 mg day ⁻¹	12	Death and MI (24)	552 (69.3)	228 (28.6)	17 (2.1)	0.67 (0.25-1.78)†	None
Simon et al., 2009 (France) (22)	2178 (mean: 70.1)	AMI	LD 300 mg MD 75 mg day ⁻¹	12	Death from any cause (225)	1561 (71.7)	564 (25.9)	53 (2.4)	0.89 (0.68-1.18)†	None
Collet et al., 2009 (France) (2)	259 (18-45)	MI	LD n.d. MD 75 mg day ⁻¹	100	Death, MI, urgent coronary revascularization (26) Stent thrombosis (12)	186 (71.8)		73 (28.2)	5.38 (2.32-12.47) 6.04 (1.75-20.80)	BMI smoking, diabetes, stent implantation, STEMI, use of proton-pump inhibitors
Mega et al., 2009 (United States) (17)	1459 (mean: 60.1)	ACS	LD 300 mg MD 75 mg day ⁻¹	15	Death from CV causes, MI, stroke (129) Stent thrombosis (18)	1064 (72.9)		395 (27.1)	1.53 (1.07-2.19) 3.09 (1.19-8.00)	None
Sibbing et al., 2009 (Germany) (4)	2485 (mean: 66.5)	CAD	LD 600 mg MD 75 mg day ⁻¹	1	Stent thrombosis (17)	1805 (73)	633 (25)	47 (2)	3.81 (1.45-10.02)	Age, diabetes, ACS, type of stent
Giusti et al., 2009 (Italy) (3)	772 (mean: 68.3)	ACS	LD 600 mg MD 75 mg day ⁻¹	6	Stent thrombosis + cardiac mortality (29) Stent thrombosis (24)	525 (68)	221 (28.6)	26 (3.4)	2.70 (1.00-8.42) 3.43 (1.01-12.78)	Residual platelet reactivity, traditional CV risk factors, clinical and procedural risk factors
Shuldiner et al., 2009 (United States) (15)	93‡ (mean: 65)	CAD	LD 300/600 mg day ⁻¹ MD 75 mg day ⁻¹	12	MI, unplanned target and nontarget lesion revascularization, hospitalization, death from CV causes (n not reported)	66 (70.9)	27 (29.1)		3.40 (1.36-8.46)	Age, gender, race

Reprinted with permission from Sofi et al. (20). †Calculated from data taken from the original text; ‡only patients who were still taking clopidogrel after 1 year.

ACS indicates acute coronary syndromes; AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; LD, loading dose; MD, maintenance dose; MI, myocardial infarction; n.d., no date; RR, risk ratio; and STEMI, ST-segment elevation myocardial infarction.

as a higher residual platelet reactivity index. In a genome-wide association study performed in a homogenous population of healthy Amish—PAPI (Pharmacogenomics of Antiplatelet Intervention)—clopidogrel reduced ADP-induced platelet aggregation to 41%, 47%, and 65% of baseline in subjects with 0, 1, and 2 CYP2C19*2 alleles, respectively (15), thereby exhibiting a gene-dose effect. However, even in this relatively homogenous population, CYP2C19*2 genotype accounted for only 12% of the variability in clopidogrel response (15).

In contrast to clopidogrel, the FDA-approved drug, prasugrel, is oxidized to its active form in a single CYP-dependent step (Figure 1). In 238 healthy subjects tested, there was no significant decrease in the plasma concentrations of active metabolite or platelet inhibition in response to prasugrel in carriers versus noncarriers of at least 1 reduced function allele for the CYP genes tested (2C19, 2C9, 2B6, 3A5, 1A2) (16). Similar observations were reported in patients with stable coronary artery disease (23). The association of these genetic variants with cardiovascular outcomes was examined in 1466 patients with ACS allocated prasugrel in TRITON-TIMI 38. No significant associations were found between any of the CYP genes tested and risk of cardiovascular death, MI, or stroke (16). Ticagrelor, which is not yet approved, is a reversible, nonthienopyridine P2Y₁₂ receptor antagonist; it is not a prodrug, and does not require biotransformation (24,25). The effect of genetic polymorphisms in CYP isoenzyme function or number for this drug remains incompletely defined. Other drugs, such as elinogrel (not yet approved), have also been studied (26).

2.1.2. Other Genetic Polymorphisms

Other genetic variations may also affect the PK, PD, and clinical efficacy of clopidogrel (27).

2.1.2.1. ABCB1

Intestinal absorption is limited by the P-glycoprotein efflux-transporter encoded by the adenosine triphosphate-binding cassette containing gene ABCB1, also known as the multidrug resistant (MDR1) gene. Compared with noncarriers (wild-type or CC genotype), the bioavailability of clopidogrel is significantly reduced among patients receiving a 300- or 600-mg LD before elective PCI who have either 1 (CT genotype) or 2 (TT genotype) copies of the ABCB1 C3435T single nucleotide polymorphism (28). In acute MI patients, the frequency of the variant TT genotype (TT 26%, CC 26%, CT 48%) was significantly higher among the 294 patients with an outcome event (death, nonfatal MI, or stroke at 1 year) compared with the 1914 patients without an event (29% versus 26%, $p=0.04$). In addition, patients with the TT genotype had significantly higher event rates at 1 year than those with the ABCB1 wild-type (CC) genotype (15.5% versus 10.7%; adjusted HR 1.72; 95% CI 1.20 to 2.47) (22). Patients who possessed 2 CYP2C19 loss-of-function alleles and at least 1 ABCB1 variant allele were at

the highest risk for a primary outcome event (HR 5.31; 95% CI 2.13 to 13.20) compared with patients who had both CYP2C19 and ABCB1 (22). In another study of 2934 ACS patients, TT homozygotes had a 72% increased risk of the composite primary end point (cardiovascular death, MI, or stroke at 15 months) compared with either CC or CT patients (HR 1.72, $p=0.002$) (29). Additional information on the frequency and consequences of combined, functionally important genetic polymorphisms is required.

2.1.2.2. OTHER CYP ISOENZYMES

The CYP3A4 and CYP3A5 enzymes also play a role in the conversion of clopidogrel to its active metabolite. In a substudy of healthy volunteers analyzed along with TRITON-TIMI 38, carrier status for a reduced function allele of CYP2C9, 3A5, and 1A2 was not associated with a consistent reduction of the PK or PD responses to clopidogrel. Carriers of a reduced function CYP2B6 allele, however, tended to have a lower plasma exposure to the active metabolite of clopidogrel and tended to have less reduction of platelet aggregation in response to clopidogrel (16,17). One other study reported that 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 (30).

2.1.2.3. P2Y₁₂ RECEPTOR

Studies have also assessed genetic variation in the gene encoding the P2Y₁₂ receptor (the binding site for clopidogrel metabolite). In the FAST-MI (Registry on Acute ST-Elevation Myocardial Infarction) study, no association was found with clopidogrel responsiveness and the genetic polymorphism encoding the P2Y₁₂ receptor (22). Other studies have also yielded similar results (31).

3. Current Status of CYP2C19 Genotyping Assays

Given the increasing importance of genetic variations, there has been increasing interest in genetic testing to identify optimal strategies of care. This feature is a central component of the new clopidogrel boxed warning. Commercial assays are available from both research and clinical laboratories. Cross validation of the techniques used and their reliability, specificity, and reproducibility are extremely limited. While results of commercial assays can be applied, they are not available in the acute phases of patient care. Point-of-care assays for the common CYP2C19 polymorphisms are not available at this time. In addition, genetic polymorphisms with gain-of-function (CYP2C19*17), and uncommon alleles with reduced function (e.g., CYP2C19*3, *4, *5) may affect clinical outcomes. An important patient care issue relates to the cost for these tests (approximately \$500), which are typically not reimbursed by major payers. Alternatives to genetic testing focus on the phenotype—specifically, platelet function. Platelet function assays can

Table 2. Pharmacodynamic Studies of Platelet Responsiveness to Different Clopidogrel Dosing Protocols

Study	Regimen	Metric	Results
ISAR-CHOICE (33) 60 elective PCI patients; C-naïve	C, 300, 600, 900 mg LD	Platelet aggregometry, active thiol metabolite of C	600 mg dose had highest active drug metabolite level and platelet suppression compared with the 300 mg dose.
von Beckerath et al. (34) 60 patients after successful PCI; 600 mg C load	C, 150 mg daily vs. 75 mg daily (MD)	30-d platelet function	C, 150 mg daily had more intense platelet inhibition.
OPTIMUS study (35) 40 patients with type 2 DM and documented suboptimal response to C	C, 150 mg daily vs. 75 mg daily (MD)	Repeat platelet function testing after 30 d	150 mg dose improved rates of platelet inhibition, but 60% of patients still had suboptimal C effect.
Fontana et al. (36) 81 patients with recent PCI and documented suboptimal platelet inhibition on C 75 mg daily	C increased to 150 mg daily C (MD)	Repeat platelet function testing after 15 d	C, 150 mg daily improved platelet inhibition.
PRINC trial (37) 60 patients undergoing PCI; C, 600 mg LD	2 h after initial C-load, either 600 mg C or placebo, then second randomization to 150 mg C vs. 75 mg C daily	Platelet inhibition at 2, 4, and 7 h, and 1 wk	600 mg load × 2 at 2 h apart produced better inhibition than 600 mg acutely; 150 mg daily results in better inhibition than 75 mg after 1 wk.
VASP-02 (38) 153 patients undergoing elective PCI	C, 150 mg versus 75 mg daily for 4 wk; after 2 wk, platelet inhibition checked and low responders increased to 150 mg daily	Platelet inhibition at 2 and 4 wk	At 2 wk, 150 mg C produced better platelet inhibition. In low responders, 150 mg C improved platelet inhibition.
Price et al. (40) 45 volunteers	C, 300, 600, 900 mg LD	Platelet inhibition at baseline and 1 through 7 h	600 mg and 900 mg had more intense platelet inhibition than 300 mg, no difference between 600 mg and 900 mg.
Montalescot et al. (ALBION) (41) 103 patients with NSTEMI	C, 300, 600, 900 mg LD	ADP-induced IPA at 24 h	LDs greater than 300 mg provided greater antiplatelet effect than 300 mg

ADP indicates adenosine diphosphate; ALBION, Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis; C, clopidogrel; DM, diabetes mellitus; IPA, inhibition of platelet aggregation; ISAR-CHOICE, Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 Higher Oral Doses for Immediate Clopidogrel Effect; LD, loading dose; MD, maintenance dose; NSTEMI, non-ST-segment elevation myocardial infarction; OPTIMUS, Optimizing Antiplatelet Therapy in Diabetes Mellitus; PCI, percutaneous coronary intervention; PRINC, Plavix Response in Coronary Intervention; and VASP-02, Vasodilator-Stimulated Phosphoprotein-02 Randomized Study.

measure the effect of ADP or P2Y₁₂ activation on platelet aggregation, receptor expression, or the level of intracellular molecules (e.g., vasodilator-stimulated phosphoprotein phosphorylation), thereby directly or indirectly measuring the platelet inhibitory effect of clopidogrel (i.e., clopidogrel responsiveness or on-treatment reactivity). Additional clinical studies are underway to test whether altering therapy in response to residual high platelet reactivity after clopidogrel administration is associated with improved clinical outcomes.

4. Alternative Dosing Regimens for Clopidogrel

Evaluation of the different strategies developed and tested to overcome clopidogrel nonresponsiveness must consider the type of study, patient population, metrics of evaluation, and duration of follow-up. Each of these variables may affect interpretation of these data and the application of a specific therapeutic approach to an individual patient. There are few data on the inhibitory effect of alternative dosing regimens in CYP2C19 intermediate and/or poor metabolizers.

Several studies have evaluated the effect of different combinations of clopidogrel LDs and MDs on platelet aggregation, metabolites of clopidogrel, and other measures

of platelet function (32–41) (Table 2). Some studies were performed specifically in patients with a documented suboptimal response to the usual dosing protocols for clopidogrel (35,36,38). However, there are less data on the effect of alternative dosing regimens in intermediate and/or poor metabolizers and a lack of data supporting a change in therapy based on genotyping alone. In general, a 600-mg LD or double LD (second 600-mg dose 2 hours later) improves the degree of acute platelet inhibition (33,37). Moreover, an MD of 150 mg daily results in a greater degree of platelet inhibition in many studies in patients with a reduced response to the usual 75-mg MD (36–38). However, even at the higher dose, some patients do not reach an optimal level of platelet inhibition *ex vivo* (35).

Fewer studies have examined patient outcomes after different clopidogrel dosing protocols including an additional 600-mg LD at the time of PCI in patients already receiving 75 mg daily (40), 600-mg versus 300-mg LD in patients with ST-segment elevation MI undergoing primary PCI (41), and 600-mg LD followed by 150 mg daily for 1 week in patients with ACS (41a) (Table 3). There was no overall benefit of reloading clopidogrel prior to PCI in patients already receiving chronic clopidogrel in the ARMYDA-4 RELOAD (Antiplatelet Therapy for Reduction of MYocardial Damage During Angioplasty-4 RELOAD) study, although patients with

Table 3. Effect of Different Clopidogrel Dosing Protocols on Patient Outcomes

Study	Regimen	Metric	Results
ARMYDA-4 RELOAD (42)* 503 stable AP or non-STEMI ACS patients on chronic C for more than 10 d	600 mg load vs. placebo	30-d MACE defined as cardiac death, MI, or TVR	No benefit in overall cohort. In non-STEMI ACS patients, 600 mg load reduced MACE (16.3% to 6.4%); no change in MACE in stable AP.
HORIZONS-AMI (43) 3602 STEMI patients	600 mg vs. 300 mg C load	30-d MACE defined as all-cause death, stroke, reinfarction, unplanned revascularization for ischemia, or major bleeding	600-mg dose was an independent predictor of lower 30-d MACE
CURRENT OASIS-7* 25,098 ACS patients (41a)	High-dose C = 600-mg loading dose, then 150 mg for 7 d, then 75 mg daily to 30 d; standard dose C = 300 mg loading dose, then 75 mg daily to 30 d	30-d MACE defined as cardiovascular death, MI, or stroke	No benefit in overall cohort. In subgroup of 17,232 PCI patients, 15% reduction in MACE in high-dose group with a 42% reduction in definite ST, but increased bleeding

*Because the overall study was negative, the results obtained in the ACS subgroup in ARMYDA-4 RELOAD and PCI subgroup in CURRENT OASIS-7 should be considered hypothesis-generating only. ACS indicates acute coronary syndromes; AP, angina pectoris; ARMYDA-4 RELOAD, Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-4 RELOAD trial; C, clopidogrel; CURRENT OASIS-7, Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions trial; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction trial; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; STEMI, ST-segment elevation myocardial infarction; and TVR, target-vessel revascularization.

ACS did appear to do better with the extra LD (42). Because the overall study was negative, the results obtained in the ACS cohort should be considered hypothesis-generating only. In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, a 600-mg dose was an independent predictor of lower 30-day MACE (43). In the CURRENT-OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Antiplatelet Strategy for Interventions-7) trial, there was no increase in efficacy of double-dose versus standard-dose clopidogrel in the overall cohort (41a). However, in patients undergoing PCI (nearly 75% of the overall cohort), MACE was significantly reduced but bleeding was also increased with double-dose clopidogrel (41a). Because the overall study was negative, the results obtained in this postrandomization subgroup of patients undergoing PCI should be considered hypothesis-generating only.

Other strategies have been tested to overcome deficits in clopidogrel responsiveness. One approach is to add a third drug to aspirin and clopidogrel to further enhance platelet inhibition. Cilostazol acts via a different pathway to selectively inhibit phosphodiesterase type 3 and affects adenosine reuptake and nitric oxide PGI₂ production by endothelial cells (44). It is approved for use in patients with peripheral vascular disease and claudication; thus, its use to enhance platelet inhibition in PCI patients is off-label. After stent placement, patients with persistently high platelet reactivity after a 300-mg LD of clopidogrel were randomized to receive either high-dose clopidogrel (150 mg daily) or cilostazol (100 mg twice daily) with the standard clopidogrel MD (45). Adjunctive cilostazol intensified platelet inhibition to a greater degree than high-dose clopidogrel in these patients and also in a separate study of patients undergoing primary PCI for ST-segment elevation MI (46). However, data on the effect of adjunctive cilostazol on clinical outcomes are conflicting. In a study of Asian patients with ACS, adjunctive cilostazol improved clinical outcomes at 6

months, but no platelet function testing was performed (47). However, in the recently reported CILON-T (Efficacy of Cilostazol on Ischemic Complications After DES Implantation) study, adjunctive cilostazol did not result in a reduction in cardiovascular events at 6 months despite improved platelet inhibition (47a). In addition, drug interactions and gastrointestinal intolerance with cilostazol may be problematic. Other isolated studies show enhanced platelet inhibition or a reduction in cardiovascular events with the addition of omega-3 fatty acids (48) or specific glycoprotein IIb/IIIa inhibitors (abciximab and tirofiban) administered acutely with aspirin and clopidogrel (49,50). However, none of these studies provide substantial proof of efficacy in large populations at risk.

The other approach has been to substitute a newer, more potent platelet inhibitor drug for clopidogrel. Prasugrel, recently approved for clinical use, still requires single-step hepatic conversion to an active metabolite before binding to the platelet P2Y₁₂ receptor. It thus far appears to have very few poor responders in patients with stable coronary artery disease (51) and in patients with ACS (52). Standard dosing of prasugrel (60 mg loading, 10 mg daily) is associated with more potent platelet inhibition than clopidogrel even at high doses (600 mg loading, 150 mg daily) (51,53–55). Moreover, when administered chronically, a 10-mg daily dose of prasugrel provides better inhibition of platelet function than 75 mg or 150 mg of clopidogrel daily. Enhanced platelet inhibition with prasugrel was documented in a small substudy of TRITON-TIMI 38 (52); significantly reduced rates of ischemic events compared with those seen with clopidogrel, including stent thrombosis, were reported in TRITON-TIMI 38 (56). There was, however, an increased rate of major bleeding, including life-threatening bleeding. The 3 groups at highest risk for bleeding in TRITON-TIMI 38 included those greater than 75 years of age, with body weight less than 60 kg, and with a history of stroke or transient ischemic attack. Prasugrel *should*

not be used in patients with qualifying ischemic stroke. In an attempt to balance the excess risk of bleeding associated with prasugrel with its benefit in reducing stent thrombosis (particularly early after stent placement), some clinicians have used an empiric strategy of prasugrel for 1 month then followed by a switch to a standard-dose clopidogrel.

Ticagrelor, although not yet available for clinical use, is an oral, reversible P2Y₁₂ receptor antagonist that blocks ADP-induced platelet aggregation and does not require metabolic activation (24). Compared with clopidogrel in a large trial of patients with ACS, ticagrelor significantly reduced the rate of the primary composite end point of death from vascular causes, MI, or stroke (25). Ticagrelor reduced the individual components of death from vascular causes and MI, but not the rate of stroke. While there was no increase in the rate of overall major bleeding, there was an increase in the rate of nonprocedure-related bleeding. Specifically in patients with a planned invasive strategy, ticagrelor had significant and clinically relevant reductions in cardiovascular and total deaths, MI, and stent thrombosis, without an increase in risk of major bleeding (57). This drug has also been found to be effective in improving platelet inhibition in patients who are nonresponders to clopidogrel (58).

5. Review of Ongoing Trials

Testing for genetic polymorphisms received considerable emphasis in the boxed warning. While CYP2C19 genetic polymorphisms have been shown in several studies to reduce clopidogrel metabolism and its PD effect and clinical effectiveness, there are no prospective studies demonstrating a clinical benefit to personalizing antiplatelet therapy based on genotype analysis. The study upon which the FDA issued the boxed warning and based its statement “to consider alternative treatment strategies” is a small unpublished crossover trial that evaluated PK and antiplatelet responses to clopidogrel in 40 healthy subjects. How these data should translate into clinical practice remains the focus of ongoing studies. Several studies of different populations, sizes, degree of methodological rigor, and follow-up are currently underway or being planned to evaluate the role of pharmacogenetic (CYP2C19) profiling of patients in their PK (active metabolite exposure) and PD (platelet function assays) responses to clopidogrel (Table 4). Two of these ongoing studies are exploring the influence of CYP2C19 in the drug interaction between clopidogrel and proton pump inhibitors, 1 with coadministration of statins (the SPICE [Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects] trial) and 1 without (the Influence of CYP2C19 Genetic Variants on Clopidogrel in Healthy Subjects study [NCT00413608]). Three trials are evaluating the role of triple antiplatelet therapy with cilostazol plus aspirin and standard dose clopidogrel versus aspirin plus high-dose clopidogrel in CYP2C19-genotyped patients with stable and ACS

(ACCEL-2C19 [Adjunctive Cilostazol Versus High Maintenance-dose Clopidogrel According to Cytochrome 2C19 Polymorphism] [NCT01012193], ACCELAMI2C19 [Adjunctive Cilostazol Versus High Maintenance-dose Clopidogrel in Acute Myocardial Infarction (AMI) Patients According to CYP2C19 Polymorphism] [NCT00915733], and ACCEL2C19 [Comparison of Platelet Inhibition With Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel According to Hepatic Cytochrome 2C19 Allele (CYP2C19) Polymorphism] [NCT00891670] trials). However, use of a surrogate end point (ex vivo platelet function assays) in these trials may limit the clinical significance of these data, as the causal relationship between laboratory measures of platelet function, and clinically relevant cardiovascular end points remains unproven. In addition, it is unknown whether platelet function tests are complementary to genotyping. Only 1 large observational, open-label study is examining genotype-guided comparison of clopidogrel 75 mg daily in extensive metabolizers (CYP2C19*1/*1) and prasugrel 5 mg or 10 mg daily (without complementary point-of-care testing of platelet function) on cardiovascular outcomes in patients with ACS (GeCCO [Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study] [NCT00995514]). Finally, a prospective randomized study—the PAPI-2 (Pharmacogenomics of Antiplatelet Intervention-2) trial—examining the role of CYP2C19*2 variant in influencing the PK, PD, and clinical response to clopidogrel is planned to be launched in the near future (A. Shuldiner, personal communication, April 2010). Whether the promise of pharmacogenetic testing in tailoring antiplatelet therapy to the individual patient will be fulfilled awaits the completion of these studies.

Platelet function testing used to tailor antiplatelet therapy has also received considerable interest. Although this field suffers from a surfeit of specific assays, definitions, and protocols, it has the advantage that point-of-care testing is currently available. There are currently 4 ongoing trials testing the hypothesis that tailoring antiplatelet therapy based on platelet responsiveness assessed in an ex vivo P2Y₁₂ assay will improve cardiovascular outcomes. The details of these trials are summarized in Table 5. Patients with high residual platelet activity are randomly allocated to standard-dose versus high-dose clopidogrel in 2 trials (GRAVITAS [Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety] and DANTE [Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition]), and to standard-dose clopidogrel versus prasugrel in 1 trial (TRIGGER-PCI [Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel]), while the ARCTIC Double Randomization of a (Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy) trial is evaluating dose adjustment of dual antiplatelet therapy with aspirin and clopidogrel on the basis of biological monitoring compared with the

Table 4. Ongoing Trials Evaluating Antiplatelet Therapy Tailored by Genotyping and/or Phenotype Assessment

Study	Design	No. of Patients	Population	Selection Criterion	Outcome	Follow-Up
Trials Evaluating Pharmacodynamic and/or Pharmacokinetic Outcomes						
GIFT (NCT00992420) PI: M.J. Price	Observational, prospective cohort study (GRAVITAS substudy) (PD study)	Up to 2000	Stable CAD or NSTEMI ACS undergoing DES	Patients with high residual platelet activity (HRPA) 12- to 24-h post-DES randomized to: 1) standard 75 mg clopidogrel, or 2) high-dose clopidogrel (additional 600 mg followed by 150 mg daily)	Association of CYP2C19 genotype with RPA (VerifyNow) on standard dose of clopidogrel or incremental change RPA on high-dose clopidogrel	6 mo
Clopidogrel Pharmacogenomics Project (NCT01097343) PI: J. Dharmavaram PI: J.S. Rossi	Randomized, open-label, crossover, phase 0 (PD/PK study)	200	Stable CAD	Screen for CYP2C19*2 LOF allele; randomize eligible patients to clopidogrel 75 mg or 150 mg daily × 30 d and then crossover	Change in RPA (VerifyNow, optical aggregometry); measurement of active metabolites	90 d
CLOVIS-2 (NCT00822666) PI: J.-P. Collet PI: G. Montalescot	Randomized, open-label, phase III, crossover (PD/PK study)	120	Post-MI, <45 y and enrolled in AFIJ registry	Comparison of 2 loading strategies of clopidogrel (300 mg vs. 900 mg) in 2 genetic profiles: wild-type 2C19*1 and carriers of 2C19*2 (homozygous or heterozygous)	Inhibition of RPA (IRPA) by optical aggregometry; measurement of active metabolites	6 h postclopidogrel loading dose
Role of CYP2C19 Polymorphism in the Drug Interaction Between Clopidogrel and Omeprazole (NCT01094275) PI: S. Nadipalli PI: T. Delao	Observational, case-crossover, phase IV (PD/PK study)	75	Healthy volunteers	Subjects with CYP2C19*2/*3 LOF allele, and age- and gender-matched wild-type control randomized to clopidogrel + omeprazole vs. clopidogrel × 1 wk, and crossover	Platelet inhibitory response to clopidogrel; measurement of active metabolites	3 wk
ELEVATE-TIMI 56 PI: J.L. Mega (58a)	Randomized treatment sequence (PD study)	275	Stable CAD	Patients on clopidogrel 75 mg and genotyped for CYP2C19 alleles will be treated with biweekly dose of clopidogrel "(75 mg to 300 mg daily, depending on genotype)."	Change in RPA (VerifyNow, VASP)	8 wk
PREDICT Pilot Study (NCT00747656) PI: M.J. Price	Observational prospective cohort (PD study)	42	Stable CAD on clopidogrel therapy	Patients with HRPA on clopidogrel 75 mg and genotyped for CYP2C19 alleles treated with double-dose clopidogrel (150 mg)	Change in RPA (VerifyNow)	7 d
ACCEL-2C19 (NCT01012193) PI: Y.-H. Jeong	Randomized, active-control, single-blind (PD study)	134	Stable CAD, elective PCI	Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 200 mg vs. cilostazol 100 mg bid + 75 mg clopidogrel + ASA 200 mg (triple therapy)	Inhibition of maximum platelet aggregation (optical aggregometry; VerifyNow)	30 d
ACCELAMI2C19 (NCT00915733) PI: I.-S. Kim	Randomized, active-control, open-label (PD study)	80	Acute MI, post-PCI	Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 100 mg vs. cilostazol 100 mg bid + 75 mg clopidogrel + ASA 100 mg (triple therapy)	Inhibition of maximum platelet aggregation (optical aggregometry; VerifyNow)	30 d

Table 4. Continued

Study	Design	No. of Patients	Population	Selection Criterion	Outcome	Follow-Up
ACCEL-2C19 (NCT00891670) PI: Y.-H. Jeong	Randomized, active-control, open-label (PD study)	80	Stable CAD, Elective PCI	Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 100 mg vs. cilostazol 100 mg bid + 75 mg clopidogrel + ASA 100 mg (triple therapy)	Maximum platelet aggregation (optical aggregometry; VerifyNow)	30 d
SPICE (NCT00930670) PI: U. Dery PI: G. Rossignol	Randomized, active-control, open-label (PD study)	320	Stable CAD, elective PCI with BMS	Subjects genotyped for CYP2C19 alleles and treated with clopidogrel randomized to statin + PPI or statin + H2RA	Change in RPA (optical aggregometry; VASP) Death, MI, stroke, or ischemia-driven TVR (secondary end point)	30 and 60 d
Influence of CYP2C19 Genetic Variants on Clopidogrel in Healthy Subjects (NCT00413608) PI: J.S. Hulot	Observational, active-control, open-label (PD/PK study)	30	Healthy volunteers	Patients genotyped for CYP2C19 variants with HRPAs on clopidogrel 75 mg ("bad responders") will be given 150 mg clopidogrel and compared with results of 75 mg clopidogrel in "good responders"	Change in RPA (optical aggregometry); measurement of active metabolites	7 d
Trials Evaluating Clinical Outcomes						
GeCCO (NCT00995514) PI: E.J. Stanek	Observational, prospective cohort, open-label, active control, noninferiority study (outcome study)	14 600	Recent NSTEMI or STEMI ACS with or without primary or delayed PCI	Genotype-guided comparison of clopidogrel (75mg daily) in extensive metabolizers (CYP2C19*1/*1) and prasugrel (5 mg or 10 mg daily)	CV death, nonfatal MI, or nonfatal stroke	6 mo

ACCEL-2C19, Adjunctive Cilostazol Versus High Maintenance-dose Clopidogrel According to Cytochrome 2C19 Polymorphism; ACCELAMI2C19, Adjunctive Cilostazol Versus High Maintenance-dose Clopidogrel in Acute Myocardial Infarction (AMI) Patients According to CYP2C19 Polymorphism; ACS, acute coronary syndromes; AFJL, Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention; ASA, acetylsalicylic acid; BMS, bare-metal stent; CAD, coronary artery disease; CLOVIS-2, Clopidogrel and Response Variability Investigation Study 2; CV, cardiovascular; CYP, cytochrome P450; DES, drug-eluting stent; GeCCO, Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study; GIFT, Genotype Information and Functional Testing Study; GRAVITAS, Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety; HRPAs, high-residual platelet activity; LOF, loss-of-function; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PD, pharmacodynamic; PI, primary investigator; PK, pharmacokinetic; PPI, proton pump inhibitor; PREDICT, Prehospital Evaluation and Economic Analysis of Different Coronary Syndrome Treatment Strategies; RPA, residual platelet activity; SPICE, Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects; STEMI, ST-segment elevation myocardial infarction; TVR, target-vessel revascularization; and VASP, vasodilator-stimulated phosphoprotein phosphorylation.

conventional, unmonitored strategy. The primary outcome in these trials is the time to first occurrence of cardiovascular complications including cardiovascular death, nonfatal MI, nonfatal stroke, stent thrombosis, or target vessel revascularization at 6 or 12 months. The routine clinical use of platelet function testing to screen clopidogrel-treated patients undergoing PCI in order to maximize efficacy while maintaining safety may be supported only after these clinical trials are completed.

Pharmacogenetic and/or PD profiling could potentially offer a tool to identify a priori patients in whom an alternative antiplatelet approach to standard-dose clopidogrel would decrease ischemic events. Options include acute administration of glycoprotein IIb/IIIa inhibitors or longer-term use of higher-dose clopidogrel, cilostazol, prasugrel, ticagrelor, or new agents such as elinogrel (26). Although the effectiveness of ticagrelor in improving cardiovascular outcomes was demonstrated in the PLATO (Platelet Inhibition And Patient Outcomes) trial, this drug is not approved by the FDA. Another promising drug, elinogrel, has only been evaluated in a phase 2 study. At the present time, prasugrel is the only new agent approved to

support PCI in patients with ACS. It must be kept in mind, however, that the use of prasugrel in high-risk genotype patients after elective PCI has not been studied. With regard to clopidogrel dose adjustment in patients with high platelet reactivity on standard clopidogrel treatment, the results are mixed. Two studies yielded improved outcomes of major adverse cardiovascular events or stent thrombosis with this approach (59,60). In contrast, 1 case series of patients with prior MI who subsequently developed stent thrombosis questioned the strategy of increasing clopidogrel dose in carriers of CYP2C19*2 as time-consuming and largely ineffective at providing adequate platelet inhibition (although prasugrel was able to suppress platelet aggregation successfully) (61). Even if the relationship between genetic polymorphisms and ischemic risk is well established, the effect on bleeding remains to be elucidated. It is possible that the relationship between genetic polymorphisms and antiplatelet effect is somewhat different for thrombosis and bleeding. Higher levels of active-metabolite generation may not necessarily translate into an optimal benefit-risk balance. As documented in the preceding text, it is difficult to interpret these current studies (41a) because of lack of

Table 5. Trials Evaluating Antiplatelet Therapy Tailored by Pharmacodynamic Assessment

Study	Design	No. of Patients	Population	Selection Criterion	Outcome	Follow-Up
GRAVITAS (NCT00645918) PI: M.J. Price	Randomized, placebo-control, multicenter	2800	Stable CAD or NSTEMI ACS undergoing PCI (DES)	Patients with HRP A 12- to 24-h post-DES randomized to: 1) standard 75 mg clopidogrel; or 2) high-dose clopidogrel (additional 600 mg followed by 150 mg daily)	CV death, nonfatal MI, or definite/probable stent thrombosis	6 mo
ARCTIC (NCT00827411) PI: G. Montalescot PI: J.-P. Collet	Randomized, active-controlled, open label, phase IV, multicenter	2500	Stable CAD, elective PCI	Patients post-DES randomized to: 1) standard dose clopidogrel plus aspirin (conventional arm); or 2) adjusted-dose clopidogrel plus aspirin based on HRP A (monitoring arm)	Death, nonfatal MI, stroke, urgent TVR, or stent thrombosis	1 y
TRIGGER-PCI (NCT00910299) Sponsor: Eli Lilly	Randomized, active-control, double blind, phase II, multicenter	2150	Stable CAD, elective PCI	Patients 24 h post-DES and 2 to 7 h postclopidogrel and HRP A randomized to: 1) prasugrel 60 mg load/10 mg daily; or 2) clopidogrel 75 mg daily	CV death or nonfatal MI	6 mo
DANTE (NCT00774475) PI: G.F. Gensini PI: R. Marcucci	Randomized, active-control, open-label, phase III, multicenter	442	NSTEMI ACS undergoing PCI	Patients with HRP A randomized to: 1) clopidogrel 75 mg maintenance (standard dose); or 2) clopidogrel 150 mg maintenance (high dose)	CV death, nonfatal MI, or TVR	6 and 12 mo

ACS indicates acute coronary syndromes; ARCTIC, Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and a Interruption Versus Continuation of Double Antiplatelet Therapy; CAD, coronary artery disease; CV, cardiovascular; DANTE, Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition; DES, drug-eluting stent; GRAVITAS, Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety; HRP A, high residual platelet activity; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PI, primary investigator; TRIGGER-PCI, Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel; and TVR, target-vessel revascularization.

concordance between the main trial findings and those obtained in patient subsets. A fundamental issue remains that it is not known whether treatment decisions predicated on the results of either genotyping or phenotyping information can impact optimization of either clinical efficacy and/or safety. Genotyping of patients enrolled in the studies listed in Table 4, and the ONSET/OFFSET (Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease) study (62), which demonstrated superior antiplatelet effects of ticagrelor compared with higher LD of clopidogrel, or the RESPOND (Response to Ticagrelor in Clopidogrel Non-responders and Responders and Effect of Switching Therapies) study (58), which showed similar platelet inhibitory effects of ticagrelor in clopidogrel responders and nonresponders alike, will likely yield valuable insights in this regard.

In summary, larger and longer-term prospective studies that include cardiovascular event outcomes are necessary to optimize predictive algorithms that may include genetic and/or platelet function testing, and their use to individualize P2Y₁₂ inhibitor therapy. However, it is important to recall that CYP2C19 polymorphism accounts for only approximately 12% of variability in clopidogrel platelet response (15) and that the positive predictive value of CYP2C19 loss-of-function genetic polymorphisms for clinical events is estimated to be between 12% (16) and 20% (2) in patients with ACS undergoing PCI. Even if slightly

better than the positive predictive values observed with the point-of-care P2Y₁₂ assay in a similar population (12%) (63–65), the predictive accuracy of these genetic polymorphisms is still low. Thus, improvement in prediction of future cardiovascular events in patients receiving antiplatelet therapy will likely benefit from development of a global risk assessment score based on traditional demographic, clinical, and procedural risk factors, genetics, and biological information rather than any single test result.

6. Conclusions

6.1. Issues for Consideration

The information on the pharmacogenomics that has formed the basis for the recent boxed warning on clopidogrel is of great importance in understanding the issues related to variability in clinical outcomes of patients with both acute and chronic coronary artery disease; in addition, this information may have applicability for patients with stroke and peripheral arterial disease, although there are no robust data in these populations. There are several critical issues that require careful consideration. As noted in the preceding text, CYP2C19 polymorphism accounts for only approximately 12% of variability in clopidogrel platelet response, and the positive predictive value of CYP2C19 loss-of-function genetic polymorphisms is estimated to be between 12% and 20% in patients with ACS undergoing PCI. In addition, there is no prospective randomized evidence to

support genotyping, a direct effect of genetic polymorphisms cannot be excluded, and there is a larger body of evidence to support platelet function testing as a risk stratifier for adverse events. These issues must be considered in the context that there are multiple unknown factors including, most importantly, the fact that the specific role of an individual genetic polymorphism in influencing outcome for the individual patient remains unknown.

1. Guideline adherence remains the cornerstone of care. Clinical judgment is required to assess individual risk and variability in response to clopidogrel. While imperfect, such judgment is essential. In addition to consideration of evidence-based guidelines, it is crucial to emphasize patient compliance with the prescribed antiplatelet regimen. Given the large interindividual variability in response to clopidogrel resulting from both clinical and genetic factors, the issues of genotyping and measurement of platelet inhibition have been raised, particularly in patients felt to be at highest risk for adverse events and in patients who have already had an adverse event despite compliance with regimens of aspirin and clopidogrel (coronary artery disease patients) or clopidogrel monotherapy (cerebrovascular ischemia patients).
2. Information on patients at risk for poor outcomes with ACCF/AHA and AHA Stroke Council Guideline-recommended therapy continues to accumulate. Some patients are identified because they have experienced an adverse outcome, such as stent thrombosis, while other patients may be considered to be at increased risk of a subsequent adverse outcome, including stent thrombosis, MI, ischemic stroke, and vascular death. This latter consideration may be based on clinical characteristics such as diabetes mellitus, chronic renal failure, or angiographic variables (e.g., diffuse 3-vessel or left-main coronary artery disease or multifocal cervicocerebral atherosclerotic disease). In the future, profiling high-risk populations may include consideration of the frequency of the genetic penetration of genetic polymorphisms in that specific population.
3. Genetic variability in CYP enzymes may affect platelet function and has been associated with adverse patient outcomes in registry experiences and clinical trials. Although CYP2C19*2 is the most common genetic variant reproducibly associated with impaired responses to clopidogrel, the specific role of the individual genetic polymorphisms in impacting outcome remains to be determined (e.g., the importance of CYP2C19*2 versus *3 or *4 for a specific patient). In addition, there are other genetic polymorphisms such as ABCB1 that may also contribute to variation in the response of individual patients to clopidogrel.

Information about the predictive value of pharmacogenomic testing is very limited, but is the focus of multiple ongoing studies. The design of such studies in terms of specific tests and patient populations (e.g., acute care

versus chronic care settings) will have major implications for the role of testing. A related issue is whether the risk from a given individual's genomic profile changes over time, depending on the specific clinical scenario (e.g., ACS versus stable angina pectoris, PCI versus medical therapy, small vessel versus large artery, atherosclerotic ischemic stroke, or carotid stenting versus medical therapy), is relevant. This question has yet to be resolved.

4. The answer to the specific question of the role of genotyping in everyday practice remains unknown at the present time. Although the boxed warning does not mandate testing, proponents would argue that there are common genetic polymorphisms that have been shown to affect the platelet response to clopidogrel as well as its clinical effectiveness in both randomized clinical trials and registry experiences. In addition, there are commercially available genetic tests that can determine CYP2C19 genotype variants although the turn-around time varies as does the cost, which is not routinely reimbursable at this time. Advocates argue that given the magnitude of the potential clinical consequences of suboptimal platelet inhibition based on genetic variation, assessment of genotypes would be justifiable. In contrast, opponents believe that there is no definitive proof at the current time that intervening on the basis of genotype improves outcome, and that there are other factors that may be more important. In addition, they would raise the question of whether genotyping should be confined to loss-of-function CYP2C19*2 or *3 (poor metabolizers), or be extended to other variants including the gain-of-function CYP2C19*17 variant (hyper-rapid or ultrarapid metabolizers). As part of this argument, opponents note that the predictive performance of CYP2C19 variant is low, ranging from 12% to 20%, and raise the question of what to do when variant genotype information is identified in patients with no clinical events. Finally, they would note that there are no point-of-care genotyping tests, which severely limits the usefulness of these data in the acute care setting. Currently, there are studies underway or in the planning stages that will address these issues to varying degrees. Despite the gaps in current knowledge, both clinicians and patients need to be aware of genetic polymorphisms that may modulate clopidogrel responsiveness and cause MACE. It is important to emphasize again that in the most recent labeling for clopidogrel, the FDA only informs physicians and patients that genetic testing is available; it neither mandates, requires, nor recommends genetic testing, thereby allowing for flexibility in clinical decisions.
5. Given the concerns about the mortality and morbidity that may be attributable to an inadequate response to antiplatelet therapy, there are a number of alternative approaches to standard guideline-based care with clopidogrel. New agents and new strategies have been used clinically and tested in a wide variety of situations. New agents such as prasugrel and ticagrelor, which are not

affected by CYP2C19 genetic variants, have been found to be more effective than standard-dose clopidogrel. This relates to the PK characteristics of these newer agents. In very high-risk clinical circumstances (e.g., prior stent thrombosis) such agents may be considered alternatives to standard ACCF/AHA and AHA Stroke Council Guideline therapy. This is particularly important in any patient suspected of treatment failure to standard-dose clopidogrel. Other treatment strategies are also being tested, including increased clopidogrel dosing or the addition of a third drug such as cilostazol to aspirin and clopidogrel. In the setting of stroke or transient ischemic neurologic symptoms, the combination of aspirin and extended release dipyridamole and aspirin monotherapy are alternatives recommended by the AHA Stroke Council guidelines for secondary prevention of stroke (66).

6.2. Recommendations for Practice

Consideration of these critical issues leads to the following recommendations for clinicians:

1. Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient. While imperfect, such careful judgment is essential.
2. Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
3. The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined (e.g., the importance of CYP2C19*2 versus *3 or *4 for a specific patient), and the frequency of genetic variability differs among ethnic groups. This has particular relevance related to the frequency of homozygotes, which occurs in approximately 2% of the population, versus heterozygotes, which occurs in approximately 30% of the population, both of whom may have increased risk.
4. Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, are both important additional considerations.
5. The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In addition, the clinical course of the majority of patients treated with clopidogrel without either genetic testing or functional testing is excellent. Clinical judgment is required to assess clinical risk and variability in patients considered to be at increased risk. Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism ("poor metabolizers") may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes. This might include, among others, patients undergoing elective high-risk PCI procedures (e.g., treatment of extensive and/or very complex disease). If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel for coronary patients, should be considered. With these other therapies, the balance of potential ischemic benefit with the known increased risk of bleeding should be considered either with alternative clopidogrel dosing or newer agents such as prasugrel. In particular, prasugrel is contraindicated in patients with stroke and TIA. For patients with ischemic stroke or TIA, alternatives to clopidogrel include aspirin or the combination of aspirin and extended-release dipyridamole, which are both recommended in the AHA Stroke Council guidelines for secondary prevention of stroke (66).
6. There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance. Clopidogrel may be switched to prasugrel, which has been found to result in decreased rates of stent thrombosis, and as noted previously, prasugrel is contraindicated for patients with stroke or TIA in patients treated with PCI for ACS, although it has not been tested in randomized trials of patients with stent thrombosis. Alternatively, the physician may make the empiric recommendation to increase the dose of clopidogrel (e.g., to 150 mg per day). There are very little data to judge the trade-off of high-dose clopidogrel versus alternative therapies on the risk-benefit ratio of safety (avoidance of bleeding) versus efficacy (prevention of a second recurrence). Functional testing may be performed and may be considered in an attempt to determine if patients are clopidogrel nonresponders. There are several different platelet function tests that can be used to assess the platelet response to clopidogrel, and the clinician should use the method with the greatest reliability and reproducibility at his or her specific facility. For stroke patients, aspirin or the combination of aspirin and extended-release dipyridamole are alternatives, as noted in the preceding text.
7. Higher LDs (600 mg versus 300 mg), double-dose loading (600 mg twice over 2 hours), and higher MDs of clopidogrel (150 mg daily) have been found to improve platelet inhibition and might be considered alternatives for high-risk patients who respond poorly to standard loading and MDs of clopidogrel, although there is uncertainty of the long-term safety and efficacy of this approach. New antiplatelet drugs such as prasugrel and, if FDA approved, ticagrelor are additional alternatives in

coronary patients with a known poor response to clopidogrel or in patients at high risk for a poor outcome from potential clopidogrel nonresponsiveness. Their use may obviate the need for additional testing. Other possibilities are adding cilostazol to standard doses of aspirin and clopidogrel (67) or using cilostazol alone (68–70). However, because platelet inhibition still may not be optimal with these regimens, follow-up platelet function testing might be considered to ensure adequate platelet inhibition. The risk-benefit ratio, in terms of safety and efficacy of each of these alternative strategies, remains to be determined by adequately powered clinical trials.

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Key Words: ACCF Expert Consensus Document ■ clopidogrel ■ FDA boxed warning ■ CYP2C19.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHERS—ACCF/AHA CLOPIDOGREL CLINICAL ALERT: APPROACHES TO THE FDA “BOXED WARNING”

Name	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David R. Holmes, Jr. (Chair)	Consultant—Cardiovascular Diseases, Mayo Clinic	None	None	None	None	None	None
Gregory J. Dehmer	Scott & White Healthcare, Professor of Medicine—Texas A&M College of Medicine	None	None	None	None	None	None
Sanjay Kaul	Director, Cardiology Fellowship Training Program—Cedars-Sinai Heart Institute Professor of Medicine—Cedars-Sinai Medical Center, and David Geffen School of Medicine at UCLA	None	None	• Johnson & Johnson	None	None	None
Dana Leifer	Associate Attending Neurologist—New York Presbyterian Hospital Associate Professor of Neurology—Weill Cornell Medical College	None	None	None	• Medtronic, CRYSTAL AF*	None	None
Patrick T. O’Gara	Associate Professor of Medicine—Brigham and Women’s Hospital Cardiovascular Medicine	None	None	None	None	None	None
C. Michael Stein	Dan May Professor of Medicine and Pharmacology—Vanderbilt Medical School Division of Clinical Pharmacology	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. *No financial relationship.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—ACCF/AHA CLOPIDOGREL CLINICAL ALERT: APPROACHES TO THE FDA “BOXED WARNING”

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Deepak L. Bhatt	Official Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	• Duke Clinical Research Institute	None	None	• AstraZeneca* • Bristol-Myers Squibb* • Cogentus • Eisai* • PLx Pharma • Sanofi-Aventis* • Takeda • The Medicines Company*		• Testimony for defendant on antithrombotic therapy in cardiovascular medicine, 2005
Paul Gurbel	Official Reviewer—American Heart Association	• Accumetrics* • AstraZeneca* • Bayer* • Medtronic* • Placor • Pozen • Schering-Plough*	None	None	• Medtronic* • Portola* • Pozen* • Sanofi-Aventis*	None	None
Julie Johnson	Official Reviewer—American Heart Association	• Medco	None	None	• National Institutes of Health*	None	None
Richard J. Kovacs	Official Reviewer—ACCF Board of Trustees	• Abbott Laboratories • Biomedical Systems • Cook-Med Institute* • ECG Scanning Services* • Eli Lilly* • Endocyte • Essentialis • XenoPort	None	None	None	None	None
Michael E. Ring	Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None
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CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; and UA, unstable angina.

APPENDIX 3. FDA DRUG SAFETY COMMUNICATION: REDUCED EFFECTIVENESS OF CLOPIDOGREL IN PATIENTS WHO ARE POOR METABOLIZERS OF THE DRUG

Safety Announcement

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a *Boxed Warning* to [sanofi-aventis, Bridgewater, NJ] for Plavix, the antiblood clotting medication. The *Boxed Warning* is about patients who do not effectively metabolize the drug (i.e., “poor metabolizers”) and therefore may not receive the full benefits of the drug.

The *Boxed Warning* in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other antiplatelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Plavix is given to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease. Plavix works by decreasing the activity of blood cells called platelets, making platelets less likely to form blood clots.

For Plavix to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug do not effectively convert Plavix to its active form. In these patients, Plavix has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death. It is estimated that 2% to 14% of the population are poor metabolizers; the rate varies based on racial background.

Healthcare professionals should be aware that a subgroup of patients are poor metabolizers and do not metabolize Plavix effectively; this can result in reduced effectiveness of Plavix. Healthcare professionals should consider use of other antiplatelet medications or alternative dosing strategies for Plavix in these patients.

Patients should not stop taking Plavix unless told to do so by their healthcare professional. They should talk with their healthcare professional if they have any concerns about Plavix, or to find out if they should be tested for being a poor metabolizer.

In May 2009, the FDA added information about poor metabolizers of Plavix to the drug label. However, based on additional data reviewed by the agency (see Data Summary in the following text), the *Boxed Warning* is now being added to highlight the reduced effectiveness of Plavix in these patients and to recommend that healthcare professionals consider use of other antiplatelet medications or

alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Additional Information for Patients

Patients currently taking Plavix should:

- Be aware that some patients do not convert Plavix to its active form as well as other patients. These patients may not get the same benefit from Plavix and are known as poor metabolizers.
- Do not stop taking Plavix unless told to do so by their healthcare professional.
- Talk with their healthcare professional if they have any concerns about Plavix.
- Talk with their healthcare professional to see if testing to determine their metabolizer status is appropriate.

Additional Information for Healthcare Professionals

The FDA recommends that healthcare professionals should:

- Be aware that some patients may be poor metabolizers of Plavix. They do not effectively convert Plavix to its active form because of low CYP 2C19 activity. The effectiveness of Plavix as a preventive therapy is reduced in these patients.
- Be aware that tests are available to determine patients CYP2C19 status.
- Consider use of other antiplatelet medications or alternative dosing strategies for Plavix in patients who have been identified as poor metabolizers.
- Be aware that although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response, an appropriate dose regimen for poor metabolizers has not been established in a clinical outcome trial.
- Review the newly approved Plavix drug label for complete information on the use of Plavix

Data Summary

The liver enzyme CYP2C19 is primarily responsible for the formation of the active metabolite of Plavix. Pharmacokinetic and antiplatelet tests of the active metabolite of Plavix show that the drug levels and antiplatelet effects differ depending on the genotype of the CYP2C19 enzyme. The following represent the different alleles of CYP2C19 that make up a patient's genotype:

- The CYP2C19*1 allele has fully functional metabolism of Plavix.
- The CYP2C19*2 and *3 alleles have no functional metabolism of Plavix. These 2 alleles account for most

of the reduced function alleles in patients of [European] (85%) and Asian (99%) descent classified as poor metabolizers.

- The CYP2C19*4, *5, *6, *7, and *8 and other alleles may be associated with absent or reduced metabolism of Plavix, but are less frequent than the CYP2C19*2 and *3 alleles.
- A patient with 2 loss-of-function alleles (as defined in the preceding text) will have poor metabolizer status.

The pharmacokinetic and antiplatelet responses to Plavix were evaluated in a crossover trial in 40 healthy subjects. Ten subjects in each of the 4 CYP2C19 metabolizer groups (ultrarapid, extensive, intermediate, and poor) were randomized to 2 treatment regimens: a 300 mg loading dose followed by 75 mg per day, or a 600 mg loading dose followed by 150 mg per day, each for a total of 5 days. After a washout period, subjects were crossed over to the alternate treatment. Decreased active metabolite exposure and increased platelet aggregation were observed in the poor metabolizers compared with that seen in the other groups. When poor metabolizers received the 600 mg loading dose followed by 150 mg daily, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen. Healthcare professionals should note that an appropriate dose regimen for patients who are poor metabolizers has not been established in clinical outcome trials (1).

More Information

Related Information

- FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. Release date: 3/12/2010
- Public Health Advisory: Updated Safety Information about a drug interaction between clopidogrel bisulfate (marketed as Plavix) and omeprazole (marketed as Prilosec and Prilosec OTC). Release date: 11/17/2009
- Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). Release date: 11/17/2009
- Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC). Release date: 11/17/2009
- Early Communication about an Ongoing Safety Review of clopidogrel bisulfate (marketed as Plavix). Release date: 1/26/2009
- Clopidogrel (marketed as Plavix) and Omeprazole (marketed as Prilosec)—Drug Interaction. Release date: 11/17/2009

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 Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

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