REVIEW

Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI

A Meta-analysis

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Content Clopidogrel, one of the most commonly prescribed medications, is a prodrug requiring CYP450 biotransformation. Data suggest its pharmacologic effect varies based on *CYP2C19* genotype, but there is uncertainty regarding the clinical risk imparted by specific genotypes.

Objective To define the risk of major adverse cardiovascular outcomes among carriers of 1 (≈26% prevalence in whites) and carriers of 2 (≈2% prevalence in whites) reduced-function *CYP2C19* genetic variants in patients treated with clopidogrel.

Data Sources and Study Selection A literature search was conducted (January 2000-August 2010) in MEDLINE, Cochrane Database of Systematic Reviews, and EMBASE. Genetic studies were included in which clopidogrel was initiated in predominantly invasively managed patients in a manner consistent with the current guideline recommendations and in which clinical outcomes were ascertained.

Data Extraction Investigators from 9 studies evaluating *CYP2C19* genotype and clinical outcomes in patients treated with clopidogrel contributed the relevant hazard ratios (HRs) and 95% confidence intervals (CIs) for specific cardiovascular outcomes by genotype.

Results Among 9685 patients (91.3% who underwent percutaneous coronary intervention and 54.5% who had an acute coronary syndrome), 863 experienced the composite end point of cardiovascular death, myocardial infarction, or stroke; and 84 patients had stent thrombosis among the 5894 evaluated for such. Overall, 71.5% were noncarriers, 26.3% had 1 reduced-function *CYP2C19* allele, and 2.2% had 2 reduced-function *CYP2C19* alleles. A significantly increased risk of the composite end point was evident in both carriers of 1 (HR, 1.55; 95% CI, 1.11-2.17; $P=.01$) and 2 (HR, 1.76; 95% CI, 1.24-2.50; $P=.002$) reduced-function *CYP2C19* alleles, as compared with noncarriers. Similarly, there was a significantly increased risk of stent thrombosis in both carriers of 1 (HR, 2.67; 95% CI, 1.69-4.22; $P<.0001$) and 2 (HR, 3.97; 95% CI, 1.75-9.02; $P=.001$) *CYP2C19* reduced-function alleles, as compared with noncarriers.

Conclusion Among patients treated with clopidogrel for percutaneous coronary intervention, carriage of even 1 reduced-function *CYP2C19* allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis.

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CLOPIDOGREL BLOCKS THE $P2Y_{12}$ adenosine diphosphate (ADP) receptor on platelets and has been shown to reduce cardiovascular events in patients presenting with an acute coronary syndrome (ACS), particularly in those undergoing percutaneous coronary intervention (PCI).[1,2] However, there is a large degree of interindividual variability in the pharmacodynamic response to clopidogrel.[3] One source of the variability is the metabolism of clopidogrel, which is a prodrug requiring biotransformation to generate its active metabolite. Cytochrome P450 (CYP) isoenzymes, specifically CYP2C19,[4] play a key role in clopidogrel metabolism, and carriers of reduced-function genetic variants in the *CYP2C19* gene have lower active clopidogrel metabolite levels and diminished platelet inhibition.[5]

Based in part on a pharmacokinetic and pharmacodynamic study in 40

For editorial comment see p 1839.

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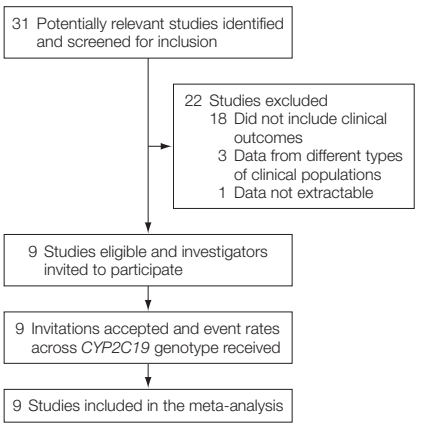
Figure 1. Study Selection Flow Diagram



healthy participants, the US Food and Drug Administration (FDA) announced a boxed warning on clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Aventis) stating that the drug has a diminished effect in individuals based on their *CYP2C19* genotype, specifically in those who harbor 2 reduced-function *CYP2C19* alleles.[6,7] Yet, there is not consensus as to whether the diminished pharmacologic response translates into worse clinical outcomes and whether the proposed increased risk of adverse cardiovascular outcomes requires 2 reduced-function *CYP2C19* alleles (present in approximately 2% of the white population) or can be seen with just 1 (present in approximately 26% of the white population).[8]

Individual clopidogrel pharmacogenetic studies have reported somewhat divergent results, and the confidence intervals (CIs) corresponding to the hazard ratios (HRs) for clinical events across different genotypes are sufficiently wide so as to not be able to address reliably the aforementioned issues. Moreover, to date, a number of studies have not generated data separately for carriers of 1 and for carriers of 2 reduced-function *CYP2C19* alleles. Therefore, to define the risk of major adverse cardiovascular events in carriers of 1 and in carriers of 2 reduced-function *CYP2C19* alleles, the investigators for each participating study agreed to perform a collaborative meta-analysis. In totality, we were able to examine the association of *CYP2C19* genotype and clinical outcomes in 9685 patients who initiated guideline-recommended treatment with clopidogrel, predominantly for PCI.

METHODS

Data Sources and Study Selection Criteria

A computerized literature search was conducted from January 2000 through August 2010 of MEDLINE, Cochrane Database of Systematic Reviews, and EMBASE using the search terms *clopidogrel* and *CYP2C19*. In addition, experts in the field were contacted and abstracts from major cardiology meetings were reviewed. The meta-analysis included studies (cohort studies and clinical trials) in which clopidogrel was initiated in predominantly invasively managed patients in a manner consistent with the current guideline recommendations.[1,2] Studies were excluded if they did not include clinical outcomes measurements.

A total of 31 studies were identified as potentially relevant and were screened for inclusion (FIGURE 1). Of these studies, 22 were subsequently excluded because they only provided pharmacodynamic or pharmacokinetic data (ie, no clinical outcomes data); data could not be extracted from what was presented in the main manuscript; or because they included patients from different clinical populations (eg, in whom treatment with clopidogrel was not guideline indicated or who were predominantly conservatively managed). Of the 9 studies that were eligible and invited, all investigators agreed to provide study-level data and participate in a collaborative meta-analysis.[9-17] Study quality was assessed independently based on elements from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[18] by 2 authors (J.L.M. and M.S.S.) with disagreements resolved by consensus.

Genotype Data, End Points, and Data Compilation

For each study, patients treated with clopidogrel were classified as carriers of zero (ie, noncarriers or wildtype), 1 (ie, heterozygotes), or 2 (eg, homozygotes or compound heterozygotes) *CYP2C19* (National Center for Biotechnology Information [NCBI] genome build 37.1, NG_008384) reduced-function alleles. Of the reduced-function alleles, *CYP2C19*2* is the most frequent variant (accounting for about 95% of the reduced-function allele carrier status).[11] Patients were categorized on the basis of *CYP2C19*2* (rs4244285) alone in 7 studies[9,10,12,14-17]; *CYP2C19*2*, **3* (rs4986893), **4* (rs28399504), and **5* (rs56337013) in 1 study[13]; and *CYP2C19*2*, **3*, **4*, **5*, and **8* (rs41291556) in 1 study (eAppendix, available at http://www.jama.com).[11]

The investigators for each participating study provided the incidence of cardiovascular death, myocardial infarction, and ischemic stroke, as well as the composite of these end points across *CYP2C19* genotypes in 9685 individuals. Investigators provided the HRs and 95% CIs for these end points for carriers of at least 1, only 1, or 2 reduced-function *CYP2C19* alleles compared with noncarriers, with adjusted HRs provided based on the investigators' determination of the need to do so in their main publication. Additionally, 6 of the 9 studies evaluated stent thrombosis, and thus analogous data pertaining to the risk of definite or probable stent thrombosis, as defined by the Academic Research Consortium criteria,[19] were provided for 5894 participants.[10-12,14-16] Outcomes were collected from 0 days to end of follow-up, 0 to 30 days, and 31 days to end of follow-up. See eAppendix for study-specific details. All of the provided data were verified by each of the participating investigators.

Statistical Analyses

We performed a meta-analysis combining HRs for each study using a random-effects model, which considers both within-study and between-study variation (given the differences in study populations' characteristics and clopidogrel dosing and therefore the potential differences in the pharmacoge-

netic association) with weighting based on inverse variance.[20] Results are presented as HRs with 95% CIs. Heterogeneity of risk was diagnosed using the Cochran *Q* statistic and the degree assessed using the I^2 measure (which reflects the percentage of the total variability due to between-study heterogeneity vs within-study variability). If heterogeneity was found, we then performed sensitivity analyses, serially excluding studies to determine the source. Additionally, sensitivity analyses were conducted examining for heterogeneity on the basis of ACS status and clopidogrel dosing. Comprehensive Meta Analysis version 2.2.048 (Biostat Inc, Englewood, New Jersey) was used for the analyses and a *P* value of less than .05 was set as the level of significance with no correction for multiple hypothesis testing given the interrelatedness of the hypotheses.

RESULTS

Overall, 9685 patients from 9 studies contributed to the cardiovascular death, myocardial infarction, or stroke analysis (TABLE 1). The average age of patients was 64.2 years and 7204 patients (74.4%) were men. A total of 8847 (91.3%) patients underwent PCI and 5278 (54.5%) had an ACS. There were 6923 patients (71.5%) with no *CYP2C19* reduced-function alleles (ie, noncarriers or wildtype), 2544 (26.3%) with 1 reduced-function *CYP2C19* allele (ie, heterozygotes), and 218 (2.2%) with 2 reduced-function *CYP2C19* alleles (eg, homozygotes or compound heterozygotes). There were no significant differences in baseline characteristics across genotypes (TABLE 2). Six studies included stent thrombosis as an end point, and thus 5894 patients with stents were

Table 1. Characteristics of Studies Included in the Meta-Analysis

Baseline Characteristics	No. of Trial Participants/Total No. (%)[a]									
	CLARITY-TIMI 28[9]	EXCELSIOR[10]	TRITON-TIMI 38[11]	AFIJI[12]	FAST-MI[13]	RECLOSE[14]	ISAR[15]	CLEAR-PLATELETS[16]	Intermountain[17]	Total[b]
Age, mean (SD), y	59.9 (10.5)	66.4 (9.1)	60.1 (11.1)	40.1 (5.1)	66.2 (13.7)	68.3 (11.0)	66.5 (10.2)	64.2 (11.5)	63.0 (11.5)	64.2
Male sex	178/227 (78.4)	622/797 (78.0)	1029/1459 (70.5)	239/259 (92.3)	1559/2208 (70.6)	576/772 (74.6)	1946/2485 (78.3)	137/228 (60.1)	918/1250 (73.4)	74.4
Diabetes	38/223 (17.0)	150/797 (18.8)	319/1459 (21.9)	27/259 (10.4)	698/2202 (31.7)	171/772 (22.2)	881/2485 (35.5)	86/228 (37.7)	354/1250 (28.3)	28.1
Smoking	99/227 (43.6)	87/797 (10.9)	556/1459 (38.1)	145/259 (56.0)	691/2202 (31.4)	266/772 (34.5)	402/2485 (16.2)	58/228 (25.4)	220/1250 (17.6)	26.1
White race	193/227 (85.0)	797/797 (100.0)	1427/1459 (97.8)	202/259 (78.0)	NA[c]	772/772 (100.0)	NA[d]	140/228 (61.4)	1250/1250 (100.0)	95.8
PCI	132/227 (58.1)	797/797 (100.0)	1459/1459 (100.0)	189/259 (73.0)	1535/2208 (69.5)	772/772 (100.0)	2485/2485 (100.0)	228/228 (100.0)	1250/1250 (100.0)	91.3
ACS	227/227 (100.0)	0/797 (0.0)	1459/1459 (100.0)	259/259 (100.0)	1174/2208 (53.2)	543/772 (70.3)	846/2485 (34.0)	0/228 (0.0)	770/1250 (61.6)	54.5
CYP2C19 Reduced-function alleles, No.										
None	150	554	1064	186	1573	525	1805	160	906	6923
1	73	226	357	64	577	221	633	63	330	2544
2	4	17	38	9	58	26	47	5	14	218
Study information										
Year published	2008	2008	2009	2009	2009	2009	2009	2009	2009	
Clopidogrel loading dose, mg	300	600	300	≥600	300-600	600	600	300-600	300-600	
Follow-up										
Median time (IQR), d	30 (30-30)	180 (180-180)	445 (356-455)	391 (102-1095)	365 (365-365)	180 (180-180)	30 (30-30)	180 (180-365)	365 (365-365)	
Maximum time, d	30	180	457	2920	365	180	30	365	365	
Complete data, %	100.0	99.1	99.3	100.0	99.4	100.0	100.0	100.0	100.0[e]	

Abbreviations: ACS, acute coronary syndrome; AFIJI, Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention; CLARITY-TIMI 28, Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28; CLEAR-PLATELETS, Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets; EXCELSIOR, Effect of Clopidogrel Loading and Risk of PCI; FAST-MI, French Registry of Acute ST-Segment Elevation and Non-ST-Elevation Myocardial Infarction; IQR, interquartile range; ISAR, Intracoronary Stenting and Antithrombotic Regimen; PCI, percutaneous coronary intervention; NA, not applicable; RECLOSE, Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38.

[a] Expansions for trial abbreviations shown in Abbreviations footnote. Intermountain is shown in upper- and lower-case lettering because trial name is not an abbreviation. All studies were deemed of comparable quality because they met key elements of the STROBE checklist.[18]

[b] The total column indicates mean for age, % for male sex, diabetes, smoking, white race, PCI, and ACS categories; and number for *CYP2C19* reduced-function allele categories.

[c] The investigators for FAST-MI note that among participants for whom race was collected, virtually all were white.

[d] The investigators for ISAR note that the patients enrolled in the study were recruited from a single center in Germany with a near exclusively white population.

[e] Complete data were available for mortality; completeness for composite end point was not available.

Table 2. Pooled Baseline Characteristics by *CYP2C19* Genotype Status[a]

Characteristics	No. of Participants (%)[b]			
		Reduced-Function *CYP2C19* Alleles		
	Overall (n = 9685)	None (n = 6923)	1 (n = 2544)	2 (n = 218)
Age, weighted mean, y	64.2	64.1	64.6	63.7
Male sex	7204 (74.4)	5180 (74.8)	1852 (72.8)	172 (78.9)
Diabetes	2724 (28.1)	1926 (27.8)	739 (29.0)	58 (27.1)
Current smoker	2524 (26.1)	1821 (26.3)	648 (25.5)	55 (25.2)
ACS at presentation	5278 (54.5)	3820 (55.2)	1339 (52.6)	119 (54.6)
PCI at presentation	8847 (91.3)	6336 (91.5)	2316 (91.0)	195 (89.4)
White race[c]	4781 (95.8)	3399 (95.9)	1277 (95.7)	105 (92.9)

Abbreviations: ACS, acute coronary syndrome; FAST-MI, French Registry of Acute ST-Segment Elevation and Non-ST-Elevation Myocardial Infarction; ISAR, Intracoronary Stenting and Antithrombotic Regimen; PCI, percutaneous coronary intervention.

[a] There were no significant differences for the categorical variables across *CYP2C19* genotype.

[b] Data are presented as No. of participants (%) unless otherwise indicated.

[c] Data on race (self-reported) were not captured uniformly in ISAR and FAST-MI (see footnotes c and d in Table 1). White race denominators for overall, none, 1, and 2 reduced-function *CYP2C19* alleles are 4992, 3545, 1334, and 113, respectively.

included in the stent thrombosis analyses. In this subset, there were 4220 patients (71.6%) with no *CYP2C19* reduced-function alleles, 1535 (26.0%) with 1 reduced-function *CYP2C19* allele, and 139 (2.4%) with 2 reduced-function *CYP2C19* alleles.

Cardiovascular Death, Myocardial Infarction, or Stroke by *CYP2C19* Genotype

Overall, 863 of the 9685 patients experienced the composite end point of cardiovascular death, myocardial infarction, or ischemic stroke. Carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers had a significantly increased risk of the composite end point (HR, 1.57; 95% CI, 1.13-2.16; $P=.006$; FIGURE 2A). In terms of individual end points, 272 patients died of a cardiovascular cause, 575 had a nonfatal myocardial infarction, and 68 had a nonfatal stroke. There was directionally consistent risk for of all the components of the composite end point associated with carriage of 1 or 2 reduced-function *CYP2C19* alleles. Specifically, for cardiovascular death, the HR was 1.84 (95% CI, 1.03-3.28; $P=.041$), for nonfatal myocardial infarction the HR was 1.45 (95% CI, 1.09-1.92; $P=.01$), and for stroke the HR was 1.73 (95% CI, 0.68-4.38; $P=.25$).

Risk in Carriers of 1 and 2 Reduced-Function *CYP2C19* Alleles

Compared with *CYP2C19* noncarriers, there was a significantly increased risk of cardiovascular death, myocardial infarction, or stroke in the 26.3% of the overall study population who carried only 1 reduced-function *CYP2C19* allele (HR, 1.55; 95% CI, 1.11-2.17; $P=.01$; Figure 2B). Similarly, there was a significantly increased risk of cardiovascular death, myocardial infarction, or stroke in the 2.2% of the overall study population who carried 2 reduced-function *CYP2C19* alleles (HR, 1.76; 95% CI, 1.24-2.50; $P=.002$; Figure 2C).

Stent Thrombosis Outcomes by *CYP2C19* Genotype

Overall, stent thrombosis occurred in 84 of the 5894 patients who had a stent implanted and were evaluated for stent thrombosis. Carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers had a significantly increased risk of stent thrombosis (HR, 2.81; 95% CI, 1.81-4.37; $P<.00001$; FIGURE 3A). Analogous to the observations for cardiovascular death, myocardial infarction, or stroke, both carriers of only 1 reduced-function *CYP2C19* allele (HR, 2.67; 95% CI, 1.69-4.22; $P<.0001$; Figure 3B) and carriers of 2 alleles (HR, 3.97; 95% CI, 1.75-9.02; $P=.001$; Figure 3C) were at significantly increased risk of stent thrombosis when compared with *CYP2C19* noncarriers.

Timing of Events

In landmark analyses, carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers had an HR of 1.36 (95% CI, 1.11-1.65) for cardiovascular death, myocardial infarction, or stroke over the first 30 days and an HR of 1.61 (95% CI, 0.88-2.94) from 31 days until the end of follow-up (FIGURE 4). For stent thrombosis, carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers had an HR of 2.94 (95% CI, 1.75-4.94) over the first 30 days and an HR of 2.80 (95% CI, 0.83-9.39) from 31 days until the end of follow-up (Figure 4).

Exploring Heterogeneity Between Studies and Among Subgroups

There was evidence of heterogeneity for the end point of cardiovascular death, myocardial infarction, or stroke when comparing carriers of only 1 reduced-function *CYP2C19* allele with noncarriers ($Q=29.22$; $P<.001$ for heterogeneity; $I^2=73\%$). Exclusion of 2 studies, FAST-MI (French Registry of Acute ST-Segment Elevation and Non-ST-Elevation Myocardial Infarction) and AFIJI (Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention), resulted in resolution of heterogeneity ($Q=4.63$; $P=.59$ for heterogeneity; $I^2=0\%$). The characteristics of patients in these 2 studies were similar to those in the other 7 studies, and the HRs for FAST-MI and AFIJI fell on either side of the summary HR. After excluding these studies, the summary HR for carriers of only 1 reduced-function *CYP2C19* allele was 1.42 (95% CI, 1.19-1.69), which was similar to the HR calculated from analyzing all 9 studies. There was no evidence of statistically significant heterogeneity for the end point of cardiovascular death, myocardial infarction, or stroke when comparing carriers of 2 reduced-function *CYP2C19* alleles with noncarriers ($Q=5.87$; $P=.44$ for heterogeneity), nor was there any significant heterogeneity in the stent thrombosis analyses (carriers of 1 reduced-

function *CYP2C19* allele vs noncarriers, $Q=4.44$ [$P=.49$ for heterogeneity]; carriers of 2 reduced-function *CYP2C19* alleles vs noncarriers, $Q=5.77$ [$P=.22$ for heterogeneity]).

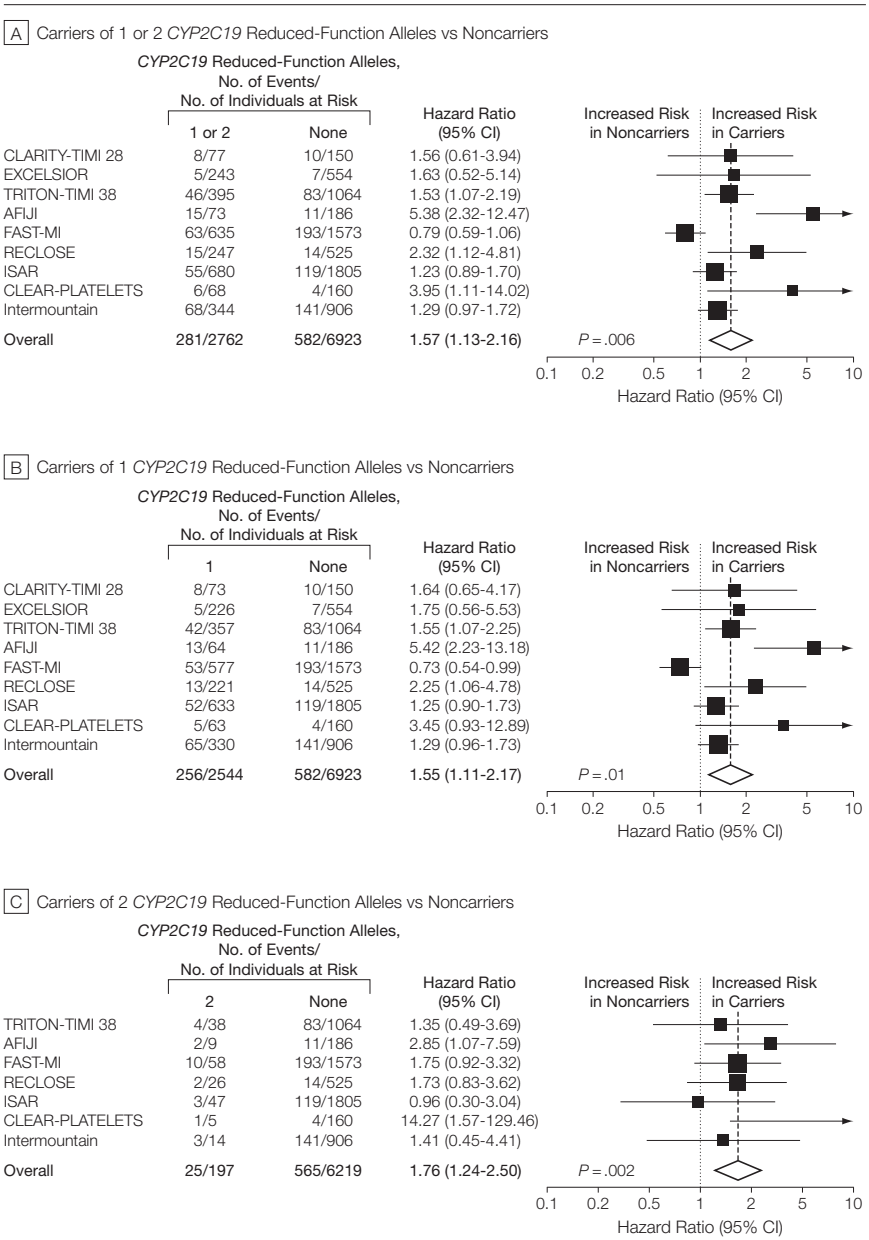
There was no evidence of heterogeneity for the end point of cardiovascular death, myocardial infarction, or stroke or for stent thrombosis across studies that had all, some, or no patients with ACS ($Q=3.82$; $P=.15$; and $Q=1.26$; $P=.53$, respectively) or across studies that used only 300 mg, 300 mg or 600 mg, or at least 600 mg of clopidogrel as the loading dose ($Q=1.61$; $P=.45$ and $Q=0.25$; $P=.88$, respectively).

COMMENT

By performing a collaborative meta-analysis with data by genotype, we found that among patients treated with clopidogrel predominantly for PCI, carriage of even 1 reduced-function *CYP2C19* allele is associated with an increased risk of adverse cardiovascular events, particularly stent thrombosis. Thus, *CYP2C19* genetic information identifies approximately 30% of the population who may be less likely to be protected from recurrent ischemic events after PCI despite treatment with standard doses of clopidogrel.

Guidelines about caring for patients with *CYP2C19* polymorphisms are starting to be developed at national levels.[6,7,21] For example, in March of 2010, the FDA issued a warning stating that there can be a diminished effect of standard doses of clopidogrel in *CYP2C19* poor metabolizers, who were defined as individuals with 2 reduced-function *CYP2C19* alleles. The proportion of the population harboring 2 reduced-function *CYP2C19* alleles is approximately 2% for whites, 4% for blacks, and 14% for Chinese individuals.[8] The FDA referenced a crossover study of 40 healthy participants who were treated with 300 mg of clopidogrel followed by 75 mg per day and with 600 mg followed by 150 mg per day. The study found that individuals with 2 reduced-function *CYP2C19* alleles, as compared with carriers of 1 or none, exhibited substantially decreased active drug metabolite levels and inhibition of platelet aggregation. However, it should be noted that a number of other pharmacokinetic and pharmacodynamic studies have also found that individuals (including both healthy individuals and, perhaps more germane, patients with coronary artery disease) who carry even 1 reduced-function *CYP2C19* allele have a blunted pharmacologic re-

Figure 2. Cardiovascular Death, Myocardial Infarction, or Ischemic Stroke by *CYP2C19* Genotype



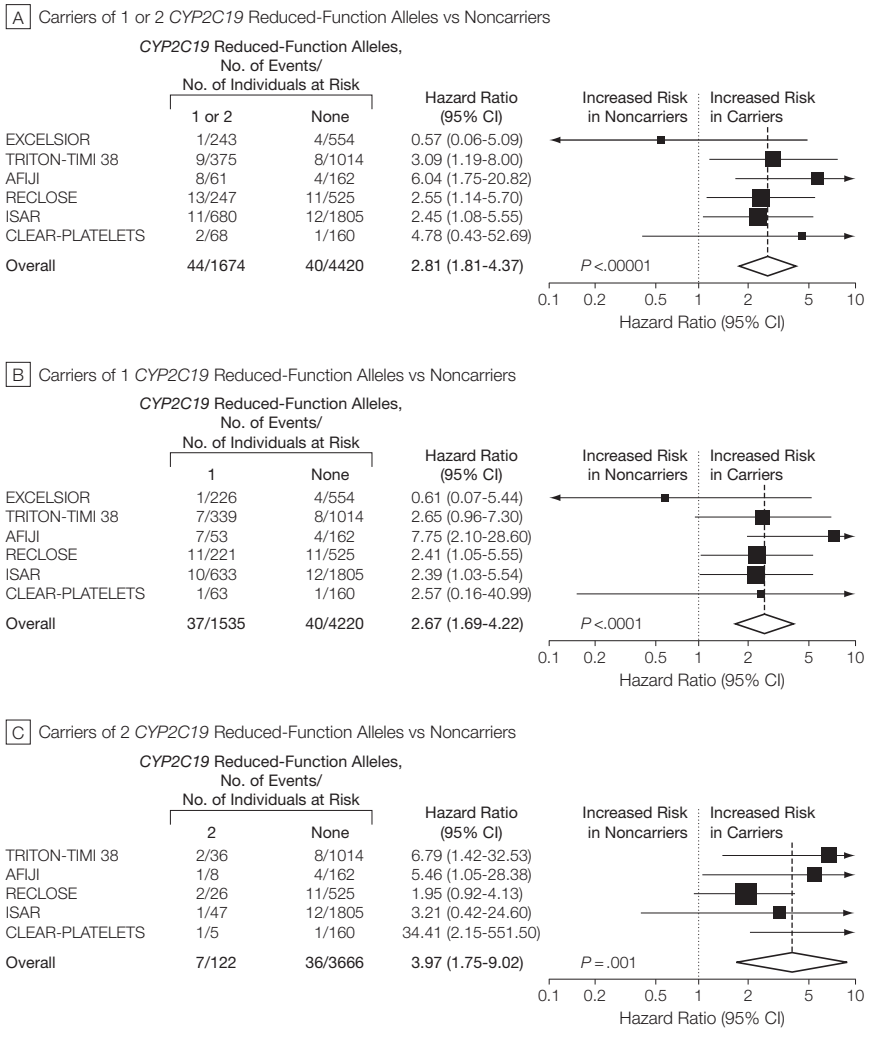
Among patients treated with clopidogrel, hazard ratios (HRs) are reported for cardiovascular death, myocardial infarction, or ischemic stroke among carriers of 1 or 2 (panel A), 1 (panel B), or 2 (panel C) reduced-function *CYP2C19* alleles vs noncarriers. Size of data markers reflects the statistical weight of the study in the meta-analysis. Data marker for the overall category indicates the 95% confidence interval (CI) for the overall HR. The number of events and of individuals at risk for events is presented for each study. Panel C, Studies with no adverse cardiovascular events among carriers of 2 reduced-function *CYP2C19* alleles were excluded from analysis.

sponse to treatment with clopidogrel, albeit less pronounced than the effect observed among carriers of 2 reduced-function alleles.[10,22-29] Thus, it is plausible that carriers of even 1 reduced-function *CYP2C19* allele as compared with noncarriers would be at increased risk of adverse cardiovascular events in the setting of treatment with standard doses of clopidogrel.

The totality of the pharmacologic data support the findings of our meta-analysis on clinical outcomes, which suggest that patients undergoing PCI treated with standard doses of clopidogrel who have either 1 or 2 reduced-function *CYP2C19* alleles are at increased risk for major adverse cardiovascular events. The observed HRs for adverse cardiovascular events of 1.55 (for carriers of 1 reduced-function *CYP2C19* allele vs noncarriers) and 1.76 (for carriers of 2 reduced-function *CYP2C19* alleles vs noncarriers) are plausible. The meta-analysis population predominantly underwent PCI, a setting in which dual antiplatelet therapy as compared with aspirin monotherapy results in risk reductions of as much as 75% to 85%.[30] In such a situation, even partial reductions in the antiplatelet effect of clopidogrel could translate into a several-fold increase in the risk of major adverse cardiovascular outcomes. As would be expected, the point estimates for the HRs were numerically higher in patients who carried 2 rather than 1 reduced-function allele, but with overlapping CIs. Moreover, the pharmacogenetic effect was more pronounced for the specific outcome of stent thrombosis than for the broader outcome of cardiovascular death, myocardial infarction, or stroke. This observation logically follows from the more pronounced risk reduction that has been documented with thienopyridines on the former vs the latter outcome.[30,31]

Three genetic studies not included in our meta-analysis (see "Methods") warrant comment and their results highlight the influence of the clinical setting on the relationship between *CYP2C19* genotype, clopidogrel, and clinical outcomes. Specifically, the most significant pharmacogenetic effect appears to be observed in patients treated with clopidogrel for PCI. In the genetic substudy from the PLATO (Platelet Inhibition and Patient Outcomes) trial, approximately two-thirds of patients underwent PCI. Although the required data from this substudy could not be incorporated directly into our meta-analysis due to the manner in which their published data were presented (ie, only presenting results by carrier state rather than by number of alleles), at 30 days the rate of cardiovascular death, myocardial infarction, or stroke among patients treated with clopidogrel was 5.7% in carriers of 1 or 2 reduced-function *CYP2C19* alleles and 3.8% in noncarriers ($P=.028$), which represents a 37% increased risk of events—similar to the current meta-analytic point estimate.[32] In landmark analyses, the investigators did not observe any increased risk after 30 days, and the rate of cardiovascular death,

Figure 3. Stent Thrombosis by *CYP2C19* Genotype



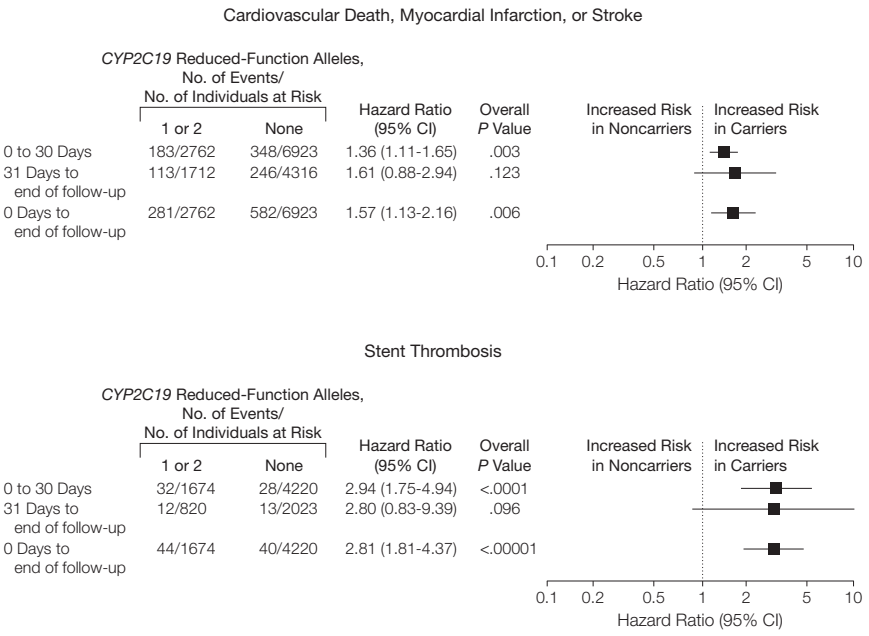
Among patients treated with clopidogrel, hazard ratios (HRs) are reported for stent thrombosis among carriers of 1 or 2 (panel A), 1 (panel B), or 2 (panel C) reduced-function *CYP2C19* alleles vs noncarriers. Size of data markers reflects the statistical weight of the study in the meta-analysis. Data marker for the overall category indicates the 95% confidence interval (CI) for the overall HR. Number of events and of individuals at risk for events is presented for each study. Panel C, Studies that had no stent thrombosis events among carriers of 2 reduced-function *CYP2C19* alleles were excluded from analysis.

myocardial infarction, or stroke by 12 months among patients treated with clopidogrel was 11.2% in carriers of 1 or 2 reduced-function *CYP2C19* alleles vs 10.0% in noncarriers. In a sensitivity analysis adding data from the PLATO genetic substudy (estimating an HR through 12 months of 1.12 for carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers to the other 9 studies in the meta-analysis, the estimated risk among patients treated with clopidogrel of cardiovascular death, myocardial infarction, or stroke associated with carriage of a *CYP2C19* reduced-function allele was largely unchanged (HR, 1.43; 95% CI, 1.11-1.84).

Patients in the genetic substudy from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial were conservatively managed with only 15.5% undergoing PCI with stenting. In this setting, the investigators observed no hazard associated with carriage of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers among patients treated with clopidogrel (HR, 0.86; 95% CI, 0.63-1.17).[33] Notably, in contrast to the 75% to 85% risk reduction resulting from the addition of a thienopyridine in patients who undergo stenting,[30] in conservatively managed patients, treatment with clopidogrel is associated with only an approximate 20% reduction in cardiovascular death, myocardial infarction, or stroke.[31] Moreover, carriage of a *CYP2C19* reduced-function allele does not completely negate the effects of clopidogrel, but rather is associated with active metabolite and platelet inhibition levels roughly 25% to 33% less than what is observed in noncarriers.[11] Taking these factors into account, one would expect carriage of a *CYP2C19* reduced-function allele to confer only a 10% to 15% increase in risk in predominantly conservatively managed patients such as those in the genetic substudy of CURE, a value that falls within their observed 95% CI. Lastly, in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, clopidogrel was not given in a manner consistent with the current guideline recommendations, and notably not all patients had established coronary disease, of those with a prior myocardial infarction the median time from that myocardial infarction to inclusion in the study was approximately 2 years, and only 22% underwent prior PCI. In this setting, no clear risk was observed with carriage of *CYP2C19* reduced-function alleles among patients treated with clopidogrel in the genetic substudy of the CHARISMA trial,[34] but as treatment with clopidogrel did not reduce adverse cardiovascular events in the overall population,[35] no pharmacogenetic interaction would be expected. In a further sensitivity analysis adding data from the CURE genetic substudy and the CHARISMA genetic substudy (estimating an HR of 1.25 for carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers) to the PLATO data and the other 9 studies in the meta-analysis, there appears to remain a significant association between carriage of 1 or 2 reduced-function *CYP2C19* alleles and cardiovascular death, myocardial infarction, or stroke (HR, 1.32; 95% CI, 1.07-1.63) in the setting of treatment with clopidogrel.

The pharmacokinetic and pharmacodynamic literature supports the notion that the mechanism underlying the observed association between *CYP2C19* reduced-function variants and clinical outcomes is reduced bioactivation of clopidogrel into its active metabolite. Nonetheless, it has been discussed whether variants in *CYP2C19* could themselves be associated with an increase in adverse cardiovascular events, regardless of treatment with clopidogrel. To that end, in the placebo group

Figure 4. Timing of Events for Cardiovascular Death, Myocardial Infarction, or Ischemic Stroke and Stent Thrombosis



Among patients treated with clopidogrel, hazard ratios (HRs) are reported for cardiovascular death, myocardial infarction, or ischemic stroke and for stent thrombosis among carriers of 1 or 2 reduced-function *CYP2C19* alleles vs noncarriers. Data markers indicate HRs and CIs across the different time points. Nine studies contributed to the end point of cardiovascular death, myocardial infarction, or stroke from 0 to 30 days, and 6 studies from 31 days to end of follow-up. Analogously, 6 studies contributed to the end point of stent thrombosis from 0 to 30 days, and 3 studies from 31 days to end of follow-up. Number of events and of individuals at risk for events is presented for each study. In the analysis, a patient could have had a nonfatal event during 0 to 30 days and a subsequent event after day 30.

of the CHARISMA study, a directionally higher hazard was observed among carriers of 2 reduced-function *CYP2C19* alleles vs noncarriers (HR, 1.82; 95% CI, 0.74-4.65).[34] In contrast, in the CURE genetic substudy, among participants in the placebo group, the rate of adverse cardiovascular events was numerically lower among carriers of a reduced-function *CYP2C19* allele (11.6%) as compared with noncarriers (13.0%).[33] Similarly, in the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28) and CLEAR-PLATELETS (Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets) studies, there was no association between *CYP2C19* genotype and adverse cardiovascular outcomes for patients not taking clopidogrel.[9,16] Furthermore, among patients in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) study treated with prasugrel (a third-generation thienopyridine that is metabolized differently than clopidogrel) and among patients in PLATO treated with ticagrelor (a nonthienopyridine $P2Y_{12}$ ADP–receptor blocker that does not undergo biotransformation to an active metabolite by the CYP2C19 enzyme), *CYP2C19* genetic variants were not associated with an increased risk of clinical outcomes.[32,36] Lastly, in genome-wide association studies for incident myocardial infarction involving over 20 000 participants, no association with *CYP2C19* was found.[37]

Tests are available to identify a patient's *CYP2C19* genotype. Although these tests are not widely used at this time, some physicians have started to use a strategy of *CYP2C19* genotyping among participants initiating treatment with clopidogrel.[38] Moving forward, point-of-care genotyping will likely be available, and this technology could further ease the implementation of *CYP2C19* testing for interested clinicians and patients.[39] Point-of-care testing is also available for platelet function testing. The relationship between pharmacogenetic and pharmacodynamic testing continues to be explored. In one study, *CYP2C19* polymorphisms appear to account for 12% of the variability in the effect of clopidogrel, as measured using ADP-induced platelet aggregation, and environmental factors account for less than 10% of the variability.[16] Compounding the complexity of the relationship, light transmittance aggregometry itself has variable reproducibility.[40] The association observed between higher platelet reactivity and adverse cardiovascular outcomes is of comparable magnitude to the pharmacogenetic findings,[41] and some, but not all studies have suggested that pharmacogenetic and platelet function testing offer independent predictive value.[14,16] Of note, it should be acknowledged that neither genotyping nor platelet function testing is a perfect discriminator of subsequent clinical outcomes, underscoring the complex, multifactorial nature of cardiovascular risk.[42] Nonetheless, prospective trials of the clinical utility of incorporating genetics and platelet function testing into treatment decisions are underway.[21,43-45]

With respect to treatment options, there are some early data suggesting that increasing the dose of clopidogrel in carriers of a *CYP2C19* reduced-function allele may enhance the degree of platelet inhibition.[7,46-49] However, all of these studies have been small, with no study having more than 20 carriers of a *CYP2C19* reduced-function allele, and with no study reporting clinical outcomes data. Larger studies that incorporate *CYP2C19* genotyping and explore the influence of higher doses of clopidogrel on platelet function parameters, as well as clinical outcomes, will be useful in further assisting with therapeutic decisions. Understanding the ability to treat patients effectively with clopidogrel across *CYP2C19* genotypes will be particularly important from a health care cost perspective, as the drug is already off patent in some countries and anticipated to go off patent in the United States and elsewhere in the near future. Additionally, there are other antiplatelet agents that may serve as particularly attractive treatment options for patients with a genetically-impaired response to clopidogrel, such as either of the third generation $P2Y_{12}$ ADP–receptor blockers prasugrel or ticagrelor,[50,51] neither of which appears to be influenced by polymorphisms in *CYP2C19*.[32,36] However, currently prasugrel is only approved by the FDA for use in ACS patients whose symptoms are to be managed with PCI, and ticagrelor is not yet approved.

There are some limitations to these analyses. First, 95.8% of the study population was white. Of note though, the effects of *CYP2C19* reduced-function alleles on platelet inhibition with clopidogrel appear to be consistent in white and Asian individuals, for example.[25,26] Second, 91.3% of the study population was treated with clopidogrel for a PCI, and as discussed previously, the impact of *CYP2C19* genotype would be expected to be, and data suggest is, considerably less in patients who do not undergo PCI, where clopidogrel has more modest efficacy. Third, most of the studies included in the meta-analysis provided information only on *CYP2C19**2. *CYP2C19**2, though, is by far the most frequent variant, accounting for approximately 95% of the reduced-function allele carrier status and the lack of genotyping beyond the *2 allele would be expected to bias toward the null, since carriers of other *CYP2C19* reduced-function alleles (eg, *CYP2C19**3) were included in the noncarriers for 7 of the studies. Likewise, there are other genes, not included in this meta-analysis, that may influence the response to clopidogrel. Fourth, for logistical reasons, individual patient-level data could not be combined. Comparative studies, however, have demonstrated excellent quantitative agreement between summary data and patient-level data when the same data sets are used for both analyses and the same exposures and outcomes are used, as was the case for the present meta-analysis.[52] Finally, the studies contributing to this meta-analysis were generally large clinical outcomes studies in which platelet function testing was not routinely performed. As such, the meta-analysis fo-

cuses on the relationship between genotype and outcomes; other studies have highlighted the predictive value of platelet function testing.[53]

In conclusion, the findings of this collaborative meta-analysis demonstrate that common genetic variants in the *CYP2C19* gene are associated with almost 1 in 3 patients not receiving ideal protection from ischemic events when treated with standard doses of clopidogrel for PCI. Given how widely clopidogrel is used to treat patients with cardiovascular disease, determination of the optimal antiplatelet treatment doses or regimens for individual patients is needed to tailor therapy appropriately.

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REFERENCES

1. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2010; 55(6):612 (dosage error in text)]. *J Am Coll Cardiol*. 2009;54(23):2205-2241.

2. Anderson JL, Adams CD, Antman EM, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction); American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction. *Circulation*. 2007;116(7):e148-e304.

3. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel. *J Am Coll Cardiol*. 2007;49(14):1505-1516.

4. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab Dispos*. 2010;38(1):92-99.

5. Giusti B, Gori AM, Marcucci R, Saracini C, Vestrini A, Abbate R. Determinants to optimize response to clopidogrel in acute coronary syndrome. *Pharmgenomics Pers Med*. 2010;3:33-50. doi:10.2147/PGPM.S5056.

6. US Food and Drug Adminitration. FDA drug safety communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor mebabolizers of the drug. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm. Accessed July 15, 2010.

7. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Plavix prescribing information. http://products.sanofi-aventis.us/PLAVIX/PLAVIX.html. Accessed July 15, 2010.

8. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet*. 2002;41(12):913-958.
9. Mega JL, Thakuria JV, Cannon CP, Sabatine MS. Sequence variations in CYP metabolism genes and cardiovascular outcomes following treatment with clopidogrel: insights from the CLARITY-TIMI 28 genomic study [abstract 1017-69 taken from the American College of Cardiology 57th Annual Scientific Session, Chicago, IL, March 29-April 1, 2008]. *J Am Coll Cardiol*. 2008;51(10)(suppl A):A178-A235. doi:10.1016/j.jacc.2008.02.007.
10. Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol*. 2008;51(20):1925-1934.
11. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360(4):354-362.
12. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009;373(9660):309-317.
13. Simon T, Verstuyft C, Mary-Krause M, et al; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360(4):363-375.
14. Giusti B, Gori AM, Marcucci R, et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. *Am J Cardiol*. 2009;103(6):806-811.
15. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur Heart J*. 2009;30(8):916-922.
16. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009;302(8):849-857.
17. Anderson JL, Mower CP, Horne BD, et al. Carriage of the CYP2C19*2 allele increases one-year risk of myocardial infarction among recipients of drug-eluting stents treated with clopidogrel [abstract 2903-8 {page A27-A28}]. *J Am Coll Cardiol*. 2009;53(10)(suppl A):A1-A99. doi:10.1016/j.jacc.2009.01.013.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808.
19. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356(10):1020-1029.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
21. Holmes DR Jr, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; Writing Committee Members. ACCF/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *Circulation*. 2010;122(5):537-557.
22. Hulot JS, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood*. 2006;108(7):2244-2247.
23. Fontana P, Hulot JS, De Moerloose P, Gaussem P. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *J Thromb Haemost*. 2007;5(10):2153-2155.
24. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost*. 2007;5(12):2429-2436.
25. Kim KA, Park PW, Hong SJ, Park JY. The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. *Clin Pharmacol Ther*. 2008;84(2):236-242.
26. Umemura K, Furuta T, Kondo K. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. *J Thromb Haemost*. 2008;6(8):1439-1441.
27. Giusti B, Gori AM, Marcucci R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics*. 2007;17(12):1057-1064.
28. Frere C, Cuisset T, Morange PE, et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. *Am J Cardiol*. 2008;101(8):1088-1093.
29. Varenhorst C, James S, Erlinge D, et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. *Eur Heart J*. 2009;30(14):1744-1752.
30. Leon MB, Baim DS, Popma JJ, et al; Stent Anticoagulation Restenosis Study Investigators. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med*. 1998;339(23):1665-1671.
31. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502.
32. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial [published online August 27, 2010]. *Lancet*.
33. Pare G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment [published online August 29, 2010]. *N Engl J Med*. doi:10.1056/NEJMoa1008410.
34. Bhatt DL, Simonsen KL, Emison ES, et al. *Charisma Genomics Substudy: Evaluation of the CYP2C19 Polymorphism in a Prospective, Randomized, Placebo-Controlled Trial of Chronic Clopidogrel Use for Primary and Secondary Prevention.* San Francisco, CA: TCT; 2009.
35. Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354(16):1706-1717.
36. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119(19):2553-2560.
37. Kathiresan S, Voight BF, Purcell S, et al; Myocardial Infarction Genetics Consortium; Wellcome Trust Case Control Consortium. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet*. 2009;41(3):334-341.
38. Damani SB, Topol EJ. The case for routine genotyping in dual-antiplatelet therapy. *J Am Coll Cardiol*. 2010;56(2):109-111.
39. Maurice CB, Barua PK, Simses D, Smith P, Howe JG, Stack G. Comparison of three commercial CYP2C9/VKORC1 genotyping assays for warfarin sensitivity [abstract G04 {page 566}]. *J Mol Diagn*. 2008;10(6):557-626. doi:10.2353/jmoldx.2008.080036.
40. Gurbel PA, Becker RC, Mann KG, Steinhubl SR, Michelson AD. Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol*. 2007;50(19):1822-1834.
41. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA*. 2010;303(8):754-762.
42. Gurbel PA, Tantry US, Shuldiner AR, Kereiakes DJ. Genotyping: one piece of the puzzle to personalize antiplatelet therapy. *J Am Coll Cardiol*. 2010;56(2):112-116.
43. Price MJ, Berger PB, Angiolillo DJ, et al. Evaluation of individualized clopidogrel therapy after drug-eluting stent implantation in patients with high residual platelet reactivity: design and rationale of the GRAVITAS trial. *Am Heart J*. 2009;157(5):818-824.
44. National Institutes of Health. Testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel (TRIGGER-PCI) (identifier: NCT00910299). ClinicalTrials Web site. http://www.clinicaltrials.gov/ct2/show/NCT00910299?term=nct00910299&rank=1. Accessed March 30, 2010.
45. National Institutes of Health. Double randomization of a monitoring adjusted antiplatelet treatment versus a common antiplatelet treatment for DES implantation, and interruption versus continuation of double antiplatelet therapy (ARCTIC) (identifier: NCT00827411). ClinicalTrials Web site. http://www.clinicaltrials.gov/ct2/show/NCT00827411?term=nct00827411&rank=1. Accessed March 30, 2010.
46. Gladding P, Webster M, Zeng I, et al. The pharmacogenetics and pharmacodynamics of clopidogrel response: an analysis from the PRINC (Plavix Response in Coronary Intervention) trial. *JACC Cardiovasc Interv*. 2008;1(6):620-627.
47. Gladding P, White H, Voss J, et al. Pharmacogenetic testing for clopidogrel using the rapid INFINITI analyzer: a dose-escalation study. *JACC Cardiovasc Interv*. 2009;2(11):1095-1101.
48. Pena A, Collet JP, Hulot JS, et al. Can we override clopidogrel resistance? *Circulation*. 2009;119(21):2854-2857.
49. Hulot JS, Wuerzner G, Bachelot-Loza C, et al. Effect of an increased clopidogrel maintenance dose or lansoprazole co-administration on the antiplatelet response to clopidogrel in CYP2C19-genotyped healthy subjects. *J Thromb Haemost*. 2010;8(3):610-613.
50. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
51. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
52. Steinberg KK, Smith SJ, Stroup DF, et al. Comparison of effect estimates from a meta-analysis of summary data from published studies and from a meta-analysis using individual patient data for ovarian cancer studies. *Am J Epidemiol*. 1997;145(10):917-925.
53. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol*. 2008;51(14):1404-1411.

