

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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CLOPIDOGREL BLOCKS THE P2Y₁₂ 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 inter-individual variability in the pharmacodynamic response to clopidogrel.³ One

For editorial comment see p 1839.

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 ($\approx 26\%$ prevalence in whites) and carriers of 2 ($\approx 2\%$ 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.

JAMA. 2010;304(16):1821-1830

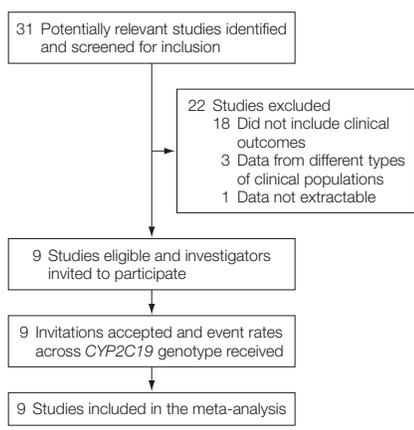
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source of the variability is the metabolism of clopidogrel, which is a prodrug requiring biotransformation to generate its active metabolite. Cytochrome P450 (CYP) isoenzymes, specifically *CYP2C19*,⁴ play a key role in clopidogrel metabolism, and 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

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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 ex-

amine 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) checklist¹⁸ 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 study¹³; 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 I² 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 clo-

pidogrel 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									Total ^b
	CLARITY-TIMI 28 ⁹	EXCELSIOR ¹⁰	TRITON-TIMI 38 ¹¹	AFIJI ¹²	FAST-MI ¹³	RECLOSE ¹⁴	ISAR ¹⁵	CLEAR-PLATELETS ¹⁶	Intermountain ¹⁷	
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 Eptifibatid 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, Intra-coronary 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.

^aExpansions 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

^bThe 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.

^cThe investigators for FAST-MI note that among participants for whom race was collected, virtually all were white.

^dThe 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.

^eComplete 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			
	Overall (n = 9685)	Reduced-Function CYP2C19 Alleles		
		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

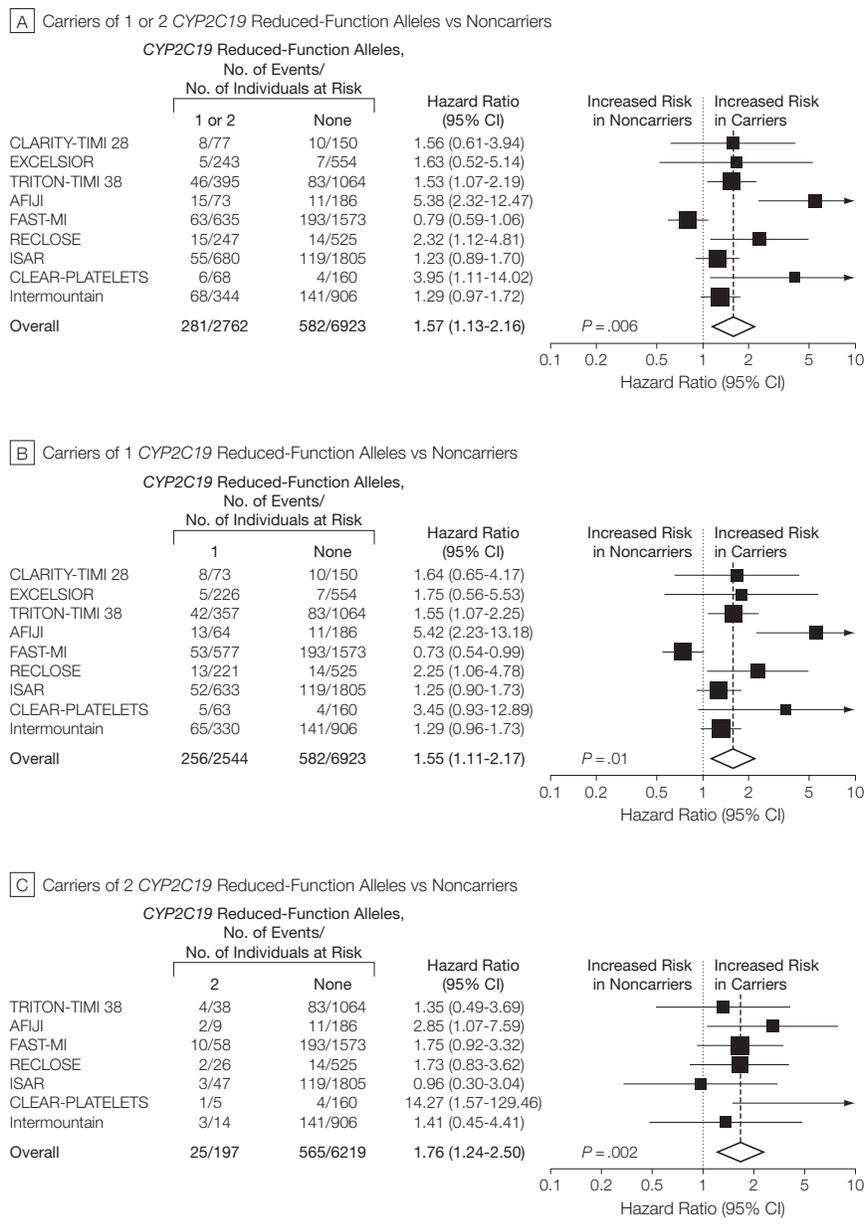
By performing a collaborative meta-analysis with data by genotype, we found that among patients treated with clopidogrel predominantly for PCI, carriage of even 1 reduced-function *CYP2C19* allele is associated with an increased risk of adverse cardiovascular events, particularly stent thrombosis. Thus, *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 individu-

als (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.

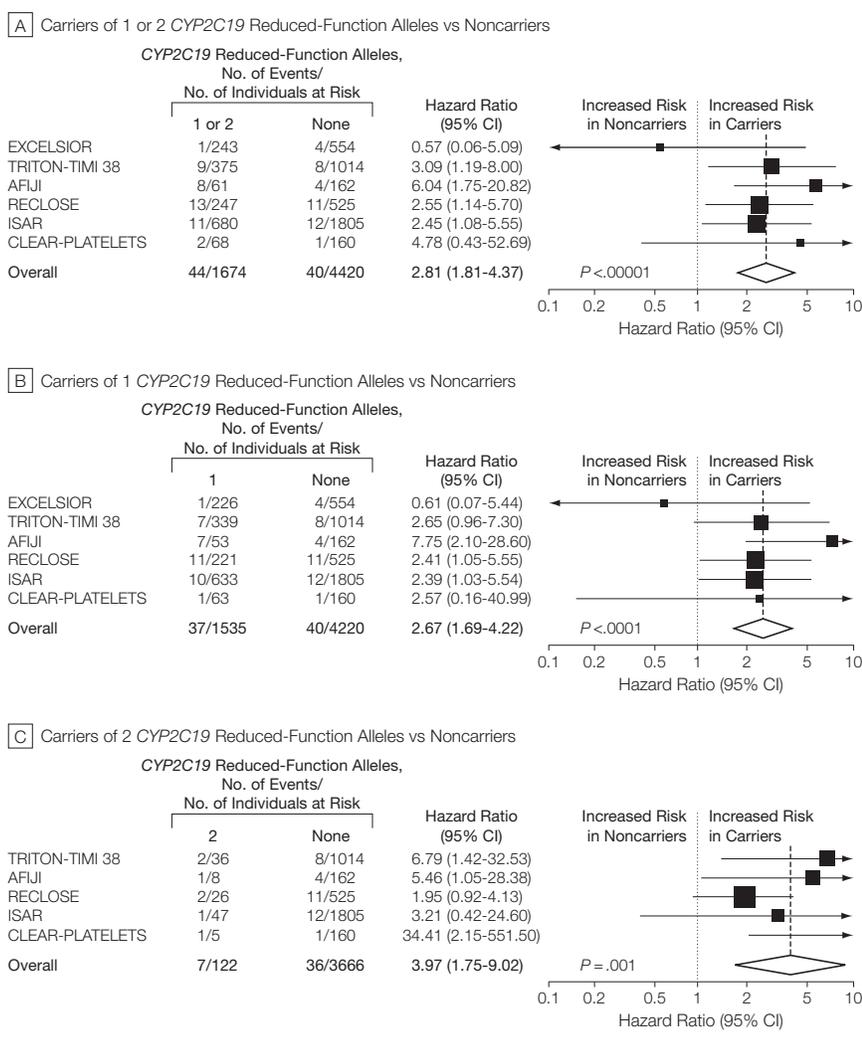
The totality of the pharmacologic data support the findings of our meta-

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

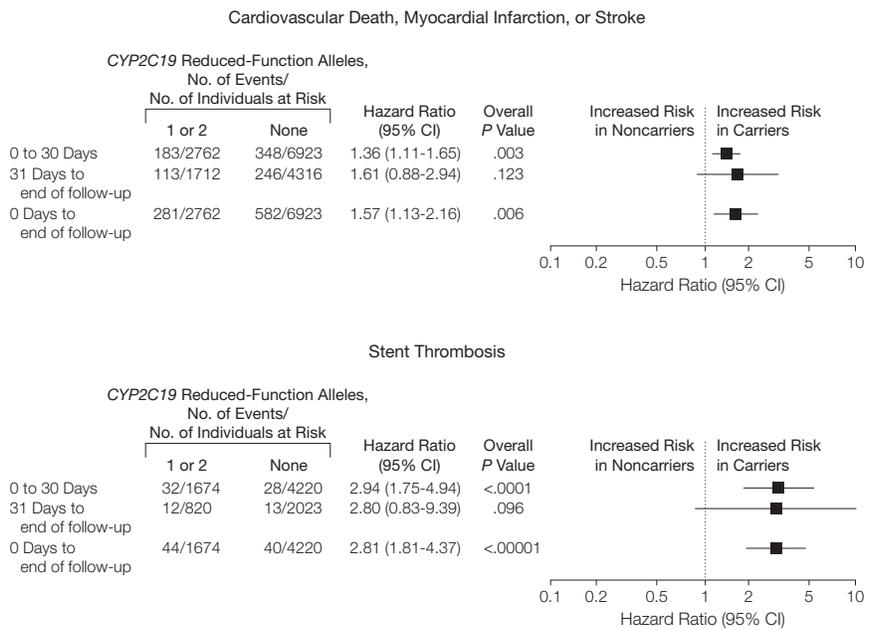


Among patients treated with clopidogrel, hazard ratios (HRs) are reported for stent thrombosis among carriers of 1 or 2 (panel A), 1 (panel B), or 2 (panel C) reduced-function CYP2C19 alleles vs noncarriers. Size of data markers reflects the statistical weight of the study in the meta-analysis. Data 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 Avoid-

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.

ance) 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

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 P2Y₁₂ 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 test-

ing 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 re-

sponse to clopidogrel, such as either of the third generation P2Y₁₂ 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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Kastrati, Montalescot, Neumann, Shen, Sibbing, Steg, Trenk, Wiviott, Sabatine.

Financial Disclosures: Dr Mega reports receiving research grant funding from Bayer Healthcare, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, and Sanofi-Aventis; research supplies from Accumetrics and Nanosphere; consulting fees from AstraZeneca, Bristol-Myers Squibb, and Sanofi-Aventis; and lecture fees from Novartis. Dr Simon reports receiving research grant funding from Servier, Pfizer, Daiichi Sankyo, Eli Lilly, Sanofi-Aventis, AstraZeneca, and Caisse d'Assurance Maladie; and consulting fees from Eli Lilly, Daiichi Sankyo, Sanofi-Aventis, Bristol-Myers Squibb, and AstraZeneca. Dr Collet reports receiving research grant funding from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, and Eli Lilly; and consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb. Dr Anderson reports receiving consulting fees from Bristol-Myers Squibb and Sanofi-Aventis. Dr Antman reports receiving research grant funding from Daiichi Sankyo and Eli Lilly; consulting fees from Sanofi-Aventis; and lecture fees from Eli Lilly and Sanofi-Aventis. Dr Cannon reports receiving research grant funding from Accumetrics, AstraZeneca, GlaxoSmithKline, Intekrin Therapeutics, Merck, and Takeda; serving on the advisory board for Bristol-Myers Squibb/Sanofi, Novartis, and Alnylam and donating the funds to charity; and serving as a clinical advisor with equity in Auto-medics Medical Systems. Dr Danchin reports receiving research grant funding from AstraZeneca, Eli Lilly, Merck, Novartis, Pfizer, Sanofi-Aventis, Servier, and The Medicines Company; lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Menarini, Merck-Serono, MSD-Schering Plough, Servier, and Sanofi-Aventis; and consulting fees from AstraZeneca, Eli Lilly, Novo, Sanofi-Aventis, and Servier. Dr Gurbel reports receiving research grant funding from Schering Plough, Millennium, AstraZeneca, Bayer, Haemonetics, Medtronic, and Boston Scientific; and honoraria from Schering Plough, AstraZeneca, Bayer, Portola, and Medtronic. Dr Hulot reports receiving research grant support from Fondation de France, INSERM, Fédération Française de Cardiologie, Biotronik, and Medco Research Institute; consulting fees from Biotronik and Medco Health Solutions; and lecture fees from Sanofi-Aventis, Daiichi Sankyo, Eli Lilly, and Bristol-Myers Squibb. Dr Montalescot reports receiving research grant funding from Abbott Vascular, Bristol-Myers Squibb, Boston Scientific, Centocor, Cordis, Eli Lilly, Fédération Française de Cardiologie, Fondation de France, Guerbet Medical, INSERM, ITC Edison, Medtronic, Pfizer, Sanofi-Aventis, Societe Francaise de Cardiologie, and Stago; consulting fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, Eli Lilly, Menarini, Novartis, Pfizer, Portola, Sanofi-Aventis Group, Schering-Plough, and The Medicines Company; and lecture fees from Abbott Vascular, Accumetrics, AstraZeneca, Bristol-Myers Squibb, Cordis, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Menarini, Merck Sharpe & Dohme, Pfizer, Sanofi-Aventis, and Schering-Plough. Dr Shen reports being employed and having ownership interest in Eli Lilly. Dr Sibbing reports receiving consulting fees from Eli Lilly and lecture fees from Dynabyte and The Medicines Company. Dr Steg reports receiving research grant funding from Servier; consulting fees from Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo/Lilly, GlaxoSmithKline, Medtronic, Merck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, and The Medicines Company; and is a stockholder in Aterovax. Dr Trenk reports receiving research grant support from Eli Lilly; consulting fees from Eli Lilly, Dai-

chi Sankyo, and AstraZeneca; and lecture fees from Eli Lilly and Daiichi Sankyo. Dr Wiviott reports receiving research grant funding from Eli Lilly, Daiichi Sankyo, and Merck-Schering Plough; honoraria from AstraZeneca, Novartis, Eli Lilly, and Daiichi Sankyo; and consulting fees from AstraZeneca, Sanofi-Aventis, Portola, and Arena. Dr Sabatine reports receiving research grant funding from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Schering Plough (now Merck), and Sanofi-Aventis; honoraria from Bristol-Myers Squibb, Sanofi-Aventis, and Eli Lilly; and consulting fees from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, and Sanofi-Aventis. The other authors reported no disclosures.

Funding/Support: Dr Mega is supported in part by grant K99/R00 HL098461-01 from the National Institutes of Health.

Role of the Sponsors: Neither the National Institutes of Health nor the sponsors of the individual studies had a role in the design and conduct of the meta-analysis; collection, management, analysis, and interpretation of the meta-analysis data; and preparation, review, or approval of the manuscript.

Online-Only Material: The eAppendix is available at <http://www.jama.com>.

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