

ORIGINAL ARTICLE

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

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ABSTRACT

BACKGROUND

Clopidogrel requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its antiplatelet effect. The genes encoding CYP enzymes are polymorphic, with common alleles conferring reduced function.

METHODS

We tested the association between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel in 162 healthy subjects. We then examined the association between these genetic variants and cardiovascular outcomes in a separate cohort of 1477 subjects with acute coronary syndromes who were treated with clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38.

RESULTS

In healthy subjects who were treated with clopidogrel, carriers of at least one *CYP2C19* reduced-function allele (approximately 30% of the study population) had a relative reduction of 32.4% in plasma exposure to the active metabolite of clopidogrel, as compared with noncarriers ($P < 0.001$). Carriers also had an absolute reduction in maximal platelet aggregation in response to clopidogrel that was 9 percentage points less than that seen in noncarriers ($P < 0.001$). Among clopidogrel-treated subjects in TRITON-TIMI 38, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with noncarriers (12.1% vs. 8.0%; hazard ratio for carriers, 1.53; 95% confidence interval [CI], 1.07 to 2.19; $P = 0.01$) and an increase by a factor of 3 in the risk of stent thrombosis (2.6% vs. 0.8%; hazard ratio, 3.09; 95% CI, 1.19 to 8.00; $P = 0.02$).

CONCLUSIONS

Among persons treated with clopidogrel, carriers of a reduced-function *CYP2C19* allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers.

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ACROSS THE SPECTRUM OF ACUTE CORONARY syndromes and in patients undergoing percutaneous coronary interventions (PCI) with stenting, dual antiplatelet therapy with aspirin and clopidogrel, a thienopyridine inhibitor of the platelet P2Y₁₂ adenosine diphosphate (ADP) receptor, is the standard of care.¹⁻³ However, the pharmacodynamic response to clopidogrel has substantial interpatient variability,⁴⁻⁶ and patients with coronary disease with lesser degrees of platelet inhibition in response to clopidogrel appear to be at increased risk for cardiovascular events.⁷⁻¹⁰

Clopidogrel is a prodrug that requires biotransformation to an active metabolite by cytochrome P-450 (CYP) enzymes (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).^{11,12} Moreover, esterases shunt the majority of clopidogrel to an inactive pathway, with the remaining prodrug requiring two separate CYP-dependent oxidative steps. The genes encoding the CYP enzymes are polymorphic, and extensive data have shown that certain alleles confer reduced enzymatic function.¹³ Data regarding in vitro metabolism and clinical outcomes suggest that the reduced-function CYP polymorphisms have an effect on the conversion to active metabolite and hence on the degree of platelet inhibition associated with clopidogrel.¹⁴⁻¹⁶

We therefore hypothesized that patients carrying a genetic variant that diminished the pharmacokinetic and pharmacodynamic response to clopidogrel would have a higher rate of ischemic events than patients who were noncarriers. To test this hypothesis, we first examined the association between functional polymorphisms in CYP genes with plasma exposure to the active metabolite of clopidogrel and platelet inhibition in healthy subjects. We then determined whether reduced-function CYP alleles were associated with a higher rate of adverse cardiovascular outcomes in a separate cohort of subjects with acute coronary syndromes who were treated with clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 (ClinicalTrials.gov number, NCT00097591).

METHODS

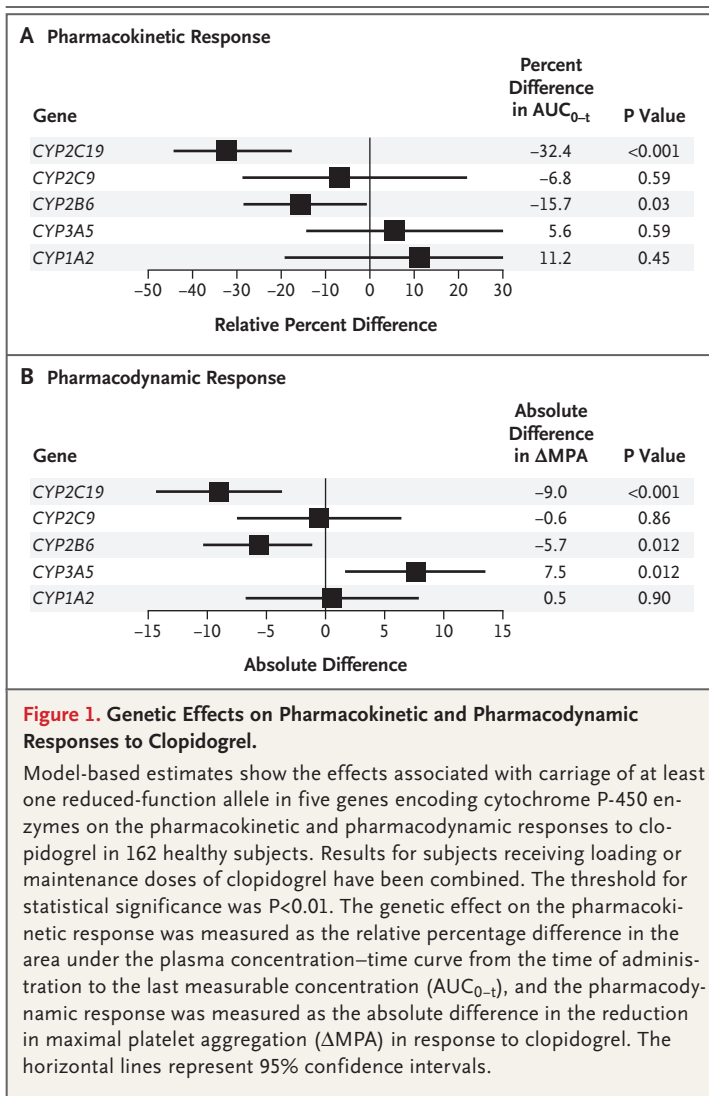
PHARMACOKINETIC AND PHARMACODYNAMIC RESPONSE IN HEALTHY SUBJECTS

We included 162 healthy subjects from six studies involving thienopyridine treatment in the pharmacokinetic and pharmacodynamic analyses (Table 1 in the Supplementary Appendix).¹⁷⁻²² Plasma concentrations of the active metabolite of clopidogrel were measured by liquid chromatography with mass spectrometry.²³ The area under the plasma concentration–time curve from the time of administration to the last measurable concentration (AUC_{0-∞}) of active metabolite was computed by non-compartmental methods of analysis with the use of the log-linear trapezoidal method. The pharmacodynamic response, which was assessed with the use of light transmission aggregometry in response to 20 μM of ADP, was expressed as an absolute reduction in maximal platelet aggregation from baseline (ΔMPA).

CLINICAL OUTCOMES

The design and primary results of TRITON-TIMI 38 have been described previously.^{24,25} Patients with acute coronary syndromes with planned PCI who were randomly assigned to treatment with clopidogrel received a 300-mg loading dose, followed by a 75-mg daily maintenance dose for up to 15 months. The primary efficacy outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke. A key prespecified secondary outcome was definite or probable stent thrombosis, as defined by the Academic Research Consortium.²⁶ Safety outcomes included TIMI major or minor bleeding not related to coronary-artery bypass grafting (CABG). All outcomes were adjudicated by a clinical events committee whose members were unaware of study-group assignments. The clopidogrel pharmacogenetic analysis included 1477 subjects who provided a DNA sample (Table 2 in the Supplementary Appendix).

All studies were approved by the institutional review board at each center, and written informed consent was obtained from all subjects. In keeping with the informed-consent and privacy policies, all genetic data resided with the sponsor (Eli Lilly)



in a deidentified database behind a firewall and were analyzed by statisticians distinct from those who had access to the clinical database. The genetic studies were designed and performed in collaboration between the TIMI Study Group and the sponsors, Eli Lilly and Daiichi Sankyo. The academic authors directed and had access to all the analyses and the full clinical database, wrote all drafts of the manuscript, decided to publish the results, and vouch for the accuracy and completeness of the data.

GENOTYPING METHODS

A total of 98% of the genotyping procedures were performed with the use of the Affymetrix Targeted Human DMET (drug-metabolizing enzymes and

transporters) 1.0 Assay (Affymetrix).^{27,28} In the case of CYP2C19*17 or a no-call on the DMET chip (2% of samples), genotyping was performed with bidirectional sequencing or exon-specific polymerase-chain-reaction amplification, followed by the use of standard agarose-gel electrophoresis to resolve restriction-fragment-length polymorphisms. A total of 54 alleles, comprising the known major functional variants, were determined with the use of clinically validated assays for CYP2C19, CYP2C9, CYP2B6, CYP3A5, CYP3A4, and CYP1A2 (Table 3 in the Supplementary Appendix). Of note, the tested alleles in CYP3A4 were not polymorphic, which left five genes for analysis. Genotypes were presumed to be in Hardy–Weinberg equilibrium if the P value was more than 0.001 (0.05/50 alleles = 0.001).

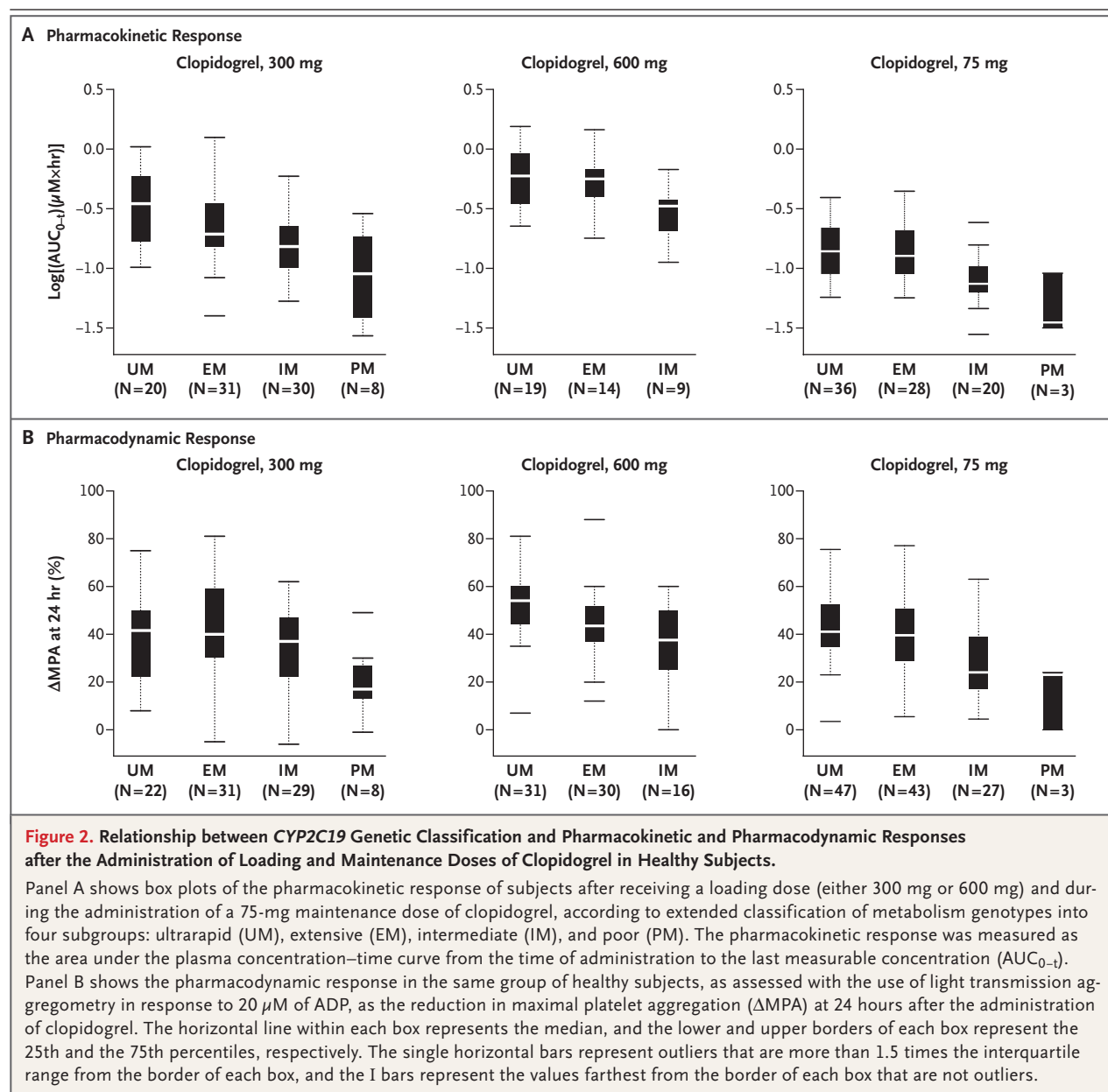
CYP GENOTYPE CLASSIFICATIONS

Each allele of the CYP genes was classified a priori by its known effect on enzymatic function according to the literature and with the use of established common-consensus star allele nomenclature.^{13,29,30} For each CYP gene, subjects were dichotomized a priori into two groups on the basis of whether they possessed at least one allele with significantly reduced function. If we observed a significant pharmacokinetic or pharmacodynamic effect, further analysis was undertaken with the use of an a priori extended categorical classification, which included ultrarapid, extensive, intermediate, and poor metabolizer genotypes. In the Supplementary Appendix, Table 4 lists the observed genotypes and their classification, and Table 5 provides the baseline characteristics in carriers and noncarriers of a reduced-function CYP2C19 allele among subjects receiving clopidogrel in TRITON–TIMI 38.

STATISTICAL ANALYSIS

Pharmacokinetic and Pharmacodynamic Responses

The associations between genetic variation and pharmacokinetic and pharmacodynamic measures were tested with the use of likelihood-ratio tests based on linear mixed-effects models, with the primary outcomes being exposure to the active metabolite of clopidogrel ($\log[AUC_{0-t}]$) and platelet inhibition (reduction in maximal platelet aggregation [ΔMPA]) in response to clopidogrel. The models contained the subject as a random effect, status as a reduced-function allele carrier as the predictor of main interest, and other fixed effects,



including study, dose, and ethnic background; for the pharmacodynamic response, also included were the time of administration, the interaction between the dose and time, and the baseline MPA. To account for other potential baseline differences, additional demographic variables (age, sex, weight, and smoking status) were included, as determined by forward selection for each model. Two-sided P values were calculated, and a significance threshold of $P < 0.01$ was used to correct for multiple hypotheses testing for the five CYP genes.

Clinical Outcomes

Rates of the outcomes were expressed as Kaplan–Meier estimates at 15 months and were compared between carriers and noncarriers of at least one reduced-function CYP allele. Consistent with the primary trial analyses, the Gehan–Wilcoxon test was used for the primary efficacy outcome and the log-rank test for other outcomes.²⁴ Hazard ratios and 95% confidence intervals were calculated on the basis of Cox proportional-hazards regression models with clinical syndrome (acute coronary

syndromes with or without ST elevation) as a stratification factor. Using the findings in healthy subjects, we tested the association between carriage of a reduced-function variant in *CYP2C19* and a higher rate of adverse clinical outcomes in subjects assigned to treatment with clopidogrel as the primary hypothesis for analysis in TRITON-TIMI 38. A two-sided P value was used to test for significance (threshold, $P < 0.05$). If a significant relationship between genotype classification and the primary efficacy outcome was identified, we then explored additional efficacy outcomes, including components of the composite primary efficacy outcome and stent thrombosis. Sensitivity analyses comparing *CYP2C19**2 carriers with noncarriers were performed in a similar manner. Other genes were investigated in an exploratory manner.

RESULTS

PHARMACOKINETIC AND PHARMACODYNAMIC RESPONSES

For the pharmacokinetic and pharmacodynamic analyses, DNA samples were available for 162 healthy subjects who were treated with clopidogrel. The mean (\pm SD) age was 34.4 ± 12.8 years, and 20% were women. After 4 hours, treatment with a 300-mg dose of clopidogrel resulted in a mean absolute reduction in platelet aggregation (Δ MPA) of 36.0 ± 20.5 percentage points.

The associations between the presence of a reduced-function CYP allele and both plasma exposure to the active metabolite of clopidogrel and platelet inhibition are presented in Figure 1. Carriers of at least one *CYP2C19* reduced-function allele (34% of the study population) had a relative reduction of 32.4% in plasma exposure to the active metabolite, as compared with noncarriers ($P < 0.001$). Carriers also had a diminished pharmacodynamic response, with an absolute Δ MPA in response to clopidogrel that was 9 percentage points less than that seen in noncarriers ($P < 0.001$), or a relative reduction of approximately 25%.

The pharmacokinetic and pharmacodynamic effects of a *CYP2C19* reduced-function allele on the response to clopidogrel were observed after a loading dose (either 300 mg or 600 mg) and during the administration of a maintenance dose (Table 6 in the Supplementary Appendix). Furthermore, when the extended *CYP2C19* genotypic classification was used (ultrarapid, extensive, intermediate, and poor metabolizer genotypes), there was a gradient of

Figure 3 (facing page). Association between Status as a Carrier of a *CYP2C19* Reduced-Function Allele and the Primary Efficacy Outcome or Stent Thrombosis in Subjects Receiving Clopidogrel.

Among 1459 subjects who were treated with clopidogrel and could be classified as *CYP2C19* carriers or noncarriers, the rate of the primary efficacy outcome (a composite of death from cardiovascular causes, myocardial infarction, or stroke) was 12.1% among carriers, as compared with 8.0% among noncarriers (hazard ratio for carriers, 1.53; 95% CI, 1.07 to 2.19) (Panel A). Among 1389 subjects treated with clopidogrel who underwent PCI with stenting, the rate of definite or probable stent thrombosis (a key prespecified secondary outcome, defined as per the Academic Research Consortium) was 2.6% among carriers and 0.8% among noncarriers (hazard ratio, 3.09; 95% CI, 1.19 to 8.00) (Panel B).

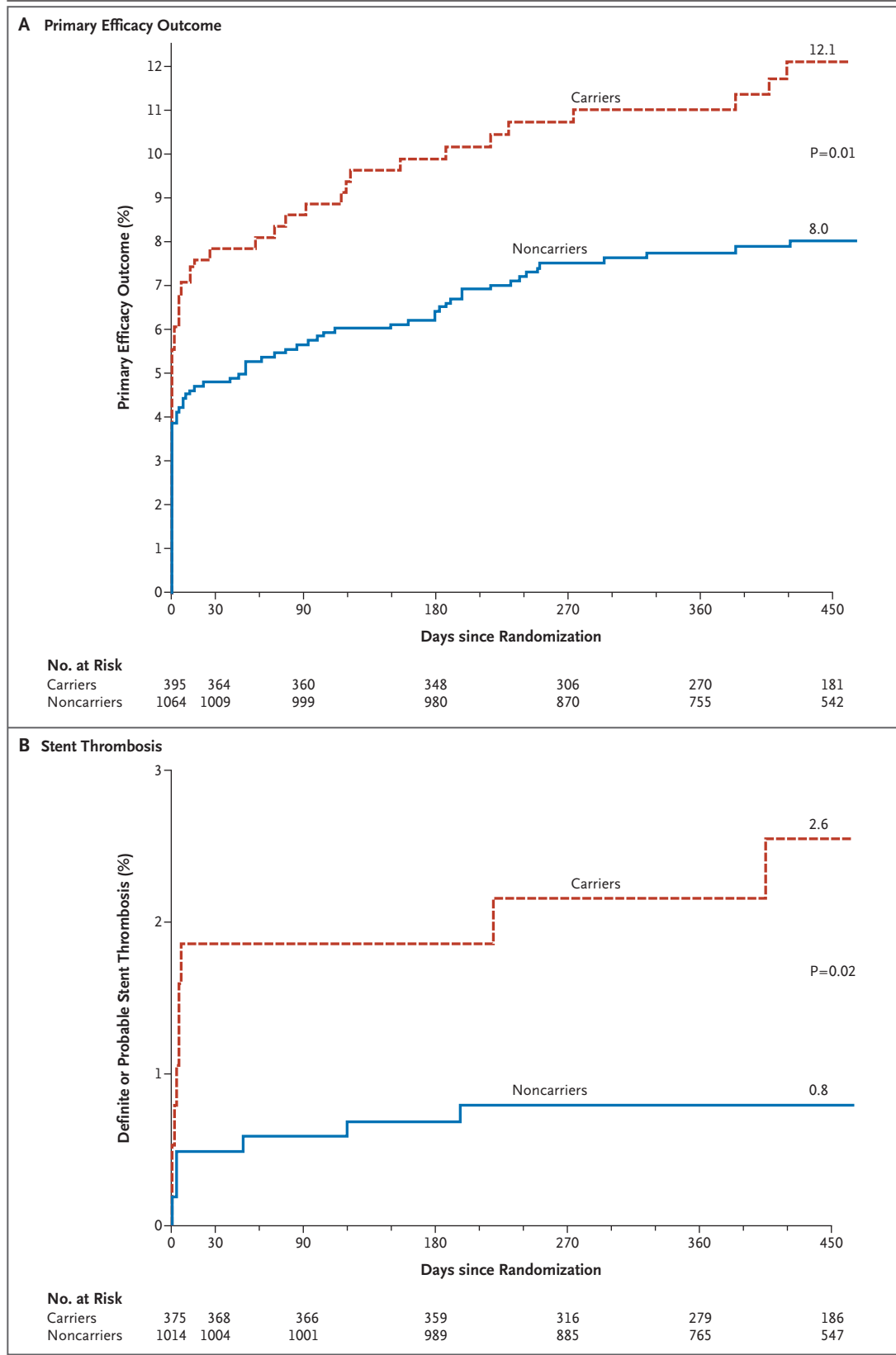
effect: subjects with the ultrarapid-metabolizer genotypes had the highest exposure to active metabolite and the greatest platelet inhibition, and subjects with the poor-metabolizer genotypes had the lowest exposure and least platelet inhibition with both loading and maintenance doses (Fig. 2).

As compared with noncarriers, carriers of a reduced-function *CYP2B6* allele tended to have lower plasma exposure to the active metabolite of clopidogrel (a relative reduction of 15.7%) and tended to have less reduction of platelet aggregation in response to clopidogrel (an absolute difference in Δ MPA of 5.7 percentage points). Carrier status for a reduced-function allele for the other three CYP genes (*CYP2C9*, *CYP3A5*, and *CYP1A2*) was not associated with a consistent attenuation of the pharmacokinetic and pharmacodynamic responses to clopidogrel.

CLINICAL OUTCOMES

DNA samples were available for 1477 subjects who were assigned to treatment with clopidogrel in TRITON-TIMI 38. Their mean age was 60.1 ± 11.1 years, 29.3% were women, 71.0% presented with non-ST-elevation acute coronary syndromes, and 29.0% presented with ST-elevation myocardial infarction.

Concordant with and extending the pharmacokinetic and pharmacodynamic findings, 395 subjects carrying at least one *CYP2C19* reduced-function allele (27.1% of the study population) were at significantly higher risk for the primary efficacy outcome of death from cardiovascular causes, myocardial infarction, or stroke than were noncarriers (12.1% vs. 8.0%; hazard ratio for car-



riers, 1.53; 95% confidence interval [CI], 1.07 to 2.19; $P=0.01$) (Fig. 3A).

A directionally consistent hazard was observed among subjects carrying a *CYP2C19* reduced-function allele for each of the components of the primary efficacy outcome, as compared with noncarriers, including death from cardiovascular causes (2.0% vs. 0.4%; hazard ratio, 4.79; 95% CI, 1.40 to 16.37), nonfatal myocardial infarction (10.1% vs. 7.5%; hazard ratio, 1.38; 95% CI, 0.94 to 2.02), and nonfatal stroke (0.88% vs. 0.24%; hazard ratio, 3.93; 95% CI, 0.66 to 23.51). The risk of stent thrombosis in carriers of a *CYP2C19* reduced-function allele was three times that among noncarriers (2.6% vs. 0.8%; hazard ratio, 3.09; 95% CI, 1.19 to 8.00; $P=0.02$) (Fig. 3B).

For *CYP2C19*, the presence of at least one copy of the *2 allele accounted for 95% of the subjects who were classified as carriers of a reduced-function allele. *CYP2C19**2 carriers had a higher rate of the primary efficacy outcome (11.7% vs. 8.3%; hazard ratio, 1.42; 95% CI, 0.98 to 2.05; $P=0.04$) and of stent thrombosis (2.7% vs. 0.8%; hazard

ratio, 3.33; 95% CI, 1.28 to 8.62; $P=0.004$) than did noncarriers.

No significant associations between any of the other CYP genotypes and the primary efficacy outcome were observed, nor did the rates of non-CABG-related TIMI major or minor bleeding differ significantly across any CYP genotype (Table 1).

DISCUSSION

Our results provide strong evidence linking CYP genetic variation to a reduced exposure to the active drug metabolite, less platelet inhibition, and less protection from recurrent ischemic events in persons receiving clopidogrel. Specifically, common polymorphisms in the *CYP2C19* gene, seen in approximately 30% of whites, 40% of blacks, and more than 55% of East Asians,³¹ significantly diminish both the pharmacokinetic and pharmacodynamic responses to clopidogrel by approximately one quarter to one third. In addition, our findings show that in patients with acute coronary syndromes treated with clopidogrel, the same

Table 1. Efficacy and Safety Outcomes at 15 Months in Subjects Treated with Clopidogrel, According to Genotype Status.*

Gene	Carriers of Reduced-Function Allele	Noncarriers of Reduced-Function Allele	Hazard Ratio (95% CI)	P Value
	no./total no. (%)			
Composite primary efficacy outcome†				
<i>CYP2C19</i>	46/395 (12.1)	83/1064 (8.0)	1.53 (1.07–2.19)	0.01
<i>CYP2C9</i>	22/230 (10.0)	107/1226 (9.0)	1.09 (0.69–1.73)	0.41
<i>CYP2B6</i>	36/370 (10.0)	68/777 (9.0)	1.11 (0.74–1.67)	0.78
<i>CYP3A5</i>	95/1130 (8.7)	14/151 (9.5)	0.89 (0.51–1.57)	0.69
<i>CYP1A2</i>	5/59 (8.5)	95/1099 (8.9)	0.97 (0.40–2.39)	0.96
Major or minor bleeding‡				
<i>CYP2C19</i>	11/393 (2.9)	30/1061 (3.0)	1.01 (0.51–2.01)	0.98
<i>CYP2C9</i>	7/229 (3.4)	34/1222 (2.9)	1.07 (0.47–2.40)	0.88
<i>CYP2B6</i>	12/370 (3.3)	22/773 (3.1)	1.08 (0.53–2.18)	0.84
<i>CYP3A5</i>	31/1125 (3.0)	5/151 (3.3)	0.77 (0.30–1.97)	0.58
<i>CYP1A2</i>	2/59 (3.4)	31/1094 (3.0)	1.29 (0.31–5.38)	0.73

* The rates of the outcomes are expressed as Kaplan–Meier cumulative estimates during a 15-month period and so are not presented as numerical percentages. Genotyping for all alleles of all genes was not successful, and not every patient could be classified as being either a carrier or a noncarrier for each gene.

† The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke. The primary efficacy outcome was assessed in 1477 patients who were assigned to treatment with clopidogrel and who provided a genetic sample.

‡ The safety outcome was assessed in 1472 patients who received treatment with clopidogrel and who provided a genetic sample.

variants in *CYP2C19* were associated with adverse clinical outcomes, including a rate of death from cardiovascular causes, myocardial infarction, or stroke that was more than 50% greater and a rate of stent thrombosis that was greater by a factor of three than the rate in noncarriers.

There are compelling biologic data to support these findings. *CYP2C19* contributes in both of the two sequential oxidative metabolic steps of clopidogrel activation. Slowing the first step would tend to shunt the prodrug preferentially to an esterase-mediated pathway forming pharmacologically inactive metabolites (Fig. 1 in the Supplementary Appendix). *CYP2C19**2 was the most frequent variant allele (95%) among the reduced-function group. This loss-of-function variant encodes a cryptic splice variant that leads to no enzymatic activity.³² Data from several studies support the observations regarding reduced-function *CYP2C19* polymorphisms and platelet aggregation among clopidogrel-treated subjects.^{10,15,33} However, these studies examined fewer polymorphisms than we did and did not have sufficient power to demonstrate an association between genotype and clinical outcome. Our study involved more extensive genotyping of the CYP genes relevant to clopidogrel metabolism and evaluated the association with exposure to the active metabolite of clopidogrel, platelet inhibition, and cardiovascular outcomes. These findings enabled us to assess the consistency in biologic effects of genetic variants across these measures.

There are several potential limitations to our study. First, although we genotyped multiple known functional variants in the relevant CYP genes in a large cohort, some rare functional variants were not observed in our population. We cannot exclude meaningful effects of these and other genetic variants that either were not identified or had incomplete functional characterization.^{34,35} Moreover, since variations in non-CYP genes may also have an effect on responsiveness to clopidogrel and the likelihood of ischemic events, such variations also merit study. Likewise, there were so few homozygotes for any allele that we could not perform meaningful analyses regarding clinical events. Second, owing to the complexity of the sample

handling and assays necessary for the pharmacokinetic and pharmacodynamic assessments, these evaluations could not be widely implemented in TRITON-TIMI 38, a large, multinational clinical trial. Thus, our platelet-aggregation studies were done in healthy subjects, not in patients with coronary disease. In addition, multiple genetic and environmental factors may contribute to platelet aggregation. However, by examining the change in platelet aggregation after the administration of clopidogrel, we attempted to control for factors that might have an effect on baseline platelet reactivity. Third, among subjects receiving clopidogrel, we might have expected to observe a lower rate of bleeding among carriers of a *CYP2C19* reduced-function allele than among noncarriers. However, given the low rate of bleeding events, the power to detect significant differences in bleeding on the basis of genotype was limited in TRITON-TIMI 38.

In conclusion, we have shown that genetic variation has an effect on pharmacologic and clinical responses to clopidogrel. Carriers of a reduced-function *CYP2C19* allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis.

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