Cytochrome P450 Gene Variants, Race, and Mortality Among Clopidogrel-Treated Patients After Acute Myocardial Infarction

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Background—Clopidogrel is recommended after acute myocardial infarction but has variable efficacy and safety, in part related to the effect of cytochrome P450 (CYP) polymorphisms on its metabolism. The effect of CYP polymorphisms on cardiovascular events among clopidogrel-treated patients after acute myocardial infarction remains controversial, and no studies to date have investigated the association of CYP variants with outcomes in black patients.

Methods and Results—Subjects (2732: 2062 whites; 670 blacks) hospitalized with acute myocardial infarction enrolled in the prospective, multicenter TRIUMPH study were genotyped for CYP polymorphisms. The majority of whites (79%) and blacks (64.4%) were discharged on clopidogrel. Among whites, carriers of the loss-of-function CYP2C19*2 allele had significantly increased 1-year mortality (adjusted hazards ratio [HR]: 1.70; confidence interval [CI]: 1.01–2.86; P=0.046) and a trend toward increased rate of recurrent MI (adjusted HR: 2.10; CI: 0.95–4.63; P=0.066). Among blacks, increased 1-year mortality was associated with the gain-of-function CYP2C19*17 allele (adjusted HR for *1/*17 versus *1/*1: 2.02; CI: 0.92–4.44; *17/*17 versus *1/*1: 8.97; CI: 3.34–24.10; P<0.0001) and the CYP1A2*1C allele (adjusted HR for *1/*1C versus *1/*1: 1.89; CI: 0.85–4.22; *1C/*1C versus *1/*1: 4.96; CI: 1.69–14.56; P=0.014). Bleeding events were significantly more common among black carriers of CYP2C19*17 or CYP1A2*1C.

Conclusions—Both loss-of-function and gain-of-function CYP polymorphisms affecting clopidogrel metabolism are associated with increased mortality among clopidogrel-treated patients after acute myocardial infarction; the specific polymorphism and the putative mechanism vary according to race. (Circ Cardiovasc Genet. 2014;7:277-286.)

Key Words: clopidogrel • genetic variation • mortality • myocardial infarction

Acutely myocardial infarction (AMI) is typically caused by platelet-mediated thrombosis at the site of a ruptured or eroded atherosclerotic plaque. Antiplatelet therapy with aspirin and clopidogrel is commonly prescribed early and continued after AMI to reduce recurrent ischemic events but may cause an increase in the risk of bleeding.1-3 Both recurrent ischemic events and bleeding have been associated with increased late mortality.4-5

Clinical Perspective on p 286

Recent studies have demonstrated wide variability of individual patient responsiveness to the inhibitory effects of clopidogrel on platelet aggregation.6-8 with potentially important implications for its clinical effectiveness and safety. After percutaneous coronary intervention (PCI) or ACS, patients with low clopidogrel responsiveness and consequent high on-treatment platelet reactivity have a higher risk of recurrent ischemic events,9-12 whereas patients with enhanced platelet inhibition have lower risk of cardiovascular events13 but a higher risk of bleeding.14 Clopidogrel, which exerts its effects by inhibiting the platelet P2Y₁₂ adenosine diphosphate receptor, is a prodrug that must be converted into its active metabolite by hepatic metabolism via multiple cytochrome (CYP) P450 isoenzymes, including CYP2C19, CYP1A2, CYP2B6, CYP2C9, and CYP3A. Functional variability in these CYP450 proteins, resulting from single nucleotide polymorphisms (SNPs) in the genes encoding them, has been shown to contribute to the observed variation in clopidogrel-induced platelet inhibition14-19 and may account, at least in part, for differences in outcome among clopidogrel-treated patients. For example, compared with individuals with 2 “wild-type” CYP2C19*1 alleles, white carriers of the loss-of-function CYP2C19*2 allele treated with clopidogrel have decreased metabolism resulting in significantly decreased levels of active metabolite,16 increased on-treatment platelet reactivity,15,17,18,20 and an increased risk of adverse ischemic events after PCI.21,22 In contrast, increased metabolism of clopidogrel among patients with a gain-of-function allele such as CYP2C19*17 results in enhanced platelet inhibition17 and is associated with an...
increased risk of bleeding after PCI. Notably, in 2010, the FDA required a "boxed warning" to be added to the label for clopidogrel concerning the diminished effectiveness of the drug in patients with decreased CYP2C19 function because of genetic polymorphisms.

These previously reported effects of CYP gene polymorphisms on clopidogrel-related platelet responsiveness and outcomes have been observed in predominantly white or Asian populations after PCI. The effect of CYP polymorphisms on cardiovascular events among clopidogrel-treated patients after an acute coronary syndrome remains controversial, and no studies to date have investigated the association of these CYP variants with outcomes in black patients. In consideration of the Institute of Medicine’s recently articulated goal to identify patient characteristics and treatments that vary by race to develop interventions that will minimize differences in care and eliminate disparities in outcomes, we investigated whether CYP variants were associated with different outcomes, including 1-year mortality, among clopidogrel-treated white and black patients after AMI in the large, prospective, multicenter Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status (TRIUMPH) cohort. Our primary aim was to investigate whether CYP2C19*2 and CYP2C19*17 variants were associated with significantly different rates of 1-year mortality in white and black post-MI patients discharged on clopidogrel. As a secondary aim, we sought to more comprehensively investigate previously reported genetic variants in the genes encoding proteins involved in clopidogrel absorption and metabolism. Toward these 2 aims, we specifically investigated variants in CYP2C19, CYP1A2, CYP2B6, CYP2C9, and CYP3A5, and ABCB1 (a gene shown to influence intestinal absorption of clopidogrel), and outcomes among patients recovering from AMI.

**Methods**

**Subjects**

Between April 11, 2005, and December 31, 2008, 4340 patients with AMI, from 24 US hospitals were prospectively enrolled into the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status (TRIUMPH) observational cohort study, as previously described. AMI patients were identified by an elevated troponin blood test and either diagnostic ECG changes or ischemic symptoms. To reach this aim, we specifically investigated variants in CYP2C19, CYP1A2, CYP2B6, CYP2C9, and CYP3A5, and ABCB1 (a gene shown to influence intestinal absorption of clopidogrel), and outcomes among patients recovering from AMI.

**Statistical Analyses**

Our primary aim was to investigate whether CYP2C19*2 (rs4244285) and CYP2C19*17 (rs12248560) variants were associated with significantly different rates of 1-year mortality in white and black post-MI patients consented to genetic testing. Of these, 2955 (99.2%) were discharged alive and were included in the present analyses. Given the large frequency differences for several genotypes of interest across race, we restricted the analyses to self-identified white and black post-MI patients discharged on clopidogrel. As a secondary aim, we sought to more comprehensively investigate previously reported genetic variants in the genes encoding proteins involved in clopidogrel absorption and metabolism. Toward these 2 aims, we specifically investigated variants in CYP2C19, CYP1A2, CYP2B6, CYP2C9, and CYP3A5, and ABCB1 (a gene shown to influence intestinal absorption of clopidogrel), and outcomes among patients recovering from AMI.

**Mortality Assessment**

One-year mortality in TRIUMPH patients discharged on clopidogrel was the primary outcome. The Social Security Administration Death Master File was queried to determine patients’ vital status as of December 31, 2010, and was available for all patients in this study. Of note, this query was performed prior to new restrictions and expunging of some records from the database.

**Cardiac Rehospitalization, Recurrent MI, and Bleeding Outcomes**

The secondary outcomes of cardiac rehospitalization, recurrent MI, and bleeding were only assessed for variants with a significant association with the primary outcome of 1-year mortality. TRIUMPH follow-up has previously been described, briefly, follow-up was scheduled on all survivors at 1, 6, and 12 months. All follow-up interviews were conducted by telephone calls from a single, specialized center. If a patient reported additional blood collection, an in-home visit was performed by trained medical personnel at 1 and 6 months. For those who did not agree to blood collection, 1- and 6-month interviews were performed by telephone from the same single, specialized center as the 12-month interview. All patients were asked to report interval events (eg, procedures, diagnostic tests, hospitalizations, and outpatient visits) occurring after the time of their last study contact. If a patient reported being hospitalized, records of that hospitalization were requested to adjudicate cardiovascular events, including MI, heart failure, or revascularization procedures. Chart abstractions were sent to 2 cardiologists for independent determination of the reason for hospitalization. If there was disagreement between the 2 cardiologists, the record was adjudicated by a third cardiologist, and, if disagreement persisted, up to 5 cardiologists independently reviewed the charts until consensus was obtained. Bleeding outcomes were documented in 2 ways. Major bleeding was adjudicated by 3 independent cardiologists. Minor ("nuisance" or BARC Type-1) bleeding was determined by interview. Any major or minor bleeding episode was counted as a bleeding outcome in this analysis.

**Genotyping Methods and QC**

DNA was isolated and purified from whole blood using the Qiagen QIAamp DNA purification kit (Qiagen, Germantown, MD). Genotyping of CYP and ABCB1 polymorphisms was performed by pyrosequencing or TaqMan assay. Pyrosequencing was performed as previously described. Polymerase chain reaction (PCR) was performed using AmpliTaq Gold PCR master mix (ABI, Foster City, CA), 1 pmole of each primer (IDT, Coralville, IA), and 1 ng DNA. Pyrosequencing primers and conditions are listed in Table I in the Data Supplement. TaqMan genotyping assays (assay IDs listed in Table II in the Data Supplement) were performed according to manufacturer’s directions (Applied Biosystems, Carlsbad, CA). The DNA segments containing the region of interest were amplified with PCR using TaqMan genotyping master mix and 5 to 10 ng DNA. Allelic discrimination was performed using sequence detection software (Applied Biosystems, Carlsbad, CA). PCR and allelic discrimination were performed using the ABI 7500 real-time PCR platform. All genotype data were transferred to a Microsoft Access database for permanent storage and merging with the clinical data sets through SAS v9.1.

For all variants, genotype call rates were greater than 92%. After pyrosequencing, the CYP2C19*2 (rs4244285) variant was found to be out of Hardy–Weinberg equilibrium in blacks (P=0.02). All samples were genotyped again using TaqMan genotyping assay. All but 3 samples matched genotypes. These 3 results were removed, but the variant remained out of Hardy–Weinberg equilibrium in blacks.
patients discharged on clopidogrel. As a secondary aim, we sought to more comprehensively investigate previously reported genetic variants in the genes encoding proteins involved in clopidogrel absorption and metabolism. Baseline and follow-up characteristics were compared by genotype. Baseline data did not differ between genotype groups except for CYP1A2*1C genotype groups in blacks where there was a statistically significant different history of CHF (although there was no linear trend one way or another [7.69% in AA homozygotes versus 13.69% in heterozygotes, and 5.7% in GG homozygotes]. P=0.018).

However, history of CHF was also included in the adjusted stratified proportional hazards models for CYP1A2*1C, described below. Categorical data are reported as frequencies and differences between groups were compared with χ² or Fisher’s exact tests, as appropriate. Continuous data are reported as mean±standard deviation (SD), and differences between groups were tested using one-way analysis of variance. Hardy–Weinberg equilibrium was assessed using χ² tests or Monte Carlo permutation with 10,000 iterations, as appropriate. Kaplan–Meier estimates and Cox proportional hazards models were used to describe the effect of genotype on patients’ survival, and log-rank P values were determined. Follow-up began at the time of discharge from the index hospitalization. To estimate the independent contribution of genotype, stratified proportional hazards models were used, adjusting for sex and the GRACE score for all outcomes except for bleeding where stratified proportional odds ratios (OR) were also adjusted for CRUSADE bleeding risk score.

According to Race

CYP2C19 expression and activity. CYP2C19 expression and activity.36

For all CYP variants, *1 (or *1A, in the case of CYP1A2) was assigned in the absence of other alleles. Metabolizer status was defined according to the classification schema described by Mega et al.37 into ultrarapid (UR), intermediate, extensive, and poor metabolizers. If metabolizer status could not be assigned according to this classification schema, the subjects were excluded from metabolizer analysis.

Analyses were performed separately in whites and blacks to minimize the risk of false-positive findings because of population stratification. Subjects reporting both white and black race (n=27) were excluded from the analysis. Our primary analysis investigated the contribution of genotype, stratified proportional hazards models were used to describe the effect of genotype on patients’ survival, and log-rank P values were determined. Follow-up began at the time of discharge from the index hospitalization. To estimate the independent contribution of genotype, stratified proportional hazards models were used, adjusting for sex and the GRACE score for all outcomes except for bleeding where stratified proportional odds ratios (OR) were also adjusted for CRUSADE bleeding risk score.33 Consistent with our previous investigations,16,18,20–22,25,34 a dominant model was used for CYP2C19 and CYP2C19*2 allele carriers versus 3% for *1/*1 homozygotes.

In white TRIUMPH subjects discharged on clopidogrel, there was 80% or more power to detect a 1-year mortality rate for patients discharged on clopidogrel, but blacks discharged on clopidogrel were less likely to also be discharged on aspirin. More than 80% of TRIUMPH patients discharged on clopidogrel received in-hospital revascularization; the majority of these being PCI (87.1% of whites and 77.4% of blacks). The 1-year mortality rate for patients discharged on clopidogrel was 3.6% (n=59) for whites and 7.2% (n=31) for blacks.

Prevalence of CYP Variants in the TRIUMPH Cohort

Frequencies of genotyped variants in white and black TRIUMPH patients (of the entire genetic cohort [including those discharged on clopidogrel and those not treated with clopidogrel] and of those only discharged on clopidogrel) are shown in Table III in the Data Supplement. All of the variants were similar in frequency to those reported in dbSNP (build 132). Most of the variants had similar frequencies in whites and blacks. However, the CYP3A5 rs776746 (G) allele, the CYP2B6*5A (T) allele, and the ABCB1 rs1045642 (C) allele were significantly more frequent in whites compared with blacks (0.97 versus 0.35 for CYP3A5 rs776746 (G) allele [P=2.73E–308]; 0.12 versus 0.03 for CYP2B6*5A (T) allele [P=7.47E–21]; 0.52 versus 0.25 for ABCB1 rs1045642 (C) allele [P=1.12E–61]). The CYP1A2*1C (A) allele and the CYP2B6*6 (T) allele were less frequent in whites compared with blacks (0.03 versus 0.28 for CYP1A2*1C (A) allele [P=3.3x10–145] and 0.24 versus 0.36 for CYP2B6*6 (T) allele [P=5.7x10–14]). CYP2C19*9 (A) allele and *13 (T) allele were rare (<1%) variants in whites and low frequency (<5%) variants in blacks.

Single Variant Association With Mortality According to Race

In white TRIUMPH subjects discharged on clopidogrel, the CYP2C19*2 variant was associated with significantly increased all-cause mortality (5.4% 1-year mortality for CYP2C19*2 allele carriers versus 3% for *1/*1 homozygotes; log-rank P=0.0216) in Kaplan–Meier analysis in our study. Baseline characteristics of these subjects are shown in Table 1. As seen in Table 1, the black subgroup consisted of more women and was slightly younger but had increased comorbidities, including diabetes mellitus, kidney disease, and heart failure. Nevertheless, the black and white subgroups had similar mean GRACE scores at discharge. The 1-year mortality rate was 4.9% for whites (n=102) and 9.7% for blacks (n=65).

Overall, 79% of whites (n=1632) and 64.4% of blacks (n=430) were discharged on clopidogrel. Characteristics of subjects discharged on clopidogrel are shown in Table 1. Similar to the entire cohort, the black subgroup consisted of more women and was slightly younger but had increased comorbidities, including diabetes mellitus, kidney disease, and heart failure. They also had more peripheral vascular disease and were more likely to have had a previous MI or cerebrovascular accident. Although the GRACE risk score was similar between whites and blacks, the CRUSADE bleeding score was significantly higher among black TRIUMPH patients discharged on clopidogrel. Discharge β-blockers and angiotensin converting enzyme/angiotensin II receptor blocker medication prescription were similar between white and black TRIUMPH patients discharged on clopidogrel, but blacks discharged on clopidogrel were less likely to also be discharged on aspirin.
Figure 1 and unadjusted (HR: 1.82; 95% confidence interval [CI]: 1.08–3.06; P = 0.0235) and adjusted (HR: 1.70; CI: 1.01–2.86; P = 0.046) analyses (Table 2). The interaction between CYP2C19*2 SNP and clopidogrel treatment for mortality in white TRIUMPH patients discharged on clopidogrel was not significant (P = 0.860). Mortality rates for each CYP2C19*2 genotype group are listed in Table IV in the Data Supplement. No other single variant (listed in Table III in the Data Supplement) was independently associated with mortality in whites.

Among black TRIUMPH patients discharged on clopidogrel, the CYP2C19*2 variant was not associated with significantly increased mortality in either unadjusted (HR: 0.66; CI: 0.29–1.47; P = 0.30) or adjusted (HR: 0.63; CI: 0.28–1.41; P = 0.26) analyses (Table 2). Among black TRIUMPH patients discharged on clopidogrel, the CYP2C19*17 variant was associated with significantly increased mortality (33.3% 1-year mortality for CYP2C19*17/*17 heterozygotes versus 9.8% for CYP2C19*17/*1 heterozygotes and 4.9% for *1/*1 homozygotes; log-rank P = 1E-05) in Kaplan–Meier analysis (Figure 2). Compared with black CYP2C19*1 homozygous individuals treated with clopidogrel, CYP2C19*17 allele carriers had greater mortality in both unadjusted (*1*/17 versus *1*/1 HR: 2.07; CI: 0.94–4.54; *17*/17 versus *1*/1 HR: 8.02; CI: 3.01–21.39; P = 0.0002) and adjusted (*1*/17 versus *1*/1 HR: 2.02; CI: 0.92–4.44; *17*/17 versus *1*/1 HR: 8.97; CI: 3.34–24.10; P < 0.0001) analyses (Table 2). Notably, patients homozygous for the *17 allele had the greatest risk and heterozygous patients had an intermediate risk, consistent with a gene dose effect. The interaction between CYP2C19*17 SNP and clopidogrel treatment for mortality in black TRIUMPH patients discharged on clopidogrel was significant (P = 0.091).

One other variant, CYP1A2*1C, was associated with significantly increased mortality (log-rank P = 0.0064) among black patients discharged on clopidogrel after AMI in Kaplan–Meier analysis (Figure 2).
CYP2C19 TRIUMPH patients discharged on clopidogrel, stratified by Figure 1.

*1A/*1A HR: 2.08; CI: 0.94–4.63; *1C/*1C versus *1A/*1A HR: 1.89; CI: 0.85–4.22; *1C/*1C versus *1A/*1A HR: 4.96; CI: 1.69–14.56; *1C allele had the greatest risk and heterozygous patients had an intermediate risk, consistent with a gene dose effect. The interaction between CYP1A2*1C SNP and clopidogrel-treated patients after AMI, we performed a pooled association analysis and determined the interaction P value between race and the relevant genetic variants. These analyses show a statistically significant interaction between race and mortality among clopidogrel-treated patients. In both unadjusted (*1A/*1C versus *1A/*1A HR: 2.08; CI: 0.94–4.63; *1C/*1C versus *1A/*1A HR: 4.96; CI: 1.69–14.56; P=0.012) and adjusted (*1A/*1C versus *1A/*1A HR: 1.89; CI: 0.85–4.22; *1C/*1C versus *1A/*1A HR: 4.96; CI: 1.69–14.56; P=0.014) analyses, patients homozygous for the CYP1A2*1C allele had the greatest risk and heterozygous patients had an intermediate risk, consistent with a gene dose effect. The interaction between CYP1A2*1C SNP and clopidogrel treatment for mortality in black TRIUMPH patients discharged on clopidogrel was significant (P=0.012).

To further substantiate a differential effect of race on the associations between CYP variants and mortality among clopidogrel-treated patients after AMI, we performed a pooled association analysis and determined the interaction P value between race and the relevant genetic variants. These analyses show a statistically significant interaction between race and mortality for CYP2C19*2 (P=0.042) and CYP2C19*17 (P=0.011).

**Single Variant Association with Cardiovascular Rehospitalization, Recurrent MI, and Bleeding**

To identify potential contributors to the significant mortality association found with CYP2C19*2, CYP2C19*17, and CYP1A2*1C variants, we determined whether variant carriers of CYP2C19*2, CYP2C19*17, and CYP1A2*1C had increased (or decreased) cardiovascular rehospitalization, recurrent MI, and bleeding events in TRIUMPH. In white TRIUMPH patients discharged on clopidogrel, there was a trend toward a increased recurrent MI among carriers of the CYP2C19*2 variant in unadjusted (HR: 2.08; CI: 0.95–4.59; P=0.0687) and adjusted (HR: 2.10; CI: 0.95–4.63; P=0.0661) models. The CYP2C19*2 variant was not associated with a significant difference in rehospitalization for all cardiovascular causes (unadjusted P=0.5034; adjusted P=0.5614) or with increased bleeding events (unadjusted P=0.283; adjusted P=0.43).

In black TRIUMPH patients discharged on clopidogrel, the CYP2C19*17 variant was not associated with a significant difference in recurrent MI (unadjusted P=0.988; adjusted P=0.999) or in cardiovascular rehospitalization (unadjusted P=0.848; adjusted P=0.785). However, bleeding events were significantly more frequent among black TRIUMPH patients homozygous for the CYP2C19*17 variant compared with those individuals without the variant (homozygote OR: 3.820; CI: 1.174–12.42; P=0.027 and heterozygote OR: 0.663; CI: 0.2850–1.5440; P=0.3419) with an overall significant genotypic effect (P=0.034).

In black TRIUMPH patients discharged on clopidogrel, the CYP1A2*1C variant was not associated with a significant difference in recurrent MI (unadjusted P=0.129; adjusted P=0.143) or in cardiovascular rehospitalization (unadjusted P=0.442; adjusted P=0.504). However, bleeding events were significantly more frequent among black TRIUMPH patient carriers of the CYP1A2*1C variant discharged on clopidogrel (OR: 2.90; CI: 1.416–5.937; P=0.0039 for heterozygotes; OR: 2.97; CI: 0.644–13.646; P=0.1638 for homozygotes; with an overall significant genotypic effect [P=0.013]).

**Metabolizer Phenotype Association With Mortality**

We sought to determine if there was an association of CYP2C19 metabolizer status with mortality among patients stratified by race in the TRIUMPH cohort. In white TRIUMPH patients discharged on clopidogrel, 44 subjects were CYP2C19 poor metabolizers, 711 subjects were extensive

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**Table 2. Unadjusted and Adjusted Hazard Ratios for Mortality in white and black Subjects Discharged on Clopidogrel by CYP2C19*2 and CYP2C19*17 Genotype**

<table>
<thead>
<tr>
<th>Variant</th>
<th>rs</th>
<th>TRIUMPH Subjects Discharged on Clopidogrel</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>rs4244285</td>
<td>1.82† 1.08–3.06 0.0235‡</td>
<td>1.7† 1.01–2.86 0.0463‡</td>
<td>1.66† 0.29–1.47 0.3049</td>
</tr>
<tr>
<td>CYP2C19*17</td>
<td>rs12248560</td>
<td>0.64§ 0.34–1.20 0.3662</td>
<td>0.76§ 0.18–3.14</td>
<td>2.07† 0.94–4.54 0.0017‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted (1*/17)</td>
<td>0.67§ 0.36–1.26 0.4608</td>
<td>2.02† 0.92–4.44 7.622E–05‡</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and HR, hazard ratio.†Carriers vs. Noncarriers.‡Significant P values.§vs. *1*/1.
metabolizers (normal), 280 subjects were intermediate metabolizers, and 494 subjects were UR metabolizers; 123 subjects were excluded from analysis because their metabolizer status could not be assigned according to the Mega classification. No significant difference in mortality by CYP2C19 metabolizer status was observed among whites discharged on clopidogrel after AMI in TRIUMPH (log-rank \( P=0.1726 \)).

In black TRIUMPH patients discharged on clopidogrel, there were 23 CYP2C19 poor metabolizer, 152 extensive metabolizer, 88 intermediate metabolizer, and 126 UR metabolizer; 49 subjects were excluded from analysis because their metabolizer status could not be assigned according to the Mega classification. As seen in Figure 4, CYP2C19 metabolizer status was significantly associated with mortality in blacks (log-rank \( P=0.0371 \)). Individuals with poor metabolizer had the highest survival (100% 1-year survival), individuals with intermediate metabolizer or extensive metabolizer had the next highest (97% and 94% 1-year survival), and individuals with UR metabolizer had the lowest 1-year survival (88% 1-year survival).

**Discussion**

Our analyses of CYP variants and outcomes among clopidogrel-treated patients after AMI revealed racial differences in the mortality association of CYP2C19 genotypes. We observed significantly increased 1-year mortality among white carriers of the loss-of-function CYP2C19*2 allele, whereas no increased mortality was observed among black CYP2C19*2 carriers. In contrast, significantly increased 1-year mortality was observed among black carriers of the gain-of-function CYP2C19*17 allele and the CYP1A2*1C allele, whereas no difference in mortality was detected among white subjects carrying either of these 2 variants. To our knowledge, this is the first report of significant associations between CYP polymorphisms and mortality among blacks and of divergent associations between mortality and CYP variants according to race.

To identify potential contributors to the observed increased mortality, we investigated the association of the same CYP polymorphisms with recurrent MI, rehospitalization for cardiac causes, and bleeding events, and also examined mortality according to genotype-predicted clopidogrel metabolizer status. In these secondary analyses, CYP2C19*2 carrier status in whites was associated with increased recurrent MI but not bleeding. In contrast, among blacks, a significant association was found between CYP2C19*17 and CYP1A2*1C with increased bleeding events. When patients were grouped according to predicted clopidogrel metabolizer phenotype, CYP2C19 metabolizer status was significantly associated with mortality in blacks but showed no association in whites. Among black AMI patients treated with clopidogrel, enhanced (UR) metabolism was associated with significantly reduced survival.

Previous studies have shown that white carriers of the loss-of-function CYP2C19*2 allele have decreased metabolism of clopidogrel and decreased levels of active metabolite, resulting in increased platelet reactivity among patients treated with clopidogrel compared with white individuals carrying 2 "wild-type" CYP2C19*1 alleles. Several previous investigations have reported that among patients presenting with acute coronary syndromes and treated with clopidogrel after PCI, white and Asian carriers of CYP2C19*2 alleles have significantly increased cardiovascular events, including MI, stroke, and death from cardiovascular causes compared with individuals with 2 CYP2C19*1 alleles. A recent investigation of post-MI patients receiving clopidogrel also reported increased cardiovascular events among CYP2C19*2 carriers. Of note, none of these previous individual studies have demonstrated a significant association between CYP2C19 genotype and all-cause mortality. Other studies have shown that the gain-of-function CYP2C19*17 variant is associated with lower adenosine diphosphate-induced platelet aggregation and a significantly increased risk of bleeding in patients undergoing PCI. Carriers of the CYP2C19*17 allele with acute coronary syndromes seem to derive more benefit during clopidogrel treatment compared with noncarriers, experiencing less subsequent cardiovascular events. These observations were also supported by 2 recent meta-analyses.
Nevertheless, the association of CYP polymorphisms with adverse cardiovascular and bleeding events has remained controversial. Meta-analyses examining the association between cardiovascular outcomes and the CYP2C19 genotype have differed in their conclusions. A meta-analysis of 19 studies involving 9685 predominantly PCI patients treated with clopidogrel reported a significantly increased risk of the composite end point of cardiovascular death, MI, or stroke in CYP2C19*2 carriers. A more recent meta-analysis of 16 prospective studies involving 20,785 subjects of Western or Asian descent with coronary artery disease on clopidogrel therapy reported an increase in adverse cardiovascular events among CYP2C19 loss-of-function allele carriers, with summary ORs of 2.18 for cardiac death ($P=0.0010$) and 1.42 for MI ($P=0.004$). In contrast, 2 other meta-analyses, one including 11 studies involving 16,360 patients and a second including 32 studies involving 42,016 patients exposed to clopidogrel concluded that CYP2C19*2 carriers had no increased risk of cardiovascular events, although a significantly increased risk of stent thrombosis after PCI was observed in those with a loss of function allele. It is important to note that none of the aforementioned studies or meta-analyses provided information on blacks.

Our finding of an association between the CYP2C19*2 allele and increased rates of MI and mortality among whites is consistent with previous reports of an increased hazard of ischemic events among carriers of loss-of-function variants for clopidogrel metabolism. Our study, however, is the first to report significantly increased 1-year mortality in clopidogrel-treated black post-MI carriers of the gain-of-function CYP2C19*17 allele and of the CYP1A2*1C allele. Notably, we observed that bleeding events were more frequent in black carriers of either of these 2 variants, leading us to speculate that the increased rate of bleeding events related to CYP genetic variability may have contributed to the adverse survival among TRIUMPH blacks with these genotypes. Supporting this contention, we also observed reduced survival among clopidogrel-treated black AMI patients with genotype-predicted enhanced or UR clopidogrel metabolism.

In addition to our findings about the more commonly studied CYP2C19*2 and *17 variants, our observation of increased mortality in black CYP1A2*1C allele carriers discharged on clopidogrel is noteworthy. This variant is much more frequent in blacks compared with whites (0.28 versus 0.03 in TRIUMPH). The CYP1A2 isoenzyme is important in detoxification of chemicals, environmental toxins, and drugs, and the CYP1A2*1C variant has been variably linked to both increased and decreased enzyme activity in white and Asian smokers and nonsmokers. However, neither the variant’s effect on enzyme activity in blacks nor its effect on clopidogrel responsiveness has been previously investigated. In view of our findings of increased bleeding events, it is intriguing to speculate that the association between CYP1A2*1C and increased mortality in blacks is related to increased clopidogrel responsiveness.

Black ancestry has been previously identified with an increased risk of bleeding among patients with ST elevation MI treated with reperfusion therapy, and among patients undergoing PCI. Two recent retrospective studies involving a total of over 80,000 patients from either the National Registry of MI (NRMI) or from 5 clinical trials reported that among patients with ST-elevation MI treated with fibrinolysis or PCI, compared with whites, blacks had an increase in both bleeding events and mortality. In a study of over 8800 patients undergoing PCI, a higher rate of bleeding was observed among blacks that remained significant after propensity adjustment for baseline characteristics. Similarly, among high-risk survivors of AMI studied in the Valsartan in Acute Myocardial Infarction (VALIANT) trial, nonwhite race was associated with a significantly increased risk of gastrointestinal bleeding, the most powerful predictor of which was use of dual antiplatelet therapy, and occurrence of gastrointestinal bleeding was associated with a significantly increased risk of all-cause death. Although some of these reports speculated that the observed increased bleeding risk according to race was a result of genotypic differences between whites and blacks, our study provides direct evidence of a specific genotypic explanation for increased bleeding risk in blacks treated with clopidogrel after AMI.

There may be significant clinical implications of these observations. Although the clinical use of CYP genetic testing has been controversial based on current evidence of the association of CYP2C19*2 with ischemic risk, the currently available studies have failed to comprehensively evaluate the potential adverse outcomes associated with CYP variants among racially diverse populations of patients treated with clopidogrel after ACS or PCI. Our results suggest select CYP variants are associated with increased mortality among clopidogrel-treated patients after AMI, and that the associated CYP variant and mechanism of increased risk may vary by race. Knowing the differences in risks associated with clopidogrel treatment, and how they vary by race, may be important in individualizing therapy to specific patients. Further study is needed to better understand how knowledge of CYP genotype might improve the management of the entire spectrum of patients who may be candidates for treatment with clopidogrel.
Our study should be interpreted in the context of several potential limitations. First, we did not measure platelet reactivity in our study. However, multiple studies have confirmed increased on-treatment platelet reactivity in CYP2C19*2 allele carriers and decreased on-treatment platelet reactivity in CYP2C19*17 allele carriers. Second, we stratified patients according to their predicted metabolizer status based on the classification suggested by Mega et al; however, the observation of an association between metabolizer classification and outcomes cannot prove cause and effect and cannot exclude the possible contribution of unmeasured confounders. In addition, although the majority of patients discharged on clopidogrel were documented to still be on clopidogrel on at least one follow-up time point, because of missing data we did not have precise information on how many subjects continued on clopidogrel for the full year. Third, as discussed in the Introduction and in the Methods sections, we performed primary and secondary analyses. As a primary analysis, our finding that the CYP2C19*17 variant was associated with significantly increased mortality among black TRIUMPH patients discharged on clopidogrel (log-rank P value = 1e−05) is highly significant. However, as a secondary analysis, our finding that the CYP1A2*1C variant was associated with significantly increased mortality among black TRIUMPH patients discharged on clopidogrel (log-rank P value = 0.0064) would just reach significance if corrected for multiple comparisons and should be replicated in future cohorts. Finally, our observations in blacks have not been independently replicated in a separate cohort. However, it should be noted that, to our knowledge, few adequately powered cohorts of genotyped subjects from outcome studies involving black AMI patients are available. For example, in the analysis of the association of CYP2C19 genotype with outcomes from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, results were only reported for patients of European and Latin American ancestry, as there were only 10 patients of African ancestry in this cohort of >5000 genotyped patients. In the report of the effect of CYP polymorphisms on response to clopidogrel from the Therapeutic Outcomes by Optimizing Platelet Inhibition by Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, the genetic cohort of 1477 subjects included only 10 patients of African ancestry, and in the meta-analysis of CYP variants among patients predominantly undergoing PCI treated with clopidogrel reported by Mega et al, there were <5% nonwhites in a cohort of >9000 patients. Nevertheless, despite lack of replication, we think there is biological and clinical plausibility for our results based on the known effects of the identified variants and the associations with specific outcome hazards observed.

In its consensus report Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare, the Institute of Medicine recommended research to identify patient characteristics and treatments that vary by race so that interventions could be developed to minimize differences in care and disparities in outcomes. Utilizing the unique opportunity provided by TRIUMPH to evaluate genetic mediators of racial disparities in outcomes among MI patients treated with clopidogrel, our investigations show that cytochrome P450 polymorphisms are associated with mortality in post-MI patients receiving clopidogrel in a race-specific manner. Understanding the mechanism by which genetic variation impacts post-MI outcomes differently in white and black patients may illuminate opportunities to improve care and, ultimately, reduce differences in outcomes by race.

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Disclosures

J.A.S. has the following potential conflicts of interest to disclose: Research Grants from Eli Lilly, EveHeart, Genentech, and Gilead; Consultant for St. Jude Medical (modest), United Healthcare (modest), Amgen (modest), Gilead (modest), Genentech (modest), Janssen (modest), and Novartis (modest); Copyrights/Patents for Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire (US Patents: 7,643,969; 7,853,456; 12/965,656; 13/615,401). Richard G. Bach has the following potential conflicts of interest to disclose: Research Grants from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, and Merck/Schering-Plough; Consultant (Clinical Event Committee Adjudication Activity only) for Roche (Significant) and Pfizer (Modest). All others have none.

References

As an antiplatelet medication, clopidogrel is commonly prescribed to reduce adverse cardiovascular events after acute myocardial infarction (AMI), but its effectiveness and safety may vary among patients because of inherited variation in cytochrome P450 (CYP) enzymes involved in its metabolism, with clinically important consequences. Select loss-of-function CYP gene (CYP) polymorphisms have previously been linked to reduced clopidogrel effectiveness for preventing recurrent ischemic events, whereas gain-of-function CYP variants have been associated with increased bleeding. We investigated the effect of CYP polymorphisms on outcomes among clopidogrel-treated patients after AMI in a real-world registry, including examining differences in these effects according to race. We observed that among clopidogrel-treated whites after AMI, carriers of the loss-of-function CYP2C19*2 allele had significantly increased 1-year mortality and a trend toward increased rate of recurrent MI, whereas among clopidogrel-treated blacks after AMI, the gain-of-function CYP2C19*17 allele and the CYP1A2*1C allele were associated with increased 1-year mortality and a higher rate of bleeding events. These results suggest that both loss-of-function and gain-of-function CYP polymorphisms affecting clopidogrel metabolism may adversely affect outcome among clopidogrel-treated patients after AMI, whereas the specific gene polymorphism and the putative mechanism of action may vary according to race. These observations have clinical implications about both racial differences in outcome among patients with AMI and the application of genetic testing to personalized antiplatelet therapy.
Cytochrome P450 Gene Variants, Race, and Mortality Among Clopidogrel-Treated Patients After Acute Myocardial Infarction
Sharon Cresci, Jeremiah P. Depta, Petra A. Lenzini, Allie Y. Li, David E. Lanfear, Michael A. Province, John A. Spertus and Richard G. Bach

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http://circgenetics.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL
**Supplemental Table S1.** Pyrosequencing Primers and Conditions.

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**Supplemental Table S3.** Frequencies of genotyped variants in Caucasian and African American TRIUMPH patients (entire cohort including those discharged on clopidogrel and those not treated with clopidogrel), TRIUMPH patients discharged on clopidogrel, dbSNP (build 132) and the test of Hardy-Weinberg equilibrium

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Supplemental Table S4. Mortality Rates for Each CYP2C19*2 Genotype Group

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Supplemental Figure S1. Linkage Disequilibrium between CYP2C19*17 SNPs in Caucasian (left panel) and African American (right panel) TRIUMPH patients. R² of LD.