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

Running title: Cresci et al.; CYP variants, clopidogrel and mortality after MI

Sharon Cresci, MD1,2; Jeremiah P. Depta, MD1; Petra A. Lenzini, MS3; Allie Y. Li, BS1; David E. Lanfear, MD, MS4; Michael A. Province, PhD3; John A. Spertus, MD, MPH5; Richard G. Bach, MD1

1Department of Medicine, Cardiovascular Division, 2Department of Genetics, 3Department of Genetics, Statistical Genomics Division, Washington University School of Medicine, Saint Louis, MO; 4Heart and Vascular Institute, Henry Ford Hospital, Detroit, MI; 5Saint Luke’s Mid America Heart Institute & the University of Missouri-Kansas City, Kansas City, MO

Correspondence:
Sharon Cresci, MD
Washington University School of Medicine
660 S. Euclid Ave., Campus Box 8086
St. Louis, MO 63110
Phone: 314-362-5363
Fax: 314-747-8560
E-mail: scresci@dom.wustl.edu

Abstract:

**Background** - Clopidogrel is recommended after acute myocardial infarction (AMI) 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 AMI remains controversial, and no studies to date have investigated the association of CYP variants with outcomes in African American patients.

**Methods and Results** - 2732 subjects (2062 Caucasians; 670 African Americans) hospitalized with AMI enrolled in the prospective, multicenter TRIUMPH study were genotyped for CYP polymorphisms. The majority of Caucasians (79%) and African Americans (64.4%) were discharged on clopidogrel. Among Caucasians, carriers of the loss-of-function CYP2C19*2 allele had significantly increased 1-year mortality (adjusted HR: 1.70; CI: 1.01 to 2.86; \(p=0.046\)), and a trend toward increased rate of recurrent MI (adjusted HR: 2.10; CI 0.95 to 4.63; \(p=0.066\)). Among African Americans, increased 1-year mortality was associated with the gain of function CYP2C19*17 allele (adjusted HR for *1/*17 vs. *1/*1: 2.02; CI: 0.92 to 4.44; *17/*17 vs. *1/*1: 8.97; CI: 3.34 to 24.10; \(p<0.0001\)) and the CYP1A2*1C allele (adjusted HR for *1/*1C vs. *1/*1: 1.89; CI: 0.85 to 4.22; *1C/*1C vs. *1/*1: 4.96; CI: 1.69 to 14.56; \(p=0.014\)). Bleeding events were significantly more common among African American 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 following AMI; the specific polymorphism and the putative mechanism vary according to race.

**Key words:** clopidogrel, pharmacogenetics cardiovascular disease, genetic variation, myocardial infarction, mortality
Introduction

Acute myocardial infarction (AMI) is typically caused by platelet-mediated thrombosis at the site of a ruptured or eroded atherosclerotic plaque. Anti-platelet therapy with aspirin and clopidogrel is commonly prescribed early and continued following 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

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. Following 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 while 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 pro-drug 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 inhibition,14-19 and may account, at least in part, for differences in outcome among clopidogrel-treated patients. For example, compared with individuals with two ‘wild-type’ CYP2C19*1 alleles, Caucasian 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

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activity, and an increased risk of adverse ischemic events after PCI. In contrast, increased metabolism of clopidogrel among patients with a gain-of-function allele such as CYP2C19*17 results in enhanced platelet inhibition and is associated with an increased risk of bleeding after PCI. Notably, in 2010, the FDA required a “boxed warning” be added to the label for clopidogrel concerning the diminished effectiveness of the drug in patients with decreased CYP2C19 function due to genetic polymorphisms.

These previously reported effects of CYP gene polymorphisms on clopidogrel-related platelet responsiveness and outcomes have been observed in predominantly Caucasian 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 African American patients. In consideration of the Institute of Medicine’s recently articulated goal to identify patient characteristics and treatments that vary by race in order 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 Caucasian and African American 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 Caucasian and/or African American 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 two 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.21

Methods
Subjects
Between April 11, 2005, and December 31, 2008, 4340 patients with AMI, from 24 U.S. 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.27-29 AMI patients were identified by an elevated troponin blood test and either diagnostic electrocardiogram (EKG) changes or ischemic symptoms. 2979 TRIUMPH patients consented to genetic testing.29 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 Caucasian and African-American patients, yielding a final sample size of 2732 subjects (2062 Caucasians; 670 African Americans). Subjects reporting both Caucasian and African American race (N=27) were excluded from the analysis. The representativeness of the TRIUMPH genetics cohort was checked (compared to the entire TRIUMPH cohort) and was confirmed (for the entire TRIUMPH cohort the rates of discharge on clopidogrel: 78.8% of Caucasians and 63.3% African Americans; 1-year mortality of 5.3% in Caucasians and 9.3% for African Americans; 1-year mortality of those subjects discharged on clopidogrel: 4.0% in Caucasians and 7.1% in African Americans) consistent with previous reports.29

Each patient was prospectively interviewed during their AMI hospitalization to ascertain their socio-demographic (including self-identified race), economic and health status characteristics. Detailed chart abstractions were performed to obtain patients’ medical history,
laboratory results, disease severity and the processes of inpatient care. TRIUMPH received Institutional Review Board approval at all participating sites and written informed consent was obtained from each participant.

**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 12/31/2010 (http://www.ntis.gov/products/ssa-dmf.asp) 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, 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 patients agreed to 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 (e.g., procedures, diagnostic tests, hospitalizations, and outpatient visits) since 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 two ways. Major bleeding was adjudicated by three 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 (Quiagen, Germantown, MD). Genotyping of *CYP* and *ABCB1* polymorphisms was performed by pyrosequencing or TaqMan® assay. Pyrosequencing was performed as previously described. PCR was carried out using Amplitaq Gold PCR master mix (ABI, Foster City, CA), 1 pmole of each primer (IDT, Coralville, IA), and 1ng DNA. Pyrosequencing primers and conditions are listed in Supplemental Table S1. TaqMan® genotyping assays (assay IDs listed in Supplemental Table S2) were performed according to manufacturer's directions (Applied Biosystems, Carlsbad, California). The DNA segments containing the region of interest were amplified with PCR using TaqMan® genotyping master mix and 5-10ng DNA. Allelic discrimination was performed using sequence detection software (Applied Biosystems, Carlsbad, California). 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 datasets 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 (HWE) in African Americans (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 HWE in African Americans.

**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 Caucasian and/or African American 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. Baseline and follow-up characteristics were compared by genotype. Baseline data did not differ between genotype groups except for *CYP1A2*1C genotype groups in African Americans 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 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 chi-square 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. HWE was assessed using chi-square tests or Monte Carlo permutation with 10000 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 score32 for all outcomes except for bleeding where stratified proportional odds ratios (OR) were also adjusted for CRUSADE bleeding risk score.33 Consistent with previous investigations,16, 18, 20-22,
a dominant model was used for CYP2C19*2 (rs4244285). For all other genotypes, we used an additive model. We genotyped both CYP2C19*17 variants, CYP2C19*17 -3402 (rs11188072) and CYP2C19*17 -806 (rs12248560), and determined linkage, in our cohort, for these two variants. Given that the two CYP2C19*17 variants were in tight LD in our cohort (Supplemental Figure S1), consistent with others’ data, we restricted our analyses to the functional, ‘defining’ CYP2C19*17 variant (CYP2C19*17 -806; rs12248560) that is responsible for a C>T transition in the CYP2C19 promoter that creates a new consensus binding site for the GATA transcription factor family, resulting in increased CYP2C19 expression and activity.

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. into ultra-rapid (UR), intermediate (IM), extensive (EM) and poor (PM) 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 Caucasians and African-Americans to minimize the risk of false positive findings due to population stratification. Subjects reporting both Caucasian and African American race (N=27) were excluded from the analysis. Our primary analysis investigated whether CYP2C19*2 (rs4244285) and/or CYP2C19*17 (rs12248560) variants were associated with significantly different rates of 1-year mortality in Caucasian and/or African American post-MI patients discharged on clopidogrel and, therefore, included only those subjects discharged on clopidogrel. If a significant association was identified, a SNP by clopidogrel treatment interaction was assessed (this secondary analysis, therefore, included subjects within the racial group that were not treated with clopidogrel). For primary effects, p-values <0.05 were considered statistically significant; interaction p-values <0.2 were considered
statistically significant.\textsuperscript{37,38} Analyses were performed with SAS version 9.2 (SAS Institute, Inc., Cary, NC) and R version 2.11.1. In TRIUMPH, given a mortality of 7.2\% in African Americans discharged on clopidogrel, there was 80\% or more power to detect a HR of 2.2 or above with a minor allele frequency of 0.21 or greater; given a mortality of 3.6\% in Caucasians discharged on clopidogrel, there was 80\% or more power to detect a HR of 2.1 or above with a minor allele frequency of 0.15 or greater.

**Results**

**TRIUMPH Genetic Cohort**

Between April 11, 2005, and December 31, 2008, 2732 subjects (2062 Caucasians; 670 African Americans) were recruited and included in our study. Baseline characteristics of these subjects are shown in Table 1. As seen in Table 1, the African American subgroup consisted of more females and was slightly younger but had increased co-morbidities, including diabetes, kidney disease and heart failure. Nevertheless, the African American and Caucasian subgroups had similar mean GRACE scores at discharge. The 1-year mortality rate was 4.9\% for Caucasians (N=102) and 9.7\% for African Americans (N=65).

Overall, 79\% of Caucasians (N=1632) and 64.4\% of African Americans (N=430) were discharged on clopidogrel. Characteristics of subjects discharged on clopidogrel are shown in Table 1. Similar to the entire cohort, the African American subgroup consisted of more females and was slightly younger but had increased co-morbidities, including diabetes, 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. While the GRACE risk score was similar between Caucasians and African Americans, the CRUSADE bleeding score was significantly higher among African American TRIUMPH patients discharged on clopidogrel. Discharge beta-
blockers and ACE/ARB medication prescription was similar between Caucasian and African American TRIUMPH patients discharged on clopidogrel, but African Americans 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 Caucasians and 77.4% of African Americans). The 1-year mortality rate for patients discharged on clopidogrel was 3.6% (N=59) for Caucasians and 7.2% (N = 31) for African Americans.

Prevalence of CYP Variants in the TRIUMPH Cohort

Frequencies of genotyped variants in Caucasian and African American TRIUMPH patients (entire cohort including those discharged on clopidogrel and those not treated with clopidogrel) are shown in Supplemental Table S3. All of the variants were similar in frequency to those reported in dbSNP (build 132). Most of the variants had similar frequencies in Caucasians and African Americans. However, the CYP3A5 rs776746 (G) allele, the CYP2B6*5A (T) allele and the ABCB1 rs1045642 (C) allele were significantly more frequent in Caucasians, as compared with African Americans (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 Caucasians, as compared with African Americans (0.03 versus 0.28 for CYP1A2*1C and 0.24 versus 0.36 for CYP2B6*6). CYP 2C19 *9 (A) allele and *13 (T) allele were rare (<1%) variants in Caucasians and low frequency (<5%) variants in African Americans.

Single Variant Association with Mortality According to Race

In Caucasian 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 vs. 3% for *1/*1 homozygotes; log-rank p= 0.0216) in Kaplan-Meier analysis (Figure 1) and unadjusted (HR: 1.82; 95% confidence interval (CI): 1.08 to 3.06; p= 0.0235) and adjusted (HR: 1.70; CI: 1.01 to 2.86; p=0.046) analyses (Table 2). The interaction between CYP2C19*2 SNP and clopidogrel treatment for mortality in Caucasian TRIUMPH patients discharged on clopidogrel was not significant (p= 0.860). Mortality rates for each CYP2C19*2 genotype group are listed in Supplemental Table S4. No other single variant (listed in Supplemental Table S3) was independently associated with mortality in Caucasians.

Among African American 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 to 1.47; p= 0.30) or adjusted (HR: 0.63; CI 0.28 to 1.41; p= 0.26) analyses (Table 2). Among African American TRIUMPH patients discharged on clopidogrel, the CYP2C19*17 variant was associated with significantly increased mortality (33.3% 1-year mortality for CYP2C19*17/*17 homozygotes vs. 9.8% for CYP2C19*17/*1 heterozygotes vs. 4.9% for *1/*1 homozygotes; log-rank p= 1e-05) in Kaplan-Meier analysis (Figure 2).

Compared with African American CYP2C19*1 homozygous individuals treated with clopidogrel, CYP2C19*17 allele carriers had greater mortality in both unadjusted (*1/*17 vs. *1/*1 HR: 2.07; CI 0.94 to 4.54; *17/*17 vs. *1/*1 HR: 8.02; CI 3.01 to 21.39; p= 0.0002) and adjusted (*1/*17 vs. *1/*1 HR: 2.02; CI 0.92 to 4.44; *17/*17 vs. *1/*1 HR: 8.97; CI 3.34 to 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 African American 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 African American patients discharged on clopidogrel following AMI in Kaplan-Meier analysis (Figure 3). In both unadjusted (*1A/*1C vs. *1A/*1A HR: 2.08; CI 0.94 to 4.63; *1C/*1C vs. *1A/*1A HR: 4.97; CI 1.70 to 14.53; p= 0.012) and adjusted (*1A/*1C vs. *1A/*1A HR: 1.89; CI 0.85 to 4.22; *1C/*1C vs. *1A/*1A HR: 4.96; CI 1.69 to 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 African American TRIUMPH patients discharged on clopidogrel was borderline significant (p= 0.122).

In order to further substantiate a differential effect of race on the associations between CYP variants and mortality among clopidogrel-treated patients following 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/or bleeding events in TRIUMPH. In Caucasian 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 to 4.59; p= 0.0687) and adjusted (HR: 2.10; CI 0.95 to 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 African American TRIUMPH patients discharged on clopidogrel, the \( CYP2C19^*17 \) (-806) 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 African American TRIUMPH patients homozygous for the \( CYP2C19^*17 \) (-806) variant compared to those individuals without the variant (homozygote OR: 3.820; CI 1.174 to 12.42; \( p = 0.027 \) and heterozygote OR: 0.663; CI 0.2850 to 1.5440; \( p = 0.3419 \) with an overall significant genotype effect (\( p = 0.034 \)).

In African American 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 African American TRIUMPH patient carriers of the \( CYP1A2^*1C \) variant discharged on clopidogrel (OR: 2.90; CI 1.416 to 5.937; \( p = 0.0039 \) for heterozygotes; OR: 2.97; CI 0.644 to 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 Caucasian TRIUMPH patients discharged on clopidogrel, 44 subjects were \( CYP2C19 \) poor metabolizers (PM), 711 subjects were extensive metabolizers (EM; normal), 280 subjects were intermediate metabolizers (IM), and 494 subjects were ultra-rapid metabolizers (UR); 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 Caucasians discharged on clopidogrel after AMI in TRIUMPH (log-rank p = 0.1726).

In African American TRIUMPH patients discharged on clopidogrel, there were 23 CYP2C19 PM, 152 EM, 88 IM and 126 UR; 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 African Americans (log-rank p = 0.0371). Individuals with PM had the highest survival (100% 1-year survival), individuals with IM or EM had the next highest (97% and 94% 1-year survival, respectively), and individuals with UR had the lowest 1-year survival (88% 1-year survival).

**Discussion**

Our analyses of CYP variants and outcomes among clopidogrel-treated patients following AMI revealed racial differences in the mortality association of CYP2C19 genotypes. We observed significantly increased 1-year mortality among Caucasian carriers of the loss-of-function CYP2C19*2 allele, while no increased mortality was observed among African American CYP2C19*2 carriers. In contrast, significantly increased 1-year mortality was observed among African American carriers of the gain of function CYP2C19*17 allele and the CYP1A2*1C allele, while no difference in mortality was detected among Caucasian subjects carrying either of these two variants. To our knowledge, this is the first report of significant associations between CYP polymorphisms and mortality among African Americans 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 Caucasians was associated with increased recurrent MI but not bleeding. In contrast, among African Americans, 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 African Americans but showed no association in Caucasians. Among African American AMI patients treated with clopidogrel, however, enhanced (UR) metabolism was associated with significantly reduced survival.

Previous studies have shown that Caucasian 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 as compared with Caucasian individuals carrying two ‘wild-type’ CYP2C19*1 alleles. Several previous investigations have reported that among ACS patients treated with clopidogrel after PCI, Caucasian and Asian carriers of CYP2C19*2 alleles have significantly increased cardiovascular events, including MI, stroke and death from cardiovascular causes when compared to individuals with two 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 ADP-induced platelet aggregation and a significantly increased risk of bleeding in patients undergoing PCI. Carriers of the CYP2C19*17 allele with acute coronary syndromes appear to derive more
benefit during clopidogrel treatment when compared to non-carriers, experiencing less subsequent cardiovascular events.\textsuperscript{13, 40} These observations were also supported by two recent meta-analyses.\textsuperscript{41, 42}

Nevertheless, the association of \textit{CYP} polymorphisms with adverse cardiovascular and bleeding events has remained controversial. Meta-analyses examining the association between cardiovascular outcomes and the \textit{CYP2C19} genotype have differed in their conclusions. A meta-analysis of 9 studies involving 9,685 predominately PCI patients treated with clopidogrel reported a significantly increased risk of the composite end point of cardiovascular death, MI or stroke in \textit{CYP2C19}*2 carriers.\textsuperscript{43} 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 \textit{CYP2C19} loss of function allele carriers, with summary odds ratios of 2.18 for cardiac death (\textit{p}= 0.0010) and 1.42 for MI (\textit{p}= 0.004).\textsuperscript{34} In contrast, two 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 \textit{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.\textsuperscript{25, 42} It is important to note that none of the aforementioned studies or meta-analyses provided information on African Americans.

Our finding of an association between the \textit{CYP2C19}*2 allele and increased rates of MI and mortality among Caucasians are 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 African American post-MI carriers of the gain of function \textit{CYP2C19}*17 allele and of the
CYP1A2*1C allele. Notably, we observed that bleeding events were more frequent in African American carriers of either of these two 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 African Americans with these genotypes. Supporting this contention, we also observed reduced survival among clopidogrel-treated African American AMI patients with genotype-predicted enhanced or UR clopidogrel metabolism.

In addition to our findings regarding the more commonly studied CYP2C19*2 and *17 variants, our observation of increased mortality in African American CYP1A2*1C allele carriers discharged on clopidogrel is noteworthy. This variant is much more frequent in African Americans compared with Caucasians (0.28 vs. 0.03, respectively 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 Caucasian and Asian smokers and non-smokers. However, neither the variant’s effect on enzyme activity in African Americans, 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 African Americans is related to increased clopidogrel responsiveness.

African American ancestry has been previously identified with an increased risk of bleeding among patients with ST elevation MI treated with reperfusion therapy46-48 and among patients undergoing PCI.49 Two recent retrospective studies involving a total of over 80,000 patients from either the National Registry of MI (NRMI)47 or from 5 clinical trials48 reported that among patients with ST-elevation MI treated with fibrinolysis or PCI, compared with Caucasians, African Americans had an increase in both bleeding events and mortality.47 In a
study of over 8800 patients undergoing PCI, a higher rate of bleeding was observed among African Americans 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, non-white race was associated with a significantly increased risk of gastrointestinal bleeding, the most powerful of which was use of dual antiplatelet therapy, and occurrence of gastrointestinal bleeding was associated with a significantly increased risk of all-cause death. While some of these reports speculated that the observed increased bleeding risk according to race was a result of genotypic differences between Caucasians and African Americans, our study provides direct evidence of a specific genotypic explanation for increased bleeding risk in African Americans treated with clopidogrel following AMI.

There may be significant clinical implications of these observations. While 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\(^15,16,20\) and decreased on-treatment platelet reactivity in CYP2C19*17 allele carriers.\(^14\) Second, we stratified patients according to their predicted metabolizer status based on the classification suggested by Mega et al.,\(^22\) 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, while the majority of patients discharged on clopidogrel were documented to still be on clopidogrel on at least one follow-up time point, due to 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, we performed primary and secondary analyses. As a primary analysis, our finding that the CYP2C19*17 variant was associated with significantly increased mortality among African American TRIUMPH patients discharged on clopidogrel (log rank p-value = 1e-05) is highly significant. However, as a secondary analysis, our finding that the CYPIA2*1C variant was associated with significantly increased mortality among African American 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 African Americans 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 African American AMI patients are available, to our knowledge. 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 more than 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 less than 5% non-whites in a cohort of more
than 9000 patients. Nevertheless, despite lack of replication, we believe 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
Health Care, 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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References:


Table 1: Baseline Characteristics of TRIUMPH Genetic Cohort and TRIUMPH Genetic Cohort Discharged on Clopidogrel (Caucasians and African Americans).

<table>
<thead>
<tr>
<th>TRIUMPH Genetic Cohort</th>
<th>TRIUMPH subjects discharged on Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caucasian (N = 2062)</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.8 ± 12.1</td>
</tr>
<tr>
<td>Female</td>
<td>573 (27.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.61 (6.2)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>763 (37.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1268 (61.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>539 (26.1)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>102 (4.9)</td>
</tr>
<tr>
<td>Hx of CHF</td>
<td>115 (5.6)</td>
</tr>
<tr>
<td>Hx of Atrial Fibrillation/flutter</td>
<td>115 (5.6)</td>
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<tr>
<td>PVD</td>
<td>91 (4.4)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>382 (18.5)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>417 (20.2)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>254 (12.3)</td>
</tr>
<tr>
<td>Prior CVA</td>
<td>80 (3.9)</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>53 (2.6)</td>
</tr>
<tr>
<td>STEMI</td>
<td>984 (47.7)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>1062 (51.5)</td>
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<tr>
<td>GRACE Risk Score</td>
<td>99.88±29.6</td>
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<tr>
<td>CRUSADE Bleeding Score</td>
<td>23.6±14.5</td>
</tr>
<tr>
<td>In-hospital revascularization</td>
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<tr>
<td>PCI</td>
<td>1456 (70.6)</td>
</tr>
<tr>
<td>CABG</td>
<td>201 (9.7)</td>
</tr>
<tr>
<td>Discharge Medications</td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>1971 (95.6)</td>
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<tr>
<td>Beta-blocker</td>
<td>1889 (91.6)</td>
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<tr>
<td>ACE/ARB</td>
<td>1525 (74)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or N (%).
ACE = angiotensin converting enzyme; ARB = Angiotensin II receptor blocker; BMI= body mass index; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; CVA = cerebral vascular accident; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack;
Table 2. Unadjusted and Adjusted Hazard Ratios for Mortality in Caucasian and African American 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>Caucasian</th>
<th>African American</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td><strong>CYP2C19*2</strong></td>
<td>rs4244285</td>
<td>unadjusted</td>
<td>1.82†</td>
<td>1.08-3.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adjusted</td>
<td>1.7†</td>
<td>1.01-2.86</td>
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<tr>
<td><strong>CYP2C19*17</strong></td>
<td>rs12248560</td>
<td>unadjusted (*/1/*17)</td>
<td>0.64‡</td>
<td>0.34-1.20</td>
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<tr>
<td></td>
<td></td>
<td>unadjusted (*17/*17)</td>
<td>0.76‡</td>
<td>0.18-3.14</td>
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<tr>
<td></td>
<td></td>
<td>adjusted (*/1/*17)</td>
<td>0.67‡</td>
<td>0.36-1.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adjusted (*17/*17)</td>
<td>0.90‡</td>
<td>0.22-3.73</td>
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</tbody>
</table>

Significant p-values in bold
†Carriers vs. Non-carriers
‡vs. *1/*1
Figure Legends:

**Figure 1.** Kaplan-Meier plot of 1-year mortality in Caucasian TRIUMPH patients discharged on clopidogrel, stratified by *CYP2C19* *C*2 (rs4244285) carrier status (p = 0.0216).

**Figure 2.** Kaplan-Meier plot of 1-year mortality in African American TRIUMPH patients discharged on clopidogrel stratified by *CYP2C19* *C*17 (rs12248560) status (p = 1e-05).

**Figure 3.** Kaplan-Meier plot of 1-year mortality in African American TRIUMPH patients discharged on clopidogrel stratified by *CYP1A2* *C*1 (rs2069514) status (p = 0.0064).

**Figure 4.** Kaplan-Meier plot of 1-year mortality in African American TRIUMPH patients discharged on clopidogrel stratified by metabolizer status (p = 0.0371).
CYP2C19*2 Carrier Status
Caucasian

Survival (%)

<table>
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<tr>
<th>Months</th>
<th>N at Risk</th>
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<tr>
<td>0</td>
<td>1169</td>
</tr>
<tr>
<td>3</td>
<td>1157</td>
</tr>
<tr>
<td>6</td>
<td>1147</td>
</tr>
<tr>
<td>9</td>
<td>1141</td>
</tr>
<tr>
<td>12</td>
<td>1134</td>
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</table>

*1/*1 *2 Carrier

p = 0.02159
CYP2C19 Metabolizer Status
African-American

Survival (%)

Months

N at Risk
UR  126  119  119  112  111
EM  152  149  147  145  143
IM  88   87   87   85   85
PM  23   23   23   23   23

p = 0.03709
### Supplemental Table S1. Pyrosequencing Primers and Conditions.

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<tr>
<th>SNP</th>
<th>Forward (5' --&gt; 3')</th>
<th>Biotinylated (5' --&gt; 3')</th>
<th>Reverse (5' --&gt; 3')</th>
<th>Internal (5' --&gt; 3')</th>
<th>Anneal T (°C)</th>
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<td>rs4244285</td>
<td>CAACCAGAGCTTGCCGATATTG</td>
<td>Biotin</td>
<td>TAAAGTCGAGGGGTTGTTG</td>
<td>CCACTATCATGTTATTTTC</td>
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<tr>
<td>rs12248560</td>
<td>TGGGCTGTTCGGCTTAGAT</td>
<td>Biotin</td>
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<tr>
<td>rs11188072</td>
<td>BiotinATTAAAAAAATGGGCAACGG</td>
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<td>TTTGATCTCTGTATGCTTCTTGG</td>
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<td>rs17884712</td>
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<tr>
<td>rs1787685</td>
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<tr>
<td>rs2069514</td>
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<td>CTGGGGCATGACAATTGCT</td>
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<td>BiotinCTGATGTTCGCCAGGCCCTT</td>
<td>AGCACAGTGATGTTGCGGTA</td>
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<tr>
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**Supplemental Table S2.** TaqMan® genotyping assay IDs.

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<td>C__25986767_70</td>
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<tr>
<td>rs3211371</td>
<td>C__30634242_40</td>
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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

<table>
<thead>
<tr>
<th>rs number</th>
<th>gene</th>
<th>alias</th>
<th>variant</th>
<th>Allele</th>
<th>TRIUMPH</th>
<th>TRIUMPH d/c on clopidogrel</th>
<th>dbSNP (build 132)</th>
<th>HWE p-value</th>
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<tbody>
<tr>
<td>rs4244285</td>
<td>CYP2C19</td>
<td>*2</td>
<td>A</td>
<td>G</td>
<td>0.15</td>
<td>0.18</td>
<td>0.15</td>
<td>0.18</td>
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<tr>
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<td>*17 (-806)</td>
<td>T</td>
<td>C</td>
<td>0.20</td>
<td>0.22</td>
<td>0.20</td>
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<tr>
<td>rs11188072</td>
<td>CYP2C19</td>
<td>*17 (-3402)</td>
<td>T</td>
<td>C</td>
<td>0.21</td>
<td>0.22</td>
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<td>*13</td>
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<td>0.03</td>
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<td>rs3211371</td>
<td>CYP2B6</td>
<td>*5A</td>
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<td>rs3745274</td>
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<td>*6</td>
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</tr>
<tr>
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<td>C</td>
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Supplemental Table S4. Mortality Rates for Each CYP2C19*2 Genotype Group

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<tr>
<th>Variant</th>
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<th>TRIUMPH subjects discharged on Clopidogrel</th>
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<td></td>
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</table>
Supplemental Figure S1. Linkage Disequilibrium between CYP2C19*17 SNPs in Caucasian (left panel) and African American (right panel) TRIUMPH patients. R² of LD.