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Clinical outcomes associated with proton pump inhibitor use among clopidogrel-treated patients within *CYP2C19* genotype groups following acute myocardial infarction

Jeremiah P. Depta, MD, MPHS¹, Petra A. Lenzini, MS², David E. Lanfear, MD, MS³, Tracy Y. Wang, MD, MHS, MSc⁴, John A. Spertus, MD, MPH⁵, Richard G. Bach, MD¹, and Sharon Cresci, MD^{1,2}

¹Washington University School of Medicine, Department of Medicine, Saint Louis, Missouri

²Washington University School of Medicine, Department of Genetics, Saint Louis, Missouri

³Heart and Vascular Institute, Henry Ford Hospital, Detroit, Michigan

⁴Duke Clinical Research Institute, Duke, Durham, North Carolina

⁵Saint Luke's Mid America Heart Institute and the University of Missouri-Kansas City, Kansas City, Missouri

Abstract

We examined clinical outcomes with proton pump inhibitors (PPI) use within *CYP2C19* genotype groups during clopidogrel treatment following acute myocardial infarction (AMI). 2062 patients were genotyped for *CYP2C19**2 and *17 variants in TRIUMPH. 12 month clinical outcomes were analyzed among patients discharged on clopidogrel within *CYP2C19**2 carrier, *CYP2C19**17 carrier, and *CYP2C19**1 homozygote genotype groups. PPI use was not associated with a difference in mortality. Among clopidogrel-treated Caucasians following AMI, PPI use was associated with a significantly higher rate of cardiac rehospitalization (HR 1.62, 95% CI 1.19-2.19; $p = 0.002$) compared with no PPI use. PPI users who were carriers of the *CYP2C19**17 variant experienced significantly higher rates of cardiac rehospitalization (HR 2.05, 95% CI 1.26-3.33; $p = 0.003$), carriers of the *CYP2C19**2 variant had a trend toward increased 1-year cardiac rehospitalization (HR 1.69, 95% CI 0.95-2.99; $P=0.07$) while no significant differences

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

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were observed among *CYP2C19**1 homozygotes. These results indicate that the risks associated with PPI use among clopidogrel-treated Caucasian post-MI patients are impacted by *CYP2C19* genotype, and suggest knowledge of genotype may be useful for personalizing PPI use among patients following AMI to reduce rehospitalization.

Keywords

cardiovascular diseases; clopidogrel; genetic variation; myocardial infarction; pharmacogenetics; *CYP2C19*

In the United States, over 900,000 individuals have an acute myocardial infarction (AMI) each year.¹ Dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP) P2Y₁₂ receptor antagonists is recommended for the secondary prevention of ischemic events following AMI.² However, adverse ischemic events following AMI remain frequent.³ Although clopidogrel is the most commonly prescribed ADP P2Y₁₂ receptor antagonist in the management of AMI,⁴ the degree of platelet inhibition with clopidogrel varies significantly between individuals.⁵ High-on treatment platelet reactivity in patients on clopidogrel is an independent risk factor for increased ischemic events following AMI.⁵ The proposed mechanisms responsible for impaired response to clopidogrel are multifactorial.⁶ However, variability in the metabolism of clopidogrel to its active metabolite has been implicated as a possible mechanism leading to clinical failure of dual antiplatelet therapy following AMI.⁷

Clopidogrel is a prodrug that is metabolized to its active metabolite by enzymes of the hepatic cytochrome P450 (CYP450) system. A number of factors influence the metabolism of clopidogrel, including drug-drug interactions and genetic polymorphisms (SNPs) in CYP450 isoenzymes, the most important of which is *CYP2C19*.⁵ Specific variants of *CYP2C19*, particularly *CYP2C19**2 and *CYP2C19**17, have been associated with marked differences in production of clopidogrel's active metabolite and resultant platelet inhibition.⁸ Previous investigations have shown that, in clopidogrel-treated AMI patients, individuals with the loss-of-function *CYP2C19**2 allele have less platelet inhibition and a higher rate of adverse cardiac events, whereas carriers of the gain-of function *CYP2C19**17 allele have the highest platelet inhibition and a potential increase in bleeding events.⁸

Proton pump inhibitors (PPIs) are also metabolized using *CYP2C19*.⁹ The pharmacodynamic effect of PPIs on clopidogrel is influenced by the drug-drug interaction that occurs at the *CYP2C19* isoenzyme.^{6, 10} Although the clinical consequences of this drug-drug interaction remain controversial,⁷ PPI use has been associated with a reduction in platelet inhibition by clopidogrel in some studies.¹¹

The clinical implications of the interplay between genetic variation in *CYP2C19* and the drug-drug interactions involving PPIs and clopidogrel are less well understood.^{6, 12} We, therefore, posed the question: in post-MI patients discharged on clopidogrel, is there a particular *CYP2C19* genotype group in which adding a PPI to clopidogrel treatment will increase adverse cardiac events? We investigated this question in the large, prospective, multicenter Translational Research Investigating Underlying disparities in acute Myocardial

infarction Patients' Health status (TRIUMPH) cohort.¹³ We specifically evaluated 1-year mortality, cardiac rehospitalization and bleeding *within CYP2C19* genotype groups in Caucasian and African-American patients discharged on clopidogrel following an AMI.

Methods

Subjects and Follow-up

From April 11, 2005 to December 31, 2008, 4340 patients with AMI were prospectively enrolled into the TRIUMPH observational cohort study from 24 medical centers in the United States, as previously described.¹³⁻¹⁵ All patients were required to have a type 1 AMI evidenced by an elevated troponin level and documented clinical ischemia (i.e. diagnostic ST changes on an ECG or ischemic signs/symptoms).¹³ 2979 TRIUMPH patients consented to genetic testing.¹⁵ Of these, 2955 (99.2%) were discharged alive and were included in the present analyses. The final sample was restricted to Caucasian (n = 1632) and African American (n = 430) patients discharged on clopidogrel following AMI (total N = 2062). Subjects discharged on PPI following AMI and/or at 1 or more follow-up interview were included in the PPI group.

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

Follow-up interviews were scheduled on all survivors at 1, 6, and 12 months after the date of discharge for the index hospitalization, as previously described.¹³ If a patient agreed to additional blood collection, an in-home visit and interview was performed by a trained medical personnel at 1 and 6 months. At 12-months, clinical follow-up was performed by telephone interview at a single specialized center. For those patients not agreeing to additional blood collection, 1 and 6 month interviews were performed by telephone from the same single specialized center used for the 12 month interview. At each interview, all patients were asked to report all interval events (e.g., procedures, diagnostic tests, hospitalizations, and outpatient visits) since their last study contact, as well as current medications on the date of interview.

Clinical Outcomes

The primary outcome of the study was all-cause mortality. For every patient in the study, all-cause mortality was assessed using the Social Security Administration Death Master File (<http://www.ntis.gov/products/ssadmf.aspx>) and was queried to determine patients' vital status as of 12/31/2010. (Of note, this query was performed prior to new restrictions and expunging of some records from the database.) Secondary outcomes were ascertained from the follow-up interviews and included the individual endpoints of cardiac rehospitalization or bleeding. 157 Caucasians and 88 African-Americans were missing information pertaining

to cardiac rehospitalization. 229 Caucasians and 105 African-Americans were missing information pertaining to bleeding. If a patient reported being hospitalized since the previous interview, 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.¹³ The bleeding outcome used for this study combined major or minor bleeding episodes.

Genotype Methods, Quality Control, and Classification

The methods used for genotyping and quality control are described in the Supplemental Methods. A dominant genetic model was used for *CYP2C19* *2 and *17. Patients were classified as *CYP2C19**1 in the absence of *2 and *17 variants. For *CYP2C19* *17, the -3402 (rs11188072) and -806 (rs12248560) variants were genotyped and linkage was determined. Given that the two *CYP2C19**17 variants were in tight linkage disequilibrium in our cohort, the analysis was restricted to the *CYP2C19**17 variant (*CYP2C19**17 -806; rs12248560) responsible for a C > T transition in the promoter that creates a consensus binding site for the GATA transcription factor family, resulting in increased *CYP2C19* expression and activity.^{16, 17}

Statistical Analyses

Analyses were performed separately in Caucasians and African-Americans to minimize the risk of false positive findings due to population stratification. In each group (Caucasians and African-Americans), baseline characteristics and clinical outcomes were compared between the PPI vs. no PPI groups and within each *CYP2C19* genotype group (i.e. *1 homozygotes and *2 or *17 carriers). Categorical data are reported as counts and percentages and compared using chi-square or Fisher's exact tests as appropriate. Continuous data are reported as mean \pm standard deviation (SD) and compared using t-tests. Hardy-Weinberg equilibrium was assessed using chi-square tests or Monte Carlo permutation with 10000 iterations, as appropriate. Follow-up began at the date of discharge from the index hospitalization. Survival function estimates (time until all-cause mortality, time until cardiac rehospitalization, and time to bleeding) were evaluated through Kaplan-Meier analysis. The log-rank test was used to identify differences in clinical outcomes between the PPI and no PPI groups overall, and within each *CYP2C19* genotype group. Cox proportional hazards models were then used to adjust for sex, GRACE score (an extensively validated score of predicting post-MI death and recurrent MI (c-statistic 0.84) from admission clinical, ECG and biomarker variables),^{18, 19} and any patient characteristic that was significantly different between PPI users vs. non-users overall and within *CYP2C19* genotype group. For primary effects, p-values < 0.05 were considered statistically significant; interaction p-values < 0.1 were considered statistically significant. Analyses were performed with SAS version 9.2 (SAS Institute, Inc., Cary, NC) and R version 2.11.1.

Results

2062 TRIUMPH patients (N = 1632 Caucasians; 430 African-Americans) were discharged on clopidogrel after MI. More than 80% of TRIUMPH patients discharged on clopidogrel had received in-hospital revascularization; the majority of these being percutaneous coronary intervention (PCI) (87.1% of Caucasians and 77.4% of African Americans). Over the study period, PPIs were used by 19% of Caucasians (N = 307) and 15% of African-Americans (N = 65). Baseline characteristics of TRIUMPH patients discharged on clopidogrel with and without the use of a PPI are shown in Table 1 (comparisons within each genotype group are shown in Supplemental Tables S1A-C). In both Caucasians and African-Americans, PPI users were older and had a higher mean GRACE risk score at discharge. In Caucasians, PPI users were more likely to be female (32.6% vs. 24.5%; $p = 0.003$) and have a higher rate of co-morbidities including hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation or flutter, history of prior PCI or coronary artery bypass grafting (CABG), and present with NSTEMI (vs. STEMI) compared with patients not using a PPI (p values ranging from 0.06 to <0.001 ; Table 1). In African-Americans, PPI users were more likely to have peripheral vascular disease (13.8% vs. 4.9%; $p = 0.006$) and a history of prior PCI (29.2% vs. 18.4%; $p = 0.04$). In both Caucasian and African-American patients, PPI users and non-users were discharged on similar secondary prevention medications, except for a lower rate of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the PPI group compared with the no PPI group among African-Americans.

As shown in Table 2, omeprazole was the most frequently reported PPI used during the study period in both Caucasian and African-American PPI users (Caucasians [C]: 62%; African-Americans [AA]: 60%) followed by pantoprazole (C: 28%; AA: 36%), esomeprazole (C: 21%; AA: 25%), lansoprazole (C: 13%; AA: 14%), and rabeprazole (C: 4%; AA: 0%). Some patients used more than one PPI. No statistically significant differences were observed between genotype groups for the use of each individual PPI (frequency of use within each genotype group is shown in Supplemental Table S2).

PPI Use was Not Associated with Significant Differences in All-Cause Mortality in Either Race

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. Unadjusted rates of all-cause mortality were not significantly different between PPI users and non-users among Caucasians (2.9% vs. 3.8%, respectively; $p = 0.48$) or African Americans (6.2% vs. 7.4%, respectively; $p = 0.64$). These findings were similar after multivariable adjustment using Cox proportional hazards models (not shown). Among Caucasian and African-American patients discharged on clopidogrel, there was no significant difference in 1-year mortality between PPI users and non-users within any particular *CYP2C19* genotype group (data not shown).

PPI Use was Associated with Significantly Increased Cardiac Rehospitalization in Caucasians with the Greatest Increase in Risk observed among *CYP2C1917 Carriers**

The 1-year cardiac rehospitalization rate was 13.6% in Caucasians (N = 201) and 15.2% in African-Americans (N = 52). There was no significant difference in 1-year cardiac rehospitalization between PPI users and non-users among African-Americans discharged on clopidogrel, overall, or *within CYP2C19* genotype groups (data not shown). In contrast, there was a significant difference in 1-year cardiac rehospitalization between PPI users and non-users among Caucasians discharged on clopidogrel in the overall group and *within CYP2C19* genotype groups (Table 3). As seen in Figure 1A, in the overall Caucasian group (i.e. not stratified by genotype group), the rate of cardiac rehospitalization was significantly higher in PPI users compared with non-users in both unadjusted and adjusted analyses (21.2% vs. 11.7%, $p < 0.0001$; adjusted HR 1.62, 95% CI 1.19-2.19; $p = 0.002$). Figures 1B – 1D show the difference in cardiac rehospitalization between PPI users and non-users in Caucasians discharged on clopidogrel *within CYP2C19* genotype groups. Within the *CYP2C19**1 homozygote genotype group, there was a significant increase in 1-year rate of cardiac rehospitalization in PPI users, compared to non-users (19.2% vs. 11.3%; $p = 0.03$; Figure 1B), in unadjusted analyses; however after adjusting for covariates, this difference was no longer significant (HR 1.51, 95% CI 0.90-2.54; $p = 0.12$; Table 3). Within the *CYP2C19**2 genotype group, PPI users had a trend toward increased 1-year cardiac rehospitalization compared to non-users (21.8% vs. 13%; unadjusted $p = 0.07$; Figure 1C; adjusted HR 1.69, 95% CI 0.95-2.99; $p = 0.07$; Table 3). Notably, as seen in Figure 1D, the most significant association was seen within *CYP2C19**17 carriers. Within this genotype group, PPI users had significantly more 1-year cardiac rehospitalization compared to non-users (23.3% vs. 10.3%; unadjusted $p = 0.0003$; adjusted HR 2.05, 95% CI 1.26-3.33; $p = 0.003$; Table 3).

Within the *CYP2C19**17 genotype group, the association of PPI use and increased 1-year cardiac rehospitalization remained significant even if those subject also carrying the *CYP2C19**2 allele (i.e. *CYP2C19**17/*2 heterozygotes; N = 106) were excluded from the analysis (adjusted HR 2.02, 95% CI 1.17- 3.47; $p = 0.01$).

PPI Use was Associated with Significantly Increased Cardiac Rehospitalization Even After Exclusion of Elective Cardiac Rehospitalization

The causes for cardiac rehospitalization were analyzed to further assess the significant differences observed in clopidogrel-treated patients with and without PPI use. In the overall Caucasian group (i.e. not stratified by *CYP2C19* genotype group), and in each *CYP2C19* genotype group, approximately one-third of the rehospitalizations were for elective procedures (CABG or valve surgery, PCI, catheterization, and defibrillator or pacemaker implantation; 34.9% in overall group; 33% in *CYP2C19* *1 homozygotes; 39% in *CYP2C19* *2 carriers; 33% in *CYP2C19* *17 carriers). After limiting cardiac rehospitalizations to non-elective admissions only (Supplemental Table S3), the rate of cardiac rehospitalization for PPI users remained significantly higher compared with non-users in clopidogrel-treated Caucasians (14.1% vs. 7.7%, $p = 0.00004$; HR 1.95, 95% CI 1.36-2.78; $p = 0.0002$) and within the clopidogrel-treated Caucasian *CYP2C19**17 genotype group (18.3% vs. 6.4%, $p = 0.00009$; HR 2.48 (95% CI 1.39-4.42; $p = 0.002$).

PPI Use was not Associated with Significantly Increased Bleeding

The rates of bleeding following AMI among clopidogrel-treated patients were not significantly different when PPI users were compared with non-users in Caucasian (PPI use: 16.5% vs. no PPI use: 14.6%, $p = 0.69$) or African-American (PPI use: 8.2% vs. no PPI use: 11%, $p = 0.51$) TRIUMPH patients.

Discussion

The aim of our study was to answer a simple question: in post-MI patients discharged on clopidogrel, is there a particular *CYP2C19* genotype group in which adding a PPI to clopidogrel treatment is associated with a higher rate of adverse cardiac events? In TRIUMPH, we found that PPI use was not associated with any differences in the rates of all-cause mortality in either race or within each *CYP2C19* genotype group. Among African-Americans, the rates of cardiac rehospitalization were not significantly different in PPI users vs. nonusers in any of the *CYP2C19* genotype groups. However, the use of a PPI was associated with significantly increased rates of cardiac rehospitalization in Caucasians, and the magnitude of this increased risk was most evident among Caucasian carriers of the *CYP2C19**17 gain of function allele. This finding remained significant after (1) adjusting for sex, GRACE score and any baseline characteristic that differed within genotype group, (2) excluding *CYP2C19**2/*17 heterozygotes and (3) limiting cardiac rehospitalizations to non-elective admissions. In TRIUMPH, 36% of Caucasians were carriers of the *CYP2C19**17 genotype. Thus, our findings have the potential to impact the clinical management of a large proportion of Caucasians following an acute MI.

Two recent studies have provided evidence of inhibition of the CYP2C19 isoenzyme by PPIs, demonstrating a decreased plasma concentration of clopidogrel's active metabolite.^{20,21} A recent randomized cross-over study of healthy *1 homozygotes demonstrated that PPIs reduce the concentration of clopidogrel's active metabolite and reduce the degree of platelet inhibition.¹⁰ Currently, the evidence regarding the effect of *CYP2C19* genetic variation on platelet inhibition in patients on a PPI and clopidogrel is limited. In a prospective double-blind cross-over randomized study, esomeprazole use significantly reduced platelet inhibition in clopidogrel-treated ACS patients who were *17 carriers or *1 homozygotes compared with placebo, but did not attenuate the antiplatelet effect in *2 carriers.²² This finding was also observed in an open-label cross-over study of healthy subjects, where platelet inhibition was significantly reduced by omeprazole and rabeprazole in *1 homozygotes but not in *2 carriers.²³ Additional studies have also shown a less pronounced effect of PPI use on *CYP2C19**2 carriers compared with *1 homozygotes.^{24, 25} These findings are supported by our study. In our study, the highest risk of cardiac rehospitalization was observed in *17 Caucasian carriers compared with the Caucasian *2 carriers and *1 homozygotes. The mechanism(s) responsible for the differential effect of various *CYP2C19* variants on platelet reactivity in clopidogrel-treated patients on a PPI are not yet understood and will require further investigation.

Previous data on the clinical significance of PPI use among clopidogrel-treated patients within *CYP2C19* genotype groups are limited and controversial. A French registry analysis of AMI patients did not find any association between PPI use and adverse cardiac events in

patients who were carriers or homozygotes for the *CYP2C19**2 allele.²⁶ A post-hoc subgroup analysis on the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 also did not find any evidence that PPI use was associated with an increase in adverse cardiac events among either *2 carriers or *1 homozygotes.¹¹ Because these studies did not report pharmacodynamic data, the PPI effect on platelet reactivity and cardiovascular outcomes within *CYP2C19* genotype groups could not be fully assessed. The Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI (POPULAR) study is the only prior study to date to analyze the PPI interaction with *CYP2C19* variants on platelet reactivity and clinical outcomes.²⁷ In this study that assessed patients after elective PCI, both *2 carriers and non-carriers had significantly higher rates of high on-treatment platelet reactivity with concurrent PPI use compared with no PPI use.²⁷ However, PPI use was not associated with an increase in 12-month adverse cardiac events in either *2 carriers or non-carriers.²⁷ An important limitation of this study, and all of the aforementioned studies, were that *17 carriers were not assessed.

Our study is the first analysis to assess clinical outcomes of PPI use in clopidogrel-treated patients within the *CYP2C19**17 genotype group. Previously, no association was observed between PPI use and adverse cardiac events among carriers of the *CYP2C19**2 allele.^{11, 26, 27} Our data supports these findings. The mechanism of this may, in part, be due to the low baseline activity of CYP2C19 in *2 carriers, where it is unlikely that a PPI would confer a further decrease in CYP2C19 activity to result in a clinically meaningful difference.^{6, 12} Given the increased CYP2C19 activity observed in *CYP2C19**17 carriers, use of CYP2C19 inhibitors such as PPIs among *CYP2C19**17 carriers may have greater potential to significantly lower enzymatic activity, resulting in reduced clopidogrel-related platelet inhibition and worse clinical outcomes. Although our data are biologically plausible, further studies are needed to confirm the mechanisms proposed by ourselves and others.

Several important limitations should be considered when interpreting our study. First, our study did not assess platelet function, thus we are not able to correlate the clinical findings of our study with measures of platelet reactivity. However, multiple studies have confirmed increased on-treatment platelet reactivity in *CYP2C19**2 allele carriers²⁸⁻³⁰ and decreased on-treatment platelet reactivity in *CYP2C19**17 allele carriers.^{30, 31} Second, compliance with clopidogrel and PPI was not assessed in our study, which could influence the clinical outcomes. However, classifying patients by discharge medication status is a well-recognized and often used approach, since most patients remain on their discharge regimen after hospitalization.³² Third, our findings regarding the *CYP2C19**17 genotype group have not been independently replicated in a separate cohort, since our study is, to our knowledge, the first study to analyze the clinical outcomes with PPI use in the *CYP2C19**17 genotype group. All of our results, however, are biologically plausible and supported by *in vitro* platelet reactivity studies; the fact that our findings in the *CYP2C19**2 and *1/*1 genotype groups are consistent with recent clinical studies and trials^{11, 26, 27} gives further credibility to our observations in the *CYP2C19**17 genotype group. Finally, despite using adjusted analyses to account for differences between the PPI and no PPI use groups in the overall

population and within each *CYP2C19* genotype group, it is still possible that unknown confounders may have contributed to the observed differences in clinical outcomes.

Conclusions

Among clopidogrel-treated Caucasians following AMI in the TRIUMPH registry, PPI use was associated with significantly increased cardiac rehospitalization. The increase in risk of rehospitalization among PPI users varied by *CYP2C19* genotype, with the greatest increase in risk observed among carriers of the gain of function *CYP2C19**17 allele. PPI use was not associated with any significant differences in all-cause mortality for clopidogrel-treated patients in either race. These results extend prior studies of the effect of PPI use on platelet function, including recent clinical trial data, and suggest the risks associated with PPI use in clopidogrel-treated Caucasian post-MI patients may be impacted by *CYP2C19* genotype. If validated, personalized treatment with PPIs based on *CYP2C19* genotype status should be considered as this may, ultimately, lead to improved post-MI outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

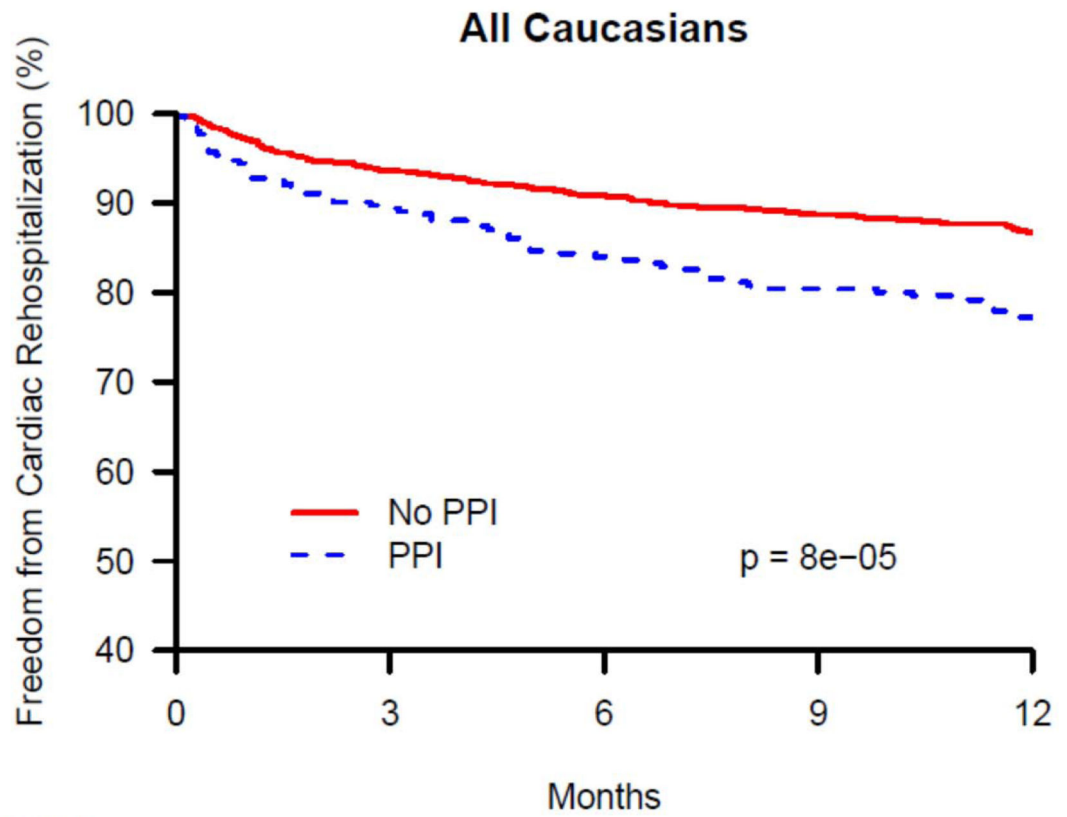
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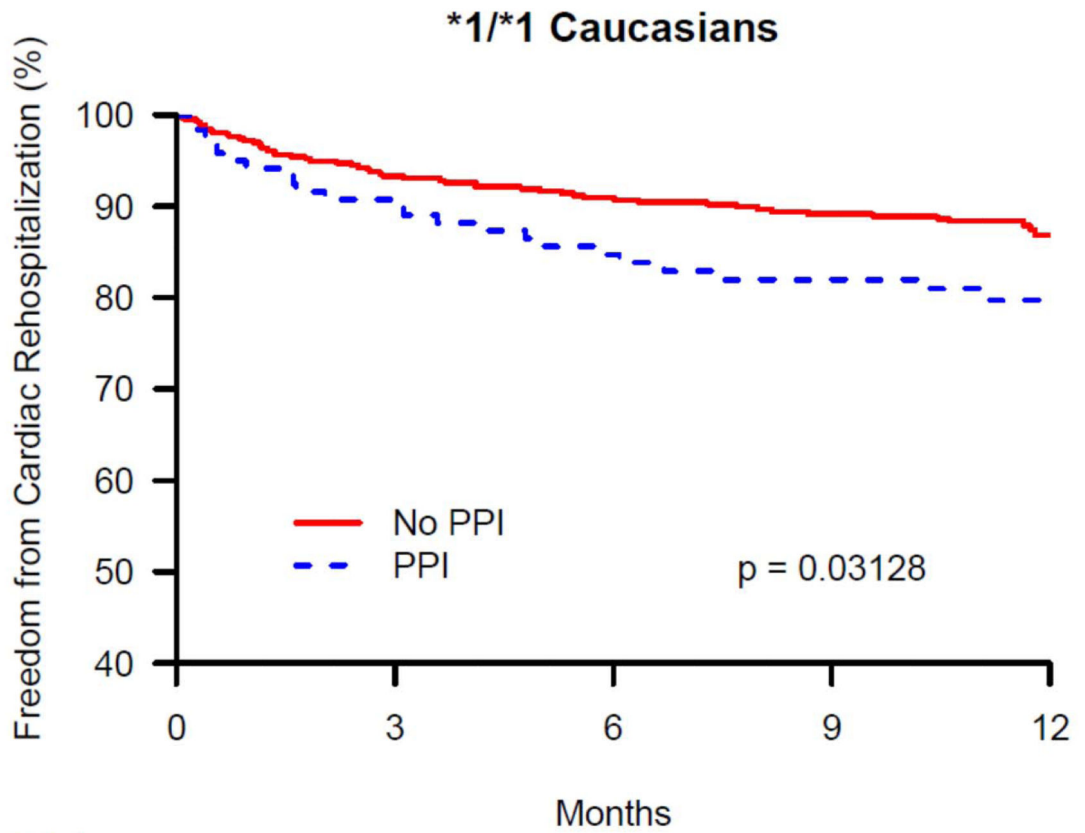
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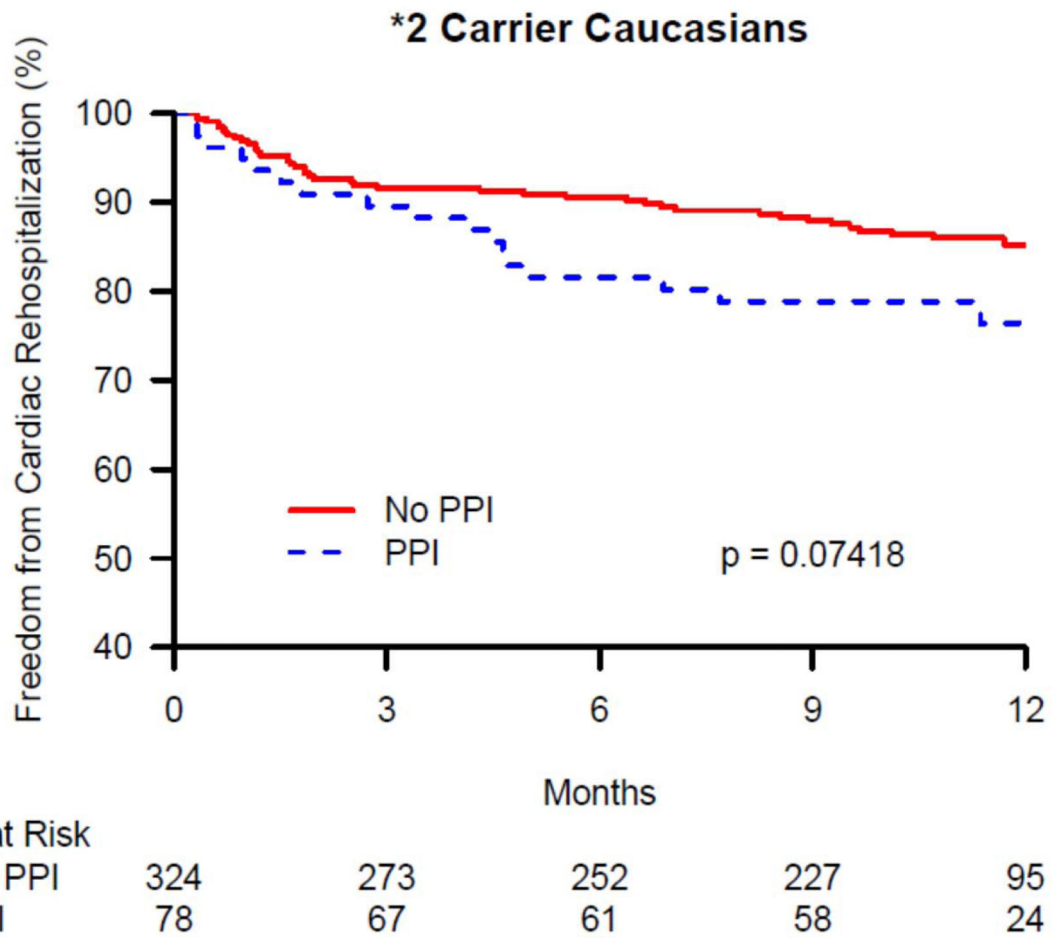
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N at Risk	0	3	6	9	12
No PPI	1190	1018	939	848	372
PPI	305	266	245	220	87



		Months				
N at Risk		0	3	6	9	12
No PPI	468	395	372	340	152	
PPI	120	106	97	85	29	



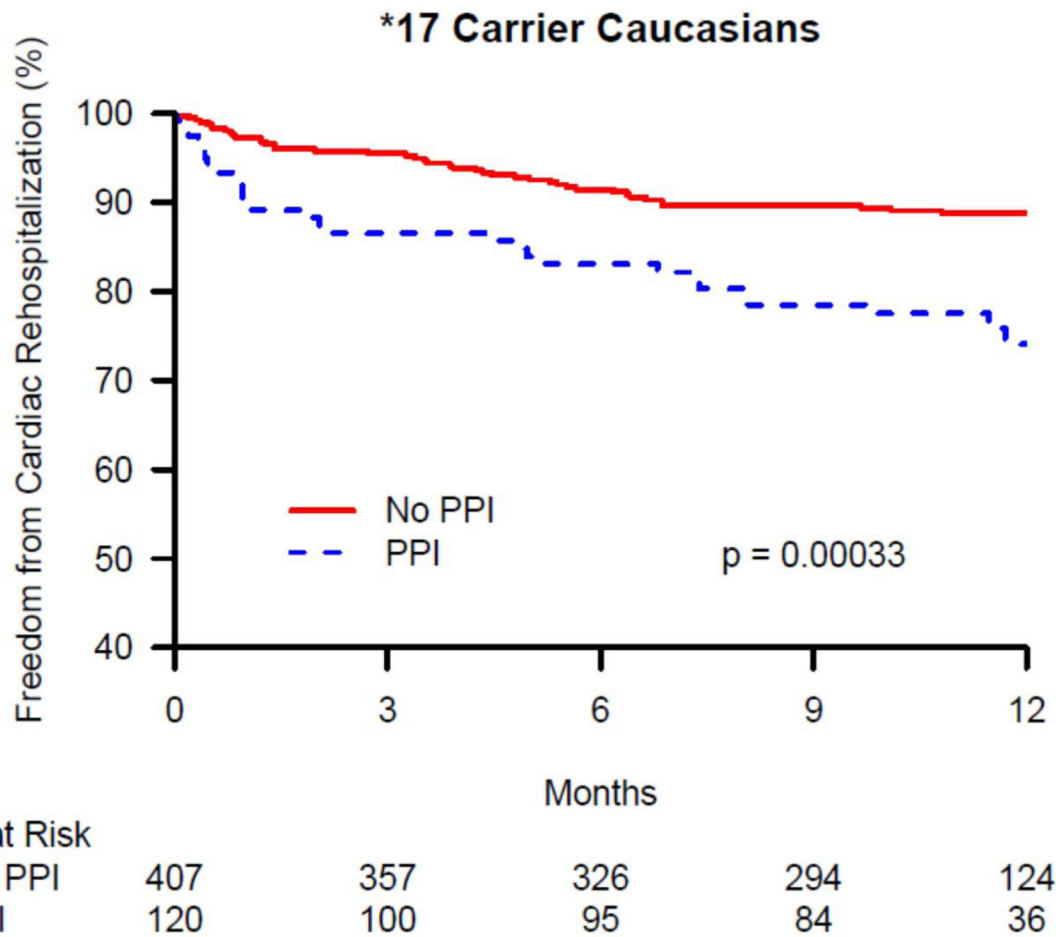


Figure 1. Kaplan-Meier analysis of cardiac rehospitalization associated with and without the use of a proton pump inhibitors (PPI) in Caucasian clopidogrel-treated genotyped TRIUMPH patients following an acute myocardial infarction. Freedom from cardiac rehospitalization are compared between PPI users and non-users within (A) all genotyped Caucasians, (B) *CYP2C19**1 homozygotes, (C) carriers of the *CYP2C19**2 allele, and (D) carriers of the *CYP2C19**17 allele. In Caucasians, PPI use was associated with significantly increased rates of cardiac rehospitalization (A) and was most significant among Caucasian carriers of the gain of function *CYP2C19**17 allele (D).

Table 1
Baseline Clinical Characteristics of Clopidogrel-Treated TRIUMPH Patients following Acute Myocardial Infarction with and without the use of a Proton Pump Inhibitor

	Caucasians		African Americans		p-value	p-value
	PPI (n = 307 patients)	No PPI (n = 1325 patients)	PPI (n = 65 patients)	No PPI (n = 365 patients)		
Age	60.4 ± 11.6	58.7 ± 12.0	60.4 ± 11.8	56.7 ± 11.8	0.02	0.02
Male	207 (67.4)	1001 (75.5)	34 (52.3)	205 (56.2)	0.003	0.56
Hypertension	202 (65.8)	754 (56.9)	51 (78.5)	282 (77.3)	0.004	0.83
Dyslipidemia	184 (59.9)	634 (47.8)	33 (50.8)	157 (43.0)	0.0001	0.25
Diabetes Mellitus	97 (31.6)	300 (22.6)	29 (44.6)	140 (38.4)	0.001	0.34
Smoking History	224 (73.2)	972 (73.9)	47 (72.3)	266 (73.9)	0.79	0.79
Congestive Heart Failure	19 (6.2)	54 (4.1)	9 (13.8)	29 (7.9)	0.11	0.12
Chronic Kidney Disease	16 (5.2)	50 (3.8)	6 (9.2)	39 (10.7)	0.25	0.72
Atrial fibrillation/flutter	22 (7.2)	47 (3.5)	0 (0.0)	10 (2.7)	0.005	0.37
Peripheral Vascular Disease	14 (4.6)	45 (3.4)	9 (13.8)	18 (4.9)	0.32	0.006
Prior Myocardial Infarction	61 (19.9)	213 (16.1)	18 (27.7)	81 (22.2)	0.11	0.33
Prior PCI	76 (24.8)	265 (20.0)	19 (29.2)	67 (18.4)	0.06	0.04
Prior CABG	55 (17.9)	128 (9.7)	5 (7.7)	33 (9.0)	<0.0001	1.00
Prior Stroke	12 (3.9)	43 (3.2)	5 (7.7)	20 (5.5)	0.56	0.56
Prior TIA	10 (3.3)	25 (1.9)	0 (0.0)	8 (2.2)	0.14	0.61
GRACE Risk Score	98.9 ± 27.8	94.7 ± 28.2	102.1 ± 29.8	92.8 ± 27.8	0.02	0.02
Clinical Presentation of AMI						
STEMI	150 (48.9)	740 (55.8)	27 (41.5)	155 (42.5)	0.03	0.89
NSTEMI	153 (49.8)	581 (43.8)	38 (58.5)	210 (57.5)	0.06	0.89
Index Hospital Revascularization						
PCI	263 (85.7)	1158 (87.4)	45 (69.2)	288 (78.9)	0.42	0.09
CABG	5 (1.6)	38 (2.9)	6 (9.2)	10 (2.7)	0.32	0.001
Discharge Medications						
Aspirin	298 (97.1)	1285 (97.0)	62 (95.4)	346 (94.8)	0.94	0.84
Clopidogrel	307 (100.0)	1325 (100.0)	65 (100.0)	365 (100.0)	1.00	1.00
Beta-blocker	286 (93.2)	1227 (92.6)	61 (93.8)	333 (91.2)	0.74	0.48

	Caucasians			African Americans		
	PPI (n = 307 patients)	No PPI (n = 1325 patients)	p-value	PPI (n = 65 patients)	No PPI (n = 365 patients)	p-value
ACEI/ARB	244 (79.5)	1043 (78.7)	0.77	41 (63.1)	302 (82.7)	0.0003
Lipid lowering medication	280 (91.2)	1230 (92.8)	0.33	59 (90.8)	338 (92.6)	0.61

Values are shown as absolute numbers (percentages) or mean ± SD.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = Transient ischemic attack.

Table 2
Type of Proton Pump Inhibitor Used During the Study Period

	Caucasians PPI users	African-Americans PPI users
Omeprazole	62%	60%
Pantoprazole	28%	36%
Esomeprazole	21%	25%
Lansoprazole	13%	14%
Rabeprazole	4%	0%

Values are shown as percentages

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Table 3
Adjusted Hazard Ratios (HR) for 1-year Cardiac Rehospitalization of Clopidogrel-treated Caucasians following AMI within *CYP2C19* genetic groups and PPI use

	<u>Caucasians</u>	
	HR (95% CI)	p-value
All Caucasians	1.62 (1.19-2.19)	0.002
<i>CYP2C19</i> *1 homozygotes	1.51 (0.90-2.54)	0.12
<i>CYP2C19</i> *2 carriers	1.69 (0.95-2.99)	0.07
<i>CYP2C19</i> *17 carriers	2.05 (1.26-3.33)	0.003

Analyses adjusted for sex, GRACE risk score, and any patient characteristic that was significantly different between PPI users vs. non-users overall (Table 1) and within *CYP2C19* genotype (Supplemental Tables 1A-C).

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