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ORIGINAL RESEARCH

CYP2C19 Genotype Is Associated With Adverse Cardiovascular Outcomes in Black Patients Treated With Clopidogrel Undergoing Percutaneous Coronary Intervention

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BACKGROUND: Cytochrome P450 2C19 (CYP2C19) intermediate and poor metabolizer patients exhibit diminished clopidogrel clinical effectiveness after percutaneous coronary intervention (PCI). However, outcome studies to date have lacked racial diversity. Thus, the impact of *CYP2C19* genotype on cardiovascular outcomes in patients treated with clopidogrel who identify as Black or African American remains unclear.

METHODS AND RESULTS: Adults among 5 institutions who self-identified as Black or African American, underwent PCI and clinical *CYP2C19* genotyping, and were treated with clopidogrel were included. Data were abstracted from health records. Major atherothrombotic (composite of death, myocardial infarction, ischemic stroke, stent thrombosis, or revascularization for unstable angina) and bleeding event rates within 1 year after PCI were compared across CYP2C19 metabolizer groups using multivariable Cox regression adjusted for potential confounders and baseline variables meeting a threshold of $P<0.10$. The population included 567 Black patients treated with clopidogrel (median age, 62 years; 46% women; 70% with an acute coronary syndrome indication for PCI). Major atherothrombotic events rates were significantly higher among clopidogrel-treated intermediate and poor metabolizers (24 of 125 [19.2%]) versus patients treated with clopidogrel without a no function allele (43 of 442 [9.7%]; 35.1 versus 15.9 events per 100 person-years; adjusted hazard ratio, 2.00 [95% CI, 1.20–3.33], $P=0.008$). Bleeding event rates were low overall (23 of 567 [4.1%]) and did not differ among the metabolizer groups.

CONCLUSIONS: Black patients with CYP2C19 intermediate and poor metabolizer phenotypes who are treated with clopidogrel exhibit increased risk of adverse cardiovascular outcomes after PCI in a real-world clinical setting. Bleeding outcomes should be interpreted cautiously. Prospective studies are needed to determine whether genotype-guided use of prasugrel or ticagrelor in intermediate and poor metabolizers improves outcomes in Black patients undergoing PCI.

Key Words: Black or African American ■ clopidogrel ■ CYP2C19 ■ genetic testing ■ percutaneous coronary intervention ■ precision medicine

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CLINICAL PERSPECTIVE

What Is New?

- Consistent with multiple previous studies in European and East Asian populations, self-reported Black or African American patients with cytochrome P450 2C19 (CYP2C19) intermediate and poor metabolizer phenotypes who were treated with clopidogrel after percutaneous coronary intervention exhibited significantly higher rates of major atherothrombotic events compared with those with nonintermediate and poor metabolizer phenotypes.

What Are the Clinical Implications?

- *CYP2C19* no function alleles are associated with diminished clopidogrel clinical effectiveness in self-reported Black or African American patients undergoing percutaneous coronary intervention in a real-world clinical setting.
- Although it is not yet determined whether genotype-guided use of alternative therapy improves adverse cardiovascular outcomes in Black patients after percutaneous coronary intervention, present data suggest clopidogrel should be avoided in CYP2C19 intermediate and poor metabolizers in accordance with Clinical Pharmacogenetics Implementation Consortium recommendations given the increased risk of major atherothrombotic events.

Nonstandard Abbreviations and Acronyms

CPIC	Clinical Pharmacogenetics Implementation Consortium
CYP2C19	cytochrome P450 2C19
IGNITE	Implementing Genomics in Practice
GUSTO	Global Use of Strategies to Open Occluded Arteries
IM	intermediate metabolizer
MACE	major adverse cardiovascular events
MAE	major atherothrombotic events
NM	normal metabolizer
PM	poor metabolizer
RM	rapid metabolizer
TRIUMPH	Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status
UM	ultrarapid metabolizer

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor (ie, clopidogrel, prasugrel, or ticagrelor) is the standard of care after a percutaneous coronary intervention (PCI) and has been shown to significantly improve outcomes by preventing major atherothrombotic events (MAE).[1,2] In patients undergoing PCI due to an acute coronary syndrome (ACS), clinical practice guidelines recommend prasugrel and ticagrelor over clopidogrel due to their superior efficacy.[1,3,4] However, these alternative agents carry an increased risk of bleeding, which contributes to clopidogrel being widely prescribed in clinical practice.[3–5]

Clopidogrel is a prodrug requiring conversion into its active metabolite by the cytochrome P450 2C19 (CYP2C19) enzyme. *CYP2C19* no function alleles (most commonly *CYP2C19*2* and *CYP2C19*3*) and the increased function *CYP2C19*17* allele are associated with interpatient variability in clopidogrel active metabolite formation and inhibition of platelet reactivity.[6] It is well established that patients treated with clopidogrel who carry 1 or 2 *CYP2C19* no function alleles, referred to as intermediate metabolizers (IMs) and poor metabolizers (PMs), respectively, have reduced clopidogrel active metabolite formation, diminished inhibition of antiplatelet reactivity, and increased risk of MAE and stent thrombosis after PCI.[7,8] The association between *CYP2C19* no function alleles and adverse outcomes in patients treated with clopidogrel has been well established, and accumulating evidence from both observational and randomized studies has demonstrated the clinical benefit of using *CYP2C19* genotype to guide selection of prasugrel or ticagrelor in *CYP2C19* no function allele carriers after PCI.[6,9] Yet, utilization of genotype-guided antiplatelet therapy in real-world clinical settings is complex as prior evidence at early adopter institutions illustrates that ≈50% of IMs are still prescribed clopidogrel.[10] In contrast, it has not been consistently demonstrated that patients treated with clopidogrel carrying 1 (rapid metabolizers [RMs]) or 2 (ultrarapid metabolizers [UMs]) copies of the increased function *CYP2C19*17* allele have higher bleeding risk. Collectively, these studies have primarily been composed of patient populations with European and East Asian ancestry and had insufficient racial and ethnic diversity.[7,8,11]

The prevalence of a *CYP2C19* no function allele is common in patients with European (≈30%) and East Asian (≈60%) ancestry, as well as in those with African ancestry (≈40%).[11] Although similar associations between *CYP2C19* no function alleles and clopidogrel clinical effectiveness would likely be expected across diverse populations, the association between CYP2C19 IM and PM status and higher risk of MAE in patients treated with clopidogrel has not been well studied in Black patients.[6,11] The prevalence of an increased function *CYP2C19*17* allele is also similar between patients with African ancestry (≈25–30%) and European ancestry (≈30%).[11] In a registry of Black patients treated with clopidogrel following a myocardial infarction (MI),

an association between the *CYP2C19*17* allele and higher bleeding risk was reported.[12] Furthermore, the same study demonstrated no association between *CYP2C19* no function alleles and mortality in Black patients treated with clopidogrel. However, these observations have not been replicated and demonstrate why additional studies evaluating the associations between CYP2C19 metabolizer phenotypes and MAE and clinically significant bleeding events in Black patients are needed. Registry data are an important source of information to establish the safety and efficacy of pharmacologic interventions among patients receiving PCI, and are a particularly important resource for studying patient populations typically underrepresented in randomized clinical trials.

Therefore, the primary objective of this analysis was to evaluate the association between CYP2C19 metabolizer phenotype and: (1) MAE and (2) clinically significant bleeding events in a real-world population of Black patients treated with clopidogrel who underwent PCI and clinical *CYP2C19* genotyping.

METHODS

Data and analytic codes that support the findings from this article are available from the authors on reasonable request.

Study Population

The study population comprised adult patients 18 years and older who underwent PCI for any indication, were genotyped for *CYP2C19* as part of clinical care, and were treated with a $P2Y_{12}$ receptor inhibitor, as previously described.[13] Patients who met these criteria (n=4335) were included from 5 institutions (University of Florida, Gainesville; University of Florida, Jacksonville; University of North Carolina, Chapel Hill; University of Maryland, Baltimore; and University of Illinois at Chicago). Of these, 2770 (63.9%) were treated with clopidogrel over the course of follow-up; rates of clopidogrel versus alternative therapy prescribing at each institution are summarized in Table S1. The study population for the current investigation comprised 567 patients treated with clopidogrel at the time of event or last follow-up whose self-reported race was documented as Black or African American in the electronic health record (EHR). Data collection was approved by the institutional review board at each institution. Written informed consent was obtained or the requirement was waived per site requirements.

Clinical *CYP2C19* genotyping was conducted using a Clinical Laboratory Improvement Amendments–certified laboratory at each site. Each site tested for the *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* alleles with additional no function alleles tested for at the University of Florida, Gainesville, University of Illinois at Chicago, and University of Maryland, Baltimore sites (Table S1). In accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC)–recommended genotype-to-phenotype classifications, CYP2C19 metabolizer phenotypes were assigned and reported in the EHR: PM (2 no function alleles), IM (1 no function allele), normal metabolizer (NM; **1/*1* genotype), RM (**1/*17* genotype), or UM (**17/*17* genotype).[6] In accordance with CPIC guideline recommendations, IMs and PMs were recommended to receive alternative antiplatelet therapy (prasugrel or ticagrelor) at each site, provided no contraindications were present, while no recommendation was made for a preferred $P2Y_{12}$ inhibitor in NMs, RMs, and UMs.[6] Provider discretion determined the ultimate prescribing decision.

Data Abstraction

Demographic, genotype, clinical, and medication data were abstracted manually from the EHR at each site using a common data collection tool, as previously described.[13,14] The data collection tool used in the current study adapted a tool previously developed by the IGNITE (Implementing Genomics in Practice) Network Pharmacogenomics Working Group.[15] Baseline data for eligible patients were collected by EHR review of the index PCI hospitalization, which was defined as the PCI performed in association with *CYP2C19* genotyping. Longitudinal data were collected from hospital and outpatient clinical encounters in the EHR, which was supplemented by telephone interviews at the University of Florida, Jacksonville site, for up to 12 months after the index PCI. The follow-up period for each patient concluded at the first occurrence of either a prespecified clinical outcome, the discontinuation of clopidogrel, the date of last-known follow-up, or the conclusion of the 12-month follow-up period. Follow-up periods for bleeding events and cardiovascular events were evaluated independently. Patients were included regardless of the length of follow-up available.

Study End Points

The primary outcome was a composite of MAE, which was defined as all-cause death, MI, ischemic stroke, stent thrombosis, or revascularization for unstable angina within 12 months following the index PCI. The secondary outcome, major adverse cardiovascular events (MACE), was the composite of cardiovascular death, MI, stent thrombosis, or ischemic stroke within 12 months after the index PCI. Clinically significant bleeding events, defined as the composite of moderate or severe/life-threatening bleeding per the Global Use of Strategies to Open Occluded Arteries (GUSTO) bleeding criteria, within 12 months following the index PCI were also evaluated as a secondary outcome.[16] Events

were identified via the EHR from provider-reported diagnoses. All clinical events were independently verified in the EHR by an interventional cardiologist or reviewed by a clinical pharmacist.

Statistical Analysis

Data were cleaned and verified at the site level and then aggregated at the University of Florida. Patient characteristics were compared among CYP2C19 metabolizer phenotype groups using χ^2 test, Mann–Whitney *U* test, or Fisher exact test as appropriate. For the analysis of MAE and MACE, patients were dichotomized into 2 CYP2C19 phenotype groups: IM/PM and NM/RM/UM (referent). For the primary analysis of bleeding events, patients were grouped by CYP2C19 phenotype status into NM (referent) and RM/UM phenotypes to determine whether the RM/UM phenotype was associated with higher risk of bleeding events, as previously described.[17] A prespecified secondary analysis of bleeding events was also conducted where RM and UM phenotypes were each compared with NM phenotypes. For each analysis, cumulative incidences of MAE, MACE, and clinically significant bleeding events were demonstrated using Kaplan–Meier curves and compared using log-rank tests, and event rates per 100 patient-years were calculated.

For each comparison, Cox proportional hazards regression was used to estimate the unadjusted hazard ratios (HRs) and 95% CIs. Multivariable Cox regression models were used to estimate adjusted HRs and 95% CIs after forcing in potential confounders identified a priori (MAE and MACE: age, sex, and ACS indication for PCI; clinically significant bleeding: age, sex, history of major hemorrhage, and anticoagulant use at discharge) and adjusting for baseline variables meeting a *P* value cutoff of <0.10 using distinct models for MAE/MACE and for clinically significant bleeding. For MAE and MACE, factors adjusted for in the model included age, sex, PCI indication (ACS versus non-ACS/elective indication), history of atrial fibrillation, aldosterone receptor antagonist at discharge, and anticoagulant use at discharge. For clinically significant bleeding events, the adjusted model included age, sex, current smoker, history of major hemorrhage, anticoagulant use at discharge, prior MI, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use at discharge. Sensitivity analyses were performed for atherothrombotic and bleeding outcomes after stratifying the baseline hazard by institution at the time of index PCI in the Cox regression model. Proportional hazards assumptions were assessed using the Grambsch-Therneau test. Statistical analyses were performed using R statistical software version 4.3 (R Foundation for Statistical Computing), and $P<0.05$ was considered significant.[18]

RESULTS

Study Population

Baseline characteristics of the 567 Black patients treated with clopidogrel included in the analysis are summarized in Table 1. The median age was 62 years, 259 (45.7%) were women, 398 (70.2%) had an ACS indication for PCI, 213 (37.6%) had prior revascularization, and 164 (28.9%) used a proton pump inhibitor at discharge. A total of 125 (22.0%) patients were CYP2C19 IM/PMs (20.8% IMs and 1.2% PMs), 205 (36.2%) were RM/UMs (31.6% RMs and 4.6% UMs), and 237 (41.7%) were NMs (Table S2).

Baseline characteristics were similar among CYP2C19 IM/PMs and NM/RM/UMs including age (63 versus 61 years; $P=0.190$), history of diabetes (52.0% versus 52.3%; $P=0.999$), and history of stroke or transient ischemic attack (17.6% versus 16.5%; $P=0.880$), with the exception of a higher prevalence of atrial fibrillation in the IM/PM group (13.6% versus 6.6%; $P=0.018$) (Table 1). Frequency of aldosterone receptor antagonist (9.6% versus 4.8%; $P=0.068$) and oral anticoagulant (15.2% versus 9.0%; $P=0.068$) use at discharge were also higher in IM/PMs, but these differences were not statistically significant. In addition, baseline characteristics among CYP2C19 NMs and RM/UMs were similar except for a higher proportion of patients with a history of MI (28.7% versus 19.9%; $P=0.042$) and prior revascularization (42.2% versus 32.5%; $P=0.046$) in the NM versus the RM/UM group, respectively (Table S3). Frequency of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use at discharge (75.9% versus 68.0%; $P=0.077$) was also higher and current smoker status (30.8% versus 38.8%; $P=0.094$) was lower in NMs versus RM/UMs, but these differences were not statistically significant.

Clinical Outcomes

All patients were treated with clopidogrel at the time of event or last follow-up by study design. The median follow-up time for IM/PMs was 212 days (interquartile range [IQR], 32–356 days) and for NM/RM/UMs was 268 days (IQR, 96–350 days). Overall, 67 (11.8%) patients experienced an MAE during follow-up. MAE occurred at a significantly higher rate in clopidogrel-treated IM/PMs versus NM/RM/UMs (35.1 versus 15.9 per 100 person-years, respectively; adjusted HR, 2.00 [95% CI, 1.20–3.33], $P=0.008$) (Table 2, Figure 1A). The secondary outcome of MACE occurred in 47 (8.3%) patients during follow-up. Like MAE, MACE occurred at a significantly higher rate among IM/PMs versus NM/RM/UMs (24.9 versus 11.1 per 100 person-years, respectively; adjusted HR, 2.06 [95% CI, 1.12–3.80], $P=0.020$) (Table 2, Figure 1B). Sensitivity analysis results for the primary

Table 1. Patient Characteristics at the Time of Index PCI in the Full Cohort of Black Patients Treated With Clopidogrel and Stratified By CYP2C19 Metabolizer Phenotype Group

	Full cohort (N=567)	CYP2C19 IM/PM (n=125)	CYP2C19 NM/RM/UM (n=442)	*P* value*
Age, y	62.0 (54.0–69.0)	63.0 (56.0–69.0)	61.0 (53.0–69.0)	0.190
Women	259 (45.7)	53 (42.4)	206 (46.6)	0.464
Hispanic	2 (0.4)	1 (0.8)	1 (0.2)	0.920
BMI, kg/m^2	30.4 (25.1–34.9)	30.5 (24.2–35.3)	30.4 (25.2–34.9)	0.923
Current smoker	193 (34.0)	40 (32.0)	153 (34.6)	0.661
ACS PCI indication	398 (70.2)	90 (72.0)	308 (69.7)	0.697
STEMI	91 (16.0)	21 (16.8)	70 (15.8)	-
NSTEMI	185 (32.6)	38 (30.4)	147 (33.3)	-
UA	122 (21.5)	31 (24.8)	91 (20.6)	-
Stent placed during PCI	535 (94.4)	115 (92.0)	420 (95.0)	0.283
Medical history				
Diabetes	296 (52.2)	65 (52.0)	231 (52.3)	0.999
Hypertension	505 (89.1)	109 (87.2)	396 (89.6)	0.552
Dyslipidemia	360 (63.5)	87 (69.6)	273 (61.8)	0.133
Prior MI	137 (24.2)	28 (22.4)	109 (24.7)	0.687
Prior revascularization	213 (37.6)	46 (36.8)	167 (37.8)	0.924
Prior stent	150 (26.5)	33 (26.4)	117 (26.5)	0.999
Prior CABG	71 (12.5)	19 (15.2)	52 (11.8)	0.383
Stroke/TIA	95 (16.8)	22 (17.6)	73 (16.5)	0.880
PVD	60 (10.6)	15 (12.0)	45 (10.2)	0.675
Heart failure	124 (21.9)	29 (23.2)	95 (21.5)	0.776
Atrial fibrillation	46 (8.1)	17 (13.6)	29 (6.6)	0.018
Gastrointestinal or intracranial hemorrhage	20 (3.5)	7 (5.6)	13 (2.9)	0.251
Active cancer	25 (4.4)	3 (2.4)	22 (5.0)	0.321
CKD	187 (33.0)	48 (38.4)	139 (31.4)	0.176
Discharge medication				
Aspirin	549 (96.8)	118 (94.4)	431 (97.5)	0.144
Statin	543 (95.8)	120 (96.0)	423 (95.7)	0.999
β-Blocker	491 (86.6)	108 (86.4)	383 (86.7)	0.999
ACEI or ARB	407 (71.8)	89 (71.2)	318 (71.9)	0.959
ARA	33 (5.8)	12 (9.6)	21 (4.8)	0.068
OAC	59 (10.4)	19 (15.2)	40 (9.0)	0.068
PPI	164 (28.9)	40 (32.0)	124 (28.1)	0.455

Data are presented as median (interquartile range) or number (percentage).

ACEI indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2); CYP2C19, cytochrome P450 2C19; IM, intermediate metabolizer; MI, myocardial infarction; NM, normal metabolizer; NSTEMI, non–ST-segment–elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PM, poor metabolizer; PPI, proton pump inhibitor; PVD, peripheral vascular disease; RM, rapid metabolizer; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina; and UM, ultrarapid metabolizer.

*The *P* value is for the comparison between the IM/PM and NM/RM/UM groups.

outcome (adjusted HR, 2.31 [95% CI, 1.36–3.92], *P*=0.002) and MACE (adjusted HR, 2.53 [95% CI, 1.34–4.79], *P*=0.004) were consistent after stratifying the baseline hazard by institution.

Overall, 23 (4.1%) patients experienced a clinically significant bleeding event during follow-up. Among these, 17 (3.8%) clinically significant bleeding events occurred in NMs, RMs, or UMs. For the primary bleeding analysis that compared CYP2C19 NMs with RM/UMs, no difference in clinically significant bleeding event rates were observed among groups (7.0 versus 5.5 per 100 person-years; adjusted HR, 1.17 [95% CI, 0.43–3.16], *P*=0.758) (Table 3; Figure 2A). Sensitivity analysis results were consistent after stratifying the baseline hazard by institution (adjusted HR, 1.25 [95% CI, 0.45–3.42], *P*=0.670). A secondary bleeding analysis that distinguished UMs and RMs was completed (Figure 2B). No significant difference in bleeding rates

Table 2. Association Between CYP2C19 IM/PM Phenotype Status and MAE and MACE Within 1 Year After PCI in Black Patients Treated With Clopidogrel

	No. of events (%)	Event rate per 100 person-y (95% CI)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)*	*P* value
MAE						
IM/PM (n=125)	24 (19.2%)	35.1 (21.1–49.2)	2.20 (1.33–3.62)	0.002	2.00 (1.20–3.33)	0.008
NM/RM/UM (n=442)	43 (9.7%)	15.9 (11.2–20.7)	Reference	-	Reference	-
MACE						
IM/PM (n=125)	17 (13.6%)	24.9 (13.1–36.7)	2.21 (1.22–4.01)	0.009	2.06 (1.12–3.80)	0.020
NM/RM/UM (n=442)	30 (6.8%)	11.1 (7.13–15.1)	Reference	-	Reference	-

Major atherothrombotic event (MAE) is a composite end point defined as all-cause mortality, myocardial infarction (MI), ischemic stroke, stent thrombosis, or revascularization for unstable angina in the 12 months following the index percutaneous coronary intervention (PCI). Major adverse cardiovascular events (MACE) is a composite end point defined as cardiovascular death, MI, stent thrombosis, or ischemic stroke within 12 months after the index PCI.

CYP2C19 indicates cytochrome P450 2C19; HR, hazard ratio, IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; and UM, ultrarapid metabolizer.

Proportional hazards were observed for all models.

*Model adjusted for age, sex, PCI indication (ie, acute coronary syndrome vs nonacute coronary syndrome/elective PCI indication), aldosterone receptor antagonist at discharge, anticoagulant at discharge, and history of atrial fibrillation.

was observed between NMs and RMs (5.5 versus 6.3 per 100 person-years; adjusted HR, 0.99 [95% CI, 0.34–2.87], *P*=0.991) (Table 3). Although a numerically higher rate of clinically significant bleeds appeared to occur in UMs (11.6 per 100 person-years), only 2 events occurred in this group, and the difference between UMs and NMs was not statistically significant (adjusted HR, 2.81 [95% CI, 0.56–14.1], *P*=0.209) (Table 3).

DISCUSSION

It is well established that *CYP2C19* no function alleles diminish clopidogrel clinical effectiveness and are associated with adverse cardiovascular outcomes in patients treated with clopidogrel after PCI.[6] However, these studies have lacked racial and ethnic diversity; therefore, the association between *CYP2C19* genotype and cardiovascular outcomes in Black patients

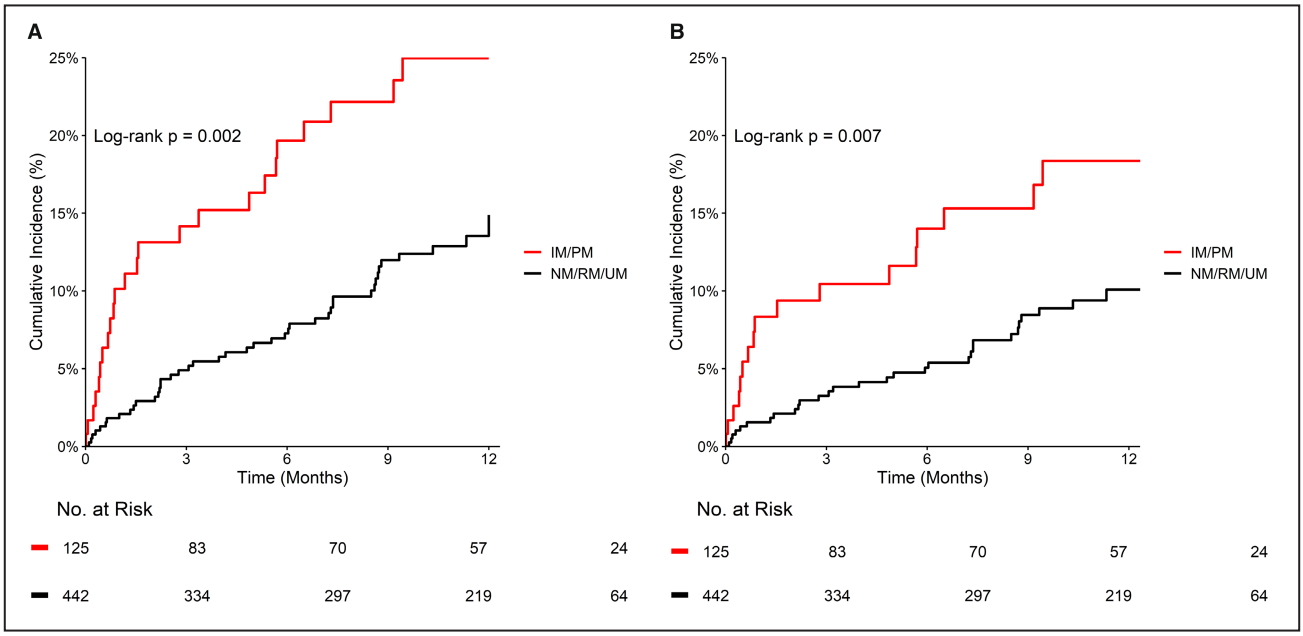

Figure 1. Time-to-event curves for major atherothrombotic events (MAE) and major adverse cardiovascular events (MACE) among Black patients treated with clopidogrel by cytochrome P450 2C19 (CYP2C19) status.
Time-to-event curves for atherothrombotic events among Black patients treated with clopidogrel by CYP2C19 status. The unadjusted log-rank *P* value for each Kaplan–Meier curve is presented. (**A**) MAE (primary end point) and (**B**) MACE (secondary end point) within 12 months after the index percutaneous coronary intervention (PCI). The Kaplan–Meier curve tails in Figure 1A were truncated at 360 days after the index PCI due to <10% of each stratum being available for follow-up. In the normal metabolizer/rapid metabolizer/ultrarapid metabolizer (NM/RM/UM) group, 1 event occurred after day 360, during which time only 17 patients (3.8%) were still in follow-up. No events occurred in the intermediate metabolizer/poor metabolizer (IM/PM) group after day 360 when only 4 (3.2%) patients were available for follow-up.

Table 3. Association Between CYP2C19 Metabolizer Phenotype Status and Clinically Significant Bleeding Events Within 1 Year After PCI in Black Patients Treated With Clopidogrel

CYP2C19 phenotype group	No. of events (%)	Event rate per 100 person-y (95% CI)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)*	*P* value
NM (n=237)	8 (3.4%)	5.45 (1.67–9.23)	Reference	-	Reference	-
RM/UM (n=206)	9 (4.4%)	7.04 (2.44–11.6)	1.30 (0.50–3.38)	0.586	1.17 (0.43–3.16)	0.758
RM† (n=180)	7 (3.9%)	6.33 (1.64–11.0)	1.17 (0.42–3.23)	0.762	0.99 (0.34–2.87)	0.991
UM† (n=26)	2 (7.7%)	11.6 (0–27.8)	2.17 (0.46–10.2)	0.328	2.81 (0.56–14.1)	0.209

Clinically significant bleeding events are defined as moderate or severe/life-threatening bleeding per the Global Use of Strategies to Open Occluded Arteries bleeding criteria within 12 months following index percutaneous coronary intervention (PCI).

CYP2C19 indicates cytochrome P450 2C19.

One covariate (sex) violated the proportional hazards assumption in the bleeding outcome analysis. After stratifying the baseline hazard by sex, similar results were observed in the primary analysis (rapid metabolizer [RM]/ultrarapid metabolizer [UM] vs normal metabolizer [NM]: adjusted hazard ratio [HR], 1.20 [95% CI, 0.44–3.25], *P*=0.721) and secondary analysis (RM vs NM: adjusted HR, 1.02 [95% CI, 0.35–2.94], *P*=0.977; UM vs NM: adjusted HR, 3.09 [95% CI, 0.61–15.7], *P*=0.174).

*Model adjusted for age, sex, history of major hemorrhage, anticoagulant at discharge, current smoker, prior myocardial infarction, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at discharge.

†RM and UM phenotypes were individually compared with NMs in a secondary analysis.

remains unclear.[11] In this real-world study of patients undergoing PCI and clinical *CYP2C19* genotyping, we report for the first time, to our knowledge, that self-reported Black or African American patients who were treated with clopidogrel and had the CYP2C19 IM/PM phenotype exhibited significantly higher rates of MAE within 1 year after PCI compared with those without a *CYP2C19* no function allele. These results are consistent with multiple previous studies in European and East Asian populations.[6–9,11] Together, these results suggest that Black IM/PM patients treated with clopidogrel are at higher risk of adverse cardiovascular outcomes after PCI and, in the absence of contraindications, would likely benefit from treatment with an alternative antiplatelet therapy such as prasugrel or ticagrelor.

Even in the presence of genotype-guided antiplatelet therapy, ≈50% of IMs are prescribed clopidogrel in real-world clinical settings. Factors associated with clopidogrel use in IM/PMs include older age, diabetes, prior stroke or transient ischemic attack, and oral anticoagulant prescription at discharge, none of which differed significantly between IM/PMs and NM/RM/UMs in our analysis.[10] Previous meta-analyses have demonstrated increased risk of MACE in clopidogrel-treated IMs and PMs of predominately European ancestry (HR, 1.57 [95% CI, 1.13–2.16]) and of East Asian ancestry (odds ratio [OR], 1.99 [95% CI, 1.64–2.42]).[7,8] The observed effect sizes in these meta-analyses appear comparable in magnitude to the results of the present analysis in Black patients for both the MAE (adjusted HR, 2.02 [95% CI, 1.22–3.37]) and MACE (adjusted HR, 2.08 [95% CI, 1.13–3.80]) end points.

Prior literature examining warfarin pharmacogenetics have demonstrated that data cannot necessarily be extrapolated from European populations to other populations given ancestral group differences in linkage disequilibrium and allele frequencies.[19] A race-stratified genetic analysis of patients with acute MI enrolled in the prospective, multicenter TRIUMPH (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status) registry did not observe a significant association between the no function *CYP2C19*2* allele and increased mortality in 430 Black patients with ACS treated with clopidogrel (adjusted HR, 0.63 [95% CI, 0.28–1.41]); whereas, in 1632 White patients treated with clopidogrel, significantly higher mortality was observed in *CYP2C19*2* allele carriers compared with noncarriers (adjusted HR, 1.70 [95% CI, 1.01–2.86]).[12] Within the TRIUMPH cohort, 77% of Black patients discharged on clopidogrel underwent PCI. In addition, TRIUMPH evaluated a primary end point of all-cause death and a secondary end point of recurrent MI, whereas our primary outcome consisted of a composite end point of MAE, which includes the outcomes of MI, stent thrombosis, ischemic stroke, and unstable angina, which have previously been more closely linked to antiplatelet therapy efficacy in clinical trials than all-cause mortality.[3,4] Consistent with the known impact of *CYP2C19* no function alleles on reduced clopidogrel active metabolite formation and inhibition of platelet reactivity, our findings suggest that Black IM/PMs are at increased risk of experiencing MAE when treated with clopidogrel after PCI.[6,11]

Recent investigation of the ancestral genetic influence on clopidogrel response suggests genes beyond *CYP2C19* may also be important in populations of African ancestry.[20] Because of inconsistencies in the evidence, the association with *CYP2C19* genotype reported in our study as well as the impact of other genes on clopidogrel-related outcomes warrants further study. In addition, studies have shown that clinical factors beyond *CYP2C19* genotype such as advanced age, obesity, chronic kidney disease, and diabetes, and concomitant medications (eg, proton pump inhibitors) impact clopidogrel effectiveness.[13,21,22] Evaluating

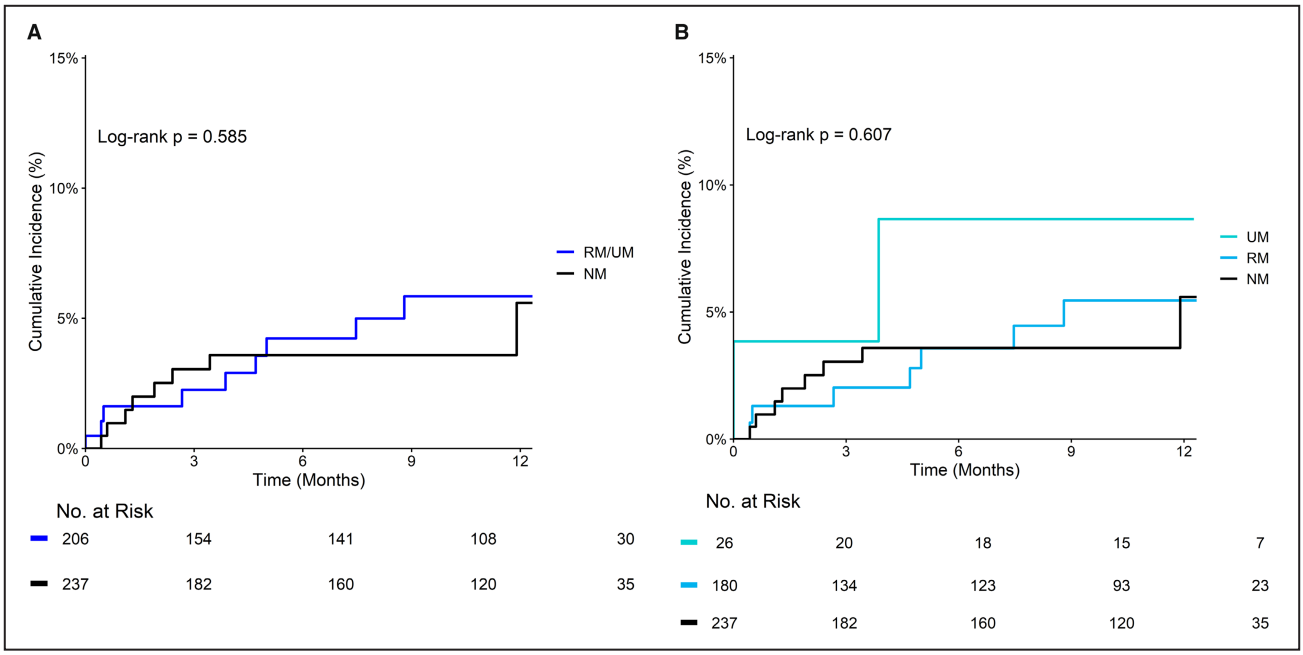

Figure 2. Time-to-event curves for clinically significant bleeding events among Black patients treated with clopidogrel by cytochrome P450 2C19 phenotype status.

Time-to-event curves for clinically significant bleeding events among normal and increased function phenotypes. The unadjusted log-rank *P* value for each Kaplan–Meier curve is presented. Clinically significant bleeding events are defined as moderate or severe/life-threatening bleeding per the Global Use of Strategies to Open Occluded Arteries bleeding criteria within 12 months following the index percutaneous coronary intervention (PCI). (**A**) Normal metabolizer (NM) vs rapid metabolizer/ultrarapid metabolizer (RM/UM) phenotypes (primary analysis) and (**B**) NM vs RM and UM phenotypes (secondary analysis).

the additive impact of these factors on outcomes was beyond the scope of the current study, but future studies with larger sample sizes may evaluate the utility of antiplatelet therapy risk prediction scores in Black patients undergoing PCI.

In addition to no function alleles, some evidence has suggested that bioactivation of clopidogrel is enhanced by the presence of the *CYP2C19*17* increased function allele, which results in augmented platelet inhibition.[6] However, clinical outcomes have not been consistently associated with the *CYP2C19*17* allele in previous studies predominantly comprising White and East Asian patients.[6,23,24] In particular, presence of the increased function *CYP2C19*17* allele after PCI has not been associated with increased risk of bleeding or decreased risk of ischemic outcomes compared with NMs when the presence of *CYP2C19* no function alleles was accounted for.[6,17,25,26] In contrast, the race-stratified genetic analysis cohort of the TRIUMPH registry demonstrated that Black patients treated with clopidogrel carrying a *CYP2C19*17*-increased function allele were at significantly higher risk of both mortality and risk of major and minor bleeding events compared with noncarriers of *CYP2C19*17*; in particular, carriers of 2 copies of the *CYP2C19*17* allele were significantly more likely to experience any major or minor bleeding (OR, 3.82 [CI, 1.17–12.4], *P*=0.027) compared with noncarriers.[12] In contrast to the TRIUMPH registry, Black RM/UMs in our analysis exhibited no apparent difference in clinically significant bleeding rates compared with clopidogrel-treated NMs. However, these results should be interpreted with caution. Our study did not assess minor bleeding and, therefore, bleeding event rates in our cohort were low; additionally, the UM phenotype group in our study included only 26 patients. Therefore, our study was likely underpowered to detect clinically significant differences between phenotype groups. Consequently, the influence of the *CYP2C19*17* allele on bleeding risk in Black patients warrants further study.

Accumulating evidence has demonstrated that a *CYP2C19* genotype–guided antiplatelet therapy strategy, which selectively uses alternative therapy with prasugrel or ticagrelor in CYP2C19 IM/PMs, decreases the occurrence of MAE after PCI without increasing major bleeding events.[6,27–29] However, the prospective studies evaluating the impact of genotype-guided antiplatelet therapy after PCI on clinical outcomes have lacked racial and ethnic diversity; among the major outcome studies that reported race and ethnicity data, only ≈6% of study participants among all of the studies were of African ancestry.[11] A recent analysis of genotype-guided antiplatelet therapy prescribing practices at 9 early adopter institutions in the United States observed no significant difference in the use of

alternative antiplatelet therapy in *CYP2C19* no function allele carriers between Black and White patients after PCI.[10] Thus, although Black patients have not been well represented in previous studies examining genotype-guided antiplatelet therapy, this study of genotype-guided prescribing suggests that CPIC guideline recommendations have been applied similarly in Black and White patients in clinical practice. The elevated risk of MAE in clopidogrel-treated IM/PMs demonstrated in the current study of Black patients with PCI suggests the need to evaluate the impact of genotype-guided antiplatelet therapy on clinical outcomes in patients of African ancestry.

Although this analysis represents the largest *CYP2C19* genotyping outcomes study of Black patients with PCI to date, several limitations are present in this study. Patients were not randomized to receive clopidogrel or alternative therapy, and genotype was considered by providers at the time of P2Y12 inhibitor prescribing. This introduces a potential selection bias in our analysis of patients treated with clopidogrel, which could vary among sites, given that providers were recommended to prescribe alternative therapy in IM/PMs; thus, the prevalence of IM/PMs in our study was lower than would typically be expected. Related to the challenges of conducting genotype association outcomes studies in underrepresented populations, the overall number of clinical events in our cohort was relatively low. In particular, the number of clinically significant bleeding events in our study was low, which introduced uncertainty and wide CIs for our secondary analysis of bleeding outcomes. Due to the low prevalence of bleeding events, this uncertainty was particularly evident in the CYP2C19 UM group. In addition, events that occurred outside of each institution's health system may have been missed if they were not available in the electronic medical record. Finally, we did not collect data on socioeconomic status, health insurance coverage, or other measures of health disparities that may have influenced the decision to prescribe clopidogrel and outcomes in our study population of patients treated with clopidogrel. Due to the focus on Black patients with PCI, clinical outcomes within other underrepresented populations such as patients of Hispanic ethnicity and comparison of outcomes among populations were not evaluated in our analysis. Together, these limitations illustrate the need for evidence generation in larger and more diverse patient populations. Targeted efforts to recruit underrepresented populations into clinical trials and registries are an important tool to close this evidence gap.[11,30–32]

In summary, the present study showed a significant association between *CYP2C19* no function alleles and increased risk for MAE in a real-world population of Black patients treated with clopidogrel after PCI. Future studies are needed to determine whether genotype-guided use of prasugrel or ticagrelor improves adverse cardiovascular outcomes in Black patients, and patients from other underrepresented populations, undergoing PCI.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

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