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Impact of the *CYP2C19*17* allele on outcomes in patients receiving genotype-guided antiplatelet therapy after percutaneous coronary intervention

Craig R. Lee, PharmD, PhD¹, Cameron D. Thomas, PharmD², Amber L. Beitelshes, PharmD, MPH³, Sony Tuteja, PharmD, MS⁴, Philip E. Empey, PharmD, PhD⁵, James C. Lee, PharmD⁶, Nita A. Limdi, PharmD, PhD, MSPH⁷, Julio D. Duarte, PharmD, PhD², Todd C. Skaar, PhD⁸, Yiqing Chen, MS², Kelsey J. Cook, PharmD², James C. Coons, PharmD⁵, Chrisly Dillon, MD, MPA⁷, Francesco Franchi, MD⁹, Jay Giri, MD, MPH⁴, Yan Gong, PhD², Rolf P. Kreutz, MD⁸, Caitrin W. McDonough, PhD, MS², James M. Stevenson, PharmD, MS⁵, Karen E. Weck, MD¹⁰, Dominick J. Angiolillo, MD, PhD⁹, Julie A. Johnson, PharmD², George A. Stouffer, MD¹⁰, Larisa H. Cavallari, PharmD² on behalf of the IGNITE Network Pharmacogenetics Working Group

¹Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC

²Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics and Precision Medicine, University of Florida, Gainesville, FL

³University of Maryland School of Medicine, Baltimore, MD

⁴University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

⁵School of Pharmacy, University of Pittsburgh, Pittsburgh, PA

⁶Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL

⁷University of Alabama at Birmingham, Birmingham, AL

⁸Indiana University School of Medicine, Indianapolis, IN

⁹Department of Medicine, Division of Cardiology, University of Florida, Jacksonville, FL

Address for Correspondence: Craig R. Lee, CB# 7569, UNC Eshelman School of Pharmacy, Chapel Hill, NC 27599-7569; Phone: 919-843-7673; craig_lee@unc.edu.

Author Contributions

C.R.L., L.H.C., C.D.T., A.L.B., S.T., P.E.E., J.C.L., N.A.L., J.D.D., T.C.S., and G.A.S. wrote the manuscript. C.R.L., L.H.C., A.L.B., S.T., P.E.E., J.C.L., N.A.L., J.D.D., T.C.S., and J.A.J. designed the research. C.R.L., L.H.C., C.D.T., A.L.B., S.T., P.E.E., J.C.L., N.A.L., J.D.D., T.C.S., K.J.C., J.C.C., C.D., F.F., J.G., R.P.K., C.W.M., J.M.S., K.E.W., D.J.A., J.A.J., and G.A.S. performed the research. C.D.T., Y.C., Y.G., and C.W.M. analyzed the data.

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¹⁰Division of Cardiology and McAllister Heart Institute, UNC School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Genotyping for *CYP2C19* no function alleles to guide antiplatelet therapy after percutaneous coronary intervention (PCI) improves clinical outcomes. Although results for the increased function *CYP2C19**17 allele are also reported, its clinical relevance in this setting remains unclear. A collaboration across nine sites examined antiplatelet therapy prescribing and clinical outcomes in 3,342 patients after implementation of *CYP2C19*-guided antiplatelet therapy. Risk of major atherothrombotic and bleeding events over 12 months after PCI were compared across *CYP2C19* metabolizer phenotype and antiplatelet therapy groups by proportional hazards regression. Clopidogrel was prescribed to a similar proportion of *CYP2C19* normal (84.5%), rapid (82.9%) and ultrarapid metabolizers (80.6%) ($P=0.360$). Clopidogrel-treated normal metabolizers (20.4 events/100 patient-years; adjusted hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.75–1.33, $P=0.993$) and clopidogrel-treated rapid or ultrarapid metabolizers (19.1 events/100 patient-years; adjusted HR 0.95, 95% CI 0.69–1.30, $P=0.734$) exhibited no difference in major atherothrombotic events compared to patients treated with prasugrel or ticagrelor (17.6 events/100 patient-years). In contrast, clopidogrel-treated intermediate and poor metabolizers exhibited significantly higher atherothrombotic event risk compared to prasugrel/ticagrelor-treated patients (adjusted HR 1.56, 95% CI 1.12–2.16, $P=0.008$). When comparing clopidogrel-treated rapid or ultrarapid metabolizers to normal metabolizers, no difference in atherothrombotic (adjusted HR 0.97, 95% CI 0.73–1.29, $P=0.808$) or bleeding events (adjusted HR 1.34, 95% CI 0.83–2.17, $P=0.224$) were observed. In a real-world setting of genotype-guided antiplatelet therapy, the *CYP2C19**17 allele did not significantly impact post-PCI prescribing decisions or clinical outcomes. These results suggest the *CYP2C19* *1/*17 and *17/*17 genotypes have limited clinical utility to guide antiplatelet therapy after PCI.

Keywords

clopidogrel; *CYP2C19*; pharmacogenomics; ultrarapid metabolizer; percutaneous coronary intervention; cardiovascular events; antiplatelet therapy

INTRODUCTION

Approximately 480,000 percutaneous coronary interventions (PCIs) are performed annually in the United States (U.S.).¹ Dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) is indicated following PCI to reduce the risk of major atherothrombotic events.²

Clopidogrel, a prodrug requiring bioactivation by the *CYP2C19* enzyme, remains the most widely prescribed P2Y₁₂ inhibitor.³ *CYP2C19* no function alleles, most notably *2, are common and significantly impair clopidogrel active metabolite formation, platelet inhibition, and clinical effectiveness after PCI.^{4,5} In contrast, *CYP2C19* genotype does not impact the clinical effects of prasugrel or ticagrelor,^{6,7} which exhibit more consistent antiplatelet effects, superior efficacy in acute coronary syndrome (ACS) patients in the absence of

CYP2C19 genotyping, and higher bleeding risk compared to clopidogrel.^{8,9} Accumulating evidence has demonstrated that genotyping and prescribing prasugrel or ticagrelor in *CYP2C19* no function allele carriers after PCI improves clinical outcomes.^{10–13}

The increased function *CYP2C19**17 allele (rs12248560) is carried by approximately 30% of the U.S. population, with individuals carrying one *17 allele and one normal function allele (*1/*17: rapid metabolizers, RM) or two *17 allele copies (*17/*17: ultrarapid metabolizers, UM) exhibiting increased *CYP2C19* expression and metabolic function compared to normal metabolizers (NM).^{5,14} The *CYP2C19**17 allele has been associated with increased active metabolite formation, enhanced inhibition of platelet aggregation, higher bleeding risk, and lower risk for ischemic events with clopidogrel.^{15–19} However, other studies have reported no significant association between the *17 allele and clopidogrel pharmacokinetics, pharmacodynamics, and ischemic and bleeding outcomes after accounting for the *2 allele.^{7,20–22} It has been postulated that the observed relationship between the *17 allele and clopidogrel's antiplatelet effects may be due to absence of the no function *2 allele rather than presence of the increased function *17 allele.^{5,20} Thus, the impact of the *CYP2C19**17 allele on clopidogrel clinical effectiveness and safety remains unclear.

Multiple institutions have successfully implemented genotype-guided antiplatelet therapy into clinical workflows.^{23,24} While *17 allele results are typically reported in addition to no function alleles on clinically implemented *CYP2C19* tests,²⁵ distinction of *CYP2C19* UMs and RMs from NMs to guide antiplatelet therapy prescribing decisions is not currently recommended due to insufficient evidence.⁵ The primary objective of this study was to investigate the impact of the *CYP2C19* UM or RM phenotypes on antiplatelet therapy selection and clinical outcomes in PCI patients who underwent *CYP2C19* genotyping in real-world clinical settings.

METHODS

Study Design and Population.

This was an expansion of a previously described multi-center investigation of *CYP2C19* genotype-guided antiplatelet therapy post-PCI.¹⁰ Seven institutions (University of Florida, Gainesville; University of North Carolina, Chapel Hill; University of Maryland, Baltimore; University of Alabama, Birmingham; University of Pittsburgh; University of Illinois, Chicago; and Indiana University) contributed data for 1,815 patients for the original analysis. The expanded dataset includes additional data for 1,002 patients from the original sites plus data for 525 patients from two additional sites (University of Pennsylvania and University of Florida, Jacksonville, as described^{26,27}). All sites had implemented clinical *CYP2C19* testing with genotype results returned via the electronic health record (EHR) for consideration during antiplatelet therapy prescribing, and participated in the NIH-funded Implementing Genomics in Practice (IGNITE) Network Pharmacogenetics Working Group.^{23,28} Data collection was approved by the Institutional Review Board at each site.

The study design was pragmatic, such that delivery of the genotype intervention was part of clinical care, the ultimate decision to order genetic testing and choice of drug therapy was

left to the discretion of the prescriber, and clinically meaningful outcome data were collected from the EHR.²⁹ All patients from each site 18 years of age who underwent PCI, *CYP2C19* genotyping, and received a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) after PCI were included, regardless of length of follow-up. A total of 3,342 patients across the nine institutions met these criteria and were included in the analysis.

***CYP2C19* Genotyping and Phenotyping.**

Genotyping was performed at each institution in a Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory. All sites genotyped for the *CYP2C19**2 and *3 no function alleles and the *17 increased function allele, with additional rare alleles genotyped at five institutions (TABLE S1). As summarized in TABLE S2, *CYP2C19* metabolizer phenotype was assigned according to standardized Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations: UM (two increased function alleles); RM (one increased and one normal function allele); NM (absence of any tested increased or no function allele), intermediate metabolizer (IM, one no function allele), or poor metabolizer (PM, two no function alleles).³⁰ Notably, patients with one no function and one increased function allele (e.g., *2/*17) were classified as IMs. Alternative antiplatelet therapy, consisting of prasugrel or ticagrelor in the absence of contraindications, was recommended over clopidogrel for IMs and PMs in accordance with CPIC recommendations.⁵ In NMs, RMs and UMs, antiplatelet therapy selection was left to the discretion of the prescriber.

Data Abstraction and Endpoints.

Demographic, clinical, genotype, and medication data were manually abstracted from the EHR at each site through review of patient encounters, including the index PCI hospitalization and subsequent hospitalizations and outpatient visits, using a common data collection form, as described.¹⁰ The index PCI (baseline) was defined as the PCI performed in association with *CYP2C19* genotyping.

The occurrence of cardiovascular and bleeding clinical events for up to 12 months following the index PCI (baseline) were determined. Events were identified based on physician-reported diagnoses abstracted from the cardiac catheterization laboratory report, hospital discharge summary notes, or outpatient clinical notes of the EHR. Antiplatelet therapy and dose at the time of each event, and at the last follow-up within 12 months, was documented. The primary outcome was major atherothrombotic events, defined as the composite of death, myocardial infarction (MI), stent thrombosis, ischemic stroke, or hospitalization for unstable angina, consistent with a recent clinical trial of genotype-guided antiplatelet therapy.³¹ The secondary outcome was clinically significant bleeding events, defined as Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate (requiring blood transfusion but not resulting in hemodynamic compromise) or severe/life-threatening (intracerebral hemorrhage or bleeding resulting in hemodynamic compromise requiring treatment).³²

Statistical Analysis.

Data were curated and aggregated at the University of Florida, Gainesville. Continuous data are presented as mean±standard deviation or median (interquartile range), and categorical

data are presented as count (%), unless otherwise indicated. Antiplatelet therapy was dichotomized (clopidogrel or prasugrel/ticagrelor) for analysis. Due to the small number of UMs and PMs, CYP2C19 metabolizer phenotype was categorized into three groups for the primary analysis: UM or RM, NM, and IM or PM. Baseline demographic and clinical factors were compared across CYP2C19-antiplatelet therapy groups using Student's t-test, chi-square, or Fisher's exact test.

The time to occurrence of an atherothrombotic or bleeding event within 12 months after the index PCI (baseline) was calculated in each patient. Patients who did not experience an event were censored at the time of last encounter in which P2Y₁₂ inhibitor treatment was documented. Event rates were reported as the number of events per 100 patient-years of follow-up. The relationship between P2Y₁₂ inhibitor therapy, CYP2C19 metabolizer phenotype, and time to occurrence of the primary and secondary clinical outcomes was evaluated by Cox proportional hazards regression, as described.^{10,33} Kaplan-Meier curves were generated, and the log-rank test was used to compare the cumulative risk of an event across groups.

In order to examine the impact of CYP2C19 metabolizer status on clopidogrel clinical effectiveness relative to alternative antiplatelet therapy, the primary analysis compared outcomes across four CYP2C19-antiplatelet therapy groups: clopidogrel-UM or RM, clopidogrel-NM, clopidogrel-IM or PM, and prasugrel or ticagrelor (regardless of CYP2C19 phenotype). Because of the known absence of an association between CYP2C19 metabolizer status and either prasugrel or ticagrelor clinical effectiveness,^{6,7} and guideline recommendations for use of prasugrel or ticagrelor as first-line therapy in ACS patients undergoing PCI,² all patients receiving prasugrel or ticagrelor were combined into a single alternative therapy reference group (alternative-combined). Secondary analyses evaluated outcomes across CYP2C19 metabolizer status within the stratum of patients treated with clopidogrel. Clopidogrel-treated NMs served as the reference group and were initially compared to clopidogrel-treated UM/RMs and clopidogrel-treated IM/PMs. An additional analysis compared outcomes across clopidogrel-treated UMs (*17/*17), RMs (e.g., *1/*17), NMs (*1/*1), IMs carrying the CYP2C19*17 allele (e.g., *2/*17), IMs not carrying the *17 allele (e.g., *1/*2), and PMs (e.g., *2/*2).

Because of the nonrandomized design, analyses were completed after adjusting for age, gender, race, and baseline covariates that differed across CYP2C19-antiplatelet groups. Covariate adjusted hazard ratio (HR) and 95% confidence intervals (CIs) for each between-group comparison were calculated. Multivariable models were created by selecting candidate covariates, described in TABLE 1, with the criterion of P<0.10 to enter the model. In the primary analysis, covariates included in the adjusted model were age (continuous), gender, race (white, black, or other), body mass index (continuous), ACS indication for PCI, drug-eluting stent at index PCI, diabetes, hypertension, chronic kidney disease (defined as an estimated glomerular filtration rate <60 ml/min), peripheral vascular disease, atrial fibrillation, heart failure, current cancer, prior stent, prior stroke or transient ischemic attack (TIA), prior gastrointestinal or intracerebral hemorrhage, and statin at discharge. In the secondary clopidogrel stratum analysis, covariates included in the adjusted model were age, gender, race, ACS indication for PCI, chronic kidney disease, peripheral vascular disease,

prior MI, prior stent, prior stroke or TIA, prior gastrointestinal or intracerebral hemorrhage, and beta-blocker at discharge.

All analyses were performed using R statistical software (version 3.6; <http://www.r-project.org/>). *P*-values <0.05 were considered statistically significant.

RESULTS

Study Population.

Baseline characteristics of the 3,342 patients included in the study are summarized in TABLE 1. The mean age was 63±12 years, 32.2% were female, and 19.7% were African-American. Comorbidities such as diabetes (40.5%), chronic kidney disease (28.8%), and atrial fibrillation (9.5%) were common. Overall, 2,290 patients (68.5%) had an ACS indication for PCI. Most patients received a drug eluting stent (85.8%) and were prescribed aspirin at discharge (97.8%) in addition to a P2Y₁₂ inhibitor.

CYP2C19 Metabolizer Status and Antiplatelet Therapy.

Among the study population, 144 (4.3%), 837 (25.0%), 1,329 (39.8%), 934 (27.9%), and 98 (2.9%) were classified as a CYP2C19 UM, RM, NM, IM, and PM, respectively, based on their *CYP2C19* genotype. The frequency of each genotype is summarized in TABLE S2.

Clopidogrel (72.1%) was the most commonly prescribed P2Y₁₂ inhibitor maintenance therapy, followed by prasugrel (17.0%) and ticagrelor (10.9%). Prasugrel or ticagrelor was prescribed to a significantly higher proportion of IM/PMs (53.9%) compared to NMs (15.5%) and UM/RMs (17.4%) (*P*<0.001, FIGURE 1), with 75 of 98 (76.5%) PMs and 481 of 934 (51.5%) IMs prescribed an alternative antiplatelet therapy. Among the IMs, 52.6% of **17* allele non-carriers (e.g., **1/*2*) and 48.3% of **17* allele carriers (e.g., **2/*17*) were prescribed prasugrel or ticagrelor (*P*=0.256). Among patients without a *CYP2C19* no function allele, clopidogrel 75 mg/day was prescribed to a similar proportion of NMs, RMs and UMs (84.5% vs. 82.9% vs. 80.6%, *P*=0.360).

There were baseline differences between antiplatelet therapy groups in age, race, indication for PCI, prevalence of multiple comorbidities including, diabetes, chronic kidney disease, peripheral vascular disease, atrial fibrillation, stroke, bleeding, and use of oral anticoagulants (TABLE 1). These differences were absent or diminished, and were only significant for race, chronic kidney disease, and prior bleeding, when comparing across CYP2C19 metabolizer status among patients prescribed clopidogrel. Aspirin use was not different across groups.

Clinical Outcomes.

During a median follow-up of 6.3 (1.0–11.0) months after PCI, 353 patients (10.6%) experienced a major atherothrombotic event. The risk of the primary outcome by CYP2C19 metabolizer status and antiplatelet therapy is shown in FIGURE 2. Compared to patients treated with prasugrel or ticagrelor, IMs or PMs treated with clopidogrel exhibited a significantly higher risk of major atherothrombotic events (17.6 vs. 33.7 events per 100 patient-years, respectively; adjusted HR 1.56, 95% CI 1.12–2.16, *P*=0.008). In contrast, clopidogrel-treated CYP2C19 NMs (20.4 events per 100 patient-years; adjusted HR 1.00,

95% CI 0.75–1.33, $P=0.993$) and clopidogrel-treated UMs or RMs (19.1 events per 100 patient-years; adjusted HR 0.95, 95% CI 0.69–1.30, $P=0.734$) exhibited no difference in risk for a major atherothrombotic event compared to patients treated with prasugrel or ticagrelor (TABLE 2).

In patients treated with clopidogrel, IM/PMs exhibited a significantly higher risk of major atherothrombotic events compared to NMs (adjusted HR 1.56, 95% CI 1.16–2.10, $P=0.003$). In contrast, no difference was observed between clopidogrel-treated UM/RMs versus NMs (adjusted HR 0.97, 95% CI 0.73–1.29, $P=0.808$). The impact of the *CYP2C19*17* allele on these associations with major atherothrombotic events was evaluated (FIGURE 3). No difference in event rate was observed across clopidogrel-treated UMs (**17/*17*), RMs (**1/*17*), and NMs (18.5, 19.3, and 20.4 events per 100 patient-years, respectively; TABLE S3). The risk of an atherothrombotic event was higher in clopidogrel-treated PMs and IMs who did not carry the **17* allele (e.g., **1/*2*) compared to NMs (adjusted HR 1.72, 95% CI 1.25–2.37, $P<0.001$). The subset of IMs who carried the **17* allele (e.g., **2/*17*), however, did not exhibit a significantly higher risk of atherothrombotic events compared to NMs (adjusted HR 1.15, 95% CI 0.67–1.97, $P=0.613$). When comparing IMs who carried the **17* allele to IMs without the **17* allele, risk of an atherothrombotic event was not significantly different (25.7 vs. 37.9 events per 100 patient-years, respectively; unadjusted HR 0.69, 95% CI 0.39–1.23; $P=0.211$; adjusted HR 0.67, 95% CI 0.37–1.21, $P=0.182$).

The secondary outcome of clinically significant bleeding was documented in 124 (3.7%) patients during the follow-up period. Overall, there was no difference in risk of developing a clinically significant bleeding event across groups (FIGURE 4, TABLE 2). In patients treated with clopidogrel, no difference in bleeding risk was observed between *CYP2C19* UM/RMs and NMs (7.9 vs. 6.0 events per 100 patient-years, respectively; adjusted HR 1.34, 95% CI 0.83–2.17, $P=0.224$) or between clopidogrel-treated UMs and RMs (7.3 and 8.0 events per 100 patient-years, respectively; TABLE S3).

DISCUSSION

The current study investigated the impact of the *CYP2C19*17* allele on antiplatelet therapy selection and outcomes following clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy across multiple centers in a real-world setting. Results illustrated that clopidogrel was prescribed at a similar rate in *CYP2C19* UMs, RMs, and NMs after PCI, and that presence of the **17* allele did not influence the frequency of alternative antiplatelet therapy selection in *CYP2C19* IMs (e.g. those with the **2/*17* genotype). Clopidogrel-treated UMs or RMs exhibited no difference in risk for a major atherothrombotic or clinically significant bleeding event compared to NMs over 12 months after PCI. In addition, cardiovascular and bleeding outcomes in clopidogrel-treated UMs or RMs and clopidogrel-treated NMs were not significantly different when compared to patients prescribed prasugrel or ticagrelor. Collectively, our results demonstrate that the *CYP2C19*17* allele does not significantly influence antiplatelet therapy selection or clinical outcomes in a real-world setting and suggest that use of the *CYP2C19* UM and RM phenotypes to guide antiplatelet therapy prescribing after PCI is likely of limited clinical utility.

Accumulating data demonstrate that use of *CYP2C19* genotyping to guide selection of prasugrel or ticagrelor in *CYP2C19* IMs and PMs after PCI lowers the risk of major atherothrombotic events compared with conventional treatment strategies without increasing bleeding risk.^{10–13,34,35} As a consequence, multiple institutions have successfully implemented *CYP2C19* genotype-guided antiplatelet therapy into clinical workflows.^{23,24,26,27,36–40} The increased function **17* allele, in addition to the **2* and **3* no function alleles, are recommended as tier 1 variants for inclusion on clinically implemented *CYP2C19* genotype tests by the Association for Molecular Pathology.²⁵ However, the impact of the **17* allele on clopidogrel clinical effectiveness and safety, and the optimal P2Y₁₂ inhibitor to use in **17* allele carriers, has remained unclear.

Several studies have reported that *CYP2C19*17* allele carriers have increased active metabolite formation, enhanced inhibition of platelet aggregation, higher bleeding risk, and lower risk for ischemic events with clopidogrel compared to non-carriers.^{15–19} In a study of 1,524 PCI patients, *CYP2C19*17* allele carriers had lower on-treatment platelet reactivity and 85% greater bleeding risk at 30 days compared to non-carriers, indicating enhanced responsiveness to clopidogrel treatment.¹⁵ Lower on-treatment platelet reactivity values were similarly shown in a study of chronic clopidogrel treatment post-PCI.¹⁶ In a study of 928 patients with MI, **17* allele carriers exhibited a 22% lower risk of clinically-driven target vessel revascularization and major ischemic events at one year compared to non-carriers.¹⁷ Importantly, these studies did not account for the impact of linkage disequilibrium between **2* and **17* allele defining variants by adjusting for the presence of the **2* allele.

Because the increased function T allele of **17* occurs on the same haplotype as the normal function G allele of **2*, it has been postulated that the observed **17* allele associations with clopidogrel response may be due to absence of the no function **2* allele rather than presence of the increased function **17* allele.^{5,20} Indeed, multiple studies have reported no significant association between the **17* allele and clopidogrel pharmacokinetics, pharmacodynamics, and outcomes after accounting for the **2* allele.^{7,20–22} Notably, in a pharmacokinetic-pharmacodynamic study performed in the Amish population, the **17* allele was marginally associated with higher clopidogrel active metabolite levels and lower post-treatment platelet aggregation, but the association was abrogated after adjustment for the **2* allele.²⁰ A retrospective genetic analysis of 3,391 clopidogrel-treated patients in the International Clopidogrel Pharmacogenomics Consortium further demonstrated that the relationship between the **17* allele and enhanced inhibition of platelet aggregation was no longer significant after adjusting for the **2* allele.²² In our pragmatic investigation of patients that underwent clinical *CYP2C19* genetic testing, while clopidogrel-treated IM/PMs (no function allele carriers) had a significantly higher risk of major atherothrombotic events compared to NMs (**1/*1*) over 12 months after PCI, clopidogrel-treated UMs (**17/*17*) or RMs (**1/*17*) exhibited no difference in atherothrombotic or bleeding events compared to NMs. Our study did not investigate clopidogrel pharmacokinetics or pharmacodynamics or clopidogrel dose-responses, and thus is limited by a lack of direct mechanistic insight into the observed clinical outcomes. However, our outcome findings in a real-world setting accounted for all tested alleles through use of *CYP2C19* metabolizer phenotypes,⁵ are consistent with these prior retrospective genotyping studies that adjusted for the **2* allele,^{20,22} and further

demonstrate that the **17* allele does not significantly alter clopidogrel effectiveness post-PCI after accounting for *CYP2C19* no function alleles.

In accordance with current CPIC recommendations,^{5,30} the combination of one no function and one increased function allele (e.g., **2/*17*) was assigned the IM phenotype across sites. In a secondary analysis that distinguished IMs with and without the **17* allele, we observed that presence of the **17* allele in IMs did not influence antiplatelet therapy prescribing. As hypothesized, clopidogrel-treated PMs and IMs without the **17* allele (e.g., **1/*2*) exhibited a significantly higher risk of atherothrombotic events compared to NMs. In contrast, the atherothrombotic event rate in the subset of IMs who carried the **17* allele (e.g., **2/*17*) was not significantly higher compared to NMs. A study evaluating the joint impact of each allele on clopidogrel's antiplatelet effects demonstrated that patients with a **2/*17* genotype had on-treatment platelet aggregation values in between those seen in **1/*2* and **1/*17* patients, indicating a potential gene-dose effect.¹⁶ Although presence of the increased function **17* allele could partially diminish the higher risk of atherothrombotic events imparted by the no function **2* allele in clopidogrel-treated patients, other studies have reported no difference in platelet reactivity between **1/*2* and **2/*17*.⁴¹ Moreover, we observed no significant difference in atherothrombotic events between the **1/*2* and **2/*17* genotypes. Thus, our data support current CPIC guidelines that classify patients with the **2/*17* genotype as an IM and recommend prasugrel or ticagrelor after PCI unless contraindicated.^{5,30} Due to the relatively low number of IMs carrying a **17* allele (n=122) in our study, statistical power for this comparison was limited, confidence intervals were wide, and the results of this secondary analysis should be interpreted with caution. Further study in a larger population is needed to more confidently determine whether the **17* allele significantly influences clopidogrel effectiveness in IMs and whether phenotypic distinction of IMs should be considered in antiplatelet therapy prescribing decisions.

Our study also demonstrated that clopidogrel-treated UMs, RMs and NMs exhibited no difference in risk for a major atherothrombotic or clinically significant bleeding event when compared to patients prescribed prasugrel or ticagrelor. These results are consistent with outcomes from the recent POPular Genetics trial in patients with ST-elevation MI.¹¹ The trial specifically demonstrated that a genotype-guided approach, with *CYP2C19* IMs and PMs treated with ticagrelor or prasugrel and all others (NMs, RMs, and UMs) treated with clopidogrel 75 mg/day, was non-inferior to universal use of ticagrelor or prasugrel for risk of developing major cardiovascular or bleeding events. The genotype-guided arm also exhibited significantly lower risk for bleeding events, which was driven by a reduction in minor bleeding. These results, together with our data, demonstrate that clopidogrel use at standard doses in patients without a *CYP2C19* no function allele is safe and effective after PCI. These data lend additional evidence in support of the current CPIC guideline recommendations,⁵ and strongly suggest that in the absence of contraindications any P2Y₁₂ inhibitor can be used after PCI in *CYP2C19* NMs, RMs and UMs.

Data from our study were generated from patients receiving genotype-guided antiplatelet therapy in a real-world clinical setting, and thus offer greater generalizability and compliment data generated from clinical trials with more rigid eligibility criteria. For example, our study population had greater racial diversity and higher prevalence of

comorbidities such as diabetes, chronic kidney disease, and history of stroke compared to recent clinical trials of biomarker-guided antiplatelet therapy.^{11,31,42} Our study also included 31% non-ACS patients for whom the impact of *CYP2C19* genotype on clopidogrel outcomes has been reported to be less than in ACS patients.^{43,44} Notably, in the setting of real-world implementation, genotype testing and dissemination of results must be integrated into the workflow without the extra resources afforded in the setting of a clinical trial. Clinical trials often allow for genetic samples to be collected and processed efficiently with changes to therapy dictated by protocols. In the real-world setting, clinicians may choose whether to act on genotype without a protocol directing their actions. In contrast to the recent POPular Genetics and TAILOR-PCI clinical trials of *CYP2C19*-guided antiplatelet therapy, neither of which considered the *CYP2C19*17* allele in their genotype-guided treatment protocols,^{11,31} our study sites reported **17* allele results in the EHR. This enabled our study to evaluate impact of the **17* allele on treatment outcomes, and to investigate for the first time whether return of **17* allele results influenced the antiplatelet therapy prescribing decision in a real-world setting. These results, however, cannot be extrapolated to other *CYP2C19* substrates.^{45,46}

Several limitations to this analysis should be noted. First, because this was a pragmatic study, randomization was not performed, and antiplatelet selection was based on individual prescriber discretion. Outcomes could have therefore been impacted by the baseline differences between *CYP2C19*-antiplatelet therapy groups. Covariate-adjusted and stratified analyses were conducted to lessen these effects. Although associations of similar magnitude were observed following adjustment, residual confounding may remain. Second, the analysis is based on medications prescribed, but there are no available data on antiplatelet therapy adherence or pharmacodynamic effects. Moreover, the frequency *CYP2C19* inhibitor use was not systematically evaluated. Thus, we cannot rule out whether differences in antiplatelet therapy adherence, aspirin responsiveness, or drug-drug interactions across groups influenced the observed outcomes. Third, clinical events were not independently adjudicated. While the manual collection of EHR data, use of common data forms, and experience of the study teams increased rigor and data quality, it is possible that some clinical events may have been mis-categorized. Events such as deaths or bleeding may have also been missed if they were not recorded in the EHR or occurred at a different healthcare system. Finally, our focus on clinically actionable bleeding (GUSTO moderate or severe/life-threatening bleeding) yielded a low number of bleeding events, and the analysis of bleeding risk in *CYP2C19* UMs or RMs was likely underpowered to detect differences between drug-phenotype groups.

In summary, our data from real-world implementation of *CYP2C19*-guided antiplatelet therapy demonstrate that the increased function **17* allele is not associated with atherothrombotic or bleeding outcomes after PCI. These data add to the existing body of evidence showing no significant impact of the **17* allele on clopidogrel's antiplatelet effects or clinical effectiveness after accounting for **2* allele, and support current CPIC guidelines that provide similar antiplatelet therapy prescribing recommendations for *CYP2C19* NMs, RMs and UMs after PCI.⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

What is the current knowledge on the topic?

The increased function *CYP2C19*17* allele confers the rapid metabolizer (RM) and ultra-rapid metabolizer (UM) phenotypes and has inconsistently been associated with increased bioactivation, antiplatelet effects, and clinical effectiveness of clopidogrel. Thus, it remains unclear whether the **17* allele is clinically actionable to guide antiplatelet therapy prescribing.

What question did this study address?

This multi-site pragmatic study examined the impact of the *CYP2C19*17* allele on major atherothrombotic and bleeding events in 3,342 patients who underwent percutaneous coronary intervention (PCI) and clinical *CYP2C19* genotyping.

What does this study add to our knowledge?

In a real-world setting of *CYP2C19* genotype-guided antiplatelet therapy, the *CYP2C19*17* allele does not influence antiplatelet therapy prescribing decisions or clinical outcomes in PCI patients once the *CYP2C19*2* and other no function alleles are accounted for.

How might this change clinical pharmacology or translational science?

These findings support current pharmacogenetic guidelines that provide similar antiplatelet therapy prescribing recommendations after PCI for patients with the *CYP2C19* UM, RM and normal metabolizer phenotypes.

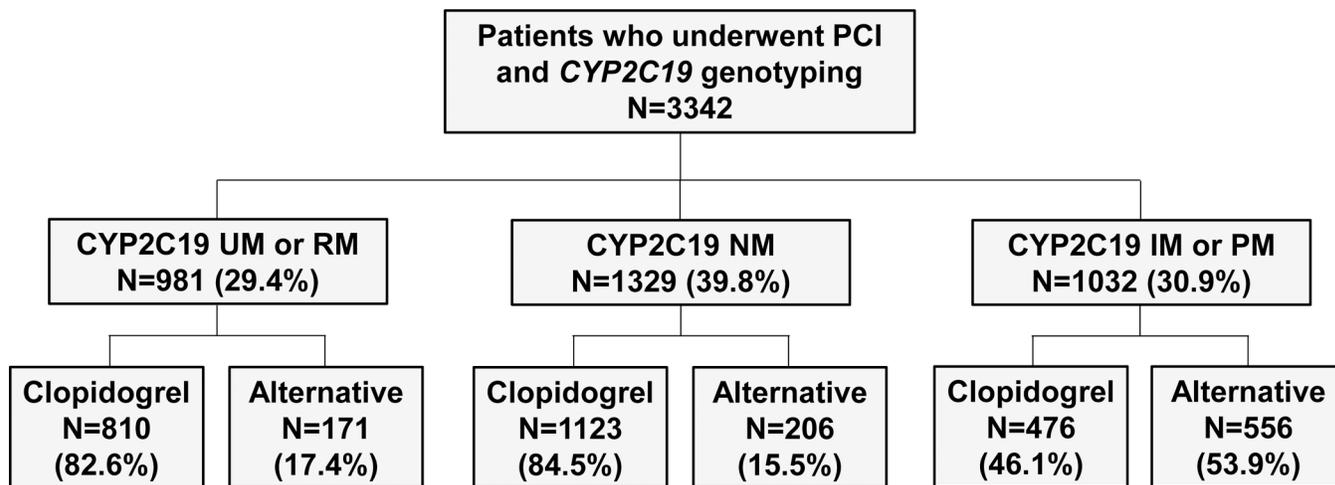
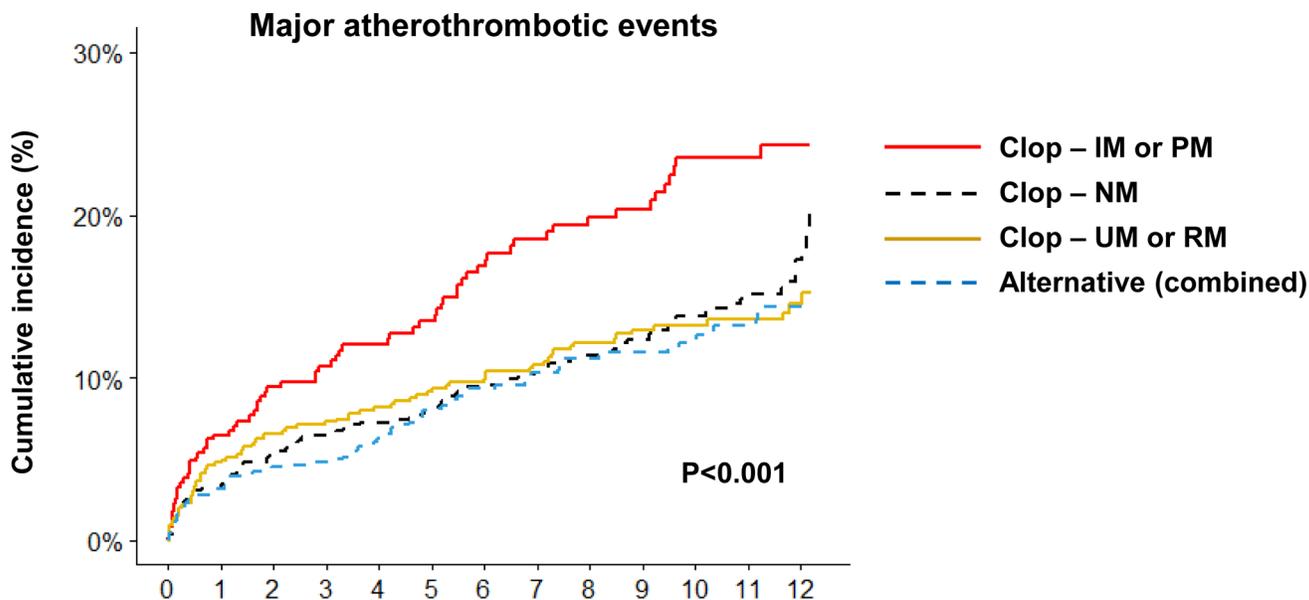


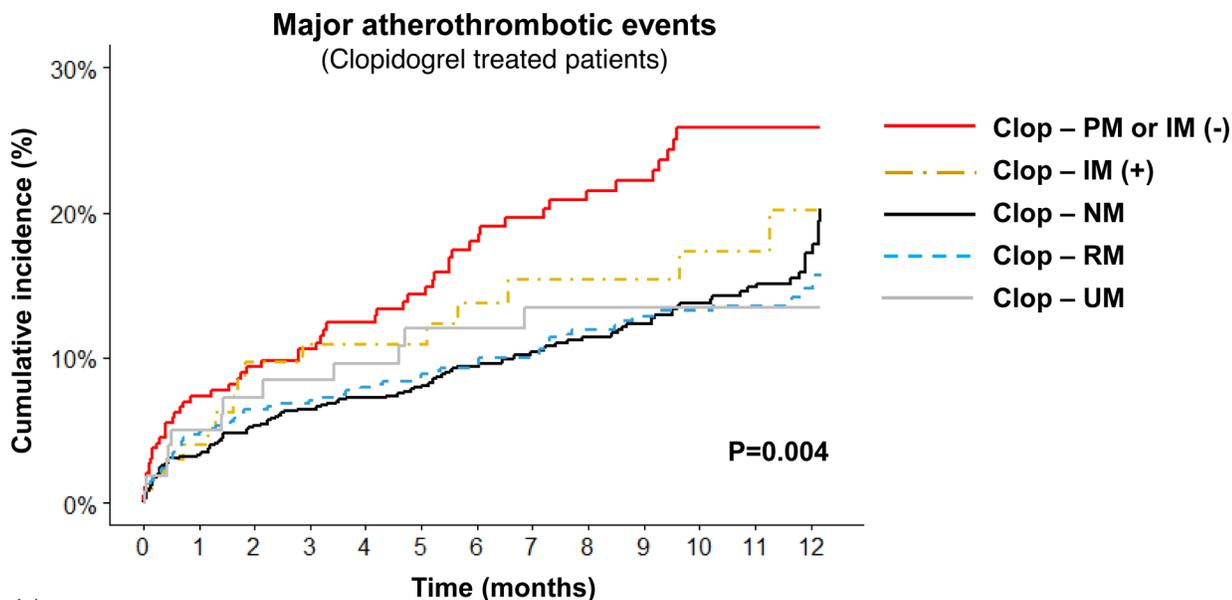
Figure 1. Study Population by CYP2C19 Metabolizer Phenotype and Antiplatelet Therapy. Flow diagram describing the number of study participants by CYP2C19 Metabolizer Phenotype (ultrarapid or rapid metabolizers [UM or RM], normal metabolizers [NM], intermediate or poor metabolizers [IM or PM]) by the prescribed P2Y₁₂ inhibitor therapy during follow-up (clopidogrel or alternative therapy).



	Time (months)						
Number at risk	0	1	2	3	4	5	6
Clop-IM/PM	476	296	250	210	171	133	71
Clop-NM	1123	759	676	611	493	367	153
Clop-UM/RM	810	548	491	441	360	284	131
Alt-combined	933	633	564	494	422	324	103

Figure 2. Cardiovascular outcomes following PCI by CYP2C19 metabolizer status and antiplatelet therapy.

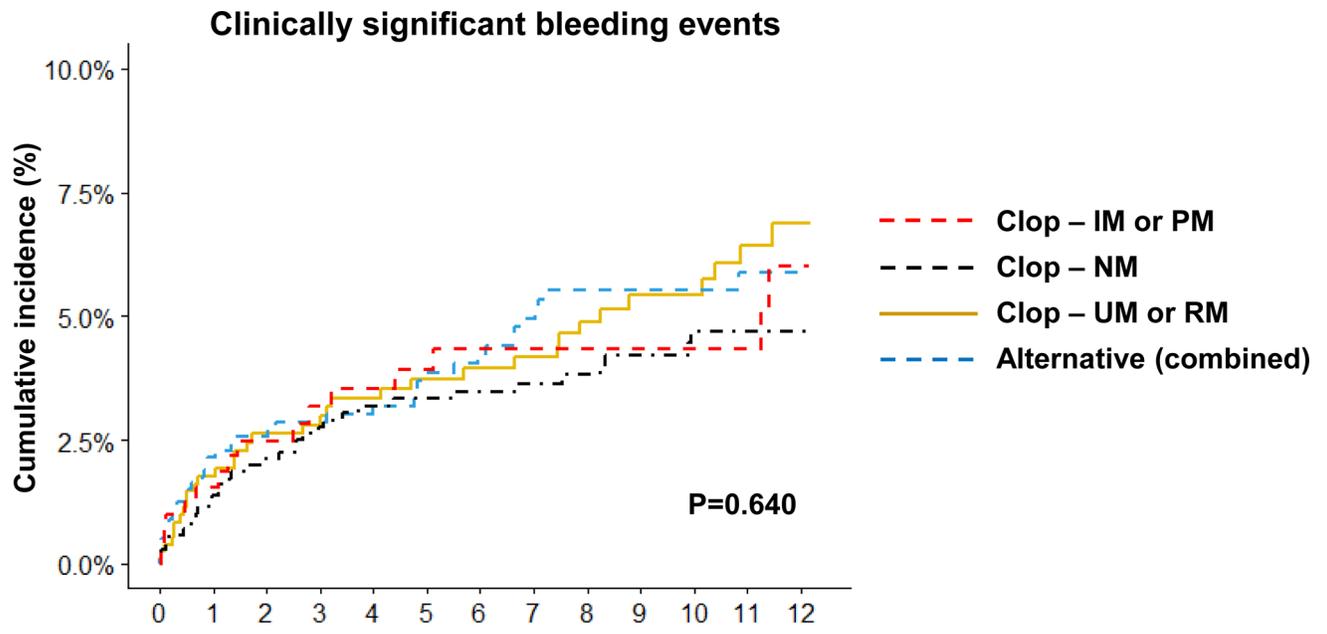
Kaplan-Meier curve for cumulative major atherothrombotic event incidence over 12 months after PCI. Data are shown across four groups: ultrarapid or rapid metabolizers prescribed clopidogrel (Clop-UM or RM); normal metabolizers prescribed clopidogrel (Clop-NM); intermediate or poor metabolizers prescribed clopidogrel (Clop-IM or PM); alternative antiplatelet therapy regardless of CYP2C19 metabolizer status (Alt-combined). The unadjusted log rank P-value for outcomes across the four groups is provided.



Number at risk							
Clop - PM or IM (-)	354	219	182	153	121	94	51
Clop - IM (+)	122	77	68	57	50	39	20
Clop - NM	1123	759	676	611	493	367	153
Clop - RM	694	467	415	376	301	235	104
Clop - UM	116	81	76	65	59	49	27

Figure 3. Cardiovascular events following PCI by CYP2C19 metabolizer and CYP2C19*17 allele status in patients treated with clopidogrel.

Kaplan-Meier curve for cumulative major atherothrombotic event incidence over 12 months after PCI in the stratum of patients treated with clopidogrel (n=2409). Data are shown across five groups: ultrarapid metabolizers (Clop-UM); rapid metabolizers (Clop-RM); normal metabolizers (Clop-NM); intermediate metabolizers carrying the *CYP2C19*17* allele (e.g., **2/*17*) (Clop-IM[+]); poor metabolizers or intermediate metabolizers not carrying the **17* allele (e.g., **1/*2*) (Clop-PM or IM[-]). Due to the very low number of CYP2C19 PMs prescribed clopidogrel, IM(-) and PM were combined for analysis. The unadjusted log rank P-value for outcomes across the five groups is provided.



	Time (months)						
Number at risk	0	1	2	3	4	5	6
Clop-IM/PM	459	292	248	216	184	150	80
Clop-NM	1113	762	682	623	510	389	171
Clop-UM/RM	809	560	506	458	381	303	140
Alt-combined	961	662	596	532	459	353	122

Figure 4. Bleeding outcomes following PCI by CYP2C19 metabolizer status and antiplatelet therapy.

Kaplan-Meier curves for cumulative clinically significant bleeding event incidence over 12 months after PCI. Data are shown across four groups, as described in Figure 2: Clop-UM or RM, Clop-NM, Clop-IM or PM, and Alt-combined. The number of patients in each group was slightly different than for the atherothrombotic endpoint as patients were stratified based on P2Y₁₂ therapy prescribed at the time of the bleeding event or last follow-up. The unadjusted log rank P-value for outcomes across the four groups is provided.

Table 1.

Study Population Characteristics at the Time of Index PCI

	All Patients	Alternative (combined)*	Clopidogrel UM or RM	Clopidogrel NM	Clopidogrel IM or PM	P-value [^]	P-value [#]
N	3342	933	810	1123	476		
Age (years)	63 ± 12	60 ± 11	64 ± 12	64 ± 12	64 ± 12	<0.001	0.636
Age 70	957 (29)	176 (19)	252 (31)	378 (34)	151 (32)	<0.001	0.466
Female	1075 (32)	250 (27)	289 (36)	368 (33)	168 (35)	<0.001	0.357
Race							
White	2448 (73)	692 (74)	603 (74)	830 (74)	323 (68)		
Black	659 (20)	171 (18)	168 (21)	204 (18)	116 (24)	0.007	0.003
Other	235 (7)	70 (7)	39 (5)	89 (8)	37 (8)		
BMI (kg/m ²)	30 ± 6	30 ± 6	30 ± 6	30 ± 6	30 ± 7	0.078	0.366
Current Smoker	969 (29)	288 (31)	231 (29)	308 (27)	142 (30)	0.364	0.609
PCI Indication							
ACS	2290 (69)	689 (74)	541 (67)	742 (66)	318 (67)		
STEMI	628 (19)	247 (26)	129 (16)	192 (17)	60 (13)		
Non-STEMI	939 (28)	275 (29)	230 (28)	297 (26)	137 (29)	<0.001	0.932
Unstable Angina	723 (22)	167 (18)	182 (23)	253 (23)	121 (26)		
Non-ACS	1052 (31)	244 (26)	269 (33)	381 (34)	158 (33)		
Drug-eluting stent at index PCI	2868 (86)	819 (88)	706 (87)	942 (84)	401 (84)	0.035	0.117
Diabetes	1354 (41)	317 (34)	343 (42)	486 (43)	208 (44)	<0.001	0.874
Hypertension	2704 (81)	700 (75)	675 (83)	927 (83)	402 (84)	<0.001	0.642
Dyslipidemia	2317 (69)	632 (68)	579 (71)	772 (69)	334 (70)	0.360	0.429
CKD [‡]	963 (29)	216 (23)	231 (29)	347 (31)	169 (36)	<0.001	0.034
PVD	335 (10)	67 (7)	83 (10)	118 (11)	67 (14)	<0.001	0.072
Heart Failure	533 (16)	115 (12)	138 (17)	191 (17)	89 (19)	0.004	0.687
Atrial Fibrillation	316 (9)	52 (6)	98 (12)	108 (10)	58 (12)	<0.001	0.143
Cancer	184 (6)	39 (4)	54 (7)	68 (6)	23 (5)	0.097	0.409
Prior MI	866 (26)	235 (25)	191 (24)	301 (27)	139 (29)	0.127	0.070
Prior Stent	770 (23)	193 (21)	172 (21)	286 (25)	119 (25)	0.027	0.083
Prior Stroke or TIA	348 (10)	53 (6)	91 (11)	131 (12)	73 (15)	<0.001	0.069

	All Patients	Alternative (combined)*	Clopidogrel UM or RM	Clopidogrel NM	Clopidogrel IM or PM	P-value [^]	P-value [#]
Prior GI Bleed or ICH	111 (3)	26 (3)	18 (2)	40 (4)	27 (6)	0.007	0.005
Discharge Meds							
Aspirin	3269 (98)	918 (98)	790 (98)	1097 (98)	464 (97)	0.552	0.961
Statin	3143 (94)	897 (96)	751 (93)	1046 (93)	449 (94)	0.009	0.532
ACEi or ARB	2245 (67)	639 (68)	557 (69)	732 (65)	317 (67)	0.289	0.257
Beta-blocker	2852 (85)	794 (85)	696 (86)	971 (86)	391 (82)	0.152	0.072
Anticoagulant	321 (10)	57 (6)	94 (12)	115 (10)	55 (12)	<0.001	0.573
Proton Pump Inhibitor	1049 (31)	277 (30)	250 (31)	377 (34)	145 (30)	0.259	0.322

Data are presented as n (%) or mean ± standard deviation

* All patients receiving prasugrel or ticagrelor, regardless of CYP2C19 phenotype, were combined into a single alternative therapy reference group

[^] P-value for comparison across four antiplatelet therapy-CYP2C19 phenotype groups: alternative (combined), clopidogrel-UM or RM, clopidogrel-NM, clopidogrel-IM or PM

[#] P-value for comparison across three CYP2C19 phenotype groups in clopidogrel-treated patients: clopidogrel-UM or RM, clopidogrel-NM, clopidogrel-IM or PM

[‡] Chronic kidney disease was defined as estimated glomerular filtration rate <60 ml/min

ACEi = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; GI = gastrointestinal; ICH = intracranial hemorrhage; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST-segment elevation MI; TIA = transient ischemic attack

Table 2. Cardiovascular and Bleeding Outcomes by CYP2C19 Metabolizer Status and Antiplatelet Therapy

Clinical outcome by P2Y ₁₂ inhibitor - CYP2C19 phenotype	Event No. (%) [*]	Event rate (per 100pt-yrs) [^]	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
<u>Major atherothrombotic events</u>						
Clopidogrel - UM or RM	80 (9.9%)	19.1	1.09 (0.80–1.48)	0.576	0.95 (0.69–1.30)	0.734
Clopidogrel - NM	117 (10.4%)	20.4	1.16 (0.88–1.54)	0.300	1.00 (0.75–1.33)	0.993
Clopidogrel - IM or PM	72 (15.1%)	33.7	1.86 (1.36–2.55)	<0.001	1.56 (1.12–2.16)	0.008
Alternative (combined) [‡]	84 (9.0%)	17.6	Reference		Reference	
<u>Clinically significant bleeding events</u>						
Clopidogrel - UM or RM	34 (4.2%)	7.9	1.04 (0.66–1.65)	0.871	0.96 (0.60–1.54)	0.865
Clopidogrel - NM	35 (3.1%)	6.0	0.78 (0.49–1.23)	0.287	0.68 (0.42–1.08)	0.104
Clopidogrel - IM or PM	16 (3.5%)	7.3	0.93 (0.52–1.67)	0.812	0.77 (0.43–1.40)	0.391
Alternative (combined) [‡]	39 (4.1%)	7.7	Reference		Reference	

^{*} Data are presented as the number (%) of patients in each group who experienced the event over 12 months of follow-up after the index PCI.

[^] The event rate was calculated as the number of events per 100 patient-years of follow-up.

[‡] All patients receiving prasugrel or ticagrelor, regardless of CYP2C19 phenotype, were combined into a single alternative therapy reference group.