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Multisite Investigation of Outcomes With Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention

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ABSTRACT

OBJECTIVES This multicenter pragmatic investigation assessed outcomes following clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy after percutaneous coronary intervention (PCI).

BACKGROUND *CYP2C19* loss-of-function alleles impair clopidogrel effectiveness after PCI.

METHODS After clinical genotyping, each institution recommended alternative antiplatelet therapy (prasugrel, ticagrelor) in PCI patients with a loss-of-function allele. Major adverse cardiovascular events (defined as myocardial infarction, stroke, or death) within 12 months of PCI were compared between patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy. Risk was also compared between patients without a loss-of-function allele and loss-of-function allele carriers prescribed alternative therapy. Cox regression was performed, adjusting for group differences with inverse probability of treatment weights.

RESULTS Among 1,815 patients, 572 (31.5%) had a loss-of-function allele. The risk for major adverse cardiovascular events was significantly higher in patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy (23.4 vs. 8.7 per 100 patient-years; adjusted hazard ratio: 2.26; 95% confidence interval: 1.18 to 4.32; $p = 0.013$). Similar results were observed among 1,210 patients with acute coronary syndromes at the time of PCI (adjusted hazard ratio: 2.87; 95% confidence interval: 1.35 to 6.09; $p = 0.013$). There was no difference in major adverse cardiovascular events between patients without a loss-of-function allele and loss-of-function allele carriers prescribed alternative therapy (adjusted hazard ratio: 1.14; 95% confidence interval: 0.69 to 1.88; $p = 0.60$).

CONCLUSIONS These data from real-world observations demonstrate a higher risk for cardiovascular events in patients with a *CYP2C19* loss-of-function allele if clopidogrel versus alternative therapy is prescribed. A future randomized study of genotype-guided antiplatelet therapy may be of value. (J Am Coll Cardiol Intv 2017;■:■–■)

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

CYP = cytochrome P450

EHR = electronic health record

HR = hazard ratio

IM = intermediate metabolizer

IPTW = inverse probability of treatment weight

LOF = loss-of-function

MACE = major adverse cardiovascular events

PCI = percutaneous coronary intervention

PM = poor metabolizer

Treatment with a $P2Y_{12}$ inhibitor plus aspirin is the standard of care following percutaneous coronary intervention (PCI) (1,2). The $P2Y_{12}$ inhibitor clopidogrel is a prodrug requiring bioactivation by cytochrome P450 (CYP) 2C19. *CYP2C19* loss-of-function (LOF) alleles lead to reduced or absent CYP2C19 activity, lower plasma concentrations of the clopidogrel active metabolite, and reduced inhibition of platelet aggregation during clopidogrel therapy (3,4). Retrospective analyses from randomized clinical trials and patient registries have demonstrated a higher risk for major adverse cardiovascular events (MACE) in clopidogrel-treated patients with versus without a *CYP2C19* LOF allele, particularly after PCI (3,5-7).

Prasugrel and ticagrelor are alternative $P2Y_{12}$ inhibitors, shown to be superior to clopidogrel in preventing cardiovascular events in patients with acute coronary syndrome (ACS) in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38) and PLATO (Platelet Inhibition and Patient Outcomes) trials, respectively (8,9). Post hoc genetic analyses from these trials showed no effect of *CYP2C19* genotype on outcomes with either prasugrel or ticagrelor (7,10). However, both drugs are more expensive than clopidogrel, which is available generically, and are associated with an increased bleeding risk. Ticagrelor is also associated with more frequent discontinuation because of side effects compared with clopidogrel (8).

Although several institutions have implemented clinical *CYP2C19* genotyping to guide antiplatelet therapy selection after PCI (11-14), the effect of this strategy on clinical outcomes is not well defined. Therefore, among patients who underwent PCI and clinical *CYP2C19* genotyping, we compared the risk for cardiovascular events between patients with *CYP2C19* LOF alleles prescribed clopidogrel 75 mg/day and those with *CYP2C19* LOF alleles prescribed alternative antiplatelet therapy. We also compared MACE risk between those with LOF alleles prescribed

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alternative therapy and those without *CYP2C19* LOF alleles treated with any $P2Y_{12}$ inhibitor.

METHODS

STUDY DESIGN. This was a multicenter investigation of clinical *CYP2C19* genotype-guided antiplatelet therapy post-PCI. The study design was pragmatic, on the basis of delivery of the genotype intervention as part of clinical care, the ultimate decision to order genetic testing and choice of drug therapy left to the discretion of the physician, unobtrusive collection of data from the electronic health record (EHR), and the focus on an objectively measured and clinically meaningful outcome (15–17). Seven institutions (the University of Florida; the University of North Carolina, Chapel Hill; the University of Maryland, Baltimore; the University of Alabama, Birmingham; the University of Illinois, Chicago; the University of Pittsburgh; and Indiana University) implemented clinical *CYP2C19* genotyping, with results returned via the EHR for consideration during antiplatelet therapy prescribing. All sites participated in the National Institutes of Health–funded Implementing Genomics in Practice Network Pharmacogenetics Working Group and contributed data (18). All patients from each site ≥18 years of age who underwent PCI and *CYP2C19* genotyping (per the strategy described in Online Table 1) and received a $P2Y_{12}$ inhibitor after PCI were included, regardless of length of follow-up. A total of 1,815 patients across the 7 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–licensed laboratory, with the test ordered prior to or at the time of PCI. All sites genotyped for the LOF *CYP2C19**2 and *CYP2C19**3 alleles, with additional rare alleles genotyped at 5 institutions (Online Table 1). *CYP2C19* LOF allele status was defined by presence of at least 1 LOF allele.

CYP2C19 phenotype was assigned similarly across sites on the basis of standardized definitions (19). Patients with 1 or 2 LOF alleles were assigned the intermediate metabolizer (IM) or poor metabolizer (PM) phenotype, respectively. Alternative antiplatelet therapy, consisting of prasugrel or ticagrelor in the absence of contraindications, was recommended for IMs and PMs, according to Clinical Pharmacogenetics Implementation Consortium guidelines (20). Ultimate antiplatelet therapy selection was left to the discretion of the prescriber.

DATA ABSTRACTION. Data abstraction procedures were approved by the institutional review board at each institution. Clinical data at baseline and for up to 12 months following the index PCI, defined as the PCI performed in association with genotyping, were manually abstracted from the EHR through review of patient encounters, including the index PCI hospitalization and subsequent hospitalizations and outpatient visits, using a common data collection form (18). The occurrence of clinical outcomes of interest, including death, myocardial infarction (ST-segment or non–ST-segment elevation myocardial infarction), ischemic stroke, stent thrombosis, and unstable angina occurring over the 12-month period after the index PCI, was determined. The date range for data abstraction was June 2012 through April 2016.

PRIMARY AND SECONDARY OUTCOMES. The primary outcome was a major adverse cardiovascular event (MACE), defined as the composite of first occurrence of myocardial infarction, ischemic stroke, or death within 12 months following the index PCI (5). Secondary outcomes were the composite of a MACE plus stent thrombosis and unstable angina and individual cardiovascular events within the MACE

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TABLE 1 Patient Characteristics at the Time of Index Percutaneous Coronary Intervention

	All Patients (n = 1,815)	LOF-Alternative (n = 346)	LOF-Clopidogrel (n = 226)	Non-LOF (n = 1,243)
Age, yrs	62.7 ± 11.8	61.4 ± 11.4	64.3 ± 11.7*	62.8 ± 11.8*
Male	1,224 (67.4)	245 (70.8)	150 (66.4)	829 (66.7)
Race				
White	1,416 (78.0)	267 (77.2)	172 (76.1)	977 (78.6)
Black	285 (15.7)	54 (15.6)	39 (17.3)	192 (15.4)
Other	114 (6.3)	25 (7.2)	15 (6.6)	74 (6.0)
BMI, kg/m^2	30.0 ± 6.2	30.1 ± 7.0	30.0 ± 6.5	29.8 ± 5.9
Current smoker	548 (30.2)	96 (27.7)	80 (35.4)	372 (29.9)
PCI indication				
ACS	1,210 (66.7)	237 (68.5)	145 (64.2)	828 (66.6)
STEMI	350 (19.3)	75 (21.7)	33 (14.6)	242 (19.5)
Non-STEMI	513 (28.3)	96 (27.7)	72 (31.8)	345 (27.7)
Unstable angina	347 (19.1)	66 (19.1)	40 (17.7)	241 (19.4)
Stable coronary disease	553 (30.5)	99 (28.6)	70 (31.0)	384 (30.9)
Other/unknown	52 (2.8)	10 (2.9)	11 (4.9)	31 (2.5)
Pre-PCI $P2Y_{12}$ inhibitor†				
Clopidogrel	1,204 (66.3)	202 (58.4)	178 (78.8)	824 (66.3)
Prasugrel	235 (12.9)	68 (19.7)	6 (2.7)	161 (13.0)
Ticagrelor	218 (12.0)	47 (13.6)	23 (10.2)	148 (11.9)
Not available	158 (8.7)	29 (8.4)	19 (8.4)	110 (8.8)
PCI type‡				
Drug-eluting stent	1,518 (83.6)	293 (84.7)	182 (80.5)	1,043 (83.9)
Bare-metal stent	275 (15.2)	46 (13.3)	40 (17.7)	189 (15.2)
Balloon angioplasty	21 (1.2)	7 (2.0)	3 (1.3)	11 (0.9)
Medical history				
Hypertension	1,449 (79.8)	260 (75.1)	183 (81.0)	1,006 (80.9)*
Diabetes	691 (38.1)	110 (31.8)	93 (41.2)*	488 (39.3)*
Dyslipidemia	1,229 (67.7)	236 (68.2)	154 (68.1)	839 (67.5)
Chronic kidney disease§	538 (29.6)	106 (30.6)	77 (34.1)	355 (28.6)
Myocardial infarction	470 (25.9)	86 (24.9)	68 (30.1)	316 (25.4)
Revascularization	779 (42.9)	137 (39.6)	103 (45.6)	539 (43.4)
Coronary artery bypass graft	313 (17.3)	61 (17.7)	43 (19.0)	209 (16.9)
Heart failure	252 (13.9)	42 (12.1)	37 (16.4)	173 (13.9)
Left ventricular EF (%)‖	51.7 ± 11.9	52.4 ± 11.4	50.2 ± 12.8	51.8 ± 11.9
Stroke or TIA	183 (10.1)	24 (6.9)	36 (15.9)*	123 (9.9)
Peripheral vascular disease	155 (8.5)	24 (6.9)	28 (12.4)*	103 (8.3)
Atrial fibrillation/flutter	159 (8.8)	27 (7.8)	25 (11.1)	107 (8.6)
Gastrointestinal bleed	54 (3.0)	14 (4.1)	10 (4.4)	30 (2.4)
Discharge medication				
Aspirin	1,782 (98.2)	342 (98.8)	220 (97.4)	1,220 (98.2)
Proton pump inhibitor	586 (32.3)	110 (31.8)	72 (31.9)	404 (32.5)
Anticoagulant agent	152 (8.4)	22 (6.4)	26 (11.5)*	104 (8.4)
Statin	1,686 (92.9)	329 (95.1)	210 (92.9)	1,147 (92.3)
ACE inhibitor or ARB	1,202 (66.2)	238 (68.8)	152 (67.3)	812 (65.3)
Beta-blocker	1,539 (84.8)	285 (82.4)	181 (80.1)	1,073 (86.3)

Values are mean ± SD or n (%). LOF-clopidogrel patients were those with at least 1 LOF allele (e.g., **2, *3*) treated with clopidogrel. LOF-alternative patients were those with at least 1 LOF allele (e.g., **2, *3*) treated with prasugrel, ticagrelor, or high-dose clopidogrel. Non-LOF patients were those with no LOF allele: **1/*1, *1/*17*, or **17/*17* genotype. *p < 0.05 compared with LOF-alternative group. †Pre-PCI $P2Y_{12}$ inhibitor was defined as the drug used for loading; if the drug used for loading was not reported, the $P2Y_{12}$ inhibitor on admission was used. ‡One patient had a stent placed, but no data were provided on the type of stent. §Chronic kidney disease was defined as estimated creatinine clearance (on the basis of the Cockcroft-Gault formula) <60 ml/min. ‖Left ventricular EF, as measured during cardiac catheterization, was available for 1,274 patients.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; EF = ejection fraction; LOF = loss-of-function; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

definition. Outcomes were identified on the basis of physician-reported diagnoses abstracted from the cardiac catheterization laboratory report, hospital discharge summary notes, or clinical notes in the event of death. Antiplatelet therapy was assessed at the time of event or last follow-up in which $P2Y_{12}$ inhibitor treatment was documented. The number of days between the index PCI and initiation of alternative antiplatelet therapy was determined in patients with an LOF allele and was available for all but 4 patients.

STATISTICAL ANALYSIS. Data were curated and aggregated at the University of Florida. The time of index PCI was considered time 0. Patients who did not experience a MACE during the 12 months post-PCI were censored at the time of the last EHR-documented follow-up in which treatment with a $P2Y_{12}$ inhibitor was documented. Event rates were calculated as the number of events divided by follow-up time (time to event or censoring) and expressed as events per 100 patient-years.

Patient characteristics and PCI features at the time of the index PCI were compared between patients with an LOF allele prescribed either clopidogrel 75 mg/day (LOF-clopidogrel group) or alternative antiplatelet therapy (LOF-alternative group) using the Student unpaired *t* test, chi-square analysis, or the Fisher exact test as appropriate. Additional comparisons were made between non-LOF patients prescribed clopidogrel or alternative antiplatelet therapy (non-LOF group) and LOF-alternative patients and between clopidogrel-treated versus alternatively treated patients in the non-LOF group. All patients were included in the MACE outcome analyses. A prespecified secondary analysis limited to patients with ACS indications (ST-segment elevation or non-ST-segment elevation myocardial infarction or unstable angina) at the index PCI was also conducted.

Kaplan-Meier plots were generated to estimate the cumulative risk for an event comparing patients in the LOF-clopidogrel versus LOF-alternative groups and also patients in the non-LOF versus LOF-alternative groups. To adjust for differences between groups, we used logistic regression to estimate the probability (propensity score) of receiving clopidogrel versus alternative antiplatelet therapy using previously reported risk factors for cardiovascular events and study site (2). Propensity scores were estimated separately for each comparison. Stabilized inverse probability of treatment weights (IPTWs) were calculated using the estimated propensity score (21). Covariate balance between groups was assessed by examining the magnitude of any residual differences between groups after applying the weights. Differences were

quantified as the weighted standardized differences, for which a threshold of 10% was used to signify a meaningful difference in covariates (21). We also examined the weights themselves to ensure that no observations were overly influential. To compare risk for primary and secondary outcomes, we constructed cause-specific Cox proportional hazard models, weighted by IPTWs. As a sensitivity analysis, we also estimated cluster robust standard errors by accounting for clustering by study site. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina).

A total sample size of 1,815 patients, with at least 30% having an LOF allele and 60% of LOF allele carriers receiving alternative therapy, provided >90% power with an alpha level of 0.05 to detect a hazard ratio (HR) of 2.0 for the occurrence of a MACE between the LOF-clopidogrel and -alternative groups.

RESULTS

PATIENT CHARACTERISTICS. Patient characteristics are summarized in **Table 1**. Among 1,815 patients, 1,210 (66.7%) presented with ACS, and 1,794 (98.8%) had stents placed at the time of PCI. The majority of patients received drug-eluting stents (83.6%) and were prescribed aspirin (98.2%) in addition to a $P2Y_{12}$ inhibitor.

Genotypes and associated phenotypes are shown in Online Table 2. The median time from index PCI to available genotype result was 1 day (interquartile range: 1 to 3 days). LOF alleles were present in 572 patients (31.5%) (**Figure 1,** Online Table 2); 518 patients (28.5%) were IMs, and 54 patients (3%) were PMs. Alternative antiplatelet therapy was prescribed to a higher proportion of patients with LOF alleles (60.5%) compared with patients without LOF alleles (15.5%; $p < 0.0001$) (**Figure 1**). A total of 58% of IMs and 87% of PMs were prescribed alternative antiplatelet therapy (Online Figure 1). Among patients with an LOF allele, the median time from genotype result to initiation of alternative antiplatelet therapy was 1 day (interquartile range: 1 to 6 days).

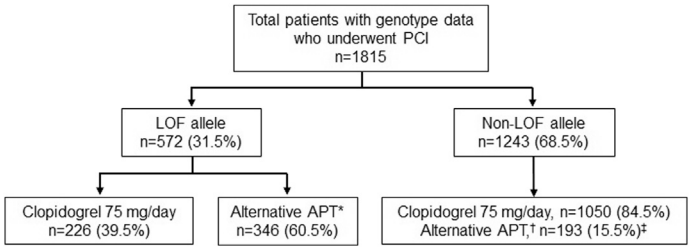
There were differences between the LOF-clopidogrel and -alternative groups in age, prevalence of diabetes, stroke, peripheral vascular disease, and use of oral anticoagulation (**Table 1**). Age and prevalence of hypertension and diabetes differed between the non-LOF and LOF-alternative groups. These imbalances were negligible after adjustment with propensity score-derived IPTWs (**Table 2**).

CLINICAL OUTCOMES. The median follow-up from index PCI to MACE or censoring was 4.8 months (interquartile range: 0.6 to 9.9 months). The occurrence of a MACE was documented in 108 patients (5.95%) over the follow-up period (event rate of 13.5 per 100 patient-years). There was a higher rate of MACE in the LOF-clopidogrel group (n = 18 events, event rate 23.4 per 100 patient-years) compared with the LOF-alternative group (n = 16 events, event rate 8.7 per 100 patient-years, log-rank $p = 0.016$) (**Table 3, Figure 2**). After propensity score adjustment, the risk for a MACE remained significantly higher in the LOF-clopidogrel versus LOF-alternative group (adjusted HR: 2.26; 95% confidence interval [CI]: 1.18 to 4.32; $p = 0.013$) (**Table 3**). There was no difference in event rates between the non-LOF and LOF-alternative groups (13.7 vs. 8.7 per 100 patient-years; log-rank $p = 0.15$; propensity score-adjusted HR: 1.14; 95% CI: 0.69 to 1.88; $p = 0.60$) (**Table 3**). Similarly, within the non-LOF group, there was no difference in MACE rates between non-LOF patients treated with clopidogrel versus non-LOF patients treated with alternative therapy after adjusting for clinical differences between groups (adjusted HR: 1.01; 95% CI: 0.52 to 1.94; $p = 0.98$) (Online Tables 3 and 4). Accounting for within-site clustering did not change the estimates for the primary outcome (Online Table 5).

In the 518 patients with the IM phenotype only, the risk for a MACE was significantly higher with clopidogrel versus alternative antiplatelet therapy (log-rank $p = 0.003$) (Online Figure 2), with event rates of 24.0 versus 6.7 per 100 patient-years, respectively. Only 7 of 54 PMs (13%) were treated with clopidogrel, precluding analysis of outcomes in this group.

Secondary outcomes are shown in **Table 3**. The risk for a MACE plus other ischemic events

FIGURE 1 Study Population by *CYP2C19* Genotype Group and Antiplatelet Therapy



*Alternative therapy in patients with 1 or 2 loss-of-function (LOF) alleles consisted of prasugrel (n = 222), ticagrelor (n = 116), or high-dose clopidogrel (150 mg/day, n = 2; 225 mg/day, n = 6). †Alternative therapy in the non-LOF group consisted of prasugrel (n = 125) or ticagrelor (n = 68). ‡$p < 0.001$ for use of alternative therapy in the non-LOF group compared with the LOF group. APT = antiplatelet therapy; PCI = percutaneous coronary intervention.

TABLE 2 Patient Characteristics After Adjustment With Inverse Probability of Treatment Weights

	LOF-Clopidogrel (n = 226)	LOF-Alternative (n = 346)	Standardized Difference*	Non-LOF (n = 1,243)	LOF-Alternative (n = 345)	Standardized Difference*
Age, yrs	62.7 ± 11.7	62.5 ± 11.4	0.02	62.5 ± 11.8	62.3 ± 11.6	0.01
Male	150 (67.5)	237 (68.9)	0.03	836 (67.6)	229 (67.0)	0.01
Race						
White	166 (75.2)	263 (76.4)	0.03	968 (78.2)	266 (77.7)	0.01
Black	39 (17.6)	55 (15.9)	0.05	193 (15.6)	53 (15.6)	0.00
BMI, kg/m^2	30.2 ± 6.3	30.1 ± 7.3	0.01	29.8 ± 5.9	29.8 ± 6.9	0.00
Current smoker	69 (31.4)	107 (31.2)	0.00	363 (29.4)	97 (28.5)	0.02
PCI indication						
Stable angina	65 (28.2)	100 (29.4)	0.03	376 (30.4)	101 (29.6)	0.02
ACS	148 (67.0)	232 (67.3)	0.01	828 (66.9)	233 (67.9)	0.02
Stent type						
Drug eluting	185 (84.3)	290 (83.8)	0.01	1,040 (84.1)	290 (84.8)	0.02
Bare metal	34 (15.0)	48 (14.1)	0.03	182 (14.7)	48 (14.0)	0.02
Medical history						
Hypertension	168 (76.0)	273 (76.4)	0.01	986 (79.7)	271 (79.2)	0.01
Diabetes	81 (36.8)	121 (35.3)	0.03	466 (37.6)	124 (36.2)	0.03
Dyslipidemia	153 (69.1)	236 (68.5)	0.01	837 (67.6)	232 (67.7)	0.00
GFR, ml/min†	74.0 ± 27.7	74.7 ± 31.5	0.02	74.5 ± 28.1	75.2 ± 31.6	0.02
MI	60 (27.1)	92 (26.8)	0.01	313 (25.4)	88 (25.8)	0.01
Revascularization	95 (43.2)	147 (42.9)	0.05	143 (41.8)	525 (42.4)	0.01
Heart failure	32 (14.8)	51 (14.8)	0.00	166 (13.5)	45 (13.2)	0.01
Stroke or TIA	23 (10.7)	33 (9.7)	0.03	114 (9.2)	28 (8.3)	0.03
PVD	21 (9.3)	31 (9.0)	0.01	99 (8.0)	26 (7.6)	0.01
Medication use						
Aspirin	217 (98.3)	339 (98.4)	0.01	1,216 (98.2)	336 (98.2)	0.00
PPI	69 (31.4)	109 (31.7)	0.01	398 (32.2)	106 (30.9)	0.05
Anticoagulant agent	19 (8.9)	28 (8.2)	0.03	98 (8.0)	24 (7.3)	0.03
Statin	209 (94.3)	325 (94.5)	0.01	1,149 (92.8)	319 (93.3)	0.02
ACE inhibitor/ARB	149 (67.4)	231 (67.3)	0.00	817 (66.0)	224 (65.4)	0.01
Beta-blocker	180 (81.5)	282 (81.8)	0.01	1,055 (85.3)	291 (85.0)	0.01

Values are mean ± SD or n (%). *Weighted absolute standardized differences were calculated using stabilized inverse probability of treatment weighting. All values are <0.1, which indicates elimination of imbalance between the 2 groups. †Estimated creatinine clearance using the Cockcroft-Gault formula.

GFR = glomerular filtration rate; MI = myocardial infarction; PPI = proton pump inhibitor; PVD = peripheral vascular disease; other abbreviations as in Table 1.

(stent thrombosis and unstable angina) was higher in the LOF-clopidogrel versus LOF-alternative group (adjusted HR: 1.82; 95% CI: 1.07 to 3.12; p = 0.027). There was no difference in the occurrence of a MACE plus ischemic events between non-LOF and LOF-alternative groups (adjusted HR: 1.09; 95% CI: 0.72 to 1.63; p = 0.69) (**Table 3**) or between non-LOF patients treated with clopidogrel versus alternative therapy (adjusted HR: 1.02; 95% CI: 0.59 to 1.78) (Online Table 4). Patients presenting with ACS at the time of index PCI (1,210 of 1,815 patients) contributed the majority of events to the analysis, including 86 of 108 events in the composite MACE outcome (80%) and 48 of 58 myocardial infarctions (83%). Consistent with the analysis of the overall study population, among patients with ACS, the LOF-clopidogrel group had a higher rate of a MACE compared with the LOF-alternative group (39.0 per 100 patient-years vs. 8.9 per 100 patient-years, respectively; adjusted HR: 2.87; 95% CI: 1.35 to 6.09; p = 0.013) (Online Figure 3, Online Table 6). The risk for a MACE plus other ischemic events (adjusted HR: 2.10; 95% CI: 1.12 to 3.90; p = 0.019) was also significantly elevated. No differences in outcomes were observed between non-LOF and LOF-alternative groups in the ACS subset. Although not an outcome of the study, moderate and severe or life-threatening bleeding events, defined according to the GUSTO (Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries) criteria, were observed in 2.3% of patients in the overall study population and were similar across groups (22).

On the basis of the prevalence of patients with LOF alleles (31.5%), the number needed to genotype to identify an LOF allele carrier for whom alternative therapy would be recommended was 3.2. With an absolute difference in the proportion of patients who had a MACE in the LOF-clopidogrel (8.0%)

TABLE 3 Primary and Secondary Outcomes by *CYP2C19* Genotype and by Antiplatelet Therapy

	LOF-Clopidogrel (n = 226)		LOF-Alternative (n = 346)		Non-LOF (n = 1,243)		Adjusted HR (95% CI) for LOF-Clopidogrel vs. LOF-Alternative	Adjusted HR (95% CI) for Non-LOF vs. LOF-Alternative
	n (%)	Event Rate*	n (%)	Event Rate*	n (%)	Event Rate*		
MACE	18 (7.96)	23.4	16 (4.62)	8.7	74 (5.95)	13.7	2.26 (1.18–4.32)	1.14 (0.69–1.88)
Death	8 (3.54)	10.4	6 (1.73)	3.3	36 (2.90)	6.6	3.76 (1.37–10.35)	1.56 (0.68–3.56)
MI	11 (4.87)	14.3	9 (2.60)	4.9	38 (3.06)	7.0	1.85 (0.77–4.45)	1.00 (0.52–1.92)
Ischemic stroke	3 (1.33)	3.9	2 (0.58)	1.1	13 (1.05)	2.4	2.81 (0.43–18.03)	2.52 (0.49–12.91)
MACE plus other ischemic events†	25 (11.06)	32.5	28 (8.09)	15.2	106 (8.53)	19.6	1.82 (1.07–3.12)	1.09 (0.72–1.63)
Stent thrombosis	4 (1.77)	5.2	4 (1.16)	2.2	13 (1.05)	2.4	1.68 (0.37–7.53)	1.01 (0.32–3.15)
Unstable angina	7 (3.10)	9.1	12 (3.47)	6.5	31 (2.49)	5.7	1.41 (0.55–3.64)	0.87 (0.44–1.70)

Unadjusted proportion of patients experiencing events during follow-up (%), event rate (per 100 patient-years), adjusted HR, and 95% CI are reported. The HR was adjusted with inverse probability weights derived from exposure propensity scores. Refer to Table 2 for variables included in the propensity score. Event rates were calculated as the number of events divided by follow-up time from index PCI to MACE or censoring in patient-years and are presented as medians. The median length of follow-up was 7.3 months (IQR: 1.5 to 10.9 months), 1.8 months (IQR: 0.2 to 8.2 months), and 4.5 months (IQR: 0.5 to 9.7 months) in the LOF-alternative, LOF-clopidogrel, and non-LOF groups, respectively ($p < 0.001$). LOF-clopidogrel patients had at least 1 LOF allele (e.g., **2, *3*) treated with clopidogrel. LOF-alternative patients had at least 1 LOF allele (e.g., **2, *3*) treated with prasugrel (n = 222), ticagrelor (n = 116), or high-dose clopidogrel (n = 8). Non-LOF patients had no LOF allele: **1/*1, *1/*17, or *17/*17* genotypes. *Median event rate expressed as events per 100 patient-years. †Composite of a MACE (defined as first occurrence of myocardial infarction, ischemic stroke, or death) plus stent thrombosis and unstable angina.

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; MACE = major adverse cardiovascular events; other abbreviations as in Tables 1 and 2.

and LOF-alternative (4.6%) groups (Table 3), the number of patients with LOF alleles needed to treat with alternative antiplatelet therapy to prevent 1 event was 29 (1 / 0.034). Therefore, the number of patients needed to genotype, with alternative antiplatelet therapy prescribed for all patients with LOF alleles, to prevent 1 cardiovascular event was 93 (29 × 3.2).

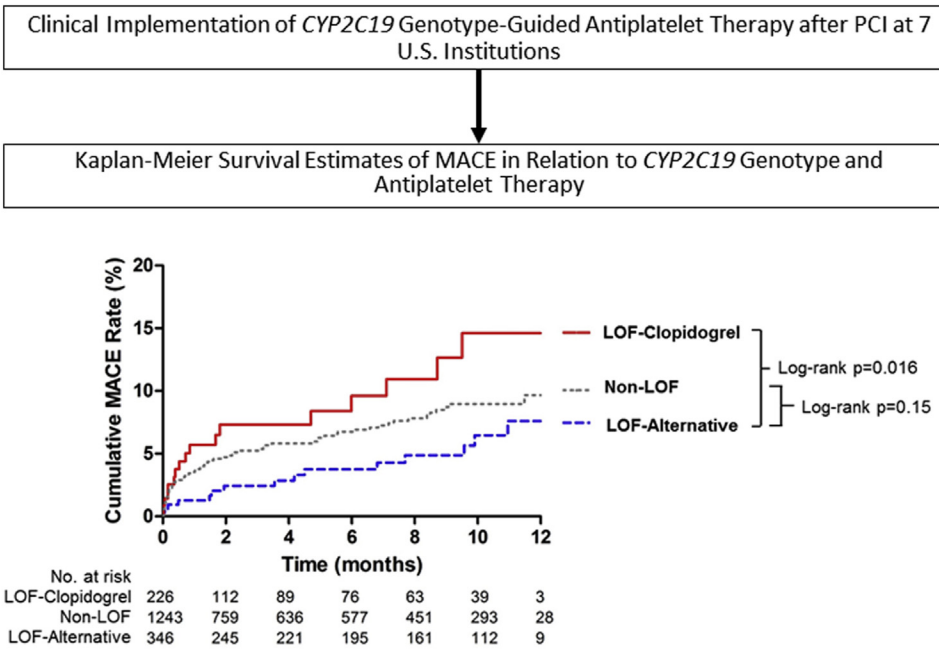
DISCUSSION

Our study is the first large multicenter study to examine outcomes after clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy. We demonstrate the feasibility of genotype-guided antiplatelet therapy after PCI across multiple institutions, with efficient return of genotype results and high uptake of alternative antiplatelet therapy in patients with an LOF allele. More important, our results show a higher risk for a MACE in patients with *CYP2C19* LOF alleles who are treated with clopidogrel versus alternative antiplatelet therapy. Most events occurred in patients with ACS indications at the index PCI, in whom the risk for a MACE was higher in LOF-clopidogrel versus LOF-alternative patients.

Retrospective genetic substudies of large clinical trials suggested worse outcomes in patients with *CYP2C19* LOF alleles treated with clopidogrel (3,5–7), but there is a paucity of data from large prospective clinical trials on outcomes with *CYP2C19* genotype-guided antiplatelet therapy. This has hindered inclusion of *CYP2C19* genotyping in clinical practice and PCI practice guidelines. Guidelines state that routine genetic testing is not recommended but might be considered in high-risk patients (Class IIb, Level of Evidence: C) (1,2). A randomized controlled trial assessing the efficacy of genotype-guided antiplatelet therapy in a target population of more than 5,000 patients began in 2013 but is not expected to be completed until 2020 (NCT01742117). Given the magnitude, time, and expense of conducting traditional randomized controlled trials, other approaches are needed to generate an evidence base quantifying clinical outcomes related to pharmacogenetic-tailored therapy. Our pragmatic approach to assessing outcomes following clinical implementation of *CYP2C19* genotyping with real-world evidence is one such approach.

Our findings are in line with recent data from the Netherlands and Spain (23,24). The Dutch study focused on patients undergoing elective PCI, who were clinically genotyped, with prasugrel recommended for PMs (23). Fewer adverse cardiovascular events were observed in PMs treated with prasugrel versus clopidogrel. The Spanish study included patients undergoing elective or emergent PCI, and recommendations for alternative therapy were made for both PMs and IMs (24). Compared with historical control subjects without genotyping, fewer adverse events were observed in patients receiving genotype-guided therapy. Our data are also consistent with those from 2 trials of Chinese patients undergoing PCI and randomized to either clopidogrel 75 mg/day or genotype-guided antiplatelet therapy, consisting of high-dose clopidogrel (150 mg/day) for IMs and high-dose clopidogrel plus cilostazol for PMs in 1 trial and ticagrelor for PMs in the other (25,26). Both studies observed significant reductions in cardiovascular events in the genotype-guided arm.

FIGURE 2 Outcomes With Clinical Implementation of *CYP2C19*-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention



Data are shown for patients with a *CYP2C19* loss-of-function (LOF) allele treated with clopidogrel (LOF-clopidogrel), patients with an LOF allele treated with alternative antiplatelet drug therapy (LOF-alternative), and patients without an LOF allele treated with either clopidogrel or alternative therapy (non-LOF). The unadjusted log-rank p values for the LOF-clopidogrel group compared with the LOF-alternative group and for the non-LOF group compared with the LOF-alternative group are provided. MACE = major adverse cardiovascular event.

The U.S. Food and Drug Administration-approved clopidogrel label warns of reduced clopidogrel effectiveness in PMs and recommends consideration of alternative antiplatelet therapy in these patients, but is silent regarding risk and recommendations in IMs (27). In our study, conducted in the context of routine clinical care, the majority of PMs (87%) were treated with alternative antiplatelet therapy, consistent with labeling recommendations, but a lower proportion of IMs were treated with alternative antiplatelet therapy (58%). This observation suggests that an IM test result is weighed less heavily than a PM result in the post-PCI antiplatelet therapy prescribing decision. However, when limiting our analysis to IMs, we observed a significantly higher rate of cardiovascular events with clopidogrel versus alternative antiplatelet therapy. These data indicate that IMs, like PMs, are at higher risk for adverse cardiovascular outcomes if treated with clopidogrel and suggest that alternative antiplatelet therapy should be considered in both IMs and PMs.

Our real-world data corroborate those from retrospective analyses of clinical trials showing a higher risk for cardiovascular events among clopidogrel-treated patients with versus without an LOF allele (3,5–7). In the absence of an LOF allele, data from the TRITON-TIMI 38 trial also suggest that the risk for adverse events may be comparable between clopidogrel and prasugrel, with a genetic substudy of the trial showing a relative risk for a MACE of 0.98 (95% CI: 0.80 to 1.20) with prasugrel compared with clopidogrel in patients without an LOF allele (28). The association between genotype and outcomes with clopidogrel appears to be indication specific, with strong and consistent associations in patients undergoing PCI, but not among lower-risk patients, such as those with atrial fibrillation or ACS managed medically (5,7,29,30). This is most clearly demonstrated in a meta-analysis showing an association between *CYP2C19* LOF genotype and risk for a MACE when analyzing studies of clopidogrel-treated patients undergoing PCI, but not when analyzing those without PCI (6).

Across institutions in our study, clopidogrel was the most commonly prescribed $P2Y_{12}$ inhibitor among patients without an *CYP2C19* LOF allele. This is consistent with other data suggesting that clopidogrel remains the predominant antiplatelet therapy in the

United States, prescribed 60% to 70% of the time according to published data through the first half of 2013 (31,32). To provide more contemporary use data, we interrogated practice patterns at Vanderbilt University Medical Center in the southeastern United States and Sanford Medical Center, which draws patients from 6 states in the Midwest. Current practice patterns in these geographic locales demonstrate that clopidogrel remains commonly prescribed following PCI, regardless of clinical context. Specifically, among 10,115 patients who underwent PCI (41% with ACS) at Vanderbilt University Medical Center from 2010 to 2015, clopidogrel use fell minimally, from 93% to 72%, during that time (unpublished data). Similarly, among 1,260 patients from Sanford Medical Center who underwent PCI at 15 catheterization laboratories during the first 9 months of 2016, 53% with ACS and 77% without ACS were discharged on clopidogrel (unpublished data).

Per PCI guidelines, the use of alternative antiplatelet agents in preference to clopidogrel after ACS and PCI is a Class IIa recommendation, on the basis of a moderate quality of evidence (1). In patients started on alternative $P2Y_{12}$ inhibitors according to PCI guidelines, *CYP2C19* genotype may still have an important role in informing therapy, especially after the 30-day post-PCI period when risk for events is highest (1). In patients with a high risk for bleeding or difficulty affording or tolerating newer agents, knowledge that a patient does not carry an LOF allele may give physicians increased confidence when considering switching the patient to the more affordable clopidogrel.

We did not directly assess why physicians chose to start some patients with an LOF allele on alternative therapy but not others. However, some speculation can be made on the basis of prescribing patterns and characteristics of treatment groups. First, the higher use of alternative therapy in PMs versus IMs suggests that physicians may heed the boxed warning in the clopidogrel labeling and place a stronger emphasis on using alternative therapy in PMs, the focus of the boxed warning. Second, the higher prevalence of stroke or transient ischemic attack history and concurrent anticoagulant agent use in the LOF-clopidogrel group versus the LOF-alternative group suggests that patient bleeding risk influenced preference for antiplatelet therapy.

STUDY LIMITATIONS. First, there was no control group of patients who did not undergo genotyping. However, some comparisons can be made with published event rates. In particular, in a genetic substudy of the TRITON-TIMI 38 trial of patients with ACS and PCI, 8% of clopidogrel-treated patients without an LOF allele and 12% with an LOF allele had a MACE (3). Rates in our study were comparable, with a MACE occurring in 7% of patients with ACS without an LOF allele (most of whom received clopidogrel) and 11% of clopidogrel-treated patients with an LOF allele.

Second, genotype-guided therapy was not randomized, because of our pragmatic design, and antiplatelet therapy selection was left to physician discretion. Thus, propensity scoring methods were used to mitigate the potential confounding effects related to differences across groups, and balance was achieved across comparison groups after weighting with IPTWs. However, residual confounding regarding the choice of antiplatelet therapy may remain.

Third, because ascertainment of outcomes was confined to the EHR without event adjudication, clinical events, including deaths, may have been missed.

Fourth, length of follow-up was variable, as is typical for the clinical setting. As such, event rates were reported.

Fifth, bleeding events were not objectively and systematically collected, given known difficulties in accurate bleeding assessment and the focus of data collection for this analysis on ischemic outcomes (33).

Finally, because of the limited number of patients who underwent elective PCI, we did not examine outcomes separately in this group.

CONCLUSIONS

We demonstrate that implementation of clinical *CYP2C19* genotyping to guide post-PCI antiplatelet therapy is feasible across multiple institutions. Our data also demonstrate that cardiovascular outcomes were worse when clopidogrel versus alternative antiplatelet therapy was prescribed after PCI in patients with an LOF allele. The higher risk for a MACE in LOF carriers prescribed clopidogrel was also evident when analyses were confined to patients with ACS and, separately, to IMs (with a single LOF allele). Our data suggest that obtaining genotype data early after PCI allows the identification of patients with *CYP2C19* LOF allele in whom alternative antiplatelet therapy would reduce risk for events. A future randomized study of genotype-guided antiplatelet therapy may be of value.

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PERSPECTIVES

WHAT IS KNOWN? *CYP2C19* LOF alleles impair clopidogrel activation and effectiveness after PCI. However, the impact of genotype-guided antiplatelet therapy on clinical outcomes is not well defined.

WHAT IS NEW? This study demonstrates that patients with 1 or 2 *CYP2C19* LOF alleles prescribed an alternative $P2Y_{12}$ inhibitor after PCI exhibit a lower risk for cardiovascular events compared with patients with 1 or 2 *CYP2C19* LOF alleles prescribed clopidogrel.

WHAT IS NEXT? Strategies to more broadly incorporate genotyping into clinical care to inform antiplatelet therapy prescribing decisions after PCI, and to evaluate the impact on health care costs, warrant further investigation.

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KEY WORDS antiplatelet therapy, cardiovascular events, clopidogrel, *CYP2C19*, percutaneous coronary intervention, pharmacogenomics

APPENDIX For supplemental tables and figures, please see the online version of this article.