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ORIGINAL ARTICLE

Clinical Outcomes and Sustainability of Using *CYP2C19* Genotype–Guided Antiplatelet Therapy After Percutaneous Coronary Intervention

See Editorial by Lewis

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BACKGROUND: *CYP2C19* loss-of-function (LOF) alleles impair clopidogrel effectiveness after percutaneous coronary intervention. The feasibility, sustainability, and clinical impact of using *CYP2C19* genotype–guided dual antiplatelet therapy (DAPT) selection in practice remains unclear.

METHODS: A single-center observational study was conducted in 1193 patients who underwent percutaneous coronary intervention and received DAPT after implementation of an algorithm that recommends *CYP2C19* testing in high-risk patients and alternative DAPT (prasugrel or ticagrelor) in LOF allele carriers. The frequency of genotype testing and alternative DAPT selection were the primary implementation end points. Risk of major adverse cardiovascular or cerebrovascular and clinically significant bleeding events over 12 months were compared across genotype and DAPT groups by proportional hazards regression.

RESULTS: *CYP2C19* genotype was obtained in 868 (72.8%) patients. Alternative DAPT was prescribed in 186 (70.7%) LOF allele carriers. *CYP2C19* testing ($P<0.001$) and alternative DAPT use in LOF allele carriers ($P=0.001$) varied over time. Risk for major adverse cardiovascular or cerebrovascular was significantly higher in LOF carriers prescribed clopidogrel versus alternative DAPT (adjusted hazard ratio, 4.65; 95% confidence interval, 2.22–10.0; $P<0.001$), whereas no significant difference was observed in those without a LOF allele (adjusted hazard ratio, 1.37; 95% confidence interval, 0.72–2.85; $P=0.347$). Bleeding event rates were similar across groups (log-rank $P=0.816$).

CONCLUSIONS: Implementing *CYP2C19* genotype–guided DAPT is feasible and sustainable in a real-world setting but challenging to maintain at a consistently high level of fidelity. The higher risk of major adverse cardiovascular or cerebrovascular associated with clopidogrel use in *CYP2C19* LOF allele carriers suggests that use of genotype-guided DAPT in practice may improve clinical outcomes.

Key Words: acute coronary syndrome ■ clopidogrel ■ cytochrome P-450 CYP2C19 ■ genetic testing ■ pharmacogenetics ■ percutaneous coronary intervention ■ precision medicine

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CLINICAL PERSPECTIVE

CYP2C19 loss-of-function alleles impair clopidogrel effectiveness after percutaneous coronary intervention (PCI). However, there remains considerable debate and uncertainty surrounding whether *CYP2C19* genetic testing should be used clinically to guide antiplatelet therapy selection in PCI patients. The current investigation offers novel insight into the feasibility, sustainability, and clinical impact of using a *CYP2C19* genotyping strategy to optimize $P2Y_{12}$ inhibitor selection after PCI in a real-world clinical setting. Results showed that *CYP2C19* genotypes were frequently ordered, efficiently returned, and routinely used to guide $P2Y_{12}$ inhibitor selection after PCI over a 2-year period; however, the frequency of genotype testing and use of alternative therapy in CYP2C19 intermediate and poor metabolizers varied significantly over time. The current study also showed that use of clopidogrel in CYP2C19 intermediate and poor metabolizers was associated with a significantly higher risk of major adverse cardiovascular and cerebrovascular events compared with alternative therapy. Our results demonstrate that implementing a *CYP2C19* genotype–guided antiplatelet therapy algorithm is feasible, sustainable, and associated with better clinical outcomes in a real-world clinical setting, but challenging to maintain at a consistently high level of fidelity. The clinical implications of our findings are that (1) clinicians need to be aware of the increased risk of major adverse cardiovascular or cerebrovascular associated with use of clopidogrel in PCI patients that carry either 1 or 2 copies of a *CYP2C19* loss-of-function allele, and (2) genotype-guided selection of antiplatelet therapy, with use of alternative therapy in CYP2C19 intermediate and poor metabolizers, should be considered in high-risk patients undergoing PCI.

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is used after percutaneous coronary intervention (PCI) and an acute coronary syndrome (ACS) to prevent major adverse cardiovascular events.[1,2] Clopidogrel remains the most commonly prescribed $P2Y_{12}$ inhibitor at most institutions, although alternative $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) are widely available.[3,4]

Clopidogrel is a prodrug that requires biotransformation by CYP enzymes (cytochromes P450), most notably CYP2C19, to generate its active metabolite. *CYP2C19* loss-of-function (LOF) polymorphisms are common and confer a reduced capacity for clopidogrel bioactivation and platelet inhibition.[5] Multiple retrospective analyses have demonstrated a significantly higher risk for major adverse cardiovascular events after PCI in clopidogrel-treated patients carrying 1 (intermediate metabolizer, IM) or 2 (poor metabolizer, PM) *CYP2C19* LOF alleles compared with clopidogrel-treated patients without a LOF allele.[6–9] In contrast, *CYP2C19* genotype does not alter the pharmacokinetics, antiplatelet effects, or clinical response to prasugrel or ticagrelor.[8,10] These alternative $P2Y_{12}$ inhibitors have shown superior efficacy compared with clopidogrel in ACS patients after PCI in clinical trials[11,12] but are more expensive and associated with an increased bleeding risk.[2,13,14] It remains unclear whether these effects are because of more potent or more consistent platelet inhibition. A secondary analysis of the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction) suggested that the overall efficacy benefit conferred by prasugrel over clopidogrel was driven by the increased risk of major adverse cardiovascular events in *CYP2C19* LOF allele carriers randomized to clopidogrel[6,10,15]; however, the impact of *CYP2C19* LOF alleles on the efficacy benefit of ticagrelor over clopidogrel in the PLATO study (Study of Platelet Inhibition and Patient Outcomes) was less dramatic.[8]

Given the lack of prospective clinical outcome data, there remains considerable debate and uncertainty surrounding whether clinical *CYP2C19* genetic testing should be routinely used to guide antiplatelet therapy selection in PCI patients.[1,5,16–18] Interest in genotype-guided antiplatelet therapy has been enhanced by a series of recent outcome-driven prospective studies, most notably a multicenter pragmatic investigation conducted by the IGNITE network (Implementing Genomics in Practice), which have suggested there is clinical benefit associated with using genotype-guided antiplatelet therapy.[19–22] Thus, an increasing number of institutions are implementing *CYP2C19* genetic testing,[23–25] despite limited data on the feasibility, sustainability, and clinical impact of using a *CYP2C19* genotyping strategy to guide $P2Y_{12}$ inhibitor selection after PCI in real-world clinical practice. The University of North Carolina implemented an algorithm incorporating *CYP2C19* genotyping in DAPT selection in 2012[26]; therefore, the objectives of this study were to (1) determine the frequency of *CYP2C19* testing and use of alternative therapy in CYP2C19 IMs and PMs over time, (2) identify the factors that influenced *CYP2C19* testing and $P2Y_{12}$ inhibitor selection, and (3) examine the relationship between $P2Y_{12}$ inhibitor, *CYP2C19* status, and clinical outcomes.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

A clinical algorithm for *CYP2C19* genotype–guided selection of antiplatelet therapy after PCI in high-risk patients (defined as ACS or high-risk coronary anatomy) was implemented at the University of North Carolina Cardiac Catheterization Laboratory in July 2012 (Figure I in the Data Supplement), as described.[26] The *CYP2C19* genotype test is ordered at the interventional cardiologist's discretion after risk stratification, and performed clinically on-site (Methods in the Data Supplement). Alternative antiplatelet therapy (prasugrel or ticagrelor) is recommended for CYP2C19 IMs and PMs, but the treatment decision is left to the discretion of the prescriber.

This single-center observational cohort study included 1193 consecutive adults ≥18 years of age who underwent PCI with coronary artery stent placement between July 1, 2012 and June 30, 2014 at the University of North Carolina Cardiac Catheterization Laboratory, and received DAPT with aspirin and a $P2Y_{12}$ inhibitor. The cohort includes 572 patients that underwent *CYP2C19* genotyping during the index PCI admission between July 1, 2012 and December 31, 2013, and were included in the IGNITE network multicenter investigation of outcomes.[19] The investigation was approved by the University of North Carolina Biomedical Institutional Review Board. Because data collection was completed by retrospective review of the electronic health record (EHR), informed consent was not required.

Data Abstraction and Study End Points

Data were manually abstracted from the EHR. The primary implementation end point was $P2Y_{12}$ inhibitor maintenance therapy, which was defined as the agent prescribed over the course of follow-up after any changes in therapy. Key secondary end points included *CYP2C19* genotype availability, initial $P2Y_{12}$ inhibitor therapy, and changes in therapy.

The primary clinical outcome was the composite of major adverse cardiovascular or cerebrovascular events (MACCE) over 12 months following the index PCI, which was defined as death, myocardial infarction, stent thrombosis, admission for ACS/unstable angina, ischemic cerebrovascular accident, or transient ischemic attack. A major secondary outcome was clinically significant bleeding, which was defined as a GUSTO (Global Use of Strategies to Open Occluded Arteries) moderate or severe/life-threatening bleeding event.[27] Events were identified using physician-reported diagnoses abstracted from the EHR and then verified by an interventional cardiologist.

Statistical Analysis

Data are presented as mean±SD, median (interquartile range), or count (%) unless otherwise indicated. To identify the key demographic and clinical factors associated with *CYP2C19* testing and $P2Y_{12}$ inhibitor selection, associations were evaluated by logistic regression using univariate and multivariable models, and the odds ratio (OR) and 95% confidence intervals (CIs) for each covariate were calculated. Interaction and stratified analyses were also completed. The sustainability of algorithm use over time was assessed by comparing genotype and medication selection end points across consecutive 6-month time intervals during the study period (index PCI during July to December 2012, January to June 2013, July to December 2013, or January to June 2014) using χ^2.

The relationship between *CYP2C19* status, prescribed $P2Y_{12}$ inhibitor therapy, and the time to occurrence of the primary (MACCE) and secondary (clinically significant bleeding) clinical outcomes were evaluated using Cox proportional hazards regression in patients with follow-up available after the index PCI admission. Time-to-event analyses were completed after adjusting for covariates that differed across groups or were associated with the clinical outcome, and the adjusted hazard ratio and 95% CIs for each between-group comparison were calculated. Covariates included in the adjusted model for MACCE included sex, race, current smoker, history of atrial fibrillation, prior stent, elevated risk of bleeding, ACS indication for PCI; drug-eluting stent at index PCI, discharge angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, discharge β-blocker, and discharge statin. Covariates included in the adjusted model for bleeding included sex, race, elevated risk of bleeding, prior stent, ACS indication for PCI, and multiple vessels stented during index PCI. To determine whether *CYP2C19* genotype modified the association between antiplatelet therapy and MACCE, the interaction between CYP2C19 phenotype (IM/PM or ultrarapid, rapid, or normal metabolizers) and antiplatelet therapy (clopidogrel or alternative) status was evaluated. Secondary analyses were completed in the strata of patients presenting with an ACS indication for their index PCI. Analyses were performed using SAS-JMP 12.0 and SAS 9.4 (SAS Institute, Cary, NC). *P* values <0.05 were considered statistically significant.

RESULTS

Study Population

This single-center observational cohort study included 1193 consecutive adults ≥18 years of age who underwent coronary artery stent placement between July 1, 2012 and June 30, 2014, and received DAPT. The mean age was 63±12 years, 67.6% were male, 20.7% were Black, and 53.8% underwent PCI for an ACS indication (Table 1). On admission, 26.0% were receiving chronic $P2Y_{12}$ inhibitor therapy and 40.1% exhibited a risk factor for bleeding.

Genotype Testing

A *CYP2C19* genotype was obtained in 868 (72.8%) patients (Figure 1A); of these, 794 (91.5%) were genotyped during the index admission. The median time from genotype order to result was 1 day, and 75% of results were available by the day after PCI. Among genotyped patients, 263 (30.2%) carried either 1 (IM) or 2 (PM) LOF alleles; 262 of which carried the **2* allele (Figure 1B).

Clinical factors indicative of high risk, including an ACS indication for PCI (OR, 2.56; 95% CI, 1.94–3.38; *P*<0.001) and stent placement in either the left anterior descending (OR, 1.60; 95% CI, 1.21–2.13; *P*=0.001) or left main (OR, 4.72; 95% CI, 1.57–20.5; *P*=0.004)

Table 1. Study Population Characteristics

Characteristic	n=1193
Age, y	63.3±12.0
Age ≥75 y	220 (18.4%)
Sex (male)	807 (67.6%)
Race	
Black	247 (20.7%)
Asian-American	7 (0.6%)
Body mass index, kg/m^2	29.9±6.4
Obese (≥30.0 kg/m^2)	505 (42.3%)
Weight <60 kg	81 (6.8%)
Current smoker	334 (28.0%)
Hypertension	997 (83.6%)
Diabetes mellitus	496 (41.6%)
Peripheral vascular disease	147 (12.3%)
Atrial fibrillation	109 (9.1%)
Heart failure	191 (16.0%)
End-stage renal disease	47 (3.9%)
Previous myocardial infarction	325 (27.2%)
Previous TIA or stroke	102 (8.5%)
Previous significant bleeding event	112 (9.4%)
Elevated bleeding risk*	478 (40.1%)
Previous coronary artery stent	466 (39.1%)
$P2Y_{12}$ inhibitor use on admission	310 (26.0%)
Clopidogrel	266 (22.3%)
Prasugrel	43 (3.6%)
Ticagrelor	1 (0.1%)
Indication for PCI	
Stable angina	551 (46.2%)
Acute coronary syndrome	642 (53.8%)
Unstable angina	204 (17.1%)
NSTEMI	297 (24.9%)
STEMI	141 (11.8%)
Stent placement by vessel at index PCI	
Left main	30 (2.5%)
Left anterior descending	497 (41.7%)
Circumflex	249 (20.9%)
Right coronary artery	359 (30.1%)
Bypass graft	27 (2.3%)
Multiple vessels stented	152 (12.7%)
Drug-eluting stent	1004 (84.2%)
Medication use at discharge	
Aspirin	1173 (98.3%)
Anticoagulant	79 (6.6%)
ACE inhibitor or ARB	801 (67.1%)
β-blocker	1009 (84.6%)
Statin	1123 (94.1%)
Proton pump inhibitor	371 (31.1%)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIA, transient ischemic attack.

*Elevated bleeding risk is a composite variable defined as one or more of the following: age ≥75 y; weight <60 kg; previous TIA or stroke event; previous significant bleeding event; current end-stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

coronary artery, were significant predictors of *CYP2C19* genotype testing during the index PCI hospitalization. In contrast, patients receiving chronic $P2Y_{12}$ inhibitor therapy on admission were significantly less likely to have a genotype test ordered (Table I in the Data Supplement).

$P2Y_{12}$ Inhibitor Therapy Selection

Clopidogrel (69.4%) was the most commonly prescribed maintenance therapy with prasugrel (30.6%) and ticagrelor (3.3%) prescribed less frequently. Consistent with the algorithm, this distribution differed substantially by CYP2C19 phenotype status (Figure 1C). CYP2C19 IMs and PMs were routinely prescribed either prasugrel (59.9%) or ticagrelor (11.8%) as maintenance therapy, with 69.5% of IMs and 83.3% of PMs receiving alternative antiplatelet therapy. In contrast, clopidogrel was commonly prescribed in patients without a *CYP2C19* LOF allele (76.4%) or without an available *CYP2C19* genotype (88.9%).

Predictors of $P2Y_{12}$ Inhibitor Therapy Selection

Clinical factors associated with prasugrel/ticagrelor selection as the initial loading therapy during the index PCI are described in Table II in the Data Supplement. CYP2C19 IM or PM phenotype was a significant independent predictor of prasugrel/ticagrelor selection as maintenance therapy (OR, 13.1; 95% CI, 8.84–19.7; $P<0.001$; Table III in the Data Supplement), as well as a change in therapy from clopidogrel to alternative therapy after the index PCI procedure (Figure II in the Data Supplement). Clinical factors, including an ACS indication for PCI (OR, 2.80; 95% CI, 1.93–4.12; $P<0.001$), left anterior descending artery stent (OR, 1.64; 95% CI, 1.16–2.34; $P=0.005$) and prasugrel/ticagrelor use on admission (OR, 18.5; 95% CI, 5.75–84.4; $P<0.001$), were also significantly associated with prasugrel/ticagrelor selection; whereas elevated bleeding risk and clopidogrel use on admission were significantly associated with clopidogrel selection (Table III in the Data Supplement).

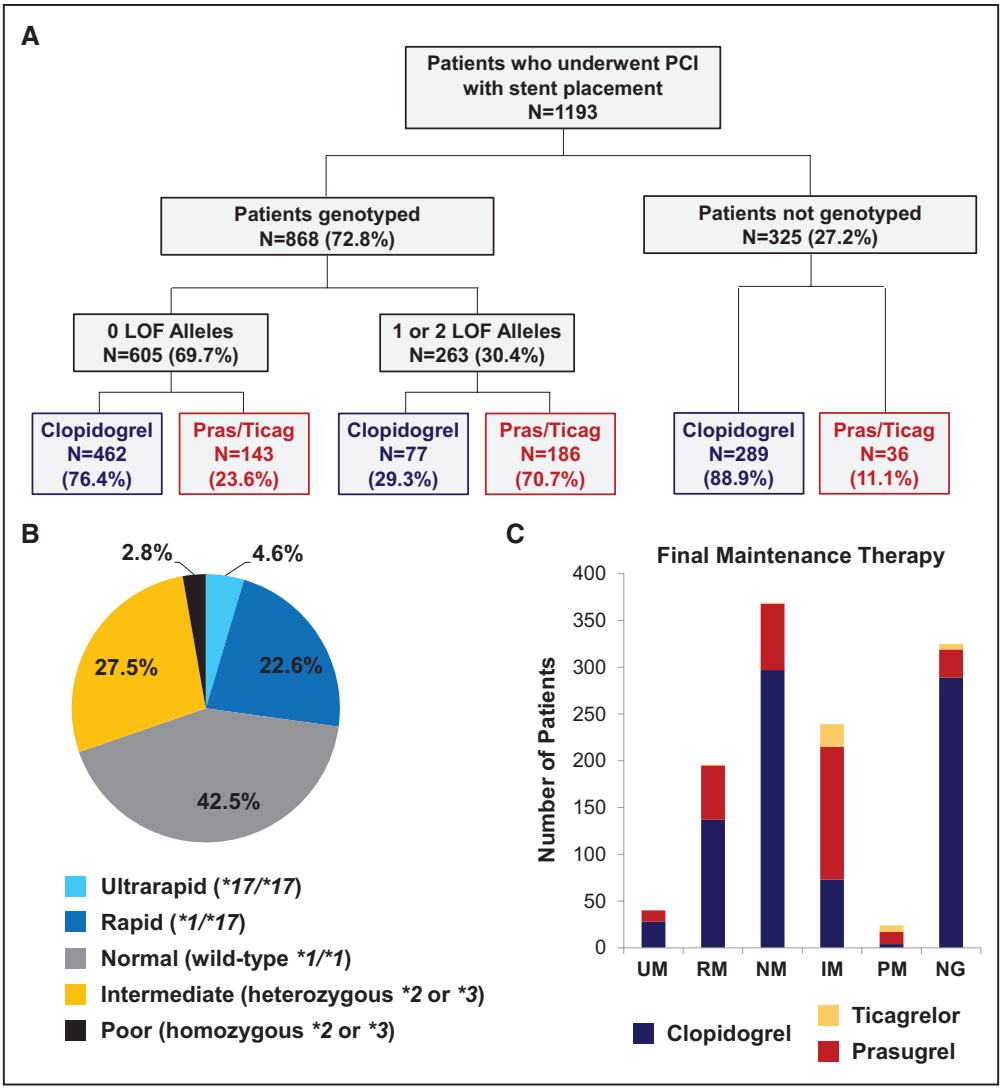


Figure 1. P2Y$_{12}$ inhibitor maintenance therapy by *CYP2C19* status.
A, Study population summary by *CYP2C19* genotype availability, loss-of-function (LOF) allele status, and maintenance therapy. **B**, CYP2C19 phenotype distribution in genotyped patients: ultrarapid (UM: n=40; 4.6%), rapid (RM: n=196; 22.6%), normal (NM: n=369; 42.5%), intermediate (IM: n=239; 27.5%); poor (PM: n=24; 2.8%) metabolizers. The IM [**1/*2*=190 (21.9%), **1/*3*=1 (0.1%), **2/*17*=48 (5.5%), **3/*17*=0 (0%)] and PM [**2/*2*=24 (2.8%), **2/*3*=0 (0%), **3/*3*=0 (0%)] phenotypes included multiple genotypes. **C**, Maintenance therapy distribution (clopidogrel, prasugrel, or ticagrelor) by CYP2C19 status (NG, not genotyped). PCI indicates percutaneous coronary intervention; Pras, prasugrel; and Ticag, ticagrelor.

CYP2C19 phenotype status also appeared to modify the association between certain clinical factors and antiplatelet therapy selection (Table IV in the Data Supplement). Although the association between ACS indication for PCI and prasugrel/ticagrelor selection was not modified by CYP2C19 phenotype status (Figure 2A), the association between elevated bleeding risk and a lower likelihood of prescribing prasugrel/ticagrelor was more pronounced in patients without a *CYP2C19* LOF allele (OR, 0.20; 95% CI, 0.12–0.33) compared with IM/PMs (OR, 0.47; 95% CI, 0.27–0.81; interaction *P*=0.023; Figure 2B). The association between left anterior descending artery stent placement and prasugrel/ticagrelor selection was only evident in patients without a LOF allele (interaction *P*=0.009; Figure 2C).

Clinical Outcomes

Clinical outcomes were evaluated in 999 patients with follow-up available after the index PCI admission (83.7% of the study population). The median (interquartile range) time from index PCI to MACCE or last follow-up was 8.7 (4.4–11.1) months. During follow-up, 119 (11.9%; 18.9 per 100 patient-years) and 38 (3.8%; 6.1 per 100 patient-years) experienced MACCE and clinically significant bleeding events, respectively. Event frequencies were lower in the strata of patients

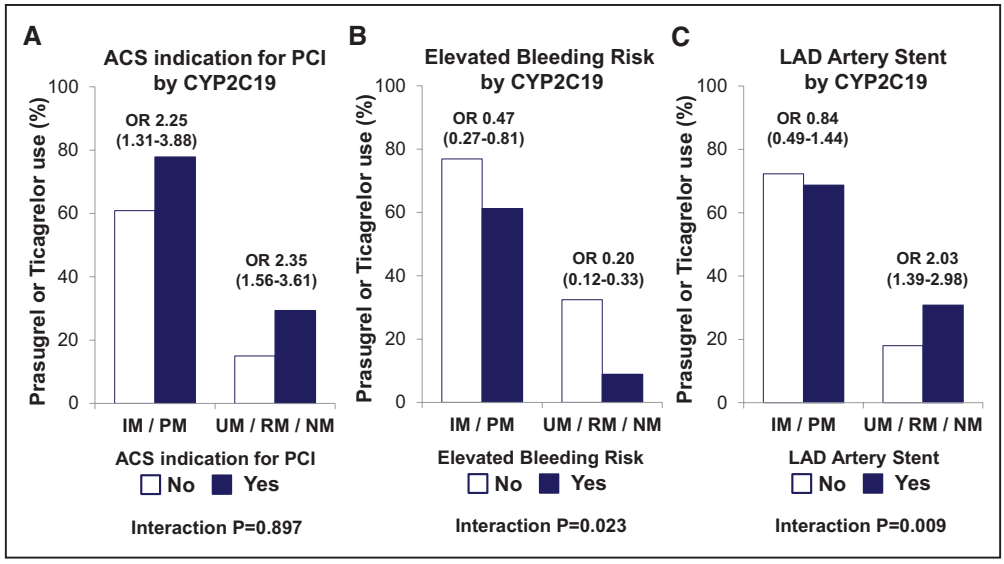


Figure 2. Prasugrel or ticagrelor selection by clinical factor and CYP2C19 phenotype status.
The frequency of alternative therapy (prasugrel or ticagrelor) use as maintenance therapy (*y* axis) in the strata of CYP2C19 intermediate or poor metabolizers (IM/PM) and ultrarapid, rapid, or normal metabolizers (UM/RM/NM) is presented according to the absence (No) and presence (Yes) of the following clinical factors: (**A**) acute coronary syndrome (ACS) indication for percutaneous coronary intervention (PCI); (**B**) elevated bleeding risk; (C) left anterior descending (LAD) artery stent placement. The odds ratio (OR; 95% confidence interval [CI]) for the association between presence of the clinical factor with prasugrel/ticagrelor selection within each CYP2C19 phenotype strata (IM/PM or UM/RM/NM), and the CYP2C19 phenotype*clinical factor interaction *P* value is provided.

that did not undergo *CYP2C19* genotyping (Table 2), which was expected because the algorithm only recommended genotyping in high-risk patients.

The risk of developing MACCE was significantly associated with CYP2C19 phenotype and the prescribed antiplatelet therapy (Table 3). Compared with CYP2C19 IM/PMs treated with alternative therapy, IM/PMs treated with clopidogrel exhibited a significantly higher risk of MACCE (11.4 versus 52.0 events per 100 patient-years, respectively; Figure 3A; adjusted hazard ratio, 4.65; 95% CI, 2.22–10.0; *P*<0.001). In contrast, no significant difference in MACCE was observed in CYP2C19 ultrarapid, rapid, or normal metabolizers treated with clopidogrel relative to alternative therapy (adjusted hazard ratio, 1.37; 95% CI, 0.72–2.85; *P*=0.347; CYP2C19*antiplatelet interaction *P*=0.018).

Table 2. Cardiovascular and Bleeding Event Type by CYP2C19 Status and $P2Y_{12}$ Inhibitor

	Not Genotyped	Genotyped	CYP2C19 IM/PM		CYP2C19 UM/RM/NM	
	All	All	Clopidogrel	Pras/Ticag	Clopidogrel	Pras/Ticag
Event Type	n=248	n=751	n=68*	n=165	n=405	n=113
MACCE	24 (9.7%)	95 (12.6%)	18 (26.5%)	13 (7.9%)	53 (13.1%)	11 (9.7%)
Death	9 (3.6%)	22 (2.9%)	5 (7.7%)	4 (2.4%)	12 (3.0%)	1 (0.9%)
Myocardial infarction	5 (2.0%)	29 (3.9%)	5 (7.7%)	5 (3.0%)	16 (4.0%)	3 (2.7%)
Stent thrombosis	0 (0.0%)	3 (0.4%)	1 (1.5%)	1 (0.6%)	1 (0.2%)	0 (0.0%)
Acute coronary syndrome/unstable angina	10 (4.0%)	44 (5.9%)	8 (11.8%)	5 (3.0%)	24 (5.9%)	7 (6.2%)
Ischemic cerebrovascular accident	3 (1.2%)	4 (0.5%)	1 (1.5%)	0 (0.0%)	2 (0.5%)	1 (0.9%)
Transient ischemic attack	1 (0.4%)	5 (0.7%)	1 (1.5%)	1 (0.6%)	2 (0.5%)	1 (0.9%)
Clinically significant bleeding events	7 (2.8%)	31 (4.1%)	2 (3.0%)	7 (4.2%)	19 (4.7%)	3 (2.7%)
GUSTO moderate	4 (1.6%)	14 (1.9%)	0 (0.0%)	4 (2.4%)	11 (2.7%)	2 (1.8%)
GUSTO severe	3 (1.2%)	17 (2.3%)	2 (3.0%)	3 (1.8%)	16 (4.0%)	1 (0.9%)

Data are presented as the number (percentage) of patients in each group that experienced the event over the course of follow-up. GUSTO indicates Global Use of Strategies to Open Occluded Arteries; IM, intermediate metabolizer; PM, poor metabolizer; Pras, prasugrel; Ticag, ticagrelor; and UM/RM/NM, ultrarapid, rapid, or normal metabolizers.

*One patient with a CYP2C19 IM phenotype receiving treatment with prasugrel experienced an early bleeding event and was subsequently switched to clopidogrel for the remainder of follow-up.

Table 3. Cardiovascular and Bleeding Event Incidence by CYP2C19 Status and $P2Y_{12}$ Inhibitor

Clinical Outcome by CYP2C19 Phenotype–Selected $P2Y_{12}$ Inhibitor	Event, n (%)*	Event Rate (Per 100 Patient-Years)†	Log-Rank *P* (Unadjusted)‡	Log-Rank *P* (Adjusted)‡	Adjusted HR (95% CI)	*P* Value
MACCE						
IM/PM–alternative	13 (7.9%)	11.4			Reference	
IM/PM–clopidogrel	18 (26.5%)	52.0			4.65 (2.22–10.0)	<0.001
UM/RM/NM–alternative	11 (9.7%)	15.0			1.25 (0.54–2.83)	0.601
UM/RM/NM–clopidogrel	53 (13.1%)	20.1	*P*<0.001	*P*<0.001	1.71 (0.95–3.32)	0.075
Clinically significant bleeding events						
IM/PM–alternative	7 (4.2%)	6.2			Reference	
IM/PM–clopidogrel	2 (3.0%)	5.9			1.04 (0.15–4.47)	0.964
UM/RM/NM–alternative	3 (2.7%)	4.2			0.81 (0.17–3.03)	0.767
UM/RM/NM–clopidogrel	19 (4.7%)	7.3	*P*=0.816	*P*=0.925	1.21 (0.51–3.19)	0.675

CI indicates confidence interval; HR, hazard ratio; IM, intermediate metabolizer; MACCE, major adverse cardiovascular and cerebrovascular events; PM, poor metabolizer; and UM/RM/NM, ultrarapid, rapid, or normal metabolizers.

*The number (percentage) in each group that experienced an event during follow-up.

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

‡Comparison of outcomes across the 4 CYP2C19 phenotype and antiplatelet therapy groups. Stratified analysis of MACCE in Blacks (adjusted log-rank *P*=0.038) and non-Blacks (adjusted log-rank *P*=0.041) demonstrated that no racial/ethnic-based differences were present. The small number of bleeding events precluded race-stratified analysis of bleeding.

There was no difference in risk of developing a clinically significant bleeding event across the CYP2C19 phenotype and antiplatelet therapy groups (Figure 3B; Table 3).

In patients with an ACS indication for their index PCI, the risk of MACCE was highest in the CYP2C19 IM/PMs treated with clopidogrel consistent with the overall study population (Figure 3C; Table V in the Data Supplement). Bleeding event rates were similar across the CYP2C19 phenotype and antiplatelet therapy groups in the ACS strata (Table V in the Data Supplement).

Sustainability of Genotype-Guided Antiplatelet Therapy Over Time

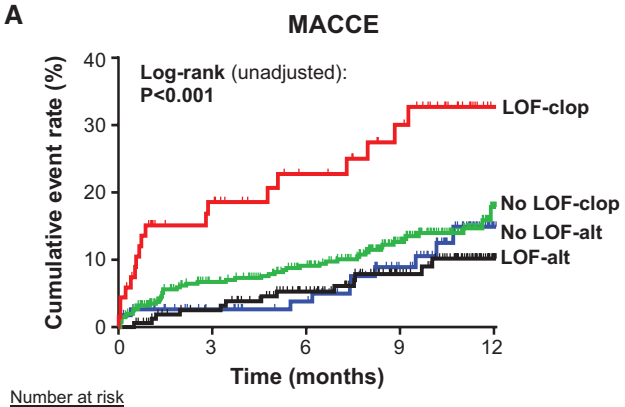
The frequency of *CYP2C19* testing and use of alternative therapy in IM/PMs varied significantly throughout the study period. Following a very high rate of genotyping during the initial 6 months (88%), the proportion genotyped decreased during the subsequent 12 months (61% to 65%) and then increased (78%) during the final 6 months (Figure 4A). These differences were driven by the frequency of genotype testing during the index PCI admission (Table VI in the Data Supplement).

The frequent use of alternative therapy in CYP2C19 IM/PMs during the initial 6 months (83%) was sustained during the subsequent 6-month period but declined to 54% before increasing to 68% during the final 6 months (Figure 4B). This was accompanied by a significant decline in the proportion of IM/PMs that underwent a change in therapy from clopidogrel to alternative therapy (Table VI in the Data Supplement). In contrast, no significant difference in alternative therapy use over time was observed in those without a *CYP2C19* LOF allele (Figure 4B).

DISCUSSION

The current investigation evaluated use of *CYP2C19* testing, $P2Y_{12}$ inhibitor selection and clinical outcomes following implementation of genotype-guided antiplatelet therapy over a 2-year period at a single academic medical center. Results showed that *CYP2C19* genotypes were frequently ordered, efficiently returned, and routinely used to guide $P2Y_{12}$ inhibitor selection after PCI. The use of clopidogrel in CYP2C19 IM/PMs was associated with a significantly higher risk of MACCE compared with alternative therapy, consistent with results from the multicenter IGNITE network study.[19] The current study also demonstrates that the frequency of genotype testing at the time of PCI and use of alternative therapy in CYP2C19 IM/PMs varied significantly over time. Taken together, these data illustrate that implementing a *CYP2C19*-guided antiplatelet therapy algorithm is feasible, sustainable, and associated with better clinical outcomes in real-world clinical practice but challenging to maintain at a consistently high level of fidelity.

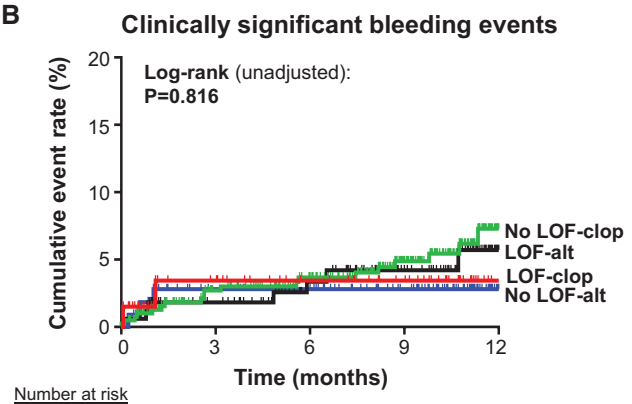
Recently, an investigation of outcomes in 1815 patients across 7 US centers conducted by the IGNITE network demonstrated that CYP2C19 IM/PMs prescribed clopidogrel had a 2.26-fold higher risk for MACCE after PCI compared with those that prescribed alternative therapy.[19] Our results, and those of the IGNITE study, are consistent with retrospective genetic



Number at risk

LOF-clop	68	48	36	28	2
No LOF-clop	405	329	295	208	20
No LOF-alt	113	93	85	61	4
LOF-alt	165	147	123	86	10
Total	751	617	539	383	36

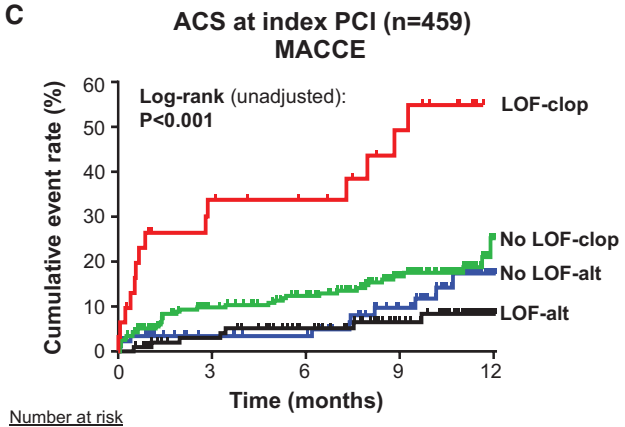
Group	Reference	Adjusted HR (95% CI)	P-value
LOF-clop	vs. **LOF-alt**	**4.65** (2.22-10.0)	**<0.001**
No LOF-clop	vs. **No LOF-alt**	**1.37** (0.72-2.85)	**0.347**
LOF-clop	vs. **No LOF-clop**	**2.71** (1.52-4.66)	**0.001**
LOF-alt	vs. **No LOF-alt**	**0.80** (0.35-1.86)	**0.601**



Number at risk

LOF-clop	67	47	36	28	2
No LOF-clop	405	324	291	206	20
No LOF-alt	113	90	83	60	4
LOF-alt	166	147	121	84	9
Total	751	608	531	378	36

Group	Reference	Adjusted HR (95% CI)	P-value
LOF-clop	vs. **LOF-alt**	**1.04** (0.15-4.47)	**0.964**
No LOF-clop	vs. **No LOF-alt**	**1.49** (0.46-6.66)	**0.530**
LOF-clop	vs. **No LOF-clop**	**0.86** (0.14-3.02)	**0.835**
LOF-alt	vs. **No LOF-alt**	**1.23** (0.33-5.85)	**0.767**



Number at risk

LOF-clop	31	19	16	10	1
No LOF-clop	235	184	166	112	11
No LOF-alt	88	70	67	49	4
LOF-alt	105	92	78	54	9
Total	459	365	327	225	25

Group	Reference	Adjusted HR (95% CI)	P-value
LOF-clop	vs. **LOF-alt**	**10.0** (3.97-27.7)	**<0.001**
No LOF-clop	vs. **No LOF-alt**	**1.37** (0.68-3.00)	**0.391**
LOF-clop	vs. **No LOF-clop**	**3.68** (1.88-6.83)	**<0.001**
LOF-alt	vs. **No LOF-alt**	**0.50** (0.18-1.35)	**0.172**

Figure 3. Cardiovascular and bleeding outcomes after percutaneous coronary intervention (PCI) by *CYP2C19* status and $P2Y_{12}$ inhibitor therapy.

Kaplan–Meier curves for (**A**) major adverse cardiovascular and cerebrovascular event (MACCE) and (**B**) clinically significant bleeding event incidence in patients that underwent *CYP2C19* testing and had follow-up available after the index PCI admission (n=751). **C**, Kaplan—Meier curve for MACCE in the strata of patients presenting with an acute coronary syndrome (ACS) indication for PCI (n=459). Data are shown across 4 *CYP2C19* genotype and antiplatelet therapy strata: intermediate or poor metabolizers carrying a loss-of-function allele prescribed clopidogrel (LOF-clop), LOF allele carriers prescribed (*Continued*)

analyses that have repeatedly demonstrated higher risk for MACCE in CYP2C19 IM/PMs treated with clopidogrel after PCI.[6–8] It is important to note that 572 of the 868 genotyped patients in our single-center analysis were included in the multicenter IGNITE network investigation. The current study extends those results, shows no difference in clinically significant bleeding across genotypes, and demonstrates that the fidelity in which *CYP2C19*-guided antiplatelet therapy is applied in practice can vary significantly over time. Our results are also consistent with 3 international prospective studies, which demonstrated that *CYP2C19* genotype–guided intensification of antiplatelet therapy in IMs and PMs significantly reduced MACCE compared with conventional therapy without genotyping and did not increase risk for bleeding.[20–22] Collectively, these studies provide an expanding evidence base demonstrating that genotype-guided selection of DAPT after PCI is associated with lower rates of MACCE without any increase in clinically significant bleeding. An ongoing randomized controlled clinical trial will assess the utility of *CYP2C19*-guided antiplatelet therapy in a prospective fashion in ≈5000 patients undergoing PCI, but will not be completed until 2020 (URL: https://www.clinicaltrials.gov. Unique identifier: NCT01742117).

The American College of Cardiology Foundation/American Heart Association PCI guidelines state that genetic testing and use of alternative therapy in genetically predisposed nonresponders might be considered in high-risk patients (Class IIb, Level of Evidence: C).[1] The Food and Drug Administration black box warning in the clopidogrel label specifically warns prescribers of reduced clopidogrel effectiveness in PMs.[16,17] The majority (20 of 24) of PMs at our institution received alternative therapy and virtually all (17 of 18) MACCE events observed in IM/PMs treated with clopidogrel occurred in IMs. These data are consistent with the IGNITE network results,[19] demonstrate that the elevated risk of adverse cardiovascular outcomes is not limited to PMs, and support the Clinical Pharmacogenetics Implementation Consortium recommendation to use alternative therapy in CYP2C19 IMs and PMs if *CYP2C19* genotype is known.[5] Furthermore, the elevated risk of MACCE in CYP2C19 IM/PMs prescribed clopidogrel was most evident in patients that underwent PCI for an ACS indication, which is consistent with the multicenter IGNITE network results.[19] These data are also consistent with prior retrospective analyses that have demonstrated the strongest associations between *CYP2C19* LOF alleles and risk of MACCE occur in higher risk strata of patients prescribed clopidogrel, such as PCI versus non-PCI and ACS versus non-ACS indications.[9,28] Collectively, our results suggest that (1) clinicians need to be aware of the risks associated with use of clopidogrel in CYP2C19 IMs and PMs, and (2) genotype-guided selection of antiplatelet therapy, with use of alternative therapy in CYP2C19 IMs and PMs, should be considered in high-risk patients undergoing PCI. Because of the low number of events, the clinical impact of genotyping in patients undergoing PCI for a non-ACS indication remains unclear and will require further study.

We observed that clinical factors indicative of high risk for future cardiovascular events, including an ACS indication for PCI and placement of a left anterior descending or left main artery stent, were the strongest predictors of genotype testing during the index PCI admission. These findings illustrate that the interventional cardiologist's decision to genotype is reactive after risk stratification, consistent with the algorithm. CYP2C19 phenotype was the strongest predictor of antiplatelet therapy selection, indicating that *CYP2C19* genotype was frequently used to guide the prescribing decision when available. However, clinical factors such as an ACS indication for PCI, risk factors for bleeding, and prior $P2Y_{12}$ inhibitor use on admission were also significantly associated with DAPT selection. Moreover, the presence of risk factors for bleeding significantly modified the association between the *CYP2C19* result and medication selection. These data illustrate that, although important, the genotype result is one of the multiple factors considered when selecting DAPT in a real-world setting, and clinicians may be reluctant to prescribe alternative therapy in IM/PMs with risk factors for bleeding. However, the significantly lower risk of MACCE observed in CYP2C19 IM/PMs prescribed alternative therapy compared with clopidogrel was not offset by a higher risk of bleeding events, which were similar across CYP2C19 phenotype and DAPT groups and consistent with other recent prospective studies.[20–22] These data suggest that the ischemic risk conferred by clopidogrel use in IM/PMs may outweigh the risk for clinically significant bleeding events conferred by alternative therapy and that placing greater weight on a CYP2C19 IM/PM result during the prescribing decision may be warranted in certain cases.

Although the feasibility of clinically implementing genotype-guided antiplatelet therapy has been demonstrated,[23,26,29,30] the sustainability of obtaining, interpreting, and using *CYP2C19* genotype to guide $P2Y_{12}$ inhibitor selection over time has not been investigated. We observed a high overall frequency of *CYP2C19* testing (73% of all PCI patients; 81%

Figure 3 Continued. alternative therapy (LOF-alt), ultrarapid, rapid or normal metabolizers without a LOF allele prescribed clopidogrel (No LOF-clop); patients without a LOF prescribed alternative therapy (No LOF-alt). The unadjusted log-rank *P* value for outcomes across the 4 groups, and the adjusted hazard ratio (HR), 95% confidence interval (CI) and *P* value for the indicated between-group comparisons, are provided.

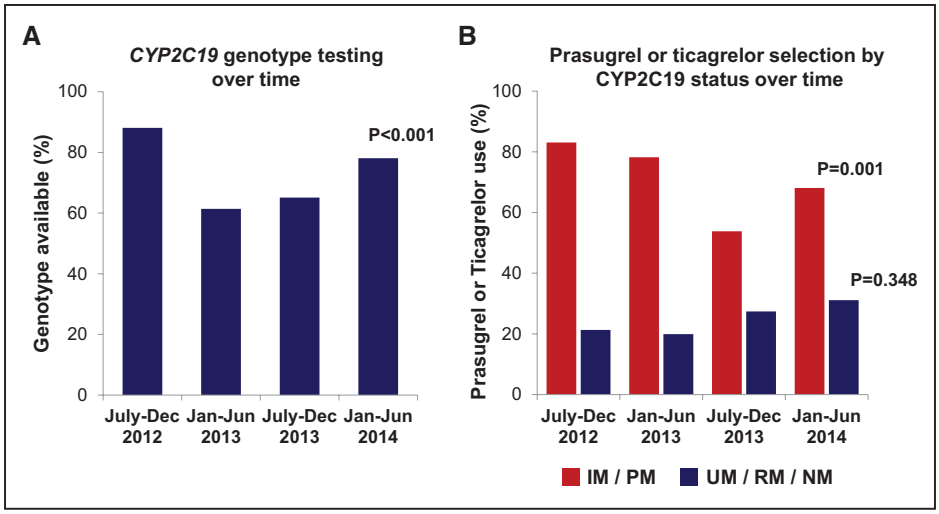


Figure 4. Frequency of *CYP2C19* genotype testing and $P2Y_{12}$ inhibitor maintenance therapy selection by CYP2C19 status over time.

The index percutaneous coronary intervention (PCI) date was categorized into 6-mo intervals. The frequency of (**A**) *CYP2C19* genotype testing and (**B**) alternative therapy (prasugrel or ticagrelor) use in the strata of CYP2C19 intermediate or poor metabolizers (IM/PM) and ultrarapid, rapid, or normal metabolizers (UM/RM/NM) in each time interval was compared. The χ^2 *P* value is provided.

of ACS patients) and use of alternative therapy in CYP2C19 IM/PMs (71% of all PCI patients; 78% of ACS patients). The feasible implementation and sustainable use of a genotype-guided algorithm at our institution was possible because of several key factors that alleviated logistical barriers. Notably, in-house genotype testing with prompt turnaround of results in the EHR, and interdisciplinary collaboration and communication among physicians, clinical pharmacists, and nurses have proven critical. Indeed, pharmacists are essential to the successful application of pharmacogenomics in clinical practice.[31] Despite the high overall use of genotype-guided antiplatelet therapy, we also observed that the proportion of PCI patients genotyped and IM/PMs prescribed alternative therapy significantly varied over time. The latter appeared driven by a significant decline in IM/PMs that underwent a change from clopidogrel to alternative therapy. These results demonstrate that implementation of an algorithm that uses genetic testing to guide drug selection is difficult to sustain at a high level in clinical practice. Because evaluation of barriers to sustained implementation via provider surveys was beyond the scope of the current study, it remains unclear what specific factors contributed to the observed fluctuations in fidelity. Although recurrent clinician education was employed, automated clinical decision support (CDS) within the EHR to alert clinicians about the genotype result was not available at our institution during the study period. Clinician education and clinical decision support have been proposed as key solutions to facilitate fidelity, sustainability, and scale of genotype-guided prescribing within and across sites.[32] Future studies are needed to evaluate the direct benefits of these strategies to overcome key implementation barriers.

The costs associated with *CYP2C19* genetic testing are also an important consideration. Recent cost-effectiveness analyses have estimated a per patient cost of $100 to 350, and the Centers for Medicare and Medicaid Services 2017 Clinical Laboratory Fee Schedule reports a reimbursement amount of $293 for *CYP2C19* testing.[33,34] These studies have collectively concluded that, from a third-party payer's perspective, *CYP2C19* genotype–guided antiplatelet therapy after PCI may be a cost-effective strategy over both a 1-year and lifetime horizon when compared with either universal clopidogrel or universal prasugrel or ticagrelor treatment without genotype testing.[33] The short-term cost-effectiveness of a genotype-guided strategy over the first 30 days after PCI has also been recently described.[34] However, these analyses have been limited by their use of clinical outcome data derived from retrospective genetic analyses of registries and clinical trials. Future studies are needed to evaluate the cost-effectiveness of implementing *CYP2C19* genotype–guided antiplatelet therapy from the health system perspective using clinical outcome and cost data derived from real-world clinical practice.

It is important to acknowledge several limitations with our study. First, data collection was completed retrospectively via EHR abstraction. Although retrospective data collection minimized influence on the practice under evaluation, we were unable to conclusively determine whether clopidogrel use in IM/PMs was a conscious clinical decision or failure to acknowledge the genotyping result. Second, genotype-guided therapy was not randomized. Thus, we cannot exclude the influence of bias

or attribute cause and effect to the observed associations between CYP2C19 phenotype, DAPT selection, and outcomes. To lessen the potential confounding effects related to differences across groups, covariate-adjusted and stratified analysis were conducted; however, residual confounding may remain and the magnitude of the observed association between clopidogrel use in IM/PMs and risk of MACCE should be interpreted with caution. Third, the analysis is based on medications prescribed, but there is no available data on adherence. Last, the data presented reflects the experience with genotype-guided antiplatelet therapy at a single academic medical center, and the results may not be generalizable to other settings and populations. Future studies in larger and more diverse populations are warranted.

CONCLUSIONS

The adverse cardiovascular outcomes associated with clopidogrel use in patients with a *CYP2C19* LOF allele suggest that the use of genotype-guided antiplatelet therapy in practice may significantly improve clinical outcomes. Given the increasing number of institutions that seek to clinically implement genotype-guided antiplatelet therapy,[23–25] our results offer insight into the feasibility, sustainability, and clinical impact of using a *CYP2C19* genotyping strategy to optimize $P2Y_{12}$ inhibitor selection in PCI patients.

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Clinical Outcomes and Sustainability of Using *CYP2C19* Genotype–Guided Antiplatelet Therapy After Percutaneous Coronary Intervention

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SUPPLEMENTAL MATERIAL

Supplemental Methods

***CYP2C19* Genotype Testing.** Genotyping for the *CYP2C19*2*, **3*, and **17* variant alleles was performed clinically on-site by the College of American Pathologists/Clinical Laboratory Improvement Amendment (CAP/CLIA)-certified UNC McLendon Molecular Genetics Laboratory using polymerase chain reaction-based TaqMan® allelic discrimination assays (Life Technologies, Foster City, CA), as described.[1] Genotype results were reviewed by a pathologist and uploaded into the 'Molecular Genetics' laboratory section of the EHR (typically within 24 to 48 hours). The genotype result is accompanied by an interpretation as well as a brief description of clopidogrel clinical pharmacology and relevance of the **2*, **3*, and **17* alleles. No active or passive alerts are available in the EHR to inform clinicians about the genotype test result when reported or a $P2Y_{12}$ inhibitor is ordered.

Data Abstraction and Study Endpoints. Data manually abstracted from the electronic health record (EHR) included demographics, medical history, indication for PCI, location of stent placement, *CYP2C19* genotype result and date, and medication use. $P2Y_{12}$ inhibitor use was collected at several time-points, including on admission for the index percutaneous coronary intervention (PCI), in the catheterization laboratory (initial loading agent), at discharge, and at inpatient and outpatient follow-up encounters for up to 12 months following the PCI. Due to the low frequency of ticagrelor use, $P2Y_{12}$ inhibitor was classified as a dichotomous variable (clopidogrel or prasugrel/ticagrelor) for statistical analysis. $P2Y_{12}$ inhibitor maintenance therapy (primary endpoint) was defined as the agent prescribed over the course of follow-up after any changes in therapy. A change in $P2Y_{12}$ inhibitor therapy (secondary endpoint) occurred when the initial agent administered at the time of PCI (loading dose) and the maintenance therapy agent were different.

Clopidogrel metabolizer phenotypes were assigned as recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC): ultrarapid (UM; **17/*17*), rapid (RM; **1/*17*), normal (NM; **1/*1*), intermediate (IM; **1/*2*, **1/*3*, **2/*17*, or **3/*17*), or poor metabolizer (PM; **2/*2*, **2/*3*, or **3/*3*).[2] CYP2C19 phenotype was collapsed into a dichotomous variable (IM/PM or UM/RM/NM) for statistical analysis. Elevated bleeding risk

was a composite variable defined as the presence of one or more of the following risk factors for bleeding on antiplatelet therapy: age ≥75 years; weight <60 kg; previous transient ischemic attack (TIA) or cerebrovascular accident (CVA); previous significant bleeding event; current end stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

Ischemic cardiovascular and bleeding events were abstracted from the EHR for up to 12 months following the index PCI. Major adverse cardiovascular or cerebrovascular events (MACCE; primary clinical outcome), defined as death, myocardial infarction, stent thrombosis, admission for acute coronary syndrome (ACS)/unstable angina, ischemic CVA, or (TIA), were identified using physician-reported diagnoses abstracted from the cardiac catheterization laboratory report, discharge summary notes, or outpatient clinic notes of the EHR. Clinically significant bleeding (secondary clinical outcome) was defined as a bleeding event documented in the EHR that (a) led to an intervention, hospitalization, prolonged hospitalized or death, and (b) was classified as a 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 resulting in hemodynamic compromise requiring treatment).[3] All MACCE and bleeding events were verified by an interventional cardiologist. $P2Y_{12}$ inhibitor therapy and dose at the time of event was recorded. It was determined that 194 of the 1193 study participants (16.3%) did not present to the UNC health care system for either follow-up clinic visits or emergent care after discharge from the index PCI admission within the 12 month follow-up period. These patients were considered lost to follow-up.

Statistical Analysis. In order to identify the factors that influenced *CYP2C19* genotype testing and $P2Y_{12}$ inhibitor selection, key covariates (including demographic factors, clinical factors and CYP2C19 phenotype status), were compared across these endpoints using a Student's t-test, chi-square test, or Fisher's exact test. Associations were evaluated by logistic regression using univariate and multivariable models. Multivariable models were created using stepwise selection with the criterion of $P<0.10$ to enter the model and $P<0.05$ to stay in the model. In order to determine whether the *CYP2C19* test result modified the association between clinical factors and $P2Y_{12}$ inhibitor selection, the interaction between CYP2C19 phenotype (IM/PM or UM/RM/NM) and clinical factor (present/absent) status was evaluated, and stratified analyses were completed.

In the clinical outcome analysis, the time to occurrence of the primary (MACCE) and secondary (clinically significant bleeding) clinical outcomes or last follow-up within 12 months following the index PCI (baseline) were calculated in each patient with available follow-up (n=999; 83.7% of the overall study population). Patients that did not experience an event were censored at the time of the last documented encounter in the EHR in which treatment with a $P2Y_{12}$ inhibitor was documented. Event rates were calculated as the number of events per 100 patient-years of follow-up (follow-up was calculated as the cumulative sum of time from index PCI to the occurrence of event or censoring). The relationship between CYP2C19 status, prescribed $P2Y_{12}$ inhibitor therapy, and the time to occurrence of the primary and secondary clinical outcomes were evaluated using Cox proportional hazards regression in the 751 patients that underwent *CYP2C19* genetic testing and had follow-up available after the index PCI admission. Since the clinical algorithm targets high-risk PCI patients for *CYP2C19* genotyping, the lower risk strata of 248 patients that did not undergo genetic testing were not included in the primary outcome analysis. Event frequencies in this stratum were calculated for descriptive purposes. Kaplan-Meier curves were generated (GraphPad Prism 6.0, GraphPad Software, La Jolla, CA) to compare the cumulative risk of an event across four CYP2C19 phenotype and antiplatelet therapy strata: IM/PMs prescribed clopidogrel, IM/PMs prescribed alternative therapy, UM/RM/NMs prescribed clopidogrel, and IM/PMs prescribed alternative therapy.

References

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Supplemental Table 1. Predictors of obtaining a *CYP2C19* genotype during the index percutaneous coronary intervention (PCI).

Variable	No Genotype [REFERENCE]	Genotype at index PCI	Genotype * at prior PCI	Odds ratio (OR) † (95% CI)	*p*-value	Adjusted OR ‡ (95% CI)	*p*-value
N	325 (27.2%)	794 (66.6%)	74 (6.2%)				
Age	65.7 ± 12.1	62.5 ± 11.8	62.1 ± 11.9	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Male	220 (67.7%)	535 (67.4%)	52 (70.3%)	0.98 (0.75-1.30)	0.919	-	
African American	77 (23.7%)	157 (19.8%)	13 (17.6%)	0.79 (0.58-1.09)	0.147	-	
Obese	136 (41.8%)	338 (42.6%)	31 (41.9%)	1.03 (0.79-1.34)	0.824	-	
Current smoker	74 (22.8%)	238 (30.0%)	22 (29.7%)	1.45 (1.08-1.97)	0.014	-	
Hypertension	298 (91.7%)	633 (79.7%)	66 (89.2%)	0.36 (0.23-0.54)	<0.001	0.46 (0.29-0.72)	<0.001
Diabetes	155 (47.7%)	303 (38.2%)	38 (51.4%)	0.68 (0.52-0.88)	0.003	-	
Peripheral vascular disease	52 (16.0%)	84 (10.6%)	11 (14.9%)	0.62 (0.43-0.91)	0.014	-	
Atrial fibrillation	35 (10.8%)	68 (8.6%)	6 (8.1%)	0.78 (0.51-1.20)	0.253	-	
Heart failure	55 (16.9%)	117 (14.7%)	19 (25.7%)	0.85 (0.60-1.21)	0.361	-	
Previous myocardial infarction	91 (28.0%)	192 (24.2%)	42 (56.8%)	0.82 (0.61-1.10)	0.185	-	
Elevated bleeding risk §	149 (45.8%)	297 (37.4%)	32 (43.2%)	0.71 (0.54-0.92)	0.009	-	
Previous coronary artery stent	148 (45.5%)	253 (31.9%)	65 (87.8%)	0.56 (0.43-0.73)	<0.001	-	
$P2Y_{12}$ inhibitor use ON ADMISSION	96 (29.5%)	160 (20.2%)	54 (73.0%)	0.60 (0.45-0.81)	<0.001	0.69 (0.50-0.94)	0.019
Index PCI							
Acute coronary syndrome	124 (38.2%)	491 (61.8%)	27 (36.5%)	2.63 (2.02-3.43)	<0.001	2.56 (1.94-3.38)	<0.001
LAD artery stent	116 (35.7%)	355 (44.7%)	26 (35.1%)	1.46 (1.12-1.91)	0.005	1.60 (1.21-2.13)	0.001
Left main artery stent	3 (0.9%)	25 (3.1%)	2 (2.7%)	3.49 (1.21-14.7)	0.034	4.72 (1.57-20.5)	0.004
Drug-eluting stent	279 (85.8%)	659 (83.0%)	66 (89.2%)	0.80 (0.55-1.15)	0.235	-	

* The 74 patients with a *CYP2C19* genotype obtained at a prior encounter, and already available in their electronic health record at the time of the index PCI are described for reference.

† Comparison of Genotype at index PCI versus No Genotype.

‡ The adjusted model was created using stepwise selection with the criterion of P<0.10 to enter the model and P<0.05 to stay in the model.

§ Elevated bleeding risk is a composite variable defined as one or more of the following: age ≥75 years; weight <60 kg; previous TIA or stroke event; previous significant bleeding event; current end stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

Supplemental Table 2. Predictors of $P2Y_{12}$ inhibitor loading therapy during the index percutaneous coronary intervention (PCI).

Variable	Clopidogrel [REFERENCE]	Prasugrel/ Ticagrelor	Odds ratio (OR) (95% CI)	*p*-value	Adjusted OR * (95% CI)	*p*-value
N	859 (72.6%)	324 (27.4%)				
Age	65.5 ± 12.0	57.6 ± 9.8	0.94 (0.93-0.95)	<0.001	0.95 (0.94-0.97)	<0.001
Male	551 (64.1%)	247 (76.2%)	1.79 (1.35-2.41)	<0.001	-	
African American	188 (21.9%)	59 (18.2%)	0.79 (0.57-1.09)	0.161	-	
Obese	354 (41.2%)	146 (45.1%)	1.17 (0.90-1.51)	0.233	-	
Current smoker	223 (26.0%)	106 (32.7%)	1.39 (1.05-1.83)	0.022	-	
Hypertension	746 (86.8%)	244 (75.3%)	0.46 (0.34-0.64)	<0.001	-	
Diabetes	390 (45.4%)	101 (31.2%)	0.54 (0.41-0.71)	<0.001	-	
Peripheral vascular disease	125 (14.6%)	21 (6.5%)	0.41 (0.25-0.64)	<0.001	-	
Atrial fibrillation	93 (10.8%)	13 (4.0%)	0.34 (0.19-0.62)	<0.001	-	
Heart failure	152 (17.7%)	37 (11.4%)	0.60 (0.40-0.87)	0.007	-	
Previous myocardial infarction	257 (29.9%)	68 (21.0%)	0.62 (0.46-0.84)	0.002	-	
Elevated bleeding risk †	413 (48.1%)	61 (18.8%)	0.25 (0.18-0.34)	<0.001	0.32 (0.22-0.46)	<0.001
Previous coronary artery stent	378 (44.0%)	86 (26.5%)	0.46 (0.35-0.61)	<0.001	-	
Clopidogrel use ON ADMISSION	254 (29.6%)	12 (3.7%)	0.09 (0.05-0.16)	<0.001	0.10 (0.05-0.18)	<0.001
Prasugrel use ON ADMISSION	6 (0.7%)	38 (11.7%)	18.9 (8.50-50.1)	<0.001	22.6 (9.18-65.4)	<0.001
Index PCI						
Acute coronary syndrome	407 (47.4%)	229 (70.7%)	2.68 (2.04-3.52)	<0.001	4.04 (2.90-5.69)	<0.001
LAD artery stent	323 (37.6%)	168 (51.9%)	1.79 (1.38-2.31)	<0.001	2.21 (1.62-3.05)	<0.001
Left main artery stent	20 (2.3%)	10 (3.1%)	1.34 (0.59-2.82)	0.468	-	
Drug-eluting stent	715 (83.2%)	283 (87.3%)	1.39 (0.97-2.04)	0.077	-	
Prior *CYP2C19* genotype available ‡	58 (6.8%)	16 (4.9%)	0.72 (0.39-1.24)	0.240	-	

* The adjusted model was created using stepwise selection with the criterion of P<0.10 to enter the model and P<0.05 to stay in the model.

† Elevated bleeding risk is a composite variable defined as one or more of the following: age ≥75 years; weight <60 kg; previous TIA or stroke event; previous significant bleeding event; current end stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

‡ In the 74 patients with a previous *CYP2C19* genotype test available in their medical record at the time of $P2Y_{12}$ inhibitor loading therapy, 62.5% (10 of 16) of those initiated on prasugrel and 13.8% (8 of 58) of those initiated on clopidogrel were CYP2C19 IMs or PMs (OR 10.4, 95% CI 3.08-39.1, P<0.001).

Supplemental Table 3. Predictors of $P2Y_{12}$ inhibitor maintenance therapy following the index PCI.

Variable	Clopidogrel [REFERENCE]	Prasugrel/ Ticagrelor	Odds ratio (OR) (95% CI)	*p*-value	Adjusted OR * (95% CI)	*p*-value
N	828 (69.4%)	365 (30.6%)				
Age	65.0±12.1	59.6±10.8	0.96 (0.95-0.97)	<0.001	0.98 (0.96-0.99)	0.007
Male	530 (64.0%)	277 (75.9%)	1.77 (1.34-2.35)	<0.001	-	
African American	186 (22.5%)	61 (16.7%)	0.69 (0.50-0.95)	0.022	-	
Obese	336 (40.6%)	169 (46.3%)	1.26 (0.98-1.62)	0.066	-	
Current smoker	225 (27.2%)	109 (29.9%)	1.14 (0.87-1.50)	0.342	-	
Hypertension	725 (87.6%)	272 (74.5%)	0.42 (0.30-0.57)	<0.001	0.50 (0.33-0.76)	0.001
Diabetes	376 (45.4%)	120 (32.9%)	0.59 (0.46-0.76)	<0.001	-	
Peripheral vascular disease	115 (13.9%)	32 (8.8%)	0.60 (0.39-0.89)	0.011	-	
Atrial fibrillation	91 (11.0%)	18 (4.9%)	0.42 (0.24-0.69)	<0.001	-	
Heart failure	146 (17.6%)	45 (12.3%)	0.66 (0.45-0.93)	0.019	-	
Previous myocardial infarction	234 (28.3%)	91 (24.9%)	0.84 (0.63-1.11)	0.232	-	
Elevated bleeding risk †	385 (46.5%)	93 (25.5%)	0.39 (0.30-0.51)	<0.001	0.36 (0.23-0.54)	<0.001
Previous coronary artery stent	355 (42.9%)	111 (30.4%)	0.58 (0.45-0.76)	<0.001	-	
Clopidogrel use ON ADMISSION	231 (27.9%)	35 (9.6%)	0.27 (0.18-0.40)	<0.001	0.29 (0.17-0.47)	<0.001
Prasugrel/Ticagrelor use ON ADMISSION	6 (0.7%)	38 (10.4%)	15.9 (7.18-42.2)	<0.001	18.5 (5.75-84.4)	<0.001
Index PCI						
Acute coronary syndrome	399 (48.2%)	243 (66.6%)	2.14 (1.66-2.77)	<0.001	2.80 (1.93-4.12)	<0.001
LAD artery stent	318 (38.4%)	179 (49.0%)	1.54 (1.20-1.98)	0.001	1.64 (1.16-2.34)	0.005
Left main artery stent	22 (2.7%)	8 (2.2%)	0.82 (0.34-1.79)	0.985	-	
Drug-eluting stent	689 (83.2%)	315 (86.3%)	1.27 (0.90-1.82)	0.173	-	
CYP2C19 genotype available	539 (65.1%)	329 (90.1%)	4.90 (3.41-7.22)	<0.001	-	
CYP2C19 IM or PM phenotype	77 (9.3%)	186 (51.0%)	7.80 (5.66-10.9)	<0.001	13.1 (8.84-19.7)	<0.001

* The adjusted model was created using stepwise selection with the criterion of P<0.10 to enter the model and P<0.05 to stay in the model.

† Elevated bleeding risk is a composite variable defined as one or more of the following: age ≥75 years; weight <60 kg; previous TIA or stroke event; previous significant bleeding event; current end stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

Supplemental Table 4. Predictors of $P2Y_{12}$ inhibitor maintenance therapy by CYP2C19 phenotype status (N=868).

Variable	Clopidogrel [REFERENCE] N=539	Prasugrel/ Ticagrelor N=329	Odds ratio (OR) (95% CI)	*p*-value	Interaction *p*-value (CYP2C19 phenotype * clinical factor)
CYP2C19 Phenotype					
IM/PM	77 (14.3%) *(29.3%)*	186 (56.5%) *(70.7%)*	7.80 (5.66-10.9)	<0.001	
UM/RM/NM	462 (85.7%) *(76.4%)*	143 (43.5%) *(23.6%)*			
ACS indication for PCI	292 (54.2%)	226 (68.7%)	1.86 (1.39-2.48)	<0.001	0.897
IM/PM	34 (44.2%) *(22.2%)*	119 (64.0%) *(77.8%)*	2.25 (1.31-3.88)	0.003	
UM/RM/NM	258 (55.8%) *(70.7%)*	107 (74.8%) *(29.3%)*	2.35 (1.56-3.61)	<0.001	
Elevated bleeding risk *	246 (45.6%)	83 (25.2%)	0.40 (0.30-0.54)	<0.001	0.023
IM/PM	40 (51.9%) *(38.8%)*	63 (33.9%) *(61.2%)*	0.47 (0.27-0.81)	0.007	
UM/RM/NM	206 (44.6%) *(91.2%)*	20 (14.0%) *(8.8%)*	0.20 (0.12-0.33)	<0.001	
LAD artery stent	220 (40.8%)	161 (48.9%)	1.39 (1.05-1.83)	0.020	0.009
IM/PM	36 (46.8%) *(31.3%)*	79 (42.5%) *(68.7%)*	0.84 (0.49-1.44)	0.525	
UM/RM/NM	184 (39.8%) *(69.2%)*	82 (57.3%) *(30.8%)*	2.03 (1.39-2.98)	<0.001	
Clopidogrel use ON ADMISSION	152 (28.2%)	34 (10.3%)	0.29 (0.19-0.43)	<0.001	0.720
IM/PM	29 (37.7%) *(54.7%)*	24 (12.9%) *(45.3%)*	0.25 (0.13-0.46)	<0.001	
UM/RM/NM	123 (26.6%) *(92.5%)*	10 (7.0%) *(7.5%)*	0.21 (0.10-0.39)	<0.001	
Prasugrel use ON ADMISSION	3 (0.6%)	25 (7.6%)	14.7 (5.10-62.1)	<0.001	0.386
IM/PM	0 (0.0%) *(0.0%)*	13 (7.0%) *(100.0%)*	-	-	
UM/RM/NM	3 (0.6%) *(20.0%)*	12 (8.4%) *(80.0%)*	14.0 (4.38-62.2)	<0.001	
Hypertension	460 (85.3%)	239 (72.6%)	0.46 (0.32-0.64)	<0.001	0.162
IM/PM	71 (92.2%) *(34.1%)*	137 (73.7%) *(65.9%)*	0.24 (0.09-0.54)	<0.001	
UM/RM/NM	389 (84.2%) *(79.2%)*	102 (71.3%) *(20.8%)*	0.47 (0.30-0.73)	<0.001	

Analysis conducted in N=868 with *CYP2C19* genotype available. Data in each cell presented as N (column %) *(row%)*.

* Elevated bleeding risk is a composite variable defined as one or more of the following: age ≥75 years; weight <60 kg; previous TIA or stroke event; previous significant bleeding event; current end stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

Supplemental Table 4 (con't). Predictors of $P2Y_{12}$ inhibitor maintenance therapy by CYP2C19 phenotype status (N=868).

Variable	Clopidogrel [REFERENCE] N=539	Prasugrel/ Ticagrelor N=329	Odds ratio (OR) (95% CI)	*p*-value	Interaction *p*-value (CYP2C19 phenotype * clinical factor)
Elevated bleeding risk (individual components) *					
Age ≥75 years	110 (20.4%)	30 (9.1%)	0.39 (0.25-0.59)	<0.001	0.003
IM/PM	16 (20.8%) *(38.1%)*	26 (14.0%) *(61.9%)*	0.62 (0.31-1.23)	0.179	
UM/RM/NM	94 (20.3%) *(95.9%)*	4 (2.8 %) *(4.1%)*	0.11 (0.03-0.28)	<0.001	
Weight < 60 kg	53 (9.8%)	10 (3.0%)	0.29 (0.14-0.55)	<0.001	0.053
IM/PM	5 (6.5%) *(38.5%)*	8 (4.3%) *(61.5%)*	0.65 (0.21-2.20)	0.466	
UM/RM/NM	48 (10.4%) *(96.0%)*	2 (1.4%) *(4.0%)*	0.12 (0.02-0.40)	<0.001	
Previous TIA/stroke	54 (10.0%)	11 (3.3%)	0.31 (0.15-0.58)	<0.001	0.954
IM/PM	10 (13.0%) *(58.8%)*	7 (3.8%) *(41.2%)*	0.26 (0.09-0.71)	0.009	
UM/RM/NM	44 (9.5%) *(91.7%)*	4 (2.8%) *(8.3%)*	0.27 (0.09-0.69)	0.004	
Current ESRD	29 (5.4%)	6 (1.8%)	0.33 (0.12-0.74)	0.006	0.210
IM/PM	4 (5.2%) *(44.4%)*	5 (2.7%) *(55.6%)*	0.50 (0.13-2.09)	0.327	
UM/RM/NM	25 (5.4%) *(96.2%)*	1 (0.7%) *(3.9%)*	0.15 (0.01-0.59)	0.004	
Prior significant bleeding event	55 (10.2%)	31 (9.4%)	0.92 (0.57-1.45)	0.708	0.194
IM/PM	10 (13.0%) *(29.4%)*	24 (12.9%) *(70.6%)*	0.99 (0.46-2.28)	0.985	
UM/RM/NM	45 (9.7%) *(86.5%)*	7 (4.9%) *(13.5%)*	0.48 (0.19-1.02)	0.056	
Anticoagulant at discharge	43 (8.0%)	16 (4.9%)	0.59 (0.32-1.04)	0.071	0.707
IM/PM	9 (11.7%) *(47.4%)*	10 (5.4%) *(52.6%)*	0.43 (0.16-1.12)	0.084	
UM/RM/NM	34 (7.4%) *(85.0%)*	6 (4.2%) *(15.0%)*	0.55 (0.20-1.25)	0.163	

Analysis conducted in N=868 with *CYP2C19* genotype available. Data in each cell presented as N (column %) *(row%)*.

* Elevated bleeding risk is a composite variable defined as one or more of the following: age ≥75 years; weight <60 kg; previous transient ischemic attack (TIA) or stroke event; previous significant bleeding event; current end stage renal disease (ESRD) requiring dialysis; or, anticoagulant prescribed at discharge.

Supplemental Table 5. Cardiovascular and bleeding event incidence by CYP2C19 phenotype status and $P2Y_{12}$ inhibitor in the strata of patients with an acute coronary syndrome indication for their index PCI procedure (n=459).

Clinical outcome by CYP2C19 phenotype – selected $P2Y_{12}$ inhibitor	Event No. (%)*	Event rate (per 100 pt-yrs) †	Log-rank P‡ (unadjusted)	Log-rank P‡ (adjusted)	Adjusted HR (95% CI)	P-value
MACCE						
IM/PM – Alternative (n=105)	7 (6.7%)	9.8			Reference	
IM/PM – Clopidogrel (n=31) §	14 (45.2%)	101.7			10.0 (3.97-27.7)	<0.001
UM/RM/NM – Alternative (n=88)	10 (11.4%)	17.7			1.99 (0.74-5.65)	0.172
UM/RM/NM – Clopidogrel (n=235)	40 (17.0%)	27.4	P<0.001	P<0.001	2.73 (1.27-6.79)	0.009
Clinically significant bleeding events						
IM/PM – Alternative (n=106)	5 (4.7%)	7.1			Reference	
IM/PM – Clopidogrel (n=30) §	1 (3.3%)	7.4			0.91 (0.05-5.87)	0.929
UM/RM/NM – Alternative (n=88)	3 (3.4%)	5.5			1.04 (0.21-4.45)	0.958
UM/RM/NM – Clopidogrel (n=235)	14 (6.0%)	9.8	P=0.804	P=0.918	1.37 (0.50-4.38)	0.557

* The number (percentage) in each group that experienced an event during follow-up.

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

‡ Comparison of outcomes across the four CYP2C19 phenotype and antiplatelet therapy strata.

§ One patient with a CYP2C19 IM phenotype receiving treatment with prasugrel experienced an early bleeding event, and was subsequently switched to clopidogrel for the remainder of follow-up.

Supplemental Table 6. Frequency of *CYP2C19* genotype testing and $P2Y_{12}$ inhibitor maintenance therapy selection over time.

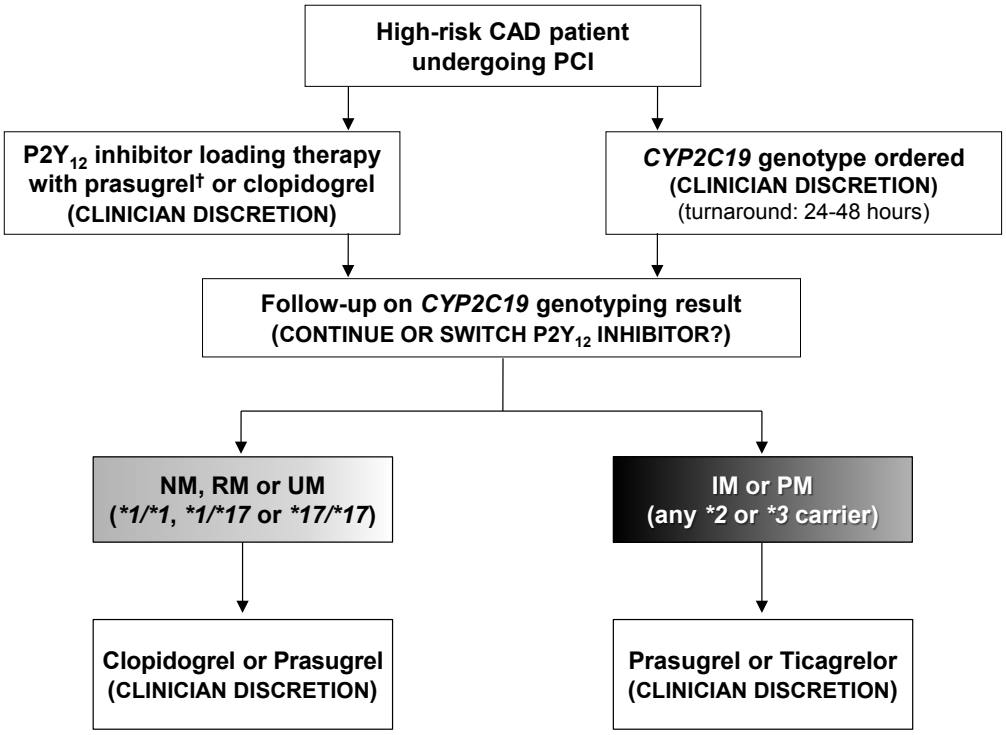
Variable	July-Dec 2012 *N=278*	Jan-June 2013 *N=311*	July-Dec 2013 *N=307*	Jan-June 2014 *N=297*	*p*-value
CYP2C19 genotype obtained	245 (88.1%)	191 (61.4%)	200 (65.1%)	232 (78.1%)	<0.001
Prior to index PCI admission *	21 (7.6%)	18 (5.8%)	25 (8.1%)	10 (3.4%)	0.055
During index PCI admission	224 (80.6%)	173 (55.6%)	175 (57.0%)	222 (74.7%)	<0.001
Genotype test result returned within 1-day of the index PCI	177 (79.0%)	128 (74.0%)	119 (68.0%)	174 (78.4%)	0.051
$P2Y_{12}$ inhibitor maintenance therapy (all patients)					
Prasugrel/ticagrelor selection	101 (36.3%)	81 (26.0%)	79 (25.7%)	104 (35.0%)	0.004
$P2Y_{12}$ inhibitor maintenance therapy (by CYP2C19 status)					
No *CYP2C19* genotype	*N=33*	*N=120*	*N=107*	*N=65*	
Prasugrel/ticagrelor selection	5 (15.2%)	11 (9.2%)	7 (6.5%)	13 (20.0%)	0.048
CYP2C19 IM/PM	*N=71*	*N=55*	*N=65*	*N=72*	
Prasugrel/ticagrelor selection	59 (83.1%)	43 (78.2%)	35 (53.8%)	49 (68.1%)	0.001
Clopidogrel → prasugrel/ticagrelor †	31 (43.7%)	24 (43.6%)	15 (23.1%)	20 (27.8%)	0.019
CYP2C19 UM/RM/EM	*N=174*	*N=136*	*N=135*	*N=160*	
Clopidogrel selection	137 (78.7%)	109 (80.1%)	98 (72.6%)	118 (73.8%)	0.348
Prasugrel/ticagrelor → clopidogrel ‡	16 (9.2%)	17 (12.5%)	12 (8.9%)	12 (7.5%)	0.536

* Patients with a *CYP2C19* genotype obtained at a prior encounter, and already available in their health record at the time of the index PCI. These prior genotypes occurred a median (IQR) of 594 (400-925) days prior to the index PCI.

† Change in therapy from clopidogrel (initial) to prasugrel or ticagrelor (maintenance).

‡ Change in therapy from prasugrel or ticagrelor (initial) to clopidogrel (maintenance).

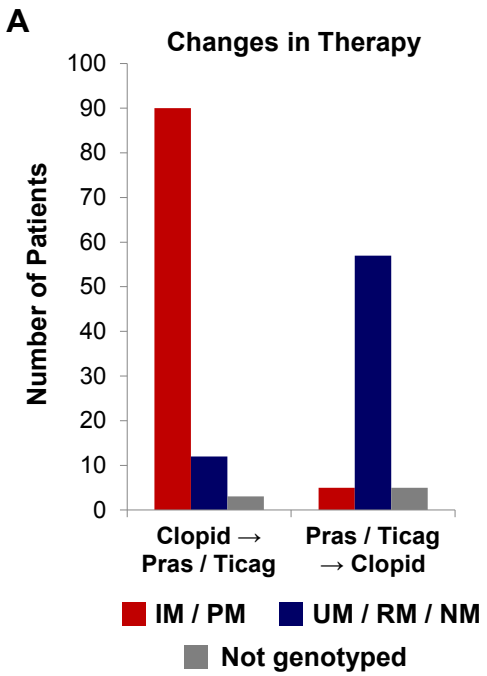
Supplemental Figure 1.



†Initiation of prasugrel is recommended in high-risk patients, excluding those:
(a) with a contraindication to prasugrel (previous TIA or CVA, age ≥75, weight <60 kg), or
(b) stable patients receiving chronic therapy with clopidogrel

Supplemental Figure 1. Algorithm for *CYP2C19* genotype-guided selection of antiplatelet therapy following PCI in high-risk patients. The algorithm implemented at our institution in July 2012 is presented. High-risk is defined as a PCI for either an acute coronary syndrome or stable CAD with high-risk anatomic findings (PCI in the left main, proximal left anterior descending, proximal left circumflex [if the artery was dominant], proximal right coronary artery [if the artery was dominant], or saphenous vein graft). After risk stratification, the interventional cardiologist administers a loading dose of either prasugrel or clopidogrel based on clinical factors and decides whether to order the *CYP2C19* genotype test, which is performed at an on-site molecular genetics laboratory during the index PCI admission (cost approximately $200). Ticagrelor can be used in high-risk patients at the prescriber's discretion. Genotype results are reviewed by a pathologist and uploaded into the laboratory section of the electronic medical record within 24-48 hours (median turnaround 1 day). Subsequently, a clinical pharmacist follows-up with the physician with a recommendation to either continue or change the current $P2Y_{12}$ inhibitor based on the genotype and patient-specific clinical factors. Alternative antiplatelet therapy, consisting of prasugrel or ticagrelor, is recommended for CYP2C19 IMs and PMs in the absence of contraindications; however, the decision is left to the discretion of the prescriber. Changes in therapy are communicated to the nursing staff and patient, and occur either prior to discharge or following discharge via phone follow-up. CAD, coronary artery disease; PM, poor metabolizer; IM, intermediate metabolizer; NM, normal metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer; TIA, transient ischemic attack; CVA, cerebrovascular accident.

Supplemental Figure 2.



Supplemental Figure 2. Changes in $P2Y_{12}$ inhibitor maintenance therapy by *CYP2C19* status. Overall, a change in $P2Y_{12}$ inhibitor therapy was observed in 174 (14.6%) patients in the study population, 164 (94.3%) of which occurred in those with an available *CYP2C19* genotype. The number of patients undergoing a change in $P2Y_{12}$ inhibitor therapy from clopidogrel to prasugrel/ticagrelor or from prasugrel/ticagrelor to clopidogrel is presented after stratification by CYP2C19 status (IM/PM: intermediate or poor metabolizers; UM/RM/NM: ultrarapid, rapid or normal metabolizers; Not genotyped). A change from clopidogrel to prasugrel/ticagrelor almost exclusively occurred in patients with the CYP2C19 IM or PM phenotype (90 of 105; 85.7%), whereas changes from prasugrel/ticagrelor to clopidogrel almost exclusively occurred in those without a *CYP2C19* LOF allele (57 of 67; 85.1%).