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Original Article

CYP2C19 genotype-directed P_2Y_{12} inhibitor antiplatelet therapy normalizes risk for major adverse cardiovascular events after percutaneous coronary intervention

Tomasz P. Stys [a], Maheedhar Gedela [a, d, *], Smitha N. Gowda [b], Valerie Bares [a], Lauren Fanta [c], Marian Petrasko [a], Catherine Hajek [b], Eric Larson [b], Adam T. Stys [a]

[a] Sanford Heart Hospital, Sanford Cardiovascular Institute, University of South Dakota Sanford School of Medicine, Sioux Falls, SD, USA
[b] Department of Internal Medicine, University of South Dakota Sanford School of Medicine, Sioux Falls, SD, USA
[c] Department of Internal Medicine, University of Wisconsin, Madison, WI, USA
[d] Mount Sinai Hospital and Icahn School of Medicine at Mount Sinai, NY, New York, USA

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ABSTRACT

Objective: To study the use of *CYP2C19* genotyping to guide $P2Y_{12}$ inhibitor selection to maximize efficacy, and attenuate risk in appropriate patients who underwent PCI for CAD.
Methods: We performed a retrospective analysis of 868 patients with CAD who received *CYP2C19* genotyping after PCI and changed $P2Y_{12}$ inhibitor based on the results. Patients were divided into two groups based on clopidogrel metabolizer status. Group I: Intermediate (IM) and poor metabolizers (PM). Group II: Ultra-rapid (UM), rapid (RM) and normal metabolizers (NM). Each group was then categorized to one of two treatment arms guided by *CYP2C19* genotype. *Category 1*: IM/PM started on clopidogrel, switched to ticagrelor or prasugrel; *2:*IM/PM started on ticagrelor/prasugrel, continued these medications; *3:* UM/RM/NM started on ticagrelor/prasugrel, switched to clopidogrel; *4:* UM/RM/NM started on clopidogrel, continued clopidogrel. Death due to cardiac causes, bleeding events, non-fatal MI, target vessel revascularization (TVR), and MACE in all four categories were considered at 1, 6 and 12 months.
Results: We did not observe significant difference between phenotypes for MACE at 1 ($p = 0.274$), 6 ($p = 0.387$), and 12 months ($p = 0.083$). Death due to cardiac causes, MI, and bleeding events were not significant at 1, 6, and 12 months. There was no significant difference in TVR at 6 ($p = 0.491$), and 12 months ($p = 0.423$) except at 1 month ($p = 0.012$).
Conclusion: CYP2C19 genotype-based intervention can be implemented effectively and reliably to guide selection of $P2Y_{12}$ inhibitor to optimize patient quality and safety when appropriate in post PCI patients.

1. Introduction

The combination of aspirin and a $P2Y_{12}$ inhibitor is the cornerstone of treatment following percutaneous coronary intervention (PCI) for coronary artery disease (CAD). Due to increased efficacy, ticagrelor and prasugrel are the $P2Y_{12}$ inhibitors of choice over clopidogrel in acute coronary syndrome (ACS).[1–4] However, the use of $P2Y_{12}$ inhibitors come at the price of increased bleeding events, especially in the setting of concomitant oral anticoagulation (OAC). The current guidelines do not support routine genotyping to tailor the $P2Y_{12}$ inhibitor. However, it may be considered in select patients with recurrent major adverse cardiovascular events (MACE) if it may alter the treatment decision.[2,5,6]

Antiplatelet effects of clopidogrel is not consistent between individuals. The incidence of clopidogrel resistance and variable response in patients undergoing PCI is 5–44%.[7,8] *CYP2C19* contributes significantly to the biotransformation of clopidogrel to its pharmacologically active metabolite. The *2 allele of *CYP2C19* is a diminished function allele causing poor platelet responsiveness to clopidogrel.[9–11] Patients homozygous or heterozygous for *CYP2C19*2* genotype who undergo PCI have increased risk for MACE.[12–14] The US Food and Drug Administration (FDA) issued a black box warning for clopidogrel alerting clinicians to consider

* Corresponding author. Cardiovascular Disease Fellow, Sanford Heart Hospital, University of South Dakota Sanford School of Medicine, 1510 Lexington Avenue, Apt 12U, New York, NY, 10029, USA.
E-mail address: maheedhargedela@gmail.com (M. Gedela).

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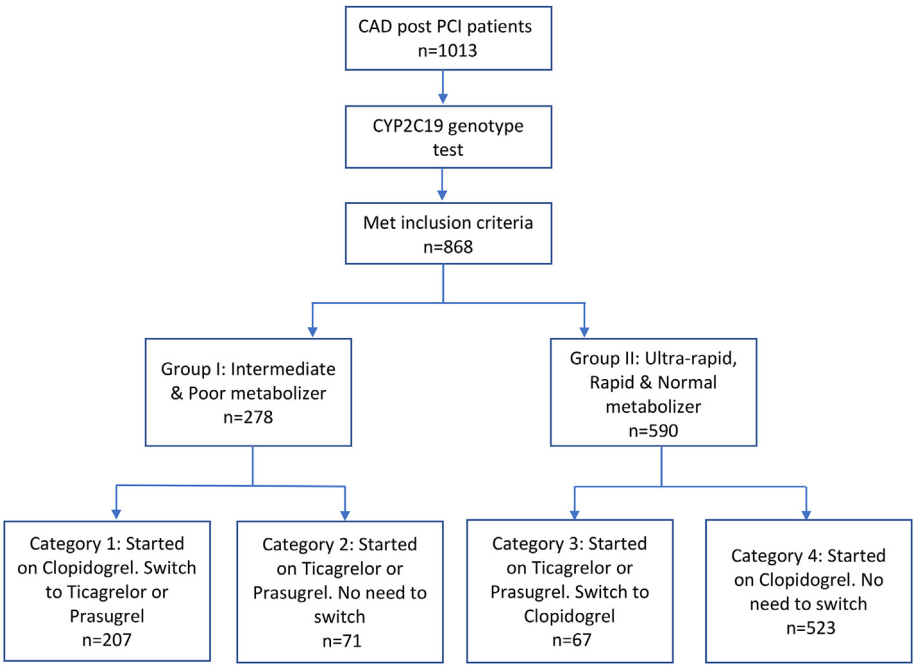

Fig. 1. Study protocol. CAD: Coronary artery disease. PCI: Percutaneous coronary intervention.

dose adjustment or alternative $P2Y_{12}$ inhibitor. Interestingly, this recommendation only included for poor metabolizer variants of *CYP2C19*.[15] However, the risk for stent thrombosis is three-fold higher and an approximately 50% increase in MACE in carriers (including intermediate metabolizers with a single loss of function (LOF) allele).[16] This finding was subsequently replicated in a practice-based cohort.[17] Further, that same group (Sanford Cardiology and Genetics) demonstrated that changing the drug from clopidogrel to ticagrelor or prasugrel normalized risk for recurrent cardiovascular events in intermediate metabolizers.[17] Current Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend that the medication be changed from clopidogrel to ticagrelor or prasugrel for intermediate as well as poor metabolizers in patients with ACS undergoing PCI.[18] We aimed to investigate the clinical outcomes when $P2Y_{12}$ inhibitor was optimized based on *CYP2C19* genotype in patients undergoing PCI for both stable ischemic heart disease (SIHD) and ACS.

2. Materials and methods

2.1. Study population and design

We conducted a retrospective study at the Sanford University Medical Center, Sioux Falls, SD, USA. We evaluated 1013 patients

Table 1
Study patients' distribution across all categories. PCI: Percutaneous coronary intervention; NC: Not categorizable.

CYP2C19 metabolizer	On Clopidogrel pre-PCI	On Clopidogrel post-PCI	Category per study protocol		Not falling into any category	
				no. of patients		no. of patients
Poor	No	No	2	6		
	No	Yes			NC	0
	Yes	No	1	19		
	Yes	Yes			NC	4
Intermediate	No	No	2	65		
	No	Yes			NC	6
	Yes	No	1	188		
	Yes	Yes			NC	6
Normal	No	No			NC	57
	No	Yes	3	44		
	Yes	No			NC	13
	Yes	Yes	4	283		
Rapid	No	No			NC	38
	No	Yes	3	18		
	Yes	No			NC	12
	Yes	Yes	4	201		
Ultra-rapid	No	No			NC	8
	No	Yes	3	5		
	Yes	No			NC	1
	Yes	Yes	4	39		
				N = 868		N = 145

Table 2
Baseline demographic, clinical and procedure characteristics.

Clinical variable	Category 1	Category 2	Category 3	Category 4	*p*-value
Age in years (mean (SD))	70.07 (12.49)	62.07 (12.20)	68.97 (11.12)	69.85 (11.29)	<0.001
Male (%)	138 (66.7)	49 (69.0)	43 (64.2)	345 (66.0)	0.939
Race					0.155
Caucasian	194 (93.7)	65 (91.5)	60 (89.6)	490 (93.7)	
African American	0 (0.0)	1 (1.4)	0 (0.0)	5 (1.0)	
American Indian	8 (3.9)	3 (4.2)	6 (9.0)	24 (4.6)	
Asian	2 (1.0)	2 (2.8)	0 (0.0)	1 (0.2)	
Declined	3 (1.4)	0 (0.0)	1 (1.5)	3 (0.6)	
Hypertension (%)	170 (82.1)	46 (64.8)	56 (83.6)	448 (85.7)	<0.001
Diabetes Mellitus (%)	77 (37.2)	25 (35.2)	20 (29.9)	200 (38.2)	0.591
Dyslipidemia (%)	167 (80.7)	46 (64.8)	51 (76.1)	419 (80.1)	0.023
Tobacco use (%)	124 (59.9)	50 (70.4)	36 (53.7)	330 (63.1)	0.193
Peripheral vascular disease (%)	44 (21.4)	11 (15.5)	6 (9.0)	132 (25.3)	0.009
Family history of heart disease (%)	126 (61.2)	40 (56.3)	40 (59.7)	352 (67.4)	0.127
Concomitant oral anticoagulant use (%)	36 (17.4)	4 (5.6)	4 (6.0)	79 (15.1)	0.018
Number of stents (mean (SD))	1.59 (0.91)	1.60 (0.81)	1.50 (0.79)	1.58 (0.87)	0.888
Diameter in mm (mean (SD))	2.97 (0.48)	2.96 (0.52)	3.13 (0.49)	2.99 (0.50)	0.129
Length in mm (mean (SD))	21.80 (8.37)	22.59 (8.28)	20.11 (7.12)	21.37 (8.39)	0.327
Vessel intervened n (%)					
Left anterior descending artery	93 (44.9)	27 (38.6)	28 (41.8)	210 (40.3)	0.67
Left circumflex artery	31 (15.0)	18 (25.7)	10 (14.9)	114 (21.9)	0.074
Right coronary artery	77 (37.2)	31 (44.3)	29 (43.3)	201 (38.6)	0.647
Left main coronary artery	7 (3.4)	1 (1.4)	2 (3.0)	27 (5.2)	0.375
Ramus intermedius	3 (1.4)	1 (1.4)	1 (1.5)	7 (1.3)	0.999
Saphenous vein graft	18 (8.7)	1 (1.4)	3 (4.5)	32 (6.1)	0.153

who underwent PCI with a drug-eluting stent (DES) for ACS and SIHD and able to take aspirin and $P2Y_{12}$ inhibitor between November 2016 and December 2017. Informed consent was obtained from all patients enrolled. The study protocol was approved by our institutional review board. We applied a clinical algorithm (Fig. 1) adjusting $P2Y_{12}$ inhibitor selection based upon *CYP2C19* genotype derived from the CPIC guidelines.[18] Additionally we included patients with SIHD undergoing PCI, a group not specifically addressed in CPIC guideline.[18] We excluded 145 patients whose management did not align with the defined clinical algorithm, resulting in 868 patients available for the analysis (Table 1). Preceding or at the time of PCI all ACS patients, according to the category (see below), received a loading dose of $P2Y_{12}$ inhibitor followed by maintenance dosing. Clopidogrel patients were loaded with either 300 mg or 600 mg and maintained on 75 mg once daily. Ticagrelor patients were loaded with 180 mg and maintained on 90 mg twice daily. Prasugrel patients were loaded with 60 mg daily and maintained on either 5 or 10 mg daily. Maintenance dosing of all three $P2Y_{12}$ antiplatelet inhibitors was continued until *CYP2C19* genotype results dictated medication changes based on *CYP2C19* genotype. All patients with SIHD undergoing PCI were loaded with clopidogrel 600 mg followed by clopidogrel 75 mg once daily as maintenance therapy until the appropriate alternative $P2Y_{12}$ antiplatelet agent was started according to the *CYP2C19* genotype.

CYP2C19 genotyping was ordered as a part of post-PCI order set and screening for *CYP2C19* alleles *2, *3, *4, *5, *6, *8, *12 and *17 was conducted through BeadXpress ADME Panel, Illumina (San Diego, CA) panel. Patients were divided into five categories according to *CYP2C19* phenotype: ultra-rapid (UM), rapid (RM), normal (NM), intermediate (IM), and poor metabolizer (PM). We combined UM, RM, and NM into group I since this group has normal antiplatelet response to clopidogrel. We combined IM and PM into group II as this group has a diminished antiplatelet response due to impaired clopidogrel active metabolite formation from a decrease or complete *CYP2C19* loss of enzyme activity. Based on the initial $P2Y_{12}$ inhibitor of choice, chosen at the discretion of interventional cardiologist, four categories were created (Fig. 1; Table 1). $P2Y_{12}$ inhibitor chosen at the time of PCI was changed as *CYP2C19* genotype results were available. In category 1($n = 207$), if clopidogrel was started and if genotype resulted as IM/PM, it was switched to ticagrelor or prasugrel. In category 2 ($n = 71$), if ticagrelor or prasugrel was started and if genotype resulted as IM/PM, they were continued on these medications. In category 3 ($n = 67$), if ticagrelor or prasugrel was started and if genotype resulted as UM/RM/NM, they were switched to clopidogrel. In category 4 ($n = 523$), if clopidogrel was started and if genotype resulted as UM/RM/NM, they continued clopidogrel.

Data were collected through review of the patient's electronic health records. Post-PCI report was used to extract procedure details. Death due to cardiovascular causes, non-fatal myocardial infarction (MI), target vessel revascularization (TVR), and bleeding events were obtained. We also divided bleeding events into Thrombolysis in Myocardial Infarction (TIMI) minor and major bleeding and Global Use of Strategies to Open Occlude Arteries (GUSTO) moderate and severe bleeding.[19] Bleeding events were determined if recorded as TIMI minor, TIMI major, GUSTO moderate, and/or GUSTO severe. MACE was defined as a composite of death due to cardiovascular causes, MI, TVR, and bleeding events. Cumulative clinical outcomes at 1, 6, and 12 months were calculated.

2.2. Statistical analysis

Continuous variables are displayed as mean (SD) and categorical variables are displayed as numbers and percentages. Analysis of variance (ANOVA) was used to analyze differences in continuous variables across the four categories. Tukey's Honest Significant Differences (HSD) method was used for post-hoc multiple comparisons when significant differences were detected. Chi-squared or Fisher's exact test was used to compare categorical variables between the four categories. Pairwise comparison between proportions with correction for multiple comparisons was done when significance was detected. Time to first occurrence of each outcome within 12 months after receiving testing results was examined by Kaplan–Meier estimates and log-rank tests. A *p*-value of less than

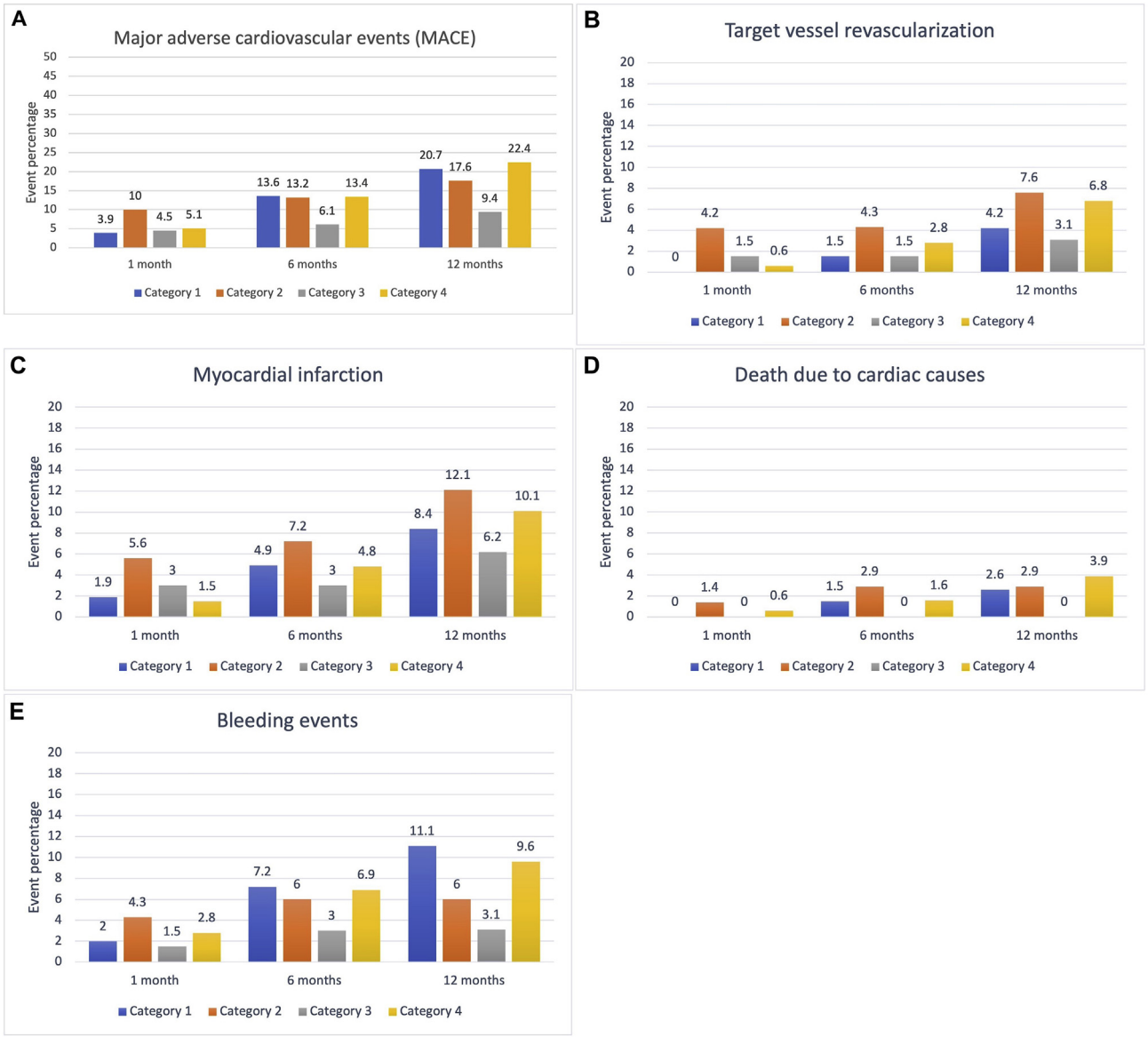

Fig. 2. (A) Major adverse cardiovascular events (B) Target vessel revascularization (C) Myocardial infarction (D) Death due to cardiac causes (E) Bleeding events across all four categories at 1, 6 and 12 months.

0.05 was considered statistically significant. R was used for all statistical analyses.[20]

3. Results

Patient demographics, clinical, and procedure characteristics were presented in Table 2. Patients in category 2 were younger compared to remaining categories. Over 60% of patients were male and nearly 90% of patients were Caucasians, with no significant difference between categories. Category 2 patients had lower hypertension than category 1 (adjusted $p = 0.021$) and category 4 (adjusted $p < 0.001$). Similarly, category 2 patients had lower dyslipidemia compared to category 1 (adjusted $p = 0.051$) and category 4 (adjusted $p = 0.032$). Category 3 patients had less peripheral vascular disease than those in category 4 (adjusted $p = 0.029$). The remaining risk factors, including diabetes mellitus, tobacco use, and family history of heart disease were not significant between the categories (Table 2). Category 1 and 4 patients were on a relatively higher proportion of OAC for other indications than category 2 and 3. After adjusting for multiple comparisons, there were no significant pairwise differences between categories. There was no significant difference between the four categories for the mean number of the DES, mean diameter, mean length of the DES or the vessel intervened.

Missing data in the analysis indicates a lost-to-follow-up ($n = 35$) or a death. There was no significant difference in MACE at 1 month ($p = 0.274$), 6 months ($p = 0.387$) and 12 months ($p = 0.083$) between the four categories (Fig. 2A) (Table 3). We observed a significant difference between categories at 1 month for TVR ($p = 0.012$). After adjusting for multiple comparisons, there was a marginally significant difference between category 1 and 2 (0% vs. 4.2%; $p = 0.097$). However, there was no significant difference in TVR at 6 months ($p = 0.491$) and 12 months ($p = 0.423$) (Fig. 2B). MI was not statistically significant across the four categories at 1 month ($p = 0.115$), 6 months ($p = 0.726$), and 12 months ($p = 0.629$) (Fig. 2C). Death due to cardiac causes was also not

Table 3
Cumulative clinical outcomes. MACE: Major adverse cardiovascular events. TIMI: Thrombolysis in Myocardial Infarction. GUSTO: Global Use of Strategies to Open Occlude Arteries.

Clinical event	No. of patients available for analysis	Category 1	Category 2	Category 3	Category 4	*p*-value[a]
Death due to cardiac causes n (%)						
1 month	863	0 (0.0)	1 (1.4)	0 (0.0)	3 (0.6)	0.370
6 months	850	3 (1.5)	2 (2.9)	0 (0.0)	8 (1.6)	0.658
12 months	819	5 (2.6)	2 (2.9)	0 (0.0)	19 (3.9)	0.453
Bleeding events n (%)						
1 month	846	4 (2.0)	3 (4.3)	1 (1.5)	14 (2.8)	0.739
6 months	819	14 (7.2)	4 (6.0)	2 (3.0)	34 (6.9)	0.723
12 months	801	21 (11.1)	4 (6.0)	2 (3.1)	46 (9.6)	0.211
Myocardial infarction n (%)						
1 month	862	4 (1.9)	4 (5.6)	2 (2.0)	8 (1.5)	0.115
6 months	843	10 (4.9)	5 (7.2)	2 (3.0)	24 (4.8)	0.726
12 months	807	16 (8.4)	8 (12.1)	4 (6.2)	49 (10.1)	0.629
Target vessel revascularization n (%)						
1 month	862	0 (0.0)	3 (4.2)	1 (1.5)	3 (0.6)	0.012
6 months	843	3 (1.5)	3 (4.3)	1 (1.5)	14 (2.8)	0.491
12 months	804	8 (4.2)	5 (7.6)	2 (3.1)	33 (6.8)	0.423
MACE n (%)						
1 month	847	8 (3.9)	7 (10.0)	3 (4.5)	26 (5.1)	0.274
6 months	825	27 (13.6)	9 (13.2)	4 (6.1)	66 (13.4)	0.387
12 months	815	40 (20.7)	12 (17.6)	6 (9.4)	110 (22.4)	0.083
TIMI minor bleeding n (%)						
1 month	846	3 (1.5)	3 (4.3)	1 (1.5)	6 (1.2)	0.212
6 months	819	11(5.6)	4 (6.0)	2 (3.0)	20 (4.1)	0.707
12 months	803	14 (7.4)	4 (6.0)	2 (3.1)	28 (5.8)	0.706
TIMI major bleeding n (%)						
1 month	846	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.4)	0.371
6 months	818	3 (1.5)	0 (0.0)	0 (0.0)	13 (2.7)	0.436
12 months	801	6 (3.2)	0 (0.0)	0 (0.0)	17 (3.5)	0.253
GUSTO moderate bleeding n (%)						
1 month	846	2 (1.0)	1 (1.4)	0 (0.0)	6 (1.2)	0.943
6 months	819	7 (3.6)	2 (3.0)	0 (0.0)	14 (2.9)	0.543
12 months	803	11 (5.8)	2 (3.0)	0 (0.0)	20 (4.1)	0.231
GUSTO severe bleeding n (%)						
1 month	846	1 (0.5)	1 (1.4)	1 (1.5)	8 (1.6)	0.604
6 months	819	4 (2.1)	1 (1.5)	1 (1.5)	16 (3.3)	0.808
12 months	803	7 (3.7)	1 (1.5)	1 (1.6)	21 (4.3)	0.685

[a] Fisher's exact test.

significant between four categories at 1 month ($p = 0.370$), 6 months ($p = 0.658$), and 12 months ($p = 0.453$) (Fig. 2D).

With respect to bleeding events, we did not observe a significant difference in clinically relevant bleeding at 1 month ($p = 0.739$), 6 months ($p = 0.723$) and 12 months ($p = 0.211$) (Fig. 2E). There was also no statistical significance in TIMI minor, TIMI major, GUSTO moderate and severe bleeding at the predefined study periods. These results were additionally confirmed as cumulative event rates based on Kaplan–Meier estimates and corresponding log-rank tests (Fig. 3) indicate no differences between four categories for each outcome within 12 months of receiving *CYP2C19* genotype results.

4. Discussion

Our study assessed the clinical application and outcomes of *CYP2C19* genotype guided $P2Y_{12}$ inhibitor selection in individuals with ACS and SIHD undergoing PCI. We demonstrated *CYP2C19* genotype-based selection of $P2Y_{12}$ inhibitor has similar event rate in all four categories and normalizes risk for ensuing MACE. Overall, 85.7% (n = 868/1013) of the patients who underwent PCI were continued on a $P2Y_{12}$ inhibitor as a maintenance therapy based on the *CYP2C19* genotype regardless of the initial loading $P2Y_{12}$ inhibitor. Excluding deaths, we were able to obtain clinical events follow-up data on 96% of included patients in our study (n = 833/868). The clinical outcomes were comparable among the categories:

1. If an IM/PM was up titrated to ticagrelor or prasugrel from clopidogrel.
2. If an IM/PM was continued on ticagrelor/prasugrel when preloaded with ticagrelor/prasugrel.
3. If an UM/RM/NM was down titrated to clopidogrel from ticagrelor or prasugrel.
4. If an UM/RM/NM was continued to clopidogrel when preloaded with clopidogrel.

CYP2C19 plays a crucial role in the conversion of clopidogrel to pharmacologically active metabolite.[9] For *CYP2C19*, the *2 allele was a major decreased function allele, and this LOF allele causes lower production of the active metabolite of clopidogrel.[10,21] Carriers of *CYP2C19*2* genotype have approximately two-fold higher ischemic cardiovascular events or death when compared to non-carriers following PCI at 1-year follow-up from decreased effectiveness of clopidogrel.[12] Having two LOF alleles increases the rate of adverse cardiovascular events 3.6 times that of non-carriers who underwent PCI for acute MI and received clopidogrel.[13]

Several studies have demonstrated the benefits of *CYP2C19*-guided therapy.[16,22,23] One of the genetic sub-study of Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial showed that *CYP2C19* genotyping could effectively identify patients who would clinically benefit from prasugrel over clopidogrel.[22] Additionally, the genetic sub-study of the PLATelet inhibition and patients Outcomes (PLATO) revealed a higher rate of ischemic events in patients with a *CYP2C19* LOF allele treated with

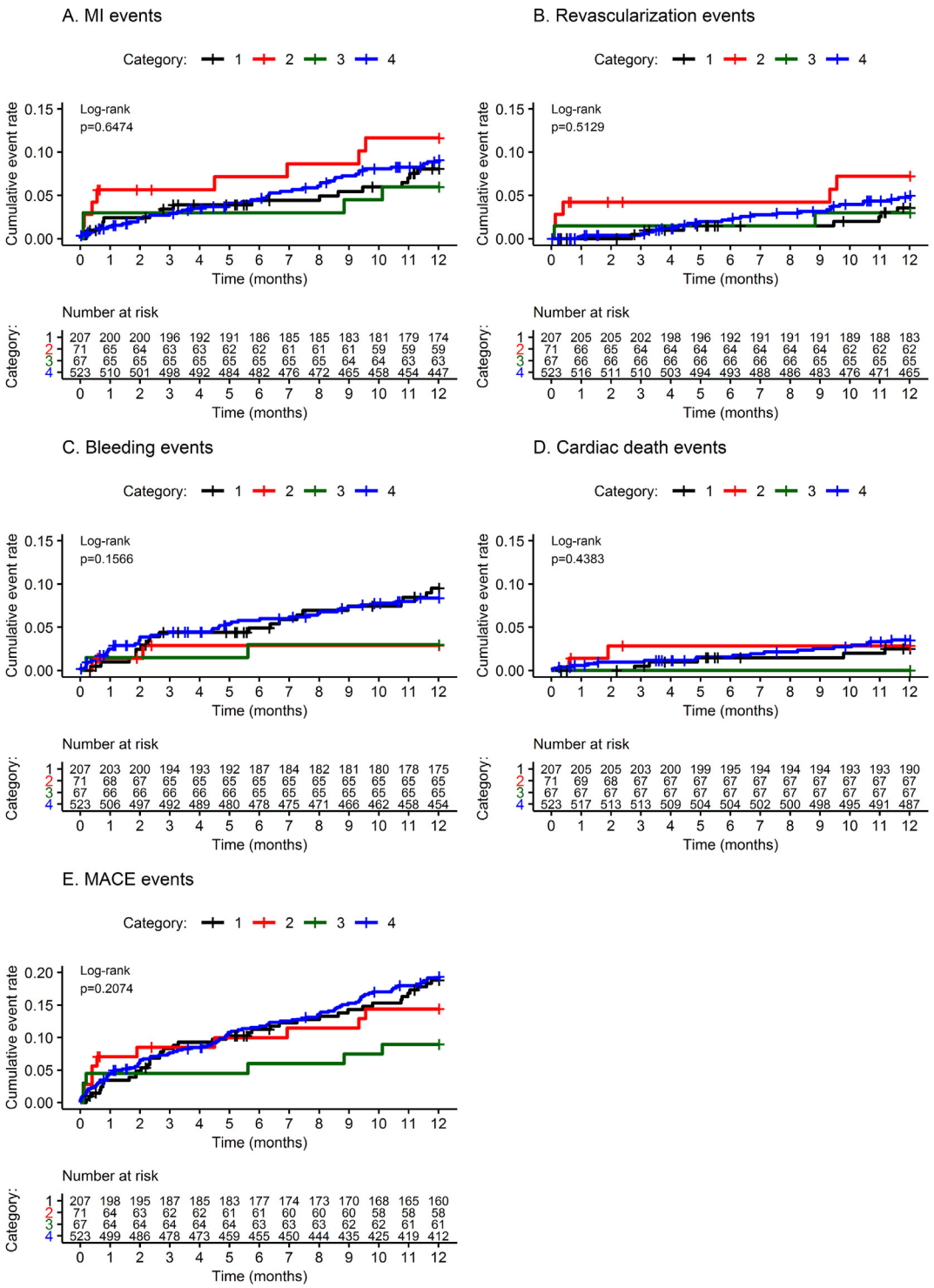

Fig. 3. Cumulative event rates within a year of CYP2C19 testing. Kaplan–Meier estimates of the cumulative incidence of myocardial infarction (A), target vessel revascularization (B), bleeding events (C), death due to cardiac causes (D), and major adverse cardiovascular events (E) by category. Vertical marks on the graph indicate censored patients and table below each graph shows the number of patients at risk by month and category. Log-rank test was used to test differences between categories. No significant differences in outcomes between categories was detected.

clopidogrel within the first 30 days post-PCI compared to those with the wild type allele. However, no difference was noted past initial 30 days.[23] In a collaborative meta-analysis of patients treated with clopidogrel for PCI, rates of MACE and stent thrombosis are notably high in patients who carry either 1 or 2 *CYP2C19* reduced function allele.[14] A large systematic review and meta-analysis of 32 studies of 42,106 participants reported no association between *CYP2C19* genotype and cardiovascular events in relation to the clopidogrel responsiveness except stent thrombosis.[24] However, most of the RCTs included in this study, the control arm was a placebo, and some of the patients were treated with medical therapy exclusively instead of PCI.

In the genotyping sub-study of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) trial, there was no significant difference in ischemic and bleeding risk when compared between continuing prasugrel versus de-escalation from prasugrel to clopidogrel in patients with ACS treated with PCI. However, de-escalation was performed in accordance with platelet reactivity by the functional testing. On contrary, we de-escalated the $P2Y_{12}$ inhibitor according to *CYP2C19* genotype. Moreover, both ticagrelor and prasugrel were used in our study rather than prasugrel only. Of note, *CYP2C19*2* genotype was a strong and independent predictor of platelet reactivity in the multivariate analysis of this trial.[25]

In the *CYP2C19* Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients – Patient Outcome after Primary PCI (POPular Genetics) trial, when clopidogrel was used in patients with *CYP2C19* without LOF allele, the combined thrombotic and bleeding outcome was not higher when compared to patients receiving ticagrelor and prasugrel at 12 months after primary PCI for STEMI.[26] Our study protocol was designed entirely based on *CYP2C19* genotype guided $P2Y_{12}$ inhibitor approach in patients with ACS and SIHD. Though there was no comparator arm comprising of patients treated with a potent $P2Y_{12}$ inhibitor without *CYP2C19* genotype in the present study, the risk for adverse cardiac events was attenuated in patients with *CYP2C19* LOF allele and adjusted to ticagrelor/prasugrel.

Our study findings are consistent with the previous multicenter study led by the IGNITE network (Implementing Genomics in Practice), that there was no difference in MACE in patients without LOF allele when treated with clopidogrel versus alternate antiplatelet agent.[17] One of the US centers in the IGNITE network has reported pragmatic execution of *CYP2C19* genotype-guided antiplatelet therapy in high-risk patients undergoing PCI, albeit maintenance of the appropriate $P2Y_{12}$ inhibitor based on the *CYP2C19* genotype and frequency of *CYP2C19* genotype testing was challenging over time.[27] Another study of 1063 ACS and elective PCI patients from the same institution published the timing, frequency, and clinical effect of swapping the $P2Y_{12}$ inhibitor with intensification in patients with a LOF allele from clopidogrel and down-titrating to clopidogrel in patients with no LOF allele/gain-of-function (GOF) allele from a potent $P2Y_{12}$ inhibitor.[28] In 49% of IM and PM initiated and continued clopidogrel, the clinical outcomes were worse compared with those who received a potent $P2Y_{12}$ inhibitor instead of clopidogrel as a maintenance therapy. Although we have used different statistical methods, our study results are in line with this study. We have not studied the clinical outcomes in patients with IM and PM who were continued on clopidogrel per the physician's discretion.

The recent Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR PCI), a multicenter, international, open-label, prospective, RCT conducted in ACS and SIHD who underwent PCI and tested the effect of genotyping when the genotyping arm was prospectively tested and prescribed ticagrelor 90 mg twice daily if they are *CYP2C19*2/*3* carriers versus retrospectively genotyped conventional arm who were receiving clopidogrel in patients with *CYP2C19*2/*3* alleles.[29] There was no significant difference in MACE or bleeding events at 12 months when the genotype-guided strategy was compared with the standard care strategy of clopidogrel regardless of LOF allele status. However, there was a potential benefit of the genotype-guided approach within three months post PCI in decreasing time to multiple recurrent ischemic events instead of "time-to-first-event", and the extended follow-up is currently ongoing. A few important observations to make a note are that the trial did not test the utility of genotype-guided de-escalation strategy, and moreover the escalation strategy in the genotyping arm exclusively used ticagrelor.

4.1. Limitations

There are several important limitations to our study. First, the current study is a retrospective analysis from a relatively narrow geographic area. We may not exclude the inherent biases associated with the study design and may not be applicable to the general population. A large, prospective RCT is required to assess the clinical algorithm we followed in the present study. Second, we only evaluated *CYP2C19* genotype effect on the genotype guided $P2Y_{12}$ inhibitor therapy in patients undergoing PCI. We cannot exclude the impact of other CYP isoenzymes with this treatment strategy, which may affect the clinical outcomes with clopidogrel. However, *CYP2C19* has a significant contribution to the biotransformation of clopidogrel to its active metabolite. Third, since we have combined IM and PM into one category, it was not feasible to assess the clinical outcomes of the usage of clopidogrel versus alternate $P2Y_{12}$ inhibitor based on the genotype separately in these two metabolizer sub-categories. Fourth, we did not exclude patients who need OAC for other indications, which may have biased some of the recorded bleeding events. However, the inclusion of OAC patients would represent a real-world setting.

5. Conclusion

The *CYP2C19* genotype-guided therapy following PCI for ACS and SIHD identifies individuals with reduced function alleles who derive limited therapeutic benefit from clopidogrel to facilitate appropriate institution of alternate $P2Y_{12}$ inhibitor to normalize risk and optimize clinical outcomes. The de-escalation to a less potent $P2Y_{12}$ inhibitor can also be performed without compromising the clinical outcomes in patients who could metabolize the clopidogrel appropriately.

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Author contribution

All authors had access to the data, participated in the preparation of the manuscript, and approved this manuscript.

Declaration of competing interest

All authors have no conflicts of interest to declare.

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