CYP2C19 genotype-directed P2Y12 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

ABSTRACT

Objective: To study the use of CYP2C19 genotyping to guide P2Y12 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 P2Y12 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/PM started on ticagrelor/prasugrel, switched to clopidogrel; 4: UM/RM/PM 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 P2Y12 inhibitor to optimize patient quality and safety when appropriate in post PCI patients. © 2021 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The combination of aspirin and a P2Y12 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 P2Y12 inhibitors of choice over clopidogrel in acute coronary syndrome (ACS).1–4 However, the use of P2Y12 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 P2Y12 inhibitor. However, it may be considered in select patients with recurrent major adverse cardiovascular events (MACE) if it may alter the treatment decision.5–9

Antiplatelet effects of clopidogrel is not consistent between individuals. The incidence of clopidogrel resistance and variable response in patients undergoing PCI is 5–44%.6,10 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.6,11 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
dose adjustment or alternative P2Y12 inhibitor. Interestingly, this recommendation only included for poor metabolizer variants of CYP2C19. 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). This finding was subsequently replicated in a practice-based cohort. 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. 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. We aimed to investigate the clinical outcomes when P2Y12 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 |
| Poor No | No | No | 2 | 6 | NC 0 |
| Yes No | Yes | No | 1 | 19 | NC 4 |
| Yes Yes | Yes | No | 2 | 65 | NC 6 |
| Intermediate | | | | | |
| No No | No | No | 3 | 44 | NC 13 |
| Yes No | Yes | No | 4 | 283 | NC 38 |
| Yes Yes | Yes | No | 3 | 18 | NC 12 |
| Normal No | No | No | 3 | 44 | NC 13 |
| Yes No | Yes | No | 4 | 283 | NC 38 |
| Yes Yes | Yes | No | 3 | 18 | NC 12 |
| Rapid No | No | No | 3 | 18 | NC 12 |
| Yes No | Yes | No | 4 | 201 | NC 8 |
| Yes Yes | Yes | No | 3 | 18 | NC 12 |
| Ultra-rapid | | | | | |
| No No | No | No | 3 | 18 | NC 12 |
| Yes No | Yes | No | 4 | 201 | NC 8 |
| Yes Yes | Yes | No | 3 | 18 | NC 12 |

Fig. 1. Study protocol. CAD: Coronary artery disease. PCI: Percutaneous coronary intervention.
who underwent PCI with a drug-eluting stent (DES) for ACS and SHD and able to take aspirin and P2Y12 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 P2Y12 inhibitor selection based upon CYP2C19 genotype derived from the CPIC guidelines. Additionally we included patients with SHD undergoing PCI, a group not specifically addressed in CPIC guideline. We excluded 145 patients whose management did not align with the defined clinical algorithm, resulting in 868 patients available for the analysis (Table 1).

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) | 0.951    |
| 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 (%)                              | 93 (44.9)  | 27 (38.6) | 28 (41.8) | 210 (40.3) | 0.67     |
| Left anterior descending artery                       | 31 (15.0)  | 18 (25.7) | 10 (14.9) | 114 (21.9) | 0.074    |
| Left circumflex artery                               | 77 (37.2)  | 31 (44.3) | 29 (43.3) | 201 (38.6) | 0.647    |
| Right coronary artery                                | 7 (3.4)    | 1 (1.4)   | 2 (3.0)   | 27 (5.2)   | 0.375    |
| Left main coronary artery                            | 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    |

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

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...
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 P2Y12 inhibitor selection in individuals with ACS and SIHD undergoing PCI. We demonstrated CYP2C19 genotype-based selection of P2Y12 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 P2Y12 inhibitor as a maintenance therapy based on the CYP2C19 genotype regardless of the initial loading P2Y12 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 pre-loaded 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.\textsuperscript{5} For CYP2C19, the *z* allele was a major decreased function allele, and this LOF allele causes lower production of the active metabolite of clopidogrel.\textsuperscript{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.\textsuperscript{13} 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.\textsuperscript{13} Several studies have demonstrated the benefits of CYP2C19-guided therapy.\textsuperscript{16,22,23} One of the genetic sub-study of Therapeutic Arteries.

### Table 3

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

| Clinical event                  | No. of patients available for analysis | Category 1 | Category 2 | Category 3 | Category 4 | p-value* |
|---------------------------------|---------------------------------------|------------|------------|------------|------------|----------|
| Death due to cardiac causes n (%) | 863                                   | 0 (0.0)    | 1 (1.4)    | 0 (0.0)    | 3 (0.6)    | 0.370    |
| Bleeding events n (%)           |                                       | 2 (1.5)    | 2 (2.9)    | 0 (0.0)    | 8 (1.6)    | 0.658    |
| Myocardial infarction n (%)     |                                       | 5 (2.6)    | 2 (2.9)    | 0 (0.0)    | 19 (3.9)   | 0.453    |
| MACE n (%)                      |                                       | 4 (2.0)    | 3 (4.3)    | 1 (1.5)    | 14 (2.8)   | 0.739    |
| TIMI minor bleeding n (%)       |                                       | 14 (7.2)   | 4 (6.0)    | 2 (3.0)    | 34 (6.9)   | 0.723    |
| TIMI major bleeding n (%)       |                                       | 21 (11.1)  | 4 (6.0)    | 2 (3.1)    | 46 (9.6)   | 0.211    |
| GUSTO moderate bleeding n (%)   |                                       | 4 (1.9)    | 4 (5.6)    | 2 (2.0)    | 8 (1.5)    | 0.115    |
| GUSTO severe bleeding n (%)     |                                       | 10 (4.9)   | 5 (7.2)    | 2 (3.0)    | 24 (4.8)   | 0.726    |
| Target vessel revascularization |                                       | 16 (8.4)   | 8 (12.1)   | 4 (6.2)    | 49 (10.1)  | 0.629    |
| 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 (%)                       | 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                               | 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                               | 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                               | 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                               | 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    |

* Fisher’s exact test.
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. 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. 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. 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.

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.
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 P2Y12 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 P2Y12 inhibitor approach in patients with ACS and SHHD. Though there was no comparator arm comprising of patients treated with a potent P2Y12 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.27 One of the US centers in the IGNITE network has reported pragmatic execution of CYP2C19 genotype guided P2Y12 inhibitor approach in high-risk patients undergoing PCI, albeit maintenance of the appropriate P2Y12 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 P2Y12 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 P2Y12 inhibitor.28 In 49% of IM and PM initiated and continued clopidogrel, the clinical outcomes were worse compared with those who received a potent P2Y12 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 who could metabolize the CYP2C19 allele. 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

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 P2Y12 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 P2Y12 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 P2Y12 inhibitor to normalize risk and optimize clinical outcomes. The de-escalation to a less potent P2Y12 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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