Clinical Outcomes after Percutaneous Coronary Intervention Over Time on the Basis of CYP2C19 Polymorphisms: Evidence from a Chinese Cohort

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Abstract

Purpose To investigate the association between CYP2C19 gene polymorphism and the risk of ischemic and bleeding complications in the different period after percutaneous coronary intervention (PCI) among patients who received clopidogrel.

Methods Between October 2015 and January 2017, CYP2C19 genotyped patients who were treated clopidogrel after PCI were enrolled this observational cohort study. Included patients were categorized as non-loss-of-function metabolizers (NLOFMs), intermediate metabolizers (IMs) and poor metabolizers (PMs) based on CYP2C19 genotype. The primary outcome was a composite of any-cause mortality, nonfatal myocardial infarction, nonfatal ischemic stroke and stent thrombosis occurring during exposure to clopidogrel. The rates of clinical outcome events were compared between CYP2C19 phenotypes. Landmark analyses were processed at 90 days and 1-year post-PCI.

Results Of 1,341 patients, 161 (12.0%) had two copy of loss-of-function (LOF) alleles, 621(46.3%) had one LOF allele, and 559 (41.7%) had no LOF allele. At the 3-month follow-up, the primary outcome events were more frequent in carriers of two LOF alleles (5.6%) than in noncarriers (1.8%) (adjusted HR 2.944, 95% CI 1.184-7.321, $p = 0.020$). A similar finding was observed among in patients with acute coronary syndrome indications at the index PCI (adjusted HR 3.046, 95% CI 1.237-7.501, $p = 0.015$). These differences did not persist within the subsequent 9 months of follow-up, among either all-comers or subjects with ACS. The incidences of bleeding outcome events were similar among CYP2C19 phenotypes throughout the follow-up period.

Conclusion These data demonstrate a higher risk for ischemic events in patients with two CYP2C19 LOF alleles who are prescribed clopidogrel, previously seen at 3 months following PCI, that is not sustained for 12 months. These findings emphasize the need to place greater weight on a PM result during early antiplatelet therapy de-escalating decisions.

Introduction

Dual antiplatelet therapy (DAPT) consisting of a P2Y12 inhibitor and aspirin is the mainstay of treatment of patients with acute coronary syndromes (ACS) and of those with chronic coronary syndrome (CCS) undergoing percutaneous coronary intervention (PCI). Clopidogrel, as a second-generation thienopyridine, has been broadly used because of its good availability and safety [1, 2]. Clopidogrel is a thienopyridine prodrug that requires a two-step oxidation process by hepatic cytochrome P450 enzymes to convert to its active metabolite. The latter irreversibly blocks the ADP binding site on the P2Y12 receptor and ultimately inhibits platelet aggregation [3]. Despite the proven efficacy of clopidogrel [4, 5], there is remarkable heterogeneity in the pharmacodynamic effect of clopidogrel. This phenomenon can be in part attributed to the variation in the cytochrome P450 (CYP) allele, especially CYP2C19*2 and CYP2C19*3 loss-of-function (LOF) alleles [6, 7].

Compared with clopidogrel, ticagrelor and prasugrel are new-generation oral P2Y12 inhibitors that have more potent, faster inhibitory effects on platelet activation and thus can more effectively prevent thrombotic events [8, 9]. However, this potent antiplatelet effect is accompanied by a higher risk of bleeding [10]. On the other hand, although DAPT is currently recommended for 1 year following PCI in patients presenting with ACS [11, 12], the ischemic benefit of intensive antiplatelet therapy was observed only during the initial period after PCI [8, 9]. In contrast, this benefit was outweighed by the increased risk of hemorrhagic complications during the additional time after the index procedure [10, 13]. Although there is no agreement on the timing, a series of DAPT de-escalating strategies (at 1 or 3 months) aimed at reducing the risk of bleeding following PCI have shown a better clinical net benefit than the traditional DAPT strategy [14–16]. Early de-escalation of antiplatelet therapy further emphasizes the importance of accurately identifying patients with a high risk of early ischemia events. This problem is more prominent in the East Asian population, which has higher frequencies of the CYP2C19 LOF allele carriers and a higher risk of bleeding [17, 18]. Therefore, elucidating the relationship between CYP2C19 LOF alleles and early ischemic events in patients after PCI is helpful to achieve the best trade-off between ischemic benefit and bleeding risk throughout antiplatelet therapy and ultimately to further optimize gene-guided tailored therapy. The objective of the present

study was to investigate whether a heightened, temporal risk for ischemic events was associated with CYP2C19 metabolic status among patients treated with clopidogrel after the index PCI.

Methods

Study Design and Population

This was a retrospective analysis data from a single centre. Consecutive patients 18 years and older who underwent CYP2C19 genotyping test during the index admission and received DAPT involving clopidogrel and aspirin after PCI at discharge were recruited in the Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, from October 2015 to January 2017. Exclusion criteria were as follows: 1) receiving long-term anticoagulation therapy (i.e., warfarin, direct thrombin inhibitor, Factor Xa inhibitor); 2) a history of cerebral hemorrhage or cavum subarachnoid bleeding; 3) a life expectancy of < 1 year; 4) clinically significant out-of-range values for platelet count or hemoglobin at admission screening; or 5) pregnancy, lactating, or planning to become pregnant within 12 months. The diagnosis of ACS had to meet ≥ 2 of the following criteria: 1) ischemic symptoms that occurred at rest and lasted for more than 20 minutes; 2) ST-segment changes (elevation or depression) of at least 1 mm in 2 contiguous leads; and 3) a rise and/or fall in cardiac biomarker troponin I or T with at least one value above the 99th percentile of the upper reference limit [19].

During the index admission, all patients were pre-treated with a 300-mg loading dose of aspirin combined with a dose of 600 mg clopidogrel prior to PCI. After discharge, patients continued to receive a maintenance dose of aspirin (100 mg daily) and clopidogrel (75 mg daily) for at least one year. During the procedure, the choice of access site, the lesions to treat and the type of stent were at the discretion of the attending physician.

The protocol of this research was granted by the Ethics Committee of the Clinical Research Center at Beijing Anzhen Hospital (no. 2021045X). The study abided by the Declaration of Declaration of Helsinki. All the patients or their legal proxies provided written informed consent.

Cyp2c19 Genotyping And Platelet Function Test

Blood samples were collected from all patients who underwent CYP2C19 genotyping at the time of admission, and deoxyribonucleic acid was extracted from leukocytes in peripheral blood. Genotyping of polymorphisms was performed with commercially available TaqMan allelic discrimination assays (Thermo Fisher Scientific, Waltham, Massachusetts). The whole process of this test was completed in strict accordance with the manufacturer's instructions. The genetic testing of three single-nucleotide polymorphisms (SNPs) for CYP2C19 included CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), and CYP2C19*17 (rs12248560). Patients were classified by predicted metabolic phenotype based on these genotype results. According to published scientific information at the time of the study, the metabolic phenotypes of CYP2C19 were categorized into non-loss-of-function metabolizers (NLOFMs, including UM: ultrarapid metabolizer, *17/*17;

RM: rapid metabolizer, *1/*17; NMs: normal metabolizer, *1/*1), intermediate metabolizers (IMs, *1/*2, *1/*3, *2/*17, or *3/*17) and poor metabolizers (PMs, *2/*2, *2/*3, or *3/*3) [20, 21].

Blood samples for the platelet function test were acquired at 12 to 24 hours following the index PCI. The effects of antiplatelet therapy were assessed by the CFMS TEG System (LEPU Medical, Beijing, China) via the arachidonic acid (AA) and adenosine diphosphate (ADP) pathways. Details of the logistics of thromboelastography have been expatiated previously [22]. Low responsiveness to clopidogrel indicated an ADP-induced platelet-fibrin clot strength (MA-ADP) > 47 mm plus an ADP-induced platelet inhibition rate < 50% [23, 24].

Follow-up And Study Outcomes

Clinical follow-up assessments of all participants were performed by means of outpatient visits or standardized telephone contacts at 3 and 12 months after PCI. Identification of all clinical outcomes was based on physician-reported diagnoses abstracted from the cardiac catheterization laboratory report, summary of hospital discharge diagnosis, or clinical notes in the event of death.

The primary outcome was a major adverse cardiovascular or cerebrovascular event (MACCE), which included death from any cause, the first occurrence of nonfatal myocardial infarction, nonfatal ischemic stroke and stent thrombosis. The secondary outcome was the composite of MACCE plus the first occurrence of urgent target-vessel revascularization (TVR). The diagnosis of myocardial infarction was according to the Third Universal Definition of Myocardial Infarction [25]. Stent thrombosis was defined according to the Academic Research Consortium [26]. Ischemic stroke was defined as a neurologic deficit caused by an ischemic event with residual symptoms lasting at least 24 hours after onset or leading to death. The bleeding outcome was clinically significant bleeding events as defined by Bleeding Academic Research Consortium (BARC) criteria (including BARC 2, BARC 3, BARC 4) [27]. BARC 2 was defined as any overt, actionable sign of bleeding that required medical intervention or evaluation but did not meet the criteria for type 3 or higher BARC bleeding; BARC 3 indicated overt bleeding plus a decrease in hemoglobin of more than 3 g/dL, intracranial hemorrhage or intraocular hemorrhage compromising vision; and BARC 4 was considered bleeding related to coronary-artery bypass grafting [27]. All outcome events were independently adjudicated by at least two cardiologists.

Statistical Analysis

Based on the data that were available at the time of the study [7], we assumed that compared with the NLOFM, the hazard ratio (HR) for the occurrence of a MACCE was 1.55 for the IM and 1.76 for the PM. Given a power of 90%, an alpha level of 0.05 and 10% loss to follow-up, we predicted that a minimum sample size of 357 would be necessary. The procedure of sample size calculation was performed with PASS version 15 (NCSS, LLC. Kaysville, UT, USA).

The baseline demographic, clinical and treatment characteristics of the three groups with different metabolic phenotypes (including non-LOF metabolizers, IMs and PMs) were compared. Discrete or categorical variables were reported as counts (percentages) and were compared by using the chi-squared test or Fisher’s exact test as appropriate. Continuous variables were presented as the mean ± standard deviation or median (interquartile range) according to their distributions and were

compared using the analysis of variance F test when the assumption of normality was met; otherwise, the Kruskal-Wallis test was used. Normality was checked with the Kolmogorov–Smirnov test and visual inspection of Q-Q plots.

All time-to-event outcomes were defined with the end of the index PCI as time zero. Kaplan-Meier plots were constructed to estimate the cumulative risk for an outcome event, and time-to-event data were compared between groups with the use of the log-rank test. The relationship between the CYP2C19 phenotype and clinical outcomes was determined by fitting a Cox proportional hazards model, and the results were expressed as HRs with 95% confidence intervals. All variables identified with a p value < 0.10 from the univariate analyses, and other variables considered to have potential prognostic value were entered into the multivariable regression model. Adjusted covariates included age, sex, coronary artery disease presentation, diabetes mellitus, hypertension, multiple-vessel disease, cerebrovascular disease, chronic kidney disease and previous myocardial infarction. Landmark analyses were used to estimate the cumulative incidence of clinical outcome events from 0 to 90 days and 91 days to 365 days after the index procedure. A secondary analysis limited to patients with ACS indications at the PCI was also conducted. All tests were 2-tailed, and a p value < 0.05 was deemed as statistically significant. Statistical analyses were conducted with SPSS 25.0 (IBM Corporation, NY, USA), and Kaplan-Meier curves were drawn using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Between October 2015 and January 2017, a total of 1502 genotyped patients were recruited after successful deployment of at least one drug-eluting stent (Fig. 1). Of these, four patients experienced outcome events during the first 24 hours after the index PCI, 11 participants switched to ticagrelor from clopidogrel under the guidance of physicians during the first year after PCI, and 146 subjects were lost to follow-up, resulting in 1341 patients being included in the primary analysis. Among 1341 patients in the final study cohort, the mean age was 58.69 ± 9.786 years and 75.2% were male. A total of 1256 patients (93.7%) presented with ACS (including 128 [9.5%] with STEMI, 138 [10.3%] with NSTEMI and 990 [73.8%] with unstable angina).

The overall baseline characteristics of the patients are listed in Table 1 according to CYP2C19 metabolic phenotypes. Based on the platelet function test results, the mean maximum amplitude of ADP-induced platelet-fibrin clot strength (MA-ADP) was highest in the PM group (36.25 [25.4–47.3] mm), intermediate (38.05 [25.8–49.7] mm) in the IM group and lowest (43.0 [28.5–54.4] mm) in the NLOFMs (p = 0.004). Patients in the NLOFM group had the highest rates of low responsiveness to clopidogrel (LRC) (n = 135, 24.2%); LRC rates were intermediate (n = 199, 32.0%) in the IM group and lowest (n = 62, 38.5%) in PMs (p < 0.001). Compared with the other two groups, the PM group had the highest proportion of LAD lesions and the lowest proportion of LCX lesions.

Table 1
Baseline Characteristics Among Patients According to CYP2C19 Phenotype

Covariates	Non-LOF Metabolizer (n = 559)	Intermediate Metabolizer (n = 621)	Poor Metabolizer (n = 161)	*p* Value
Demographics				
Age, yrs	58.8 ± 10.0	58.5 ± 9.9	58.9 ± 8.6	0.866
Female	139 (24.9)	151 (24.3)	43 (26.7)	0.822
Body mass index, kg/m^2	26.0 ± 3.10	26.0 ± 3.4	25.8 ± 3.2	0.842
Cardiovascular risk factors				
Current or previous smoker	193 (34.5)	214 (34.5)	58 (36.0)	0.929
Family history of CAD	70 (12.5)	88 (14.2)	23 (14.3)	0.679
Previous PCI	127 (22.7)	124 (20.0)	36 (22.4)	0.491
Previous CABG	15 (2.7)	21 (3.4)	2 (1.2)	0.332
Previous myocardial infarction	68 (12.2)	66 (10.6)	26 (16.1)	0.153
Comorbidities				
Diabetes mellitus	187 (33.5)	210 (33.8)	60 (37.3)	0.655
Hypertension	357 (63.9)	395 (63.6)	104 (64.6)	0.973
Hyperlipidemia	255 (45.6)	285 (45.9)	66 (41.0)	0.519
Cerebrovascular disease	44 (7.9)	43 (6.9)	18 (11.2)	0.201
Peripheral arterial disease	13 (2.3)	17 (2.7)	5 (3.1)	0.830
Chronic kidney disease	73 (13.1)	73 (11.8)	16 (9.9)	0.532
Coronary artery disease presentation				0.006
Stable coronary disease	40 (7.2)	36 (5.8)	9 (5.6)	
Acute coronary syndrome	519 (92.8)	585 (94.2)	152 (94.4)	
Unstable angina	435 (77.8)	445 (71.7)	110 (68.3)	
Non-STEMI	40 (7.2)	72 (11.6)	26 (16.1)	
STEMI	44 (7.9)	68 (11.0)	16 (9.9)	
Coronary angiography				

Values were mean ± SD, No. (%) or median (IQR).

non-LOF metabolizer non-loss-of-function metabolizer, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *CABG* coronaryartery bypass grafting, *non-STEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, *PLT* platelet count, *IQR* interquartile range, *ADP* adenosine diphosphate, MA_{ADP} the maximum amplitude of ADP-induced platelet-fibrin clot strength, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker.

[a] Low responsiveness to clopidogrel was defined as the ADP-induced platelet-fibrin clot strength (MA_{ADP}) > 47 mm plus an ADP-induced platelet inhibition rate < 50%.

Covariates	Non-LOF Metabolizer (n = 559)	Intermediate Metabolizer (n = 621)	Poor Metabolizer (n = 161)	*p* Value
Left main artery	19 (3.4)	27 (4.3)	6 (3.7)	0.697
Left anterior descending artery	410 (73.3)	421 (67.8)	129 (80.1)	0.004
Circumflex artery	197 (34.9)	255 (41.1)	50 (31.1)	0.020
Right coronary artery	215 (38.5)	244 (39.3)	52 (32.3)	0.259
Multiple-vessel disease	199 (35.6)	220 (35.4)	55 (34.2)	0.944
Number of stents implanted per patient	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.747
Baseline laboratory evaluation				
PLT, × 10^9/L	213.4 ± 50.6	213.8 ± 47.6	216.6 ± 52.7	0.775
ADP-induced platelet inhibition rate	51.3 (32.7–72.8)	49.7 (27.0-72.6)	37.5 (17.7–61.7)	< 0.001
MA_{ADP}, mm	36.3 (25.4–47.3)	38.05 (25.8–49.7)	43.0 (28.5–54.4)	0.004
Number of low responsiveness to clopidogrel [a]	135 (24.2)	199 (32.0)	62 (38.5)	< 0.001
Concomitant medication				
Statin	497 (88.9)	560 (90.2)	142 (88.2)	0.676
Beta-blocker	400 (71.6)	456 (73.4)	124 (77.0)	0.374
ACE inhibitor or ARB	339 (60.6)	384 (61.8)	82(50.9)	0.039
Proton pump inhibitor	141 (25.2)	150 (24.2)	41 (25.5)	0.891

Values were mean ± SD, No. (%) or median (IQR).

non-LOF metabolizer non-loss-of-function metabolizer, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *CABG* coronaryartery bypass grafting, *non-STEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, *PLT* platelet count, *IQR* interquartile range, *ADP* adenosine diphosphate, MA_{ADP} the maximum amplitude of ADP-induced platelet-fibrin clot strength, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker.

[a] Low responsiveness to clopidogrel was defined as the ADP-induced platelet-fibrin clot strength (MA_{ADP}) > 47 mm plus an ADP-induced platelet inhibition rate < 50%.

Genotypes And Phenotypes

The distribution of genotypes and associated phenotypes is shown in Table 2. The frequencies of the CYP2C19*1, *2, *3, and *17 alleles were 63.4%, 29.8%, 5.4% and 1.4%, respectively. Among all recruited patients, 621 subjects (46.3%) who carried 1 copy of the LOF CYP2C19 allele were defined as IMs, 161 participants (12.0%) who had 2 copies of the LOF CYP2C19 alleles were regarded as PMs, and 559 patients (41.7%) without any LOF CYP2C19 allele were considered NLOFMs.

Table 2
Distribution of CYP2C19 Alleles and Genotypes Among Patients

Allele	Frequency No. (%)	Genotype	Frequency No. (%)	Phenotype	Frequency No. (%)
*1	1701 (63.4)	*1/*1	535 (39.9)	NLOFM	559 (41.7)
*2	799 (29.8)	*1/*2	510 (38.0)	IM	621 (46.3)
*3	144 (5.4)	*1/*3	98 (7.3)	PM	161 (12.0)
*17	38 (1.4)	*1/*17	23 (1.7)		
		*2/*2	121 (9.0)		
		*2/*3	36 (2.7)		
		*2/*17	11 (0.8)		
		*3/*3	4 (0.3)		
		*3/*17	2 (0.2)		
		*17/*17	1 (0.1)		

NLOFM non-loss-of-function metabolizer, was the composite of ultrarapid metabolizer (*17/*17), rapid metabolizer (*1/*17) and normal metabolizer (*1/*1); *IM* intermediate metabolizer (*1/*2, *1/*3, *2/*17, or *3/*17); *PM* poor metabolizer (*2/*2, *2/*3, or *3/*3).

Clinical Outcomes

The median time from indexed procedure to clinical outcome events or censoring was 392 days (interquartile range: 379 to 405 days). Over the follow-up period, death from any cause, the first occurrence of nonfatal myocardial infarction, nonfatal ischemic stroke or stent thrombosis (the primary outcome) occurred in 76 cases (5.67%), the secondary outcome consisting of death from any cause, the first occurrence of nonfatal myocardial infarction, nonfatal ischemic stroke, stent thrombosis or urgent TVR occurred in 90 cases (6.71%), and the occurrence of clinically significant bleeding events was documented in 41 cases (3.06%).

The 12-month composite clinical outcomes and the landmark analysis of time-to-first event within and after 90 days are shown in Table 3. In the 1-year analysis, the rates of the primary outcome were not significantly different between groups (NLOFM 4.7%; IM 6.0%; PM 8.1%; log-rank $p = 0.213$). Similarly, the secondary outcome rates were not significantly different among groups (NLOFM 5.5%; IM 7.1%; PM 9.3%; log-rank $p = 0.193$) in the 365-day analysis. From the 12-month landmark analysis, there were significant differences in the primary outcome and secondary outcome between different metabolizer groups at the initially reported 90-day follow-up period (primary outcomes: NLOFM 1.8%, IM 2.3%, PM 5.6%, log-rank $p = 0.019$; secondary outcomes: NLOFM 6.2%, IM 2.3%, PM 1.8%, log-rank $p = 0.005$) (Fig. 2, Online Figure S1). However, those differences did not persist at 91–365 days of follow-up (primary outcomes: NLOFM 2.9%, IM 3.8%, PM 2.6%, log-rank $p = 0.631$; secondary outcomes: NLOFM 3.8%, IM 4.9%, PM 3.3%, log-rank $p = 0.529$). Furthermore, there was no in-group difference in bleeding outcome between the three groups in any time period (Table 3).

Table 3
Clinical Outcomes and Individual Components According to CYP2C19 Phenotype

Outcomes	0-365 Days				0–90 Days				91–365 Days			
	NLOFM	IM	PM	p Value [a]	NLOFM	IM	PM	p Value	NLOFM	IM	PM	p Value
Primary Outcome [b]	26 (4.7)	37 (6.0)	13 (8.1)	0.213	10 (1.8)	14 (2.3)	9 (5.6)	0.019	16 (2.9)	23 (3.8)	4 (2.6)	0.631
Death from Any Cause	7 (1.3)	11 (1.8)	8 (5.0)	0.009	3 (0.5)	7 (1.1)	6 (3.7)	0.004	4 (0.7)	4 (0.7)	2 (1.3)	0.708
Myocardial Infarction	13 (2.3)	15 (2.4)	4 (2.5)	0.990	5 (0.9)	6 (1.0)	2 (1.2)	0.922	8 (1.5)	9 (1.5)	2 (1.3)	0.99
Stent Thrombosis	5 (0.9)	8 (1.3)	1 (0.6)	0.688	2 (0.4)	1 (0.2)	1 (0.6)	0.599	3 (0.5)	7 (1.2)	0 (0.0)	0.254
Ischemic Stroke	1 (0.2)	3 (0.5)	0 (0.0)	0.482	0 (0.0)	0 (0.0)	0 (0.0)	—	1 (0.2)	3 (0.5)	0 (0.0)	0.482
Secondary Outcome [c]	31 (5.5)	44 (7.1)	15 (9.3)	0.193	10 (1.8)	14 (2.3)	10 (6.2)	0.005	21 (3.8)	30 (4.9)	5 (3.3)	0.529
Urgent TVR	5 (0.9)	7 (1.1)	2 (1.2)	0.893	0 (0.0)	0 (0.0)	1 (0.6)	0.026	5 (0.9)	7 (1.1)	1 (1.7)	0.821
Bleeding Outcome [d, e]	18 (3.2)	17 (2.7)	6 (3.7)	0.772	5 (0.9)	2 (0.3)	2 (1.2)	0.311	13 (2.3)	15 (2.4)	4 (2.5)	0.991

Values were No. (%).

NLOFM non-loss-of-function metabolizer, *IM* intermediate metabolizer, *PM* poor metabolizer, *TVR* target-vessel revascularization.

[a] The *p* values were evaluated with log-rank test in Kaplan–Meier analysis.

[b] Primary outcome was the composite of death from any cause, myocardial infarction, definite or probable stent thrombosis and ischemic stroke.

[c] Secondary outcome was the composite of death from any cause, myocardial infarction, ischemic stroke, definite or probable stent thrombosis and urgent target-vessel revascularization.

[d] Bleeding outcome was clinically significant bleeding events as defined by Bleeding Academic Research Consortium (BARC) criteria (including BARC 2, BARC 3, BARC 4)

[e] BARC was the criteria for grading and categorizing bleeding events, BARC 2 was defined as any overt, actionable sign of bleeding that requires medical intervention or evaluation, but not meet criteria for type 3 or higher BARC bleeding; BARC 3 indicated overt bleeding plus a decrease in hemoglobin of more than 3 g/dL, intracranial hemorrhage or intraocular hemorrhage compromising vision; BARC 4 was bleeding related to coronary-artery bypass grafting.

As presented in Table 4, a higher risk of primary outcomes was observed among PMs than among NLOFMs (adjusted HR 2.944, 95% CI 1.184–7.321, $p = 0.020$) during the first 90 days following the index PCI. Likewise, PMs had significantly higher rates of secondary outcomes than NLOFMs (adjusted HR 3.309, 95% CI 1.363–8.033, $p = 0.008$). According to the individual components of the clinical outcomes listed in Online Table S1, the between-group differences in clinical outcomes were driven by a higher incidence of all-cause mortality (adjusted HR 7.600, 95% CI 1.826–31.627 $p = 0.005$). In the analysis of subsequent time periods, HRs of primary outcome for PMs compared with NLOFMs were 1.192 (95% CI 0.231–6.152, $p =$

0.834) at 3–6 months of follow-up, 1.206 (95% CI 0.123–11.833, $p = 0.872$) at 6–9 months of follow-up and 0.432 (95% CI 0.052–3.610, $p = 0.439$) at 9–12 months of follow-up. Additionally, the incidences of all clinical outcomes were similar between IMs and NLOFMs throughout the follow-up period (Table 4).

Table 4
Primary Outcome, Secondary Outcome and Bleeding Outcome with CYP2C19 Phenotype

Outcomes	0-365 Days		0–90 Days		91–365 Days	
	Hazard Ratio (95% CI) [a]	p Value [a]	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Primary Outcome [b]						
NLOFM	Reference	—	Reference	—	Reference	—
IM	1.308 (0.788–2.170)	0.299	1.232 (0.544–2.790)	0.616	1.641 (0.560–4.808)	0.366
PM	1.698 (0.865–3.3315)	0.124	2.944 (1.184–7.321)	0.020	1.194 (0.393–3.630)	0.754
Secondary Outcome [c]						
NLOFM	Reference	—	Reference	—	Reference	—
IM	1.310 (0.824–2.083)	0.253	1.234 (0.546–2.794)	0.613	1.372 (0.785-2.400)	0.267
PM	1.677 (0.898–3.131)	0.105	3.309 (1.363–8.033)	0.008	0.884 (0.332–2.353)	0.805
Bleeding Outcome [d, e]						
NLOFM	Reference	—	Reference	—	Reference	—
IM	0.885 (0.455–1.721)	0.718	0.366 (0.069–1.951)	0.239	1.075 (0.510–2.266)	0.849
PM	1.152 (0.455–2.918)	0.766	1.172 (0.208–6.610)	0.857	1.086 (0.352–3.346)	0.886

CI confidence interval, *NLOFM* non-loss-of-function metabolizer, *IM* intermediate metabolizer, *PM* poor metabolizer.

[a] Hazard Ratios, confidence intervals and *p* values were calculated by means of Cox proportional hazard regression models adjusting for age, sex, coronary artery disease presentation, diabetes mellitus, hypertension, multiple-vessel disease, cerebrovascular disease, chronic kidney disease and previous myocardial infarction.

[b] Primary outcome was the composite of death from any cause, myocardial infarction, definite or probable stent thrombosis and ischemic stroke.

[c] Secondary outcome was the composite of death from any cause, myocardial infarction, definite or probable stent thrombosis, ischemic stroke and urgent target-vessel revascularization.

[d] Bleeding outcome was clinically significant bleeding events as defined by Bleeding Academic Research Consortium (BARC) criteria (including BARC 2, BARC 3, BARC 4)

[e] The BARC criteria were used for grading and categorizing bleeding events, BARC 2 referred to any overt, actionable sign of bleeding that requires medical intervention or evaluation, but not meet criteria for type 3 or higher BARC bleeding; BARC 3 indicated overt bleeding plus a decrease in hemoglobin of more than 3 g/dL, intracranial hemorrhage or intraocular hemorrhage compromising vision; BARC 4 was bleeding related to coronary-artery bypass grafting.

Patients who underwent PCI with the ACS indication accounted for the majority of events in the analysis, including 73 of 86 events in the composite MACCE outcome (84.9%) and 40 of 41 clinical bleeding events (97.6%). In line with the analysis of the overall study population, among subjects with ACS, an early MACCE occurred more often in PMs than in NLOFMs (adjusted HR 3.046, 95% CI 1.237–7.501, $p = 0.015$) (Online Table S2). A higher early risk of a component of MACCE plus

urgent TVR was also been found among PMs (adjusted HR 3.309, 95% CI 1.363–8.033, $p = 0.008$). Nevertheless, after the first 90 days, nevertheless, the differences in clinical outcome event risk among the groups were attenuated in the ACS subset (Online Table S2).

Discussion

In this monocentric retrospective cohort study, we evaluated the efficacy of clopidogrel among patients with different CYP2C19 phenotypes. The results demonstrated that among patients who were prescribed clopidogrel after PCI, carriers of two CYP2C19 LOF alleles were associated with a significantly higher risk of experiencing combined death from any cause, myocardial infarction, stent thrombosis or ischemic stroke within 90 days following the index PCI than NLOFMs. Notwithstanding, these higher MACCE rates of PMs did not persist post-procedure at 91–365 days of follow-up. Moreover, most clinical outcome events occurred in subjects who presented with ACS, among whom a higher risk for MACCE in PMs was similarly confined to the first 3 months following PCI. In addition, no in-group differences in bleeding events were observed at any follow-up time among the overall population or ACS patients. Finally, at the initial stage of clopidogrel administration, the proportion of patients with high platelet activity among the PMs was higher than that among the NLOFMs.

Our finding pertaining to the time period of high MACCE risk extends the results of previous studies examining the relationship between genetic polymorphisms and clinical outcome during DAPT. The genetic sub-study of the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial investigated the effects of CYP2C19 genotype on outcomes between and within clopidogrel and ticagrelor treatment groups [28]. Time-dependent interactions between phenotypes and the effects of clopidogrel on clinical events were observed, with significantly higher MACCE rates among patients with the CYP2C19 LOF allele at prophase after PCI than among those without it, but there was no significant difference between the genotype groups thereafter. In TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial, the largest randomized controlled trial (RCT) of CYP2C19 genotype-guided antiplatelet therapy to date, fewer adverse clinical events were found in the genotype-guided arm at the 0- to 3-month follow-up, and the initial superiority of this antiplatelet agent section strategy was lost by the time of the 1-year follow-up [29]. In this study, we also found that the difference in ischemic risk between phenotypes was attenuated after 90 days' follow-up, which may be related to the fewer events in the low-risk stage of thrombosis than in the high-risk period of thrombosis.

Although multiple lines of evidence support the association between CYP2C19 LOF (*2 and *3) alleles and ischemic events in patients treated with clopidogrel, homozygous carriers of LOF alleles are at higher risk than heterozygous carriers [7, 30, 31]. Conclusions from recent RCTs and meta-analyses, nevertheless, have not yet reached agreement on the clinical efficacy of gene-guided antiplatelet therapy [19, 29, 32]. Due to the lack of sufficient evidence, the current guidelines and consensus state that routine genetic testing is not recommended for tailoring DAPT [11, 33, 34].

Robust evidence originating from RCTs demonstrated that new-generation platelet inhibitors are superior to clopidogrel in reducing ischemic events, which results in current guidelines favoring more potent platelet inhibitors, including ticagrelor and prasugrel, over clopidogrel when DAPT is clinically indicated [12, 34]. However, the more prominent reduction in ischemic events of the new drugs was only seen only early on [8, 9, 35], while an increasing hemorrhagic risk occurred during the maintenance phase [10]. This rationale makes the concept of de-escalation of antiplatelet therapy has gradually aroused people's interest (i.e., intensive antiplatelet therapy is used only in the early phase following the procedure and is replaced with less potent antiplatelet therapy thereafter). Accumulative evidence has demonstrated a higher net benefit for the de-escalation strategy than for conventional antiplatelet therapy [14–16, 36]. However, a higher incidence of net adverse clinical events (including MACCEs and bleeding events) following an unreasonable downgrade switching of P2Y12 inhibitors in early phases of ACS was found in an observational, prospective study [37]. In conclusion, determining a reasonable and tailored time for patients with different ischemic risk to downgrade switching may be warranted during antiplatelet therapy.

The difference in early ischemic risk between CYP2C19 genotypes found in our study is mechanistically supportive of placing greater weight on a PM result during the platelet inhibitor de-escalating decision.

The POPular Genetics (Patient Outcome after Primary PCI) trial is a multicentre RCT aimed at determining whether patients undergoing PCI benefit from genotype-guided selection of P2Y12 inhibitors [38]. In the genotype-guided group, carriers of an LOF CYP2C19 allele were prescribed ticagrelor or prasugrel, whereas noncarriers received clopidogrel. Ultimately, genotype-guided therapy has not only been proven to be noninferior to standard treatment with prasugrel or ticagrelor in terms of preventing thrombotic events, but also resulted in a lower risk of hemorrhagic complications. This implies that the superiority of new-generation drugs compared with clopidogrel might partially be explained by eliminating the interindividual variability of pharmacodynamic effects. On the other hand, in keeping with our conclusions, several studies have shown that patients who received clopidogrel had similar rates of bleeding events, irrespective of CYP2C19 genotypes [20, 28]. In contrast, in a retrospective study focusing on patients with two LOF alleles, the risk of bleeding events was significantly higher in the ticagrelor group than in the clopidogrel group [39]. This seems to shed light on de-escalating strategies for the LOF alleles carriers.

It is worth noting that the East Asian population has a higher frequency of the CYP2C19 LOF allele carriers than the Caucasian and African American populations (50 to 60% among East Asians vs. 30% among Caucasians and African Americans) [31, 40], which was also confirmed in our study (58.3%). Moreover, the incidence of hemorrhagic events among East Asian patients receiving antiplatelet therapy seems to be greater than that among Caucasians [41, 42]. In contrast to well-established strategies of either DAPT de-escalation or gene guidance based on clinical outcome data from Caucasian patients, there is a paucity of data on East Asian patients who have a risk profile for both thrombosis and hemorrhage events that is different from that of Caucasians. Further studies that aim to provide insight into these gaps in evidence are necessary.

The monotonic increase in the incidence of low responsiveness to clopidogrel from NLOFMs to IMs to PMs in the present study is prominent. This finding is consistent with some studies of CYP2C19 variants and platelet function. Albeit it has been widely confirmed that high platelet reactivity during treatment is the direct cause of ischemic events in carriers of CYP2C19 LOF alleles, no clinical benefits were found in studies incorporating platelet function test results into antiplatelet therapy adjustments [43–45]. The high rates of longitudinal intraindividual variation in clopidogrel responder status might weaken the predictive information of platelet function testing [46, 47].

Limitations

There are several limitations in our study that merit being mentioned. In the present study, we analysed only patients who had CYP2C19 genotype results. However, the specific reasons for processing the CYP2C19 genotype test decided by the physician were unclear, which means that potential bias might exist in this cohort. Moreover, not all of genetic polymorphisms, including ABCB1 and PON1, that may be associated with clopidogrel responsiveness were analysed in our study. In addition, our study did not independently analyse carriers of the gain-of-function CYP2C19 allele (*17), mainly because the data on this allele are still controversial [33, 48]. In accordance with other follow-up studies, the use of death from any cause instead of cardiovascular mortality may affect the interpretation of the results. However, full information on the cause of death is rarely acquired; thus, cardiovascular mortality could not be reported in this study. Given that the number of bleeding events was small, the power to detect significant differences between bleeding between groups was probably limited in our study. Further specific studies on bleeding events are required to provide insight into these gaps in evidence.

Conclusions

The findings of the current study demonstrated that the higher risk for poor metabolizers prescribed clopidogrel is mainly to three months after PCI. This difference in ischemic risk between CYP2C19 phenotypes was also evident when analyses were

confined to patients with ACS. Nevertheless, the significantly high ischemic risk of LOF allele carriers was attenuated during the subsequent 9 months among both all-comer patients and subjects with ACS. Of note, there was no in-group difference in bleeding outcome between the three groups in any time period. Our data support the application potent antiplatelet therapy for patients with two CYP2C19 LOF alleles in the first 90 days following PCI and are thought to provoke the de-escalating of DAPT thereafter.

Declarations

Conflict of Interest

All authors declare that there are no conflicts of interests to disclose.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Beijing Anzhen Hospital (IRB number: 2021045X) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to Participate and for Publication

All patients signed informed consent to participate and for the publication of the data in anonymous form.

Author contribution

Study conception and design: Yang Zhang, Yong Zeng and Quan Li. Acquisition, analysis, or interpretation of data: Yang Zhang, Quan Li. Determination of clinical events: Yong Zeng, Quan Li, Yicong Ye and Xiliang Zhao. Drafted the manuscript: All authors. Handled funding and supervision: Yong Zeng and Quan Li.

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Availability of Data and Materials

Data and materials will be available upon reasonable request.

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Supplementary material

The online version of this article contains supplementary material, which is available at.

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Figures

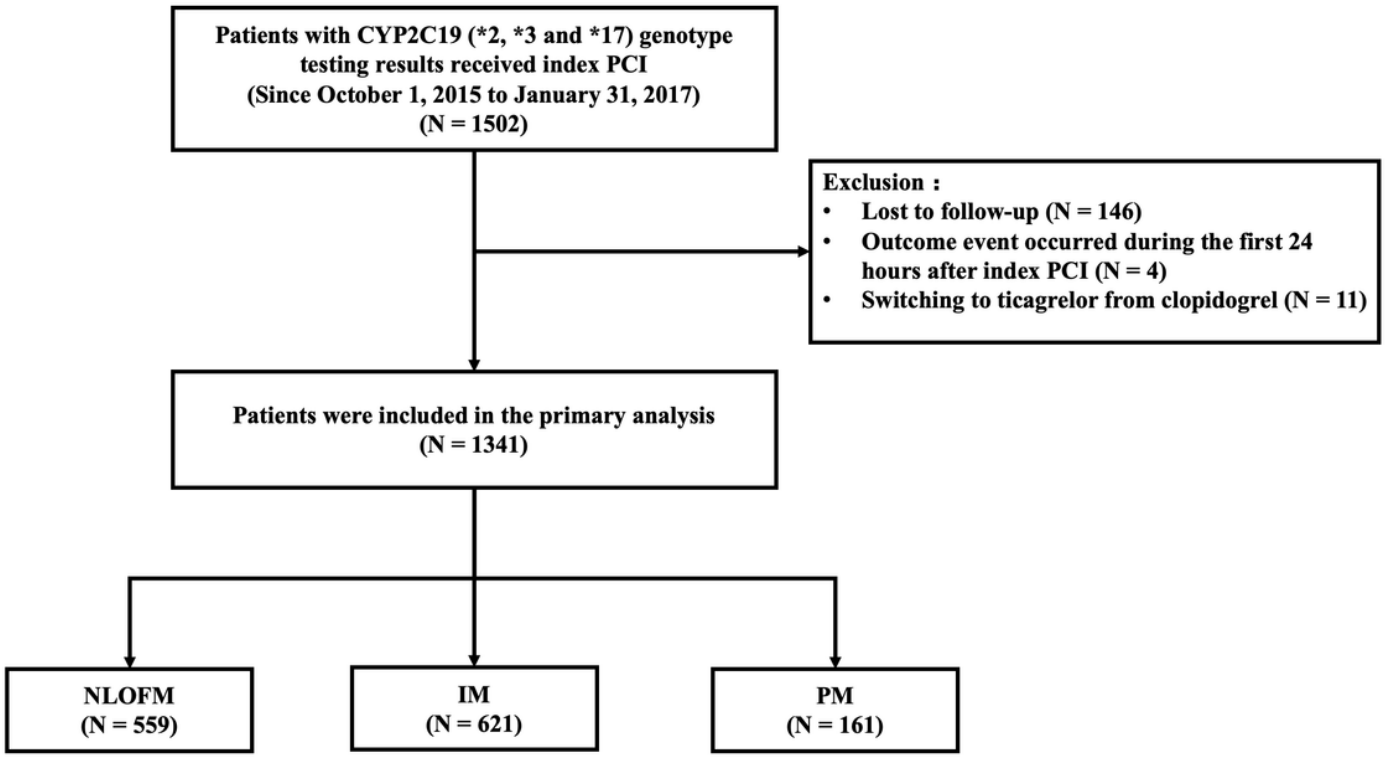

Figure 1

Flow Diagram of the Cohort Selection NLOFM non-loss-of-function metabolizer, IM intermediate metabolizer, PM poor metabolizer, PCI percutaneous coronary intervention.

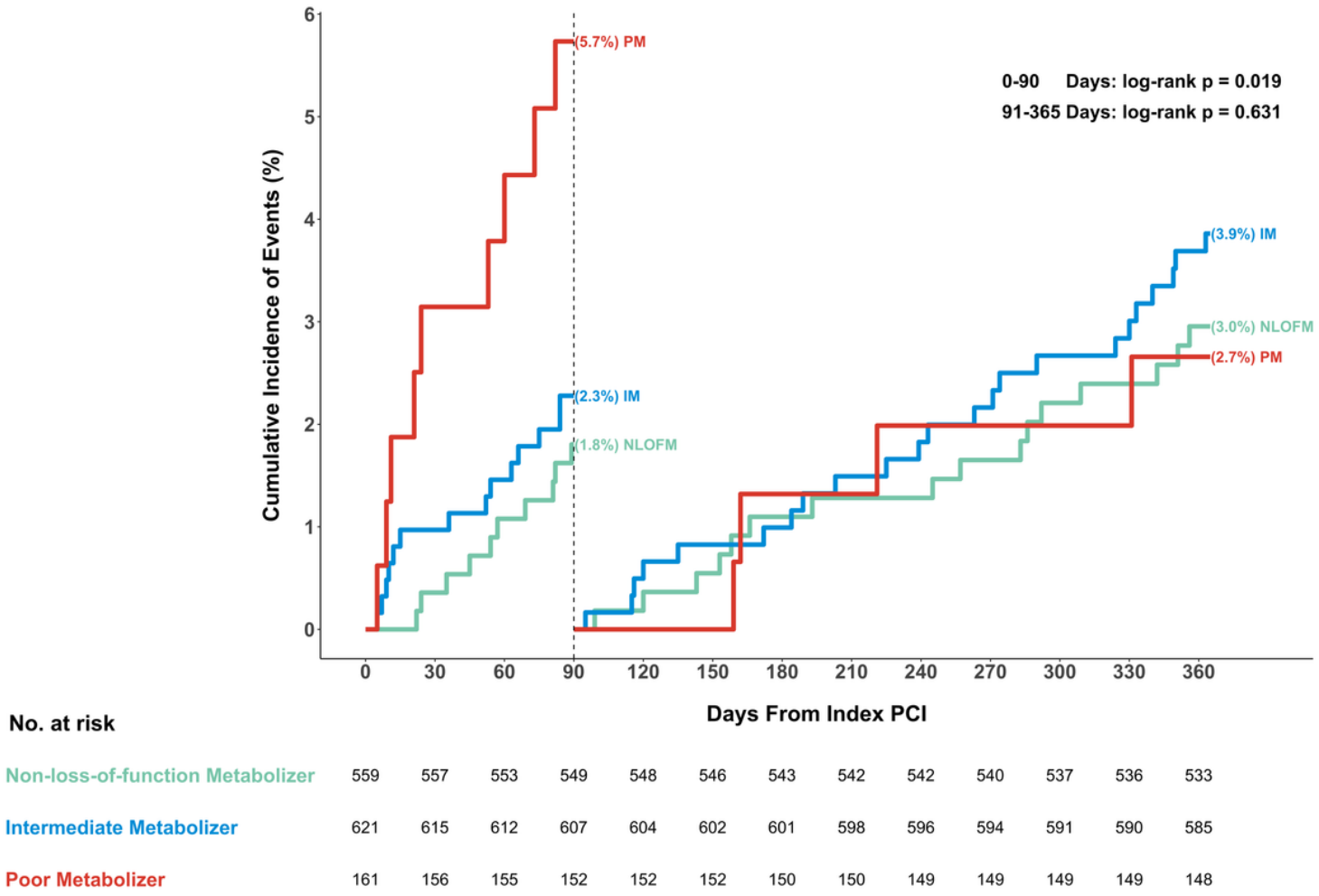

Figure 2

Incidence Curves for the Primary Outcome Event rates (%) were the Kaplan-Meier event rate. NLOFM non-loss-of-function metabolizer, IM intermediate metabolizer, PM poor metabolizer, PCI percutaneous coronary intervention. The primary outcome was the composite of death from any cause, myocardial infarction, definite or probable stent thrombosis and ischemic stroke. Landmark analysis was conducted at 90 days after index percutaneous coronary intervention.

Supplementary Files

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