CYP2C19 genotype has prognostic value in specific populations following coronary stenting

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Background: The prognostic value of the CYP2C19 genotype in post-percutaneous coronary intervention (PCI) patients remains controversial. The recently-published, limited-sample PHARMCLO trial indicates a personalized pharmacogenomic approach may reduce adverse events. This study aimed to determine the prognostic value of CYP2C19 genotypes.

Methods: The original cohort consisted of 10,724 PCI patients in 2013. 756 patients with genotyped CYP2C19 were included in our analysis. The CYP2C19 genotype prognostic value was tested based on different clinical factors. The primary endpoint was major adverse cardio- and cerebro-vascular event (MACCE).

Results: MACCE 2-years post-PCI occurred in 19 patients (17.4%) in poor metabolizers (PM, CYP2C19 *2/*2, *2/*3, *3/*3), 43 patients (12.2%) in intermediate metabolizers (IM, CYP2C19 *1/*2 or *1/*3) and 27 patients (9.2%) in extensive metabolizers (EM, CYP2C19 *1/*1). PM was an independent MACCE predictor compared with EM (HR: 1.960, 95% CI: 1.139–3.372), but the difference between IM and PM was not significant (HR: 1.314, 95% CI: 0.843–2.048). Major bleeding (BARC grade ≥3) was not significantly different between the three groups (2.5% *vs.* 2.1% *vs.* 0.8%, P=0.133). Subgroup analysis showed that the CYP2C19 genotype prognostic value was present in the following subgroups: male, age >60 years, body mass index (BMI) >24 kg/m^2, SYNTAX score >15, current smokers, and patients without chronic kidney disease.

Conclusions: Utilizing CYP2C19 genotype to guide post-PCI antiplatelet therapy might be appropriate in patients with the following characteristics: male, age >60 years, BMI >24 kg/m^2, SYNTAX score >15, current smokers, and non-chronic kidney disease (CKD) patients.

Keywords: Pharmacogenomics; antiplatelet; percutaneous coronary intervention; clopidogrel

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Introduction

Dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitors is the main approach to preventing ischemic events after the percutaneous coronary intervention (PCI) procedure (1). However, the most widely-used P2Y12 receptor inhibitor, clopidogrel, exhibits individual differences in efficacy (2). Genetic polymorphisms play an important role in individual drug reactions. Clopidogrel conversion to the active drug form is regulated by the CYP450 system, which presents multiple genetic polymorphisms (3). Numerous previous clinical pharmacogenomic studies determined that CYP2C19 loss-of-function (LOF) alleles (including the *2 and *3 alleles) are associated with high on-treatment platelet reactivity (4-7). In addition, other genetic variants associated with clopidogrel metabolism (*PON1* and *ABCB1*) may also contribute to the individual antiplatelet efficacy of clopidogrel (8,9).

Previous studies and meta-analyses showed that the CYP2C19 LOF allele in clopidogrel-treated PCI patients is associated with higher ischemic risk, including early stent thrombosis (4,10-13). However, some other studies presented contradictory results (14-16). In addition to genetic polymorphisms, clopidogrel responses are also influenced by other factors. Some drugs, including proton pump inhibitors, statins, calcium channel blockers, and warfarin, could alter clopidogrel pharmacodynamics by competing for metabolic enzymes (17,18). Clinical factors such as age, gender, diabetes, body mass index (BMI), renal dysfunction, and hyperlipidemia may also contribute to the individual clopidogrel response (19-22). How these factors comprehensively influence clopidogrel reactivity is of great significance.

The present study aimed to evaluate the prognostic value of CYP2C19 genotypes in patients with different clinical characteristics, including gender, age, BMI, synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score, smoking status, diabetes mellitus, and chronic kidney disease. We provide evidence that the CYP2C19 genotype can inform optimal antiplatelet treatment with clopidogrel. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7724).

Methods

Study design and participants

This is a retrospective, single-center cohort study. The detailed study design is shown in *Figure 1*. The corresponding and first author had full access to all study data, and take responsibility for data integrity and analysis. The original cohort consisted of 10,724 PCI patients who were admitted to Fuwai Hospital, the National Center of Cardiovascular Diseases (Beijing, China), throughout 2013. Within this cohort, 756 patients taking CYP2C19 genotype test were eligible. Because ticagrelor was made available in the Chinese market at the end of 2012, only 4 subjects in our original cohort used this medication to replace clopidogrel. Another 9 patients took double-dosage clopidogrel or triple-antiplatelet medication with cilostazol before discharge. These 12 patients were excluded from our analysis because different antiplatelet strategies have confounding effects on the predictive value of CYP2C19 genotypes. Two-year follow-up was completed after PCI with either a subsequent visit or by telephone. Exclusion criteria included aspirin or clopidogrel allergy, bleeding disorder, chronic oral anticoagulation drugs such as warfarin, contraindication to antiplatelet therapy, severe anemia, tumor, or severe immune system disorder. Baseline information and clinical profiles were retrieved from medical records. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage. Diabetes mellitus was defined as at least 200 mg/dL blood glucose after a 2-hour glucose tolerance test, fasting glucose ≥126 mg/dL (≥7.0 mM), HbA1c ≥6.5%, physician-diagnosed diabetes, and/or use of diabetic medication.

All the participants provided signed informed consent for the original cohort study and subsequent analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Fuwai Hospital (No. 2016-847) and individual consent for this retrospective analysis was waived.

DNA extraction and CYP2C19 genotyping

CYP2C19 genotypes were tested by gene sequencing in the Central Laboratory of Fuwai Hospital during hospitalization. We extracted DNA from peripheral blood with a Thermo Kingfisher Flex system (BOKUN BIOTECH, China). DNA was stored at −80 ℃ until analysis. CYP2C19*2 and *3 were genotyped using a CYP2C19*2 and *3 Gene Detection Fluorescence PCR Capillary Electrophoresis Sequencing Analysis Kit (Beijing SinoMDgene Technology Co., Ltd) and was performed on

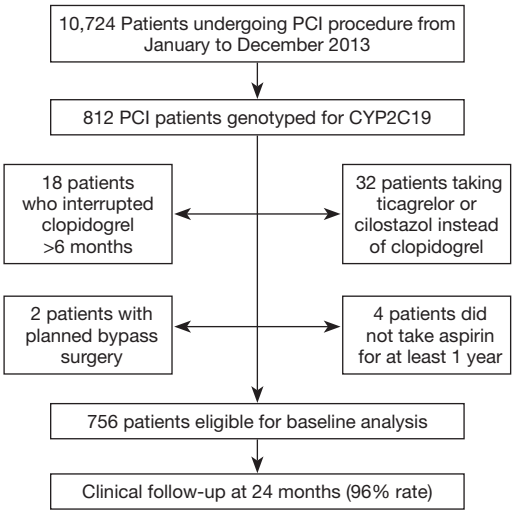

Figure 1 Study flow diagram.

an ABI 3500xL Dx DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Genotypes were confirmed independently by two professionals. 5% of sequence data was verified by resequencing. CYP2C19*2 and *3 alleles were defined as "LOF" alleles. Patients with *1/*1 alleles were defined as extensive metabolizers (EM), those with a single *2 or *3 allele (i.e., *1/*2 or *1/*3) were defined as intermediate metabolizers (IM), and those with two *2 or *3 alleles (i.e., *2/*2, *2/*3 or *3/*3) were defined as poor metabolizers (PM).

Antiplatelet treatment, follow-up, study endpoints, and subgroup analysis strategy

All 756 post-PCI patients received a 300 mg loading dose of clopidogrel and aspirin before PCI, followed by a daily 100 mg maintenance dose of aspirin and 75 mg clopidogrel for at least 1 year. Clinical and telephone follow-up was conducted on Day 30 and Months 6, 12, and 24 to monitor ischemic and bleeding endpoints.

The primary endpoint of our study was major adverse cardiovascular and cerebrovascular event (MACCE, a composite of all-cause death, myocardial infarction, target vessel revascularization, and cerebrovascular events). An independent event committee of two cardiologists was responsible for events adjudication. Academic Research Consortium (ARC) (23)-defined stent thrombosis was also recorded. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) (24) type 3 and 5 bleeding events. Acute myocardial infarction was diagnosed in accordance with the universal definition proposed in 2012. Target vessel revascularization was clinically driven. Stroke was defined as focal neurologic function loss caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death.

Variables included in the multivariate Cox analysis and used for subgroup stratification were selected by reviewing previous studies about potential factors contributing to the individual clopidogrel response. Finally, we took gender, age, BMI, SYNTAX score, smoking status, diabetes mellitus, and chronic kidney disease into the multivariate model. The threshold of age was selected based on the WHO definition of old age (60 years). BMI >24 kg/m^2 is according to the Chinese overweight standard. SYNTAX tertiles were used to define high-risk (upper tertile, >15) and intermediate-low risk groups (medium-lower tertile, ≤15).

Statistical analysis

All continuous variables are presented as mean ± SD. Analysis of variance (ANOVA) was used to compare means across multiple groups. Non-continuous and categorical variables are presented as frequencies or percentages and were compared using Chi-square tests or Fisher's exact tests. Kaplan-Meier curve analysis was used to calculate time to clinical endpoints. Between-group differences were evaluated by log-rank tests. The Cox proportional hazards model was further applied to estimate hazard ratios, and the proportional hazards assumptions were tested by log minus log plot. All patient data were censored at the date of the last available information. Cox analysis was performed to establish clinical variables associated with clinical events. The interaction between CYP2C19 genotypes and clinical risk factors was tested using Cox analysis. A two-sided P value <0.05 indicated statistical significance. Statistical analysis was performed using SPSS version 21 software (IBM Institute Inc., USA).

Results

Baseline study population characteristics

From January to December 2013, we recruited 756 eligible PCI patients and determined their CYP2C19 genotypes. All the patients included in the present study underwent PCI procedure with 2nd generation DES (new-generation DES). The utilization of intravenous ultrasound imaging

Table 1 Baseline study population characteristics stratified by CYP2C19 genotype

	EM, N=294	IM, N=353	PM, N=109	P value
Age (years)	57.47±10.12	58.07±10.19	56.44±10.09	0.331
Male	209 (71.1%)	270 (76.5%)	83 (76.1%)	0.263
BMI (kg/m^2)	26.28±3.25	25.97±3.12	25.82±3.6	0.335
Diabetes mellitus	101 (34.4%)	112 (31.7%)	35 (32.1%)	0.767
Hypertension	192 (65.3%)	237 (67.1%)	65 (59.6%)	0.355
Dyslipidemia	207 (70.4%)	249 (70.5%)	78 (71.6%)	0.973
CKD	111 (47.6%)	145 (49.7%)	38 (48.7%)	0.900
Peripheral arterial disease	12 (4.1%)	7 (2.0%)	2 (1.8%)	0.219
AMI presentation	69 (23.5%)	83 (23.5%)	27 (24.8%)	0.959
Previous MI	35 (13.8%)	50 (16.7%)	15 (16.9%)	0.617
Previous stroke	30 (10.2%)	44 (12.5%)	7 (6.4%)	0.191
Previous PCI	62 (24.5%)	104 (29.5%)	32 (29.4%)	0.122
Previous CABG	11 (3.7%)	20 (5.7%)	6 (5.5%)	0.502
Bleeding history	2 (0.7%)	3 (0.8%)	1 (0.9%)	0.379
Current smoking	155 (52.7%)	185 (52.4%)	57 (52.3%)	0.703
SYNTAX score	10 [7–17]	10 [6–17]	10 [5–17]	0.613
C type lesions	164 (55.8%)	201 (56.9%)	53 (48.6%)	0.538
Trans-radial approach	249 (84.7%)	286 (81.0%)	89 (81.7%)	0.493
No. of stents	1.93±1.07	1.9±1.12	1.77±0.96	0.420
Stent length (mm)	34.47±18.5	34.37±19.06	32.12±15.42	0.497
LVEF (%)	62.61±6.11	62.83±7.18	62.16±6.02	0.657
Statins	264 (89.9%)	324 (91.8%)	100 (91.7%)	0.651
Beta-blockers	248 (84.4%)	304 (86.1%)	88 (80.7%)	0.004
Calcium-channel blockers	170 (57.8%)	202 (57.2%)	70 (64.2%)	0.504
Proton pump inhibitors	38 (12.9%)	50 (14.1%)	15 (13.8%)	0.617
ACEi/ARB	203 (69.0%)	255 (72.2%)	76 (69.7%)	0.173

Values are mean ± SD or n (%). Continuous variables were compared using one-way ANOVA and Bonferroni post-hoc analysis. Categorical variables were compared using Chi-square test. EM, extensive metabolizers, CYP2C19 genotype *1/*1; IM, intermediate metabolizers, CYP2C19 genotype *1/*2 or *1/*3; PM, poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3; BMI, body mass index; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

could be found in about 10% in the whole cohort. Based on CYP2C19 genotyping results, 294 patients (38.9%) were included in the EM group (i.e., *1/*1), 353 patients (46.7%) in the IM group (i.e., *1/*2 or *1/*3), and 109 patients (14.4%) in the PM group (i.e., *2/*2, *2/*3 or *3/*3). During the 2-year follow-up period, adverse event and vital status information was available for 96% of the total study population. Baseline subject characteristics are presented in *Table 1*. Most comorbidities, medications, and PCI procedure parameters were well matched, except for beta-blocker use (84.4% in EM, 86.1% in IM, and 80.7% in PM, P=0.004). The transradial approach was used in

Table 2 Univariate Cox survival analysis for MACCE events among different CYP2C19 genotypes

	IM *vs.* EM			PM *vs.* EM		
	HR	95% CI	P value	HR	95% CI	P value
Whole cohort	1.314	0.843–2.048	0.227	1.960	1.139–3.372	0.015
Male	1.394	0.827–2.351	0.213	2.068	1.098–3.895	0.024
Female	1.105	0.469–2.603	0.819	1.676	0.572–4.906	0.346
SYNTAX score >15	1.683	0.845–3.350	0.139	2.791	1.273–6.119	0.010
SYNTAX score ≤15	1.071	0.595–1.928	0.819	1.342	0.611–2.948	0.463
Age >60	1.353	0.682–2.687	0.387	2.736	1.248–5.998	0.012
Age ≤60	1.284	0.717–2.300	0.400	1.461	0.679–3.142	0.332
BMI >24	1.525	0.902–2.578	0.115	2.648	1.390–5.042	0.003
BMI ≤24	0.880	0.380–2.036	0.765	0.980	0.356–2.695	0.968
DM	1.510	0.713–3.196	0.282	2.176	0.875–5.412	0.094
Non-DM	1.222	0.705–2.119	0.476	1.858	0.945–3.654	0.073
Current smoking	1.415	0.775–2.586	0.259	2.024	0.967–4.238	0.062
Non-smoking	1.212	0.628–2.336	0.567	1.887	0.847–4.200	0.120
CKD	0.960	0.466–1.977	0.912	1.350	0.513–3.552	0.543
Non-CKD	1.603	0.911–2.818	0.101	2.372	1.219–4.613	0.011

EM, extensive metabolizers, CYP2C19 genotype *1/*1; IM, intermediate metabolizers, CYP2C19 genotype *1/*2 or *1/*3; PM, poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3; BMI, body mass index; CKD, chronic kidney disease; MI, myocardial infarction; DM, diabetes mellitus.

84.7%, 81.0%, and 81.7% of patients in the three groups, respectively (P=0.493). Total stent length per patient was 34.47±18.5, 34.37±19.06, and 32.12±15.42 mm, respectively (P=0.497). Acute myocardial infarction occurrence at admission was not statistically different (23.5%, 23.5%, and 24.8%; P=0.959). Similar SYNTAX scores were found among the three groups (P=0.613).

Clinical outcomes in the whole cohort

The primary endpoint of MACCE events (defined as a composite of all-cause death, myocardial infarction, target vessel revascularization or stroke) two years post-PCI occurred in 19 patients (17.4%) in the PM group, 43 patients (12.2%) in the IM group, and 27 patients (9.2%) in the EM group. In univariate Cox analysis, PM was an independent predictor for MACCE events compared with EM (see *Table 2*; HR: 1.960, 95% CI: 1.139–3.372, P=0.015), but the difference between the IM and PM groups was not significant (see *Table 2*; HR: 1.314, 95% CI: 0.843–2.048, P=0.227). After adjusting for potential confounders including age, gender, diabetes, body mass index, renal dysfunction, smoking, and SYNTAX score, PM was still the most significant MACCE predictor (see *Table 3*; HR: 1.957, 95% CI: 1.132–3.384, P=0.016). Again, no significantly increased adverse event risk was detected between PM and EM groups (HR: 1.344, 95% CI: 0.861–2.098, P=0.194). *Figure 2* shows the cumulative Kaplan-Meier MACCE estimates among the three groups (PM *vs.* EM: log-rank P=0.014; IM *vs.* EM: log-rank P=0.223).

No significant difference was detected in the major bleeding rates (BARC grade ≥3) between the three groups (2.1% in PM, 2.3% in IM, and 2.6% in EM). Regarding in-stent thrombosis, the very low incidence in the study cohort might explain the lack of significant differences. There was 1 case (0.9%) in PM, 6 cases (1.7%) in IM, and 2 cases (0.7%) in EM.

Subgroup analysis of CYP2C19 genotype prognostic value

To evaluate the prognostic value of CYP2C19 genotypes in patients with different clinical characteristics, subgroup

Table 3 Multivariate Cox survival analysis for MACCE events among different CYP2C19 genotypes

	IM *vs.* EM			PM *vs.* EM		
	HR	95% CI	P value	HR	95% CI	P value
Whole cohort	1.344	0.861–2.098	0.194	1.957	1.132–3.384	0.016
Male	1.434	0.849–2.422	0.178	2.067	1.087–3.391	0.027
Female	1.145	0.480–2.729	0.760	1.447	0.481–4.353	0.511
SYNTAX score >15	1.717	0.861–3.423	0.125	2.952	1.329–6.558	0.008
SYNTAX score ≤15	1.122	0.621–2.028	0.703	1.394	0.628–3.093	0.415
Age >60	1.380	0.693–2.749	0.360	2.721	1.215–6.093	0.015
Age ≤60	1.278	0.711–2.298	0.412	1.585	0.726–3.462	0.248
BMI >24	1.566	0.923–2.657	0.096	2.391	1.249–4.577	0.008
BMI ≤24	0.947	0.405–2.216	0.901	0.977	0.343–2.781	0.965
DM	1.580	0.744–3.357	0.234	2.109	0.834–5.330	0.115
Non-DM	1.239	0.714–2.151	0.446	1.714	0.861–3.410	0.125
Current smoking	1.462	0.798–2.678	0.218	2.153	1.017–4.560	0.045
Non-smoking	1.199	0.619–2.323	0.591	1.819	0.801–4.132	0.153
CKD	0.972	0.470–2.012	0.939	1.078	0.397–2.923	0.883
Non-CKD	1.613	0.915–2.845	0.098	2.412	1.231–4.727	0.010

EM, extensive metabolizers, CYP2C19 genotype *1/*1; IM, intermediate metabolizers, CYP2C19 genotype *1/*2 or *1/*3; PM, poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3; BMI, body mass index; CKD, chronic kidney disease; MI, myocardial infarction; DM, diabetes mellitus.

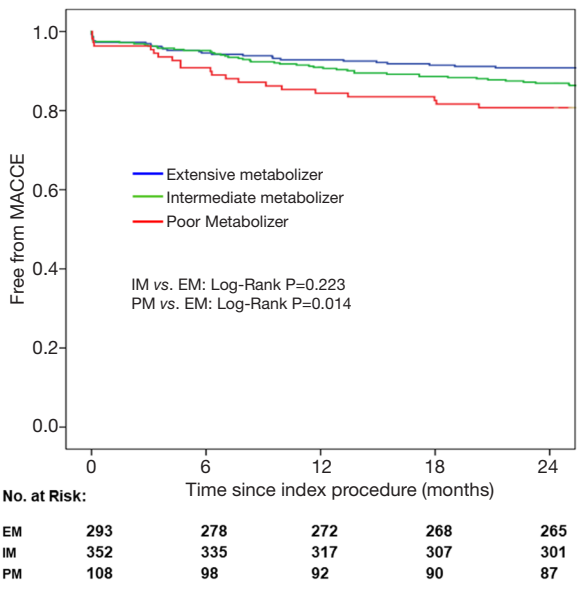

Figure 2 Cumulative Kaplan-Meier estimates of the primary endpoints (MACCE) in the whole cohort. MACCE, major adverse cardiac and cerebrovascular events. EM, extensive metabolizers, CYP2C19 genotype *1/*1; IM, intermediate metabolizers, CYP2C19 genotype *1/*2 or *1/*3; PM, poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3.

analysis was performed at the following levels: male or female, age >60 years or ≤60 years, BMI >24 kg/m^2 or ≤24 kg/m^2, SYNTAX score >15 or ≤15, smoking or non-smoking, diabetes mellitus (DM) or non-DM. The multivariate Cox analysis presented in *Table 3* was also adjusted for the above confounders.

The prognostic value of the PM genotype, which has been detected in the whole cohort, differed in patients with different characteristics (*Tables 2,3*). A significant CYP2C19 genotype prognostic value (PM *vs.* EM) was found in the following subgroups (*Figure 3*): male (HR: 2.067, 95% CI: 1.087–3.391, P=0.027), age >60 years (HR: 2.721, 95% CI: 1.215–6.093, P=0.015), BMI >24 kg/m^2 (HR: 2.391, 95% CI: 1.249–4.577, P=0.008), SYNTAX score >15 (HR: 2.952, 95% CI: 1.329–6.558, P=0.008), current smoking (HR: 2.153, 95% CI: 1.017–4.560, P=0.045), and non-CKD (HR: 2.412, 95% CI: 1.231–4.727, P=0.010). In patients without these clinical characteristics, no significant correlation was found between CYP2C19 genotype and clinical prognosis. *Figures 4* and *5* show the cumulative Kaplan-Meier estimates of MACCE in different subgroups. Interestingly, the CYP2C19 prognostic value (PM *vs.* EM) was similar

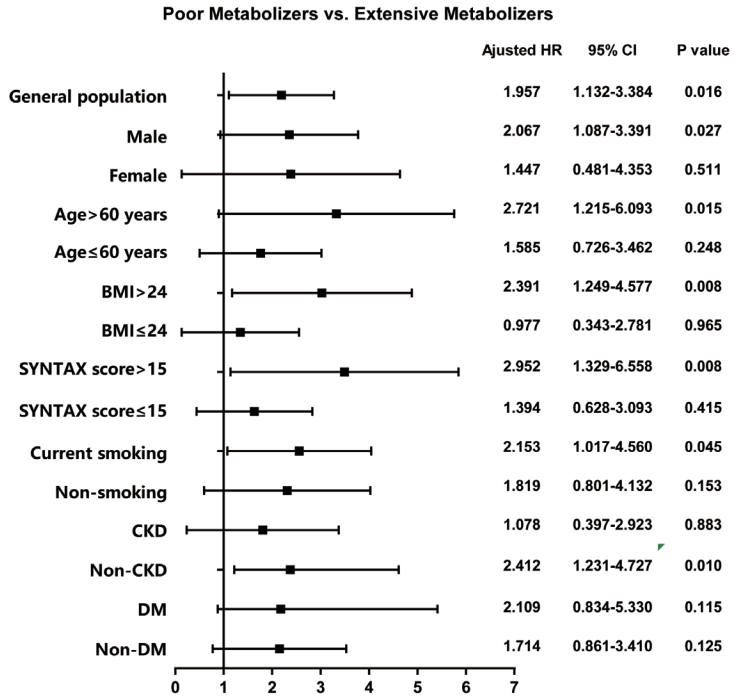

Figure 3 Hazard ratios from CYP2C19 genotype prognostic value subgroup analysis. Extensive metabolizers, CYP2C19 genotype *1/*1; poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus.

in patients with DM (HR: 2.109, 95% CI: 0.834–5.330, P=0.115) or without DM (HR: 1.714, 95% CI: 0.861–3.410, P=0.125).

Discussion

The prognostic value of CYP2C19 genotypes in post-PCI patients is still controversial. A recently-published study (25) named the PHARMCLO trial indicated that personalized pharmacogenomic approaches may reduce adverse events. However, the study was only conducted in a limited sample population. Our results suggest that the CYP2C19 predictive value manifests in patients with the following characteristics: male, age >60 years, BMI >24 kg/m^2, SYNTAX score >15, current smokers, and non-CKD. These findings support the idea that utilizing the CYP2C19 genotype to guide post-PCI antiplatelet therapy in specific populations might be appropriate.

It was previously reported that platelet aggregation increases gradually when haplotypes *1, *2, and *3 were replicated by diplotypes (3). CYP2C19 LOF alleles *2 and *3 are all associated with platelet aggregation risk. Similarly, platelet aggregation activity showed a slight uptrend along with increased LOF alleles. However, it was also reported that clopidogrel responses can be influenced by other factors. The other two genetic variants associated with clopidogrel metabolism (*PON1* and *ABCB1*) could contribute to the individual antiplatelet efficacy of clopidogrel (8,9). Some drugs, including proton pump inhibitors, statins, calcium channel blockers, warfarin, and others, could alter the clopidogrel pharmacodynamics by competing with metabolic enzymes (17,18). Clinical factors such as age, gender, diabetes, BMI, renal dysfunction, and hyperlipidemia may also contribute to the individual clopidogrel response (11,19,20). With complex confounding factors, previous studies evaluating the prognostic value of CYP2C19 did not present a convincing conclusion to guide clinical applications.

In early 2020, Angiolillo DJ and his colleagues published the development and validation of ABCD-GENE score, which is a useful tool to identify patients at high risk for high on-treatment platelet reactivity (26). Combining 4 clinical factors including age, BMI, CKD and diabetes and 1 genetic factor (CYP2C19 LOF), the ABCD-GENE score was validated in the external cohorts, including a Japan cohort (27). These findings supported the view derived

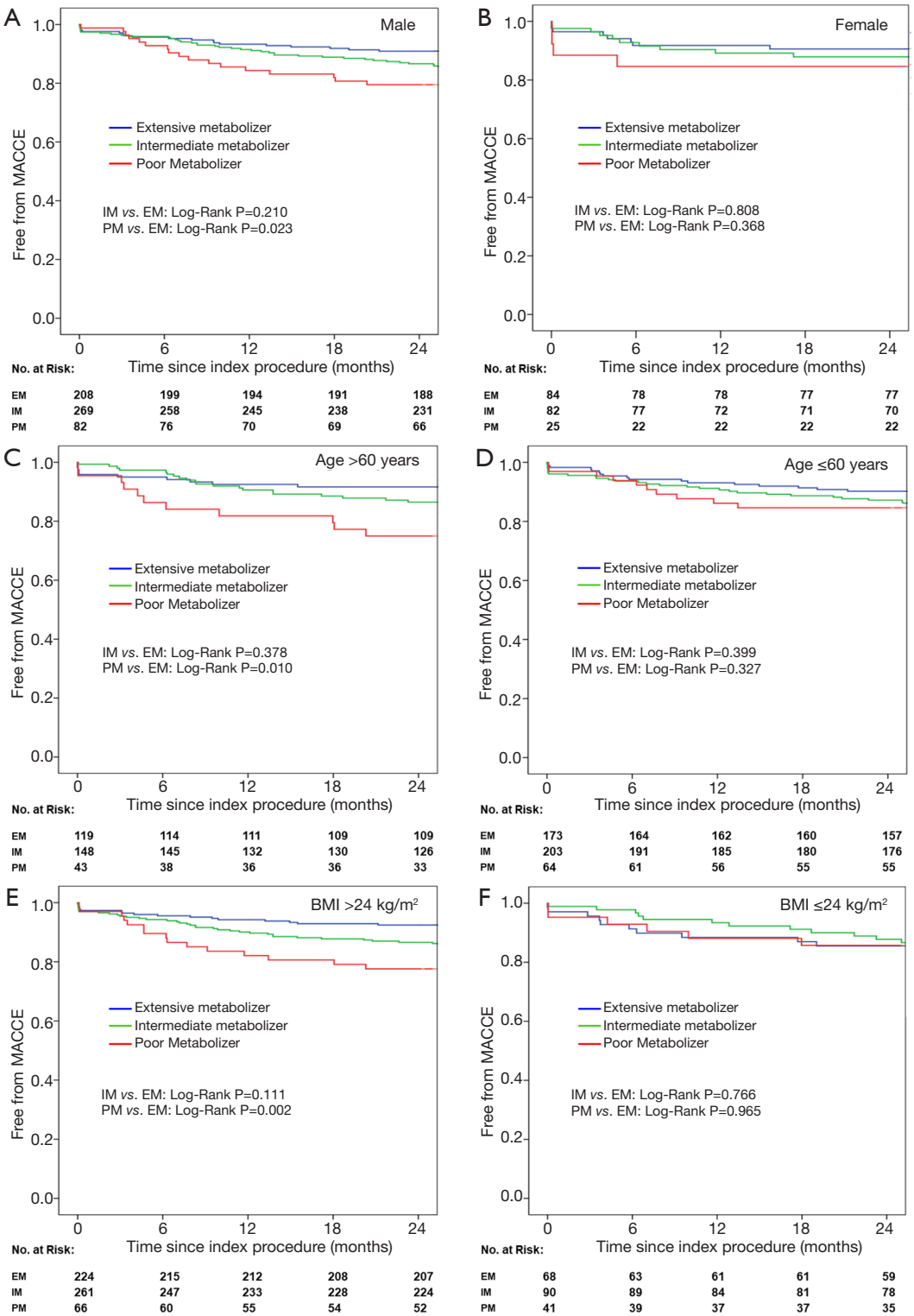

Figure 4 Cumulative Kaplan-Meier MACCE Estimates in Sex, Age, and BMI Subgroups. (A) male subgroup; (B) female subgroup; (C) age >60 years subgroup; (D) age ≤60 years subgroup; (E) BMI >24 kg/m^2 subgroup; (F) BMI ≤24 kg/m^2 subgroup. EM, extensive metabolizers, CYP2C19 genotype *1/*1; IM, intermediate metabolizers, CYP2C19 genotype *1/*2 or *1/*3; PM, poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3.

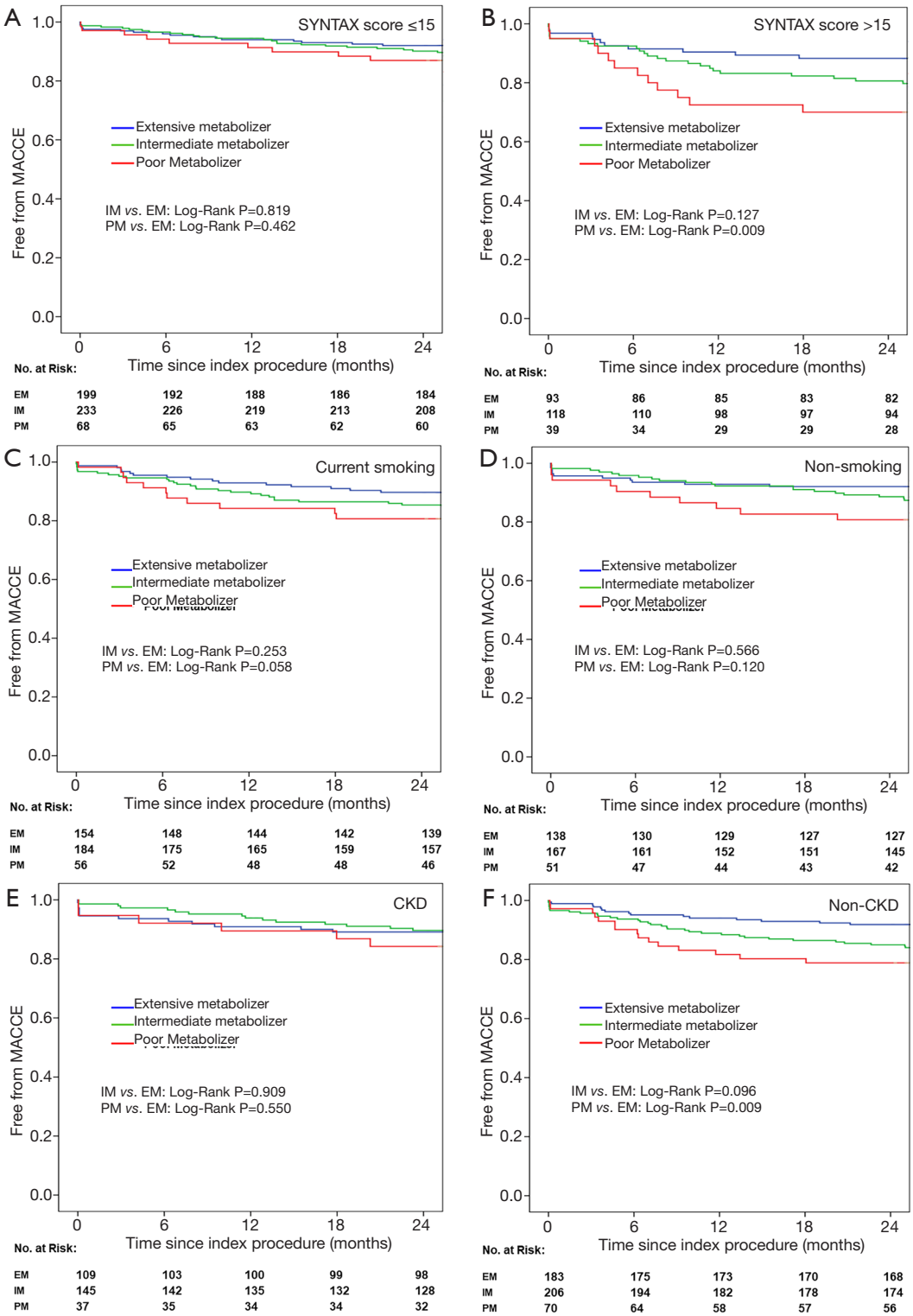

Figure 5 Cumulative Kaplan-Meier MACCE Estimates in SYNTAX score, smoking, and CKD subgroups. (A) SYNTAX score ≤15 subgroup; (B) SYNTAX score >15 subgroup; (C) current smoking subgroup; (D) non-smoking subgroup; (E) CKD subgroup; (F) non-CKD subgroup. EM, extensive metabolizers, CYP2C19 genotype *1/*1; IM, intermediate metabolizers, CYP2C19 genotype *1/*2 or *1/*3; PM, poor metabolizers, CYP2C19 genotype *2/*2, *2/*3, or *3/*3.

from our study: CYP2C19 genotype should be interpreted and applicated based on specific clinical settings. In recent years, two large-scale clinical trials of CYP2C19 genotype-guided antiplatelet therapy following percutaneous coronary intervention offer new insight of the clinical utility of genotyping strategy to personalize antiplatelet therapy selection. The POPular Genetics trial published in 2019 found that CYP2C19 genotype–guided strategy for selection of oral P2Y12 inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding (28). In the TAILOR-PCI trial published in 2020, among CYP2C19 LOF carriers undergoing PCI, genotype-guided selection of an oral P2Y12 inhibitor, compared with conventional clopidogrel therapy, resulted in no statistically significant difference in a composite ischemic endpoint (29). The above two trials indicated that the separate utilization of CYP2C19 genotype in general PCI population might not be reasonable.

In the PHARMCLO trial, researchers evaluated whether selecting antiplatelet therapy (clopidogrel, prasugrel, or ticagrelor) on the basis of patient genetic and clinical characteristics leads to better clinical outcomes. Although the study was prematurely terminated because of lacking *in vitro* diagnosis certification, this trial still suggests improved outcomes after evaluation of genetic factors. An obviously different strategy taken in this study is that although all the patients in the pharmacogenomic group received genotyping tests, the final decision was left to doctors after comprehensively balancing ischemic/bleeding risk. Taking clinical characteristics into account, pharmacogenomic information became an important decision-making factor. The further questions are: (I) Is pharmacogenomic guidance applicable for all PCI patients? and (II) If not, who should receive pharmacogenomic testing? Our study provides preliminary indications for these questions.

Bliden *et al.* reported that current smokers on clopidogrel therapy displayed significantly lower platelet aggregation and adenosine diphosphate (ADP)-stimulated active glycoprotein (GP) IIb/IIIa expression compared with non-smokers (30), indicating that smoking might be an important cause of response variability to clopidogrel therapy. Cigarette smoking induces cytochrome P450 (31), which is involved in clopidogrel metabolism. In addition, smoking also influences the long-term benefit of clopidogrel therapy in PCI patients (19). In our study, CYP2C19 genotyping could better predict future clinical events in current smokers following PCI procedures.

In 2014, Tabata *et al.* found that kidney function status modified the effects of CYP2C19 polymorphisms on clinical outcome in patients following coronary stent implantation (21). Including 154 CKD patients and 177 non-CKD patients, CYP2C19 LOF allele carriers were identified as independent cardiovascular event predictors only in the non-CKD group. CKD is also a prognostic factor in PCI patients. Moreover, previous clinical observations suggest that CKD itself contributes to high residual platelet reactivity. Thus, the CKD contribution to platelet reactivity and adverse clinical events might outweigh the influence of the CYP2C19 genotype in CKD patients.

Higher rates of cardiovascular events were predicted by CYP2C16 genotype in other populations in our study, including males, age >60 years, BMI >24 kg/m^2, and SYNTAX score >15. Differing adverse event rates might explain some previous controversies regarding the effects of CYP2C19 LOF alleles on clinical outcome in patients receiving DAPT. In patients with traditional high-risk predictors (male, aged, high SYNTAX score, high BMI), the adverse event incidence increased, causing a more significant difference of clinical outcomes among genotype subgroups than in the low-risk population. In other words, using CYP2C19 genotypes is more suitable in populations with high adverse cardiovascular event risk.

Increasing evidence indicates that East Asian patients have different risk profiles for thrombophilia and bleeding compared with Caucasian patients. Thus, a different 'therapeutic window' of antiplatelet therapy might be appropriate in East Asian patients (32-35). The CYP2C19 LOF genotype is almost twice as prevalent in Asian populations compared to Caucasian populations, thus contributing to the high prevalence of low clopidogrel responsiveness in Asians (36). However, the incidence of adverse ischemic outcomes or stent thrombosis after PCI is similar or lower than in white patients, and is called the "East Asian paradox" (33). Our study findings indicate that in East Asian PCI patients, CYP2C19 genotypes might be an effective tool for predicting clinical outcomes and selecting an appropriate intensity of antiplatelet therapy.

There were several limitations in the present study. First, as showed in *Figure 1*, only about 800 patients of the total PCI cohort took genotype test, leading to the unavoidable selection bias of the present study. This limits its homogeneity in the general PCI population Second, the individual variability in clopidogrel responsiveness was multifactorial. CYP2C19*2 explained only about 12% of the

potential variation in clopidogrel responses. Other potential genetic mutations were not included in our research, such as CYP2C19*17, PON1, and ABCB1. Third, this is a single-center study with a limited sample size. Although a single-center design helps maintain standard procedures (PCI, genotype, medication and follow-up), a multi-center design with a larger sample could provide more replicable data. Finally, more than 70% of subjects in this study were male. This gender disparity might lead to a relatively inadequate statistical power in female subgroups.

Conclusions

Our results indicate that CYP2C19 genotype has a greater prognostic value in PCI patients with one of the following clinical characteristics: male, age >60 years, BMI >24 kg/m^2, SYNTAX score >15, current smoking, and no chronic kidney disease. The study findings support the idea that a personalized approach using CYP2C19 genotyping to guide post-PCI antiplatelet therapy might be appropriate.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the participants provided signed informed consent for the original cohort study and subsequent analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Fuwai Hospital (No. 2016-847) and individual consent for this retrospective analysis was waived.

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