High Platelet Reactivity Combined with *CYP2C19* Genotype in Predicting Outcomes in East Asian Patients Undergoing Percutaneous Coronary Intervention

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Loss-of-function (LoF) alleles of cytochrome P450 2C19 (*CYP2C19*), which are prevalent in East Asians, are linked to high platelet reactivity (HPR) phenotype and poor prognosis. We aimed to investigate the incremental predictive value of HPR combined with *CYP2C19* genotype in predicting outcomes after drug-eluting stent (DES) implantation. The patients treated with platelet function and genotype-related long-term prognosis in drug-eluting stent (PTRG-DES) consortium enrolled a total of 13,160 Korean patients treated with DES who had platelet function test (PFT) or *CYP2C19* genotype, of which, 6,717 patients with PFT and genotype together were categorized. HPR was defined as VerifyNow ≥252 P2Y12 reaction unit. The primary outcome was the incidence of major adverse cardiac and cerebrovascular event (MACCE) 5 years after treatment. The patients with both HPR and *CYP2C19* LoF/LoF had the highest MACCE rates (6.2%) and increased MACCE risk (adjusted hazard ratio: 1.89, 95% confidence interval: 1.20–2.91, *P* = 0.006) compared with those without both HPR and *CYP2C19* LoF/LoF. There was no effect of interaction between HPR and *CYP2C19* genotype on the primary outcome (*P* = 0.424). Adding combined HPR and *CYP2C19* genotype to the conventional model had an incremental influence in predicting MACCE and stent thrombosis. Compared to the model including HPR or *CYP2C19* genotype alone, a combination model significantly improved the risk stratification for stent thrombosis but not MACCE. In DES-treated East Asian patients, the combined evaluation of PFT results and *CYP2C19* genotyping might improve risk prediction of ischemic events during clopidogrel treatment.

Study Highlights

WHAT IS THE CURRENT KNOWLEGE ON THE TOPIC?

☑ Loss-of-function (LoF) alleles of cytochrome P450 2C19 (*CYP2C19*) are linked to a high platelet reactivity (HPR) phenotype and poor prognosis in drug-eluting stent (DES)-treated patients receiving clopidogrel. The frequency of *CYP2C19* LoF alleles and the level of platelet reactivity differ between East Asians and Whites. Nevertheless, the prognostic implications of combined platelet reactivity and the *CYP2C19* genotype are undetermined, specifically in East Asians.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Do data on HPR phenotypes and *CYP2C19* genotypes have incremental predictive value compared with each alone in DES-treated patients receiving clopidogrel?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Combined risk stratification with HPR and *CYP2C19* LoF alleles outperformed the model, including each alone in predicting stent thrombosis but not the composite ischemic primary end point.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ In DES-treated patients at high risk for thrombosis and bleeding, comprehensive analysis of HPR and *CYP2C19* genotype might be valuable to attain the optimal therapeutic window of platelet reactivity by adjusting the intensity and duration of $P2Y_{12}$ inhibition.

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Dual antiplatelet therapy (DAPT) using aspirin and clopidogrel remains a standard of care in patients with stable ischemic heart disease or acute coronary syndromes who are at high bleeding risk after percutaneous coronary intervention (PCI).[1–6] Because the cytochrome P450 (*CYP2C19*) pathway is involved in the two-step biotransformation of clopidogrel, carriage of *CYP2C19* loss-of-function (LoF) allele (*2 or *3) is significantly linked to the prevalence of a high platelet reactivity (HPR) phenotype and consequently a worse clinical outcome.[7–13] As thrombotic and hemorrhagic events are related to increased risks of morbidity and mortality, achieving an optimal therapeutic window of post-PCI platelet reactivity is crucial to reduce ischemic events while avoiding serious bleeding complications.[6,14,15] The requirement of an optimal antiplatelet effect differs according to the disease acuity and phases after PCI, the risk of excessive bleeding vs. ischemia, the demographic risk factors, and the patient's ethnicity.[15–18]

Compared with that in White patients, the frequency of *CYP2C19* LoF carriage and the level of on-clopidogrel platelet reactivity were higher in East Asian patients (~65 vs. 30%, respectively). However, the risk of ischemic events following PCI was similar or even lower in East Asians than that in Whites, which is often described as the "East Asian Paradox."[18,19] The prognostic implications of a comprehensive assessment of the HPR phenotype and the *CYP2C19* genotype remain poorly characterized in East Asians. We hypothesized that combined stratification of HPR phenotypes and *CYP2C19* genotypes would better predict post-PCI clinical outcomes during clopidogrel treatment than individual stratification. Therefore, we aimed to investigate the additive impacts of HPR phenotypes and *CYP2C19* genotypes on atherothrombotic events in East Asian patients undergoing PCI. We also evaluated the discriminative capability of HPR phenotype and genetic testing results to predict adverse outcome during clopidogrel treatment among these patients.

METHODS

Data source and study population

The platelet function and genotype-related long-term prognosis in drug-eluting stent (DES)-treated patients (PTRG-DES) consortium ($n = 13,160$) is a nationwide, multicenter, large-scale registry endorsed by the Korean Society of Interventional Cardiology (**Table S1**). It was specifically designed to determine the relationship between platelet function testing (PFT)/genotyping and subsequent clinical events in East Asian patients with coronary artery disease after DES implantation (ClinicalTrials.gov Identifier: NCT04734028).[20] From July 2003 to August 2018, consecutive patients at each center were successfully treated with one (or more) DES approved by the US Food and Drug Administration (FDA) or Conformité Européenne (CE) mark. The patients that were adequately loaded with clopidogrel were eligible for enrollment, regardless of patient or lesion complexity. The exclusion criteria included occurrence of a major complication during the procedure, fibrinolytic therapy, a need for oral anticoagulant, and the use of potent $P2Y_{12}$ inhibitorsl such as ticagrelor or prasugrel. In this analysis, we used the patient data with available *CYP2C19* genotyping results following DES implantation (the PTRG-genotype cohort; $n = 8,163$). In the final cohort of our analysis, 6,717 patients (82.3% of the PTRG-genotype cohort) also underwent PFT evaluation, which was conducted using the VerifyNow P2Y12 assay kit (Accriva, San Diego, CA, USA). This study complied with the Declaration of Helsinki and was approved by the institutional review board of each participating center, who waived the requirement for written informed consent for access to an institutional registry.

Procedures and test methods

All PCI procedures were performed in accordance with the conventional standard of care.[21] Patients who were not taking aspirin or clopidogrel before undergoing the procedure received the appropriate loading doses (300 mg and 300–600 mg, respectively). Following the PCI procedure, the patients were administered a daily maintenance dose of 100 mg aspirin and 75 mg clopidogrel. The patients were recommended to maintain aspirin therapy indefinitely and clopidogrel for at least 1 year; however, the duration of DAPT administration and choice of single antiplatelet agent, aspirin or clopidogrel, was determined by the attending physician according to the clinical situation. The treating physicians were aware of not *CYP2C19* genotype but PFT result. Antiplatelet therapy modifications, such as prasugrel or ticagrelor, were also at the discretion of the attending physicians at each participating center. However, our registry did not include those who switched from clopidogrel to prasugrel or ticagrelor. All other treatments were as per the standard of care, and clinical outcomes were evaluated until the last outpatient visit.

CYP2C19 genotyping

The genomic deoxyribonucleic acid (DNA) was extracted from mononuclear cells with the commercial DNA kit and the DNA extracts were stored at −20°C until used. The genotype of each single nucleotide polymorphism (SNP) was determined by pyrosequencing using a PSQ 96MA Pyrosequencer (Pyrosequencing AB, Uppsala, Sweden) or ABI PRISM 3100 genetic analyzer (Applied Biosystems[20]; **Table S2**). SNPs measured were *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *CYP2C19*17* (rs12248560).

The *CYP2C19* genotypes were classified into 3 genotypically predicted metabolizer status groups according to the number of *CYP2C19* LoF alleles present (**Tables S3**, **S4**)[13,22]: (1) extensive metabolizers (EMs) for individuals not carrying the LoF allele (*1/*1, *1/*17, or *17/*17); (2) intermediate metabolizers (IMs) for carriers of one LoF allele (*1/*2, *1/*3, *2/*17, or *3/*17); and (3) poor metabolizers (PMs) for carriers of two LoF alleles (*2/*2, *2/*3, or *3/*3).

Platelet function testing – VerifyNow P2Y12 Reaction unit assay

Platelet reactivity was measured after an adequate period to ensure the full anti-platelet effect using the VerifyNow assay kit (Accriva). Before the blood sampling for PFT, clopidogrel was given as: (1) a dose of 600 mg after 6-hour intervals; (2) a dose of 300 mg after 12-hour intervals; or (3) a dose of 75 mg 5 days before conducting the PCI procedure. This VerifyNow assay is a whole-blood, point-of-care, turbidimetric optical detection assay designed to measure agonist-induced platelet aggregation and was done according to manufacturer's recommendations.[23] Blood samples were collected in 3.2% citrate Vacuette tubes (Greiner Bio-One Vacuette North America, Monroe, NC, USA). VerifyNow P2Y12 reaction unit (PRU) data were collected as continuous measures. The criterion for HPR was defined as "PRU ≥ 252," based on a previous analysis by the PTRG-DES consortium,[24] which was in accordance with the highest tertile and corresponded well to the criteria used in previous publications involving East Asian patients.[9,16,18]

Primary outcome measures

The primary outcome was the incidence of a composite of major adverse cardiac and cerebrovascular events (MACCEs), including all-cause death, non-fatal myocardial infarction (MI), definite stent thrombosis, and non-fatal stroke within 5 years. The secondary outcome was the incidence of individual components of the primary outcome. Major bleeding was defined according to the criteria recommended by the Bleeding Academic Research Consortium (bleeding type 3–5).[25]

All deaths were considered to have occurred from cardiovascular causes unless a definite non-cardiovascular cause could be established. MI was defined as increased cardiac troponin values with ischemic symptoms or ischemic changes on electrocardiogram, imaging evidence of recent loss of viable myocardium, or new regional wall motion abnormalities that were not related to the procedure. Stent thrombosis (definite) was defined according to the Academic Research Consortium criteria.[26] Stroke was defined as evidence of neurological deficits requiring hospitalization and clinically documented lesions on the brain (detected by computed tomography or magnetic resonance imaging).

Statistics

Continuous variables were expressed as means ± standard deviations (SDs) or as medians (interquartile ranges (IQRs)), whereas categorical variables were presented as absolute numbers and frequencies (%). The Student's unpaired *t*-test and the Mann–Whitney *U* test were used for parametric continuous and nonparametric continuous variables, respectively. Comparisons between categorical variables were performed using Pearson's chi-square test or Fisher's exact test. Kaplan–Meier survival analyses were used to compare event rates and the results were compared using the log-rank test. In addition, to explain early and late relative effects of the HPR phenotypes and the *CYP2C19* genotypes, landmark analyses were performed based on the 1-year landmarks and confirmed using the Kaplan–Meier curves. Clinical follow-ups were censored on the day of the first cardiovascular event corresponding to the day of the clinical end point. For patients without a clinical event, clinical follow-up was censored either at the last clinic visit while undergoing clopidogrel therapy or on the day of clopidogrel discontinuation.[27] We conducted multivariate Cox regression analyses to estimate the adjusted hazard ratio (aHR) and 95% confidence interval (CI) to: (1) examine the association between combined HPR phenotypes and *CYP2C19* genotypes, and the incidences of primary outcome and stent thrombosis, and (2) adjust for potential confounders: age ≥ 75 years, sex, body mass index < 18.5, diabetes mellitus, hypertension, dyslipidemia, current smoker, presentation of acute myocardial infarction (AMI), congestive heart failure, chronic kidney disease ≥ stage 3, anemia (hemoglobin < 13 g/dL for men; < 12 g/dL for women), and multivessel disease. Discrimination was assessed using the integrated area under the curve (iAUC) in consideration of the follow-up period, and the difference in iAUC values was confirmed using the bootstrap method (the dataset was resampled 1,000 times for comparison with the standard model). We also calculated the net reclassification index (NRI) and the integrated discrimination improvement (IDI) values to evaluate the additive predictive power of the HPR phenotype, the *CYP2C19* genotypes, and a combination of both over that of the conventional clinical model for estimation of the risks of MACCE and stent thrombosis within 5 years of the intervention in all subjects. Statistical significance was set at a 2-sided *P* value < 0.05. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), RStudio, and R version 4.2.1.

RESULTS

Participants

Among a total of 13,160 patients in the PTRG-DES consortium, 6,717 had both *CYP2C19* genotyping and PFT results (**Figure S1**). We classified these patients into 6 groups according to presence of HPR and *CYP2C19* genotype as follows: (1) no HPR/*CYP2C19* EMs as reference ($n = 1961$; 29.2%); (2) no HPR/*CYP2C19* IMs ($n = 2{,}603$; 30.7%); (3) no HPR/*CYP2C19* PMs ($n = 444$; 6.6%); (4) HPR/*CYP2C19* EMs ($n = 568$; 8.5%); (5) HPR/*CYP2C19* IMs ($n = 1{,}168$; 17.4%); and (6) HPR/*CYP2C19* PMs ($n = 513$; 7.6%).

Distribution of P2Y12 PRUs and baseline characteristics

The mean, median, and inter-tertile range values of PRUs in on-clopidogrel patients were 217, 219, and 188–252, respectively. The mean PRU values for *CYP2C19* EMs (37.7%), *CYP2C19* IMs (48.1%), and *CYP2C19* PMs (14.2%) were 195, 225, and 252, respectively (**Table S4**, **Figure S2**). The prevalence of HPR was the highest in *CYP2C19* PMs, followed by that in *CYP2C19* IMs and *CYP2C19* EMs (53.6, 36.1, and 22.5%, respectively; $P < 0.001$).

The baseline characteristics of the 6 groups are presented in **Table 1**. Stable angina (41.1%) was the most frequent clinical presentation in all six groups. The mean age of the patients was 64.4 years, out of which 65.7% were men. More women and elderly patients were included in the group of individuals with HPR than those in the group of patients without HPR. The prevalence of risk factors such as smoking, diabetes mellitus, hypertension, and chronic kidney disease differed among the six groups. The group of patients with HPR included fewer smokers, but a higher proportion of patients with diabetes mellitus, hypertension, and chronic kidney disease than the group of patients without HPR. There were no differences in left ventricular ejection fractions, platelet counts, cholesterol levels, or hemoglobin A_{1c} levels among the groups of patients. The six groups showed mostly similar angiographic and procedural characteristics. Discharge medications did not differ

Table 1 Baseline characteristics

	Overall (*n* = 6,717)	No HPR/*CYP2C19* EM (*n* = 1961)	No HPR/*CYP2C19* IM (*n* = 2063)	No HPR/*CYP2C19* PM (*n* = 444)	*P* value	HPR/*CYP2C19* EM (*n* = 568)	HPR/*CYP2C19* IM (*n* = 1,168)	HPR/*CYP2C19* PM (*n* = 513)	*P* value	*P* value[a]
PRU, mean ± SD	217.4 ± 78.4	163.8 ± 58.8	182.9 ± 51.5	189.7 ± 52.9	< 0.001	300.9 ± 41.1	299.2 ± 38.9	306.3 ± 41.6	0.004	< 0.001
PRU, median (25th–75th)	219 (168–270)	173 (125–211)	193 (155–221)	204 (169–227)	< 0.001	292 (269–323)	290 (269–320)	298 (272–335)	0.004	< 0.001
Index presentation, *n* (%)					0.953				0.479	0.861
Stable angina	2,759 (41.1)	816 (41.6)	856 (41.5)	172 (38.7)		225 (39.6)	485 (41.5)	205 (40.0)		
Unstable angina	2,265 (33.7)	659 (33.6)	697 (33.8)	160 (36.0)		177 (31.2)	393 (33.7)	179 (34.9)		
NSTEMI	1,014 (15.1)	290 (14.8)	300 (14.5)	65 (14.6)		106 (18.7)	173 (14.8)	80 (15.6)		
STEMI	679 (10.1)	196 (10.0)	210 (10.2)	47 (10.6)		60 (10.6)	117 (10.0)	49 (9.6)		
Age, years	64.4 ± 10.8	63.2 ± 10.9	62.9 ± 10.7	62.0 ± 10.9	0.138	68.0 ± 10.3	67.3 ± 10.0	66.4 ± 10.5	0.286	< 0.001
Male, *n* (%)	4,415 (65.7)	1,349 (68.8)	1,503 (72.9)	340 (76.6)	< 0.001	298 (52.5)	640 (54.8)	285 (55.6)	0.547	< 0.001
Body mass index, kg/m^2	24.6 ± 3.1	24.6 ± 3.1	24.6 ± 3	24.9 ± 3.1	0.191	24.5 ± 3.2	24.5 ± 3.2	24.4 ± 3.2	0.763	0.207
Risk factors, *n* (%)										
Smoking	1,646 (24.5)	513 (26.2)	602 (29.2)	132 (29.7)	0.068	94 (16.6)	195 (16.7)	110 (21.4)	0.044	< 0.001
Diabetes mellitus	2,249 (33.5)	603 (30.8)	683 (33.1)	134 (30.2)	0.206	213 (37.5)	431 (36.9)	185 (36.1)	0.887	< 0.001
Hypertension	4,044 (60.2)	1,151 (58.7)	1,211 (58.7)	235 (52.9)	0.065	386 (68.0)	746 (63.9)	315 (61.4)	0.071	< 0.001
Dyslipidemia	4,415 (65.7)	1,278 (65.2)	1,399 (67.8)	288 (64.9)	0.162	361 (63.6)	757 (64.8)	332 (64.7)	0.869	0.282
Chronic kidney disease	1,460 (21.7)	367 (18.7)	390 (18.9)	86 (19.4)	0.949	174 (30.6)	315 (27.0)	128 (25.0)	0.099	< 0.001
Medical history, *n* (%)										
History of congestive heart failure	546 (8.8)	178 (9.1)	183 (8.9)	45 (10.1)	0.702	36 (6.3)	73 (6.3)	31 (6.0)	0.979	0.004
Previous MI	545 (8.1)	149 (7.6)	175 (8.5)	40 (9.0)	0.463	50 (8.8)	88 (7.5)	43 (8.4)	0.628	0.778
Previous PCI	1,056 (15.7)	310 (15.8)	319 (15.5)	68 (15.3)	0.941	94 (16.6)	176 (15.1)	89 (17.4)	0.455	0.867
Previous CABG	86 (1.3)	31 (1.6)	34 (1.7)	1 (0.2)	0.069	7 (1.2)	9 (0.8)	4 (0.8)	0.602	0.052
Previous stroke	488 (7.3)	128 (6.5)	160 (7.8)	22 (5.0)	0.069	47 (8.3)	86 (7.4)	45 (8.8)	0.575	0.133
Laboratory measurements										
LV ejection fraction, %	58.8 ± 11.0	58.7 ± 11.0	59.2 ± 10.9	58.4 ± 10.9	0.309	57.7 ± 11.0	58.6 ± 11.0	59.2 ± 11.1	0.112	0.144
WBC, ×10^3/mm^3	7.8 ± 2.8	7.8 ± 2.8	8.0 ± 2.9	8.0 ± 2.9	0.178	7.7 ± 3.0	7.7 ± 2.9	7.5 ± 2.6	0.286	0.004
Hemoglobin, g/dL	13.6 ± 1.9	13.8 ± 1.8	14.0 ± 1.8	14.2 ± 1.9	< 0.001	12.5 ± 1.9	12.8 ± 1.7	12.9 ± 1.7	< 0.001	< 0.001
Platelet, ×10^3/mm^3	236.5 ± 76.8	236.5 ± 77.8	237.1 ± 74.1	225.6 ± 68.2	0.840	233.9 ± 82.2	238.5 ± 78.2	226.4 ± 59.1	0.384	0.798
GFR, mL/min/1.73 m^2	78.2 ± 26.6	80.0 ± 24.8	79.9 ± 25.1	80.1 ± 26.1	0.983	73.6 ± 30.5	75.4 ± 28.8	74.8 ± 29.0	0.486	< 0.001
Total cholesterol, mg/dL	174.0 ± 44.8	174.5 ± 45.6	174.7 ± 43.8	176.9 ± 44.4	0.589	172.7 ± 44.3	172.6 ± 44.8	171.1 ± 46.4	0.810	0.315
Triglyceride, mg/dL	143.1 ± 102.5	147.9 ± 119	146.7 ± 95.7	147.4 ± 115.3	0.944	132.4 ± 87.9	138.2 ± 89.7	128.9 ± 86.8	0.134	< 0.001
HDL-cholesterol, mg/dL	43.0 ± 11.6	43.0 ± 11.7	43.0 ± 11.4	43.3 ± 11.4	0.872	43.1 ± 11.9	42.6 ± 12.0	43.1 ± 11.4	0.602	0.865
LDL-cholesterol, mg/dL	105.1 ± 38.5	105.1 ± 39.2	105.1 ± 37.3	108.9 ± 36.0	0.161	104.5 ± 38.3	104.4 ± 39.9	103.7 ± 39.6	0.941	0.408

(Continued)

Table 1 (Continued)

	Overall (*n* = 6,717)	No HPR/*CYP2C19* EM (*n* = 1961)	No HPR/*CYP2C19* IM (*n* = 2063)	No HPR/*CYP2C19* PM (*n* = 444)	*P* value	HPR/*CYP2C19* EM (*n* = 568)	HPR/*CYP2C19* IM (*n* = 1,168)	HPR/*CYP2C19* PM (*n* = 513)	*P* value	*P* value[a]
Hemoglobin A_{1c}, %	6.5 ± 1.3	6.4 ± 1.3	6.4 ± 1.3	6.6 ± 1.4	0.369	6.6 ± 1.4	6.5 ± 1.2	6.6 ± 1.2	0.527	0.180
Procedural characteristics										
Treated lesions										
Left main coronary artery	312 (4.6)	99 (5.1)	90 (4.4)	22 (5.0)	0.574	26 (4.6)	51 (4.4)	24 (4.7)	0.954	0.924
Left anterior descending artery	3,999 (59.5)	1,179 (60.1)	1,246 (60.4)	253 (57.0)	0.402	301 (53.0)	704 (60.3)	316 (61.6)	0.005	0.020
Left circumflex artery	1945 (29.0)	544 (27.7)	579 (28.1)	138 (31.1)	0.361	181 (31.9)	347 (29.7)	156 (30.4)	0.657	0.272
Right coronary artery	2,551 (38.0)	738 (37.6)	798 (38.7)	150 (33.8)	0.154	233 (41.0)	430 (36.8)	202 (39.4)	0.213	0.208
Others	109 (1.6)	37 (1.9)	34 (1.7)	13 (2.9)	0.197	9 (1.6)	12 (1.0)	4 (0.8)	0.418	0.063
ACC/AHA lesion: type B2/C	2,833 (42.2)	809 (41.3)	855 (41.4)	182 (41.0)	0.982	250 (44.0)	510 (43.7)	227 (44.3)	0.973	0.529
Multivessel disease, *n* (%)	2,403 (35.9)	682 (34.8)	732 (35.5)	144 (32.4)	0.470	214 (37.7)	433 (37.1)	198 (38.6)	0.837	0.251
Multivessel PCI, *n* (%)	2,413 (35.9)	685 (34.9)	734 (35.6)	144 (32.4)	0.451	216 (38.0)	435 (37.2)	199 (38.8)	0.827	0.213
Complex PCI, *n* (%)	1,695 (25.2)	512 (26.1)	544 (26.4)	104 (23.4)	0.430	148 (26.1)	262 (22.4)	125 (24.4)	0.236	0.143
Second generation DES	6,405 (95.4)	1876 (95.7)	1981 (96.0)	426 (96.0)	0.845	527 (92.8)	1,102 (94.4)	493 (96.1)	0.062	0.012
Number of stents, *n*	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.7	0.274	1.6 ± 0.8	1.6 ± 0.7	1.6 ± 0.8	0.160	0.279
Stent length, mm	35.6 ± 22.0	35.3 ± 22.2	36.4 ± 22.1	34.1 ± 20.4	0.085	36.0 ± 21.6	34.6 ± 21.7	36.5 ± 22.6	0.178	0.121
Stent diameter, mm	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	0.984	3.0 ± 0.4	3.0 ± 0.5	3.0 ± 0.5	0.857	0.997
Concomitant medications at discharge, *n* (%)										
Aspirin	6,636 (98.8)	1942 (99.0)	2036 (98.7)	442 (99.6)	0.235	559 (98.4)	1,154 (98.8)	503 (98.1)	0.482	0.278
Clopidogrel	6,717 (100.0)	1961 (100.0)	2063 (100.0)	444 (100.0)	–	568 (100.0)	1,168 (100.0)	513 (100.0)	–	–
Beta blocker	4,171 (62.1)	1,230 (62.7)	1,268 (61.5)	276 (62.2)	0.712	341 (60.0)	732 (62.7)	324 (63.2)	0.488	0.833
Angiotensin blockade	3,899 (58.0)	1,135 (57.9)	1,200 (58.2)	236 (53.2)	0.141	340 (59.9)	687 (58.8)	301 (58.7)	0.901	0.354
Calcium channel blocker	2030 (30.2)	601 (30.7)	620 (30.1)	118 (26.6)	0.238	182 (32.0)	347 (29.7)	162 (31.6)	0.547	0.483
Statin	5,920 (88.1)	1740 (88.7)	1819 (88.2)	404 (91.0)	0.235	490 (86.3)	1,012 (86.6)	455 (88.7)	0.427	0.123
Proton pump inhibitor	1,135 (16.9)	286 (14.6)	312 (15.1)	61 (13.7)	0.729	123 (21.7)	254 (21.8)	99 (19.3)	0.499	<0.001
DAPT at 1year	5,001 (74.5)	1,444 (73.6)	1,544 (74.8)	312 (70.3)	0.132	445 (78.4)	883 (75.6)	373 (72.7)	0.098	0.050
Clopidogrel monotherapy	486 (7.2)	140 (7.1)	144 (7.0)	36 (8.1)	0.704	36 (6.3)	85 (7.3)	45 (8.8)	0.305	0.666
Clopidogrel (DAPT + monotherapy)	5,487 (81.7)	1,584 (80.8)	1,688 (81.8)	348 (78.4)	0.228	481 (84.7)	968 (82.9)	418 (81.5)	0.369	0.113

(Continued)

among the six groups, except the use of proton pump inhibitors. The rates of clopidogrel administration at 1, 3, and 5 years were 81.7%, 71.0%, and 69.4%, respectively, without differences across the groups.

Outcomes according to combined HPR and *CYP2C19* genotype

The primary outcome was observed in 266 patients (4.0%) during the follow-up period (**Table 2**). Median (IQR) follow-up days were 382 (363–1,163). The HPR/*CYP2C19* PM group showed the highest rate of MACCE (6.2%), whereas patients with no HPR/*CYP2C19* EMs had the lowest (2.9%, $P < 0.001$). The differences in rates of MACCE were mainly due to all-cause death and stent thrombosis. The Kaplan–Meier curves for 5-year primary outcome revealed that the cumulative MACCE events was more frequent in patients with HPR/*CYP2C19* EMs, HPR/*CYP2C19* IMs, or HPR/*CYP2C19* PMs than those with no HPR/*CYP2C19* EMs (**Figure 1**). In a landmark analysis (**Figure S3**), the cumulative incidence of MACCE within 1 year of PCI was different across the groups ($P < 0.001$); however, these differences in MACCE occurrence values were not observed beyond the 1-year period ($P = 0.61$). There was no effect of interactions between HPR and *CYP2C19* genotype on the primary outcome and stent thrombosis (**Figure 2**).

HPR was associated with a higher incidence of both MACCE and stent thrombosis, whereas *CYP2C19* IM/PM was linked to a greater occurrence of stent thrombosis only (**Table 3**). Compared with the reference group, the HPR/*CYP2C19* PM and HPR/*CYP2C19* EM groups showed an increased risk of 5-year MACCE after adjusting for various clinical and laboratory-associated factors. The HPR/*CYP2C19* IM and HPR/*CYP2C19* PM groups were associated with an increased risk of stent thrombosis compared with the reference group. Combining HPR and *CYP2C19* PM was associated with the greatest risk for MACCE (aHR: 1.87, 95% CI: 1.20 to 2.91, $P = 0.006$) and stent thrombosis (aHR: 3.83, 95% CI: 1.15 to 12.78, $P = 0.029$). No significant differences were found in the incidences of major bleeding events between the groups. Sensitivity analyses using western HPR cutoff of > 208 PRU[22] showed the consistent results with the primary analysis using HPR cutoff of ≥ 252 PRU (**Tables S5**, **S6**). Additionally, when stratifying the cohort into those with and without acute coronary syndrome (ACS), the composite outcome and stent thrombosis incidents differ between stable angina and ACS, as shown in **Tables S7** and **S8**. The risks of MACCE and stent thrombosis according to the HPR/*CYP2C19* genotype were also different between them, depicted in **Tables S9** and **S10**. However, there was no effect of interaction on the primary composite outcome between stable angina and ACS ($P = 0.558$).

Discriminatory value and reclassification of combined HPR phenotype- and *CYP2C19* genotype-based model

Table 4 depicts the iAUC, NRI, and IDI values estimated using the conventional model combined with HPR phenotypes and/or *CYP2C19* genotypes to predict the risks of 5-year MACCE and stent thrombosis. Prediction of MACCE using the conventional

Table 1 (Continued)

	Overall ($n = 6,717$)	No HPR/*CYP2C19* EM ($n = 1961$)	No HPR/*CYP2C19* IM ($n = 2063$)	No HPR/*CYP2C19* PM ($n = 444$)	*P* value	HPR/*CYP2C19* EM ($n = 568$)	HPR/*CYP2C19* IM ($n = 1,168$)	HPR/*CYP2C19* PM ($n = 513$)	*P* value	*P* value[a]
DAPT at 3years	3,889 (57.9)	1,116 (56.9)	1,192 (57.8)	237 (53.8)	0.236	337 (59.3)	708 (60.6)	299 (58.3)	0.649	0.128
Clopidogrel monotherapy	882 (13.1)	261 (13.3)	269 (13.0)	63 (14.2)	0.809	71 (12.5)	144 (12.3)	74 (14.4)	0.477	0.833
Clopidogrel (DAPT + monotherapy)	4,771 (71.0)	1,377 (70.2)	1,461 (70.8)	300 (67.6)	0.397	408 (71.8)	852 (72.9)	373 (72.7)	0.886	0.285
DAPT at 5years	3,553 (52.9)	1,002 (51.1)	1,103 (53.5)	222 (50.0)	0.210	298 (52.5)	652 (55.8)	276 (53.8)	0.392	0.129
Clopidogrel monotherapy	1,106 (16.5)	344 (17.5)	334 (16.2)	72 (16.2)	0.489	90 (15.9)	178 (15.2)	88 (17.2)	0.613	0.639
Clopidogrel (DAPT + monotherapy)	4,659 (69.4)	1,346 (68.6)	1,437 (69.7)	294 (66.2)	0.350	388 (68.3)	830 (71.1)	364 (71.0)	0.471	0.400

Continuous variables were expressed in mean ± SD or median (IQR) as indicated.
ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft; CYP, cytochrome P415; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; EM, extensive metabolizer; HPR, high platelet reactivity; IM, intermediate metabolizer; GFR, glomerular filtration rate; LV, left ventricle; MI, myocardial infarction; NSTEMI, non-ST-segment myocardial infarction; PCI, percutaneous coronary intervention; PM, poor metabolizer; PRU, P2Y12 reaction unit; STEMI, ST-segment myocardial infarction; WBC, white blood cell.
[a]*P* value for 6 groups.

Table 2 Five-year outcomes according to combined HPR and *CYP2C19* genetic testing

	Entire cohort (n = 6,717)	No HPR/*CYP2C19* EM (n = 1961)	No HPR/*CYP2C19* IM (n = 2063)	No HPR/*CYP2C19* PM (n = 444)	*P* value	HPR/*CYP2C19* EM (n = 568)	HPR/*CYP2C19* IM (n = 1,168)	HPR/*CYP2C19* PM (n = 513)	*P* value	*P* value[a]
MACCE	266 (4.0)	57 (2.9)	69 (3.3)	16 (3.6)	0.632	35 (6.2)	57 (4.9)	32 (6.2)	0.392	<0.001
All-cause death	141 (2.1)	27 (1.4)	32 (1.6)	8 (1.8)	0.774	21 (3.7)	33 (2.8)	20 (3.9)	0.431	<0.001
Non-fatal MI	71 (1.1)	16 (0.8)	20 (1.0)	5 (1.1)	0.780	8 (1.4)	14 (1.2)	8 (1.6)	0.825	0.639
Stent thrombosis, definite	27 (0.4)	0 (0.0)	6 (0.3)	3 (0.7)	0.008	3 (0.5)	10 (0.9)	5 (1.0)	0.680	0.001
Non-fatal stroke	61 (0.9)	18 (0.9)	18 (0.9)	5 (1.1)	0.879	7 (1.2)	8 (0.7)	5 (1.0)	0.508	0.901
Major bleeding	204 (3.0)	52 (2.7)	57 (2.8)	13 (2.9)	0.942	26 (4.6)	37 (3.2)	19 (3.7)	0.338	0.224

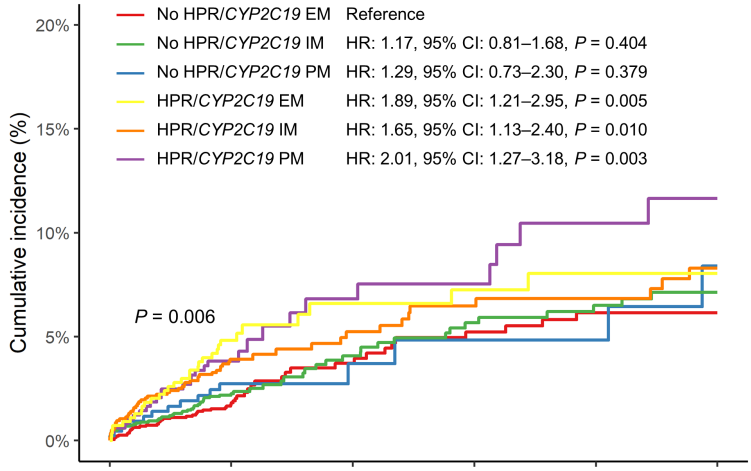
EM, extensive metabolizer; HPR, high platelet reactivity; IM, intermediate metabolizer; MACCE, major adverse cardiac and cerebrovascular events (a composite of all-cause death, myocardial infarction, stroke, and stent thrombosis); MI, myocardial infarction; PM, poor metabolizer; ST, stent thrombosis.
[a]*P* value for 6 groups.

model resulted in an iAUC value of 0.672 (95% CI: 0.650 to 0.709). Compared with the conventional model, combining the conventional model with HPR + *CYP2C19* genotypes significantly increased an iAUC for MACCE (0.679, 95% CI: 0.660 to 0.719, $P = 0.039$) and stent thrombosis (0.837, 95% CI: 0.828 to 0.930, $P < 0.001$). Combined stratification over individual stratification tended to improve prognostication but missed statistical significance in predicting 5-year MACCE. In contrast, combined stratification outperformed the conventional model with each test alone in predicting stent thrombosis. The combination of HPR phenotype and *CYP2C19* genotypes with the conventional model did not result in significant NRI or IDI values for MACCE. However, individual HPR or genetic data and a combination of both resulted in significant NRI values for stent thrombosis.

DISCUSSION

The present study underlines the prognostic implications of the combination of HPR phenotyping and *CYP2C19* genotyping information of DES-treated Korean patients undergoing clopidogrel therapy. This is the first study to comprehensively evaluate the additive effects of the *CYP2C19* genotype on clinical outcomes in East Asians with a high prevalence of the *CYP2C19* LoF allele(s) (~65% prevalence of *2 or *3 alleles). The key findings were as follows: (1) patients with HPR and 2 copies of *CYPC19* LoF alleles had an unfavorable composite outcome while undergoing clopidogrel treatment after PCI compared with those without HPR and *CYP2C19* LoF alleles; (2) 1 year after PCI, the prognostic effects of HPR phenotypes and *CYP2C19* genotypes on clinical outcomes were diminished; (3) combined HPR phenotype and the *CYP2C19* LoF alleles was associated with an increased risk of 5-year MACCE and stent thrombosis; and (4) compared with HPR phenotypes or CYP2C19 genotypes alone, incorporating both data into the conventional model significantly increased iAUC for predicting the risk of stent thrombosis but not MACCE.

DAPT strategies may be chosen according to the clinical setting (stable coronary artery disease vs. acute coronary syndrome), the stage of the disease (early vs. long-term treatment), and patient risk for ischemic and bleeding complications. The use of PFT and genetic testing have been proposed as optional tools to aid clinical decision of choosing the P2Y12 inhibitors.[22] Despite the robustness of the evidence for the HPR phenotype and *CYP2C19* LoF alleles as poor prognostic indicators during clopidogrel treatment, particularly when considering adequately powered randomized trials, their routine assessment is not recommended in the current guidelines.[1,22] The limited clinical benefits of the PFT-guided escalation of $P2Y_{12}$ inhibitors could be explained as follows. First, as laboratory-defined PFT is mainly determined by the level of adenosine diphosphate-induced platelet reactivity observed in patients undergoing $P2Y_{12}$ inhibitor treatment, it may not precisely reflect the effects of other platelet activation pathways where molecules such as thromboxane A_2, thrombin, collagen, and epinephrine are involved. Second, PFT-guided escalation to potent $P2Y_{12}$ inhibitors may not be required in PCI-treated patients with a low ischemic risk profile. Indeed, the escalation strategy of switching



Number at risk

No HPR/*CYP2C19* EM	1961	1209	415	350	278	216
No HPR/*CYP2C19* IM	2063	1287	462	376	312	257
No HPR/*CYP2C19* PM	444	261	97	73	61	45
HPR/*CYP2C19* EM	568	361	172	134	103	83
HPR/*CYP2C19* IM	1168	759	329	270	214	174
HPR/*CYP2C19* PM	513	311	130	106	80	66

Figure 1 Kaplan–Meier curves for 5-year ischemic composite outcomes according to the combined HPR phenotypes and *CYP2C19* genotypes. CI, confidence interval; CYP, cytochrome P450; EM, extensive metabolizer; HPR, high platelet reactivity; HR, hazard ratio; IM, intermediate metabolizer; PM, poor metabolizer; PRU, P2Y12 reaction unit.

from clopidogrel to prasugrel in low-risk patients with the HPR phenotype did not show effective reduction in ischemic events, and the trial was halted because of a lower-than-expected incidence of clinical events.[28] Third, the prognostic implication and optimal therapeutic window of PFT may be different according to a given clinical acuity, such as AMI, elapsed time following PCI, baseline characteristics (e.g., gender, body mass index, and anemia), and ethnicity.[6,9,16,18,29] East Asian patients have higher on-clopidogrel PRUs values, but similar or somewhat lower thrombotic events than White patients. A recent expert consensus statement has suggested that East Asian patients may have a different cutoff value for HPR phenotype and a weak correlation between PFT results and

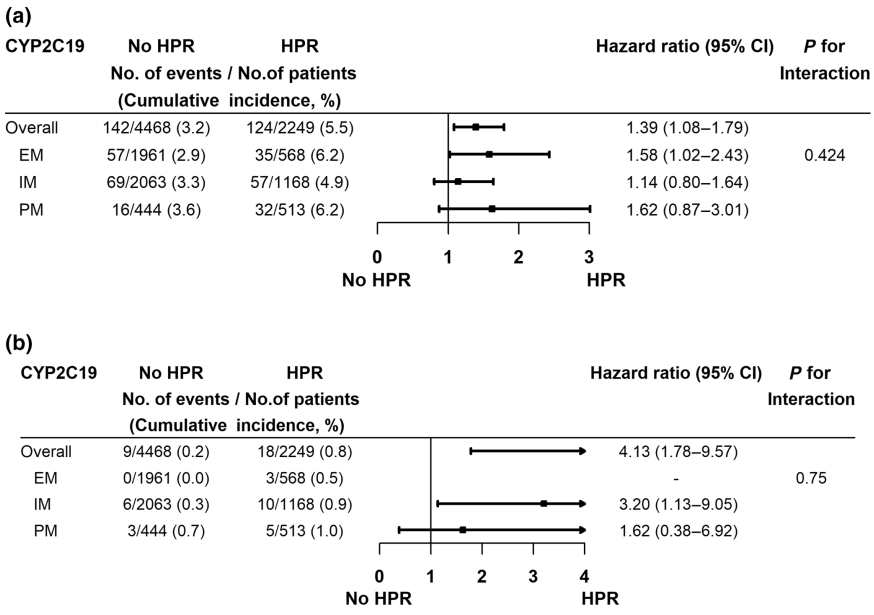


Figure 2 The effect of HPR on outcomes across *CYP2C19* genotype subgroups. CI, confidence interval; other abbreviations as in Figure 1. CI, confidence interval; CYP, cytochrome P450; EM, extensive metabolizer; HPR, high platelet reactivity; HR, hazard ratio; IM, intermediate metabolizer; PM, poor metabolizer; PRU, P2Y12 reaction unit.

Table 3 Hazard ratios of 5-year outcomes according to HPR, *CYP219* genetic testing, and a combination of both

	MACCE			Stent thrombosis		
Adjusted model	**Adjusted HR**	**95% CI**	***P* value**	**Adjusted HR**	**95% CI**	***P* value**
Conventional model[a] + HPR						
No HPR	Reference			Reference		
HPR	1.37	1.06–1.76	0.016	4.16	1.79–9.65	<0.001
Conventional model[a] + *CYP2C19* IM/PM						
CYP2C19 EM	Reference			Reference		
CYP2C19 IM	1.07	0.82–1.41	0.608	6.19	1.42–26.95	0.015
CYP2C19 PM	1.35	0.95–1.93	0.097	11.04	2.34–52.05	0.002
Conventional model[a] + HPR + *CYP2C19* IM/PM						
No HPR/*CYP2C19* EM	Reference					
No HPR/*CYP2C19* IM	1.17	0.82–1.66	0.379	Reference[b]		
No HPR/*CYP2C19* PM	1.16	0.65–2.04	0.619	2.42	0.60–9.70	0.213
HPR/*CYP2C19* EM	1.54	1.00–2.38	0.049	1.29	0.25–6.57	0.757
HPR/*CYP2C19* IM	1.32	0.91–1.92	0.142	3.16	1.12–8.95	0.030
HPR/*CYP2C19* PM	1.87	1.20–2.91	0.006	3.83	1.15–12.78	0.029

CI, confidence interval; EM, extensive metabolizer; HPR, high platelet reactivity; HR, hazard ratio; IM, intermediate metabolizer; MACCE, major adverse cardiac and cerebrovascular event; PM, poor metabolizer.
[a]Conventional model included age ≥ 75, sex, body mass index < 18.5, diabetes mellitus, hypertension, dyslipidemia, current smoker, anemia, chronic kidney disease stage ≥ 3, presentation with acute myocardial infarction, congestive heart failure, multivessel disease. [b]This group was set as a reference since there was no incidence of stent thrombosis in the HPR/*CYP2C19* EM group.

clinical outcomes compared with that of White patients.[18] For example, the PTRG-DES consortium has recently suggested "PRU ≥ 252" as the criterion for HPR following DES implantation,[24] whereas "PRU > 208" has been recommended as the criterion for HPR by the Western expert consensus.[22] However, recent meta-analysis[30] overcoming sample size limitation of single randomized controlled trials demonstrated that a strategy of a guided selection of antiplatelet therapy is associated with improved outcomes as compared with standard selection of antiplatelet therapy among patients undergoing PCI. Guided selection of antiplatelet therapy improved both composite and individual efficacy outcomes with a favorable safety profile, driven by a reduction in minor bleeding and supporting the use of platelet function or genetic testing to optimize the selection of agent in patients undergoing PCI.[30] Another meta-analysis[31] using clopidogrel as a treatment reference reported that a guided approach in ACS was the only strategy associated with reduced MACCE without any significant trade-off in bleeding.

Higher levels of platelet reactivity in East Asians during clopidogrel treatment may be mainly related to the high prevalence of *CYP2C19* LoF alleles (up to 65% of patients); this fact was validated again in the present study. Because on-clopidogrel platelet reactivity is determined by not only the presence of *CYP2C19* LoF alleles[11] but also other factors, such as demography, clinical conditions, and race, there is a discrepancy in the association between the HPR phenotype and the *CYP2C19* genotype. In the present analysis, 46.4% (444/957) of patients with *CYP2C19* PMs did not have HPR phenotype. Thus, we investigated the additive prognostic value of combining HPR and genotyping tests compared with each one alone. A combined presence of HPR and 2-copy *CYP2C19* LoF alleles was found to be an independent predictor for MACCE and stent thrombosis after fully adjusting for conventional covariates. We also evaluated and compared the discriminatory capabilities of HPR phenotyping, *CYP2C19* genotyping, and a combination of both with that of the conventional model in predicting the risk of MACCE and stent thrombosis. The HPR phenotyping or the CYP2C19 genotyping data alone did not provide significant NRI or IDI values for predicting the risk of MACCE compared with the conventional model. Adding combined HPR phenotypes and CYP2C19 genotypes did not increase iAUC for MACCE but increased iAUC for stent thrombosis compared with each one alone. Interestingly, the landmark analysis revealed that the prognostic value of combined HPR and genetic tests was confined to 1 year after PCI. One-year post-PCI, the prognostic effect of *CYP2C19* LoF allele and/or HPR phenotype presence would diminish or even eradicate in patients on clopidogrel therapy. Our results partly coincide with the results of the Harmonizing Optimal Strategy for Treatment of coronary artery diseases-EXtended Antiplatelet Monotherapy (HOST-EXAM) trial[32] conducted in Korean patients, in which clopidogrel monotherapy was found to be superior to aspirin monotherapy in preventing thrombotic events 6–18 months after DES implantation.

Considering the cost-effectiveness of both PFT and genetic testing, our results are in accordance with the current guidelines that do not recommend universal use of these tests in patients undergoing PCI.[1,22] However, the rate of stent thrombosis after DES implantation was more precisely predicted by the combined model incorporating combined HPR phenotyping and *CYP2C19*

Table 4 Integrated AUC, NRI, and IDI for 5-year MACCE and stent thrombosis

	iAUC	*P* value	NRI	*P* value	IDI	*P* value
MACCE						
Conventional model[a]	0.672 (0.650–0.709)		Reference		Reference	
Conventional model + HPR	0.676 (0.656–0.713)	0.103[b]	0.051 (−0.018–0.133)	0.129	0.001 (−0.001–0.006)	0.448
Conventional model + *CYP2C19* IM/PM	0.674 (0.655–0.712)	0.121[b]	0.030 (−0.035–0.104)	0.388	0.001 (0.000–0.005)	0.318
Conventional model + HPR+*CYP2C19* IM/PM	0.679 (0.660–0.719)	0.039[b]	0.077[c]	0.083[d]	0.046 (−0.016–0.126)	0.209	0.001 (−0.001–0.008)	0.408
Stent thrombosis						
Conventional model[a]	0.736 (0.715–0.868)		Reference		Reference	
Conventional model + HPR	0.785 (0.756–0.897)	0.052[b]	0.275 (0.022–0.427)	0.030	0.003 (−0.014–0.041)	0.229
Conventional model + *CYP2C19* IM/PM	0.801 (0.785–0.903)	0.014[b]	0.428 (0.110–0.486)	0.010	0.004 (−0.001–0.060)	0.060
Conventional model + HPR+*CYP2C19* IM/PM	0.837 (0.828–0.930)	<0.001[b]	0.005[c]	0.031[d]	0.293 (0.113–0.451)	<0.001	0.005 (−0.004–0.055)	0.119

AUC, area under the curve; HPR, high platelet reactivity; iAUC, integrated area under the curve; IDI, integrated discrimination improvement; IM, intermediate metabolizer; MACCE, major adverse cardiac and cerebrovascular event; NRI, net reclassification index; PM, poor metabolizer.
[a]Conventional model included age ≥ 75 years old, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, current smoker, anemia, chronic kidney disease, presentation with acute myocardial infarction, congestive heart failure, multivessel disease. [b]*P* value vs. conventional model. [c]*P* value vs. conventional model + HPR. [d]*P* value vs. conventional model + *CYP2C19* IM/PM.

genotyping data than by the conventional model with each one alone; DES-treated patients (including East Asian patients) with a high ischemic risk may benefit from PFT- and/or genotype-guided escalation of $P2Y_{12}$ inhibitor therapy. Furthermore, information on the *CYP2C19* genotype may be valuable in the case of ACS patients with high bleeding risk, as patients not having the *CYP2C19* LoF allele can be de-escalated from potent $P2Y_{12}$ inhibitors to clopidogrel therapy.[33,34] Indeed, in the Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial, there were no differences in the rates of ischemic events in *CYP2C19* EMs on clopidogrel or prasugrel therapy.[35] The clinical utility and the role of PFTs and/or *CYP2C19* genetic tests in complex cases of patients having both high ischemic and high bleeding risks should be explored in future investigations. The cost-effectiveness of phenotypic and genotypic testing should also be examined in future studies.

The present study had some limitations. First, the observations of the current study can be used only for the generation of hypothesis, as this study was performed in a non-randomized, observational manner. However, the sample size of the present analysis was as large as that of previous trials, where PFTs and outcomes in White patients undergoing clopidogrel treatment were investigated.[6] In contrast to the above study, our cohort comprised East Asians, in whom *CYP2C19* LoF alleles were more prevalent than those in European patients. Therefore, our findings provide information exclusively on East Asian patients undergoing clopidogrel treatment following PCI. Moreover, our PCI cohort was unique because comprehensive information on HPR phenotypes and *CYP2C19* genotypes was available for 6,717 patients who underwent PCI with DES implantation. Second, although PRU levels can change over time, only information on a single measurement of PRU was available. Finally, despite the presence of several tools for platelet function tests, such as adenosine diphosphate–induced light transmittance aggregometry, the VerifyNow was the only tool used for platelet function test in this study.

In conclusion, the combined analysis of HPR phenotypes and *CYP2C19* genotypes was significantly associated with MACCE within 5 years of PCI in DES-treated East Asian patients on clopidogrel therapy. However, it did not provide an enhanced risk stratification compared with each one alone. As for stent thrombosis, these tests were independently associated with an increased risk and enhanced risk stratification. Further research is warranted to investigate the clinical benefits of tailored antiplatelet treatment based on combined information of PFT and *CYP2C19* genotype analyses in East Asian patients.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

Dr. Jeong has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals, and Yuhan Pharmaceuticals, as well as research grants or support from Yuhan Pharmaceuticals and U&I Corporation, outside the submitted work. Dr. Song has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Bayer Korea, and Samjin Pharmaceutical, outside the submitted work. Dr. Joo has received honoraria for lectures from AstraZeneca, Hanmi, Samjin, Dong-A, HK inno. N Pharmaceuticals, and DIO Medical Ltd, outside the submitted work. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.E.K., H.S.J., D.A.G., U.S.T., P.A.G., Y.H.J., and S.G.A. wrote the manuscript. J.H.L., J.W.L., Y.J.Y., Y.H.J., and S.G.A. designed the research. B.K.K., H.J.J., K.Y.C., Y.P., Y.B.S., J.W.S., S.Y.L., J.R.C., A.Y.H., H.S.K., M.H.K., E.S.S., D.S.L., Y.H.J., and S.G.A. performed the research. S.E.K., H.S.J., T.H.G., and S.G.A. analyzed the data.

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