Platelet Function and Genotype after DES Implantation in East Asian Patients: Rationale and Characteristics of the PTRG-DES Consortium

Ae-Young Her[1]*, Young-Hoon Jeong[2]*, Byeong-Keuk Kim[3], Hyung Joon Joo[4], Kiyuk Chang[5], Yongwhi Park[6], Young Bin Song[7], Sung Gyun Ahn[8], Jung-Won Suh[9], Sang Yeup Lee[10], Jung Rae Cho[11], Hyo-Soo Kim[12], Moo Hyun Kim[13], Do-Sun Lim[4], Eun-Seok Shin[14], and On Behalf of the PTRG-DES Consortium Investigators

[1]Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon;
[2]CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital and Department of Internal Medicine, Chung-Ang University College of Medicine, Gwangmyeong;
[3]Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul;
[4]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Korea University College of Medicine, Seoul;
[5]Division of Cardiology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul;
[6]Department of Internal Medicine, Gyeongsang National University School of Medicine and Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon;
[7]Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul;
[8]Department of Cardiology, Yonsei University Wonju Severance Christian Hospital, Wonju;
[9]Department of Internal Medicine, Seoul National University College of Medicine and Department of Cardiology, Seoul National University Bundang Hospital, Seongnam;
[10]Division of Cardiology, Chung-Ang University Gwangmyeong Hospital and Department of Internal Medicine, Chung-Ang University College of Medicine, Gwangmyeong;
[11]Cardiology Division, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul;
[12]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul;
[13]Department of Cardiology, Dong-A University Hospital, Busan;
[14]Division of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea.

Purpose: Platelet function test (PFT) results and genotype hold unique prognostic implications in East Asian patients. The aim of the PTRG-DES (Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated Patients with coronary artery disease) consortium is to assess the clinical impact thereof on long-term clinical outcomes in Korean patients with coronary artery disease during dual antiplatelet therapy (DAPT) including clopidogrel.

Materials and Methods: Searching publications on the PubMed, we reviewed clopidogrel treatment studies with PFT and/or genotype data for potential inclusion in this study. Lead investigators were invited to share PFT/genotype results, patient characteristics, and clinical outcomes to evaluate relationships among them.

Results: Nine registries from 32 academic centers participated in the PTRG-DES consortium, contributing individual patient data from 13160 patients who underwent DES implantation between July 2003 and August 2018. The PTRG-PFT cohort was composed of 11714 patients with available VerifyNow assay results. Platelet reactivity levels reached 218±79 P2Y12 reaction units (PRU), and

high on-clopidogrel platelet reactivity based on a consensus-recommended cutoff (PRU >208) was observed in 55.9%. The PTRG-Genotype cohort consisted of 8163 patients with candidate genotypes related with clopidogrel responsiveness. Of those with cytochrome P450 (CYP) 2C19 genotype, frequencies of carrying one and two loss-of-function allele (s) (*2 or *3) were 47.9% (intermediate metabolizers) and 14.2% (poor metabolizers), respectively.

Conclusion: The PTRG-DES consortium highlights unique values for on-clopidogrel platelet reactivity and CYP2C19 phenotype that may be important to developing optimal antiplatelet regimens in East Asian patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT04734028.

Key Words: East Asia, platelet function, genotype, drug-eluting stent, coronary artery disease

INTRODUCTION

Following percutaneous coronary intervention (PCI) in patients with significant coronary artery disease (CAD), dual antiplatelet therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ receptor inhibitor is the cornerstone of pharmacologic treatment to improve clinical prognosis.[1,2] Since platelet inhibition levels have been shown to be associated with the risks of post-PCI atherothrombotic and bleeding complications, tailored DAPT approaches guided by platelet function test (PFT) or genotyping (e.g., escalation, de-escalation, or switching) have been proposed and tested in multiple clinical trials.[3]

Compared with Caucasian patients, East Asian patients show unique antiplatelet effects and clinical outcomes (different therapeutic window of platelet inhibition), greater resistance to atherothrombotic events, and more vulnerability to bleeding at the same level of platelet reactivity ("East Asian Paradox").[4,5] Therefore, numerous clinical trials and analysis have suggested different efficacy and safety profiles during individual $P2Y_{12}$ inhibitor treatment (clopidogrel, prasugrel or ticagrelor) in East Asian patients treated with PCI.[4,6-8] However, consensus documents by expert groups recommend different strategies in selecting a DAPT regimen for East Asian patients.[9,10]

The PTRG-DES (Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated patients with coronary artery disease) consortium was established to determine the linkage of PFT and genotyping with long-term prognosis during clopidogrel treatment in a large-scale East Asian cohort treated with drug-eluting stent (DES). This article describes the framework for the organization and characteristics of the PTRG-DES consortium. Upcoming publications from various sub-analyses of this consortium is expected to divulge information important to developing individualized treatment regimens for East Asian patients requiring antiplatelet therapy.

MATERIALS AND METHODS

Study design and patients

An organizing committee of PTRG-DES investigators was established to define scientific goals. The organizing committee invited the lead investigators of clopidogrel-related prospective clinical registries published in the PubMed as of January 2018 to participate. Criteria for participation included available on-clopidogrel PFT or genotyping data and, for outcome analysis, availability of baseline characteristics and clinical prognosis in CAD patients treated with DES implantation.

In total, nine prospective registries from 32 Korean academic centers have joined the PTRG-DES consortium, contributing data from 13160 DES patients treated between July 2003 and August 2018 in Supplementary Table 1 (only online). We obtained 11714 PFT results measured by the VerifyNow assay (PTRG-PFT cohort) and 8163 genotyping results related with clopidogrel responsiveness (PTRG-Genotype cohort) (Fig. 1). The type and number of patients in the PFT and/or genotyping datasets are provided in Supplementary Table 2 (only online). The PTRG-DES consortium is supported by the Platelet-Thrombosis Research Group under the Korean Society of Interventional Cardiology. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The institutional review board of each participating center approved the registry and waived the requirement for written informed consent for access to institutional registries. The study was performed in accordance with the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.
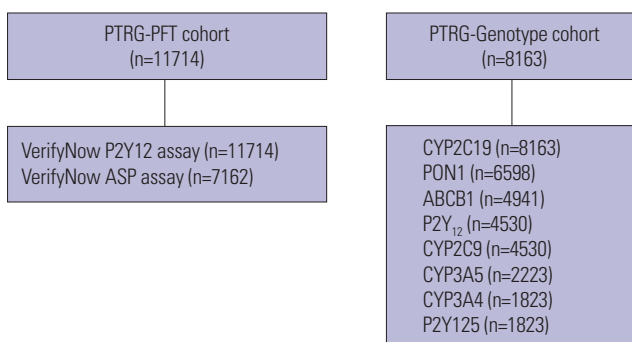

Fig. 1. Cohorts of the PTRG-DES consortium. ABCB1, ATP Binding Cassette Subfamily B Member 1; CYP, cytochrome P450; PFT, platelet function test; PON1, Paraoxonase 1; PTRG-DES, Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated patients with coronary artery disease.

Procedures and test methods

Consecutive patients at each center who were successfully treated with one or more DESs approved by the US Food and Drug Administration (FDA) or CE mark and who were adequately loaded with aspirin and clopidogrel were eligible for enrollment, regardless of patient or lesion complexity. The major exclusion criteria were the occurrence of a major complication during the procedure, fibrinolytic therapy, and need for oral anticoagulant or potent $P2Y_{12}$ inhibitor, such as ticagrelor or prasugrel.

All PCI procedures were performed according to the standard technique.[11] Following a PCI procedure, patients were administered 100 mg of aspirin and 75 mg of clopidogrel a day. Patients were recommended to maintain aspirin indefinitely and clopidogrel for at least 1 year, and all other treatments were per standard of care. Clinical outcomes were evaluated until the last outpatient visit.

Platelet function test

Platelet reactivity was measured after an adequate period to ensure the full anti-platelet effect using the VerifyNow assay (Accriva, San Diego, CA, USA) during the peri-procedural period (from "just after the insertion of the arterial sheath" to "within 24 hr after DES implantation").[12] Aspirin was given as either 1) a coated oral dose of 300 mg at least 6 hr or 2) a dose of 100 mg at least 5 days before PCI. Clopidogrel was given as either 1) a dose of 600 mg at least 6 hr, 2) a dose of 300 mg at least 12 hr, or 3) a dose of 75 mg at least 5 days before PCI. If eptifibatide or tirofiban was used during PCI, a 24-hr washout period was required before VerifyNow testing. No patients receiving abciximab were enrolled because of a long washout period.

This VerifyNow assay is a whole-blood, point-of-care, turbidimetric optical detection assay designed to measure agonist-induced platelet aggregation. Blood samples were collected in 3.2% citrate Vacuette tubes (Greiner Bio-One Vacuette North America, Monroe, NC, USA). The measurement protocol followed the manufacturer's recommendations, the details of which have been described elsewhere.[13] We collected the following PFT data as continuous measures: VerifyNow P2Y12 baseline reactivity (BASE) and P2Y12 reaction units (PRU) and VerifyNow aspirin reaction units (ARU). Additionally, based on Western consensus documents in which cutoffs for high platelet reactivity (HPR) were identified, we initially defined the criteria of HPRs during DAPT with clopidogrel [>208 PRU to adenosine diphosphate (ADP) and >550 ARU to arachidonic acid].[3]

Genotyping

For genotyping, whole peripheral blood was obtained from patients. Genomic deoxyribonucleic acid (DNA) was extracted from mononuclear cells with the DNA kit and stored at -20°C until ready for use. The genotype of each single nucleotide polymorphism (SNP) was determined by pyrosequencing using a PSQ 96MA Pyrosequencer (Pyrosequencing AB, Uppsala, Sweden)[14] or ABI PRISM® 3100 genetic analyzer (Thermo Fisher Scientific Inc., Agawam, MA, USA).[15] SNPs were measured at cytochrome P450 (CYP) 2C19*2 (rs4244285), CYP2C19*3 (rs4986893), CYP2C19*17 (rs12248560), CYP2C9*3 (rs1057910), ABCB1 (rs 1045642), paraoxonase-1 (PON1) (rs662), and $P2Y_{12}$ (rs6809699).

The CYP2C19 phenotypes were classified into three groups according to the number of CYP2C19 loss-of-function (LOF) alleles: 1) extensive metabolizers, for individuals not carrying a LOF variant (*1/*1, *1/*17, or *17/*17); 2) intermediate metabolizers, for carriers of one LOF allele (*1/*2, *1/*3, *2/*17, or *3/*17); and 3) poor metabolizers, for carriers of two LOF alleles (*2/*2, *2/*3, or *3/*3).[3]

Clinical outcomes and definitions

An independent clinical events committee masked to PFT and genotyping results adjudicated all clinical events using original source documents. The primary ischemic endpoint was occurrence of major adverse cardiac and cerebrovascular events (MACCE), including all-cause death, myocardial infarction (MI), definite stent thrombosis (ST), or stroke. In addition, major bleeding was defined as Bleeding Academic Research Consortium (BARC) bleeding type 3–5 (Supplementary Table 3, only online).[16]

All deaths were considered to be of cardiovascular (CV) cause unless a definite non-CV cause could be established. MI was defined as increased cardiac troponin values with ischemic symptoms or ischemic changes on electrocardiogram or imaging evidence of recent loss of viable myocardium or new regional wall motion abnormality that were not related to the procedure. ST (definite) was defined according to Academic Research Consortium criteria.[17] Stroke was defined as evidence of a neurological deficit requiring hospitalization and clinically documented lesions on brain computed tomography or magnetic resonance imaging.

Statistical analysis

Data at the individual patient level were used to calculate prevalence, mean values, and event rates for the total cohort with two-sided 95% confidence intervals (CIs). If there were crucial issues after validation of the PTRG-DES central database, individual data were sent to the principal investigator of the respective registry to confirm the data, perform corrections, and provide additional data.

The Kolmogorov-Smirnov test was performed to analyze the normal distribution of continuous variables. Continuous variables are expressed as a mean±SD or as a median (interquartile range), while categorical variables are presented as absolute numbers and frequencies (%). Student's unpaired t-test for parametric continuous variables and the Mann-Whitney U test for non-parametric continuous variables were used. Comparisons between categorical variables were performed using the Pearson chi-square test or Fisher exact test when the Cochran rule was not met for categorical variables. To assess the relationship between the criteria of HPR and subsequent

Table 1. Baseline Characteristics of the Patients (n=13160)

Variables	Value
Index presentation	
Stable angina	5684 (43.2)
Unstable angina	3750 (28.5)
Non-ST-segment elevation MI	2009 (15.3)
ST-segment elevation MI	1717 (13.0)
Age, yr	64.4±10.9
Male	8848 (67.2)
Body mass index, kg/m^2	24.5±3.1
Risk factors*	
Hypertension	7933 (60.3)
Dyslipidemia	8303 (63.1)
Smoking	3578 (27.2)
Diabetes mellitus	4619 (35.1)
Insulin-treated	459 (3.5)
Chronic kidney disease	2875 (21.8)
Current dialysis	191 (1.5)
Anemia	3345 (25.4)
Previous history	
History of congestive heart failure	1072 (8.1)
Previous MI	971 (7.4)
Previous PCI	1737 (13.2)
Previous CABG	163 (1.2)
Previous stroke	921 (7.0)
Laboratory measurements	
LV ejection fraction, %	58.8±10.6
WBC, ×10^3/mm^3	7.8±3.0
Hemoglobin, g/dL	13.6±1.8
Platelet, ×10^3/mm^3	243.7± 80.0
GFR, mL/min/1.73 m^2 (MDRD)	77.3±26.6
HbA$_{1c}$, %	6.5±1.4
Total cholesterol, mg/dL	173.6±44.0
LDL-cholesterol, mg/dL	106.5±42.6
HDL-cholesterol, mg/dL	43.9±12.5
Triglyceride, mg/dL	142.3± 96.6
Angiographic feature	
ACC/AHA lesion	
A/B1 type	5626 (42.8)
B2/C type	7534 (57.2)
Number of diseased vessels	
One	7755 (58.9)
Two	3517 (26.7)
Three	1888 (14.3)
Multivessel disease	5405 (41.1)
Bifurcation lesion	1508 (11.5)
Chronic total occlusion lesion	897 (6.8)
Procedural data	
Multivessel PCI	3234 (24.6)
Treated lesions	
Left main coronary artery	659 (5.0)
Left anterior descending artery	7757 (58.9)

Table 1. Baseline Characteristics of the Patients (continued) (n=13160)

Variables	Value
Left circumflex artery	3933 (29.9)
Right coronary artery	5018 (38.1)
Stent type†	
1st generation DES	1934 (14.7)
≥2nd generation DES	11226 (85.3)
Number of stent, n	1.6±0.8
Stent length, mm	35.1±21.9
Stent diameter, mm	3.03±0.44
Concomitant medications	
Aspirin	12831 (97.5)
Clopidogrel	13160 (100.0)
Cilostazol	1292 (9.8)
Beta blocker	7627 (58.0)
Angiotensin blockade	8063 (61.3)
Calcium channel blocker	3118 (23.7)
Statin	11607 (88.2)
Proton pump inhibitor	2235 (17.0)

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LV, left ventricular; WBC, white blood cell; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; HbA$_{1c}$, hemoglobin A$_{1c}$; LDL, low density lipoprotein; HDL, high density lipoprotein; ACC, American College of Cardiology; AHA, American Heart Association; DES, drug-eluting stent.

Continuous variables are expressed as a mean±SD.

*Hypertension was diagnosed according to one of the following: 1) history of hypertension diagnosed and treated with medication, diet, and/or exercise; 2) blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic on at least two occasions; or 3) currently on antihypertensive pharmacologic therapy. Dyslipidemia was diagnosed according to one of the following: 1) total cholesterol ≥200 mg/dL; 2) LDL-cholesterol ≥130 mg/dL; 3) HDL-cholesterol <40 mg/dL; or 4) triglycerides ≥150 mg/dL. Current smoker was defined as the use of tobacco within 1 year of admission; diabetes mellitus was diagnosed according to one of the following: 1) a history of diabetes, regardless of duration of disease, or need for antidiabetic agents; 2) a fasting blood glucose ≥126 mg/dL; or 3) glycosylated hemoglobin ≥6.5%. Chronic kidney disease was diagnosed according to one of the following: 1) GFR <60 mL/min/1.73 m^2 (MDRD); 2) on dialysis; or 3) history of a renal transplantation. Anemia was defined as hemoglobin level <12 g/dL in women and 13 g/dL in men; †First-generation DES indicates durable polymer-based paclitaxel-eluting stents (PES: Taxus, Pico) or sirolimus-eluting stents (SES: Cypher). Second-generation DESs include next-generation DESs, including everolimus-eluting stent (EES: Promus, Xience), zotarolimus-eluting stent (ZES: Endeavor, Resolute, Onyx), biolimus-eluting stent (BES: Biolimus A9), and polymer-free SES. If a patient was treated with first- and second-generation DESs together, this patient was considered as implantation with first-generation DES.

clinical outcomes, we compared time-to-event data with log-rank tests and presented them as Kaplan-Meier estimates. A p value <0.05 was considered statistically significant. All statistical analyses were performed with IBM/SPSS v24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics
Between July 2003 to August 2018, 13160 patients treated with

DESs in South Korea were enrolled (PTRG-PFT: n=11714 and PTRG-Genotype: n=8163). After DES implantation, clopidogrel was prescribed in all patients, and 97.5% (n=12831) of patients was discharged with aspirin.

A high-risk cohort was enrolled, with a large proportion of patients having diabetes (35.1%), index presentation with acute coronary syndrome (ACS) (56.8%), and complex lesion (American College of Cardiology/American Heart Association lesion B2 or C type: 57.2%) (Table 1). Most of these patients received 2nd generation DESs (n=11226, 85.3%), and stents were implanted for 1.6 lesions per patient, with a total stent length of 35.1 mm.

Platelet function test and genotype

From the PTRG-PFT cohort, the mean values of the VerifyNow P2Y$_{12}$ assay were 218±79 PRU (n=11714) and 298±59 PRU at BASE (n=10487), and that of the VerifyNow aspirin assay was 444±69 ARU (n=7162). The prevalences of HPR to ADP and arachidonic acid (consensus-recommended definition)[3] were 55.9% (>208 PRU) and 10.9% (>550 ARU), respectively. The cutoffs of upper tertiles were 253 PRU and 461 ARU, respectively.

The distributions of genotypes and associated phenotypes in the PTRG-Genotype cohort (n=8163) are shown in Table 2. Like previous data from East Asian countries,[14,15,18] more than 60% of the enrolled subjects carried at least one copy of the CYP2C19 LOF allele (62.0%). Extensive metabolizers represented 38.0% (n=3098), whereas intermediate and poor metabolizers accounted for 47.9% (n=3906) and 14.2% (n=1159), respectively.

Clinical outcomes

During the median follow-up duration of 21 months (interquartile range: 12 to 61 months) (up to 199 months), MACCE and major bleeding events occurred in 6.8% (n=899, mean time of 25 months) and 3.3% (n=431, mean time of 20 months), respectively (Fig. 2 and Table 3). The risk of MACCE increased over time, whereas events of major bleeding were observed more frequently in the early phase (up to 1 year).

Patients who suffered from MACCE showed higher PRU and ARU levels than those without MACCE (Fig. 3). Subjects with HPR to ADP (>208 PRU) exhibited a higher risk of MACCE occurrence than those without HPR (8.4% vs. 4.9%, *p*<0.001), while there was no significant difference in MACCE risk between patients with vs. without HPR to arachidonic acid (>550 ARU) (6.4% vs. 5.0%, *p*=0.084) (Fig. 4). Rates of MACCE, however, did not differ across CYP2C19 phenotypes (4.4% vs. 4.6% vs. 5.3% in extensive vs. intermediate vs. poor metabolizers, *p*=0.261) (Fig. 5).

DISCUSSION

The PTRG-DES consortium, to our knowledge, is the largest

Table 2. Distribution of CYP2C19 Alleles, Genotype and Phenotype (PTRG-Genotype Cohort: n=8163)

Allele	Frequency no. (%)	Genotype	Frequency no. (%)	Phenotype	Frequency no. (%)
*1	9950 (60.9)	*1/*1	3011 (36.9)	Extensive metabolizer	3098 (38.0)
*2	4486 (27.5)	*1/*2	2786 (34.1)	Intermediate metabolizer	3906 (47.9)
*3	1738 (10.6)	*1/*3	1055 (12.9)	Poor metabolizer	1159 (14.2)
*17	152 (0.9)	*1/*17	87 (1.1)		
		*2/*2	606 (7.4)		
		*2/*3	440 (5.4)		
		*2/*17	48 (0.6)		
		*3/*3	113 (1.4)		
		*3/*17	17 (0.2)		
		*17/*17	0 (0)		

CYP, cytochrome P450.

PCI cohort with the longest clinical follow-up to evaluate the relation between platelet reactivity/genotype and clinical outcomes. The main findings of this consortium are as follows: 1) East Asian patients showed a higher level of platelet reactivity during clopidogrel treatment than Western patients (218 vs. 188 PRU in PTRG-DES vs. ADAPT-DES)[13]; 2) East Asian patients exhibited a higher prevalence of CYP2C19 LOF allele carriage (62%) than Western patients;[19] and 3) East Asian patients showed different risk ratios (RR) of MACCE and major bleeding occurrence according to the time period during clopidogrel treatment.[13]

Following large-scale placebo-controlled randomized clinical trials (RCTs) showing a net clinical benefit for potent P2Y$_{12}$ inhibitor (prasugrel or ticagrelor) vs. clopidogrel use in ACS patients,[20,21] Jeong[22] proposed a new concept for East Asian patients against Western guidelines. Based on a unique risk-benefit ratio (or therapeutic zone of platelet reactivity) and pharmacodynamic profile in East Asian patients,[4,5] Jeong[22] suggested that potent P2Y$_{12}$ inhibitor vs. clopidogrel would have a different effect than that observed in the Western population. Subsequently, clinical data from several registries[6,23,24] and a small-sized RCT[8] from East Asian countries have suggested diminished clinical benefits and an increased bleeding risk for potent P2Y$_{12}$ inhibitor use in East Asian patients with ACS, compared with clopidogrel.

Antiplatelet strategies for East Asian patients differ across consensus documents and clinical guidelines.[9,10,25] Substantial clinical evidence from large-scale PFT/genotype-based registries and RCTs are required to establish unwavering treatment guidelines for East Asians patients. Therefore, we believe that this PTRG-DES consortium will be able to suggest reliable linkage of platelet function and genotyping with clinical outcomes in East Asian populations. Since the present consortium is the largest PFT cohort of DES-treated all-comers with a long-term follow-up, our results are expected to overcome the limitations
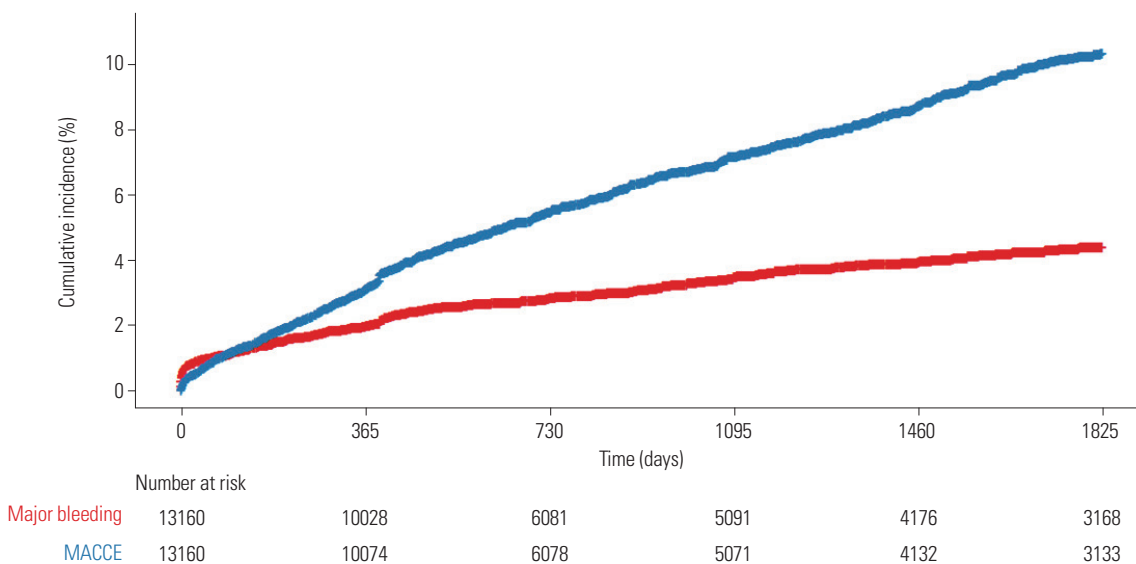
Fig. 2. Kaplan-Meier analysis for MACCE and major bleeding events (PTRG-DES consortium; n=13160). The blue line represents cumulative event rates of MACCE and the red line represents cumulative event rates of major bleeding events during follow-up period in this consortium. MACCE, major adverse cardiac and cerebrovascular events; PTRG-DES, Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated Patients with coronary artery disease.

Table 3. Prevalence of MACCE and Major Bleeding Events during Follow-Up (PTRG-DES: n=13160)

MACCE		Major bleeding	
All-cause death	512 (3.9)	BARC type 3	414 (3.1)
CV death	165 (1.3)	3a	297 (2.3)
Non-CV death	347 (2.6)	3b	67 (0.5)
		3c	50 (0.4)
Non-fatal MI	201 (1.5)	BARC type 4	7 (0.1)
Stent thrombosis (definite)	69 (0.5)	BARC type 5	10 (0.1)
		5a	3 (0.0)
		5b	7 (0.1)
Non-fatal stroke	238 (1.8)		

MACCE, major adverse cardiac and cerebrovascular events; PTRG-DES, Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated Patients with coronary artery disease; BARC, Bleeding Academic Research Consortium; CV, cardiovascular; MI, myocardial infarction.
Data are presented as n (%).

of previous East Asian studies related with cohort size, follow-up duration, and heterogenicity of disease entity.

The use of guided antiplatelet strategies (platelet function and genetic testing) in PCI-treated patients with high-risk profiles has aimed to improve clinical outcomes by tailoring antiplatelet potency and duration to the individual patient.[3] Early clinical RCTs did not find any clinical benefit with a guided approach, however. Caveats in trial designs, such as the inclusion of low-risk patients, inadequate identification of high-risk patients by a guided method, and undecided optimal selection of potent $P2Y_{12}$ inhibitors, could contribute to these disappointing results. Nevertheless, a recent meta-analysis (n=20743; 11 RCTs and three observation studies) demonstrated that guid-

ed selection of antiplatelet therapy vs. standard therapy was associated with reductions in ischemic events (RR 0.78, 95% CI 0.63–0.95, p=0.015) and bleeding (RR 0.88, 95% CI 0.77–1.01, p=0.069).[26]

Compared with Western individuals, East Asian patients follow different guided cutoffs (e.g., high or low platelet reactivity) and enhanced platelet inhibition by standard-dose potent $P2Y_{12}$ inhibitor.[4,5] In addition, research suggests that the association between CYP2C19 genotyping and clinical outcomes during clopidogrel treatment can differ according to ethnicity. In the Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI) trial, despite the same treatment with clopidogrel in patients carrying the CYP2C19 LOF allele, Caucasian patients showed an increased risk of ischemic events by about 1.8-fold than East Asian patients (7.3% vs. 4.1%).[27] A genotype-guided strategy (mainly with ticagrelor) vs. conventional treatment reduced the risk of 1-year ischemic event after index PCI by 1.4% (2.7% vs. 4.1%) and 2.6% (4.7% vs. 7.3%) in the East Asians and Caucasians, respectively. There are unmet needs to establish cutoffs of high-risk phenotypes and optimal escalation strategies balancing clinical efficacy and safety.

In the present analysis, ARU (i.e., aspirin responsiveness) showed a limited relationship with clinical events. For aspirin resistance, recent data have mostly suggested an imprecise clinical impact on clinical outcomes,[3] which may be related with the weak and indirect inhibition of thromboxane pathway by aspirin. Based on this observation, numerous clinical trials have tested the clinical benefit of early aspirin discontinuation from the initial DAPT regimen. In addition, CYP2C19 phenotype did not show a close relationship with clinical events in this cohort. Since genetic variants are just one influential factor af-

fecting the antiplatelet effect of clopidogrel, their contribution to clinical events would be diminished in East Asian patients. East Asian patients show a unique risk-benefit ratio during antiplatelet treatment and a relatively weak relationship between platelet

reactivity and atherothrombotic events.[4-6]

There are several limitations to this study that warrant consideration. This study has an innate limitation regarding its observational nature with registry data. However, with the exten-
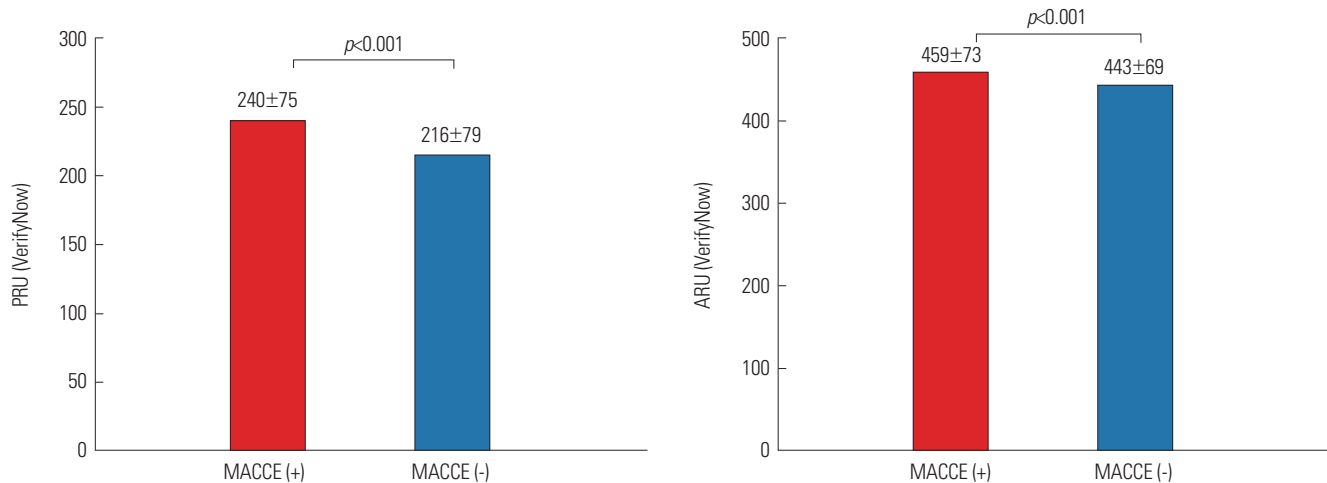

Fig. 3. PRU and ARU levels in patients with (red) vs. without (blue) ischemic events (MACCE). PRU, P2Y12 reaction unit; ARU, aspirin reaction unit; MACCE, major adverse cardiac and cerebrovascular events.
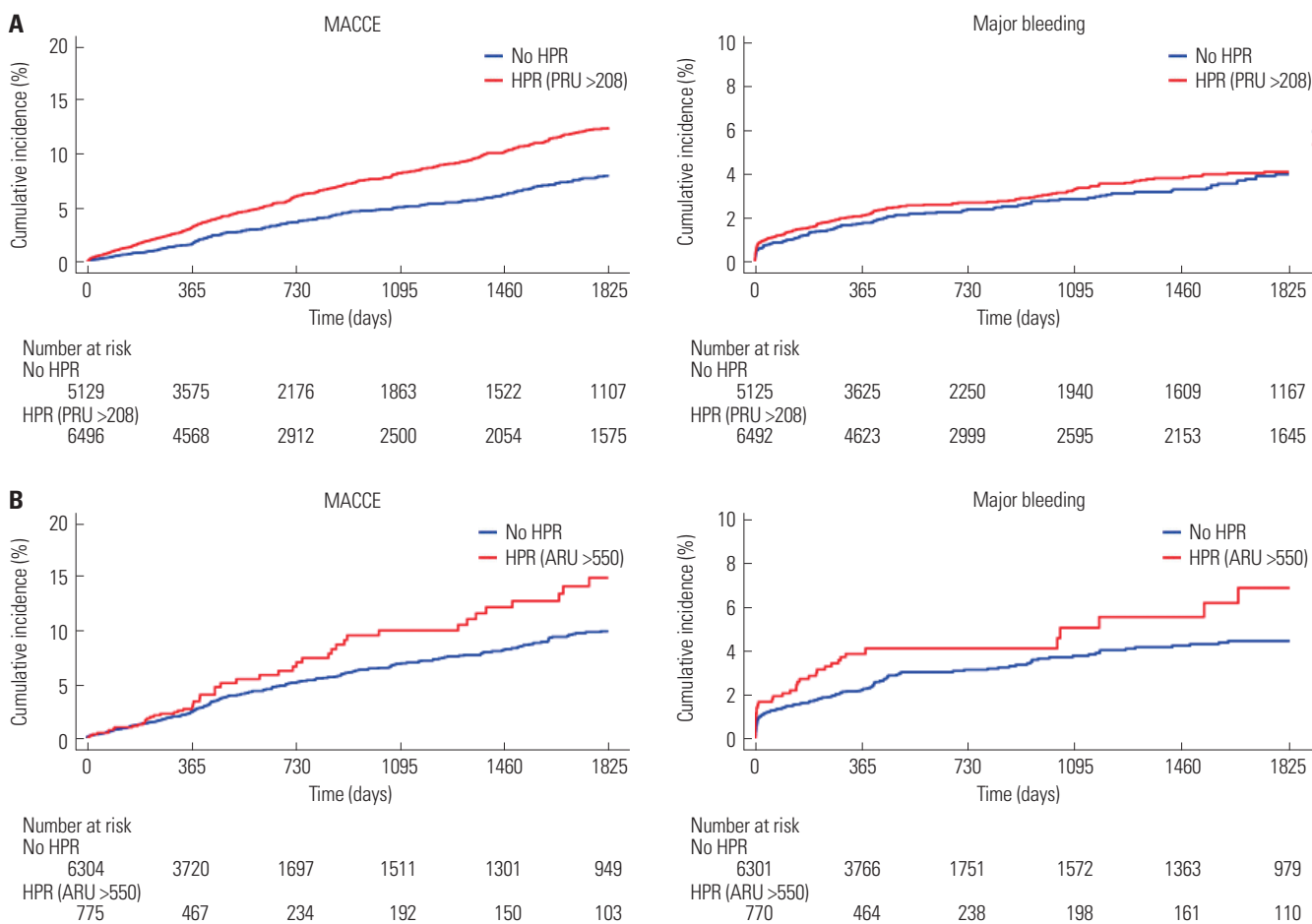

Fig. 4. Kaplan-Meier analysis for the association between HPR and MACCE and major bleeding events. (A) HPR to ADP (PRU >208) and MACCE and major bleeding events. (B) HPR to arachidonic acid (ARU >550) and MACCE and major bleeding events. HPR, high platelet reactivity; MACCE, major adverse cardiac and cerebrovascular events; ADP, adenosine diphosphate; PRU, P2Y12 reaction units; ARU, aspirin reaction units.
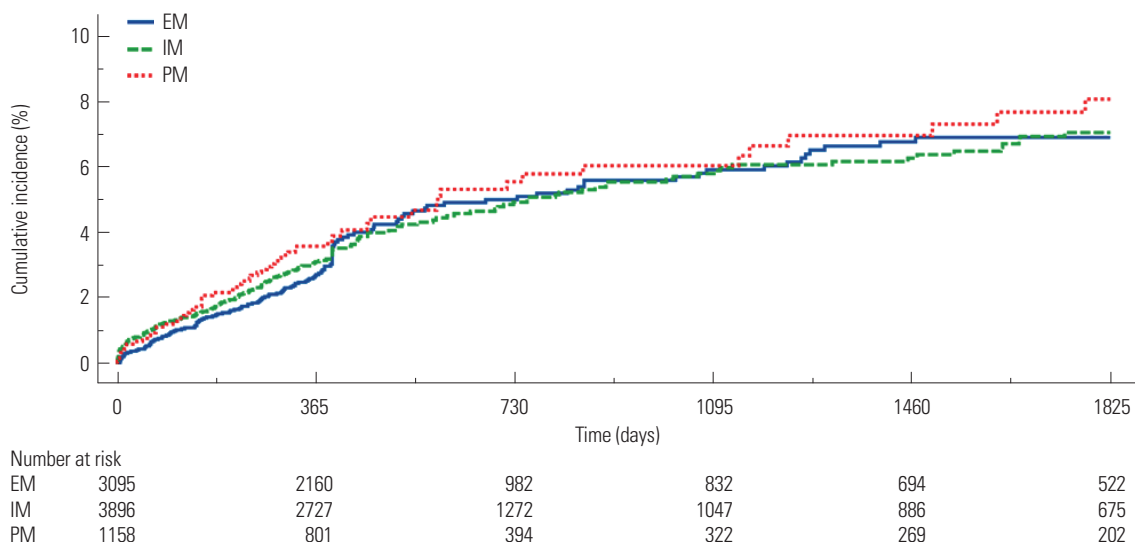
Fig. 5. Kaplan-Meier analysis for the association between CYP2C19 phenotype and MACCE. MACCE, major adverse cardiac and cerebrovascular events; EM, extensive metabolizers; IM, intermediate metabolizers; PM, poor metabolizers.

Number at risk

EM	3095	2160	982	832	694	522
IM	3896	2727	1272	1047	886	675
PM	1158	801	394	322	269	202

sive sensitivity analyses, confounders were adjusted to minimize bias from different baseline characteristics. Nonetheless, unmeasured confounders might still be present, and the extent to which unmeasured confounders contribute to the relation between platelet reactivity, genotyping, and adverse clinical outcomes is uncertain. One-point platelet function may not reflect dynamic changes over time. Lastly, the results of the present study may be limited to the boundaries of measurements and cannot be directly extended to the selection of an optimal antiplatelet strategy.

In conclusion, the PTRG-DES consortium indicates that East Asian patients have a higher level of on-clopidogrel platelet reactivity and higher prevalence of CYP2C19 LOF allele carriage, compared with Western patients, as well as a different RR of MACCE and major bleeding occurrence according to the time period during clopidogrel treatment. This registry will provide important "real-world" information regarding the linkage of platelet function and genotype with clinical events in a large cohort of clopidogrel-treated East Asian patients to better develop optimal antiplatelet strategies in this ethnicity.

DATA SHARING STATEMENT

The data generated in this study are available from the corresponding authors upon reasonable request.

ACKNOWLEDGEMENTS

AUTHOR CONTRIBUTIONS

Conceptualization: Ae-Young Her, Young-Hoon Jeong, Yongwhi Park, and Eun-Seok Shin. Data curation: Ae-Young Her, Young-Hoon Jeong, Hyung Joon Joo, and Yongwhi Park. Formal analysis: Ae-Young Her, Young-Hoon Jeong, and Jung Rae Cho. Funding acquisition: Moo Hyun Kim, Do-Sun Lim, and Eun-Seok Shin. Investigation: Ae-Young Her, Young-Hoon Jeong, Byeong-Keuk Kim, Kiyuk Chang, Young Bin Song, Sung Gyun Ahn, Jung-Won Suh, Sang Yeup Lee, Hyo-Soo Kim, Moo Hyun Kim, Do-Sun Lim, and Eun-Seok Shin. Methodology: Ae-Young Her, Young-Hoon Jeong, Hyung Joon Joo, Yongwhi Park, and Jung Rae Cho. Project administration: Yongwhi Park. Resources: Kiyuk Chang, Hyo-Soo Kim, Moo Hyun Kim, Do-Sun Lim, and Eun-Seok Shin. Software: Ae-Young Her and Young-Hoon Jeong. Supervision: Kiyuk Chang, Hyo-Soo Kim, Moo Hyun Kim, Do-Sun Lim, and Eun-Seok Shin. Validation: Byeong-Keuk Kim, Yongwhi Park, Young Bin Song, and Jung-Won Suh. Visualization: Ae-Young Her, Young-Hoon Jeong, and Eun-Seok Shin. Writing—original draft: Ae-Young Her and Young-Hoon Jeong. Writing—review & editing: Ae-Young Her, Young-Hoon Jeong, and Eun-Seok Shin. Approval of final manuscript: all authors.

ORCID iDs

Ae-Young Her   https://orcid.org/0000-0002-9990-6843
Young-Hoon Jeong   https://orcid.org/0000-0003-0403-3726
Byeong-Keuk Kim   https://orcid.org/0000-0003-2493-066X
Hyung Joon Joo   https://orcid.org/0000-0003-1846-8464
Kiyuk Chang   https://orcid.org/0000-0003-3456-8705
Yongwhi Park   https://orcid.org/0000-0003-3626-9717
Young Bin Song   https://orcid.org/0000-0003-3986-9152
Sung Gyun Ahn   https://orcid.org/0000-0002-1528-2739
Jung-Won Suh   https://orcid.org/0000-0002-0397-6071
Sang Yeup Lee   https://orcid.org/0000-0003-1386-349X
Jung Rae Cho   https://orcid.org/0000-0002-9803-6612
Hyo-Soo Kim   https://orcid.org/0000-0003-0847-5329
Moo Hyun Kim   https://orcid.org/0000-0003-3468-6453
Do-Sun Lim   https://orcid.org/0000-0001-5751-5177
Eun-Seok Shin   https://orcid.org/0000-0002-9169-6968

REFERENCES

1. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2016;68:1082-115.

2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017;39:213-60.

3. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 2019;12:1521-37.

4. Kim HK, Tantry US, Smith SC Jr, Jeong MH, Park SJ, Kim MH, et al. The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. Thromb Haemost 2021;121:422-32.

5. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol 2014;11:597-606.

6. Kang J, Han JK, Ahn Y, Chae SC, Kim YJ, Chae IH, et al. Third-generation P2Y12 inhibitors in East Asian acute myocardial infarction patients: a nationwide prospective multicentre study. Thromb Haemost 2018;118:591-600.

7. Kang J, Park KW, Palmerini T, Stone GW, Lee MS, Colombo A, et al. Racial differences in ischaemia/bleeding risk trade-off during anti-platelet therapy: individual patient level landmark meta-analysis from seven RCTs. Thromb Haemost 2019;119:149-62.

8. Park DW, Kwon O, Jang JS, Yun SC, Park H, Kang DY, et al. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. Circulation 2019;140:1865-77.

9. Kim HK, Ahn Y, Chang K, Jeong YH, Hahn JY, Choo EH, et al. 2020 Korean Society of Myocardial Infarction expert consensus document on pharmacotherapy for acute myocardial infarction. Korean Circ J 2020;50:845-66.

10. Tan JW, Chew DP, Abdul Kader MAS, Ako J, Bahl VK, Chan M, et al. 2020 Asian Pacific Society of cardiology consensus recommendations on the use of P2Y12 receptor antagonists in the Asia-Pacific region. Eur Cardiol 2021;16:e02.

11. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology appropriate use criteria task force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:2212-41.

12. Jeong YH, Bliden KP, Antonino MJ, Park KS, Tantry US, Gurbel PA. Usefulness of the VerifyNow P2Y12 assay to evaluate the antiplatelet effects of ticagrelor and clopidogrel therapies. Am Heart J 2012;164:35-42.

13. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614-23.

14. Joo HJ, Ahn SG, Park JH, Park JY, Hong SJ, Kim SY, et al. Effects of genetic variants on platelet reactivity and one-year clinical outcomes after percutaneous coronary intervention: a prospective multicentre registry study. Sci Rep 2018;8:1229.

15. Kim HS, Chang K, Koh YS, Park MW, Choi YS, Park CS, et al. CYP2C19 poor metabolizer is associated with clinical outcome of clopidogrel therapy in acute myocardial infarction but not stable angina. Circ Cardiovasc Genet 2013;6:514-21.

16. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.

17. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction. Eur Heart J 2018;40:237-69.

18. Li C, Zhang L, Wang H, Li S, Zhang Y, You L, et al. Gene variants in responsiveness to clopidogrel have no impact on clinical outcomes in Chinese patients undergoing percutaneous coronary intervention-A multicenter study. Int J Cardiol 2017;240:360-6.

19. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.

20. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.

21. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

22. Jeong YH. "East asian paradox": challenge for the current antiplatelet strategy of "one-guideline-fits-all races" in acute coronary syndrome. Curr Cardiol Rep 2014;16:485.

23. Sun Y, Li C, Zhang L, Yu T, Ye H, Yu B, et al. Clinical outcomes after ticagrelor and clopidogrel in Chinese post-stented patients. Atherosclerosis 2019;290:52-8.

24. You SC, Rho Y, Bikdeli B, Kim J, Siapos A, Weaver J, et al. Association of ticagrelor vs clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. JAMA 2020;324:1640-50.

25. Nakamura M, Kimura K, Kimura T, Ishihara M, Otsuka F, Kozuma K, et al. JCS 2020 guideline focused update on antithrombotic therapy in patients with coronary artery disease. Circ J 2020;84:831-65.

26. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Lancet 2021;397:1470-83.

27. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. JAMA 2020;324:761-71.