Prognostic Implication of *CYP2C19* Genotype According to Clinical Risk Stratification After Drug-Eluting Stent Implantation

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The impact of *CYP2C19* genotype in relation to clinical risk is unclear during clopidogrel treatment following drug-eluting stent (DES) implantation. This study aimed to evaluate the prognostic significance of *CYP2C19* genotypes based on clinical risk stratification in DES-treated patients. From the nationwide multicenter PTRG-DES (Platelet function and genoType-Related long-term progGosis in DES-treated patients) consortium, patients were classified according to the presence of *CYP2C19* loss-of-function (LoF) allele: rapid or normal metabolizers (RMs/NMs) vs. intermediate or poor metabolizers (IMs/PMs), and clinical risk was stratified using the CHADS-P_2A_2RC and TRS 2°P scores. The primary endpoint (1°EP) was a composite of cardiac death, myocardial infarction, and stent thrombosis during a 3-year follow-up. Among clopidogrel-treated patients with *CYP2C19* genotyping (n = 8,163), IMs/PMs (62.1%) demonstrated an increased risk of 1°EP compared with RMs/NMs (hazard ratio [HR]: 1.48; 95% confidence interval [CI]: 1.05–2.07; Log-rank P < 0.001), Most notable in those with high CHADS-P2A2RC (≥ 4) and TRS 2°P (≥ 3) scores (HR_{adj}: 1.68; 95% CI: 1.01–2.80; P = 0.047 and HR_{adj}: 1.63; 95% CI: 1.05–2.54; P = 0.029, respectively). In patients with low scores, there was no difference in 1°EP between IMs/PMs vs. RMs/NMs; however, an interaction was observed between acute and chronic coronary syndromes for both low CHADS-P_2A_2RC (HR_{adj}: 2.12; 95% CI: 1.11–4.03 and HR_{adj}: 0.68; 95% CI: 0.34–1.36; $P_{interaction}$ = 0.017) and TRS 2°P scores (HR_{adj}: 2.34; 95% CI: 1.07–5.12 and HR_{adj}: 0.52; 95% CI: 0.22–1.17; $P_{interaction}$ = 0.008). Among clopidogrel-treated patients, the carriage of the *CYP2C19* LoF allele was associated with higher ischemic risk, particularly in those with high clinical risk or an acute coronary syndrome presentation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ During clopidogrel-based DAPT, carriage of *CYP2C19 loss-of-function* (*LoF*) allele (**2* or **3*) is associated with worse clinical outcomes in PCI-treated patients presenting with ACS.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Limited evidence exists to support genotype-guided selection of P2Y12 inhibitors based on clinical or lesion-related risk profiles following PCI.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ From the PTRG-DES consortium (n = 8,163), carriage of CYP2C19 LoF allele was associated with an increased risk of ischemic events, particularly in those with high clinical or lesional risk (CHADS- P2A2RC ≥ 4 or TRS 2°P ≥ 3) or an acute coronary syndrome presentation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Clinical application of CYP2C19 genotyping requires careful assessment of each patient's bleeding and ischemic risks. High ischemic risk can be defined by the presenting disease entity and by clinical and lesional risk phenotypes.

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Clinical trial registration: Platelet function and genotype-related long-term prognosis in DES-treated patients with coronary artery disease [PTRG-DES]; NCT04734028.

The platelet adenosine diphosphate (ADP) $P2Y_{12}$ receptor plays a pivotal role in platelet activation by amplifying the effects of various agonists[1,2] and underscores its critical role in thrombosis and hemostasis, making it a key therapeutic target. Dual antiplatelet therapy (DAPT), aspirin and a $P2Y_{12}$ inhibitor, is a main antiplatelet strategy following percutaneous coronary intervention (PCI). Several oral $P2Y_{12}$ inhibitors are commercially available—clopidogrel, prasugrel, and ticagrelor—each with distinct pharmacokinetic and pharmacodynamic profiles, leading to different safety and efficacy clinical outcomes.[3,4] The use of potent oral $P2Y_{12}$ inhibitors, compared with clopidogrel, can lead to an increased risk of bleeding complications when applied universally. These observations have led to the concept of a "therapeutic window of platelet inhibition" in PCI-treated patients with significant coronary artery disease (CAD).[1,2,5]

The wide variability in individual responses to clopidogrel can be attributed to demographic, metabolic (including drug–drug interactions), clinical, procedural, and genetic factors. Clopidogrel, a prodrug, is converted to an active metabolite through a two-step oxidation process mediated by the hepatic cytochrome P450 (*CYP*) enzyme system.[6] The *CYP2C19* enzyme is involved in both metabolic steps of clopidogrel biotransformation.[7] Polymorphisms in the *CYP2C19* gene, particularly those resulting in loss-of-function (LoF) alleles, significantly influence this biotransformation process. This genetic variation can lead to decreased pharmacokinetic and pharmacodynamic effects of clopidogrel,[8] thereby reducing platelet inhibition and potentially increasing the risk of cardiovascular (CV) events.[9,10]

Comprehensive evidence from pharmacokinetic, pharmacodynamic, clinical outcomes, and meta-analyses supports the use of *CYP2C19* genetic testing to guide DAPT strategies to improve clinical outcomes in high-risk CAD patients.[1,2,11,12] Recent clinical guidelines recommend a genotype-guided approach for selecting a $P2Y_{12}$ inhibitor in patients with acute coronary syndrome (ACS), rather than extending this strategy to those with chronic coronary syndrome (CCS) following PCI.[13] The factors determining ischemic risk profile are diverse, including not only the disease entity (ACS vs. CCS) but also clinical risk factors and PCI complexity.[14]

Limited evidence exists to support genotype-guided selection of $P2Y_{12}$ inhibitors in patients with high ischemic risk, as defined by traditional CV risk factors, following the implantation of contemporary drug-eluting stents (DES). Therefore, we conducted the current analysis to investigate whether the prognostic significance of the *CYP2C19* genotype varies based on clinical risk stratifications using widely adopted clinical risk scores, such as the CHADS-P_2A_2RC[15] and Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention (TRS 2°P) scores.[16]

METHODS

Study population

The PTRG-DES (Platelet function and genoType-Related long-term proGnosis in DES-treated patients) consortium comprises nine prospective registries from 32 Korean academic centers, endorsed by the Korean Society of Interventional Cardiology (NCT04734028).[17] This consortium was specifically designed to determine the relationship between platelet reactivity or genotyping and clinical events following DES implantation in Korean patients with significant CAD. A total of 13,610 patients from July 2003 to August 2018 were eligible.

The organizing committee invited the lead investigators of clopidogrel-treated prospective clinical registries published in PubMed to participate. Consecutive patients at each center who were successfully treated with one or more DES approved by the U.S. Food and Drug Administration or CE mark and were adequately loaded with clopidogrel, were eligible for enrollment, regardless of patient or lesion complexity. The exclusion criteria were the occurrence of a major complication during the procedures, PCI strategies other than DES (balloon angioplasty only or use of bare-metal stents), and use of any $P2Y_{12}$ inhibitor other than Clopidogrel. Patients who underwent fibrinolytic therapy or needed oral anticoagulants were also excluded.[17]

In this analysis, we enrolled patients with available *CYP2C19* genotyping during clopidogrel treatment following DES implantation (*PTRG-Genotype* cohort). Finally, 8,163 patients were enrolled and classified into two groups according to the presence of *CYP2C19* LoF allele(s): (i) rapid metabolizers (RMs) or normal metabolizers (NMs); and (ii) intermediate metabolizers (IMs) or poor metabolizers (PMs) (**Figure S1**).

Patient management and procedures

Patient management, including PCI procedures, was conducted according to current standard practices. The operator determined the PCI strategy and choice of medications. Following the procedures, patients received aspirin (100 mg daily) and clopidogrel (75 mg daily). Patients were advised to continue aspirin indefinitely, and to receive clopidogrel based on their disease entity, and individual ischemic and bleeding risk profiles. Since *CYP2C19* genotyping was performed solely for research purposes, its results were not used to guide the selection of antiplatelet therapy. The use of potent $P2Y_{12}$ inhibitors was prohibited due to the

consortium's inclusion criteria. The final regimen and duration of antiplatelet therapy were left to the operator's discretion, based on guidelines and the patient's estimated ischemic and bleeding risks.

CYP2C19 genotyping

CYP2C19 genotypes were determined by single-nucleotide polymorphism (SNP) analysis using commercialized analyzers, including the PSQ 96MA Pyrosequencer (Pyrosequencing AB), the ABI PRISM 3100 genetic analyzer (Applied Biosystems), or the Spartan RX system (Spartan Bioscience) (**Table S1**). SNPs of the major alleles present in Korean patients, including *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *CYP2C19*17* (rs12248560) were analyzed.

The patients were classified into different genetically predicted CYP2C19 metabolizer status.[13] IMs had 1 *LoF* allele with 1 normal function allele, or 1 *LoF* allele with 1 gain-of-function (GoF) allele that may not compensate for the effect of the LoF allele, whereas PMs had 2 LoF alleles. RMs included *CYP2C19*1/*17*, NMs included *CYP2C19*1/*1*, and IMs included *CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17*, and *CYP2C19*3/*17*. PMs included *CYP2C19*2/*2, CYP2C19*2/*3*, and *CYP2C19*3/*3* (**Table S2**). No patients had the *CYP2C19*17/*17* genotype.

Clinical risk stratification

Various predictive risk scores for primary and secondary prevention are available in CV medicine. This analysis utilized two widely used, well-validated predictive risk scores for stratifying clinical risk.

CHADS-P_2A_2RC score. This system was recently developed to identify patients without atrial fibrillation at high risk a experiencing their first arterial thromboembolic event.[15] Compared with the 2019 ESC guideline, this score improved risk classification and may particularly identify low-risk patients with limited benefit from potent antithrombotic treatment.[18] This predictive model allocates one point for each of the following factors: congestive heart failure, hypertension, age between 65 and 74 years, diabetes mellitus (DM), active smoking, renal disease, and multivessel obstructive CAD. Two points for age ≥ 75 years and peripheral artery disease (PAD) are assigned. "High ischemic risk" was allocated in cases of a CHADS-P_2A_2RC score of ≥ 4.[19]

TRS 2°P score. This model was developed for risk prediction of patients with known CAD. The Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS 2°P) score is the aggregate of nine variables: age ≥ 75 years, diabetes mellitus, hypertension, current smoking, PAD, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction (defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2). Patients were stratified into "high ischemic risk" according to TRS2°P score of ≥3.[16]

Clinical outcomes and follow-up

The primary outcome was the occurrence of major adverse cardiovascular events (MACE: a composite of cardiac death, myocardial infarction [MI], and definite stent thrombosis) at 3 years after the index procedure. Bleeding events were adjudicated by the Bleeding Academic Research Consortium (BARC) classification. Major bleeding events were defined as BARC 3–5 bleedings at 3 years after the index procedure.[20] All outcome measurements were defined according to the Academic Research Consortium definitions.

For these time-to-event analyses, censoring was applied at the occurrence of the first clinical event or at the date of clopidogrel discontinuation to clarify the association between clinical outcomes and CYP2C19 genotyping.

Statistical analysis

Categorical variables are presented as numbers, relative frequencies, and, percentages and were compared using the Chi-square test. Continuous variables are expressed as either mean ± SD for normally distributed data or as median (IQR) for non-normally distributed data, determined by normality analysis using Q-Q plots and the Kolmogorov–Smirnov test. For parametric continuous variables, Student's unpaired *t*-test was utilized, while the Mann–Whitney rank sum test was applied for nonparametric continuous variables. The analysis of variance (ANOVA) test was employed to compare four groups.

The cumulative incidence of events at 3 years was calculated using Kaplan–Meier estimates, and clinical outcomes among the groups were compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. For this model, the proportional hazards assumption for *CYP2C19* genotype and clinical risk phenotype was validated using the Schoenfeld residual method. After excluding variables from clinical risk scores, multivariable Cox proportional hazards models were constructed using known key variables such as sex, body mass index, presentation with ACS, dyslipidemia, history of CABG, use of β-blocker, angiotensin blockade, and statin.

HRs for *CYP2C19* genotype and clinical risk phenotype in relation to MACE, cardiac death, MI, and stent thrombosis were calculated. Subgroup analyses for the specific group were conducted as part of an exploratory data analysis.

All probability values were two-sided. *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 26.0 for Windows (IBM) and R version 4.3.1 (R Foundation for Statistical Computing).

Ethics statement

The Institutional Review Board of each participating center approved the registry and waived the requirement for written informed consent for accessing an institutional registry. This study was performed in accordance with Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

RESULTS

Baseline characteristics are presented in **Table S3**. Among a total of 8,163 patients, the mean age was 64.2 ± 10.8 years, and 65.1% of patients were male. Index presentation with ACS was observed in 56.7% ($n = 4,630$,); 24.1% of the patients underwent multivessel PCI. The median follow-up duration was 377 days (IQR: 351, 860 days). During the follow-up, MACE and major bleeding occurred in 161 (3.2%) and 260 (4.4%) patients, respectively (**Table S4**).

Characteristics and outcomes according to CYP2C19 phenotype

Of total cohort, 3,098 (37.9%) patients were RMs or NMs, and 5,065 (62.1%) patients were IMs or PMs (**Figure S1**). There were no significant differences in demographics, CV risk factors, lesion and procedural characteristics, and discharge medications between the groups (**Table S3**). At the 3-year follow-up, patients carrying *CYP2C19* LoF alleles showed a significantly higher incidence of ischemic events, whereas major bleeding did not differ between the groups (**Figure 1a**), but the incidence of major bleeding was not different between the groups (4.6% vs. 4.3%; unadjusted HR: 0.99; 95% CI: 0.76–1.30; Log-rank $P = 0.969$) (**Figure 1b**).

Characteristics and outcomes according to clinical risk group

When classified by the CHADS-P_2A_2RC score, the distribution of patients was seen at **Figure 2a**. CHADS-P_2A_2RC scores

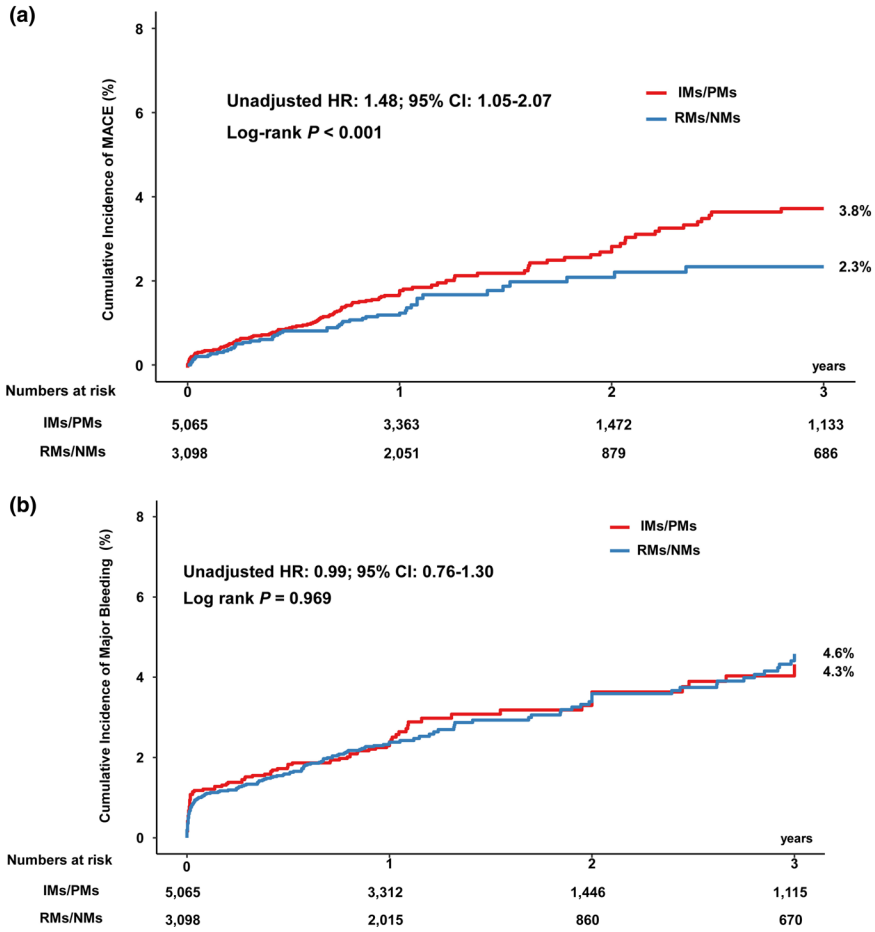


Figure 1 Cumulative incidence of (**a**) MACE and (**b**) major bleeding at 3 years based on CYP2C19 phenotype. Cumulative incidence of (**a**) MACE (a composite of cardiac death, myocardial infarction, and stent thrombosis) and (**b**) major bleeding (BARC type 3- 5) was compared between the rapid metabolizer (RM) or normal metabolizer (NM) vs. intermediate metabolizer (IM) or poor metabolizer (PM) over a 3-year follow-up period. BARC, Bleeding Academic Research Consortium; CI, confidence interval *CYP2C19*, hepatic cytochrome P450;HR, hazard ratio; MACE, major adverse cardiovascular event.

were proportionally associated with higher risks of both ischemic and bleeding events (P for trend < 0.001). When stratified according to the CHADS-P2A 2RC score, the high clinical risk group (CHADS-P2A 2RC ≥ 4: n = 1,924 [23.5%]) had a higher prevalence of CV risk factors compared with the low-clinical risk group (CHADS-P2A 2RC ≤ 3: n = 6,239 [76.5%]). Additionally, the high clinical risk group had a higher proportion of female patients, ACS and multivessel PCI compared with the low clinical risk group (**Table 1**). At the 3-year follow-up, the high clinical risk group showed higher rates of MACE (6.0% vs. 2.3%; Log-rank P < 0.001) and major bleeding (8.8% vs. 3.0%; Log-rank P < 0.001) compared with the low clinical risk group (**Figure S2**).

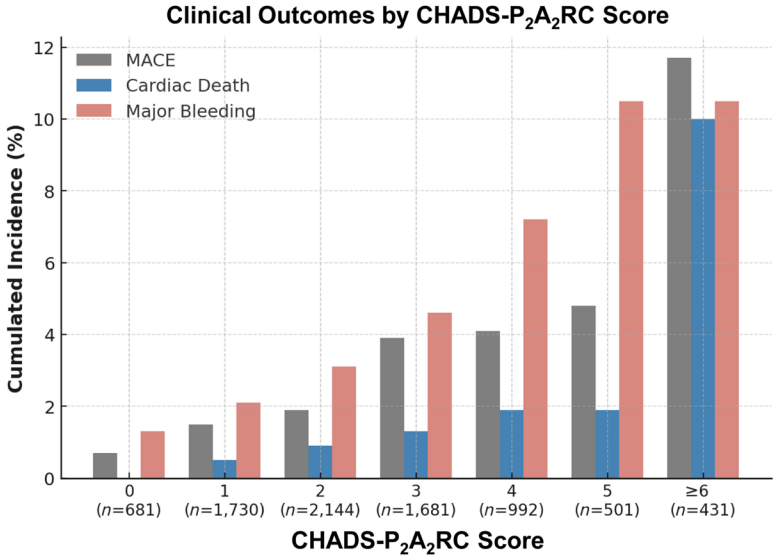
When evaluated by the TRS 2°P score, the distribution of patients was seen at **Figure 2b**. As the TRS 2°P score increased, the cumulative rates of MACE, cardiac death, and major bleeding (P for trend < 0.001) rose (**Figure 2b**). When stratified the individuals according to TRS 2°P score, the high clinical risk group (TRS 2°P ≥ 3: n = 3,723 [45.6%]) showed a higher prevalence of CV risk factors compared with the low clinical risk group (TRS 2°P ≤ 2: n = 4,440 [54.4%]) (**Table 1**). Additionally, the high clinical risk group had a higher proportion of male patients, dyslipidemia ACS and multivessel PCI compared with the low clinical risk group. At the 3-year follow-up, the high clinical risk group showed increased risks of MACE (4.9% vs. 2.0%; Log-rank P < 0.001) and major bleeding (6.6% vs. 2.9%; Log-rank P < 0.001) compared with the low clinical risk group (**Figure S3**).

Prognostic implication of CYP2C19 phenotype according to clinical risk

The prevalence of LoF allele carriage (IMs/PMs) was comparable between the low and high CHADS-P_2A_2RC groups (62.4% and 61.9%). When we compared clinical outcomes according to the clinical risk group and CYP2C19 phenotype, the presence of high clinical risk and IMs/PMs exhibited an additive effect on MACE and cardiac death (**Figure 3a,b**). *CYP2C19* LoF carriers with high clinical risk (CHADS-P_2A_2RC ≥4) showed the highest risk for MACE (7.3% vs. 1.9%; adjusted HR: 3.55; 95% CI: 2.24–5.64; P < 0.001) compared with noncarriers with low clinical risk (CHADS-P_2A_2RC ≤ 3) (**Table 2**, **Figure 3a**), which was related to the increased rates of cardiac death, MI, and definite stent thrombosis (**Table 2**, **Figure 3b**). The prognostic impact of CYP2C19 LoF carriage on MACE occurrence was significant

(a)

Variable of Prediction	Score
CHF	1
Hypertension	1
Age between 65 and 74 years	1
Diabetes mellitus	1
Active **S**moking	1
Peripheral artery disease	2
Age ≥ 75 years	2
Renal failure	1
Multivessel **C**AD	1
Total Score	**10**



(b)

Variable of Prediction	Score
Age ≥ 75 years	1
Diabetes mellitus	1
Hypertension	1
Current smoking	1
Peripheral artery disease	1
Prior stroke	1
Prior CABG	1
Heart failure	1
Renal dysfunction	1
Total Score	**9**

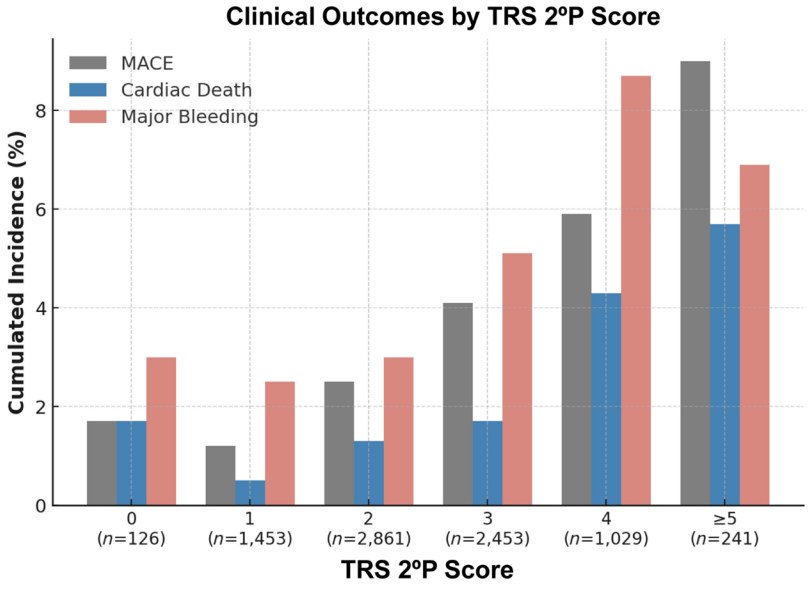


Figure 2 (**a**) CHADS-P_2A_2RC and (**b**) TRS 2°P scores: variables, distribution, and cumulated incidence of clinical events. CABG, coronary bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; TRS 2°P, thrombolysis in myocardial infarction (TIMI) risk score for secondary prevention.

in the high-risk group (adjusted HR: 1.68; 95% CI: 1.01–2.80; $P = 0.047$), not in the low-risk group (adjusted HR: 1.31; 95% CI: 0.83–2.07; $P = 0.242$) ($P_{interaction} = 0.479$) (**Table 2**). The risk of major bleeding was significantly associated with the clinical risk group, rather than the *CYP2C19* phenotype (**Figure 3c**). In the 1-year landmark analysis, the cumulative incidence of MACE and cardiac death continued to diverge even beyond the first year, particularly in patients with high clinical risk and *CYP2C19* LoF allele (MACE: 4.0% vs. 1.4%; and cardiac death: 2.4% vs. 0.6% in the high-risk group) (**Figure S4**).

The incidence of IMs/PMs was similar between the low and high TRS2°P groups (62.6% and 61.6%), respectively. When comparing clinical outcomes based on clinical risk group and *CYP2C19* phenotype, the presence of high clinical risk and IMs/PMs showed an additive effect on the occurrence of MACE and cardiac death (**Figure 4a,b**). CYP2C19 LoF carriers with high clinical risk (TRS2°P ≥ 3) exhibited the highest risk for MACE (5.9% vs. 1.7%; adjusted HR: 2.82; 95% CI: 1.72–4.64; $P < 0.001$) compared with non-carriers with low-clinical risk (TRS2°P ≤ 2) (**Table 2**, **Figure 4a**), which was driven by the increased rates of cardiac death, MI, and definite stent thrombosis (**Table 2**, **Figure 4b**). Clinical impact of *CYP2C19* LoF carriage on MACE was significant in the high-risk group (adjusted HR: 1.63; 95% CI: 1.05–2.54; $P = 0.029$), not in the low-risk group (adjusted HR: 1.23;

Table 1 Baseline characteristics according to clinical risk scores

Variable	Total (n=8,163)	Low CHADS-P_2A_2RC (≤3) (n=6,239, 76.5%)	High CHADS-P_2A_2RC (≥4) (n=1,924, 23.5%)	P-value	Low TRS 2°P (≤2) (n=4,440, 54.4%)	High TRS 2°P (≥3) (n=3,723, 45.6%)	P-value
Age, year	64.2 (10.8)	61.8 (10.1)	71.9 (9.1)	<0.001	62.3 (10.0)	66.4 (11.3)	<0.001
Male	5,312 (65.1)	4,194 (67.2)	1,118 (58.1)	<0.001	2,777 (62.5)	2,535 (68.1)	<0.001
IM/PMs	5,065 (62.0)	1,200 (62.4)	3,865 (61.9)	0.76	2,332 (62.6)	2,733 (61.6)	0.326
Body mass index, kg/m^2	24.6 (3.1)	24.7 (3.0)	24.2 (3.2)	<0.001	24.6 (3.0)	24.6 (3.2)	0.204
Index presentation							
Chronic coronary syndrome	3,533 (43.3)	2,789 (44.7)	744 (38.7)	<0.001	1,916 (43.2)	1,617 (43.4)	0.817
Acute coronary syndrome	4,630 (56.7)	3,450 (55.3)	1,180 (61.3)		2,524 (56.8)	2,106 (56.6)	
Risk factors							
Smoking	1,939 (23.8)	1,399 (22.4)	540 (28.1)	<0.001	625 (14.1)	1,314 (35.3)	<0.001
Hypertension	4,928 (60.4)	3,288 (52.7)	1,640 (85.2)	<0.001	1,809 (40.7)	3,119 (83.8)	<0.001
Diabetes mellitus	2,811 (34.4)	1,685 (27.0)	1,126 (58.5)	<0.001	673 (15.2)	2,138 (57.4)	<0.001
Dyslipidemia	5,163 (63.2)	3,947 (63.3)	1,216 (63.2)	0.982	2,714 (61.1)	2,449 (65.8)	<0.001
Chronic kidney disease	1,903 (23.3)	709 (11.4)	1,194 (62.1)	<0.001	1,167 (26.3)	736 (19.8)	<0.001
History of peripheral disease	1,063 (13.0)	199 (3.2)	864 (44.9)	<0.001	243 (5.5)	820 (22.0)	<0.001
History of congestive heart failure	738 (9.0)	352 (5.6)	386 (20.1)	<0.001	115 (2.6)	623 (16.7)	<0.001
Previous MI	677 (8.3)	481 (7.7)	196 (10.2)	0.001	359 (8.1)	318 (8.5)	0.482
Previous PCI	1,225 (5.0)	866 (3.9)	359 (18.7)	<0.001	641 (14.4)	584 (15.7)	0.123
Previous CABG	99 (1.2)	69 (1.1)	30 (1.6)	0.142	19 (0.4)	80 (2.1)	<0.001
Previous stroke	596 (7.3)	387 (6.2)	209 (10.9)	<0.001	75 (1.7)	521 (14.0)	
Laboratory findings							
LV ejection fraction, %	58.8±10.9	59.9±10.0	55.6±12.6	<0.001	59.5±10.0	58.1±11.7	<0.001
WBC, ×10^3/mm^3	7.8±2.9	7.7±2.8	8.1±3.1	<0.001	7.7±2.9	7.9±2.9	<0.001
Hemoglobin, g/dL	13.5±1.9	13.8±1.7	12.6±2.1	<0.001	13.6±1.8	13.4±2.0	<0.001
Platelet, ×10^3/mm^3	252.2±86.5	258.3±87.8	232.2±78.7	<0.001	251.4±86.5	253.1±86.4	0.378
GFR (MDRD), mL/min/1.73 m^2	76.2±25.8	81.5±23.0	58.8±26.9	<0.001	75.6±25.5	76.8±26.3	0.042
Total cholesterol, mg/dL	174.4±43.2	177.1±42.9	165.6±42.9	<0.001	178.2±42.6	170.0±43.5	<0.001
Triglyceride, mg/dL	141.7±99.0	145.6±102.6	128.9±85.1	<0.001	143.5±101.8	139.5±95.5	0.08
HDL-cholesterol, mg/dL	43.0±11.1	43.6±11.1	41.0±10.9	<0.001	43.8±11.2	42.1±11.0	<0.001
LDL-cholesterol, mg/dL	104.1±36.0	106.2±35.7	97.4±35.9	<0.001	106.9±35.7	100.9±36.1	<0.001
HbA1c, %	6.5±1.3	6.4±1.3	6.8±1.4	<0.001	6.3±1.3	6.7±1.4	<0.001
Angiographic feature							
ACC/AHA lesion							
Type A	540 (6.6)	422 (6.8)	118 (6.1)	0.513	322 (7.3)	218 (5.9)	<0.001
Type B1	3,732 (45.7)	2,868 (46.0)	864 (44.9)		1,954 (44.0)	1,778 (47.8)	
Type B2	2,166 (26.5)	1,647 (26.4)	519 (27.0)		1,177 (26.5)	989 (26.6)	
Type C	1,725 (21.1)	1,302 (20.9)	423 (22.0)		987 (22.2)	738 (19.8)	
Number of diseases vessels							
1	4,889 (59.9)	3,819 (61.2)	1,070 (55.6)	<0.001	2,677 (60.3)	2,212 (59.4)	
2	2,164 (26.5)	1,636 (26.2)	528 (27.4)		1,159 (26.1)	1,005 (27.0)	
3	1,110 (13.6)	784 (2.6)	326 (16.9)		604 (13.6)	506 (13.6)	

(Continued)

Table 1 (Continued)

Variable	Total (n=8,163)	Low CHADS-P_2A_2RC (≤3) (n=6,239, 76.5%)	High CHADS-P_2A_2RC (≥4) (n=1,924, 23.5%)	P-value	Low TRS 2°P (≤2) (n=4,440, 54.4%)	High TRS 2°P (≥3) (n=3,723, 45.6%)	P-value
Multivessel disease	3,274 (40.1)	2,420 (38.8)	854 (44.4)	<0.001	1,763 (39.7)	1,511 (40.6)	0.433
Bifurcation lesion	617 (7.6)	476 (7.6)	141 (7.3)	0.699	377 (8.5)	240 (6.4)	0.001
Chronic total occlusion lesion	563 (6.9)	426 (6.8)	137 (7.1)	0.696	280 (6.3)	283 (7.6)	0.024
Procedure data							
Multivessel PCI	1,969 (24.1)	1,434 (23.0)	535 (27.8)	<0.001	1,028 (23.2)	941 (25.3)	0.027
Treated lesions							
Left main coronary artery	399 (4.9)	279 (4.5)	120 (6.2)	0.002	208 (4.7)	191 (5.1)	0.38
Left anterior descending artery	4,796 (58.8)	3,706 (59.4)	1,090 (56.7)	0.035	2,655 (59.8)	2,141 (57.5)	0.038
Left circumflex artery	2,444 (29.9)	1,818 (29.1)	626 (32.5)	0.005	1,311 (29.5)	1,133 (30.4)	0.387
Right coronary artery	3,109 (38.1)	2,279 (36.5)	830 (43.1)	<0.001	1,661 (37.4)	1,448 (38.9)	0.176
Number of stents	1.6±0.7	1.5±0.7	1.6±0.8	<0.001	1.5±0.7	1.6±0.7	<0.001
Stent length, mm	34.4±20.9	33.8±20.4	36.5±22.6	<0.001	33.3±20.1	35.8±21.9	<0.001
Stent diameter, mm	3.0±0.4	3.0±0.5	3.0±0.4	<0.001	3.0±0.5	3.0±0.4	<0.001
Discharge medications							
Aspirin	8,058 (98.7)	6,168 (98.9)	1,890 (98.2)	0.043	4,389 (98.9)	3,669 (98.5)	0.268
Clopidogrel	8,163 (100.0)	6,239 (100.0)	1,924 (100.0)	1.000	4,440 (100.0)	3,723 (100.0)	1.000
Beta-blocker	5,129 (62.8)	3,900 (62.5)	1,229 (63.9)	0.29	2,743 (61.8)	2,386 (64.1)	0.033
Angiotensin blocker	5,035 (61.7)	3,790 (60.7)	1,245 (64.7)	0.002	2,532 (57.0)	2,503 (67.2)	<0.001
Calcium channel blocker	2,331 (28.6)	1,687 (27.0)	644 (33.5)	<0.001	1,205 (27.1)	1,126 (30.2)	0.002
Statin	7,148 (87.6)	5,493 (88.0)	1,655 (86.0)	0.021	3,846 (86.6)	3,302 (88.7)	0.005
Proton pump inhibitor	1,379 (16.9)	1,001 (16.0)	378 (19.6)	<0.001	714 (16.1)	665 (17.9)	0.035

Data are shown as mean±standard deviation or number(%).ACS, acute coronary syndrome; CRP, C-reactive protein; GFR, glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IM/PM, intermediate or poor metabolizer; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction unit; RAAS, renin-angiotensin aldosterone system; WBC, white blood cell.

95% CI: 0.72–2.11; P=0.453) ($P_{interaction}$=0.434) (**Table 2**). The risk of major bleeding was primarily associated with clinical risk group, rather than *CYP2C19* phenotype (**Figure 4c**). In the 1-year landmark analysis, the cumulative incidence of MACE and cardiac death continued to diverge even beyond the first year, particularly in patients with high clinical risk and CYP2C19 LoF allele (3.7% vs. 1.6% for MACE; and 1.9% vs. 0.6% for cardiac death in the high-risk group) (**Figure S5**).

Prognostic implication of CYP2C19 phenotype according to clinical risk and disease entity

The prognostic implication of being an IM or PM was significant in ACS patients (adjusted HR: 1.90; 95% CI: 1.21–2.94; P=0.004), but not in those with CCS (adjusted HR: 0.97; 95% CI: 0.56–1.67; P=0.966) ($P_{interaction}$=0.045) (**Figure 5a**). In the high-risk group, CYP2C19 LoF carriage increased the risk of MACE irrespective of the disease entity (ACS vs. CCS) ($P_{interaction}$=0.953 in CHADS-P2A 2RC ≥4 and $P_{interaction}$=0.904 in TRS2°P ≥ 3) (**Figure 5b,c**). Among the low clinical risk group, the prognostic implication of *CYP2C19 LoF* carriage was different according to the disease entity. In patients with CHADS-P_2A_2RC ≤ 3, CYP2C19 LoF carriage significantly increased the risk of MACE in ACS patients (adjusted HR: 2.12; 95% CI: 1.11–4.03; P=0.021), but not in CCS patients (adjusted HR: 0.68; 95% CI: 0.34–1.36; P=0.333) ($P_{interaction}$=0.017). A similar trend was observed in individuals with TRS2°P ≤ 2 (adjusted HR: 2.34; 95% CI: 1.07–5.12; P=0.033 in ACS patients and adjusted HR: 0.52; 95% CI: 0.22–1.17; P=0.136 in CCS patients) ($P_{interaction}$=0.008) (**Figure 5b,c**).

DISCUSSION

This nationwide, multicenter study assessed the prognostic impact of genetically predicted CYP2C19 phenotype according to clinical risk stratification using the CHADS-P_2A2RC and TRS 2°P scores during clopidogrel-based DAPT after DES implantation. Key findings include: (i) Over 60% of Korean patients carried CYP2C19 LoF alleles; (ii) LoF carriage was linked to a higher 3-year risk of post-PCI ischemic events; (iii) High-risk patients, defined by either CHADS-P_2A_2RC ≥ 4 or TRS 2°P ≥ 3, had greater ischemic and bleeding risks; and (iv) The adverse effect of LoF alleles was especially evident in high-risk patients and in low-risk patients presenting with ACS.

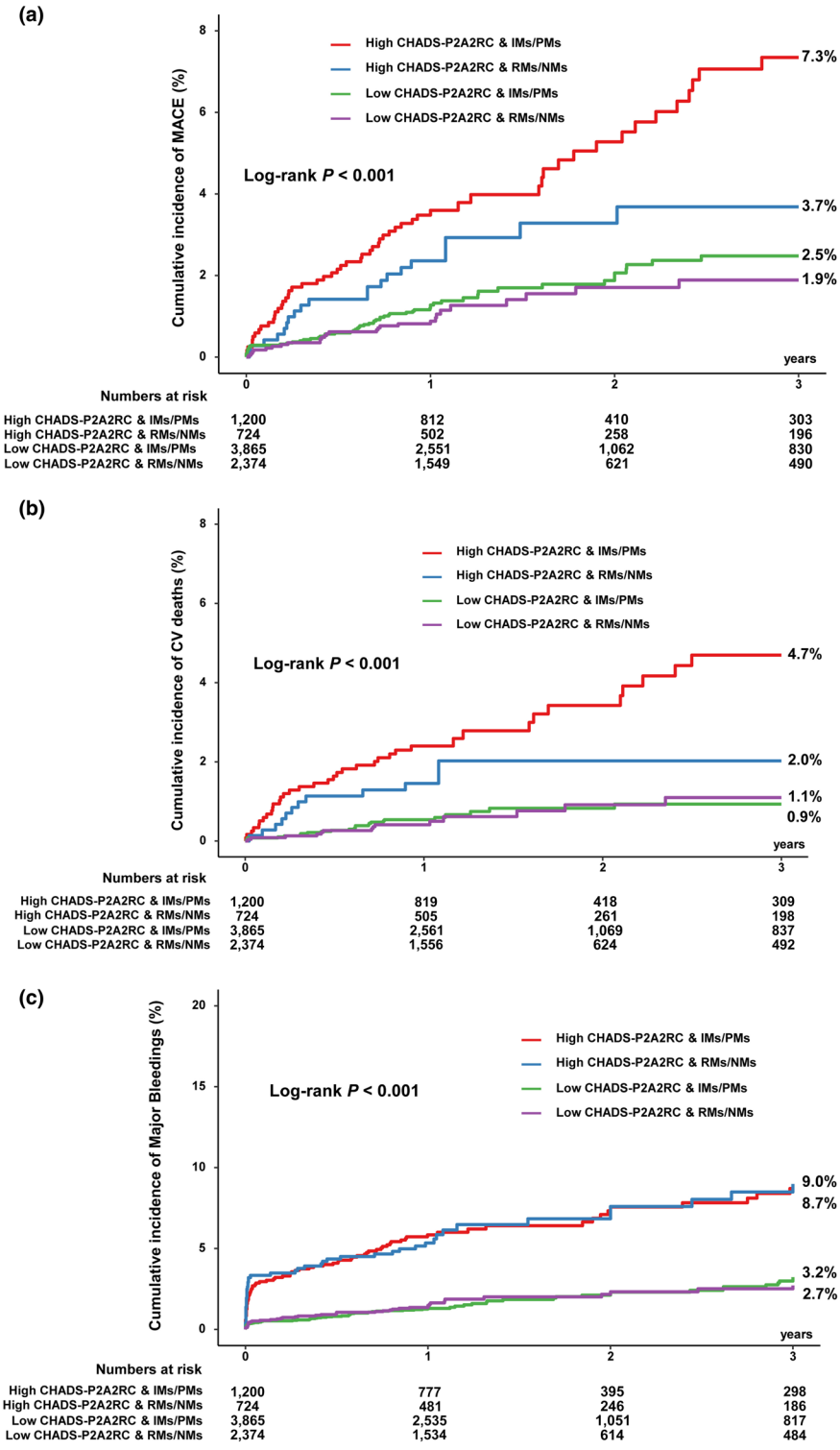


Figure 3 Cumulative incidence of (**a**) MACE, (**b**) cardiac death, and (**c**) major bleeding at 3 years according to CHADS-P_2A_2RC and *CYP2C19* phenotype. Cumulative incidence of (**a**) MACE (a composite of cardiac death, myocardial infarction, and stent thrombosis), (**b**) cardiac death, and (**c**) major bleeding (BARC type 3 or 5) was compared across the four groups stratified by CHADS-P_2A_2RC score (high [≥ 4] vs. low [≤ 3]) and *CYP2C19* phenotype (rapid metabolizer [RM] or normal metabolizer [NM] vs. intermediate metabolizer [IM] or poor metabolizer [PM]) over a 3-year follow-up period. BARC, Bleeding Academic Research Consortium; CYP2C19, hepatic cytochrome P450; MACE, major adverse cardiovascular event.

Table 2 Comparison of clinical risk according to CYP2C19 phenotypes and clinical risk score

	Risk Scores	Genotyping	Cumulative Incidence	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value			Cumulative Incidence	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
MACE	CHADS-$P_2A_2RC \leq 3$	RM/NM	1.9	Reference				TRS2°P ≤ 2	RM/NM	1.7	Reference			
		IM/PM	2.5	1.31 (0.83–2.07)	0.242				IM/PM	2.2	1.23 (0.72–2.11)	0.453		
	CHADS-$P_2A_2RC \geq 4$	RM/NM	3.7	2.10 (1.18–3.76)	0.012	Reference		TRS2°P ≥ 3	RM/NM	3.1	1.74 (0.97–3.11)	0.062	Reference	
		IM/PM	7.3	3.55 (2.24–5.64)	<0.001	1.68 (1.01–2.80)	0.047		IM/PM	5.9	2.82 (1.72–4.64)	<0.001	1.63 (1.05–2.54)	0.029
Cardiac death	CHADS-$P_2A_2RC \leq 3$	RM/NM	1.1	Reference				TRS2°P ≤ 2	RM/NM	1.2	Reference			
		IM/PM	0.9	1.05 (0.54–2.04)	0.878				IM/PM	0.9	1.00 (0.48–2.05)	0.995		
	CHADS-$P_2A_2RC \geq 4$	RM/NM	2.0	2.43 (1.12–5.28)	0.024	Reference		TRS2°P ≥ 3	RM/NM	1.5	1.50 (0.69–3.27)	0.301	Reference	
		IM/PM	4.7	4.41 (2.37–8.20)	<0.001	1.82 (0.95–3.50)	0.072		IM/PM	3.3	2.62 (1.37–5.00)	0.003	1.75 (0.96–3.21)	0.07
Myocardial infarction	CHADS-$P_2A_2RC \leq 3$	RM/NM	0.9	Reference				TRS2°P ≤ 2	RM/NM	0.8	Reference			
		IM/PM	1.1	1.14 (0.59–2.18)	0.697				IM/PM	1.1	1.34 (0.61–2.97)	0.467		
	CHADS-$P_2A_2RC \geq 4$	RM/NM	1.7	1.61 (0.67–3.84)	0.287	Reference		TRS2°P ≥ 3	RM/NM	1.7	1.86 (0.79–4.36)	0.155	Reference	
		IM/PM	3.2	2.70 (1.37–5.29)	0.004	1.70 (0.75–3.82)	0.201		IM/PM	2.4	2.42 (1.14–5.13)	0.021	1.31 (0.68–2.52)	0.42
Stent thrombosis	CHADS-$P_2A_2RC \leq 3$	RM/NM	0.3	Reference				TRS2°P ≤ 2	RM/NM	0.1	Reference			
		IM/PM	0.6	3.06 (1.05–8.95)	0.041				IM/PM	0.3	5.03 (0.63–40.18)	0.128		
	CHADS-$P_2A_2RC \geq 4$	RM/NM	0.6	8.49 (0.01–9.99)	0.996	Reference		TRS2°P ≥ 3	RM/NM	0.4	3.29 (0.34–32.67)	0.303	Reference	
		IM/PM	1	4.54 (1.39–14.81)	0.012	4.11 (0.01–9.99)	0.998		IM/PM	1.3	13.83 (1.86–103.00)	0.01	4.20 (1.25–14.11)	0.02
Major bleeding	CHADS-$P_2A_2RC \leq 3$	RM/NM	2.7	Reference				TRS2°P ≤ 2	RM/NM	2.8	Reference			
		IM/PM	3.2	0.99 (0.67–1.46)	0.949				IM/PM	3.0	0.93 (0.61–1.43)	0.752		
	CHADS-$P_2A_2RC \geq 4$	RM/NM	8.7	3.53 (2.32–5.38)	<0.001	Reference		TRS2°P ≥ 3	RM/NM	6.4	2.00 (1.30–3.08)	0.002	Reference	
		IM/PM	9.0	3.48 (2.38–5.09)	<0.001	0.99 (0.69–1.43)	0.965		IM/PM	6.7	2.04 (1.38–3.01)	<0.001	1.02 (0.73–1.43)	0.916

Adjusted covariates included sex, body mass index, presentation with ACS, dyslipidemia, and the use of β-blockers, angiotensin blockers, and statins.

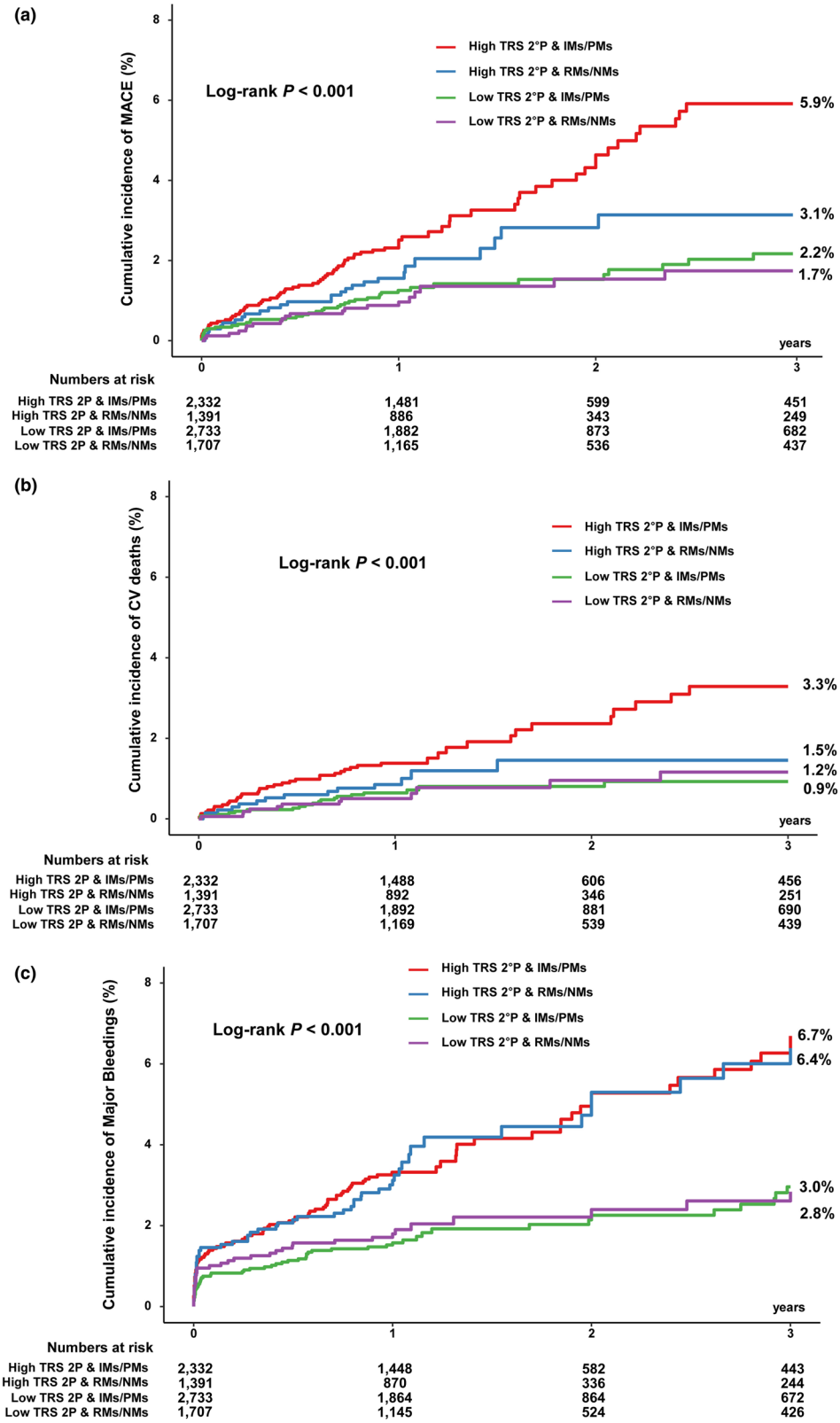


Figure 4 Cumulative incidence of (**a**) MACE, (**b**) cardiac death, and (**c**) major bleeding at 3 years based on TRS 2°P score and CYP2C19 phenotype. Cumulative incidence of (**a**) MACE (a composite of cardiac death, myocardial infarction, and stent thrombosis), (**b**) cardiac death, and (**c**) major bleeding (BARC type 3 or 5) was compared across the four groups stratified by TRS 2°P score (high [≥3] vs. low [≤2]) and *CYP2C19* phenotype (rapid metabolizer [RM] or normal metabolizer [NM] vs. intermediate metabolizer [IM] or poor metabolizer [PM]) over a 3-year follow-up period. BARC, Bleeding Academic Research Consortium; CYP2C19, hepatic cytochrome P450; MACE, major adverse cardiovascular event; TRS 2°P, thrombolysis in myocardial infarction (TIMI) risk score for secondary prevention.

The 2022 CPIC guideline strongly recommends standard-dose prasugrel or ticagrelor in *CYP2C19* IM/PM with ACS or undergoing PCI, based on high-quality evidence.[1,2] However, the role of genotype-guided $P2Y_{12}$ inhibitor selection in patients with varying ischemic risk after DES implantation remains unclear. In ACS, guided de-escalation from potent $P2Y_{12}$ inhibitors to clopidogrel may reduce bleeding in clopidogrel responders (RMs/NMs). In CCS, guided escalation to potent inhibitors may reduce ischemic events in LoF allele carriers (IMs/PMs), provided that the bleeding risk, as assessed by established criteria, does not outweigh the ischemic benefit. This study demonstrates that integrating CYP2C19 phenotype with clinical risk scores, such as CHADS-P2A2RC and TRS 2°P, can effectively identify patients at high ischemic risk. These findings support a personalized antiplatelet strategy that incorporates genetic, clinical, and disease-specific factors.

Prediction of post-PCI ischemic events by clinical risk scores

Assessing the risk of ischemic or bleeding complications in patients undergoing PCI is crucial for determining the appropriate intensity and duration of antiplatelet therapy. Several well-established factors were associated with the risk of atherothrombotic events following PCI.[14] In ACS patients, thrombotic risk peaks in the first month post-PCI and diminishes thereafter. Additionally, procedural factors, such as PCI complexity, are closely associated with the risk of thrombotic events extending through mid-term follow-up.[21] However, clinical risk factors had a greater and more prolonged effect on outcomes than procedural risk. The present analysis also showed a prolonged prognostic impact of clinical risk stratification on the occurrence of ischemic and bleeding complications following DES implantation. Therefore, the clinical benefit of genotype-guided selection of $P2Y_{12}$ inhibitors may be enhanced in high-risk patients identified through validated clinical risk scores, such as CHADS-P_2A_2RC and TRS 2°P.

The CHADS-P_2A_2RC score was specifically developed to enhance the identification of CCS patients who are at a high risk of thrombotic events.[19] This scoring system is supported by evidence indicating its effectiveness in more accurately identifying high-risk patients who could benefit from intensified antiplatelet strategies compared with the ESC criteria.[22] The proportion of patients identified as high-risk phenotype was 33.9% using the ESC criteria[22] compared with 24.9% with the CHADS-P_2A_2RC score. Furthermore, the CHADS-P_2A_2RC score has been shown to enhance risk classification effectively and may be particularly useful in identifying low-risk patients with limited benefit from treatment. This score enabled correct downward risk reclassification of ~8% without events, yielding an improved specificity of 9.7%, a loss of sensitivity of 4.4%, and an overall net reclassification index of 0.053.[18] The present analysis identified a 23.5% prevalence of the high-risk group (CHADS-P_2A_2RC ≥ 4), which was significantly associated with an increased risk of both 3-year ischemic (HR: 2.71; 95% CI: 1.99–3.69; Log-rank $P < 0.001$) and bleeding complications (HR: 3.67; 95% CI: 2.83–4.75; Log-rank $P < 0.001$) compared with the low-risk group (**Figure S1**). Bleeding complications peaked within the first month post-PCI and stabilized thereafter. Since escalating $P2Y_{12}$ inhibitors based on *CYP2C19* phenotype in the high-risk group may increase bleeding risk, large-scale clinical evidence is needed before its implementation in clinical practice.

The TRS 2°P score is a simple 9-point risk stratification tool developed to predict recurrent CV events in stable patients with a history of MI.[16] Previous studies have demonstrated the prognostic value of TRS 2°P following PCI for long-term secondary prevention, assessing both thrombotic and bleeding outcomes.[21,23,24] The present analysis identified 45.6% of patients as high-risk phenotype (TRS 2°P ≥ 3), which increased the risk of both 3-year ischemic (HR: 2.18; 95% CI: 1.58–3.01; Log-rank $P < 0.001$) and bleeding events (HR: 2.10; 95% CI: 1.61–2.74; Log-rank $P < 0.001$). These findings further emphasize the importance of utilizing TRS 2°P as a reliable predictor of adverse outcomes including ischemic and bleeding complications.

CYP2C19 genotyping-guided selection of Oral $P2Y_{12}$ inhibitor

Carriers of *CYP2C19* LoF alleles exhibit reduced generation of clopidogrel's active metabolite, leading to higher rates of HPR and an increased risk of thrombotic events following PCI.[13] *CYP2C19* genotyping offers the key advantage of providing stable, lifelong information, as an individual's genotype remains unchanged over time. A genotyping-guided approach enables personalized escalation or de-escalation of antiplatelet therapy compared with standard $P2Y_{12}$ inhibitor therapy. In the ACS setting, a genotyping-guided strategy enables selective de-escalation from a potent $P2Y_{12}$ inhibitor to clopidogrel in noncarriers of *CYP2C19* LoF alleles. Conversely, in the CCS setting, this strategy allows for selective escalation from clopidogrel to a potent $P2Y_{12}$ inhibitor among carriers of *CYP2C19* LoF alleles. Despite its promising potential, the clinical implementation of guided antiplatelet therapy in routine practice remains limited, primarily due to the absence of strong recommendation from clinical guidelines, mixed findings from clinical trials, and insufficient pharmacogenetic education.[1,25,26]

The current study highlights a key finding: the prognostic impact of *CYP2C19* phenotype was significant in DES-treated patients with high clinical risk, but not in those with low clinical risk. Additionally, the clinical impact of *CYP2C19* phenotype remained relevant in individuals with low clinical risk when presenting with ACS. Collectively, these findings suggest that the carriage of the *CYP2C19*-LoF allele can be associated with an increased ischemic risk in patients with high ischemic risk, such as those with ACS or high clinical risk scores. These findings may also inform management in CCS patients. Additionally, because genotyping analyzes a patient's fixed genetic information, it can be performed regardless of whether the patient is currently taking antiplatelet therapy, such as clopidogrel. For CCS patients with high clinical risk, the genotyping-guided escalation strategy offers a rationale for switching to a potent P2Y12 inhibitor in LoF allele carriers, particularly in those with high clinical risk. Nevertheless, large-scale clinical trials are warranted to confirm the utility of this strategy prior to widespread adoption.

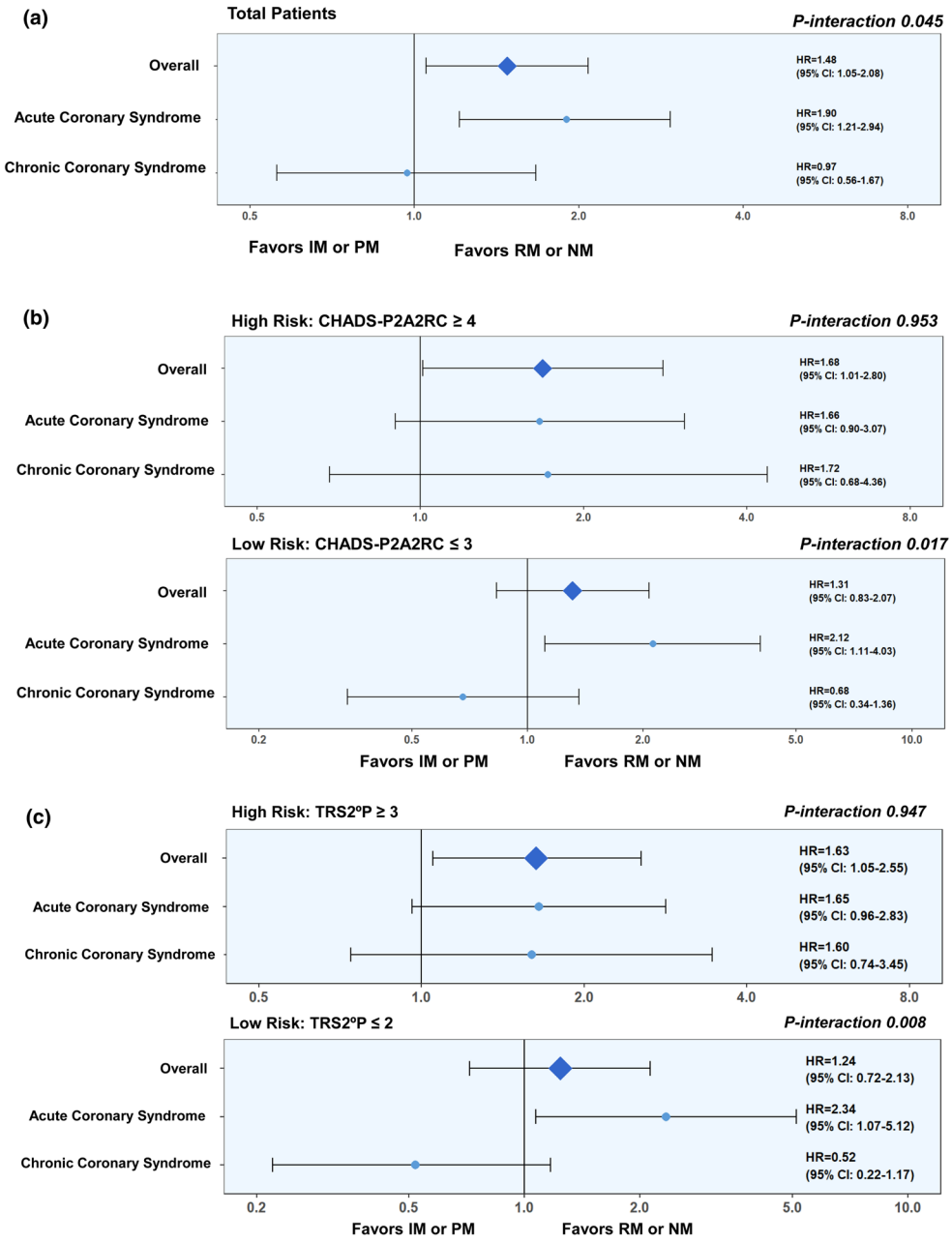


Figure 5 Prognostic implication of *CYP2C19* phenotype according to clinical risk stratification and disease entity. Adjustment was performed by variables such as sex, body mass index, dyslipidemia, and the use of β-blocker, angiotensin blocker, and statin. CI, confidence interval; CYP2C19, hepatic cytochrome P450; HR, hazard ratio; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; TRS 2°P, thrombolysis in myocardial infarction (TIMI) risk score for secondary prevention.

"East Asian Paradox" and antiplatelet prescription

More than 60% of East Asian patients carry *CYP2C19* LoF alleles, reflecting the marked decreased response to clopidogrel. It is noteworthy that clopidogrel remains still widely used in East Asia despite this high prevalence, largely due to the so-called "East Asian Paradox"—that is, a relatively lower ischemic but higher bleeding risk during antithrombotic therapy in this population.[5] Meanwhile, in East Asian patients with ACS, potent $P2Y_{12}$ inhibitors have not shown a clear ischemic advantage over clopidogrel but have consistently increased bleeding. For example, in a Korean AMI cohort, ticagrelor or prasugrel was associated with a higher rate of major bleeding without a statistically significant reduction in ischemic events compared with clopidogrel.[27] Likewise, a randomized trial in Korean ACS patients demonstrated that ticagrelor significantly increased bleeding risk but did not reduce composite ischemic outcomes compared with clopidogrel.[28]

In this context, this analysis is particularly important for assessing the association between *CYP2C19* genotype and clinical outcomes in a selected cohort of East Asian patients undergoing DES implantation. We identified a clear genotype–outcome relationship

in patients with high clinical risk, and this association persisted beyond 1 year. However, using standard-dose ticagrelor or prasugrel is unlikely to overcome this challenge. Instead, de-escalation or abbreviated DAPT strategies have demonstrated greater clinical benefit in East Asian patients than in Western patients,[5] underscoring the importance of genotype- and clinical risk–guided antiplatelet therapy to optimize the balance between ischemic protection and bleeding safety in this population.

Limitations

First, as this study was based on a large-scale consortium of prospective registries, unmeasured confounders and potential selection bias may have influenced the results. *CYP2C19* genotyping was performed in patients who remained event-free at the time of enrollment, which may have contributed to the relatively low event rates, even among those with ACS. However, exclusion of early-event patients was likely minimal and is unlikely to have introduced substantial selection bias. The overall low event rates observed in this analysis are more likely attributable to the characteristics of this cohort. East Asian PCI populations have consistently shown lower ischemic event rates than Caucasian cohorts, a well-recognized feature of the "East Asian paradox".[5] Second, although data on DAPT duration and regimen were available, reasons for regimen selection and adherence were unclear, as the analysis relied on registry data. Third, given the unique ischemic and bleeding profiles of East Asian populations, our findings may not directly generalize to the clinical use of prasugrel or ticagrelor in these patients with CYP2C19-LoF alleles.[5] These findings, derived from an East Asian population with distinct genetic and bleeding characteristics, should be interpreted with caution when extrapolated to other ethnic groups. Fourth, our analysis did not demonstrate an association between *CYP2C19* genotype and major bleeding. Unlike minor bleeding,[29] major bleeding is multifactorial and may be influenced by the antiplatelet effect, comorbid conditions, and the anatomo-physiologic background. Finally, the duration of clopidogrel therapy was determined at the discretion of the treating physician, based on the patient's clinical condition and individual ischemic and bleeding risk profiles. Because clopidogrel discontinuation could potentially affect outcomes, we also censored follow-up at the date of discontinuation to minimize its impact on the observed clinical events. Meanwhile, ~20% of patients apparently continued clopidogrel beyond 3 years according to the attending physician's discretion. This variability in time of clopidogrel treatment may reflect a real-world practice.

CONCLUSIONS

In this large-scale, real-world analysis of DES-treated patients receiving clopidogrel-based dual antiplatelet therapy, high clinical risk (CHADS-P_2A_2RC ≥ 4 or TRS 2°P ≥ 3) was associated with worse clinical outcomes compared with low clinical risk. Among clopidogrel-treated patients, carriage of the CYP2C19 LoF allele was linked to increased CV risk, particularly in those at high clinical risk. In low-risk patients, the prognostic relevance of the LoF allele carriage was mainly observed in those presenting with ACS.

SUPPORTING INFORMATION

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

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Hyun Woong Park conceived and designed the study, performed the statistical analyses, interpreted the data, and drafted the manuscript. Young-Hoon Jeong contributed to the study design, data management, statistical analyses, and interpretation of results, and assisted in drafting and revising the manuscript. Jae-Hwan Lee, Jin-Ok Jeong, Hyo-Soo Kim, Moo Hyun Kim, Do-Sun Lim, Eun-Seok Shin, Diana A. Gorog, Udaya S. Tantry, Paul A. Gurbel, and contributed to the conception of the study, interpretation of the data, and critical revision of the manuscript for important intellectual content. Byeong-Keuk Kim, Hyung Joon Joo, Kiyuk Chang, Jin-Yong Hwang, Young Bin Song, Sung Gyun Ahn, Jung-Won Suh, Woong Gil Choi, Jung Rae Cho, Jeehoon Kang, and Sang Yeub Lee were responsible for patient enrollment, data acquisition and verification, and critically reviewed the manuscript for important intellectual content. Young-Hoon Jeong provided overall supervision, had final responsibility for the decision to submit the manuscript for publication, and acts as the guarantor of the work. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data will be shared on reasonable requests to the corresponding author, if required.

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