

ORIGINAL RESEARCH

Sex Differences in Prognostic Implications of CYP2C19 Genotype After Drug-Eluting Stent Implantation

Soo-Jin Kim , MD, PhD; Ae-Young Her , MD, PhD; Hyung Joon Joo , MD, PhD; Kiyuk Chang , MD, PhD; Byeong-Keuk Kim , MD, PhD; Young Bin Song , MD, PhD; Sung Gyun Ahn , MD, PhD; Jung-Won Suh , MD, PhD; Sang Yeup Lee , MD, PhD; Jung Rae Cho , MD, PhD; Hyo-Soo Kim , MD, PhD; Young-Hoon Jeong , MD, PhD; Moo Hyun Kim , MD, PhD; Do-Sun Lim , MD, PhD; Eun-Seok Shin , MD, PhD

BACKGROUND: Dual-antiplatelet therapy is standard after percutaneous coronary intervention, but clopidogrel responsiveness varies with *CYP2C19* loss-of-function alleles. Whether the genotype conveys different prognostic significance between sexes is uncertain.

METHODS: We analyzed 4630 East-Asian patients with acute coronary syndrome in the PTRG-DES (Platelet Function- and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) consortium with available *CYP2C19* genotyping. Patients were classified as rapid/normal metabolizers versus intermediate/poor metabolizers. The primary end point was cardiac death, myocardial infarction, or definite stent thrombosis within 5 years.

RESULTS: Among 4630 patients with acute coronary syndrome, 1708 (36.9%) were women. The prevalence of intermediate/poor metabolizer phenotypes was similar in women (61.8%) and men (62.5%). After multivariable adjustment for clinical, laboratory, and procedural confounders, intermediate/poor metabolizer carriers had a significantly higher risk of the 5-year primary outcome in men compared with rapid/normal metabolizer carriers (adjusted hazard ratio [HR], 3.27 [95% CI, 1.58–6.74]; $P=0.001$). In contrast, no significant association was observed in women (adjusted HR, 1.21 [95% CI, 0.58–2.52]; $P=0.615$). Intermediate/poor metabolizer status was also associated with a higher risk of 5-year cardiac death in men only (adjusted HR, 7.01 [95% CI, 2.01–24.48]; $P=0.002$). Significant interactions between sex and *CYP2C19* metabolizer status were observed for both the primary outcome (P for interaction=0.034) and cardiac death (P for interaction=0.049).

CONCLUSIONS: *CYP2C19* loss-of-function allele status was a significant predictor of long-term adverse cardiovascular outcomes in men but not in women, suggesting a sex-specific prognostic difference in patients with acute coronary syndrome undergoing percutaneous coronary intervention.

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Key Words: coronary artery disease ■ *CYP2C19* genotype ■ drug-eluting stent ■ female ■ sex

Correspondence to: Eun-Seok Shin, MD, PhD, Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, 25 Daehakbyeongwon-ro, Dong-gu, Ulsan 44033, Republic of Korea. Email: sesim1989@gmail.com

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CLINICAL PERSPECTIVE

What Is New?

- In 4630 East-Asian patients with acute coronary syndrome receiving clopidogrel-based dual-antiplatelet therapy, *CYP2C19* loss-of-function alleles conferred a 3-fold higher 5-year risk of ischemic events in men, whereas no excess risk was evident in women.

What Are the Clinical Implications?

- Genotype-guided escalation of P2Y₁₂ inhibition may be most beneficial in male carriers of *CYP2C19* loss-of-function alleles, whereas alternative risk determinants should be explored in women.

Nonstandard Abbreviations and Acronyms

HPR	high platelet reactivity
IM	intermediate metabolizer
LOF	loss of function
MACE	major adverse cardiovascular event
NM	normal metabolizer
PM	poor metabolizer
PRU	P2Y ₁₂ reaction unit
RM	rapid metabolizer
ST	stent thrombosis

Dual-antiplatelet therapy, typically comprising aspirin and a P2Y₁₂ receptor antagonist, such as clopidogrel, is the standard treatment following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).^{1,2} Clopidogrel is a prodrug that requires metabolic activation primarily via the cytochrome P450 enzyme system, with *CYP2C19* playing a pivotal role in this bioactivation process.³ Genetic polymorphisms in *CYP2C19* can significantly alter the metabolic efficiency of clopidogrel, thereby affecting its antiplatelet activity and clinical efficacy. In particular, carriers of loss-of-function (LOF) alleles, such as *CYP2C19**2 and *CYP2C19**3, exhibit reduced enzymatic activity, leading to impaired conversion to the active metabolite and attenuated platelet inhibition. These individuals, categorized as poor metabolizers, are consequently at increased risk for adverse cardiovascular events, including stent thrombosis and recurrent ischemia.^{4–6}

Recent trials have demonstrated the benefit of genotype-guided antiplatelet therapy compared with conventional treatment approaches in patients with

ACS, particularly in optimizing therapy for those carrying LOF alleles.^{7–9} Although the association between *CYP2C19* polymorphisms and clopidogrel response has been well documented, the potential influence of sex-based biological differences remains under-explored. Pharmacokinetic and pharmacodynamic variability, related to differences in drug absorption, metabolism, and platelet reactivity, along with ethnic and genetic diversity, may contribute to sex-specific outcomes in patients treated with clopidogrel. These factors, with genetic diversity, may affect the clinical relevance of *CYP2C19* variants in a sex-dependent manner.

Therefore, this study aimed to investigate whether *CYP2C19* LOF alleles are associated with sex-specific differences in long-term clinical outcomes among East Asian patients with ACS undergoing PCI and receiving clopidogrel-based antiplatelet therapy.

METHODS

Transparency and Openness Statement

The data that support the findings of this study are not publicly available because of institutional and ethical restrictions. The analytic methods and study materials are available from the corresponding author on reasonable request.

Study Population

The PTRG-DES (Platelet Function- and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) consortium was a prospective multicenter registry from 32 hospitals in Korea.¹⁰ The participating registries and centers are listed in [Table S1](#). A total of 13 160 patients who underwent successful PCI for significant coronary artery disease at 9 PCI registries between July 2003 and August 2018 were recruited. In this study, we included 4630 patients who presented with ACS and had available *CYP2C19* genotyping data during long-term antiplatelet therapy following drug-eluting stent implantation. Patients were stratified by sex into female and male groups and further categorized according to *CYP2C19* metabolizer status: rapid or normal metabolizers (RMs/NMs) versus intermediate or poor metabolizers (IMs/PMs) based on the presence of *CYP2C19* LOF alleles ([Figure 1](#)).

Ethics Statement

The study protocol was approved by the Institutional Review Board of each participating center, and the requirement for written informed consent was waived because of the observational nature of the registry-based study.

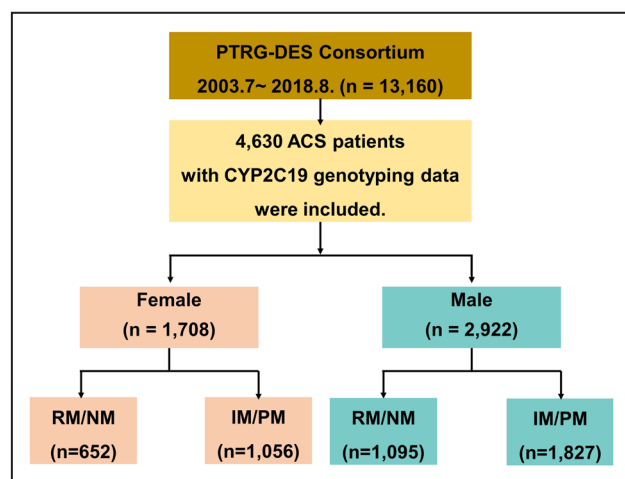


Figure 1. Study flow.

From the PTRG-DES Consortium (July 2003–August 2018; n=13 160), 4630 patients with ACS with CYP2C19 genotyping data were included. Among them, 1708 were women (652 RM/NM and 1056 IM/PM) and 2922 were men (1095 RM/NM and 1827 IM/PM). ACS indicates acute coronary syndrome; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; PTRG-DES, Platelet Function- and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease; and RM, rapid metabolizer.

Patient Management and Procedure

Patients who had not been taking aspirin or clopidogrel before the procedure were administered a loading dose of aspirin (300 mg) and clopidogrel (300–600 mg) as part of the preprocedural preparation. All PCI procedures were conducted according to standard protocols. After the PCI, patients received a maintenance regimen consisting of 100 mg of aspirin and 75 mg of clopidogrel daily. Patients were advised to continue aspirin indefinitely and clopidogrel for at least 12 months. The total duration of dual-antiplatelet therapy was individualized based on the patient's clinical profile and physician judgment.

CYP2C19 Genotyping

Peripheral blood or oral mucosa samples were collected from patients for genetic analysis. DNA was extracted from mononuclear cells in the blood using a specialized DNA extraction kit and stored at -20°C until analysis. Genetic mutations were analyzed by single-nucleotide polymorphism testing using commercial platforms available at each institution, such as the PSQ 96MA Pyrosequencer, ABI PRISM 3100 Genetic Analyzer, or the Spartan RX system.^{11–13} Details of the site-specific genotyping method are provided in Table S2. Patients were classified according to their CYP2C19 genotype. IMs were defined as individuals carrying 1 LOF allele (CYP2C19 *2 or *3) along with 1 normal or gain-of-function allele. PMs were defined as individuals with 2 LOF alleles. These classifications were based on

established genotype–phenotype correlations.^{4,11,13,14} The detailed information is provided in Table S3.

Study End Point

The primary end point was the occurrence of major adverse cardiovascular events (MACEs), including cardiac death, myocardial infarction (MI), and stent thrombosis (ST) for 5 years after PCI. The secondary end points were cardiac death, MI, ST, all-cause mortality, repeat revascularization, stroke, and major bleeding (Bleeding Academic Research Consortium grade 3–5).¹⁵

Cardiac death was defined as death resulting from MI, cardiac perforation, or pericardial tamponade, occurrences of arrhythmias or irregularities in heart conduction, or a stroke within postprocedure 30 days or linked to the procedure. It also included deaths resulting from procedural complications. Otherwise, it was characterized as a death case where cardiac causes could not be excluded. MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings associated with MI combined with an increase in creatine kinase-MB above the upper normal limit or troponin T/I greater than the 99th percentile of the upper normal limit, unrelated to an interventional procedure.¹⁶ ST was defined as definite ST according to the Academic Research Consortium criteria.¹⁷ Stroke included any new embolic, thrombotic, or hemorrhagic stroke events with neurologic deficits that persisted for at least 24 hours.

Statistical Analysis

Categorical variables were presented as percentages and compared using the χ^2 test or Fisher exact test. Continuous variables were presented as mean $\pm$ SD, and means were compared using Student *t*-test. Time-to-event data were presented as Kaplan–Meier estimates and compared using the log-rank test. Hazard ratios (HRs) and 95% CIs were generated using the Cox proportional hazards regression model. In the subgroup analysis, the relationship between intermediate or poor metabolizer status and clinical outcomes was examined using Cox regression analysis. To evaluate the risk of MACEs in the female group, an additional analysis was conducted by dividing patients with available platelet reactivity data into 4 subgroups. Based on a previous study that identified a cutoff value of P2Y12 reaction unit (PRU) for ischemic events, high platelet reactivity (HPR) to clopidogrel was defined as a PRU value of ≥ 252 in this study.¹⁸ Univariate and multivariate regression analyses were performed to identify independent predictors of clinical outcomes. Multivariate analysis was adjusted for the following variables: age, body mass index, hypertension, diabetes, dyslipidemia, smoking, chronic kidney disease, history of congestive heart failure, previous myocardial infarction, previous percutaneous coronary intervention, previous

stroke, PRU, white blood cell count, hemoglobin, platelet count, number of diseased vessels, multivessel disease, bifurcation lesion, chronic total occlusion lesion, multivessel PCI, involvement of the left main coronary artery, left anterior descending artery, left circumflex artery, or right coronary artery, use of first-generation drug-eluting stents, second-generation drug-eluting stents, number of stents, and use of aspirin, clopidogrel, β -blockers, calcium channel blockers, and statins. The same analyses were also conducted in the male group to compare sex-based differences. Interaction terms between sex and CYP2C19 metabolizer status were included in multivariate Cox regression models to evaluate effect modification. Significance was assessed using the Wald test for interaction. All tests were 2 sided, and $P < 0.05$ was considered statistically significant. The analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and R version 3.6.1.

RESULTS

Baseline Characteristics by Group

Baseline characteristics are presented in Table 1. Among the total of 4630 patients, 1708 (36.9%) were women and 2922 (63.1%) were men. The follow-up duration was 1004.8 ± 681.4 days for women and 777.79 ± 615.9 days for men. On average, women were older than men (67.4 versus 62.1 years). The prevalence of hypertension and chronic kidney disease was slightly higher in women, whereas the proportion of smokers was greater in men. Women also showed higher PRU levels compared with men (Table 1).

In the female group, NM was 37% (636 patients), RM was 1% (16 patients), IM was 47% (802 patients), and PM was 15% (254 patients). In the male group, NM was 37% (1070 patients), RM was 1% (25 patients), IM was 48% (1408 patients), and PM was 14% (419 patients). When categorized as NM/RM versus IM/PM, the distribution in women was 38% (652 patients) versus 62% (1056 patients), and in men, it was 38% (1095 patients) versus 62% (1827 patients), showing no statistically significant difference between sexes.

There were no significant differences in baseline clinical characteristics, angiographic or procedural data, or discharge medications between the RM/NM and IM/PM groups in either the female or male populations. However, the VerifyNow PRU levels were higher in the IM/PM group compared with the RM/NM group in both sexes (Tables 1 and 2).

Five-Year Clinical Outcomes According to Sex and CYP2C19 Genotype

The 5-year incidence of MACEs was similar between sexes in the overall population, occurring in 42

female patients (2.5%) and 72 male patients (2.5%). The follow-up duration of the overall population was 861.5 ± 650.1 days. Among subgroups, MACEs occurred in 2.7% of women with IM/PM, 2.0% of women with RM/NM, 3.1% of men with IM/PM, and 1.5% of men with RM/NM (Figure 2). In the female group, multivariate-adjusted Cox regression analysis showed no significant association between the IM/PM phenotype and the risk of MACEs compared with the RM/NM group (adjusted HR, 1.21 [95% CI, 0.58–2.52]; $P = 0.615$). However, in the male group, the IM/PM phenotype was significantly associated with an increased risk of MACEs compared with the RM/NM group (adjusted HR, 3.27 [95% CI, 1.58–6.74]; $P = 0.001$). A formal interaction test confirmed a significant sex-based difference in association between CYP2C19 phenotype and MACE risk (P for interaction = 0.034) (Figure 3). In the ST events, the male IM/PM group showed the highest number of events, with 14 cases (0.8%), and the incidence was significantly different among the 4 groups ($P = 0.033$) (Figure S1). However, this difference was not statistically significant after multivariate analysis in female and male groups (HR, 2.17 [95% CI, 0.86–5.46]; $P = 0.101$) (Figure 3). Both male and female IM/PM groups showed a higher MI event rate of 1.3% compared with the RM/NM groups, but the differences were not statistically significant (Figure S2; Figure 3).

Interestingly, both female and male IM/PM groups showed a relatively higher incidence of cardiac death. In the female group, cardiac death occurred in 1.5% of the IM/PM group compared with 0.9% in the RM/NM group, whereas in the male group, it occurred in 1.6% of the IM/PM group compared with 0.8% in the RM/NM group (Figure S3). In multivariate analysis, the IM/PM group in women was not identified as an independent risk factor for cardiac death (HR, 1.70 [95% CI, 0.53–5.45]; $P = 0.372$), whereas in men, the IM/PM phenotype was found to be an independent predictor of cardiac death (HR, 7.01 [95% CI, 2.01–24.48]; $P = 0.002$) (Figure 3).

In this analysis, no significant association was observed between CYP2C19 metabolizer status and Bleeding Academic Research Consortium 3 to 5 bleeding events in either sex. In the female group, Bleeding Academic Research Consortium 3 to 5 bleeding occurred in 4.7% of the IM/PM group and 3.7% of the RM/NM group, whereas in the male group, it occurred in 3.4% of the IM/PM group and 3.5% of the RM/NM group (Figure S4).

Five-Year Clinical Outcomes According to CYP2C19 Genotype and HPR in Women

Among the 1467 female patients with available HPR test results, patients were reclassified into 4 groups

Table 1. Baseline Characteristics

Characteristic	Women				Men			
	Overall (n=1708)	RM/NM (n=652)	IM/PM (n=1056)	P value	Overall (n=2922)	RM/NM (n=1095)	IM/PM (n=1827)	P value
Age, y	67.4±10.2	67.3±10.5	67.5±9.9	0.742	62.1±11.4	62.2±11.5	62.1±11.4	0.905
Body mass index, kg/m ²	24.3±3.1	24.3±3.1	24.4±3.2	0.756	24.5±3.0	24.5±3.0	24.5±3.1	0.891
Risk factors								
Hypertension	1078 (63.1)	427 (65.5)	651 (61.6)	0.110	1604 (54.9)	599 (54.7)	1005 (55.0)	0.873
Diabetes	615 (36.0)	231 (35.4)	384 (36.4)	0.696	926 (31.7)	349 (31.9)	577 (31.6)	0.870
Dyslipidemia	1037 (60.7)	387 (59.4)	650 (61.6)	0.366	1872 (64.1)	678 (61.9)	1194 (65.4)	0.061
Smoking	196 (11.5)	76 (11.7)	120 (11.4)	0.854	1092 (37.4)	384 (35.1)	708 (38.8)	0.046
Chronic kidney disease	659 (38.6)	250 (38.3)	409 (38.7)	0.873	528 (18.1)	200 (18.3)	328 (18.0)	0.832
History of peripheral artery disease	198 (11.6)	71 (10.9)	127 (12.0)	0.476	439 (15.0)	158 (14.4)	281 (15.4)	0.486
History of congestive heart failure	162 (9.5)	55 (8.4)	107 (10.1)	0.245	314 (10.7)	124 (11.3)	190 (10.4)	0.435
Previous MI	176 (10.3)	64 (9.8)	112 (10.6)	0.602	218 (7.5)	77 (7.0)	141 (7.7)	0.495
Previous PCI	329 (19.3)	132 (20.2)	197 (18.7)	0.418	383 (13.1)	143 (13.1)	240 (13.1)	0.952
Previous stroke	126 (7.4)	47 (7.2)	79 (7.5)	0.834	193 (6.6)	70 (6.4)	123 (6.7)	0.721
Laboratory findings								
VerifyNow PRU	232.6±81.5	205.0±80.6	249.7±77.3	<0.001	208.4±78.1	187.0±80.4	221.1±73.9	<0.001
HPR (PRU >208)	943 (55.2)	278 (42.6)	665 (63.0)	<0.001	1235 (42.3)	345 (31.5)	890 (48.7)	<0.001
WBC count, ×10 ³ /mm ³	7.9±2.9	7.8±2.9	8.0±3.0	0.418	8.6±3.3	8.6±3.2	8.6±3.3	0.670
Hemoglobin, g/dL	12.7±1.7	12.8±1.7	12.7±1.7	0.203	14.0±1.9	14.0±1.9	14.0±1.9	0.604
Platelet, ×10 ³ /mm ³	242.5±80.2	241.7±82.2	243.0±78.9	0.751	249.1±87.7	248.7±91.5	249.3±85.4	0.872
GFR (MDRD), mL/min per 1.73 m ²	68.0±26.2	68.5±25.8	67.6±26.4	0.503	80.1±26.0	80.6±25.9	79.7±26.0	0.370
HbA1c, %	6.5±1.3	6.6±1.4	6.5±1.3	0.693	6.4±1.3	6.4±1.4	6.3±1.3	0.237
Total cholesterol, mg/dL	178.4±44.6	177.8±43.4	178.8±45.4	0.683	176.0±44.1	175.4±42.9	176.4±44.8	0.593
LDL cholesterol, mg/dL	108.3±46.1	109.0±57.5	107.9±37.3	0.656	108.3±38.2	107.9±38.8	108.5±37.8	0.662
HDL cholesterol, mg/dL	44.4±11.4	44.6±11.3	44.2±11.4	0.467	41.9±10.9	42.1±11.4	41.8±10.6	0.538
Triglyceride, mg/dL	132.9±87.0	133.9±96.5	132.3±80.5	0.722	141.9±101.3	140.5±99.5	142.8±102.4	0.560
LV ejection fraction, %	57.9±11.5	58.0±11.1	57.9±11.7	0.765	56.9±10.9	56.6±10.7	57.2±11.1	0.200

Values are number (percentage) or mean±SD.

GFR indicates glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HPR, high platelet reactivity; IM, intermediate metabolizer; LDL, low-density lipoprotein; LV, left ventricular; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NM, normal metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; PRU, P2Y12 reaction unit; RM, rapid metabolizer; and WBC, white blood cell.

based on HPR status and *CYP2C19* metabolizer phenotype. The distribution was as follows: 402 patients in the non-HPR and RM/NM group, 447 in the non-HPR and IM/PM group, 159 in the HPR and RM/NM group, and 459 in the HPR and IM/PM group. In multivariate Cox regression analysis for MACEs, compared with the non-HPR and RM/NM group, the HPR and IM/PM group showed an HR of 1.25 (95% CI, 0.51–3.06; $P=0.63$), which was not statistically significant as an independent risk factor. In contrast, a similar analysis in the male cohort revealed that the HPR and IM/PM group had a significantly higher risk of MACEs compared with the non-HPR and RM/NM

group (HR, 11.78 [95% CI, 3.56–38.93]; $P<0.0001$), indicating a statistically significant independent association (Table S4).

DISCUSSION

CYP2C19 genotyping is known to influence the efficacy of antiplatelet agents, and its association with clinical outcomes has been reported.⁹ This study aimed to investigate whether these associations differ by sex. In this post hoc analysis of a large East Asian cohort with ACS undergoing PCI, the overall 5-year incidence of MACEs was low and comparable between

Table 2. Angiographic and Procedural Characteristics

Characteristic	Women				Men			
	Overall (n=1708)	RM/NM (n=652)	IM/PM (n=1056)	P value	Overall (n=2922)	RM/NM (n=1095)	IM/PM (n=1827)	P value
Angiographic feature								
ACC/AHA lesion								
Type A	77 (4.5)	38 (5.8)	39 (3.7)	0.147	150 (5.1)	65 (5.9)	85 (4.7)	0.217
Type B1	661 (38.7)	245 (37.6)	416 (39.4)		1334 (45.7)	487 (44.5)	847 (46.4)	
Type B2	475 (27.8)	188 (28.8)	287 (27.2)		757 (25.9)	274 (25.0)	483 (26.4)	
Type B3	495 (29.0)	181 (27.8)	314 (29.7)		681 (23.3)	269 (24.6)	412 (22.6)	
No. of diseased vessels								
1	939 (55.0)	357 (54.8)	582 (55.1)	0.636	1727 (59.1)	640 (58.4)	1087 (59.5)	0.757
2	480 (28.1)	178 (27.3)	302 (28.6)		806 (27.6)	303 (27.7)	503 (27.5)	
3	289 (16.9)	117 (17.9)	172 (16.3)		389 (13.3)	152 (13.9)	237 (13.0)	
Multivessel disease	769 (45.0)	295 (45.2)	474 (44.9)	0.885	1195 (40.9)	455 (41.6)	740 (40.5)	0.577
Bifurcation lesion	161 (9.4)	55 (8.4)	106 (10.0)	0.271	221 (7.6)	80 (7.3)	141 (7.7)	0.684
Chronic total occlusion lesion	119 (7.0)	48 (7.4)	71 (6.7)	0.615	207 (7.1)	85 (7.8)	122 (6.7)	0.269
Procedural data								
Multivessel PCI	451 (26.4)	169 (25.9)	282 (26.7)	0.721	751 (25.7)	277 (25.3)	474 (25.9)	0.698
Treated lesions								
Left main coronary artery	85 (5.0)	36 (5.5)	49 (4.6)	0.416	131 (4.5)	53 (4.8)	78 (4.3)	0.470
Left anterior descending artery	1013 (59.3)	369 (56.6)	644 (61.0)	0.073	1688 (57.8)	630 (57.5)	1058 (57.9)	0.843
Left circumflex artery	540 (31.6)	206 (31.6)	334 (31.6)	0.988	915 (31.3)	330 (30.1)	585 (32.0)	0.288
Right coronary artery	705 (41.3)	280 (42.9)	425 (40.2)	0.271	1161 (39.7)	450 (41.1)	711 (38.9)	0.244
Stent type								
First-generation DES	1490 (87.2)	565 (86.7)	925 (87.6)		2526 (86.4)	935 (85.4)	1591 (87.1)	
Second-generation DES	218 (12.8)	87 (13.3)	131 (12.4)	0.572	396 (13.6)	160 (14.6)	236 (12.9)	0.195
No. of stents	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.741	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.335
Stent length, mm	34.0±21.4	33.4±21.8	34.3±21.1	0.379	35.1±21.5	34.8±21.3	35.3±21.5	0.591
Stent diameter, mm	2.9±0.4	2.9±0.4	2.9±0.4	0.840	3.1±0.5	3.1±0.5	3.1±0.5	0.176
Discharge medications								
Aspirin	1673 (98.0)	639 (98.0)	1034 (97.9)	0.899	2886 (98.8)	1078 (98.4)	1808 (99.0)	0.224
Clopidogrel	1708 (100.0)	652 (100.0)	1056 (100.0)	NA	2922 (100.0)	1095 (100.0)	1827 (100.0)	NA
β-Blocker	1034 (60.5)	387 (59.4)	647 (61.3)	0.432	1974 (67.6)	742 (67.8)	1232 (67.4)	0.854
RAAS inhibitors	869 (50.9)	349 (53.5)	520 (49.2)	0.085	1843 (63.1)	706 (64.5)	1137 (62.2)	0.224
Calcium channel blocker	523 (30.6)	208 (31.9)	315 (29.8)	0.367	737 (25.2)	285 (26.0)	452 (24.7)	0.438
Statin	1296 (75.9)	493 (75.6)	803 (76.0)	0.841	2641 (90.4)	1003 (91.6)	1638 (89.7)	0.085
Proton pump inhibitor	297 (17.4)	102 (15.6)	195 (18.5)	0.135	565 (19.3)	198 (18.1)	367 (20.1)	0.184

Values are number (percentage), mean±SD, or median (interquartile range).

ACC indicates American College of Cardiology; AHA, American Heart Association; DES, drug-eluting stent; IM, intermediate metabolizer; NM, normal metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; RAAS, renin-angiotensin-aldosterone system; and RM, rapid metabolizer.

female and male patients. However, when stratified by *CYP2C19* metabolizer status, a clear sex-specific pattern was observed. *CYP2C19* IM/PM status was associated with a significantly higher risk of MACEs and

cardiac death in male patients, whereas no such association was observed in female patients. In contrast, no statistically significant associations were observed for myocardial infarction, stent thrombosis, or Bleeding

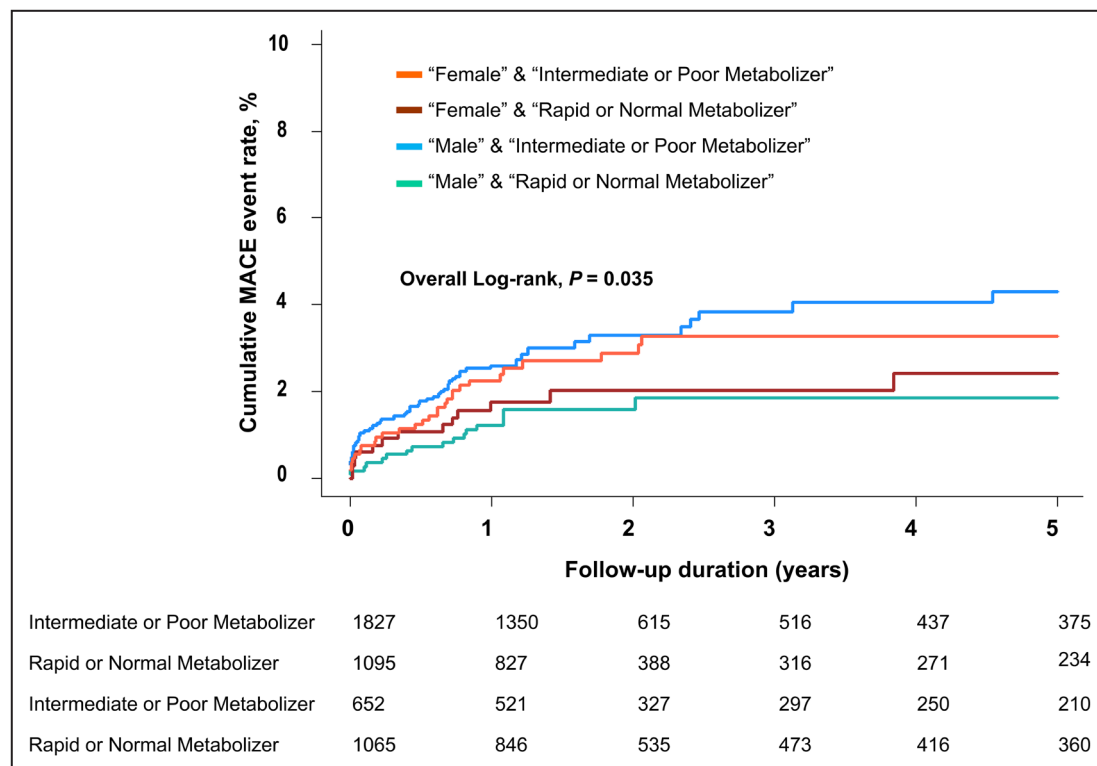


Figure 2. Kaplan–Meier curve according to sex and CYP2C19 genotyping for MACEs.

Kaplan–Meier curves show the cumulative incidence of MACEs over 5 years according to sex and CYP2C19 metabolizer phenotype. The cumulative incidence of MACEs was highest in male IM/PM carriers, whereas female RM/NM and male RM/NM groups had the lowest rates. The overall difference among the 4 groups was statistically significant (log-rank $P=0.035$). IM indicates intermediate metabolizer; MACE, major adverse cardiovascular event; NM, normal metabolizer; PM, poor metabolizer; and RM, rapid metabolizer.

Academic Research Consortium 3 to 5 bleeding events across subgroups, potentially reflecting limited statistical power because of the low incidence of these events. These findings indicate a sex-specific difference in the prognostic relevance of CYP2C19 LOF alleles in this clinical setting.

Sex Differences in Clinical Impact According to CYP2C19 Genotype

Previous studies have reported that CYP2C19 poor metabolizer status is associated with reduced production of epoxyeicosatrienoic acids, contributing to an increased risk of diabetic retinopathy, coronary artery disease, and MI, particularly in women. These associations have been especially linked to microvascular dysfunction.^{19–21} However, this study focused on patients diagnosed with coronary artery disease who underwent PCI, providing a different clinical context. In this setting, the role of CYP2C19 genotyping as a predictor of secondary clinical events after PCI was observed only in men, suggesting a sex-specific divergence in the clinical impact of CYP2C19 LOF alleles.

The TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial evaluated a CYP2C19 genotype-guided Antiplatelet strategy in patients with undergoing PCI and was conducted primarily in a Western population, in which the prevalence of CYP2C19 LOF alleles was relatively low compared with East Asian populations: ~28.5% for IMs and 3% for PMs. However, the study included 23% East Asian participants, among whom the prevalence of LOF alleles was 59.7%, consistent with the rate observed in the present study. In a post hoc sex-based analysis of the TAILOR-PCI study, no significant sex differences were observed in the prevalence of CYP2C19 LOF alleles. When analyzing the interaction between sex and receipt of CYP2C19 genotype guided optimal P2Y12 inhibitor therapy based on genotype, women who received optimal therapy had a significantly higher risk of major adverse cardiovascular events compared with men (women: 6.8% versus men: 4.0%; adjusted HR, 1.48 [95% CI, 1.08–2.03]).⁹ In contrast, among patients who did not receive optimal therapy, no sex-based difference in major adverse cardiovascular event incidence was observed (women: 5.7% versus men: 5.7%; adjusted HR, 1.41 [95% CI,

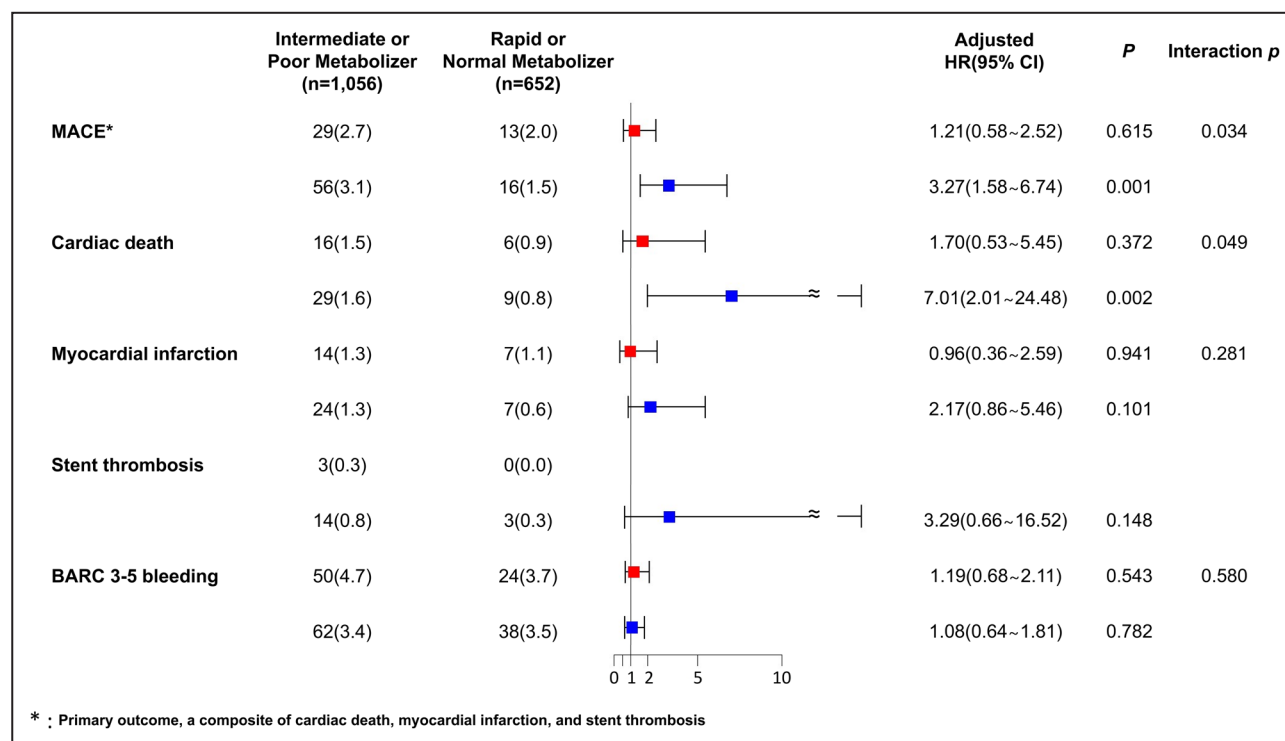


Figure 3. Association between sex, CYP2C19 genotyping, and outcomes.

This figure shows adjusted hazard ratios for 5-year outcomes by sex and CYP2C19 metabolizer status. Male IM/PM carriers had a significantly higher risk of MACEs (HR, 3.27 [95% CI, 1.58–6.74]), whereas the risk was not significant in female IM/PM carriers (HR, 1.21 [95% CI, 0.58–2.52]). No significant differences were observed in individual outcomes, such as cardiac death, MI, or stent thrombosis. BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio; IM, intermediate metabolizer; MACE, major adverse cardiovascular event; MI, myocardial infarction; and PM, poor metabolizer.

0.90–2.21)). These findings align with the results of our study, where the prognostic value of *CYP2C19* genotype was more evident in men than women. And this highlighted the need to consider sex-specific factors when applying personalized antiplatelet strategies. Notably, this study represents a follow-up analysis of a large-scale cohort within an East Asian population, and it clearly demonstrates that the prognostic significance of *CYP2C19* genotyping, previously shown to be more pronounced in patients with ACS, also extends to sex-based differences in clinical outcomes.²²

In predicting clinical outcomes after PCI, HPR appeared to be a differential impact risk between sexes. In a previous study, HPR was identified as an independent predictor of 1-year major adverse cardiac and cerebrovascular events and all-cause mortality in men, but not in women.²³ This underscores the challenge of identifying a single independent prognostic factor in female patients. Similarly, in the present study, the *CYP2C19* genotype emerged as a significant predictor of clinical outcomes in men, but not in women, reinforcing the potential for sex-specific differences in risk stratification following PCI. Additionally, although a previous study reported that combined evaluation of platelet function test results and *CYP2C19* genotyping

improved the prediction of cardiovascular events during clopidogrel treatment, our additional analysis showed that although HPR and *CYP2C19* variation were independent predictors of cardiovascular events in men, they were not in women.²⁴ These findings suggest that a combined assessment of platelet function and *CYP2C19* genotype may help refine individualized dual-antiplatelet therapy strategies, particularly in male patients at higher ischemic risk.

This discrepancy may be partly explained by the fact that female patients were generally older and had a higher prevalence of cardiovascular risk factors, such as diabetes, hypertension, and chronic kidney disease, compared with men. However, even after adjusting for these variables, it remained challenging to identify an independent prognostic marker in women. This suggests that the complex interplay of sex hormone fluctuations, inflammatory responses, and other biological factors unique to women may contribute to the observed differences in outcome predictability.

Study Limitations

As this analysis was based on data from a multicenter consortium, the potential influence of unmeasured

confounding factors cannot be excluded. Additionally, the post hoc nature of the analysis limits the ability to draw causal inferences and should be considered hypothesis generating. Furthermore, the absolute number of clinical events was relatively small, particularly after stratification by sex. Given the limited number of events relative to the number of covariates included in the multivariable models, there is a potential risk of overfitting and residual confounding, which may have influenced the observed associations. As a result, the observed differences between female and male patients may partly reflect differences in statistical power rather than true biological heterogeneity. Finally, similar to other cardiovascular clinical trials, the representation of female participants was relatively low, comprising ~37% of the study population, which may limit the generalizability of sex-specific findings.

CONCLUSIONS

In this sex-based analysis of patients with ACS from the PTRG-DES consortium, the prevalence of *CYP2C19* LOF alleles, including PM and IM phenotypes, did not differ significantly between women and men. However, among patients who underwent PCI with drug-eluting stents, *CYP2C19* LOF status was associated with high risks of 5-year MACEs and cardiac death in male patients, but not in female patients. Notably, the interaction between sex and *CYP2C19* LOF status was statistically significant, suggesting a sex-specific difference in the prognostic value of *CYP2C19* genotyping in this clinical context. These findings should be interpreted with caution given the limited number of events and warrant confirmation in independent cohorts.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea (S.-J.K.); Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Korea (A.-Y.H.); Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea (H.-J.J., D.-S.L.); Division of Cardiology, Department of Internal Medicine, College of Medicine, Catholic University of Korea, Seoul, Korea (K.C.); Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea (B.-K.K.); Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (Y.B.S.); Department of Cardiology, Yonsei University Wonju Severance Christian Hospital, Wonju, Korea (S.G.A.); Department of Internal Medicine, Seoul National University College of Medicine and Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea (J.-W.S.); Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea (S.-Y.L., Y.-H.J.); Cardiology Division, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea (J.R.C.); Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea (H.-S.K.); Department

of Cardiology, Dong-A University Hospital, Busan, Korea (M.H.K.); and Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea (E.-S.S.).

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Disclosures

None.

Supplemental Material

Table S1–S4

Figures S1–S4

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