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ORIGINAL RESEARCH

Prognostic Impact of *CYP2C19* Genotypes on Long-Term Clinical Outcomes in Older Patients After Percutaneous Coronary Intervention

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BACKGROUND: Carriers of *CYP2C19* loss-of-function alleles have increased adverse events after percutaneous coronary intervention, but limited data are available for older patients. We aimed to evaluate the prognostic impact of *CYP2C19* genotypes on clinical outcomes in older patients after percutaneous coronary intervention.

METHODS AND RESULTS: The study included 1201 older patients (aged ≥75 years) who underwent percutaneous coronary intervention and received clopidogrel-based dual antiplatelet therapy in South Korea. Patients were grouped on the basis of *CYP2C19* genotypes. The primary outcome was 3-year major adverse cardiac events, defined as a composite of cardiac death, myocardial infarction, and stent thrombosis. Older patients were grouped into 3 groups: normal metabolizer (36.6%), intermediate metabolizer (48.1%), and poor metabolizer (15.2%). The occurrence of the primary outcome was significantly different among the groups (3.1, 7.0, and 6.2% in the normal metabolizer, intermediate metabolizer, and poor metabolizer groups, respectively; *P*=0.02). The incidence rate of all-cause death at 3 years was greater in the intermediate metabolizer and poor metabolizer groups (8.1% and 9.2%, respectively) compared with that in the normal metabolizer group (3.5%, *P*=0.03) without significant differences in major bleeding. In the multivariable analysis, the intermediate metabolizer and poor metabolizer groups were independent predictors of 3-year clinical outcomes.

CONCLUSIONS: In older patients, the presence of any *CYP2C19* loss-of-function allele was found to be predictive of a higher incidence of major adverse cardiac events within 3 years following percutaneous coronary intervention. This finding suggests a need for further investigation into an optimal antiplatelet strategy for older patients.

REGISTRATION: URL: https://clinicaltrials.gov. Identifier: NCT04734028.

Key Words: aged ■ cytochrome P-450 2C19 ■ genetics ■ genotype ■ percutaneous coronary intervention ■ polymorphism

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CLINICAL PERSPECTIVE

What Is New?

- In older patients (aged ≥75 years) taking clopidogrel-based dual antiplatelet therapy, the presence of any *CYP2C19* loss-of-function allele is predictive of a higher incidence of major adverse cardiac events within a 3-year period of percutaneous coronary intervention, independent of platelet reactivity levels.

What Are the Clinical Implications?

- Testing for *CYP2C19* polymorphism in older patients may be useful for identifying those at an elevated risk of ischemic events and those who would benefit the most from tailored therapy based on their genotype.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
DES	drug-eluting stent
IM	intermediate metabolizer
LOF	loss-of-function
MACE	major adverse cardiac event
NM	normal metabolizer
PHARMCLO	Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes
PM	poor metabolizer
POPular Genetics	Genotype Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients
PTRG-DES	Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent–Treated Patients
PRU	$P2Y_{12}$ reaction unit
TAILOR-PCI	Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention

Clopidogrel is a prodrug that requires bioactivation into its active metabolite by the liver enzyme CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19). The polymorphism-driven metabolic activity of CYP2C19 significantly influences the pharmacokinetics of clopidogrel by altering its metabolic conversion, which in turn indirectly affects its pharmacodynamic properties.[1,2] The substantial variability in response to clopidogrel limits its effectiveness in patients undergoing percutaneous coronary intervention (PCI) for significant coronary artery disease.[3] When treated with clopidogrel, carriers of any *CYP2C19* loss-of-function (LOF) allele (*2 or *3) showed a reduction in the biotransformation of clopidogrel, decreased platelet inhibition, and an increased number of adverse ischemic events.[3,4] Based on evidence from therapeutic comparison trials, current guidelines recommend prasugrel or ticagrelor for patients with acute coronary syndrome,[5] which are more potent but have also been shown to increase the risk of bleeding. It is important to note that genomic data are not incorporated into these guidelines. There is a paucity of data to support the use of more potent $P2Y_{12}$ inhibitors in patients undergoing PCI for chronic coronary syndrome,[6] and clopidogrel remains the most widely prescribed platelet inhibitor due to its lower cost, availability, and safety profiles in daily clinical practice.[7–10]

Older patients receiving dual antiplatelet therapy (DAPT) are more susceptible to bleeding complications after PCI,[11–13] and clopidogrel is preferred in older patients with acute coronary syndrome because of a lower bleeding profile than that with prasugrel or ticagrelor.[14] Nevertheless, the major cardiovascular community has not yet adopted routine *CYP2C19* testing,[15] and the current guidelines provide insufficient evidence-based recommendations for the optimal DAPT strategy in older patients.[5] This population has also been underrepresented in clinical trials evaluating genotype-guided DAPT strategies,[16–18] and little is known about the clinical implications of *CYP2C19* polymorphism in older patients (aged ≥75 years) taking clopidogrel-based DAPT. Therefore, in this multicenter, observational study, we aimed to investigate the long-term outcomes according to *CYP2C19* genotypes in older adults.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Source of Data and Study Population

The PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent–Treated

Patients) consortium is a multicenter, nationwide, real-world registry of patients who underwent PCI with drug-eluting stent (DES) implantation and received DAPT with aspirin and clopidogrel (NCT04734028). This registry did not include individuals with acute coronary syndrome who were treated with ticagrelor or prasugrel. Detailed information about the study protocol has been previously published.[19–21] Briefly, 13 160 consecutive patients from 32 academic centers in South Korea were enrolled between July 2003 and August 2018. The exclusion criteria were as follows: (1) major complications during the index PCI or before platelet function testing, or if coronary bypass surgery was planned; (2) PCI strategy without DES implantation; and (3) requirement of an oral anticoagulant or a more potent $P2Y_{12}$ inhibitor.

Of the 13 160 patients, a total of 1201 older patients (aged ≥75 years) were selected for the main analysis after excluding patients without $P2Y_{12}$ reaction unit (PRU) values and those without *CYP2C19* genotype results (Figure S1). Patients who were rapid metabolizers (*1/*17, *2/*17, and *3/*17) of CYP2C19 were also excluded because of their confounding effects.[22] There were no individuals with the *17/*17 genotype in the PTRG-DES registry. Study patients were classified into 3 groups according to the *CYP2C19* genotype: normal metabolizer (NM; *1/*1), intermediate metabolizer (IM; *1/*2 and *1/*3), and poor metabolizer (PM; *2/*2, *2/*3, and *3/*3).

Platelet Function Test and Genotyping

Platelet reactivity expressed as PRU was measured using the VerifyNow assay (Accriva, San Diego, CA) during the periprocedural period after ensuring an adequate period of full antiplatelet effects.[23] A PRU cutoff of 252 was selected for data analysis on the basis of our previous reports from the PTRG-DES registry.[20]

For genotyping, pyrosequencing of each single nucleotide polymorphism was performed using commercialized analyzers: PSQ 96MA Pyrosequencer (Pyrosequencing AB, Uppsala, Sweden), ABI PRISM 3100 genetic analyzer (Applied Biosystems, Foster City, CA), or Spartan RX system (Spartan Bioscience, Ottawa, Canada), as previously reported.[24–26] Major Korean alleles included *CYP2C19**2 (rs4244285), *CYP2C19**3 (rs4986893), and *CYP2C19**17 (rs12248560). The physicians and patients were blinded to the residual platelet reactivity and genotype results.

Procedures and Managements

PCI with DES implantation was performed in accordance with the guidelines of the Korean Society of Interventional Cardiology. Parenteral anticoagulation was performed during PCI to maintain an activated clotting time of 250 to 300 seconds. If the patients were naïve to aspirin or clopidogrel at enrollment, loading doses of aspirin (300 mg at least 2 hours before PCI) and clopidogrel (300 mg at least 12 hours before PCI; 600 mg at least 6 hours before PCI) were administered. Patients receiving abciximab were excluded because a long washout period was needed for the PRU assay. DAPT with maintenance doses of aspirin and clopidogrel was recommended for at least 12 months after the index PCI. However, the duration of DAPT was left to the discretion of caring physicians. *CYP2C19* genotyping was systematically performed for research purposes only, and the genotype results were not used to select an antiplatelet regimen.[21]

Study Variables and Outcomes

The primary outcome was the occurrence of major adverse cardiac events (MACEs), defined as the composite of cardiac death, myocardial infarction (MI), and stent thrombosis at 3 years after the index PCI. The key secondary outcomes were all-cause death and major bleeding events (Bleeding Academic Research Consortium grade 3–5). Other secondary outcomes included single components constituting the composite of MACEs, cerebrovascular accidents, and any revascularization. MI was defined as an increase in creatine kinase–myoglobin binding above the upper normal limit or troponin T/I levels >99th percentile of the upper normal limit, with concomitant ischemic symptoms, electrocardiographic changes, or abnormal imaging findings suggestive of ischemia. Periprocedural MI was not included in the definition of MI. Stent thrombosis was defined as a definite stent thrombosis according to the Academic Research Consortium criteria. Cardiac death was attributed to deaths due to MI, cardiac perforation, pericardial tamponade, arrhythmia or conduction abnormality, stroke within 30 days of the index PCI, and procedural complications or any case of death in which a cardiac cause could not be excluded. Cerebrovascular accidents included any new embolic, thrombotic, or hemorrhagic stroke with neurologic deficits that persisted for at least 24 hours. Any revascularization included PCI or coronary bypass surgery on either the target- or nontarget vessels.

Demographic, angiographic, and procedural data were collected through patient interviews or by reviewing medical records. Anemia was defined as a hemoglobin level <13 g/dL in men and <12 g/dL in women. Chronic kidney disease was diagnosed as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Follow-up visits were performed through office visits or telephone contact, if necessary. All clinical events from each participating center were reviewed and adjudicated by an independent committee that was blinded to the genetics and PRU results. The institutional review board of each participating center approved the

PTRG-DES registry (Korea University Anam Hospital; 2018AN0283) and waived the requirement of written informed consent for access to an institutional registry.

Statistical Analysis

Continuous variables were reported as means±SD and categorical variables as numbers (percentages). For continuous variables, group comparisons were made using parametric analysis (1-way ANOVA), while categorical variables were compared using the χ^2 test or Fisher's exact test. Cumulative incidence rates were calculated based on Kaplan–Meier estimates, and intergroup comparisons were assessed using the log-rank test. The entire follow-up duration was used to analyze time-to-event outcomes, and the patients were censored at the time of death or the last available follow-up. Only the first event was included for patients with multiple events reported for the same outcome. A multivariable Cox proportional hazard regression model was used to analyze the influence of different covariates on the time-to-event outcomes by calculating hazard ratios (HRs) and 95% CIs. By integrating major clinical or procedural risk factors identified from previous studies,[20,21] variables with clinical relevance were included in the multivariable model to determine independent predictors of MACEs. The model included male sex, body mass index, diabetes, hypertension, peripheral artery disease, chronic kidney disease, smoking, prior PCI, presentation of acute MI at the index PCI, anemia, PRU ≥252, left ventricular ejection fraction (per 1% increase), statin, proton pump inhibitors, discontinuation of DAPT within 1 year, and *CYP2C19* polymorphisms. The relationships between age and the adjusted risk of MACEs were explored using restricted cubic splines. Statistical analyses were performed using the R statistical software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with a value of $P<0.05$ considered statistically significant.

RESULTS

Among the 6597 patients with both PRU and genotype results, 1201 patients (18.2%) were aged ≥75 years (Figure S1). The median age of older patients (aged ≥75 years) was 78 years (mean, 79.1±3.6), 49.4% were men, and 28.7% presented with acute MI. The median PRU was 242 (mean, 240±78) in older patients.

Baseline and Procedural Characteristics of Older Patients

Older patients included 440 (36.6%) individuals with NM, 578 (48.1%) with IM, and 183 (15.2%) with PM. There were no significant differences in baseline characteristics between the genotype groups (Table 1). Except for the PRU values and glycosylated hemoglobin levels, laboratory findings were also similar between the groups according to the *CYP2C19* genotype. On-treatment PRU was significantly different across the groups (NM, 214.6±79.8 versus IM, 249.3±70.2 versus PM, 268.1±79.3; $P<0.001$), and the distribution of PRU in older patients is presented in Figure 1A. Scatterplots of the relationship between age and PRU values in the overall patients (n=6597) are shown in Figure 1B. Age showed a weak but significant correlation with PRU values ($r=0.214$, $P<0.001$).

Regarding procedural data, PCI of the left anterior descending artery was more frequent in the IM and PM groups in older patients (Table 2). First-generation DESs were used in 4.6% (306/6597) of the overall cohort and in 4.0% (48/1201) of the older patients. Within 1 year of the index PCI, 24.5% of older patients discontinued DAPT and deescalated to either aspirin monotherapy or clopidogrel monotherapy. In older patients, the rate of 1-year DAPT discontinuation was higher in IMs at 27.2% and PMs at 28.4%, compared with NMs (19.5%). However, throughout the entire follow-up period, the proportion of patients maintaining DAPT did not differ significantly among the genotype subgroups in older patients.

CYP2C19 Polymorphism and Clinical Outcomes in Older Patients

The cumulative incidence rates of the primary and secondary outcomes according to the genotype subgroups are presented in Table 3. Three years after the index PCI, composite MACEs occurred in 3.1%, 7.0%, and 6.2% of older patients in the NM, IM, and PM groups, respectively (Figure 2). All-cause death was also significantly higher in the PM and IM groups of older patients. Despite the higher PRU values, the PM and IM groups showed similar incidences of major bleeding events when compared with that in the NM group.

After multivariable adjustment, older patients in the PM group showed an increased risk of 3-year MACEs (adjusted HR, 3.66 [95% CI, 1.38–9.70]; $P=0.009$), and the IM group also showed an increased risk of 3-year MACEs (adjusted HR, 2.71 [95% CI, 1.16–6.34]; $P=0.022$) compared with the NM group. The multivariable-adjusted independent predictors of 3-year MACEs in older patients were diabetes, chronic kidney disease, left ventricular ejection fraction, discontinuation of DAPT within 1 year of the index PCI, and IM/PM genotypes (Table 4). Anemia and statin use showed a borderline association with 3-year MACEs, whereas PRU ≥252 did not reach statistical significance after adjustment (adjusted HR, 0.95 [95% CI, 0.51–1.77]; $P=0.88$). The PRU value in older patients

Table 1. Baseline Characteristics in Overall and Older Patients

	Overall patients (n=6597)				Older patients (n=1201)			
	NM (n=2460)	IM (n=3180)	PM (n=957)	*P* value	NM (n=440)	IM (n=578)	PM (n=183)	*P* value
Index presentation								
Acute MI, n (%)	632 (25.7)	783 (24.6)	241 (25.2)	0.655	134 (30.5)	163 (28.2)	48 (26.2)	0.528
Age, y	64.2±10.9	64.5±10.6	64.4±10.9	0.579	79.3±3.8	78.9±3.6	79.0±3.4	0.213
≥75, n (%)	440 (17.9)	578 (18.2)	183 (19.1)	0.701				
Male sex, n (%)	1606 (65.3)	2106 (66.2)	625 (65.3)	0.726	215 (48.9)	300 (51.9)	93 (50.8)	0.629
Body mass index, kg/m^2	24.5±3.1	24.6±3.1	24.6±3.2	0.929	23.7±3.4	23.5±3.2	23.4±3.1	0.530
Risk factors, n (%)								
Hypertension	1491 (60.6)	1926 (60.6)	550 (57.5)	0.191	317 (72.0)	416 (72.0)	123 (67.2)	0.419
Dyslipidemia	1594 (64.8)	2123 (66.8)	620 (64.8)	0.243	255 (58.0)	367 (63.5)	112 (61.2)	0.199
Smoking	597 (24.3)	784 (24.7)	242 (25.3)	0.821	52 (11.8)	63 (10.9)	29 (15.8)	0.198
Diabetes	795 (32.3)	1095 (34.4)	319 (33.3)	0.246	145 (33.0)	195 (33.7)	67 (36.6)	0.676
Chronic kidney disease	522 (21.2)	693 (21.8)	214 (22.4)	0.744	170 (38.6)	203 (35.1)	70 (38.3)	0.473
Anemia	634 (25.8)	803 (25.3)	262 (27.4)	0.419	213 (48.4)	270 (46.7)	89 (48.6)	0.829
Previous history, n (%)								
History of PAD	331 (13.5)	479 (15.1)	131 (13.7)	0.198	82 (18.6)	124 (21.5)	36 (19.7)	0.532
History of CHF	209 (8.5)	253 (8.0)	76 (7.9)	0.738	50 (11.4)	60 (10.4)	19 (10.4)	0.869
Previous MI	196 (8.0)	259 (8.1)	83 (8.7)	0.795	32 (7.3)	50 (8.7)	14 (7.7)	0.712
Previous PCI	397 (16.1)	491 (15.4)	157 (16.4)	0.679	79 (18.0)	92 (15.9)	37 (20.2)	0.369
Previous CABG	37 (1.5)	41 (1.3)	5 (0.5)	0.067	5 (1.1)	9 (1.6)	2 (1.1)	0.806
Previous stroke	174 (7.1)	244 (7.7)	67 (7.0)	0.627	54 (12.3)	65 (11.2)	24 (13.1)	0.759
Lab measurements								
VerifyNow PRU	194.7±79.2	225.0±73.3	252.2±74.9	<0.001	214.6±79.8	249.3±70.2	268.1±79.3	<0.001
PRU≥252	547 (22.2)	1151 (36.2)	513 (53.6)	<0.001	139 (31.6)	289 (50.0)	115 (62.8)	<0.001
LV ejection fraction, %	58.4±11.0	59.0±10.9	58.8±11.0	0.202	57.1±11.8	58.1±12.0	58.3±13.0	0.388
WBC, ×10^3/mm^3	7.8±2.9	7.9±2.9	7.7±2.7	0.347	7.5±2.8	7.7±2.7	7.7±3.1	0.709
Hemoglobin, g/dL	13.5±1.9	13.6±1.8	13.5±1.9	0.602	12.4±1.8	12.6±1.7	12.4±1.8	0.306
Platelet, ×10^3/mm^3	235.3±78.5	237.7±75.9	234.3±75.2	0.346	223.8±79.4	229.9±69.2	229.9±69.8	0.384
GFR, mL/min/1.73 m^2	78.7±26.4	78.2±26.3	77.3±27.8	0.360	68.8±26.0	70.1±25.9	69.7±25.9	0.708
HbA_{1c}, %	6.5±1.3	6.4±1.3	6.6±1.3	0.308	6.3±1.0	6.2±0.9	6.7±1.4	0.005
Total cholesterol, mg/dL	174.2±45.5	173.9±44.1	173.8±45.5	0.961	169.6±40.2	168.8±43.8	163.8±42.9	0.293
LDL cholesterol, mg/dL	105.5±44.7	104.8±38.2	106.1±38.0	0.650	103.2±34.8	102.1±37.2	99.6±36.8	0.552
HDL cholesterol, mg/dL	43.1±11.8	42.8±11.6	43.2±11.4	0.638	43.3±11.5	42.9±13.2	44.1±11.6	0.541
Triglyceride, mg/dL	144.5±113.4	143.7±93.7	137.6±101.5	0.218	116.6±68.1	120.7±72.1	114.1±68.5	0.472

Values are presented as numbers (percentages) or means±SD. CABG indicates coronary artery bypass graft; CHF, congestive heart failure; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IM, intermediate metabolizer; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; NM, normal metabolizer; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, poor metabolizer; PRU, $P2Y_{12}$ reaction unit; and WBC, white blood cell.

did not show a statistically significant relationship with the unadjusted risk of 3-year MACEs in the spline curve (Figure S2).

Aging and Clinical Outcomes in Overall Patients

Overall, the median age of the overall patients (n=6597) was 65 years (mean, 64.4±10.8), and 5396 patients were aged <75 years. The cumulative incidence of 3-year MACEs was significantly higher in older patients (Table S1). After adjustment with the Cox regression model, age ≥75 years was an independent factor predictive of 3-year MACE in overall patients (adjusted HR, 1.52 [95% CI, 1.04–2.24]; *P*=0.03; Table S2). Age as a continuous variable showed a significant linear relationship with the unadjusted and adjusted risks of 3-year MACEs in the overall patients (Figure 3).

DISCUSSION

We evaluated the clinical impact of *CYP2C19* genotypes on the occurrence of MACEs in older patients

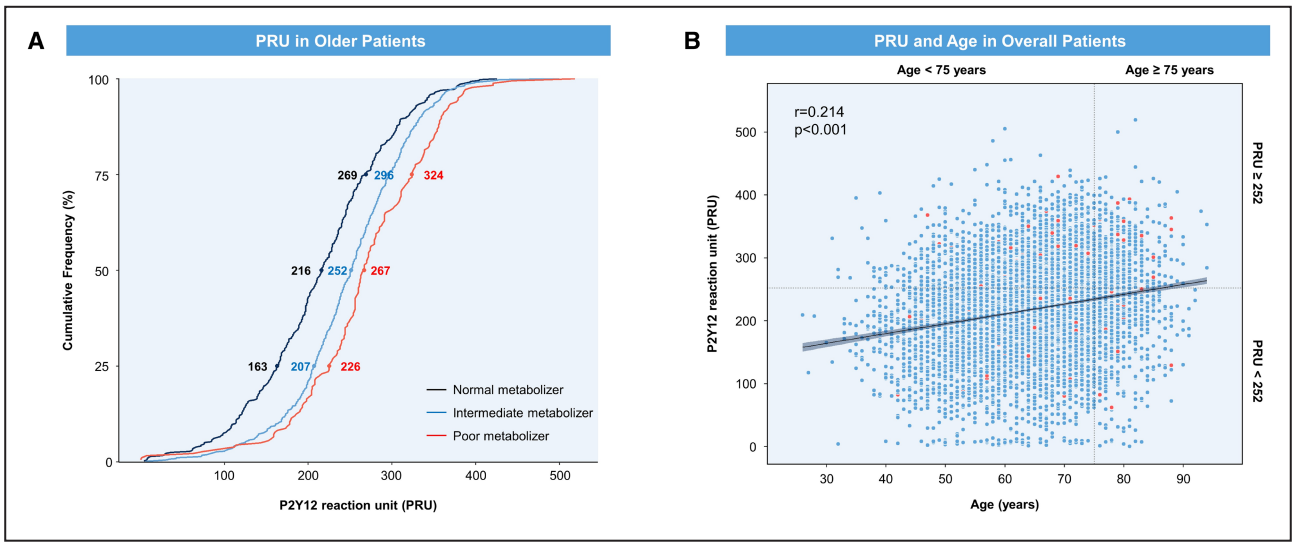

Figure 1. Distribution of $P2Y_{12}$ reaction units.
(**A**) Distribution of $P2Y_{12}$ reaction unit in patients aged ≥75 y. (**B**) Relationship between $P2Y_{12}$ reaction unit and age in overall patients. PRU indicates $P2Y_{12}$ reaction unit.

(aged ≥75 years) who underwent PCI with successful DES implantation and received DAPT with aspirin and clopidogrel. The main findings of our study include the following: (1) both IM and PM genotypes were linked to an increased risk of 3-year MACEs in older patients; (2) after adjusting for clinical variables and PRU, both IM and PM genotypes were independent predictors of 3-year MACEs in older patients; and (3) the occurrence of major bleeding events was similar among the different *CYP2C19* genotypes.

We have previously reported a genetic study of 811 older patients (aged ≥75 years).[27] The primary end point was a composite of MI and death at 1 year. Regarding the *CYP2C19* allele, the PM group had a significantly higher risk for the primary end point (HR, 2.43 [95% CI, 1.12–5.24]; *P*=0.024) than the IM/NM group. In contrast, the present study demonstrated that in 1201 older patients, the IM group had an increased risk of adverse ischemic events, along with a similar risk of bleeding events when compared with the NM group. Both the IM and PM groups were significant predictors in the adjusted multivariable model, whereas PRU was not an independent predictor of 3-year MACEs in older patients.

Older patients are more vulnerable to ischemic events and bleeding complications,[11] possibly due to age-related changes in platelet count and function.[28] Aging is also linked to a decrease in liver size and mass, as well as hepatic blood flow,[29] resulting in variable pharmacokinetic and pharmacodynamic responses to drugs such as clopidogrel.[30] While platelet count decreases with age in multiple ethnic groups,[31,32] changes in platelet responsiveness are less well understood and have little evidence in older population. One analysis of 54 patients with stable angina (aged 45–92 years) showed that age was negatively correlated with platelet aggregation, which explains the increased occurrence of bleeding complications in older patients.[33] Compared with younger patients, older patients also have an increased risk of ischemic events due to an impaired response to clopidogrel.[34] In addition, although the activities of various cytochrome P450 enzymes do not generally decline with old age,[35,36] a few studies with omeprazole have shown that aging has a significant effect on the activities of the *CYP2C19* allele.[37,38] There is, however, a gap in knowledge regarding the effectiveness of clopidogrel when administered to older individuals (aged ≥75 years) with various *CYP2C19* polymorphisms. Our study demonstrated that age was significantly correlated with on-treatment PRU during clopidogrel-based DAPT. We also found significant differences in on-treatment PRU levels between the *CYP2C19* genotype subgroups in older patients (aged ≥75 years).

It is well established that having even 1 LOF *CYP2C19* allele significantly increases the risk of adverse ischemic events in patients treated with clopidogrel after PCI.[3,4] However, prospective clinical trials evaluating *CYP2C19* genotype-guided strategies for the use of $P2Y_{12}$ inhibitors have been inconclusive,[16–18] and older patients have been underrepresented in these trials. The PHARMCLO (Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes) trial included 28.4% (252/888) of older patients (>80 years) and found that ischemic end points occurred more frequently in the standard-of-care arm compared with the pharmacogenomic arm (*P*<0.001).[17] The *CYP2C19* POPular Genetics (Genotype Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients) trial included 14.6% (363/2488) older patients

Table 2. Procedural Characteristics in Overall and Older Patients

	Overall patients (n=6597)				Older patients (n=1201)			
	NM (n=2460)	IM (n=3180)	PM (n=957)	*P* value	NM (n=440)	IM (n=578)	PM (n=183)	*P* value
Angiographic feature, n (%)								
ACC/AHA lesion								
A/B1 type	1419 (57.7)	1837 (57.8)	548 (57.3)	0.962	252 (57.3)	327 (56.6)	97 (53.0)	0.608
B2/C type	1041 (42.3)	1343 (42.2)	409 (42.7)		188 (42.7)	251 (43.4)	86 (47.0)	
Number of diseased vessels								
1	1574 (64.0)	2030 (63.8)	614 (64.2)	0.638	287 (65.2)	358 (61.9)	106 (57.9)	0.365
2	607 (24.7)	820 (25.8)	233 (24.3)		103 (23.4)	156 (27.0)	50 (27.3)	
3	279 (11.3)	330 (10.4)	110 (11.5)		50 (11.4)	64 (11.1)	27 (14.8)	
Multivessel disease	881 (35.8)	1146 (36.0)	342 (35.7)	0.978	152 (34.5)	220 (38.1)	77 (42.1)	0.187
Bifurcation lesion	175 (7.1)	229 (7.2)	63 (6.6)	0.805	30 (6.8)	47 (8.1)	17 (9.3)	0.539
Chronic total occlusion lesion	189 (7.7)	219 (6.9)	67 (7.0)	0.501	26 (5.9)	32 (5.5)	10 (5.5)	0.960
Procedural data, n (%)								
Multivessel PCI	886 (36.0)	1150 (36.2)	343 (35.8)	0.982	153 (34.8)	220 (38.1)	77 (42.1)	0.211
Treated lesions								
Left main coronary artery	124 (5.0)	139 (4.4)	46 (4.8)	0.489	26 (5.9)	28 (4.8)	10 (5.5)	0.752
Left anterior descending artery	1438 (58.5)	1917 (60.3)	569 (59.5)	0.382	233 (53.0)	347 (60.0)	117 (63.9)	0.016
Left circumflex artery	706 (28.7)	917 (28.8)	294 (30.7)	0.469	129 (29.3)	150 (26.0)	52 (28.4)	0.473
Right coronary artery	950 (38.6)	1205 (37.9)	352 (36.8)	0.601	182 (41.4)	235 (40.7)	69 (37.7)	0.692
PCI for LM or LAD	1515 (61.6)	1989 (62.5)	593 (62.0)	0.758	250 (56.8)	363 (62.8)	123 (67.2)	0.031
Number of stents, n	1.6±0.8	1.6±0.8	1.6±0.8	0.792	1.6±0.8	1.6±0.7	1.7±0.8	0.192
Stent length, mm	35.5±22.1	35.7±21.9	35.4±21.6	0.942	35.7±22.4	35.3±22.2	36.3±21.2	0.859
Stent diameter, mm	3.0±0.4	3.0±0.5	3.0±0.5	0.905	2.9±0.4	2.9±0.4	2.9±0.4	0.536
DES type								
First-generation	122 (5.0)	146 (4.6)	38 (4.0)	0.460	20 (4.5)	23 (4.0)	5 (2.7)	0.575
Newer-generation	2338 (95.0)	3034 (95.4)	919 (96.0)		420 (95.5)	555 (96.0)	178 (97.3)	
Concomitant medications, n (%)								
Aspirin	2432 (98.9)	3140 (98.7)	945 (98.7)	0.913	434 (98.6)	572 (99.0)	179 (97.8)	0.497
Cilostazol	185 (7.5)	279 (8.8)	82 (8.6)	0.224	40 (9.1)	46 (8.0)	20 (10.9)	0.453
β Blocker	1530 (62.2)	1966 (61.8)	600 (62.7)	0.880	256 (58.2)	352 (60.9)	115 (62.8)	0.497
Angiotensin blockade	1429 (58.1)	1851 (58.2)	537 (56.1)	0.494	275 (62.5)	341 (59.0)	112 (61.2)	0.518
Calcium channel blocker	766 (31.1)	948 (29.8)	280 (29.3)	0.437	136 (30.9)	169 (29.2)	61 (33.3)	0.559
Statin	2163 (87.9)	2781 (87.5)	859 (89.8)	0.157	221 (50.2)	296 (51.2)	88 (48.1)	0.760
Proton pump inhibitor	397 (16.1)	554 (17.4)	160 (16.7)	0.440	82 (18.6)	120 (20.8)	38 (20.8)	0.674
Antiplatelet regimen within 1 year								
Dual antiplatelet therapy	1836 (74.6)	2388 (75.1)	685 (71.6)	0.087	354 (80.5)	421 (72.8)	131 (71.6)	0.008
Discontinuation of DAPT	624 (25.4)	792 (24.9)	272 (28.4)		86 (19.5)	157 (27.2)	52 (28.4)	
Aspirin monotherapy	450 (18.3)	564 (17.7)	189 (19.7)		47 (10.7)	92 (15.9)	30 (16.4)	
Clopidogrel monotherapy	174 (7.1)	228 (7.2)	81 (8.5)		39 (8.9)	65 (11.2)	22 (12.0)	
Others	0 (0.0)	0 (0.0)	2 (0.2)		0 (0.0)	0 (0.0)	0 (0.0)	
Antiplatelet regimen beyond 1 year								
Dual antiplatelet therapy	1171 (47.6)	1587 (49.9)	458 (47.9)	0.192	219 (49.8)	282 (48.8)	95 (51.9)	0.760
Aspirin monotherapy	802 (32.6)	998 (31.4)	305 (31.9)		115 (26.1)	163 (28.2)	46 (25.1)	
Clopidogrel monotherapy	484 (19.7)	595 (18.7)	192 (20.1)		106 (24.1)	133 (23.0)	42 (23.0)	
Others	3 (0.1)	0 (0.0)	2 (0.2)		0 (0.0)	0 (0.0)	0 (0.0)	

Values are presented as numbers (percentages) or means±SD. ACC/AHA indicates American College of Cardiology/ American Heart Association; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; IM, intermediate metabolizer; LAD, left anterior descending artery; LM, left main; NM, normal metabolizer; PCI percutaneous coronary intervention; and PM, poor metabolizer.

Table 3. Incidence of the Primary and Secondary Outcomes at 3 Years After the Index PCI

	Overall patients				Older patients			
	NM (n=2460)	IM (n=3180)	PM (n=957)	Log-rank P	NM (n=440)	IM (n=578)	PM (n=183)	Log-rank *P* value
Primary and key secondary outcomes								
MACE	38 (2.2)	78 (3.5)	25 (3.0)	0.038	9 (3.1)	29 (7.0)	11 (6.2)	0.018
All-cause death	44 (2.9)	59 (3.0)	24 (3.3)	0.380	12 (3.5)	32 (8.1)	13 (9.2)	0.026
Major bleeding	76 (3.7)	89 (3.7)	28 (3.6)	0.798	24 (6.1)	31 (7.3)	10 (5.7)	0.999
Other secondary outcomes								
Cardiac death	19 (1.1)	40 (2.1)	16 (2.2)	0.063	3 (1.0)	23 (5.9)	9 (7.1)	0.002
Myocardial infarction	21 (1.2)	33 (1.6)	10 (1.5)	0.768	6 (2.1)	10 (3.0)	3 (1.7)	0.861
Stent thrombosis	3 (0.1)	16 (0.5)	8 (0.8)	0.007	0 (0.0)	2 (0.3)	3 (1.7)	0.014
Cerebrovascular accident	23 (1.6)	21 (0.7)	10 (1.5)	0.364	12 (4.9)	6 (1.4)	2 (1.1)	0.116
Any revascularization	177 (10.7)	202 (9.6)	60 (10.0)	0.350	27 (7.5)	34 (8.8)	11 (9.8)	0.998

Values are presented as numbers (percentages) (the Kaplan–Meier estimate of cumulative incidence). HR indicates hazard ratio; IM, intermediate metabolizer; NM, normal metabolizer; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; and PM, poor metabolizer.

(aged ≥75 years) and showed that genotype-guided therapy was noninferior to prasugrel or ticagrelor in preventing adverse ischemic events (P<0.001 for noninferiority) and superior in preventing bleeding events (P=0.04).[16] There was no significant interaction between treatment group and prespecified age subgroup (aged ≥75 versus <75 years). While the POPular Genetics trial tested a genotype-guided deescalation strategy, the TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention) trial tested a genotype-guided uptitration strategy and included 14.3% (757/5276) older patients (aged ≥75 years). The TAILOR-PCI study did not demonstrate significant differences in a composite of ischemic end points between genotype-guided therapy and conventional clopidogrel therapy when assessed as time to first event (P=0.06).[18] However, a recent analysis of all observed events (first and subsequent ischemic events) found that the genotype-guided uptitration treatment showed a significant reduction in the cumulative incidence of ischemic events at 12 months (P=0.011).[39] Although our study cannot provide direct evidence to support the use of prasugrel or ticagrelor in older patients with any *CYP2C19* LOF allele, both IM and PM genotypes were strongly linked to an increased risk of 3-year composite ischemic events.

In older patients, clopidogrel treatment has been a reasonable alternative to ticagrelor or prasugrel in those aged ≥70 years presenting with non–ST-segment–elevation acute coronary syndrome, because it leads to fewer bleeding events without an increase in coprimary net clinical benefit outcome.[7] Subgroup analysis in the older patients (aged ≥70 years) from the combined POPular Genetics and Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular Age) trial cohort also confirmed similar rates in atherothrombotic and lower bleeding events in the clopidogrel group of LOF noncarriers when compared with the ticagrelor group.[40] Older adults could be safely deescalated to clopidogrel-based DAPT without risking inefficacy, provided that their genotype is considered. Thus, we suggest that testing for *CYP2C19* polymorphism in older patients could be useful for identifying those at an elevated risk of ischemic events (LOF carriers) and those who would most likely experience a reduction in bleeding events with tailored therapy (LOF noncarriers). This is particularly important if these older patients are being considered for a deescalation strategy with clopidogrel monotherapy, as it may inadvertently increase the risk of thrombotic events following the early discontinuation of DAPT.[41,42] In our study, the decision to discontinue DAPT was made without considering genotyping results. Thus, the observed association between LOF genotypes and higher rates of 1-year discontinuation of DAPT in older patients should be interpreted with caution, as it is purely observational. Furthermore, we considered the confounding effect of early discontinuation of DAPT and adjusted the multivariable analysis to consolidate the link between *CYP2C19* genotypes and clinical outcomes.

Previously, a high on-treatment PRU (≥252) was significantly correlated with the risk of adverse clinical outcomes in our large-scale East Asian cohort.[20] However, in the present analysis, PRU showed an insignificant association with 3-year MACEs in older patients, despite the differences in PRU levels among the *CYP2C19* genotype subgroups. PRU assessed at a single time point appears to have limitations in predicting the risk of future ischemic events and that *CYP2C19* genotypes could be more powerful predictors of clinical outcomes in older patients. PRU may be more variable in older patients due to age-related physiological changes, more frequent comorbidities, and possible drug–drug interactions from polypharmacy.

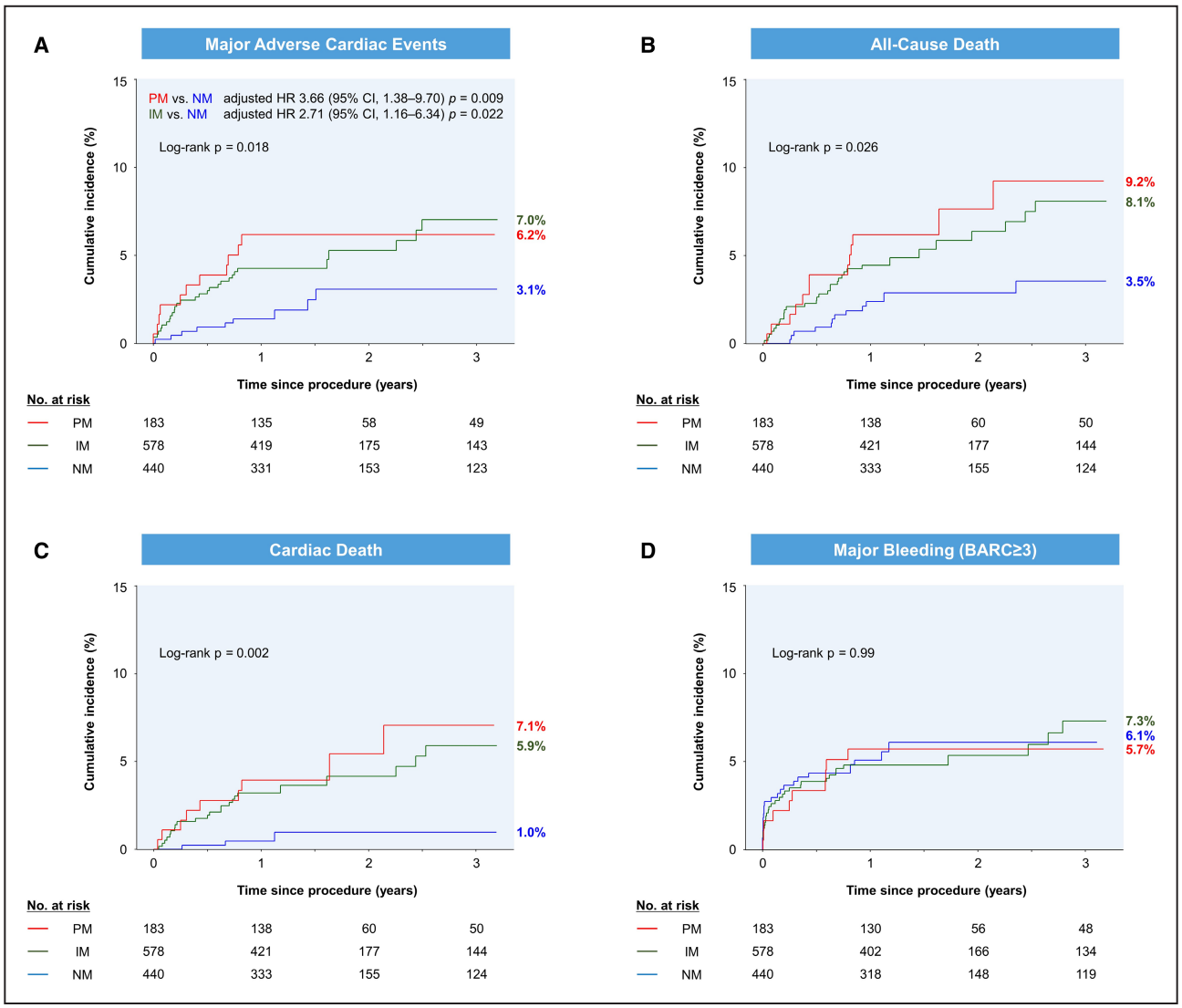

Figure 2. Cumulative incidence of primary and secondary outcomes.
Cumulative incidence of 3-year (**A**) major adverse cardiac events, (**B**) all-cause death, (**C**) cardiac death, and (**D**) major bleeding (BARC grade 3–5) events based on the *CYP2C19* genotype groups. BARC indicates Bleeding Academic Research Consortium; NM, normal metabolizer; IM, intermediate metabolizer; and PM, poor metabolizer.

Limitations

To our knowledge, the present study was able to explore and document the impact of *CYP2C19* genotypes on clopidogrel responses in the largest number of older patients to date. However, this study had some limitations: First, the study design of the observational registry had an inherent selection bias and limited long-term follow-up. The study findings are to be considered hypothetical or theory based, which therefore only contributes to the evidence or hypothesis being generated. To note, a selection bias might have arisen because genotyping was an integral part of registry enrollment, rather than a separate and randomized process. Additionally, unmeasured confounders have yet to be considered and cannot be excluded. Second, PRU was assessed shortly after PCI at a single time point, and multiple PRU results, including before the index PCI and during the follow-up, were not available. Thus, no direct evidence exists that a higher incidence of cardiac death in the IM or PM groups may be elicited by a higher on-treatment PRU. It is possible that *CYP2C19* polymorphisms may directly affect adverse clinical outcomes independent of clopidogrel metabolism and associated platelet reactivity. Third, the inclusion period of the PTRG-DES registry was long and included significant changes in clinical practice, including the evolution of drug therapy. Ticagrelor and prasugrel were introduced to the Korean market in July 2011 and July 2010, respectively, and they only became covered by the national insurance program from

Table 4. Risk of the Primary Outcome (MACE) in Older Patients (n=1201)

Variables	Univariable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Male sex	1.34 (0.76–2.37)	0.305	1.36 (0.72–2.59)	0.341
Body mass index ≥25 kg/m^2	0.69 (0.36–1.32)	0.265	0.85 (0.42–1.73)	0.648
Diabetes	2.24 (1.28–3.93)	0.005	1.90 (1.02–3.54)	0.043
Hypertension	1.64 (0.82–3.29)	0.163	1.05 (0.50–2.19)	0.902
Peripheral artery disease	2.19 (1.22–3.95)	0.009	1.05 (0.52–2.11)	0.896
Chronic kidney disease	2.46 (1.38–4.40)	0.002	2.29 (1.15–4.58)	0.019
Current smoker	2.45 (1.28–4.70)	0.007	1.41 (0.64–3.13)	0.394
Prior percutaneous coronary intervention	1.48 (0.77–2.85)	0.235	1.42 (0.70–2.90)	0.333
Presentation as acute MI	1.68 (0.95–2.98)	0.074	1.24 (0.64–2.43)	0.525
Anemia	1.74 (0.98–3.10)	0.058	1.80 (0.94–3.48)	0.077
Platelet reactivity unit ≥252	1.51 (0.86–2.65)	0.152	0.95 (0.51–1.77)	0.883
LV ejection fraction (per 1% increase)	0.96 (0.94–0.98)	<0.001	0.97 (0.94–0.99)	0.006
Statin	2.81 (0.87–9.07)	0.084	2.98 (0.90–9.86)	0.075
Proton pump inhibitor	1.84 (1.00–3.38)	0.050	1.61 (0.83–3.15)	0.161
Discontinuation of DAPT within 1 year	3.65 (2.08–6.39)	<0.001	4.08 (2.19–7.62)	<0.001
Intermediate metabolizer (vs normal metabolizer)	2.54 (1.20–5.37)	0.015	2.71 (1.16–6.34)	0.022
Poor metabolizer (vs normal metabolizer)	3.06 (1.27–7.38)	0.013	3.66 (1.38–9.70)	0.009

DAPT indicates dual antiplatelet therapy; HR, hazard ratio; LV, left ventricular; MACE, major adverse cardiac event; and MI, myocardial infarction.

March 2013 for ticagrelor and July 2012 for prasugrel. Patients who were prescribed with the more potent $P2Y_{12}$ inhibitors, either before or after enrollment, were excluded from the registry. Finally, our analysis was restricted to the Korean population, further limiting its generalizability. In the present analysis, 63.4% of older patients had a *CYP2C19* LOF allele (IM, 48.1%; and PM, 15.2%). While the rate of any *CYP2C19* LOF allele was greater than the findings reported in multicenter observational studies of Western populations,[43,44] it remained comparable to the incidence observed in the TAILOR-PCI trial. East Asians comprised 23% of the patients in the TAILOR-PCI trial, where the rate of *CYP2C19* LOF alleles was 59.7%.[18]

CONCLUSIONS

Among older patients (aged ≥75 years) taking clopidogrel-based DAPT after PCI with successful

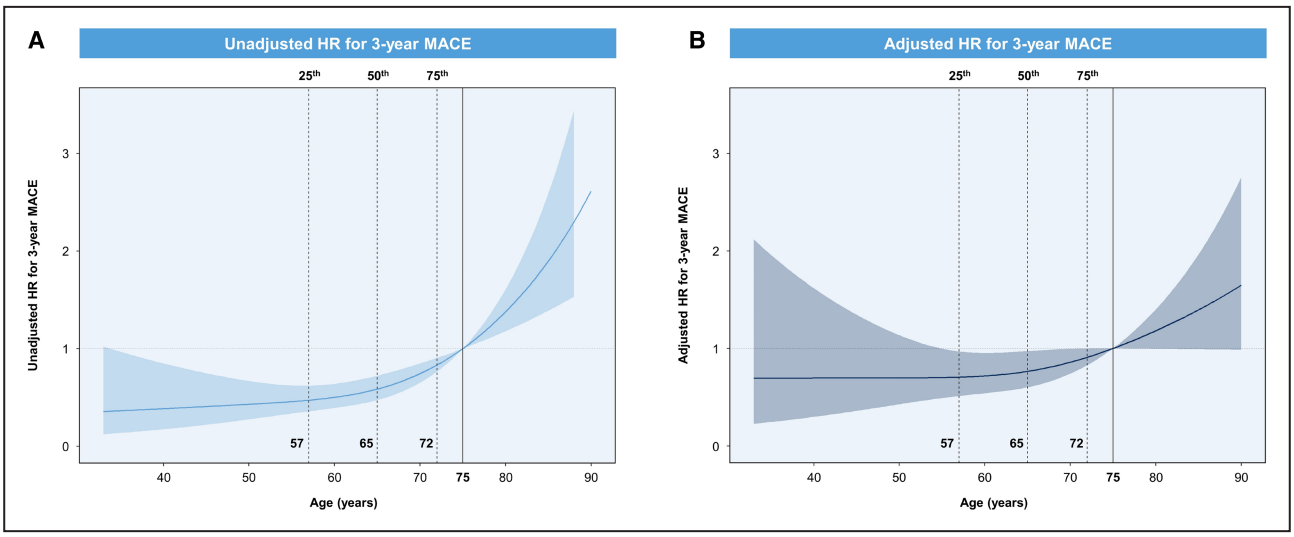

Figure 3. Spline curve for age and the primary outcome.
Spline curve for the association of age as a continuous variable with the (**A**) unadjusted and (**B**) adjusted risk of 3-year MACEs. HR indicates hazard ratio; and MACEs, major adverse cardiac events.

DES implantation, carriers of any *CYP2C19* LOF allele were linked to an increased risk of 3-year MACEs. After adjustment, *CYP2C19* genotypes were significant predictors of clinical outcomes, whereas PRU was not. To define an optimal antiplatelet therapy for older patients, additional randomized studies focusing on the impact of *CYP2C19* genotyping in conjunction with multiple platelet reactivity traits are needed.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1

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