

Effect of Calcium Channel Blockers on Antiplatelet Activity of Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention: Insights from the PTRG-DES Consortium

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Abstract

Aims: Calcium channel blockers (CCBs) are frequently co-administered with clopidogrel in cardiovascular disease. Although an inhibitory drug interaction exists between them, comprehensive large-scale studies for its validation are lacking. We investigated interactions between CCBs and clopidogrel using a large-scale national registry of patients who underwent percutaneous

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Data Availability Statement included at the end of the article



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coronary intervention (PCI). **Methods and Results:** The Platelet function and genoType-Related long-term Prognosis-Platelet Function Test consortium investigates the association between platelet function test and long-term prognosis during dual antiplatelet therapy including clopidogrel in patients using drug-eluting stents. We compared the *ex vivo* platelet reactivity using the VerifyNow P2Y₁₂ test and clinical outcomes between CCB users and non-users. Between 2003 and 2018, 11 714 patients were enrolled and categorized into two groups according to CCB usage. A composite endpoint encompassing all-cause mortality, myocardial infarction, stent thrombosis, or stroke was defined as a major adverse cardiac and cerebrovascular event (MACCE). During the 5-year follow-up period, no significant differences were observed in P2Y₁₂ reaction units (215.8 ± 84.7 vs 218.4 ± 76.7 , $P = .156$), MACCEs, major bleeding, or high platelet reactivity rates, even after adjusting for propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). When limited to the high platelet reactivity cohort (≥ 252 PRU), the results remained consistent for MACCE [PSM-adjusted, HR: 0.923 (0.644-1.323), P -value .663; IPTW-adjusted, HR: 1.300 (0.822-2.056), P -value .262]. **Conclusions:** CCB and clopidogrel co-administration does not appear to significantly impact clopidogrel responsiveness or clinical outcomes. Despite these promising results, further investigation may be warranted. **Clinical trial registration:** Platelet Function and genoType-Related Long-term progGosis in DES-treated Patients: A Consortium From Multi-centered Registries [PTRG-DES]; NCT04734028

Keywords

calcium channel blockers, cardiovascular disease, clopidogrel, platelet function test, long-term prognosis

Introduction

Patients with cardiovascular disease, particularly those who have undergone percutaneous coronary intervention (PCI), are often administered antiplatelet agents, such as clopidogrel. These patients also require additional medications to manage comorbidities, such as hypertension, diabetes, and hyperlipidemia. Clopidogrel can interact with other drugs, affecting its efficacy and safety.¹

Clopidogrel is a prodrug that is primarily converted by cytochrome P450 (CYP) 3A4 and 2C19 in the liver into its active metabolite. The active metabolite exerts its pharmacological effects by blocking the adenosine diphosphate P2Y₁₂ receptor and inhibiting platelet activation and recruitment.² The potential interaction between clopidogrel and calcium channel blockers (CCBs) has been a topic of interest in clinical research.³⁻⁵ The findings of several studies that investigated the influence of CCBs on the effectiveness of clopidogrel were conflicting. Some have suggested a potential interaction between CCBs and clopidogrel, whereas others have reported the absence of any substantial association between the two.⁶⁻⁸

Previous research has shown that coadministration of CCBs is associated with decreased platelet inhibition by clopidogrel, indicating that CCBs may reduce the effectiveness of clopidogrel through CYP3A4-mediated interactions.⁴ Furthermore, a study assessing ADP-inducible platelet reactivity by light transmission aggregometry and the VerifyNow P2Y₁₂ assay, found that patients with concomitant CCB therapy showed significantly higher on-treatment platelet reactivity than those without CCB medication, confirming CCB therapy as an independent predictor of reduced clopidogrel-mediated platelet inhibition.⁵ However, these studies were performed on a limited number of patients and large-scale clinical studies are lacking. Additionally, studies examining the impact on major adverse cardiac and cerebrovascular event (MACCE) with long-term follow-up are also lacking. Population-based cohort study in western Denmark involving 13 001 patients found

that concomitant use of CCBs did not modify the protective effect of clopidogrel and was not associated with increased cardiovascular risk among patients using clopidogrel after coronary stent implantation.⁶ Similarly, in a cohort study of 1608 consecutive patients, it was found that concomitant CCB therapy did not alter clopidogrel-mediated platelet aggregation and did not have a measurable impact on stent thrombosis and mortality after coronary stenting.⁷ Therefore, we aimed to examine the potential interactions between CCBs and clopidogrel using a large-scale national registry of patients who underwent PCI.

Methods and Materials

Data Collection

The Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated patients with coronary artery disease (PTRG-DES) consortium conducted a prospective multicenter registry (ClinicalTrials.gov identifier: NCT04734028). This study included 13 160 patients who underwent successful PCI for significant coronary artery disease in nine registries in Korea between July 2003 and August 2018.⁹

In the PTRG-DES cohort, 11 714 patients underwent the VerifyNow P2Y₁₂ test during antiplatelet therapy. Patients at each center who had been successfully treated with one or more drug-eluting stents (DES), which were adequately loaded with aspirin and clopidogrel, regardless of the complexity of their medical condition or lesion were enrolled in the study. All PCI procedures were performed according to the standard technique.^{10,11} Following PCI, patients were administered 100 mg of aspirin and 75 mg of clopidogrel daily. Patients were recommended to continue taking aspirin indefinitely and clopidogrel for at least one year, and all other treatments were per standard of care. The clinical outcomes were evaluated at the last outpatient visit.

The patient population taking dihydropyridine (DHP) or non-DHP calcium channel blockers (CCB) at the time of hospitalization was defined as the CCB users. The institutional review board of each participating center approved the registry and waived the requirement for written informed consent for access to institutional registries. This study was performed in accordance with the Good Clinical Practice Guidelines and principles of the Declaration of Helsinki.

Platelet Function Test

Platelet reactivity was measured after an adequate period to ensure the full antiplatelet effect using the VerifyNow assay (Accriva, San Diego, CA, USA) during the peri-procedural period (from “just after the insertion of the arterial sheath” to “within 24 h after DES implantation”).¹² Aspirin and clopidogrel were administered according to standardized guidelines for loading and maintenance doses.¹³ Aspirin was given as either 1) a coated oral dose of 300 mg at least 6 h; or 2) a dose of 100 mg at least 5 days before PCI. Clopidogrel was given as either 1) a dose of 600 mg at least 6 h; 2) a dose of 300 mg at least 12 h; or 3) a dose of 75 mg at least 5 days before PCI.

The VerifyNow assay is a whole-blood, point-of-care, turbidimetric optical detection assay designed to measure agonist-induced platelet aggregation. Blood samples were collected in 3.2% citrate Vacuette™ tubes (Greiner Bio-One Vacuette North America, Monroe, NC, USA). The measurement protocol followed the manufacturer’s recommendations as previously described.¹¹ In this study, platelet function tests (PFTs) for clopidogrel were presented in terms of P2Y12 reaction units (PRU). Based on a previous study that established an optimal cutoff value for PRU related to ischemic events in Korea,¹⁴ high platelet reactivity (HPR) on clopidogrel was defined as a PRU value of 252 or higher.

Clinical Outcomes and Definitions

An independent clinical events committee, blinded to the PFT and genotyping results, adjudicated all clinical events using the source documents. The primary ischemic endpoint encompassed significant adverse cardiac and cerebrovascular events (MACCEs), including all-cause mortality, myocardial infarction (MI), definite stent thrombosis (ST), or stroke up to 5 years. Major bleeding was defined as type 3-5 bleeding according to the Bleeding Academic Research Consortium.¹⁵

All deaths were considered to be of cardiovascular (CV) cause unless a definite non-CV cause was established. MI was defined as increased cardiac troponin levels with ischemic symptoms or ischemic changes on electrocardiography, imaging evidence of recent loss of viable myocardium, or the appearance of a new regional wall motion abnormality unrelated to the procedure. ST (definite) was defined according to the Academic Research Consortium criteria.¹² Stroke was defined as the presence of neurological deficits necessitating hospitalization and clinically documented lesions observable on brain computed tomography or magnetic resonance imaging.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD), while categorical variables are presented as numbers and frequencies. Laboratory measurements and clinical parameters were analyzed using Student’s t-test and Fisher’s exact test. Survival analysis was conducted to evaluate time-to-event outcomes and estimate survival curves using the Kaplan–Meier method. The log-rank test was used to compare survival curves between groups and determine the statistical significance of the observed discrepancies. Additionally, Cox proportional hazards regression analysis was performed to investigate the independent impact of the variables on survival outcomes. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were generated using Cox proportional hazards regression models. Multivariate analysis was conducted using variables from the univariate analysis, employing the stepwise forward selection method.

Given that this study was conducted as a registry analysis, propensity score matching (PSM) was employed to address potential associations between CCBs and clinical events. Control variables, including age, sex, body mass index (BMI), the clinical presentation of MI, smoking status, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), peripheral artery disease (PAD), congestive heart failure, prior history of MI or cerebrovascular events (CVAs), platelet reactivity unit, hemoglobin levels, creatinine levels, low-density lipoprotein (LDL) cholesterol levels, the complexity of coronary arterial disease (as categorized by ACC/AHA lesion type), risk of PCI assessed by the complex high-risk indicated percutaneous coronary intervention (CHIP-PCI) criteria,¹⁶ and concomitant medications (aspirin, cilostazol, beta-blockers [BBs], renin-angiotensin system [RAS]-inhibitors, and statins), were considered.

The inverse probability of treatment weighting (IPTW) methodology was applied to account for potential confounding factors. Cox proportional hazards regression analysis stratified by propensity score was used to adjust for HRs associated with the events of interest. Statistical significance was set at $P < .05$. All statistical analyses were performed using the SPSS (version 23.0; IBM, Armonk, NY, USA) and R programming (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Baseline Characteristics

Patients were divided into two subgroups based on CCB administration, with CCBs administered to 2817 patients (24.0%). Significant differences were observed among the baseline characteristics between the two groups, including age, sex, BMI, clinical presentation: predisposing factors such as HTN, DM, hyperlipidemia, CKD, and previous histories of myocardial infarction, PCI, CABG, and CVA. However, there were no significant differences in congestive heart failure and peripheral

artery disease. Propensity score matching (PSM) significantly reduced the differences between the two groups (with a C-statistic of 0.675) regarding patient characteristics like age, sex, BMI, predisposing factors, laboratory tests, angiographic features, and medication use, as well as conditions, such as previous histories of MI, PCI, CABG, and CVA, but not PAD. This was further supported by IPTW analysis. For factors such as age, sex, congestive heart disease, PAD, and past medical history, the standardized mean differences (SMD) were below 0.1, indicating that the method effectively balanced these variables between the CCB and non-CCB groups (Table 1).

Platelet Function Test

PRU values were not significantly different between the CCB and non-CCB groups, with mean values of 215.8 ± 84.7 and 218.4 ± 76.7 , respectively. Moreover, no substantial variations were observed within patients with HPR based on the utilization of CCB (Table 1 and Figure 1).

Furthermore, after implementing the PSM and IPTW methods, no statistically significant disparities in patients with HPR were detected between the two groups. These findings indicate that the concurrent administration of CCB and clopidogrel effectively reduces the impact of other variables, facilitating a more precise evaluation of their influence on MACCE.

MACCEs According to Calcium Channel Blocker Administration

The occurrence of MACCEs was 6.84% ($n = 801$) in the total population and was not significantly different between the CCB-users and non-users (6.4% and 7.0%, respectively; HR: 0.988; 95% CI: 0.837-1.166; $P = .884$) (Table 2). The MACCEs between the two groups were not significantly different after the PSM (HR: 0.905; 95% CI: 0.717-1.142; $P = .401$) and the IPTW (HR: 1.252; 95% CI: 0.930-1.687; $P = .139$) matchings.

This trend persisted even among patients with HPR, and CCB usage did not appear to affect MACCE, and major bleeding based on, as no significant differences were observed between the two groups, even after adjusting using the PSM and IPTW methods (Table 3).

Table 4 presents the results of the univariate and multivariate Cox regression analysis for MACCEs. In the univariate analysis, several variables significantly impacted MACCEs, such as age, DM, HTN, CKD, and CVA. However, the multivariate analysis demonstrated that PAD, a history of CVA, and anemia, but not the use of CCB, significantly influenced MACCEs.

As a subgroup analysis, we conducted further analysis to evaluate the impact of CCB use on platelet reactivity and the MACCE across various CYP2C19 genotype subgroups. A total of 6717 patients had both genotype data and PRU level. The CYP2C19 genotypes were classified into three genotypically predicted metabolizer status groups according to the number of CYP2C19 loss-of-function (LoF) alleles present: (1) extensive metabolizers (EMs) for individuals not carrying

the LoF allele ($*1/*1$, $*1/*17$, or $*17/*17$); (2) intermediate metabolizers (IMs) for carriers of one LoF allele ($*1/*2$, $*1/*3$, $*2/*17$, or $*3/*17$); and (3) poor metabolizers (PMs) for carriers of two LoF alleles ($*2/*2$, $*2/*3$, or $*3/*3$).

Prior study has shown that the CYP2C19 genotype significantly influences 5-year MACCE outcomes in the PTRG registry.¹⁷ Therefore, we analyzed whether there were differences in platelet reactivity and MACCE based on CCB use within each CYP2C19 genotype subgroup. As shown in Supplementary Table 1, there were no significant differences in platelet reactivity between CCB users and non-users within each subgroup [197.0 ± 79.7 versus 193.6 ± 79.5 in the EM group ($P = .322$); 224.9 ± 74.7 versus 225.0 ± 72.6 in the IM group ($P = .954$); 258.9 ± 75.6 versus 249.5 ± 74.5 in the PM group ($P = .077$), respectively]. Supplementary Figure 1 indicates that the use of CCBs did not significantly impact MACCE outcomes within each genotype subgroup (HR: 1.221; 95% CI: 0.807-1.848; $P = .344$ in the EM group, HR: 1.385; 95% CI: 0.976-1.965; $P = .068$ in the IM group, HR: 0.738; 95% CI: 0.386-1.412; $P = .359$ in the PM group, respectively). Subgroup analysis based on metabolizer type revealed no significant differences in platelet reactivity and MACCE outcomes based on the use of CCBs.

Other Clinical Outcomes

Survival analysis was performed to evaluate additional clinical events, including all-cause death, MI, ST, stroke, and major bleeding events. Kaplan–Meier survival plots were generated based on the original patient information (Figure 2). As shown in Table 2, in the CCB and non-CCB groups, respectively, the incidence of all-cause death was 3.3% ($n = 92$) and 3.9% ($n = 350$), showing no significant difference (HR: 0.891; 95% CI: 0.708-1.121; $P = .324$); the incidence of MI was 1.6% ($n = 46$) and 1.7% ($n = 147$), showing no significant difference (HR: 1.052; 95% CI: 0.756-1.466; $P = .763$); the incidence of ST was 0.5% and 0.6%, showing no significant difference (HR: 0.837; 95% CI: 0.454-1.542; $P = .568$); the incidence of stroke was 1.9% ($n = 53$) and 1.8% ($n = 161$), showing no significant difference (HR: 1.106; 95% CI: 0.810-1.508; $P = .527$); and the incidence of major bleeding events was 3.2% ($n = 91$) and 3.0% ($n = 269$), showing no significant difference (HR: 1.132; 95% CI: 0.893-1.436; $P = .306$).

The Kaplan–Meier survival curves for the PSM-matched groups are presented in Figure 3. No significant differences were found in other clinical outcomes, including all-cause death, MI, ST, stroke, and the risk of major bleeding. Furthermore, survival analysis after IPTW did not reveal any significant differences in the clinical outcomes (Figure 4). The adjusted HRs, 95% CIs, and P -values for the outcomes are provided in Table 2.

Discussion

In this study, we comprehensively analyzed the clinical data of patients treated with drug-eluting stents to evaluate the effects of CCBs on the efficacy of clopidogrel in terms of laboratory

Table 1. Baseline Characteristics.

	Before PSM, IPTW				After PSM		After IPTW									
	CCB (n = 2817)		No CCB (n = 8897)		P-value	CCB (n = 2071)		No CCB (n = 2071)		P-value	CCB (n = 1615)		No CCB (n = 3833)		P-value	SMD
Age (years)	65.1 ± 10.5		64.1 ± 11.0		<.001	65.1 ± 10.8		65.2 ± 10.7		.946	64.9 ± 10.6		64.10 (10.89)		.020	0.070
Male sex (%)	1841 (65.4%)		6110 (68.7%)		.001	1329 (64.2%)		1330 (64.2%)		1.000	1011 (62.6%)		2529 (66.0%)		.018	0.071
BMI (kg/m ²)	24.8 ± 3.2		24.4 ± 3.1		<.001	24.9 ± 3.2		24.8 ± 3.1		.566	24.9 ± 3.2		24.5 ± 3.1		<.001	0.127
Clinical presentation					<.001					.169					<.001	0.313
Stable angina	1299 (46.1%)		3611 (40.6%)			905 (43.7%)		848 (40.9%)			696 (43.1%)		1430 (37.3%)			
Unstable angina	1011 (35.9%)		2455 (27.6%)			743 (35.9%)		764 (36.9%)			640 (39.6%)		1254 (32.7%)			
Non-ST segment elevation MI	317 (11.3%)		1543 (17.3%)			260 (12.6%)		264 (12.7%)			188 (11.6%)		678 (17.7%)			
ST segment elevation MI	190 (6.7%)		1288 (14.5%)			163 (7.9%)		195 (9.4%)			91 (5.6%)		471 (12.3%)			
Predisposing factors																
Hypertension	2021 (71.7%)		5028 (56.5%)		<.001	1479 (71.4%)		1485 (71.7%)		.863	1126 (69.7%)		2172 (56.7%)		<.001	0.273
Diabetes mellitus	1056 (37.5%)		3001 (33.7%)		<.001	779 (37.6%)		784 (37.9%)		.898	597 (37.0%)		1235 (32.2%)		.001	0.100
Dyslipidemia	1871 (66.4%)		5684 (63.9%)		.015	1461 (70.5%)		1423 (68.7%)		.211	1145 (70.9%)		2661 (69.4%)		.293	0.032
Chronic kidney disease	752 (26.7%)		1680 (18.9%)		<.001	541 (26.1%)		542 (26.2%)		1.000	421 (26.1%)		745 (19.4%)		<.001	0.159
LV ejection fraction(%)	60.8 ± 9.9		58.2 ± 10.7		<.001	60.8 ± 10.0		61.2 ± 9.9		.232	60.8 ± 10.1		58.1 ± 11.2		<.001	0.253
Congestive heart disease	195 (6.9%)		685 (7.7%)		.186	132 (6.4%)		118 (5.7%)		.396	109 (6.7%)		341 (8.9%)		.010	0.080
Peripheral artery disease	348 (12.4%)		1105 (12.4%)		.952	260 (12.6%)		188 (9.1%)		<.001	223 (13.8%)		554 (14.5%)		.562	0.019
Previous Myocardial infarction	232 (8.2%)		607 (6.8%)		.013	170 (8.2%)		167 (8.1%)		.910	145 (9.0%)		290 (7.6%)		.089	0.051
Previous history of PCI	516 (18.3%)		1052 (11.8%)		<.001	381 (18.4%)		363 (17.5%)		.491	322 (19.9%)		290 (7.6%)		<.001	0.174
Previous history of CABG	51 (1.8%)		99 (1.1%)		.002	40 (1.9%)		29 (1.4%)		.225	34 (2.1%)		43 (1.1%)		<.001	0.078
Previous CVA	244 (8.7%)		569 (6.4%)		<.001	182 (8.8%)		188 (9.1%)		.785	131 (8.1%)		258 (6.9%)		.080	0.053
Laboratory measurements																
Hemoglobin (g/dL)	13.4 ± 1.9		13.6 ± 1.8		<.001	13.5 ± 1.9		13.5 ± 1.8		.396	13.5 ± 1.9		13.6 ± 1.8		.005	0.082
Creatinine (mg/dL)	1.2 ± 1.2		1.0 ± 0.9		<.001	1.2 ± 1.2		1.2 ± 1.3		.560	1.2 ± 1.2		1.0 ± 1.0		<.001	0.116

(continued)

Table 1. (continued)

	Before PSM, IPTW			After PSM			After IPTW		
	CCB (n = 2817)	No CCB (n = 8897)	P-value	CCB (n = 2071)	No CCB (n = 2071)	P-value	CCB (n = 1615)	No CCB (n = 3833)	P-value SMD
LDL Cholesterol (mg/dL)	101.0 ± 43.1	108.6 ± 43.3	<.001	100.6 ± 44.2	100.0 ± 37.1	.679	100.9 ± 45.3	107.4 ± 38.9	<.001 0.154
HbA1C (%)	6.6 ± 1.4	6.6 ± 1.4	.790	6.6 ± 1.4	6.7 ± 1.4	.066	6.5 ± 1.4	6.5 ± 1.3	.456 0.042
P2Y12 reaction units (PRU)	215.8 ± 84.7	218.4 ± 76.7	.156	214.5 ± 82.4	211.7 ± 75.1	.267	217.3 ± 77.3	215.6 ± 77.7	.458 0.022
High platelet activity (≥252 PRU)	981 (34.8%)	3020 (33.9%)	.403	690 (33.3%)	633 (30.6%)	.062	530 (32.8%)	1242 (32.4%)	.790 0.009
Angiographic features ACC/AHA lesion									
A/B1 type	1476 (52.4%)	3762 (42.3%)	<.001	1129 (54.5%)	1090 (52.6%)	.236	977 (60.5%)	2189 (57.1%)	.131 0.071
B2/C type	1341 (47.6%)	5135 (57.7%)		942 (45.5%)	981 (47.4%)		638 (39.5%)	1645 (42.9%)	
Multi-vessel disease	1056 (37.5%)	3475 (39.1%)	.141	804 (38.8%)	751 (36.3%)	.095	591 (36.6%)	1331 (34.7%)	.198 0.039
Complex PCI	720 (25.6%)	2432 (27.3%)	.068	569 (27.5%)	605 (29.2%)	.228	423 (26.2%)	993 (25.9%)	.853 0.007
Concomitant medication									
Aspirin	2795 (99.2%)	8614 (96.8%)	<.001	2052 (99.1%)	2058 (99.4%)	.471	1600 (99.1%)	3779 (98.6%)	.189 0.045
Cilostazol	288 (10.2%)	931 (10.5%)	.742	173 (8.4%)	154 (7.4%)	.300	119 (7.4%)	330 (8.6%)	.142 0.046
RAS inhibitor	1683 (59.7%)	5244 (58.9%)	.463	1253 (60.5%)	1283 (62.0%)	.355	948 (58.7%)	2194 (57.2%)	.334 0.030
Beta-blocker	1529 (54.3%)	5140 (57.8%)	.001	1157 (55.9%)	1194 (57.7%)	.259	950 (58.8%)	2442 (63.7%)	.001 0.100
Statin	2505 (88.9%)	7874 (88.5%)	.561	1823 (88.0%)	1852 (89.4%)	.169	1420 (87.9%)	3359 (87.6%)	.799 0.009

Values are presented as the mean ± standard deviation or number with percentage (%).

Abbreviations: PSM, propensity score matching; IPTW, inverse probability of treatment weighting; CCB, calcium channel blocker; SMD, standard mean difference; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CVA, cardiovascular adverse event; LDL, low-density lipoprotein; ACC/AHA, the American College of Cardiology and American Heart Association; CHIP-PCI, Complex high-risk indicated percutaneous coronary intervention; RAS, renin-angiotensin system.

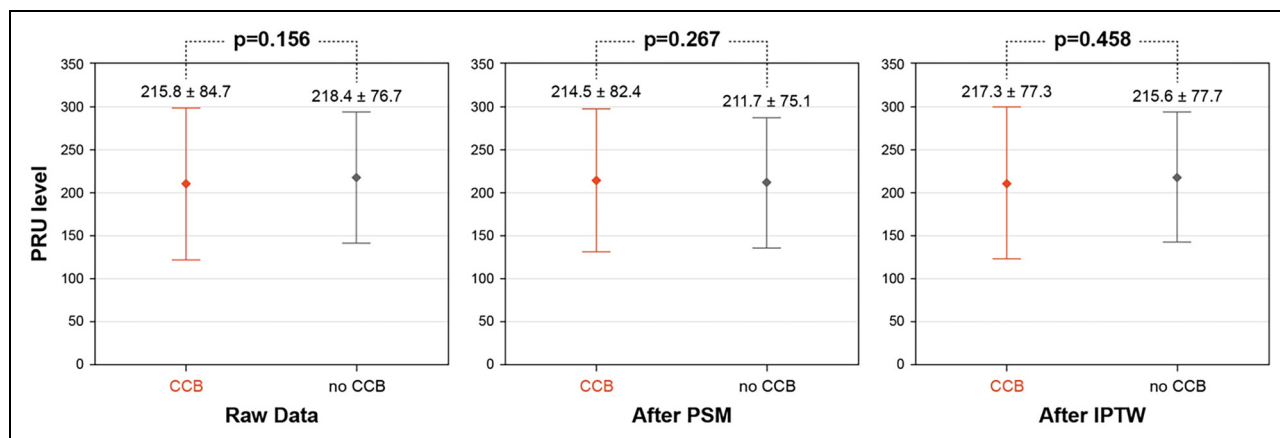


Figure 1. Clopidogrel responsiveness according to CCB administration.

Table 2. Comparison of Major Adverse Cardiac and Cerebrovascular Events (MACCEs) Between Two Groups.

	CCB (n = 2817)	No CCB (n = 8897)	Unadjusted analysis		PSM-adjusted analysis		IPTW-adjusted analysis	
			HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
MACCE	181 (6.4%)	620 (7.0%)	0.988 (0.837-1.166)	.884	0.905 (0.717-1.142)	.401	1.252 (0.930-1.687)	.139
All-cause death	92 (3.3%)	350 (3.9%)	0.891 (0.708-1.121)	.324	0.812 (0.590-1.118)	.202	1.094 (0.718-1.668)	.675
Non-fatal MI	46 (1.6%)	147 (1.7%)	1.052 (0.756-1.466)	.763	1.078 (0.669-1.736)	.758	1.403 (0.784-2.512)	.255
Stent thrombosis, definite	13 (0.5%)	49 (0.6%)	0.837 (0.454-1.542)	.568	0.821 (0.340-1.980)	.660	0.657 (0.198-2.183)	.493
Non-fatal stroke	53 (1.9%)	161 (1.8%)	1.106 (0.810-1.508)	.527	1.159 (0.738-1.821)	.521	1.677 (0.961-2.925)	.069
Major bleeding	91 (3.2%)	269 (3.0%)	1.132 (0.893-1.436)	.306	1.185 (0.841-1.668)	.332	1.136 (0.804-1.607)	.470

Abbreviations: CCB, calcium channel blocker; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiovascular events; MI, myocardial infarction

measurement and long-term clinical prognosis. To the best of our knowledge, this is the largest cohort study encompassing both PFTs and clinical outcome data that scrutinized the interplay between CCBs and clopidogrel. The key findings were as follows: (1) CCBs did not attenuate the *ex vivo* efficacy of clopidogrel; (2) the incidence of HPR did not differ between CCB users and non-users; and (3) the co-administration of CCBs with clopidogrel did not increase MACCEs and major bleeding episodes during long-term follow-up, regardless of HPR status.

Current guidelines for ST-segment elevation MI (STEMI) and non-ST-segment elevation acute coronary syndromes classify BBs as Class I indications.¹⁸ CCBs are recommended for patients for whom BBs are contraindicated. Despite this recommendation, CCBs are frequently prescribed, particularly in regions such as Korea and Japan, where the incidence of variant angina is higher than that in Western countries, and the prevalence of acute coronary syndrome is increasing.¹⁹

The latest recommendations for BB use in patients with chronic coronary disease (CCD) are as follows²⁰: (1)

Prolonged BB therapy is not recommended to enhance outcomes in patients with CCD who have not experienced an MI in the past year, have a left ventricular ejection fraction $\leq 50\%$, or lack another primary indication for BB therapy. (2) For initial antianginal therapy, either a CCB or BB is recommended. Given these recommendations, it is crucial to thoroughly investigate the potential interactions between CCBs and clopidogrel.

Recent review articles investigated the concurrent use of clopidogrel and CCB, demonstrating that although variability in clopidogrel-induced antiplatelet effects can impact clinical outcomes, especially in patients undergoing coronary stenting, most studies evaluating the clinical implications of clopidogrel-drug interactions have not shown significant effects. Guidelines have been established recommending the prescription of PPIs, which significantly interact with clopidogrel, to patients who are on dual antiplatelet therapy and have a history of gastrointestinal bleeding. However, clear guidelines on the concurrent use of CCB and clopidogrel have not yet been established.

Table 3. Comparison of Adverse Clinical Events Based on the Use of CCBs in Patients with High Clopidogrel Responsiveness (≥ 252 PRU).

	CCB (n = 981)	No CCB (n = 3020)	Unadjusted analysis		PSM-adjusted analysis		IPTW-adjusted analysis	
			HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
MACCE	100 (10.2%)	250 (8.3%)	1.031 (0.808-1.315)	.807	0.923 (0.644-1.323)	.663	1.300 (0.822-2.056)	.262
All-cause death	53 (5.4%)	171 (5.7%)	1.038 (0.763-1.413)	.811	1.066 (0.671-1.693)	.786	1.666 (0.925-3.002)	.089
Non-fatal MI	23 (2.3%)	58 (1.9%)	1.315 (0.811-2.133)	.267	1.243 (0.613-2.523)	.546	1.793 (0.704-4.566)	.221
Stent thrombosis, definite	8 (0.8%)	29 (1.0%)	0.850 (0.389-1.860)	.685	0.807 (0.271-2.401)	.700	0.756 (0.187-3.063)	.695
Non-fatal stroke	17 (1.7%)	67 (2.2%)	0.832 (0.489-1.417)	.499	0.691 (0.307-1.557)	.373	1.140 (0.436-2.977)	.790
Major bleeding	36 (3.7%)	105 (3.5%)	1.128 (0.773-1.648)	.532	0.556 (0.906-3.356)	.096	1.304 (0.726-2.343)	.374

Abbreviations: CCB, calcium channel blocker; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiovascular events; MI, myocardial infarction.

Table 4. Univariable and Multivariable Cox Regression Analysis for MACCEs.

	Univariable (n = 11 714)		Multivariable (n = 11 714)	
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age	0.905 (0.884-0.927)	<.001	1.036 (1.022-1.049)	<.001
BMI	0.905 (0.884-0.927)	<.001	1.070 (0.896-0.974)	.002
DM	1.404 (1.221-1.614)	<.001	1.331 (1.047-1.692)	.196
Hypertension	1.550 (1.336-1.798)	<.001	0.846 (0.538-1.329)	.468
Dyslipidemia	0.952 (0.826-1.097)	.498	0.997 (0.994-1.001)	.123
CKD	2.054 (1.780-2.370)	<.001	1.044 (0.788-1.384)	.763
PAD	2.015 (1.673-2.428)	<.001	2.576 (1.334-4.974)	.005
CHF	1.722 (1.361-2.179)	<.001	0.700 (0.417-1.162)	.166
Previous CVA	1.963 (1.584-2.432)	<.001	1.738 (1.241-2.434)	.001
Previous MI	1.198 (0.949-1.512)	.128	1.050 (0.720-1.534)	.800
Anemia (Hb < 13 g/dL(M), Hb < 12 g/dL(F))	2.019 (1.751-2.327)	<.001	1.414 (1.073-1.862)	.014
Aspirin	0.633 (0.449-0.893)	.009	0.833 (0.454-1.529)	.556
Beta-blocker	1.049 (0.911-1.207)	.507	1.010 (0.788-1.294)	.937
Cilostazol	1.319 (1.057-1.646)	.014	0.899 (0.554-1.459)	.668
RAS blocker	1.441 (1.243-1.671)	<.001	1.461 (0.799-2.672)	.217
Calcium Channel Blocker	0.988 (0.837-1.166)	.884	1.007 (0.767-1.320)	.959

Abbreviations: BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; PAD, peripheral artery disease; CHF, congestive heart failure; CVA, cardiovascular adverse event; MI, myocardial infarction; RAS, renin-angiotensin system.

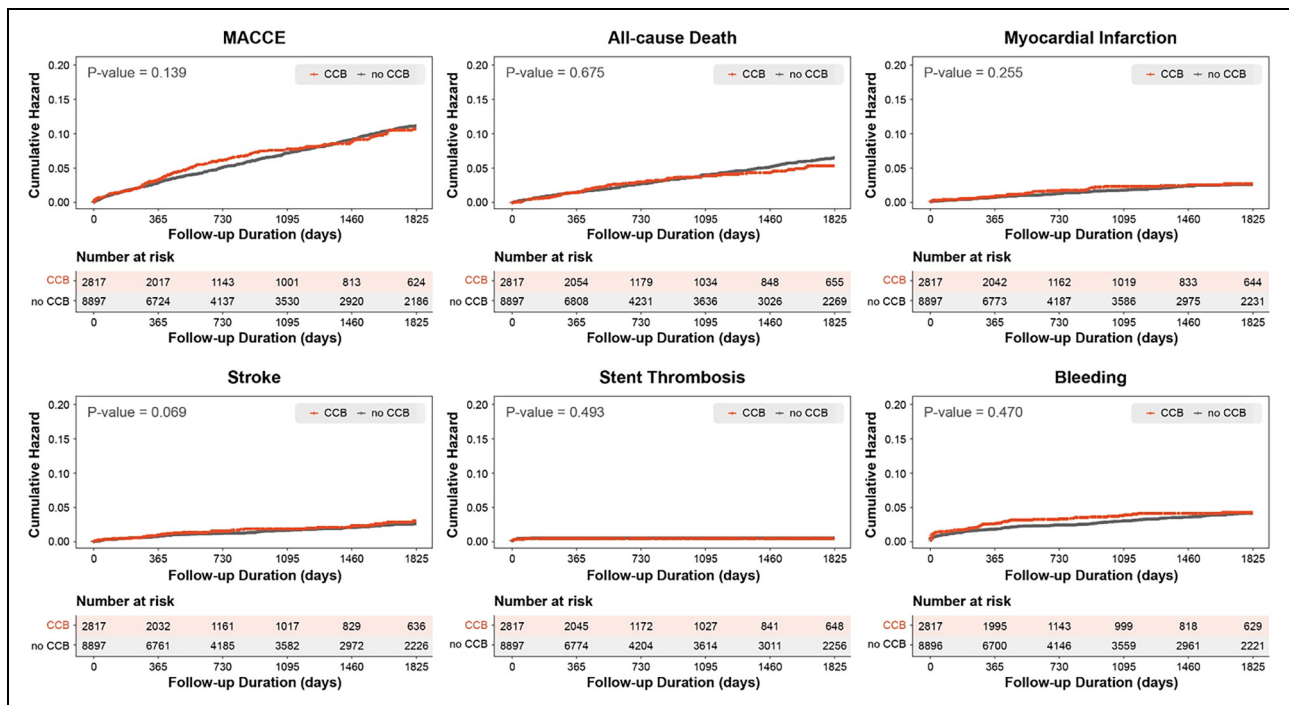


Figure 2. Kaplan–Meier analysis results of the cumulative incidence of events before PSM & IPTW.

Abbreviations: PSM, propensity score matching; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiovascular events.

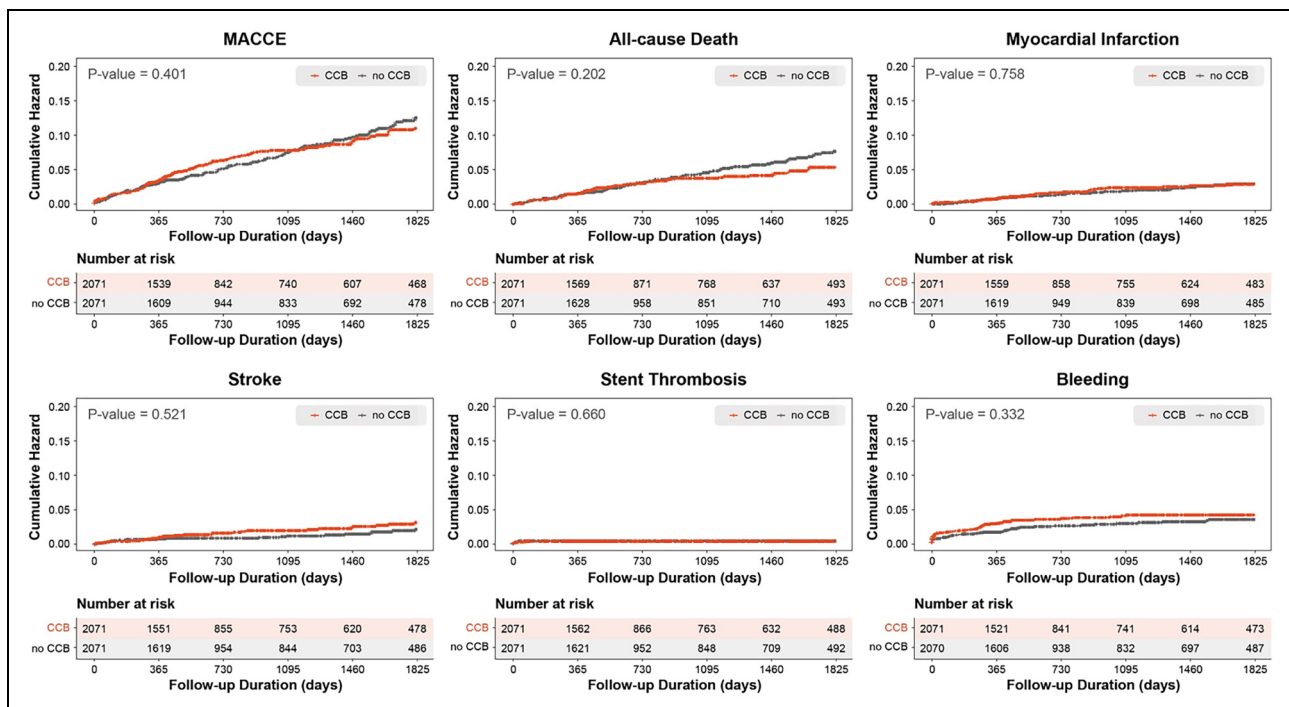


Figure 3. Kaplan–Meier analysis results of the cumulative incidence of events after PSM.

Abbreviations: PSM, propensity score matching; MACCE, major adverse cardiovascular events.

Based on these large-scale studies, the need for randomized trials to provide clarity in this area persists.^{21,22}

CCBs are extensively metabolized in the liver, mainly by cytochrome P450 3A4, resulting in the production of inactive

metabolites, thereby competing with clopidogrel for the enzyme. This reduces the antiplatelet effect of clopidogrel. Furthermore, drug transporter P-glycoprotein (P-gp) and the metabolizing enzyme CYP3A often share a wide range of

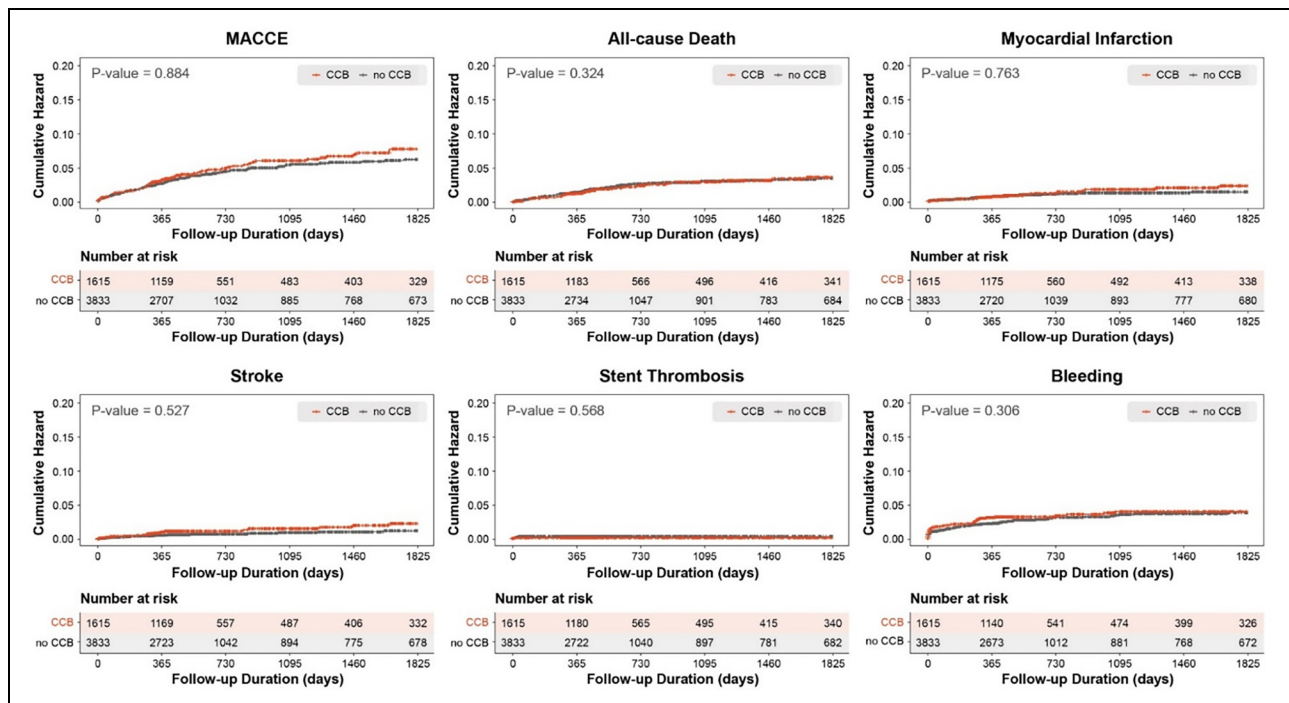


Figure 4. Kaplan–Meier analysis results of the cumulative incidence of events after IPTW. Abbreviations: IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiovascular events.

substrates and modulators, and they are frequently co-located within cells. This dual action of transport and metabolism significantly influences the disposition of drugs.^{22,23}

Siller-Matula et al showed that the platelet reactivity index and ADP-induced platelet aggregation were higher in patients receiving concomitant clopidogrel and CCB and that the intake of CCBs was associated with adverse clinical outcomes.⁴ These findings are consistent with other studies, which showed that the concomitant use of P-gp-inhibiting and non-P-gp-inhibiting CCBs increases the antiplatelet effect of clopidogrel.^{5,24}

Sarafoff et al investigated the relationship between platelet reactivity and outcomes after coronary stenting in 1608 patients.⁷ They found that median platelet aggregation values, the clinical endpoint of death, and ST were not significantly different between patients receiving CCB and those not receiving them. Moreover, Olesen et al performed a study on 56 800 patients, of whom 24 923 were treated with clopidogrel and 13 380 were treated with CCBs. They found that the risk associated with the use of CCBs increased in both groups.²⁴ Additionally, a randomized, controlled, open-label trial showed that concomitant administration of amlodipine did not significantly alter PRU values or the degree of platelet inhibition.²⁵

Our study had several limitations. First, it was based on an observational registry, which may have introduced biases and unmeasured factors influencing clinical outcomes. Efforts were made to overcome these limitations by using PSM or IPTW to adjust for potential confounders. Second, the registry only included PFT data at a single point using the VerifyNow method. However, previous studies have used PRU measured during the index hospitalization as a surrogate marker for

predicting long-term prognosis after stenting.^{26,27} Third, medication information was obtained only from discharge records following the index admission, including the exact duration of CCB use, and prescription changes over time were not considered. Additionally, patient compliance and physician discretion might influence clinical outcomes, even though each patient adhered to standard therapy guidelines. This limitation is inherent in large-scale nationwide cohort studies. However, this limitation can be mitigated by the fact that most patients follow standard care regimens after PCI, maintaining consistent medication use without significant changes in the early post-PCI period. Fourth, this study lacked information regarding the specific types of CCBs used (DHP vs non-DHP). While some evidence suggests that CCB types may have different interactions with other medications,²⁸ previous studies have analyzed CCBs without distinguishing between these two types and there also have no significant interactions with clopidogrel.^{4,22} Our approach is consistent with existing studies, though further research may provide additional insights. Lastly, only East Asians were included in this cohort; therefore, our findings may not be generalizable to other ethnic groups.

Conclusion

In this large prospective multicenter cohort registry, we found no evidence of clinically significant drug-drug interactions between CCBs and clopidogrel. This result remained consistent even after minimizing confounding variables using PSM and IPTW. According to our study, the concomitant use of CCBs and clopidogrel does not seem to present safety concerns.

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Declaration of Conflicting Interests

Dr. Jeong has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals, and Yuhan Pharmaceuticals, as well as research grants or support from Yuhan Pharmaceuticals and U&I Corporation. Dr. Song has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Bayer Korea, and Samjin Pharmaceutical. Dr. Joo has received honoraria for lectures from AstraZeneca, Hanmi, Samjin, Dong-A, HK Inno. N Pharmaceuticals, and DIO Medical Ltd. The other authors have no potential conflicts of interest to disclose.

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Data Availability Statement

PTRG data underlying this article cannot be shared publicly because of data protection agreements but can be available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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