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ORIGINAL RESEARCH

Clopidogrel Vs Aspirin Monotherapy for Secondary Prevention After Percutaneous Coronary Intervention

A Nationwide Cohort Study

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ABSTRACT

BACKGROUND After guideline-recommended dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI), long-term antiplatelet monotherapy is advised, but the optimal agent in real-world practice remains uncertain.

OBJECTIVES The authors aimed to compare efficacy and safety of clopidogrel versus aspirin monotherapy in stable post-PCI patients.

METHODS Using the Korean nationwide claims and health examination database, we identified PCI-treated patients maintained on clopidogrel or aspirin monotherapy between 2009 and 2019. The co-primary outcomes were major adverse cardiovascular events (a composite of cardiovascular death, myocardial infarction or ischemic stroke) and major bleeding.

RESULTS Among 133,454 patients receiving DAPT, 67,652 (50.7%) continued with clopidogrel monotherapy and 65,802 (49.3%) continued with aspirin monotherapy. The median durations of DAPT and monotherapy duration were 1.0 year (IQR: 0.8-1.2) and 3.3 years (IQR: 1.3-6.2), respectively. After stabilized inverse probability of treatment weighting, clopidogrel monotherapy was associated with lower risks of major adverse cardiovascular events (HR: 0.759; 95% CI: 0.733-0.785; $P < 0.0001$) and major bleeding (HR: 0.895; 95% CI: 0.848-0.945; $P < 0.0001$) compared with aspirin monotherapy. Clopidogrel monotherapy was associated with lower risks of cardiovascular death (HR: 0.605; 95% CI: 0.573-0.638; $P < 0.0001$), myocardial infarction (HR: 0.921; 95% CI: 0.877-0.968; $P = 0.0011$), and ischemic stroke (HR: 0.674; 95% CI: 0.624-0.729; $P < 0.0001$) than aspirin monotherapy. The treatment effects were consistent across prespecified subgroups and DAPT durations.

CONCLUSIONS In the stable post-PCI period, clopidogrel monotherapy may be preferred over aspirin monotherapy for long-term prevention due to its efficacy and safety. (JACC Asia. 2026;6:1353–1366) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CCS = chronic coronary syndrome

CV = cardiovascular

DAPT = dual antiplatelet therapy

DES = drug-eluting stent

ICD-10-CM = International Classification of Diseases-10th Revision-Clinical Modification

IPTW = inverse probability of treatment weighting

MACE = major adverse cardiovascular event

MI = myocardial infarction

NHIS = National Health Insurance Service

PCI = percutaneous coronary intervention

PPI = proton pump inhibitor

RCT = randomized clinical trials

SAPT = single antiplatelet therapy

SMD = standardized mean difference

In patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), guidelines recommend the use of dual antiplatelet therapy (DAPT) to prevent recurrent cardiovascular (CV) events, with the treatment duration adjusted based on clinical presentation, bleeding risk, and ischemic risk.[1-3] Following the completion of the guideline-recommended duration of DAPT, long-term treatment with antiplatelet monotherapy is recommended. Aspirin has traditionally been the first-line agent for single antiplatelet therapy (SAPT), supported by historical evidence, its status as the standard of care, broad availability, low cost, and potential benefit of reducing colorectal cancer risk.[4,5] Recent guidelines, however, recognize $P2Y_{12}$ inhibitor as a viable alternative, particularly in patients with a history of myocardial infarction (MI) or remote PCI.[1-3]

Large-scale randomized clinical trials (RCTs) comparing $P2Y_{12}$ inhibitor with aspirin as monotherapy for the prevention of post-PCI CV events have shown mixed results regarding efficacy and safety.[6-11] Recent meta-analyses in patients with established CAD have shown that monotherapy with either clopidogrel or ticagrelor is more effective than aspirin in reducing ischemic events. Notably, clopidogrel monotherapy was linked to a lower risk of major bleeding, whereas ticagrelor monotherapy showed a borderline increase compared with aspirin monotherapy.[12-14] Despite these findings, evidence from real-world clinical practice directly comparing the long-term benefits of different $P2Y_{12}$ inhibitor monotherapies is still limited.

Although RCTs with strict inclusion and exclusion criteria are essential for establishing high-quality evidence on antiplatelet agents, well-designed post-approval observational studies can complement these findings by providing insights in broader, real-world populations.[15-18] In this present study, we aimed to compare the efficacy and safety of clopidogrel vs aspirin monotherapy for secondary prevention using a nationwide population-based cohort of Korean patients who underwent PCI.

METHODS

DATA SOURCES. This study used the National Health Claims Database maintained by the National Health Insurance Service (NHIS) of Korea, a mandatory single-payer system covering approximately 97.1% of the population.[15] Each individual is assigned a unique 13-digit resident identification code, enabling accurate longitudinal tracking of health care services. The NHIS database includes detailed information on diagnoses coded according to the International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM), treatments, procedures, surgeries, prescriptions, hospital admissions, and discharge summaries for all insured individuals under the National Health Insurance Act.[15,16] Researchers with approved study protocols from the NHIS Data Sharing Service are granted full access to the database, highlighting its transparency and utility for public health research. The study protocol was approved by the Institutional Review Board of Chung-Ang University (institutional review board no. 1041078-202201-HR-050). Informed consent was waived because all patient data were anonymized and deidentified before analysis.

COHORT DESIGN AND STUDY POPULATION. We constructed a study cohort comprising 591,646 patients diagnosed with CAD who underwent PCI between January 2009 and December 2019 (**Figure 1**). Baseline characteristics—including age, sex, comorbidities, and concomitant medications—were collected. Detailed definitions of comorbidities are provided in Supplemental Table 1.[17,18] To identify the subjects who received SAPT for chronic maintenance following PCI (n = 224,277), we initially applied the following exclusion criteria: 1) continuation of DAPT regimen; 2) uncertain duration and type of DAPT; 3) unclear diagnostic information at the time of PCI; 4) ischemic or bleeding events occurring during DAPT; and 5) insufficient patient data.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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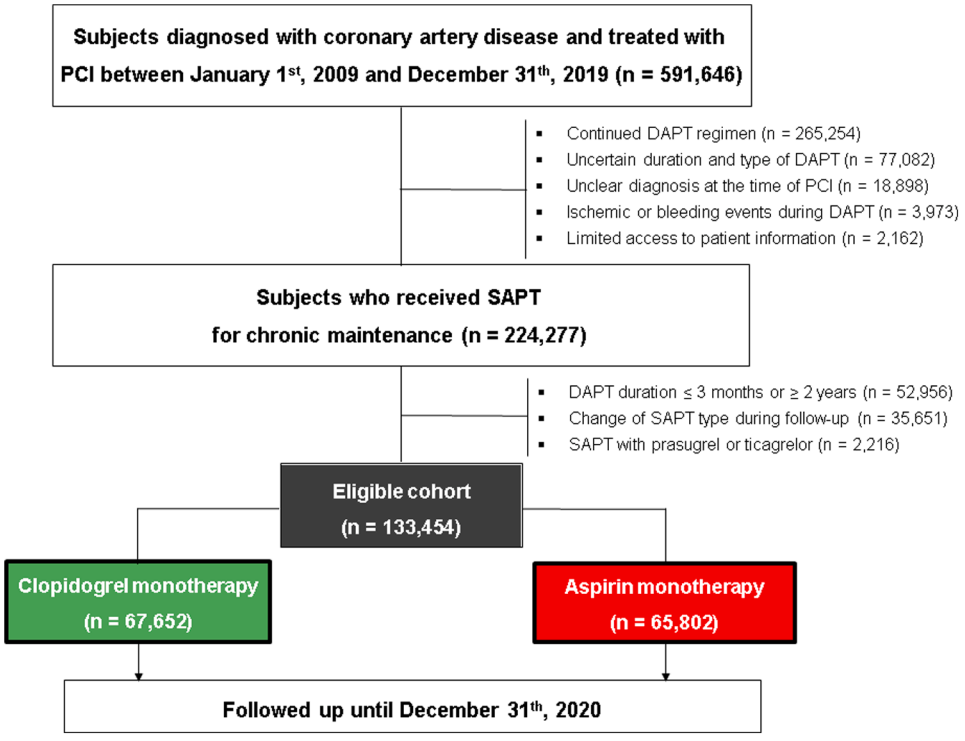
FIGURE 1 Flowchart of the Study Population



This flowchart summarizes the selection of the study cohort from a nationwide database. Among 591,646 patients with coronary artery disease who underwent percutaneous coronary intervention (PCI), those with continued dual antiplatelet therapy (DAPT), uncertain treatment exposure, events during DAPT, or insufficient data were excluded. The final cohort comprised 133,454 patients receiving single antiplatelet therapy (SAPT) with clopidogrel or aspirin and was followed through December 31, 2020.

To define the final cohort maintained on either clopidogrel or aspirin monotherapy, we applied additional exclusion criteria: 1) a DAPT duration of ≤3 months or ≥2 years; 2) switching of SAPT agent during the follow-up period; and 3) SAPT with prasugrel or ticagrelor. This final study cohort thus comprised 133,454 PCI-treated patients who were maintained on monotherapy with either clopidogrel 75 mg once daily (clopidogrel group: n = 67,652) or aspirin 100 mg once daily (aspirin group: n = 65,802).

STUDY OUTCOMES AND DEFINITIONS. The primary effectiveness outcome was major cardiovascular events (MACEs), defined as a composite of CV death, MI, and ischemic stroke. The primary safety outcome was major bleeding.[17,19] The secondary outcomes included the individual components of MACEs and major bleeding (gastrointestinal + intracranial origin). Detailed definitions of the effectiveness and safety outcomes based on ICD-10-CM codes are summarized in Supplemental Table 2.[17,18] Participants were followed from the index date, defined as the date of monotherapy initiation after DAPT discontinuation, until the occurrence of an outcome event or censoring. For the MACE analysis, event time was defined as the earliest occurrence of any MACE component, and cause of death was verified through linkage with the National Death Index provided by the Korean National Statistical Office, using each individual's unique identification code. According to the ICD-10-CM codes for primary cause of death, mortality was categorized into CV disease (disease of the circulatory system: I00-I99; sudden death: R96) and other (non-CV disease) causes (all other ICD-10-CM codes). Major bleeding was defined as the first bleeding episode and included fatal bleeding, bleeding requiring both hospitalization and transfusion, or bleeding occurring at critical sites (intracranial, intraspinal, intra-articular, intraocular, pericardial, retroperitoneal, or intramuscular with compartment syndrome), Bleeding sites included the gastrointestinal tract, intracranial region, urogenital system, respiratory tract, nasal cavity, intraocular

region, and other anatomical locations.[17,19] For both endpoints, participants were censored at death when it was not the outcome of interest or at the end of the study period.

SUBGROUP ANALYSIS. Several subgroup analyses were performed to compare monotherapy with clopidogrel vs aspirin: age strata (<65 or ≥65 years), sex, index disease acuity (acute coronary syndrome [ACS] or chronic coronary syndrome [CCS]), selected comorbidities (hypertension, diabetes, and renal disease), concomitant medications (index DAPT regimen and proton pump inhibitors [PPIs]), and DAPT duration (abbreviated and standard). The significance of the interaction terms was assessed using the likelihood ratio test comparing models with and without the interaction terms. For all subgroup analyses, multivariable Cox proportional hazards models were adjusted with the same covariates as in the primary analysis.

Abbreviated DAPT was defined as DAPT administered for ≤6 months in patients with CCS or ≤12 months in those with ACS.[1-3] In contrast, standard DAPT was defined as therapy given for >6 months for CCS or >12 months for ACS. The significance of the interaction terms was assessed using the likelihood ratio test comparing models with and without the interaction terms. Abbreviated DAPT was defined as DAPT administered for ≤6 months in patients with CCS or ≤12 months in those with ACS.[1-3] In contrast, standard DAPT was defined as therapy given for >6 months for CCS or >12 months for ACS.

For all subgroup analyses, multivariable Cox proportional hazards models were adjusted with the same covariates as in the primary analysis.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median with IQR (25th-75th percentile), and categorical variables are expressed as frequencies with percentages. Baseline and procedural characteristics were compared using the chi-square test for categorical variables and Student's *t*-test for continuous variables. Statistical significance was reported using *P* values.

To compare the clinical effectiveness and safety between the aspirin and clopidogrel groups while accounting for differences in baseline characteristics, we performed an inverse probability of treatment weighting (IPTW) analysis using stabilized weights derived from propensity scores.[20] Propensity scores were estimated using a logistic regression model including age, sex, hypertension, diabetes, dyslipidemia, chronic kidney disease, smoking status, peripheral artery disease, past cardiovascular history (previous MI, PCI, bypass surgery, and stroke), clinical indication for PCI, durations of SAPT and DAPT, DAPT strategy (abbreviated vs standard), and concomitant medications such as beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, statin, and PPI. Covariate balance between the groups was assessed using standardized mean differences (SMDs), with an absolute SMD ≤0.1 indicating a negligible imbalance (Supplemental Figure 1).[21] Kaplan-Meier curves were constructed using IPTW-adjusted weights to visualize survival differences within the pseudo-population generated by the weighted sample. Weighted survival curves and cumulative incidence over time were estimated using the IPTW-modified Kaplan-Meier estimator. Adjusted HRs for clinical endpoints were calculated using Cox proportional hazards regression models incorporating IPTW, with the aspirin group serving as the reference. Between-group differences were assessed using weighted Cox models with robust standard errors. The proportional hazards assumption was evaluated through log-minus-log survival plots and Schoenfeld residuals, which showed no significant deviations, supporting the validity of the Cox models. Statistical significance was assessed using a 2-sided $P < 0.05$. All statistical analyses used SAS version 9.4. (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS. From the initial cohort of 591,646 patients diagnosed with CAD and treated with PCI, a final cohort of 133,454 patients was identified who received either clopidogrel (n = 67,652; 50.7%) or aspirin monotherapy (n = 65,802; 49.3%) for chronic maintenance therapy (**Figure 1**). Throughout the study period, the use of clopidogrel monotherapy steadily increased, surpassing that of aspirin monotherapy from 2016 (Supplemental Figure 2).

Baseline characteristics, including the comorbidities and medication history of the cohort population, before and after stabilized IPTW are presented in **Tables 1 and 2**. Before IPTW adjustment, patients receiving clopidogrel monotherapy were generally older and were less frequently treated with a DAPT regimen containing a potent $P2Y_{12}$ inhibitor, beta-blocker, or PPI compared with those receiving aspirin monotherapy. After applying stabilized IPTW, baseline characteristics were well balanced between the 2 groups, with all SMDs <0.01, indicating negligible imbalance. The mean age of the participants was 63.8 ± 16.3 years, and approximately two-thirds initially presented with ACS. The median duration of DAPT administration was 1.0 year (IQR: 0.8-1.2),

TABLE 1 Baseline Characteristics of the Study Participants Before Inverse Probability of Treatment Weighting

	Total (N = 133,454)	Clopidogrel (n = 67,652)	Aspirin (n = 65,802)	SMD
Age, y	63.8 ± 16.4	64.4 ± 11.6	63.8 ± 16.5	0.11
<40	2,280 (1.7)	1,064 (1.6)	1,216 (1.8)	
40-49	13,226 (9.9)	6,185 (9.1)	7,041 (10.7)	
50-59	33,635 (25.2)	16,305 (24.1)	17,330 (26.3)	
60-69	39,553 (29.6)	19,991 (29.5)	19,562 (29.7)	
70-79	33,087 (24.8)	17,391 (25.7)	15,696 (23.9)	
≥80	11,673 (8.7)	6,716 (9.9)	4,957 (7.5)	
Male (%)	95,815 (71.8)	47,814 (70.7)	48,001 (72.9)	0.05
CV risk factor				
Hypertension	62,626 (46.9)	31,638 (46.8)	30,988 (47.1)	<0.01
Diabetes mellitus	34,940 (26.2)	18,039 (26.7)	16,901 (25.7)	0.02
Dyslipidemia	18,797 (14.1)	9,683 (14.3)	9,114 (13.9)	0.01
Current smoking	24,438 (18.3)	12,290 (18.2)	12,148 (18.5)	0.12
Chronic kidney disease	2,813 (2.1)	1,581 (2.3)	1,232 (1.9)	0.03
Peripheral artery disease	5,570 (4.2)	2,909 (4.3)	2,661 (4.0)	0.01
Past medical history				
Previous MI	4,017 (3.0)	1,921 (2.8)	2,096 (3.2)	0.02
Previous PCI	626 (0.5)	207 (0.3)	419 (0.6)	0.05
Previous CABG	256 (0.2)	132 (0.2)	124 (0.2)	<0.01
Previous stroke	7,884 (5.9)	4,297 (6.4)	3,587 (5.5)	0.04
Clinical indication for PCI				0.07
Silent ischemia	2,821 (2.1)	1,585 (2.3)	1,237 (1.9)	
Stable angina	40,992 (30.7)	20,869 (30.8)	20,123 (30.6)	
Unstable angina	36,584 (27.4)	19,417 (28.7)	17,167 (26.1)	
Acute MI	53,056 (39.8)	25,781 (38.1)	27,275 (41.5)	
Index DAPT regimen				0.19
Aspirin + clopidogrel	114,780 (86.0)	60,319 (89.2)	54,461 (82.8)	
Aspirin + prasugrel	5,186 (3.9)	2,197 (3.2)	2,989 (4.5)	
Aspirin + ticagrelor	13,488 (10.1)	5,136 (7.6)	8,352 (12.7)	
DAPT duration, years (IQR)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	0.03
Abbreviated DAPT	46,657 (35.0)	23,362 (34.5)	23,295 (35.4)	0.02
Standard DAPT	86,797 (65.0)	44,290 (65.5)	42,507 (64.6)	
SAPT duration, years (IQR)	3.3 (1.4-6.2)	2.5 (1.1-4.9)	4.4 (1.9-7.3)	0.51
Concomitant medications				
Beta-blocker	81,754 (61.3)	39,619 (58.6)	42,135 (64.0)	0.11
ACEI or ARB	71,593 (53.6)	34,766 (51.4)	36,827 (56.0)	0.09
Statin	111,866 (83.8)	56,423 (83.4)	55,443 (84.3)	0.02
Proton pump inhibitor	56,186 (42.1)	25,025 (37.0)	31,161 (47.4)	0.21

Values are mean ± SD or n (%). A difference of standardized mean difference (SMD) < 0.1 indicates a relatively small imbalance.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass grafting; CV = cardiovascular; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy.

with 34.9% of patients receiving an abbreviated DAPT regimen. The median duration of SAPT was 3.3 years (IQR: 1.3-6.2), during which 42.2% of participants received a prescription for a PPI.

CLINICAL OUTCOMES. During the follow-up period, absolute clinical outcomes between the groups are shown in Supplemental Table 3. In an IPTW cohort, the occurrence of the primary effectiveness outcome (MACE) was significantly lower in the clopidogrel group (4.4% vs 5.7% in the aspirin group; HR: 0.759; 95% CI: 0.733-0.785; $P < 0.0001$) (Table 3, Figure 2A). With respect to the primary safety outcome, clopidogrel vs aspirin monotherapy was also associated with a lower risk of major bleeding (1.9% vs 2.1%; HR: 0.895; 95% CI: 0.848-0.945; $P < 0.0001$) (Table 3, Figure 3A).

With regard to the secondary outcomes, the clopidogrel group showed significantly lower risks of individual clinical endpoints compared with the aspirin group (Table 3): CV death (HR: 0.605; 95% CI: 0.573-0.638) (Figure 2B), MI (HR: 0.921; 95% CI: 0.877-0.968) (Figure 2C), ischemic stroke (HR: 0.674;

TABLE 2 Baseline Characteristics of the Study Participants After Inverse Probability of Treatment Weighting

	Total	Clopidogrel	Aspirin	SMD
Age, y	63.8 ± 16.3	63.8 ± 16.3	63.8 ± 16.4	<0.01
<40	1.7%	1.7%	1.7%	
40-49	9.9%	9.9%	9.9%	
50-59	25.1%	25.2%	24.9%	
60-69	29.7%	29.5%	29.8%	
70-79	24.9%	24.7%	25.1%	
≥80	8.8%	9.0%	8.6%	
Male (%)	71.7%	71.7%	71.7%	<0.01
CV risk factor				
Hypertension	47.1%	47.1%	47.0%	<0.01
Diabetes mellitus	26.2%	26.2%	26.2%	<0.01
Dyslipidemia	14.1%	14.1%	14.1%	<0.01
Current smoking	18.3%	18.2%	18.3%	<0.01
Chronic kidney disease	2.1%	2.1%	2.1%	<0.01
Peripheral artery disease	4.2%	4.2%	4.2%	<0.01
Past medical history				
Previous MI	3.1%	3.1%	3.1%	<0.01
Previous PCI	0.5%	0.5%	0.5%	<0.01
Previous CABG	0.2%	0.2%	0.2%	<0.01
Previous stroke	6.0%	6.0%	6.0%	<0.01
Clinical indication for PCI				<0.01
Silent ischemia	2.1%	2.1%	2.1%	
Stable angina	31.1%	31.2%	31.1%	
Unstable angina	27.2%	27.2%	27.2%	
Acute MI	39.5%	39.5%	39.6%	
Index DAPT regimen				<0.01
Aspirin + clopidogrel	86.0%	86.0%	86.0%	
Aspirin + prasugrel	3.9%	3.9%	3.9%	
Aspirin + ticagrelor	10.1%	10.2%	10.1%	
DAPT duration, years (IQR)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	<0.01
Abbreviated DAPT	34.9%	34.9%	34.9%	<0.01
Standard DAPT	65.1%	65.1%	65.1%	
SAPT duration, years (IQR)	3.3 (1.3-6.2)	3.3 (1.3-6.2)	3.3 (1.3-6.2)	<0.01
Concomitant medication				
Beta-blocker	61.1%	61.1%	61.1%	<0.01
ACEI or ARB	53.6%	53.5%	53.6%	<0.01
Statin	83.7%	83.7%	83.7%	<0.01
Proton pump inhibitor	42.2%	42.3%	42.2%	<0.01

Values are mean ± SD or n (%). A difference of standardized mean difference (SMD) < 0.1 indicates a relatively small imbalance.

Abbreviations as in Table 1.

95% CI: 0.624-0.729) (Figure 2D), and major bleeding (gastrointestinal + intracranial location) (HR: 0.903; 95% CI: 0.854-0.955) (Figure 3B).

SUBGROUP ANALYSES. With respect to the primary effectiveness outcome, the beneficial effect of clopidogrel monotherapy compared with aspirin monotherapy was generally consistent across all prespecified subgroups (Figure 4). No statistically significant interactions were observed between treatment effects and subgroup variables. During the study period, patients with an ACS phenotype had a higher risk of MACE compared with those with a CCS phenotype ($P < 0.001$). However, clopidogrel monotherapy was associated with a significantly lower risk of MACE than aspirin monotherapy in both the ACS group (HR: 0.800; 95% CI: 0.770-0.830; $P < 0.0001$) and the CCS group (HR: 0.698; 95% CI: 0.650-0.749; $P < 0.0001$), with no significant interaction according to clinical presentation (P for interaction = 0.7531).

Furthermore, the duration of DAPT before switching to SAPT did not modify the clinical benefit of clopidogrel monotherapy over aspirin. The HR for MACE was 0.844 (95% CI: 0.801-0.889; $P < 0.0001$) in the abbreviated DAPT arm and 0.708 (95% CI: 0.677-0.740; $P < 0.0001$) in the standard DAPT arm (P for interaction = 0.4129) (Figure 5A). In terms with major bleeding, there was no statistical difference between the treatments in the abbreviated DAPT arm (HR: 0.941; 95% CI: 0.858-1.032; $P = 0.1964$), whereas clopidogrel monotherapy significantly reduced bleeding risk compared with aspirin monotherapy in the standard DAPT arm (HR: 0.884; 95% CI: 0.824-0.949; $P = 0.0006$) (P for interaction = 0.2528) (Figure 5B).

DISCUSSION

From the large-scale nationwide cohort of 591,646 Korean patients diagnosed with CAD who underwent PCI, we identified the eligible cohort of 133,454 patients who maintained monotherapy with either clopidogrel 75 mg once daily (n = 67,652) or aspirin 100 mg once daily (n = 65,802). Leveraging the comprehensive and longitudinal prescription tracking capabilities of the Korean NHIS database, we assessed the clinical effectiveness and safety of long-term maintenance monotherapy with clopidogrel and aspirin in real-world PCI-treated patients. The main findings of our study are as follows: 1) clopidogrel monotherapy demonstrated a steady upward trend over time in real-world practice; 2) clopidogrel monotherapy was associated with a significant reduction in ischemic outcomes compared with aspirin monotherapy, with consistent benefits observed across individual components, including CV death, MI, and ischemic stroke; 3) clopidogrel monotherapy was also associated with a lower risk of major bleeding events (Central Illustration); and 4) the beneficial effect of clopidogrel monotherapy on both ischemic and bleeding outcomes was consistent across all prespecified subgroups, including clinical presentation (ACS vs CCS) and DAPT duration before SAPT initiation (abbreviated vs standard).

$P2Y_{12}$ INHIBITOR VS ASPIRIN FOR SECONDARY PREVENTION OF CV DISEASE. Although DAPT strategy has been a post-PCI cornerstone medical

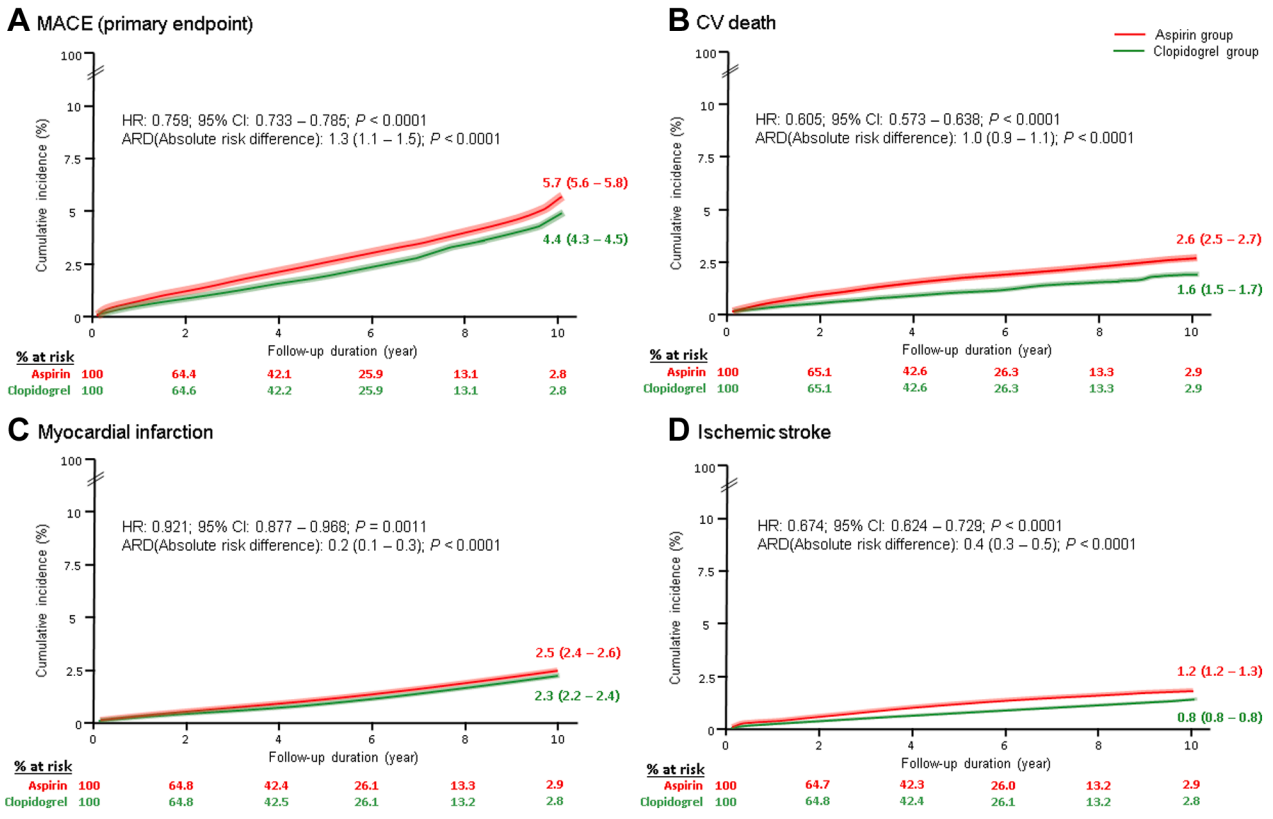
TABLE 3 Outcome Rates and HR After Inverse Probability of Treatment Weighting Matching

	Clopidogrel (%)	Aspirin (%)	HR (95% CI)[a]	*P* Value
Effectiveness outcomes				
MACE[b]	4.4 (4.29-4.51)	5.7 (5.57-5.83)	0.759 (0.733-0.785)	<0.0001
Cardiovascular death	1.6 (1.53-1.67)	2.6 (2.51-2.69)	0.605 (0.573-0.638)	<0.0001
Myocardial infarction	2.3 (2.22-2.38)	2.5 (2.42-2.58)	0.921 (0.877-0.968)	0.0011
Ischemic stroke	0.8 (0.76-0.84)	1.2 (1.15-1.25)	0.674 (0.624-0.729)	<0.0001
Safety outcomes				
Major bleeding (total)	1.9 (1.82-1.98)	2.1 (2.02-2.18)	0.895 (0.848-0.945)	<0.0001
Major bleeding (gastrointestinal + intracranial)	1.7 (1.63-1.77)	1.9 (1.83-1.97)	0.903 (0.854-0.955)	0.0004

[a]Adjusted HRs for clinical endpoints were calculated using Cox proportional hazards regression models incorporating inverse probability of treatment weighting, with the aspirin group serving as the reference. [b]MACEs were defined as a composite of cardiovascular death, myocardial infarction, or ischemic stroke.
MACE = major adverse cardiovascular event.

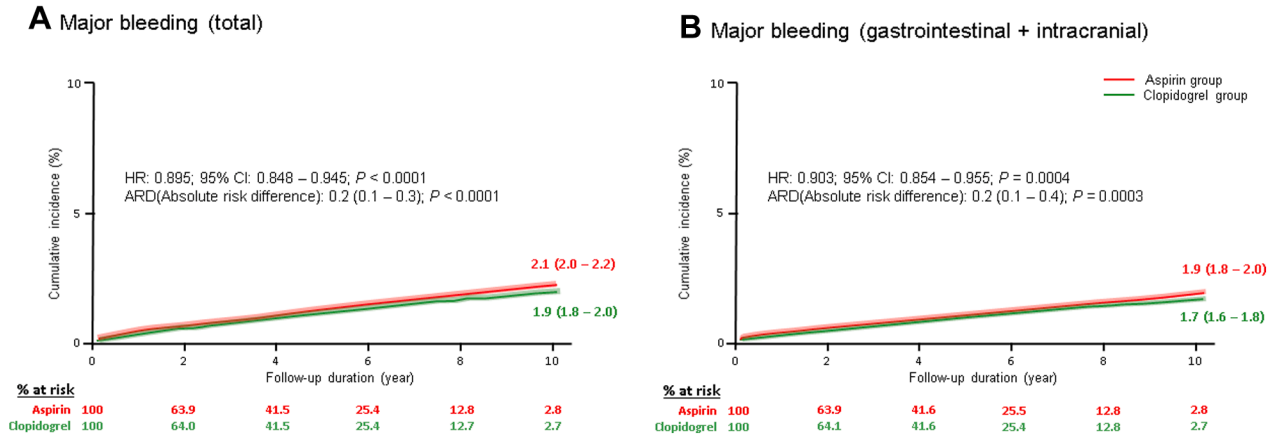
therapy during the guideline-directed duration, SAPT is typically continued for a much longer period as part of lifelong secondary prevention. Acetylsalicylic acid (aspirin) was first synthesized in 1853 and, many years later, was found to inhibit platelet cyclooxygenase-1, thereby suppressing thromboxane A_2 production and reducing the risk of CV events. Meta-analyses conducted by the Anti-Thrombotic Trialists' Collaboration have demonstrated that aspirin use reduced ischemic events in patients with

FIGURE 2 Cumulative Risk of Effectiveness Outcomes After IPTW



Cumulative incidence curves after stabilized inverse probability of treatment weighting (IPTW) are shown for major adverse cardiovascular events (MACE) (A), cardiovascular (CV) death (B), myocardial infarction (C), and ischemic stroke (D). Clopidogrel monotherapy was associated with a lower cumulative incidence than aspirin monotherapy across all outcomes. Red indicates aspirin, green indicates clopidogrel, and the shaded bands represent 95% CIs. ARD = absolute risk difference.

FIGURE 3 Cumulative Risk of Safety Outcomes After IPTW



Cumulative incidence curves after stabilized IPTW are shown for total major bleeding (A) and major bleeding of gastrointestinal or intracranial origin (B). Clopidogrel monotherapy was associated with a lower bleeding risk than aspirin monotherapy. Red indicates aspirin, green indicates clopidogrel, and the shaded bands represent 95% CIs. Abbreviations as in Figure 2.

CAD, albeit with an associated but acceptable increase in bleeding risk.[5,22] However, several key limitations of these meta-analyses may constrain their applicability to current practice. These include the enrollment of a limited patient population, the use of aspirin dosages higher than those currently recommended, and outdated pharmacological and procedural practices that do not reflect modern standards of care.[22]

The ADP $P2Y_{12}$ receptor is a key mediator of the hemostatic response, playing a crucial role in amplifying platelet activation initiated by other agonists, such as thromboxane A_2, thrombin, and collagen.[23,24] Although thromboxane A_2 and ADP act synergistically in platelet aggregation, ADP-$P2Y_{12}$ signaling is pivotal for sustaining glycoprotein IIb/IIIa activation, amplifying responses to diverse agonists and stabilizing platelet-rich thrombus formation. In addition to their central antiplatelet effects, $P2Y_{12}$ inhibitors exert off-target actions through $P2Y_{12}$-independent mechanisms, such as increasing plasma adenosine levels. Emerging evidence suggests that $P2Y_{12}$ receptor inhibitors may modulate inflammation, stabilize atherosclerotic plaques, prevent vasoconstriction, reduce reperfusion injury, and improve endothelial function.[22-24] For example, clopidogrel monotherapy was associated with improved endothelial function, enhanced platelet inhibition, and reduced coagulation activity compared with aspirin.[25] These findings suggest potential pleiotropic effects of $P2Y_{12}$ inhibition on endothelial function and overall hemostatic profiles in patients treated with PCI, which may help support the observed CV mortality benefit associated with clopidogrel in the present study.

Recent RCTs have compared the clinical outcomes of clopidogrel monotherapy vs aspirin for chronic maintenance therapy following drug-eluting stent (DES) implantation, demonstrating differences in efficacy and safety profiles between the 2 agents. The STOPDAPT (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy) trials[9,10] were not primarily designed to compare clopidogrel vs aspirin monotherapy, but rather to investigate the safety of shortened DAPT durations or non-aspirin-based strategies. In contrast, HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy)[7,8] and SMART-CHOICE 3 (Smart Angioplasty Research Team: Choice of Optimal Anti-Thrombotic Strategy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents 3)[11] were explicitly designed to evaluate direct head-to-head comparisons between clopidogrel and aspirin monotherapy in a chronic maintenance setting. The extended follow-up of the HOST-EXAM trial (n = 4,717; median follow-up of 5.8 years [IQR: 4.8-6.2]) demonstrated a sustained benefit of clopidogrel over aspirin in reducing the primary endpoint (12.8% vs 16.9%; HR: 0.74; 95% CI:

FIGURE 4 Subgroup Analysis of MACE

Subgroup	Clopidogrel (%)	Aspirin (%)	HR (95% CI)	P value	$P_{interaction}$
Age					0.5957
< 65 years	2.3 (2.2 – 2.4)	2.9 (2.8 – 3.0)	0.793 (0.743 – 0.848)	<0.0001	
≧ 65 years	6.6 (6.4 – 6.8)	8.8 (8.6 – 9.0)	0.773 (0.742 – 0.804)	<0.0001	
Sex					0.8296
Male	2.7 (2.6 – 2.9)	3.1 (2.9 – 3.3)	0.770 (0.737 – 0.805)	<0.0001	
Female	1.9 (1.7 – 2.1)	2.2 (2.0 – 2.4)	0.781 (0.740 – 0.824)	<0.0001	
Index presentation					0.7531
ACS	5.1 (4.9 – 5.2)	6.5 (6.4 – 6.7)	0.800 (0.770 – 0.832)	<0.0001	
CCS	2.9 (2.8 – 3.1)	4.2 (4.0 – 4.4)	0.698 (0.650 – 0.749)	<0.0001	
Hypertension					0.1730
Yes	5.0 (4.8 – 5.2)	6.8 (6.6 – 7.0)	0.760 (0.726 – 0.796)	<0.0001	
No	3.8 (3.7 – 3.9)	4.8 (4.6 – 5.0)	0.791 (0.752 – 0.833)	<0.0001	
DM					0.1524
Yes	5.3 (5.1 – 5.6)	7.0 (6.7 – 7.2)	0.806 (0.758 – 0.856)	<0.0001	
No	4.0 (3.9 – 4.1)	5.3 (5.2 – 5.4)	0.761 (0.730 – 0.793)	<0.0001	
CKD					0.3144
Yes	7.9 (6.9 – 8.9)	10.7 (9.6 – 11.9)	0.770 (0.644 – 0.921)	0.0043	
No	4.3 (4.2 – 4.4)	5.6 (5.5 – 5.8)	0.776 (0.749 – 0.803)	<0.0001	
$P2Y_{12}$ inhibitor used before SAPT					0.3253
Aspirin + clopidogrel	4.6 (4.5 – 4.8)	6.1 (6.0 – 6.3)	0.770 (0.743 – 0.798)	<0.0001	
Aspirin + ticagrelor	2.0 (1.6 – 2.4)	2.5 (2.1 – 3.0)	0.802 (0.613 – 1.049)	0.1066	
Aspirin + prasugrel	2.9 (2.6 – 3.2)	3.6 (3.3 – 3.9)	0.837 (0.732 – 0.957)	0.0094	
PPI use					0.1390
Yes	3.7 (3.5 – 3.8)	4.8 (4.6 – 4.9)	0.803 (0.764 – 0.843)	<0.0001	
No	5.3 (5.1 – 5.5)	7.1 (6.9 – 7.3)	0.758 (0.723 – 0.795)	<0.0001	

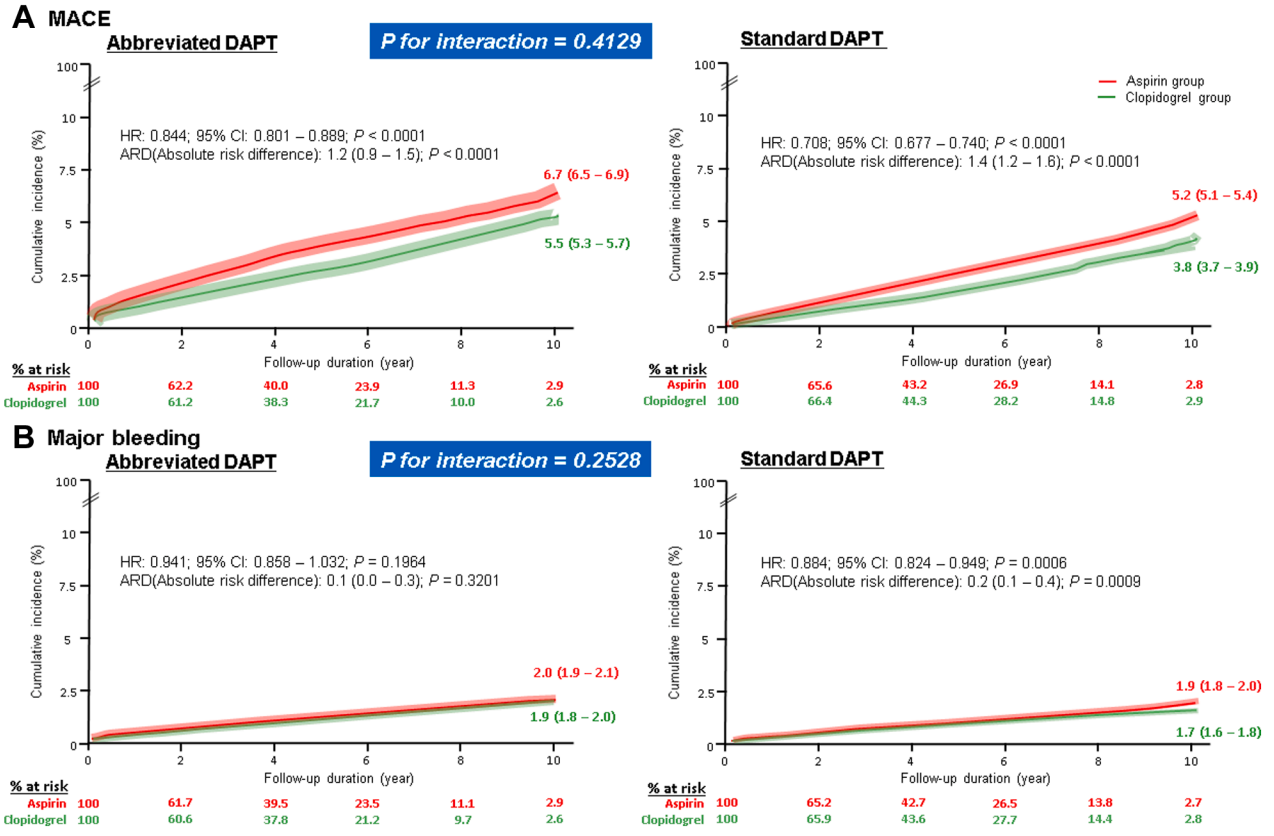
Forest plot of HRs for MACEs across prespecified subgroups after stabilized inverse probability of treatment weighting. Clopidogrel monotherapy was associated with a lower risk than aspirin monotherapy, with no significant interaction across subgroups. Squares indicate HRs, horizontal lines indicate 95% CIs, and the dashed vertical line indicates the null value. ACS = acute coronary syndrome; CCS = chronic coronary syndrome; CKD = chronic kidney disease; DM = diabetes mellitus; PPI = proton pump inhibitor; other abbreviation as in Figure 2.

0.63-0.86; $P < 0.001$). Clopidogrel was associated with a significant reduction in thrombotic events (8.1% vs 11.9%; HR: 0.66; 95% CI: 0.55-0.79; $P < 0.001$) as well as in bleeding events of Bleeding Academic Research Consortium type 2 or higher (4.5% vs 6.1%; HR: 0.74; 95% CI: 0.57-0.94; $P = 0.016$).[8] The SMART-CHOICE 3 trial, including patients at high risk of recurrent ischemic events (n = 5,542; median follow-up of 2.3 years [IQR: 1.6-3.0]), demonstrated that clopidogrel monotherapy significantly reduced the risk of the primary endpoint compared with aspirin monotherapy (4.4% vs 6.6%; HR: 0.71; 95% CI: 0.54-0.93; $P = 0.013$). Clopidogrel was also associated with a lower risk of MI (1.0% vs 2.2%; HR: 0.54; 95% CI: 0.33-0.90) and a trend toward reduced all-cause mortality (2.4% vs 4.0%; HR: 0.71; 95% CI: 0.49-1.02), showing no significant differences in bleeding events of Bleeding Academic Research Consortium type 2 or higher (3.0% vs 3.0%; HR: 0.97; 95% CI: 0.67-1.42).[11]

A recent meta-analysis including 7 RCTs (n = 28,982) compared clinical benefit of clopidogrel vs aspirin monotherapy in patients with established CAD.[12] MACE was lower in patients assigned to clopidogrel than in those assigned to aspirin (HR: 0.86; 95% CI: 0.77-0.96; $P = 0.0082$). However, the rate of major bleeding (HR: 0.94; 95% CI: 0.74-1.21; $P = 0.64$) did not differ. Among these, 4 RCTs including East Asian patients receiving contemporary DES demonstrated a significant reduction in MACE with clopidogrel monotherapy compared with aspirin monotherapy. However, the 3 RCTs that enrolled non-East Asian patients were highly heterogeneous in treatment strategies (eg, aspirin dose, medical vs interventional management) and showed no clear difference in ischemic events between therapies. Notably, the CAPRIE (randomized, blinded trial of Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events)—conducted nearly 3 decades ago—accounts for ~90% of the Western RCT evidence.

Given several important differences with the present large-scale nationwide cohort—including relatively small sample sizes, presence of high-risk comorbidities, and limited follow-up durations—

FIGURE 5 Cumulative Risk of Outcomes According to DAPT Duration

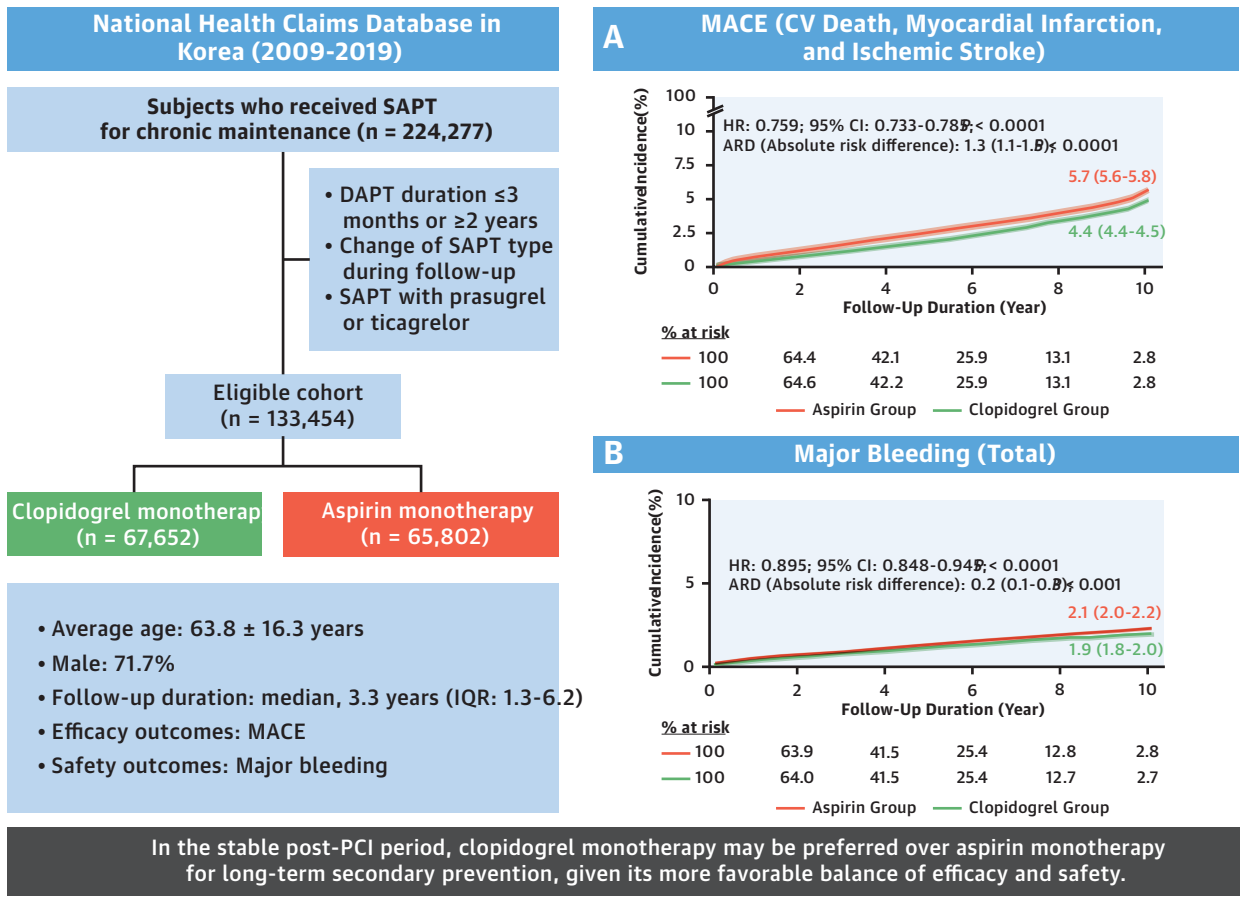


Cumulative incidence curves for MACEs (A) and major bleeding (B) are shown according to abbreviated or standard DAPT duration. Clopidogrel monotherapy was associated with a lower risk of MACEs in both strata, whereas the reduction in major bleeding was more evident after standard DAPT duration. Abbreviations as in Figures 1 and 2.

recent RCTs and meta-analyses may not adequately reflect the current real-world clinical practice and may have been underpowered to detect statistically significant differences in clinical outcomes between the treatments. The present nationwide cohort study included relatively low-risk patients who underwent PCI in real-world clinical practice (n = 133,454)—about 5 times the sample size of a recent meta-analysis[12]—and demonstrated statistically significant superiority of clopidogrel monotherapy over aspirin monotherapy in terms of long-term efficacy and safety for the secondary prevention of CV events over a follow-up period of up to 10 years. A post hoc subgroup analysis of a meta-analysis suggested that $P2Y_{12}$ inhibitor monotherapy, compared with aspirin, provided a greater net clinical benefit in Asian patients than in Caucasian patients (*P* for interaction = 0.023), primarily driven by significant reductions in the risks of stroke and major bleeding among Asian patients.[7,12] In addition, the present study reported a higher prevalence of prior stroke (6.0%) compared with the HOST-EXAM and SMART-CHOICE 3 trials, which reported rates of 2.6% and 4.5%, respectively.[8,11] Taken together, differences in the ethnicity and baseline characteristics of the enrolled cohorts may influence the incidence of individual clinical outcome components and the observed benefit of the tested antiplatelet strategy.

$P2Y_{12}$ INHIBITOR VS ASPIRIN FOR PREVENTION OF BLEEDING EVENTS. The CAPRIE trial was one of the first RCTs comparing clopidogrel 75 mg once daily and aspirin 325 mg once daily, which enrolled more than 19,000 patients with established atherosclerosis, defined as the presence of a recent ischemic stroke, a recent MI, or symptomatic peripheral

CENTRAL ILLUSTRATION **Monotherapy With Clopidogrel or Aspirin for Secondary Prevention Following Percutaneous Coronary Intervention**



Cho JH, et al. JACC Asia. 2026;6(8):1353–1366.

Using the Korean National Health Claims Database (2009–2019), we identified 133,454 patients receiving chronic single antiplatelet therapy (SAPT) after percutaneous coronary intervention (PCI), including 67,652 on clopidogrel monotherapy and 65,802 on aspirin monotherapy. After stabilized inverse probability of treatment weighting, clopidogrel monotherapy was associated with lower cumulative incidence of major adverse cardiovascular events (MACEs) and major bleeding than aspirin monotherapy. These findings suggest that clopidogrel monotherapy may be preferred over aspirin for long-term secondary prevention during the stable period after PCI. ARD = absolute risk difference; CV = cardiovascular; DAPT = dual antiplatelet therapy.

arterial disease. At a mean follow-up of just less than 2 years, the modest clinical benefit of clopidogrel monotherapy—a risk reduction of 8.7%—was observed alongside lower rates of intracranial hemorrhage (0.33% vs 0.47%) and gastrointestinal bleeding (0.52% vs 0.72%) in favor of clopidogrel.[26] Similarly, the HOST-EXAM and SMART-CHOICE 3 trials demonstrated that the superior safety profile of 75-mg clopidogrel, compared with 100-mg aspirin, was primarily driven by reductions in intracranial hemorrhage and gastrointestinal ulceration or bleeding.[8,11] In the present study, clopidogrel monotherapy was associated with a significant reduction in the risk of intracranial bleeding compared with aspirin monotherapy, whereas no significant differences were observed in gastrointestinal bleeding events (Supplemental Table 3).

Differences in the risk of gastrointestinal ulcer or bleeding observed across studies may be partly explained by variations in PPI use, particularly during aspirin therapy in East Asian patients who have a high prevalence of *Helicobacter pylori* infection.[27]

The HOST-EXAM and SMART-CHOICE 3 trials reported relatively low PPI prescription rates (6.6% and 20.5%, respectively).[7,11] In contrast, the STOPDAPT-2 and STOPDAPT-3 trials reported markedly higher PPI usage rates (77.9% and 87.8%, respectively), which may account for the lack of significant differences in gastrointestinal bleeding risk between clopidogrel and aspirin monotherapy following DES implantation.[9,10] In the present nationwide cohort study, the PPI prescription rate was 42.2%. Consistent with the findings from the STOPDAPT-2 and STOPDAPT-3 trials,[9,10] the PPI prescription rate was lower during clopidogrel monotherapy than during aspirin monotherapy, as PPIs were often discontinued concurrently when switching to clopidogrel following DAPT. Further research is warranted to clarify the risk of gastrointestinal bleeding associated with long-term clopidogrel monotherapy according to PPI administration.

$P2Y_{12}$ INHIBITOR VS ASPIRIN MONOTHERAPY FOLLOWING ABBREVIATED DAPT. Following PCI, current guidelines recommend DAPT with aspirin and a $P2Y_{12}$ inhibitor for 6 months in patients with CCS and for 12 months in those with ACS. Further risk stratification to determine optimal DAPT duration is advised based on individual bleeding and ischemic risk profiles.[1-3] Based on clinical evidence, the consensus statement supports that abbreviation of DAPT duration after 1 to 6 months, followed by monotherapy with aspirin or a $P2Y_{12}$ inhibitor, reduces bleeding without an increase in ischemic events in patients at high bleeding risk, particularly those without high ischemic risk.[28,29]

A recent network meta-analysis including patients with ACS undergoing PCI (15 RCTs; n = 35,326) demonstrated that surface under the cumulative ranking ranked 1-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy as the best for reducing major bleeding (relative risk [RR]: 0.47; 95% CI: 0.26-0.74) and 3-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy as optimal for reducing MACE (RR: 0.85; 95% CI: 0.56-1.21) compared with 12 months of DAPT.[30] However, such meta-analyses involve indirect comparisons and include a diverse type of $P2Y_{12}$ inhibitors. In the present study, abbreviated DAPT followed by clopidogrel monotherapy reduced the risk of ischemic event without increasing the bleeding risk compared with abbreviated DAPT followed by aspirin monotherapy. In real-world clinical practice, when a patient's bleeding risk is assessed to outweigh the ischemic risk, an abbreviated DAPT regimen followed by clopidogrel monotherapy may be a suitable SAPT for long-term secondary prevention, as it may mitigate early post-PCI ischemic events without increasing bleeding risk compared with aspirin monotherapy.

STUDY LIMITATIONS. First, this study was an observational, retrospective cohort study using a nationwide claims database, which carries inherent risks such as coding errors, missing data, and the lack of clinically relevant data due to unmeasured variables, or concomitant over-the-counter drug use that usually cannot be captured in such data sources. In addition, we could not reliably classify stent generations to identify detailed PCI strategies, and we were unable to fully assess temporal changes in guideline-directed medical therapy over the study period. Therefore, residual confounding related to evolving devices and practice patterns cannot be excluded, and these factors may have introduced bias into our results. The primary outcomes were not independently adjudicated, introducing a substantial risk of bias and potential misclassification of endpoints. However, the definition and coding of clinically relevant outcomes in the present study were validated in recent clinical studies using the NHIS database.[15-18] Second, this study may have selection or ascertainment bias. Although all measured baseline differences were accounted for using the IPTW matching, unmeasured confounder might still influence the observed results. Patients receiving short DAPT (≤3 months) were excluded, thereby limiting the inclusion of individuals with an extremely high bleeding risk in the current analysis. Consistent with contemporary clinical practice, we prespecified the exclusion of DAPT durations ≤3 months to reduce heterogeneity and potential misclassification, and to minimize the possibility that extreme bleeding risk or patient frailty—rather than the choice of chronic monotherapy—would drive long-term outcomes. Third, our study reported fewer ischemic and bleeding events compared with previous RCTs.[7-11] The study participants belong to an East Asian population, where a lower risk of recurrent CV events is characteristic.[27] In addition, as a real-world, population-based cohort study, clinicians may have been less likely to de-escalate from DAPT to SAPT in patients perceived to be at high ischemic risk. Indeed, among approximately 590,000 patients who underwent PCI between 2009 and 2019, ~45% continued on DAPT without transitioning to SAPT. These characteristics may lead to unique clinical outcomes in the present study compared with recent RCTs,[7-11] where antiplatelet de-escalation is protocol-

mandated. Fourth, the present study enrolled only East Asian patients, among whom the prevalence of cytochrome P450 (CYP) 2C19 polymorphism is high (~ 65%).[27] Given that clopidogrel metabolism is substantially affected by carriage of this polymorphism, the findings may reflect different clinical efficacy and safety in non-East Asian or more genetically diverse populations. However, a Korean multicenter cohort (n = 8,163) demonstrated that the polymorphism's prognostic impact was confined to ACS and to the first year post-PCI.[31] Finally, the study did not incorporate phenotype or genetic testing for clopidogrel responsiveness, as routine platelet function or genotyping is not currently recommended in clinical practice.[32]

CONCLUSIONS

In this nationwide cohort study, clopidogrel monotherapy for chronic maintenance was associated with a lower incidence of adverse clinical outcomes—including CV death, MI, ischemic stroke, and major bleeding—compared with aspirin monotherapy in patients who underwent PCI. These observed effects of clopidogrel monotherapy were consistent across all prespecified subgroups, including clinical presentation and the duration of DAPT. Long-term clopidogrel monotherapy may be a preferable alternative to aspirin monotherapy for secondary prevention in real-world clinical practice.

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KEY WORDS aspirin, cardiovascular event, clopidogrel, dual antiplatelet therapy, percutaneous coronary intervention

APPENDIX For supplemental figures and tables, please see the online version of this paper.