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Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention
The SMART-CHOICE Randomized Clinical Trial

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IMPORTANCE Data on P2Y12 inhibitor monotherapy after short-duration dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention are limited.

OBJECTIVE To determine whether P2Y12 inhibitor monotherapy after 3 months of DAPT is noninferior to 12 months of DAPT in patients undergoing PCI.

DESIGN, SETTING, AND PARTICIPANTS The SMART-CHOICE trial was an open-label, noninferiority, randomized study that was conducted in 33 hospitals in Korea and included 2993 patients undergoing PCI with drug-eluting stents. Enrollment began March 18, 2014, and follow-up was completed July 19, 2018.

INTERVENTIONS Patients were randomly assigned to receive aspirin plus a P2Y12 inhibitor for 3 months and thereafter P2Y12 inhibitor alone (n = 1495) or DAPT for 12 months (n = 1498).

MAIN OUTCOMES AND MEASURES The primary end point was major adverse cardiac and cerebrovascular events (a composite of all-cause death, myocardial infarction, or stroke) at 12 months after the index procedure. Secondary end points included the components of the primary end point and bleeding defined as Bleeding Academic Research Consortium type 2 to 5. The noninferiority margin was 1.8%.

RESULTS Among 2993 patients who were randomized (mean age, 64 years; 795 women [26.6%]), 2912 (97.3%) completed the trial. Adherence to the study protocol was 79.3% of the P2Y12 inhibitor monotherapy group and 95.2% of the DAPT group. At 12 months, major adverse cardiac and cerebrovascular events occurred in 42 patients in the P2Y12 inhibitor monotherapy group and in 36 patients in the DAPT group (2.9% vs 2.5%; difference, 0.4% [1-sided 95% CI, −∞% to 1.3%]; P = .007 for noninferiority). There were no significant differences in all-cause death (21 [1.4%] vs 18 [1.2%]; hazard ratio [HR], 1.18; 95% CI, 0.63-2.21; P = .61), myocardial infarction (11 [0.8%] vs 17 [1.2%]; HR, 0.66; 95% CI, 0.31-1.40; P = .28), or stroke (11 [0.8%] vs 5 [0.3%]; HR, 2.23; 95% CI, 0.78-6.43; P = .14) between the 2 groups. The rate of bleeding was significantly lower in the P2Y12 inhibitor monotherapy group than in the DAPT group (2.0% vs 3.4%; HR, 0.58; 95% CI, 0.36-0.92; P = .02).

CONCLUSIONS AND RELEVANCE Among patients undergoing percutaneous coronary intervention, P2Y12 inhibitor monotherapy after 3 months of DAPT compared with prolonged DAPT resulted in noninferior rates of major adverse cardiac and cerebrovascular events. Because of limitations in the study population and adherence, further research is needed in other populations.

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Current standard antiplatelet therapy after percutaneous coronary intervention (PCI) with drug-eluting stents is dual antiplatelet therapy (DAPT) with aspirin plus a P2Y12 inhibitor followed by aspirin monotherapy.[1,2] However, the optimal duration of DAPT after PCI remains controversial. Although 3 or 6 months of DAPT followed by aspirin monotherapy was comparable to 12 months of DAPT in several randomized studies, such as the OPTIMIZE and EXCELLENT trials,[3,4] a short duration of DAPT was associated with an increased risk of myocardial infarction and stent thrombosis in meta-analyses.[5,6] Conversely, prolonged DAPT increases the risk of bleeding, which offsets the benefit from reducing recurrent ischemic events.[5,7,8] Therefore, neither prolonged DAPT nor short-duration DAPT followed by aspirin monotherapy is fully satisfactory. To develop novel antiplatelet strategies that maintain efficacy for ischemic events while reducing the bleeding risk after PCI is of paramount importance.

P2Y12 inhibitor monotherapy has recently been suggested as a new alternative antiplatelet strategy in patients with atherosclerotic cardiovascular disease.[9] Clopidogrel reduced the risk of subsequent ischemic events with a similar risk of bleeding compared with aspirin in patients with atherosclerotic cardiovascular disease or those undergoing PCI.[10,11] Compared with DAPT, clopidogrel monotherapy was not associated with an increased thrombotic risk in high-risk patients with recent ischemic stroke or transient ischemic attack.[12] Moreover, several studies reported that clopidogrel monotherapy conferred a lower risk of bleeding than DAPT.[12,13] These results suggest that P2Y12 inhibitor monotherapy may be comparable to DAPT for the prevention of recurrent ischemic events, with a lower risk of bleeding in patients undergoing PCI. Therefore, the Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) trial sought to compare P2Y12 inhibitor monotherapy after 3 months of DAPT with 12 months of DAPT in patients receiving current-generation drug-eluting stents.

Methods

Study Design

This trial was an investigator-initiated, multicenter, open-label, noninferiority, randomized study performed at 33 sites in Korea. The trial was designed by the steering committee and was coordinated by the Academic Clinical Research Organization of Samsung Medical Center (Seoul, Korea). The open-label design was selected because of limited funding; therefore, we took several precautions to minimize the possibility of bias. First, to prevent crossovers from the allocated treatment to the alternative treatment, we emphasized the importance of adherence to the protocol to the investigators during trial preparation and throughout the duration of the study via newsletters and telephone communications. Second, we regularly monitored adherence to the protocol of study participants and investigators. Third, an independent clinical event adjudication committee, whose members were unaware of the study-group assignments, adjudicated all the clinical outcomes. The institutional review board at each participating center approved the trial protocol. All participants provided written informed consent. The independent data and safety monitoring board oversaw the safety of the trial. The full protocol and statistical analysis plan for this trial are available in Supplement 1. The rationale and design of this study have been previously published.[14]

Eligible patients were aged 20 years or older and had 1 or more coronary artery stenoses of 50% or greater in a native coronary artery with visually estimated diameter of 2.25 mm or greater and 4.25 mm or smaller amenable to stent implantation, and underwent PCI. Patients with known hypersensitivity or contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, everolimus, or sirolimus were excluded. Additional exclusion criteria included hemodynamic instability or cardiogenic shock; active pathologic bleeding, including gastrointestinal or genitourinary bleeding; drug-eluting stent implantation within 12 months before the index procedure; women of childbearing potential; noncardiac comorbid conditions with a life expectancy less than 2 years; or conditions that may result in protocol nonadherence. A complete list of the inclusion and exclusion criteria is provided in eTable 1 in Supplement 2.

Randomization and Study Procedures

Patients were randomly assigned to the P2Y12 inhibitor monotherapy group (aspirin plus a P2Y12 inhibitor for 3 months and thereafter a P2Y12 inhibitor alone) or to the DAPT group (aspirin plus a P2Y12 inhibitor for at least 12 months) in a 1:1 ratio. Enrollment and random assignment were conducted at the index procedure or at a follow-up visit within 3 months after the index procedure. Randomization was performed with a web-based response system (http://www.ecrf.kr/smartchoice) in blocks of 4 and was stratified by clinical presentation (stable ischemic heart disease or acute coronary syndrome), enrolling center, type of P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), and type of stent used. To minimize the bias from different stent devices, the stents used were limited to cobalt-chromium everolimus-eluting stents (Xience Prime, Xience

Key Points

Question Is P2Y12 inhibitor monotherapy for 9 months after 3 months of dual antiplatelet therapy (DAPT) noninferior to 12 months of DAPT in patients undergoing percutaneous coronary intervention?

Findings In this randomized clinical trial including 2993 patients, the rate of all-cause death, myocardial infarction, or stroke at 12 months was 2.9% with P2Y12 inhibitor monotherapy and 2.5% for patients receiving DAPT. The 1-sided confidence limit of this difference was within the noninferiority margin of 1.8%.

Meaning Although in this study P2Y12 inhibitor monotherapy after a short duration of DAPT resulted in a noninferior rate of major cardiovascular events compared with prolonged DAPT, further research is needed in other populations.

Expedition, or Xience Alpine; Abbott Vascular), platinum-chromium everolimus-eluting stents (Promus Element, Promus Premier, or SYNERGY; Boston Scientific), or sirolimus-eluting stents with biodegradable polymer (Orsiro; Biotronik). For each patient, all lesions had to be treated with the identical type of stent; however, other stents were allowed in case of device failure or situations in which the operators decided otherwise, considering the best interests of the patient.

Percutaneous coronary intervention was conducted according to standard techniques. The length and diameter of the stent were not restricted. Intravascular imaging or fractional flow reserve was also conducted according to the operators' discretion. All patients received 300 mg of aspirin and a 300- or 600-mg clopidogrel loading dose orally at least 12 hours before PCI, unless they had previously received these antiplatelet medications. However, if administration of a loading dose was not possible 12 hours in advance, a 600-mg loading dose of clopidogrel was given as early as possible before intervention. For patients with acute coronary syndrome, 60 mg prasugrel or 180 mg ticagrelor as well as clopidogrel was used. After the procedure, patients received DAPT with aspirin 100 mg once daily plus clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily for 3 months in both groups. The administration of aspirin was stopped at 3 months after the index procedure in the P2Y12 inhibitor monotherapy group but was continued indefinitely in the DAPT group. A P2Y12 inhibitor was prescribed continuously in both groups.

It was recommended that all patients receive optimal pharmacologic therapy, including statins, β-blockers, or renin-angiotensin system blockade, if indicated, following clinical guidelines.[15,16] Clinical follow-up was performed at 3, 6, and 12 months after index PCI. At follow-up, data about patients' clinical status, all interventions received, outcome events, and adverse events were recorded. In particular, information on the use of aspirin or a P2Y12 inhibitor was assessed at each follow-up. Patients who discontinued antiplatelet therapy as a result of clinically significant active bleeding or for other procedures were monitored carefully for cardiac events, and, once they were stabilized, their allocated antiplatelet therapy was restarted as soon as possible.

Study End Points

The primary end point was major adverse cardiac and cerebrovascular events, defined as a composite of all-cause death, myocardial infarction, or stroke at 12 months after the index procedure. Secondary end points included the components of the primary end point, cardiac death, target lesion revascularization, target vessel revascularization, any revascularization, stent thrombosis, Bleeding Academic Research Consortium bleeding type of at least 2 or 3, and a composite of death, myocardial infarction, cerebrovascular event, or any revascularization at 12 months after the index procedure, and each component of primary and secondary end points at 2 and 3 years.

All deaths were considered cardiac unless a definite noncardiac cause could be established. Myocardial infarction was define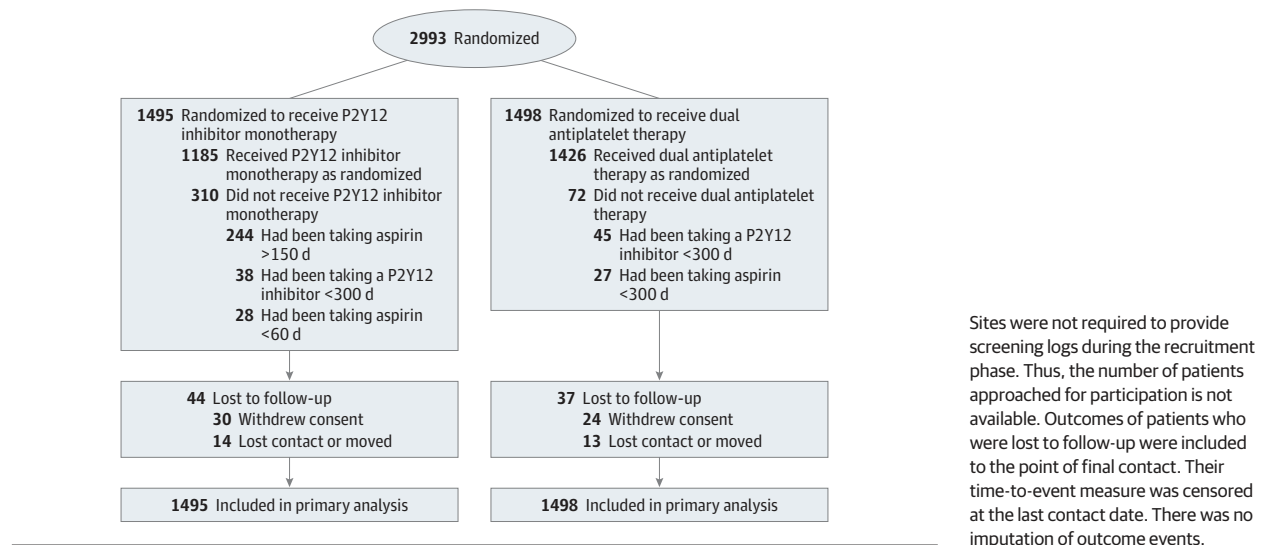d as elevated cardiac enzyme levels (cardiac troponin or myocardial band fraction of creatine kinase) above the upper reference limit with ischemic symptoms or electrocardiographic findings indicative of ischemia. However, periprocedural enzyme-level elevation within 48 hours after the index procedure without concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia was excluded in the assessment of end points.[17] Stroke was defined as any nonconvulsive focal or global neurologic deficit of abrupt onset lasting for more than 24 hours or leading to death, which was caused by ischemia or hemorrhage within the brain. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium classification.[17] Bleeding was defined as Bleeding Academic Research Consortium type 2 to 5 bleeding.[18] Major bleeding was defined as Bleeding Academic Research Consortium type 3, 4, and 5 bleeding. For a post hoc analysis, net adverse clinical and cerebral events were defined as major adverse cardiac and cerebrovascular events plus Bleeding Academic Research Consortium type 2 to 5 bleeding.

Statistical Analysis

The sample size was calculated for noninferiority comparison between P2Y12 inhibitor monotherapy and DAPT in regard to the primary outcome of major adverse cardiac and cerebrovascular events (statistical analysis plan in Supplement 1). According to data from previous trials, the event rate of major adverse cardiac and cerebrovascular events in the DAPT group at 12 months after the index procedure was estimated to be 4.0%.[3,19] Selection of the noninferiority margin (ie, the limit below which the upper limit of a 1-sided 95% CI would consider monotherapy to be noninferior to DAPT) was complicated by the limited information available from existing trials at study design. We chose the noninferiority margin in accordance with clinical judgment and other relevant studies with a noninferiority design. There was consensus among the steering committee that the noninferiority margin should be less than a 50% increase compared with the expected event rate of the standard treatment group, and the noninferiority margin of 2 trials that were available up to that time was equivalent to a 40% increase in the expected event rate.[3,20] It is generally desirable to choose a smaller value for the noninferiority margin, but the feasibility of study recruitment was another important consideration. Therefore, we chose the noninferiority margin of 1.8% that was equivalent to a 45% increase in the expected event rate. With a sampling ratio of 1:1 allowing for 2% attrition in each group during 12 months, a total of 3000 patients (1500 per group) would provide 80% power at a 1-sided type I error of 5%. If the upper limit of the 1-sided 95% CI of the difference were less than the prespecified noninferiority margin, P2Y12 inhibitor monotherapy would be considered noninferior to DAPT.

The analysis of the primary end point followed the intention-to-treat principle, with inclusion of all randomized patients according to original group allocation. A per-protocol analysis excluded patients who did not receive the assigned treatment, according to regular assessments of study participants every 3 months with time-to-event methods. Cumulative event rates were estimated with the Kaplan-Meier

Figure 1. Randomization and Patient Flow in the Study Comparing P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention

Sites were not required to provide screening logs during the recruitment phase. Thus, the number of patients approached for participation is not available. Outcomes of patients who were lost to follow-up were included to the point of final contact. Their time-to-event measure was censored at the last contact date. There was no imputation of outcome events.

method and compared with log-rank tests. Analyses of secondary end points and subgroup analyses were performed with 2-tailed superiority hypothesis testing, with α = .05 and with 2-sided 95% CIs. A post hoc landmark analysis was performed with a landmark of aspirin discontinuation at 3 months. As a post hoc sensitivity analysis, repeated analysis using adherence as a time-varying exposure and a frailty term for site differences was performed. The proportion of patients with at least 1 missing datum was 1.7%, and no imputation methods were used to infer missing data of baseline variables. Patients who were lost to follow-up were censored at the time of the last known contact. Prespecified subgroups included acute coronary syndrome; diabetes mellitus; implanted stent type; type of P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor); chronic kidney disease, defined as estimated glomerular filtration rate less than 60 mL/min/m^2; and multivessel PCI. Prespecified subgroup analyses of the primary end point were performed to evaluate the consistency of treatment effects of P2Y12 inhibitor monotherapy compared with DAPT, using Cox regression models with tests for interaction. Because of the potential for type I error caused by multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Categoric variables are presented as numbers and percentages and compared with the χ^2 test or Fisher exact test. Continuous variables are presented as mean (SD) and compared with the t test. P values and CIs were 2-tailed except those for noninferiority testing of the primary end point. All analyses were performed with SAS version 9.2.

Results

From March 18, 2014, to July 7, 2017, a total of 2993 patients were enrolled. Of these, 1495 patients were randomly assigned to receive P2Y12 inhibitor monotherapy and 1498 were randomly assigned to receive 12-month DAPT (**Figure 1**). Study participants were followed until the development of an event, death, or July 19, 2018, whichever came first. The median time from the index event to randomization was 1 day (interquartile range, 0 to 13) in the P2Y12 inhibitor monotherapy group and 1 day (interquartile range, 0 to 11) in the DAPT group. All baseline demographic, clinical, angiographic, and procedural characteristics were well balanced in the 2 groups (**Table 1**). The mean age was 64 years, 26.6% of all patients were women, 37.5% had diabetes mellitus, 58.2% presented with acute coronary syndrome, and 49.5% had multivessel disease. Medications at discharge from the index PCI were similar in both groups (eTable 2 in Supplement 2).

Antiplatelet Therapy

Overall adherence to the study protocol was 79.3% in the P2Y12 inhibitor monotherapy group and 95.2% in the DAPT group. The rates of P2Y12 inhibitor use were similar in both groups: 96.4% at 6 months and 95.0% at 12 months in the P2Y12 inhibitor monotherapy group and 98.1% at 6 months and 96.6% at 12 months in the DAPT group. The median duration of aspirin was 96 days (interquartile range, 88-118 days) in the P2Y12 inhibitor monotherapy group and 365 days (interquartile range, 363-365) in the DAPT group. The proportion of patients receiving aspirin beyond 3 months in the P2Y12 inhibitor monotherapy group was 14.4% at 6 months and 8.9% at 12 months. Clopidogrel was used as the P2Y12 inhibitor in 1149 patients (76.9%) in the P2Y12 inhibitor monotherapy group and 1163 (77.6%) in the DAPT group. Potent P2Y12 inhibitors, prasugrel or ticagrelor, were used in 346 patients (23.1%) in the P2Y12 inhibitor monotherapy group and 335 (22.4%) in the DAPT group.

End Points

Follow-up for the primary end point was complete for 1451 (97.1%) of patients in the P2Y12 inhibitor monotherapy group

Table 1. Characteristics of Patients at Baseline

Characteristic	No. (%)	
	P2Y12 Inhibitor Monotherapy (n = 1495)	Dual Antiplatelet Therapy (n = 1498)
Age, mean (SD), y	64.6 (10.7)	64.4 (10.7)
Men	1087 (72.7)	1111 (74.2)
Women	408 (27.3)	387 (25.8)
Body mass index, mean (SD)[a]	24.5 (3.1)	24.7 (3.2)
Comorbidities		
Hypertension	921 (61.6)	919 (61.3)
Dyslipidemia	673 (45.1)	679 (45.5)
Diabetes mellitus	570 (38.2)	552 (36.8)
Current smoking	424 (28.4)	367 (24.5)
Previous revascularization	172 (11.5)	177 (11.8)
Previous stroke	99 (6.6)	102 (6.8)
Previous myocardial infarction	62 (4.1)	65 (4.3)
Chronic renal failure	44 (2.9)	53 (3.5)
Left ventricular ejection fraction, mean (SD), %	60.0 (10.9)	59.9 (10.7)
Clinical presentation		
Stable angina	625 (41.8)	625 (41.8)
Unstable angina	467 (31.2)	491 (32.8)
Non-ST-segment elevation myocardial infarction	239 (16.0)	230 (15.4)
ST-segment elevation myocardial infarction	164 (11.0)	150 (10.0)
Transradial approach	1091 (73.0)	1091 (72.8)
Multiple vessels disease	749 (50.1)	734 (49.0)
No. of lesion treated	1849	1885
Location of lesions		
Left main	23 (1.2)	35 (1.9)
Left anterior descending artery	903 (48.8)	950 (50.4)
Left circumflex	399 (21.6)	376 (19.9)
Right coronary artery	524 (28.3)	524 (27.8)
Lesion complexity		
Calcified	235 (15.7)	229 (15.3)
Bifurcation	199 (13.3)	181 (12.1)
Thrombotic	110 (7.4)	112 (7.5)
Use of intravascular ultrasonography	372 (25.0)	406 (27.2)
Treated lesions per patient		
1	1065 (71.2)	1041 (69.5)
2	329 (22.0)	351 (23.4)
3	86 (5.8)	91 (6.1)
≥4	15 (1.0)	15 (1.0)
Multilesion intervention	430 (28.8)	457 (30.5)
Multivessel intervention	337 (22.5)	368 (24.6)
No. of stents per patient		
1	975 (65.2)	978 (65.3)
2	380 (25.4)	374 (25.0)
3	102 (6.8)	115 (7.7)
≥4	38 (2.6)	31 (2.0)
Stent length per patient, mean (SD), mm	38.0 (22.5)	37.8 (22.9)
Type of drug-eluting stents		
Cobalt-chromium everolimus eluting	525 (35.1)	526 (35.1)
Platinum-chromium everolimus eluting	489 (32.7)	478 (31.9)
Sirolimus-eluting with biodegradable polymer	481 (32.2)	491 (32.8)
Zotarolimus eluting	0	1 (0.1)
Paclitaxel-cilostazol eluting	0	1 (0.1)

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

Table 2. Outcomes at 12 Months

Outcome	No. (%)		Estimate of Difference, % (95% 1-Sided CI)	P Value
	P2Y12 Inhibitor Monotherapy (n = 1495)[a]	Dual Antiplatelet Therapy (n = 1498)[a]		
Primary End Point				
MACCE[b]	42 (2.9)	36 (2.5)	0.4 (−∞ to 1.3)	.007 (noninferiority)
Secondary End Points			Hazard Ratio (95% CI)	
All-cause death	21 (1.4)	18 (1.2)	1.18 (0.63 to 2.21)	.61
Myocardial infarction	11 (0.8)	17 (1.2)	0.66 (0.31 to 1.40)	.28
Stroke	11 (0.8)	5 (0.3)	2.23 (0.78 to 6.43)	.14
Cardiac death	11 (0.8)	13 (0.9)	0.86 (0.38 to 1.91)	.70
Stent thrombosis	3 (0.2)	2 (0.1)	1.51 (0.25 to 9.02)	.65
Bleeding BARC type 2-5	28 (2.0)	49 (3.4)	0.58 (0.36 to 0.92)	.02
Major bleeding[c]	12 (0.8)	14 (1.0)	0.87 (0.40 to 1.88)	.72
Post Hoc Analysis				
Death or myocardial infarction	31 (2.1)	32 (2.2)	0.98 (0.60 to 1.61)	.94
Cardiac death or myocardial infarction	21 (1.5)	27 (1.9)	0.79 (0.45 to 1.39)	.50
Net adverse clinical and cerebral events[d]	65 (4.5)	81 (5.6)	0.81 (0.58 to 1.12)	.20

Abbreviations: BARC, Bleeding Academic Research Consortium; MACCE, major adverse cardiac and cerebrovascular events.
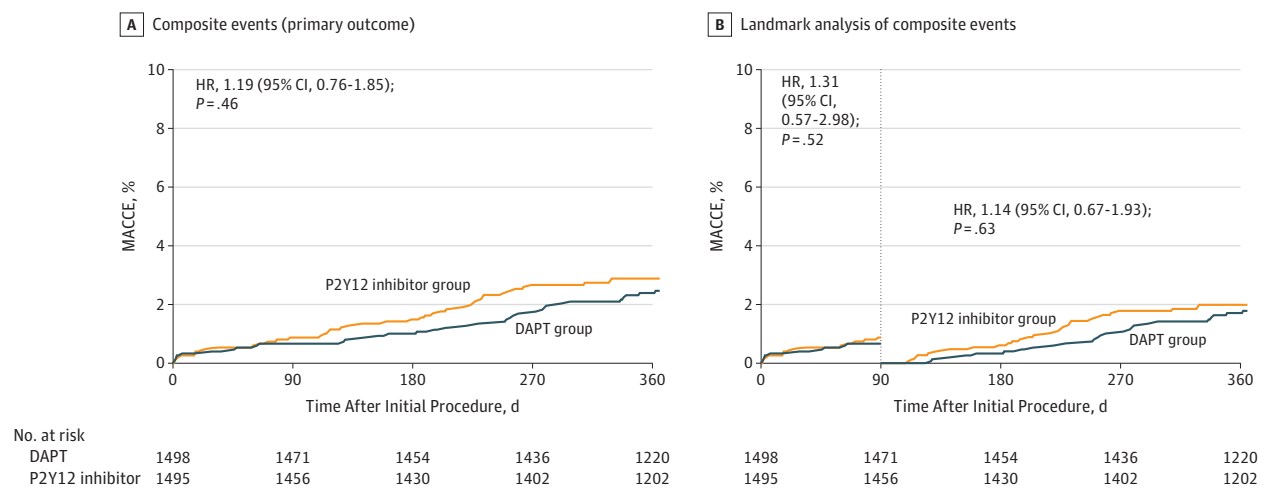
[a] Data are presented for the intention-to-treat population. The percentages are Kaplan-Meier estimates.

[b] A composite of all-cause mortality, myocardial infarction, or stroke.

[c] BARC type 3 to 5 bleeding.

[d] MACCE plus BARC type 2 to 5 bleeding.

Figure 2. Time-to-Event Curves for the Major Adverse Cardiovascular and Cerebrovascular Events and Landmark Analysis at 3 Months

A   Composite events (primary outcome)

HR, 1.19 (95% CI, 0.76-1.85); P = .46

B   Landmark analysis of composite events

HR, 1.31 (95% CI, 0.57-2.98); P = .52

HR, 1.14 (95% CI, 0.67-1.93); P = .63

| No. at risk					
DAPT	1498	1471	1454	1436	1220
P2Y12 inhibitor	1495	1456	1430	1402	1202

A, Results of the analysis of the primary end point of major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) at 12 months. B, Results of the landmark analysis at 3 months (the point after which one group received P2Y12 inhibitor only and the other received DAPT) for the primary end point. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses. Hazard ratios are for the patients in the P2Y12 inhibitor monotherapy group. DAPT indicates dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events. MACCE was defined as a composite of all-cause death, myocardial infarction, or stroke. The median length of patient follow-up was 365 days (25th and 75th percentile, 365 and 365) in the P2Y12 inhibitor monotherapy group and 365 days (25th and 75th percentile, 365 and 365) in the DAPT group.

and 1461 (97.5%) in the DAPT group. At 12 months, the primary end point of major adverse cardiac and cerebrovascular events occurred in 42 patients in the P2Y12 inhibitor monotherapy group and 36 in the DAPT group. Cumulative rates of major adverse cardiac and cerebrovascular events at 12 months were 2.9% for the P2Y12 inhibitor monotherapy group and 2.5% for the DAPT group (difference, 0.4% [1-sided 95% CI, −∞% to 1.3%]; P = .007 for noninferiority), meeting criteria for noninferiority of P2Y12 inhibitor monotherapy to DAPT (**Table 2, Figure 2**A; eFigure 1 in Supplement 2). In the per-protocol

analysis, major adverse cardiac and cerebrovascular events occurred in 36 of 1185 patients in the P2Y12 inhibitor monotherapy group and 35 of 1426 in the DAPT group. Cumulative rates of major adverse cardiac and cerebrovascular events at 12 months were 3.1% for the P2Y12 inhibitor monotherapy group and 2.5% for the DAPT group (difference, 0.6% [1-sided 95% CI, −∞% to 1.5%]; P = .02 for noninferiority) (eTable 3 and eFigure 2 in Supplement 2), meeting criteria for noninferiority P2Y12 inhibitor monotherapy to DAPT in the per-protocol analysis.

Figure 3. Time-to-Event Curves for the Bleeding and Landmark Analysis at 3 Months
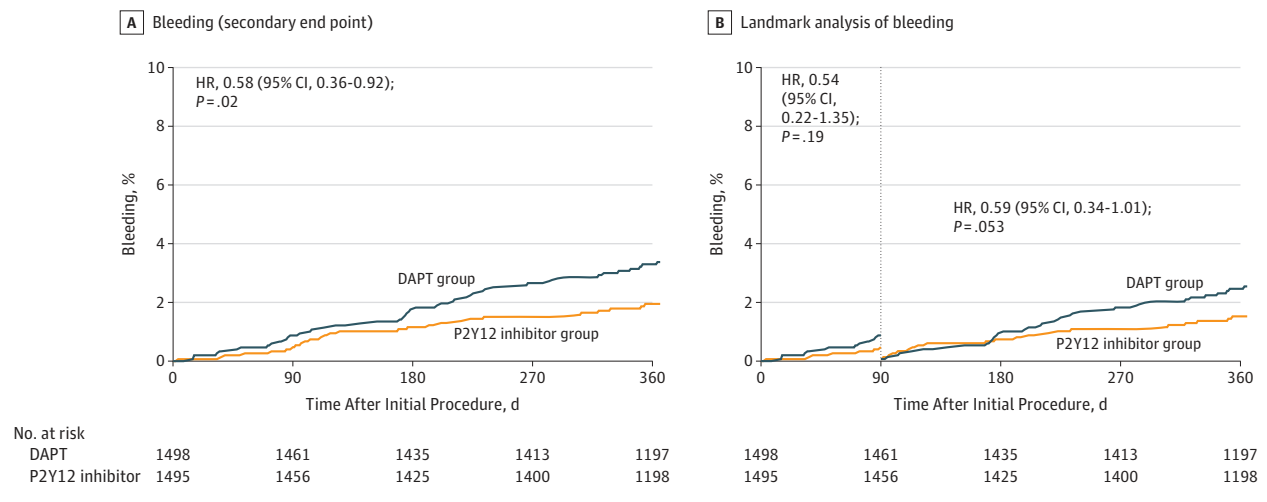
A, Results of the analysis of the bleeding at 12 months. B, Results of the landmark analysis at 3 months (the point after which one group received P2Y12 inhibitor only and the other received DAPT) for bleeding. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses. Hazard ratios are for the patients in the P2Y12 inhibitor monotherapy group. DAPT indicates dual antiplatelet therapy; HR, hazard ratio.

There were no significant differences in the cumulative rates of the components of the primary end point at 12 months for all-cause death, myocardial infarction, and stroke (Table 2; eFigures 3-5 in Supplement 2). The risk of stent thrombosis was not significantly different between the 2 groups (Table 2). The results from the per-protocol analysis were similar to those from the intention-to-treat analysis (eTable 3 in Supplement 2). A post hoc landmark analysis showed that the risk of major adverse cardiac and cerebrovascular events between 3 and 12 months was not significantly different between the groups (hazard ratio, 1.14; 95% CI, 0.67-1.93; P = .63) (Figure 2B). A post hoc analysis using adherence as a time-varying exposure and a frailty term for site differences gave similar results (hazard ratio, 1.26; 95% CI, 0.79-2.00; P = .33). The rate of bleeding was significantly lower in the P2Y12 inhibitor monotherapy group than in the DAPT group (2.0% vs 3.4%; hazard ratio, 0.58; 95% CI, 0.36-0.92; P = .02) (Table 2 and **Figure 3**A). There was no significant difference in the risk of bleeding between the groups in the post hoc 3-month landmark analysis (hazard ratio, 0.59; 95% CI, 0.34-1.01; P = .053) (Figure 3B). The rate of major bleeding did not differ significantly between the 2 groups (Table 2). In the per-protocol analysis, the risk of bleeding was significantly lower in the P2Y12 inhibitor monotherapy group than in the DAPT group (1.8% vs 3.1%; hazard ratio, 0.58; 95% CI, 0.34-0.97; P = .04) (eTable 3 and eFigure 2 in Supplement 2).

The treatment effects of the P2Y12 inhibitor monotherapy compared with DAPT were consistent across various subgroups for the major adverse cardiac and cerebrovascular events, including the subgroups according to clinical presentation (acute coronary syndrome vs stable ischemic heart disease) and type of P2Y12 inhibitors (eFigure 6 in Supplement 2). In post hoc subgroup analyses in regard to the risk of bleeding, the results were consistent across various subgroups (eFigure 7 in Supplement 2).

Discussion

In this randomized trial, P2Y12 inhibitor monotherapy after 3 months of DAPT was noninferior to 12-month DAPT for the primary end point of major adverse cardiac and cerebrovascular events at 12 months after the index procedure, and was associated with a lower rate of bleeding.

There are several plausible explanations for these results. First, aspirin might provide little additional inhibition of platelet aggregation in the presence of a P2Y12 inhibitor. P2Y12 receptor activation is important to platelet thromboxane A2 production, and P2Y12 inhibition can result in a substantial degree of inhibition of thromboxane A2.[21,22] It was also reported that P2Y12 inhibitor monotherapy inhibited hemostatic system activation to a similar extent compared with DAPT.[23] Second, the risk of bleeding was significantly lower with P2Y12 inhibitor monotherapy than with DAPT in the present study. Reduction of bleeding after PCI is of great importance because it has a strong relationship with subsequent all-cause mortality and major adverse cardiovascular events.[24] In addition to bleeding-related death, interruption of antiplatelet therapy because of bleeding may be associated with an increase in thrombotic events. Third, second-generation drug-eluting stents with documented safety that significantly reduced stent thrombosis and myocardial infarction compared with the first-generation drug-eluting stents were exclusively used.[6] In the present study, the rate of stent thrombosis was low and similar in both groups. Three-month DAPT in the P2Y12 inhibitor monotherapy group might be adequate to prevent stent thrombosis after implantation of current-generation drug-eluting stents.

In the GLOBAL LEADERS trial, the researchers compared ticagrelor plus aspirin for 1 month followed by ticagrelor alone for 23 months vs 12 months of standard DAPT followed by

12 months of aspirin alone in patients undergoing PCI.[25] Although the trial was large and well conducted, generalizability is limited by the exclusive use of ticagrelor even in patients with stable ischemic heart disease. On the contrary, in this trial, there was no restriction on type of P2Y12 inhibitors and clinical presentation. As a result, clopidogrel was the predominant P2Y12 inhibitor in the patients in the trial. Response to clopidogrel shows wide individual variability, and there might be concerns that clopidogrel monotherapy is inadequate to prevent recurrent ischemic events in the substantial portion of patients with high platelet reactivity with clopidogrel.[26,27] However, there was no significant interaction between type of P2Y12 inhibitors and the treatment effects of the 2 antiplatelet regimens on the major adverse cardiac and cerebrovascular events in the present study.

Limitations

This study has several limitations. First, the noninferiority margin of 1.8% (corresponding to a 45% increase with respect to the expected event rate and a 72% increase with respect to the observed event rate) was relatively wide and this study might be underpowered. However, the noninferiority margin of major trials on duration of DAPT was equivalent to a 20% to 67% increase in the expected event rate and a 47% to 133% increase in the observed event rate of the standard treatment group.[3,4,20,28-32] Therefore, the noninferiority margin of this trial was not exceptionally wide, but was typical compared with that of the previous trials on DAPT duration. Second, the present study was an open-label trial, not placebo controlled, and was conducted in a low risk-population. Although several precautions were taken to maximize adherence and minimize treatment crossovers, the possibility of biases toward noninferiority originating from an open-label intervention or from low adherence in the monotherapy group could not be excluded. However, intention-to-treat and per-protocol analyses showed similar conclusions, suggesting that any potential biases caused by differential adherence and treatment crossover are likely small. Third, not all consecutive patients were considered for enrollment and the number of patients screened was not available. Selection bias for enrollment of patients with relatively low risk may limit application of the results of this study in other populations. In the SMART-DATE trial that compared 6-month DAPT with the conventional 12-month or longer duration of DAPT in patients with acute coronary syndrome, myocardial infarction significantly increased with 6-month DAPT.[31] Although more than half of patients presented with acute coronary syndrome in this trial, the safety of P2Y12 inhibitor monotherapy after a short duration of DAPT in patients with a high-risk profile needs to be confirmed in a future study, such as the TWILIGHT trial.[33]

Conclusions

Among patients undergoing percutaneous coronary intervention, P2Y12 inhibitor monotherapy after 3 months of DAPT compared with prolonged DAPT resulted in noninferior rates of major adverse cardiac and cerebrovascular events. Because of limitations in the study population and adherence, further research is needed in other populations.

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