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$P2Y_{12}$ inhibitor monotherapy in complex percutaneous coronary intervention: A post-hoc analysis of SMART-CHOICE randomized clinical trial

Ji Woong Roh[1, 2], Joo-Yong Hahn[3], Ju-Hyeon Oh[4], Woo Jung Chun[4], Yong Hwan Park[4], Woo Jin Jang[5], Eul-Soon Im[6], Jin-Ok Jeong[7], Byung Ryul Cho[8], Seok Kyu Oh[9], Kyeong Ho Yun[9], Deok-Kyu Cho[2], Jong-Young Lee[10], Young-Youp Koh[11], Jang-Whan Bae[12], Jae Woong Choi[13], Wang Soo Lee[14], Hyuck Jun Yoon[15], Seung Uk Lee[16], Jang Hyun Cho[17], Woong Gil Choi[18], Seung-Woon Rha[19], Hee-Yeol Kim[1], Joo Myung Lee[2], Taek Kyu Park[2], Jeong Hoon Yang[2], Jin-Ho Choi[2], Seung-Hyuck Choi[2], Sang Hoon Lee[2], Hyeon-Cheol Gwon[2], Dong-Bin Kim[1], Young Bin Song[2]

[1]Division of Cardiology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine and Cardiovascular Center, Yongin Severance Hospital, Yongin, Korea; [3]Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Division of Cardiology, Samsung Changwon Hospital, Department of Internal Medicine, Sungkyunkwan University School of Medicine, Korea; [5]Division of Cardiology, Department of Internal Medicine, Ewha Womans University Medical Center Seoul Hospital, Seoul, Republic of Korea; [6]Division of Cardiology, Dongsuwon General Hospital, Suwon, Korea; [7]Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea; [8]Division of Cardiology, Kangwon National University Hospital, Chuncheon, South Korea; [9]Department of Cardiology, Wonkwang University School of Medicine, Iksan, South Korea; [10]Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Korea; [11]Division of Cardiology, Department of Internal Medicine, Chosun University Hospital, Gwangju, Korea; [12]Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea; [13]Department of Cardiology, Seoul Eulji Hospital, Eulji University College of Medicine, Seoul, Korea; [14]Department of Internal Medicine, College of Medicine, Chung-Ang University, Seoul, Korea; [15]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea; [16]Division of Cardiology, Kwangju Christian Hospital, Gwangju, Korea; [17]Division of Cardiology, Department of Internal Medicine, Saint Carollo Hospital, Suncheon, Korea; [18]Division of Cardiology, Department of Internal Medicine, Konkuk University Chungju Hospital, Konkuk University College of Medicine, Chungju, Korea; [19]Department of Cardiology, Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea

Address for correspondence: Dong-Bin Kim, MD, Division of Cardiology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, tel: 82-32-340-7019, fax: 82-32-340-7227, e-mail: dbkimmd@catholic.ac.kr; Young Bin Song, MD, Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, tel: 82-02-3410-3419, fax: 82-02-3410-3849, e-mail: youngbin.song@gmail.com

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Abstract

Background: *It remains unclear whether $P2Y_{12}$ monotherapy, especially clopidogrel, following short-duration dual antiplatelet therapy (DAPT) is associated with favorable outcomes in patients undergoing complex percutaneous coronary intervention (PCI). Therefore, this study analyzed the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel (78%), in complex PCI following short-term DAPT.*

Methods: *The post-hoc analysis of the SMART-CHOICE trial involving 2,993 patients included 498 cases of complex PCIs, defined by at least one of the following features: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with ≥ 2 stents implanted, and a total stent length of ≥ 60 mm. The primary endpoint was major adverse cardiac and cerebrovascular event (MACCE), defined as the composite of all-cause death, myocardial infarction, and stroke. The primary safety endpoint included bleeding, defined as Bleeding Academic Research Consortium (BARC) types 2 to 5.*

Results: *Complex PCI group had a higher risk of MACCE (4.0% vs. 2.3%, hazard ratio [HR] = 1.74, 95% confidence interval [CI]: 1.05–2.89, p = 0.033) and a similar risk of BARC types 2–5 bleeding (2.6% vs. 2.6%, HR = 1.02, 95% CI: 0.56–1.86, p = 0.939) compared with those without complex PCIs. Patients undergoing complex PCIs, followed by $P2Y_{12}$ inhibitor monotherapy and 12 months of DAPT exhibited similar rates of MACCE (3.8% vs. 4.2%, HR = 0.92, 95% CI: 0.38–2.21, p = 0.853).*

Conclusions: *$P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, following 3 months of DAPT did not increase ischemic events in patients with complex PCIs.* (Cardiol J 2021; 28, 6: 855–863)

Key words: clopidogrel, high-risk, percutaneous coronary intervention

This article is accompanied by the editorial on page 804

Introduction

With the development of new-generation drug-eluting stents (DES), several studies including GLOBAL-LEADERS, TWILIGHT, TICO, and the SMART-CHOICE trial have reported the safety and effectiveness of $P2Y_{12}$ monotherapy following short-term dual antiplatelet therapy (DAPT) [1–4]. However, short-term DAPT therapy in complex percutaneous coronary intervention (PCI) remains a concern. The concept of complex PCI has been recently proposed [5]. However, there is currently no universal definition of a complex PCI. In general, complex PCI includes bifurcation with 2 stent implants, ≥ 3 stents implanted, ≥ 3 lesions treated, and total stent length ≥ 60 mm or stent with chronic total occlusion lesions [6]. Patients with complex PCIs carry a higher risk of ischemic adverse events that is proportional to their burden and severity of coronary artery disease [7], and require longer DAPT to prevent ischemic events [8]. Although prolonged DAPT is associated with a potential benefit in preventing ischemic events, it also increases bleeding risk, which is correlated with the morbidity and mortality of patients [9]. Sub-group analyses of complex PCI focusing on monotherapy with ticagrelor, but not clopidogrel which is used more in real-world practice showing favorable ischemic outcomes [6, 10].

The aim of this present sub-study of the SMART-CHOICE trial was to investigate the effectiveness and safety of $P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel (78%), following short-term DAPT in patients with complex PCI compared with 12 months of DAPT.

Methods

Study design

This study involved a post-hoc analysis of the SMART-CHOICE trial, a multicenter, prospective open-label randomized clinical trial (NCT02079194). The study design and protocol have been reported in detail elsewhere [2]. In brief, the trial randomly assigned patients to two groups before PCI: (i) 3 months of DAPT (acetylsalicylic acid [ASA] and a $P2Y_{12}$ inhibitor), followed by 9 months of $P2Y_{12}$ inhibitor monotherapy, and (ii) 12 months of DAPT. The trial was designed and coordinated by the Academic Clinical Research Organization of Samsung Medical Center (Seoul, Korea). The trial randomized a total of 2,993 patients at 33 hospitals. This trial was approved by the Institutional Review Board of each center. The study followed the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the trial. Patients and the public were not involved in the design of conduct in this research.

Study proceedings

In the present analysis, complex PCI was defined by at least one of the following angiographic characteristics: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and a total stent length of ≥ 60 mm. These five high-risk features of complex percutaneous procedures for ischemic events have been reported in previous studies [10].

Study endpoints

The primary efficacy endpoint included major adverse cardiac and cerebrovascular event (MACCE) defined as a composite of all-cause death, myocardial infarction (MI), and stroke at 1 year after the index procedure. The primary safety endpoint was bleeding defined as Bleeding Academic Research Consortium (BARC) types 2 to 5 at 12 months after the index procedure.

Definitions

Unless a definite noncardiac cause could be established, cardiac disease was assumed as the default cause of death. Myocardial infarction was defined as elevated cardiac enzyme levels (cardiac troponin or myocardial band fraction of creatine kinase) above the upper reference limits with ischemic symptoms or electrocardiographic findings indicative of ischemia. However, periprocedural enzyme elevations within 48 hours after the index procedure without concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia were excluded from the endpoint assessment. Stroke was defined as any nonconvulsive focal or global neurologic deficit of abrupt onset lasting more than 24 hours or leading to death caused by cerebral ischemia or hemorrhage. Stent thrombosis was defined as definite or probable type according to the Academic Research Consortium classification [11]. Major bleeding was defined as BARC types 3, 4, and 5 [12].

Statistical analysis

Categoric variables are presented as numbers and percentages and were compared using the χ^2 test or the Fisher exact test. Continuous variables are presented as the mean ± standard deviation and compared using the Student t-test. The cumulative incidence of clinical events up to 1 year was calculated using the Kaplan-Meier method and compared using the log-rank test. The hazard ratio (HR), with a 95% confidence interval (CI) was derived from a Cox regression model. Subgroup analyses of the outcomes were performed to evaluate the effects of P2Y$_{12}$ inhibitor monotherapy compared with DAPT using Cox regression models with tests for interaction. All tests were two-sided and a p-value of < 0.05 was considered statistically significant. All analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

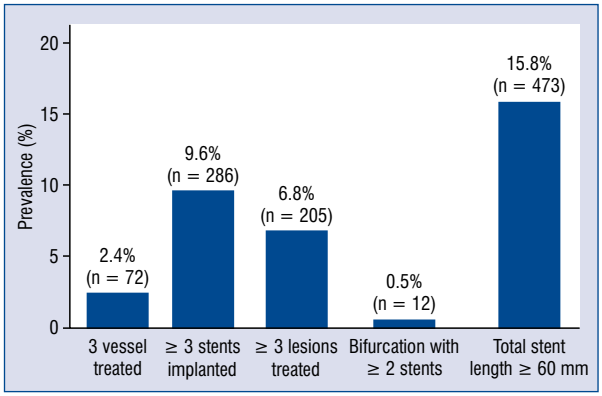

Figure 1. Prevalence of complex percutaneous coronary intervention components.

Results

The SMART-CHOICE trial randomized a total of 2,993 patients including 498 treated with complex PCIs and 2,495 undergoing non-complex PCIs. The prevalence of complex PCI components in the overall population is shown in Figure 1. The baseline clinical and procedural characteristics according to PCI complexity are summarized in Table 1. Of the patients, 76.3% (380/498) who underwent complex PCIs and 83.8% (1961/2495) of those who underwent non-complex PCIs were exposed to clopidogrel-based therapy. Patients undergoing complex PCIs manifested higher rates of hypertension, diabetes mellitus, and chronic renal failure, but lower rate of prior revascularization, and low ejection fraction. Angiographically, the complex PCI group had more diseased, treated lesions, and total stents implanted, with increased usage of intravascular ultrasound.

At 1 year, the patients who underwent complex PCIs carried higher rates of MACCE (4.0% vs. 2.3%, HR = 1.74, 95% CI: 1.05–2.89, p = 0.033), all-cause death (2.6% vs. 1.0%, HR = 2.52, 95% CI: 1.30–4.90, p = 0.007), cardiac death (1.6% vs. 0.6%, HR = 2.51, 95% CI: 1.08–5.88, p = 0.033), and stent thrombosis (0.6% vs. 0.1%, HR = 7.53, 95% CI: 1.26–45.06, p = 0.027). However, BARC bleeding types 2–5 showed similar rates (2.6% vs. 2.6%, HR = 1.02, 95% CI: 0.56–1.86, p = 0.939) in the complex and non-complex PCI groups (Table 2, Fig. 2).

Table 1. Baseline and procedural characteristics in patients according to percutaneous coronary intervention (PCI) complexity

	Complex PCI (n = 498)	Non-complex PCI (n = 2495)	P value
Age [years]	64.4 ± 10.7	64.5 ± 10.7	0.755
Male	376 (75.5%)	1822 (73.0%)	0.220
Body mass index	24.7 ± 3.1	24.6 ± 3.1	0.340
Hypertension	340 (68.3%)	1500 (60.1%)	0.001
Diabetes mellitus	218 (43.8%)	904 (36.3%)	0.002
Dyslipidemia	222 (44.6%)	1130 (45.5%)	0.767
Current smoking	127 (25.5%)	664 (26.7%)	0.630
Prior myocardial infarction	18 (3.6%)	109 (4.4%)	0.520
Prior revascularization	44 (8.8%)	305 (12.2%)	0.037
Prior stroke	41 (8.2%)	160 (6.4%)	0.168
Chronic renal failure	28 (5.6%)	69 (2.8%)	0.002
LVEF [%]	58.1 ± 11.9	60.3 ± 10.5	< 0.001
Acute coronary syndrome	288 (57.8%)	1453 (58.3%)	0.891
Shorter DAPT	260 (52.2%)	1235 (49.5%)	0.350
Clopidogrel based therapy	380 (76.3%)	1961 (83.8%)	0.258
Procedural characteristics			
No. of diseased lesion/patient	2.39 ± 0.85	1.23 ± 0.47	< 0.001
No. of lesions stented/patient	2.37 ± 0.78	1.18 ± 0.38	< 0.001
No. of stents implanted/patient	2.75 ± 0.78	1.22 ± 0.43	< 0.001
Target vessels:			
Left main	9 (1.8%)	49 (2.0%)	0.957
Left anterior descending	382 (76.7%)	1471 (59.0%)	< 0.001
Left circumflex	235 (47.2%)	540 (21.6%)	< 0.001
Right coronary	313 (62.9%)	735 (29.5%)	< 0.001
Trans radial approach	367 (73.7%)	1815 (72.7%)	0.704
Use of IVUS	156 (31.5%)	622 (25.0%)	0.004

DAPT — dual antiplatelet therapy; IVUS — intravascular ultrasound; LVEF — left ventricular ejection fraction

Table 2. Clinical outcomes in patients according to percutaneous coronary intervention (PCI) complexity.

	Complex PCI (n = 498)	Non-complex PCI (n = 2495)	Univariate hazard ratio	P value
MACCE	20 (4.0%)	58 (2.3%)	1.74 (1.05–2.89)	0.033
Bleeding BARC type 2–5	13 (2.6%)	64 (2.6%)	1.02 (0.56–1.86)	0.939
All death:	13 (2.6%)	26 (1.0%)	2.52 (1.30–4.90)	0.007
Cardiac death	8 (1.6%)	16 (0.6%)	2.51 (1.08–5.88)	0.033
Non-cardiac death	5 (1.0%)	10 (0.4%)	2.52 (0.86–7.38)	0.091
Myocardial infarction	6 (1.2%)	22 (0.9%)	1.38 (0.56–3.40)	0.487
Stroke	3 (0.6%)	13 (0.5%)	1.16 (0.33–4.07)	0.816
Stent thrombosis	3 (0.6%)	2 (0.1%)	7.53 (1.26–45.06)	0.027
Major bleeding*	2 (0.4%)	24 (1.0%)	0.42 (0.10–1.77)	0.236

*BARC type 3 to 5 bleeding; BARC — Bleeding Academic Research Consortium; MACCE — major adverse cardiac and cerebrovascular event

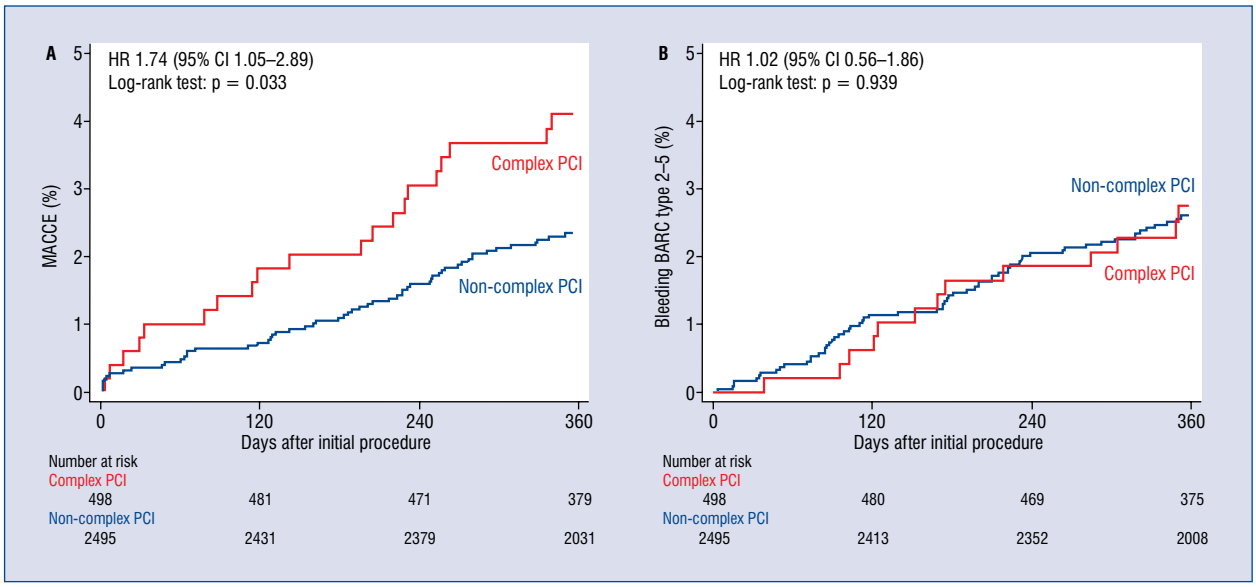

Figure 2. Cumulative incidence of events at 1 year on crude analysis according to complex and non-complex percutaneous coronary interventions (PCI); **A.** Major adverse cardiovascular and cerebrovascular events (MACCE); **B.** Bleeding Academic Research Consortium (BARC) types 2–5; CI — confidence interval; HR — hazard ratio.

Baseline characteristics according to the antiplatelet regimen used in patients with complex and non-complex PCIs are presented in Table 3. No significant differences were found in any variables. The effects of DAPT and P2Y$_{12}$ inhibitor monotherapy in the complex and non-complex PCI groups are presented in Table 4 and Figure 3. In non-complex PCI, P2Y$_{12}$ monotherapy showed similar MACCE rates (2.6% vs. 2.1%; HR = 1.27; 95% CI: 0.76–2.14; p = 0.359) and significantly lower BARC 2–5 bleeding rates (1.9% vs. 3.3%; HR = 0.57; 95% CI: 0.34–0.96; p = 0.033) compared with the DAPT group. Similar MACCE rates were found among patients exposed to P2Y$_{12}$ inhibitor monotherapy and DAPT (3.8% vs. 4.2%; HR = 0.92; 95% CI: 0.38–2.21; p = 0.853). P2Y$_{12}$ monotherapy was associated with lower BARC 2–5 bleeding rates compared with the DAPT group without statistical significance (1.9% vs. 3.4%; HR = 0.58; 95% CI: 0.19–1.77; p = 0.340). The interaction was not statistically significant between complex and non-complex PCI groups with MACCE (interaction p = 0.483) and BARC bleeding types 2–5 (interaction p = 0.904).

Discussion

The current study compared the clinical outcomes of patients treated with P2Y$_{12}$ inhibitor monotherapy, mostly clopidogrel, following 3 months of DAPT and 12 months of standard DAPT according to the PCI complexity. The findings of this study were as follows. First, patients undergoing complex PCIs carried a higher risk of ischemic and similar risk of bleeding events than those with non-complex PCIs. Second, patients with complex PCIs treated with P2Y$_{12}$ inhibitor monotherapy, mostly clopidogrel, following short-term DAPT showed favorable ischemic outcomes comparable to those 12 months of DAPT.

Regarding new-generation DESs, compared with standard DAPT, patients treated with PCI undergoing P2Y$_{12}$ inhibitor monotherapy following short-term DAPT showed non-inferior ischemic outcomes [2]. P2Y$_{12}$ inhibitor monotherapy reduced the risk of bleeding compared with DAPT [13]. These results suggest that P2Y$_{12}$ inhibitor monotherapy after short-term DAPT might be comparable to long-term DAPT for preventing ischemic events, with a lower risk of bleeding in patients undergoing PCIs with new-generation DESs. However, the risk-benefit profile of antiplatelet therapy regimens and their duration in patients with complex PCI remains disputed.

The concept of complex PCI has recently been proposed along with improvement in PCI techniques, adjunct pharmacological therapy, and the development of new-generation DES. However, currently, there is no universal definition of complex PCI in terms of angiographic or lesion characteristics. In the present study, the definition proposed by Serruys et al. [10], was used.

Table 3. Baseline and procedural characteristics stratified according to percutaneous coronary intervention (PCI) complexity and randomized regimen.

	Complex PCI (n = 498)			Non-complex PCI (n = 2495)		
	$P2Y_{12}$ monotherapy (n = 260)	DAPT (n = 238)	P	$P2Y_{12}$ monotherapy (n = 1235)	DAPT (n = 1260)	P
Age [years]	64.7 ± 10.5	64.0 ± 10.9	0.458	64.6 ± 10.8	64.4 ± 10.6	0.695
Male	191 (73.5%)	185 (77.7%)	0.316	896 (72.6%)	926 (73.5%)	0.628
Body mass index	24.6 ± 3.3	24.8 ± 2.9	0.680	24.5 ± 3.1	24.7 ± 3.2	0.101
Hypertension	177 (68.1%)	163 (68.5%)	0.978	744 (60.3%)	756 (60.0%)	0.914
Diabetes mellitus	119 (45.8%)	99 (41.6%)	0.397	451 (36.6%)	453 (36.0%)	0.766
Dyslipidemia	115 (44.2%)	107 (45.0%)	0.942	558 (45.3%)	572 (45.7%)	0.904
Current smoking	67 (25.8%)	60 (25.2%)	0.968	357 (29.0%)	307 (24.4%)	0.072
Prior myocardial infarction	9 (3.5%)	9 (3.8%)	0.987	53 (4.3%)	56 (4.4%)	0.929
Prior revascularization	19 (7.3%)	25 (10.5%)	0.272	153 (12.4%)	152 (12.1%)	0.840
Prior stroke	22 (8.5%)	19 (8.0%)	0.975	77 (6.2%)	83 (6.6%)	0.789
Chronic renal failure	16 (6.2%)	12 (5.0%)	0.731	28 (2.3%)	41 (3.3%)	0.168
LVEF [%]	58.3 ± 10.9	57.9 ± 11.6	0.657	60.2 ± 10.1	60.2 ± 9.8	0.950
Acute coronary syndrome	142 (54.6%)	146 (61.3%)	0.153	728 (58.9%)	725 (57.6%)	0.163
Clopidogrel based therapy	198 (76.2%)	182 (76.5%)	0.934	967 (78.3%)	994 (78.9%)	0.720
Procedural characteristics						
No. of diseased lesion/patient	2.39 ± 0.95	2.39 ± 0.79	0.336	1.23 ± 0.40	1.23 ± 0.51	0.307
No. of lesions stented/patient	2.37 ± 0.58	2.37 ± 0.91	0.144	1.18 ± 0.41	1.18 ± 0.36	0.381
No. of stents implanted/patient	2.75 ± 0.82	2.75 ± 0.71	0.347	1.22 ± 0.41	1.22 ± 0.45	0.662
Target vessels:						
Left main	5 (1.9%)	4 (1.7%)	0.419	20 (1.6%)	29 (2.3%)	0.279
Left anterior descending	193 (74.2%)	189 (79.4%)	0.208	710 (57.5%)	761 (60.4%)	0.151
Left circumflex	123 (47.3%)	112 (47.1%)	0.853	276 (22.3%)	264 (21.0%)	0.425
Right coronary	156 (60.0%)	157 (66.0%)	0.199	368 (29.8%)	367 (29.1%)	0.746
Trans radial approach	191 (73.5%)	176 (73.9%)	0.983	900 (72.9%)	915 (72.6%)	0.922
Use of IVUS	82 (31.7%)	74 (31.2%)	0.954	290 (23.6%)	332 (26.4%)	0.110

DAPT — dual antiplatelet therapy; IVUS — intravascular ultrasound; LVEF — left ventricular ejection fraction

The study pooled patient-level data from 6 randomized controlled trials and compared long--term (≥ 12 months) and short-term (3 or 6 months) DAPT following ASA monotherapy in patients undergoing complex PCIs. The results showed that long-term DAPT significantly reduced MACCEs compared with short-term DAPT in the complex PCI group. That study also found that the benefit of long-term DAPT was increased additively with each increase in procedural complexity. However, the ischemic benefit of extended DAPT was offset by an increased risk of bleeding [14].

$P2Y_{12}$ inhibitor monotherapy has been suggested as a new alternative antiplatelet strategy to ASA because it reduced the cardiovascular events and gastrointestinal bleeding [15]. Recently, 4 large randomized clinical trials showed favorable results with $P2Y_{12}$ inhibitor monotherapy after short-term DAPT. Among them, sub-analyses of the Global Leaders and TWILIGHT trials showed efficacy and safety of ticagrelor monotherapy in complex PCI. A post-hoc study of the Global Leaders trial revealed that 23 months of ticagrelor monotherapy following 1 month of DAPT provided a net clinical benefit for patients with complex PCIs [10]. The post-hoc study of the TWILIGHT trial showed that ticagrelor monotherapy was associated with a lower incidence of bleeding without an increased risk of ischemic events compared with continuing ticagrelor plus ASA for 12 months among patients undergoing complex PCIs [6]. In contrast to the previous 2 sub-studies, the present study used

Table 4. Comparison of clinical outcomes in patients stratified according to percutaneous coronary intervention (PCI) complexity and randomized regimen.

	Percent (number)		Hazard ratio	P value	Interaction p
	$P2Y_{12}$ monotherapy	DAPT			
MACCE:					
Complex	3.8% (10/260)	4.2% (10/238)	0.92 (0.38–2.21)	0.853	0.483
Non-complex	2.6% (32/1235)	2.1% (26/1260)	1.27 (0.76–2.14)	0.359	
Bleeding BARC type 2–5:					
Complex	1.9% (5/260)	3.4% (8/238)	0.58 (0.19–1.77)	0.340	0.904
Non-complex	1.9% (23/1235)	3.3% (41/1260)	0.57 (0.34–0.96)	0.033	
All death:					
Complex	3.1% (8/260)	2.1% (5/238)	1.48 (0.48–4.51)	0.494	0.646
Non-complex	1.1% (13/1235)	1.0% (13/1260)	1.03 (0.48–2.22)	0.942	
Cardiac death:					
Complex	1.9% (5/260)	1.3% (3/238)	1.54 (0.37–6.42)	0.557	0.671
Non-complex	0.5% (6/1235)	0.8% (10/1260)	0.62 (0.23–1.70)	0.351	
Non-cardiac death:					
Complex	1.2% (3/260)	0.8% (2/238)	1.39 (0.23–8.31)	0.719	0.210
Non-complex	0.6% (7/1235)	0.2% (3/1260)	2.40 (0.62–9.27)	0.205	
Myocardial infarction:					
Complex	0.8% (2/260)	1.7% (4/238)	0.46 (0.09–2.53)	0.375	0.306
Non-complex	0.7% (9/1235)	1.0% (13/1260)	0.71 (0.31–1.67)	0.438	
Stroke:					
Complex	0% (0/260)	1.3% (3/238)	0.01 (0.01–153.1)	0.369	0.126
Non-complex	0.9% (11/1235)	0.2% (2/1260)	5.69 (1.26–25.67)	0.024	
Stent thrombosis:					
Complex	0.8% (2/260)	0.4% (1/238)	1.82 (0.17–20.11)	0.624	0.320
Non-complex	0.1% (1/1235)	0.1% (1/1260)	1.02 (0.06–16.36)	0.987	
Major bleeding:					
Complex	0% (0/260)	0.8% (2/238)	0.01 (0.01–125.1)	0.464	0.721
Non-complex	1.0% (12/1235)	1.0% (12/1260)	1.03 (0.46–2.30)	0.939	

BARC — Bleeding Academic Research Consortium; DAPT — dual antiplatelet therapy; MACCE — major adverse cardiac and cerebrovascular event

$P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, in more than three-quarters of the total study population following 3 months of DAPT. Although clopidogrel is most often used after PCI in real-world clinical practice, clopidogrel monotherapy may be inadequate in preventing ischemic events associated with complex PCIs due to less potency and wide individual variability of the drug response.

Although the current study involved only East Asians who carry a lower ischemic risk than Westerners, $P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, did not increase the ischemic risk compared with 12 months of DAPT. However, patients with $P2Y_{12}$ monotherapy carrying non-complex lesions showed significantly lower bleeding rates (1.9% vs. 3.3%; HR = 0.57, 95% CI: 0.34–0.96; p = 0.033) than patients with 12 months of DAPT, although the patients with complex PCIs did not show significantly lower bleeding rates (1.9% vs. 3.3%; HR = 0.58, 95% CI: 0.19–0.77; p = 0.340). The p-value for the interaction between the two treatment arms was close to one, which is thought to be a type II statistical error due to the small sample size, and $P2Y_{12}$ monotherapy also might have a favorable effect on bleeding events in complex PCIs.

An expert consensus suggested that the selection and duration of the antiplatelet agents should be individualized by balancing ischemic and bleeding risks. Accordingly, three scoring systems were developed, including the PRECISE-DAPT score to

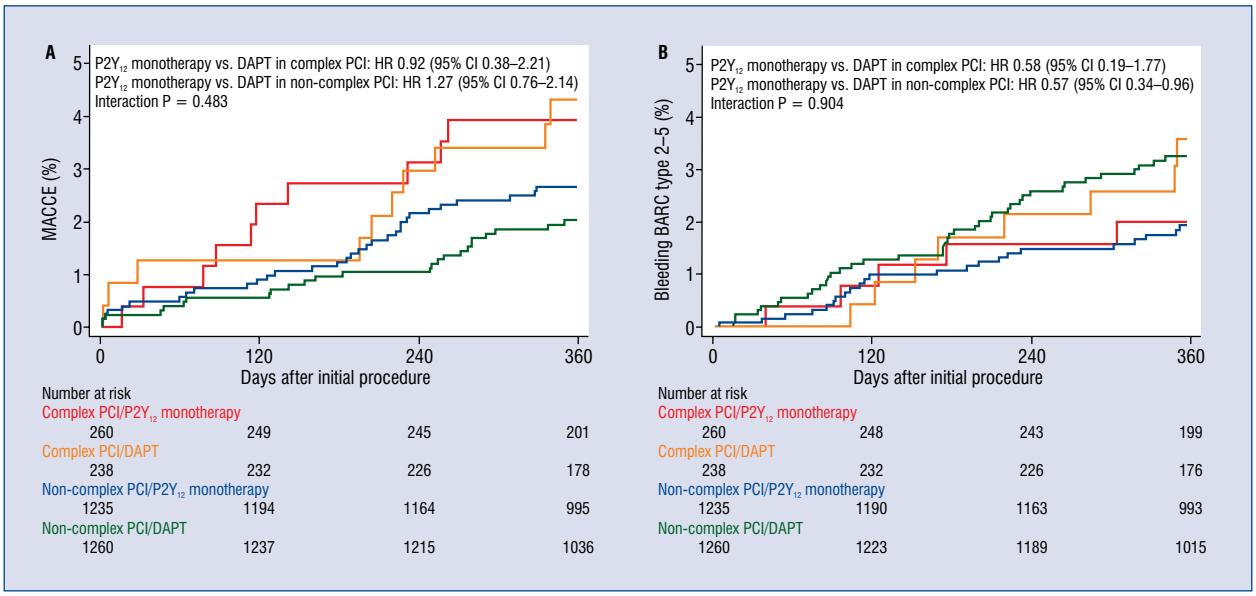

Figure 3. Cumulative incidence of events at 1 year after randomization according to randomization group (dual antiplatelet therapy [DAPT] vs. $P2Y_{12}$ monotherapy) in subjects with and without complex percutaneous coronary interventions (PCI); **A.** Major adverse cardiovascular and cerebrovascular events (MACCE); **B.** Bleeding Academic Research Consortium (BARC) types 2–5; CI — confidence interval; HR — hazard ratio.

facilitate the selection and duration of antiplatelet agents for patients with high bleeding risk (PRECISE-DAPT score ≥ 25) [16]. In a study of patients who underwent complex PCI and using PRECISE-DAPT score, the long-term DAPT was associated with net adverse clinical events (NACE) only if the bleeding risk was low (PRECISE-DAPT score < 25) and no ischemic benefit and significantly higher bleeding events in patients with high bleeding risk (PRECISE-DAPT score ≥ 25) [17]. In the present study of complex PCI stratified according to PRECISE-DAPT score, the high bleeding risk group was associated with higher rates of MACCE and NACE. In particular, the high bleeding risk group, unlike the low bleeding risk group, manifested fewer BARC type 2–5 bleeding events and a HR 0.35 in the $P2Y_{12}$ monotherapy group, without statistical significance due to the possibility of type 2 error associated with small sample size (**Suppl. Table 1**). Another significant feature in this study was that intravascular ultrasound was used more in the complex PCI group, which may have affected lower ischemic events in the $P2Y_{12}$ monotherapy group. Recently, the European Bifurcation Club proposed an algorithm for DAPT duration after PCI for bifurcation with a higher risk of both procedural and long-term adverse events. They proposed that decisions of DAPT duration should be based on the clinical presentation, bleeding risk, stenting strategy, and the possible use of intracoronary imaging. When confirming coronary imaging during PCI, the duration of DAPT should be reduced [18].

Limitations of the study

The present study has notable strengths associated with a well-randomized study design involving mainly clopidogrel but also had several limitations. First, the present study on complex PCI was not pre-specified in the protocol. Therefore, the current findings must only be interpreted as hypothesis-generating. Confirmatory randomized trials for complex PCI with proper antiplatelet therapy are still needed in the future. Second, the complexity of coronary anatomy and lesions were site-reported, not reviewed by an angiographic core laboratory. Thus, they might not have included all angiographic markers of lesion complexity or risk. Third, in bleeding events of complex PCI, $P2Y_{12}$ inhibitor monotherapy resulted in fewer bleeding events without statistical significance due to type II error associated with a small sample size. Unfortunately, the advantage of $P2Y_{12}$ monotherapy with fewer bleeding events in complex PCIs could not be established. Fourth, the study findings cannot be generalized to Western patients because all patients were East Asians who were relatively resistant to ischemic events but more susceptible to bleeding events.

Conclusions

In conclusion, compared with patients treated with non-complex PCIs, patients with complex PCIs carried a higher risk of ischemic events at 1 year. P2Y$_{12}$ inhibitor monotherapy, mostly with clopidogrel, following 3 months of DAPT resulted in favorable ischemic events comparable to the standard 12 months of DAPT regimen for complex PCIs. These findings need to be considered as hypothesis-generating. This study should be viewed as a dedicated prospective trial of proper antiplatelet regimen for complex PCI.

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