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Determinants and Clinical Outcomes of Extended Dual Antiplatelet Therapy over 3 Years after Drug-Eluting Stent Implantation: A Retrospective Analysis

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Purpose: Although current guidelines recommend the administration of dual antiplatelet therapy (DAPT) for up to 12 months after the implantation of a drug-eluting stent (DES), extended DAPT is frequently used in real-world practice.

Materials and Methods: From the Korean Multicenter Angioplasty Team registry, we identified a total of 1414 patients who used DAPT for >3 years after DES implantation (extended-DAPT group) and conducted a landmark analysis at 36 months after the index procedure. We evaluated the determinants for and long-term outcomes of extended DAPT and compared the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of all-cause death, myocardial infarction, stent thrombosis, and stroke, between the extended-DAPT group and the guideline-DAPT group [DAPT <1 year after DES implantation (n=1273)].

Results: Multivariate analysis indicated the occurrence of acute coronary syndrome as the most significant clinical determinant of the use of extended DAPT. Bifurcation, stent diameter ≤3.0 mm, total stented length ≥28 mm, and use of first-generation DESs were also significant angiographic and procedural determinants. MACCE rates were similar between the extended-DAPT group and the guideline-DAPT group in crude analysis [hazard ratio (HR), 1.08; 95% confidence interval (CI), 0.69–1.68; p=0.739] and after propensity matching (HR, 1.22; 95% CI, 0.72–2.07; p=0.453). Major bleeding rates were comparable between the two groups.

Conclusion: In patients undergoing percutaneous coronary intervention, indefinite use of DAPT does not show superior outcomes to those of guideline-DAPT. Major bleeding rates are also similar.

Key Words: Antiplatelet therapy, drug-eluting stent, percutaneous coronary intervention

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INTRODUCTION

The duration of dual antiplatelet therapy (DAPT) in the drug-eluting stent (DES) era remains controversial.[1] Current clinical practice guidelines recommend the use of DAPT for 6 to 12 months after DES implantation.[2] However, in real-world practice, the use of DAPT for more than 12 months, the use of extended DAPT for more than 3 years, and nearly indefinite use of DAPT are common for various reasons. A recent large randomized controlled trial indicated that the use of DAPT be-

yond 1 year after DES implantation significantly reduced the risk of stent thrombosis (ST) and major adverse events, but increased the risk of bleeding, which was associated with an increase in mortality.[3] Therefore, we sought to investigate the major clinical, angiographic, and procedural determinants for extended-DAPT use (DAPT >3 years), and to compare the long-term clinical outcomes between patients who used DAPT for more than 3 years and those who used DAPT for up to 12 months.

MATERIALS AND METHODS

Between April 2003 and March 2012, patients who underwent percutaneous coronary intervention (PCI) using DESs and met the study criteria were enrolled in the Korean Multicenter Angioplasty Team registry.[4] A total of a 4081 patients were identified for analysis after excluding patients with the following conditions: 1) major adverse events such as death, myocardial infarction (MI), ST, repeated revascularization, stroke, or major bleeding; 2) clinical follow-up duration of <3 years; and 3) unclear DAPT duration (Fig. 1). Patients were classified into three groups according to DAPT duration after DES implantation as follows: patients who used DAPT for more than 3 years (extended-DAPT group; n=1414); patients who used DAPT for 1–3 years (intermediate-DAPT; n=1394); and patients who discontinued DAPT and switched to single antiplatelet therapy within 12 months according to clinical guidelines (guideline-DAPT group; n=1273). To evaluate the major determinants for long-term outcomes of extended DAPT use, various baseline clinical, angiographic, and procedural characteristics and clinical outcomes of the extended-DAPT group were compared to those of the guideline-DAPT group. To compare the clinical outcomes, a landmark analysis was performed 3 years after the index procedure. In this study, DAPT was defined as the combination of aspirin and clopidogrel, and patients who received other P2Y12 inhibitors were not included. The Institutional Review Board or ethics committee approved the study protocol (4-2018-0759), and all patients provided written informed consent before participating in the study.

Data were recorded using standard case report forms, and procedural angiographies were forwarded to the coordinating center. Baseline clinical and angiographic data were collected for all patients, including age, sex, traditional coronary risk factors, past medical history, and clinical presentation.

Follow-up included visits to the outpatient clinic at 30 days and 3 months after the procedure and every 3 to 6 months thereafter. Patients who were lost to regular clinical follow-up were contacted by telephone and asked about their clinical status.

The primary endpoints were 1) major clinical, angiographic, and procedural determinants for extended-DAPT use (DAPT >3 years) and 2) the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of all-cause death, MI, ST, and stroke. The secondary endpoints were 1) net adverse clinical events (NACE), defined as the composite of all-cause death, MI, ST, stroke, and major bleeding; 2) the composite of cardiac death, MI, and ST; and 3) individual components of MACCE and NACE.

All events were defined according to the Academic Research Consortium and an expert consensus document that defined the third universal definition for MI.[5,6] Deaths were classified as being due to cardiac or noncardiac causes.[5] MI was defined as a creatine kinase myocardial band fraction elevation above the upper limit of normal (ULN) or troponin T/I >99th percentile of the ULN, with concomitant ischemic symptoms, electrocardiographic findings, or abnormal imaging findings indicative of myocardial ischemia unrelated to an interventional procedure.[5,6] ST was defined as definite or probable ST.[5] Stroke was defined as brain cell death caused by ischemia based on pathological, imaging, or other objective evidence of cerebral focal ischemic injury in a defined vascular distribution or clinical evidence of cerebral focal ischemic injury based on symptoms persisting ≥24 hours or until death; other etiologies were excluded.[7] Strokes were determined to be either hemorrhagic or ischemic using imaging studies. Major bleeding was defined as type 3 or 5 according to the Bleeding Academic Research Consortium criteria.[8] Congestive heart failure was defined as left ventricle ejection fraction <40%.[9] Bifurcation lesions were defined as Medina classification (1.1.1), (1.0.1), or (0.1.1) lesions.[10] The DAPT scoring system assigned 1 point each for MI at presentation, prior MI or PCI, diabetes, stent diameter <3 mm, cigarette smoking, and paclitaxel-eluting stent; 2 points each for the history of congestive heart failure/low ejection fraction (<30%) and vein graft intervention; -1 point for age 65–75 years; and -2 points for age ≥75 years.[11]

Continuous variables are expressed as a mean±standard deviation, and categorical data are presented as frequencies. For group comparisons, Pearson's chi-square test, Fisher's chi-exact test, or Wilcoxon rank-sum test were used, as appropriate. Time-to-event data are presented using Kaplan-Meier estimates. The rates for each event during the follow-up period were analyzed using Kaplan-Meier method. Log-rank test was used to compare survival rates. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated from a Cox proportional hazards model. To identify the determinants for the use of extended-DAPT, we performed univariate and multivariate analyses. Any variable with p value<0.10 in univariate analysis was included in the multivariate models. To reduce bias between the two groups in comparison, propensity score matching was used. Propensity score adjusting was used in the logistic regression models, with DAPT continuation at 36 months used as the dependent variable along with 27 independent variables. A two-sided p value<0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistical software (SPSS version 23.0 for Windows, IBM Corp., Armonk, NY, USA).

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RESULTS

Among the eligible patients (n=4081), 1414 (34.6%) were included in the extended-DAPT group and 1273 were included in the guideline-DAPT group (Fig. 1). The baseline clinical characteristics of both groups are presented in Table 1. Compared to the guideline-DAPT group, the extended-DAPT group had higher incidences of prior MI, PCI, and bypass surgery; and acute coronary syndrome (ACS); and a lower left ventricular ejection fraction.

Angiographic and procedural characteristics are provided in Table 2. Compared to the guideline-DAPT group, the extended-DAPT group had higher proportions of individuals with lesions with multi-vessel disease, in-stent restenosis, bifurcation, and number of lesions treated ≥2. The extended-DAPT group had a greater number of stents implanted, longer- and smaller-sized stents used, and a more frequent use of first-generation DESs compared to the guideline-DAPT group.

DAPT scores were higher in the extended-DAPT group than in the guideline-DAPT group (p<0.01), and the proportion of patients with DAPT scores greater than 2 points was higher in the extended-DAPT group (50.3% vs. 29.3%, p<0.01) (Supplementary Table 1, only online).

In multivariate analyses for the determinants of extended use of DAPT, ACS presentation was the most significant clinical

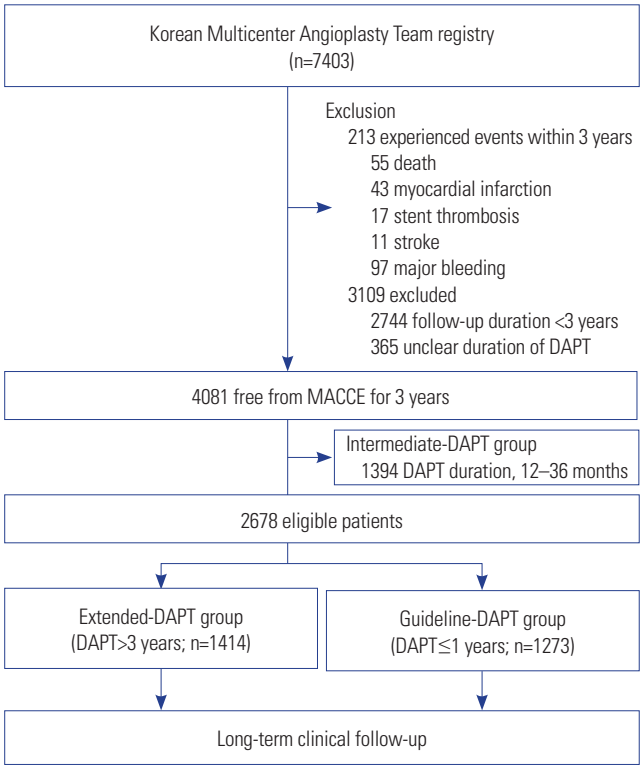

Fig. 1. Study at a glance. DAPT, dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebrovascular events.

Table 1. Clinical Characteristics

Characteristics	Extended-DAPT (n=1414)	Guideline-DAPT (n=1273)	*p* value
Age (yr)	62.8±9.8	62.7±9.9	0.809
Male	927 (66)	858 (67)	0.456
Body mass index (kg/m^2)	24.8±3.0	24.8±2.9	0.950
Current smoker	308 (22)	301 (24)	0.249
Dyslipidemia or statin use before procedure	1160 (82)	1057 (83)	0.498
Hypertension	879 (62)	808 (64)	0.484
Diabetes mellitus	447 (32)	387 (30)	0.498
Chronic kidney disease	39 (3)	23 (2)	0.101
Congestive heart failure	38 (3)	27 (2)	0.340
Left ventricular ejection fraction (%)	57.8±13.4	61.4±12.3	<0.001
Prior stroke	116 (8)	107 (8)	0.850
Prior myocardial infarction	157 (11)	71 (6)	<0.001
Previous percutaneous coronary intervention	265 (19)	136 (11)	<0.001
Prior bypass surgery	59 (4)	35 (3)	0.045
Clinical presentation			<0.001
Acute coronary syndrome	652 (46)	492 (39)	
Acute myocardial infarction	301 (21)	249 (20)	
Unstable angina	351 (25)	243 (19)	
Stable angina	762 (54)	781 (61)	
Medications at discharge			
β-blockers	849 (60)	741 (58)	0.330
Angiotensin-converting enzyme or angiotensin-receptor blockers	789 (56)	724 (57)	0.583
Statin	1376 (97)	1235 (97)	0.642

DAPT, dual antiplatelet therapy.
Data are presented as the mean±SD or percentage (%).

Table 2. Angiographic and Procedural Characteristics

Characteristics	Extended-DAPT (n=1414)	Guideline-DAPT (n=1273)	*p* value
Multi-vessel (2- or 3-vessel) disease	980 (69)	742 (58)	<0.001
Treated vessel			0.596
Left anterior descending	813 (58)	761 (60)	
Left circumflex	227 (16)	184 (15)	
Right coronary	365 (26)	320 (25)	
Graft	9 (1)	8 (1)	
Left main artery involvement	121 (9)	112 (9)	0.825
Chronic total occlusion	71 (6)	57 (5)	0.243
In-stent restenosis	69 (9)	30 (3)	<0.001
Bifurcation	385 (50)	366 (36)	<0.001
Calcification (moderate or severe)	131 (11)	127 (11)	0.853
Number of lesions treated ≥2	549 (39)	345 (27)	<0.001
Total number of stents implanted	1.6±0.7	1.5±0.6	<0.001
Total stent length	40.5±21.3	32.8±17.6	<0.001
Total stent length ≥28 mm	968 (69)	675 (53)	<0.001
Stent diameter	3.0±0.4	3.1±0.4	<0.001
Stent diameter ≤3.0 mm	1106 (78)	571 (45)	<0.001
Type of drug-eluting stents			<0.001
First-generation	1078 (76)	313 (25)	<0.001
Sirolimus-eluting	762	256	
Paclitaxel-eluting	316	57	
Second-generation	269 (19)	932 (73)	
Everolimus-eluting	5	288	
Zotarolimus-eluting	199	379	
Biolimus-eluting	15	265	
Mixed use of the first- and second-generation	67 (5)	28 (2)	
Glycoprotein II_b/III_A blocker use	21 (4)	20 (3)	0.391

DAPT, dual antiplatelet therapy.
Data are presented as the mean±SD or percentage (%).

determinant. Of the angiographic and procedural variables, bifurcation, total stent length ≥28 mm, stent diameter ≤3.0 mm, and use of first-generation DESs were significant determining factors for the extended use of DAPT (Table 3).

During follow-up (median duration, 120 months), there were 79 MACCEs (2.9%; 36 all-cause deaths, 29 MI, 6 ST, 22 strokes) after DES implantation, and no significant difference was noted between the extended-DAPT and guideline-DAPT groups in both the crude- and propensity-matched analyses (Table 4 and Fig. 2). The rates of MACCE and NACE were not significantly different between the two groups in either the crude- or propensity-matched analyses. The rates of composite all-cause death, MI, and ST were also not significantly different between the two groups in both the crude- and propensity-matched analyses. The rates of major bleeding were similar between the two groups (p=0.185). In propensity-matched analyses, the extended-DAPT group showed a trend toward having a higher major bleeding rate compared to the guideline-DAPT group, although the difference was not statistically significant (p=0.070)

We also performed subgroup analyses while focusing on the major determining factors for extended-DAPT (Fig. 3). In the subgroup analyses of composite of all-cause death, MI, and ST, a significant interaction was not noted. In multivariate analysis for the composite of all-cause death, MI, and ST, age (per year) and total stent length ≥28 mm were significant risk factors (Supplementary Table 2, only online).

DISCUSSION

The principal findings of the current study are as follows: 1) In real-world practice, extended DAPT is frequently used in patients without MACCE and with DES implantation (approximately 1/3 of patients). 2) Significant determinants for the extended use of DAPT for more than 3 years were ACS, bifurcation, small diameter and long length of DES, and use of first-generation DESs. 3) In patients undergoing PCI, the outcomes after extended-DAPT, defined as indefinite use of DAPT with aspirin and clopidogrel, did not show superiority over those after the guideline-DAPT, and major bleeding rates were similar. 4) In patients treated with first-generation DESs, extended use of DAPT was significantly associated with lower MACCE rates compared to the use of guideline-DAPT.

Antiplatelet treatment is a cornerstone in the management of patients with DES implantation for preventing ST.[2] However, even with the designated duration recommended in current guidelines, the optimal DAPT duration after DES implantation still remains debatable.[3,12,13] Both prolonged DAPT for longer than 1 year and short-term DAPT for 3–6 months have been proposed. A recent randomized DAPT trial demonstrated that the use of DAPT beyond 1 year after the placement of a DES significantly reduced the risks of ST (1.4% vs. 0.4%) and MACCE (5.9% vs. 4.3%) compared to using aspirin therapy alone. A previous meta-analysis also indicated that DAPT for 1 year after DES implantation reduced the occurrence of MI and ST, but increased mortality due to an increased risk of non-cardiovascular mortality.[14] In the current real-world registry study, 34.6% of patients who had not experienced MACCE for 3 years still received DAPT at 3 years. Similarly, the patterns of nonadherence to antiplatelet regimens in stented patients (PARIS) registry investigating DAPT patterns in post-PCI patients indicated that 42.0% of patients were still receiving DAPT at 2 years.[15] Thus, there appear to be some conflict between the guideline recommendations and the actual use in recent clinical trials. In addition, the incidence and determinants for the extended use of DAPT have not been clearly established in real-world practice.

Many scoring systems have been suggested for determining the duration of DAPT.[11,16,17] In particular, DAPT, PARIS, and the Predicting Bleeding Complications In Patients Undergoing

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Table 3. Univariate and Multivariate Analyses of Determinants for the Extended Use of DAPT

Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Clinical variables				
Age (yr)	1.00 (0.99–1.01)	0.809	1.00 (0.98–1.01)	0.462
Body mass index (kg/m^2)	1.01 (0.97–1.03)	0.950		
Male	1.06 (0.90–1.25)	0.456	1.26 (0.95–1.67)	0.114
Hypertension	0.95 (0.81–1.11)	0.484		
Diabetes mellitus	1.06 (0.90–1.25)	0.498		
Chronic kidney disease	1.54 (0.92–2.60)	0.103		
Current smoker	0.90 (0.75—1.08)	0.250		
Acute coronary syndrome presentation	1.38 (1.18–1.61)	<0.001	1.37 (1.06–1.79)	0.018
Prior percutaneous coronary intervention	1.93 (1.54–2.41)	<0.001	1.43 (0.92–2.21)	0.113
Prior bypass surgery	1.54 (1.01–2.36)	0.047	1.22 (0.59–2.53)	0.598
Prior myocardial infarction	2.12 (1.58–2.83)	<0.001	1.55 (0.96–2.49)	0.072
Prior heart failure	1.27 (0.77–2.10)	0.341		
Prior stroke	0.97 (0.74–1.28)	0.850		
Angiographic variables				
Treated lesion number ≥2	1.71 (1.45–2.01)	<0.001	0.91 (0.65–1.30)	0.613
Multivessel disease	1.62 (1.38–1.89)	<0.001	1.16 (0.85–1.58)	0.345
Left main involvement	0.97 (0.74–1.27)	0.825		
In-stent restenosis	3.38 (2.18–5.24)	<0.010	2.04 (0.99–4.20)	0.053
Bifurcation	1.78 (1.47–2.15)	<0.001	1.55 (1.19–2.02)	0.001
Chronic total occlusion	1.24 (0.87–1.77)	0.244		
Procedural variables				
Total stent length ≥28 mm	1.92 (1.64–2.25)	<0.001	1.54 (1.12–2.12)	0.007
Stent diameter ≤3.0 mm	4.42 (3.73–5.22)	<0.001	3.33 (2.51–4.43)	<0.001
First-generation drug-eluting stents	11.91 (9.93–14.29)	<0.001	11.43 (8.78–14.87)	<0.001

DAPT, dual antiplatelet therapy; OR, odds ratio; CI, confidence interval.
*Any variable with $p<0.10$ in univariate analysis was included in the multivariate models.

Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score have focused on clinical determinants for the optimal duration of DAPT. In the current study, the proportion of patients with a DAPT score of more than 2 points was significantly higher in the extended-DAPT group, and the initial clinical presentation of ACS was the most significant clinical factor that determined the duration of DAPT. Indeed, previous studies have reported that the use of extended DAPT in ACS patients reduces recurrent ischemic events, and that a significant proportion of patients experience adverse cardiac events beyond the first year after ACS.[18]

Lesion- or procedural-complexity could be considered when determining DAPT duration. However, these are not considered in the current scoring systems that are used to determine DAPT duration. In contrast, lesion- and procedural-complexity were identified as major determinants for the use of extended DAPT in this study. Stent-related predictors were also significant determining factors for DAPT duration. In the current study, the total stented length of ≥28 mm, minimal stent diameter of ≤3.0 mm, and the use of first-generation DES were major determining factors. Previous meta-analyses indicated that the most significant predictors of ST include longer stent length [odds ratio (OR), 1.3; 95% CI, 1.2–1.5, per 10 mm] and final minimal lumen diameter with stent (OR, 04; 95% CI, 0.2–0.7, per 1 mm).[19] Another study on the etiology of very-late ST also indicated that patients with very-late ST had longer lesions and stents.[20] Therefore, physicians tend to use extended DAPT. A significant angiographic predictor in this study was the occurrence of a bifurcation lesion. This may have been related to the increasing concerns caused by a higher risk of ST after the use of the two-stent technique or malapposed metal burden in the jailed side branch from the use of a cross-over single stent. A previous study reported that the risk of all-cause death or MI was significantly lower in the ≥12-month DAPT group than in the <12-month DAPT group after PCI for bifurcation lesions using DES.[21]

Table 4. Clinical Outcomes at 10 Years (Median Follow-Up Duration)

Crude analysis	Extended-DAPT (n=1414)	Guideline-DAPT (n=1273)	HR (95% CI)	*p* value
Follow-up duration (month)	111.11±18.8	103.0±18.0		
MACCE (all-cause death, MI, ST, and stroke)	44 (3.3)	35 (3.2)	1.08 (0.69–1.68)	0.739
NACE (all-cause death, MI, ST, stroke, and major bleeding)	60 (4.7)	43 (4.4)	1.10 (0.74–1.64)	0.629
Composite of all-cause death, MI, and ST	32 (2.4)	30 (2.8)	0.91 (0.55–1.49)	0.700
Death	22 (1.7)	14 (1.4)	1.31 (0.67–2.56)	0.434
Cardiovascular death	2 (0.1)	4 (0.4)	0.41 (0.07–2.24)	0.303
Non-cardiovascular death	20 (1.5)	10 (1.0)	1.67 (0.78–3.58)	0.186
MI	14 (1.1)	15 (1.3)	0.80 (0.39–1.66)	0.553
ST	3 (0.2)	3 (0.3)	0.84 (0.17–4.19)	0.832
Total stroke	13 (1.0)	9 (0.8)	1.25 (0.53–2.92)	0.611
Ischemic stroke	11 (0.8)	8 (0.7)	1.18 (0.47–2.94)	0.726
Hemorrhagic stoke	2 (0.1)	3 (0.3)	0.60 (0.10–3.56)	0.569
Major bleeding	19 (1.5)	9 (1.2)	1.71 (0.77–3.80)	0.185
Propensity score matching analysis	**Extended DAPT (n=677)**	**Guideline DAPT (n=1149)**	**HR (95% CI)**	***p* value**
Follow-up duration, months	108.4±21.7	102.8±18.4		
MACCE (all-cause death, MI, ST, and stroke)	24 (3.8)	33 (3.2)	1.22 (0.72–2.07)	0.453
NACE (all-cause death, MI, ST, stroke, and major bleeding)	36 (6.1)	39 (4.2)	1.43 (0.90–2.25)	0.128
Composite of all-cause death, MI, and ST	16 (2.5)	28 (2.8)	0.96 (0.52–1.78)	0.895
Death	12 (1.9)	13 (1.3)	1.51 (0.69–3.31)	0.306
Cardiovascular death	1 (0.2)	4 (0.5)	0.39 (0.04–3.52)	0.402
Non-cardiovascular death	11 (1.8)	9 (0.8)	2.02 (0.84–4.88)	0.119
MI	7 (1.1)	14 (1.4)	0.84 (0.34–2.09)	0.713
ST	2 (0.3)	3 (0.3)	1.07 (0.18–6.42)	0.944
Total stroke	8 (1.3)	8 (0.8)	1.64 (0.61–4.39)	0.324
Ischemic stroke	8 (1.3)	8 (0.8)	1.64 (0.61–4.39)	0.324
Hemorrhagic stoke	0	0	-	-
Major bleeding	12 (2.1)	8 (1.2)	2.29 (0.93–5.63)	0.070

DAPT, dual antiplatelet therapy; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; NACE, net adverse clinical events; MI, myocardial infarction; ST, stent thrombosis.
Data are presented as the mean±SD or number (%) and percentages, along with Kaplan-Meier estimates.

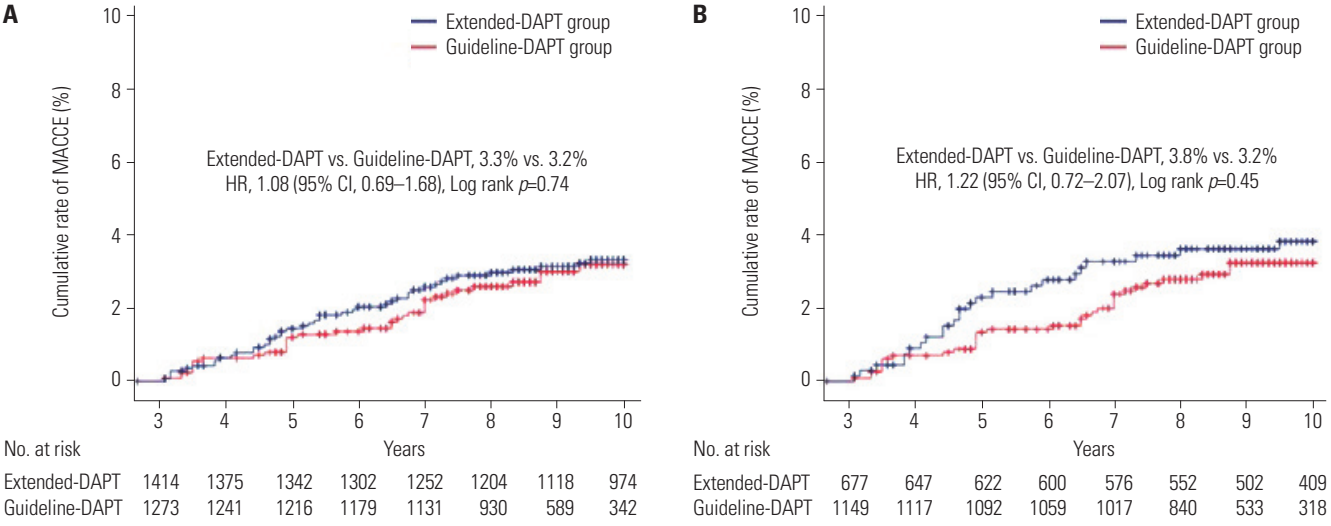

Fig. 2. Cumulative MACCE rates according to Kaplan-Meier analyses. (A) Crude-analysis. (B) Propensity score matching analysis. DAPT, dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebrovascular events.

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	Extended-DAPT		Guideline-DAPT		HR (95% CI)	*p* value for interaction
	No. of events	No. of patients	No. of events	No. of patients		
All patients	16	677	28	1149	0.96 (0.52–1.78)	
Bifurcation						
Yes	4	209	8	340	0.80 (0.24–2.68)	0.77
No	12	468	20	809	1.02 (0.50–2.09)	
Acute coronary syndrome						
Yes	9	304	14	446	0.94 (0.41–2.17)	0.98
No	7	373	14	703	0.93 (0.37–2.30)	
Stent diameter (mm)						
≤3.0	9	404	15	569	0.85 (0.37–1.94)	0.72
>3.0	7	273	13	580	1.09 (0.44–2.75)	
Total stentlength (mm)						
≥28	12	398	21	633	0.91 (0.45–1.85)	0.89
<28	4	279	7	516	1.07 (0.31–3.65)	
Stent generation						
First	11	408	11	334	0.82 (0.36–1.90)	0.91
Second	5	269	17	815	0.88 (0.32–2.38)	
Sex						
Male	12	459	23	779	0.68 (0.43–1.73)	0.55
Female	4	218	5	370	1.42 (0.38–5.30)	
Hypertension						
Yes	11	426	22	736	0.85 (0.41–1.76)	0.52
No	5	251	6	413	1.37 (0.42–4.50)	
Diabetes mellitus						
Yes	6	212	14	351	0.70 (0.27–1.83)	0.41
No	10	465	14	798	1.22 (0.54–2.74)	
Multi-vessel disease						
Yes	3	22	1	23	1.06 (0.51–2.21)	0.59
No	13	655	27	1126	0.73 (0.23–2.33)	

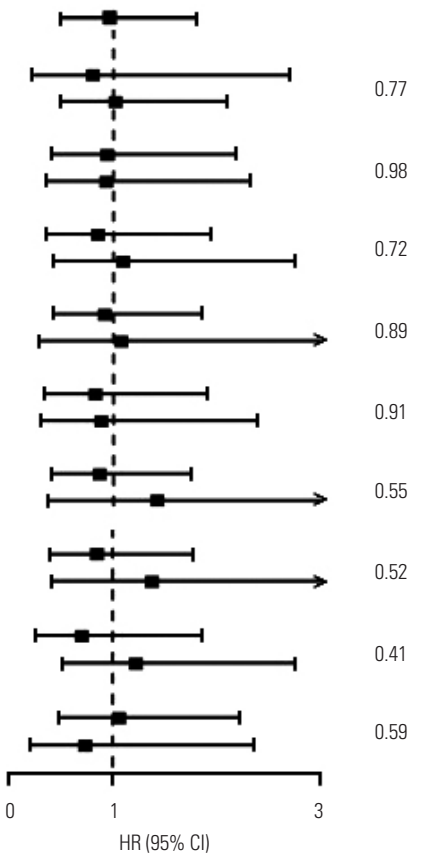

Fig. 3. Subgroup analyses. HRs for NACE from Cox regression models investigating extended-DAPT versus guideline-DAPT are shown for patient subgroups. DAPT, dual antiplatelet therapy; HR, hazard ratio; CI, confidence interval; NACE, net adverse clinical events.

The type of DES was also a significant determining factor for the extended use of DAPT. Some registry data have indicated a continually increasing risk of ST several years after first-generation DES implantation.[22] Currently available registry data suggest a lower rate of ST in patients who received second-generation DESs compared to those who received first-generation DESs.[23] In the patients who received first-generation DESs in this study, there was a lower rate of MACCE in the extended-DAPT group compared to the guideline-DAPT group. A previous study (ARTIC-Generation; Clinical Outcome of First- vs. Second-Generation DES According to DAPT Duration) also indicated worse clinical outcomes with first-generation DESs compared to second-generation DESs, a difference that appeared to persist even with prolonged DAPT (6.2% vs. 2.6%; HR, 2.31; 95% CI, 1.31–4.07; p=0.004).[24] In the current study, extended DAPT use led to a significant reduction in MACCE in patients who were treated with first-generation DESs. Based on the results of this study and other studies, extended DAPT could be carefully considered for patients treated with first-generation DESs.

There are several concerns regarding extended DAPT, such as increased major bleeding [ARCTIC-Interruption (Dual-Antiplatelet Treatment beyond 1 Year after Drug-Eluting Stent Implantation): 12-month vs. 18–30 month DAPT, <0.5% vs. 1%, p=0.073; DAPT: 12-month vs. 30-month DAPT, 1.6% vs. 2.5%, p=0.001; PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study): 24-month vs. 6-month DAPT, 7.4% vs. 3.5%, p=0.0002].[3,13,25]

However, in the current study, extended DAPT did not significantly increase the risk of major bleeding after propensity matching (2.1% vs. 1.2%, p=0.07). Therefore, extended DAPT could be used in patients at high thrombotic risk without excessively increasing the risk of major bleeding. In clinical practice, the duration of DAPT may be tailored after careful evaluation of both bleeding and ischemic risk, while taking into consideration the clinical presentation, lesion complexity, and procedural factors.

The strength of this study lies in its use of population-based, real-world registries. However, this study had several limitations. First, this was a retrospective analysis of registry data. Second, since the current study included only patients who did not experience a major event during 3 years after PCI and were compliant with the designated therapy, the study results were only relevant to patients who achieved that milestone. In

interpreting the results of the current study, the group of subjects should not be expanded, and the results should be interpreted with caution. Third, neither medication adherence nor tolerability was evaluated. Fourth, as the patients enrolled in this study were event-free for 3 years, there was a possibility that the patients at low risk of bleeding or cardiovascular events were enrolled. Fifth, patients who had used DAPT for >3 years were classified into the extended-DAPT group, but this classification was arbitrary. Careful attention would be needed for interpretation of the current results. Notwithstanding, 86.4% of the patients in the extended-DAPT group actually used DAPT for more than 5 years. Sixth, the classification of the guideline, intermediate, and extended-DAPT groups may be an arbitrary classification. The guideline-DAPT group was developed for comparison with the extended-DAPT group, and was classified according to the duration of DAPT use. Seventh, we could not achieve perfect matching or control of all of the confounding variables, even though we conducted propensity score matching analysis to reduce bias. However, we were able to exclude all of the extremes in each group. Finally, this study only included thienopyridine P2Y12 inhibitors. Therefore, additional studies comparing the extended DAPT using new antiplatelet agents, such as ticagrelor and prasugrel, with standard DAPT should be performed to further guide clinical practice.

In conclusion, the significant predictors for the use of extended DAPT for more than 3 years were ACS, bifurcation, small stent diameter, long length of DES, and first-generation DES in the real world. In patients undergoing PCI, indefinite use of DAPT did not show superiority in reducing the clinical events compared to the guideline-DAPT. Moreover, major bleeding rates were similar. Notably, however, in patients who were treated with first-generation DESs, extended-DAPT was associated with significantly lower MACCE rates compared to guideline-DAPT.

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