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Original article

Dual antiplatelet therapy after percutaneous coronary intervention for left main coronary artery disease

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ABSTRACT

Introduction and objectives: There are scarce data on the optimal duration and prognostic impact of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with second-generation drug-eluting stents for left main coronary artery (LMCA) disease. The aim of this study was to investigate the practice pattern and long-term prognostic effect of DAPT duration in patients undergoing PCI with second-generation drug-eluting stents for LMCA disease.
Methods: Using individual patient-level data from the IRIS-MAIN and KOMATE registries, 1827 patients undergoing PCI with second-generation drug-eluting stents for LMCA disease with valid information on DAPT duration were included. The efficacy outcome was major adverse cardiovascular events (MACE, a composite of cardiac death, myocardial infarction, and stent thrombosis) and the safety outcome was TIMI major bleeding.
Results: DAPT duration was $<$ 6 months (n = 273), 6 to 12 months (n = 477), 12 to 24 months (n = 637), and $\geq$ 24 months (n = 440). The median follow-up duration was 3.9 [interquartile range, 3.01-5.00] years. Prolonged DAPT duration was associated with lower incidences of MACE. In multigroup propensity score analysis, adjusted HR for MACE were significantly higher for DAPT $<$ 6 months and DAPT 6 to 12 months than for DAPT 12 to 24 months (HR, 4.51; 95%CI, 2.96-6.88 and HR 1.92; 95%CI, 1.23-3.00). There was no difference in HR for major bleeding among the assessed groups.
Conclusions: DAPT duration following PCI for LMCA disease is highly variable. Although the duration of DAPT should be considered in the context of the clinical situation of each patient, $<$ 12 months of DAPT was associated with higher incidence of MACE. Registration identifiers: NCT01341327; NCT03908463.

Tratamiento antiagregante plaquetario doble tras la intervención coronaria percutánea del tronco coronario izquierdo

Palabras clave:
Tratamiento antiagregante plaquetario doble
Enfermedad del tronco coronario izquierdo
Stents farmacoactivos

RESUMEN

Introducción y objetivos: Son escasos los datos sobre la duración y el impacto pronóstico del tratamiento antiagregante plaquetario doble (TAPD) tras una intervención coronaria percutánea (ICP) del tronco coronario izquierdo (TCI) con *stents* farmacoactivos de segunda generación. El objetivo de este estudio es investigar los patrones de prescripción y el efecto pronóstico a largo plazo de la duración del TAPD en pacientes sometidos a ICP del TCI con *stents* farmacoactivos segunda generación.
Métodos: A partir de los datos individuales de los registros IRIS-MAIN y KOMATE, se incluyó a 1.827 pacientes sometidos a ICP del TCI con *stents* farmacoactivos de segunda generación de los que hubiese información válida sobre la duración del TAPD. El objetivo de eficacia fue la aparición de eventos

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cardiovasculares adversos mayores (MACE) (un combinado de muerte cardiaca, infarto de miocardio y trombosis del *stent*) y el de seguridad fue la presencia de hemorragia mayor según TIMI.
Resultados: Las duraciones del TAPD fueron < 6 meses (n = 273), de 6-12 meses (n = 477), de 12-24 meses (n = 637) y ≥ 24 meses (n = 440). La mediana de la duración del seguimiento fue de 3,9 [intervalo intercuartílico, 3,01-5,00] años. El TAPD prolongado se asoció con menor incidencia de MACE. En el análisis de puntuación de propensión multigrupo, las HR ajustadas de los MACE fueron significativamente mayores con los TAPD de menos de 6 meses y de 6-12 meses (HR = 4,51; IC95%, 2,96-6,88) frente al TAPD de 12-24 meses (HR = 1,92; IC95%, 1,23-3,00). No hubo diferencias en la HR de hemorragia mayor entre los grupos evaluados.
Conclusiones: La duración del TAPD tras la ICP para la enfermedad del TCI es muy variable. Aunque debe considerarse en función de la situación clínica de cada paciente, un TAPD de menos de 12 meses se asoció con mayor incidencia de MACE.

Abreviaturas

DAPT: dual antiplatelet therapy
DES: drug-eluting stent
LMCA: left main coronary artery
MACE: major adverse cardiovascular events
PCI: percutaneous coronary intervention
ST: stent thrombosis

INTRODUCTION

Recent extended follow-up of landmark randomized clinical trials have shown that percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is associated with similar incidences of hard endpoints and mortality to those of coronary artery bypass grafting in patients with left main coronary artery (LMCA) disease and low-to-intermediate anatomic complexity.[1–3] Current practice guidelines usually recommend the duration of dual antiplatelet therapy (DAPT) in patients undergoing PCI with DES on the basis of initial clinical presentation, including DAPT for at least 6 months for chronic stable angina and 12 months for acute coronary syndrome (ACS).[4] However, there are limited data on the optimal duration of DAPT in patients receiving PCI for complex lesions, including multivessel, bifurcation, and chronic total occlusions, or LMCA disease.

Although some prior studies suggested that prolonged duration of DAPT might be associated with better clinical outcomes in patients undergoing complex PCI,[5,6] the proportion of LMCA-PCI was limited, and most studies used first-generation DES. In this clinical context, we investigated the practice pattern and long-term prognostic effect of DAPT duration in patients undergoing PCI with second-generation DES for LMCA disease using merged individual patient-level data from 2 large, real-world, contemporary PCI registries.

METHODS

Participants and study design

The design and enrollment characteristics of 2 multicenter registries (IRIS-MAIN and KOMATE) have been published previously.[7,8] Briefly, the IRIS-MAIN is a nonrandomized, multinational, observational registry gathering data on consecutive patients with unprotected LMCA disease. Another study population was derived from the KOMATE registry, which includes 8 coronary intervention centers in Korea. Both data sources had an "all-comers" design to evaluate the characteristics, treatments, and clinical outcomes of patients with LMCA disease in the real-world setting. Among merged individual-level data, we only included patients with LMCA who were treated with second-generation DES with available accurate information on postprocedural DAPT duration. The exclusion criteria were minimal; patients who underwent bare-metal stent (BMS) or first-generation DES. In addition, we excluded patients in whom we could not accurately judge the effectiveness of DAPT (patients with follow-up loss within 30 days, patients with in-hospital events within 30 days). A flow diagram of the current analysis is shown in figure 1. This study was approved by the institutional review board of each participating center for merged data use and all patients provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the research ethics committee of each participating center, and written informed consent was obtained by all participants.

PCI procedures and data collection

All PCI procedures were conducted in accordance with local guidelines using standard techniques. Intraprocedural anticoagulation was maintained with unfractionated or low molecular weight heparin to achieve an activated clotting time of 250 to 300 s. Other procedural factors, such as access location, stent strategy, stent technique, and use of intravascular ultrasound, were left to the operator's discretion. Although the duration of DAPT (aspirin plus $P2Y_{12}$ inhibitors [clopidogrel, ticagrelor, or prasugrel]) was usually recommended according to the current practice guidelines,[4] the final duration was left to the treating physician's discretion with consideration of the patient's clinical and procedural characteristics and other comorbid medical conditions. The DAPT duration criterion was allowed up to 2 months in addition to the date of use, considering the time of the outpatient department visit. All clinical, angiographic, procedural, and outcome data were collected using a web-based reporting system. To identify the status of antiplatelet therapy, the dates and duration of prescribed antiplatelet agents were obtained from the electronic prescribing system of each hospital. Additional information was obtained by further inquiry into medical records or telephone contact, if necessary.

Clinical outcomes and definitions

The efficacy outcome of the study was major adverse cardiovascular events (MACE), defined as a composite of cardiac death, fatal or nonfatal acute myocardial infarction, and stent

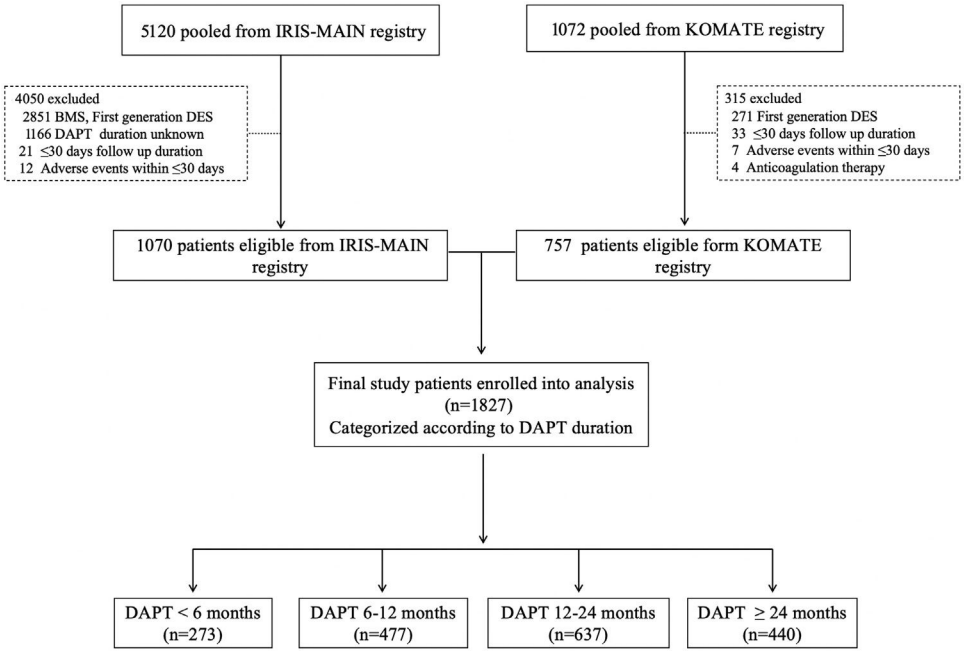

Figure 1. Study flow chart. BMS, bare-metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; IRIS-MAIN, Interventional Cardiology Research Incorporation Society-Left Main Revascularization Study; KOMATE, Korean Multicenter Angioplasty Team Study.

thrombosis events. The secondary outcomes were all-cause mortality and target vessel revascularization. Fatal or nonfatal acute myocardial infarction was defined as an increase in the creatine kinase-myocardial band or troponin level to the 99th percentile of the upper limit of normal with ischemic symptoms or electrocardiographic findings indicative of ischemia not related to the index procedure (ie, procedural myocardial infarction was disregarded). Stent thrombosis was defined as definite stent thrombosis according to the Academic Research Consortium definition.[9] The safety outcome was major bleeding. Bleeding events were defined as minor or major bleeding as per the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria.[10] All clinical outcomes were independently adjudicated by an independent group of clinicians who were unaware of DAPT duration and types of DES.

Statistical analysis

Continuous variables are reported as mean ± standard deviation and were analyzed using 1-way ANOVA. Categorical variables are reported as frequencies (percentages) and were analyzed using chi-square tests. Survival curves were prepared using Kaplan-Meier analysis and analyzed using log-rank tests. Cox proportional hazard regression analysis was used to identify independent predictors of primary endpoints and to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) for clinical outcomes. To minimize confounding and residual selection bias in observational treatment comparisons, a propensity score weighting method was applied to control imbalances in various baseline characteristics across different groups of DAPT duration. For multigroup comparisons, multiple propensity scores were estimated using the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) method, and the corresponding inverse probabilities of treatment weight (the reciprocals of the propensity scores) were estimated by using generalized boosted models through an iterative estimation procedure.[11] To calculate the propensity score, key clinical, anatomic, and procedural characteristics, such as age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, ACS, chronic kidney disease, multivessel disease, stent strategy, previous PCI, and intravascular ultrasound, were included. The balance of the pretreatment covariates was assessed, and significant improvement in baseline was achieved after weighting. Furthermore, the performance of this propensity model was confirmed by comparing the distributions of standardized mean differences of covariates and propensity scores between these groups before and after inverse probabilities of treatment weight.

Cox regression models with test for interaction were used to evaluate the consistency of treatment effects in multiple subgroups. The statistical analysis was performed using IBM SPSS version 23.0 (IBM, United States) and R software version 3.5.2 (R Project for Statistical Computing).

RESULTS

Pattern of DAPT duration and baseline characteristics

From July 2006 to August 2017, 1827 patients with LMCA lesions treated by PCI with second-generation DES and with valid data on DAPT duration were included in the final analytic datasets (figure 1). The practice pattern of DAPT duration in these patients is shown in figure 2. The median DAPT duration was 398 (interquartile range [IQR], 360-730) days for the entire population. According to DAPT duration, patients were categorized into 4 groups: DAPT < 6 months (n = 273), 6 to 12 months (n = 477), 1224 months (n = 637), and ≥ 24 months (n = 440). The median DAPT durations were 99 (IQR, 36.7-180) days in DAPT < 6 months, 365 (IQR, 341-365) days in DAPT 6 to 12 months, 523.5 (IQR, 397-730) days in DAPT 12 to 24 months, and 1095 (IQR, 1004-1316.5) days in DAPT ≥ 24 months, respectively. Since we enrolled patients for a long period of time (2006-2017), we investigated the pattern of DAPT duration according to the 2 different periods (2006-2011 and 2012-2017). The median duration of DAPT was longer in the

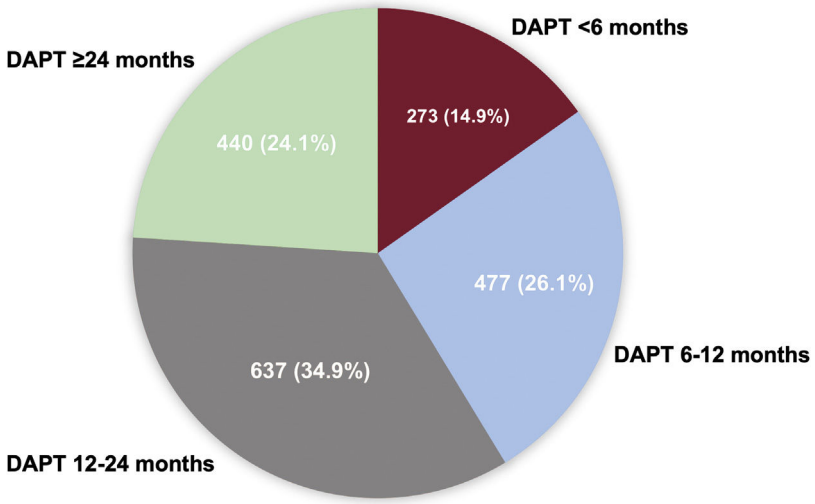

Figure 2. Distribution of participants according to DAPT duration. Values are presented as No. (%). DAPT, dual antiplatelet therapy.

2006 to 2011 period (IQR, 497days) than in the 2012 to 2017 period (IQR 381 days). The pattern of DAPT between the 2 periods was the same as shown in figure 1 of the supplementary data.

The baseline clinical characteristics of the study population are shown in table 1. The clinical characteristics were similar between the 4 groups, except for dyslipidemia and history of previous PCI. DAPT duration tended to be significantly shorter in patients with stable angina than in those with ACS. The DAPT and procedural characteristics of the study population are shown in table 2. Regarding $P2Y_{12}$ inhibitors, most patients received clopidogrel (94.6%), and ticagrelor and prasugrel was used in 4.1% and 1.3% of the patients, respectively.

The percentage of multivessel disease was the lowest in the DAPT < 6 months group, and the highest in the DAPT ≥ 24 months group. The extent of CAD was similar between the 4 groups. Distal bifurcation involvement was lowest in the DAPT < 6 months group and highest in the DAPT ≥ 24 months group. The average stent diameter and postdilatation balloon diameter were largest in the DAPT ≥ 24 months group. Postdilatation balloon pressure was the highest in the DAPT ≥ 24 months group. Patients who underwent PCI with intravascular ultrasound were significantly more likely to receive DAPT for ≥ 24 months.

Clinical outcomes according to DAPT duration

The median length of follow-up among all patients was 47.9 [36.7-60.8) months. The number of patients lost to follow-up was

Table 1
Baseline patient characteristics according to DAPT duration.

	Total population (N = 1 827)	DAPT < 6 mo (n = 273)	DAPT 6-12 mo (n = 477)	DAPT 12-24 mo (n = 637)	DAPT ≥ 24 mo (n = 440)	SMD (unmatched)	*P* (unmatched)	SMD (after PS weighting)	*P* (after PS weighting)
Age, y	64.3 ± 10.6	65.0 ± 11.3	63.5 ± 10.7	64.8 ± 10.7	64.1 ± 9.7	0.077	.136	0.008	.997
Male sex	1,395 (76.4)	205 (75.1)	380 (79.7)	479 (75.2)	331 (75.2)	0.057	.27	0.014	.983
Diabetes mellitus	609 (33.3)	87 (31.9)	158 (33.1)	204 (32)	160 (36.4)	0.049	.461	0.028	.914
Hypertension	1,146 (62.7)	165 (60.4)	302 (63.3)	401 (63)	278 (63.2)	0.025	.865	0.012	.993
Dyslipidemia	1,120 (61.3)	189 (69.2)	292 (61.2)	354 (55.6)	285 (64.8)	0.153	< .0001	0.041	.763
Chronic kidneys disease	137 (7.5)	20 (7.3)	34 (7.1)	53 (8.3)	30 (6.8)	0.031	.796	0.019	.949
Smoking	422 (23.1)	57 (20.9)	130 (27.3)	141 (22.1)	94 (21.4)	0.076	.091	0.029	.895
Previous PCI	326 (17.8)	45 (16.5)	72 (15.1)	109 (17.1)	100 (22.7)	0.105	.017	0.017	.970
Previous CABG	60 (3.3)	6 (2.2)	19 (4)	20 (3.1)	15 (3.4)	0.032	.612	0.039	.791
Clinical indication for PCI									
Stable angina	450 (24.6)	45 (16.5)	119 (25)	187 (29.3)	99 (22.5)	0.162	< .0001	0.058	.421
Acute coronary syndrome	1377 (75.4)	228 (83.5)	358 (75)	450 (70.7)	341 (77.5)	0.131	.001	0.036	.777
Unstable angina	1060 (77)	171 (75)	271 (75.7)	340 (75.6)	278 (81.5)	0.112	.008	0.072	.370
NSTEMI	222 (16.1)	41 (18)	66 (18.4)	72 (16)	43 (12.6)	0.096	.103	0.074	.181
STEMI	95 (6.9)	16 (7)	21 (5.9)	38 (8.4)	20 (5.9)	0.050	.58	0.045	.679
Mean ejection fraction, %	59.5 ± 12.5	59.0 ± 13.1	59.8 ± 13.1	59.4 ± 13.3	59.7 ± 10.2	0.059	.871	0.065	.402

CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; NSTEMI, non-ST-elevation acute myocardial infarction; PCI, percutaneous coronary intervention; SMD, standardized mean difference; STEMI, ST-segment elevation myocardial infarction. Values are presented as No. (%) or mean ± standard deviation.

Table 2
DAPT and procedural characteristics according to DAPT duration.

	Total population (n = 1827)	DAPT < 6 mo (n = 273)	DAPT 6-12 mo (n = 477)	DAPT 12-24 mo (n = 637)	DAPT ≥ 24 mo (n = 440)	SMD (unmatched)	*P* (unmatched)	SMD (after PS weighting)	*P* (after PS weighting)
DAPT duration, d	589.3 ± 443.9	105.1 ± 64.1	336.9 ± 52.7	546.3 ± 145.4	1,225.6 ± 400.2	3.181	< .0001	3.224	< .0001
DAPT score	0.52 ± 1.30	0.45 ± 1.36	0.74 ± 1.36	0.48 ± 1.27	0.39 ± 1.21	0.134	< .0001	0.042	.627
$P2Y_{12}$ inhibitor						0.074	.299	0.070	.284
Clopidogrel	1,729 (94.6)	255 (93.4)	458 (96)	596 (93.6)	420 (95.5)				
Ticagrelor	75 (4.1)	14 (5.1)	17 (3.6)	31 (4.9)	13 (3)				
Prasugrel	23 (1.3)	4 (1.5)	2 (0.4)	10 (1.6)	7 (1.6)				
Multivessel disease	1,281 (70.1)	177 (64.8)	339 (71.1)	447 (70.2)	318 (72.3)	0.067	.186	0.056	.369
Disease extent									
Left main only	133 (7.3)	25 (9.3)	34 (7.2)	41 (6.4)	33 (7.5)	0.056	.502	0.028	.873
Left main with 1-VD	459 (25.3)	73 (27.2)	114 (24.2)	173 (27.2)	99 (22.5)	0.066	.281	0.047	.554
Left main with 2-VD	667 (36.7)	88 (32.8)	184 (39.1)	219 (34.4)	176 (40)	0.087	.094	0.054	.446
Left main with 3-VD	557 (30.7)	82 (30.6)	139 (29.5)	204 (32)	132 (30)	0.028	.816	0.031	.847
RCA involvement	805 (44.3)	120 (44.8)	202 (42.9)	286 (44.9)	197 (44.8)	0.018	.911	0.040	.818
Left main lesion location									
Ostium of shaft	651 (35.8)	111 (41.4)	165 (35)	209 (32.8)	166 (37.7)	0.092	.072	0.087	.143
Distal bifurcation	1,244 (68.1)	182 (66.7)	325 (68.1)	435 (68.3)	302 (68.6)	0.017	.955	0.017	.975
Stent technique						0.109	.003	0.039	.742
1-stent strategy	1,512 (83.3)	216 (80.6)	381 (80.9)	558 (87.7)	357 (81.1)				
2-stent strategy	303 (16.7)	52 (19.4)	90 (19.1)	78 (12.3)	83 (18.9)				
Total stent number per patient	2.21 ± 1.22	2.17 ± 1.26	2.19 ± 1.16	2.16 ± 1.23	2.32 ± 1.24	0.073	.156	0.068	.344
Average stent diameter in MV, mm	3.57 ± 0.43	3.51 ± 0.47	3.47 ± 0.47	3.66 ± 0.38	3.63 ± 0.39	0.175	< .0001	0.168	< .001
Average stent length in MV, mm	21.88 ± 7.64	21.85 ± 7.63	21.89 ± 7.83	20.95 ± 7.38	22.92 ± 7.62	0.106	.008	0.116	.028
Postdilatation balloon diameter, mm	3.71 ± 0.56	3.67 ± 0.56	3.63 ± 0.58	3.71 ± 0.55	3.81 ± 0.54	0.174	< .0001	0.134	< .001
Postdilatation balloon pressure, mmHg	15.61 ± 4.60	15.13 ± 4.47	15.17 ± 4.12	15.83 ± 4.74	16.09 ± 4.94	0.104	.011	0.115	.031
FKBI	848 (46.5)	164 (60.3)	213 (44.7)	250 (39.3)	221 (50.2)	0.219	< .0001	0.191	< .001
IVUS	1107 (60.7)	160 (58.8)	264 (55.3)	395 (62.1)	288 (65.5)	0.103	.013	0.027	.901

DAPT, dual antiplatelet therapy; FKBI, final kissing-balloon inflation; IVUS, intracoronary ultrasound; MV, main vessel; RCA, right coronary artery; VD, vessel disease. Values are presented as No. (%) or mean ± standard deviation.

73 out of 1827 (3.99%). First, we fit Cox proportional-hazards log-linear models adjusted by baseline and procedural parameters with thin-plate spline curves to DAPT duration (figure 3). When we analyzed the risk of MACE and major bleeding according to DAPT duration as a continuous variable, risk of MACE progressively decreased, but the risk of major bleeding increased with >12 months of DAPT. We investigated Cox proportional-hazards log-linear models with thin-plate spline curves to DAPT duration according to stent strategies and with or without bifurcation lesions. Regardless of these factors, the results remained consistent (figure 2 of the supplementary data).

The cumulative incidences of clinical outcomes according to the categories of DAPT duration are shown in table 3 and in figure 2 of the supplementary data. The cumulative rates of MACE occurred more frequently in the DAPT < 6 months group than in other DAPT groups (lowest for the DAPT ≥ 24 months [1.6%] and highest for the

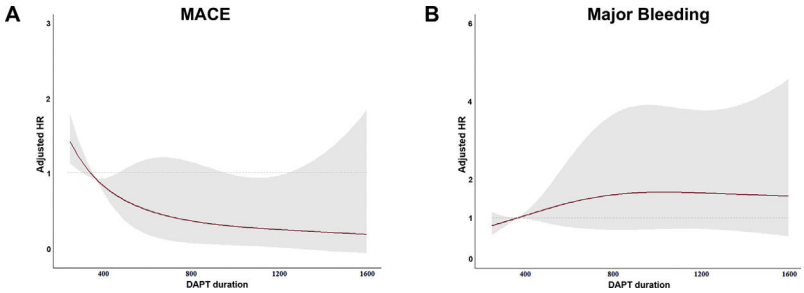

Figure 3. Spline curves. Duration-response relationships between DAPT duration and MACE (A), and between DAPT duration and major bleeding (B) after PS weighting tested by a log-linear model with thin-plate spline curves. DAPT, dual antiplatelet therapy; HR, hazard ratio; MACE, major adverse cardiovascular event; PS, propensity score.

Table 3
Clinical outcomes according to DAPT duration.

	DAPT < 6 mo (n = 273)	DAPT 6-12 mo (n = 477)	DAPT 12-24 mo (n = 637)	DAPT ≥ 24 mo (n = 440)	*P*
*Major adverse cardiovascular event**	5.1 (2.0-8.0)	3.1 (2.0-5.0)	2.0 (1.0-3.0)	1.6 (0.0-3.0)	.02
Cardiac death	3.7 (1.0-6.0)	2.5 (1.0-4.0)	1.1 (0.0-2.0)	1.1 (0.0-2.0)	.03
Myocardial infarction	2.6 (1.0-4.0)	1.0 (0.0-2.0)	1.7 (1.0-3.0)	1.1 (0.0-2.0)	.35
Stent thrombosis	1.5 (0.0-3.0)	0.6 (0.0-1.0)	0.3 (0.0-1.0)	0.2 (0.0-1.0)	.12
All-cause death	12.5 (9.0-16.0)	6.7 (4.0-9.0)	5.3 (4.0-7.0)	3.9 (2.0-6.0)	< .0001
Target vessel revascularization	11.0 (7.0-15.0)	5.0 (3.0-7.0)	4.4 (3.0-6.0)	8.4 (6.0-11.0)	< .0001
Major bleeding	1.1 (0.0-2.0)	1.3 (0.0-2.0)	2.8 (2.0-4.0)	3.6 (2.0-5.0)	.07
Minor bleeding	5.9 (3.0-9.0)	4.0 (2.0-6.0)	2.8 (2.0-4.0)	3.2 (2.0-5.0)	.14

DAPT, dual antiplatelet therapy.
Values are presented as cumulative rate (95% confidence interval). Cumulative rates (95% confidence intervals) of events are based on Kaplan-Meier estimates.
* Major adverse clinical event was defined as cardiac death, myocardial infarction, or stent thrombosis.

DAPT < 6 months [5.1%]). There was no difference in the cumulative incidence of major bleeding (lowest for the DAPT < 6 months [1.1%] and highest for DAPT ≥ 24 months [3.6%]).

The distributional balance of propensity scores according to DAPT duration before and after weighting is shown in figure 4 of the supplementary data. The adjusted risks for adverse clinical events according to the different categories of DAPT duration after application of multiple treatment propensity score weighting are shown in figure 4. With DAPT 12 to 24 months as the reference group, adjusted hazard ratios for MACE were significantly higher for DAPT < 6 months and DAPT 6 to 12 months than for DAPT 12 to 24 months (HR, 4.51; 95%CI, 2.96-6.88 and HR 1.92; 95%CI, 1.23-3.00). Major bleeding events tended to be more likely in the ≥ 24 month group than in the other shorter DAPT groups. Multivariate analysis revealed that diabetes mellitus and chronic kidney disease were independent predictors of MACE (table 1 of the supplementary data).

DISCUSSION

In this pooled individual patient-level analysis from 2 large-sized, contemporary, real-world registries, DAPT duration was highly variable. Although DAPT duration should be considered in the context of the clinical situation of each patient, < 12 months of DAPT was associated with a higher incidence of MACE.

LMCA lesions are one of the most complex anatomic subsets in real-world clinical settings. Recent clinical studies suggested that PCI with second-generation DES for LMCA disease provided favorable procedural and long-term clinical outcomes.[2,3] However, there have been few studies on long-term duration and the effect of DAPT in the contemporary PCI practice with second-generation DES for the treatment of LMCA disease. In a recent study, DAPT for > 12 months after an index procedure was associated with a reduced risk of ischemic events among patients with LMCA bifurcation stenting compared with DAPT for ≤ 12 months.[12] However, that study might have been hampered by the use of first-generation DES, the exclusion of LMCA ostial and shaft lesions, and nonassessment of bleeding events. Moreover, since events occurring within 12 months were excluded, the exact relationship between shorter or longer DAPT duration and clinical events could not be assessed. In contrast, in the recent EXCEL trial report, continuation of DAPT beyond 12 months was not found to be associated with a reduced risk of ischemic events (death, myocardial infarction, or stroke) after PCI with everolimus-eluting

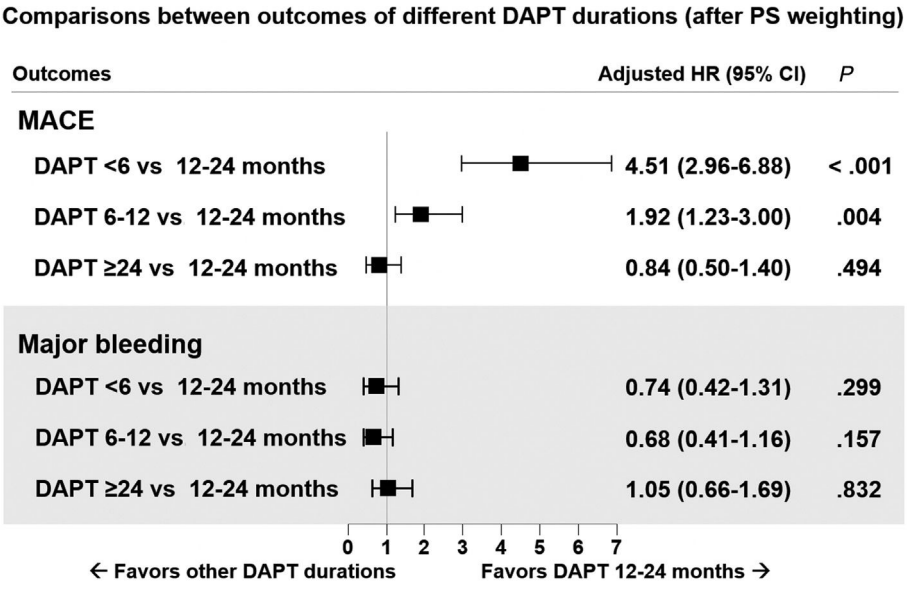

Figure 4. Central illustration. Comparison between outcomes of different DAPT durations in propensity score analyses. Adjusted HR. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; PS, propensity score.

stents in patients with LMCA disease.[13] However, that study was a subgroup analysis including a relatively limited number of patients, and, again, there was no assessment of bleeding events. In the current study, we investigated clinical outcomes including ischemic and bleeding events according to different durations of DAPT in patients receiving PCI with contemporary second-generation DES for LMCA disease using 2 large-scaled real-world registries. Following PCI, DAPT was maintained in most patients (84.8%) for at least 6 months according to the current guidelines. After multiple treatment propensity score weighting, with DAPT 12 to 24 months as the reference group, DAPT for < 12 months was significantly associated with a higher risk of MACE without a clinical benefit or reducing major bleeding.

Recently, several randomized clinical trials have reported the potential benefit of reduced DAPT duration in patients receiving contemporary second-generation DES.[14,15] Most studies have shown that antiplatelet monotherapy was associated with a lower incidence of clinically relevant bleeding compared with DAPT but with a higher risk of ischemic events. However, the observed results of several studies regarding the shortening of DAPT in complex PCI groups were conflicting and the number of patients with LMCA disease was too small to provide clinically meaningful insights. In the RAIN registry subgroup analysis, the incidence of MACE was significantly higher in the ≤ 3 months DAPT group compared with the 3 to 12 and > 12 months DAPT groups, which was mainly driven by the differences in myocardial infarction and stent thrombosis.[16] Theoretically, despite the use of second-generation DES, PCI for LMCA disease is more likely to develop stent malapposition due to their large diameter and bifurcation compared with non-LMCA lesions, which might result in insufficient strut coverage and a potential risk of thrombus formation. In previous studies, especially among patients with a 2-stent strategy, implying a high probability of stent malapposition and underexpansion, fatal ischemic events substantially increased when DAPT was discontinued.[17] A similar association between shorter DAPT and higher ischemic events was also observed in our study, which might be of paramount clinical significance with regard to the optimal DAPT duration in patients with complex PCI for LMCA disease. In the IDEAL-LM trial, PCI with the biodegradable polymer-coated platinum-chromium DES followed by 4 months of DAPT was noninferior to durable polymer cobalt-chromium DES followed by 12 months of DAPT with respect to MACE at 2 years. However, due to lower than predicted event rates, the trial is underpowered, and the individual components of MACE all trended to be numerically higher in the biodegradable polymer-DES with 4 months of DAPT.[18]

Several score systems (eg, DAPT score, PRECISE-DAPT score) and validation studies have been designed to determine optimal DAPT duration.[19,20] In a previous study, DAPT > 12 months was associated with a lower MACE rate than DAPT ≤ 12 months in a population with DAPT score ≥ 2, but not in a population with DAPT score < 2.[12] The efficacy and safety of a short DAPT duration of DAPT after LMCA PCI requires further investigation and future studies should focus on individual patient risk of ischemic and bleeding events.

Limitations

There are several limitations of our study. First, although multiple propensity score treatment analysis was performed, this study was an observational, nonrandomized study; therefore, it might be vulnerable to inherent limitations, including selection bias and unmeasured confounders. Thus, the overall observed findings should be interpretated as provisional and hypothesis-generating only. These findings should be confirmed or refuted through large randomized clinical trials. Second, owing to the limited number of clinical events, our study was underpowered to detect clinically relevant differences regarding hard clinical endpoints including death, stent thrombosis, or major bleeding. Third, we were not able to classify bleeding endpoints to other classifications such as the International Society on Thrombosis and Hemostasis (ISTH) or Bleeding Risk Estimation and the new Bleeding Academic Research Consortium (BARC) classification due to the limited information of our multicenter observational data. Fourth, we could not systematically measure detailed information on atherosclerotic burden and complexity, such as SYNTAX score. Fifth, the study population was enrolled over a wide period (2006-2017). This may have introduced some heterogeneity in the study population due to changes in clinical practice and improvements in PCI technology. Sixth, we did not include data on oral anticoagulation agents. Finally, in the current study, potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, were less frequently used. In a recent study, novel $P2Y_{12}$ inhibitor monotherapy was shown to reduce major bleeding events without increasing ischemic events in patients with complex PCI.[21] This concept should be further tested in patients with complex PCI including LMCA disease.

CONCLUSIONS

In this merged individual patient-level analysis of 2 large-scale real-world registries, although the duration of DAPT should be considered in the context of the clinical situation of each patient, DAPT for < 12 months was significantly associated with a higher risk of MACE in patients undergoing PCI with second-generation DES for LMCA disease. Future randomized clinical trials are warranted to determine the optimal duration of DAPT for patients receiving complex PCI including LMCA disease.

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AUTHORS' CONTRIBUTIONS

S. Cho, D.Y. Kang, J.S. Kim, and D.W. Park designed the study; T.S. Kang, J.M. Ahn, P.H. Lee, S.J. Kim, S.W. Lee, Y.H. Kim, C.W. Lee, S.W. Park, S.J. Lee, S.J. Hong, C.M. Ahn, B.K. Kim, Y.G. Ko, D. Choi, Y. Jang, M.K. Hong, and S.J. Park assisted with data acquisition and interpretation; S. Cho and I.S. Kim performed statistical analyses; S. Cho, D.Y. Kang, J.S.Kim, D.W. Park, and C.M. Ahn contributed to the discussion; S. Cho, and J.S. Kim drafted the manuscript; S. Cho, J.S. Kim, and D.W. Park revised the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None.

WHAT IS KNOWN ABOUT THE TOPIC?

- Although some prior studies suggested that prolonged duration of DAPT might be associated with better clinical outcomes in patients undergoing complex PCI, the proportion of LMCA-PCI was limited and most studies used first-generation DES.

WHAT DOES THIS STUDY ADD?

- In this pooled individual patient-level analysis of 2 large-sized, contemporary, real-world registries, we observed that DAPT duration was highly variable. Although DAPT duration should be considered in the context of the clinical situation of each patient, <12 months of DAPT was associated with a higher incidence of MACE.
- Further randomized clinical trials are needed to determine the optimal duration of DAPT in patients undergoing PCI for LMCA disease.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2022.07.007

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