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ORIGINAL ARTICLE
Coronary Revascularization

Optimal Duration for Dual Antiplatelet Therapy After Left Main Coronary Artery Stenting

Jungho Choi, MD, PhD; In-Soo Kim, MD; Sungsoo Cho, MD, PhD; Jung-Sun Kim, MD, PhD; Sung-Jin Hong, MD; Dong-Ho Shin, MD; Chul-Min Ahn, MD, PhD; Byeong-Keuk Kim, MD, PhD; Young-Guk Ko, MD, PhD; Donghoon Choi, MD, PhD; Myeong-Ki Hong, MD, PhD; Yangsoo Jang, MD, PhD

Background: Coronary interventions using drug-eluting stents (DESs) of left main coronary artery (LMCA) lesions have shown favorable clinical outcomes. However, duration of dual antiplatelet therapy (DAPT) after LMCA interventions has not yet been investigated.

Methods and Results: From a multicenter Korean Multicenter Angioplasty Team (KOMATE) registry, 1,004 patients who received DES implantations for LMCA lesions and did not experience major adverse cardiovascular events (including major bleeding) for 1 year after coronary intervention were analyzed. Patients were divided into 2 groups; DAPT ≤12 (n=503) and >12 months (n=501). The primary endpoint was number of net clinical adverse events (NACEs), composite of cardiac deaths, myocardial infarctions, stent thrombosis and major bleeding events. During a 4.5-year follow-up period after LMCA interventions, the DAPT >12 months group showed a lower NACE rate than the DAPT ≤12 months group (adjusted-HR 0.53 [0.29–0.99], P=0.045). For patients who maintained DAPT >12 months, rate of cardiac deaths, myocardial infarctions, and stent thrombosis events were lower than in patients who had DAPT ≤12 months (adjusted-HR 0.35 [0.17–0.73], P=0.005) without increased major bleeding (P=0.402).

Conclusions: For patients who can continue DAPT without major bleeding events, prolonged DAPT (>12 months) after LMCA stenting demonstrated better long-term efficacy outcomes than DAPT ≤12 months with comparable safety.

Key Words: Dual antiplatelet therapy; Duration; Left main coronary artery disease; Percutaneous coronary intervention

Left main coronary artery (LMCA) diseases are associated with high cardiovascular mortality and coronary artery bypass grafting (CABG) was regarded as a standard revascularization strategy for these patients.[1] Over the past 20 years, there were significant developments in percutaneous coronary intervention (PCI). Although favorable results from previous studies have suggested PCI as an alternative therapeutic strategy, the optimal duration of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation remains uncertain for these patients with LMCA disease.[2–6] Extended DAPT for >12 months has been shown to reduce ischemic events, such as myocardial infarction (MI), stent thrombosis (ST), and ischemic stroke, but resulted in an increased number of bleeding events.[7] However, DAPT for >12 months has not been recommended for all patients who receive DES implantations because of the improved performance of second-generation DESs and concerns regarding the possibility of clinically significant bleeding.[8,9] Although several studies have reported that longer duration DAPT could result in beneficial clinical outcomes in cases of complex coronary lesions, including LMCA, the number of patients with LMCA in these studies has not been large enough to determine whether these beneficial outcomes reach the level of clinical relevance.[10,11] LMCA lesions generally result in large areas of myocardial ischemia and are associated with worse clinical outcomes.[12–14] Therefore, determining the optimal DAPT duration is more important

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Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul (J.C., J.-S.K., S.-J.H., D.-H.S., C.-M.A., B.-K.K., Y.-G.K., D.C., M.-K.H., Y.J.); Division of Cardiology, Department of Internal Medicine, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon (J.C.); Division of Cardiology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul (I.-S.K.); and Division of Cardiovascular Medicine, Department of Internal Medicine, Dankook University Hospital, Dankook University College of Medicine, Cheonan (S.C.), Korea

The first two authors contributed equally to this work (J.C., I.-S.K.).

Mailing address: Jung-Sun Kim, MD, PhD, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei-ro 50-1, Seodaemun-gu, Seoul 03722, Korea. E-mail: kjs1218@yuhs.ac

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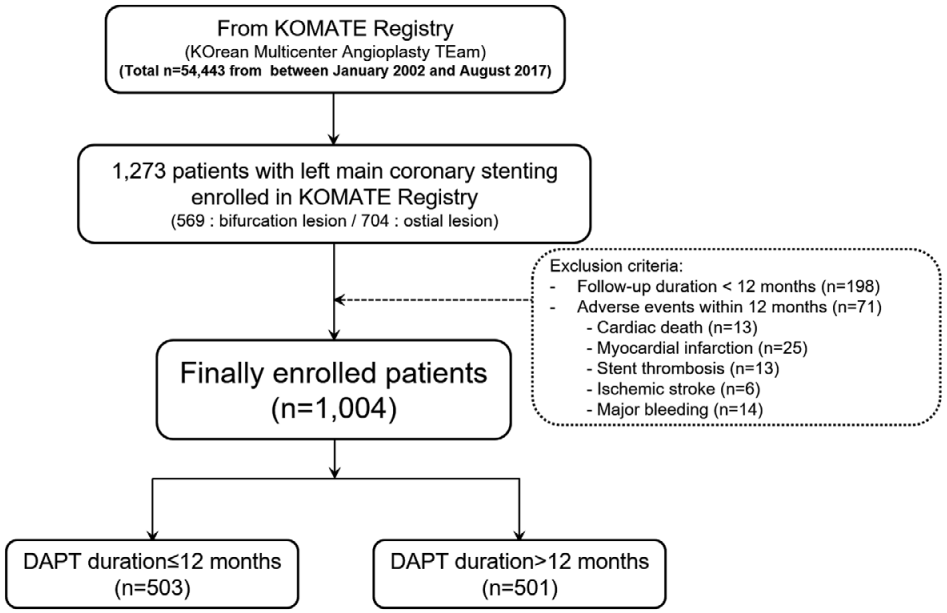

Figure 1. Study cohort and included patients from the KOMATE registry. KOMATE, Korean Multicenter Angioplasty Team; DAPT, dual antiplatelet therapy.

after LMCA stenting than for any other subset of coronary artery disease. We attempted to investigate the long-term clinical outcomes of extended DAPT for >12 months after DES implantations in patients with LMCA.

Methods

This multicenter cohort study registered with the ClinicalTrials.gov (number NCT03908463; Korean Multicenter Angioplasty Team (KOMATE) registry [retrospective and prospective registry]) was about the optimal duration of DAPT after DES implantation for patients with LMCA diseases, and was performed according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement reporting guidelines (**Supplementary Table 1**).[15]

Study Population

The study population was derived from the KOMATE registry, which includes 8 coronary intervention centers in Korea. Between January 2002 and August 2017, 1,273 of 54,443 consecutive patients who received DES implantations for LMCA lesions, including bifurcated (n=569) or ostial/shaft lesions (n=704), were assessed for eligibility. Those patients who were followed for <12 months (n=198), or presented with adverse events (cardiac death, MI, ST, ischemic stroke, and bleeding events) within 12 months after DES implantations to treat LMCA (n=71), were excluded in the final analysis. The resulting 1,004 patients with LMCA lesions were divided into 2 groups: 503 patients (50.1%) discontinued 1 antiplatelet agent (usually $P2Y_{12}$ inhibitor) within 12 months of implantation (DAPT ≤12 months group), and 501 patients (49.9%) continued to use aspirin and a $P2Y_{12}$ inhibitor for >12 months (DAPT >12 months group), with a median 4.5-year follow-up duration (**Figure 1**). The duration of DAPT was determined at the discretion of the treating physician. This study was carried out in accordance with the Declaration of Helsinki, approved by the Institutional Review Board at Severance Hospital of the Yonsei University Health System, and written informed consent was obtained from all patients. To adjust for potential confounders, we used the inverse probability of treatment weighting (IPTW) as described below.

Pre-Procedural Medication and Procedure Process

Patients received aspirin and $P2Y_{12}$ inhibitors according to current guidelines.[16] During the PCI, anticoagulation was mediated by unfractionated heparin or low molecular-weight heparin to achieve an activated clotting time between 250 and 300s. The early generation of DESs used in this study included the paclitaxel-eluting stent, the sirolimus-eluting stent, and the zotarolimus-eluting, stent-SPLINT. The current generation of DESs included the zotarolimus-eluting stent, RESOLUTE; the everolimus-eluting stent; and the biolimus-eluting stent. The stent strategy, stenting technique, and the use of intravascular ultrasound devices were decided by the operating doctor. After discharge, patients were followed at 6, 12, and 18 months by direct visit to outpatient departments, and thereafter at 6-month intervals. The duration of DAPT was determined for each patient by the physician, based on baseline and pre-procedural characteristics.

Clinical Outcomes and Definitions

The primary endpoint was the number of net adverse clinical events (NACEs), which was defined as the combined incidences of cardiac deaths, MIs, STs, and major bleeding events. Cardiac death was defined as the immediate cause of death recorded on the death certificate, focusing on MI

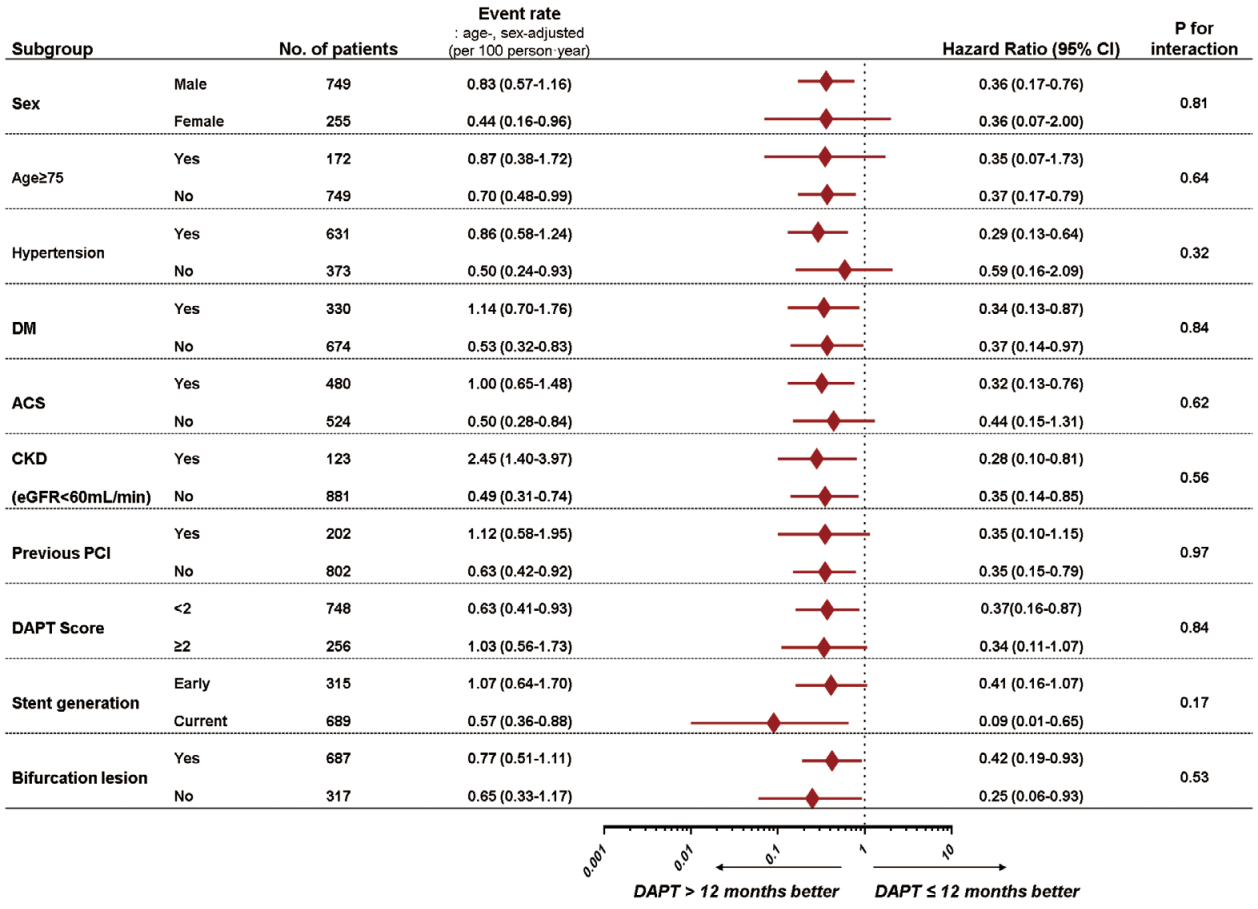

Figure 2. Effect of DAPT duration >12 months on net clinical adverse events (NACEs) in different subgroups. The hazard ratios (HRs; logarithmic scale) were adjusted by baseline and procedural parameters. DAPT, dual antiplatelet therapy; CI, confidence interval; ACS, acute coronary syndrome; DM, diabetes mellitus; CKD, chronic kidney disease; GFR, glomerular filtration rate; PCI, percutaneous coronary intervention

and heart failure. Acute MI was defined according to the Third Universal Definition[17] as an increase in the levels of cardiac biological markers, such as the creatine kinase-myocardial band or troponin, to the 99th percentile of the upper limit of the normal range, accompanied by ischemic symptoms or electrocardiographic ischemic changes, which were not related to the index procedure. ST was defined as either definite ST or probable ST, according to the Academic Research Consortium definitions.[18] Stroke was defined as ischemic stroke. Bleeding events were classified as either minor or major bleeding events, as determined by the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria.[19] Any intracranial bleeding was treated as a major bleeding event according to the TIMI bleeding criteria, and supplementary information such as brain imaging was used.[19] To evaluate the advantages and disadvantages of longer DAPT durations, the number of NACEs were measured for each group.

Adjustment of Differences Between 2 Groups

Patients with DAPT durations >12 months and those with DAPT durations ≤12 months were expected to differ with regards to their pre-procedural characteristics. Therefore, we gathered available baseline characteristic data from our registry to make comparative adjustments. Propensity scores, which were used to assess the probability that a patient would be selected to receive DAPT for >12 months, based on the baseline and pre-procedural characteristics of each patient, were developed using logistic regressions to adjust for baseline differences between groups.[20] Then, the IPTW, based on propensity scores, was used as the primary tool to adjust for baseline differences between patients in the DAPT >12 months and the DAPT ≤12 months groups.[21] Each patient who received DAPT for >12 months was weighted by the inverse of the probability that the patient would be selected to receive DAPT for >12 months and vice versa. We also confirmed the performance of this propensity model by comparing the distributions of the standardized mean differences (SMDs) for both covariates and propensity scores between these groups, both before and after IPTW was performed.

Statistical Analysis

Cumulative event rates were assessed based on Kaplan-Meier censoring estimates, and comparisons of clinical outcomes between the DAPT >12 months and the DAPT

Table 1. Baseline and Procedural Characteristics of the Patients (Before and After PS Weighting)

Variables	Entire population (n=1,004)	Unweighted (before PS weighting)				After PS weighting (IPTW)			
		DAPT ≤12-months (n=503)	DAPT >12-months (n=501)	SMD	P value	DAPT ≤12-months (n=503)	DAPT >12-months (n=501)	SMD	P value
Age (mean, SD)	64.1±10.8	64.8±10.8	63.4±10.7	0.123	0.052	64.1±10.8	64.3±10.7	0.022	0.754
Male, n (%)	749 (74.6)	375 (74.6)	374 (74.7)	0.002	0.972	372 (74.3)	373 (74.4)	0.002	0.980
Current smokers, n (%)	235 (23.4)	108 (21.5)	127 (25.3)	0.092	0.147	129 (25.6)	118 (23.6)	0.047	0.515
EF (%, SD)	59.2±14.8	59.6±15.2	58.9±14.5	0.047	0.342	59.3±15.5	59.2±14.2	0.004	0.473
HTN, n (%)	631 (62.8)	307 (61.0)	324 (64.7)	0.075	0.234	329 (65.4)	318 (63.5)	0.040	0.572
DM, n (%)	330 (32.9)	160 (31.8)	170 (33.9)	0.045	0.475	170 (33.7)	165 (33.0)	0.015	0.836
Dyslipidemia, n (%)	515 (51.3)	247 (49.1)	268 (53.5)	0.088	0.165	254 (50.4)	253 (50.5)	0.002	0.974
CKD (eGFR <60 mL/min/1.73 m^2), n (%)	123 (12.3)	56 (11.1)	67 (13.4)	0.068	0.280	64 (12.8)	61 (12.1)	0.020	0.786
Previous stroke, n (%)	76 (7.6)	39 (7.8)	37 (7.4)	0.014	0.826	37 (7.3)	38 (7.5)	0.009	0.894
Presented as ACS, n (%)	480 (47.8)	242 (48.1)	238 (47.5)	0.012	0.848	245 (48.8)	240 (47.9)	0.020	0.781
Previous PCI, n (%)	202 (20.1)	94 (19.4)	108 (21.6)	0.072	0.257	112 (22.2)	104 (20.8)	0.033	0.646
Previous CABG, n (%)	67 (6.7)	30 (6.0)	37 (7.4)	0.057	0.368	37 (7.3)	33 (6.5)	0.029	0.698
Medications†									
Aspirin, n (%)	992 (98.8)	500 (99.4)	492 (98.2)	0.068	0.279	495 (98.5)	492 (98.3)	0.018	0.812
Clopidogrel, n (%)	936 (93.2)	460 (91.5)	476 (95.0)	0.055	0.383	475 (93.4)	471 (91.8)	0.018	0.808
Prasugrel, n (%)	5 (0.5)	3 (0.6)	2 (0.4)	0.001	0.910	1 (0.2)	1 (0.2)	0.006	0.921
Ticagrelor, n (%)	63 (6.3)	40 (8.0)	23 (4.6)	0.007	0.998	32 (6.4)	35 (8.0)	0.040	0.349
Statin, n (%)	967 (96.3)	492 (97.8)	475 (94.8)	0.140	0.027	490 (97.4)	480 (95.8)	0.034	0.572
ACE inhibitors, n (%)	233 (23.2)	111 (22.1)	122 (24.4)	0.178	0.005	114 (22.6)	112 (23.3)	0.017	0.809
ARB, n (%)	355 (35.4)	181 (36.0)	174 (34.7)	0.099	0.116	188 (37.3)	175 (34.9)	0.054	0.443
β-blockers, n (%)	684 (68.1)	338 (67.2)	346 (69.1)	0.178	0.005	324 (64.5)	332 (66.2)	0.039	0.588
Antiplatelet agents used at DAPT cessation									
Aspirin, n (%)	748 (74.5)	374 (74.4)	374 (74.7)	0.007	0.914	384 (76.3)	374 (74.6)	0.040	0.562
Clopidogrel, n (%)	424 (42.2)	158 (31.4)	266 (53.1)	0.476	0.001	204 (40.6)	222 (44.3)	0.098	0.129
Ticagrelor and Prasugrel, n (%)	7 (0.7)	6 (1.2)	1 (0.2)	0.120	0.058	6 (1.2)	1 (0.2)	0.106	0.094
Procedural parameters									
DAPT score ≥2, n (%)	256 (25.5)	127 (25.2)	129 (25.7)	0.011	0.856	126 (25.1)	128 (25.6)	0.013	0.853
Stent generation (current), n (%)	689 (68.9)	431 (85.7)	258 (51.5)	0.791	0.001	354 (70.4)	369 (73.6)	0.072	0.318
Puncture access									
Radial, n (%)	235 (23.4)	140 (27.8)	95 (19.0)	0.221	0.001	125 (24.8)	113 (22.6)	0.053	0.440
Femoral, n (%)	769 (76.6)	363 (72.2)	406 (81.0)	0.210	0.002	378 (75.2)	388 (77.4)	0.052	0.451
Bifurcation lesion, n (%)	684 (68.4)	354 (70.2)	334 (66.7)	0.076	0.232	349 (69.4)	351 (70.0)	0.011	0.871
Ostial lesion, n (%)	430 (42.8)	221 (43.9)	209 (41.7)	0.045	0.478	216 (43.0)	232 (46.3)	0.067	0.339
IVUS/OCT use, n (%)	495 (49.3)	262 (52.1)	233 (46.5)	0.112	0.077	257 (51.1)	238 (47.5)	0.094	0.136
Minimal stent diameter (mm, SD)	3.41±0.37	3.42±0.37	3.41±0.38	0.017	0.789	3.42±0.37	3.41±0.38	0.044	0.530
Two-stent PCI,‡ n (%)	72 (7.2)	31 (6.2)	41 (8.2)	0.078	0.215	31 (6.2)	39 (7.9)	0.066	0.344

ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HTN, hypertension; IPTW, inverse probability of treatment weighting; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PS, propensity score; SD, standard deviation; SMD, standardized mean difference. †Medication at hospital discharge. ‡Two-stent strategy used for a left main bifurcation lesion.

≤12 months groups were performed using the log-rank test. Because differences in patient characteristics could affect the clinical outcomes, the following analyses to adjust for potential confounders were used.

First, a multivariable-adjusted Cox proportional hazard regression analysis was used. In the multivariable-adjusted models, baseline and procedural covariates were selected if they were significantly different between the 2 groups or had predictive values. The variables included in the multivariable model were age, sex, baseline ejection fraction, hypertension, diabetes, chronic kidney disease, dyslipidemia, smoking status, previous PCI history, DES type (early- or current-generation), lesion complexity (bifurcation lesion or 2-stent strategy for these bifurcation lesions), and DAPT score.[22] The proportionality assumption was assessed by linear estimates of the hazard ratio for the duration–response relationship between DAPT duration and each outcome, which were tested by a log-linear model

Table 2. Comparison of Clinical Outcomes, According to DAPT Duration (A: Overall Patients, n=1,004; B: Patients Who Received Current-Generation DES Analysed as Sensitivity Analysis, n=689)

Outcomes	DAPT ≤12 months, no. of patients (%/year)	DAPT >12 months, no. of patients (%/year)	DAPT >12 months vs. ≤12 months: multivariable-adjusted† (before PS-weighting)		DAPT >12 months vs. ≤12 months: multivariable-adjusted† (after PS-weighting, IPTW)	
			HR (95% CI)	P value	HR (95% CI)	P value
A: Overall patients (n=1,004)	**n=503**	**n=501**				
NACE	29 (1.30)	19 (0.62)	0.345 (0.168–0.706)	0.004	0.534 (0.289–0.987)	0.045
Efficacy outcomes						
Cardiac death, MI or ST	27 (1.21)	12 (0.39)	0.204 (0.090–0.464)	<0.001	0.353 (0.172–0.728)	0.005
Cardiac death or MI	26 (1.16)	11 (0.40)	0.181 (0.077–0.430)	<0.001	0.350 (0.166–0.742)	0.006
Cardiac death	15 (0.67)	6 (0.19)	0.144 (0.045–0.459)	0.001	0.418 (0.161–1.087)	0.074
MI	17 (0.76)	9 (0.29)	0.238 (0.089–0.641)	0.004	0.422 (0.176–1.017)	0.054
ST	9 (0.40)	4 (0.13)	0.206 (0.047–0.908)	0.037	0.301 (0.087–1.044)	0.059
TLR	12 (0.54)	18 (0.58)	1.065 (0.444–2.554)	0.887	1.121 (0.507–2.478)	0.778
Stroke	7 (0.31)	16 (0.52)	2.060 (0.693–6.122)	0.194	1.810 (0.718–4.561)	0.208
Safety outcomes						
TIMI major bleeding	5 (0.22)	8 (0.26)	1.850 (0.491–6.975)	0.363	1.626 (0.522–5.062)	0.402
TIMI minor bleeding	12 (0.54)	12 (0.39)	0.915 (0.377–2.219)	0.844	0.731 (0.296–1.806)	0.497
B: Current-generation DES (n=689)	**n=431**	**n=258**				
NACE	22 (1.14)	4 (0.26)	0.31 (0.11–0.91)	0.033	0.273 (0.089–0.839)	0.023
Efficacy outcomes						
Cardiac death, MI or ST	20 (1.03)	1 (0.06)	0.09 (0.01–0.65)	0.017	0.071 (0.009–0.552)	0.011
Cardiac death or MI	19 (0.94)	1 (0.06)	0.09 (0.01–0.67)	0.019	0.076 (0.010–0.590)	0.014
Cardiac death	10 (0.51)	1 (0.06)	0.10 (0.02–1.37)	0.097	0.215 (0.023–1.969)	0.174
MI	12 (0.63)	1 (0.06)	0.14 (0.02–1.08)	0.059	0.099 (0.012–0.824)	0.032
ST	6 (0.31)	0 (0.0)	0.02 (0.01–0.62)	0.295	0.016 (0.001–13.989)	0.999
TLR	7 (0.36)	7 (0.44)	1.76 (0.62–5.02)	0.291	1.770 (0.589–5.316)	0.309
Stroke	6 (0.31)	6 (0.37)	1.81 (0.58–5.62)	0.305	2.149 (0.662–6.977)	0.203
Safety outcomes						
TIMI major bleeding	4 (0.20)	4 (0.26)	1.77 (0.44–7.07)	0.422	1.186 (0.210–6.689)	0.847
TIMI minor bleeding	9 (0.47)	7 (0.44)	1.36 (0.51–3.65)	0.544	1.280 (0.464–3.526)	0.634

CI, confidence interval; DES, drug eluting stent; HR, hazard ratio; MI, myocardial infarction; NACE, net adverse clinical event, which was defined as a composite of cardiac death, MI, ST, and major bleeding event; ST, stent thrombosis; TLR, target lesion revascularization; TIMI, Thrombolysis in Myocardial Infarction. Other abbreviations as in Table 1. †Variables included in these multivariable-adjusted models before and after PS weighting: age, sex, baseline ejection fraction, HTN, diabetes, CKD, dyslipidemia, smoking status, previous PCI history, DES type (current- or early-generation), lesion complexity (bifurcation lesion and 2-stent PCI), and DAPT score.

with a thin-plate spline for DAPT duration, adjusting for age, sex, clinical (hypertension, diabetes, chronic kidney disease, dyslipidemia, previous PCI history, and smoking intake habit), and procedural (stent type and bifurcation lesion) variables.

Second, to adjust for significant differences in the patient characteristics between the 2 groups, the inverse probability of weighted Cox proportional hazard regression analysis was used.[21] For the IPTW adjustment, the inverse of the propensity score was adjusted by using the proportional hazard regression model. After IPTW adjustment, the balance between the 2 groups was evaluated by SMDs, and the groups were regarded as being successfully balanced if the SMDs were within ±0.1 across all matched covariates.[21] To avoid drawing biased results and to investigate the robustness of this study, we performed multivariable adjusted Cox proportional hazard regression analysis by using the following populations: IPTW, 1:1 propensity score-matched, and unmatched population. We also performed the following 2 sensitivity analyses.

Two sensitivity analyses (**Supplementary File**) were performed to investigate the robustness of our primary analysis: (1) we excluded patients with early-generation DESs because the stent generation is a major confounding factor when analyzing post-procedural outcomes. Therefore, only those 689 patients with current-generation DESs were included in this sensitivity analysis; and (2) another sensitivity analysis was performed with the entire population (n=1,273), including patients who were followed for <12 months or presented with adverse events within 12 months after DES implantation at LMCA lesions.

To assess the optimal DAPT duration after LMCA stenting, we investigated several cut-off durations and estimated the sensitivity and specificity of predicting NACEs and ischemic events (cardiac death, MI, or ST), according to each cut-off duration. Then, we determined the optimal DAPT duration to be the one with the highest Youden index value (Youden's index = sensitivity + specificity − 1).[23] A P value of <0.05 was considered to be statistically significant. The event rates shown in **Figure 2** are represented as 'age- and sex-adjusted event rates per 100 persons·year' to provide more accurate comparisons among groups because the follow-up time periods differed among groups. Age and sex adjustments were calculated

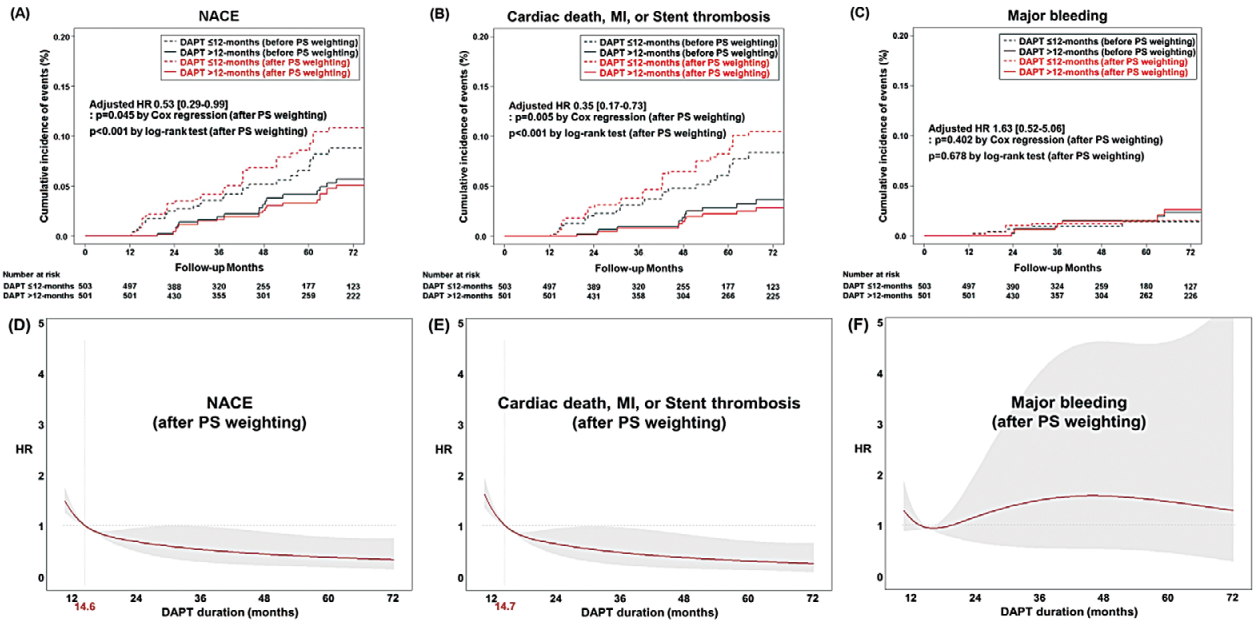

Figure 3. (**A**–**C**) Kaplan-Meier curves of (**A**) NACEs, (**B**) ischemic outcomes (cardiac death, MI, and ST), and (**C**) major bleeding events. (**D**–**F**) Duration–response relationships between DAPT durations and (**D**) NACEs, (**E**) ischemic outcomes (cardiac death, MI, or ST), and (**F**) major bleeding events, after PS weighting and testing using a log-linear model with thin-plate splines (clinical- and pre-procedural parameter-adjusted HRs). DAPT, dual antiplatelet therapy; HR, hazard ratio; MI, myocardial infarction; NACE, net adverse clinical event; PS, propensity score; ST, stent thrombosis.

by using age and sex stratification, using 5-year age groups. All statistical analyses were performed with R software (version 3.5.2; R Project for Statistical Computing).

Results

Baseline Characteristics

Of the 1,273 patients who received DES implantations of LMCA lesions, 1,004 patients met the inclusion criteria and were analyzed in this study. Among them, 503 patients discontinued either aspirin or the $P2Y_{12}$ inhibitor within 12 months, and 501 patients maintained DAPT for >12 months after DES implantation. The median DAPT durations were 9.1 and 29.9 months for the DAPT ≤12 months and DAPT 12 months groups, respectively. Because the groups were expected to differ with regards to patient characteristics, we performed propensity score-based inverse probability weighting to adjust for these differences, after which the SMDs of the clinical variables did not differ between the 2 groups (**Table 1** and **Supplementary Table 2** for 1:1 propensity score matched population). Approximately half of the patients presented with acute coronary syndrome at the time of LMCA stent implantation.

The propensity score distributions for the 2 groups are shown in **Supplementary Figure 1**.

Clinical Outcomes According to DAPT Duration

After a median of 4.5 years of follow up after the index PCI, NACEs occurred in 48 patients (4.5%), and significantly fewer NACEs occurred in the DAPT >12 months group than in the DAPT ≤12 months group (19 patients vs. 29 patients, 3.8% vs. 5.8%; multivariable-adjusted HR 0.53 [0.29–0.99], P=0.045, **Table 2A** and **Figure 3**; crude HRs were described in **Supplementary Table 3**) despite longer follow-up duration (median 63.8 and 54.4 months for the DAPT >12 and ≤12 months groups, respectively). Cardiac death, MI, or ST events occurred in 39 patients (3.9%), and a significantly fewer number of these events occurred in the DAPT >12 months group than in the DAPT ≤12 months group (12 patients vs. 27 patients, 2.4% vs. 5.4%; adjusted hazard ratio for DAPT >12 months=0.35 [0.17–0.73], P=0.005). Individually, cardiac death, MI, and ST were observed less frequently in the DAPT >12 months group than in the DAPT ≤12 months group (**Supplementary Figure 2**; cardiac death: 1.2% vs. 3.0%; adjusted HR=0.42 [0.16–1.09], P=0.074; MI: 1.8% vs. 3.4%; adjusted HR=0.42 [0.18–1.02], P=0.054; and ST: 0.8% vs. 1.8%; adjusted HR=0.30 [0.09–1.04], P=0.059). In addition, the incidence of major bleeding and stroke events were not statistically different between these groups (major bleeding: 1.6% vs. 1.0%; adjusted HR=1.63 [0.52–5.06], P=0.402; and stroke: 3.2% vs. 1.4%; adjusted H=1.81 [0.72–4.56], P=0.208). No differences were observed for the incidence of target lesion revascularization and minor bleeding between the 2 groups (target lesion revascularization: 3.6% vs. 2.4%; adjusted HR=1.12 [0.51–2.48], P=0.778; and any bleeding: 3.8% vs. 3.4%; adjusted HR=1.06 [0.51–2.24], P=0.870) (**Supplementary Figure 3**).

The distributions of ischemic events according to DAPT duration showed an increased number of ischemic events in the DAPT ≤12 months group compared with the DAPT >12 months group (**Supplementary Figure 4**).

We fit baseline- and pre-procedural, parameter-adjusted, Cox proportional-hazard, log-linear models with thin-plate

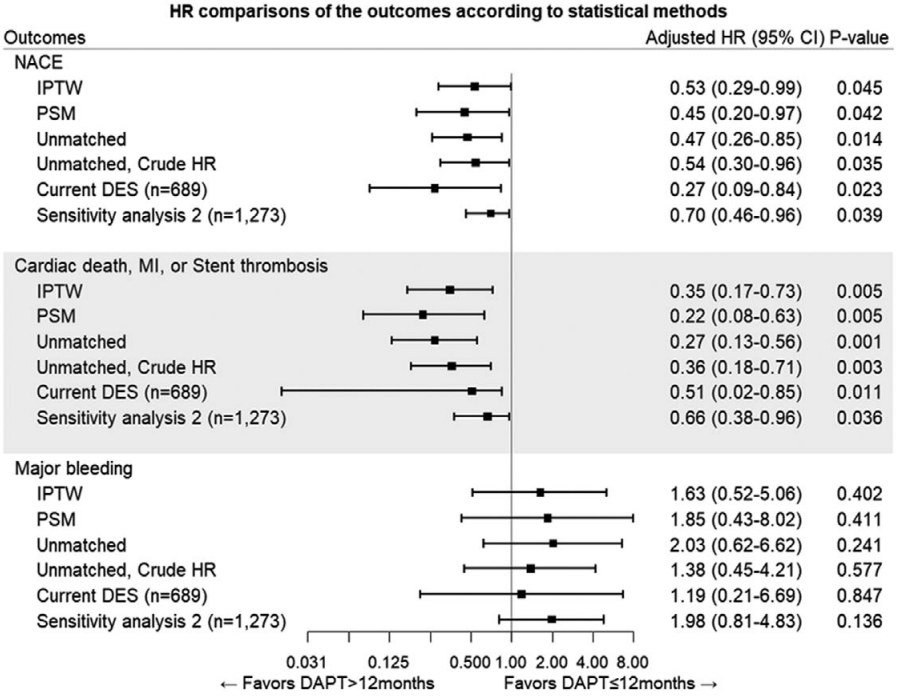

Figure 4. Forest plot for HR comparisons of the outcomes according to statistical methods. CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NACE, net adverse clinical event; PSM, 1:1 propensity score matching.

spline curves according to DAPT duration, and the prolongation of DAPT duration was significantly associated with decreased risks for NACEs and ischemic outcomes (cardiac death, MI, or ST) (**Figure 3**). NACEs and ischemic events (cardiac death, MI, or ST) were significantly reduced in patients who received DAPT for >14.6 months and DAPT for >14.7 months compared to the opposites, respectively (**Figure 3**). Two sensitivity analyses for patients who received current-generation DES (n=689) and for the entire population (n=1,273) also showed consistent results (**Supplementary Figure 5**). We briefly described these results as a forest plot for HR comparisons of the outcomes according to statistical methods (**Figure 4**).

Supplementary Figure 6 shows the receiver operating characteristic curves, based on DAPT duration, associations between DAPT duration, and the occurrence of NACEs or ischemic outcomes (cardiac death, MI, or ST). The DAPT duration concordance indices plural of concordance index of the prediction models for NACEs and ischemic outcomes (cardiac death, MI, or ST) were 0.75 [0.67–0.83] and 0.73 [0.64–0.83], respectively. The specific DAPT durations that were associated with decreased risks for these outcomes were >15 months for both NACEs and ischemic outcomes, based on the highest Youden's index values (Youden's index: 0.420 at DAPT ≥15 months) (**Supplementary Figure 6**, **Supplementary Tables 4** and **5**).

Subgroup Analysis

The NACE rate was consistently lower in the DAPT >12 months group than in the DAPT ≤12 months group, across several subgroups (**Figure 2**). No significant interactions were found between subgroups (**Figure 1**).

Clinical Outcomes for Current-Generation DESs

To perform a sensitivity analysis, we excluded those patients who received early-generation DESs and only analyzed patients who received current-generation DESs (n=689). Consistently, the results showed that the rates of NACEs (adjusted HR 0.273 [0.089–0.839] after PS-weighting: propensity score weighting, P=0.023) and ischemic outcomes (cardiac death, MI, or ST; adjusted HR=0.071 [0.009–0.552] after PS-weighting, P=0.011) were significantly lower in the DAPT >12 months group (n=258) than in the DAPT ≤12 months group (n=431), without significant increases in the major bleeding rate (P=0.847) during a similar follow-up duration (47.4 and 48.6 months, respectively) (**Table 2B**).

Discussion

The results of our study can be summarized as follows:

(1) Patients with a prolonged duration of DAPT, >12 months, showed a lower rate of NACEs than patients with a DAPT duration <12 months.

(2) The number of ischemic events was reduced in patients who received DAPT for >12 months compared with those who received DAPT ≤12 months, without increasing the number of major bleeding events.

(3) With current-generation DESs, the number of NACEs and ischemic outcomes (cardiac death, MI, or ST) were significantly reduced in patients who received DAPT for >12 months than in patients who received DAPT

for ≤12 months.

Under current guidelines, PCI is recommended as an alternative strategy to CABG for patients with LMCA disease, especially ostial and shaft lesions. However, no randomized study has examined the optimal duration of DAPT after LMCA stenting. LMCA lesions frequently require complex procedural processes because of unique anatomical factors, including large vessel sizes and distal bifurcated lesions, in addition to the clinical importance of LMCA.[16]

Although no studies have directly examined LMCA lesions, several studies have examined the beneficial effects of prolonged DAPT. In a retrospective analysis of the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial, 336 patients who underwent coronary stenting in the LMCA and/or the proximal left descending coronary artery showed consistent benefits with prolonged DAPT compared with patients who received 6 months of DAPT.[10] A previous study that performed a post hoc, patient-level, pooled analysis of randomized, controlled trials showed that patients who received complex PCI, including for LMCA lesions, and prolonged DAPT (≥1 year) had significantly reduced risks of ischemic events compared with patients who received shorter periods of DAPT (3 or 6 months).[24] However, only 49 patients with LMCA lesions were included among 1,680 patients treated with complex PCI, which does not represent the real-world clinical occurrence of LMCA lesions; however, the current study analyzed a relatively large, real-world patient population to evaluate the role of prolonged DAPT after LMCA lesions, and considering the complexity of LMCA lesions. Previous results from the Coronary Bifurcation Stenting (COBIS) II registries showed that the risk of all-cause death or MI was significantly lower in the DAPT >12 months group than in the DAPT ≤12 months group after PCI of bifurcation lesions with DESs, but this analysis primarily included non-LMCA lesions, and the proportion of early-generation DESs was higher than current-generation DESs.[25]

Several studies have attempted to determine the optimal DAPT duration for second-generation DESs, balancing safety and efficacy. However, few studies have assessed the optimal duration of DAPT in patients with LMCA lesions or examined whether the prolonged use of DAPT is necessary when using second-generation DESs.[24] Compared with a previous similar study,[26] this study included all LMCA lesions including ostial and shaft, as well as bifurcation lesions. Interestingly, extended DAPT duration (>12 months) showed comparable beneficial effect in non-bifurcation lesions after LMCA stenting. However, determining the optimal DAPT duration must consider bleeding risks, as well as ischemic risks, because DAPT-related bleeding is the most common complication after stent implantation and is associated with lower survival rates.[27] More interestingly, we developed a spline model of NACEs, cardiac deaths, MIs, STs, and major bleeding events to identify the optimal duration of DAPT. The curve shows an abrupt decrease in the hazard ratio for NACEs, cardiac death, MI, and ST and an increase in major bleeding events after 15 months of DAPT. In addition, >15 months of DAPT was shown to reduce NACEs and represents the best cut-off time point, based on the highest Youden's index value in this analysis, which was a similar result to that returned by the spline model. This finding suggests at least 15 months of DAPT may provide beneficial effects that balance the potential for ischemic and bleeding events. During the subgroup analysis, no significant interactions were observed for any group, indicating that the LMCA lesion is a more crucial factor for determining the optimal DAPT duration than other clinical and anatomical factors. For bifurcation lesions, a recent study showed that DAPT for <12 months increased the incidence of thrombotic adverse events in patients with bifurcation lesions treated with a 2-stent strategy but not for patients treated with a 1-stent strategy.[28] However, the current study demonstrated that a longer duration of >12 months of DAPT resulted in better clinical outcomes than a duration of ≤12 months of DAPT, irrespective of the presence of bifurcation. This result might be due to the higher chance of acute malapposition for non-LMCA lesions, due to ostial location and large vessel diameter, even for non-bifurcation lesions. However, patients treated with a 2-stent strategy represented only 7% of the population in this registry, which may limit our ability to determine the benefits of longer DAPT durations in patients treated with a 2-stent strategy; this result showed a discrepancy compared with the findings from a previous study.[26]

Limitations and Future Clinical Applications

Our study had the following limitations. (1) Although the patients were enrolled from a large-scale, multicenter registry, this was an observational study and the patient characteristics were expected to differ between the 2 groups. However, inverse probability weighting and propensity score-matched analysis for these patients was used to adjust for differences in baseline and pre-procedural parameters, based on propensity scores, and a multivariable-adjusted Cox regression analysis was also performed after propensity score weighting or matching to compare the outcomes between these groups, and overall results were consistent (**Figure 4**). (2) To compare the DAPT effect accurately, we excluded patients who were followed for <12 months or presented with adverse events within 12 months after the index procedure; therefore, the number of major bleeding events was quite low although these patients were enrolled from a large-scale multicenter registry. However, during the overall 3.8-year follow up among the entire 1,273 patients, 51 (1.05%/year) MI and 27 (0.56%/year) major bleeding events occurred, and 25 (1.96%) and 14 (1.09%) patients experienced MI and major bleeding within initial 12 months after coronary intervention, respectively; these findings are similar to those found in previous studies.[29–31] Any (major or minor) bleeding events were not significantly increased in the DAPT >12 months group compared with the ≤12 months group (3.8% vs. 3.4%, **Supplementary Figures 3** and **7**). (3) We prescribed the antiplatelet agents as per the guidelines;[16] the proportion of patients who received novel antiplatelet agents was quite low. However, among 480 patients with acute coronary syndrome, 408 patients (85%) were enrolled before 2015, and 68 patients were prescribed ticagrelor and prasugrel in our cohort (**Table 1**). (4) This study included 689 patients (68.6%) with current-generation DES and ~30% patients were treated with early-generation DES; however, the sensitivity analysis for patients with current-generation DES also showed consistency (**Table 2B** and **Supplementary Figure 5**). (5) Although this study showed favorable results about prolonged DAPT after LMCA stenting in patients who can continue DAPT without major bleeding events, recent studies (GLOBAL Leaders[32] and TWILIGHT[33] trials) also

showed favorable outcomes with short DAPT after coronary stenting in complex coronary artery lesions. Future prospective studies would be needed to investigate these issues.

Conclusions

This study investigated the effects of prolonged DAPT (>12 months) after LMCA stenting for patients who can continue DAPT without major bleeding events, and found a lower incidence of NACEs and ischemic outcomes with comparable safety, compared with patients who have DAPT for ≤12 months. Moreover, these results were also shown consistently for patients with current-generation DES. A prospective randomized trial that includes a large number of patients using only current-generation DESs is necessary.

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Disclosures

The authors have no conflicts of interest to disclose.

IRB Information

This study was approved by the Institutional Review Board at Severance Hospital of the Yonsei University Health System (4-2018-0759).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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