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Long-Term Clinical Outcomes and Optimal Stent Strategy in Left Main Coronary Bifurcation Stenting

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CME/MOC Objective for This Article: At the end of the activity the reader should be able to: 1) compare the clinical outcomes of 1- vs. 2-stent strategy for left main coronary artery (LMCA) bifurcation stenting according to stent generation; 2) describe the predictors of major adverse cardiovascular events (MACE) after treating LMCA bifurcation lesions; and 3) appraise the optimal stent strategy and techniques for LMCA bifurcation stenting: which patients need to be treated with a 2-stent strategy?

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Long-Term Clinical Outcomes and Optimal Stent Strategy in Left Main Coronary Bifurcation Stenting

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ABSTRACT

OBJECTIVES This study sought to investigate the long-term clinical effects of stent generation and stent strategy for left main coronary artery (LMCA) bifurcation lesion treatment.

BACKGROUND Limited data are available to assess long-term clinical outcomes after stenting, including use of current-generation drug-eluting stent (C-DES) for treatment of LMCA bifurcation lesions.

METHODS A total of 1,353 patients who were recorded in 2 multicenter real-world registries were treated by either early-generation drug-eluting stent (E-DES) (n = 889) or C-DES (n = 464). Primary endpoint was major adverse cardiovascular events (MACE). MACE was defined as a composite of cardiac death or myocardial infarction, stent thrombosis, and target lesion revascularization rates during 3-year follow-up. The authors further performed propensity-score adjustment for clinical outcomes.

RESULTS During 3-year follow-up, the overall MACE rate was 8.7%. Use of a 1-stent strategy resulted in better clinical outcomes than use of a 2-stent strategy (4.7% vs. 18.6%, hazard ratio [HR]: 3.71; 95% confidence interval [CI]: 2.55 to 5.39; $p < 0.001$). Use of C-DES resulted in a lower MACE rate compared with using E-DES (4.6% vs. 10.9%, HR: 0.55; 95% CI: 0.34 to 0.89; $p = 0.014$), especially for the 2-stent strategy. For patients with C-DES, the presence of chronic kidney disease and pre-intervention side branch diameter stenosis ≥50% were significant independent predictors of MACE.

CONCLUSIONS Intervention of LMCA bifurcation lesions using DES implantation demonstrated acceptable long-term clinical outcomes, especially in C-DES patients. Use of a 1-stent strategy resulted in better clinical benefits than using a 2-stent strategy. (J Am Coll Cardiol Intv 2018;11:1247–58) © 2018 by the American College of Cardiology Foundation.

Coronary artery bypass graft (CABG) surgery has been the standard treatment for left main coronary artery (LMCA) disease for approximately 30 years, and percutaneous coronary intervention (PCI) has become an emerging alternative treatment option (1,2). However, along with the rapid development of medical technology, current guidelines indicate that PCI with drug-eluting stent (DES) is an optimal revascularization strategy for treatment of LMCA disease (3). Randomized clinical trials (RCTs) revealed that PCI using DES might be a reasonable treatment strategy for LMCA disease (4–7). However, most studies on LMCA bifurcation lesion stenting have examined early-generation DES (E-DES), whereas only a few existing studies have explored the optimal stent strategy for LMCA bifurcation lesion treatment using real-world practice data (8,9). In addition, limited data are available to be used in treatment guidelines for PCI outcomes of LMCA bifurcation lesion, compared with those for LMCA ostial or trunk lesion (10).

We investigated the long-term clinical effects of applying stent strategy and current-generation DES (C-DES) in LMCA bifurcation stenting, using large sample size datasets from 2 multicenter real-world registries.

METHODS

STUDY POPULATION. The KOMATE (Korean Multicenter Angioplasty Team) multicenter registry of DES implantation comprises data from 8 major coronary intervention centers. The COBIS (Coronary Bifurcation Stenting) II registry is a retrospective multicenter

registry dedicated to bifurcation lesion PCI (using DES) treatment cases. Sixteen major coronary intervention centers in Korea submit patient data to the COBIS II registry. From February 2002 to September 2013, a total of 1,353 patients were selected as the study population. Data for 569 patients with LMCA bifurcation lesions were taken from the KOMATE registry; among them, 496 patients (87.2%) were treated by a 1-stent strategy PCI, and 73 patients (12.8%) were treated by a 2-stent strategy PCI. Data for the remaining 784 patients were taken from the COBIS II registry; among them, 470 patients (59.9%) were treated by a 1-stent strategy PCI, and 314 patients (40.1%) were treated by a 2-stent strategy PCI (**Figure 1**). Inclusion criteria were the entire LMCA bifurcation lesions treated solely using DES due to either stable coronary artery disease or acute coronary syndrome (ACS). Exclusion criteria were cardiogenic shock and cardiopulmonary resuscitation. LMCA bifurcation lesions were classified according to the Medina classification: 1,1,1 type, 1,0,1 type, and 0,1,1 type were defined as true bifurcation lesions (11).

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The KOMATE registry is based on real clinical practice, and regulatory authorities require only written informed consent for coronary intervention studies. Written informed consent was obtained from every patient. The COBIS II registry was funded by the Korean Society of Interventional Cardiology. Local institutional review board at each hospital has approved the study protocol and waived the requirement for informed consent for access to each institution's PCI registry.

PCI PROCEDURE. PCI procedures were performed according to current practice guidelines. All patients received loading doses of aspirin (300 mg/day) and clopidogrel (300 mg or 600 mg) before PCI. Aspirin was continued indefinitely, and clopidogrel duration was left to the operator's discretion. Factors such as the access location, type of DES, and use of intravascular ultrasound and final kissing balloon inflation were all left to the operator's discretion. In addition, decisions to treat bifurcation lesions by a 1- or 2-stent strategy were made by individual operators. E-DES used in this study included paclitaxel-eluting stents (TAXUS, Boston Scientific, Natick, Massachusetts), sirolimus-eluting stents (CYPHER, Cordis, Fremont, California), and zotarolimus-eluting stent-SPLINT (ENDEAVOR SPLINT, Medtronic, Minneapolis, Minnesota). C-DES included everolimus-eluting stents (XIENCE, Abbott Vascular, Santa Clara, California), zotarolimus-eluting stent-RESOLUTE (RESOLUTE INTEGRITY, Medtronic), and biolimus-eluting stents (NOBORI, Terumo, Tokyo, Japan).

FOLLOW-UP, DATA COLLECTION, AND ANALYSIS. Clinical, angiographic, procedural, and outcome data were collected using a web-based reporting system. Additional information was obtained by further inquiry into medical records or telephone contact, if necessary. An independent clinical event adjudicating committee reviewed all data on outcomes reported from participating centers. Every patient in both registries received clinical follow-ups of up to 3 years (median follow-up duration 28.73 months; interquartile range: 12.00 to 48.02 months).

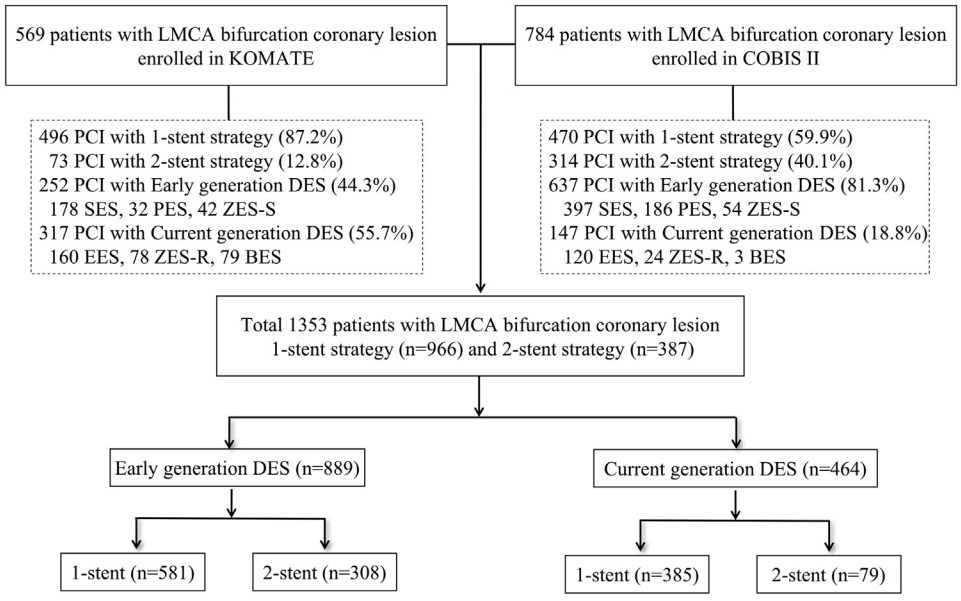
QUANTITATIVE CORONARY ANGIOGRAPHY. Quantitative coronary angiographic (QCA) analysis of patients in the KOMATE registry was performed using an off-line QCA system (CAAS system, Pie Medical Imaging, Maastricht, the Netherlands) at the angiography core laboratory (Cardiovascular Research Center, Yonsei University Medical Center, Seoul, South Korea). QCA analysis for patients in the COBIS II registry was performed using Centricity CA 1000 (GE, Waukesha, Wisconsin) at the angiography core laboratory (Cardiac and Vascular Center, Samsung Medical Center, Seoul, South Korea). We measured reference diameter and minimal luminal diameter at the LMCA (proximal vessel [PV]), left anterior descending (LAD) coronary artery (main branch [MB]), and left circumflex coronary (LCx) artery (side branch [SB]). Coronary artery disease was defined as coronary artery stenosis with lumen diameter reduction of 50%. Lesion length and bifurcation angle were also measured.

CLINICAL OUTCOMES AND DEFINITIONS. The primary endpoint was major adverse cardiovascular events (MACE), which were defined as a composite of cardiac death, fatal or nonfatal acute myocardial infarction (MI), stent thrombosis (ST), and target lesion revascularization (TLR). Fatal or nonfatal acute MI was defined as an increase in creatine kinase-myocardial band or troponin level to the 99th percentile of the upper limit of the normal range with ischemic symptoms or electrocardiographic findings indicative of ischemia, which was not related to the index procedure. ST was defined as definite ST

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CABG = coronary artery bypass
C-DES = current-generation drug-eluting stent(s)
CI = confidence interval
CKD = chronic kidney disease
DES = drug-eluting stent(s)
DK = double kissing
DS = diameter stenosis
E-DES = early-generation drug-eluting stent(s)
HR = hazard ratio
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
LMCA = left main coronary artery
MACE = major adverse cardiovascular event(s)
MB = main branch
MI = myocardial infarction
PCI = percutaneous coronary intervention
POT = proximal optimization technique
PV = proximal vessel
QCA = quantitative coronary angiographic analysis
RCT = randomized clinical trial
SB = side branch
ST = stent thrombosis
TLR = target lesion revascularization

FIGURE 1 Overview of Study Scheme



BES = biolimus-eluting stent(s); COBIS = Coronary Bifurcation Stenting; EES = everolimus-eluting stent(s); KOMATE = Korean Multicenter Angioplasty Team; LMCA = left main coronary artery; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); ZES-R = zotarolimus-eluting stent-RESOLUTE; ZES-S = zotarolimus-eluting stent-SPLINT.

according to the Academic Research Consortium definitions. TLR was defined as a repeat PCI of a lesion within 5 mm of the original stent deployment (12).

STATISTICAL ANALYSIS. Results for continuous variables were expressed as mean ± SD, and compared by the Student's *t*-test. Categorical variables were reported as frequencies (percentages), and compared by the chi-square test. Survival curves were prepared after Kaplan-Meier analysis, and compared by the log-rank test. Cox proportional hazards models were used to identify independent predictors of primary endpoints. The models were also used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical outcomes. Propensity-score matching was used to reduce selection bias associated with stent strategy and potential confounding factors in the observational study, and to adjust significant differences in the patients' baseline characteristics or procedure data. Propensity scores were estimated using multiple logistic regression analysis. Included covariates were age, sex, hypertension, diabetes, acute coronary syndrome, multivessel disease, chronic kidney disease, dyslipidemia, smoking, previous PCI, and previous CABG surgery. Patients were matched based on the closest possible value of propensity score (nearest neighbor matching). A matching caliper of 0.05 SDs of the logit of estimated propensity score was enforced, in order to make sure that matches of poor fit were excluded. We then performed a 1:2 propensity-score matching iteration. In subgroup analyses, tests of interaction were used to confirm differential clinical outcomes of stent strategy. Statistical Package for the Social Sciences (SPSS 20.0, SPSS, Chicago, Illinois) was used for all statistical evaluations. Values of $p < 0.05$ were considered to indicate statistically significant results.

RESULTS

PATIENT CLINICAL, ANGIOGRAPHIC, AND PROCEDURE CHARACTERISTICS. The entire study population included mostly male patients (74.1%), as well as those with multivessel disease (63.9%) and hypertension (60.2%) (Table 1). The mean SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score was 22.96 ± 8.77. A total of 889 (65.7%) patients were treated using PCI with E-DES; 387 (34.3%) patients were treated using PCI with C-DES. ACS was more common in patients with E-DES; multivessel disease was more common in C-DES patients. Compared with patients who

received E-DES, a greater percentage of patients who received C-DES underwent a 1-stent strategy procedure.

The 2-stent strategy group also had a higher prevalence of ACS, multivessel disease, previous PCI, and higher SYNTAX score compared with 1-stent strategy group (Table 2). In C-DES group, patients who underwent 2-stent strategy procedure had an even greater prevalence of ACS and multivessel disease compared with those who underwent 1-stent strategy procedure. Patients who underwent 2-stent strategy procedure had more true bifurcation lesions, and more frequently underwent final kissing balloon inflation and intravascular ultrasound (IVUS) in both E-DES and C-DES groups. Comparison of baseline characteristics between 1- and 2-stent strategies applied in the stent population after propensity-score matching is shown in Online Table S1.

QCA ANALYSIS. In both the E-DES and C-DES groups, patients who underwent a 2-stent strategy procedure had significantly smaller PV and SB minimal lumen diameters, greater percentages of MB and SB diameter stenosis (DS), and longer SB lesion length than patients who underwent a 1-stent strategy procedure (Table 3). The angles between the MBs and SBs were similar in both stent strategy groups. Comparison of QCA analysis between 1- and 2-stent strategies applied in the stent population after propensity-score matching is shown in Online Table S2.

CLINICAL OUTCOMES ACCORDING TO DES GENERATION AND STENT STRATEGY. During the median follow-up period of 25.90 months (interquartile range: 11.00 to 45.02 months), MACE rate was 8.7% in the entire population of LMCA bifurcation lesion patients. MACE differences between stent generation and stent strategy are shown in the Figure 2. In the entire population, use of a 2-stent strategy resulted in higher rate of MACE, cardiac death or MI, and TLR, compared with using a 1-stent strategy. In the E-DES group, use of a 2-stent strategy resulted in a higher rate of MACE compared with using a 1-stent strategy, mainly due to higher TLR rate (HR: 3.81; 95% CI: 2.49 to 5.83; $p < 0.001$). In the C-DES group, the 2-stent strategy tended to result in a higher MACE rate, but the result was not statistically significant (HR: 2.31; 95% CI: 0.95 to 5.59; $p = 0.065$) (Figure 2, Table 4). After 1:2 matching between 1- and 2-stent strategies in the entire population and E-DES groups using the propensity score, a 2-stent strategy still led to a significantly higher rate of MACE compared with a 1-stent strategy. In the C-DES group, use of a 2-stent strategy resulted in a similar rate of MACE compared with using a 1-stent strategy according to propensity-score matched analysis (HR: 1.28; 95% CI: 0.37 to 4.44; $p = 0.698$) (Table 4). In 1-stent strategy group, MACE rates were similar between the E-DES and C-DES groups (5.6% vs. 3.4%, respectively, HR: 0.90; 95% CI: 0.47 to 1.74; $p = 0.758$). In 2-stent strategy group, MACE rates tended to be higher in E-DES groups, but the difference was not statistically significant (20.7% vs. 10.4%,

TABLE 1 Patient Clinical, Angiography, and Procedure Characteristics

	Entire Population (N = 1,353)	Early Generation (n = 889)	Current Generation (n = 464)	p Value
Age, yrs	63.42 ± 10.43	63.27 ± 10.35	63.72 ± 10.58	0.458
Male	1,002 (74.1)	658 (74.0)	344 (74.1)	0.961
SYNTAX score	22.96 ± 8.77	22.79 ± 9.19	23.30 ± 7.90	0.308
ACS	683 (50.5)	466 (52.4)	217 (46.8)	0.048
Multivessel disease	865 (63.9)	536 (60.3)	329 (70.9)	<0.001
Smoking	438 (32.4)	257 (28.9)	181 (39.0)	<0.001
DM	448 (33.1)	290 (32.6)	158 (34.1)	0.596
HTN	815 (60.2)	521 (58.6)	294 (63.4)	0.09
CKD	57 (4.2)	40 (4.5)	17 (3.7)	0.468
Dyslipidemia	593 (43.8)	365 (41.1)	228 (49.1)	0.004
Pre-PCI	280 (20.7)	193 (21.7)	87 (18.8)	0.202
Pre-CABG	54 (4.0)	28 (3.1)	26 (5.6)	0.029
LVEF	55.31 ± 19.30	54.88 ± 19.74	56.04 ± 18.53	0.313
True bifurcation*	563 (41.6)	371 (41.7)	192 (41.4)	0.900
Medina				0.097
1,1,1	410 (30.3)	264 (29.7)	146 (31.5)	
1,0,1	79 (5.8)	50 (5.6)	29 (6.3)	
0,1,1	74 (5.5)	57 (6.4)	17 (3.7)	
1,0,0	138 (10.2)	91 (10.2)	47 (10.1)	
1,1,0	339 (25.1)	208 (23.4)	131 (28.2)	
0,1,0	258 (19.1)	178 (20.0)	80 (17.2)	
0,0,1	55 (4.1)	41 (4.6)	14 (3.0)	
Stent type				<0.0001
SES	575 (42.5)	575 (64.7)		
PES	218 (16.1)	218 (24.5)		
EES	280 (20.7)		280 (60.3)	
ZES-S	96 (7.1)	96 (10.8)		
ZES-R	102 (7.5)		102 (22.0)	
BES	82 (6.1)		82 (17.7)	
Stent technique				<0.0001
1-stent strategy	966 (71.4)	581 (65.4)	385 (83.0)	
2-stent strategy	387 (28.6)	308 (34.6)	79 (17.0)	<0.0001
T-stenting	135 (10.0)	111 (12.5)	24 (5.2)	
Crush	164 (12.1)	128 (14.4)	36 (7.8)	
Kissing or V stent	13 (1.0)	10 (1.1)	3 (0.6)	
Culotte	66 (4.9)	57 (6.4)	9 (1.9)	
Others	9 (0.6)	2 (0.2)	7 (1.5)	
Kissing	592 (43.8)	452 (50.8)	140 (30.2)	<0.0001
IVUS	770 (56.9)	500 (56.2)	270 (58.2)	0.492

Values are mean ± SD or n (%). *True bifurcation = Medina classification 1,1,1 type, 1,0,1 type, and 0,1,1 type.

ACS = acute coronary syndrome(s); BES = biolimus-eluting stent; CABG = coronary bypass graft; CKD = chronic kidney disease; DM = diabetes mellitus; EES = everolimus-eluting stent(s); HTN = hypertension; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); ZES-R = zotarolimus-eluting stent-RESOLUTE; ZES-S = zotarolimus-eluting stent-SPLINT.

TABLE 2 Patient Clinical, Angiography, and Procedure Characteristics According to DES Generation and Stent Strategy

	Early-Generation DES (n = 889)			Current-Generation DES (n = 464)		
	1-Stent (n = 581)	2-Stent (n = 308)	p Value	1-Stent (n = 385)	2-Stent (n = 79)	p Value
Age, yrs	63.2 ± 10.4	63.5 ± 10.2	0.89	63.3 ± 10.3	65.9 ± 11.7	0.042
Male	440 (75.7)	218 (70.8)	0.11	281 (73.0)	63 (79.7)	0.211
SYNTAX score	21.4 ± 8.9	25.4 ± 9.1	<0.0001	23.0 ± 7.9	24.6 ± 7.9	0.118
ACS	277 (47.7)	189 (61.4)	<0.0001	170 (44.2)	47 (59.5)	0.013
Multivessel disease	277 (47.7)	259 (84.1)	<0.0001	261 (67.8)	68 (86.1)	0.001
Smoking	183 (31.5)	74 (24.0)	0.019	151 (39.2)	30 (38.0)	0.836
DM	189 (32.5)	101 (32.8)	0.937	140 (36.4)	18 (22.8)	0.02
HTN	339 (58.3)	182 (59.7)	0.83	242 (62.9)	52 (65.8)	0.618
CKD	25 (4.3)	15 (4.9)	0.698	16 (4.2)	1 (1.3)	0.213
Dyslipidemia	247 (42.5)	118 (38.3)	0.226	200 (51.9)	28 (35.4)	0.008
Pre-PCI	106 (18.2)	87 (28.2)	0.001	76 (19.7)	11 (13.9)	0.228
Pre-CABG	20 (3.4)	8 (2.6)	0.492	23 (6.0)	3 (3.8)	0.444
LVEF, %	54.7 ± 20.4	55.2 ± 18.3	0.78	56.3 ± 18.6	54.9 ± 18.4	0.559
True bifurcation*	147 (25.3)	224 (72.7)	<0.0001	133 (34.5)	59 (74.7)	<0.0001
Medina			<0.0001			<0.0001
1,1,1	103 (17.7)	161 (52.3)		106 (27.5)	40 (50.6)	
1,0,1	30 (5.1)	20 (6.5)		19 (4.9)	10 (12.7)	
0,1,1	14 (2.4)	43 (14.0)		8 (2.1)	9 (11.4)	
1,0,0	84 (14.5)	7 (2.3)		46 (11.9)	1 (1.3)	
1,1,0	173 (29.8)	35 (11.4)		128 (33.2)	3 (3.8)	
0,1,0	162 (27.9)	16 (5.2)		71 (18.4)	9 (11.4)	
0,0,1	15 (2.6)	26 (8.4)		7 (1.8)	7 (8.9)	
Stent type			0.004			0.214
SES	375 (64.5)	200 (64.9)				
PES	130 (22.4)	88 (28.6)				
ZES-S	76 (13.1)	20 (6.5)				
ZES-R				81 (21.0)	21 (26.6)	
EES				231 (60.0)	49 (62.0)	
BES				73 (19.0)	9 (11.4)	
Stent technique						
1-stent technique	581 (100.0)		<0.001	385 (100.0)		<0.001
2-stent technique						
T-stenting		111 (36.0)			24 (30.4)	
Crush		128 (41.6)			36 (45.6)	
Kissing or V stent		10 (3.2)			3 (3.8)	
Culotte		57 (18.5)			9 (11.4)	
Others		2 (0.6)			7 (8.9)	
Kissing	183 (31.5)	269 (87.3)	<0.0001	72 (18.7)	68 (86.1)	<0.0001
IVUS	309 (53.2)	191 (62.0)	0.012	218 (56.6)	52 (65.8)	0.131
Main vessel						
Total stent length, mm	28.8 ± 14.83	29.39 ± 14.69	0.57	31.6 ± 17.0	25.9 ± 12.8	0.001
Maximal stent diameter, mm	3.42 ± 0.34	3.35 ± 0.34	0.004	3.47 ± 0.4	3.38 ± 0.45	0.11
Side branch						
Total stent length, mm		23.17 ± 11.69			19.54 ± 7.12	
Maximal stent diameter, mm		3.13 ± 0.37			3.04 ± 0.41	

Values are mean ± SD or n (%). *True bifurcation = Medina classification 1,1,1 type, 1,0,1 type, and 0,1,1 type.
DES = drug-eluting stent(s); DM = diabetes mellitus; HTN = hypertension; other abbreviations as in Table 1.

respectively; HR: 0.54; 95% CI: 0.26 to 1.12; p = 0.098) (Figure 3).

MULTIVARIATE ANALYSIS OF PREDICTORS FOR CLINICAL OUTCOMES OF LMCA BIFURCATION LESION TREATMENT. Independent predictors for MACE were use of 2-stent strategy and presence of chronic kidney disease (CKD) in the entire population and the E-DES group. In the C-DES group, the strongest predictors for MACE were pre-intervention SB DS >50% (HR: 5.24; 95% CI: 2.20 to 12.46; p < 0.0001) and

TABLE 3 Quantitative Coronary Angiographic Analysis

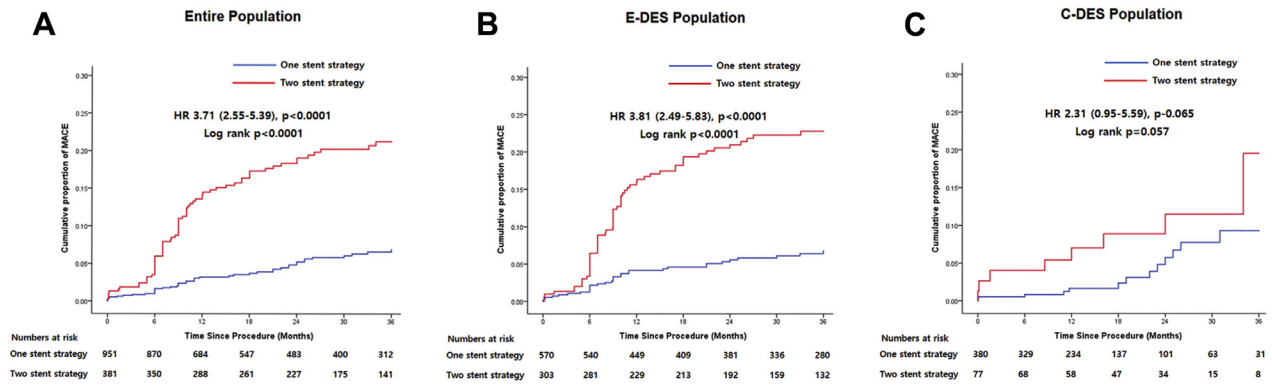
	Early-Generation DES (n = 889)			Current-Generation DES (n = 464)		
	1-Stent (n = 581)	2-Stent (n = 308)	p Value	1-Stent (n = 385)	2-Stent (n = 79)	p Value
Bifurcation angle, degrees	84.11 ± 29.50	83.00 ± 25.66	0.561	85.32 ± 28.72	82.05 ± 28.41	0.345
Pre-intervention						
PV RD, mm	3.87 ± 0.72	3.86 ± 0.65	0.834	3.87 ± 0.56	3.80 ± 0.49	0.314
MB RD, mm	3.39 ± 12.42	2.72 ± 0.54	0.342	2.83 ± 0.53	2.76 ± 0.52	0.285
SB RD, mm	2.88 ± 0.64	2.75 ± 0.49	0.001	2.69 ± 0.67	2.66 ± 0.53	0.705
PV MLD, mm	2.42 ± 1.02	2.10 ± 0.89	<0.0001	2.32 ± 0.93	2.06 ± 1.00	0.027
MB MLD, mm	1.57 ± 0.79	1.47 ± 0.62	0.039	1.68 ± 0.85	1.49 ± 0.72	0.07
SB MLD, mm	2.18 ± 0.79	1.42 ± 0.62	<0.0001	2.13 ± 0.78	1.44 ± 0.75	<0.0001
MB DS, %	56.87 ± 23.63	61.47 ± 19.57	0.002	44.13 ± 29.86	55.49 ± 23.58	0.002
SB DS, %	26.86 ± 20.87	52.23 ± 20.71	<0.0001	21.57 ± 22.4	48.82 ± 25.71	<0.0001
MB lesion length, mm	20.61 ± 14.31	21.56 ± 16.14	0.371	24.50 ± 15.50	17.36 ± 13.31	<0.0001
SB lesion length, mm	6.28 ± 10.1	10.7 ± 9.75	<0.0001	6.16 ± 6.53	10.07 ± 8.76	<0.0001
Post-intervention						
PV RD, mm	3.91 ± 0.66	3.92 ± 0.70	0.811	3.91 ± 0.58	3.80 ± 0.54	0.125
MB RD, mm	3.05 ± 0.56	2.87 ± 0.57	<0.0001	2.92 ± 0.54	2.86 ± 0.44	0.322
SB RD, mm	2.89 ± 0.64	2.82 ± 0.51	0.114	2.66 ± 0.67	2.76 ± 0.48	0.127
PV MLD, mm	3.56 ± 0.53	3.66 ± 0.61	0.018	3.43 ± 0.59	3.58 ± 0.53	0.03
MB MLD, mm	3.10 ± 0.49	2.99 ± 0.44	0.001	3.12 ± 0.52	2.99 ± 0.48	0.041
SB MLD, mm	2.14 ± 0.72	2.67 ± 0.52	<0.0001	2.01 ± 0.78	2.54 ± 0.62	<0.0001

Values are mean ± SD.
DES = drug-eluting stent(s); DS = diameter stenosis; MB = main branch; MLD = minimal luminal diameter; PV = proximal vessel; RD = reference diameter; SB = side branch.

presence of CKD (HR: 5.00; 95% CI: 1.46 to 17.12; p = 0.01) (Table 5). In the C-DES group, performing IVUS served as an independent predictor for reduction of cardiac death or MI.

SUBGROUP ANALYSIS. We analyzed MACE rates according to pre-specified clinical and QCA parameter subgroups. In the entire population and the E-DES group, use of a 1-stent strategy consistently resulted in better clinical outcomes in all subgroups, compared with using a 2-stent strategy (Online Figures S1 and S2). However, in the C-DES group, the 2-stent strategy resulted in better outcomes when the DS of the SB was >50%; when SB stenosis was >65%, improvement was statistically significant (Online Figure S3).

FIGURE 2 Kaplan-Meier Curves According to Stent Strategy Used for LMCA Bifurcation Lesion Treatment Using E-DES or C-DES



Cumulative incidence of MACE in the entire population **(A)**, E-DES population **(B)**, and C-DES population **(C)**. C-DES = current-generation drug-eluting stent(s); E-DES = early-generation drug-eluting stent(s); HR = hazard ratio; LMCA = left main coronary artery; MACE = major adverse cardiovascular event(s).

TABLE 4 HRs for 2-Stent Strategy, Clinical Outcomes

	1-Stent Strategy	2-Stent Strategy	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Propensity-Score Matched HR (95% CI)	p Value
Entire population	951	381						
MACE	45 (4.7)	71 (18.6)	3.71 (2.55-5.39)	<0.0001	3.40 (1.97-5.86)	<0.0001	3.52 (2.30-5.41)	<0.0001
Cardiac death or MI	20 (2.1)	22 (5.8)	2.44 (1.33-4.48)	0.004	1.75 (0.86-3.56)	0.123	1.97 (1.04-3.76)	0.039
TLR	31 (3.3)	55 (14.4)	4.11 (2.65-6.39)	<0.0001	3.66 (1.96-6.85)	<0.0001	4.23 (2.51-7.15)	<0.0001
Stent thrombosis	5 (0.5)	4 (1.0)	1.70 (0.46-6.36)	0.428	1.74 (0.47-6.52)	0.409	1.35 (0.34-5.42)	0.672
Early-generation stent	571	304						
MACE	32 (5.6)	63 (20.7)	3.81 (2.49-5.83)	<0.0001	3.63 (2.00-6.60)	<0.0001	4.21 (2.43-7.28)	<0.0001
Cardiac death or MI	12 (2.1)	17 (5.6)	2.56 (1.22-5.35)	0.013	2.07 (0.89-4.83)	0.093	2.61 (1.12-6.10)	0.027
TLR	23 (4.0)	49 (16.1)	4.12 (2.51-6.76)	<0.0001	4.04 (2.05-7.96)	<0.0001	5.31 (2.65-10.66)	<0.0001
Stent thrombosis	3 (0.5)	2 (0.7)	1.18 (0.20-7.08)	0.854	1.25 (0.21-7.49)	0.81	1.29 (0.18-9.18)	0.797
Current-generation stent, n	380	77						
MACE	13 (3.4)	8 (10.4)	2.31 (0.95-5.59)	0.065	1.22 (0.42-3.50)	0.714	1.28 (0.37-4.44)	0.698
Cardiac death or MI	8 (2.1)	5 (6.5)	2.59 (0.84-7.97)	0.096	1.89 (0.49-7.27)	0.357	4.13 (0.43-40.17)	0.22
TLR	8 (2.1)	6 (7.8)	2.53 (0.88-7.34)	0.086	1.75 (0.48-6.42)	0.398	0.95 (0.26-3.57)	0.95
Stent thrombosis	2 (0.5)	2 (2.6)	3.79 (0.53-27.34)	0.186	3.67 (0.50-26.92)	0.201		

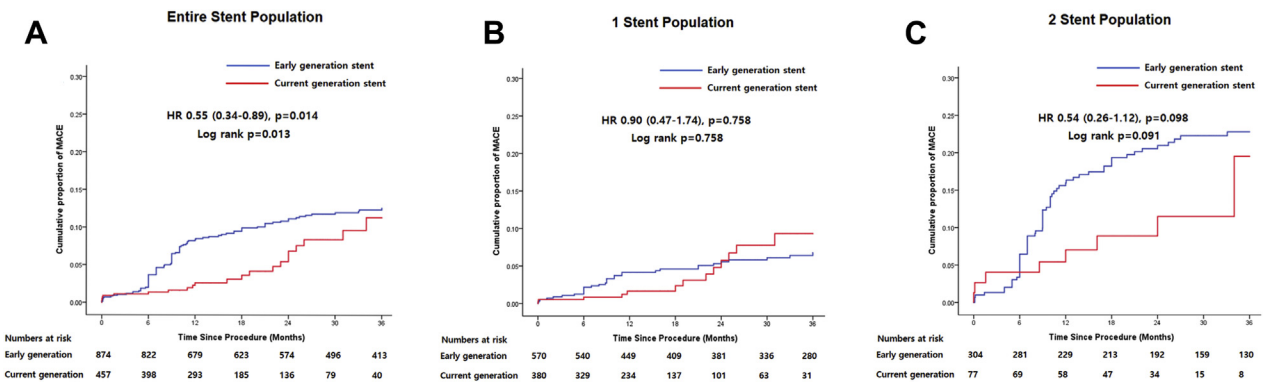
Values are n or n (%), unless otherwise indicated.
CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization.

TLR RATES AND PATTERNS FOR LMCA BIFURCATION LESIONS ACCORDING TO STENT GENERATION AND STENT STRATEGY. TLR rates were 9.6% (E-DES 85 of 889 patients) and 4.5% (C-DES 21 of 464 patients) for LMCA bifurcation lesions. In the E-DES group, the TLR rate was significantly lower in patients who underwent a 1-stent strategy compared with a 2-stent strategy patients (5.7% vs. 16.9%, respectively; $p < 0.0001$). In the E-DES group, the TLR site was mainly along the PV to the MB after using a 1-stent strategy, whereas it was near the SB after using a 2-stent strategy (Online Figure S4A). In the C-DES group, the TLR rate was lower in patients who underwent a 1-stent strategy compared with a 2-stent strategy group, but the difference was not statistically significant (2.1% vs. 7.8%, respectively; $p = 0.086$). TLR site was mainly along the PV to the MB after application of both the 1- and 2-stent strategies (Online Figure S4B).

DISCUSSION

The main findings of analyses for the 2 large multicenter registries with LMCA bifurcation lesion data were as follows: 1) PCI using DES in patients with LMCA bifurcation lesions was associated with

FIGURE 3 Kaplan-Meier Curves According to Stent Generation Used for LMCA Bifurcation Lesion Treatment



Cumulative incidence of MACE in the entire population **(A)**, 1-stent strategy population **(B)**, and 2-stent strategy population **(C)**. HR = hazard ratio; LMCA = left main coronary artery; MACE = major adverse cardiovascular event(s).

TABLE 5 Predictors for Clinical Outcomes According to Stent Generation in Overall Population of Patients With LMCA Bifurcation Lesions

	Entire Population		Early-Generation Stent		Current-Generation Stent	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
MACE						
2-stent strategy	3.80 (2.62–5.47)	<0.0001	3.88 (2.53–5.94)	<0.0001		
Pre % DS SB ≥50%					5.24 (2.20–12.46)	<0.0001
CKD	3.02 (1.66–5.49)	<0.0001	2.43 (1.22–4.82)	0.011	5.00 (1.46–17.12)	0.01
Cardiac death or MI						
ACS	3.19 (1.46–6.95)	0.004	3.36 (1.27–8.89)	0.015		
IVUS					0.20 (0.06–0.74)	0.016
CKD	3.03 (1.28–7.14)	0.011	3.23 (1.16–9.01)	0.025		
Age >75 yrs	2.88 (1.48–5.61)	0.002	2.36 (1.02–5.46)	0.046	4.34 (1.45–12.95)	0.009
2-stent strategy	2.20 (1.20–4.05)	0.011	2.26 (1.08–4.76)	0.031		
Cardiac death						
CKD	4.79 (1.62–14.22)	0.005	5.14 (1.45–18.21)	0.011		
ACS	3.97 (1.35–11.68)	0.012	5.69 (1.29–25.02)	0.021		
Age >75 yrs					6.52 (1.31–32.51)	0.022
Pre % DS MB ≥75%					6.06 (1.22–30.21)	0.028
Pre % DS SB ≥50%	3.17 (1.41–7.15)	0.005	2.56 (0.97–6.74)	0.057		
MI						
Age >75 yrs	3.12 (1.26–7.76)	0.014				
ACS	2.85 (1.04–7.80)	0.042				
IVUS					0.93 (0.01–0.78)	0.028
TLR						
2-stent strategy	4.39 (2.80–6.88)	<0.0001	4.09 (2.49–6.71)	<0.0001		
CKD	2.67 (1.29–5.53)	0.008			4.98 (1.09–22.63)	0.038
Pre % DS SB ≥50%					4.61 (1.58–13.42)	0.005

LMCA = left main coronary artery; other abbreviations as in Tables 1, 3, and 4.

satisfactory clinical outcomes; the MACE rate was 8.7% at 3 years of follow-up; 2) a 1-stent strategy resulted in better clinical outcomes compared with a 2-stent strategy for LMCA bifurcation lesion treatment; and 3) independent predictors for MACE were the use of 2-stent strategy and CKD in E-DES patients, and pre-intervention SB diameter stenosis >50% and CKD in C-DES patients.

PCI WITH DESs IN LMCA BIFURCATION LESION PATIENTS: OPTIMAL REVASCULARIZATION STRATEGY. PCI with DES in patients with LMCA disease results in favorable clinical outcomes. This method has become an alternative revascularization strategy for eligible patients, in addition to bringing remarkable developments in DES technology, procedural techniques, and drugs (13). In the EXCEL (Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease) study comparing PCI with C-DES and CABG, the primary endpoint rate (death, stroke, or MI) was 15.4% in the PCI group for a 3-year follow-up duration. In LMCA bifurcation lesion subgroup analysis (80.5% of total population), the event rate was 15.6% compared with 14.8% shown in the non-bifurcated LM lesion group (6). In our study, the MACE rate was 10.1% for the 3-year follow-up duration, despite including only bifurcation lesions. This result indicates that PCI with DES is a good option to use as an optimal revascularization strategy.

LMCA BIFURCATION STENTING ACCORDING TO STENT GENERATION AND STENT STRATEGY. The success of revascularization in coronary bifurcation patients depends on bifurcation morphology, plaque distribution, and myocardial territory between the MB and SB. The size and territory of the SB in non-LMCA bifurcation are usually smaller compared with the MB, so revascularization of the MB is often more important. However, in patients with LMCA bifurcation lesions, MB (from the left main trunk to the LAD) and SB (LCx) revascularization are important (14,15). Therefore, it is not desirable to treat LMCA bifurcation lesions by using the same criteria for non-LM bifurcation lesions. Results from previous studies of LMCA bifurcation lesion patients were analyzed as subgroups of entire coronary bifurcation, and patient numbers were relatively small (9,16). Few RCTs have compared the use of 1- and 2-stent strategies in patients with LMCA bifurcation lesions. However, analyses of multicenter registries

revealed that a 1-stent strategy offered better clinical outcomes than a 2-stent strategy (8,9). In the EXCEL substudy, over a 3-year follow-up, rates of cardiac death, ischemia-driven TLR, as well as the primary composite endpoint of death, MI, or stroke, were more common with a planned 2-stent strategy compared with a provisional 1-stent strategy, which showed a strong benefit toward the 1-stent strategy (17). Only the use of double kissing (DK)-crush technique during application of the 2-stent strategy improved clinical outcomes, compared with using other 2-stent techniques and a 1-stent strategy (18–20). In our study, due to a significantly lower TLR rate, the 1-stent strategy had better clinical outcome than the 2-stent strategy when E-DES was used. When C-DES was used, the 1-stent strategy still resulted in a lower MACE rate compared with the 2-stent strategy, but the difference was not statistically significant. Differences between E-DES and C-DES results were associated with improvements in stent profile (e.g., platform, polymer, strut thickness) and device types (e.g., IVUS, fractional flow reserve, noncompliant balloon). Development of PCI technique (e.g., proximal optimization technique [POT] and final kissing balloon inflation) and operator experience may have contributed to improvement in clinical outcomes after using the 2-stent strategy. The results of Song et al. (21) suggested that the use of C-DES, noncompliant balloon, or final kissing balloon was associated with better long-term outcomes in patients with bifurcation lesions who were treated by a 2-stent strategy in the Korean Bifurcation Pooled Cohort study. In particular, POT can provide optimization of stent diameter to LMCA diameter, in addition to correcting stent malapposition and reducing ellipticity of the stented segment (22). However, the recommended POT was not applied at the time of the procedure in the current registry.

PREDICTORS OF CLINICAL OUTCOMES IN LMCA BIFURCATION: CLINICAL, LESION, AND PROCEDURAL FACTORS. Results of a registry study of treatment of LMCA bifurcation lesions using E-DES have shown that the use of a 2-stent strategy, old age, ACS, and impaired renal function were associated with poor prognosis; final kissing balloon inflation was associated with a good prognosis (8). In another study, true bifurcation, high EURO score, and small LMCA vessel size were independent predictors of poor clinical outcomes (23). In our study, use of a 2-stent strategy and CKD were independent predictors of MACE when E-DES was used. A pre-intervention SB DS >50% and presence of CKD were independent predictors of MACE when C-DES was used. A pre-intervention SB DS >50% was not only a predictor for MACE, but also a significant independent predictor of cardiac death and TLR occurrence.

OPTIMAL STENT STRATEGY AND TECHNIQUES FOR LMCA BIFURCATION STENTING: WHICH PATIENTS WOULD NEED 2-STENT STRATEGY? Fatal consequences can occur from jailed SB lesions when the provisional 1-stent strategy is unconditionally performed for treatment of LMCA bifurcation lesions (14,15). It is very important to identify those who may experience fatal outcomes from the patients who are at high risk of developing jailed SB lesions. However, even in recent RCT studies of LMCA disease, no data on optimal stent strategy or stent technique in a PCI group were reported (6,7). Few studies have been performed to determine which LMCA bifurcation lesion patients should be treated by a 2-stent strategy. According to expert opinions, Park et al. (24) considered a 2-stent strategy for LMCA bifurcation lesions in the LCx with Medina classification (1,1,1 or 1,0,1 or 0,1,1), large LCx (≥2.5 mm diameter), diseased left dominant coronary system, narrow angle between the LAD and LCx, and concomitant diffuse disease in the LCx. A recent review article that cited the results of previous DEFNITION (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts) study data has reported that an intensive 2-stent strategy is required for cases with a SB >70% and lesion length >10 mm (16,25). However, because the number of patients with LMCA bifurcation included in DEFINITION study was small, there are limitations to using these criteria as an absolute reference standard. In the recently published DKCRUSH-V (Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions) RCT, DK crush technique showed a better clinical outcome than a provisional stent in true bifurcation lesions (Medina classification 1,1,1 and 0,1,1 type) (20). However, because additional SB stents were implanted in 47.1% of the provisional stent groups, the result should be carefully interpreted. Nevertheless, this study suggested that an appropriate 2-stent technique may be an optimal treatment strategy for true bifurcation. In our data, use of a 1-stent strategy consistently resulted in better clinical outcomes for all subgroups, compared with using a 2-stent strategy in the E-DES group. In the C-DES group, use of a 2-stent strategy resulted in better outcomes when

the pre-intervention DS of the SB was >50%; the results were statistically significant when SB stenosis was >65%. Although our overall data showed that a 1-stent strategy offered a better clinical outcome than a 2-stent strategy, the 2-stent strategy showed better results in severe cases of pre-intervention SB DS. If the pre-intervention SB DS is >65%, switching to a 2-stent strategy procedure (T-stenting, T-and-protrusion stenting, or culotte technique) or planned 2-stent strategy (mini crush or DK crush) procedure may be considered. Our results also provide strong evidence to support the algorithm for LMCA bifurcation lesion intervention that was proposed by Rab et al. (25). The ongoing EBC MAIN study (European Bifurcation Club Left Main Study; NCT02497014) RCT comparing 1 versus 2 stents (DK crush or culotte) will provide additional information on the optimal treatment of LMCA bifurcation lesions.

STUDY LIMITATIONS. First, because we used non-randomized comparisons, selection bias might have affected the results. Second, we could not include and control some variables, such as improvements in bifurcation PCI technique (POT) and device used (fraction flow reserve and atherectomy). Third, the number of patients who received a 2-stent strategy procedure with C-DES was too small to provide the power needed to obtain statistically significant results. Fourth, the sample size was too small to evaluate low-frequency events such as ST and MI, despite using 2 of the largest data registries available.

CONCLUSIONS

Our study using data of 1,353 patients from 2 large multicenter registries, KOMATE and COBIS II, has found that PCI with DES for treatment of LMCA bifurcation lesions had acceptable procedural and satisfactory long-term clinical outcomes, especially when C-DES was used. For both E-DES and C-DES procedures, a 1-stent strategy showed better clinical benefits than a 2-stent strategy. Therefore, a 1-stent strategy should be considered first for treatment of LMCA bifurcation lesions.

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PERSPECTIVES

WHAT IS KNOWN? PCI with DES in LMCA disease shows favorable clinical outcomes, and the method has become an alternative revascularization strategy in eligible patients. However, limited data are available to assess long-term clinical outcomes after DES including C-DESs in LMCA bifurcation lesion.

WHAT IS NEW? We have reported that PCI with DES is a good treatment option for LMCA bifurcation lesions, with regard to both long-term safety and efficacy. For both E-DES and C-DES procedures, using a 1-stent strategy led to better clinical benefits than applying a 2-stent strategy.

WHAT IS NEXT? Future clinical studies including larger randomized trials of optimal revascularization strategy are required to compare newer-generation stenting versus surgery. Also, the use of 1- and 2-stent strategies should be further studied to evaluate the clinical outcomes for LMCA bifurcation lesions.

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KEY WORDS bifurcation lesion, left main coronary artery, percutaneous coronary intervention

APPENDIX For supplemental figures and tables, please see the online version of this paper.

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