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Differential Prognostic Impact of Treatment Strategy Among Patients With Left Main Versus Non–Left Main Bifurcation Lesions Undergoing Percutaneous Coronary Intervention

Results From the COBIS (Coronary Bifurcation Stenting) Registry II

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Objectives The authors sought to investigate whether the impact of treatment strategies on clinical outcomes differed between patients with left main (LM) bifurcation lesions and those with non-LM bifurcation lesions.

Background Few studies have considered anatomic location when comparing 1- and 2-stent strategies for bifurcation lesions.

Methods We compared the prognostic impact of treatment strategies on clinical outcomes in 2,044 patients with non-LM bifurcation lesions and 853 with LM bifurcation lesions. The primary outcome was target lesion failure (TLF) defined as a composite of cardiac death, myocardial infarction (MI), and target lesion revascularization.

Results The 2-stent strategy was used more frequently in the LM bifurcation group than in the non-LM bifurcation group (40.3% vs. 20.8%, $p < 0.01$). During a median follow-up of 36 months, the 2-stent strategy was not associated with a higher incidence of cardiac death (hazard ratio [HR]: 1.24; 95% confidence interval [CI]: 0.72 to 2.14; $p = 0.44$), cardiac death or MI (HR: 1.12; 95% CI: 0.58 to 2.19; $p = 0.73$), or TLF (HR: 1.39; 95% CI: 0.99 to 1.94; $p = 0.06$) in the non-LM bifurcation group. In contrast, in patients with LM bifurcation lesions, the 2-stent strategy was associated with a higher incidence of cardiac death (HR: 2.43; 95% CI: 1.05 to 5.59; $p = 0.04$), cardiac death or MI (HR: 2.09; 95% CI: 1.08 to 4.04; $p = 0.03$), as well as TLF (HR: 2.38; 95% CI: 1.60 to 3.55; $p < 0.01$). Significant interactions were present between treatment strategies and bifurcation lesion locations for TLF ($p = 0.01$).

Conclusions The 1-stent strategy, if possible, should initially be considered the preferred approach for the treatment of coronary bifurcation lesions, especially LM bifurcation lesions. (Korean Coronary Bifurcation Stenting [COBIS] Registry II; NCT01642992) (J Am Coll Cardiol Intv 2014;7:255–63)

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Coronary bifurcation lesions are 1 of the most challenging lesion subsets to treat and are known to have lower angiographic success rates, a higher risk of procedural complications, and a greater restenosis rate than nonbifurcation lesions, even in the drug-eluting stent (DES) era (1,2). A number of studies comparing the 1- and 2-stent strategies for bifurcation lesions have been performed (3–5), but there are limited data comparing the efficacy and safety of these strategies according to the anatomic location of the bifurcation lesion. Therefore, we sought to investigate whether the impact of treatment strategies on clinical outcomes differed between patients with left main (LM) bifurcation lesions and those with non-LM bifurcation lesions using data from a dedicated bifurcation multicenter real-world registry.

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Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
LM = left main
MI = myocardial infarction
MLD = minimal lumen diameter
MV = main vessel
PCI = percutaneous coronary intervention
RD = reference diameter
SB = side branch

Methods

Study population. The COBIS (Coronary Bifurcation Stenting) Registry II is a retrospective multicenter registry dedicated to bifurcation lesions treated with percutaneous coronary intervention (PCI) with DES. From January 2003 through December 2009, 2,897 consecutive patients were enrolled from 18 major coronary intervention centers in the Republic of Korea. The inclusion criteria were coronary bifurcation lesions treated solely with DES, a main vessel (MV) diameter ≥2.5 mm, and a side branch (SB) diameter ≥2.3 mm. The exclusion criteria were cardiogenic shock, cardiopulmonary resuscitation, and protected LM disease. This registry was funded by the Korean Society of Interventional Cardiology. The local institutional review board at each hospital approved this study and waived the requirement for informed consent for access to each institution's PCI registry.

Percutaneous coronary intervention. All interventions were performed according to current standard guidelines. All patients received dual oral antiplatelet therapy with 300 mg aspirin and either 300 or 600 mg clopidogrel before PCI unless they had previously received these medications. Intravenous heparin was administered to maintain an activated clotting time of 250 to 300 s. The access, type of DES, and use of intravascular ultrasound or glycoprotein IIb/IIIa receptor inhibitors were all left to the operator's discretion. Decisions to treat bifurcation lesions by a 1- or 2-stent technique were made by the individual operators. Aspirin was continued indefinitely, and the duration of clopidogrel treatment was also left to the operator's discretion.

Data collection and analysis. Clinical, angiographic, procedural, and outcome data were collected with the use of a Web-based reporting system. Additional information was obtained by further inquiry into medical records or telephone contact, if necessary. All baseline and procedural cine coronary angiograms were reviewed and quantitatively analyzed at the angiographic core laboratory (the Cardiac and Vascular Center, Samsung Medical Center, Seoul, Republic of Korea) using standard qualitative and quantitative analyses and definitions (6). We determined the minimal lumen diameter (MLD) and reference diameter (RD) for each vessel. The percentage of diameter stenosis was calculated as: 100 × (RD − MLD)/RD. The bifurcation angle was defined as the angle between the distal MV and the SB at its origin using the angiographic projection with the widest separation of the 2 branches (7). Bifurcation lesions were classified according to the Medina classification, in which the proximal MV, distal MV, and SB components of the bifurcation are each assigned a score of 1 or 0 depending on the presence or absence of >50% stenosis (8). Medina classification type 1.1.1, 1.0.1, and 0.1.1 lesions were defined as true bifurcation lesions.

Study outcomes and definitions. The primary endpoint of the study was target lesion failure, defined as a composite of cardiac death, spontaneous myocardial infarction (MI), and target lesion revascularization during follow-up. Secondary endpoints were the individual components of the primary endpoint, composite of cardiac death or spontaneous MI, stent thrombosis, and target vessel revascularization.

All deaths were considered cardiac unless a definite noncardiac cause could be established. MI was defined as elevated cardiac enzymes (troponin or creatine kinase-myocardial band) greater than the upper limit of the normal with ischemic symptoms or electrocardiographic findings indicative of ischemia that was not related to the index procedure. Target lesion revascularization was defined as repeat PCI of the lesion within 5 mm of stent deployment or bypass graft surgery of the target vessel. Target vessel revascularization was the repeat revascularization of the target vessel by PCI or bypass graft surgery. Stent thrombosis was assessed based on the definitions of the Academic Research Consortium (9). An independent clinical event

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adjudicating committee reviewed all outcome data reported from the participating centers.

Statistical analyses. Continuous variables are presented as mean ± SD or the median and interquartile range and were compared using the *t* test or Wilcoxon rank sum test for continuous variables. Categorical variables are reported as frequencies (percentages) and were compared using the chi-square or Fisher exact test, as appropriate. Survival curves were constructed using Kaplan-Meier estimates and were compared using the log-rank test.

To ensure a rigorous adjustment for significant difference in patient characteristics according to treatment strategy and to avoid model overfitting based on few events in the endpoints, we used a weighted Cox proportional hazards model using inverse probability of treatment weighting (10). A propensity score analysis was performed with a logistic regression model from which the probability for the 2-stent strategy was calculated for each patient. In the weighted Cox multivariable model with inverse probability of treatment weighting methods, the weights for patients undergoing the 2-stent strategy were the inverse of 1 − propensity score, and weights for patients not undergoing the 2-stent strategy were the inverse of the propensity score. We also tested the significance of interactions between treatment strategy and location of bifurcation lesion on outcomes in these models.

All reported p values are 2-tailed, and $p < 0.05$ was considered significant. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics. Of the 2,897 patients registered in the COBIS II registry, 2,044 patients (70.6%) had a non-LM bifurcation lesion and 853 (29.4%) had an LM bifurcation lesion. The 2-stent strategy was used more frequently in the LM bifurcation group than in the non-LM bifurcation group (40.3% vs. 20.8%, $p < 0.01$).

Baseline demographic, clinical, angiographic, and procedural characteristics according to bifurcation lesion locations and treatment strategies are shown in Tables 1 and 2. In the non-LM bifurcation group, patients undergoing the 2-stent strategy had a higher prevalence of left anterior descending artery bifurcation lesions and previous PCI than those undergoing the 1-stent strategy. In the LM bifurcation group, patients undergoing the 2-stent strategy were older and had a higher prevalence of previous PCI and acute coronary syndrome on admission than those undergoing the 1-stent strategy. Compared with patients undergoing the 1-stent strategy, those undergoing the 2-stent strategy were more likely to have multivessel disease and true bifurcation lesions on Medina classification and more frequently underwent final kissing balloon dilation, intravascular ultrasound, and remote-site intervention in both non-LM and LM bifurcation groups. The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score was significantly greater in patients undergoing the 2-stent strategy than in those undergoing the 1-stent strategy in both groups. Among the 2-stent group, the crush technique was used most frequently,

Table 1. Baseline Clinical Characteristics

	Non-LM Bifurcation (n = 2,044)			LM Bifurcation (n = 853)		
	1-Stent (n = 1,618)	2-Stent (n = 426)	p Value	1-Stent (n = 509)	2-Stent (n = 344)	p Value
Age, yrs	61.8 ± 10.3	61.3 ± 10.7	0.32	62.6 ± 10.0	64.0 ± 9.7	0.05
≥65 yrs	637 (39.4)	170 (39.9)	0.84	208 (40.9)	155 (45.1)	0.22
Male	1,152 (71.2)	296 (69.5)	0.49	387 (76.0)	248 (72.1)	0.20
Acute coronary syndrome	1,078 (66.6)	279 (65.5)	0.66	250 (49.1)	217 (63.1)	<0.01
Current smoker	437 (27.0)	100 (23.5)	014	121 (23.8)	75 (21.8)	0.50
Diabetes mellitus	445 (27.5)	122 (28.6)	0.64	166 (32.6)	107 (31.1)	0.64
Hypertension	936 (57.8)	242 (56.8)	0.70	290 (57.0)	207 (60.2)	0.35
Dyslipidemia	535 (33.1)	123 (28.9)	0.10	138 (27.1)	110 (32.0)	0.13
Family history of CAD	46 (2.8)	10 (2.3)	0.58	20 (3.9)	6 (1.7)	0.07
Peripheral vascular disease	18 (1.1)	2 (0.5)	0.23	9 (1.8)	10 (2.9)	0.27
Previous myocardial infarction	86 (5.3)	30 (7.0)	0.17	27 (5.3)	30 (8.7)	0.50
Previous cerebrovascular event	83 (5.1)	24 (5.6)	0.68	51 (10.0)	31 (9.0)	0.62
Previous PCI	170 (10.5)	67 (15.7)	<0.01	91 (17.9)	86 (25.0)	0.01
Chronic kidney disease	40 (2.5)	10 (2.3)	0.88	19 (3.7)	12 (3.5)	0.85
LVEF, %*	57.3 ± 11.1	58.9 ± 12.0	0.03	59.6 ± 11.5	59.0 ± 11.8	0.50
<50%	283 (20.7)	62 (18.0)	0.26	59 (14.3)	50 (18.2)	0.17

Values are mean ± SD or n (%). *LVEF was available in 688 LM bifurcation patients and 1,079 non-LMB patients.
CAD = coronary artery disease; LM = left main; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Angiographic and Procedural Characteristics

	Non-LM Bifurcation (n = 2,044)			LM Bifurcation (n = 853)		
	1-Stent (n = 1,618)	2-Stent (n = 426)	p Value	1-Stent (n = 509)	2-Stent (n = 344)	p Value
Vessel involved			<0.01			
LAD/diagonal	1,191 (73.6)	360 (84.5)				
LCX/OM	308 (19.0)	41 (9.6)				
RCA bifurcation	119 (7.4)	25 (5.9)				
Multivessel disease	729 (45.1)	200 (46.9)	0.49	230 (45.2)	283 (82.3)	<0.01
SYNTAX score	14.9 ± 7.6	16.7 ± 7.6	<0.01	21.1 ± 9.2	25.0 ± 9.4	<0.01
Low score (0–22)	1,354 (83.7)	347 (81.5)		309 (60.7)	128 (37.2)	
Intermediate score (23–32)	222 (13.7)	63 (14.8)		152 (29.9)	152 (44.2)	
High score (≥33)	42 (2.6)	16 (3.8)		48 (9.4)	64 (18.6)	
Medina classification			<0.01			<0.01
True bifurcation	814 (50.3)	330 (77.5)		114 (22.4)	244 (70.9)	
1.1.1	502 (31.0)	189 (44.4)		79 (15.5)	168 (48.8)	
1.0.1	130 (8.0)	30 (7.0)		23 (4.5)	28 (8.1)	
0.1.1	182 (11.2)	111 (26.1)		12 (2.4)	48 (14.0)	
Nontrue bifurcation	804 (49.7)	96 (22.5)		395 (77.6)	100 (29.1)	
1.0.0	250 (15.5)	8 (1.9)		80 (15.7)	8 (2.3)	
0.1.0	290 (17.9)	25 (5.9)		170 (33.4)	23 (6.7)	
1.1.0	243 (15.0)	24 (5.6)		125 (24.6)	35 (10.2)	
0.0.1	21 (1.3)	39 (9.2)		20 (3.9)	34 (9.9)	
Stent type			<0.01			0.01
SES	744 (46.0)	237 (55.6)		248 (48.7)	185 (53.8)	
PES	509 (31.5)	120 (28.2)		105 (20.6)	88 (25.6)	
EES	175 (10.8)	37 (8.7)		97 (19.1)	39 (11.3)	
ZES	189 (11.7)	32 (7.5)		58 (11.4)	30 (8.7)	
Others	1 (0.1)	0		1 (0.2)	2 (0.6)	
Stenting technique						
1-stent technique	1,618 (100.0)	—		509 (100.0)	—	
2-stent techniques	—	426 (100)		—	344 (100.0)	
T-stenting	—	153 (35.9)		—	124 (36.0)	
Crush	—	226 (53.1)		—	143 (41.6)	
Kissing or V stenting	—	36 (8.5)		—	60 (17.4)	
Culottes	—	9 (2.1)		—	12 (3.5)	
Others	—	2 (0.5)		—	5 (1.5)	
Final kissing balloon inflation	502 (31.0)	348 (81.7)	<0.01	191 (37.5)	308 (89.5)	<0.01
Guidance of intravascular ultrasound	434 (26.8)	203 (47.7)	<0.01	273 (53.6)	213 (61.9)	0.02
Remote site intervention	426 (26.3)	133 (31.2)	0.04	122 (24.0)	118 (34.3)	<0.01
Main vessel						
Total stent length, mm	28.9 ± 11.9	30.0 ± 11.3	0.09	27.4 ± 13.4	28.6 ± 13.8	0.20
Maximal stent diameter, mm	3.10 ± 0.38	3.15 ± 0.34	0.03	3.46 ± 0.38	3.37 ± 0.36	<0.01
Side branch						
Total stent length, mm	—	21.6 ± 7.6	—	—	22.6 ± 11.0	—
Maximal stent diameter, mm	—	2.74 ± 0.25	—	—	3.14 ± 0.38	—

Values are n (%) or mean ± SD.

EES = everolimus-eluting stent(s); LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main; OM = obtuse marginal branch; PES = paclitaxel-eluting stent(s); RCA = right coronary artery; SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

followed by the T-stenting technique, kissing, or V-stenting technique, and culottes stenting technique in both non-LM and LM bifurcation groups.

Quantitative coronary angiographic analysis. In both LM and non-LM bifurcation groups, patients who underwent the 2-stent strategy had significantly smaller RD and MLD of the SB, a greater percentage of diameter stenosis of the SB, and a longer lesion length of the MV and SB than those in the 1-stent strategy group (Table 3). In the non-LM bifurcation group, the angle between the MV and SB was

Table 3. Quantitative Coronary Angiographic Analysis

	Non-LM Bifurcation (n = 2,044)			LM Bifurcation (n = 853)		
	1-Stent (n = 1,618)	2-Stent (n = 426)	p Value	1-Stent (n = 509)	2-Stent (n = 344)	p Value
Bifurcation angle, °	54.0 (43.0 to 68.0)	50.0 (40.0 to 62.0)	<0.01	81.2 (62.9 to 102.2)	78.2 (64.1 to 99.8)	0.30
Pre-intervention						
MV RD, mm	2.9 (2.7 to 3.2)	2.9 (2.6 to 3.1)	0.04	3.4 (3.0 to 3.7)	3.3 (3.0 to 3.6)	0.01
SB RD, mm	2.4 (2.3 to 2.5)	2.4 (2.2 to 2.5)	<0.01	2.8 (2.5 to 3.3)	2.7 (2.4 to 3.0)	<0.01
MV MLD, mm	0.9 (0.6 to 1.2)	0.9 (0.6 to 1.3)	<0.01	1.2 (0.8 to 1.6)	1.2 (0.9 to 1.5)	0.43
SB MLD, mm	1.3 (0.9 to 1.8)	0.9 (0.5 to 1.2)	<0.01	2.2 (1.6 to 2.6)	1.2 (0.9 to 1.6)	<0.01
MV diameter stenosis, %	70.1 ± 14.4	67.1 ± 17.0	<0.01	63.6 ± 17.7	63.6 ± 16.0	0.98
SB diameter stenosis, %	44.7 ± 22.5	62.8 ± 19.2	<0.01	28.9 ± 22.3	53.1 ± 19.1	<0.01
MV lesion length, mm	16.4 (10.5 to 24.3)	18.8 (11.0 to 28.5)	0.01	12.3 (7.8 to 22.6)	14.8 (9.2 to 24.5)	<0.01
SB lesion length, mm	1.1 (0 to 6.0)	9.3 (4.6 to 16.1)	<0.01	0 (0 to 2.3)	6.9 (3.5 to 14.1)	<0.01
Post-intervention						
MV RD, mm	3.0 (2.7 to 3.2)	2.9 (2.7 to 3.2)	<0.01	3.4 (3.0 to 3.8)	3.4 (3.0 to 3.7)	0.38
SB RD, mm	2.4 (2.3 to 2.5)	2.4 (2.3 to 2.5)	0.04	2.8 (2.5 to 3.3)	2.8 (2.4 to 3.2)	0.01
MV MLD, mm	2.6 (2.3 to 2.9)	2.6 (2.3 to 2.9)	0.95	2.9 (2.6 to 3.3)	2.8 (2.5 to 3.1)	<0.01
SB MLD, mm	1.34 (1.0 to 1.8)	2.2 (1.9 to 2.4)	<0.01	2.2 (1.8 to 2.6)	2.5 (2.3 to 3.0)	<0.01
MV residual stenosis, %	14.1 ± 13.2	12.3 ± 11.4	<0.01	14.0 ± 12.9	16.5 ± 11.1	<0.01
SB residual stenosis, %	44.3 ± 22.3	8.9 ± 15.9	<0.01	25.0 ± 18.8	6.8 ± 15.0	<0.01
MV acute gain, mm	1.68 (1.3 to 2.0)	1.6 (1.2 to 2.0)	0.02	1.8 (1.3 to 2.2)	1.6 (1.3 to 2.0)	0.11
SB acute gain, mm	0 (−0.3 to 0.3)	1.3 (1.0 to 1.6)	<0.01	0 (−0.3 to 0.3)	1.4 (1.0 to 1.7)	<0.01

Values are median (interquartile range) or mean ± SD.
LM = left main; MLD = minimal lumen diameter; MV = main vessel; RD = reference diameter; SB = side branch.

significantly smaller in patients in whom the 2-stent strategy was used than in those who underwent the 1-stent strategy, but in the LM bifurcation group, the angle between the MV and SB was similar.

Clinical outcomes according to bifurcation lesion locations and treatment strategies. Complete clinical follow-up data for major clinical events were obtained in 96.0% and 97.4% of patients who underwent the 1- and 2-stent strategies for non-LM bifurcation lesions (p = 0.18), and 96.3% and 96.5% for LM bifurcation lesions (p = 0.85), respectively. The median follow-up was 37 months (interquartile range: 25 to 53 months) in the non-LM bifurcation group and 35 months (interquartile range: 25 to 50 months) in the LM bifurcation group.

During the entire study period, 182 primary composite events occurred, including 20 cardiac deaths, 33 spontaneous MIs, and 147 target lesion revascularizations in the non-LM bifurcation group. In the LM bifurcation group, 114 primary composite events occurred, including 22 cardiac deaths, 20 spontaneous MIs, and 83 target lesion revascularizations. Observed clinical outcomes according to bifurcation lesion location and treatment strategy are shown

Table 4. Clinical Outcome Rates According to Treatment Strategy in Patients With LM Bifurcation Lesions and Non-LM Bifurcation Lesions

	Non-LM Bifurcation (n = 2,044)				LM Bifurcation (n = 853)			
	1-Stent (n = 1,618)	2-Stent (n = 426)	HR (95% CI)	p Value	1-Stent (n = 509)	2-Stent (n = 344)	HR (95% CI)	p Value
Target lesion failure	130 (8.0)	52 (12.2)	1.51 (1.10–2.09)	0.01	41 (8.1)	73 (21.2)	2.77 (1.89–4.06)	<0.01
Cardiac death	16 (1.0)	4 (0.9)	0.91 (0.30–2.72)	0.86	8 (1.6)	14 (4.1)	2.51 (1.05–5.98)	0.03
Spontaneous myocardial infarction	22 (1.4)	11 (2.6)	1.77 (0.86–3.65)	0.12	8 (1.6)	12 (3.5)	2.22 (0.91–5.43)	0.08
Cardiac death or myocardial infarction	36 (2.2)	14 (3.3)	1.40 (0.75–2.59)	0.29	16 (3.1)	24 (7.0)	2.21 (1.17–4.16)	0.01
Definite or probable stent thrombosis	8 (0.5)	5 (1.2)	2.26 (0.74–6.91)	0.15	3 (0.6)	11 (3.2)	5.35 (1.49–19.2)	0.01
Target lesion revascularization	104 (6.4)	43 (10.1)	1.56 (1.09–2.23)	0.01	29 (5.7)	54 (15.7)	2.89 (1.84–4.54)	<0.01
Target vessel revascularization	150 (9.3)	53 (12.4)	1.32 (0.97–1.81)	0.08	50 (9.8)	77 (22.4)	2.45 (1.72–3.50)	<0.01

Values are n (%) unless otherwise indicated.
CI = confidence interval; HR = hazard ratio; LM = left main.

in Table 4. In the non-LM bifurcation group, treatment with the 2-stent strategy was associated with a higher incidence of target lesion failure and target lesion revascularization, but not cardiac death and the composite of cardiac death or MI (Fig. 1).

In contrast, among patients with the LM bifurcation lesions, patients who underwent the 2-stent strategy had a higher incidence of cardiac death, the composite of cardiac death or MI, target lesion revascularization, and target lesion failure (Fig. 2). In addition, definite or probable stent thrombosis occurred more frequently in the 2-stent group than in the 1-stent group.

After adjustments of clinical covariates using an inverse probability of treatment weighting method (Table 5), the adjusted risks for primary (hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 0.99 to 1.94; p = 0.06) and any secondary endpoints were not significantly different according to treatment strategy except for target lesion revascularization in patients with non-LM bifurcation lesions. On the other hand, in the LM bifurcation group, the adjusted risks for the primary endpoint (HR: 2.38; 95% CI: 1.60 to 3.55; p < 0.01) and all secondary endpoints were significantly higher in patients treated with the 2-stent strategy than in those treated with the 1-stent strategy. There were statistically significant interactions between treatment strategies and bifurcation lesion locations for covariate-adjusted risks of target lesion failure (p = 0.01), target lesion revascularization (p = 0.03), and target vessel revascularization (p < 0.01). There was also a nonsignificant trend in the interaction between treatment strategy and bifurcation lesion location for the composite of cardiac death or MI (p = 0.06).

Discussion

In the present study, we compared the prognostic impact of treatment strategy on clinical outcomes according to bifurcation lesion location (LM vs. non-LM bifurcation lesion)

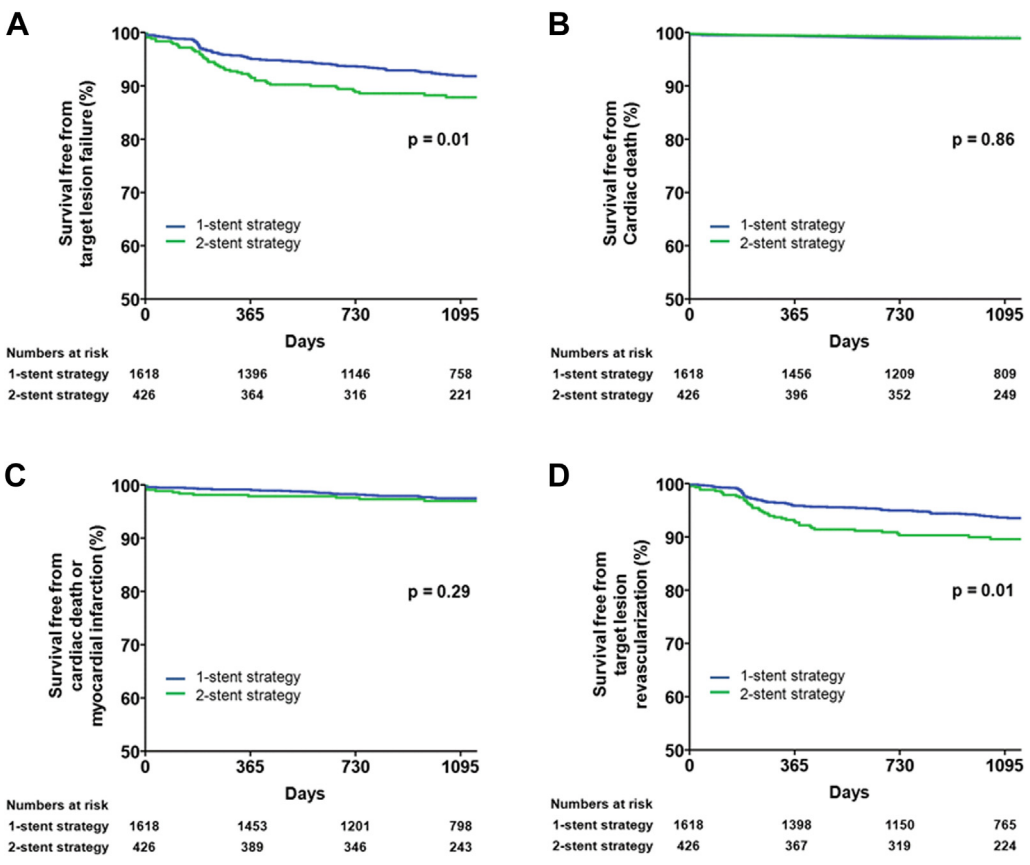

Figure 1. Kaplan-Meier Curves in Patients With Non-LM Bifurcation Lesions

(A) Kaplan-Meier curves for target lesion failure in patients undergoing the 1-stent strategy versus the 2-stent strategy. **(B)** Kaplan-Meier curves for cardiac death in patients undergoing the 1-stent strategy versus the 2-stent strategy. **(C)** Kaplan-Meier curves for cardiac death or myocardial infarction in patients undergoing the 1-stent strategy versus the 2-stent strategy. **(D)** Kaplan-Meier curves for target lesion revascularization in patients undergoing the 1-stent strategy versus the 2-stent strategy. LM = left main.

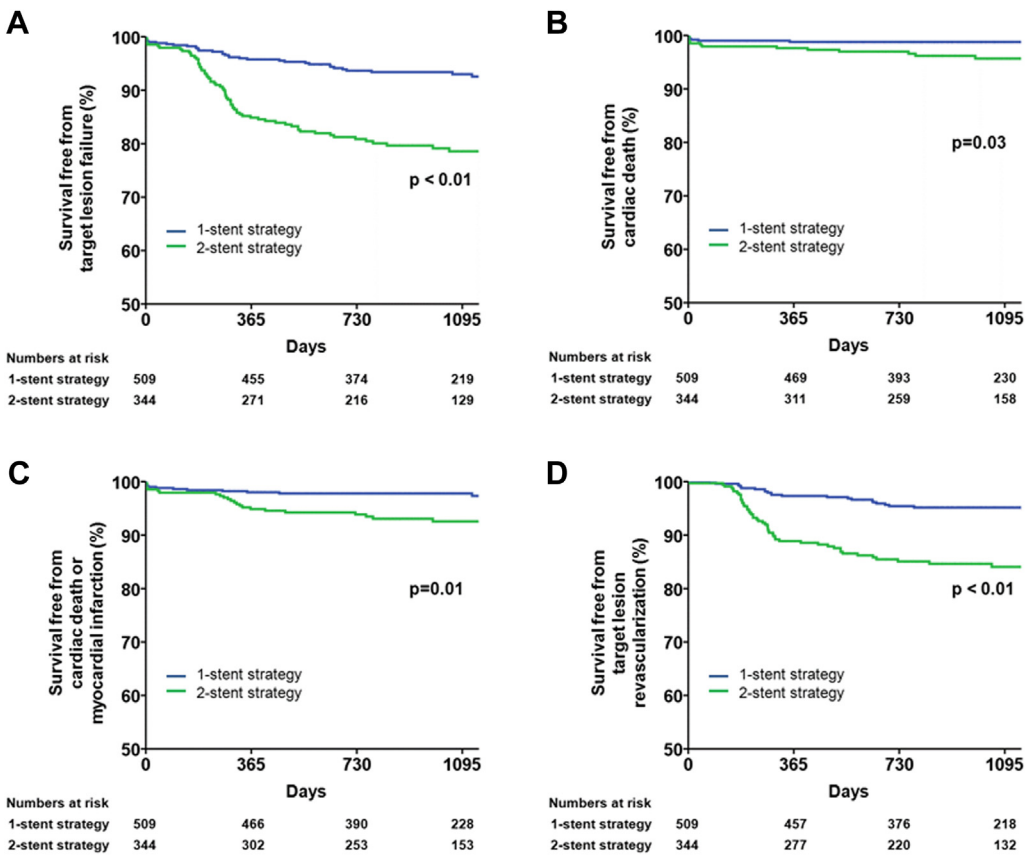

Figure 2. Kaplan-Meier Curves in Patients With LM Bifurcation Lesions

Kaplan-Meier curves for **(A)** target lesion failure, **(B)** cardiac death, **(C)** cardiac death or myocardial infarction, and **(D)** target lesion revascularization in patients undergoing the 1-stent strategy versus the 2-stent strategy. LM = left main.

using data from a large, multicenter, dedicated bifurcation registry. The main findings of the present study are that compared with the 1-stent strategy, the 2-stent strategy was associated with higher risks of cardiovascular events in patients with LM bifurcation lesion, whereas this association was attenuated in those with non-LM bifurcation lesions, and that significant interactions were present between treatment strategy and bifurcation lesion location in the adjusted risks of target lesion failure, target lesion revascularization, and target vessel revascularization.

Table 5. Adjusted Hazard Ratios for the 2-Stent Technique for the Clinical Outcomes Using Inverse Probability of Treatment Weighting Method

	Non-LM Bifurcation (n = 2,044)		LM Bifurcation (n = 853)		
	HR (95% CI)	p Value	HR (95% CI)	p Value	Interaction p Value
Target lesion failure	1.39 (0.99–1.94)	0.06	2.38 (1.60–3.55)	<0.01	<0.01
Cardiac death	1.24 (0.72–2.14)	0.44	2.43 (1.05–5.59)	0.04	0.12
Spontaneous myocardial infarction	1.40 (0.64–3.09)	0.40	3.32 (1.23–8.98)	0.02	0.25
Cardiac death or myocardial infarction	1.12 (0.58–2.19)	0.73	2.09 (1.08–4.04)	0.03	0.06
Definite or probable stent thrombosis	1.95 (0.64–5.98)	0.24	4.58 (1.43–14.7)	0.01	0.12
Target lesion revascularization	1.48 (1.02–2.13)	0.04	2.44 (1.50–3.96)	<0.01	0.04
Target vessel revascularization	1.26 (0.92–1.74)	0.15	2.12 (1.45–3.08)	<0.01	<0.01

Abbreviations as in Table 4.

Coronary bifurcation lesions are complex, and their treatment continues to be the subject of substantial debate, even in the DES era (1,2). Previous randomized trials comparing the 1-stent strategy with the elective 2-stent strategy (mainly in patients with non-LM bifurcation lesions) consistently found no significant differences in the major adverse cardiovascular event rate (3–5). In contrast, several observational studies including only patients with LM bifurcation lesions have shown that, compared with the 1-stent strategy, the 2-stent strategy was associated with higher rates of cardiac death, MI, or target lesion revascularization (11,12). Even though this discrepancy between previous studies may be attributable to a selection bias in the observational studies as a result of more complex lesions in the 2-stent group, there are limited data regarding whether the impact of treatment strategy on clinical outcomes would differ between patients with LM bifurcation lesions and those with non-LM bifurcation lesions. In addition, considering that LM bifurcation lesions are increasingly treated with PCI in real-world practice, it is very important to investigate whether treatment strategies are of similar prognostic value for different bifurcation lesion locations. One previous study addressed this issue, but has several limitations; the registry studied was not dedicated to treatment of bifurcation lesions, follow-up was relatively short, and the authors only compared the LM and left anterior descending artery strata (13). Therefore, we examined the long-term comparative efficacy and safety of the 1- versus 2-stent treatment strategies according to different bifurcation lesion locations using data from the COBIS II registry. The COBIS II registry is a large, nationwide multicenter registry dedicated solely to coronary bifurcation lesions treated only with DES.

The present study found that the 2-stent strategy had a strong association with adverse cardiovascular events including cardiac death or MI, stent thrombosis, and target lesion revascularization in patients with LM bifurcation lesions. These findings are in line with findings from previous studies that compared different strategies of revascularization for LM bifurcation lesions (11,12,14). On the other hand, for the treatment of non-LM bifurcation lesions, this association was attenuated, with no significant difference in cardiac mortality, MI risk, and target lesion failure, although there was still a higher risk of target lesion revascularization in patients treated with the 2-stent strategy. Moreover, significant interactions were observed between treatment strategy and bifurcation lesion location in the adjusted risks of target lesion failure, target lesion revascularization, and target vessel revascularization.

There are several possible explanations for the differences in clinical outcomes according to stenting strategy between LM and non-LM bifurcation lesions. First, a high bifurcation angle has been known to be an independent predictor of increased major adverse cardiac events, especially in the crush or culottes stenting technique, whereas no such association was observed in the 1-stent group (15). In the present study, the LM bifurcation group had a higher bifurcation angle compared with the non-LM bifurcation group, and the crush technique was used most frequently in both groups. Second, it is well-known that proper stent expansion is crucial to prevent restenosis and thrombosis (16,17). Several bench studies have shown that a higher bifurcation angle is associated with less expansion and apposition of the SB stent (18,19). In addition, a previous intravascular ultrasound imaging study evaluating 403 patients treated with PCI for LM bifurcation lesions found that the frequency of stent underexpansion in the 2-stent group was twice as high as that in the 1-stent group, which could explain the higher risk of adverse cardiovascular events in patients treated with the 2-stent strategy (20).

The main point of the present study is that, if possible, the 1-stent strategy should initially be considered as the preferred approach for the treatment of coronary bifurcation lesions, especially in patients with LM bifurcation lesions. In the present study, ~60% of patients with LM bifurcation lesions were treated with the 1-stent strategy, which is consistent with previous reports (11,12). We previously reported that the 1-stent strategy with provisional SB stenting for LM bifurcation lesions was feasible and effective and that the crossover rate to the 2-stent technique was only 12.5% when SB stenting was performed only if there was diameter stenosis >50% or type B or greater dissection after main vessel stenting followed by kissing balloon dilation (21). Therefore, the 1-stent strategy may be performed in the majority of patients with LM bifurcation lesions and is associated with favorable clinical outcomes. However, considering the higher risk of stent thrombosis, cardiac death, and MI as well as repeat revascularization observed in patients treated with the 2-stent technique compared with those treated with the 1-stent technique, a careful surgical evaluation should take place in patients with LM bifurcation lesions requiring an elective 2-stent technique.

Study limitations. Our study's nonrandomized, observational design may have significantly affected the results due to confounding factors. The selection of treatment strategy and stent type was at the discretion of the operators. Some baseline and angiographic characteristics were unfavorable to the 2-stent group compared with the 1-stent group. This may contribute to differences in adverse outcomes between the 2 groups, and the impact of the 2-stent strategy on adverse clinical outcomes could become more relevant in patients with LM bifurcation lesions. Although we strove to reduce treatment-selection bias for treatment strategy and potential confounding using various risk-adjusted and inverse probability of treatment weighting, unmeasured confounders may be present. Another limitation is that a substantial portion of patients were treated with first-

generation DES, which were found to be inferior to newer generation DES with regard to the occurrence of adverse clinical events. Our findings should be confirmed by adequately powered, randomized trials using newer generation DES.

Conclusions

There was a substantial interaction between treatment strategy and bifurcation lesion location for cardiovascular events. The 1-stent strategy, if anatomically suitable, should be considered the primary strategy for the treatment of coronary bifurcation lesions, especially LM bifurcation lesions. Randomized, controlled trials with a large sample size are needed to confirm these findings.

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Key Words: angioplasty ■ bifurcation lesions ■ drug-eluting stent(s) ■ left main.