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Original Studies

Comparison of Single- Versus Two-Stent Techniques in Treatment of Unprotected Left Main Coronary Bifurcation Disease

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Background: This study sought to compare 3-year outcomes of single- versus two-stent techniques in patients with distal unprotected left main coronary artery (LMCA) disease treated with drug-eluting stents (DES). Methods and Results: A total of 392 patients with distal unprotected LMCA disease who underwent DES implantation with single- (n = 234) or two- (n = 158) stent techniques were evaluated. The primary end point was major adverse cardiac events (MACE), defined as the composite of death, myocardial infarction (MI), and target lesion revascularization (TLR). The two-stent group was more likely to have extensive coronary artery stenosis. After adjustment with weighted Cox model using the inverse probability of treatment weighting, the 3-year risk of death was similar in the single- and two-stent groups (hazard ratio [HR], 0.77, 95% confidence interval [CI], 0.28–2.13, P = 0.62). However, the 3-year risks of MI (HR, 0.38, 95% CI, 0.19–0.78, P = 0.008), TLR (HR, 0.16, 95% CI, 0.05–0.57, P = 0.005), and MACE (HR, 0.89, 95% CI, 0.22–0.67, P = 0.0007) were significantly lower in the single-stent group. Conclusion: Compared with the two-stent technique, the single-stent technique showed more favorable long-term clinical outcomes in patients with distal unprotected LMCA disease who received DES.

Key words: percutaneous coronary angioplasty; stents; left main; bifurcation

INTRODUCTION

The introduction of drug-eluting stents (DES) has significantly reduced the rate of repeat revascularization for patients with unprotected left main coronary artery (LMCA) disease, as compared with bare-metal stents (BMS) [1–3]. However, distal LMCA disease remained a technical challenge and was associated with poorer clinical outcomes than nondistal lesions [2,4]. The optimally effective technique for treatment of bifurcation lesions in patients with distal unprotected LMCA disease is unclear [2,5]. Bifurcation lesions present a wide spectrum of anatomical complexity, ranging from simple lesions that can be treated with a single-stent technique to complex lesions that require a two-stent technique. Our previous retrospective analysis showed that, compared with the two-stent technique, the single-stent technique was technically easier and more effective in improving long-term clinical outcomes in patients with distal unprotected LMCA disease containing a normal left circumflex coronary artery [5]. That study, however,

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involved a limited number of patients from a single center and had a short follow-up period. A more recent study showed that the single-stent technique was associated with lower rates of 2-year major adverse events than the two-stent technique in patients with distal unprotected LMCA disease [6]. Although large, this study was weakened by a lack of angiographic analysis, which should be considered in the adjustment technique. We have therefore compared 3-year clinical outcomes of the single-stent and two-stent techniques in patients with distal unprotected LMCA disease undergoing percutaneous coronary intervention (PCI) using DES.

METHODS

Study Population and Procedures

As previously reported, the MAIN-COMPARE (revascularization for unprotected left MAIN coronary artery stenosis: COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) registry includes patients with distal unprotected LMCA disease who received DES ($n = 467$) as the index procedure at 12 major cardiac centers in Korea between May 2003 and June 2006 [7]. This analysis involved 392 (84%) consecutive patients whose baseline angiographies could be analyzed. Patients who had prior coronary artery bypass grafting (CABG), underwent concomitant valvular or aortic surgery, had ST-segment myocardial infarction (MI) requiring emergent stenting, or presented with cardiogenic shock were excluded. The local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

Patients underwent PCI, rather than CABG, according to the preference of the patient or physician, as well as contraindications for or disagreement with CABG [7]. Beginning in March 2003, DES implantation has been the exclusive treatment for LMCA disease at all participating centers. The choice of sirolimus- (Cypher and Cypher Select; Cordis; Johnson & Johnson) or paclitaxel- (Taxus Express and Liberté; Boston Scientific) eluting stents was at the discretion of each physician. Stent implantation techniques for patients with LMCA disease have been described [1,7]. Interventions for any other significant coronary artery disease were performed according to current practice guidelines. For LMCA bifurcation lesions, the single-stent technique, in which a stent was placed across the side branches (usually the left circumflex artery), was preferred in patients with diminutive or normal-looking side branches. Two-stent techniques, consisting of T-stenting, kissing stenting, culotte stenting, crush stenting, or V-stenting, were considered in patients with diseased side branches. A selection of stenting strategy was mostly determined by intravascular ultrasound (IVUS) as well as angiographic findings. The use of predilation or an intraaortic balloon pump was at the discretion of each physician. Postdilation with high-pressure inflation after stenting was performed in selected patients with suboptimal expansion or stent inapposition, as assessed by angiography or IVUS. Debulking devices, including cutting balloon angioplasty, rotablator, or debulking coronary atherectomy, were used in selected patients with severe calcified or fibrous plaques at the discretion of each physician.

All patients receiving DES were prescribed aspirin (200 mg) plus clopidogrel 75 mg (after a loading dose of 300 or 600 mg) before or during the coronary intervention. After the procedure, aspirin was continued indefinitely and clopidogrel was continued for at least 6 months [8]. Extended use of clopidogrel beyond 6 months was at the discretion of each physician.

Study Endpoints and Definitions

The primary endpoint of this analysis was major adverse cardiac events (MACE), defined as the composite of death, MI, and target lesion revascularization (TLR) at 3 years. All components of the primary end point were considered as secondary end points. Patients' baseline demographic, clinical, angiographic, and procedural characteristics were collected using a dedicated internet-based reporting system. Occurrences of death, MI, TLR, target vessel revascularization (TVR), and stent thrombosis were ascertained during hospitalization, at 6 months and 1 year after the procedure, and annually for up to 3 years. All events were based on clinical diagnosis by attending physicians and were centrally adjudicated by an independent group of clinicians.

All deaths were considered of cardiac origin unless a noncardiac origin was established clinically or at autopsy. The diagnosis of acute MI and periprocedural MI were based on the universal definition of MI [9]. TLR was defined as repeat revascularization with PCI or coronary artery bypass surgery for restenosis of the entire segment involving the implanted stent and 5 mm distal and proximal to the stent. TVR was defined as any repeat revascularization in the treated vessel, including any segments of the left anterior descending artery and the left circumflex artery [10].

To compare baseline anatomical complexity in patients undergoing the single-stent and two-stent techniques, the SYNTAX score for each patient was independently calculated at the Angiographic Core Laboratory of the CardioVascular Research Foundation, Seoul, Korea. The total score for each patient was determined by adding the score for each individual diseased segment, defined as segments with $\geq$50% stenosis in vessels $\geq$1.5 mm in diameter, as recommended [11].

Statistical Analysis

Baseline clinical, angiographic and procedural characteristics of groups of patients receiving single- and two-stent techniques are presented as median and interquartile range (IQR) and compared using the Wilcoxon rank sum test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables, as appropriate. Unadjusted cumulative rates of individual and composite outcomes were estimated by the Kaplan–Meier method and compared by log-rank test.

Crude and adjusted risks for adverse outcomes were compared by univariate and multivariate Cox proportional hazards regression analyses. Multiple regression analysis was performed using the two-stent technique as the reference category and the indicator variable for the single-stent technique. Variables with P-values ≤ 0.20 and clinically relevant covariates, regardless of their statistical relevance in univariate analyses, were candidates for inclusion in multivariate Cox proportional hazards models. The final models were determined by backward elimination.

To reduce the impact of treatment-selection bias and potential confounding factors in an observational study, we used weighted Cox proportional hazard models with robust standard errors to compare hazard rates of outcomes in the single- and two-stent groups. Weighted Cox's models were constructed using the inverse probability of treatment weighting (IPTW) approach [12]. In the IPTW model, weights were stabilized by marginal probability for both treatment strategies. That is, stabilized weights for patients treated with two-stent techniques were the product of the marginal probability for the two-stent group and the inverse of (1-propensity score), and those for patients treated with the single-stent technique were the product of the marginal probability for the single-stent group and the inverse of the propensity score [13].

All P values are two-sided, and P values less than 0.05 were considered statistically significant. SAS software, version 9.1 (SAS Institute, Cary, NC) was used for statistical analysis.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Baseline Clinical and Procedural Characteristics

A total of 392 consecutive patients with distal unprotected LMCA disease who received DES were included in this analysis; 234 were treated with a single-stent technique and 158 with two-stent techniques. The baseline demographic, clinical, angiographic, and procedural characteristics of the two groups are listed in Tables I and II. There were no significant between group differences in demographic and clinical characteristics. Compared with patients in the single-stent group, those in the two-stent group were more likely to have more complex coronary anatomies, three-vessel diseases, and right coronary stenosis and to be treated with glycoprotein IIb/IIIa inhibitors, kissing balloon dilatation, and multiples stents. In the two-stent group, 72 patients (45.6%) were treated with crush stenting, 55 with simultaneous kissing stenting (34.8%), 25 with T-stenting (15.8%), 4 with V-stenting (2.5%), and 2 with culotte stenting (1.3%) (Table II). Using the SYNTAX score calculation, true bifurcation lesions (i.e., types C, D, F, and G) were identified in 78 patients (33.3%) in the single-stent group and in 84 (53.2%) in the two-stent group ($P < 0.001$). Consequently, the overall SYNTAX score was higher in the two-stent group. However, the median scores outside the LMCA segment were comparable in the single- (8.0, IQR, 1.0 to 16.0) and two- (10.0, IQR, 2.0 to 17.0, $P = 0.06$) stent groups. IVUS guidance in DES implantation was 179 patients (76.5%) in the single-stent group and 117 (74.1%) in the two-stent group (Table II).

Unadjusted Outcomes

Figure 1 shows the crude outcomes of patients treated with single- and two-stent techniques. The two groups had a similar 3-year unadjusted incidence of death (5.8% vs. 7.6%, $P = 0.65$). However, the 3-year unadjusted incidences of MI (7.3% vs. 16.6%, $P = 0.007$), which was primarily related to the periprocedural MI (6.8% vs. 13.9%, $P = 0.02$), TLR (2.2% vs. 8.4%, $P = 0.005$), and MACE (14.3% vs. 27.4%, $P = 0.002$) were significantly lower in the single-stent group (Fig. 1).

Stent thrombosis occurred in three patients in the two-stent group, on days 0, 5, and 22 after the index procedure, but in none of the patients in the single-stent group. Stent thrombosis in the three patients was angiographically confirmed, presenting as MI, consisting of one patient with non-ST segment MI and two with ST segment MI.

Adjusted Outcomes

After adjusting for possible confounders using a multivariate Cox regression model, we found that the 3-year adjusted risks of death in the single- and two-stent groups were similar (hazard ratio [HR], 0.87, 95% confidence interval [CI], 0.32–2.36, $P = 0.79$). In contrast, the 3-year adjusted risks of MI (HR, 0.48, 95% CI, 0.26–0.89, $P = 0.021$), TLR (HR, 0.25, 95% CI, 0.09–0.71, $P = 0.009$), and MACE (HR, 0.52, 95% CI, 0.32–0.83, $P = 0.006$) were significantly lower in the single-stent

TABLE I. Baseline Clinical Characteristics

Variable	One-stent (n = 234)	Two-stent (n = 158)	P
Age (years)	71.3 (63.8–76.5)	71.2 (64.3–76.5)	0.11*
Male gender	170 (72.6)	121 (76.6)	0.38
Diabetes			
Any diabetes	85 (36.5)	46 (29.1)	0.13
Insulin treatment	15 (6.4)	12 (7.6)	0.65
Hypertension	127 (54.7)	88 (56.1)	0.78
Hyperlipidemia	83 (35.8)	56 (35.9)	1.00
Current smoker	56 (23.9)	29 (18.4)	0.19
Family history of CAD	20 (8.5)	8 (5.1)	0.19
Previous myocardial infarction	25 (10.8)	17 (10.8)	0.99
Previous coronary angioplasty	52 (22.3)	40 (25.5)	0.47
Previous congestive heart failure	3 (1.3)	2 (1.3)	1.00
Previous stroke	21 (9.1)	15 (9.6)	0.89
Peripheral vascular disease	5 (2.2)	4 (2.5)	1.00
Chronic lung disease	7 (3.0)	6 (3.8)	0.66
Chronic kidney disease	7 (3.0)	7 (4.5)	0.46
Left ventricular ejection fraction (%)	60.0 (55.8–71.0)	68.0 (62.0–72.0)	0.16*
EuroSCORE	3.0 (2.0–5.0)	3.0 (2.0–7.0)	0.47*
Electrocardiographic findings			0.99
Sinus rhythm	223 (95.3)	151 (95.6)	
Atrial fibrillation	5 (2.1)	3 (1.9)	
Other	6 (2.6)	4 (2.5)	
Clinical presentation			0.10
Silent ischemia	8 (3.4)	1 (0.6)	
Stable angina	83 (35.5)	54 (34.2)	
Unstable angina	107 (46.3)	88 (56.1)	
NSTEMI	36 (15.4)	15 (9.5)	

Abbreviations: CAD, coronary artery disease; NSTEMI, non ST-segment elevation myocardial infarction. The values are presented with median (interquartile range) and number (percentage).
*By Wilcoxon rank sum test.

group. These results were also seen following the second adjustment using the standard IPTW method (Table III).

DISCUSSION

The major finding of this study was that, among patients with distal unprotected LMCA disease, the 3-year adjusted risk of death was similar when single- or two-stent techniques were used, whereas the 3-year adjusted risks of MI, TLR, and MACE were significantly lower when the single-stent technique was used.

Distal unprotected LMCA lesions are associated with a poorer prognosis because these lesions invariably involve two major ostial lesions in the left anterior descending and left circumflex arteries, [2,4,14] making coronary artery bypass graft surgery the preferred method of treatment. With the introduction of DES and the use of new adjuvant medications, including clopidogrel, statins, antiplatelet agents, and glycoprotein IIb/IIIa inhibitors, and new devices, especially IVUS guidance, stenting with DES has increasingly been performed by experienced interventional cardiologists for patients with unprotected LMCA disease. PCI has been shown to be safe for patients with distal unprotected LMCA disease at low to intermediate risk [2,10,15–17].

Despite the development of treatment modalities, the most appropriate stent technique for distal unprotected LMCA disease is still unclear [2,5]. The single-stent strategy has been associated with improved clinical outcomes that were mainly driven by short duration of procedure, low X-ray dose, and lower rates of procedure-related myocardial necrosis in patients with non-left main bifurcated lesions [18–21]. In contrast, few studies have compared single- and two-stent techniques in patients with LMCA disease [5,6,22]. Although we previously reported that the single-stent method was more effective in reducing repeat revascularization in patients with normal left circumflex artery, that study was limited by the small number of patients [5]. More recently, a comparison of the two-stent technique in 317 patients and the single-stent technique in 456 patients disclosed no differences in the incidence of death or MI, however, the single stent technique was associated with lower rates of TLR and MACE [6]. These results were generally in agreement with ours, except that we found that the single-stent technique was associated with a lower risk of MI, which was mainly driven by periprocedural MI. Our study, however, included angiographic information, which was qualitatively measured in an independent core laboratory. The SYNTAX score, which

TABLE II. Baseline Angiographic and Procedural Characteristics

Variable	One-stent (n = 234)	Two-stent (n = 158)	P
SYNTAX score, total	23.5 (17.0–32.5)	27.0 (19.0–33.5)	0.007*
ACC/AHA lesion type B2 or C	195 (83.3)	145 (91.8)	0.016
Bifurcation types[a]	162 (69.2)	115 (72.8)	<0.001
Type A, B, E	84 (35.9)	31 (19.6)	
Type C, D, F, G	78 (33.3)	84 (53.2)	
Angulation <70[b]	26 (11.1)	20 (12.7)	0.64
Trifurcation types	72 (30.8)	43 (27.2)	0.37
1 diseased segment	9 (3.8)	1 (0.6)	
2 diseased segments	20 (8.5)	9 (5.7)	
3 diseased segments	15 (6.4)	14 (8.9)	
4 diseased segments	28 (12.0)	19 (12.0)	
Total occlusion	1 (0.4)	1 (1.3)	0.57
Significant lesion (50–99% stenosis)	234 (100)	158 (100)	1.00
Lesion length >20 mm	157 (67.1)	157 (99.4)	<0.001
Heavy calcification	15 (6.4)	11 (7.0)	0.63
Thrombus	8 (3.4)	4 (2.5)	0.77
Extent of diseased vessel			<0.001
LMCA only	26 (11.1)	11 (7.0)	
LMCA plus single-vessel disease	80 (34.2)	8 (5.1)	
LMCA plus two-vessel disease	66 (28.2)	60 (38.0)	
LMCA plus three-vessel disease	62 (26.5)	79 (50.0)	
Right coronary artery disease	97 (41.5)	83 (52.5)	0.031
Restenotic lesion	13 (5.6)	7 (4.4)	0.62
Use of glycoprotein IIb/IIIa inhibitors	14 (6.0)	19 (12.0)	0.035
Use of intra-aortic balloon pump	10 (4.3)	10 (6.3)	0.37
Guidance of intravascular ultrasound	179 (76.5)	117 (74.1)	0.39
Direct stenting	45 (19.2)	27 (17.1)	0.58
Final kissing balloon dilatation	95 (40.6)	113 (71.5)	<0.001
Bifurcation stenting			-
Crush	–	72 (45.6)	
Kissing	–	55 (34.8)	
T-stenting	–	25 (15.8)	
V-stenting	–	4 (2.5)	
Culotte	–	2 (1.3)	
Number of stents at LMCA	1.33 ± 0.59	1.35 ± 0.54	0.81
Total stent length at LMCA (mm)	28.0 (18.0–41.0)	51.0 (41.0–66.0)	<0.001*
Stent diameter at LMCA (mm)	3.50 (3.25–3.50)	3.17 (3.00–3.25)	<0.001*

Abbreviations: LMCA, left main coronary artery. The values are presented with median (interquartile range) and number (percentage).
*By Wilcoxon rank sum test.
[a]Type A, pre-branch stenosis not involving the ostium of the side branch; Type B, post side branch stenosis of the main vessel not involving the origin of the side branch; Type C, stenosis encompassing the side branch but not involving its ostium; Type D, stenosis involving the main vessel and ostium of the side branch; Type E, stenosis involving only the ostium of the side branch; Type F, stenosis directly involving the main vessel (pre-side branch) and the ostium of the side branch; Type G, stenosis directly involving the main vessel (post-side branch) and the ostium of the side branch.
[b]Bifurcation with a steep angle (<70°) between the side branch and the distal main vessel.

was measured to indicate angiographic complexity in the two treatment groups, may play a role in the adjustment of potential confounders when stenting procedures were compared in a nonrandomized registry [23].

After rigorous two-step adjustments, we confirmed that the single-stent technique was associated with more favorable long-term outcomes, as determined by the 3-year risks of MI, TLR, and MACE. Patients treated with the two-stent technique have been regarded as having more complex lesions and a greater plaque burden, which caused the higher risks of adverse clinical outcomes. We therefore adjusted the angiographic findings for important confounders during multivariate and IPTW analysis, as well as adjusting for important clinical variables. The choice of treatment modality for each patient with distal LMCA disease was based on a combination of several factors, including coronary anatomy, operator's preference, and plaque burden in the bifurcation lesion. Although we found that patients treated with the two-stent technique had more complex anatomy in their bifurcation lesions, there were no significant differences in other angiographic variables between two groups. Thus, if possible, the single-stent technique should first be considered for patients with distal LMCA disease.

Compared with other studies, approximately three fourths of the patients in our study received IVUS

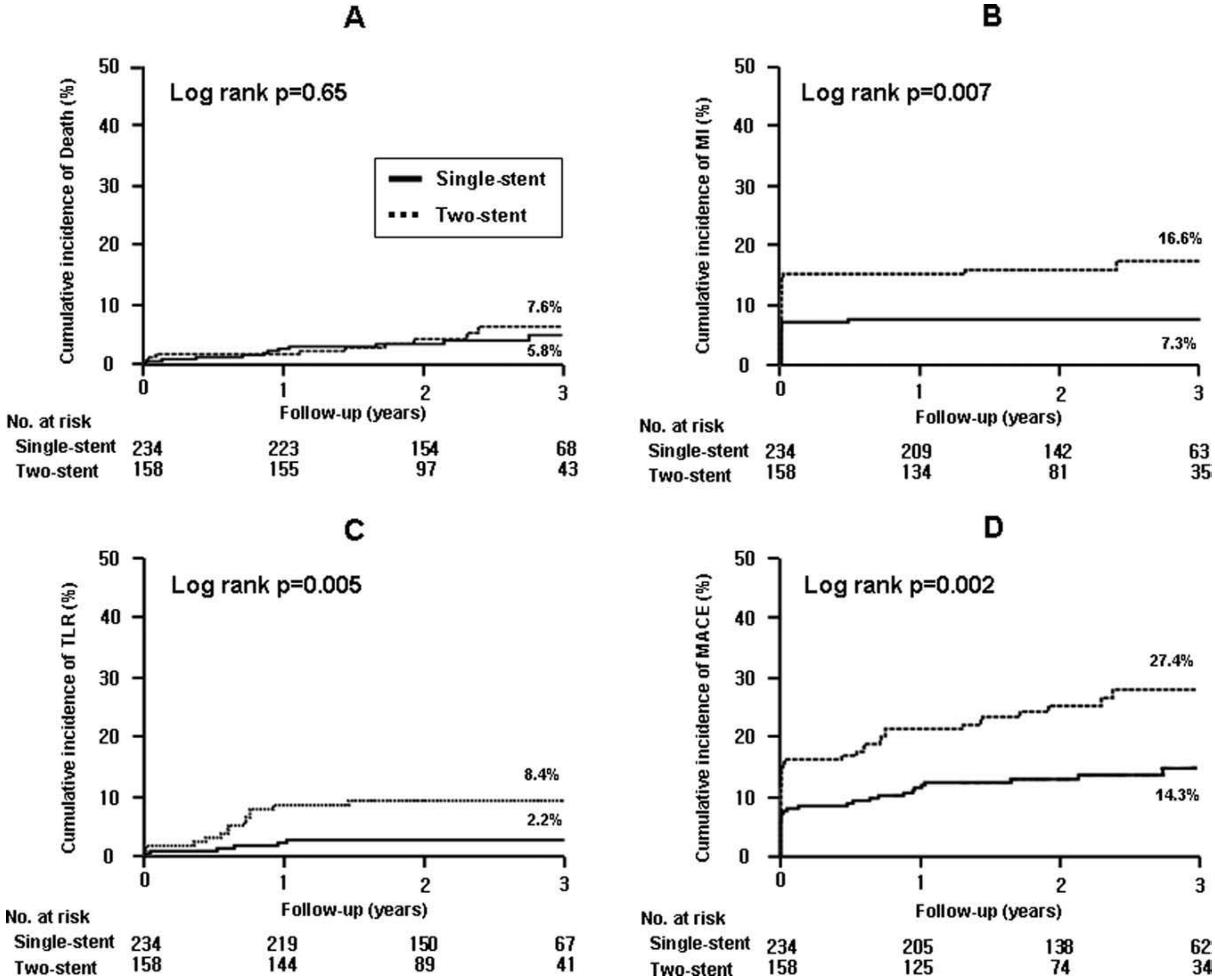

Fig. 1. Kaplan–Meier 3-year incidence curves of (A) death, (B) myocardial infarction (MI), (C) target lesion revascularization (TLR), and (D) major adverse cardiac events (MACE), including death, MI or TLR, in patients with distal left main lesions receiving drug-eluting stents.

TABLE III. Three-Year Clinical Outcomes in the Unadjusted, Covariate-Adjusted Cox Proportional Analysis, and Adjusted With Inverse Probability Treatment Weight Methods in Patients Treated With the Single-Stent Versus the Two-Stent Technique

	Crude		Multivariate		Adjusted with IPTW	
Outcome	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Death	0.818 (0.339–1.972)	0.654	0.874 (0.323–2.364)	0.79†	0.772 (0.280–2.132)	0.62
MI	0.440 (0.237–0.814)	0.009	0.482 (0.260–0.894)	0.021‡	0.379 (0.185–0.777)	0.008
TLR	0.254 (0.091–0.713)	0.009	0.254 (0.091–0.713)	0.009	0.163 (0.046–0.573)	0.005
TVR	0.316 (0.158–0.633)	0.001	0.267 (0.129–0.550)	0.0003§	0.248 (0.111–0.556)	0.0007
MACE	0.485 (0.303–0.776)	0.003	0.518 (0.323–0.831)	0.006‖	0.387 (0.224–0.671)	0.0007

Abbreviations: IPTW, inverse probability treatment weight; CI, confidence interval; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiac events.

*Hazard ratios for single-stent relative to two-stent techniques.

†Adjusted for peripheral vascular disease, chronic kidney disease, left ventricular ejection fraction, EuroSCORE, electrocardiographic findings, and SYNTAX score.

‡Adjusted for hyperlipidemia, SYNTAX score.

§Adjusted for age, insulin treated diabetes, and previous stroke.

‖Adjusted for chronic kidney disease, left ventricular ejection fraction, SYNTAX score, and use of intra-aortic balloon pump.

guidance. IVUS was used before and during PCI to determine the degree of stenosis, plaque distribution, and anatomic configuration with side branches, as well as to assess the correct stent size and length, and the appropriate stent technique. In our study, a selection of stenting strategy between single- versus two-stenting, was mostly determined by IVUS examination as well as angiograhpic appearance of the LMCA bifurcation [24,25]. This strategy of IVUS guidance might improve the outcomes [26] and be useful to clarify the diseased side branch, in which the two-stent technique was considered in first strategy.

Our study had several limitations. First, despite rigorous adjustment using standard and weighted-Cox regression employing IPTW, unmeasured confounders, procedure bias, or selection bias may have been present. Second, although including baseline qualitative angiographic assessment such as the SYNTAX score system in a core laboratory, quantitative angiographic assessment was not fully performed. However, details on the bifurcation lesions were clarified together with procedural characteristics, with most of the angiographic data included in our analysis. Third, despite the high proportion of patients who underwent IVUS-guided stenting, we did not perform a detailed analysis of IVUS parameters.

In conclusion, we confirmed that stenting with DES can be a safe and effective alternative to CABG for distal LMCA stenosis. Regarding the stenting technique, single-stent technique should be considered as the first-line strategy after a careful evaluation of lesions with angiography and IVUS.

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