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ORIGINAL ARTICLE
Coronary Intervention

Comparison of 2-Stenting Strategies Depending on Sequence or Technique for Bifurcation Lesions in the Second-Generation Drug-Eluting Stent Era

— Analysis From the COBIS (Coronary Bifurcation Stenting) III Registry —

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Background: It has not been determined which specific 2-stenting strategy is the best for bifurcation lesions. Our aim was to investigate the clinical outcomes of various 2-stenting strategies in the era of 2nd-generation drug-eluting stents (2G-DES).

Methods and Results: We analyzed 454 patients who finally underwent 2-stenting for a bifurcation lesion, from among 2,648 patients enrolled in the COBIS III registry. The primary outcome was target lesion failure (TLF). Patients were analyzed according to stenting sequence (provisional [main vessel stenting first] vs. systemic [side branch stenting first]) and stenting technique (crush vs. T vs. culotte vs. kissing/V stenting). Overall, 4.4 years' TLF after 2-stenting treatment for bifurcation lesion was excellent: TLF 11.2% and stent thrombosis 1.3%. There was no difference in TLF according to 2-stenting strategy (11.1% vs. 10.5%, P=0.990 for provisional and systemic sequence; 8.6% vs. 14.4% vs. 12.9% vs. 12.2%, P=0.326 for crush, T, culotte, kissing/V technique, respectively). Only left main (LM) disease and a shorter duration of dual antiplatelet therapy (DAPT) were associated with TLF. The distribution of DAPT duration differed between patients with and without TLF, and the time-point of intersection was 2.5 years. Also, the side branch was the most common site of restenosis.

Conclusions: The stenting sequence or technique did not affect clinical outcomes, but LM disease and shorter DAPT were associated with TLF, in patients with bifurcation lesions undergoing 2-stenting with 2G-DES.

Key Words: 2-stenting technique; Adjunctive pharmacotherapy; Bifurcation; Drug-eluting stents; Left main disease

The treatment of bifurcation lesions remains one of the most challenging aspects in the field of interventional cardiology. Following technical improvements of percutaneous coronary intervention (PCI), more bifurcation lesions are becoming potential candidates for PCI. Current consensus recommends the provisional 1-stenting technique for bifurcation lesions, but recent

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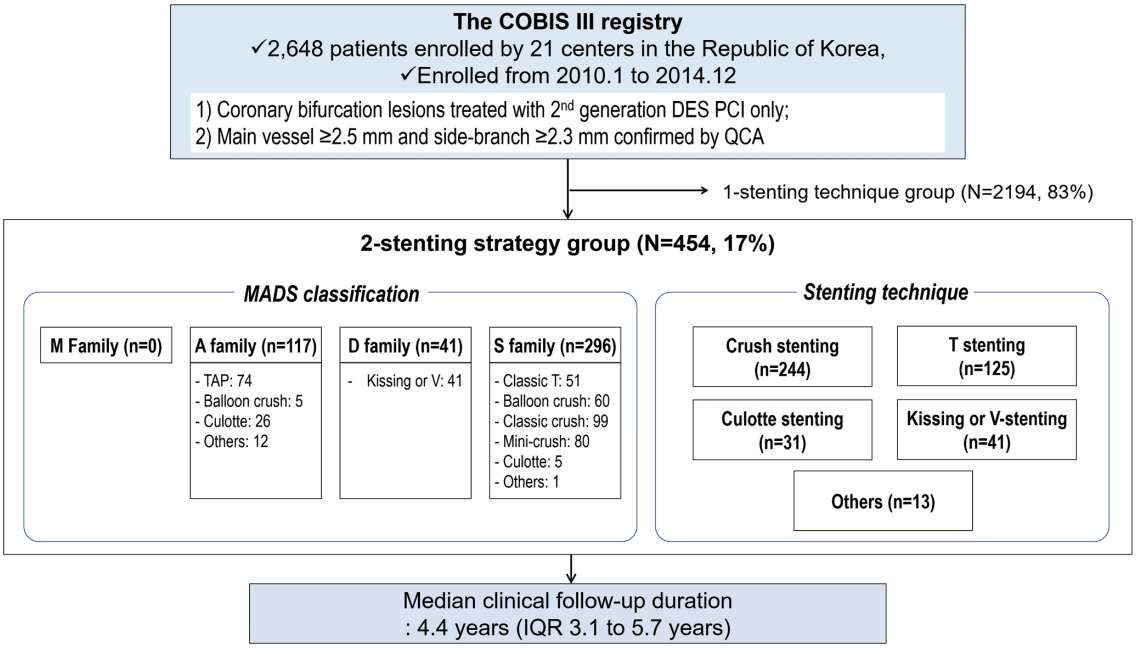

Figure 1. Study flowchart of the COBIS registry. COBIS, COronary BIfurcation Stenting; DES, drug-eluting stent; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

studies have shown that a 2-stenting technique should be considered when clinically necessary.[1] The recent European Bifurcation Club consensus states that an upfront 2-stenting technique should be used in very complex lesions with large, calcified side branches (SBs) with ostial disease extending >5 mm from the carina, and in bifurcations with SBs that should be secured by stenting once they are accessed.[1] However, when a 2-stenting technique is deemed necessary, it is still debated which specific stenting strategy and technique should be preferred,[2,3] mainly because of contradictory results derived from previous trials,[4–8] leading clinicians to apply the most personally familiar technique.[9] Moreover, the specific stenting strategy is determined through the clinical decision making of the physician. Therefore, comparing outcomes of the final stenting strategy would provide practical feedback to clinicians regarding the best strategy. Accordingly, in a large registry-based population composed of patients who underwent PCI with 2nd-generation drug-eluting stents (2G-DES) for bifurcation lesions, we evaluated the prognostic effect of different 2-stenting strategies on clinical outcomes. First, we compared the clinical outcomes after different sequences of 2-stenting, because it is important in real-world practice to decide whether the first stent should be implanted into the main vessel (MV), so-called the provisional 2-stenting sequence, or the SB, so-called systematic 2-stenting sequence. Second, we also compared the performance of 4 different techniques of 2-stenting: crush, T, culotte, and kissing/V stenting.

Methods

Study Design and Patient Population

This study was based on the COBIS (COronary BIfurcation Stenting) III registry, which is a retrospective, multicenter, observational, real-world registry of patients with bifurcation lesions who underwent PCI with 2G-DES (**Figure 1**, Clinicaltrials.gov, NCT03068494). A total of 2,648 patients from 21 tertiary medical centers were con-

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Table 1. Comparison of Baseline Clinical Characteristics of Patients Between the 2-Stenting Sequence and Specific 2-Stenting Techniques

	Total 2-stenting	2-stenting sequence[a]		P value
		Provisional	Systemic	
n	454	117 (25.8%)	296 (65.2%)	
Sex (male)	331 (72.9%)	85 (72.6%)	218 (73.6%)	0.933
Age (years)	65.02±11.06	65.32±10.67	64.55±11.02	0.518
Clinical diagnosis, n (%)				0.231
Stable angina	179 (39.4%)	46 (39.3%)	124 (41.9%)	
Unstable angina	152 (33.5%)	38 (32.5%)	97 (32.8%)	
NSTEMI	89 (19.6%)	19 (16.2%)	57 (19.3%)	
STEMI	34 (7.5%)	14 (12.0%)	18 (6.1%)	
Hypertension, n (%)	254 (55.9%)	61 (52.1%)	167 (56.4%)	0.497
Diabetes mellitus, n (%)	176 (38.8%)	45 (38.5%)	111 (37.5%)	0.945
Dyslipidemia, n (%)	174 (38.3%)	45 (38.5%)	110 (37.2%)	0.894
Current smoker, n (%)	119 (26.2%)	37 (31.6%)	72 (24.3%)	0.164
CRF, n (%)	20 (4.4%)	5 (4.3%)	13 (4.4%)	>0.999
Previous stroke, n (%)	27 (5.9%)	8 (6.8%)	17 (5.7%)	0.848
Previous MI, n (%)	21 (4.6%)	3 (2.6%)	16 (5.4%)	0.326
Previous PCI, n (%)	66 (14.5%)	18 (15.4%)	43 (14.5%)	0.946
Previous CABG, n (%)	1 (0.2%)	0 (0.0%)	1 (0.3%)	>0.999
LVEF, (%)	58.38±9.76	59.48±10.17	58.08±9.62	0.246
Laboratory tests				
Hemoglobin (mg/dL)	13.25±1.97	13.17±2.04	13.34±1.89	0.891
Creatinine (mg/dL)	1.18±1.25	1.03±0.65	1.19±1.31	0.122
Pre-PCI CK-MB (mg/dL)	18.18±52.81	20.89±47.85	18.74±58.03	0.751
Post-PCI CK-MB (mg/dL)	22.88±68.00	24.35±60.24	18.15±50.82	0.357
Pre-PCI Troponin I (mg/dL)	5.35±19.69	5.76±13.95	5.66±22.73	0.967
Post-PCI Troponin I (mg/dL)	10.38±36.78	8.36±19.35	8.89±39.02	0.873
Discharge medications				
Aspirin, n (%)	442 (97.6%)	115 (98.3%)	288 (97.6%)	>0.999
P2Y12 inhibitor, n (%)	442 (97.6%)	114 (97.4%)	289 (98.0%)	0.718
Clopidogrel, n (%)	410 (91.5%)	107 (93.0%)	266 (91.1%)	0.660
Prasugrel, n (%)	17 (3.8%)	5 (4.3%)	10 (3.4%)	0.771
Ticagrelor, n (%)	16 (3.6%)	3 (2.6%)	13 (4.4%)	0.573
DAPT, n (%)	439 (96.9%)	114 (97.4%)	287 (97.0%)	>0.999
DAPT duration (median [IQR]), days	121.1 [81.8, 164.3]	124.50 [97.83, 171.33]	120.04 [76.08, 158.67]	0.082

Data are presented as mean±standard deviation, or n (%). [a]For the 2-stenting sequence (provisional or systematic), patients with kissing/V stenting (n=41) were excluded. [b]For the 2-stenting technique (crush vs. T vs. culotte vs. kissing/V), patients with other stenting techniques (n=13) were excluded. CVA, cerebrovascular accident; CRF, chronic renal failure; DAPT, dual antiplatelet treatment; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

(**Table 1** continued the next page.)

secutively enrolled in the registry, during an enrollment period from January 2010 to December 2014. The registry included patients who were at least 19 years old and had any type of coronary bifurcation lesion in the major epicardial artery treated solely with 2G-DES, a MV diameter ≥2.5 mm, and an SB diameter ≥2.3 mm confirmed by core laboratory quantitative coronary angiography (QCA) analysis. The major exclusion criteria were cardiogenic shock or cardiopulmonary resuscitation during hospitalization, protected left main (LM) disease, and severe left ventricular systolic dysfunction (ejection fraction <30%). The registry was supported by the Korean Bifurcation Club and Korean Society of Interventional Cardiology. The study complied with the provisions of the Declaration of Helsinki, and was approved by the institutional review board at each center. The requirement for written informed consent was waived due to the retrospective nature of the study. This work was supported by the Korean Bifurcation Club and Korean Society of Interventional Cardiology.

Clinical Endpoints

Clinical follow-up was performed for a median 4.4 years (interquartile range [IQR] 3.1–5.7 years). The primary analysis outcome of the present study was the occurrence of target lesion failure (TLF), defined as the composite of cardiac death, spontaneous myocardial infarction (MI), and clinically driven target lesion revascularization (TLR). Secondary endpoints included the individual components of the primary endpoint, all-cause death, target vessel revascularization, stent thrombosis (ST) and bleeding

	2-stenting technique[b]				P value
	Crush	T	Culotte	Kissing/V	
n	244 (53.7%)	125 (27.5%)	31 (6.8%)	41 (9.0%)	
Sex (male)	177 (72.5%)	95 (76.0%)	22 (71.0%)	28 (68.3%)	0.771
Age (years)	64.18±10.87	65.33±11.19	65.42±10.48	67.49±12.30	0.384
Clinical diagnosis, n (%)					NA
Stable angina	95 (38.9%)	58 (46.4%)	12 (38.7%)	9 (22.0%)	
Unstable angina	88 (36.1%)	38 (30.4%)	8 (25.8%)	17 (41.5%)	
NSTEMI	46 (18.9%)	18 (14.4%)	6 (19.4%)	13 (31.7%)	
STEMI	15 (6.1%)	11 (8.8%)	5 (16.1%)	2 (4.9%)	
Hypertension, n (%)	136 (55.7%)	67 (53.6%)	17 (54.8%)	26 (63.4%)	0.748
Diabetes mellitus, n (%)	81 (33.2%)	55 (44.0%)	16 (51.6%)	120 (48.8%)	0.037
Dyslipidemia, n (%)	83 (34.0%)	57 (45.6%)	12 (38.7%)	19 (46.3%)	0.123
Current smoker, n (%)	58 (23.8%)	40 (32.0%)	8 (25.8%)	10 (24.4%)	0.394
CRF, n (%)	9 (3.7%)	8 (6.4%)	0 (0.0%)	2 (4.9%)	0.429
Previous stroke, n (%)	13 (5.3%)	10 (8.0%)	1 (3.2%)	2 (4.9%)	0.749
Previous MI, n (%)	10 (4.1%)	6 (4.8%)	2 (6.5%)	2 (4.9%)	0.823
Previous PCI, n (%)	31 (12.7%)	20 (16.0%)	7 (22.6%)	2 (4.9%)	0.411
Previous CABG, n (%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	5 (12.2%)	>0.999
LVEF, (%)	57.91±9.53	59.70±10.44	58.78±8.18	57.57±9.73	0.479
Laboratory tests					
Hemoglobin (mg/dL)	13.35±1.82	13.20±2.07	13.15±2.20	12.85±2.25	0.579
Creatinine (mg/dL)	1.12±1.14	1.28±1.37	0.90±0.34	1.58±1.87	0.006
Pre-PCI CK-MB (mg/dL)	17.82±58.19	21.08±52.09	10.66±33.05	8.90±17.60	0.173
Post-PCI CK-MB (mg/dL)	17.71±51.28	17.82±37.84	35.05±97.09	53.67±148.14	0.394
Pre-PCI Troponin I (mg/dL)	5.55±23.25	4.98±15.23	6.04±15.60	2.57±7.10	0.461
Post-PCI Troponin I (mg/dL)	8.97±42.13	6.51±15.67	9.86±20.41	24.83±53.46	0.205
Discharge medications					
Aspirin, n (%)	238 (97.9%)	121 (96.8%)	31 (100.0%)	39 (95.1%)	0.483
P2Y12 inhibitor, n (%)	239 (98.4%)	121 (96.8%)	30 (96.8%)	39 (95.1%)	0.333
Clopidogrel, n (%)	219 (90.5%)	112 (91.8%)	29 (96.7%)	37 (90.2%)	0.784
Prasugrel, n (%)	7 (2.9%)	7 (5.6%)	1 (3.3%)	2 (4.9%)	0.540
Ticagrelor, n (%)	13 (5.4%)	2 (1.6%)	1 (3.3%)	0 (0.0%)	0.193
DAPT, n (%)	237 (97.5%)	120 (96.0%)	30 (96.8%)	39 (95.1%)	0.556
DAPT duration (median [IQR]), days	120.4 [78.9, 164.1]	125.1 [78.5, 158.6]	121.2 [100.2, 179.5]	120.6 [87.5, 163.0]	0.759

events. All clinical events were verified by an independent clinical event adjudicating committee, which comprised independent experts in interventional cardiology who had not participated in patient enrollment. Definitions of outcome measures in this study are specified in **Supplementary File 1**.

Statistical Analysis

Data are presented as numbers and frequencies for categorical variables and as mean±standard deviation for continuous variables. Clinical and procedural characteristics were compared between patients who had undergone stenting using different techniques. For comparison among groups, the χ^2 (or Fisher exact test when any expected count was <5 for a 2×2 table) test for categorical variables and unpaired Student's t-test or one-way analysis of variance for continuous variables were applied. To estimate independent factors to predict endpoints, a multivariable Cox proportional hazards regression was performed. Due to the difference in angiographic characteristics between comparison groups, we used 2 different matching processes: the propensity score matching (PSM) method and the inverse probability weighted (IPW) Cox proportional hazard regression model. Factors included in the PSM analysis were bifurcation location in the coronary artery, true bifurcation lesions based on the Medina classification, lesion lengths of the MV and SB, reference diameters of the MV and SB, and MLD of the MV and SB before PCI. Event rates were calculated based on Kaplan-Meier censoring estimates and compared using the log-rank test. The Breslow test was used to compare the different stent technique groups. All probability values were 2-sided and $P<0.05$ was considered statistically significant. Statistical tests were performed using R (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

From the total population of the COBIS III registry, 2194 patients (82.9%) received a 1-stenting technique and 454 patients (17.1%) finally received a 2-stenting technique.

Table 2. Clinical Outcomes of Different Sequences of 2-Stenting Technique

	2-stenting	2-stenting sequence[a]		P value	2-stenting technique[b]				P value
		Provisional	Systemic		Crush	T	Culotte	Kissing/V	
n	454	117 (25.8%)	296 (65.2%)		244 (53.7%)	125 (27.5%)	31 (6.8%)	41 (9.0%)	
All-cause death, n (%)	22 (4.8%)	4 (3.4%)	15 (5.1%)	0.645	9 (3.7%)	9 (7.2%)	1 (3.2%)	3 (7.3%)	0.351
Cardiac death, n (%)	10 (2.2%)	3 (2.6%)	6 (2.0%)	0.717	3 (1.2%)	5 (4.0%)	1 (3.2%)	1 (2.4%)	0.229
Non-cardiac death, n (%)	12 (2.6%)	1 (0.9%)	9 (3.0%)	0.294	6 (2.5%)	4 (3.2%)	0 (0.0%)	2 (4.9%)	0.592
MI, n (%)	8 (1.8%)	3 (2.6%)	5 (1.7%)	0.693	5 (2.0%)	1 (0.8%)	2 (6.5%)	0 (0.0%)	0.221
Target vessel MI, n (%)	6 (1.3%)	3 (2.6%)	3 (1.0%)	0.358	3 (1.2%)	1 (0.8%)	2 (6.5%)	0 (0.0%)	0.129
Any revascularization, n (%)	69 (15.2%)	18 (15.4%)	45 (15.2%)	>0.999	35 (14.3%)	23 (18.4%)	3 (9.7%)	8 (19.5%)	0.510
TLR, n (%)	38 (8.4%)	10 (8.5%)	25 (8.4%)	>0.999	18 (7.4%)	13 (10.4%)	3 (9.7%)	4 (9.8%)	0.678
TVR, n (%)	49 (10.8%)	13 (11.1%)	33 (11.1%)	>0.999	23 (9.4%)	18 (14.4%)	3 (9.7%)	5 (12.2%)	0.523
Stent thrombosis, n (%)	6 (1.3%)	1 (0.9%)	5 (1.7%)	>0.999	4 (1.6%)	1 (0.8%)	1 (3.2%)	0 (0.0%)	0.512
Target lesion failure,* n (%)	48 (10.6%)	13 (11.1%)	31 (10.5%)	0.990	21 (8.6%)	18 (14.4%)	4 (12.9%)	5 (12.2%)	0.326

Data are presented as n (%). *Composite of cardiac death, MI, and target lesion revascularization. [a]For the 2-stenting sequence (provisional or systematic), patients with kissing/V stenting (n=41) were excluded. [b]For the 2-stenting technique (crush vs. T vs. culotte vs. kissing/V), patients with other stenting techniques (n=13) were excluded. MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

The 2-stenting technique population was classified according to the stenting sequence using the MADS classification, and by the specific stenting technique (**Figure 1**). The systematic sequence with SB-first was twice more applied (65.2%) compared with the provisional sequence with MV first, and the crush technique (53.7%) was the most commonly applied technique. Baseline characteristics of patients receiving each stenting sequence and technique are shown in **Table 1**. Overall, there was no difference in the baseline characteristics of patients receiving each treatment strategy. Lesion and procedural characteristics of the patients receiving different stenting strategies are shown in **Supplementary Table 1**, and the QCA analysis results are shown in **Supplementary Table 2**. The patients receiving the systematic sequence with SB-first had a smaller MLD of the SB, while those receiving the provisional sequence with MV first had a longer lesion length in the MV. Also, the crush technique was used in lesions with a smaller MLD of the SB. After PCI, the crush technique achieved a larger MLD of the MV, whereas the culotte technique achieved a larger MLD of the SB.

Using a multivariable logistic regression model, we evaluated the major determinants of the systematic sequence with SB-first. The systematic sequence was performed when the SB MLD was smaller (HR_{adj} 2.128, 95% confidence interval (CI) 1.300–3.460, P=0.003, per 1 mm decrease in MLD), and when the MV lesion length was shorter (HR_{adj} 1.028, 95% CI 1.005–1.050, P=0.015, per 1 mm decrease of the MV lesion length).

Clinical Outcomes

The cumulative TLF rate during the median follow-up of 4.4 years (IQR 3.1–5.7 years) is shown in **Table 2** and **Figure 2**. There was no difference in the TLF rate between 2 different 2-stenting sequence or 4 different 2-stenting techniques, which was consistent with other secondary outcomes. By multivariate analysis (**Table 3**, **Supplementary Table 3**), the 2-stenting sequence or 2-stenting technique was not an independent predictor of TLF, but LM bifurcation disease and shorter duration of DAPT were associated with TLF after 2-stenting for a bifurcation lesion.

Regarding the antiplatelet regimen, 23 patients (5.1%) experienced early DAPT interruption during the follow-up period (were either treated with single antiplatelet therapy (SAPT) immediately after PCI or switched from DAPT to SAPT during the follow-up period), while the remaining 431 patients (94.9%) were treated with DAPT during the total period. The TLF event rate was significantly higher in patients who experienced early DAPT interruption (30.4% [7 events out of 23 patients] vs. 9.7% [42 events out of 431 patients], P=0.002) **Figure 3A** shows the antiplatelet usage pattern and duration of the 23 patients with early DAPT interruption, and the TLF event time-point for each 7 individual cases. Moreover, **Figure 3B** shows the distribution of DAPT duration by population density, according to TLF occurrence. Patients who experienced TLF events were prescribed a shorter duration of DAPT, compared with those who did not experience TLF events (median DAPT duration: 3.7 years (IQR 1.2 years, 5.0 years) vs. 4.0 years (IQR 2.9 years, 5.5 years), P=0.028, for TLF (+) and TLF (−) patients, respectively). The time-point of intersection was 2.5-years, implying TLF occurred more often in patients with DAPT duration <2.5 years. Using 2.5-years as the cutoff value of DAPT duration, patients with DAPT duration <2.5 years experienced a significantly higher rate of TLF than the other group with DAPT duration ≥2.5 years (18.8% [19/101] vs. 8.5% [30/353], P=0.003). **Supplementary Table 4** shows the event rate of each individual component of TLF, showing that cardiac death and TLR events were significantly higher in the "DAPT duration ≥2.5 years" group. The occurrence of bleeding events was not significantly different between the 2 groups (5.0% [5/101] vs. 3.1% [11/353], P=0.366, in the DAPT duration <2.5 years and ≥2.5 years respectively). Cumulative incidence of bleeding events is shown in **Supplementary Figure 1**.

Additionally, we performed a PSM analysis of the angiographic characteristics of the provisional and systematic sequence groups, analyzing a total of 117 pairs in a 1:1 matched fashion. Baseline clinical and angiographic char-

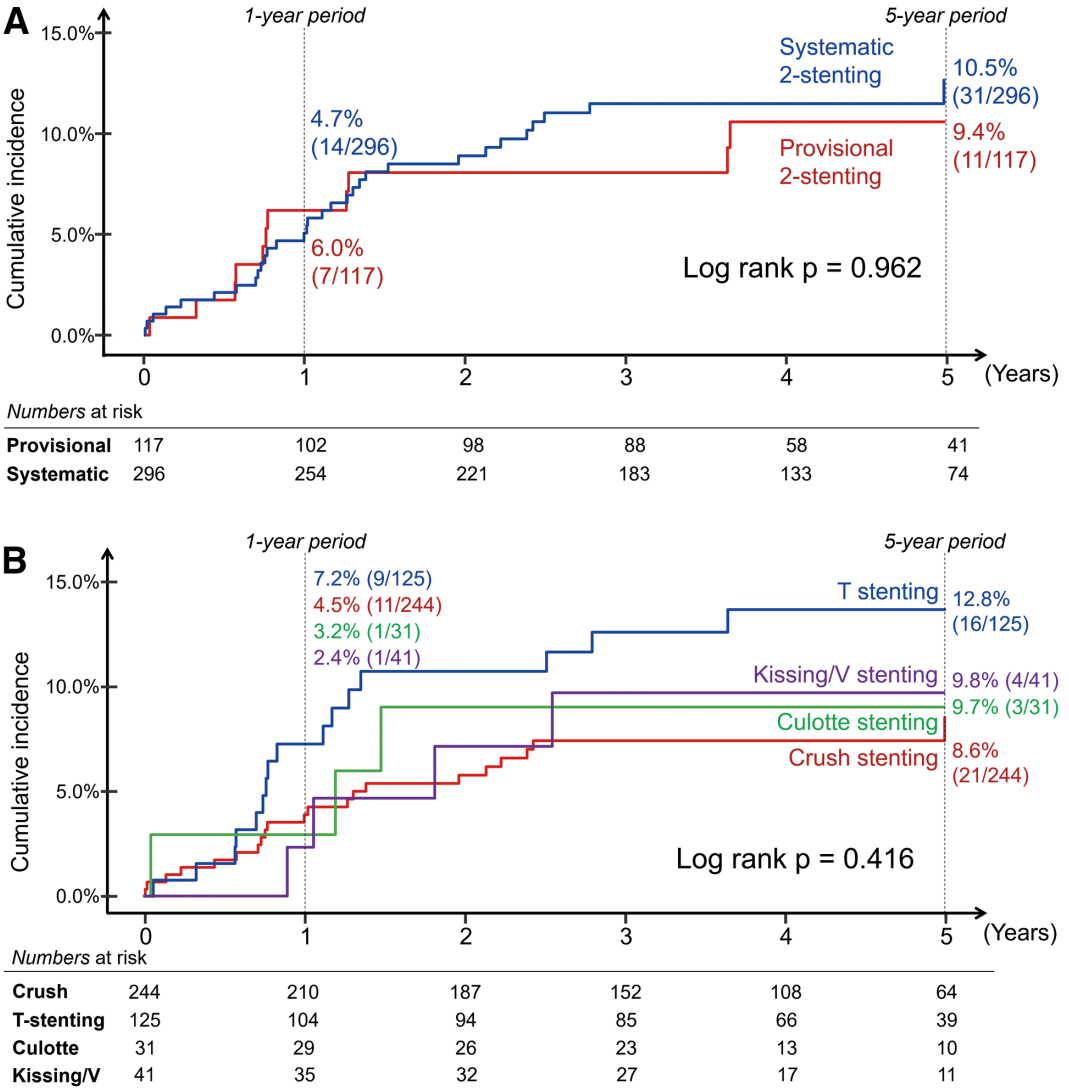


Figure 2. Cumulative incidence of target lesion failure (TLF) for 5 years between 2 different sequences and among 4 different techniques of 2-stenting strategy. Kaplan-Meier curves are shown for TLF in the provisional (MV-first) and systematic (SB-first) sequence groups (**A**), and in the 2-stenting technique (crush, T, culotte, and kissing/V stenting technique) groups (**B**). Clinical events show no difference in the TLF rate between different strategy groups. MV, main vessel; SB, side branch.

acteristics of the PSM population are shown in **Supplementary Tables 5,6**. The cumulative TLF rate of the PSM population was 11.1% (13/117) vs. 12.0% (14/117) for the provisional and systematic sequence groups, respectively, with no significant difference (P>0.999). The independent predictors of TLF in the PSM analysis, as well as in the IPW analysis, did not include the 2-stenting strategy (**Table 3**). Independent predictors in the PSM or IPW analysis were identical to those in the multivariate Cox regression model, which suggests the robustness of the results.

Subgroup Analysis

As a sensitivity analysis, we performed subgroup analysis according to various angiographic characteristics. Specifically, according to the presence of LM disease, the incidence of clinical events is shown in **Figure 4**. In the LM bifurcation disease subgroup, the clinical outcome was similar between 2 different sequences and among 4 different techniques of 2-stenting. In the non-LM bifurcation subgroup, however, the sequence of 2-stenting may have had some influence on outcomes, with all clinical events occurring with the systematic sequence (SB first) of 2-stenting. Among the 4 different techniques of 2-stenting, TLF did not occur in patients receiving the culotte 2-stenting technique. Otherwise, there was no significant interaction for the risk of TLF between the 2-stenting techniques (**Supplementary Table 7**, **Supplementary Figure 2**).

Restenosis Pattern After 2-Stenting According to the Stenting Sequence and Technique

Among the total population, TLR incidence was similar between 2 different sequences and among the 4 different

Table 3. Independent Predictors of TLF in the PSM and IPTW Analyses

	Adjusted hazard ratio	95% CI	P value
Total population			
Stenting sequence (systemic vs. provisional)	1.541	0.628–3.779	0.345
Stenting technique (reference: crush technique)			
T-stenting	1.659	0.854–3.223	0.135
Culotte	1.197	0.342–4.192	0.778
Kissing/V	0.760	0.098–5.870	0.792
LM disease	4.014	1.779–9.055	<0.001
DAPT duration (per 1-month increase)	0.658	0.546–0.794	<0.001
PSM analysis (117 pairs)			
Stenting sequence (systemic vs. provisional)	1.427	0.582–3.498	0.437
Stenting technique (reference: crush technique)			
T-stenting	1.901	0.795–4.548	0.149
Culotte	1.662	0.417–6.628	0.472
Kissing/V	1.397	0.157–12.448	0.765
LM disease	4.494	1.976–10.217	<0.001
DAPT duration (per 1-month increase)	0.986	0.980–0.993	<0.001
IPTW analysis			
Stenting sequence (systemic vs. provisional)	0.798	0.425–1.500	0.484
Stenting technique (reference: crush technique)	NA	NA	NA
LM disease	3.192	1.568–6.500	0.001
DAPT duration (per 1-month increase)	0.988	0.980–0.995	0.002

Other variables, such as clinical presentation as acute coronary syndrome, diabetes mellitus, chronic kidney disease, intravascular ultrasound usage, true bifurcation lesions based on the Medina classification, lesion length of the MV and SB, and MLD of the MV and SB before PCI, were not significant predictors of TLF. DAPT, dual antiplatelet treatment; LM, left main; MLD, minimum lumen diameter; MV, main vessel; PCI, percutaneous coronary intervention; SB, side branch; TLR, target lesion revascularization.

techniques of 2-stenting (**Table 2**). For further analysis, the site-specific location of TLR was evaluated (**Figure 5**). Regardless of the sequence of 2-stenting, the SB was the main TLR site (53.3% vs. 60.7%, P=0.640, in the provisional and systematic stenting sequence groups, respectively). When classified by the 4 different techniques of 2-stenting, however, the location of TLR was mainly the SB in the crush or T stenting groups, while it was evenly distributed to the MV and SB in the culotte or kissing/V stenting groups.

Discussion

In this study, we analyzed the effect of 2 different sequences of 2-stenting (provisional and systematic 2-stenting) and 4 different techniques of 2-stenting (crush, T, culotte, kissing/V stenting) on long-term clinical outcomes of patients who underwent PCI with 2G-DES for bifurcation lesions. The main findings can be summarized as follows. (1) Baseline clinical characteristics were similar between groups. The only difference was the distribution of lesion severity: systematic SB-first stenting was performed in patients with a smaller MLD in the SB, whereas provisional MV first stenting was performed in those having a long lesion in the MV. (2) TLF rates for 4.4 years were comparable between the 2 different sequences of 2-stenting and among the 4 different techniques of 2-stenting in the crude analysis, and in the PSM analysis. (3) Presence of LM bifurcation and a shorter duration of DAPT were associated with TLF, but neither the sequence nor the technique of 2-stenting was a predictors of TLF. (4) In LM bifurcation subgroup, TLF incidence was comparable regardless of sequence or technique of 2-stenting, whereas in the non-LM subgroup, TLF did not occur in the provisional sequence with MV first group or the culotte technique group. (5) The site of TLR was mainly the SB, regardless of the sequence of 2-stenting and crush or T stenting, while it was evenly distributed to the MV and SB in the culotte and kissing/V stenting groups.

Current Guidelines for Bifurcation Lesions

Previous studies and guidelines suggest 1-stenting with a provisional approach is the preferred strategy for the treatment of bifurcation lesions.[1,2] However, along with improvements in new-generation DES and the adoption of various adjunctive treatment strategies, the 2-stenting technique has shown improved outcomes. Based on previous study results,[5,10,11] the current guideline admits the following exceptions for when the 2-stenting technique is preferred: presence of a large SB (≥2.75 mm) with a long ostial SB lesion (>5 mm) or anticipated difficulty in accessing an important SB after main branch stenting, and true distal LM bifurcations.[1] Additionally, previously reported predictors of SB occlusion included not only the SB disease severity and lesion length, but also the MV lesion location, severity and clinical presentation.[12] Therefore, we can infer that various factors should be considered when deciding the stenting strategy. Moreover, our study population comprisedpatients who eventually received a 2-stenting technique. Because the lesion length and MLD of the SB in our cohort were 10.75±7.66 mm and 0.90±0.56 mm, respectively, we can assume that the lesion severity was

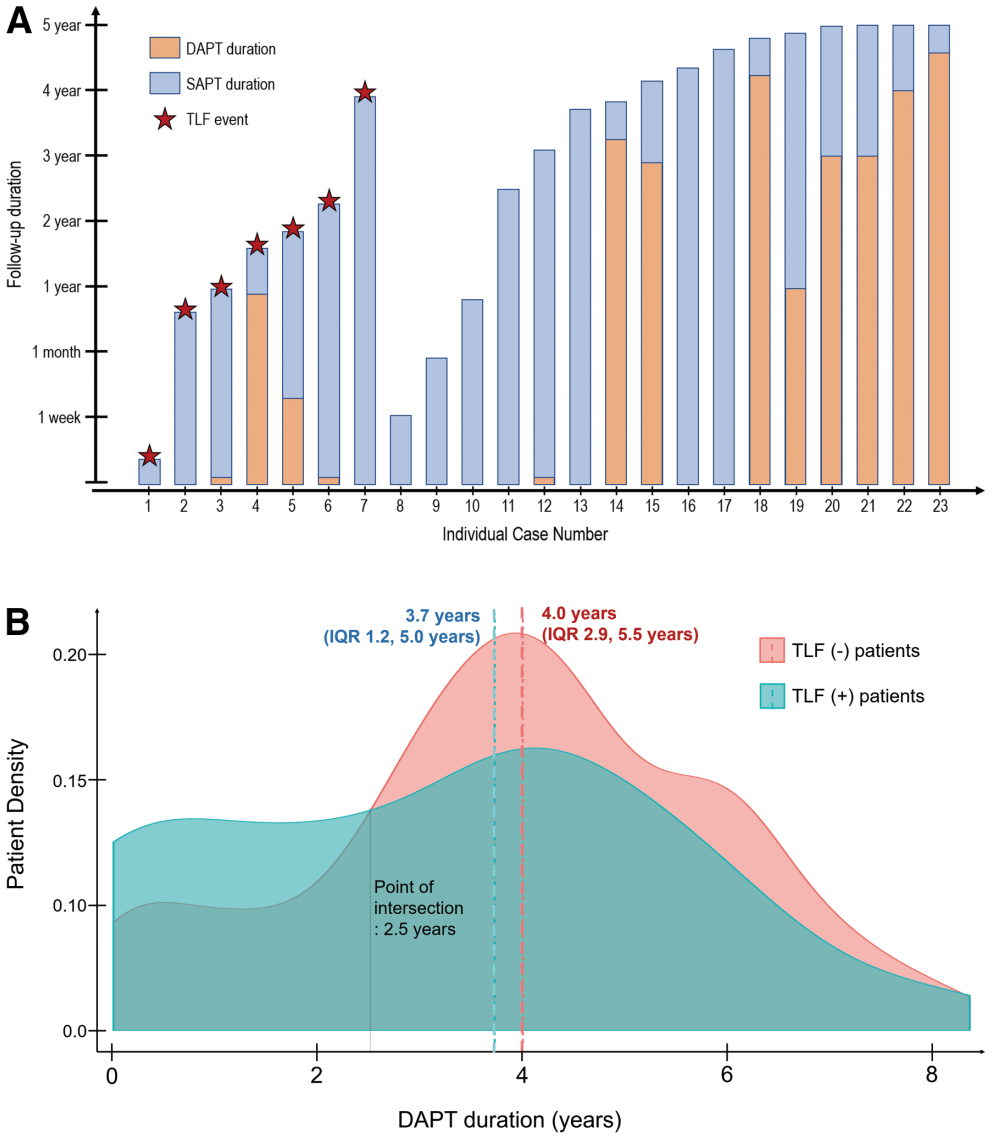


Figure 3. Different distribution in dual antiplatelet therapy (DAPT) duration according to target lesion failure (TLF), and different clinical course according to the duration of DAPT. Among the total population, 23 patients (5.1%) experienced early DAPT interruption during the follow-up period, and 7 TLF events occurred in this population. (**A**) Antiplatelet usage patterns and duration. The total bar height indicates the follow-up duration, with the duration of DAPT and SAPT shown. The TLF event time-point for each of the 7 individual cases is shown as a red star. (**B**) DAPT duration plotted for all patients, according to TLF occurrence. Patients who were free from TLF events were prescribed a longer duration of DAPT, compared with those who experienced TLF events. The time-point of intersection was 2.5 years. SAPT, single antiplatelet therapy.

complex, which may support the adoption of a 2-stenting technique. On the other hand, other clinical trials have shown inconsistent results with regard to the best specific technique.[4,6–8] Also, in reality, it is still an issue whether to consider an upfront 2-stenting strategy, or to treat the bifurcation lesion under a provisional strategy. To give an answer to this question, we compared the long-term clinical outcomes of various strategies of 2-stenting: the 2 different sequences of 2-stenting (provisional and systematic 2-stenting) and the 4 different techniques (crush, T, culotte, kissing/V stenting technique) in the patients dedicated to a bifurcation lesion receiving PCI with 2G-DES.

Comparable Results Among Various 2-Stenting Strategies for Bifurcation Lesions (Stenting Sequence and Technique)

In our study, there was no difference in the clinical characteristics of the patients in 2-stenting strategy groups. The only difference was the distribution of lesion severity: the systematic SB-first stenting sequence was performed in patients with a more severe SB lesion (smaller MLD in the SB) while the provisional MV first stenting was performed in those having a severe MV lesion (longer MV lesion length). This reflects that the choice of the stenting sequence is a clinical decision based on necessity, not a random decision. Rather than proposing a specific technique, the oper-

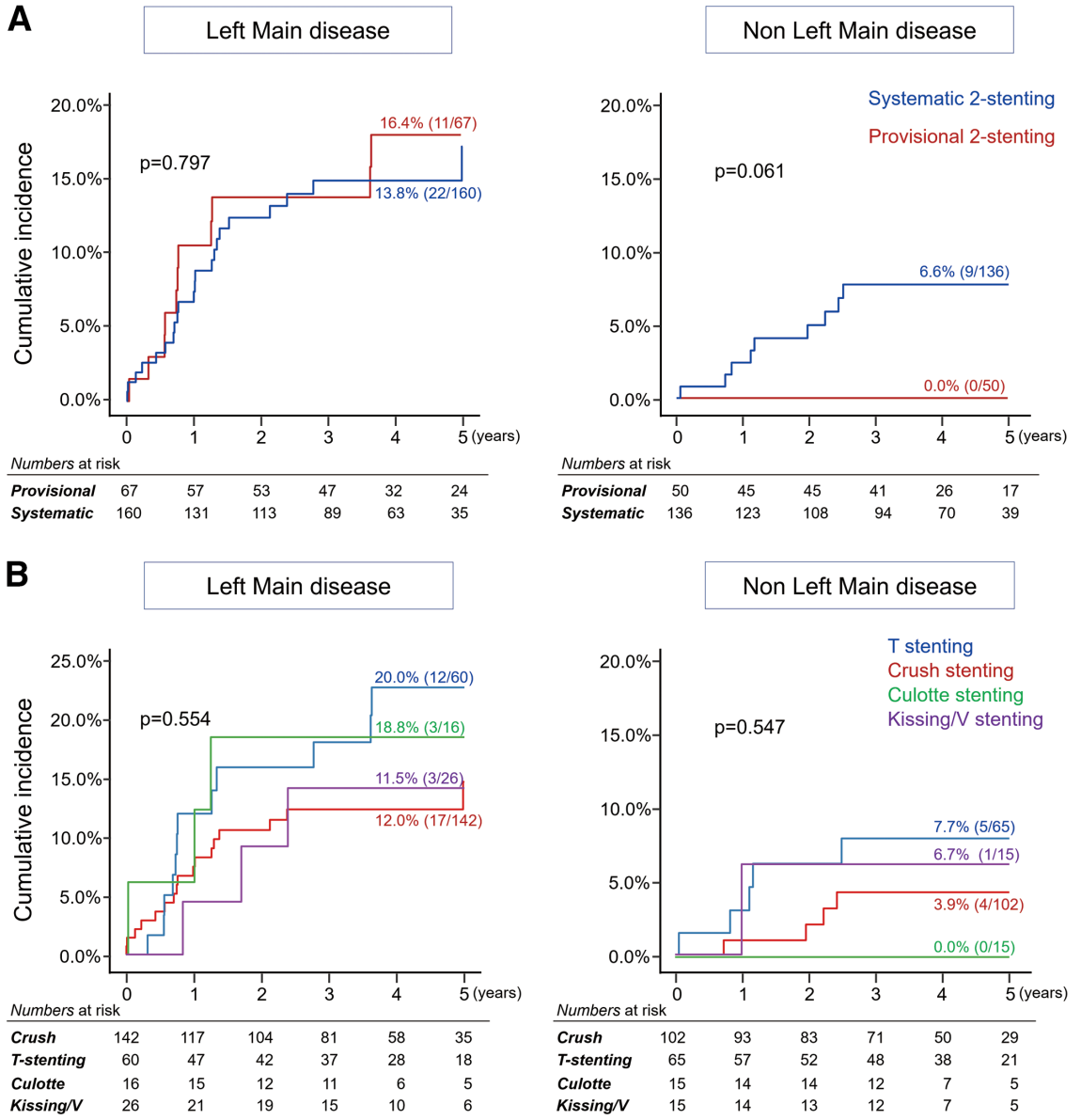
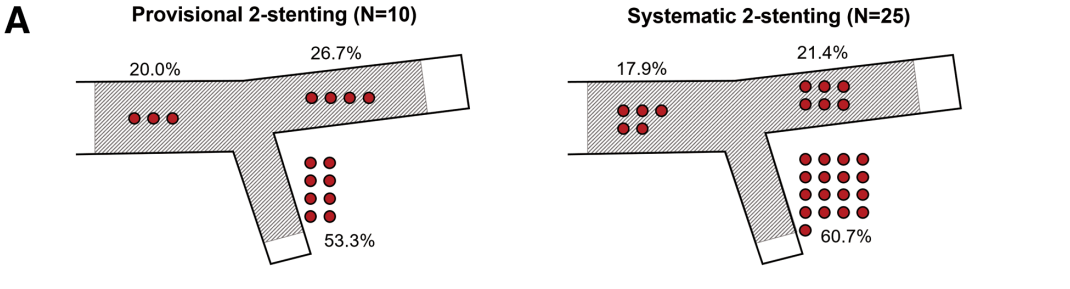


Figure 4. Cumulative incidence of target lesion failure (TLF) for 5 years in left main (LM) vs. non-LM subgroups according to 2-stenting strategy. Kaplan-Meier curves of TLF are shown for LM and non-LM disease subgroups. The clinical outcome incidence was similar for each stenting sequence (**A**) and stenting technique (**B**). Regarding the stenting sequence, clinical events occurred similarly for both stenting sequences in the LM disease subgroup, while all clinical events occurred in the systematic sequence group of the non-LM disease subgroup.

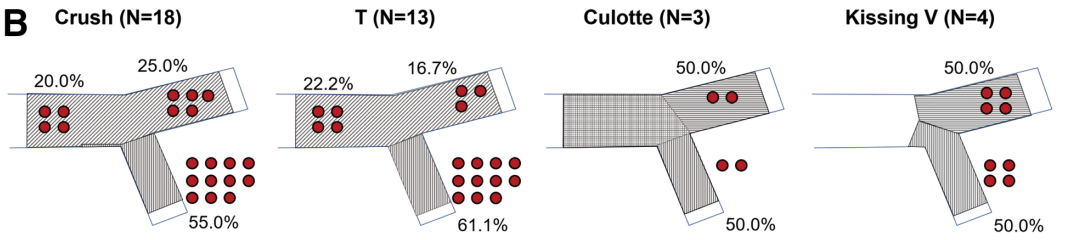
ator should select the most adequate technique with regard to the patient's clinical/lesion characteristics and his/her personal experience.[9] Regarding the comparison of 1- and 2-stenting strategies, and of various 2-stenting techniques (culotte, DK mini-crush, T-stenting), the ongoing EBC MAIN trial (NCT02497014) will be able to provide clearer clinical evidence.[13] Interestingly, usage of intravascular ultrasound (IVUS) was not an independent predictor of clinical outcome. It is well known that accurate morphological assessment of the MV and SB before and after PCI is important for optimizing the bifurcation PCI procedure by guiding stent sizing and landing points, and evaluating stent expansion etc.[14] Although IVUS-guided PCI is recommended for bifurcation PCI in the current guidelines, we were unable to observe an improvement in the IVUS group regarding the 5-year TLF. However, the impact direction (hazard ratio) of IVUS usage was <1, implying a beneficial effect of IVUS usage, but may be due to the non-randomized small sample size of our study.

Association of Shorter DAPT With TLF

The DAPT duration is a modifiable factor after treatment of bifurcation lesions, unlike the other independent predictor which is LM disease. From our study, DAPT duration



	Total Two Stenting (N=35/413, 8.5%)	Provisional Two Stenting (N=10/117, 8.5%)	Systemic Two Stenting (N=25/296, 8.4%)
Proximal vessel only	4 (11.4%)	0	4 (16%)
Main branch only	5 (14.3%)	2 (20%)	3 (12%)
Side branch only	18 (51.4%)	3 (30%)	15 (60%)
Proximal vessel to Main branch	1 (2.9%)	0	1 (4%)
Proximal vessel to Side branch	3 (8.6%)	3 (30%)	0
Main branch to Side branch	8 (22.8%)	2 (20%)	2 (8%)



	Crush (N=18/244, 7.4%)	T (N=13/125, 10.4%)	Culotte (N=3/31, 9.7%)	Kissing/V (N=4/41, 9.8%)
Proximal vessel only	3 (16.7%)	1 (7.7%)	0	0
Main branch only	3 (16.7%)	1 (7.7%)	1 (33.3%)	0
Side branch only	10 (55.6%)	6 (46.2%)	1 (33.3%)	0
Proximal vessel to Main branch	1 (5.6%)	0	0	0
Proximal vessel to Side branch	0	3 (23.1%)	0	0
Main branch to Side branch	1 (5.6%)	2 (15.4%)	1 (33.3%)	4 (100%)

Figure 5. Location of restenosis leading to target lesion revascularization according to 2-stenting strategy. The specific locations of in-stent restenosis leading to target lesion failure (TLF) are presented as dots, according to the stenting sequence (**A**) and stenting technique (**B**). (In diffuse restenosis cases with multiple sites, all sites are marked with dots.) The most common site of TLR was the side branch, regardless of the stenting strategy.

<2.5 years brought a significant increase in TLF risk. The clinical implication of this is notable, because the physician can acknowledge 2-stenting treatment for a bifurcation lesion as a unique indication for longer DAPT in the current trend of shorter DAPT duration. A similar message was also derived from our previous study, which reported that prolonged DAPT (DAPT maintenance ≥1 year) is necessary to improve safety issues in patients who undergo LM bifurcation PCI with a 2-stenting technique.[15] Other studies also stress the importance of longer DAPT to decrease major adverse cardiac events, especially in complex PCI, which includes "bifurcation with 2 stents implanted".[16,17] In 2-stenting lesions, subclinical thrombus attachment on the overlapping stent struts, metallic neocarinas, and malapposed struts at the bifurcation segment can occur and which may lead to delayed endothelialization of the stented segment. Moreover, the necessity of a 2-stenting technique implies high atherosclerotic burden of the coronary tree, which may require stronger antiplatelet therapy. Therefore, longer DAPT may be needed to reduce adverse clinical events in patients with 2-stenting for bifurcation lesions. On the other hand, the concept of "high bleeding risk" (HBR) is currently gaining importance, regarding those patients who are vulnerable to bleeding events when using a longer DAPT. It is very important to decrease underexpansion, malapposition and stent deformation in HBR patients, because this may lead to a shorter DAPT duration. These factors can be detected by using more detailed imaging examinations, such as optical coherence tomography, and therefore, our study stressed the clinical implication of more detailed imaging of HBR patients undergoing complex bifurcation PCI.

Different Approaches in LM vs. Non-LM Bifurcation Lesions

Overall, the TLF rate in LM bifurcation lesions was higher

than that of non-LM bifurcations, which can be explained by unique lesion and clinical features. First, LM bifurcation lesions differ from non-LM bifurcations in several anatomical characteristics such as a large-sized proximal vessel with a rapidly tapering MV caliber, larger territory of the SB, a complex bifurcation angle (3D T-shaped), and frequent involvement of a trifurcation lesion (i.e., the ramus intermedius branch). These various and complex anatomical features make LM bifurcations vulnerable to unfavorable stenting results such as stent malapposition and formation of a thick metal carina. Second, patients with LM bifurcations have more clinical risk factors compared with non-LM bifurcation patients. Our results showed a distinct clinical event pattern according to the bifurcation location. In the LM bifurcation subgroup, TLF was comparable between the provisional and systematic strategies, but in the non-LM bifurcation subgroup, all TLF occurred in the systematic group. This suggests that crush or classic T stenting (SB first) may be worse than culotte or TAP (MV first). This may be explained by the clinical relevance or size of the SB in LM and non-LM bifurcations. The systematic strategy is usually applied to severely diseased and small SB, which would be more difficult in the diagonal branch of the non-LM bifurcation subgroup than the circumflex artery in the LM bifurcation subgroup. Thus, the systematic SB-first strategy might show worse outcomes than the provisional MV first strategy, especially in the non-LM bifurcation subgroup.

Unique Feature of Location of TLR According to 2-Stenting Strategy for Bifurcation Lesions

By describing the site of TLR in each group, the SB was shown to be the most vulnerable site of restenosis, regardless of the sequence of 2-stenting. This may be due to the geographic anatomy of the SB ostium, which has an extreme angulation and often a large plaque burden. This site is prone to stent malapposition/underexpansion and overhanging stent struts, leading to lower shear stress or turbulent flow on the strut surface, known to activate platelets and the coagulation cascade.[18,19] Also, the neocarina formed by metallic struts modulates the local hemodynamics, generating an imbalance in shear stress that can potentially promote stent restenosis and thrombosis.[20] Collectively, the abovementioned factors are intrinsic factors that are not modified by the stenting technique, and therefore, irrespective of the stenting sequence, the SB may be the most vulnerable site of restenosis. From the clinicians' viewpoint, various adjunctive therapies, such as stent optimization maneuvers, using imaging tools, and meticulous medical treatment, including DAPT agents, should be considered for 2-stenting bifurcation patients.

In terms of the 4 different techniques of 2-stenting, the site of TLR differed slightly according to the technique. In the crush or T stenting group, the main site of TLR was absolutely the SB, whereas in the culotte or kissing/V stenting group, it was equally distributed to the MV and SB. This information may be useful for the treatment of LM bifurcation patients with a big left circumflex artery with bad morphology, where the effect of restenosis is huge and chance of restenosis is high.

Study Limitations

Our study has several limitations that should be discussed. First, this was an observational analysis of a retrospective registry, which may have hidden confounding factors or allocation biases that could affect the results. Obviously, the specific 2-stenting strategy and adjunctive treatment for bifurcation lesions, such as DAPT duration, were determined by the treating physician's preference, which created an asymmetric distribution of patients in the groups. Therefore, we should not interpret our results in the manner of a randomized trial. However, we still believe that our results are meaningful because we could compare the stenting strategies that incorporated the physician's intention. Also, we performed meticulous analyses to compensate for this asymmetric distribution. Second, as can be seen in **Figure 1**, the T, culotte and crush techniques were each performed by the MV-first or SB-first stenting strategy, which was based on the physician's preference. This may lead to ambiguity in the comparison between stenting sequences and stenting techniques. However, we believe that our analysis reflects how 2-stenting is performed in real-world practice, and the results should be interpreted on the basis of real-world practice. Third, the dominance of the systematic 2-stent approach over the provisional approach, in a population including non-true bifurcations (37%) and non-LM lesions (45%), is not consistent with the current recommendation from worldwide consensus. Our study results should be interpreted based on the study population's characteristics. Fourth, patients who received bailout stenting in the provisional 1-stenting strategy were classified as the corresponding 2-stenting group. With regard to that bailout stenting often being performed as the MV-first stenting sequence, this could have contributed to the results of our analysis. Fifth, during the enrollment period of our registry, the "proximal optimization technique" and the DK-crush technique were not in widespread use. Although these treatment options are often recommended for current bifurcation treatment, we acknowledge that the penetration rate of these techniques in real-world registries is still low. Finally, the sample size was not large in the subgroup analysis of LM and non-LM bifurcation lesions, so this result should be interpreted with caution.

Conclusions

From the COBIS III registry, which included patients with bifurcation lesions receiving a 2-stenting strategy, TLF and ST rates were excellent for around 5 years with the contemporary DES. In this study, the outcome was not affected by technical factors of 2-stenting treatment for bifurcation lesions, such as different sequences or techniques of 2-stenting, but was worsened by the presence of LM disease and a shorter duration of DAPT.

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Disclosures

H.-S.K. is a member of *Circulation Journal*'s Editorial Team. Other authors declare no disclosures or conflicts of interest with any industry.

IRB Information

The present study was approved by the Institutional Review Board of Seoul National University Hospital (reference no. 1702-099-832).

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Supplementary Files

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