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Comparing Two-Stent Strategies for Bifurcation Coronary Lesions: Which Vessel Should be Stented First, the Main Vessel or the Side Branch?

Dong-Ho Shin[1,*], Kyung Woo Park[1,*], Bon-Kwon Koo[1], Il-Young Oh[1], Jae-Bin Seo[2], Hyeon-Cheol Gwon[3], Myung-Ho Jeong[4], In-Whan Seong[5], Seung Woon Rha[6], Ju-Young Yang[7], Seung-Jung Park[8], Jung Han Yoon[9], Kyoo-Rok Han[10], Jong-Sun Park[11], Seung-Ho Hur[12], Seung-Jea Tahk[13] and Hyo-Soo Kim[1]

[1]Department of Internal Medicine, Cardiovascular Center, Seoul National University Hospital, Seoul; [2]Department of Internal Medicine, Boramae Medical Center, Seoul; [3]Department of Internal Medicine, Samsung Medical Center, Seoul; [4]Department of Internal Medicine, Chonnam National University Hospital, Gwangju; [5]Department of Internal Medicine, Chungnam National University Hospital, Daejeon; [6]Department of Internal Medicine, Korea University Medical Center, Seoul; [7]Department of Internal Medicine, National Health Insurance Corporation Ilsan Hospital, Goyang; [8]Department of Internal Medicine, University of Ulsan Asan Medical Center, Seoul; [9]Department of Internal Medicine, Wonju Christian Hospital, Wonju; [10]Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul; [11]Department of Internal Medicine, Yeungnam University Medical Center, Daegu; [12]Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu; [13]Department of Internal Medicine, Ajou Univeristy Hospital, Suwon, Korea

*Dong-Ho Shin and Kyung Woo Park contributed equally to this work.

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Address for Correspondence:
Hyo-Soo Kim, MD
Cardiovascular Center, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82.2-2072-2226, Fax: +82.2-766-8904
E-mail: hyosoo@snu.ac.kr

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This study compared two-stent strategies for treatment of bifurcation lesions by stenting order, 'main across side first (A-family)' vs 'side branch first (S-family). The study population was patients from 16 centers in Korea who underwent drug eluting stent implantation with two-stent strategy (A-family: 109, S-family: 140 patients). The endpoints were cardiac death, myocardial infarction (MI), stent thrombosis (ST), and target lesion revascularization (TLR) during 3 years. During 440.8 person-years (median 20.2 months), there was 1 cardiac death, 4 MIs (including 2 STs), and 12 TLRs. Cumulative incidence of cardiac death, MI and ST was lower in A-family (0% in A-family vs 4.9% in S-family, $P = 0.045$). However, TLR rates were not different between the two groups (7.1% vs 6.2%, $P = 0.682$). Final kissing inflation (FKI) was a predictor of the hard-endpoint (hazard ratio 0.061; 95% CI 0.007-0.547, $P = 0.013$), but was not a predictor of TLR. The incidence of hard-endpoint of S-family with FKI was comparable to A-family, whereas S-family without FKI showed the poorest prognosis (1.1% vs 15.9%, retrospectively; $P = 0.011$). In conclusion, 'A-family' seems preferable to 'S-family' if both approaches are feasible. When two-stent strategy is used, every effort should be made to perform FKI, especially in 'S-family'.

Key Words: Bifurcation; Coronary Artery Disease; Drug-Eluting Stents; Percutaneous Coronary Intervention

INTRODUCTION

Despite the evolution of percutaneous coronary intervention (PCI) since its introduction in 1977, and the recent wide spread use of drug eluting stents (DES), coronary bifurcation lesions still remain one of the most difficult and challenging lesion subsets to treat, with a high rate of adverse events (1-3). Currently, the standard approach for bifurcation lesions is provisional stenting, since no significant benefit from the routine complex or two-stent strategy has been demonstrated (4-8). However, many in-

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terventional cardiologists acknowledge that there exist certain situations in which the two-stent strategy is needed (9). Therefore, a substantial proportion of bifurcation lesions are treated using the two-stent strategy in real world practice (1, 9, 10), and considerable crossovers from one-stent to two-stent strategies occur even in randomized controlled trials (5, 8).

However, there is a paucity of data comparing the different methods of the two-stent strategy, and the choice of treatment strategy is currently left to the operator's discretion. The complexity and the numerous subtypes within the two-stent strategy technique seem to make it difficult to compare different techniques. In this respect, The 'MADS classification', a new classification of techniques for bifurcation lesion treatment proposed by Louvard et al., appears to provide simple contrasts and useful information regarding procedural sequences (11, 12). It classifies different techniques according to which segment is initially stented; main proximal first (M), main across side first (A), distal first (D), and side branch first (S).

In the present study, we sought to compare two-stent strategies from the data of the Korean multicenter coronary bifurcation stenting registry using the MADS classification, 'main across side first (A family)' vs 'side branch first (S family)'.

MATERIALS AND METHODS

The Coronary Bifurcation Stenting registry

The Coronary BIfurcation Stenting registry (COBIS) is a multicenter registry of bifurcation lesions treated in 17 major cardiovascular centers in Korea, sponsored by the Korean Society of Interventional Cardiology (13). Utilizing an electronic case report form and a centralized database, consecutive patients treated with DES for coronary bifurcation lesions between January 2004 and June 2006 entered in the registry. All data was managed by independent data managers from a core center and completeness and validity of data was confirmed by multiple queries and monitoring.

Study population

The inclusion criteria of the COBIS registry were : 1) DES implantation in the coronary bifurcation lesion between January 2004 and June 2006, 2) main vessel (MV) diameter ≥ 2.5 mm and side branch (SB) diameter ≥ 2.0 mm. Exclusion criteria were cardiogenic shock, ST-segment elevation acute myocardial infarction (MI) within 48 hr, life expectancy < 1 yr, or left main bifurcation. Dedicated bifurcation stents are not approved in Korea and were not included in this registry. Among the patients in the COBIS registry, those treated with the two-stent strategy, defined by the presence of stents at both the MV and the SB ostium, were eligible for the present study. The final analytic cohort consisted of the patients treated with 'A family' and 'S family'.

Stent implantation procedure

All patients were pretreated with dual antiplatelet therapy consisting of aspirin and clopidogrel. A loading dose of clopidogrel was administered before the index procedure if patients were not pretreated. Heparin was administered according to local hospital protocols, and activated clotting time control was not mandatory. Glycoprotein IIb/IIIa receptor inhibitors were used at the discretion of the operator. Aspirin was continued indefinitely, and clopidogrel was continued for at least 6 months according to local practice. The access, devices including type of DES, and stenting techniques were all left to the operator's discretion. Intravascular ultrasound (IVUS) was not used routinely. Bifurcation lesions were classified as stated by the Medina classification, which consists of giving three consecutive binary values (1 or 0) according to whether each of the proximal MV, distal MV, and SB segments respectively is compromised (14). Type (1, 1, 1), (1, 0, 1), and (0, 1, 1) lesions were regarded as true bifurcation lesions. Angiographic success was defined as achievement of TIMI 3 flow with a final residual stenosis < 30% for MV and < 50% for SB.

All baseline and procedural cine coronary angiograms were stored digitally on compact discs or hard disks in Digital Imaging and Communication in Medicine format. Lesion and procedural characteristics of all cineangiograms were reviewed and qualitatively analyzed at the angiographic core laboratory in the Cardiac and Vascular Center, Samsung Medical Center, Seoul, Korea (13).

Follow-up and clinical outcomes

Clinical follow-up was performed at each participating center by medical record review or telephone interview. Follow-up events included death, cardiac death, MI, cerebrovascular event, stent thrombosis (ST), repeated PCI, and coronary artery bypass grafting at 3-yr follow-up.

We analyzed the composite events of cardiac death, MI, and ST as the composite hard endpoint, and target lesion revascularization (TLR) as the repeated procedure endpoint. All deaths were considered cardiac unless a definite non-cardiac cause could be established. MI was defined as documented non-fatal MI adjudicated by either new abnormal Q-wave or predefined enzymatic changes (15). Definite and probable ST according to the Academic Research Consortium definition was regarded as ST (16). TLR was defined as repeat PCI of the lesion within 5 mm of stent deployment or bypass graft surgery of the target vessel. All events were adjudicated by independent investigators that were unaware of the purpose of the study.

Statistical analysis

Continuous variables were described as mean and standard deviation, and the Student t-test was used to analyze the difference between the two groups. Categorical variables were reported as

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Table 1. Baseline characteristics of the participants

Baseline characteristics	Total (n = 249)	A family (n = 109)	S family (n = 140)	*P* value
Female	93 (37.3%)	40 (36.7%)	53 (37.9%)	0.808
Age (yr)	62.90 ± 10.4	62.9 ±10.7	61.5 ±9.4	0.281
Current smoking	60 (24.1%)	26 (23.9%)	34 (24.3%)	0.905
Acute coronary syndrome at the index procedure	145 (58.2%)	53 (48.6%)	92 (65.7%)	0.005*
Previous MI	22 (8.8%)	8 (7.3%)	14 (10.0%)	0.450
History of stroke	9 (3.6%)	4 (3.7%)	5 (3.6%)	0.978
Hypertension	144 (57.8%)	67 (61.5%)	77 (55.0%)	0.348
Diabetes	66 (26.5%)	28 (25.7%)	38 (27.1%)	0.764
Dyslipidemia†	76 (30.5%)	30 (27.5%)	46 (32.9%)	0.341
Chronic renal insufficiency	6 (2.4%)	2 (1.8%)	4 (2.9%)	0.697
Creatinine (mg/dL)	1.08 ± 0.74	0.94 ± 0.23	1.05 ± 0.88	0.165
Cholesterol (mg/dL)	182.04 ± 11.38	168.8 ± 42.7	173.7 ± 39.5	0.350
Low-density lipoprotein (mg/dL)	107.01 ± 36.78	109.3 ± 41.2	105.1 ± 32.9	0.398
High-density lipoprotein (mg/dL)	43.85 ± 12.73	45.9 ± 13.6	42.2 ± 11.8	0.028*
Ejection fraction (%)	59.86 ± 11.38	60.2 ± 10.1	59.6 ± 12.2	0.758
Periprocedural aspirin‡	229 (92.0%)	98 (89.9%)	131 (93.6%)	0.205
Periprocedural clopidogrel‡	226 (90.4%)	97 (89.0%)	129 (92.1%)	0.291
Periprocedural cliostazol‡	39 (15.6%)	5 (4.6%)	34 (24.3%)	< 0.001*
Periprocedural abciximab‡	8 (3.2%)	7 (6.4%)	1 (0.7%)	0.023*
Angiographic findings				
No. of lesions	250	110	140	
Location of diseased vessels				
Left anterior descending coronary artery	216 (86.4%)	89 (80.9%)	127 (90.7%)	0.021*
Left circumflex coronary artery	23 (9.2%)	12 (10.9%)	11 (7.9%)	
Right coronary artery	11 (4.4%)	9 (8.2%)	2 (1.4%)	
Medina classification				0.035*
001	13 (5.2%)	8 (7.3%)	5 (3.6%)	
010	18 (7.2%)	12 (10.9%)	6 (4.3%)	
011	46 (18.4%)	18 (16.4%)	28 (20.0%)	
100	6 (2.4%)	4 (3.6%)	2 (1.4%)	
101	13 (5.2%)	6 (5.5%)	7 (5.0%)	
110	9 (3.6%)	7 (6.4%)	2 (1.4%)	
111	145 (58.0%)	55 (50.0%)	90 (64.3%)	
True bifurcation (011, 101, 111)	204 (81.6%)	79 (71.8%)	125 (89.3%)	< 0.001*
Total occlusion of MV	15 (6.0%)	8 (7.3%)	7 (5.0%)	0.453
Thrombus in MV	8 (3.2%)	4 (3.6%)	4 (2.9%)	0.734
Total occlusion of SB	12 (4.8%)	7 (6.4%)	5 (3.6%)	0.305
Thrombus in SB	4 (1.6%)	3 (2.7%)	1 (0.7%)	0.323
Procedural information				
Reference diameter of MV (mm)	2.97 ± 0.46	2.86 ± 0.51	3.09 ± 0.35	0.001*
Minimal luminal diameter of MV (mm)	0.73 ± 0.43	0.71 ± 0.44	0.74 ± 0.42	0.646
Lesion length of MV (mm)	19.50 ± 8.71	15.83 ± 8.01	23.54 ± 7.63	< 0.001*
Reference diameter of SB (mm)	2.41 ± 0.40	2.23 ± 0.40	2.61 ± 0.28	< 0.001*
Minimal luminal diameter of SB (mm)	0.82 ± 0.47	0.87 ± 0.50	0.76 ± 0.43	0.147
Lesion length of SB (mm)	11.61 ± 8.87	8.22 ± 9.23	15.47 ± 6.63	< 0.001*
Intravascular ultrasound guidance	116 (46.4%)	78 (70.9%)	38 (27.1%)	< 0.001*
Stent type				
Sirolimus-eluting stent	364 (68.4%)	166 (70.0%)	198 (67.1%)	0.530
Paclitaxel-eluting stent	165 (31.0%)	69 (29.1%)	96 (32.5%)	
Bare-metal stent§	3 (0.6%)	2 (0.8%)	1 (0.3%)	
No. of stents in MV	1.25 ± 0.48	1.24 ± 0.45	1.26 ± 0.50	0.648
No. of stents in SB	1.03 ± 0.18	1.03 ± 0.16	1.04 ± 0.19	0.708
Mean diameter of MV stents (mm)	3.17 ± 0.34	3.22 ± 0.34	3.13 ± 0.33	0.036*
Mean diameter of SB stents (mm)	2.74 ± 0.29	2.74 ± 0.30	2.74 ± 0.28	0.943
Cumulative length of MV stents (mm)	30.66 ± 11.73	31.21 ± 11.75	30.22 ± 11.73	0.513
Cumulative length of SB stents (mm)	21.64 ± 8.73	21.11 ± 9.64	22.05 ± 7.97	0.414
Final kissing inflation	193 (77.2%)	99 (90.0%)	94 (67.1%)	< 0.001*

Values were presented as the number of patients (%) or mean ± standard deviation.*P value < 0.05; †dyslipidemia was defined by total cholesterol > 200 mg/dL, LDL > 130 mg/dL, HDL < 30 mg/dL, triglycerides > 150 mg/dL, or use of lipid-lowering agents for the history of dyslipidemia; ‡including chronic use and loading before the index PCI; §implanted along with drug-eluting stents for the bifurcation lesions. MI, Myocardial infarction; MV, Main vessel; SB, Side branch; PCI, Percutaneous coronary intervention.

proportions and were compared with the chi-square test or Fisher's exact test. We estimated the crude cumulative incidences of the events of interest with the Kaplan-Meier method. The log-rank test was used to assess the significance of the differences between the incidences.

To adjust the differences of baseline characteristics between the strategies, the propensity score as a probability of the use of 'S family' for each patient was calculated using a non-parsimonious multivariate logistic regression model in which baseline characteristics such as demographics, past medical history, laboratory values, angiographic findings and procedural information were incorporated (variables above 'Stent type' in Table 1; c-statistics 0.849). Because the propensity score model is used to minimize selection bias at the time when a specific treatment is chosen, the factors specified after determinations of stenting order were excluded from the calculation (i.e. variables below 'Stent type' in Table 1), Thereafter, we calculated adjusted survival using two weight methods of inverse-probability weight (IPW) and standardized mortality/morbidity ratio (SMR) weight transformed from the propensity scores. Adjusted survival using IPW was utilized to overcome limitations inherent to a Cox model (17-19), while SMR-weighted analysis has been shown to provide similar results to propensity-score matching (20). Conventional and weighted Cox regression model were used to compare TLR.

Statistical analyses were performed with R version 2.8.1 (R Development Core Team, Vienna, Austria, http://www.R-project.org). All *P* values are two-sided and results with a *P* value less than 0.05 were considered statistically significant.

Ethics statement

The study fully complied with the Declaration of Helsinki and was approved by the institutional review board of each participating center including Seoul National University Hospital, and the requirement for informed consent was waived (Clinicaltrials.gov number: NCT00851526).

RESULTS

Study population and procedural outcomes

Among 1,691 bifurcation lesions in 1,668 patients from the registry, 293 lesions in 292 patients were treated with two-stent strategies. The final analytic cohort was composed of 250 lesions from 249 patients, 110 lesions (109 patients) in the A family and 140 lesions in the S family (Fig. 1). The detailed technique compositions of families are also listed in Fig. 1.

Table 1 summarizes baseline clinical, angiographic, and procedural characteristics of the patients and lesions. There were no significant differences between the 2 groups in classical risk factors of coronary heart disease such as sex, age, smoking, hypertension and dyslipidemia. However, patients that were treated using the S family, were more likely to have acute coronary syndrome, lower high-density lipoprotein levels, left anterior descending coronary artery lesions, and true bifurcation lesions than the A family. They were also less likely to receive IVUS guidance and periprocedural abciximab, and more likely to receive periprocedural cilostazol. Regarding procedural parameters, the S family was associated with a larger reference diameter and longer lesion length in both the parent vessel and SB, smaller mean stent diameter in the MV, lower proportion of final kissing inflation (FKI).

Immediately after PCI, the S family was associated with a larger reference diameter and minimal luminal diameter of the side branch, higher SB procedural success rate, and fewer acute clo-

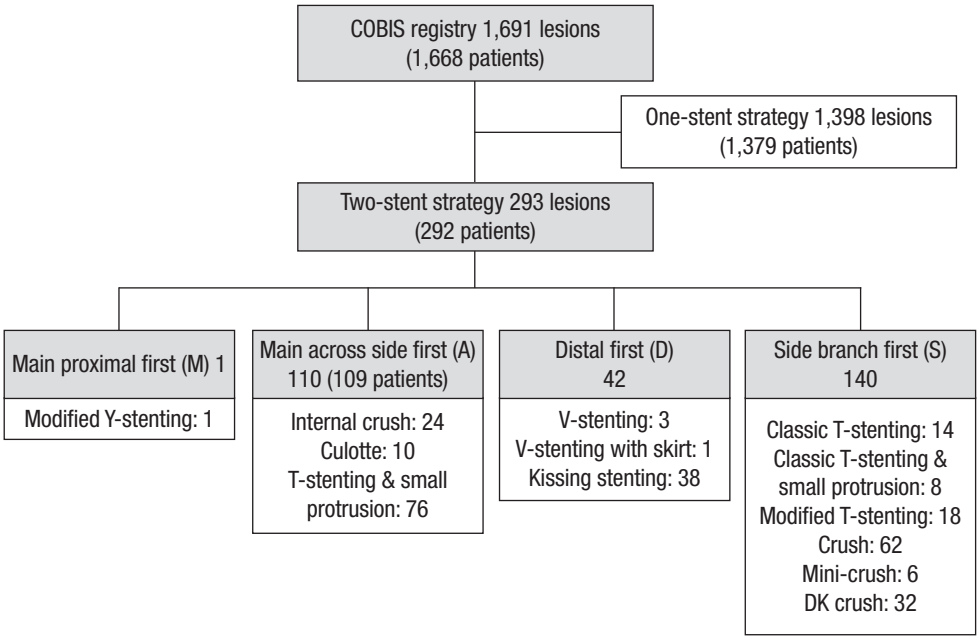

Fig. 1. COBIS registry and stenting strategies for bifurcation lesions.

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sure of the SB (Table 2).

Follow-up and clinical outcomes after the A and S families

During 440.8 person-years of follow-up (median 20.2 months), there was 1 cardiac death, 4 MIs (including 2 STs which presented as MI), and 12 TLRs. All cases of cardiac death, MI, and ST occurred exclusively in the S family group, despite longer use of anti-platelet agents (Table 2). Cumulative incidence of the composite hard endpoint in the S family was 4.9% and differed from that in the A family (Fig. 2A). Hazard ratio (HR) was not reported as there were no events for patients with A family. Conversely, there was no significant difference in TLR between the 2 strategies (7.1% in A family vs 6.2% in S family, multivariate HR of the S family 1.01; 95% CI 0.09-11.7, $P = 0.99$, Fig. 2B).

To adjust the differences in baseline characteristics and possible allocation bias, we calculated the propensity score as a probability of the use of 'S family' for each patient and adopted propensity-based weight analysis with IPW and SMR weight, which resulted in better balances between the groups as distributions of the propensity scores became similar (Supplementary Fig. 1). Even after adjustment, the cumulative incidence of cardiac death, MI, and ST in the A family was still lower than that observed in the S family (Fig. 3). Regarding TLR, HRs of the S family were 1.07 (95% CI 0.25-4.54, $P = 0.93$) and 1.32 (95% CI 0.54-3.25, $P = 0.55$)

Table 2. Post-procedural results and follow-up

Post-procedural results	Total (n = 249)	A family (n = 109)	S family (n = 140)	*P* value
Reference diameter of MV (mm)†	3.19 ± 0.41	3.17 ± 0.47	3.21 ± 0.35	0.506
Minimal luminal diameter of MV (mm)†	2.86 ± 0.47	2.76 ± 0.54	2.97 ± 0.35	0.003*
Lesion length of MV (mm)†	18.18 ± 10.08	16.64 ± 9.50	19.15 ± 10.42	0.332
Reference diameter of SB (mm)†	2.57 ± 0.31	2.46 ± 0.31	2.68 ± 0.26	< 0.001*
Minimal luminal diameter of SB (mm)†	2.28 ± 0.41	2.19 ± 0.40	2.38 ± 0.40	0.004*
Lesion length of SB (mm)†	12.41 ± 9.83	11.80 ± 12.66	12.79 ± 7.76	0.739
Procedural success of MV	248 (99.2%)	108 (98.2%)	140 (100.0%)	0.109
Procedural success of SB	242 (96.8%)	102 (92.7%)	140 (100.0%)	0.001*
Acute closure of MV	1 (0.4%)	1 (0.9%)	0 (0.0%)	0.258
Acute closure of SB	11 (4.4%)	10 (9.1%)	1 (0.7%)	0.001*
Follow-up				
Follow-up duration ≥ 1 yr	236 (94.8%)	106 (97.2%)	130 (92.9%)	0.119
Follow-up duration ≥ 2 yr	92 (36.9%)	38 (34.8%)	54 (38.6%)	0.512
Follow-up duration (days)†	660.2 ± 254.5	658.3 ± 242.2	661.6 ± 264.7	0.921
Duration of aspirin use (months)†	19.66 ± 9.47	18.30 ± 9.08	20.73 ± 9.67	0.044*
Duration of clopidogrel use (months)†	14.32 ± 8.31	12.69 ± 7.05	15.62 ± 9.00	0.004*
Duration of cilostazol use (months)†	1.91 ± 5.45	0.99 ± 3.76	2.64 ± 6.40	0.012*
Clinical outcomes				
Cardiac death‡	1 (0.8%)	0	1 (1.4%)	
Myocardial infarction‡	4 (2.4%)	0	4 (4.2%)	
Stent thrombosis‡	2 (1.0%)	0	2 (1.8%)	
Target lesion revascularization‡	12 (6.6%)	6 (7.1%)	6 (6.2%)	

*P value < 0.05; †mean ± standard deviation; ‡cumulative incidence (calculated with the Kaplan-Meier method). MV, Main vessel; SB, Side branch.

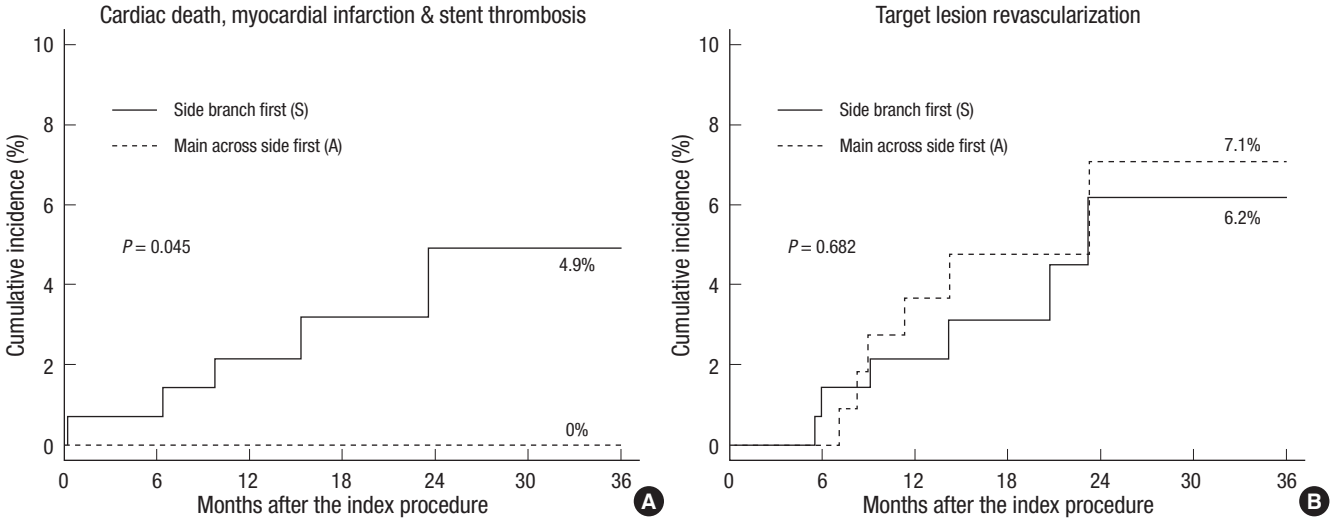

Fig. 2. Clinical outcomes of the A and S family. (**A**) Cardiac death, myocardial infarction and stent thrombosis; (**B**) Target lesion revascularization.

in the propensity-adjusted analysis and IPW-weighted analysis, respectively (Supplementary Fig. 2 for adjusted incidence).

Final kissing inflation and clinical outcomes

Among the variables specified after the decision of stenting order, the use of FKI was a significant prognostic factor for the composite hard endpoint (univariate HR 0.061; 95% CI 0.007-0.547, $P = 0.013$, Fig. 4A). FKI was performed in 99 lesions (90.0%) in the A family and 94 (67.1%) in the S family. In the A family, there was no difference in the hard endpoint between those who received FKI and those who did not, since FKI was performed in most patients and there were no hard events after using the A family. However, in the S family, patients who received FKI showed a significantly lower rate of hard endpoints than those who did not (Fig. 4B), suggesting that at least in the S family, FKI is important to improve clinical results. This difference remained significant even after the adjustment with propensity-based weight analysis (Supplementary Fig. 3). In particular, the clinical outcome of the S family with FKI was comparable with the A family (Fig. 4B, Supplementary Fig. 3). These results were the same when the data was reanalyzed using only patients with true bifurcating lesions (Supplementary Fig. 4).

In contrast to the hard endpoints, FKI was not an independent predictor of target lesion revascularization (HR 2.68, 95% CI 0.33-21.7, $P = 0.36$ from propensity-adjusted model; HR 0.70, 95% CI 0.24-2.04, $P = 0.52$ from the IPW-weighted model).

DISCUSSION

Comparing the long term clinical outcome of two-stent strate-

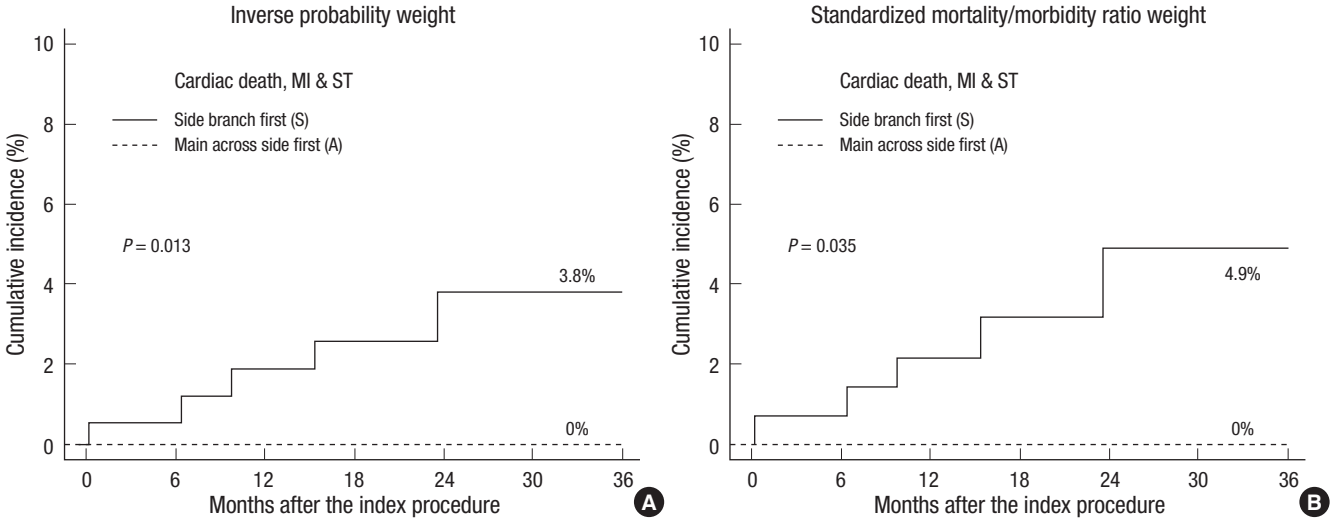

Fig. 3. Adjusted incidences of cardiac death, myocardial infarction and stent thrombosis using inverse probability weight (**A**) and standardized mortality/morbidity ratio weight (**B**). MI, myocardial infarction; ST, stent thrombosis.

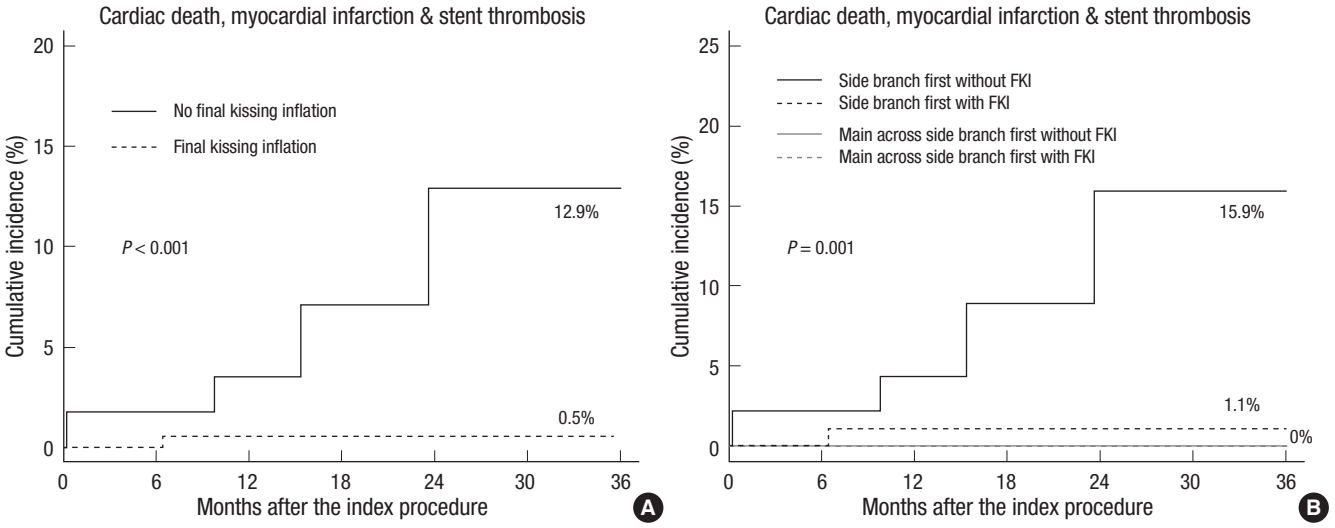

Fig. 4. Cardiac death, myocardial infarction and stent thrombosis by whether final kissing inflation or not (**A**), and by the combination of "A or S family" and FKI (**B**). FKI, Final kissing inflation.

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gies for treatment of significant bifurcation coronary disease according to the order of stent implantation (A: main across side first vs S: side branch first), we found that the cumulative incidence of the composite of cardiac death, MI and ST was higher in the S family than those in the A family, while no significant differences were found regarding the risk of repeat revascularization. In addition, FKI was important in improving the hard endpoints especially in the S family. The patients that received FKI in the S family showed clinical results similar to those in the A family.

To the best of our knowledge, this is the first study using the MADS classification proposed by Louvard et al. to compare clinical outcomes of bifurcation strategies (11). Classical classifications of the bifurcation strategies mainly involve stenting shapes (such as T, crush, culottes) or intention-to-treat (provisional vs complex strategy). The former, usually called 'technique', helps us to understand geometric structure and its possible influence. Conversely, it also provokes some confusion since there are too many techniques to remember although only a few of them seem to be performed popularly. A classification consisting of many subclasses makes it difficult to perform comparisons with each other, and in that case, it helps to combine similar elements into a few categories.

Concerning intention-to-treat, it aids in planning of bifurcation lesion treatment as it corresponds to the stenting order. 'Provisional' itself, however, implies that there are certain conditions in which one or more stents are needed for a side branch even after the decision to perform the simple strategy. Therefore, it does not exactly agree with the classification of 'one-stent' vs 'two-stent'. If we assume the condition in which an interventional cardiologist thinks SB stenting is needed, regardless of being provisional or planned, 'provisional strategy' corresponds to the A family and 'complex strategy' to the S family.

In the present study, we defined the 'two-stent strategy' by the presence of stent at the side branch ostium, not by intention-to-treat, presuming that SB stenting was required. To categorize various techniques, we applied the MADS classification, which could enhance the comparability of the two-stent strategy and may provide useful information to plan how to treat a bifurcation lesion regarding the stenting order.

From our results, the A family, i.e. main across side first, seems preferable to the S family in a condition which needs SB stenting. Interestingly, this corresponds well to the current recommendation of provisional stenting in which a main vessel stenting is performed first (3).

There have been 3 studies comparing the two-stent strategies. However, it would be difficult to compare the results of those studies with that of the present study, since the previous comparisons were not regarding stenting order. In the Nordic study, investigators compared the 'culotte (regardless of the stenting order)' vs the 'crush' technique (21), and the remaining two studies compared the 'classical crush' technique with the 'double-kissing crush' techniques, which can be considered as a scheme comparing the 'S vs S family' (22, 23). None of these studies showed significant differences in hard endpoints according to the type of technique. However, there was more in-stent restenosis of the SB (21) and increased TLR (22, 23) in the 'crush' group during relatively short follow-up periods of 8 months.

Most trials of treatment strategy for bifurcation lesions compared the one-stent (or provisional) strategy with the two-stent (or complex) strategy, and they reported no differences in clinical outcomes (4-8). This might have resulted from the limited power of these studies due to the small number of participants as well as the short duration of follow-up. Most studies reported data up to 6-8 months and only one study showed data up to 2 yr (7). In fact, at a short-term follow-up of 6 months in the present study, the incidence difference of the hard endpoints was only 0.7% without a statistical significance. However, the curves continued to diverge beyond 6 months and the difference in hard end points assessed with the log-rank test was significant at two-year follow-up. Among observational studies, there was only one report that showed higher rates of MI and ST after 2-DES implantation without a difference in TLR (10).

FKI is considered to be important in improving clinical outcome after bifurcation lesion treatment . Therefore, we analyzed each stenting strategy according to whether or not FKI was performed. In the S family, FKI considerably reduced the incidence of cardiac death, MI and ST. As for the A family, there was no difference between the patients that received FKI when compared to those that did not. However, since most patients in the A family (90%) were treated with FKI, it is difficult to make any conclusions as to the role of FKI in the A family. We could not evaluate the interaction between the strategies and FKI either because there was no hard endpoint events in the A family regardless of FKI.

FKI is reported to reduce restenosis and TLR after intervention of bifurcation lesions, and thus is strongly recommended especially after the two-stent strategy (3, 24-26). In the present study, the FKI was performed more frequently in the A family than in the S family. Since there have been little evidence that a specific strategy is better than another for bifurcation lesions, it might be also possible to interpret our results as the difference in FKI that resulted in the difference in hard endpoints between the A and S family. However, it is important to note that it was the same interventional cardiologists who did fewer FKI after the S family than after the A family, suggesting that the difference in FKI between the A and S groups might result from the chosen strategies themselves with different stent geometry at the time of SB wiring which can be impeded by the presence of a SB stent. Furthermore, in the S family we have to take more labor to re-wire SB for FKI after MV stenting, whereas in A family we can do FKI immediately after the second stenting without additional

rewiring procedure. Such kind of procedure characteristics may influence the rate of FKI in association with the specific strategies, A vs S. If this is the case, we should not consider an initial strategy and FKI separately, but rather as one package.

Compared to previous reports, it is also notable that FKI (or the A family) resulted in improving the clinical outcome of the composite hard endpoint and not the need for repeated revascularization. Since stent under-expansion and suboptimal stent scaffolding can be associated with increased risk for ST, MI, or cardiac death, it is reasonable to think that FKI, which can minimize such phenomena, could improve hard endpoints. In previous studies, it has not been proven whether the choice of certain strategies or the performance of FKI is associated with better outcome regarding hard endpoints. This is probably due to the wide confidence intervals of the effect estimates, which result from a limited power owing to a small number of patients analyzed and relatively short duration of follow up. There was a report that the 2-DES implantation with a significantly lower proportion of FKI resulted in more MI and ST than the 1-DES implantation with FKI (10).

This is an observational study, and is susceptible to residual bias due to unmeasured confounding factors. Most importantly, we only analyzed the A family with successful SB stenting cases, which means those cases with failed SB stenting were excluded, leading to overestimation of the benefits of the A family. In addition, about 70% of the A and S groups were 'T-stenting & small protrusion technique' and 'crush technique & its' variants', respectively, so that the clinical outcome of each technique could be biased toward the representative technique. More clinical data with various techniques is needed to substantiate the findings. Second, the quantitative coronary analysis was not performed using a dedicated program for bifurcation lesions, and lacked information regarding the bifurcation angles. Because the bifurcation angle is reported to influence outcome (25, 27, 28), it would have been better if we had information regarding the angles. Third, a considerable number of lost follow-ups can also be another source of selection bias especially beyond 1 yr. In the survival analysis, censoring is supposed to be non-informative, i.e. missing at random. However, censoring can be influenced by physical status and socioeconomic status, and, therefore, can be informative. In our registry, censoring distributions of the 2 groups were homologous (Supplementary Fig. 5), and are expected to have little influence over the results. Finally, this study was not a prospective randomized trial, but an analysis of a real-world cohort of patients receiving intervention for bifurcation lesions. Although-, we performed extensive statistical analysis to correct for confounding factors, such as propensity score analysis and weight methods, our data and analysis is vulnerable to confounding factors that were otherwise unrecognized but inherent in this type of study. Nevertheless, the present study has merits in that it reflects the real world practice as the COBIS registry is the largest bifurcation registry consisting of more than 1,600 patients except one (29). In particular, the low proportion of successful FKI after the S family and its possible clinical consequences alert us to the importance of FKI after a 2-stent strategy.

If both the A and S approaches are feasible for intervention of a bifurcation lesion, the A family, i.e. main across side first, seems preferable to the S family, i.e. side branch first. When the two-stent strategy is used, every effort should be made to perform FKI, especially in the S family.

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AUTHOR SUMMARY

Comparing Two-Stent Strategies for Bifurcation Coronary Lesions: Which Vessel Should be Stented First, the Main Vessel or the Side Branch?

Dong-Ho Shin, Kyung Woo Park, Bon-Kwon Koo, Il-Young Oh, Jae-Bin Seo, Hyeon-Cheol Gwon, Myung-Ho Jeong, In-Whan Seong, Seung Woon Rha, Ju-Young Yang, Seung-Jung Park, Jung Han Yoon, Kyoo-Rok Han, Jong-Sun Park, Seung-Ho Hur, Seung-Jea Tahk and Hyo-Soo Kim

For treatment of complex coronary bifurcation lesions, we compared two-stent strategies according to stenting order; 'main across side first (A-family)' vs 'side branch first (S-family)'. Patients of A-family showed fewer events of cardiac complications than those with S-family, while target lesion revascularization (TLR) rates were similar between the two groups. Final kissing inflation (FKI) was another independent predictor of prognosis, but was not a predictor of TLR. The prognosis of S-family with FKI was comparable with the A-family, whereas the S-family without FKI showed the poorest prognosis. If both approaches are feasible, 'A-family' seems preferable to 'S-family'. When the two-stent strategy is used, every effort should be made to perform FKI, especially in the 'S-family'.

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