ORIGINAL RESEARCH

5-Year Outcome of Simple Crossover Stenting in Coronary Bifurcation Lesions Compared With Side Branch Opening

Cheol Hyun Lee, MD,[a] Chang-Wook Nam, MD,[a] Yun-Kyeong Cho, MD,[a] Hyuck-Jun Yoon, MD,[a] Kwon-Bae Kim, MD,[a] Hyeon-Cheol Gwon, MD,[b] Hyo-Soo Kim, MD,[c] Woo Jung Chun, MD,[d] Seung Hwan Han, MD,[e] Seung-Woon Rha, MD,[f] In-Ho Chae, MD,[g] Jin-Ok Jeong, MD,[h] Jung Ho Heo, MD,[i] Junghan Yoon, MD,[j] Do-Sun Lim, MD,[k] Jong-Seon Park, MD,[l] Myeong-Ki Hong, MD,[m] Sung Yun Lee, MD,[n] Kwang Soo Cha, MD,[o] Doo-Il Kim, MD,[p] Jang-Whan Bae, MD,[q] Kiyuk Chang, MD,[r] Byung-Hee Hwang, MD,[s] So-Yeon Choi, MD,[t] Myung Ho Jeong, MD,[u] Ki Hong Choi, MD,[b] Young Bin Song, MD,[b] Soon-Jun Hong, MD,[k] Joon-Hyung Doh, MD,[n] Bon-Kwon Koo, MD,[c] Seung-Ho Hur, MD[a]

ABSTRACT

BACKGROUND The optimal side branch (SB) treatment strategy after simple crossover stenting in bifurcation lesions is still controversial.

OBJECTIVES The purpose of this study was to compare the long-term outcomes of a 1-stent strategy with simple crossover alone versus with an additional SB–opening procedure in patients with left main (LM) and non-LM coronary bifurcation lesions.

METHODS Patients who underwent percutaneous coronary intervention with a 1-stent strategy for bifurcation lesions including LM were selected from the COBIS (Coronary Bifurcation Stenting) III registry and divided into the simple crossover–alone group and SB-opening group. Clinical outcomes were assessed by the 5-year rate of target lesion failure (a composite of cardiac death, target vessel myocardial infarction, and target lesion repeat revascularization).

RESULTS Among 2,194 patients who underwent the 1-stent strategy, 1,685 (76.8%) patients were treated with simple crossover alone, and 509 (23.2%) patients were treated with an additional SB-opening procedure. Although the baseline SB angiographic disease was more severe in the SB-opening group, the final lumen diameter of the SB was larger. The 5-year observed target lesion failure rate was similar between the 2 groups (7.0% in the simple crossover vs. 6.7% in SB-opening group; hazard ratio: 0.99; 95% confidence interval: 0.66 to 1.48; p = 0.947), even in the subgroup analyses including LM (9.5% vs. 11.3%; p = 0.442) and true bifurcation (5.3% vs. 7.8%; p = 0.362). The results were not changed after an inverse probability of treatment weighting adjustment. There was no difference in the overall and SB-related target lesion revascularization rate in both groups.

CONCLUSIONS The long-term clinical outcome of the 1-stent strategy with simple crossover alone for coronary bifurcation lesions was acceptable compared to those of additional SB-opening procedures. (Korean Coronary Bifurcation Stenting [COBIS] Registry III [COBIS III]; NCT03068494) (JACC: Asia 2021;1:53–64) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Keimyung University Dongsan Hospital, Daegu, Korea; [b]Sungkyunkwan University Samsung Medical Center, Seoul, Korea; [c]Seoul National University Hospital, Seoul, Korea; [d]Sungkyunkwan University Samsung Changwon Hospital, Seoul, Korea; [e]Gachon University Gil Hospital, Incheon, Korea; [f]Korea University Guro Hospital, Seoul, Korea; [g]Seoul National University Bundang Hospital, Seongnam, Korea; [h]Chungnam National University Hospital, Daegeon, Korea; [i]Kosin University Gospel Hospital, Busan, Korea; [j]Yonsei University Wonju Severance Christian Hospital, Wonju, Korea; [k]Korea University Anam Hospital, Seongnam, Korea; [l]Yeungnam University Medical Center, Daegu, Korea; [m]Yonsei University Severance Cardiovascular Hospital, Seoul, Korea; [n]Inje University Ilsan Paik Hospital, Goyang, Korea; [o]Pusan National University Hospital, Pusan, Korea; [p]Inje University Haeundae Paik Hospital, Busan, Korea; [q]Chungbuk National University Hospital, Cheongju, Korea; [r]Seoul St. Mary's Hospital, Seoul, Korea; [s]St. Paul's Hospital, The Catholic University of Korea, Seoul, Korea; [t]Ajou University Hospital, Suwon, Korea; and the [u]Chonnam National University Hospital, Gwangju, Korea.

With the results of randomized trials, which demonstrated that the routine 2-stent strategy did not show better clinical outcomes than the 1-stent strategy in bifurcation lesions (1,2), the usual percutaneous coronary intervention (PCI) strategy for coronary bifurcation disease is a provisional approach. However, the standard technique of the provisional strategy is not clear, and there are limited data on the long-term outcome of the side branch (SB) treatment strategy after the 1-stent strategy with simple main vessel (MV) crossover in bifurcation lesions. Because there were several studies showing completely opposite results about the clinical outcome after SB opening (3-6), and a functional anatomic discrepancy has been confirmed in the angiographically compromised SB after simple crossover stenting in bifurcation lesions (7-9), a routine SB-opening procedure after simple MV crossover stenting in non-left main (LM) bifurcation lesions is generally not recommended (10). There are also limited clinical outcome data on the role of SB-opening procedures after the 1-stent strategy in LM bifurcation lesions (8). Therefore, the present study sought to compare the long-term outcomes of the 1-stent strategy with simple crossover alone versus with an additional SB-opening procedure in a real-world, large bifurcation registry including LM and non-LM bifurcation lesions.

METHODS

STUDY DESIGN AND POPULATION. The COBIS III (Coronary Bifurcation Stenting III) registry is a retrospective, multicenter, observational, real-world registry of patients with bifurcation lesions who underwent PCI with second-generation drug-eluting stents (DES) (NCT03068494). Between January 2010 and December 2014, a total of 2,648 patients were consecutively enrolled from 21 centers in the Republic of Korea. In the analysis of this study, the patients who underwent PCI with the 1-stent strategy without additional SB stenting were enrolled. The patients who underwent the 2-stent strategy were excluded, and their features are described in Supplemental Tables 1 and 2. The patients were divided into 2 groups, including a simple crossover-alone group and SB-opening group, and the 5-year clinical outcomes were compared. This registry included patients who were at least 19 years old and had any type of coronary bifurcation lesion in a major epicardial artery treated solely with second-generation DESs and an MV diameter of ≥2.5 mm and SB diameter of ≥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 LM disease, and severe left ventricular systolic dysfunction (ejection fraction: <30%). This registry was supported by the Korean Bifurcation Club and Korean Society of Interventional Cardiology. The Institutional Review Board of each hospital approved the study protocol and waived the requirement for written informed consent due to the retrospective nature of the study.

PCI PROCEDURE. Coronary interventions were performed in accordance with the relevant standard guidelines at the time of each procedure. All patients received loading doses of aspirin (300 mg) and P2Y$_{12}$ inhibitors (clopidogrel 300 to 600 mg, prasugrel 60 mg, or ticagrelor 180 mg) before the PCI unless they had previously received these antiplatelet medications. Anticoagulation was performed using low-molecular-weight heparin or unfractionated heparin to achieve an activated clotting time of 250 to 300 s during the PCI. The treatment strategies after a 1-stent technique (proximal optimization technique [POT], final kissing inflation [FKI] with or without POT, and only SB opening), access site, type of DES, use of glycoprotein IIb/IIIa inhibitors, and use of intravascular imaging or an invasive physiologic assessment were all left to the operators' discretion. After the procedure, 100 mg of aspirin was continued indefinitely, and the maintenance duration of clopidogrel (75 mg/day), prasugrel (10 mg/day), or ticagrelor (90 mg twice daily) was also at the operators' discretion.

DATA COLLECTION AND QCA ANALYSIS. Information about the patient demographics, medications, laboratory data, angiographic data, procedural data, and outcomes was collected using a web-based reporting system. Additional information was

TABLE 1 Baseline Characteristics of Patients

	Simple Crossover (n = 1685)	SB Opening (n = 509)	p Value
Age, yrs	63.38 ± 11.09	63.67 ± 10.58	0.595
Men	1,282 (76.1)	400 (78.6)	0.267
Hypertension	961 (57.0)	289 (56.8)	0.960
Diabetes mellitus	562 (33.4)	167 (32.8)	0.861
Dyslipidemia	628 (37.3)	207 (40.7)	0.183
Current smoker	527 (31.3)	152 (29.9)	0.582
Previous PCI	187 (11.1)	70 (13.8)	0.120
Previous stroke	122 (7.2)	28 (5.5)	0.207
Previous heart failure	11 (0.7)	4 (0.8)	0.760
Ejection fraction, %	58.43 ± 10.17	59.41 ± 8.77	0.048
Clinical presentation			0.091
Stable angina	636 (37.7)	214 (42.0)	
Acute coronary syndrome	1,049 (62.3)	295 (58.0)	
Discharge medications			
Aspirin	1,660 (98.5)	500 (98.6)	0.998
P2Y$_{12}$ inhibitor	1,664 (98.8)	502 (99.0)	0.804
Beta-blocker	1,035 (61.4)	285 (56.0)	0.032
Calcium-channel blocker	130 (7.7)	44 (8.7)	0.544
ACE inhibitor or ARB	1,050 (62.3)	297 (58.3)	0.119
Statin	1,514 (89.9)	449 (88.2)	0.330

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; PCI = percutaneous coronary intervention.

obtained by further inquiry into the medical records or by telephone contact, if necessary.

All baseline and procedural coronary angiograms were reviewed and analyzed quantitatively by an angiographic core laboratory (Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Republic of Korea) with a validated automated edge-detection system (Centricity CA 1000, GE, Waukesha, Wisconsin). Bifurcation lesions were classified according to the Medina classification and divided into 3 segments for a QCA analysis: proximal MV, distal MV, and SB (11). True bifurcation lesions were defined as Medina classification types 1.1.1, 1.0.1, and 0.1.1. For both the pre- and post-procedures, the minimum lumen diameter (MLD), reference vessel diameter (RVD), and lesion length for each vessel were measured, and the percent diameter stenosis (%DS) for each vessel was calculated as: 100 × (RVD − MLD)/RVD.

STUDY OUTCOMES AND DEFINITIONS. The primary clinical outcome was a target lesion failure (TLF)—the composite endpoint of death from cardiac causes, a target vessel myocardial infarction (MI), or target lesion repeat revascularization (TLR). Various secondary clinical outcomes were also assessed, including death (any cause, cardiac cause, or noncardiac cause), MI (any cause or target vessel MI), target vessel revascularization, TLR, and stent thrombosis. Death was considered as having a cardiac cause unless an unequivocal noncardiac cause could

be established. A spontaneous MI was defined as an elevation of a creatine kinase-myocardial band or a troponin level greater than the upper limit of normal with concomitant ischemic symptoms or electrocardiography findings indicative of ischemia that was not related to the index procedure. TLR was defined as a repeat revascularization with a PCI or coronary artery bypass surgery for restenosis of the entire segment involving the implanted stent and within 5 mm of the distal and proximal margins of the stent and SB ostium. The definition of a stent thrombosis was assessed according to the Academic Research Consortium definition (12).

STATISTICAL ANALYSIS. Continuous variables were compared between the groups using Student's *t*-test and are presented as the mean ± SD. Categorical data were compared between the groups using the chi-square test and are presented as numbers and relative frequencies. The cumulative incidence of clinical events are presented as a Kaplan-Meier estimate, and the significance level was assessed with a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard models, and the proportional hazards assumptions of the HRs in the Cox proportional hazards models were graphically inspected in the "log minus log" plot and were also tested by Schoenfeld residuals. We fitted weighted Cox proportional hazards models

TABLE 2   Baseline Lesion and Procedural Characteristics

	Simple Crossover (n = 1,685)	SB Opening (n = 509)	p Value
Location of bifurcated vessel			<0.001
LM	489 (29.0)	193 (37.9)	
LAD	796 (47.2)	241 (47.3)	
LCx	276 (16.4)	50 (9.8)	
RCA	124 (7.4)	25 (4.9)	
Medina classification			<0.001
0.0.1	14 (0.8)	31 (6.1)	
0.1.0	468 (27.8)	90 (17.7)	
0.1.1	113 (6.7)	42 (8.3)	
1.0.0	263 (15.6)	26 (5.1)	
1.0.1	97 (5.8)	38 (7.5)	
1.1.0	340 (20.2)	65 (12.8)	
1.1.1	390 (23.1)	217 (42.6)	
True bifurcation (SB disease)	600 (35.6)	297 (58.3)	<0.001
DES type			0.039
EES	799 (47.4)	236 (46.4)	
ZES	459 (27.2)	151 (29.7)	
BES	339 (20.1)	110 (21.6)	
Others	88 (5.2)	12 (2.4)	
Maximal diameter of MV stents, mm	3.34 ± 0.62	3.42 ± 0.62	0.014
Cumulative length of MV stents, mm	28.87 ± 13.79	27.36 ± 12.52	0.022
Final kissing balloon	0 (0.0)	391 (76.8)	<0.001
Proximal optimization technique	485 (28.8)	146 (28.7)	0.998
Use of intravascular ultrasound	601 (35.7)	215 (42.2)	0.008
QCA			
Pre-procedure			
Reference diameter of PV, mm	3.56 ± 0.62	3.63 ± 0.61	0.116
Reference diameter of MV, mm	3.22 ± 0.48	3.26 ± 0.46	0.106
Reference diameter of SB, mm	2.57 ± 0.44	2.63 ± 0.43	0.013
MLD of PV, mm	1.79 ± 1.18	1.73 ± 1.04	0.306
MLD of MV, mm	0.81 ± 0.48	0.86 ± 0.43	0.022
MLD of SB, mm	1.65 ± 0.82	1.44 ± 0.81	<0.001
Diameter stenosis of PV, %	50.60 ± 29.69	52.52 ± 26.71	0.166
Diameter stenosis of MV, %	74.83 ± 14.40	73.51 ± 12.53	0.046
Diameter stenosis of SB, %	37.49 ± 26.06	46.61 ± 25.90	<0.001
Lesion length of MV, mm	19.40 ± 10.38	16.82 ± 8.94	<0.001
Lesion length of SB, mm	3.80 ± 5.94	5.20 ± 5.90	<0.001
Final			
MLD of PV, mm	3.59 ± 0.60	3.67 ± 0.58	0.007
MLD of MV, mm	2.77 ± 0.49	2.78 ± 0.42	0.758
MLD of SB, mm	1.52 ± 0.81	1.69 ± 0.70	<0.001
Diameter stenosis of PV, %	11.26 ± 9.02	10.16 ± 9.00	0.015
Diameter stenosis of MV, %	15.26 ± 10.36	15.86 ± 9.22	0.213
Diameter stenosis of SB, %	42.56 ± 26.23	37.21 ± 21.84	<0.001

Values are n (%) or mean ± SD. The number, length, and diameter of the stents were all calculated per lesion.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main; MLD = minimal lumen diameter; MV = main vessel; PV = parent vessel; QCA = quantitative coronary angiography; RCA = right coronary artery; other abbreviations as in **Figures 1 and 3**.

using the inverse probability of treatment weighting (IPTW) approach (13). The propensity scores were estimated without regard to the outcomes with a multiple logistic regression analysis. The distribution of the propensity score is provided in Supplemental Figure 1 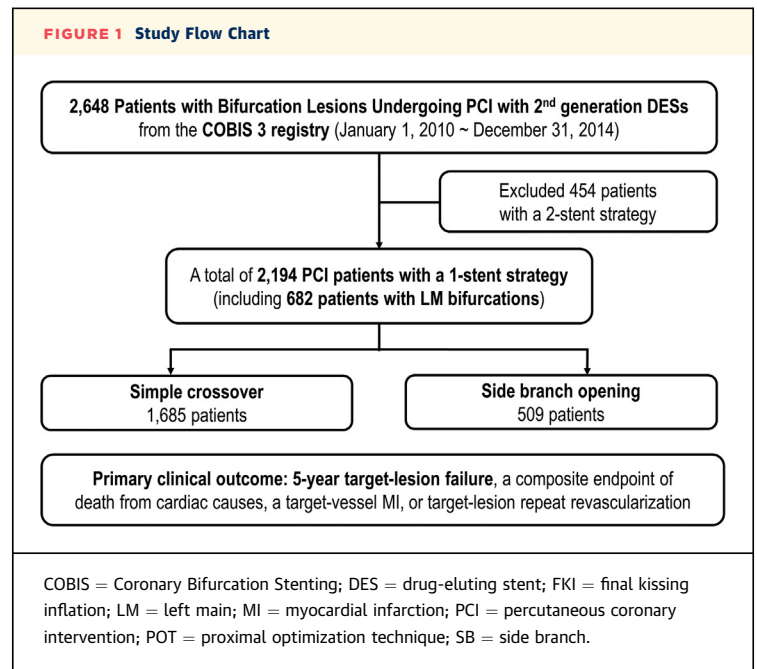for both groups. A full nonparsimonious model was developed that includes the covariates in Tables 1 and 2 except QCA data. All probability values are 2-sided, and p values of <0.05 were considered statistically significant. Statistical analyses were performed using R statistical software, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS AND LESIONS.

A total of 2,194 patients who underwent PCI with the 1-stent strategy for bifurcation lesions were enrolled from the COBIS III registry. Among them, 1,685 (76.8%) patients were treated with simple crossover alone, and 509 (23.2%) patients were treated with an additional SB-opening procedure (Figure 1). The baseline demographics and clinical characteristics of the study population are shown in Table 1. There was no significant difference in the patients' clinical characteristics except the ejection fraction between the 2 groups. Table 2 shows the lesion characteristics and procedural results of the study population. At the lesion level before the PCI, the RVD of the SB, MLD of the MV, and %DS of the SB were smaller, and the lesion length of the SB was shorter in the simple crossover group. In addition, the incidence of a true bifurcation was lower in the simple crossover group (simple crossover vs. SB opening: 35.6% vs. 58.3%, p < 0.001). The final MLD of the SB was smaller (1.52 mm vs. 1.69 mm; p < 0.001) and % DS of the SB was larger (42.56% vs. 37.21%; p < 0.001) in the simple crossover group. Intravascular ultrasound was used more frequently in the SB-opening group than the simple crossover group (45.2% vs. 35.7%; p = 0.008).

CLINICAL IMPACT OF THE ADDITIONAL SB-OPENING PROCEDURE AFTER SIMPLE CROSSOVER STENTING.

The median duration of the clinical follow-up was 53 months (interquartile range: 37 to 68 months). The 5-year observed TLF rate in the 1-stent strategy with simple crossover group did not statistically differ from that of the SB-opening group (simple crossover vs. SB opening: 7.0% vs. 6.7%; HR: 0.99; 95% CI: 0.66 to 1.48; p = 0.947), and the result did not change after an IPTW adjustment. The incidence of 5-year cardiac death (3.0% vs. 2.8%; HR: 0.93; 95% CI: 0.50 to 1.72; p = 0.822), target vessel MI (0.8% vs. 1.4%; HR: 1.38; 95% CI: 0.54 to 3.57; p = 0.501), and TLR (4.0% vs. 3.5%; HR: 0.92; 95% CI: 0.52 to 1.63; p = 0.776) did not differ between the 2 groups (Table 3, Figure 2).

Figure 3 presents the subgroup analyses of the primary endpoint. We found little evidence of the HRs differing across each subgroup, including use of intravascular ultrasound and POT. The overall TLR rates were similar in both groups. Among them, there was also no difference in SB-related TLR events (55.7% of the simple crossover group and 66.7% in the SB-opening group; p = 0.165) (Figure 4).

FIGURE 1 Study Flow Chart

2,648 Patients with Bifurcation Lesions Undergoing PCI with 2nd generation DESs from the COBIS 3 registry (January 1, 2010 ~ December 31, 2014)

Excluded 454 patients with a 2-stent strategy

A total of 2,194 PCI patients with a 1-stent strategy (including 682 patients with LM bifurcations)

Simple crossover 1,685 patients

Side branch opening 509 patients

Primary clinical outcome: 5-year target-lesion failure, a composite endpoint of death from cardiac causes, a target-vessel MI, or target-lesion repeat revascularization

COBIS = Coronary Bifurcation Stenting; DES = drug-eluting stent; FKI = final kissing inflation; LM = left main; MI = myocardial infarction; PCI = percutaneous coronary intervention; POT = proximal optimization technique; SB = side branch.

CLINICAL IMPACT OF THE ADDITIONAL SB-OPENING PROCEDURE AFTER SIMPLE CROSSOVER STENTING IN LM AND TRUE BIFURCATION LESIONS.

When only the LM bifurcation lesions were stratified, the 5-year rates of TLF (simple crossover vs. SB opening: 9.5% vs. 11.3%; HR: 1.24; 95% CI: 0.72 to 2.14; p = 0.442) and TLR (4.8% vs. 7.3%; HR: 1.53; 95% CI: 0.75 to 3.14; p = 0.241) were not different, and the same results were shown after an IPTW adjustment (Table 4, Figure 5). Although the incidence of a target vessel revascularization was higher in the SB-opening group, there was no statistical significance after an IPTW adjustment (7.1% vs. 11.9%; IPTW-adjusted HR: 1.30; 95% CI: 0.59 to 2.89; p = 0.519). Although a numerically high rate of stent thrombosis was observed in the LM simple crossover group, there was only 1 ostial left circumflex-related stent thrombosis, and the clinical presentation at the index procedure was acute coronary syndrome in all cases.

When only the true bifurcation was stratified, the SB-opening group did not exhibit an improvement in the clinical outcome compared to the simple crossover group in the 5-year TLF (simple crossover vs. SB opening: 5.3% vs. 7.8%, HR: 1.29; 95% CI: 0.74 to 2.26; p = 0.362).

DISCUSSION

The major findings from the present study, which investigated the long-term outcomes of a 1-stent

TABLE 3   Unadjusted and Adjusted Clinical Outcomes According to an Additional SB-Opening Procedure

	Event Rates* at 5 Years		Unadjusted		IPTW Adjusted	
	Simple Crossover (n = 1,685)	SB Opening (n = 509)	HR† (95% CI)	p Value	HR† (95% CI)	p Value
Primary outcome						
Target lesion failure‡	95 (7.0)	29 (6.7)	0.99 (0.66-1.48)	0.947	0.68 (0.37-1.26)	0.218
Secondary outcomes						
Death from any cause	77 (5.4)	17 (3.9)	0.75 (0.46-1.23)	0.252	0.77 (0.37-1.62)	0.494
Cardiac	43 (3.0)	12 (2.8)	0.93 (0.5-1.72)	0.822	0.98 (0.41-2.38)	0.970
Noncardiac	32 (2.3)	5 (1.1)	0.53 (0.23-1.26)	0.150	0.52 (0.13-2.04)	0.346
MI	22 (1.5)	11 (2.4)	1.36 (0.68-2.74)	0.386	1.45 (0.51-4.08)	0.482
Target vessel MI	12 (0.8)	6 (1.4)	1.38 (0.54-3.57)	0.501	1.36 (0.33-5.55)	0.670
Any revascularization	133 (9.7)	42 (9.7)	1.01 (0.72-1.42)	0.955	0.83 (0.49-1.42)	0.502
Target lesion	52 (4.0)	15 (3.5)	0.92 (0.52-1.63)	0.776	0.59 (0.24-1.43)	0.244
Target vessel	86 (6.4)	30 (7.0)	1.15 (0.76-1.72)	0.514	0.75 (0.4-1.38)	0.351
Definite stent thrombosis	16 (1.0)	3 (0.7)	0.76 (0.26-2.26)	0.626	0.98 (0.21-4.59)	0.985

Values are n (%) unless noted otherwise. *Event rates are based on Kaplan-Meier estimates. †HRs are for the SB-opening group compared with the simple crossover group. ‡Target lesion failure was defined as a composite of death by cardiac causes, target vessel MI, or target lesion revascularization.

HR = hazard ratio; IPTW = inverse probability of treatment weighting; other abbreviation as in **Figures 1 and 3**.

strategy with simple crossover alone versus with an additional SB-opening procedure for coronary bifurcation lesions, are as follows:

- There were various different baseline angiographic characteristics between the 2 groups, and the SB-opening group showed better post-procedural angiographic results in the SB.
- However, an additional procedure for SB opening did not exhibit improvement in the long-term clinical outcomes compared to simple crossover alone, and the results did not change after an IPTW adjustment.
- Even in the various subgroup analyses, including LM and true bifurcation lesion subsets, the outcomes were not different between the 2 groups.
- There were similar 5-year overall and SB-related TLR rates in both groups.

In the treatment of bifurcation lesions, a provisional strategy is generally recommended, because the 1-stent strategy had better or similar long-term clinical outcomes than the 2-stent strategy in several randomized and registry trials (1,2,14,15). Apart from the 1-stent strategy for bifurcation lesions, there is still controversy over a SB-opening treatment after simple MV stenting because of conflicting results. In the Nordic-Baltic Bifurcation Study III, the CROSS (Choice of Optimal Strategy for Bifurcation Lesions With Normal Side Branch) study, and the COBIS I study, SB opening by FKI after simple MV stenting did not show a better clinical outcome compared to simple crossover alone. Furthermore, the simple crossover group had a reduced use of

contrast media and shorter procedure and fluoroscopy times (4,5,16). On the other hand, in the COBIS II study, which included LM and non-LM bifurcation lesions, SB opening with FKI was associated with a favorable long-term clinical outcome, mainly driven by the reduction in TLR in the MV (adjusted HR: 0.51; 95% CI: 0.28 to 0.93; p = 0.03) as a result of an increase in the MLD of the MV (3). Because of this limited clinical evidence about the role of SB opening after simple crossover stenting, a routine SB opening is mandatorily recommended only with the 2-stent strategy (17), and there is controversy over the 1-stent strategy.

The current study was a large, multicenter, real-world registry of patients with bifurcation lesions including LM bifurcation lesions. In this registry, physicians choose SB opening for the patients with large SB territory or complex anatomy such as LM or true bifurcation lesions and preferred to complete the procedure with simple crossover alone in the patients who had low ejection fraction or presented with acute coronary syndrome. Although the SB opening could improve the immediate angiographic results in the SB, the 5-year clinical outcomes of SB opening after simple crossover stenting did not differ compared to the simple crossover group after an IPTW adjustment, even in various subgroup analyses, including the LM and true bifurcation lesions. An additional important finding of our current study was that there were similar overall TLR rates in both groups and no difference in SB-related TLR events by analyzing the angiographic locations of the patients who had TLR (**Central Illustration**). SB-related TLR events were

FIGURE 2 Outcomes According to Additional SB Opening After Simple Crossover Stenting
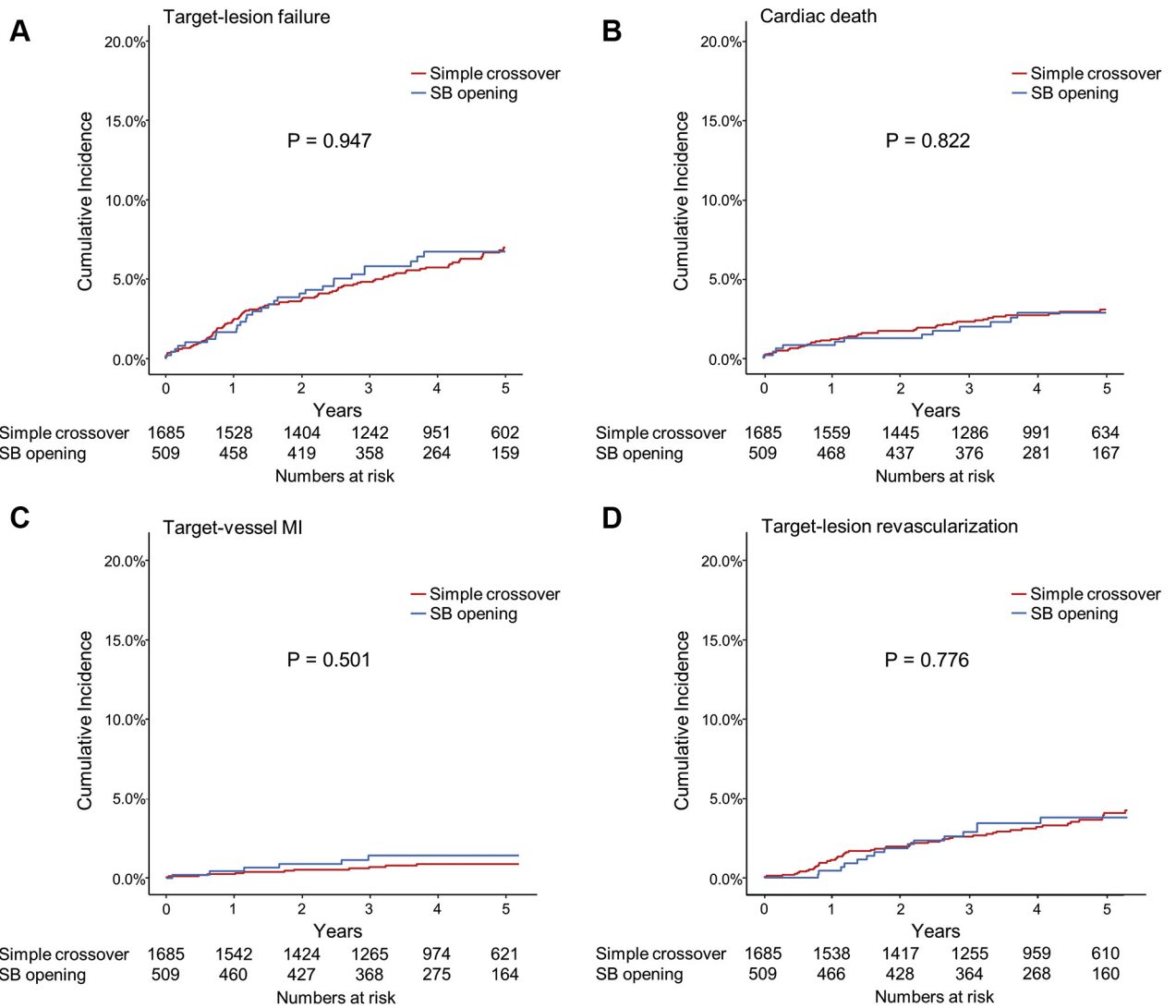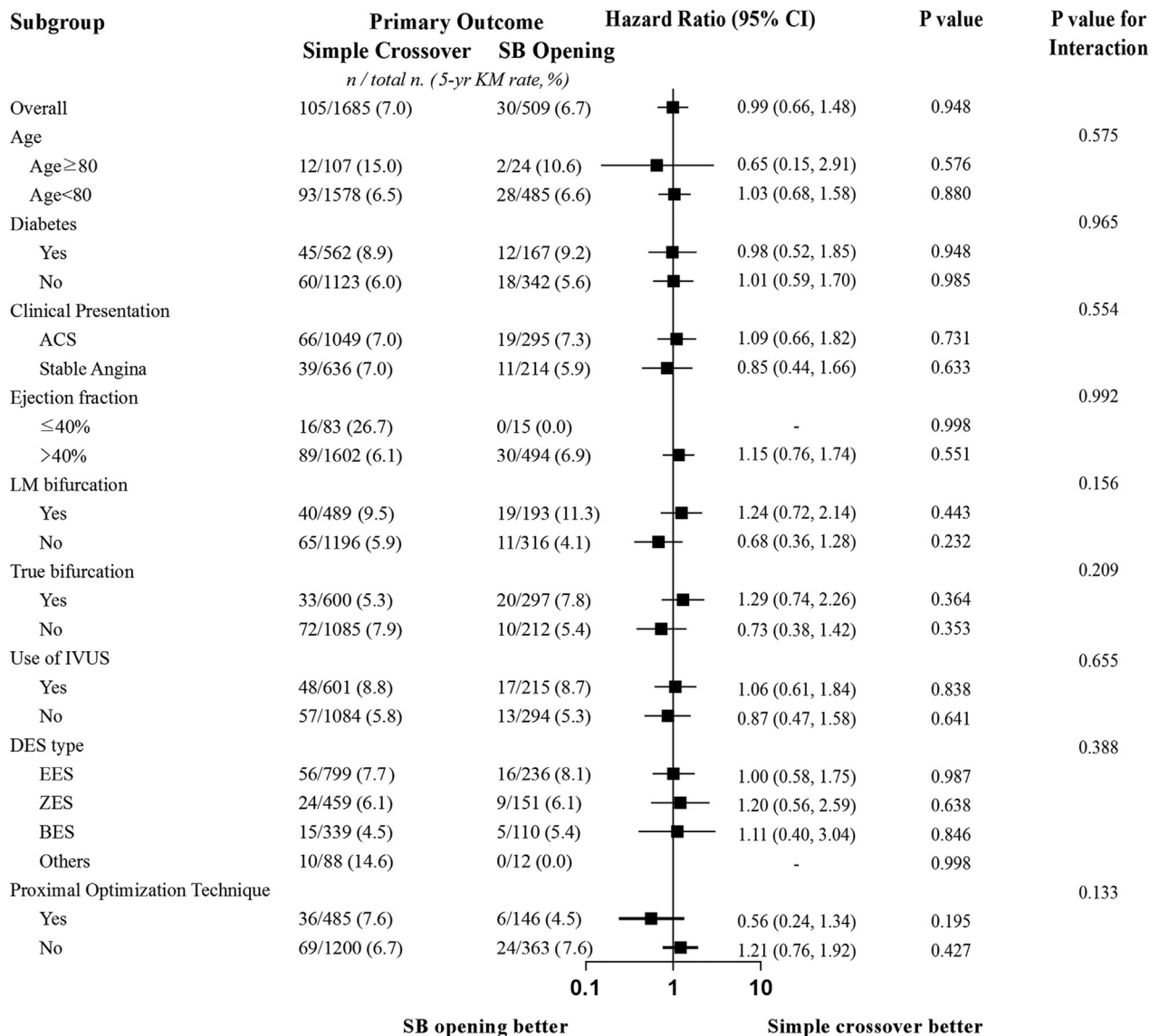

The 5-year cumulative-incidence curves are shown for target-lesion failures according to an additional SB-opening procedure after the 1-stent strategy with simple crossover. Target-lesion failure was defined as a composite of death from **(A)** cardiac causes, target vessel MI, or target vessel revascularization; **(B)** cardiac death; **(C)** target vessel MI, **(D)** and target lesion revascularization. Abbreviations as in **Figure 1**.

consistently similar in previous studies such as CROSS (routine SB opening with FKI vs. leave alone: 1.3% vs. 1.3%; p = 0.97), COBIS I (FKI vs. non-FKI: 2.1% vs. 0.0%), and COBIS II studies (FKI vs. non-FKI: 2.1% vs. 2.2%; p = 0.62) (3,5,16). Therefore, the routine additional SB-opening procedure may not prevent an SB-related TLR event after the 1-stent strategy in coronary bifurcation lesions. However, the current study included patients who had relatively simple bifurcation lesions, such as mild to moderate stenosis and short lesion length of the SB,

and excluded patients who had been treated with a 2-stent strategy because of highly complex bifurcation lesions, such as tight stenosis with longer lesion length in a large SB. This concept should be cautiously applied and not used for all bifurcation lesions.

The issue of the SB-opening procedure was well demonstrated by an optical coherence tomography study. An inappropriate rewiring location over the ostial SB strut guided by only angiography may lead to a worse result after the SB opening with FKI (18,19).

FIGURE 3 Subgroup Analysis

Subgroup	Primary Outcome		Hazard Ratio (95% CI)	P value	P value for Interaction
	Simple Crossover	SB Opening			
	n / total n. (5-yr KM rate, %)				
Overall	105/1685 (7.0)	30/509 (6.7)	0.99 (0.66, 1.48)	0.948	
Age					0.575
Age≥80	12/107 (15.0)	2/24 (10.6)	0.65 (0.15, 2.91)	0.576	
Age<80	93/1578 (6.5)	28/485 (6.6)	1.03 (0.68, 1.58)	0.880	
Diabetes					0.965
Yes	45/562 (8.9)	12/167 (9.2)	0.98 (0.52, 1.85)	0.948	
No	60/1123 (6.0)	18/342 (5.6)	1.01 (0.59, 1.70)	0.985	
Clinical Presentation					0.554
ACS	66/1049 (7.0)	19/295 (7.3)	1.09 (0.66, 1.82)	0.731	
Stable Angina	39/636 (7.0)	11/214 (5.9)	0.85 (0.44, 1.66)	0.633	
Ejection fraction					0.992
≤40%	16/83 (26.7)	0/15 (0.0)	-	0.998	
>40%	89/1602 (6.1)	30/494 (6.9)	1.15 (0.76, 1.74)	0.551	
LM bifurcation					0.156
Yes	40/489 (9.5)	19/193 (11.3)	1.24 (0.72, 2.14)	0.443	
No	65/1196 (5.9)	11/316 (4.1)	0.68 (0.36, 1.28)	0.232	
True bifurcation					0.209
Yes	33/600 (5.3)	20/297 (7.8)	1.29 (0.74, 2.26)	0.364	
No	72/1085 (7.9)	10/212 (5.4)	0.73 (0.38, 1.42)	0.353	
Use of IVUS					0.655
Yes	48/601 (8.8)	17/215 (8.7)	1.06 (0.61, 1.84)	0.838	
No	57/1084 (5.8)	13/294 (5.3)	0.87 (0.47, 1.58)	0.641	
DES type					0.388
EES	56/799 (7.7)	16/236 (8.1)	1.00 (0.58, 1.75)	0.987	
ZES	24/459 (6.1)	9/151 (6.1)	1.20 (0.56, 2.59)	0.638	
BES	15/339 (4.5)	5/110 (5.4)	1.11 (0.40, 3.04)	0.846	
Others	10/88 (14.6)	0/12 (0.0)	-	0.998	
Proximal Optimization Technique					0.133
Yes	36/485 (7.6)	6/146 (4.5)	0.56 (0.24, 1.34)	0.195	
No	69/1200 (6.7)	24/363 (7.6)	1.21 (0.76, 1.92)	0.427	

0.1   1   10

SB opening better   Simple crossover better

Hazard ratios are for the SB opening compared to the simple crossover. ACS = acute coronary syndrome; BES = biolimus-eluting stent; CI = confidence interval; EES = everolimus-eluting stent; IVUS = intravascular ultrasound; ZES = zotarolimus-eluting stent; other abbreviations as in **Figure 1**.

Computational fluid dynamics analysis also demonstrated that the SB-opening procedure increased the very low wall shear stress area in the MV, suggesting the possibility of neointimal hyperplasia progression (20). Similarly, a recent meta-analysis showed that SB opening with an FKI strategy increased the risk of MV restenosis (21).

Although the SB-opening procedure with FKI can provide an optimal expansion of the MV, POT has replaced this effect, which can not only make an optimal stent expansion but also restore the elliptical deformation of the stent struts and reduce the malapposition of the stent proximal segment (22). In addition, the incidence of POT was similar in both groups of the current study. However, this concept should be confirmed by an independent study focused on the POT itself.

Furthermore, previous fractional flow reserve studies in a jailed SB after simple MV stenting well demonstrated the discrepancy between angiographic

jailing of the SB and the functional significance. An additional SB opening procedure could not achieve a better outcome compared to only medical therapy in a jailed SB deferred by fractional flow reserve guidance (7,10). Even after LM simple crossover stenting, similar results were observed in the jailed left circumflex lesions (8,9). In that study, the angiographic acute luminal gain of the MV, not that of the SB after stenting, and the functional significance of a jailed SB were reported as major determinants of the long-term clinical outcome after simple crossover stenting (8). Therefore, the maximal optimization of the MV might be more important than the SB-opening procedure itself in a bifurcation PCI with simple crossover stenting. An SB opening with additional complex procedures, which need more resources and have a risk of procedural complications, might be waived by a provisional strategy with a functional evaluation and be performed in ischemic and clinically relevant SBs.

STUDY LIMITATIONS. First, this was a non-randomized, retrospective, observational study, which may have affected the results because of confounding factors. Although we performed multiple sensitivity analyses, including an IPTW adjustment, to
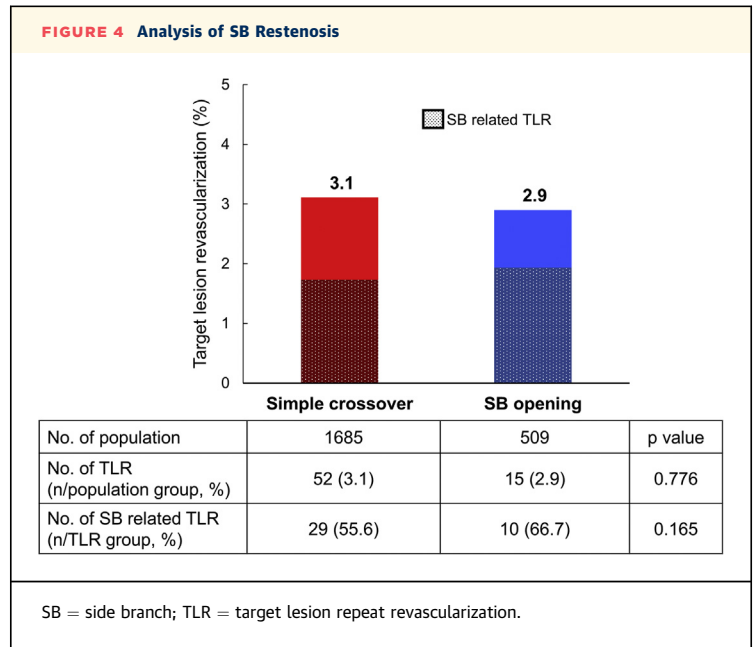
reduce the potential confounders, we could not correct for the unmeasured variables. Second, the choice of treatment strategy, use of intravascular imaging, vascular access, type of stent, and concomitant

FIGURE 4 Analysis of SB Restenosis

No. of population	1685	509	p value
No. of TLR (n/population group, %)	52 (3.1)	15 (2.9)	0.776
No. of SB related TLR (n/TLR group, %)	29 (55.6)	10 (66.7)	0.165

SB = side branch; TLR = target lesion repeat revascularization.

TABLE 4 Unadjusted Clinical Outcomes According to an Additional SB-Opening Procedure for LM or True Bifurcation Lesions

	Event Rates* at 5-year		Unadjusted		IPTW Adjusted	
	Simple Crossover	SB Opening	HR† (95% CI)	p Value	HR† (95% CI)	p Value
LM lesion	489	193				
Target lesion failure‡	37 (9.5)	19 (11.3)	1.24 (0.72-2.14)	0.442	0.92 (0.41-2.06)	0.836
Death from any cause	33 (8.2)	7 (4.1)	0.49 (0.22-1.11)	0.086	0.83 (0.27-2.56)	0.741
Cardiac	20 (5.1)	5 (3.0)	0.60 (0.23-1.59)	0.303	0.79 (0.19-3.36)	0.755
Noncardiac	12 (3.1)	2 (1.1)	0.33 (0.08-1.46)	0.145	0.84 (0.13-5.41)	0.854
MI	8 (1.9)	8 (4.7)	2.27 (0.88-5.88)	0.092	3.62 (1.05-12.44)	0.041
Target-vessel MI	6 (1.4)	5 (3.0)	1.82 (0.58-5.74)	0.306	2.44 (0.51-11.56)	0.261
Any revascularization	43 (11.2)	25 (15.0)	1.50 (0.93-2.43)	0.100	1.50 (0.73-3.09)	0.271
Target lesion	18 (4.8)	12 (7.3)	1.53 (0.75-3.14)	0.241	1.34 (0.47-3.81)	0.580
Target vessel	27 (7.1)	20 (11.9)	1.87 (1.07-3.28)	0.029	1.30 (0.59-2.89)	0.519
Definite stent thrombosis	7 (1.6)	0 (0)	0.32 (0.04-2.56)	0.282	1.44 (0.24-8.7)	0.692
True bifurcation	1,196	316				
Target-lesion failure†	26 (5.3)	19 (7.8)	1.29 (0.74-2.26)	0.362	0.93 (0.43-2.01)	0.854
Death from any cause	29 (5.8)	11 (4.4)	0.74 (0.38-1.43)	0.372	0.68 (0.27-1.76)	0.432
Cardiac	16 (3.1)	9 (3.7)	1.07 (0.5-2.29)	0.856	1.10 (0.39-3.11)	0.864
Noncardiac	13 (2.8)	2 (0.8)	0.29 (0.07-1.28)	0.103	0.13 (0.03-0.57)	0.007
MI	6 (1.3)	4 (1.5)	1.06 (0.32-3.53)	0.921	0.46 (0.14-1.56)	0.214
Target vessel MI	3 (0.5)	3 (1.2)	1.56 (0.35-6.99)	0.559	0.64 (0.14-2.88)	0.561
Any revascularization	41 (8.2)	23 (9.4)	0.98 (0.6-1.6)	0.928	0.63 (0.3-1.3)	0.210
Target lesion	11 (2.4)	8 (3.4)	1.24 (0.52-2.97)	0.622	0.55 (0.22-1.33)	0.181
Target vessel	23 (4.8)	15 (6.3)	1.17 (0.62-2.19)	0.632	0.58 (0.28-1.19)	0.140
Definite stent thrombosis	4 (0.7)	2 (0.8)	1.28 (0.3-5.35)	0.739	2.09 (0.37-11.85)	0.405

Values are n or n (%), unless noted otherwise. *Event rates are based on Kaplan-Meier estimates. †Hazard ratios are for the SB-opening group compared to the simple crossover group. ‡Target lesion failure was defined as a composite of death by cardiac causes, target vessel MI, or target lesion revascularization.

Abbreviations as in **Figures 1 and 3**.

FIGURE 5   Outcomes According to Additional SB Opening, Stratified by LM and True Bifurcation Lesions
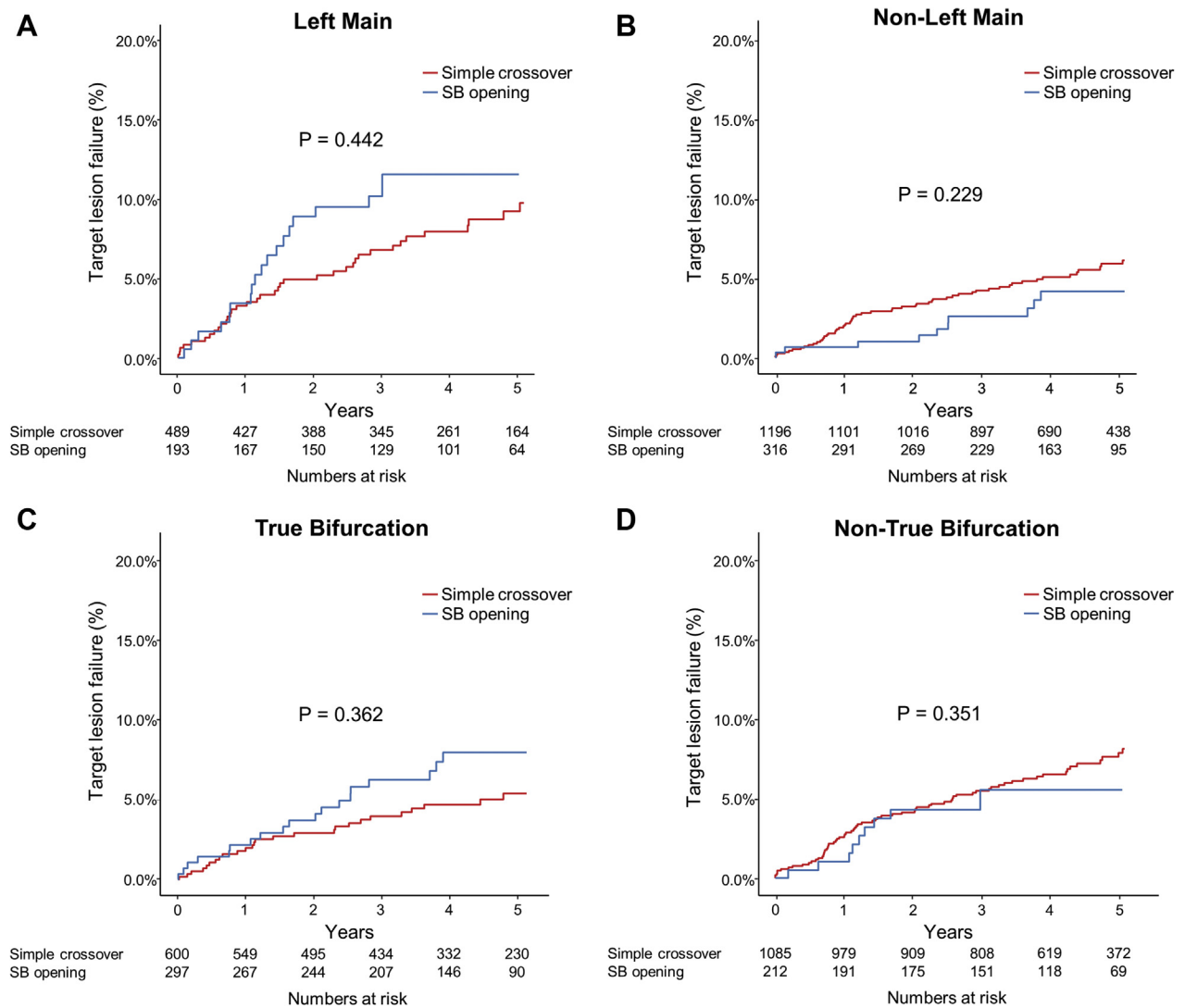
In each figure, the 5-year of cumulative-incidence curves are shown for the target lesion failure according to an additional SB-opening procedure after the 1-stent strategy with simple crossover. Target lesion failure was defined as a composite of death from cardiac causes, target vessel myocardial infractions, or target-vessel revascularization with **(A)** LM bifurcation lesions, **(B)** non-LM bifurcation lesions, **(C)** true bifurcation lesions, and **(D)** non–true bifurcation lesions. Abbreviations as in **Figure 1**.

medications might have reflected individual physicians' preferences. For this reason, information on the rate and clinical outcomes of bail-out stenting on the SB after single stenting were limited. Third, because of the low rate of POT, the procedural optimization of the SB-opening group may not have been complete. However, that was a similar ratio in the simple crossover group, which was a result of comparing similar conditions. However, our data showed the long-term clinical outcome for the previously underreported effects of the SB-opening procedure after the 1-stent

strategy with simple crossover and could play a hypothesis-generating role for future research and reduce unnecessary procedures with bifurcation lesions of coronary artery disease.

CONCLUSIONS

The long-term clinical outcomes of the simple crossover 1-stent strategy without an additional SB-opening procedure in patients with coronary bifurcation lesions was acceptable, even for LM or true

CENTRAL ILLUSTRATION Outcomes After Simple Crossover Stenting in Coronary Bifurcation Lesions According to Additional Side Branch Opening
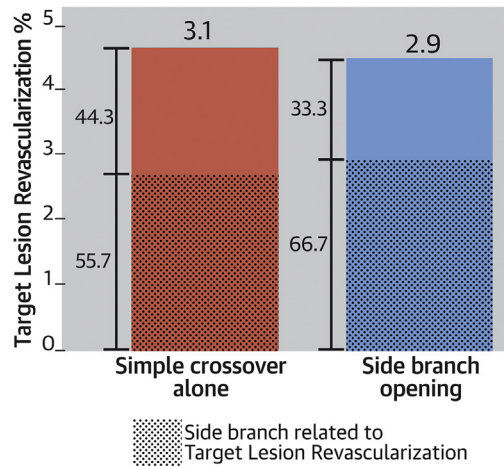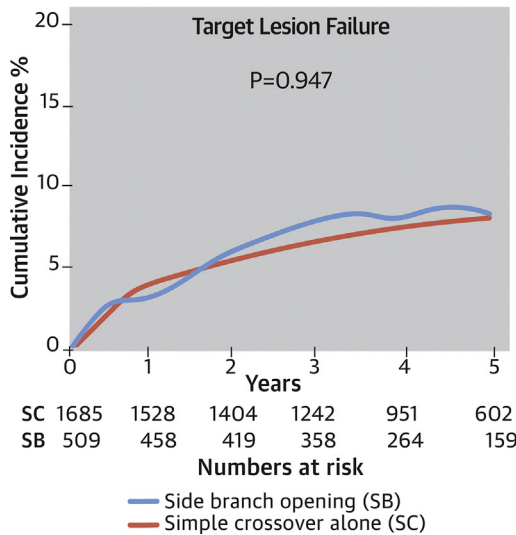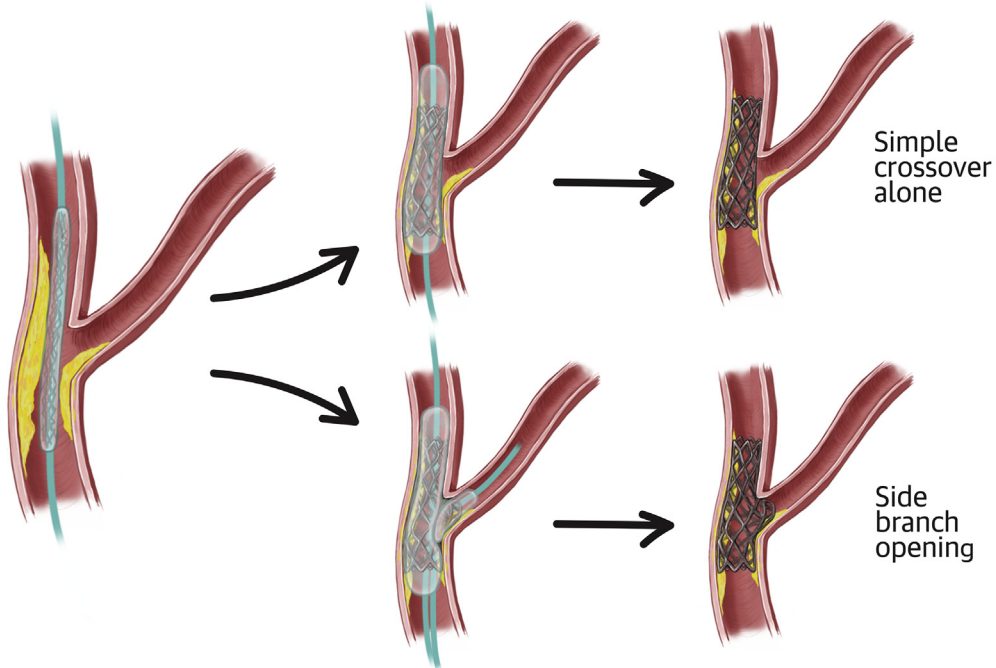
Lee, C.H. et al. JACC: Asia. 2021;1(1):53–64.

An additional side branch–opening procedure after simple main vessel stenting for coronary bifurcation lesions did not exhibit an improvement in the 5-year observed target lesion failure rate compared to simple crossover alone. Furthermore, similar overall and SB-related target lesion revascularization rates were seen in both groups. Therefore, the long-term clinical outcomes after the 1-stent strategy with simple crossover for coronary bifurcation lesions was acceptable.

bifurcation lesions. Therefore, an additional complex procedure for SB opening may not be mandatory for simple crossover stenting bifurcation lesions.

ADDRESS FOR CORRESPONDENCE: Dr. Chang-Wook Nam, Department of Internal Medicine, College of Medicine, Keimyung University Dongsan Hospital, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea. E-mail: ncwcv@dsmc.or.kr. OR Dr. Seung-Ho Hur, Department of Internal Medicine, College of Medicine, Keimyung University Dongsan Hospital, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea. E-mail: shur@dsmc.or.kr.

PERSPECTIVES

COMPENTENCY IN MEDICAL KNOWLEDGE: This study investigated the long-term outcomes of a 1-stent strategy with simple crossover alone versus with additional an SB-opening procedure for coronary bifurcation lesions. The 5-year observed TLF rate was similar between the simple crossover–alone and SB-opening groups, and there were similar 5-year overall and SB-related TLR rates in both groups. SB opening with additional complex procedures, which need more resources and have a risk of procedural complications, might be waived by a provisional strategy and be performed only in ischemic and clinically relevant SB.

TRANSLATIONAL OUTLOOK: Further large randomized studies are needed to clarify the impact of an additional SB-opening procedure in more complex bifurcation lesions.

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KEY WORDS bifurcation disease, clinical outcome, percutaneous coronary intervention

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