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ORIGINAL ARTICLE
Coronary Intervention

Long-Term Clinical Outcomes and Its Predictors Between the 1- and 2-Stent Strategy in Coronary Bifurcation Lesions

— A Baseline Clinical and Lesion Characteristic-Matched Analysis —

Albert Youngwoo Jang, MD; Minsu Kim, MD; Pyung Chun Oh, MD; Soon Yong Suh, MD; Kyounghoon Lee, MD; Woong Chol Kang, MD; Ki Hong Choi, MD; Young Bin Song, MD; Hyeon-Cheol Gwon, MD; Hyo-Soo Kim, MD; Woo Jung Chun, MD; Seung-Ho Hur, MD; Seung-Woon Rha, MD; In-Ho Chae, MD; Jin-Ok Jeong, MD; Jung Ho Heo, MD; Junghan Yoon, MD; Soon Jun Hong, MD; Jong-Seon Park, MD; Myeong-Ki Hong, MD; Joon-Hyung Doh, MD; Kwang Soo Cha, MD; Doo-Il Kim, MD; Sang Yeub Lee, MD; Kiyuk Chang, MD; Byung-Hee Hwang, MD; So-Yeon Choi, MD; Myung Ho Jeong, MD; Chang-Wook Nam, MD; Bon-Kwon Koo, MD; Seung Hwan Han, MD

Background: Differences in the impact of the 1- or 2-stent strategy in similar coronary bifurcation lesion conditions are not well understood. This study investigated the clinical outcomes and its predictors between 1 or 2 stents in propensity score-matched (PSM) complex bifurcation lesions.

Methods and Results: We analyzed the data of patients with bifurcation lesions, obtained from a multicenter registry of 2,648 patients (median follow up, 53 months). The patients were treated by second generation drug-eluting stents (DESs). The primary outcome was target lesion failure (TLF), composite of cardiac death, target vessel myocardial infarction (TVMI), and ischemia-driven target lesion revascularization (TLR). PSM was performed to balance baseline clinical and angiographic discrepancies between 1 and 2 stents. After PSM (N=333 from each group), the 2-stent group had more TLRs (hazard ratio [HR] 3.14, 95% confidence interval [CI] 1.42–6.97, P=0.005) and fewer hard endpoints (composite of cardiac death and TVMI; HR 0.44, 95% CI 0.19–1.01, P=0.054), which resulted in a similar TLF rate (HR 1.40, 95% CI 0.83–2.37, P=0.209) compared to the 1-stent group. Compared with 1-stent, the 2-stent technique was more frequently associated with less TLF in the presence of main vessel ($p_{interaction}$=0.008) and side branch calcification ($p_{interaction}$=0.010).

Conclusions: The 2-stent strategy should be considered to reduce hard clinical endpoints in complex bifurcation lesions, particularly those with calcifications.

Key Words: 1-stent; 2-stent; Bifurcation lesion; Complex lesion; Predictors

The optimal stenting technique between the 1- or 2-stent strategy in coronary bifurcation lesions is still controversial, especially in complex bifurcation lesions.[1] Operators generally implement the 2-stent technique in patients with more complex lesions, such as lesions with true bifurcation, severe side branch (SB) diameter stenosis (DS), larger SB reference diameter (RD), or greater SB lesion length.[2–4] Thus, lesions requiring a 2-stent strategy are intrinsically more complex and prone to procedural complications, which may lead to a poorer long-term outcome compared with the 1-stent strategy.[3–8]

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Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon (A.Y.J., M.K., P.C.O., S.Y.S., K.L., W.C.K., S.H.H.); Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (K.H.C., Y.B.S., H.-C.G.); Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul (H.-S.K., B.-K.K.); Division of Cardiology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon (W.J.C.); Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu (S.-H.H.); Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, Seoul (S.-W.R.); Division of Cardiology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do (I.-H.C.); Division of Cardiology, Department of Medicine, Chungnam National University Hospital, Daejeon (J.-O.J.); Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan (J.H.H.); Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju (J.Y.);
(Footnote continued the next page.)

Previous data, including randomized trials and registries, generally favor the 1-stent strategy.[3–8] Seminal randomized trials showed that simple stenting was associated with improved procedural success and composite clinical events.[4,5] These data, however, need to be interpreted with caution due to the following characteristics: (1) less severe SB branch profiles in the simple stenting group (1-stent/provisional);[4–7] (2) enrolled patients with small SBRDs (SBRD ≥2.0 mm for NORDIC I and the British Bifurcation Coronary [BBC] trial); (3) visual estimations used for evaluating lesion characteristics;[4–7] and (4) operator selection bias resulting in less severe angiographic lesions allocated to the 1-stent group in registries.[3,8] Such issues indicate that previous studies may be confounded by the enrollment of patients intrinsically advantageous to the simple stenting strategy. Additionally, these data have not evaluated patients for second generation drug-eluting stents (DESs) or predictors in determining the outcomes.[4–7]

To minimize the confounding effect of baseline angiographic characteristics favorable to the 1-stent strategy, we performed propensity score matching (PSM). In this study, we comparatively analyzed the outcomes and its predictors between the 1- and 2-stent groups treated with second generation DESs, after matching baseline clinical and angiographic lesion characteristics using large real-world, multicenter registry data.

Methods

Study Design and Patients

The COBIS (Coronary Bifurcation Stenting) III registry is a retrospective, multicenter, observational, and real-world registry that consecutively enrolled patients with bifurcation lesions who underwent percutaneous coronary intervention (PCI) using a second generation DES (Clinicaltrials.gov, NCT03068494).[9] A total of 2,648 patients were consecutively enrolled across 21 centers in the Republic of Korea between January 2010 and December 2014. The inclusion and exclusion criteria were as described previously.[9] This registry was supported by the Korean Bifurcation Club and the Korean Society of Interventional Cardiology. Written informed consent was waived by each institutional review board due to the retrospective nature of the study. The current study was approved by institutional review boards (IRBs) from each participating centers, including the IRB of our own institute (Gachon University Gil Medical Center; IRB approval number: GBIRB2017-070).

Procedures, Data Collection, and Quantitative Coronary Angiography (QCA) Analysis

Patient data including demographics, medication, laboratory data, angiographic characteristics, and procedural specifics were collected into a web-based reporting system. Clinical outcomes were obtained via medical records. Patients lost during follow up were interviewed via telephone.

All angiographic data were reviewed and quantitatively analyzed by the angiographic core laboratory (Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Republic of Korea). A dedicated automated edge-detection system (Centricity CA 1000; GE, Waukesha, WI, USA) was used for QCA analysis. Bifurcation lesions were categorized using the Medina classification. All lesions were divided into 3 segments for QCA analysis: proximal main vessel (MV), distal MV, and SB.[10] True bifurcation lesions were defined as lesions with Medina classification type 1.1.1, 1.0.1, and 0.1.1. Angiographic parameters such as the bifurcation angle (defined as the angle between the distal MV and the SB at its origin using the angiographic projection with the widest separation of the 2 branches), minimum lumen diameter (MLD), RD, lesion length, percent DS, and presence of coronary artery calcification (CAC) for each vessel were evaluated at both pre- and post-procedure. CAC was defined as moderate or severe CAC, which was identified as readily apparent radiopacities within the vascular wall during the cardiac cycle or without cardiac motion, before contrast injection at the site of the stenosis.[11] The implementation of a proximal optimization technique (POT) before and/or after SB ballooning was regarded as positive for the variable POT.

Definition of Study Endpoints

The 1- and 2-stent groups were defined according to the final number of stents implanted in the bifurcation lesions. The primary endpoint was target lesion failure (TLF), which was defined as a composite of cardiac death, target vessel myocardial infarction (TVMI), and ischemia-driven target lesion revascularization (TLR). Secondary endpoints included the individual components of the primary endpoint, all-cause death, spontaneous myocardial infarction (MI), target vessel revascularization (TVR), and stent thrombosis. All clinical events were verified by an independent clinical event adjudicating committee of experts in interventional cardiology who had not participated in patient enrollment.

Deaths were regarded to be of cardiac origin, unless there was definite evidence of non-cardiac cause. Spontaneous

Division of Cardiology, Department of Internal Medicine, Korea University Anam Hospital, Seoul (S.J.H.); Division of Cardiology, Department of Internal Medicine, Yeungnam University Medical Center, Daegu (J.-S.P.); Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul (M.-K.H.); Division of Cardiology, Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang (J.-H.D.); Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan (K.S.C.); Division of Cardiology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Goyang (D.-I.K.); Division of Cardiology, Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju (S.Y.L.); Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul (K.C.); Division of Cardiology, Department of Internal Medicine, St. Paul's Hospital, The Catholic University of Korea, Seoul (B.-H.H.); Division of Cardiology, Department of Internal Medicine, Ajou University Hospital, Suwon (S.-Y.C.); Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Gwangju (M.H.J.); and Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegoo (C.-W.N.), Republic of Korea

Mailing address: Seung Hwan Han, MD, Division of Cardiology, Department of Internal Medicine, Gachon University Gil Hospital, 21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Republic of Korea. E-mail: shhan@gilhospital.com; heartist@gmail.com

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Table 1. Demographic Data of the Pre- and Post-Matched Population

	Pre-matched			Post-PSM matched			
	1-stent (N=2,194)	2-stent (N=454)	P value	1-stent (N=333)	2-stent (N=333)	P value	SMD
Demographic data							
Age (years)	63±11	65±12	0.006	64±10	64±11	0.704	0.029
Men	1,682 (76.7)	331 (72.9)	0.100	250 (75.1)	247 (74.2)	0.859	0.021
HTN	1,250 (57.0)	254 (55.9)	0.726	192 (57.7)	189 (56.8)	0.876	0.018
DM	729 (33.2)	176 (38.8)	0.027	124 (37.2)	125 (37.5)	1.000	0.006
Current smoker	679 (30.9)	119 (26.2)	0.052	95 (28.5)	98 (29.4)	0.864	0.02
Dyslipidemia	835 (38.1)	174 (38.3)	0.957	131 (39.3)	134 (40.2)	0.874	0.018
CKD	83 (3.8)	20 (4.4)	0.624	15 (4.5)	15 (4.5)	1.000	<0.001
Previous PCI	257 (11.7)	66 (14.5)	0.111	46 (13.8)	48 (14.4)	0.911	0.017
Previous MI	92 (4.2)	21 (4.6)	0.774	15 (4.5)	17 (5.1)	0.856	0.028
Previous stroke	150 (6.8)	27 (5.9)	0.557	23 (6.9)	19 (5.7)	0.632	0.049
Presented as ACS	1,344 (61.3)	275 (60.6)	0.826	200 (60.1)	201 (60.4)	1.000	0.006
Laboratory and echocardiographic data							
Creatinine (mg/dL)	1.1±1.2	1.2±1.3	0.254	1.2±1.5	1.1±1.1	0.578	0.043
LDL-C (mg/dL)	105±37	103±38	0.353	107±35	105±39	0.560	0.051
LVEF (%)	59±10	58±10	0.604	59±10	58±10	0.590	0.045
Discharge medication							
Aspirin	2,162 (98.5)	443 (97.6)	0.202	325 (97.6)	325 (97.6)	1.000	<0.001
P_2Y_{12} inhibitor	2,168 (98.8)	443 (97.6)	0.068				
Clopidogrel	2,045 (93.2)	416 (91.6)	0.274	312 (93.7)	309 (92.8)	0.758	0.036
Ticagrelor	63 (2.9)	16 (3.5)	0.553	13 (3.9)	11 (3.3)	0.835	0.032
Prasugrel	83 (3.8)	17 (3.7)	1.000	8 (2.4)	10 (3.0)	0.811	0.037

Data are expressed as mean±standard deviation or n (%). ACS, acute coronary syndrome; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PSM, propensity score matching; SMD, standardized mean difference.

MI was defined as an elevation of creatine kinase-myocardial band or 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 repeat PCI of the lesion within 5 mm of stent deployment.

Statistical Analysis

Continuous variables were compared between groups using the Student's t-test and are presented as mean±standard deviation. Categorical data were compared between groups using the Chi-squared test and are presented as numbers and relative frequencies. For all analyses, a 2-sided $P<0.05$ was considered statistically significant. For the evaluation of clinical outcomes between groups, we performed PSM to balance the different pre-procedural clinical and angiographic properties between the 1-stent and 2-stent groups. By definition of PSM, all procedural decisions and attributes that emerged after deciding the 1- or 2-stent strategy, such as POT, final kissing balloon inflation (FKB), or the use of intravascular ultrasound (IVUS), were not included in the matching process.[12] Statistical analyses were performed using R Statistical Software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). Patients were censored either at the time of the event or at 5 years (1,825 days).

Propensity scores for each group were calculated using logistic regression. Two groups were matched for 28 pre-procedural clinical or angiographic parameters, including age, sex, hypertension, diabetes mellitus, current smoking, dyslipidemia, chronic kidney disease (CKD), acute coronary syndrome (ACS), primary PCI, previous MI, previous PCI, left ventricular ejection fraction (LVEF), serum creatinine, low-density lipoprotein cholesterol, multi-vessel disease, left main (LM) bifurcation, bifurcation angle, true bifurcation, pre-procedural MVRD and SBRD, MV/SB DS, MV/SB lesion length, total occlusion of MV/SB, and CAC of MV/SB. Both groups were matched one-to-one with a caliper width of 0.1, using the nearest neighbor method. Longitudinal survival data with or without PSM were analyzed using Kaplan-Meier plots. Standardized mean difference (SMD) is the most conventionally used method to confirm whether matching is adequately balanced. A SMD of <0.1 after PSM is considered as adequately balanced between baseline covariates.

Predictor analysis for long-term clinical outcome was performed using a stepwise Cox proportional hazards regression model in all COBIS III patients, after adjusting for baseline clinical and angiographic lesion characteristics. Adjusted hazard ratios (HR_{adj}) and 95% confidence intervals (CI) after multivariable adjustment (baseline clinical and angiographic lesion characteristics) were calculated for each group. Covariates that were either statistically significant in the univariate Cox analysis or those with clinical relevance were included in the multivariable Cox analysis. Continuous variables included in the predictor analysis were dichotomized based on median values. The P value for interaction was calculated to determine

Table 2. Pre- and Post-Matched Angiographic Characteristics

	Pre-PSM			Post-PSM			
	1-stent (N=2,194)	2-stent (N=454)	P value	1-stent (N=333)	2-stent (N=333)	P value	SMD
Angiographic characteristics							
LM bifurcation	682 (31.1)	253 (55.7)	<0.001	144 (43.2)	151 (45.3)	0.640	0.042
Bifurcation angle (°)	71.2±21.9	72.2±21.9	0.381	71.1±22.5	71.5±21.8	0.833	0.016
MV CAC	393 (17.9)	141 (31.1)	<0.001	84 (25.2)	89 (26.7)	0.724	0.034
SB CAC	133 (6.1)	67 (14.8)	<0.001	34 (10.2)	37 (11.1)	0.802	0.029
Multi-vessel disease	1,302 (59.3)	345 (76.0)	<0.001	235 (70.6)	236 (70.9)	1.000	0.007
MV total occlusion	227 (10.3)	30 (6.6)	0.018	26 (7.8)	25 (7.5)	1.000	0.011
SB total occlusion	81 (3.7)	27 (5.9)	0.037	21 (6.3)	14 (4.2)	0.297	0.094
Location of bifurcation (%)			<0.001			0.002	0.299
LAD	1,037 (47.3)	171 (37.7)		134 (40.2)	156 (46.8)		
LCX	326 (14.9)	24 (5.3)		37 (11.1)	22 (6.6)		
LM	682 (31.1)	253 (55.7)		144 (43.2)	151 (45.3)		
RCA	149 (6.8)	6 (1.3)		18 (5.4)	4 (1.2)		
True bifurcation (Medina class type 1.1.1, 1.0.1, and 0.1.1), n (%)	897 (40.9)	358 (78.9)	<0.001	269 (80.8)	266 (79.9)	0.845	0.023
RD of MV (mm)	3.2±0.5	3.3±0.5	0.011	3.2±0.5	3.3±0.5	0.275	0.085
RD of SB (mm)	2.6±0.4	2.7±0.5	0.001	2.6±0.4	2.6±0.4	0.678	0.032
DS of MV (%)	74.5±14.0	69.3±17.6	<0.001	71.5±15.6	70.7±16.3	0.514	0.051
DS of SB (%)	39.6±26.3	66.7±18.9	<0.001	62.8±21.1	63.4±19.6	0.712	0.029
Lesion length of MV (mm)	18.8±10.1	17.0±11.5	0.002	18.0±9.1	18.0±11.9	0.977	0.002
Lesion length of SB (mm)	4.1±5.9	10.7±7.7	<0.001	9.5±7.1	9.5±7.2	0.933	0.007
MLD of MV (mm)	0.8±0.5	1.0±0.6	<0.001	0.9±0.5	1.0±0.6	0.349	0.073
MLD of SB (mm)	1.6±0.8	0.9±0.6	<0.001	1.0±0.7	1.0±0.6	0.681	0.032

Data are expressed as mean ± standard deviation or n (%). CAC, coronary artery calcification; DS, diameter stenosis; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; MLD, minimal lumen diameter; MV, main vessel; PSM, propensity score matching; RCA, right coronary artery; RD, reference diameter; SB, side branch; SMD, standardized mean difference.

whether there was a significant difference between the hazard ratio of the 1- and 2-stent group predictors.

Results

Baseline Characteristics

A total of 2,648 patients with bifurcation lesions were enrolled in the COBIS III registry. Of the total patients, 2,194 (82.9%) patients were treated with the 1-stent strategy whereas the remaining 454 (17.1%) patients were treated with 2 stents, based on the discretion of the operator. After matching, 333 patients were allocated to each group, among which all 28 baseline demographic/angiographic characteristics and discharge medications were balanced to a SMD of <0.1 (**Tables 1** and **2**). The study flowchart is shown in **Supplementary Figure**.

Angiographic Characteristics

Pre- and post-matched angiographic characteristics are presented in **Table 2**. In the pre-matched analysis, the 2-stent group had more lesions involving the LM vessel (55.7% vs. 31.1%, P<0.001). Additionally, patients treated with 2 stents had more true bifurcation lesions (78.9% vs. 40.9%, P<0.001), MV CAC (31.1% vs. 17.9%, P<0.001), SB CAC (14.8% vs. 6.1%, P<0.001), SB total occlusion (5.9% vs. 3.7%, P=0.037), and the presence of multi-vessel disease (76.0% vs. 59.3%, P<0.001), whereas MV total occlusions (10.3% vs. 6.6%, P=0.018) were more frequent in the 1-stent group. In the pre-matched QCA analysis, the 2-stent group had a significantly larger SBRD, RD of the MV, SBDS, DS of the MV, and MV/SB lesion length compared with the 1-stent group (**Table 2**). These angiographic discrepancies between the 1-stent and 2-stent groups were balanced after PSM (SMD <0.1 for all). After PSM, patients had more complex bifurcation lesions compared with pre-PSM. There were more MV CAC (26.0% vs. 20.2%), SB CAC (10.7% vs. 7.6%), multi-vessel diseases (70.7% vs. 62.2%), and true bifurcations (80.3% vs. 47.4%) than pre-PSM (P<0.05 for all).

Procedural Characteristics

Procedural characteristics and final angiographic results between the 1- and 2-stent groups before and after PSM showed significant differences (**Table 3**). Before PSM, 39.2% of patients received trans-radial intervention, and >50% of patients were guided by IVUS. In the 2-stent group, crush, t-stenting, culotte, and the kissing technique were performed in 53.7%, 27.5%, 6.8%, and 9.0%, respectively (**Table 3**). Detailed analysis on this notion was previously described.[13] POT or RePOT was performed in a similar proportion in the 1- (29.8%) and 2-stent groups (32.2%), respectively.

Table 3. Pre- and Post-Matched Procedural and Post-Procedural Characteristics

	Pre-PSM			Post-PSM		
	1-stent (N=2,194)	2-stent (N=454)	P value	1-stent (N=333)	2-stent (N=333)	P value
Procedural characteristics						
Transradial access	1,329 (60.6)	178 (39.2)	<0.001	207 (62.2)	116 (34.8)	<0.001
IVUS-guided	816 (37.2)	247 (54.4)	<0.001	130 (39.0)	170 (51.1)	0.002
NC Balloon for MV	380 (17.3)	135 (29.7)	<0.001	70 (21.0)	90 (27.0)	0.085
NC Balloon for SB	97 (4.4)	93 (20.5)	<0.001	20 (6.0)	59 (17.7)	<0.001
Final kissing balloon	391 (17.8)	398 (87.7)	<0.001	103 (30.9)	290 (87.1)	<0.001
POT or RePOT	654 (29.8)	146 (32.2)	0.349	114 (34.2)	110 (33.0)	0.806
NC balloon (in MV or SB)	390 (17.8)	144 (31.7)	<0.001	72 (21.6)	98 (29.4)	0.026
Stent technique (%)			<0.001			<0.001
1-stent	2,194 (100.0)	–		333 (100.0)	0 (0.0)	
Crush	–	244 (53.7)		0 (0.0)	177 (53.2)	
T-stenting	–	125 (27.5)		0 (0.0)	97 (29.1)	
Culotte	–	31 (6.8)		0 (0.0)	26 (7.8)	
Kissing	–	41 (9.0)		0 (0.0)	22 (6.6)	
Others	–	13 (2.9)		0 (0.0)	11 (3.3)	
Cumulative length of MV stents (mm)	28.3±13.2	31.3±15.3	<0.001	27.6±12.5	31.3±14.7	<0.001
Cumulative length of SB stents (mm)	–	21.3±8.7	–	–	20.3±7.8	–
Maximal diameter of MV stents (mm)	3.4±0.6	3.4±0.7	0.510	3.14±0.66	3.1±0.7	0.681
Maximal diameter of SB stents (mm)	–	2.8±0.4	–	–	2.8±0.4	–
Minimal diameter of MV stents (mm)	3.2±0.7	3.2±0.7	0.425	3.06±0.65	3.0±0.7	0.297
Minimal diameter of SB stents (mm)	–	2.7±0.7	–	–	2.7±0.7	–
MV occlusion during PCI	45 (2.1)	9 (2.0)	1.000	11 (3.3)	7 (2.1)	0.473
SB occlusion during PCI	82 (3.7)	11 (2.4)	0.213	27 (8.1)	3 (0.9)	<0.001
Post-procedural characteristics						
Post-RD of MV (mm)	3.3±0.5	3.4±0.5	<0.001	3.3±0.5	3.4±0.5	<0.001
Post-RD of SB (mm)	2.6±0.4	2.7±0.4	<0.001	2.6±0.4	2.7±0.4	<0.001
Post-MLD of MV (mm)	2.8±0.5	2.8±0.4	0.170	2.8±0.5	2.8±0.4	0.170
Post-MLD of SB (mm)	1.6±0.8	2.4±0.5	<0.001	1.6±0.8	2.4±0.5	<0.001
Post-DS of MV (%)	15.4±10.1	16.6±9.0	0.009	15.4±10.1	16.6±9.0	0.009
Post-DS of SB (%)	41.3±25.4	11.1±11.6	<0.001	41.3±25.4	11.1±11.6	<0.001

Data are expressed as mean±standard deviation or n (%). –, not applied; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; POT, proximal optimization technique. Other abbreviations as in Tables 1,2.

Table 4. Comparison of Long-Term Clinical Outcomes Between the 1- and 2-Stent Groups

	Pre-PSM				Post-PSM			
	1-stent (N=2,194)	2-stent (N=454)	HR (95% CI)	Log-rank P	1-stent (N=333)	2-stent (N=333)	HR (95% CI)	Log-rank P
Primary endpoint								
TLF	151 (6.9)	51 (11.2)	1.77 (1.29–2.43)	<0.001	24 (7.2)	33 (9.9)	1.40 (0.83–2.37)	0.209
Secondary endpoint								
Cardiac death	66 (3.0)	11 (2.4)	0.83 (0.42–1.63)	0.494	13 (3.9)	6 (1.8)	0.47 (0.18–1.23)	0.122
TVMI	21 (1.0)	6 (1.3)	1.43 (0.58–3.55)	0.437	3 (0.9)	4 (1.2)	1.29 (0.29–5.78)	0.737
TLR	78 (3.6)	36 (7.9)	2.87 (1.94–4.25)	<0.001	8 (2.4)	25 (7.5)	3.14 (1.42–6.97)	0.005
TVR	124 (5.7)	51 (11.2)	2.14 (1.54–2.96)	<0.001	17 (5.1)	33 (9.9)	1.95 (1.09–3.51)	0.025
ST	22 (1.0)	6 (1.3)	1.36 (0.55–3.36)	0.503	4 (1.2)	3 (0.9)	0.79 (0.17–3.53)	0.752
Cardiac death +TVMI	84 (3.8)	15 (3.3)	0.96 (0.55–1.67)	0.895	20 (6.0)	10 (3.0)	0.44 (0.19–1.01)	0.054
Cardiac death +TVMI+ST	89 (4.1)	17 (3.7)	0.97 (0.57–1.65)	0.901	21 (6.3)	11 (3.3)	0.50 (0.23–1.11)	0.087

Data are expressed as n (%). CI, confidence interval; HR, hazard ratio; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction; TVR, target vessel revascularization; ST, stent thrombosis.

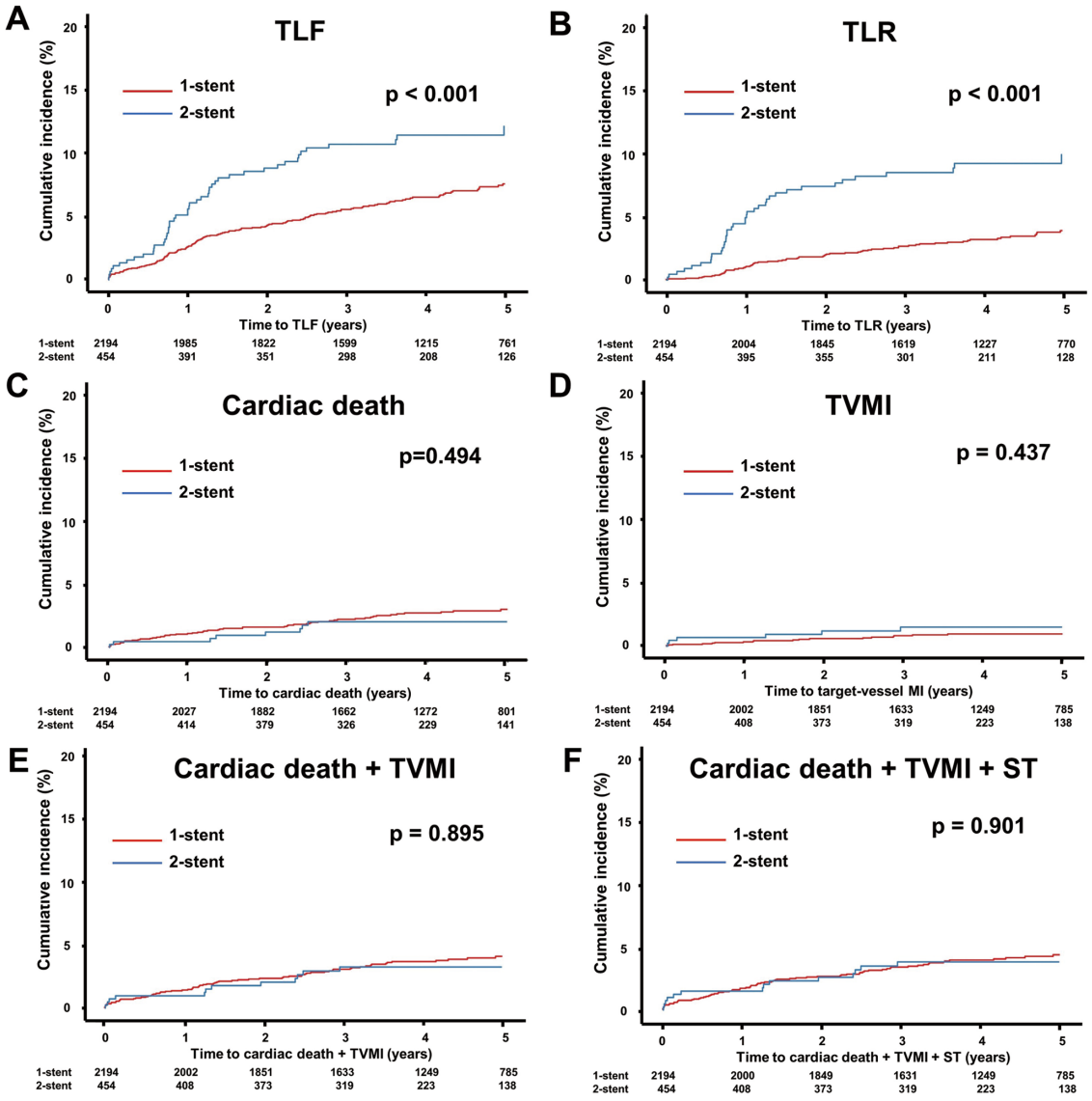

Figure 1. Comparison of 5-year clinical outcomes between the 1-stent and 2-stent strategies in the pre-matched population. Kaplan-Meier curves comparing the risk of TLF (**A**), TLR (**B**), cardiac death (**C**), and TVMI (**D**), cardiac death+TVMI (**E**), and cardiac death+TVMI+ST (**F**). ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction.

In the post-matched analysis, the 1-stent group had more radial access, and a higher post-procedure DS of the SB. The 2-stent group included more IVUS-guided procedures as well as use of a non-compliant (NC) balloon of the MV and SB and FKB procedures. The 2-stent group had a longer cumulative MV stent length, post-procedural RD of the MV/SB, MLD of the SB, more angiographic success in the SB, but greater DS of the MV compared with the 1-stent group.

Long-Term Clinical Outcomes Between the 1- and 2-Stent Strategies

In the pre-matched analysis, the 2-stent group had significantly more TLF (11.2% vs. 6.9%, HR 1.77, 95% CI 1.29–2.43, log-rank P<0.001) with more TLR (7.9% vs. 3.6%, HR 2.87, 95% CI 1.94–4.25, log-rank P<0.001) (**Table 4**, **Figure 1**). After PSM, the 2-stent group had more TLRs (7.5% vs. 2.4%, HR 3.14, 95% CI 1.42–6.97, log-rank P=0.005), but had similar rates of TLF (9.9% vs. 7.2%, HR 1.40, 95% CI 0.83–2.37, log-rank P=0.209) with numerically less cardiac deaths (1.8% vs. 3.9%, HR 0.47, 95% CI 0.18–1.23, log-rank P=0.122) and a composite of hard endpoints, such as cardiac death+TVMI (3.0% vs. 6.0%, HR 0.44, 95% CI 0.19–1.01, log-rank P=0.054) and cardiac death+TVMI+ST (3.3% vs. 6.3%, HR 0.50, 95% CI 0.23–1.11, log-rank P=0.087) compared to the 1-stent group (**Table 4**, **Figure 2**).

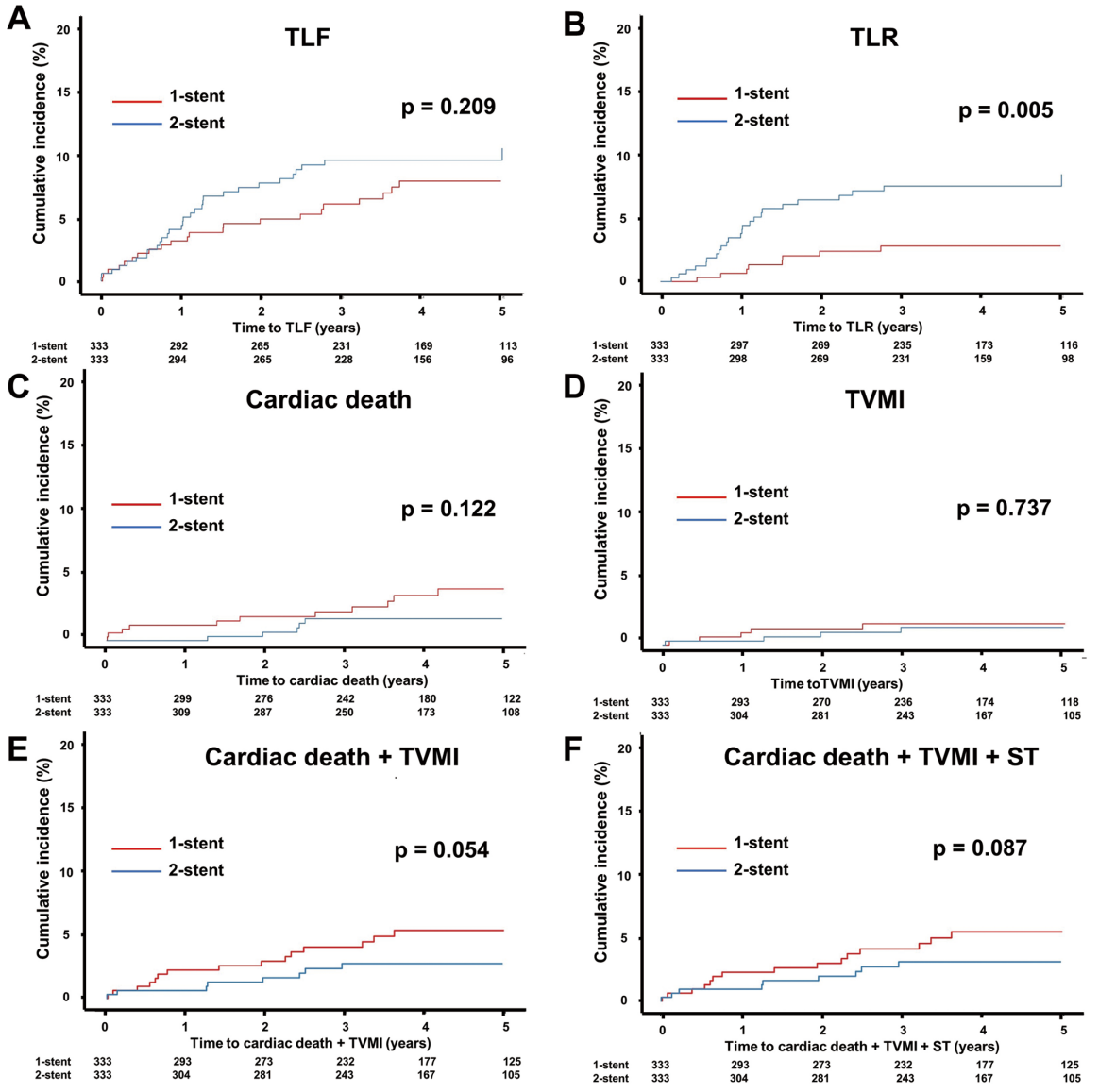

Figure 2. Comparison of 5-year clinical outcomes between the 1-stent and 2-stent strategies in the post-matched population. Kaplan-Meier curves comparing the risk of TLF (**A**), TLR (**B**), cardiac death (**C**), and target-vessel MI (**D**), cardiac death+TVMI (**E**), and cardiac death+TVMI+ST (**F**). ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction.

Predictors of TLF in the 1- and 2-Stent Strategies

In the multivariate predictor analysis adjusted for baseline clinical and angiographic lesion characteristics, CKD (HR_{adj} 1.96, 95% CI 1.05–3.66, P=0.035), LM lesions (HR_{adj} 1.68, 95% CI 1.14–2.48, P=0.008), and SB CAC (HR_{adj} 1.87, 95% CI 1.44–3.08, P=0.013), LVEF ≤40% (HR_{adj} 2.42, 95% CI, 1.49–3.95, P<0.001) were independent ominous predictors for long-term clinical outcomes in all COBIS III patients (**Figure 3**, **Supplementary Table**).

The presence of CKD (HR_{adj} 2.28, 95% CI 1.19–4.36, P=0.013), SB CAC (HR_{adj} 2.47, 95% CI 1.40–4.33, P=0.002), and LVEF ≤40% (HR_{adj} 2.21, 95% CI 1.26–3.87, P=0.005) were associated with poor outcomes in the 1-stent group. In the 2-stent group, NC balloon use in the MV or SB (HR_{adj} 0.44, 95% CI 0.20–0.98, P=0.045) was a favorable predictor, whereas LM lesions (HR_{adj} 6.92, 95% CI 2.48–19.32, P<0.001) and LVEF ≤40% (HR_{adj} 5.69, 95% CI 1.85–17.45, P<0.001) were predictive of poor outcomes. There was significant interaction between stenting strategy and the presence of MV or SB CAC for covariate-adjusted risks of TLF ($p_{interaction}$<0.05), which was suggestive of a lower chance of TLF when the 2-stent strategy was selected in the presence of MV or SB CAC compared with the 1-stent strategy. There were no interactions between the presence of SB lesion length ≥10 mm or complex lesions and the 1-/2-stent strategy (**Figure 3**, **Supplementary Table**).

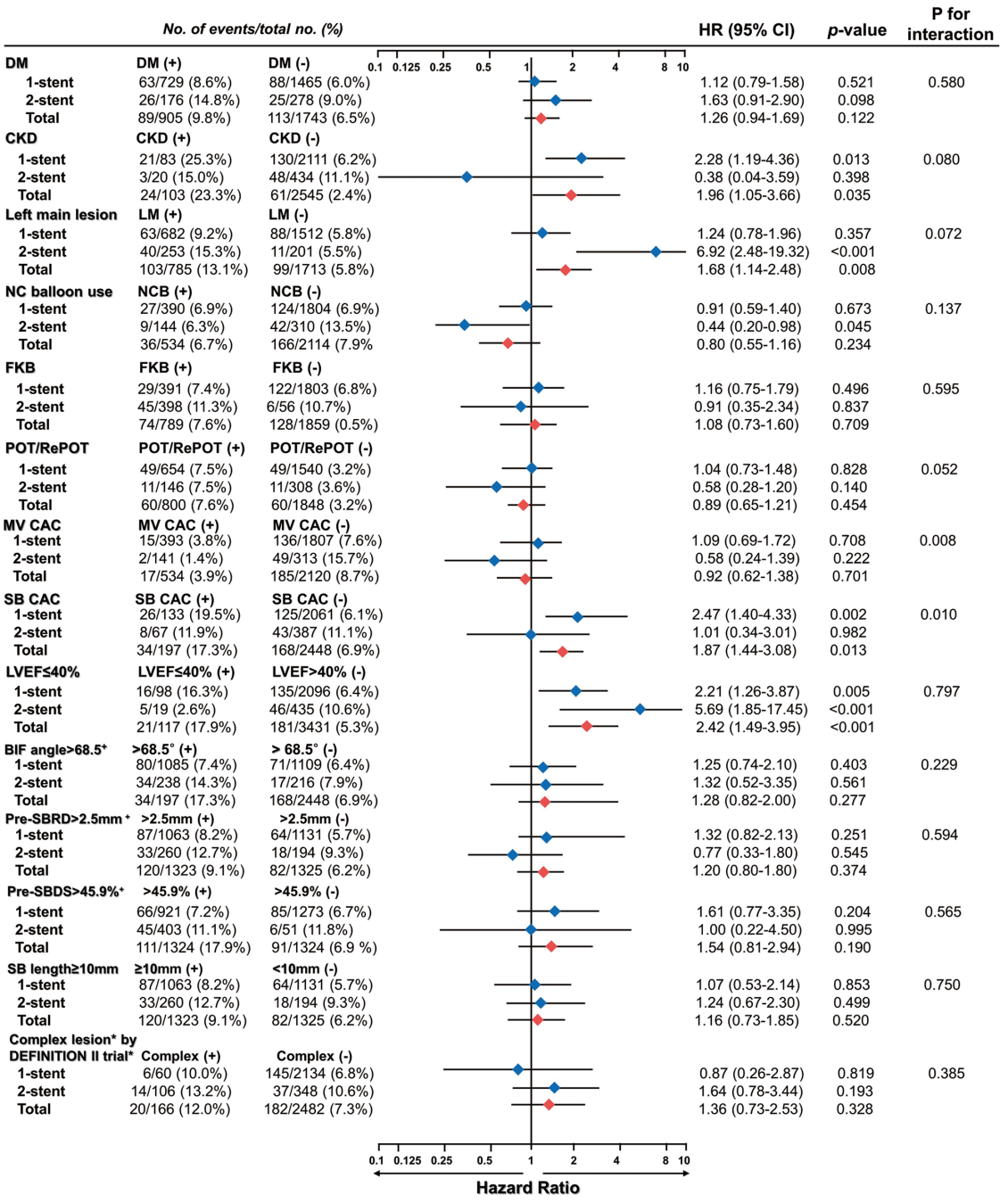

Figure 3. Multivariate cox regression predictor analysis for target lesion failure (TLF). The adjusted hazards ratios (HR) and 95% confidence interval (CI) of each stenting strategy is shown. The P-interaction between stenting strategies is demonstrated. ⁺Subgroup analysis was based on the median values of bifurcation angle, pre-SBRD, and pre-SBDS. *Complex bifurcation lesions were defined as any 1 major criterion (SB lesion length ≥10 mm with diameter stenosis of SB≥70% for distal LM bifurcation lesions or diameter stenosis of SB≥90% for non-LM bifurcation lesions) plus any 2 minor criteria (moderate-to-severe calcification, multiple lesions, bifurcation angle <45 or >70, MV RVD <2.5 mm, thrombus-containing lesions, or MV lesion length ≥25 mm) on visual estimation. This definition was adopted from the DEFINITION II trial.[14] Predictors were adjusted for baseline clinical parameters (age, sex, hypertension, diabetes mellitus, current smoking, dyslipidemia, CKD, ACS, primary PCI, previous MI, previous PCI, LVEF <40%, creatinine, P_2Y_{12} inhibitors) and angiographic parameters (multi-vessel disease, left main (LM) lesion, bifurcation angle, true bifurcation, RD of MV/SB, DS of MV/SB, lesion length of MV/SB, total occlusion of MV/SB, and CAC of MV/SB). ACS, acute coronary syndrome; BIF, bifurcation; CAC, coronary artery calcification; CI, confidence interval; CKD, chronic kidney disease; DES, drug-eluting stent; DM, diabetes mellitus; DS, diameter stenosis; FKB, final kissing balloon; HR, hazard ratio; LVEF, left ventricular ejection fraction; MV, main vessel; MI, myocardial infarction; NC, non-compliant; NCB, non-compliant balloon; PCI, percutaneous coronary intervention; POT, proximal optimization technique; RD, reference diameter; SB, side branch.

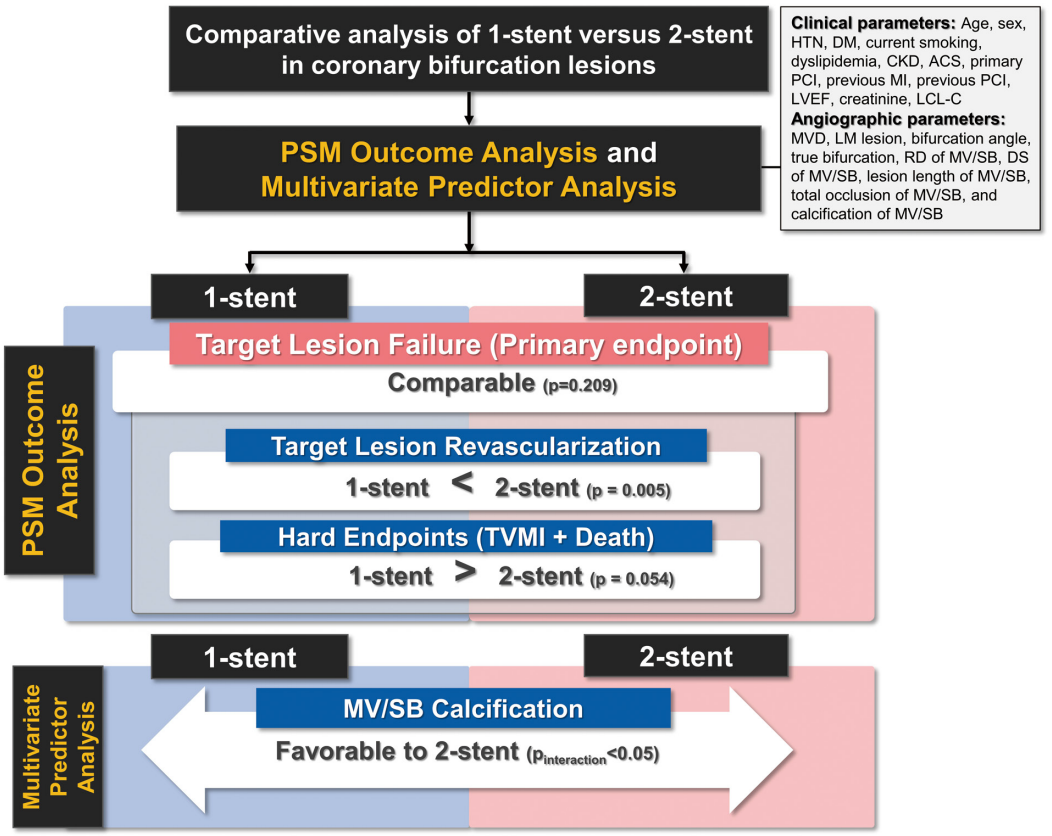

Figure 4. Outcomes and predictors between the 1- and 2-stent strategy in matched coronary bifurcation lesions. ACS, acute coronary syndrome; CAC, coronary artery calcification; CKD, chronic kidney disease; DES, drug-eluting stent; DS, diameter stenosis; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MV, main vessel; MVD, multi-vessel disease; NC, non-compliant; PCI, percutaneous coronary intervention; PSM, propensity score matching; RD, reference diameter; SB, side branch.

Complex lesions were defined based on the DEFINITION II study.[14]

Discussion

In this study, we comparatively analyzed the long-term clinical outcomes and its predictors of the 1- and 2-stent strategy in complex bifurcation lesions after PSM. As all complex lesions requiring 2 stents were matched one-to-one to the 1-stent group, we regarded all matched lesions as complex bifurcation lesions. Novel findings of the current analysis were as follows: (1) TLF rate in the 2-stent strategy was similar compared with the 1-stent strategy, with more TLR and numerically few cardiac deaths and the composite of hard endpoints (cardiac death+TVMI); and (2) the 2-stent strategy was associated with a significantly lower chance of TLF in the presence of MV or SB CAC, compared to the 1-stent group (**Figure 4**).

Previous randomized trials demonstrated provisional stenting strategy as the optimal technique in bifurcation lesions.[4–7] However, these results are concerning for several reasons. First, different baseline bifurcation lesion characteristics between the 1- and 2-stent groups were present in the enrolled patients. Second, many patients had a small SB. Third, visual estimation used to measure lesion characteristics was inaccurate. Fourth, only first-generation DESs were used.[4–7] Understanding such limitation is crucial because the enrolled patients in previous studies may be intrinsically favorable to the 1-stent strategy.[6,7]

After PSM, the angiographic properties in the 1-stent group became more complex, as demonstrated by the significantly higher rate of MV and SB CAC, true bifurcation (41% increased to 81%), longer SB lesion lengths (4.1 increased to 9.5 mm), and a more severe SBDS (40% increased to 63%) compared to pre-PSM. Therefore, we attempted to compare the performance of 1-stent vs. 2-stent in complex lesions that generally require a 2-stent strategy after PSM. In this context, the trend of more cardiac deaths and TVMI in the 1-stent strategy group may be because the post-PSM population receive only 1 stent to a complex lesion (more true bifurcations, more severe CAC and DS in the SBs together with longer SB lesions) that potentially requires an additional stent to the SB. Our results indicates that the 2-stent technique may perform as well as the 1-stent technique in complex bifurcation lesions, if not better. However, this should not be construed as 2 stents being superior to 1 stent in non-complex lesions.

The SB lesion length may be a factor influencing out-

comes of stenting strategy in bifurcation lesions. Recently, the DEFINITION II trial investigating complex bifurcation lesions showed that the planned 2-stent strategy (n=328) using the double kissing crush technique or culotte stenting technique reduced the incidence of 1-year TLF, which was largely driven by less TVMI compared to the provisional group (n=325). The SB lesion length was approximately 14 mm in this study.[14] The DK CRUSH V (Double Kissing and Double Crush Versus Provisional T Stenting Technique for the Treatment of Unprotected Distal Left Main True Bifurcation Lesions: A Randomized, International, Multi-Center Clinical Trial) study also showed an advantage of the 2-stent strategy (double kissing crush or culotte technique) over provisional stenting in unprotected LM disease. The SB lesion length was approximately 17 mm and the median SYNTAX score was 31.[15] Meanwhile, the recently published EBC MAIN (European bifurcation club left main) study demonstrated similar results between the provisional and 2-stent strategy in LM bifurcation lesions.[16] The discrepancy of findings between the EBC MAIN and the DEFINITION II and DK CRUSH V trials may be explained by several reasons. First, the SB lesion length was shorter than the previous 2 trials (7 mm in EBC MAIN vs. 14 mm in DEFINITION II and 17 mm in DK CRUSH II). Second, the SB lesion length was significantly shorter in the provisional stenting group (5.8 mm vs. 7.9 mm) in the EBC MAIN study, which was intrinsically favorable to the provisional stenting group. The current cohort was in the gray zone between the previous 3 trials in terms of SB lesion length; the post-PSM SB lesion length of our cohort (9.5 mm) was shorter than that in the DEFINITION II and DK CRUSH V trials and longer than that in the EBC MAIN trial. Bifurcation lesions with short SB lesions may have a small plaque burden in the SB, leading to a low event rate. Thus, the benefit of an additional stent to the short SB lesion may be smaller than that for long SB lesions. Although we failed to demonstrate a significant P interaction between SB lesion length and the 1-/2- stenting strategy, we believe that the sample size in the 2-stent group with SB lesion length ≥10 mm was significantly underpowered to derive statistical meaning. For instance, there were only 260 (9.8%) and 106 patients (4.0%) among the total 2,648 patients who had 2 stents in the presence of SB lesion length ≥10 mm and complex lesions, respectively (**Figure 3**). Future analysis of real-world data in this regard with sufficient power is warranted.

The presence of CAC increases the likelihood of procedural failure and complication after coronary intervention, as well as an increased risk of SB occlusion.[11,17] DES implantation improves acute and long-term event-free survival in calcified lesions compared to the bare metal stent and balloon angioplasty,[11,17] suggesting that inserting a second stent to the SB with calcified lesions may be necessary. Our data also demonstrates that a 2-stent strategy with second generation DES reduced the catastrophic hard endpoint (cardiac death+TVMI) in complex calcified bifurcation lesions. There were more stent optimizations conducted in the 2-stent group, including POT/rePOT, FKB, and NC balloon use, which is especially important in bifurcation lesions with a high burden of CAC. The risk of SB dissection or rupture associated with FKB and NC balloon in the 1-stent group may hamper SB optimization, which may subsequently translate to a higher hard endpoint rate in the 1-stent group.

The procedural characteristics were not included in the covariates of our PSM and multivariate predictor analysis, because the original hypothesis was to investigate the performance of the 2-stent technique compared with the 1-stent technique under similar clinical and angiographic circumstances. Moreover, PSM by definition does not include actions following the decision of treatment strategy, such as POT, FKB, NC balloon, or the use of IVUS.[12] A previous study by Choi et al of the COBIS III registry showed that the 1-stent strategy was associated with better outcomes,[9] although the analysis centered more on adjusting outcomes with procedural characteristics and not for the angiographic features such as vessel RD, bifurcation angle, or CAC profiles. Our data therefore indicate that the previously demonstrated poorer outcomes associated with the 2-stent technique may potentially be related to more severe patients and lesions being intrinsically suitable for the 2-stent strategy, but not the inferiority of the 1-stent technique itself.

The study has the limitations intrinsic to studies of a retrospective nature. As the current investigation was non-randomized and observational, we believe that there may have been confounding factors behind the 1- and 2-stent groups. Although we performed PSM to minimize this effect, we believe that there might be unmeasurable confounding factors that remain. The results in our analysis can also be misleading to non-complex bifurcation lesions that fundamentally do not require 2 stents. As patients with less severe SB characteristics were intrinsically excluded (1,861 out of 2,194 in the 1-stent group) during the PSM process, our results showed that the 2-stent strategy can be a legitimate option in bifurcation lesions with hostile SBs. In the current study, the presence of MV or SB CAC was validated by an independent angiographic core laboratory to minimize bias. However, further investigations using intravascular imaging are necessary to confirm our findings. As previously mentioned, IVUS imaging and NC balloon for SB and/or FKB were not included in the multivariable Cox analysis because the need for these procedures is usually decided after the selection of a 1-/2-stent strategy. In addition, the 2-stent strategy intrinsically requires a greater number of such procedures (IVUS, NC balloon, and FKB). Additionally, we were not able to include the effect of drug-coated balloons in this study because there were no cases using the device. Finally, we were not able to include LM and non-LM subgroup outcome analysis because the study was severely underpowered for deriving meaningful results after PSM.

Conclusions

The 2-stent strategy may be strongly considered for reducing catastrophic hard endpoints in complex bifurcation lesions, especially in those with significant CAC.

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Disclosures

H.-S.K. is a member of *Circulation Journal*'s Editorial Team.

IRB Information

This study was approved by the Gachon University Gil Medical Center: GBIRB2017-070. Trial Registration: ClinicalTrials.gov, NCT03068494.

Data Availability

Data are not available due to patient health information privacy.

References

1. Sawaya FJ, Lefevre T, Chevalier B, Garot P, Hovasse T, Morice MC, et al. Contemporary approach to coronary bifurcation lesion treatment. *JACC Cardiovasc Interv* 2016; **9:** 1861–1878.
2. Burzotta F, Lassen JF, Lefevre T, Banning AP, Chatzizisis YS, Johnson TW, et al. Percutaneous coronary intervention for bifurcation coronary lesions: The 15(th) consensus document from the European Bifurcation Club. *EuroIntervention* 2021; **16:** 1307–1317.
3. Palmerini T, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, et al. Impact of bifurcation technique on 2-year clinical outcomes in 773 patients with distal unprotected left main coronary artery stenosis treated with drug-eluting stents. *Circ Cardiovasc Interv* 2008; **1:** 185–192.
4. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: The Nordic bifurcation study. *Circulation* 2006; **114:** 1955–1961.
5. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: The British Bifurcation Coronary Study: Old, new, and evolving strategies. *Circulation* 2010; **121:** 1235–1243.
6. Behan MW, Holm NR, Curzen NP, Erglis A, Stables RH, de Belder AJ, et al. Simple or complex stenting for bifurcation coronary lesions: A patient-level pooled-analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study. *Circ Cardiovasc Interv* 2011; **4:** 57–64.
7. Behan MW, Holm NR, de Belder AJ, Cockburn J, Erglis A, Curzen NP, et al. Coronary bifurcation lesions treated with simple or complex stenting: 5-year survival from patient-level pooled analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study. *Eur Heart J* 2016; **37:** 1923–1928.
8. Kandzari DE, Gershlick AH, Serruys PW, Leon MB, Morice MC, Simonton CA, et al. Outcomes among patients undergoing distal left main percutaneous coronary intervention. *Circ Cardiovasc Interv* 2018; **11:** e007007.
9. Choi KH, Song YB, Lee JM, Park TK, Yang JH, Hahn JY, et al. Prognostic effects of treatment strategies for left main versus non-left main bifurcation percutaneous coronary intervention with current-generation drug-eluting stent. *Circ Cardiovasc Interv* 2020; **13:** e008543.
10. Gwon HC. Understanding the coronary bifurcation stenting. *Korean Circ J* 2018; **48:** 481–491.
11. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Genereux P. Coronary artery calcification: Pathogenesis and Prognostic Implications. *J Am Coll Cardiol* 2014; **63:** 1703–1714.
12. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, et al. Comparison of propensity score methods and covariate adjustment. *J Am Coll Cardiol* 2017; **69:** 345–357.
13. Kang J, Han JK, Yang HM, Park KW, Kang HJ, Gwon HC, et al. 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. *Circ J* 2021; **85:** 1944–1955.
14. Zhang JJ, Ye F, Xu K, Kan J, Tao L, Santoso T, et al. Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: The DEFINITION II trial. *Eur Heart J* 2020; **41:** 2523–2536.
15. Chen SL, Zhang JJ, Han Y, Kan J, Chen L, Qiu C, et al. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V randomized trial. *J Am Coll Cardiol* 2017; **70:** 2605–2617.
16. Hildick-Smith D, Egred M, Banning A, Brunel P, Ferenc M, Hovasse T, et al. The European bifurcation club Left Main Coronary Stent study: A randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). *Eur Heart J* 2021; **42:** 3829–3839.
17. Perfetti M, Fulgenzi F, Radico F, Toro A, Procopio A, Maddestra N, et al. Calcific lesion preparation for coronary bifurcation stenting. *Cardiol J* 2019; **26:** 429–437.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-22-0163