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Long-Term Clinical Outcomes of Final Kissing Ballooning in Coronary Bifurcation Lesions Treated With the 1-Stent Technique

Results From the COBIS II Registry (Korean Coronary Bifurcation Stenting Registry)

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ABSTRACT

OBJECTIVES This study investigated the impact of final kissing ballooning (FKB) after main vessel (MV) stenting on outcomes in patients with coronary bifurcation lesions after application of the 1-stent technique.

BACKGROUND Although FKB has been established as the standard method for bifurcation lesions treated with a 2-stent strategy, its efficacy in a 1-stent approach is highly controversial.

METHODS This study enrolled 1,901 patients with a bifurcation lesion with a side branch diameter ≥2.3 mm, treated solely with the 1-stent technique using a drug-eluting stent from 18 centers in Korea between January 1, 2003 and December 31, 2009. The primary outcome was major adverse cardiac events (MACE)—cardiac death, myocardial infarction, or target lesion revascularization. Propensity score-matching analysis was also performed.

RESULTS FKB was performed in 620 patients and the post minimal lumen diameter of the MV and side branch was larger in the FKB group than in the non-FKB group. During follow-up (median 36 months), the incidence of MACE (adjusted hazard ratio [HR]: 0.68, 95% confidence interval [CI]: 0.46 to 0.99; p = 0.048) was lower in the FKB group than the non-FKB group. After propensity score matching (545 pairs), the FKB group had a lower incidence of MACE (adjusted HR: 0.50, 95% CI: 0.30 to 0.85; p = 0.01), and target lesion revascularization in the MV (adjusted HR: 0.51, 95% CI: 0.28 to 0.93; p = 0.03) and both vessels (adjusted HR: 0.47, 95% CI: 0.25 to 0.90; p = 0.02) than in the non-FKB group.

CONCLUSIONS In coronary bifurcation lesions, we demonstrated that the 1-stent technique with FKB was associated with a favorable long-term clinical outcome, mainly driven by the reduction of target lesion revascularization in the MV or both vessels as a result of an increase in minimal lumen diameter. (Korean Coronary Bifurcation Stenting Registry II [COBIS II]: NCT01642992) (J Am Coll Cardiol Intv 2015;8:1297–307) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

FKB = final kissing ballooning

HR = hazard ratio

MACE = major adverse cardiac event(s)

MI = myocardial infarction

MLD = minimal luminal diameter

MV = main vessel

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

RD = reference diameter

SB = side branch

TLR = target lesion revascularization

Provisional stenting of the side branch (SB) after main vessel (MV) stenting is now a standard approach to coronary bifurcation lesions because the elective 2-stent technique offers few advantages over the 1-stent technique (1–3). In addition, the 2-stent technique has been associated with increased use of contrast, longer procedure time, and higher rates of procedure-related myocardial infarction (1,4). Although final kissing ballooning (FKB) is currently considered mandatory in 2-stent techniques such as culotte and crush approaches (5,6), the effects of FKB on clinical and angiographic outcomes after only MV stenting are controversial (7,8). Randomized trials have found no short-term or long-term benefits of FKB (2,9), and a retrospective study reported harmful effects of FKB with the 1-stent technique (7). However, most relevant studies are limited by small sample size, an inadequate short-term follow-up period, exclusion of left main bifurcation lesions, or a small SB. Therefore, we investigated whether routine FKB after successful stenting of the MV would improve long-term outcomes in patients with coronary bifurcation lesions, including left main bifurcation lesions, in a large-scale, multicenter registry.

METHODS

STUDY POPULATION. The COBIS II (Korean Coronary Bifurcation Stenting Registry) is a retrospective multicenter registry of individuals with coronary bifurcation lesions who underwent percutaneous coronary intervention (PCI) with a drug-eluting stent. We enrolled patients from 18 major coronary intervention centers in Korea between January 1, 2003 and December 31, 2009. Only patients with a coronary bifurcation lesion treated solely with drug-eluting stents, an MV diameter ≥2.5 mm, and an SB diameter ≥2.3 mm confirmed by core lab quantitative coronary angiography (QCA) analysis were included. Patients with cardiogenic shock, any experience with cardiopulmonary resuscitation, or protected left main disease were excluded. This registry was sponsored by the Korean Society of Interventional Cardiology. The local institutional review board at each hospital approved this study and waived the requirement for informed consent in all enrolled patients.

To assess the effects of FKB after MV stenting on clinical outcomes in patients undergoing the provisional approach, we selected patients treated with the 1-stent technique for 1 bifurcation lesion included in the COBIS II database (n = 2,127). Experienced investigators (H.C.G. and J.H.Y.) confirmed whether to do FKB by reviewing all patient angiograms. We excluded cases with total occlusion in the SB before MV stenting (n = 88), a bail-out SB intervention for Thrombolysis In Myocardial Infarction (TIMI) flow grade <3 (n = 134), or a dissection classified as type B or worse (n = 4) in the SB after MV stenting. Finally, 1,901 patients who met the selection criteria were included in this analysis (**Figure 1**).

PERCUTANEOUS CORONARY INTERVENTION PROCEDURE. All patients received loading doses of aspirin (300 mg) and clopidogrel (300 to 600 mg) before the coronary intervention unless they had previously received these antiplatelet medications. Anticoagulation therapy during PCI was performed according to current practice guidelines stipulated by the Korean Society of Interventional Cardiology. The treatment strategy, stenting techniques, selection of drug-eluting stent type, and use of glycoprotein IIb/IIIa receptor inhibitors or intravascular ultrasound were all left to the operator's discretion. Aspirin was continued indefinitely, and the duration of thienopyridine treatment was also at the operator's discretion.

DEFINITIONS. Death was defined as any post-procedure death and was considered to be of cardiac origin unless there was documentation of another cause. Myocardial infarction (MI) was defined as the presence of electrocardiography findings indicative of ischemia that were not related to the index procedure, as well as chest discomfort associated with creatinine kinase-myocardial band fraction or troponin-T/troponin I greater than the upper limit of normal. Target lesion revascularization (TLR) was

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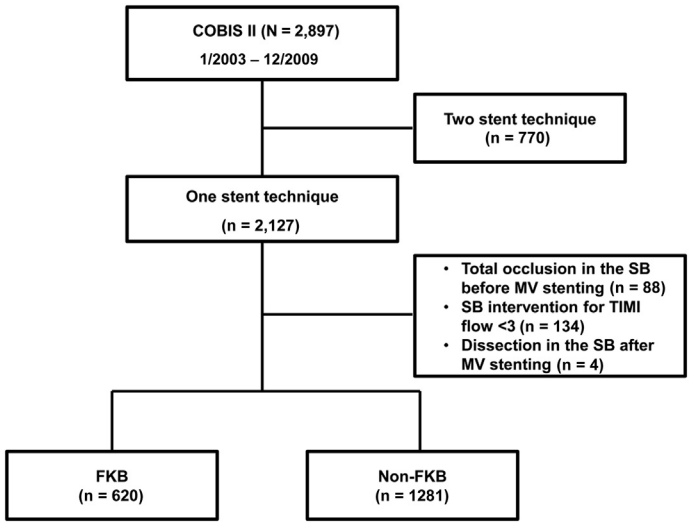
defined as a repeat PCI of the lesion within 5 mm of stent deployment or bypass graft surgery of the target vessel. The peri-procedural period included the first 48 h after PCI. Stent thrombosis was defined according to the Academic Research Consortium as definite, probable, or possible. The timing of stent thrombosis was classified as early (within 1 month after the index procedure), late (between 1 month and 1 year), or very late (after 1 year) (10). Angiographic success was defined as the achievement of residual stenosis <30% with TIMI flow grade 3 in the MV and residual stenosis <50% with TIMI flow grade 3 in the SB. Bifurcations were classified according to the Medina classification, in which the proximal MV, distal MV, and SB components of the bifurcation are each assigned a score of 1 or 0 depending on the presence or absence of >50% stenosis (11). Medina classification type 1.1.1, 1.0.1, and 0.1.1 lesions were defined as true bifurcation lesions.

CLINICAL FOLLOW-UP AND ENDPOINTS. Clinical, laboratory, procedural, angiographic, and outcome data were collected from an Internet-based reporting system. Additional information was gathered by contacting general practitioners, reviewing hospital records, and conducting telephone interviews. The primary outcome of this study was major adverse cardiac events (MACE) during follow-up, defined as a composite event of cardiac death, MI, or TLR. The secondary outcomes were the individual components of the primary endpoint, all-cause death, and stent thrombosis.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS. All baseline and procedural cine coronary angiograms were analyzed quantitatively at the angiographic core laboratory of the Cardiac and Vascular Center, Samsung Medical Center (Seoul, Korea), using standard qualitative and quantitative analyses with an automatic edge-detection system (Centricity CA 1000, GE, Waukesha, Wisconsin) (12). Besides the Centricity Cardiology CA1000, the angiography of the bifurcations was analyzed using the Cardiovascular Angiography Analysis System (CAAS version 5.10, Pie Medical Imaging, Maastricht, the Netherlands). QCA was rechecked off-line by 2 experienced analysts (H.C.G. and J.H.Y.), independent of each other. For QCA (Figure 2), bifurcation lesions were divided into the proximal reference, MV proximal (proximal to SB take-off), MV middle (<5 mm distal to take-off), MV distal, MV distal reference, SB ostial (<5 mm distal to take-off), SB distal, and SB reference segments. The minimal luminal diameter (MLD) and reference diameter (RD) before and immediately after the procedure were measured in matched views. For the MV, the RD was the average of the proximal and distal reference lumen diameters. For SB, the RD was the distal reference lumen diameter.

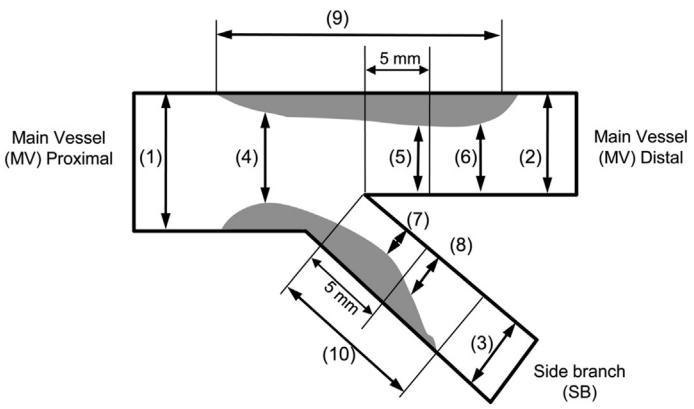
FIGURE 1 Scheme of Group Distribution in the Registry



1,901 patients who met the selection criteria were included in final analysis. COBIS II = Korean Coronary Bifurcation Stenting Registry II; FKB = final kissing ballooning; MV = main vessel; SB = side branch; TIMI = Thrombolysis In Myocardial Infarction.

STATISTICAL ANALYSIS. All values are presented as the mean ± SD or median (interquartile range). Comparisons between continuous variables were made using the Student *t*-test or the Wilcoxon

FIGURE 2 Schematic Diagram of QCA Analysis



The quantitative coronary angiographic (QCA) analysis assessed the following: (1) MV proximal reference diameter (RD); (2) MV distal RD; (3) SB distal RD; (4) MV proximal minimal lumen diameter (MLD); (5) MV middle MLD; (6) MV distal MLD; (7) SB ostium MLD; (8) SB distal MLD; (9) MV lesion length; and (10) SB lesion length. Abbreviations as in Figure 1.

rank-sum test when applicable. Categorical data were tested using Fisher exact test or the chi-square test. Event-free survival was estimated by the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazard model was used to compare the risks of adverse cardiac events between the FKB and the non-FKB groups. We checked log-linearity for linear trends, Shoenfeld residual test for proportional hazards assumption, and variance inflation factor (<5) for multicollinearity in multivariable Cox regression. Furthermore, we tried to include an interaction term, but no interaction terms were statistically significant. Propensity scores were estimated using multiple logistic-regression analysis. A full nonparsimonious model that included all variables in Tables 1 and 2, as well as the baseline QCA variables in Table 3, was developed. The covariate balance achieved by matching was assessed by calculating the absolute standardized differences in covariates between the FKB and non-FKB groups. Pairs were matched by the nearest neighbor matching method, a greedy algorithm among patients with an individual propensity score. An absolute standardized difference of <10% for the measured covariate suggests appropriate balance between the groups. In the propensity score-matched population, continuous variables were compared with a paired *t* test or the Wilcoxon signed-rank test, as appropriate; categorical variables were compared with McNemar or Bowker test of symmetry, as appropriate. The reduction in the risk of negative outcome was compared using a stratified Cox regression model with prognostic covariates having an absolute standardized difference >10.0%. Cumulative incidence rates of individual clinical outcomes and composite outcomes were estimated by the Kaplan-Meier method and compared by the paired Prentice-Wilcoxon test. Statistical analyses were performed with SAS (version 9.2, SAS Institute Inc., Cary, North Carolina). All tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

BASELINE, ANGIOGRAPHIC, AND PROCEDURAL CHARACTERISTICS. Overall population. Among the 1,901 eligible patients, FKB was performed in 620 patients (32.6%). In the FKB group, angiographic success was achieved in 514 patients (82.9%). Baseline patient characteristics are shown in Table 1, and angiographic and procedural characteristics are shown in Table 2. Compared with patients in the

TABLE 1 Baseline Patient Characteristics

	Total Population				Propensity-Matched Population			
	FKB (n = 620)	Non-FKB (n = 1,281)	p Value	Standardized Difference	FKB (n = 545)	Non-FKB (n = 545)	p Value	Standardized Difference
Age, yrs	61.8 ± 10.1	62.3 ± 10.2	0.30	-5.1	61.8 ± 10.1	62.4 ± 9.9	0.90	-6.5
Male	438 (70.7)	939 (73.3)	0.22	-5.8	379 (69.5)	384 (70.5)	0.79	-2.0
Medical history								
Diabetes mellitus	176 (28.4)	390 (30.4)	0.36	-4.6	149 (27.3)	162 (29.7)	0.42	-5.3
Hypertension	367 (59.2)	739 (57.7)	0.53	3.1	325 (59.6)	298 (54.7)	0.11	10.1
Dyslipidemia	207 (33.4)	381 (29.7)	0.11	7.7	188 (34.5)	170 (31.2)	0.26	7.0
Smoking	153 (24.7)	338 (26.4)	0.43	-4.0	131 (24.0)	140 (25.7)	0.57	-3.8
Chronic kidney disease	12 (1.9)	42 (3.3)	0.10	-9.7	11 (2.0)	17 (3.1)	0.35	-8.0
Family history of coronary artery disease	21 (3.4)	34 (2.7)	0.37	4.1	18 (3.3)	14 (2.6)	0.60	4.1
Previous history of MI	29 (4.7)	69 (5.4)	0.51	-3.4	25 (4.6)	25 (4.6)	0.99	0
Previous history of PCI	87 (14.0)	147 (11.5)	0.11	7.4	75 (13.8)	64 (11.7)	0.34	5.8
Previous history of CABG	3 (0.5)	11 (0.9)	0.57	-5.4	2 (0.4)	6 (1.1)	0.29	-10.6
Previous history of CVA	35 (5.7)	88 (6.9)	0.31	-5.3	35 (6.4)	32 (5.9)	0.80	2.4
Peripheral vascular disease	6 (1.0)	16 (1.3)	0.59	-2.9	5 (0.9)	9 (1.7)	0.42	-7.5
Left ventricular ejection fraction	60.0 ± 10.4	57.5 ± 9.7	<0.001	23.9	59.6 ± 10.8	59.2 ± 8.9	0.39	3.8
Serum creatinine, mg/dl	1.10 ± 0.89	1.10 ± 0.84	0.871	-0.8	1.09 ± 0.86	1.11 ± 0.98	0.917	-2.1
Clinical presentation			<0.001				0.71	
Stable angina	243 (39.2)	476 (37.2)			218 (40.0)	214 (39.3)		
Unstable angina	263 (42.4)	424 (33.1)		18.8	219 (40.2)	212 (38.9)		2.6
ST-segment elevation MI	46 (7.4)	175 (13.7)		-23.8	45 (8.3)	51 (9.4)		-4.2
Ischemic cardiomyopathy or silent ischemia	13 (2.1)	25 (2.0)		1.0	10 (1.8)	11 (2.0)		-1.3
Non-ST-segment elevation MI	55 (8.9)	181 (14.1)		-18.5	53 (9.7)	57 (10.5)		-2.6

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; CVA = cerebrovascular accident; FKB = final kissing ballooning; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Angiographic and Procedural Characteristics

	Total Population				Propensity-Matched Population			
	FKB (n = 620)	Non-FKB (n = 1,281)	p Value	Standardized Difference	FKB (n = 545)	Non-FKB (n = 545)	p Value	Standardized Difference
Bifurcation location			0.002				0.52	
Left main bifurcation	184 (29.7)	308 (24.0)			158 (29.0)	140 (25.7)		
Left anterior descending artery/diagonal	342 (55.2)	704 (55.0)		0.4	304 (55.8)	327 (60.0)		-8.5
Left circumflex/obtuse marginal artery	64 (10.3)	204 (15.9)		-18.4	57 (10.5)	51 (9.4)		3.6
Right coronary artery bifurcation	30 (4.8)	65 (5.1)		-1.1	26 (4.8)	27 (5.0)		-0.9
Calcification, SB	35 (5.7)	61 (4.8)	0.410	3.8	30 (5.5)	26 (4.8)	0.68	3.2
Medina classification			<0.001				0.97	
True bifurcation	310 (50.0)	452 (35.3)			260 (47.7)	259 (47.5)		
1.1.1	203 (32.7)	260 (20.3)			164 (30.1)	164 (30.1)		
1.0.1	47 (7.6)	79 (6.2)		5.3	41 (7.5)	38 (7.0)		2.1
0.1.1	60 (9.7)	113 (8.8)		2.9	55 (10.1)	57 (10.5)		-1.2
Nontrue bifurcation	310 (50.0)	829 (64.7)			285 (52.3)	286 (52.5)		
1.0.0	61 (9.8)	245 (19.1)		-31.2	57 (10.5)	65 (11.9)		-4.9
0.1.0	121 (19.5)	334 (26.1)		-16.5	116 (21.3)	110 (20.2)		2.8
1.1.0	109 (17.6)	231 (18.0)		-1.2	98 (18.0)	100 (18.4)		-1.0
0.0.1	19 (3.1)	19 (1.5)		9.2	14 (2.6)	11 (2.0)		3.2
SB pre-dilation before MV stenting	146 (23.6)	190 (14.8)	<0.001	20.5	116 (21.3)	110 (20.2)	0.71	2.6
Use of intravascular ultrasound	204 (32.9)	453 (35.4)	0.290	-5.2	179 (32.8)	190 (34.9)	0.52	-4.3
Total stent length, mm	27.7 ± 11.7	28.8 ± 12.6	0.13	-9.3	28.1 ± 12.1	28.6 ± 12.9	0.89	-3.5
Maximal stent diameter, mm	3.24 ± 0.41	3.17 ± 0.42	<0.001	15.8	3.23 ± 0.41	3.21 ± 0.42	0.70	3.9

Values are n (%) or mean ± SD.
FKB = final kissing ballooning; MV = main vessel; SB = side branch.

non-FKB group, those in the FKB group had a higher prevalence of high left ventricular ejection fraction, left main bifurcation lesion, true bifurcation, SB predilation, and large stent diameter. However, they had a lower prevalence of left circumflex/obtuse marginal artery bifurcation, as well as ST-segment elevation MI and non-ST-segment elevation MI at initial presentation. First-generation drug-eluting stents such as the sirolimus-eluting stent and paclitaxel-eluting stent were similarly implanted in both groups (464 patients [74.8%] in the FKB group and 942 [73.5%] in the non-FKB group [p = 0.54]). In addition, 109 patients (17.6%) in the FKB group and 235 (18.3%) in the non-FKB group discontinued dual antiplatelet therapy for <12 months; there was no significant difference between the 2 groups (p = 0.69).

Propensity-matched population. After propensity-score matching for the entire population, 545 matched pairs of patients were created (Tables 1 and 2). The C-statistic for the propensity score model was 0.76, suggesting that the use of FKB was relatively random; this improves the reliability of our analysis. There were no significant differences in baseline, angiographic, or procedural characteristics between the FKB and non-FKB groups for propensity-matched subjects.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS. Minimum intraobserver agreements of QCA variables using the intraclass coefficient were 0.98 (H.C.G.) and 0.97 (J.H.Y.), and minimum interobserver variability was 0.80. In the overall population, lesion length was shorter and proximal RD was larger in the MV of the FKB group than those of non-FKB group. Lesion length was longer, distal RD was larger, and ostial MLD was smaller in the SB of the FKB group compared with those in the non-FKB group (Table 3). After MV stenting (before FKB), the middle MLD of the MV and the ostial MLD of the SB were significantly smaller in the FKB group. After FKB, the MV proximal, middle, and distal MLD; SB ostial; and distal MLD were significantly larger in the FKB group than in the non-FKB group. These QCA results after FKB were maintained in the propensity-matched populations.

CLINICAL OUTCOMES. Overall population. The median follow-up duration was 36 months (interquartile range: 25 to 50 months) and 152 MACE occurred. Table 4 shows the cumulative clinical outcomes of the study groups. The incidence of MACE was significantly lower in the FKB group than in the non-FKB group (FKB vs. non-FKB: 6.8 vs. 8.6%; p = 0.048) (Figure 3A). The incidence of all-cause death, cardiac death, and stent thrombosis was not significantly different between the 2 groups, but the incidence of MI was (0.6% vs. 1.8%; p = 0.03). In the

TABLE 3 QCA Data

	Total Population				Propensity-Matched Population			
	FKB (n = 620)	Non-FKB (n = 1,281)	p Value	Standardized Difference	FKB (n = 545)	Non-FKB (n = 545)	p Value	Standardized Difference
Baseline								
Main vessel								
Lesion length	17.10 ± 11.0	18.20 ± 11.78	0.05	-10.0	17.38 ± 11.31	17.48 ± 11.09	0.73	-0.9
Proximal RD	3.52 ± 0.67	3.39 ± 0.63	<0.001	20.4	3.50 ± 0.66	3.44 ± 0.66	0.74	7.6
Distal RD	2.76 ± 0.48	2.71 ± 0.48	0.06	9.4	2.74 ± 0.48	2.74 ± 0.49	0.97	0.2
Proximal MLD	1.75 ± 0.91	1.75 ± 0.97	0.92	-0.5	1.76 ± 0.92	1.70 ± 0.97	0.71	6.3
Middle MLD	1.35 ± 0.66	1.41 ± 0.74	0.07	-9.2	1.35 ± 0.66	1.33 ± 0.67	0.67	3.4
Distal MLD	1.92 ± 0.79	1.72 ± 0.84	<0.001	25.1	1.88 ± 0.79	1.83 ± 0.84	0.54	6.3
Side branch								
Lesion length	3.71 ± 5.33	3.03 ± 5.73	0.01	12.7	3.64 ± 5.42	3.62 ± 5.61	0.87	0.4
Distal RD	2.60 ± 0.42	2.55 ± 0.43	0.02	11.6	2.59 ± 0.42	2.55 ± 0.45	0.29	10.2
Ostial MLD	1.57 ± 0.74	1.71 ± 0.71	<0.001	-19.0	1.59 ± 0.75	1.57 ± 0.71	0.89	2.9
Distal MLD	2.05 ± 0.68	1.98 ± 0.67	0.05	9.5	2.02 ± 0.69	1.96 ± 0.71	0.27	9.6
After MV stenting								
Main vessel								
Proximal MLD	3.07 ± 0.54	3.05 ± 0.57	0.66	2.2	3.07 ± 0.55	3.02 ± 0.58	0.85	9.2
Middle MLD	2.75 ± 0.53	2.81 ± 0.54	0.04	-10.1	2.76 ± 0.54	2.71 ± 0.56	0.72	9.6
Distal MLD	2.76 ± 0.49	2.76 ± 0.52	0.91	-0.6	2.76 ± 0.49	2.72 ± 0.54	0.85	8.6
Side branch								
Ostial MLD	1.21 ± 0.72	1.52 ± 0.75	<0.001	-42.7	1.26 ± 0.73	1.25 ± 0.69	0.71	1.3
Distal MLD	2.02 ± 0.68	1.99 ± 0.65	0.36	4.4	2.02 ± 0.69	1.96 ± 0.68	0.67	7.8
Final								
Main vessel								
Proximal MLD	3.29 ± 0.57	3.07 ± 0.57	<0.001		3.27 ± 0.57	3.04 ± 0.59	<0.001	
Middle MLD	2.87 ± 0.50	2.81 ± 0.53	0.03		2.86 ± 0.50	2.72 ± 0.56	0.001	
Distal MLD	2.84 ± 0.48	2.77 ± 0.52	0.003		2.83 ± 0.48	2.73 ± 0.55	0.04	
Side branch								
Ostial MLD	1.84 ± 0.62	1.58 ± 0.73	<0.001		1.85 ± 0.62	1.36 ± 0.69	<0.001	
Distal MLD	2.16 ± 0.58	2.01 ± 0.65	<0.001		2.15 ± 0.59	1.99 ± 0.68	0.04	

Values are mean ± SD.

MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RD = reference diameter; other abbreviations as in Tables 1 and 2.

multivariable regression analysis, the FKB group had a significantly lower risk of MACE (adjusted hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.46 to 0.99; p = 0.048), but the incidence of MI was not significantly different between the 2 groups (Table 4). The definite or probable stent thrombosis rate was not significantly different between the groups (0.5% vs. 0.3%; p = 0.72).

Propensity-matched population. After 1:1 propensity-score matching, FKB was associated with a lower incidence of MACE (6.8% vs. 9.7%; adjusted HR: 0.50, 95% CI: 0.30 to 0.85; p = 0.01) and TLR (5.9% vs. 7.9%; adjusted HR: 0.51, 95% CI: 0.28 to 0.91; p = 0.02) (Table 5, Figure 3B). However, the incidence of MI was not significantly different between the 2 groups. The incidence of TLR in the MV (5.7% vs. 7.3%; adjusted HR: 0.51, 95% CI: 0.28 to 0.93; p = 0.03) and in both vessels (4.2% vs. 7.0%; adjusted HR: 0.47, 95% CI: 0.25 to 0.90; p = 0.02) was lower in the FKB group. The rate of TLR at the SB was also numerically lower in the FKB group but was not significantly different between the 2 groups. There was no significant clinical center effects (p values ranging from 0.117 to ~0.527).

Subgroup analysis. To determine whether the observed outcomes related to FKB in the overall and propensity-matched populations were consistent, we calculated the unadjusted HR for MACE in various complex subgroups (Figure 4). There were no significant interactions between the use of FKB and MACE among all the subgroups. Compared with the non-FKB group, the association of FKB with better MACE outcome was consistent across various subgroups including women and patients with acute coronary syndrome, non-left main bifurcation lesions, and true bifurcations; these associations were also consistent in propensity-matched population subgroups (Figure 5).

TABLE 4 Clinical Outcomes in FKB Group Compared With Non-FKB Group During Follow-Up Period

	FKB (n = 620)	Non-FKB (n = 1,281)	Unadjusted HR (95% CI)	p Value	Adjusted HR* (95% CI)	p Value
All-cause death	19 (3.1)	42 (3.3)	0.86 (0.50–1.48)	0.59	0.86 (0.47–1.58)	0.63
Cardiac death	4 (0.6)	15 (1.2)	0.53 (0.18–1.60)	0.26	0.56 (0.17–1.90)	0.35
MI	4 (0.6)	23 (1.8)	0.32 (0.11–0.91)	0.03	0.48 (0.16–1.45)	0.19
Stent thrombosis†	3 (0.5)	4 (0.3)	1.50 (0.34–6.71)	0.60	1.36 (0.25–7.28)	0.72
Target lesion revascularization	36 (5.8)	84 (6.6)	0.78 (0.53–1.16)	0.22	0.71 (0.47–1.09)	0.12
Main vessel	35 (5.6)	81 (6.3)	0.79 (0.53–1.17)	0.24	0.71 (0.46–1.09)	0.11
Side branch	13 (2.1)	28 (2.2)	0.85 (0.44–1.64)	0.62	0.67 (0.33–1.38)	0.28
Both vessels	25 (4.0)	66 (5.2)	0.70 (0.44–1.11)	0.13	0.66 (0.40–1.08)	0.10
MACE‡	42 (6.8)	110 (8.6)	0.70 (0.49–0.99)	0.048	0.68 (0.46–0.99)	0.048

Values are n (%) unless otherwise indicated. *Adjusted covariates include age, diabetes mellitus, left ventricular ejection fraction, clinical manifestation, bifurcation location, Medina classification, SB pre-dilation before main vessel stenting, proximal reference diameter of MV, distal MLD of MV, lesion length of SB, distal RD of SB, ostium MLD of SB, middle MLD of MV after MV stenting, and ostium MLD of SB after MV stenting. †Stent thrombosis was defined as definite or probable. ‡Major adverse cardiac events included cardiac death, recurrent MI, and target lesion revascularization.

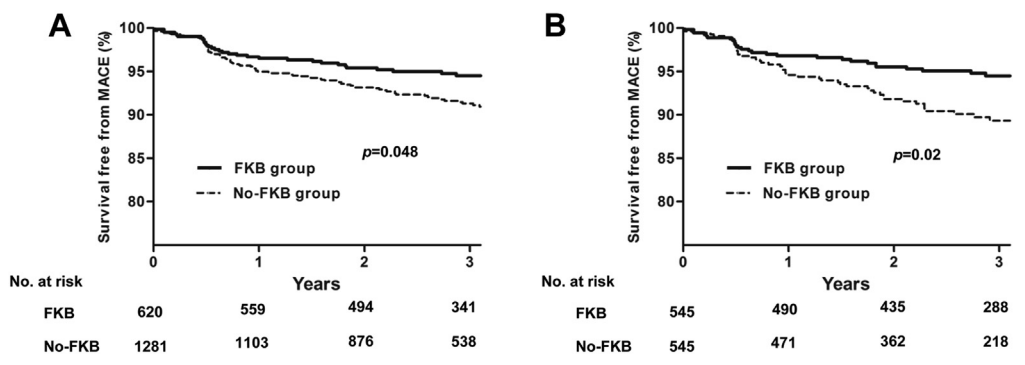
CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; other abbreviations as in Tables 1 to 3.

DISCUSSION

In the present study, we investigated the association of FKB with clinical outcome in patients with coronary bifurcation lesions treated with the 1-stent technique using data from a large, multicenter registry in Korea. The FKB group had a lower risk of MACE than did the non-FKB group. This result was maintained in propensity-matched populations and was mainly driven by a reduction of TLR in the main vessel or in both vessels (the MV and the SB). Furthermore, the association of FKB with favorable MACE outcome was consistent across various subgroups. However, there were no significant differences between the groups in terms of the rates of hard endpoints such as cardiac death, MI, or stent thrombosis.

The provisional stenting technique remains the preferred strategy in the majority of coronary bifurcation lesions based on several randomized controlled trials and meta-analyses, although the optimal stenting technique for bifurcation lesions has been debated (1,4,13). It is not known whether the MV stent should always be opened at the SB ostium by FKB in cases in which decreased TIMI flow or severe dissection do not occur in the SB. In addition, the results regarding geometric change after SB opening through MV stent from observational studies are inconsistent (14–16). Meticulous bench testing by Ormiston et al. (14) demonstrated that balloon dilation through the struts of a stent distorted the stent and induced stenosis in the stent immediately distal to the SB, which was restored by simultaneous FKB using an

FIGURE 3 Unadjusted Kaplan-Meier Curves in FKB Versus Non-FKB Groups



(A) Kaplan-Meier curves for major adverse cardiac events (MACE) in final kissing ballooning (FKB) **(solid line)** versus non-FKB groups **(dashed line)** in all patients. **(B)** Kaplan-Meier curves for MACE in FKB versus non-FKB groups in propensity-matched populations.

TABLE 5 Clinical Outcomes in FKB Group Compared With Non-FKB Group in Propensity-Matched Population During Follow-Up Period

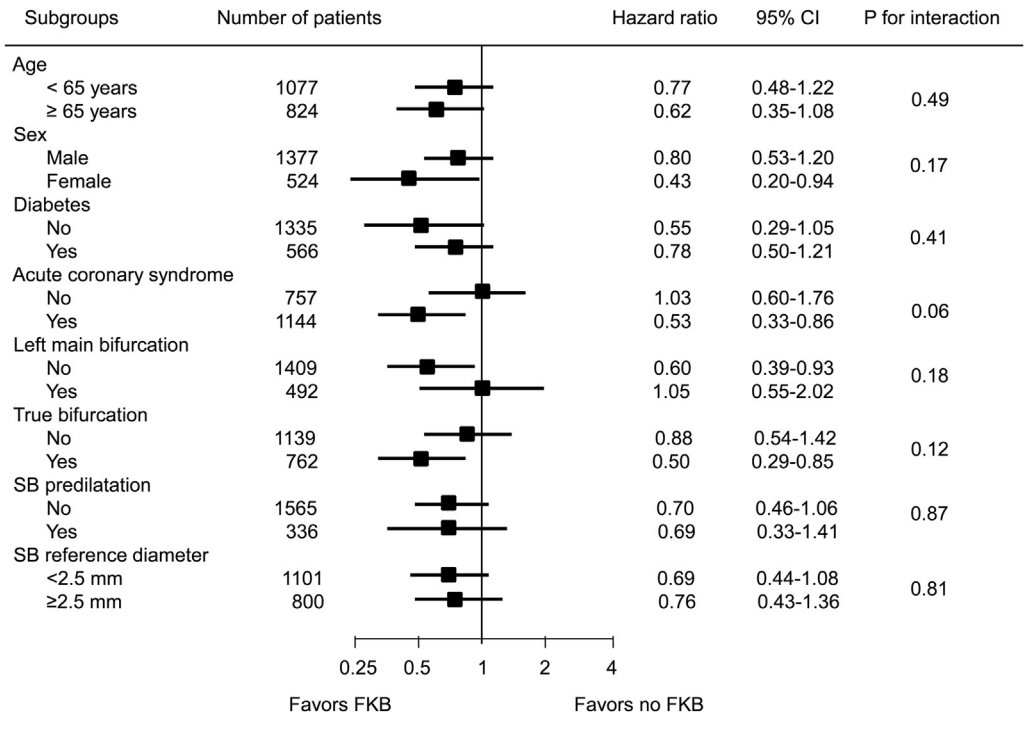
	FKB (n = 545)	Non-FKB (n = 545)	Unadjusted HR (95% CI)	p Value	Adjusted HR* (95% CI)	p Value
All-cause death	17 (3.1)	20 (3.7)	0.67 (0.30–1.48)	0.32	0.68 (0.28–1.63)	0.39
Cardiac death	3 (0.6)	8 (1.5)	0.43 (0.11–1.66)	0.22	0.50 (0.11–2.29)	0.37
MI	4 (0.7)	5 (0.9)	0.50 (0.09–2.73)	0.42	0.18 (0.01–20.36)	0.48
Stent thrombosis†	3 (0.6)	4 (0.7)	0.72 (0.16–3.23)	0.67	0.77 (0.17–3.45)	0.73
Target lesion revascularization	32 (5.9)	43 (7.9)	0.53 (0.30–0.94)	0.03	0.51 (0.28–0.91)	0.02
Main vessel	31 (5.7)	40 (7.3)	0.53 (0.30–0.96)	0.04	0.51 (0.28–0.93)	0.03
Side branch	12 (2.2)	18 (3.3)	0.57 (0.24–1.36)	0.21	0.57 (0.24–1.37)	0.21
Both vessels	23 (4.2)	38 (7.0)	0.47 (0.25–0.88)	0.02	0.47 (0.25–0.90)	0.02
MACE‡	37 (6.8)	53 (9.7)	0.54 (0.32–0.89)	0.02	0.50 (0.30–0.85)	0.01

Values are n (%) unless otherwise indicated. *Adjusted covariates include hypertension, history of coronary artery bypass graft, and distal RD of SB. †Stent thrombosis was defined as definite or probable. ‡Major adverse cardiac events included cardiac death, recurrent MI, and target lesion revascularization.

Abbreviations as in Tables 1 to 4.

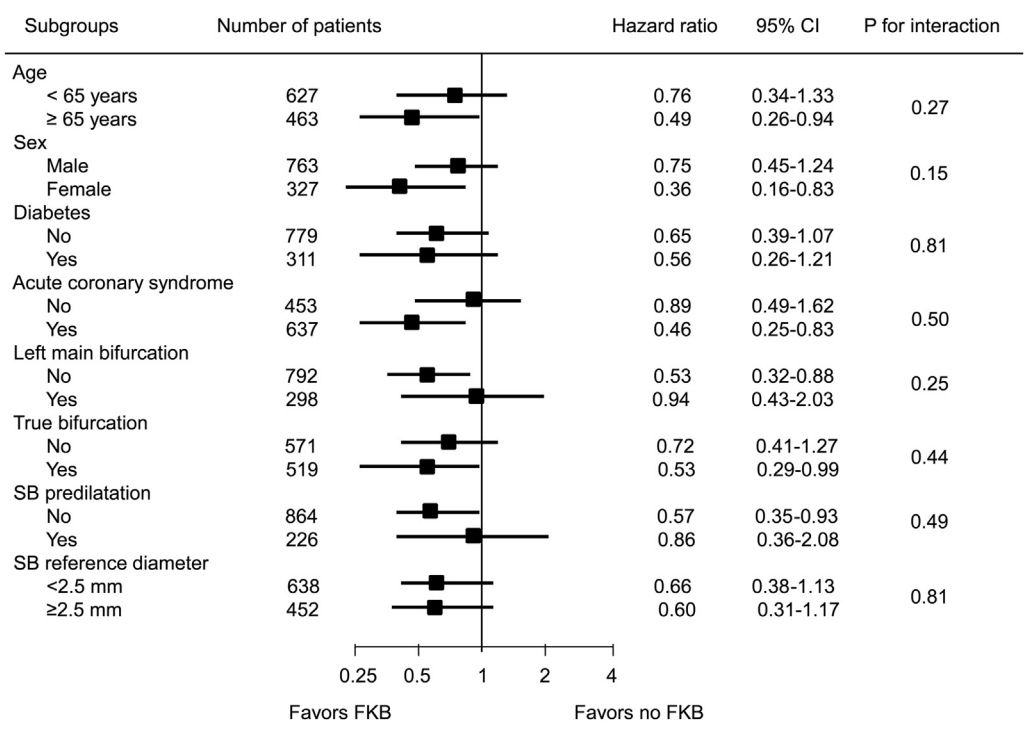
in vitro model. In addition, comprehensive volumetric intravascular ultrasound studies demonstrated that, in the bifurcation lesion, SB dilation significantly reduced the MV stent volume area under the SB origin and distorted MV stent symmetry, which was restored after FKB (16). In a previous study, dilation of the SB actually resulted in a reduction in the cross-sectional area under the SB origin from 5.9 ± 1.2 mm^2 initially to 5.2 ± 1.2 mm^2. After KB inflation, the cross-sectional area partially recovered (to 5.6 ± 1.2 mm^2) (15). Moreover, our final QCA data showed that proximal, middle, and distal MLD in the MV and SB were larger in the FKB group compared with those in the non-FKB group. These results suggest that FKB might reduce the rate of in-stent restenosis and subsequently the rate of TLR by increasing luminal gain in the MV and SB.

FIGURE 4 Comparative Unadjusted HR of MACE for Subgroups in All Populations



There were no significant interactions between the use of FKB and MACE among various subgroups in all populations. CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

FIGURE 5 Comparative Unadjusted HR of MACE for Subgroups in Propensity-Matching Population



There were no significant interactions between the use of FKB and MACE among various subgroups in propensity-matching populations. Abbreviations as in Figures 1, 3, and 4.

Until now, the benefit of FKB has been demonstrated only in bifurcation lesions treated with the 2-stent technique, mostly using the culotte or crush technique (5,6,17). Therefore, several clinical studies have investigated both the clinical and angiographic effects of routine FKB in patients with coronary bifurcation lesions treated with the 1-stent technique (2,7–9). However, these studies have reported conflicting results. Our previous study (COBIS I) reported that FKB increased the long-term risk of TLR, most of which occurred in the MV and may have harmed the MV stent (7). The current study (COBIS II) included 492 patients (17%) who were enrolled in COBIS I. The COBIS II study included coronary bifurcation lesions with a larger size of MV and SB compared with the COBIS I study. The big difference between the COBIS II and COBIS I studies in terms of clinical outcomes is that, in the FKB group, the incidence of TLR in the MV and in both vessels was lower in the COBIS II study, in contrast to the higher incidence of TLR in the COBIS I study. These contrary results can be attributed to several factors. First, after FKB, the MV middle and distal MLD was not different between the FKB and non-FKB groups in the COBIS I study, but was larger in the FKB than non-FKB group in the COBIS II study. FKB appears to make less of a difference in MLD in smaller vessels, whereas dilation of larger vessels with a larger balloon produces a bigger luminal gain. If FKB causes MV stent deformity and subsequently increases the incidence of binary restenosis in MV stents, the possibility of ischemia-driven TLR would be higher in the FKB group with same-sized MLD. However, in cases of a larger MLD with FKB, the influence of binary restenosis by stent deformity might be relatively small because a similar degree of late loss produces greater diameter stenosis in smaller lumens than in larger ones. Both studies obviously showed that SB ostial and distal MLD after FKB increased in the FKB group, but found no significant difference in TLR of the SB between FKB and non-FKB groups. Koo et al. (18) reported that diagonal branch occlusion caused fewer symptoms, fewer electrocardiogram changes, less arrhythmogenic potential, and better collateral recruitability than left anterior descending artery occlusion did. Our study included more than 50% of left anterior descending artery/diagonal bifurcation lesions. Therefore, we suggest that restenosis of SB may not translate into ischemia-driven TLR, which is why there was no significant difference in terms of TLR of the SB between

both groups even though post-MLD of SB was larger in the FKB group than in the non-FKB group.

STUDY LIMITATIONS. First, the nonrandomized nature of the registry data could have resulted in selection bias. Several baseline characteristics were significantly different between groups, and the decision to perform FKB in each patient was made at the operator's discretion. Although we performed a propensity score-matched analysis to adjust for these potential confounding factors, we were not able to correct for unmeasured variables. Second, angiographic follow-up and TLR were performed according to each institution's strategy and each operator's discretion. In particular, we did not know the relationship between binary restenosis and TLR because we did not have information on intravascular ultrasound before and after FKB or at follow-up angiography. Third, adverse clinical events were not centrally adjudicated in our registries. All events were identified by the patients' physicians and confirmed by the principal investigator of each hospital. Fourth, the results of stent thrombosis in the present study should be considered cautiously. Although the vital status of all patients, including those lost to follow-up, was confirmed with the Korean national database using a citizen registration number that is unique to each individual, we cannot exclude the possibility of under-reporting of clinical outcomes other than death such as nonfatal MI and stent thrombosis. Fifth, in real-world practice, there are considerations of strategy and timing of FKB depending on the preference of the operator. Accordingly, in a substantial portion treated without previously enlarging the stent struts with a single balloon, TLR might not be associated with the geometrical distortion of the stent struts. Sixth, given the observed clinical event rates, a properly powered study would include more than 7,461 patients (FKB vs. non-FKB, α-error: 0.05, β-error: 0.2). Accordingly, the study was considerably underpowered and subgroup analysis was not conclusive. Lastly, the outcomes of FKB with second- or third-generation stents because of improved SB access will need to be tested in a future trial.

CONCLUSIONS

In a large, multicenter Korean registry trial studying coronary bifurcation lesions, we demonstrated that the 1-stent technique with FKB was associated with a favorable long-term clinical outcome, mainly driven by the reduction of TLR in the MV or both vessels as a result of an increase in MLD. These findings need to be confirmed in a future large-scale randomized trial.

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PERSPECTIVES

WHAT IS KNOWN? Although FKB is currently considered mandatory in 2-stent techniques, the effects of FKB on clinical and angiographic outcomes after only MV stenting are controversial. In addition, most relevant studies are limited by small sample size, an inadequate short-term follow-up period, exclusion of left main bifurcation lesions, or a small SB.

WHAT IS NEW? In coronary bifurcation lesions, we demonstrated that the 1-stent technique with FKB was associated with a favorable long-term clinical outcome, mainly driven by the reduction of TLR in the MV or both vessels as a result of an increase in MLD.

WHAT IS NEXT? Angiographic follow-up and TLR were performed according to each institution's strategy and each operator's discretion. Therefore, our results need to be confirmed in a future prospective randomized trial.

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