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CLINICAL RESEARCH

CORONARY

Optimal Strategy for Provisional Side Branch Intervention in Coronary Bifurcation Lesions

3-Year Outcomes of the SMART-STRATEGY Randomized Trial

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ABSTRACT

OBJECTIVES This study compared the long-term follow-up results of conservative versus aggressive strategies for provisional side branch (SB) intervention in coronary bifurcation lesions.

BACKGROUND The appropriate criteria for provisional SB ballooning or stenting have not been established.

METHODS A total of 258 patients with a large bifurcation lesion were randomized to a conservative or aggressive SB intervention strategy. Different criteria applied for the initiation of SB intervention after main vessel stenting in the conservative and aggressive groups were Thrombolysis In Myocardial Infarction flow grade lower than 3 versus a stenosis diameter >75% for non-left main bifurcations, and a stenosis diameter >75% versus a stenosis diameter >50% for left main bifurcations. The primary endpoint was target vessel failure (TVF), defined as a composite of cardiac death, spontaneous myocardial infarction, or target vessel revascularization at 3 years.

RESULTS At 3 years, TVF occurred in 11.7% of the conservative group versus 20.8% of the aggressive group ($p = 0.049$). Although no significant differences were observed in the incidence of TVF between groups at 1 year (9.4% vs. 9.2%; $p = 0.97$), landmark analysis between 1 and 3 years showed significantly less TVF in patients assigned to the conservative strategy (2.6% vs. 12.7%; $p = 0.004$). The crossover to the 2-stent technique was an independent predictor of TVF (hazard ratio: 5.42, 95% confidence interval: 2.03 to 14.5; $p < 0.001$). There was no interaction between left main bifurcation and treatment effects for TVF (p for interaction = 0.8).

CONCLUSIONS A conservative strategy compared with an aggressive strategy for provisional SB intervention is associated with long-term benefits for patients with a large bifurcation lesion. (Optimal Strategy for Side Branch Stenting in Coronary Bifurcation Lesion; NCT00794014) (J Am Coll Cardiol Intv 2016;9:517–26) © 2016 by the American College of Cardiology Foundation.

Provisional side branch (SB) intervention after main vessel (MV) stenting is the default strategy for most bifurcation lesions in real-world practice (1,2). However, the appropriate criteria for provisional SB ballooning or stenting after MV stenting have not been established. Previous studies found that the rate of crossover to a 2-stent technique during provisional SB intervention was highly variable,

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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

IVUS = intravascular ultrasound

LM = left main

MI = myocardial infarction

MV = main vessel

PCI = percutaneous coronary intervention

SB = side branch

TBR = target bifurcation revascularization

TLR = target lesion revascularization

TVF = target vessel failure

TVR = target vessel revascularization

ranging from 2% to 30%, depending on the criteria for the SB stenting (3-7). In the randomized SMART-STRATEGY (SMart Angioplasty Research Team-Optimal STRATEGY for Provisional Side Branch Intervention in Coronary Bifurcation Lesions) trial, different strategies for provisional SB intervention were compared in patients undergoing percutaneous coronary intervention (PCI) for bifurcation lesions. The trial results demonstrated that a conservative strategy for provisional SB intervention was associated with a lower rate of crossover to the 2-stent technique and a lower incidence of procedure-related myocardial necrosis compared with an aggressive strategy but had similar short-term clinical outcomes (8). The aim of the present study was to compare 3-year clinical outcomes in patients with coronary bifurcation lesions treated with a conservative or an aggressive strategy for provisional SB intervention.

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METHODS

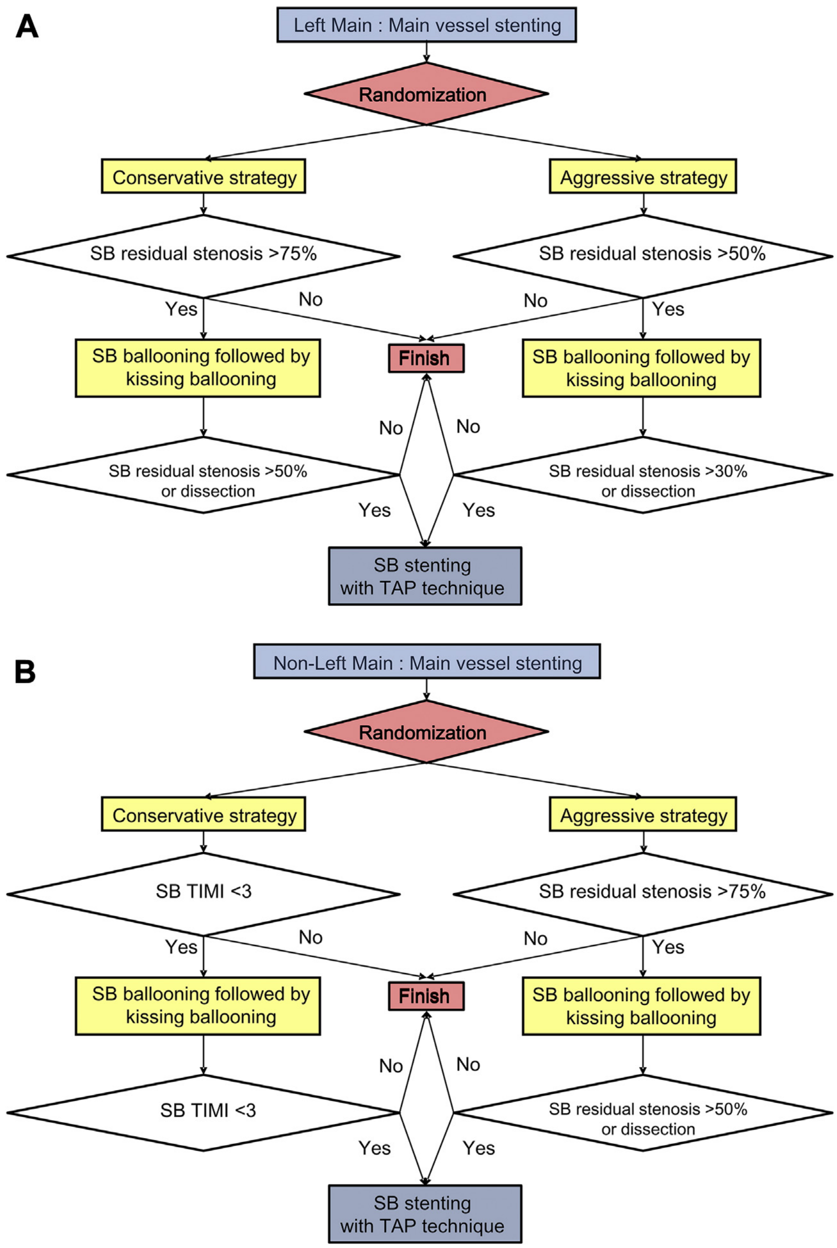
STUDY DESIGN AND PATIENTS. This prospective, randomized, nonblinded, single-center trial enrolled patients with coronary bifurcation lesions who underwent PCI with drug-eluting stents (DES) from July 2007 to December 2010. The protocol was approved by the local institutional review board, and written informed consent was obtained from all participants. The design, exclusion and inclusion criteria, and data collection methods of the SMART-STRATEGY trial were previously described (8). In brief, patients with stable coronary artery disease or non-ST-segment elevation acute coronary syndrome and a de novo coronary bifurcation lesion including an unprotected left main (LM) bifurcation lesion were included. The MV diameter was ≥2.5 mm, and the SB diameter was ≥2.3 mm by visual estimation. Patients with hemodynamic instability, left ventricular ejection fraction <25%, and primary PCI were excluded.

Patients were stratified by the presence or absence of an LM bifurcation lesion and were randomized 1:1 to a conservative or aggressive strategy for provisional SB intervention after MV stenting (**Figure 1**). For LM bifurcation lesions, the conservative strategy was SB ballooning followed by kissing ballooning for an SB stenosis diameter >75% after MV stenting and SB stenting for an SB stenosis diameter >50% or type B or greater dissection after SB ballooning. The aggressive strategy was SB ballooning followed by kissing ballooning for an SB stenosis diameter >50% after MV stenting and SB stenting for an SB stenosis diameter >30% or type B or greater dissection after SB ballooning. For non-LM bifurcation lesions, the conservative strategy was SB ballooning followed by kissing ballooning for Thrombolysis In Myocardial Infarction flow grade lower than 3 in the SB after MV stenting and SB stenting for Thrombolysis In Myocardial Infarction flow grade lower than 3 in the SB after SB ballooning. The aggressive strategy was SB ballooning followed by kissing ballooning for an SB stenosis diameter >75% after MV stenting and SB stenting for an SB stenosis diameter >50% after SB ballooning. For all cases of SB stenting, the T-stenting and small protrusion technique (9) was used exclusively, and final kissing balloon inflation was mandatory. All procedures were performed under intravascular ultrasound (IVUS) guidance whenever possible (see the Online Appendix for details).

STUDY ENDPOINTS AND FOLLOW-UP. The primary endpoint was the occurrence of target vessel failure (TVF), defined as a composite of cardiac death, spontaneous myocardial infarction (MI), or target vessel revascularization (TVR) at 3-year follow-up. Secondary endpoints included the individual components of the primary endpoint, all-cause death, stent thrombosis, target lesion revascularization (TLR), and target bifurcation revascularization (TBR) at 3-year follow-up. All deaths were considered cardiac unless a definite noncardiac cause could be established. Spontaneous MI was defined as elevated cardiac enzymes (troponin or myocardial band fraction of creatine kinase) greater than the upper limit of the normal that occurred along with ischemic symptoms or electrocardiography findings indicative of ischemia unrelated to the index procedure. TVR was defined as repeat revascularization of the target vessel by PCI or bypass graft surgery. TLR was defined as repeat PCI of the lesion within 5 mm of stent deployment or bypass graft surgery of the target vessel. TBR was defined as repeat revascularization with a stenosis diameter ≥50% within 5 mm proximal or distal to carina of bifurcation. Stent thrombosis was assessed according to the definitions of the Academic Research Consortium as definite, probable, or possible stent thrombosis (10).

Data on all-cause death, cardiac death, spontaneous MI, stent thrombosis, TLR, TBR, TVR, and TVF were obtained through office visits or telephone contact at 1, 3, 9, and 12 months after the index procedure and every 6 months thereafter. For validation, information about vital status was obtained through

FIGURE 1 Trial Profile

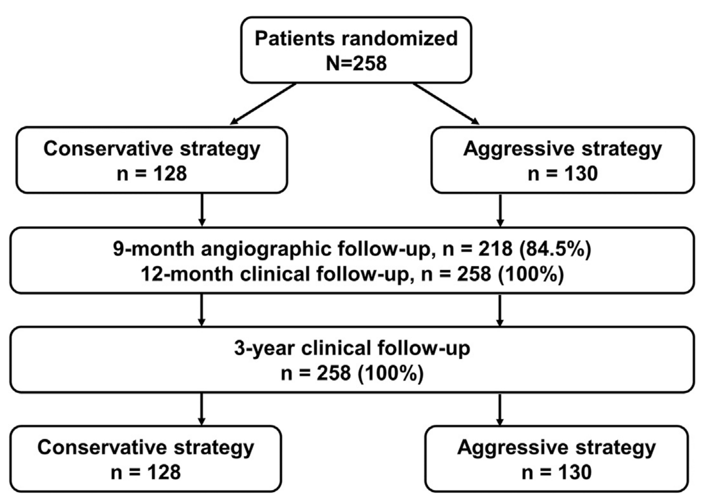


Patients were stratified by the presence or absence of a left main bifurcation lesion and were randomized 1:1 to conservative or aggressive strategy for provisional side branch (SB) intervention after main vessel stenting. **(A)** Left main bifurcation lesion. **(B)** Non-left main bifurcation lesion. SB = side branch; TAP = T-stenting and small protrusion; TIMI = Thrombolysis In Myocardial Infarction.

December 31, 2013, from the National Population Registry of the Korea National Statistical Office using a unique personal identification number.

STATISTICAL ANALYSIS. All data were analyzed by the intention-to-treat principle. Categorical variables were summarized as numbers with percentages and compared using Pearson's chi-square or the Fisher exact test. Continuous variables were expressed as the median with interquartile range and compared using an independent t test or the Wilcoxon rank sum test. Time-to-event hazard curves were presented

FIGURE 2 Three-Year Follow-Up Patient Flow Diagram of the SMART-STRATEGY Study



A total of 258 patients with bifurcation lesions were included in the present study. Clinical follow-up data at 3 years were available for all patients: 128 in the conservative group and 130 in the aggressive group.

with Kaplan-Meier estimates and compared using a log-rank test. To assess events occurring between 1 and 3 years, a landmark analysis was performed. We performed multivariable Cox regression to ascertain variables independently associated with 3-year outcomes. Proportional hazard assumptions were confirmed by Schoenfeld's test, and no relevant violation was found. Clinically relevant covariates were included in the multivariable models and were the following: age, acute coronary syndrome, diabetes mellitus, previous MI, previous PCI, LM bifurcation, true bifurcation, remote site intervention, second-generation DES (vs. first-generation DES), MV stent length (per 10 mm), crossover to 2-stent technique, and kissing balloon inflation. A p value <0.05 by a 2-tailed test was considered significant. The SAS version 9.1 (SAS Institute, Cary, North Carolina) was used for all analyses.

RESULTS

BASELINE CLINICAL AND PROCEDURAL CHARACTERISTICS. A total of 258 patients with bifurcation lesions were included in the present study. Clinical follow-up data at 3 years were available for all patients: 128 in the conservative group and 130 in the aggressive group. Figure 2 shows the patient flow diagram. Baseline clinical and procedural characteristics were well matched between groups (Tables 1 and 2). An LM bifurcation lesion was noted in 114 patients (44.2%) and a true bifurcation lesion in 171 (66.3%). IVUS was used similarly in 252 patients (97.7%), and the type of implanted DES did not differ between groups. SB intervention after MV stenting was performed differently according to the treatment strategy. SB balloon dilation was less frequently required in the conservative group than in the aggressive group (25.8% vs. 68.5%; $p < 0.001$). Additional stents were less frequently implanted in the SB in the conservative group than in the aggressive group (7.0% vs. 30.0%; $p < 0.001$). Only 1 patient randomized to the aggressive strategy failed to receive the assigned treatment because of rewiring failure.

CLINICAL OUTCOMES. Clinical event rates at 1 and 3 years and between 1 and 3 years in patients receiving conservative versus aggressive strategies are shown in Table 3 and Figure 3. From randomization through 3 years, the conservative strategy was associated with a lower incidence of TVF (11.7% vs. 20.8%; $p = 0.049$) (Figure 3A). No significant differences were observed in the incidence of TVF between groups at 1 year (9.4% vs. 9.2%; $p = 0.97$) (Figure 3B). In a landmark analysis between 1 year and 3 years, significantly fewer TVF events occurred in patients assigned to the conservative strategy (2.6% vs. 12.7%; $p = 0.004$) (Figure 3B). During the 3-year follow-up period, the conservative group had a significantly lower incidence of the composite of cardiac death or MI (0.8% vs. 6.2%; $p = 0.036$), with numerically lower rates of TVR. The incidence of TLR at 3 years was similar in the 2 groups (Figure 3C), but the conservative group showed lower rates of 3-year TLR than the aggressive group in a landmark analysis of TLR at 1 year after randomization (Figure 3D). Stent thrombosis occurred in 2 patients (0.8%), both in the aggressive group, despite the use of dual antiplatelet therapy. One patient died of probable stent thrombosis 10 months after stenting of both branches for an LM bifurcation lesion. The other patient presented with unstable angina from thrombotic occlusion 28 months after MV stenting for LM bifurcation.

INDEPENDENT PREDICTORS OF TVF AND TLR AT 3-YEAR FOLLOW-UP. Multivariable Cox regression models with a backward elimination method were used to determine the independent predictors of TVF and TLR at 3-year follow-up (Table 4). The covariates included are shown in Online Tables 1 and 2. The crossover to the 2-stent technique was the independent predictor of TVF (hazard ratio: 5.42, 95% confidence interval: 0.03 to 14.5; $p < 0.001$) and TLR (HR: 15, 95% confidence interval: 0.00 to 9.88; $p = 0.049$). The use of second-generation DES versus first-generation DES was

TABLE 1 Baseline Clinical Characteristics

	Conservative (n = 128)	Aggressive (n = 130)	p Value
Age, yrs	61.8 ± 10.1	61.5 ± 10.2	0.83
Male	105 (82.0)	108 (83.1)	0.83
Clinical presentation			0.51
Silent ischemia	13 (10.2)	7 (5.4)	
Stable angina	80 (62.5)	82 (63.1)	
Unstable angina	26 (20.3)	31 (23.8)	
Myocardial infarction	9 (7.0)	10 (7.7)	
Hypertension	70 (54.7)	75 (57.7)	0.63
Diabetes mellitus	37 (28.9)	33 (25.4)	0.53
Dyslipidemia	16 (12.5)	17 (13.1)	0.89
Current smoking	33 (25.8)	23 (17.7)	0.12
Family history of coronary artery disease	17 (13.3)	19 (14.6)	0.76
Cerebrovascular accident	5 (3.9)	10 (7.7)	0.19
Chronic renal failure	2 (1.6)	4 (3.1)	0.68
Previous myocardial infarction	7 (5.5)	5 (3.8)	0.54
Previous percutaneous coronary intervention	14 (10.9)	9 (6.9)	0.26
Previous coronary bypass graft surgery	0	1 (0.8)	>0.99
Left ventricular ejection fraction, %*	60.5 ± 7.3	59.3 ± 10.7	0.41

Values are mean ± SD or n (%). *Available in 84 patients (65.6%) with conservative strategy and 77 patients (59.2%) with aggressive strategy.

independently associated with lower rates of TVF and TLR at 3-year follow-up (Online Table 3).

IVUS PREDICTORS OF TLR WITHIN 1 YEAR AND AFTER 1 YEAR. TLR occurred similarly in both the MV and SB within 1 year, but predominantly in the MV after 1 year (Online Figure 1). To propose mechanistic explanations, we investigated pre- and post-procedural IVUS predictors of TLR within 1 year and after 1 year. The predictors of TLR within 1 year were a small pre-procedural minimal lumen area (MLA) at the SB, a large pre-procedural percentage of plaque burden at the minimal lumen area site of SB, and a large post-procedural percentage of plaque burden at the minimal lumen area site of SB (Online Table 4). However, pre- and post-procedural IVUS findings of the MV and SB could not predict the occurrence of TLR after 1 year (Online Table 5). The percentages of neointimal area in the proximal MV and distal MV at 9-month follow-up were associated with TLR after 1 year (Figure 4).

CLINICAL OUTCOMES IN LM AND NON-LM BIFURCATION LESIONS. Clinical event rates at 3 years in patients receiving the conservative versus aggressive strategy according to LM bifurcation lesion are shown in Table 5. There was no interaction between treatment strategy and TVF rate across the LM bifurcation lesions (p for interaction = 0.8). In 114 patients

TABLE 2 Procedural Characteristics

	Conservative (n = 128)	Aggressive (n = 130)	p Value
Target vessel			0.91
Left main bifurcation	57 (44.5)	57 (43.8)	
Non-left main bifurcation	71 (55.5)	73 (56.2)	
LAD/diagonal	52 (40.6)	66 (50.8)	
LCX/OM	10 (7.8)	3 (2.3)	
RCA bifurcation	9 (7.0)	4 (3.1)	
Medina classification			0.74
True bifurcation	82 (64.1)	89 (68.5)	0.46
1.1.1	68 (53.1)	76 (58.5)	
1.0.1	8 (6.3)	4 (3.1)	
0.1.1	6 (4.7)	9 (6.9)	
Nontrue bifurcation	46 (35.9)	41 (31.5)	0.46
1.0.0	2 (1.6)	2 (1.5)	
0.1.0	26 (20.3)	19 (14.6)	
1.1.0	17 (13.3)	19 (14.6)	
0.0.1	1 (0.8)	1 (0.8)	
Remote site intervention	39 (30.5)	35 (26.9)	0.53
IVUS guidance	124 (96.9)	128 (98.5)	0.45
Type of stent used			0.57
Sirolimus-eluting stent	60 (46.9)	62 (47.7)	
Everolimus-eluting stent	40 (31.3)	35 (26.9)	
Other drug-eluting stents	28 (21.9)	33 (25.4)	
Main vessel			
No. of stents per lesion	1.2 ± 0.4	1.2 ± 0.4	0.41
Total stent length, mm	24.9 ± 5.6	25.1 ± 5.3	0.76
Maximal stent diameter, mm	3.3 ± 0.4	3.3 ± 0.4	0.45
Maximal balloon pressure, atm	15.1 ± 3.4	14.7 ± 3.1	0.24
Side branch			
Balloon inflation	33 (25.8)	89 (68.5)	<0.001
Kissing balloon inflation	33 (25.8)	89 (68.5)	<0.001
Stent implantation	9 (7.0)	39 (30.0)	<0.001
No. of stents per lesion	1.0 ± 0.0	1.0 ± 0.2	0.64
Total stent length, mm	18.4 ± 7.8	17.7 ± 5.6	0.73
Maximal stent diameter, mm	2.8 ± 0.2	2.9 ± 0.4	0.46
Maximal balloon pressure, atm	14.3 ± 3.0	15.7 ± 2.6	0.17
Treatment according to randomization	128 (100)	129 (99.2)	>0.99

Values are n (%) or mean ± SD.
IVUS = intravascular ultrasound; LAD = left anterior descending artery; LCX = left circumflex artery; OM = obtuse marginal; RCA = right coronary artery.

(44%) with LM bifurcation lesions, TVF rate was numerically lower in the conservative group than the aggressive group (14.0% vs. 22.8%), but the differences were not significant (HR: 1.69, 95% CI: 0.70 to 4.07). In 144 patients (56%) with non-LM bifurcation lesions, the TVF rate was also insignificantly lower in the conservative group than the aggressive group (9.9% vs. 19.2%, hazard ratio: 2.02, 95% confidence interval: 0.81 to 5.00).

DISCUSSION

We compared different strategies for provisional SB ballooning and stenting in patients undergoing

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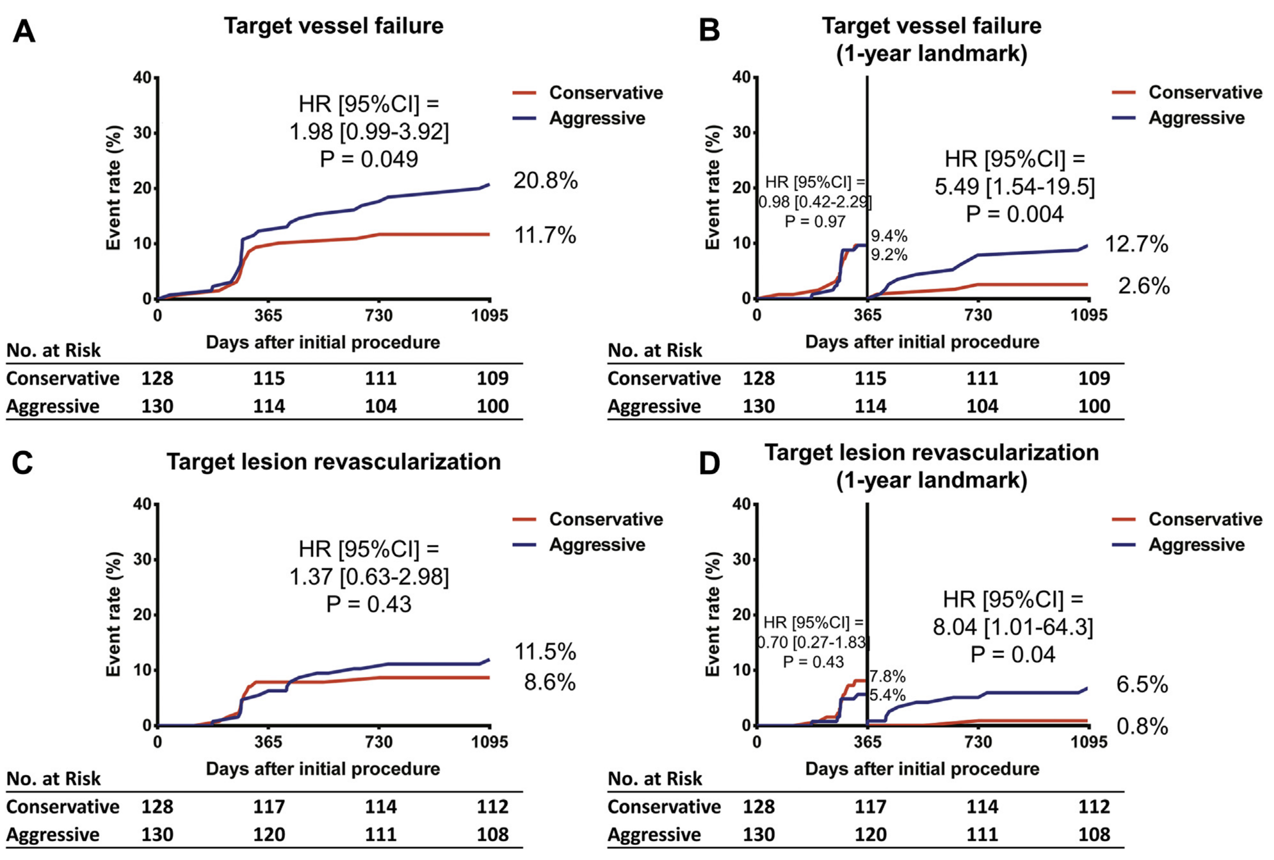
TABLE 3 Clinical Outcomes at 1-Year, From 1 Year to 3 Years, and at 3-Year Follow-Up According to Treatment Strategy

	1 Year			1 Year to 3 Years			3 Years		
Outcome	Conservative	Aggressive	p Value	Conservative	Aggressive	p Value	Conservative	Aggressive	p Value
TVF*	12 (9.4)	12 (9.2)	0.97	3 (2.6)	15 (12.7)	0.004	15 (11.7)	27 (20.8)	0.049
Cardiac death or MI	0	1 (0.8)	>0.99	1 (0.8)	7 (5.4)	0.07	1 (0.8)	8 (6.2)	0.036
Cardiac death	0	1 (0.8)	>0.99	1 (0.8)	3 (2.3)	0.62	1 (0.8)	4 (3.1)	0.37
Spontaneous MI	0	0	–	0	4 (3.1)	0.12	0	4 (3.1)	0.12
Definite or probable ST	0	1 (0.8)	>0.99	0	1 (0.8)	>0.99	0	2 (1.5)	0.50
TBR	6 (4.7)	4 (3.1)	0.50	1 (0.8)	5 (4.0)	0.21	7 (5.5)	9 (6.9)	0.63
TLR	10 (7.8)	7 (5.4)	0.43	1 (0.8)	8 (6.5)	0.04	11 (8.6)	15 (11.5)	0.43
For main vessel	5 (3.9)	4 (3.1)	0.75	0	8 (6.3)	0.007	5 (3.9)	12 (9.2)	0.08
For side branch	5 (3.9)	4 (3.1)	0.75	1 (0.8)	3 (2.4)	0.62	6 (4.7)	7 (5.4)	0.80
TVR	12 (9.4)	11 (8.5)	0.80	2 (1.7)	10 (8.4)	0.02	14 (10.9)	21 (16.2)	0.22

Values are n (%). *Defined as a composite of cardiac death, spontaneous MI, or TVR.
MI = myocardial infarction; ST = stent thrombosis; TBR = target bifurcation revascularization; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization.

FIGURE 3 Clinical Outcomes at 3-Year Follow-Up



Time-to-event curves in patients randomized to conservative versus aggressive strategy. **(A)** Target vessel failure through 3 years. **(B)** Target vessel failure through 1 year and from 1 year through 3 years (landmark analysis). **(C)** Target lesion revascularization through 3 years. **(D)** Target lesion revascularization through 1 year and from 1 year through 3 years (landmark analysis). CI = confidence interval; HR = hazard ratio.

TABLE 4 Independent Predictors of TVF and TLR at 3-Year Follow-Up

	Hazard Ratio (95% CI)	p Value
TVF		
Crossover to 2-stent (vs. 1-stent) technique	5.42 (2.03–14.5)	<0.001
Remote site intervention	2.43 (1.28–4.64)	0.007
Stent length of main vessel (per 10 mm)	1.93 (1.06–3.54)	0.03
Second-generation DES (vs. first-generation DES)	0.48 (0.24–0.96)	0.04
TLR		
Crossover to 2-stent (vs. 1-stent) technique	3.15 (1.00–9.88)	0.049
Remote site intervention	2.53 (1.10–5.82)	0.03
Second-generation DES (versus first-generation DES)	0.32 (0.13–0.79)	0.01

Multivariable Cox regression models were adjusted by clinically relevant variables (see Online Tables 3 and 4).

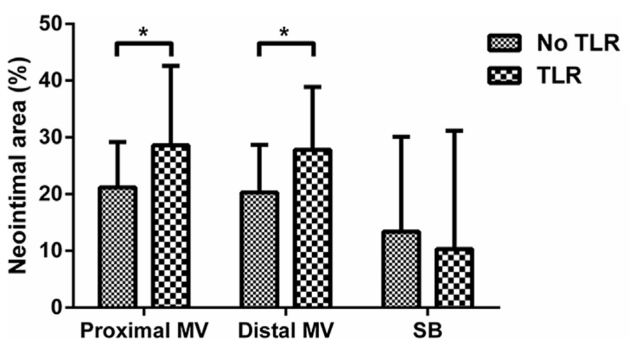
CI = confidence interval; DES = drug-eluting stent; other abbreviations as in Table 3.

coronary bifurcation intervention from the prospective, randomized SMART-STRATEGY trial. The principal findings were the following: 1) compared with an aggressive strategy, long-term clinical benefits were seen in patients treated with a conservative strategy for provisional SB intervention; 2) the clinical benefits of a conservative strategy for provisional SB intervention appeared remarkably in the landmark analysis between 1 year and 3 years, mainly driven by the difference of TLR for MV; 3) it is possible that MV TLR resulted from neointimal hyperplasia on the MV stent; 4) the crossover to the 2-stent technique was an independent predictor of TVF and TLR at 3-year follow-up; 5) the use of second-generation DES was independently associated with lower rates of TVF and TLR at 3-year follow-up; 6) a conservative strategy for provisional SB intervention in LM bifurcation was still feasible and effective during 3-year follow-up.

Simple MV stenting with provisional SB intervention is considered the standard approach for the treatment of most bifurcation lesions (11–14). However, when and how to perform SB ballooning or stenting after MV stenting is still debated. Previous studies comparing a provisional approach with an elective 2-stent approach used different criteria for SB stenting, resulting in highly variable rates of crossover to a 2-stent technique during provisional SB intervention (3–7). In addition, routine final kissing balloon dilation did not improve clinical outcomes in patients treated with MV stenting (15–17). The SMART-STRATEGY trial enrolled patients with large bifurcation lesions including LM bifurcation lesions to compare different strategies for provisional SB intervention in patients undergoing coronary bifurcation PCI. A conservative strategy for provisional SB intervention, compared with an aggressive strategy, was associated with a lower rate of crossover to a 2-stent technique and a lower incidence of procedure-related myocardial necrosis (8). Although no significant difference in 1-year TVF was seen in the 2 groups, significantly fewer TVF events were observed in patients treated with the conservative strategy between 1 and 3 years. It is mainly driven by the difference of TLR for MV. On follow-up IVUS, the percentages of neointimal area in the proximal MV and distal MV at 9 months were associated with TLR after 1 year. It is possible that other factors, such as stent deformation caused by kissing balloon inflation and an overlapping stent strut, might contribute to late adverse clinical events more than 1 year after stent implantation. Compared with the conservative strategy, crossover to a 2-stent technique was required more frequently in the aggressive strategy group. As a result, most TLR after 1 year might occur in the MV of patients treated with the aggressive strategy.

Different strategies for SB intervention resulted in the discrepancies in procedural steps between the 2 groups. Kissing balloon inflation and crossover to a 2-stent technique were implemented less frequently in the conservative group than the aggressive group, which might explain the long-term superiority of the conservative strategy observed in this randomized trial. In the multivariable analysis, the crossover to the 2-stent technique was the most powerful independent predictor of TVF, but kissing balloon

FIGURE 4 Association Between Percentage of Neointimal Area at 9-Month Follow-Up and TLR After 1 Year



The percentages of neointimal area in the proximal MV and distal MV at 9-month follow-up were associated with TLR after 1 year. *p <0.05. MV = main vessel; SB = side branch; TLR = target lesion revascularization.

TABLE 5 Clinical Outcomes at 3-Year Follow-Up in Left Main and Non-Left Main Bifurcation

	Left Main Bifurcation			Non-Left Main Bifurcation			
	Conservative (n = 57)	Aggressive (n = 57)	Hazard Ratio (95% CI)	Conservative (n = 71)	Aggressive (n = 73)	Hazard Ratio (95% CI)	Interaction p Value
TVF*	8 (14.0)	13 (22.8)	1.69 (0.70–4.07)	7 (9.9)	14 (19.2)	2.02 (0.81–5.00)	0.80
Cardiac death or MI	0	4 (7.0)	–	1 (1.4)	4 (5.5)	3.98 (0.44–35.6)	1.00
Cardiac death	0	3 (5.3)	–	1 (1.4)	1 (1.4)	0.97 (0.06–15.5)	1.00
Spontaneous MI	0	1 (1.8)	–	0	3 (4.1)	–	–
Definite or probable ST	0	2 (3.5)	–	0	0	–	–
TBR	5 (8.8)	7 (12.3)	1.47 (0.47–4.64)	2 (2.8)	2 (2.7)	0.96 (0.14–6.83)	0.71
TLR	6 (10.5)	7 (12.3)	1.21 (0.41–3.59)	5 (7.0)	8 (11.0)	1.58 (0.52–4.82)	0.74
For main vessel	2 (3.5)	4 (7.0)	2.07 (0.38–11.3)	3 (4.2)	8 (11.0)	2.68 (0.71–10.1)	0.81
For side branch	4 (7.0)	6 (10.5)	1.58 (0.45–5.61)	2 (2.8)	1 (1.4)	0.48 (0.04–5.29)	0.39
TVR	8 (14.0)	10 (17.5)	1.30 (0.51–3.31)	6 (8.5)	11 (15.1)	1.84 (0.68–4.98)	0.63

Values are n (%). *Defined as a composite of cardiac death, spontaneous MI, and TVR.
Abbreviations as in Tables 3 and 4.

inflation was not associated with long-term clinical outcomes. These findings might suggest that a 2-stent technique itself has an adverse effect on long-term clinical outcomes of patients with coronary bifurcation lesions, irrespective of patient or lesion complexity. Two stents had greater metal burden, leading to an increased risk of MI (18). In addition, the 2-stent techniques are more complex and might be associated with suboptimal stent expansion, leading to a higher risk of adverse cardiovascular events (11–14). The use of second-generation DES was associated with lower rates of TVF and TLR at 3-year follow-up. It is coincident with the long-term results of recently published studies comparing the first- and second-generation DES (19,20). To clarify the clinical benefit of the newer generation DES, randomized, controlled trials are warranted.

LM bifurcation has a large SB with a large amount of subtended myocardium compared with a non-LM bifurcation lesion, and the approach to keep the SB just patent might be limited. Therefore, we chose different criteria for the conservative strategy for provisional SB intervention: the initiation of an SB intervention was a stenosis diameter >75% in the SB after MV stenting. This criterion was derived from a functional study that most lesions with a stenosis diameter <75% in the SB after MV stenting are not associated with ischemia and thus do not require further intervention (21). In the present study, there was no significant interaction between treatment strategy and TVF across the LM bifurcation lesions, and the favorable result of conservative strategy for a provisional SB intervention in overall population might apply to the LM and non-LM bifurcation subgroups. It might be caused from more crossovers to the 2-stent technique in the aggressive approach compared with the conservative approach in both LM and non-LM bifurcation lesions. According to recent registry data, use of the 1-stent technique for the treatment of LM bifurcation lesions was associated with a significant reduction in major adverse cardiac events compared with the 2-stent technique (22–24). Considering the recent registry findings and our long-term follow-up results, a conservative strategy might be feasible for a provisional SB intervention for most LM bifurcation lesions. Adequately powered randomized, controlled trials including LM bifurcation lesions are required to confirm the efficacy and safety of a conservative strategy for provisional SB intervention.

STUDY LIMITATIONS. First, the statistical power was low because of a lower than expected event rate. In particular, the rate of stent thrombosis appeared quite low, despite a bifurcation lesion, a large proportion of first-generation DES, and long duration of follow-up. A possible explanation for the low event rate was that stent implantation in all patients was optimized by IVUS. IVUS guidance during PCI for bifurcation lesions might have helped reduce the event rate (25–27). Second, this study was designed to include coronary bifurcation lesions with an MV diameter ≥2.5 mm and an SB diameter ≥2.3 mm by visual estimation, not quantitative coronary angiographic analysis. As a result, this study included coronary bifurcation lesions with an SB diameter smaller than 2.3 mm by quantitative coronary angiographic analysis. Visual assessment is more variable and less precise compared with quantitative coronary angiographic analysis, and bifurcation-dedicated software packages are suitable for quantitative assessment of bifurcations before and after intervention (28,29). Third, because the study was an open-label trial, both patients and operators were not blinded to the strategy used, which might have introduced bias in symptom assessment at follow-up. In addition, routine angiographic follow-up at 9 months may have had a delayed oculostenotic impact on the outcomes. Fourth, many patients were treated with the first-generation DES, which are not used currently. Our findings should be tested in a large-scale confirmatory trial using newer generation DES. Fifth, the provisional approach in coronary bifurcation lesions usually means provisional SB stenting after MV stenting. In this study, our strategies for provisional SB intervention included SB ballooning followed by kissing ballooning after MV stenting. Finally, T-stenting and a small protrusion technique were exclusively used in all cases of SB stenting. Thus, extrapolating the findings of this study to other 2-stent techniques might not be appropriate.

CONCLUSIONS

In patients with a large coronary bifurcation lesion undergoing bifurcation stenting via a provisional approach, a conservative strategy for provisional SB intervention was associated with better 3-year clinical outcomes compared with an aggressive strategy. The conservative strategy might be considered the preferred approach for provisional SB intervention.

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PERSPECTIVES

WHAT IS KNOWN? Although the 1-stent technique with a provisional SB intervention is now regarded as the standard technique for most bifurcation lesions, the appropriate criteria for SB ballooning or stenting have not been established.

WHAT IS NEW? The conservative strategy for provisional SB intervention had better long-term clinical outcomes compared with the aggressive strategy, mainly due to lower crossover rate to the 2-stent technique. The clinical benefits of a conservative strategy for provisional SB intervention appeared remarkably in the landmark analysis between 1 and 3 years, mainly driven by the difference of TLR for MV.

WHAT IS NEXT? A large-scale confirmatory study is needed to determine optimal strategies for provisional SB intervention in coronary bifurcation lesions using newer generation DES.

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KEY WORDS bifurcation, coronary artery disease, side branch, treatment strategy

APPENDIX For supplemental material and tables, please see the online version of this article.