

Comparison of First- and Second-Generation Drug-Eluting Stents for Bifurcation Stenting Followed by the Final Kissing-Balloon Technique

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ABSTRACT

Introduction: Percutaneous coronary intervention (PCI) for bifurcated lesions is challenging. We assessed the procedural performance and clinical outcomes of first- and second-generation drug-eluting stents (DES) in bifurcation stenting followed by the final kissing-balloon (FKB) technique.

Methods: We retrospectively analyzed 192 patients (222 lesions) who underwent PCI for bifurcated lesions. In all cases, lesions were stented, followed by FKB. Clinical outcomes were compared for the two generations—first generation (80 patients/88 lesions) vs. second generation (112 patients/134 lesions). The primary endpoint was target-lesion failure (TLF), defined as cardiac death, target-lesion revascularization, or target-lesion-related stent thrombosis at 2 years.

Results: TLF incidence was higher for first-generation DES than for second-generation DES (12.5% vs. 2.7%; $P = 0.001$). A Cox proportional hazard analysis revealed that first-generation DES (hazard ratio [HR]: 6.32, 95% confidence interval [CI]: 1.72-23.1, $P = 0.005$), age ≥ 75 years (HR: 1.55, 95% CI: 1.17-2.03, $P = 0.001$), and left main trunk PCI (HR: 3.89, 95% CI: 1.30-11.5, $P = 0.01$) were independent predictors of TLF after bifurcation stenting followed by FKB. Notably, age ≥ 75 years (HR: 1.70, 95% CI: 1.27-2.28, $P < 0.01$) and left main trunk PCI (HR: 4.72, 95% CI: 1.35-16.5, $P = 0.01$) were associated with an increased TLF for patients who were treated with first-generation DES. No prognostic factor of TLF was found for patients with second-generation DES.

Conclusions: In bifurcation stenting followed by FKB, outcomes are better for second-generation DES than for first-generation DES.

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KEYWORDS: percutaneous coronary intervention, drug-eluting stent, bifurcation stenting, final kissing-balloon technique, target-lesion revascularization

Introduction

Percutaneous coronary intervention (PCI) is more chal-

lenging for bifurcated lesions than for non-bifurcated lesions because bifurcation stenting is associated with increased risk of target-lesion failure (TLF) after PCI.^{1,2)} In

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addition to lesion difficulties with respect to optimal stent placement, hemodynamics at bifurcations, such as increased shear stress and induced flow perturbation, lead to poorer outcomes.³⁾

The final kissing-balloon (FKB) technique is commonly used for dilating lesions at bifurcations. It requires simultaneous or sequential inflation of two coronary balloons, i.e., in the main vessel and side branch, after deploying a coronary stent.^{4,5)} FKB seems to be better for maintaining blood flow after well-conditioned stent placement in bifurcations; however, some studies found that FKB is associated with higher incidences of cardiovascular events, including cardiac mortality, repeat revascularization, and stent thrombosis, when first-generation drug-eluting stents (DES) are used.^{6,7)} Second-generation DES have improved clinical and procedural outcomes for patients with coronary artery disease.^{8,9)} Improvements in stent strut, polymer biocompatibility, and drug elution have contributed to reduce the incidence of serious adverse events after stent implantation. However, few studies have compared the outcomes after bifurcation PCI with first- or second-generation DES. To address this shortcoming, we assessed the procedural performance and 2-year clinical outcomes of first- and second-generation DES at bifurcations followed by FKB.

Methods

Study sample

We retrospectively analyzed clinical data for 1,305 consecutive patients with angina (1,434 lesions) who underwent PCI with DES; 192 patients (222 lesions) had undergone elective PCI for bifurcated lesions during the period from May 2006 to May 2013. The analysis used information included in a prospective database at Toho University Omori Medical Center.

The inclusion criteria were the following: (1) a coronary bifurcation lesion treated with first- or second-generation DES; (2) main-vessel diameter >2.5 mm and a clinically important side branch in bifurcation (>2.0 mm) or a need for wire insertion for protection or treatment; and (3) treatment with FKB after main-vessel stent deployment. Lesions treated with the two-stent approach were not excluded. The two-stent approach was provisionally selected when closure or flow-limiting dissection occurred in the side-branch ostium after stent deployment in the main vessel. The exclusion criteria were the following: (1) treatment failure; (2) use of a bare-metal stent; and (3) a diagno-

sis of acute coronary syndrome, including myocardial infarction and unstable angina. Diagnostic angiograms were scored according to the SYNTAX score algorithm at the core laboratory.¹⁰⁾

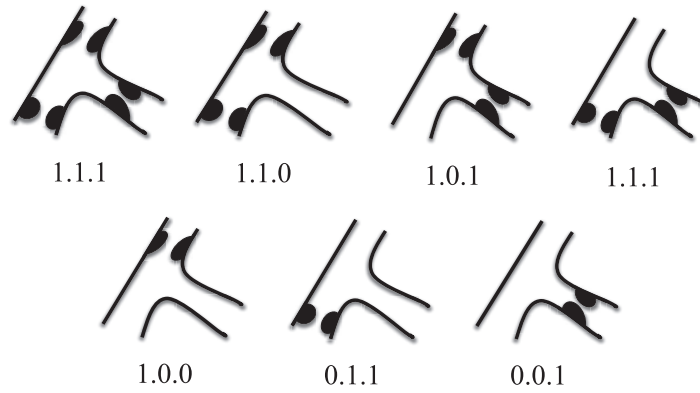
First-generation DES were used from May 2006 until November 2011. These included sirolimus-eluting stents (SES; CYPHER; Cordis/Johnson & Johnson, Warren, NJ, USA) and paclitaxel-eluting stents (PES; TAXUS; Boston Scientific, Natick, MA, USA). Second-generation DES were used between May 2009 and May 2013. These included zotarolimus-eluting stents (ZES; Endeavor and Resolute Integrity; Medtronic, Santa Rosa, CA, USA), everolimus-eluting stents (EES; XIENCE PRIME, XIENCE V, and XIENCE Xpedition; Abbott Vascular, Santa Clara, CA, USA, or PROMUS and PROMUS Element; Boston Scientific), and biolimus-eluting stents (BES; NOBORI; Terumo, Tokyo, Japan).

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the relevant ethics committee of Toho University Omori Medical Center (No. M17092). Informed consent was obtained from all patients.

PCI and angiography

PCI was performed according to the current standard guidelines.¹¹⁾ Patients received 100 mg aspirin and either 150 mg clopidogrel or 200 mg ticlopidine before PCI if dual antiplatelet therapy had not been previously prescribed. Intravenous fractured heparin (100 U/kg) was administered for anticoagulation during PCI. PCI strategies for bifurcation—including stenting techniques, type of stent, and additional FKB after stenting—were selected by the operators. All PCI were done by five well-experienced interventionists during the study period, so performance was not different between patients. All patients were on dual antiplatelet therapy (DAPT) before PCI, and as shown in the method section, we continued DAPT in the study population. In the follow-up after discharge, patients were treated as outpatients in the department of cardiovascular medicine at Toho University Omori Medical Center. When patients were referred to local clinics, they regularly underwent cardiovascular examinations such as blood testing, ECG, and UCG at our department in the follow-up periods.

Systematic follow-up angiography was mandatory at 6 to 12 months postoperatively. Quantitative coronary angiography (QCA) was analyzed off-line after the main-vessel stenting and FKB by an experienced investigator using



	1.1.1.	1.1.0	1.0.1	0.1.1	1.0.0.	0.1.0	0.0.1
1st-gen DES, n (%)	30 (34.1%)	4 (4.5%)	20 (22.7%)	24 (27.2%)	2 (2.3%)	7 (8.0%)	1 (1.1%)
2nd-gen DES, n (%)	47 (35.1%)	12 (9.0%)	22 (16.4%)	33 (24.6%)	4 (3.0%)	13 (9.7%)	3 (2.2%)

Fig. 1 Lesion characteristics according to the Medina classification.

validated, commercially available, edge detection software (CCIP 310 system; Gadelius Medical Co., Tokyo, Japan). The reference diameter and minimal lumen diameter were measured for the proximal main vessel and the side-branch vessel. Lesion length was also measured. For the main vessel, the reference diameter was the average of the proximal and distal reference lumen diameters. The percent diameter stenosis was calculated using the following equation: $100 \times (\text{reference diameter} - \text{minimal lumen diameter}) / \text{reference diameter}$. Diastolic frame was taken at the angle with the least shrinkage of the lesion, and the image was recorded in the same angle before and after treatment. Medina classification is expressed as 1 or 0, according to the presence or absence of $>50\%$ diameter stenosis in the proximal main vessel, distal main vessel, and side-branch components of the bifurcation (Fig. 1). Medina classification was based on visual inspection by the operator. A true bifurcated lesion was defined as one significantly involving both the main vessel and side-branch ostium. Thus, lesions with Medina classifications of (1.1.1), (1.0.1), and (0.1.1) were considered true bifurcations.

Clinical follow-up and endpoints

The primary endpoint of this study was the incidence of TLF at 2 years, including cardiac death, target-lesion revascularization (TLR), and target-lesion-related stent thrombosis.

Statistical analysis

Data were analyzed using the Statistical Package for EZR for Windows (version 1.35, Saitama, Japan). Data were expressed as mean \pm standard deviation. The Kolmogorov-

Smirnov test was used to assess the normality of the distribution. Continuous variables were compared using the Student's *t*-test. For data with a non-normal distribution, the non-parametric Mann-Whitney *U* test was used for comparisons between groups. The chi-square test or Fisher exact test was used to analyze categorical variables. Survival free from major events was analyzed by Kaplan-Meier analysis, and the resulting curves were compared with the log-rank test. Cox proportional hazards analysis was performed to identify independent predictors of TLF during the entire observation period. The multi-variable Cox proportional hazards model was built by stepwise variable selection with entry and exit criteria set at the $P < 0.15$ level.

Results

Baseline and clinical characteristics of patients

Between May 2006 and May 2013, 197 patients received PCI with FKB. We had two failure cases in the first-generation DES group and three cases in the second-generation DES group. There was no statistical difference between them. Therefore, a total of 192 patients (222 lesions) were studied. The baseline characteristics of the patients are shown in Table 1. The baseline characteristics matched well between the first-generation DES group and second-generation DES group, except for stent selection. All patients were successfully treated by bifurcation PCI with FKB. First-generation DES were used for 80 patients (88 lesions [SES = 56, PES = 32]), and second-generation DES were used for 112 patients (134 lesions [SES = 82,

Table 1 Baseline characteristics of the study population.

Characteristic	1st-gen DES (n = 80 pts, 88 lesions)	2nd-gen DES (n = 112, 134 lesions)	P value
<i>Clinical</i>			
Age, years	67.6 ± 10.1	66.5 ± 10.8	0.48
Age ≥75 years, %	18 (22.5)	36 (18.8)	0.25
Female, %	12 (15.0)	28 (24.8)	0.1
Hypertension, %	48 (60.0)	78 (69.0)	0.28
Diabetes mellitus, %	34 (42.5)	58 (51.3)	0.25
Dyslipidemia, %	53 (66.3)	76 (67.3)	1.0
History of smoking, %	56 (70.0)	71 (62.8)	0.36
Prior PCI, %	45 (56.3)	57 (50.4)	0.47
Serum creatinine, mg/dl	1.43 ± 1.92	1.29 ± 2.02	0.64
CKD, %	28 (35.0)	22 (34.5)	0.88
Ejection fraction, %	60.9 ± 13.9	62.2 ± 11.9	0.5
Ejection fraction <50%	16 (20.0)	21 (18.8)	0.85
Follow-up duration, months	23.1 ± 4.2	23.2 ± 3.1	0.23
<i>Medications</i>			
Dual antiplatelet therapy, %	79 (98.9)	110 (98.2)	1.0
Beta blockers, %	33 (41.3)	58 (51.8)	0.19
RAAS inhibitors, %	61 (76.2)	82 (73.2)	0.73
Statins, %	55 (68.8)	78 (69.6)	1.0
<i>Angiography</i>			
Left main trunk, %	16 (20.0)	31 (27.7)	0.4
Left anterior descending, %	49 (55.7)	64 (47.7)	0.21
Left circumflex, %	16 (18.1)	32 (23.9)	0.32
Right coronary artery, %	7 (7.9)	7 (5.2)	0.57
True bifurcation, %	74 (84.0)	102 (76.2)	0.17
Multi-vessel disease, %	57 (64.7)	86 (64.1)	1.0
SYNTAX score	13.9 ± 8.8	12.1 ± 7.4	0.11
<i>Quantitative coronary angiography</i>			
Late loss, mm	0.45 ± 0.51	0.19 ± 0.5	<0.001
Lesion length, mm	21.1 ± 9.13	22.2 ± 6.62	0.3
Reference diameter, mm	2.94 ± 0.69	2.79 ± 0.65	0.09
Minimal luminal diameter, mm	1.03 ± 0.57	0.92 ± 0.62	0.16
<i>Procedural parameters</i>			
Two-stent approach, %	38 (43.8)	44 (32.3)	0.12
Final kissing balloon technique, %	88 (100)	134 (100)	1.0
Main vessel stent diameter ≥3.5 mm, %	16 (18.1)	19 (14.1)	0.45
Main vessel total stent length ≥24 mm, %	35 (39.7)	60 (44.7)	0.49
Fluoroscopy time, min	30.3 ± 11.8	31.1 ± 10.2	0.70
<i>Clinical outcome</i>			
TLF, %	12 (12.5)	3 (2.7)	0.001
Cardiac death, %	5 (6.3)	0 (0)	<0.01
TLR, %	9 (10.2)	3 (2.2)	0.01
Target lesion-related stent thrombosis	2 (2.3)	1 (0.74)	0.57

Abbreviations: 1st-gen DES, first-generation drug-eluting stent; 2nd-gen DES, second-generation drug-eluting stent; HR, hazard ratio; 95% CI, 95% confidence interval; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; RAAS, renin angiotensin aldosterone system; IVUS, intravascular ultrasound; TLF, target lesion failure; TLR, target lesion revascularization.

ZES= 14, BES = 38]).

Culprit bifurcated lesions were located in the left main trunk (LMT; n = 47; 21.1%), left anterior descending (n =

113; 50.9%), left circumflex (n = 48; 21.6%), and right coronary artery (n = 14; 6.3%). There was no significant difference between groups in conventional coronary risk fac-

tors, including sex, age, or presence of hypertension, diabetes, chronic kidney disease, or dyslipidemia.

Past history of coronary revascularization was similar for the first- and second-generation DES groups. There was no significant difference between groups in terms of prescribed medications, including DAPT, beta-blockers, statins, or inhibitors of the renin-angiotensin-aldosterone system (angiotensin-converting enzyme inhibitors and angiotensin-II-receptor blockers). The two-stent approach was used for 43.8% of patients in the first-generation DES group and for 32.3% of patients in the second-generation DES group. There was no significant difference in the diameter of the stent used for the main vessel: the stent diameter was greater than 3.5 mm for 18.1% of first-generation DES and 14.1% of second-generation DES. Stent length in the main vessel was similar between the two groups.

QCA data revealed no significant difference in lesion length between groups. There was no significant difference in minimum lesion diameter between groups. At follow-up coronary angiography, late loss was significantly greater for the first-generation DES group than for the second-generation DES group (0.19 ± 0.50 mm vs. 0.45 ± 0.51 mm, respectively; $P < 0.001$).

Clinical outcomes at 2 years

The mean follow-up duration was 23.3 ± 3.3 months. Kaplan-Meier analysis revealed an overall cumulative TLF incidence of 7.8% at 2 years (12.5% for the first-generation DES group and 2.7% for the second-generation DES group; $P = 0.009$; Fig. 2A). Among the components of TLF, the rate of cardiac death for the first-generation DES group was significantly higher than that for the second-generation DES group (6.3% vs. 0%, $P = 0.0008$; Fig. 2B). In the first-generation DES group, cardiac death included two deaths by heart failure and three sudden deaths. TLR rate was also significantly higher for the first-generation DES group than for the second-generation DES group (10.2% vs. 2.2%, $P = 0.01$; Fig. 2C). There was no significant difference in the incidence of target-lesion-related stent thrombosis between the two groups (2.3% vs. 0.74%, $P = 0.57$; data not shown).

Independent predictors of TLF

Cox proportional hazards analysis revealed that implantation of first-generation DES was an independent predictor of TLF after adjustment for age ≥ 75 , smoking, and LMT PCI for patients who underwent bifurcation PCI with FKB (Table 2).

Analysis of the differences in clinical and procedural variables for first-generation DES and second-generation DES showed that age ≥ 75 , LMT PCI, and true bifurcation were independent predictors of TLF for the first-generation DES group (Table 3). No predictive factors of TLF were found for the second-generation DES group.

Discussion

We investigated whether second-generation DES are superior to first-generation DES for bifurcation stenting followed by FKB for patients with angina. TLF incidence was significantly higher at 2 years in the first-generation DES group.

Despite recent progress in PCI for coronary artery disease, PCI is more challenging for bifurcations than for other lesions, as indicated by increased TLF, including in-stent restenosis, repeat revascularization, and stent thrombosis.^{12,13} Therefore, cardiovascular interventionalists continue to improve bifurcation PCI.^{2,14,15} The principal aims are to optimize apposition and prevent deformation and distortion of deployed stents. FKB is one of the common bifurcation strategies which is generally considered for side-branch vessels with a diameter greater than 2.5 mm and considerable cardiac muscle distribution to save.^{16,17} There is also an advantage for future revascularization in side branches to secure an access route from the dilated main-vessel stent strut. However, only few studies have found the efficacy of first-generation DES in bifurcation stenting with FKB.^{18,19} Indeed, introduction of first-generation DES followed by FKB for bifurcation lesions is associated with increased TLF as a consequence of overdilation-induced injury of the side branch, strut deformity, polymer disruption of the DES, or main-vessel stent malapposition opposite the side branch.⁶ Theoretically, this mechanical adverse effect of FKB to the deployed stent might equally occur across any stent generations. However, we found that TLF incidence was significantly higher for the first-generation DES group compared with the second-generation DES group. The difference in TLR rate between the groups is most likely attributable to increased binary restenosis—defined by QCA with higher late loss—in the first-generation DES group. We had two patients who had stent thrombosis in the first-generation DES and one in the second-generation DES. In addition, we could not exclude the possibility that cardiac death might be attributable to TLF for two patients in the first-generation DES group. Cox proportional hazards

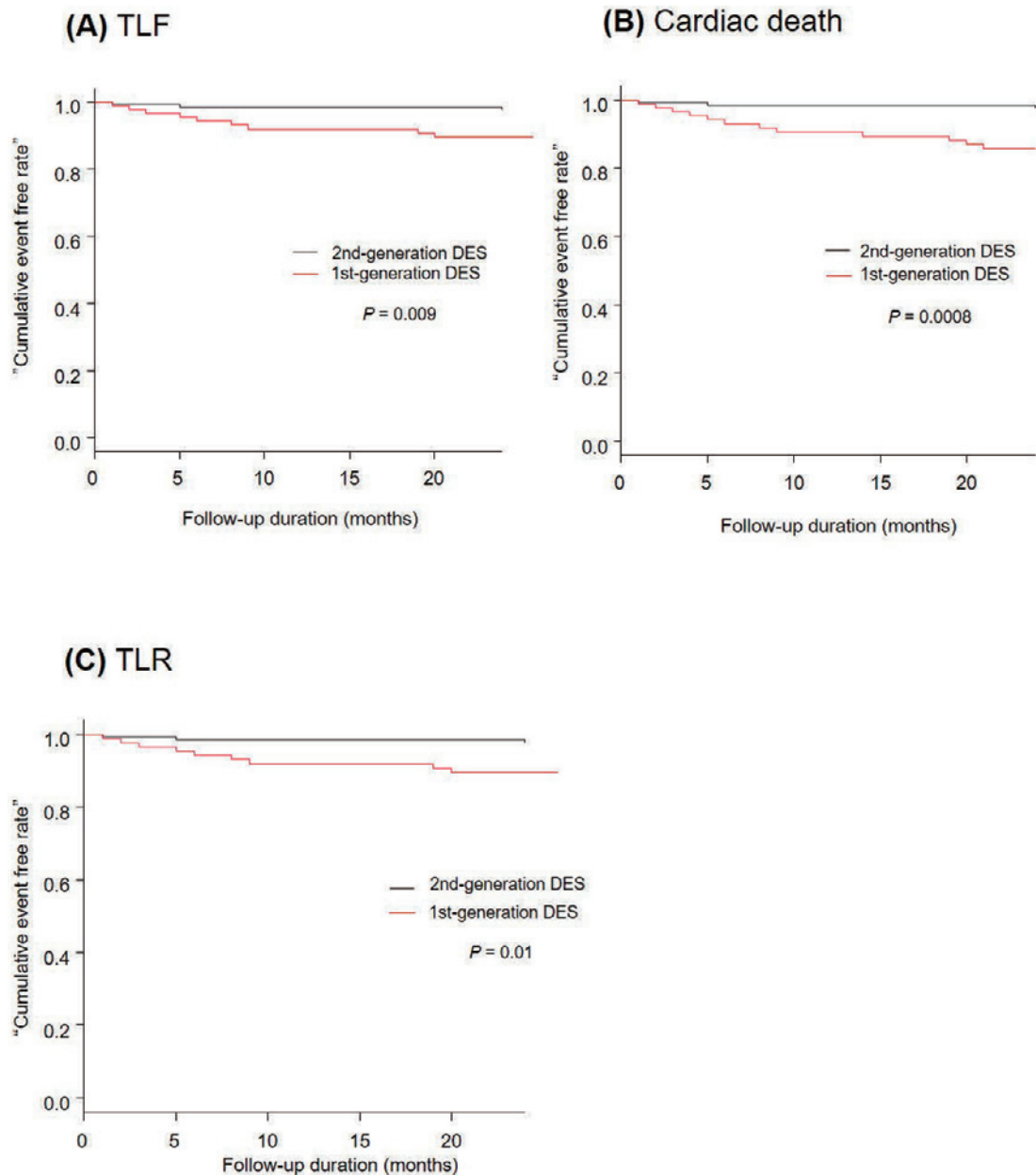


Fig. 2 Kaplan-Meier analyses for TLF (A) and its components, cardiac death (B), and TLR (C).

analysis of TLF incidence revealed that use of first-generation DES was significantly associated with increased TLF. PCI for LMT was also associated with increased TLF, as previously reported.^{17,20} Of importance, the introduction of the two-stent technique was not associated with the difference in outcome between the groups. This was perhaps because the two-stent technique was performed for the side branch bail-out, equally leading to the increasing TLF incidence irrespective of the stent generations. We found that the introduction rates of the two-stent technique among TLF cases were equally high between the two groups (33.3% for the first-generation DES

group and 33.3% for the second-generation DES group).

Finally, for the first-generation DES group, age and LMT PCI were associated with increased TLF in the multivariate analysis. These are the known risk factors of poor cardiovascular outcome demonstrated by previous studies that evaluated the efficacy of first-generation DES in bifurcation PCI.²⁰⁻²² By contrast, we did not identify any involvement of the known predictive factors of cardiovascular events, such as the elderly and diabetes, after the second-generation DES implantation.^{23,24} In comparison with coronary artery bypass, the efficacy and indication of PCI for the LMT lesion have been disputed. According to

Table 2 Independent predictors of TLF by Cox proportional hazard analysis.

Independent predictors of TLF	Univariate analysis		Multivariate analysis	
	HR, 95% CI	P value	HR, 95% CI	P value
Age ≥ 75	1.53, 1.17-2.00	0.001	1.55, 1.17-2.03	0.001
Female	0.63, 0.14-2.80	0.54		
Creatinine	1.02, 0.80-1.31	0.81		
CKD	0.42, 0.11-1.50	0.18		
Hypertension	1.38, 0.44-4.34	0.57		
Dyslipidemia	1.09, 0.37-3.19	0.87		
Diabetes	0.95, 0.34-2.63	0.92		
History of smoking	3.67, 0.83-16.3	0.08		
Ejection fraction	1.01, 0.96-1.05	0.64		
1 st -generation DES	6.52, 1.84-23.1	0.003	6.32, 1.72-23.1	0.005
Multi-vessel disease	1.08, 0.37-3.17	0.88		
LMT	2.57, 0.91-7.22	0.07	3.89, 1.30-11.5	0.01
Prior PCI	1.58, 0.54-4.62	0.40		
True bifurcation	0.68, 0.21-2.15	0.51		
Large stent (≥ 3.5 mm)	0.79, 0.18-3.53	0.76		
Stent Length ≥ 24 mm	1.57, 0.56-4.33	0.38		
Two-stent approach	0.83, 0.28-2.45	0.74		
Beta blockers	1.27, 0.46-3.50	0.64		
Statins	0.80, 0.27-2.36	0.69		
RAAS inhibitors	0.89, 0.28-2.81	0.85		
Dual antiplatelet therapy	1.41, 0.06-30.2	0.82		
SYNTAX score	1.05, 0.98-1.11	0.12	1.03, 0.94-1.12	0.45

Abbreviations: TLF, target lesion failure; HR, hazard ratio; 95% CI, 95% confidence interval; CKD, chronic kidney disease; DES, drug eluting stent; LMT, left main trunk; PCI, percutaneous coronary intervention; RAAS, renin angiotensin aldosterone system.

Table 3 Independent predictors of TLF for the first-generation DES group for bifurcation PCI.

Independent predictors of TLF in 1 st -generation DES for bifurcation PCI		
	HR, 95% CI	P value
Age ≥ 75	1.70, 1.27-2.28	<0.01
LMT	4.72, 1.35-16.5	0.01
True bifurcation	0.23, 0.06-0.85	0.02
SYNTAX score	1.00, 0.90-1.12	0.92

Abbreviations: TLF, target lesion failure; DES, drug-eluting stent; PCI, percutaneous coronary intervention; HR, hazard ratio; 95% CI, 95% confidence interval; LMT, left main trunk.

the SYNTAX trial, cardiovascular events increase after PCI in patients with higher SYNTAX scores as compared with coronary artery bypass.²⁵⁾ We found that the SYNTAX score tends to be higher in patients who developed TLF, particularly in the first-generation DES group. Of importance, we found that patients with an LMT lesion had a

greater SYNTAX score in both groups (first-generation DES group: 9.66 ± 5.13 vs 22.9 ± 6.14 , $P < 0.01$; second-generation DES group: 9.97 ± 5.21 vs 25.8 ± 6.49 , $P < 0.01$). The small sample size for the overall population, including the very low event rate in the second-generation DES group, might affect the result. Therefore, a larger study is required to compare the efficacy of different stent generations in the bifurcation PCI, particularly among patients with the LMT lesion with a higher SYNTAX score.

Study limitations

First, this study was a post-hoc analysis performed at a single center, which greatly limited the statistical power. Second, we compared the outcomes of first- and second-generation DES in the treatment of bifurcation. Although all patients underwent additional FKB, we did not investigate the actual effectiveness of FKB. Future studies should compare the outcomes of bifurcation PCI with second-generation DES—with or without FKB. Third, we cannot exclude the possibility of an association between the ocular-stenotic reflex and the indications for coronary

intervention. This study required systematic follow-up angiography within 6 to 12 months after PCI, and TLR may not be fully caused by ischemic symptoms even though all vessel stenoses were evaluated by QCA. Fourth, the baseline lesion characteristics in the bifurcation might affect the different outcomes between the groups. We found that a numerically greater number of lesions were classified as Medina (1-1-1) among patients with TLF in the first-generation DES group as compared with those in the second-generation DES group (50% vs 33.3%).

Conclusions

The outcomes for bifurcation stenting followed by FKB are better for second-generation DES than for first-generation DES.

Conflicts of interest: None declared.

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