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Original Article

Comparison of First- and Second-Generation Drug-Eluting Stents for Bifurcation Stenting

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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 underwent stenting, 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 (15.0% vs. 2.7%; $P<0.01$). The first-generation DES (hazard ratio [HR]: 6.41, 95% confidence interval [CI]: 1.75-23.5, $P<0.01$) and SYNTAX score (HR: 1.07, 95% CI: 1.01-1.13, $P = 0.02$) were predictors of TLF after bifurcation stenting followed by FKB. PCI for the left main trunk (HR: 6.22, 95% CI: 1.55-25.0, $P = 0.01$) and SYNTAX score (HR: 1.09, 95% CI: 1.02-1.17, $P = 0.02$) were found to be associated with increased TLF for patients who were treated with first-generation DES, but 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 challenging 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 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 simulta-

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neous or sequential inflation of two coronary balloons, i.e., in the main vessel and the side branch, after deployment of 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 (DESs) are used.[6, 7] Second-generation DESs 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 reduction of 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 were conducted in the side branch ostium after stent deployment in the main vessel. Exclusion criteria were the following: (1) treatment failure, (2) use of a bare-metal stent, and (3) a diagnosis of acute coronary syndrome including myocardial infarction and unstable angina. Diagnostic angiograms were scored according to the SYNTAX score algorithm.[10]

First-generation DESs were used from May 2006 to 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 DESs 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). The comprehensive agreement was obtained from all patients in the form of opt-out on the website of Toho University Omori Medical Center.

PCI and angiography

PCI was performed according to the guidelines in 2006.[11] Patients were recommended to receive 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. Therefore, performance of PCI was not different between patients.

All of patients were on dual antiplatelet therapy (DAPT) before PCI, and DAPT was recommended to continue for at least 12 months. 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 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

	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 (27.3%)	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%)

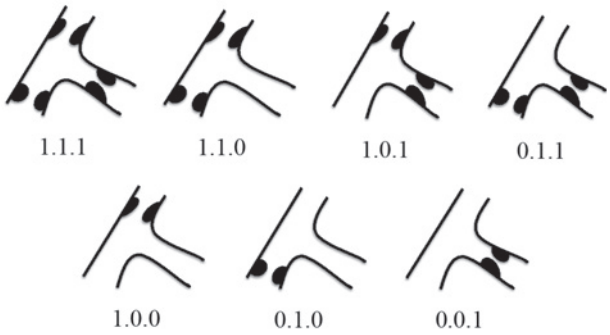

Fig. 1 Lesion characteristics according to the Medina classification.

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 × (reference diameter − minimal lumen diameter) × 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 ± standard deviation. The Kolmogorov-Smirnov test was used to assess the normality of the distribution. Continuous variables were compared using 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-squared test or Fisher exact test was used to analyze categorical variables. Survival free from major events was analyzed using a Kaplan-Meier analysis, and the resulting curves were compared with the log-rank test. The categorical or continuous factors were subjected to a univariate logistic regression analysis to identify predictors of TLF.

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 the groups. Therefore, a total of 192 patients (222 lesions) were studied. The baseline characteristics of the patients are listed in Table 1. The baseline characteristics matched well between the first-generation DES group and the second-generation DES group, except for stent selection. All patients were successfully treated by bifurcation PCI with FKB. First-generation DESs were used for 80 patients (88 lesions [SES = 56, PES = 32]), and second-generation DESs were used for 112 patients (134 lesions [EES = 82, ZES= 14, BES = 38]). DAPT was prescribed in most of the patients (98.4%).

Culprit bifurcated lesions were located in the left main trunk (LMT) (n = 47; 21.2%), 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 factors including sex, age, or presence of hypertension, diabetes, chronic kidney disease, or dyslipidemia.

History of coronary revascularization was similar for the first- and second-generation DES groups. There was no significant difference between groups in terms of pre-

Table 1 Baseline characteristics of the study population.

Characteristic	1st-gen DES (n = 80 pts, 88 lesions)	2nd-gen DES (n = 112 pts, 134 lesions)	*P* value
Clinical			
Age, years	67.6 ± 10.1	66.5 ± 10.8	0.48
Age ≥75 years, %	18 (22.5)	36 (32.1)	0.25
Female, %	12 (15.0)	28 (25.0)	0.10
Hypertension, %	48 (60.0)	78 (69.6)	0.28
Diabetes mellitus, %	34 (42.5)	58 (51.8)	0.25
Dyslipidemia, %	53 (66.3)	76 (67.9)	1.00
History of smoking, %	56 (70.0)	71 (63.4)	0.36
Prior PCI, %	45 (56.3)	57 (50.9)	0.47
Serum creatinine, mg/dl	1.43 ± 1.92	1.29 ± 2.02	0.64
CKD, %	28 (35.0)	38 (33.9)	0.88
Ejection fraction, %	60.9 ± 13.9	62.2 ± 11.9	0.50
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
Medications			
Dual antiplatelet therapy, %	79 (98.8)	110 (98.2)	1.00
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)	1.00
Angiography			
Left main trunk, %	16 (18.2)	31 (23.1)	0.40
Left anterior descending, %	49 (55.7)	64 (47.8)	0.21
Left circumflex, %	16 (18.2)	32 (23.9)	0.32
Right coronary artery, %	7 (8.0)	7 (5.2)	0.57
True bifurcation, %	74 (84.1)	102 (76.1)	0.17
Multi-vessel disease, %	57 (64.8)	86 (64.2)	1.00
SYNTAX score	13.9 ± 8.8	12.1 ± 7.4	0.11
Quantitative coronary angiography			
Late loss, mm	0.45 ± 0.51	0.19 ± 0.5	<0.01
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
Procedural parameters			
Two-stent approach, %	38 (43.8)	44 (32.8)	0.12
Final kissing balloon technique, %	88 (100)	134 (100)	1.0
Main vessel stent diameter ≥3.5 mm, %	16 (18.2)	19 (14.2)	0.45
Main vessel total stent length ≥24 mm, %	35 (39.8)	60 (44.8)	0.49
Fluoroscopy time, min	30.3 ± 11.8	31.1 ± 10.2	0.70
Clinical outcome			
TLF, %	12 (15.0)	3 (2.7)	<0.01
Cardiac death, %	5 (6.3)	0 (0)	<0.01
TLR, %	9 (10.2)	3 (2.2)	0.03
Target lesion–related stent thrombosis	2 (2.3)	1 (0.75)	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.

scribed 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 32.8% of patients in the second-generation

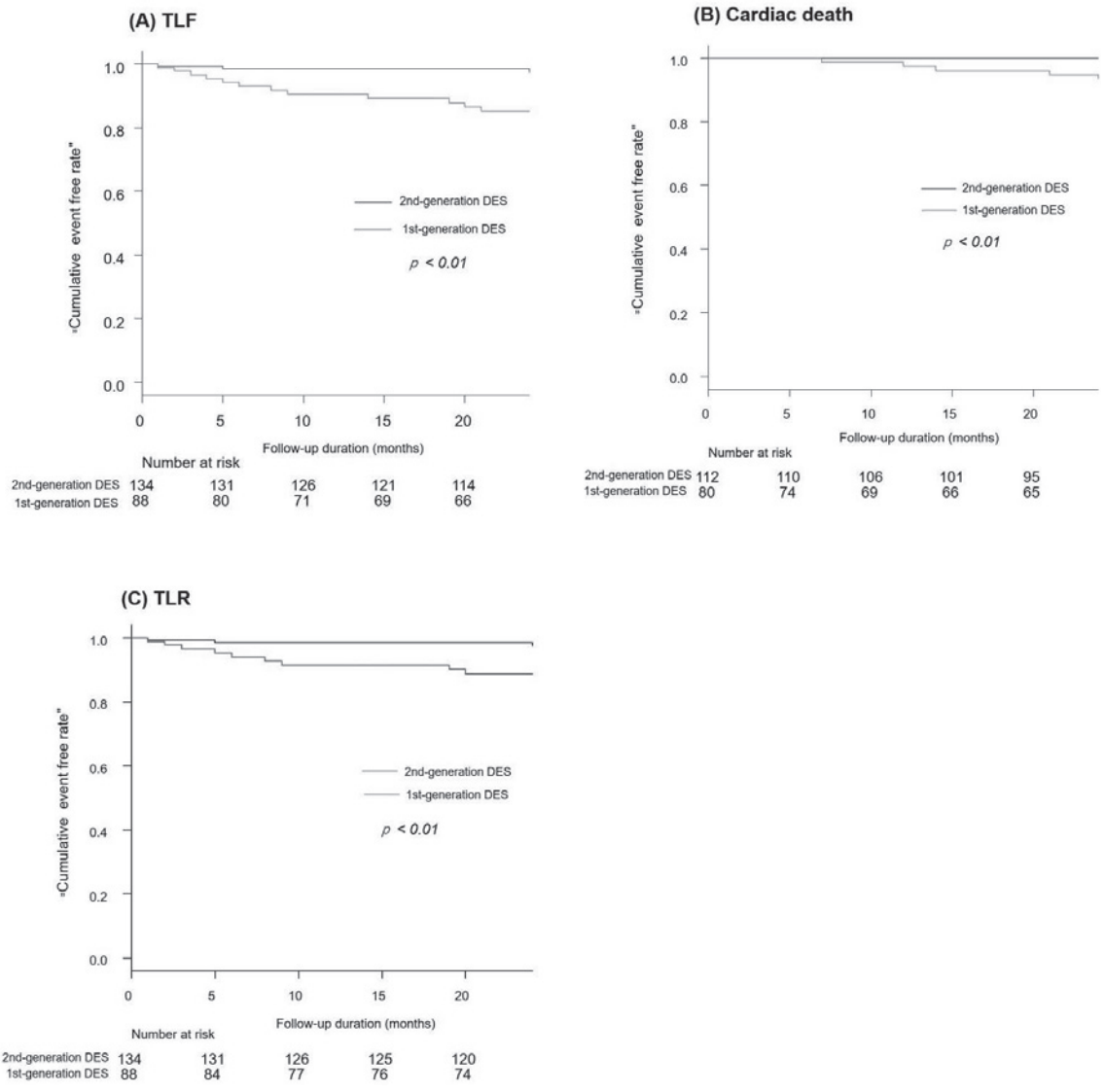

Fig. 2 Kaplan–Meier analyses for TLF (A) and its components, cardiac death (B), and TLR (C).

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 18.2% of first-generation DESs and 14.2% of second-generation DESs. 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 (0.45 ± 0.51 mm vs. 0.19 ± 0.50 mm, respectively; $P<0.01$).

Clinical outcomes at 2 years

The mean follow-up duration was 23.3 ± 3.3 months. The Kaplan-Meier analysis revealed an overall cumulative TLF incidence of 6.8% at 2 years 15.0 % for the first-generation DES group and 2.7% for the second-generation DES group ($P<0.01$; 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%, $P<0.01$; 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. 0.75%, $P = 0.57$; data not shown).

Table 2 Predictors of TLF.

Univariate analysis				
Predictors	n	Event rate (%)	HR, 95% CI	*P* value
Age ≥75 yrs/Age <75 yrs	54/138	3 (5.6)/12 (8.7)	0.78, 0.21–2.89	0.71
Female/Male	40/152	2 (5.0)/13 (8.6)	0.56, 0.12–2.60	0.46
Creatinine			1.01, 0.78–1.31	0.95
CKD (+)/CKD (−)	66/126	3 (4.5)/12 (9.5)	0.45, 0.12–1.66	0.23
Hypertension (+)/Hypertension (−)	126/66	11 (8.7)/4 (6.1)	1.48, 0.45–4.85	0.52
Dyslipidemia (+)/Dyslipidemia (−)	129/63	5 (3.4)/10 (15.9)	0.71, 0.24–2.10	0.54
Diabetes	92/100	7 (7.6)/8 (8.0)	0.95, 0.33–2.72	0.92
Smoking (+)/Smoking (−)	127/65	13 (10.2)/2 (3.1)	3.59, 0.79–16.4	0.10
Ejection Fraction			1.01, 0.97–1.05	0.70
1st-generation DES/2nd -generation DES	80/112	12 (15.0)/3 (2.7)	6.41, 1.75–23.5	<0.01
Multi-vessel disease (+)/Multi-vessel disease (−)	118/74	10 (8.5)/5 (6.8)	1.28, 0.42–3.90	0.67
LMT (+)/LMT (−)	40/152	6 (15.0)/9 (5.9)	2.80, 0.94–8.41	0.07
Prior PCI (+)/Prior PCI (−)	102/90	10 (9.8)/5 (5.6)	1.85, 0.61–5.63	0.28
True bifurcation (+)/True bifurcation (−)	156/36	11 (7.1)/4 (11.1)	0.61, 0.18–2.03	0.42
Large stent (≥3.5 mm) (+)/Large stent (≥3.5 mm) (−)	31/161	2 (6.5)/13 (8.1)	0.79, 0.17–3.67	0.76
Stent length ≥24 mm (+)/Stent length ≥24 mm (−)	84/108	8 (9.5)/7 (6.5)	1.52, 0.53–4.37	0.44
Two-stent approach (+)/Two-stent approach (−)	70/122	5 (7.1)/10 (8.2)	0.86, 0.28–2.63	0.79
Beta blocker (+)/Beta blocker (−)	91/101	8 (8.8)/7 (6.9)	1.32, 0.46–3.81	0.60
Statin (+)/Statin (−)	133/59	10 (7.5)/5 (8.5)	0.88, 0.29–2.69	0.82
RAAS inhibitor (+)/RAAS inhibitor (−)	143/49	11 (7.7)/4 (8.2)	0.94, 0.28–3.09	0.92
DAPT (+)/DAPT (−)	189/3	15 (7.9)/0 (0)	N/A	N/A
SYNTAX score			1.07, 1.01–1.13	0.02

※Incidence of TLF components (n, %)
TLF: 15 (6.8), Cardiac death: 5 (2.6), TLR: 12 (5.4), Target lesion–related stent thrombosis: 3 (1.4).
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.

Predictors of TLF

The univariate logistic regression analysis showed the use of first-generation DES, and SYNTAX scores were associated with TLF incidence (Table 2). In terms of the type of DES, the event rate of first-generation DESs was higher compared to that of second-generation DESs. Patients with events had an increased SYNTAX score compared to those without events (17.33 ± 10.62 vs. 11.57 ± 6.71, p = 0.02), whereas the creatinine level (1.54 ± 1.75 mg/dl vs. 1.41 ± 1.96 mg/dl, p = 0.83) and LVEF (61.13 ± 12.15% vs. 60.9 ± 14.34%, p = 0.96) did not differ between patents with and without events. Other clinical parameters also did not differ between the event and non-event groups (Table 2). In addition, there was a tendency toward statistical significance by LMT PCI for predicting TLF.

Analyses of the differences in clinical and procedural variables for first-generation DESs and second-generation DESs showed that LMT PCI and the SYNTAX score were predictors of TLF for the first-generation DES group (Table 3). No predictive factors of TLF were found for the second-generation DES group (Table 4).

Discussion

We investigated whether second-generation DESs are superior to first-generation DESs 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 interventionists 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 common bifurcation strategies that is generally considered for side branch vessels with diameters greater than 2.5 mm and

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

Univariate analysis				
Predictors	n	Event rate (%)	HR, 95% CI	*P* value
Age ≥75 yrs/Age <75 yrs	18/62	3 (16.7)/9 (14.5)	1.18, 0.28–4.91	0.82
Female/Male	12/68	2 (16.7)/10 (14.7)	1.16, 0.22–6.10	0.86
Creatinine			1.03, 0.77–1.40	0.83
CKD (+)/CKD (−)	28/52	3 (10.7)/9 (17.3)	0.57, 0.14–2.32	0.44
Hypertension (+)/Hypertension (−)	48/32	9 (18.8)/3 (9.4)	2.15, 0.53–8.68	0.28
Dyslipidemia (+)/Dyslipidemia (−)	27/53	4 (14.8)/8 (15.1)	1.02, 0.28–3.76	0.97
Diabetes	34/46	4 (11.8)/8 (17.4)	0.63, 0.17–2.31	0.49
Smoking (+)/Smoking (−)	56/24	10 (17.9)/2 (8.3)	2.39, 0.48–11.9	0.29
Ejection Fraction			1.00, 0.96–1.04	1.00
Multi-vessel disease (+)/Multi-vessel disease (−)	50/30	8 (16.0)/4 (13.3)	1.24, 0.34–4.53	0.75
LMT (+)/LMT (−)	12/68	5 (41.7)/7 (10.3)	6.22, 1.55–25.0	0.01
Prior PCI (+)/Prior PCI (−)	45/35	9 (20.0)/3 (8.6)	2.67, 0.66–10.7	0.24
True bifurcation (+)/True bifurcation (−)	67/13	8 (11.9)/4 (30.8)	0.31, 0.08–1.23	0.09
Large stent (≥3.5 mm) (+)/Large stent (≥3.5 mm) (−)	14/66	2 (14.2)/10 (15.2)	0.89, 0.18–3.76	0.79
Stent length ≥24 mm (+)/Stent length ≥24 mm (−)	33/47	6 (18.2)/6 (12.8)	1.52, 0.44–5.20	0.51
Two-stent approach (+)/Two-stent approach (−)	34/46	4 (11.8)/8 (17.4)	0.63, 0.17–2.31	0.49
Beta blocker (+)/Beta blocker (−)	33/47	6 (18.2)/6 (12.8)	1.52, 0.44–5.20	0.51
Statin (+)/Statin (−)	55/25	8 (14.5)/4 (16.0)	0.89, 0.24–3.30	0.87
RAAS inhibitor (+)/RAAS inhibitor (−)	61/19	9 (14.8)/3 (15.8)	0.92, 0.22–3.83	0.91
DAPT (+)/DAPT (−)	79/1	12 (15.2)/0 (0)	N/A	N/A
SYNTAX score			1.09, 1.02–1.17	0.02

※Incidence of TLF components (n, %)
TLF: 12 (15.0), Cardiac death: 5 (6.3), TLR: 9 (10.2), Target lesion–related stent thrombosis: 2 (2.3).
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.

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 that efficacy of first-generation DESs in bifurcation stenting with FKB.[18, 19] Indeed, introduction of first-generation DESs 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 the 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. The logistic regression analysis of the TLF incidence revealed that use of first-generation DESs was significantly associated with increased TLF. PCI for LMT and the SYNTAX score were also related to increased TLF, as previously reported.[17, 20] It is possible that improvements in second-generation DESs regarding strut thickness, polymer biocompatibility, stent malapposition, and drug elution are responsible for the lower TLF rate. Of importance, the introduction of the two-stent technique was not associated with the difference in the 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). Although patients with first-generation DESs had higher stent thrombosis compared

Table 4 Predictors of TLF for the second-generation DES group for bifurcation PCI.

Univariate analysis				
Predictors	n	Event rate (%)	HR, 95% CI	*P* value
Age ≥75 yrs/Age <75 yrs	36/76	0 (0)/3 (4.0)	0.00, 0.00–infinite	1.00
Female/Male	28/84	0 (0)/3 (3.6)	1.16, 0.22–6.10	0.86
Creatinine			0.08, 0.0003–21.6	0.37
CKD (+)/CKD (−)	38/74	0 (0)/3 (4.1)	0.00, 0.00–infinite	1.00
Hypertension (+)/Hypertension (−)	78/34	2 (2.6)/1 (2.9)	0.91, 0.08–10.3	0.28
Dyslipidemia (+)/Dyslipidemia (−)	76/36	1 (1.3)/2 (5.6)	0.44, 0.04–4.99	0.51
Diabetes	58/54	3 (5.2)/0 (0)	0.00, 0.00–infinite	0.99
Smoking (+)/Smoking (−)	71/41	3 (4.2)/0 (0)	0.00, 0.00–infinite	1.00
Ejection Fraction			1.09, 0.95–1.24	0.20
Multi-vessel disease (+)/Multi-vessel disease (−)	86/26	2 (2.3)/1 (3.8)	1.25, 0.11–14.3	0.86
LMT (+)/LMT (−)	31/81	1 (3.2)/2 (2.5)	1.60, 0.14–18.3	0.71
Prior PCI (+)/Prior PCI (−)	57/55	1 (1.8)/2 (3.6)	0.46, 0.04–5.18	0.53
True bifurcation (+)/True bifurcation (−)	102/10	3 (2.9)/0 (0)	0.00, 0.00–infinite	0.99
Large stent (≥3.5 mm) (+)/Large stent (≥3.5 mm) (−)	19/93	0 (0)/3 (3.2)	0.00, 0.00–infinite	0.99
Stent length ≥24 mm (+)/Stent length ≥24 mm (−)	60/52	2 (3.3)/1 (1.9)	2.36, 0.21–26.8	0.49
Two-stent approach (+)/Two-stent approach (−)	44/68	1 (2.3)/2 (2.9)	0.97, 0.09–11.1	0.98
Beta blocker (+)/Beta blocker (−)	58/54	2 (3.4)/1 (1.9)	1.96, 0.17–22.3	0.59
Statin (+)/Statin (−)	78/34	2 (2.6)/1 (2.9)	0.87, 0.08–9.91	0.91
RAAS inhibitor (+)/RAAS inhibitor (−)	82/30	2 (2.4)/1 (3.3)	0.69, 0.06–7.92	0.77
DAPT (+)/DAPT (−)	110/2	3 (2.7)/0 (0)	1.43, 0.00–1960	0.92
SYNTAX score			1.07, 0.95–1.20	0.26

※Incidence of TLF components (n, %)
TLF: 3 (2.7), Cardiac death: 0 (0), TLR: 3 (2.2), Target lesion–related stent thrombosis: 1 (0.75).
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.

to those with second-generation DESs, this did not reach statistical significance. Higher incidence in stent thrombosis (2%) by first-generation DESs was reported in a prior study,[21] which is in line with our current study.

Finally, to further identify the difference in predictive factors for TLF across the stent generations, we added the separate analysis in each stent group. For the first-generation DES group, LMT PCI, and the SYNTAX score were associated with increased TLF in the univariate analysis. This is consistent with the previous reports that evaluated the efficacy of first-generation DES in bifurcation PCI.[20, 22, 23] By contrast, we did not identify any involvement of the known predictive factors of cardiovascular events, such as the old age and diabetes, after the second-generation DES implantation.[24, 25] In comparison with coronary artery bypass, the efficacy and indication of PCI for the LMT lesion have been disputed. According to the SYNTAX trial, cardiovascular events increase after PCI in patients with a higher SYNTAX score as compared with coronary artery bypass.[26] We found that the SYNTAX score was higher in patients who developed TLF, particularly in the first-generation DES group (11.60 ± 6.96 vs. 17.8 ± 11.4, p = 0.01). Of importance, we found that patients with an LMT lesion had a greater SYNTAX score in both groups (first-generation DES group: 10.1 ± 6.21 vs. 22.9 ± 6.15, $P<0.01$, second-generation DES group: 10.7 ± 6.39 vs. 25.8 ± 6.50, $P<0.01$). Although the treatment strategy was made with cardiovascular surgeons according to the current guideline, we possibly excluded potential candidates for coronary artery bypass grafting considering their lower surgical durability because of aging or other reasons. Therefore, this might affect the higher incidence after PCI among patients with a higher SYNTAX score. We also assume that a higher SYNTAX score contributed to the higher mortality rate in the first-generation DES group as compared to the previous report.[27] 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 lesions 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 DESs 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 DESs—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, baseline lesion characteristics in the bifurcation might affect the different outcome between the groups. We found that the numerically greater number of lesions was 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 (58.3% vs. 33.3%). Fifth, because of the low event rate and the lack of information, the association between the incidence of target-lesion-related stent thrombosis and DAPT duration was not investigated. According to the previous report, the incidence of stent thrombosis among patients who received the first-generation DESs was higher than those treated by the second-generation DESs.[20] However, we assume that the incidence of stent thrombosis might influence the outcome in our study population because we could not exclude the possibility that sudden cardiac death was attributable to TLF among two patients in the first-generation DES group. The further investigation on the optimal management of antiplatelet therapy after bifurcation PCI is required. In the current study, the SYNTAX score was a predictor of TLF for patients with first-generation DESs. As coronary artery bypass grafting (CABG) is commonly recommended among patients with a higher SYNTAX score, CABG could avoid higher events among such patients, in particular those with first-generation DESs.

Conclusions

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

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References

1) Brilakis ES, Lasala JM, Cox DA, Bowman TS, Starzyk RM, Dawkins KD. Two-Year outcomes after utilization of the TAXUS paclitaxel-eluting stent in bifurcations and multivessel stenting in the ARRIVE registries. J Interv Cardiol. 2011; 24: 342-50.
2) Yanagi D, Shirai K, Takamiya Y, Fukuda Y, Kuwano T, Ike A, et al. Results of provisional stenting with a Sirolimus-eluting stent for bifurcation lesion: multicenter study in Japan. J Cardiol. 2008; 51: 89-94.
3) Zhang JJ, Chen SL, Hu ZY, Kan J, Xu HM, Shan SJ, et al. Contradictory shear stress distribution prevents restenosis after provisional stenting for bifurcation lesions. J Interv Cardiol. 2010; 23: 319-29.
4) Kim YH, Park DW, Suh IW, Jang JS, Hwang ES, Jeong YH, et al. Long-term outcome of simultaneous kissing stenting technique with sirolimus-eluting stent for large bifurcation coronary lesions. Catheter Cardiovasc Interv. 2007; 70: 840-6.
5) Yu CW, Yang JH, Song YB, Hahn JY, Choi SH, Choi JH, et al. 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). JACC Cardiovasc Interv. 2015; 8: 1297-307.
6) Yamawaki M, Muramatsu T, Kozuma K, Ito Y, Kawaguchi R, Kotani J, et al. Long-term clinical outcome of a single stent approach with and without a final kissing balloon technique for coronary bifurcation. Circ J. 2014; 78: 110-21.
7) Tamura T, Kimura T, Morimoto T, Nakagawa Y, Furukawa Y, Kadota K, et al. Three-year outcome of sirolimus-eluting stent implantation in coronary bifurcation lesions: the provisional side branch stenting approach versus the elective two-stent approach. EuroIntervention. 2011; 7: 588-96.
8) Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, et al. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: a pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY). JACC Cardiovasc Interv. 2014; 7: 20-8.
9) Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). JACC Cardiovasc Interv. 2013; 6: 1263-6.
10) Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005; 1: 219-27.
11) Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: ex-

ecutive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006; 11: 1341-81.
12) Latib A, Colombo A. Bifurcation disease: what do we know, what should we do? JACC Cardiovasc Interv. 2008; 1: 218-26.
13) Dzavik V, Kharbanda R, Ivanov J, Ing DJ, Bui S, Mackie K, et al. Predictors of long-term outcome after crush stenting of coronary bifurcation lesions: importance of the bifurcation angle. Am Heart J. 2006; 152: 762-9.
14) Ormiston JA, Currie E, Webster MW, Kay P, Ruygrok PN, Stewart JT, et al. Drug-eluting stents for coronary bifurcations: insights into the crush technique. Catheter Cardiovasc Interv. 2004; 63: 332-6.
15) Jim MH, Ho HH, Ko RL, Siu CW, Yiu KH, Chow WH. Long-term clinical and angiographic outcomes of the sleeve technique on non-left-main coronary bifurcation lesions. EuroIntervention. 2009; 5: 104-8.
16) Rahman S, Leesar T, Cilingiroglu M, Effat M, Arif I, Helmy T, et al. Impact of kissing balloon inflation on the main vessel stent volume, area, and symmetry after side-branch dilation in patients with coronary bifurcation lesions: a serial volumetric intravascular ultrasound study. JACC Cardiovasc Interv. 2013; 6: 923-31.
17) Gwon HC, Hahn JY, Koo BK, Song YB, Choi SH, Choi JH, et al. Final kissing ballooning and long-term clinical outcomes in coronary bifurcation lesions treated with 1-stent technique: results from the COBIS registry. Heart. 2012; 98: 225-31.
18) Korn HV, Yu J, Ohlow MA, Huegl B, Schulte W, Wagner A, et al. Interventional therapy of bifurcation lesions: a TIMI flow-guided concept to treat side branches in bifurcation lesions--a prospective randomized clinical study (Thueringer bifurcation study, THUEBIS study as pilot trial). Circ Cardiovasc Interv. 2009; 2: 535-42.
19) Liu G, Ke X, Huang ZB, Wang LC, Huang ZN, Guo Y, et al. Final kissing balloon inflation for coronary bifurcation lesions treated with single-stent technique: A meta-analysis. Herz. 2017.
20) Cho Y, Koo BK, Song YB, Hahn JY, Choi SH, Gwon HC, et al. Comparison of the first- and second-generation limus-eluting stents for bifurcation lesions from a Korean multicenter registry. Circ J. 2015; 79: 544-52.
21) Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovasc Interv. 2013; 12: 1267-74.
22) Gwon HC, Choi SH, Song YB, Hahn JY, Jeong MH, Seong IW, et al. Long-term clinical results and predictors of adverse outcomes after drug-eluting stent implantation for bifurcation lesions in a real-world practice: the COBIS (Coronary Bifurcation Stenting) registry. Circ J. 2010; 74: 2322-8.
23) Giustino G, Baber U, Aquino M, Sartori S, Stone GW, Leon MB, et al. Safety and Efficacy of New-Generation Drug-Eluting Stents in Women Undergoing Complex Percutaneous Coronary Artery Revascularization: From the WIN-DES Collaborative Patient-Level Pooled Analysis. JACC Cardiovasc Interv. Apr. 2016; 9: 674-84.
24) Abdel-Wahab M, Neumann FJ, Serruys P, Silber S, Leon M, Mauri L, et al. ncidence and predictors of unplanned non-target lesion revascularisation up to three years after drug-eluting stent implantation: insights from a pooled analysis of the RESOLUTE Global Clinical Trial Program. EuroIntervention. 2016; 12: 465-72.
25) Niccoli G, Stuteville M, Sudhir K, Li D, Montone RA, Bolognese L, et al. Incidence, time course and predictors of early vs. late target lesion revascularisation after everolimus-eluting stent implantation: a SPIRIT V substudy. EuroIntervention. 2013; 9: 353-9.
26) Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. EuroIntervention. N Engl J Med. 2009; 360: 961-72.
27) Manuel P, Francesco B, Carlo T, Alfonso M, Jose SL, Giampaolo N, et al. Three-year follow-up of patients with bifurcation lesions treated with sirolimus- or everolimus-eluting stents: SEAside and CORpal cooperative study. Rev Esp Cardiol. 2014; 10: 797-803.