Temporal changes in characteristics, treatment strategies, and outcomes of coronary bifurcation lesion interventions

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Objectives **Coronary bifurcations are common in daily practice of percutaneous coronary intervention and remain one of the most challenging lesions, but it is still unknown how characteristics, treatment strategy, and outcomes have changed over the last decade of drug-eluting stents (DES) era. We evaluated characteristics of treatment pattern and outcomes for patients with bifurcation disease over time in real-world clinical practice.**

Patients and methods **A total of 7282 patients with coronary bifurcation lesions were pooled from the Interventional Cardiology Research Incorporation Society-Drug-Eluting Stents registry and the Interventional Research Incorporation Society-Left MAIN registry. Primary outcome was a target-vessel failure (TVF), defined as a composite of cardiac death, target-vessel myocardial infarction, or clinically indicated target-vessel revascularization.**

Results **Among the total population, 2232 (30.7%) had left main bifurcation lesions. The use of one-stent strategy was more frequent in conjunction with second-generation DES (86.2 vs. 13.8%) than with first-generation DES (65.4 vs. 34.6%). Two-stent strategy was associated with a higher risk of TVF as compared with one-stent strategy [adjusted hazard ratio (HR): 1.28, 95% confidence interval (CI): 1.12–1.47, $P < 0.001$]. However, the risk of TVF with two-stent strategy relative to one-stent strategy has decreased from the first-generation DES (HR: 1.56, 95% CI: 1.22–1.99, $P < 0.001$) to the second-generation DES (HR: 1.12, 95% CI: 0.94–1.34, $P = 0.19$).**

Conclusion **For patients with bifurcation disease, stenting strategy has become more simpler and percutaneous coronary intervention outcomes have more improved over time. One-stent strategy relative to two-stent strategy was associated with better clinical outcomes, but the advantage of one-stent strategy was less pronounced with the use of second-generation DES.** *Coron Artery Dis* **30:33–43**

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Introduction

In the contemporary practice of percutaneous coronary interventions (PCIs), bifurcation lesions account for 15–20% of all coronary lesion subsets. Bifurcation PCI remains one of the most challenging procedures with respect to procedural complexity and a relatively higher rate of adverse clinical events, as compared with non-bifurcation PCI [1]. Nevertheless, during the past decade, PCI outcomes for bifurcation lesions have steadily improved through advancements of device technology, procedural techniques, and background antithrombotic agents [2,3]. Especially, with the widespread adoption of drug-eluting stents (DES) with a lower risk of angiographic and clinical restenosis, PCI for complex bifurcation lesions has become more technically feasible and shows favorable short-term and long-term clinical outcomes. Moreover, newer-generation DES, as compared with first-generation devices, are associated with better efficacy and safety outcomes [4,5], and therefore the benefits associated with the use of newer-generation DES may be more pronounced for complex lesion subset such as coronary bifurcations.

Although PCI procedures for bifurcation lesions have substantially improved in recent decade, limited data are available on the long-term trends of patient characteristics, stenting strategy, stent type, and associated clinical effects over time. Understanding such changes may be

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important for helping clinical decision making and planning future medical progress toward improved management of bifurcation disease. Using a pooled database from two large-scaled observation registries, we therefore evaluated secular changes of characteristics, PCI pattern, and long-term clinical outcomes in a real-world population with bifurcation lesions.

Patients and methods

Study population, procedures, and data collection

The study population was pooled from two large-scaled, independent, multicenter, observational studies of the Interventional Cardiology Research Incorporation Society-Drug-Eluting Stents (IRIS-DES) registry (NCT01186133) and the Interventional Research Incorporation Society-Left MAIN Revascularization (IRIS-MAIN) registry (NCT01341327). Details of the design and the organization of the IRIS-DES and the IRIS-MAIN studies have been published elsewhere [6,7], and the key features are summarized in Supplementary Table 1 (Supplemental digital content 1, *http://links.lww.com/MCA/A205*). In brief, the IRIS-DES involves a prospective, multicenter recruitment of unrestricted patients undergoing PCI with DES in Korea and consists of several different DES arms of first-generation and second-generation devices between July 2007 and July 2016. The current analysis includes patients treated with five different types of DES. The IRIS-MAIN is a prospective, multinational registry involving consecutive patients with unprotected left main (LM) disease who were treated with PCI, bypass surgery, or medical therapy alone between March 2003 and March 2016. For the present analysis, patients with bifurcation lesions who were treated with DES were pooled from the databases of the two registries. These registries were supported by the Cardiovascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design, conduct, or analysis of the study. The study protocol was approved by the ethics committee at each participating center, and all patients provided written, informed consent.

In both registries, PCI was performed according to standard techniques at the discretion of the treating physician. These registries did not specify PCI treatment and therefore each operator was responsible for the decision to choose a specific stenting strategy for bifurcation treatment. Because this study was not randomized and observational, we did not systematically capture the operator's initial intention for provisional versus complex two-stents strategy. Thus, comparison between simple strategy and complex two-stents strategy was performed on the basis of the final result of the procedure (one vs. two stents). Periprocedural anticoagulation was administered according to standard regimens. All patients undergoing PCI received a loading dose of aspirin and $P2Y_{12}$ receptor inhibitors before or during the intervention. After the procedure, aspirin was continued indefinitely and $P2Y_{12}$ inhibitors were prescribed for at least 6–12 months. Treatment beyond this duration was at the discretion of the physician.

For the IRIS-DES and IRIS-MAIN registries, all of the baseline characteristics and outcome data were collected using a dedicated, electronic case report form by specialized personnel at each participating center. Clinical follow-up of the patients was performed according to per-protocol follow-up visits. The Internet-based system provides each center with immediate and continuous feedback on the processes and quality of care measures. Monitoring and verification of registry data are periodically performed in the participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea).

Clinical outcomes and definitions

The primary clinical outcome of the current analysis was target-vessel failure [a composite of death from cardiac causes, target-vessel myocardial infarction (MI), or clinically indicated target-vessel revascularization (TVR)]. Secondary clinical outcomes included death (cardiac or noncardiac), MI (Q-waver or non-Q-wave), repeat revascularization (TVR or non-TVR), and stent thrombosis.

Death was considered as cardiac unless an unequivocal noncardiac cause could be established. The protocol definition of MI was prespecified and was based on the universal definition of MI [6,8]. Procedure-related MI was defined as the presence of new Q waves or an elevation of creatine kinase-myocardial band isoenzyme three times the normal upper limit. Spontaneous MI was defined as any increase of cardiac enzyme above the upper range limit with or without the development of Q waves on ECG. In addition, alternative criteria of MI, defined post-hoc, were examined on the basis of the Society for Cardiovascular Angiography and Interventions (SCAI) definition [9]. Using this definition, we specified post-hoc an alternative definition of the target-vessel failure: a composite of death from cardiac causes, SCAI-defined target-vessel MI, or clinically indicated TVR. Repeat revascularization included any type of percutaneous or surgical revascularization procedure and was categorized as TVR or non-TVR. Definite stent thrombosis was defined according to the Academic Research Consortium criteria [10]. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee, whose members were blinded as to the study devices.

Statistical analysis

All analyses were performed for patients with all bifurcation lesions, those with non-LM bifurcation lesions, and those with LM bifurcation lesions. Categorical outcomes were compared by the χ^2-test, unless the expected number of values in any cell of the 2×2 contingency table was less than 5, in which case the Fisher exact test

was used. Continuous variables are presented as mean ± SD and were compared by the *t*-test. Cumulative incidence rates of primary and secondary clinical outcomes were estimated by the Kaplan–Meier method and tested by the log-rank statistic.

Multivariable Cox proportional-hazards regression modeling was used to examine the independent effect of the change of DES generation (first-generation vs. second-generation DES) on clinical outcomes of bifurcation PCI [11]. In addition, we determine whether there are differences in clinical outcomes between simple strategy and complex two-stents strategy according to the bifurcation location (all, non-LM, or LM) and the type of DES (all, first-generation or second-generation DES). After unadjusted analyses were initially performed, multivariable Cox regression analyses were performed to adjust potential confounders identified by the investigators using a literature search and a priori based on clinical knowledge. These covariates included age, sex, presence or absence of diabetes, history or no history of MI, history or no history of PCI, presence or absence of chronic renal failure, clinical presentation (stable angina, unstable angina, or MI), ejection fraction, bifurcation location (LM, left anterior descending, left circumflex, or right coronary artery), disease extent (one, two, or three vessels), and use or nonuse of intravascular ultrasound. The proportional-hazards assumption was tested by examination of log–log survival curves and partial Schoenfeld residuals, and no significant violations were found. All reported *P* values are two sided and have not been adjusted for multiple testing. All the analyses were performed with the use of SAS software, version 9.3 (SAS Institute, Cary, North Carolina, USA).

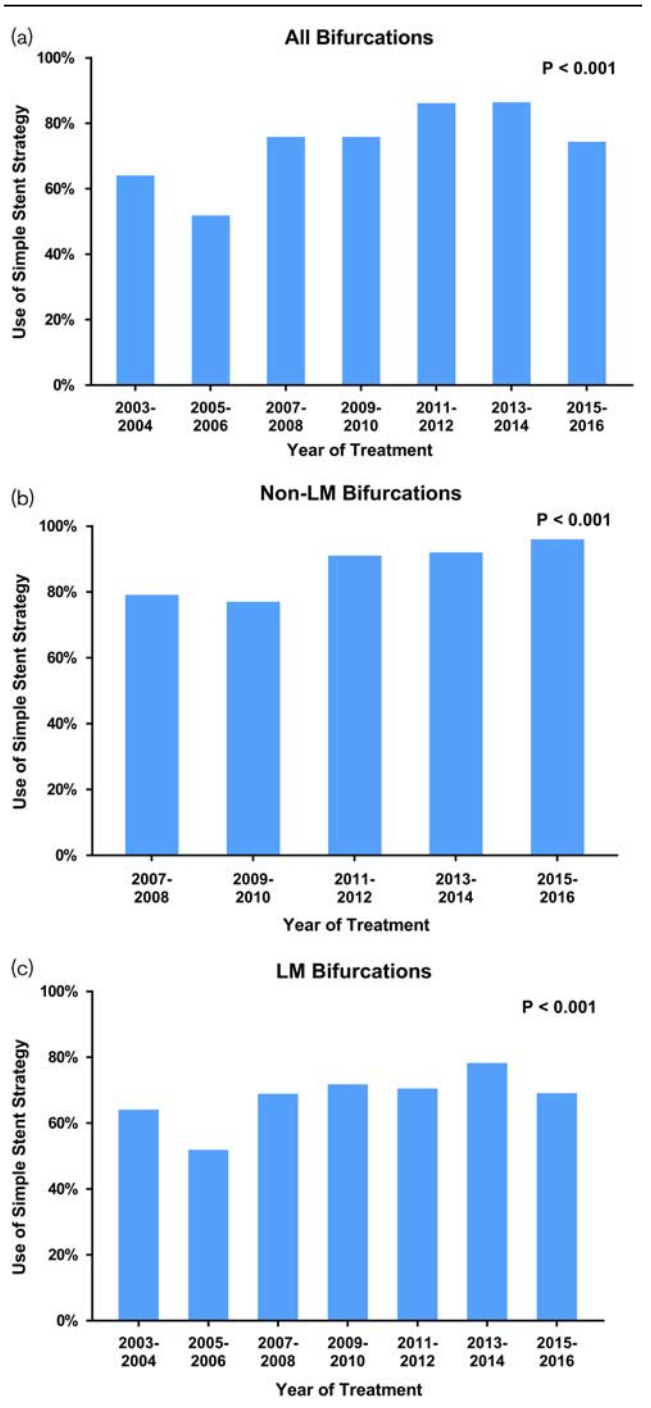
Results

Patient characteristics and treatment strategy

Of the 17 196 patients enrolled in the IRIS-DES registry and the 5833 patients enrolled in the IRIS-MAIN registry, 7282 patients with bifurcation lesions were included in the current analysis (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/MCA/A205*). Among them, 5050 (69.3%) patients had non-LM bifurcation lesions and 2232 (30.7%) had LM bifurcation lesions. Baseline characteristics of the patients with non-LM bifurcations versus LM bifurcations are summarized in Supplementary Tables 2 and 3 (Supplemental digital content 1, *http://links.lww.com/MCA/A205*).

Use of simple stent strategy for bifurcation lesion according to the year of treatment is shown in Fig. 1. The use of the simple stent strategy showed a gradual increase in all bifurcation, non-LM and LM bifurcation lesion over time. Changes of the patients' characteristics and medications from first-generation DES to second-generation DES are shown in Table 1. Over the time, there was an increase of age, less patients had previous history of MI or PCI, and more patients had peripheral vascular diseases and tended to present with unstable angina or MI. Ejection fraction was getting to be lower, and use of β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, or statin has

Fig. 1



Use of simple stent strategy for bifurcation lesion over time. Changes of use of simple stent strategy according to the year of treatment for all bifurcations (a), non-LM bifurcations (b), and LM bifurcations (c). LM, left main.

Table 1 Baseline demographics and clinical characteristics stratified by bifurcation location and generation of drug-eluting stents[a]

	All bifurcations ($N=7282$)			Non-LM bifurcations ($N=5050$)			LM bifurcations ($N=2232$)		
Characteristics	First-generation DES ($N=1380$)	Second-generation DES ($N=5902$)	P	First-generation DES ($N=929$)	Second-generation DES ($N=4121$)	P	First-generation DES ($N=451$)	Second-generation DES ($N=1781$)	P
Age (years)	62.8 ± 10.5	64.0 ± 10.6	< 0.001	62.9 ± 10.5	63.6 ± 10.7	0.05	62.6 ± 10.5	64.9 ± 10.2	< 0.001
Sex (male)	991 (71.8)	4325 (73.3)	0.28	636 (68.5)	2935 (71.2)	0.10	355 (78.7)	1390 (78.0)	0.81
BMI (kg/m^2)	24.7 ± 2.9	24.6 ± 3.1	0.35	24.7 ± 2.9	24.7 ± 3.1	0.63	24.6 ± 2.7	24.4 ± 3.1	0.30
Hypertension	829 (60.1)	3672 (62.2)	0.15	564 (60.7)	2523 (61.2)	0.80	265 (58.8)	1149 (64.5)	0.03
Diabetes mellitus	484 (35.1)	1958 (33.2)	0.19	306 (32.9)	1315 (31.9)	0.57	178 (39.5)	643 (36.1)	0.20
Requiring insulin	80 (5.8)	268 (4.5)	0.06	56 (6.0)	165 (4.0)	0.01	24 (5.3)	103 (5.8)	0.79
Current smoking	379 (27.5)	1655 (28.0)	0.69	254 (27.3)	1219 (29.6)	0.19	125 (27.7)	436 (24.5)	0.18
Hyperlipidemia	457 (44.3)	2136 (46.0)	0.33	402 (43.3)	1837 (44.6)	0.49	55 (53.4)	299 (57.2)	0.55
Previous MI	94 (6.8)	303 (5.1)	0.02	54 (5.8)	178 (4.3)	0.06	40 (8.9)	125 (7.0)	0.22
Previous PCI	224 (16.2)	654 (11.1)	< 0.001	130 (14.0)	353 (8.6)	< 0.001	94 (20.8)	301 (16.9)	0.06
Previous stroke	108 (7.8)	435 (7.4)	0.60	74 (8.0)	293 (7.1)	0.40	34 (7.5)	142 (8.0)	0.84
Previous heart failure	30 (2.2)	144 (2.4)	0.63	22 (2.4)	94 (2.3)	0.97	8 (1.8)	50 (2.8)	0.29
Atrial fibrillation	48 (3.5)	171 (2.9)	0.29	36 (3.9)	125 (3.0)	0.22	12 (2.7)	46 (2.6)	> 0.99
Family history of CAD	89 (6.4)	457 (7.7)	0.11	42 (4.5)	296 (7.2)	0.004	47 (10.4)	161 (9.1)	0.42
Chronic lung disease	33 (2.4)	147 (2.5)	0.91	22 (2.4)	99 (2.4)	> 0.99	11 (2.4)	48 (2.7)	0.89
Chronic renal failure	46 (3.3)	224 (3.8)	0.46	35 (3.8)	143 (3.5)	0.73	11 (2.4)	81 (4.5)	0.06
Peripheral vascular disease	16 (1.2)	181 (3.1)	< 0.001	7 (0.8)	106 (2.6)	0.001	9 (2.0)	75 (4.2)	0.04
Clinical presentation			< 0.001			< 0.001			0.009
Stable angina	702 (50.9)	2535 (43.0)		459 (49.4)	1715 (41.6)		243 (53.9)	820 (46.0)	
Unstable angina	430 (31.2)	1989 (33.7)		283 (30.5)	1335 (32.4)		147 (32.6)	654 (36.7)	
MI	248 (18.0)	1378 (23.3)		187 (20.1)	1071 (26.0)		61 (13.5)	307 (17.2)	
Ejection fraction									
Mean (%)	59.2 ± 9.3	58.6 ± 10.0	0.06	58.6 ± 9.5	58.5 ± 9.9	0.91	60.4 ± 8.6	58.8 ± 10.3	0.002
Data missing	151 (10.9)	534 (9.0)		109 (11.7)	352 (8.5)		42 (9.3)	182 (10.2)	
In-hospital or discharge medications									
Aspirin	1356 (98.5)	5796 (98.6)	0.93	917 (99.1)	4061 (98.6)	0.29	439 (97.3)	1735 (98.6)	0.10
ADP receptor antagonist									
Clopidogrel	1358 (98.4)	5602 (94.9)	< 0.001	917 (98.7)	3957 (96.0)	< 0.001	441 (97.8)	1645 (92.4)	< 0.001
Ticagrelor	–	100 (1.7)	< 0.001	–	54 (1.3)	< 0.001	–	46 (2.6)	0.01
Prasugrel	–	20 (0.3)	0.03	–	3 (0.1)	0.41	–	17 (1.0)	0.04
β-Blocker	786 (57.0)	3586 (60.8)	0.01	548 (59.0)	2556 (62.0)	0.09	238 (52.8)	1030 (57.8)	0.06
Calcium channel blocker	738 (53.5)	2457 (41.6)	< 0.001	466 (50.2)	1704 (41.3)	< 0.001	272 (60.3)	753 (42.3)	< 0.001
ACE inhibitor or ARB	521 (37.8)	3007 (50.9)	< 0.001	411 (44.2)	2096 (50.9)	< 0.001	110 (24.4)	911 (51.2)	< 0.001
Statin	778 (56.4)	4478 (75.9)	< 0.001	689 (74.2)	3555 (86.3)	< 0.001	89 (19.7)	923 (51.8)	< 0.001
Status of DAPT									
DAPT at discharge	1349 (97.8)	5689 (96.4)	0.011	913 (98.3)	3986 (96.7)	0.01	436 (96.7)	1703 (95.6)	0.32
DAPT at 6 months	1270 (92)	5172 (87.6)	< 0.001	880 (94.7)	3679 (89.3)	< 0.001	390 (86.5)	1493 (83.8)	0.17
DAPT at 1 year	1062 (77.0)	4143 (70.2)	< 0.001	759 (81.7)	2947 (71.5)	< 0.001	303 (67.2)	1196 (67.2)	0.99
DAPT at 2 year	702 (50.9)	2372 (40.2)	< 0.001	476 (51.2)	1652 (40.1)	< 0.001	226 (50.1)	720 (40.4)	< 0.001
DAPT at 3 year	589 (42.7)	1665 (28.2)	< 0.001	410 (44.1)	1196 (29.0)	< 0.001	179 (39.7)	469 (26.3)	< 0.001

Values are mean ± SD or n (%).

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a]P values comparing first-generation DES and second-generation DES in each stratum of all, non-LM, or LM bifurcations.

significantly increased. The time duration of dual antiplatelet therapy during follow-up has been shortened over time with second-generation DES.

Changes in angiographic and procedural characteristics are shown in Table 2. For non-LM bifurcation lesions, three-quarter of patients had lesions on left anterior descending artery. Over the time, the proportion of true bifurcation lesion has decreased. In the era of first-generation DES, 64% had true bifurcation lesions and 35% were treated with complex two-stents strategy. In the era of second-generation DES, 50% had true bifurcation lesions, but only 14% were treated with complex two-stents strategy. As such, more patients have been treated with simple one-stent strategy than complex two-stents strategy (Fig. 2). This pattern was consistent for patients with non-LM bifurcation lesions and those with LM bifurcation lesions. Because of inclusion nature of the IRIS-DES registry, sirolimus-eluting stents were mostly included as the first-generation DES. In the second-generation DES, more than half of patients were treated with everolimus-eluting stents.

Clinical outcomes

The median duration of follow-up was 3.6 years (interquartile range: 2.0–4.1 years). As shown in Supplementary Fig. 2 and Table 4 (Supplemental digital content 1, *http://links.lww.com/MCA/A205*), the 3-year rate of target-vessel failure was significantly lower in patients treated with second-generation DES than in those treated with

Table 2 Baseline angiographic and procedural characteristics stratified by bifurcation location and generation of drug-eluting stents[a]

Characteristic	All bifurcations ($N=7282$)			Non-LM bifurcations ($N=5050$)			LM bifurcations ($N=2232$)		
	First-generation DES ($N=1380$)	Second-generation DES ($N=5902$)	P	First-generation DES ($N=929$)	Second-generation DES ($N=4121$)	P	First-generation DES ($N=451$)	Second-generation DES ($N=1781$)	P
Bifurcation lesion			0.047			0.09			NA
LM	451 (32.7)	1781 (30.2)		–	–		451 (100.0)	1781 (100.0)	
LAD	729 (52.8)	3099 (52.5)		729 (78.5)	3099 (75.2)		–	–	
LCX	152 (11.0)	796 (13.5)		152 (16.4)	796 (19.3)		–	–	
RCA	48 (3.5)	226 (3.8)		48 (5.2)	226 (5.5)		–	–	
Disease extent			0.001			0.01			0.11
One-vessel disease	585 (42.4)	2808 (47.6)		585 (63.0)	2808 (68.1)		–	–	
Two-vessel disease	624 (45.2)	2496 (42.3)		290 (31.2)	1113 (27.0)		334 (74.1)	1383 (77.7)	
Three-vessel disease	171 (12.4)	598 (10.1)		54 (5.8)	200 (4.9%)		117 (25.9)	398 (22.3)	
Medina classification			< 0.001			< 0.001			< 0.001
True bifurcation	879 (63.7)	2920 (49.5)		546 (58.8)	1746 (42.4)		333 (73.8)	1174 (65.9)	
1.1.1	766 (55.5)	2419 (41.0)		451 (48.5)	1324 (32.1)		315 (69.8)	1095 (61.5)	
1.0.1	36 (2.6)	228 (3.9)		33 (3.6)	210 (5.1)		3 (0.7)	18 (1.0)	
0.1.1	77 (5.6)	273 (4.6)		62 (6.7)	212 (5.1)		15 (3.3)	61 (3.4)	
Nontrue bifurcation	501 (36.3)	2982 (50.5)		383 (41.2)	2375 (57.6)		118 (26.2)	607 (34.1)	
1.0.0	56 (4.1)	408 (6.9)		38 (4.1)	331 (8.0)		18 (4.0)	77 (4.3)	
0.1.0	70 (5.1)	400 (6.8)		69 (7.4)	390 (9.5)		1 (0.2)	10 (0.6)	
1.1.0	365 (26.4)	2050 (34.7)		266 (28.6)	1531 (37.2)		99 (22.0)	519 (29.1)	
0.0.1	10 (0.7)	124 (2.1)		10 (1.1)	123 (3.0)		–	1 (0.1)	
Stenting strategy			< 0.001			< 0.001			< 0.001
Simple crossover	902 (65.4)	5090 (86.2)		624 (67.2)	3755 (91.1)		278 (61.6)	1335 (75.0)	
Two-stent strategy	478 (34.6)	812 (13.8)		305 (32.8)	366 (8.9)		173 (38.4)	446 (25.0)	
DES type			< 0.001			< 0.001			< 0.001
First-generation									
SES	1366 (99.0)	–		929 (100.0)	–		437 (96.9)	–	
PES	14 (1.0)	–		0 (0.0)	–		14 (3.1)	–	
Second-generation									
CoCr-EES	–	2146 (36.4)		–	1514 (36.7)		–	632 (35.5)	
PtCr-EES	–	1186 (20.1)		–	755 (18.3)		–	431 (24.2)	
PC-ZES	–	341 (5.8)		–	–		–	341 (19.1)	
Re-ZES	–	1211 (20.5)		–	1018 (24.7)		–	193 (10.8)	
BES	–	970 (16.4)		–	834 (20.2)		–	136 (7.6)	
Others	–	48 (0.8)		–	–		–	48 (2.7)	
Use of IVUS	1230 (89.1)	3790 (64.2)	< 0.001	831 (89.5)	2482 (60.2)	< 0.001	399 (88.5)	1308 (73.4)	< 0.001

Values are *n* (%).

BES, biolimus-eluting stents; CoCr-EES, cobalt-chromium everolimus-eluting stents; DES, drug-eluting stents; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; NA, not available; PC-ZES, phosphorylcholine polymer-based zotarolimus-eluting stents; PES, paclitaxel-eluting stents; PtCr-EES, platinum–chromium everolimus-eluting stents; RCA, right coronary artery; Re-ZES, resolute zotarolimus-eluting stents; SB, side branch; SES, sirolimus-eluting stents.

[a]*P* values comparing first-generation DES and second-generation DES in each stratum of all, non-LM, or LM bifurcations.

first-generation DES, mainly driven by lower rates of non-Q-wave MI and TVR; these patterns are similar for non-LM and LM bifurcations (but not always statistically significantly for each subgroup). The event rates of clinical outcomes according to non-LM versus LM bifurcations are shown in Supplementary Table 5 (Supplemental digital content 1, *http://links.lww.com/MCA/A205*).

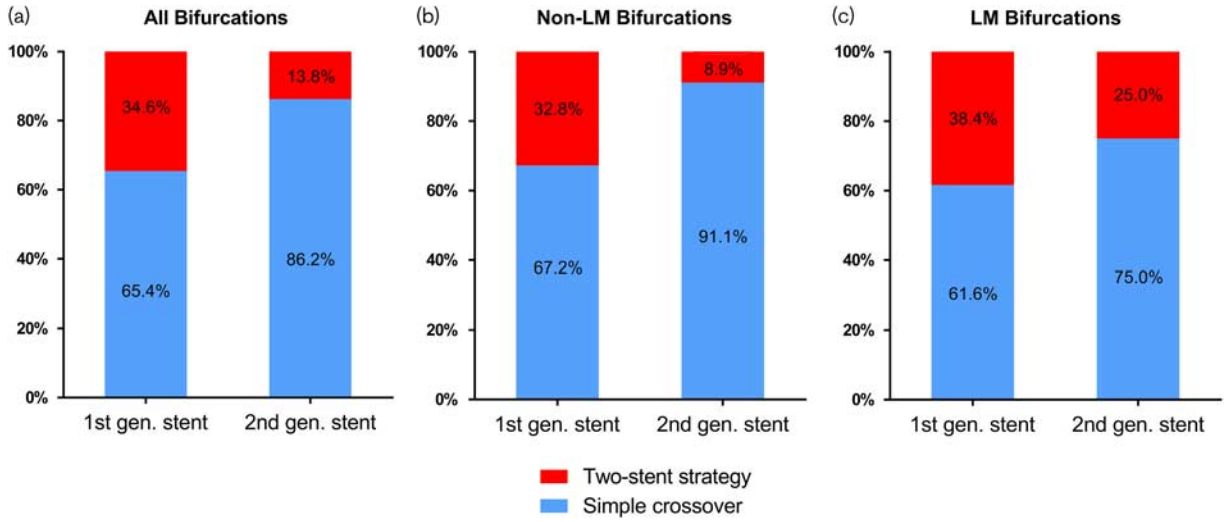
Unadjusted and adjusted HRs for clinical outcomes are summarized in Table 3. After multivariable adjustment of baseline covariates, the risk of target-vessel failure was consistently lower in the second-generation DES group than in the first-generation DES group, combined with lower risk of MI and TVR. A similar trend was also observed for patients with non-LM bifurcation and those with LM bifurcation lesions.

Simple versus complex stenting strategy

The rate of target-vessel failure during the 3-year follow-up period was significantly lower in patients treated with simple one-stent strategy than in those with complex two-stent strategy (Table 4). This difference was largely attributable to the significant reduction in the incidence of non-Q-wave MI and TVR associated with simple strategy. This pattern was more prominent for patients with LM bifurcations rather than for those with non-LM bifurcations. Overall findings were unchanged after multivariable correction for key clinical covariates (Table 5).

As shown in Fig. 3 and Supplementary Table 6 (Supplemental digital content 1, *http://links.lww.com/MCA/A205*), after multivariable adjustment, the adjusted risk of target-vessel failure was significantly higher with complex stenting strategy during all time period. However, the adjusted HRs for the risk of target-vessel failure with complex strategy relative to simple strategy gradually decreased over time from the first-generation DES to the second-generation DES, suggesting that the gap in the treatment effect between simple versus complex strategy has been narrowed with second-generation DES.

Fig. 2



Proportion of Bifurcation stenting strategy according to the generation of drug-eluting stents. Changes of relative proportion of simple one-stent and complex two-stents strategy from the first-generation DES to the second-generation DES for all bifurcations (a), non-LM bifurcations (b), and LM bifurcations (c). DES, drug-eluting stents; LM, left main.

Post-hoc analysis using different definition of myocardial infarction

We also performed post-hoc analyses using the SCAI definition of MI. As compared with the protocol definition of MI, overall incidence of SCAI-defined MI was substantially lower. Using the SCAI definition of MI, there were no significant differences in the 3-year rates of MI and target-vessel failure between the first-generation and second-generation DES (Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/MCA/A205*). These findings were consistent after multivariable adjustment (Table 3). In addition, the 3-year rate of SCAI-defined MI was similar between simple one-stent strategy and complex two-stent strategy (Table 4). The 3-year rate of alternatively defined target-vessel failure also did not significantly differ. After multivariable adjustment of clinical covariates, overall findings remained (Table 5).

Discussion

In the present pooled analysis of two large, multicenter, prospective cohort studies, we found that there were remarkable changes in patient characteristics, stenting strategy, and the related clinical outcomes among patients with non-LM and LM bifurcation disease over the last decade from the first-generation DES to the second-generation DES. The major findings are that (i) simple one-stent strategy has been more frequently applied relative to complex two-stent strategy over time; (ii) PCI with contemporary second-generation DES compared with first-generation DES reduced the 3-year rates of target-vessel failure, MI, and TVR; and (iii) simple stenting strategy compared with complex stenting strategy was associated with better clinical outcomes. However, this treatment difference has been narrowed over time from first-generation DES to second-generation DES.

Previous studies comparing first-generation versus second-generation DES in bifurcation lesions suggested that use of contemporary second-generation DES was associated with better clinical outcomes as compared with first-generation device, largely because of a lower rate of MI or repeat revascularization [12,13]. These findings were also consistent in our study. Newer-generation DES has been developed that used novel stent materials, thinner strut platforms, and delivery systems, with more biocompatible polymers (both durable and bioresorbable) than their predecessors [14]. Such improvement of stent technology might explain a reduction of MI, TVR, and target-vessel failure. In addition, technical advance for PCI optimization, integrated use of functional or imaging tools, and more experienced bifurcation PCI strategy over time might contribute to improvement of bifurcation PCI outcomes [2,3].

In our study, stenting technique has been simplified for bifurcation treatment over time. In the past decade, many clinical trials and meta-analyses have compared the use of one-stent versus two-stents techniques with DES for non-LM and LM bifurcation lesions [15–17]. Although multiple techniques for complex stenting have been proposed and some studies suggested no difference in clinical outcomes between provisional and two-stents strategy [18,19], the majority of studies have shown no advantage of complex stenting regardless of the lesion location or bifurcation type. On the basis of such evidences, a simple stenting with provisional side-branch (SB) treatment has become the preferred strategy in the majority of bifurcation lesions.

Table 3 Unadjusted and adjusted hazard ratios for primary and secondary clinical outcomes stratified by bifurcation location and generation of drug-eluting stents[a]

	HR (95% CI), *P* value (second-gen DES vs. first-gen DES)					
	All bifurcations (*N* = 7282)		Non-LM bifurcations (*N* = 5050)		LM bifurcations (*N* = 2232)	
Outcomes	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Primary outcomes						
Target-vessel failure[b]	0.86 (0.75–0.99), 0.03	0.86 (0.74–0.99), 0.03	0.87 (0.72–1.04), 0.12	0.88 (0.80–0.97), 0.02	0.90 (0.73–1.11), 0.31	0.81 (0.66–1.01), 0.06
Secondary outcomes						
Death from any cause	1.08 (0.83–1.41), 0.56	0.90 (0.69–1.18), 0.46	0.86 (0.63–1.19), 0.37	0.79 (0.57–1.11), 0.18	1.72 (1.07–2.74), 0.02	1.15 (0.71–1.86), 0.56
Cardiac	1.13 (0.82–1.55), 0.45	0.94 (0.68–1.30), 0.71	0.89 (0.60–1.31), 0.55	0.79 (0.53–1.19), 0.26	1.81 (1.04–3.14), 0.04	1.24 (0.70–2.17), 0.46
Noncardiac	0.97 (0.60–1.58), 0.91	0.83 (0.51–1.37), 0.47	0.81 (0.45–1.44), 0.46	0.82 (0.45–1.51), 0.52	1.49 (0.61–3.61), 0.38	0.97 (0.39–2.42), 0.95
MI	0.77 (0.65–0.90), 0.001	0.76 (0.65–0.89), 0.001	0.78 (0.63–0.97), 0.03	0.80 (0.64–1.01), 0.06	0.78 (0.61–1.00), 0.05	0.71 (0.55–0.91), 0.01
Q-wave	1.17 (0.55–2.50), 0.68	1.27 (0.58–2.75), 0.55	1.22 (0.47–3.18), 0.68	1.61 (0.61–4.25), 0.34	1.08 (0.31–3.80), 0.90	0.96 (0.27–3.38), 0.95
Non-Q-wave	0.75 (0.63–0.88), 0.001	0.74 (0.62–0.88), 0.001	0.76 (0.61–0.95), 0.02	0.76 (0.60–0.96), 0.02	0.77 (0.60–0.99), 0.04	0.70 (0.55–0.91), 0.01
Any revascularization	0.93 (0.77–1.13), 0.49	0.96 (0.79–1.17), 0.71	1.14 (0.88–1.47), 0.32	1.18 (0.91–1.54), 0.22	0.69 (0.51–0.93), 0.02	0.69 (0.51–0.94), 0.02
TVR	0.77 (0.62–0.97), 0.03	0.83 (0.74–0.94), 0.13	0.87 (0.64–1.18), 0.36	0.96 (0.70–1.31), 0.78	0.70 (0.50–0.98), 0.04	0.70 (0.49–0.99), 0.04
Non-TVR	1.46 (1.00–2.14), 0.05	1.37 (0.92–2.03), 0.12	1.89 (1.17–3.05), 0.01	1.79 (1.10–2.93), 0.02	0.66 (0.34–1.31), 0.24	0.70 (0.36–1.35), 0.32
Definite stent thrombosis	0.97 (0.36–2.60), 0.95	0.70 (0.27–1.84), 0.50	1.60 (0.36–7.09), 0.54	1.13 (0.24–5.42), 0.88	0.52 (0.13–2.10), 0.36	0.49 (0.12–2.08), 0.33
Post-hoc analyses						
MI (SCAI-defined)[c]	0.87 (0.68–1.13), 0.30	0.96 (0.73–1.28), 0.80	1.06 (0.73–1.52), 0.77	1.25 (0.84–1.87), 0.28	0.75 (0.52–1.07), 0.11	0.75 (0.50–1.11), 0.15
Q-wave	1.13 (0.53–2.42), 0.76	1.43 (0.63–3.25), 0.40	1.15 (0.44–3.00), 0.78	1.57 (0.59–4.18), 0.37	1.10 (0.31–3.85), 0.88	1.37 (0.31–6.12), 0.68
Non-Q-wave	0.84 (0.64–1.10), 0.22	0.91 (0.67–1.23), 0.53	1.04 (0.70–1.55), 0.84	1.19 (0.76–1.85), 0.44	0.72 (0.49–1.04), 0.08	0.71 (0.47–1.07), 0.10
Alternatively defined target-vessel failure[d]	0.98 (0.83–1.17), 0.84	1.03 (0.85–1.24), 0.78	1.02 (0.81–1.29), 0.84	1.10 (0.86–1.42), 0.44	0.98 (0.75–1.27), 0.87	0.93 (0.70–1.24), 0.63

Adjusted hazard ratios are adjusted for age, sex, diabetes, previous MI, previous PCI, chronic renal failure, clinical presentation, ejection fraction, bifurcation location, disease extent, and use of intravascular ultrasound.
DES, drug-eluting stents; gen, generation; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCAI, the Society for Cardiovascular Angiography and Interventions; TVR, target-vessel revascularization.
[a]Hazard ratios are for the second-generation DES group as compared with the first-generation DES group.
[b]Target-vessel failure was defined as death from cardiac causes, target-vessel MI, or clinically indicated TVR.
[c]MI was defined post-hoc according to the SCAI definition [10].
[d]The alternative-defined target-vessel failure, defined post-hoc, was a composite of death from cardiac causes, target-vessel MI (SCAI-defined), or clinically indicated TVR.

Table 4 Three-year event rates of primary and secondary clinical outcomes stratified by bifurcation location and stenting strategy[a]

	All bifurcations ($N=7282$)			Non-LM bifurcations ($N=5050$)			LM bifurcations ($N=2232$)		
	Simple strategy ($N=5992$)	Complex strategy ($N=1290$)		Simple strategy ($N=4379$)	Complex strategy ($N=671$)		Simple strategy ($N=1613$)	Complex strategy ($N=619$)	
Outcome	Event rate at 3 year (%, 95% CI)		P	Event rate at 3 year (%, 95% CI)		P	Event rate at 3 year (%, 95% CI)		P
Primary outcomes									
Target-vessel failure[b]	16.6 (15.6–17.6)	22.0 (19.7–24.3)	<0.001	14.8 (13.7–15.9)	16.4 (13.6–19.2)	0.15	21.5 (19.4–23.6)	28.5 (24.7–32.3)	0.011
Secondary outcomes									
Death from any cause	5.6 (5.0–6.2)	5.1 (3.8–6.4)	0.44	5.0 (4.3–5.7)	3.7 (2.2–5.2)	0.17	7.2 (5.8–8.6)	6.7 (4.5–8.9)	0.53
Cardiac	4.1 (3.6–4.6)	3.5 (2.4–4.6)	0.33	3.6 (3–4.2)	2.3 (1.1–3.5)	0.10	5.5 (4.2–6.8)	5.0 (3.1–6.9)	0.54
Noncardiac	1.5 (1.2–1.8)	1.6 (0.9–2.3)	0.93	1.4 (1.0–1.8)	1.4 (0.5–2.3)	0.98	1.9 (1.2–2.6)	1.8 (0.6–3.0)	0.85
MI	10.4 (9.6–11.2)	15.8 (13.8–17.8)	<0.001	8.1 (7.3–8.9)	12.7 (10.2–15.2)	0.007	14.6 (12.8–16.4)	19.1 (16.0–22.2)	0.001
Q-wave	0.7 (0.5–0.9)	0.6 (0.2–1.0)	0.60	0.7 (0.4–1.0)	0.6 (0.0–1.2)	0.90	0.9 (0.4–1.4)	0.5 (−0.1 to 1.1)	0.45
Non-Q-wave	9.7 (8.9–10.5)	15.2 (13.2–17.2)	<0.001	8.2 (7.4–9.0)	12.2 (9.7–14.7)	0.011	13.8 (12.1–15.5)	18.7 (15.6–21.8)	0.01
Any revascularization	9.1 (8.3–9.9)	11.4 (9.6–13.2)	0.01	9.0 (8.0–10.0)	9.2 (6.9–11.5)	0.79	9.2 (7.6–10.8)	14.0 (11.0–17.0)	0.004
TVR	5.9 (5.2–6.6)	8.7 (7.1–10.3)	<0.001	5.4 (4.7–6.1)	5.8 (4.0–7.6)	0.61	7.2 (5.8–8.6)	12.2 (9.4–15.0)	0.001
Non-TVR	3.4 (2.9–3.9)	3.0 (2.0–4.0)	0.41	3.8 (3.2–4.4)	3.6 (2.1–5.1)	0.84	2.1 (1.3–2.9)	2.1 (0.8–3.4)	0.74
Definite stent thrombosis	0.4 (0.2–0.6)	0.2 (−0.1 to 0.5)	0.49	0.4 (0.2–0.6)	0.0 (0.0–0.0)	0.12	0.4 (0.1–0.7)	0.5 (−0.1 to 1.1)	0.79
Post-hoc analyses									
MI (SCAI-defined)[c]	4.9 (4.3–5.4)	5.4 (4.2–6.7)	0.37	4.0 (3.4–4.6)	3.8 (2.3–5.2)	0.79	7.2 (5.9–8.5)	7.3 (5.2–9.4)	0.96
Q-wave	0.7 (0.5–0.9)	0.5 (0.1–1.0)	0.66	0.6 (0.4–0.9)	0.6 (0.0–1.2)	0.99	0.8 (0.4–1.3)	0.5 (−0.1 to 1.1)	0.42
Non-Q-wave	4.2 (3.7–4.7)	4.9 (3.7–6.1)	0.25	3.4 (2.9–4.0)	3.2 (1.8–4.5)	0.78	6.4 (5.2–7.6)	6.8 (4.7–8.8)	0.74
Alternatively defined target-vessel failure[d]	11.5 (10.6–12.3)	12.6 (10.7–14.5)	0.18	10.3 (9.3–11.2)	8.0 (5.9–10.1)	0.12	14.9 (13.0–16.7)	18.1 (14.8–21.4)	0.12

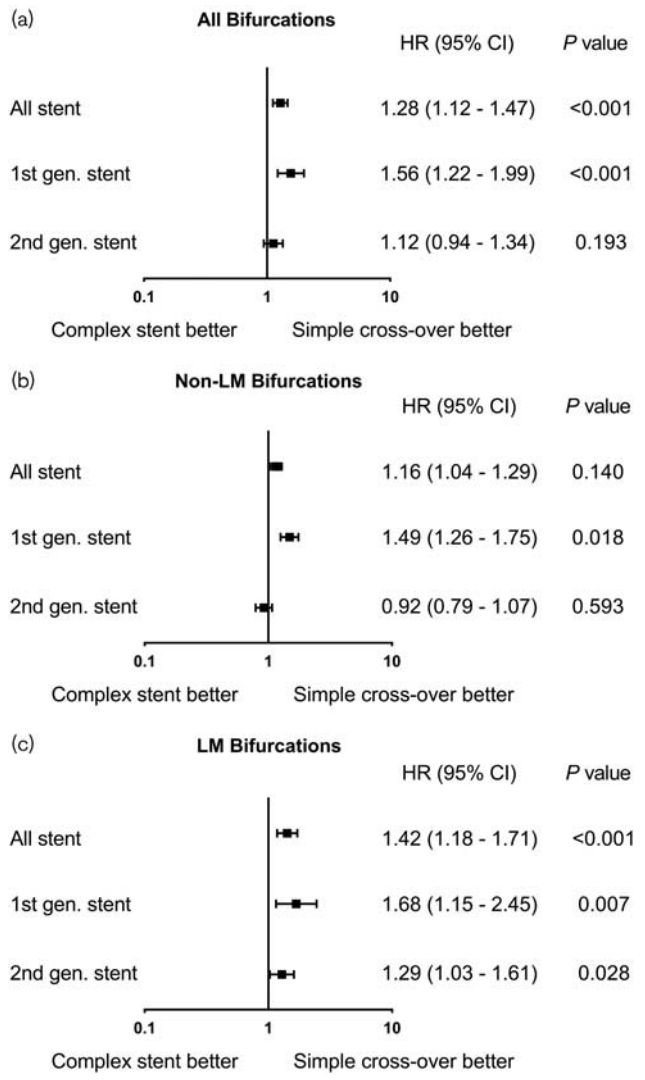
DES, drug-eluting stents; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; TVR, target-vessel revascularization.
[a]Cumulative rates (95% CI) of events are based on Kaplan–Meier estimates.
[b]Target-vessel failure was defined as death from cardiac causes, target-vessel MI, or clinically indicated TVR.
[c]MI was defined post-hoc according to the SCAI definition [10].
[d]The alternative-defined target-vessel failure, defined post-hoc, was a composite of death from cardiac causes, target-vessel MI (SCAI-defined), or clinically indicated TVR.

Table 5 Unadjusted and adjusted hazard ratios for primary and secondary clinical outcomes stratified by bifurcation location and stenting strategy[a]

	HR (95% CI), *P* value (complex vs. simple strategy)					
	All bifurcations (*N* = 7282)		Non-LM bifurcations (*N* = 5050)		LM bifurcations (*N* = 2232)	
Outcomes	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Primary outcome						
Target-vessel failure[b]	1.40 (1.22–1.60), 0.01	1.28 (1.12–1.47), <0.001	1.16 (0.95–1.42), 0.16	1.16 (1.04–1.29), 0.14	1.37 (1.13–1.65), 0.01	1.42 (1.18–1.71), <0.001
Secondary outcomes						
Death from any cause	0.89 (0.67–1.19), 0.44	0.82 (0.61–1.10), 0.18	0.74 (0.48–1.14), 0.17	0.78 (0.51–1.21), 0.27	0.88 (0.60–1.31), 0.53	0.86 (0.58–1.27), 0.45
Cardiac	0.84 (0.60–1.19), 0.33	0.76 (0.54–1.08), 0.12	0.63 (0.36–1.09), 0.10	0.67 (0.38–1.16), 0.15	0.87 (0.55–1.37), 0.54	0.84 (0.53–1.33), 0.46
Noncardiac	1.02 (0.61–1.71), 0.93	0.99 (0.59–1.68), 0.98	1.01 (0.50–2.04), 0.98	1.06 (0.52–2.16), 0.87	0.93 (0.43–2.00), 0.85	0.91 (0.42–1.96), 0.80
MI	1.57 (1.34–1.83), 0.01	1.41 (1.21–1.66), <0.001	1.47 (1.16–1.86), 0.01	1.45 (1.29–1.64), <0.001	1.34 (1.08–1.68), 0.01	1.41 (1.14–1.74), <0.001
Q-wave	0.81 (0.36–1.80), 0.60	0.79 (0.35–1.77), 0.57	0.94 (0.33–2.67), 0.90	0.87 (0.31–2.47), 0.79	0.62 (0.18–2.17), 0.45	0.71 (0.50–1.01), 0.60
Non-Q-wave	1.62 (1.38–1.91), 0.01	1.46 (1.24–1.72), <0.001	1.51 (1.19–1.93), 0.01	1.51 (1.33–1.70), <0.001	1.39 (1.10–1.74), <0.001	1.45 (1.17–1.79), <0.001
Any revascularization	1.29 (1.06–1.56), 0.01	1.25 (1.05–1.50), 0.02	1.04 (0.79–1.37), 0.79	1.04 (0.79–1.38), 0.78	1.52 (1.14–2.03), <0.001	1.57 (1.18–2.10), <0.001
TVR	1.54 (1.23–1.93), 0.01	1.40 (1.25–1.58), <0.001	1.10 (0.77–1.56), 0.61	1.08 (0.90–1.29), 0.68	1.72 (1.25–2.36), <0.001	1.79 (1.30–2.46), <0.001
Non-TVR	0.85 (0.58–1.24), 0.41	0.96 (0.65–1.39), 0.81	0.95 (0.61–1.49), 0.84	0.99 (0.63–1.55), 0.95	0.89 (0.43–1.82), 0.74	0.89 (0.43–1.85), 0.76
Definite stent thrombosis	0.65 (0.19–2.19), 0.49	0.65 (0.19–2.23), 0.50	0.04 (0.00–23.04), 0.32	NA	1.31 (0.33–5.24), 0.70	1.67 (0.40–6.95), 0.48
Post-hoc analyses						
MI (SCAI-defined)[c]	1.13 (0.87–1.47), 0.37	0.97 (0.73–1.29), 0.85	0.95 (0.62–1.44), 0.79	0.88 (0.56–1.38), 0.57	1.01 (0.71–1.43), 0.96	1.05 (0.73–1.52), 0.78
Q-wave	0.83 (0.37–1.86), 0.66	0.84 (0.37–1.91), 0.68	0.99 (0.35–2.85), 0.99	0.92 (0.32–2.66), 0.88	0.60 (0.17–2.11), 0.43	0.72 (0.20–2.58), 0.62
Non-Q-wave	1.18 (0.89–1.55), 0.26	1.00 (0.74–1.35), 0.99	0.94 (0.59–1.48), 0.78	0.87 (0.53–1.43), 0.59	1.06 (0.74–1.53), 0.75	1.10 (0.74–1.61), 0.64
Alternatively defined target-vessel failure[d]	1.13 (0.94–1.35), 0.18	1.01 (0.84–1.22), 0.92	0.79 (0.60–1.06), 0.12	0.76 (0.56–1.03), 0.08	1.21 (0.95–1.53), 0.12	1.27 (0.99–1.64), 0.06

Adjusted hazard ratios are adjusted for age, sex, diabetes, previous MI, previous PCI, chronic renal failure, clinical presentation, ejection fraction, bifurcation location, disease extent, and use of intravascular ultrasound.
DES, drug-eluting stents; LM, left main; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; TVR, target-vessel revascularization.
[a]Hazard ratios are for complex stenting strategy as compared with simple stenting strategy.
[b]Target-vessel failure was defined as death from cardiac causes, target-vessel MI, or clinically indicated TVR.
[c]MI was defined post-hoc according to the SCAI definition [10].
[d]The alternative-defined target-vessel failure, defined post-hoc, was a composite of death from cardiac causes, target-vessel MI (SCAI-defined), or clinically indicated TVR.

Fig. 3



Adjusted risk of target-vessel failure according to stenting strategy over time stratified by generation of drug-eluting stents for all bifurcation (a), non-LM bifurcations (b), and LM bifurcations (c). Adjusted hazard ratios are for complex stenting strategy as compared with simple stenting strategy. Target-vessel failure was defined as death from cardiac causes, target-vessel MI, or clinically indicated TVR. Models are adjusted for age, sex, diabetes, previous MI, previous PCI, chronic renal failure, clinical presentation, ejection fraction, bifurcation location, disease extent, and use of intravascular ultrasound. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target-vessel revascularization.

This practice pattern was also observed in our large-sized, longitudinal, real-world registry.

In the clinical viewpoint, although angiographic narrowing of SB is common after simple-crossover stenting, there is a substantial discrepancy between functional significance and % diameter stenosis of jailed SB; most of such SB stenosis are functionally nonsignificant [20,21]. In addition, the prerequisites of clinical benefit with PCI over medical therapy require the presence of moderate to large amounts of inducible ischemia [22,23]. However, only a few SB can cause moderate to severe ischemia and thus 'leave-it-alone' strategy for functionally insignificant SB narrowing might be clinically reasonable. With such clinical concept, more frequent adoption of simple stenting strategy might reduce unnecessary SB intervention and be one of important factors contributing to improved outcomes of bifurcation PCI over time.

Interestingly, in our study, the difference in treatment effect between simple and complex stenting has been narrowed from the first-generation DES to the second-generation DES. This trend was also noted in large-sized, bifurcation pooled cohorts [13]. With contemporary second-generation DES, improved stent design and thinner strut allowing easy accessibility and full expansion of SB ostium as well as more potent anti-restenotic effect might translate into enhanced feasibility and improved outcomes of complex stenting strategy. In addition, evolving two-stents techniques with continuous refinement and increasing expertise significantly contributed to improved PCI results after complex stenting. All these factors have influenced the gap in treatment effect between simplex and complex strategy to be progressively narrowed over time. Current findings suggest that stenting strategy should be individualized according to the anatomic or functional significance of SB and its clinical relevance and, if SB is considered to be stented, initially planned complex stenting strategy with contemporary second-generation DES can be a reasonable approach for complex bifurcation lesion.

Using the protocol definition of MI used in our study, the presence of periprocedural MI was significantly associated with an increased risk of mortality [24], implying the prognostic significance of our MI definition. However, there is disagreement about how to define a 'clinically relevant MI' after PCI [9]. In the current study, using less stringent MI definition, comparative outcomes (MI or target-vessel failure) between groups (first-generation vs. second-generation DES and simple vs. complex strategy) were statistically significant; however, these outcome differences were attenuated by using more stringent, SCAI-defined MI. Because uniform definition of MI in complex PCI situation is still lacking, further studies are required to improve standardization of MI definition for future PCI trials.

Our study has some potential limitations. First, because of a nature of nonrandomized, observational study, overall findings are to be considered hypothetical and hypotheses-generating only. Second, because defining of bifurcation lesion, patient selection, and treatment strategy was mainly based on the operator discretion, the study findings are subject to selection bias. Especially, comparison between simple and complex two-stents strategy was based on the final result of the procedure, not operator's initial intention. Comparative outcomes between simple and complex strategy might be significantly affected by residual confounding and unmeasured variables. Third, because the database merged two

clinical studies, interstudy variability in care may exist that could have influenced the results. Fourth, because detailed information on two-stents techniques was not fully available in all patients, we could not determine whether clinical outcomes were different according to specific techniques of complex stenting. Finally, in our study, the incidence of stent thrombosis was extremely low. As compared with the Western population, a relatively low rate of stent thrombosis might be explained in part by differences in clinical or lesion characteristics, interventional practice, or race or ethnic groups, as previously noted [6,25]. Owing to a few number of thrombotic events, our study was underpowered to detect any clinical relevance with regard to safety outcomes.

Conclusion

Over the last decade from first-generation to second-generation DES, baseline characteristics, stenting strategy, and PCI outcomes have substantially changed in patients with non-LM and LM bifurcation disease. Simple stenting strategy has been more frequently used and clinical outcomes have been improved over time. Overall, simple strategy as compared with complex strategy was associated with a lower rate of target-vessel failure, but this treatment gap has progressively narrowed with contemporary second-generation DES.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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