

Long-Term Outcomes After Stent Implantation for Left Main Coronary Artery (from the Multicenter Assessing Optimal Percutaneous Coronary Intervention for Left Main Coronary Artery Stenting Registry)



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We assessed long-term outcomes after left main coronary artery (LMCA) stenting based on lesion types and stenting strategies. In the Assessing Optimal percutaneous coronary Intervention for Left Main Coronary Artery stenting registry, we evaluated 1,607 consecutive patients undergoing stent implantation for unprotected LMCA lesions (bifurcation lesions: $n = 1318$ and nonbifurcation lesions: $n = 289$). Among the bifurcation lesions, 1,281 lesions were treated with stenting across the bifurcation (bifurcation 1-stent strategy: $n = 999$ or bifurcation 2-stent strategy: $n = 282$). Among the nonbifurcation lesions, 219 lesions were treated with nonbifurcation stenting. The median follow-up duration was 4.6 (95% CI 4.5 to 4.8) years. The 5-year risk of bifurcation lesions relative to nonbifurcation lesions was neutral for target lesion revascularization (TLR) (adjusted hazard ratio [HR] 0.82, 95% CI 0.55 to 1.23, $p = 0.34$) and all-cause death (adjusted HR 1.22, 95% CI 0.87 to 1.71, $p = 0.26$). The risk of the bifurcation 1-stent strategy relative to nonbifurcation stenting in nonbifurcation lesions was also neutral for TLR (adjusted HR 1.19, 95% CI 0.74 to 1.90, $p = 0.47$) and all-cause death (adjusted HR 0.81, 95% CI 0.56 to 1.18, $p = 0.27$). However, the bifurcation 2-stent strategy was associated with worse clinical outcomes than the bifurcation 1-stent strategy in TLR (adjusted HR 1.76, 95% CI 1.23 to 2.52, $p = 0.002$) and definite or probable stent thrombosis (crude HR 3.50, 95% CI 1.32 to 9.33, $p = 0.01$), despite neutral risk for all-cause death (adjusted HR 1.00, 95% CI 0.74 to 1.36, $p = 0.99$). There was no definite or probable very late stent thrombosis up to 5 years. In conclusion, long-term outcomes after stent implantation for unprotected LMCA lesions were not dependent on the bifurcation lesion types but related to the bifurcation stenting strategies with worse outcomes for the bifurcation 2-stent strategy. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;119:355–364)

Stent implantation in patients with left main coronary artery (LMCA) disease has been widely performed as an alternative to coronary artery bypass grafting (CABG), especially in those with less extensive coronary artery

disease.^{1–3} However, despite improvement in devices and techniques, LMCA stenting remains challenging, and the cumulative incidence of target lesion revascularization (TLR) is reported to be significantly higher in bifurcation lesions than in nonbifurcation lesions.⁴ Moreover, it is reported that not only the rate of TLR^{5,6} but also that of cardiac death tended to be higher in patients with bifurcation lesions treated with the 2-stent strategy than in those treated with the 1-stent strategy.⁷ Considering the wide variations in LMCA bifurcation morphologies and bifurcation stenting techniques, the effects of lesion types (bifurcation or nonbifurcation) and stenting strategies (1 stenting or 2 stenting for bifurcation lesions or nonbifurcation stenting for nonbifurcation lesions) on clinical outcomes should be further clarified. Therefore, we assessed long-term clinical outcomes after LMCA stenting based on lesion types and stenting strategies.

Methods

The Assessing Optimal percutaneous coronary Intervention for Left Main Coronary Artery stenting registry is

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See page 363 for disclosure information.

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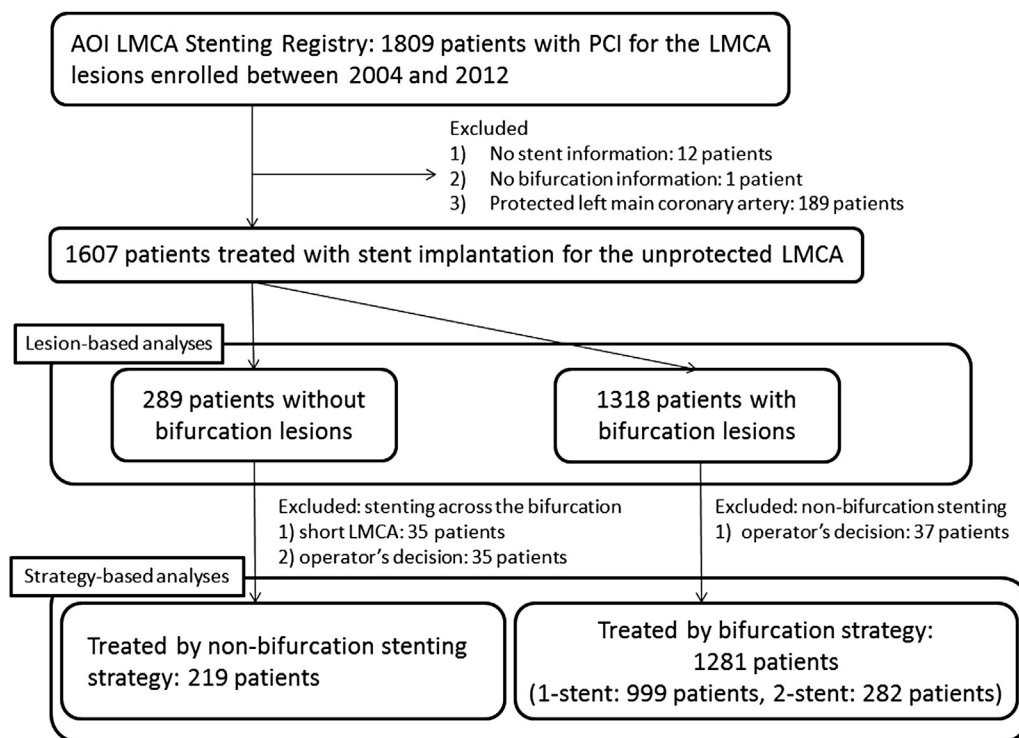


Figure 1. Study flow chart.

an investigator-initiated multicenter registry conducted in 6 centers in Japan from 2004 to 2012, retrospectively enrolling 1,809 consecutive patients undergoing coronary stent implantation for significant LMCA lesions, which were angiographically defined as at least 50% stenosis in the LMCA. Patients with previous CABG were included if a significant stenosis or an obstruction had developed in the bypass graft for the left coronary artery.

Aspirin (100 mg/day) and ticlopidine (200 mg/day) or clopidogrel (75 mg/day) were prescribed to all patients after the procedure. According to each institutional protocol, the recommended durations of dual antiplatelet therapy were at least 8 to 12 months after drug-eluting stent (DES) implantation and at least 1 month after bare-metal stent implantation; however, the actual durations were decided by each cardiologist. We collected data on patient, lesion, and procedural characteristics by reviewing medical records and follow-up information by reviewing medical records or contacting patients, relatives, or local physicians. Clinical follow-up was censored by death and lost to follow-up or at 5 years after the procedure. The median follow-up duration was 4.6 (95% CI 4.5 to 4.8) years.

The study was approved by each institutional ethics committee and was conducted in accordance with the provisions of the Declaration of Helsinki and the ethical guidelines for epidemiological studies in Japan. Written informed consent was waived according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, whereas no patient refused to participate in the study when being contacted for follow-up.

Coronary angiograms were carefully evaluated for lesion types and stenting strategies by the experienced

interventional cardiologists at each center. Bifurcation lesion was defined as a coronary artery narrowing adjacent to and involving the origin of a significant side branch, according to the proposition of the European Bifurcation Club.⁸ The Medina classification was used to assess each bifurcation lesion.⁹ Of the 1,809 LMCA lesions, 1,318 lesions (72.9%) were classified as bifurcation lesions, and 289 lesions (16.0%) as nonbifurcation lesions, excluding 13 patients (0.7%) without sufficient data for evaluation and 189 patients with protected LMCA (Figure 1). LMCA stenting across the bifurcation was performed in 1,281 patients with LMCA bifurcation lesions. We excluded 37 patients with LMCA bifurcation lesions in whom stenting across the bifurcation was not performed based on the discretion of the operators. LMCA stenting across the bifurcation was further classified into the bifurcation 1-stent (n = 999) and bifurcation 2-stent (n = 282) strategies. The bifurcation 2-stent strategy was defined as deploying at least 1 stent both in the main and side vessels of the LMCA lesion. Nonbifurcation stenting was defined as stent implantation without crossing the bifurcation in patients with nonbifurcation LMCA lesions (n = 219). We excluded 70 patients with stenting across the bifurcation despite the absence of LMCA bifurcation lesions (Figure 1). During the study period, we used the following 3 types of stent: bare-metal stent, first-generation DES (G1-DES), and second-generation DES (G2-DES). G1-DES included Cypher (sirolimus eluting; Cordis, Johnson & Johnson, Miami, Florida), Taxus (paclitaxel eluting; Boston Scientific, Natick, Massachusetts), and Endeavor (zotarolimus eluting; Medtronic, Santa Rosa, California) stents. G2-DES included Xience (everolimus eluting; Abbot Vascular, Santa Clara, California), BioMatrix (biolimus eluting; Biosensors,

Table 1
Baseline patient, lesion, and procedural characteristics and medications
according to lesion types: bifurcation versus nonbifurcation lesions

Variable	Entire cohort (N = 1607)	Non-bifurcation (N = 289)	Bifurcation (N = 1318)	p Value
Age (years)	71.9±10.3	70.7±10.3	72.1±10.2	0.046
Age ≥ 80 years*	395 (25%)	49 (17%)	346 (26%)	0.001
Men	1207 (75%)	212 (73%)	995 (76%)	0.45
Hypertension	1185 (74%)	217 (75%)	968 (74%)	0.58
Diabetes mellitus*	661 (41%)	110 (38%)	551 (42%)	0.24
Insulin-treated diabetes	164 (10%)	32 (11%)	132 (10%)	0.60
Dyslipidemia	846 (53%)	150 (52%)	696 (53%)	0.77
Current smoker	281 (18%)	47 (16%)	234 (18%)	0.54
eGFR (mL/min/1.73m ²)	58.0±24.0	57.0±25.5	58.2±23.7	0.66
Hemodialysis*	96 (6%)	23 (8%)	73 (6%)	0.12
eGFR < 60 and non-HD*	698 (43%)	119 (41%)	579 (44%)	0.39
Previous PCI*	683 (43%)	113 (39%)	570 (43%)	0.20
Previous myocardial infarction	437 (27%)	57 (20%)	380 (29%)	0.002
Previous heart failure*	212 (13%)	37 (13%)	175 (13%)	0.83
Malignancy*	163 (10%)	19 (7%)	144 (11%)	0.03
Stroke*	206 (13%)	33 (11%)	173 (13%)	0.43
Peripheral vascular disease*	213 (13%)	47 (16%)	166 (13%)	0.10
LVEF (%)†	56.2±13.7	55.9±14.6	56.3±13.5	0.81
Euro score	5.8±3.6	5.9±3.9	5.8±3.6	0.81
Clinical presentation*				0.89
Stable CAD	1104 (69%)	202 (70%)	902 (68%)	
UAP/NSTEMI	320 (20%)	55 (19%)	265 (20%)	
STEMI	183 (11%)	32 (11%)	151 (12%)	
Decompensated heart failure	152 (10%)	28 (10%)	124 (10%)	0.94
Shock vital*	133 (8%)	23 (8%)	110 (8%)	0.83
Extent of CAD				<0.001
Left main only	186 (12%)	107 (37%)	79 (6%)	
Left main + 1-vessel	475 (30%)	100 (35%)	375 (29%)	
Left main + 2-vessels	606 (38%)	59 (20%)	547 (42%)	
Left main + 3-vessels	340 (21%)	23 (8%)	317 (24%)	
Multi-vessel (Left main + ≥2-vessels)*	946 (59%)	82 (28%)	864 (66%)	<0.001
CTO in the RCA	197 (12%)	14 (5%)	183 (14%)	<0.001
SYNTAX score‡	25.8±10.1	19.0±8.5	27.3±9.8	<0.001
LMCA characteristics				
Bifurcation lesion	1318 (82%)	0 (0%)	1318 (100%)	<0.001
True bifurcation	685 (43%)	0 (0%)	685 (52%)	<0.001
Medina classification				
(1,0,0)			161 (12%)	
(0,1,0)			62 (5%)	
(0,0,1)			29 (2%)	
(1,1,0)			380 (29%)	
(1,0,1)			85 (6%)	
(0,1,1)			26 (2%)	
(1,1,1)			574 (44%)	
True trifurcation	51 (3%)	0 (0%)	51 (4%)	<0.001
Calcified lesion*	230 (14%)	28 (10%)	202 (15%)	0.01
In-stent restenosis lesion	47 (3%)	8 (3%)	39 (3%)	0.86
Procedural characteristics				
Arterial access site				0.88
Femoral	1123 (70%)	203 (70%)	920 (70%)	
Radial or brachial	484 (30%)	86 (30%)	398 (30%)	

Table 1
(continued)

Variable	Entire cohort (N = 1607)	Non-bifurcation (N = 289)	Bifurcation (N = 1318)	p Value
Guiding catheter size				<0.001
6 Fr	284 (18%)	103 (36%)	181 (14%)	
≥7 Fr	1262 (82%)	180 (64%)	1082 (86%)	
Use of mechanical support				0.04
IABP	233 (15%)	31 (11%)	202 (15%)	
PCPS	45 (3%)	6 (2%)	39 (3%)	0.41
Stenting across the bifurcation	1351 (84%)	70 (24%)	1281 (97%)	<0.001
Two stenting	282 (18%)	0 (0%)	282 (21%)	<0.001
Use of rotablator	104 (7%)	10 (4%)	94 (7%)	0.02
Stent types*				<0.001
Bare metal stent	318 (20%)	93 (32%)	225 (17%)	
G1-DES	763 (48%)	121 (42%)	642 (49%)	
G2-DES	526 (33%)	75 (26%)	451 (34%)	
Use of intracoronary imaging modalities				
IVUS*	1067 (66%)	184 (64%)	883 (67%)	0.28
OCT	48 (3%)	6 (2%)	42 (3%)	0.32
None	499 (31%)	99 (34%)	400 (30%)	0.19
Number of stents per lesion	1.4±0.7	1.1±0.4	1.5±0.7	<0.001
Stent size (MV) (mm)	3.3±0.4	3.5±0.3	3.3±0.4	<0.001
Stent size (MV) ≥ 3.5 mm*	1002 (62%)	232 (80%)	770 (58%)	<0.001
Stent length (MV) (mm)	23.7±12.6	14.3±6.7	25.7±12.6	<0.001
Stent length (MV) ≥ 30 mm*	314 (20%)	8 (3%)	306 (23%)	<0.001
Final balloon size (MV) (mm)	3.4±0.5	3.7±0.6	3.3±0.5	<0.001
Stent size (SV) (mm)	2.9±0.4		2.9±0.4	
Stent length (SV) (mm)	20.1±6.8		20.1±6.8	
Maximum balloon size (SV) (mm)	2.8±0.5	2.6±0.6	2.8±0.5	0.17
Medications				
Aspirin	1550 (97%)	281 (97%)	1269 (97%)	0.90
Thienopyridine	1525 (96%)	277 (96%)	1248 (96%)	0.83
Warfarin	147 (9%)	25 (9%)	122 (9%)	0.71
Statins*	1006 (63%)	154 (53%)	852 (65%)	<0.001
β-blockers*	437 (27%)	67 (23%)	370 (28%)	0.09
ACE-I/ARB*	884 (55%)	150 (52%)	734 (56%)	0.24
Proton pump inhibitor	690 (43%)	108 (37%)	582 (45%)	0.03
H2-blocker	230 (14%)	37 (13%)	193 (15%)	0.39

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; CTO = chronic total occlusion; eGFR = estimated glomerular filtration rate; G1-DES = first-generation drug-eluting stent; G2-DES = second-generation drug-eluting stent; HD = hemodialysis; IABP = intraaortic balloon pumping; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MV = main vessel; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; PCPS = percutaneous cardiopulmonary support; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; SV = side vessel; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery; UAP = unstable angina pectoris.

* Indicates potential independent risk-adjusting variables selected for Cox proportional hazards models.

† Calculated in 213 patients in the nonbifurcation lesion arm and in 986 patients in the bifurcation lesion arm.

‡ Calculated in 284 patients in the nonbifurcation lesion arm and in 1,285 patients in the bifurcation lesion arm.

Table 2
Baseline patient, lesion, and procedural characteristics and medications
according to stenting strategies

Variable	Non-bifurcation Stenting (N = 219)	Bifurcation 1-stent (N = 999)	Bifurcation 2-stent (N = 282)	p Value
Age (years)	70.7±10.0	72.2±10.2	72.0±10.3	0.24
Age ≥ 80 years*	36 (16%)	260 (26%)	75 (27%)	0.009
Men	161 (74%)	768 (77%)	199 (71%)	0.08
Hypertension	166 (76%)	736 (74%)	203 (72%)	0.63
Diabetes mellitus*	83 (38%)	423 (42%)	107 (38%)	0.26
Insulin-treated diabetes	24 (11%)	96 (10%)	33 (12%)	0.54
Dyslipidemia	117 (53%)	527 (53%)	152 (54%)	0.94
Current smoker	35 (16%)	182 (18%)	49 (17%)	0.72
eGFR (ml/min/1.73m ²)	55.9±25.0	58.8±23.3	57.3±25.2	0.28
Hemodialysis*	17 (8%)	48 (5%)	22 (8%)	0.07
eGFR < 60 and non-HD*	94 (43%)	437 (44%)	120 (43%)	0.93
Previous PCI*	85 (39%)	440 (44%)	111 (39%)	0.19
Previous myocardial infarction	42 (19%)	288 (29%)	78 (28%)	0.01
Previous heart failure*	28 (13%)	137 (14%)	34 (12%)	0.75
Malignancy*	14 (6%)	110 (11%)	30 (11%)	0.12
Stroke*	26 (12%)	126 (13%)	42 (15%)	0.53
Peripheral vascular disease*	36 (16%)	132 (13%)	30 (11%)	0.16
LVEF (%)†	55.6±14.4	56.5±13.3	55.7±13.8	0.53
Euro score	6.1±4.0	5.8±3.6	5.8±3.6	0.90
Clinical presentation*				0.30
Stable CAD	150 (69%)	690 (69%)	189 (67%)	
UAP/NSTEMI	43 (20%)	186 (19%)	67 (24%)	
STEMI	26 (12%)	123 (12%)	26 (9%)	
Decompensated heart failure	21 (10%)	96 (10%)	24 (9%)	0.86
Shock vital*	20 (9%)	85 (9%)	23 (8%)	0.93
Extent of CAD				<0.001
Left main only	86 (39%)	73 (7%)	4 (1%)	
Left main + 1-vessel	66 (30%)	341 (34%)	25 (9%)	
Left main + 2-vessels	48 (22%)	380 (38%)	148 (53%)	
Left main + 3-vessels	19 (9%)	205 (21%)	105 (37%)	
Multi-vessel (Left main + ≥2-vessels)*	67 (31%)	585 (59%)	253 (90%)	<0.001
CTO in the RCA	13 (6%)	132 (13%)	48 (17%)	0.001
SYNTAX score‡	19.2±9.1	26.5±9.4	30.8±10.2	<0.001
LMCA characteristics				
Bifurcation lesion	0 (0%)	999 (100%)	282 (100%)	<0.001
True bifurcation	0 (0%)	433 (43%)	242 (86%)	<0.001
Medina classification				
(1,0,0)		142 (14%)	14 (5%)	
(0,1,0)		52 (5%)	2 (1%)	
(0,0,1)		15 (2%)	3 (1%)	
(1,1,0)		356 (36%)	21 (7%)	
(1,0,1)		57 (6%)	25 (9%)	
(0,1,1)		19 (2%)	2 (1%)	
(1,1,1)		357 (36%)	215 (76%)	
True trifurcation	0 (0%)	33 (6%)	18 (6%)	0.02
Calcified lesion*	22 (10%)	149 (15%)	50 (18%)	0.053
In-stent restenosis lesion	8 (4%)	24 (2%)	12 (4%)	0.21
Procedural characteristics				
Arterial access site				0.06
Femoral	151 (69%)	711 (71%)	180 (64%)	
Radial or brachial	68 (31%)	288 (29%)	102 (36%)	

Table 2
(continued)

Variable	Non-bifurcation Stenting (N = 219)	Bifurcation 1-stent (N = 999)	Bifurcation 2-stent (N = 282)	p Value
Guiding catheter size				<0.001
6 Fr	82 (38%)	164 (17%)	11 (4%)	
≥7 Fr	133 (62%)	791 (83%)	265 (96%)	
Use of mechanical support				
IABP	26 (12%)	158 (16%)	36 (13%)	0.20
PCPS	6 (3%)	27 (3%)	10 (4%)	0.75
Stenting across the bifurcation	0 (0%)	999 (100%)	282 (100%)	<0.001
Two stenting	0 (0%)	0 (0%)	282 (100%)	<0.001
Use of rotablator	7 (3%)	71 (7%)	22 (8%)	0.08
Stent types*				<0.001
Bare metal stent	80 (37%)	177 (18%)	37 (13%)	
G1-DES	89 (41%)	487 (49%)	137 (49%)	
G2-DES	50 (23%)	335 (34%)	108 (38%)	
Use of intracoronary imaging modalities				
IVUS*	132 (60%)	690 (69%)	171 (61%)	0.004
OCT	3 (1%)	36 (4%)	6 (2%)	0.14
None	84 (38%)	274 (27%)	110 (39%)	<0.001
Number of stents per lesion	1.1±0.4	1.3±0.6	2.3±0.7	<0.001
Stent size (MV) (mm)	3.5±0.3	3.3±0.3	3.2±0.4	<0.001
Stent size (MV) ≥ 3.5 mm*	185 (85%)	610 (61%)	131 (47%)	<0.001
Stent length (MV) (mm)	12.5±5.9	25.7±12.2	27.4±14.0	<0.001
Stent length (MV) ≥ 30 mm*	4 (2%)	227 (23%)	79 (28%)	<0.001
Final balloon size (MV) (mm)	3.8±0.6	3.4±0.5	3.3±0.5	<0.001
Stent size (SV) (mm)			2.9±0.4	
Stent length (SV) (mm)			20.1±6.8	
Maximum balloon size (SV) (mm)		2.6±0.4	2.9±0.5	
Medications				
Aspirin	212 (97%)	959 (97%)	274 (98%)	0.67
Thienopyridine	208 (95%)	943 (95%)	269 (96%)	0.83
Warfarin	20 (9%)	92 (9%)	28 (10%)	0.93
Statins*	114 (52%)	649 (65%)	176 (62%)	0.002
β-blockers*	50 (23%)	279 (28%)	77 (27%)	0.31
ACE-I/ARB*	109 (50%)	559 (56%)	152 (54%)	0.24
Proton pump inhibitor	82 (37%)	435 (44%)	128 (46%)	0.14
H2-blocker	29 (13%)	143 (15%)	45 (16%)	0.66

The abbreviations are the same as in Table 1.

* Indicates potential independent risk-adjusting variables selected for Cox proportional hazards models.

† Calculated in 157 patients in the nonbifurcation strategy arm, in 756 patients in the bifurcation 1-stent strategy arm, and in 199 patients in the bifurcation 2-stent strategy arm.

‡ Calculated in 214 patients in the nonbifurcation strategy arm, in 973 patients in the bifurcation 1-stent strategy arm, and in 275 patients in the bifurcation 2-stent strategy arm.

Morges, Switzerland), Nobori (biolimus eluting; Terumo, Tokyo, Japan), Promus Element (everolimus eluting; Boston Scientific), and Resolute (zotarolimus eluting; Medtronic) stents.

The coprimary outcome measures were TLR (for efficacy) and all-cause death (for safety) at 5 years. The secondary outcome measures included cardiac death, sudden death, myocardial infarction (MI), definite or probable stent

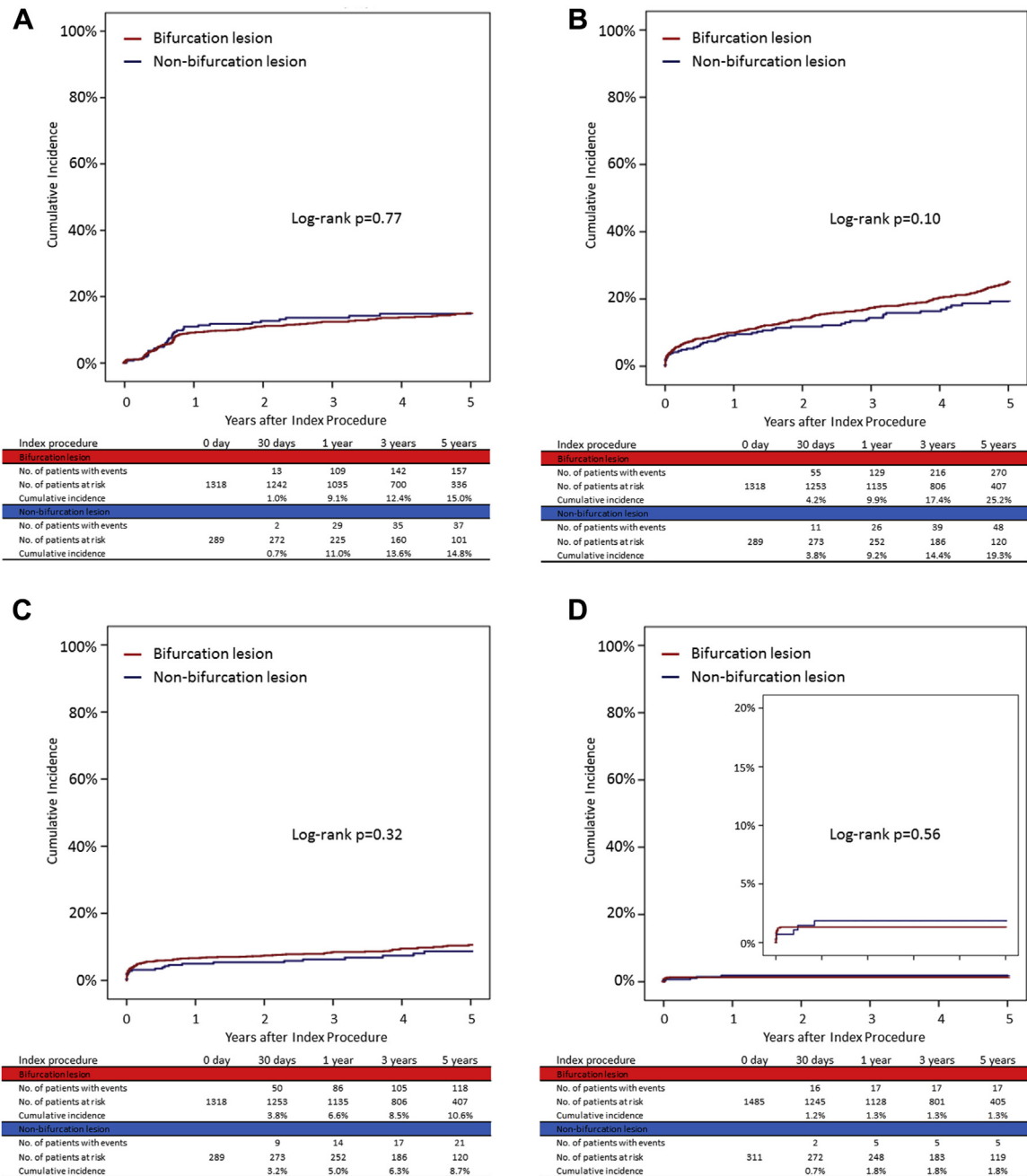


Figure 2. Clinical outcomes according to lesion types: bifurcation and nonbifurcation lesions. (A) Target lesion revascularization; (B) all-cause death; (C) cardiac death; (D) definite or probable stent thrombosis.

thrombosis (ST), stroke, and any coronary revascularization at 5 years. Cardiac death included any kind of death except for obvious noncardiac death. MI was defined as ischemic symptoms and/or ischemic changes of electrocardiogram along with elevated cardiac enzymes (troponin or creatine kinase-MB fraction) greater than the upper limit of normal. ST was defined according to the Academic Research Consortium definitions.¹⁰ ST was further classified according to the timing as early (≤ 30 days), late (31 days to 1 year), and very late (>1 year). ST of interest in the present study was restricted to ST in LMCA lesion. TLR was defined as repeat percutaneous coronary intervention (PCI) or CABG for

restenosis or thrombosis of the target lesions within the stent or within 5-mm proximal or distal to the stent including the ostium and/or the treated segment of the side branch.

Data were presented as mean $\pm$ SD or median and interquartile range for continuous variables and numbers with percentage for categorical variables. Continuous variables were compared using the Student *t* test or Wilcoxon rank-sum test as appropriate. Categorical variables were compared using the chi-square test. The cumulative incidences of clinical events were estimated by the Kaplan-Meier curves and were compared using the log-rank test. Cox proportional hazard models were constructed to adjust

Table 3

Five-year clinical outcomes according to lesion types: bifurcation and nonbifurcation lesions

	Number of Patients With at Least 1 Event (Cumulative 5-year incidence)		Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
	Non-bifurcation (N = 289)	Bifurcation (N = 1318)				
TLR	37 (14.8%)	157 (15.0%)	0.95 (0.66-1.36)	0.77	0.82 (0.55-1.23)	0.34
All-cause death	48 (19.3%)	270 (25.2%)	1.29 (0.95-1.75)	0.11	1.22 (0.87-1.71)	0.26
Cardiac death	21 (8.7%)	118 (10.6%)	1.27 (0.80-2.01)	0.32	1.27 (0.76-2.12)	0.37
Sudden death	5 (2.1%)	23 (2.4%)	1.05 (0.40-2.76)	0.92	NA	-
Myocardial infarction	8 (3.8%)	34 (3.5%)	0.97 (0.45-2.10)	0.94	NA	-
Stent thrombosis	5 (1.8%)	17 (1.3%)	0.74 (0.27-2.02)	0.56	NA	-
Definite	4 (1.5%)	13 (1.0%)	0.71 (0.23-2.18)	0.55	NA	-
Probable	1 (0.3%)	4 (0.3%)	0.87 (0.10-7.82)	0.90	NA	-
Stroke	9 (4.0%)	52 (5.4%)	1.34 (0.66-2.73)	0.42	NA	-
Ischemic	7 (3.2%)	35 (3.9%)	1.16 (0.52-2.62)	0.72	NA	-
Hemorrhagic	2 (0.8%)	17 (1.6%)	1.90 (0.44-8.22)	0.39	NA	-
Any coronary revascularization	80 (33.9%)	359 (34.3%)	1.00 (0.78-1.27)	0.99	0.75 (0.57-0.98)	0.04

CI = confidence interval; HR = hazard ratio; NA = not applicable; TLR = target lesion revascularization.

The risks of bifurcation lesion relative to nonbifurcation lesion for individual end points were expressed as HRs and 95% CI. Stent thrombosis denotes that occurred in the left main coronary artery.

for the potential confounders. We evaluated the risk of bifurcation lesion relative to nonbifurcation lesion as well as those of the nonbifurcation stenting and the bifurcation 2-stent strategy relative to the bifurcation 1-stent strategy for individual end points, which were expressed as hazard ratios (HRs) and 95% CIs. The risk-adjusting variables in the Cox proportional hazard models included 20 clinically relevant factors listed in Table 1 and also 3 periods based on when stent implantation was performed: 2004 to 2006 (bate-metal stent period), 2007 to 2009 (G1-DES period), and 2010 to 2012 (G2-DES period) because treatment strategies and other related factors changed over time. Proportional hazard assumptions for the variables were assessed on the plots of log (time) versus log (−log [survival]) stratified by each variable and were verified to be acceptable for all the variables. Cox proportional hazard models for sudden death, MI, ST, and stroke were not constructed due to their small numbers of patients with event. To evaluate TLR and ST events beyond 1 year after the procedure, a landmark analysis at 1 year was conducted, excluding patients having individual end point events before the landmark point. All statistical analyses were performed by a physician (M.O.) and by a statistician (T.M.) with SPSS (IBM SPSS Statistics 23, IBM, Armonk, New York). Two-tailed p values less than 0.05 were considered statistically significant.

Results

The study patients were mainly elderly patients and included a large proportion of patients with diabetes mellitus, previous PCI, stable coronary artery disease, and multivessel disease. The mean SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score was relatively high. The dominant access site was the femoral artery. Most patients were treated with DES. Intracoronary imaging, mostly intravascular ultrasound, was used in approximately 2/3 of patients (Table 1). The differences in baseline characteristics among the 3 periods are listed in Supplementary Table 1.

Patients with bifurcation lesions compared with those with nonbifurcation lesions were older and had more complex clinical and angiographic characteristics such as previous MI, right coronary artery disease, multivessel disease, and heavily calcified lesions. The SYNTAX score was significantly greater in patients with bifurcation lesions than in those with nonbifurcation lesions (Table 1). Patients treated with the bifurcation 2-stent strategy had more complex clinical and angiographic characteristics, such as multivessel disease and heavily calcified lesions, than those treated with the nonbifurcation stenting or the bifurcation 1-stent strategy. The SYNTAX score was significantly higher in patients treated with the bifurcation 2-stent strategy than in those treated with the nonbifurcation stenting or the bifurcation 1-stent strategy (Table 2).

The cumulative 5-year incidence of TLR was similar between patients with and without bifurcation lesions. Even after adjusting confounders, the risk of the bifurcation lesions relative to the nonbifurcation lesions remained neutral for TLR (Figure 2 and Table 3). The cumulative 5-year incidence of all-cause death trended to be higher in patients with bifurcation lesions than in those with nonbifurcation lesions. However, after adjusting confounders, the risk of the bifurcation lesions relative to the nonbifurcation lesions was not significant for all-cause death (Figure 2 and Table 3). The cumulative 5-year incidence of and the adjusted risk for cardiac death were also not significantly different between patients with bifurcation and nonbifurcation lesions (Figure 2 and Table 3). The cumulative 5-year incidences of sudden death, MI, definite or probable ST, stroke, and any coronary revascularization were not significantly different between patients with and without bifurcation lesions. Patients with nonbifurcation lesions had a higher adjusted risk for any coronary revascularization (Figure 2 and Table 3).

The cumulative 5-year incidence of TLR was significantly higher in patients treated with the bifurcation 2-stent strategy than in those treated with the nonbifurcation

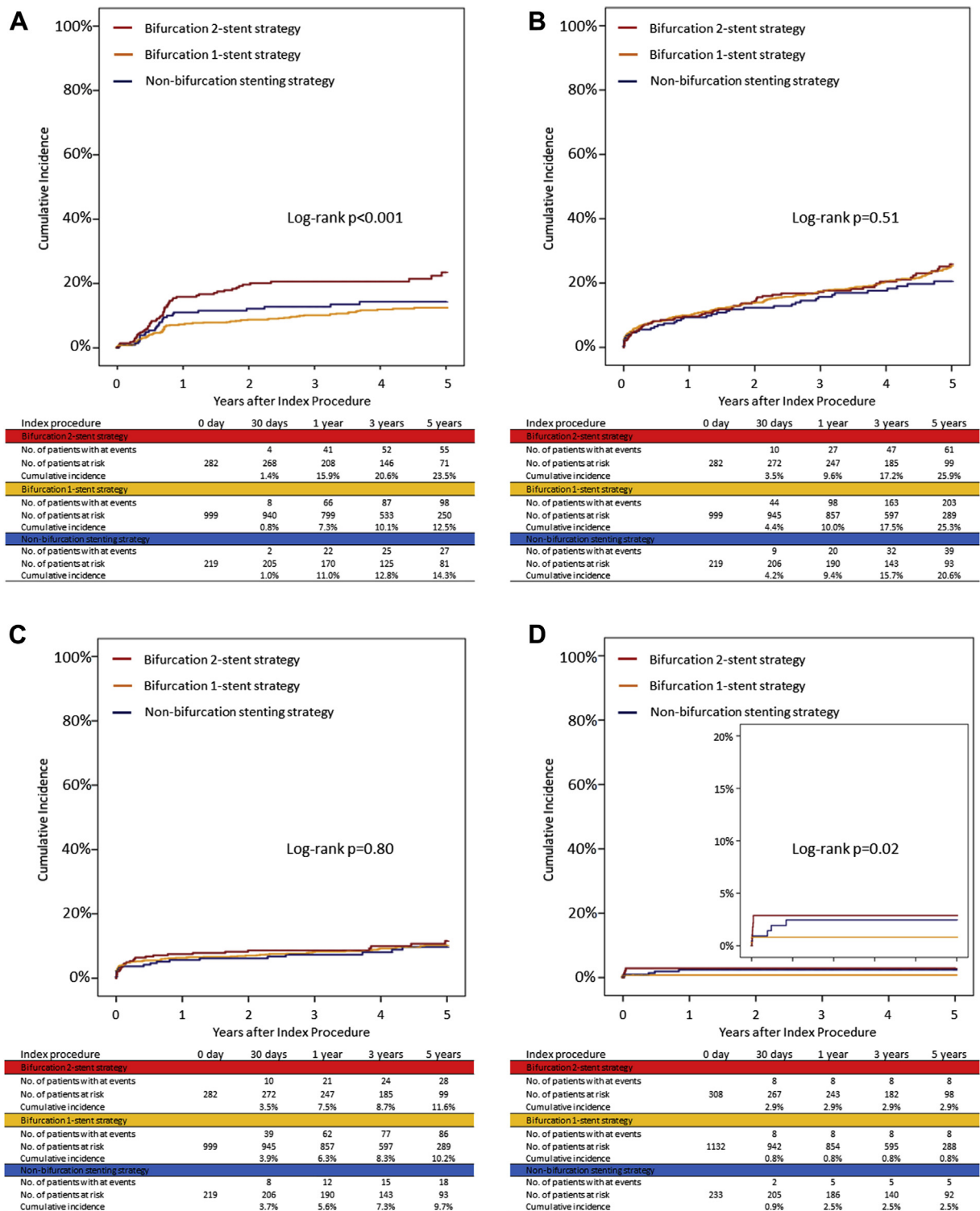


Figure 3. Clinical outcomes according to stenting strategies: noncrossover stenting, bifurcation 1-stent, and bifurcation 2-stent strategies. (A) Target lesion revascularization; (B) all-cause death; (C) cardiac death; (D) definite or probable stent thrombosis.

stenting or the bifurcation 1-stent strategy (Figure 3 and Table 4). After adjusting confounders, the excess risk of the bifurcation 2-stent strategy relative to the bifurcation 1-stent strategy for TLR was significant, whereas the risk of the nonbifurcation stenting relative to the bifurcation 1-stent

strategy for TLR was neutral (Table 4). Beyond 1 year, the TLR rate in the bifurcation 2-stent strategy attenuated and became no significantly different from those in the other 2 strategies (Supplementary Figure 1). The cumulative 5-year incidences of and adjusted risks for all-cause death

Table 4

Five-year clinical outcomes according to stenting strategies: noncrossover stenting, bifurcation 1-stent, and bifurcation 2-stent strategies

	Number of Patients with at Least 1 Event (Cumulative 5-year Incidence)			Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
	Non-bifurcation Stenting (N = 219)	Bifurcation 1-stent (N = 999)	Bifurcation 2-stent (N = 282)				
TLR	27 (14.3%)	98 (12.5%)	55 (23.5%)	1) 1.24 (0.81-1.90) 2) 2.05 (1.47-2.85)	0.32 <0.001	1) 1.19 (0.74-1.90) 2) 1.76 (1.23-2.52)	0.47 0.002
All-cause death	39 (20.6%)	203 (25.3%)	61 (25.9%)	1) 0.82 (0.58-1.16) 2) 1.01 (0.76-1.35)	0.27 0.93	1) 0.81 (0.56-1.18) 2) 1.00 (0.74-1.36)	0.27 0.99
Cardiac death	18 (9.7%)	86 (10.2%)	28 (11.6%)	1) 0.92 (0.55-1.53) 2) 1.12 (0.73-1.71)	0.75 0.62	1) 0.88 (0.50-1.53) 2) 1.27 (0.79-2.02)	0.64 0.32
Sudden death	5 (2.8%)	14 (2.0%)	9 (4.0%)	1) 1.54 (0.56-4.29) 2) 2.19 (0.95-5.05)	0.41 0.07	NA NA	- -
Myocardial infarction	7 (4.4%)	22 (3.1%)	11 (5.1%)	1) 1.36 (0.58-3.20) 2) 1.70 (0.82-3.50)	0.47 0.15	NA NA	- -
Stent thrombosis	5 (2.5%)	8 (0.8%)	8 (2.9%)	1) 2.86 (0.94-8.75) 2) 3.50 (1.32-9.33)	0.07 0.01	NA NA	- -
Definite	4 (2.0%)	6 (0.6%)	6 (2.2%)	1) 3.06 (0.86-10.8) 2) 3.51 (1.13-10.9)	0.08 0.03	NA NA	- -
Probable	1 (0.5%)	2 (0.2%)	2 (0.7%)	1) 2.28 (0.21-25.2) 2) 3.50 (0.49-24.8)	0.50 0.21	NA NA	- -
Stroke	8 (4.4%)	35 (4.6%)	15 (7.5%)	1) 0.98 (0.46-2.12) 2) 1.48 (0.81-2.71)	0.96 0.21	NA NA	- -
Ischemic	6 (3.3%)	23 (3.1%)	10 (5.3%)	1) 1.12 (0.45-2.74) 2) 1.48 (0.70-3.10)	0.81 0.30	NA NA	- -
Hemorrhagic	2 (1.1%)	12 (1.5%)	5 (2.1%)	1) 0.74 (0.17-3.32) 2) 1.43 (0.50-4.04)	0.70 0.51	NA NA	- -
Any coronary revascularization	61 (33.5%)	252 (31.7%)	94 (41.2%)	1) 1.10 (0.83-1.46) 2) 1.35 (1.06-1.71)	0.49 0.01	1) 1.34 (0.98-1.82) 2) 1.04 (0.81-1.34)	0.06 0.76

The risks of (1) nonbifurcation stenting and (2) bifurcation 2-stent strategy relative to bifurcation 1-stent strategy for individual end points were expressed as HRs and 95% CI. Stent thrombosis denotes that occurred in the left main coronary artery. The abbreviations are the same as in Table 3.

and cardiac death were comparable among the 3 strategies (Figure 3 and Table 4). The cumulative 5-year incidence of definite or probable ST was significantly higher in patients treated with the bifurcation 2-stent strategy than in those treated with the bifurcation 1-stent strategy (Figure 3 and Table 4). The excess ST rate in the bifurcation 2-stent strategy was exclusively seen within 1 year after the procedure. Remarkably, very late ST did not occur irrespective of the stenting strategies (Supplementary Figure 1). The characteristics of patients with definite ST are listed in Supplementary Table 2. The cumulative 5-year incidence of any coronary revascularization was significantly higher in patients treated with the bifurcation 2-stent strategy than in those treated with the bifurcation 1-stent strategy (Table 4). However, after adjusting confounders, the risk for any coronary revascularization was neutral among the 3 strategies. The cumulative 5-year incidences of sudden death, MI, and stroke were similar among the 3 strategies.

Discussion

The primary findings of this multicenter registry were as follows: (1) the long-term efficacy and safety outcomes after stent implantation for LMCA lesions were comparable between bifurcation and nonbifurcation lesions; (2) clinical outcomes were also comparable between the nonbifurcation stenting and the bifurcation 1-stent strategy, whereas the

bifurcation 2-stent strategy was associated with significantly higher risk for TLR and ST than the bifurcation 1-stent strategy; and (3) definite or probable very late ST did not occur regardless of the stenting strategies up to 5 years.

Previous studies have reported that the cumulative incidence of TLR after LMCA stenting was significantly higher in bifurcation lesions than in nonbifurcation lesions,^{4,11,12} whereas our study, having a longer follow-up and a larger number of patients, demonstrated that the cumulative 5-year incidence of TLR after LMCA stenting was comparable between the bifurcation and nonbifurcation lesions. The bifurcation 2-stent strategy for LMCA lesions, particularly that using G1-DES, is reported to be a significant predictor of TLR.^{4,6,13} The rate of the bifurcation 2-stent strategy for LMCA bifurcation lesions in our study was only 20% compared with 31% to 50% in the previous studies, suggesting that a lower rate of the bifurcation 2-stent strategy brings better clinical outcomes. Recently, it has been reported that clinical outcomes in non-LMCA bifurcation lesions are equivalent between the bifurcation 1-stent and 2-stent strategies,¹⁴ whereas the LMCA bifurcation is an independent risk factor of target vessel failure in bifurcation lesions treated with the bifurcation 2-stent strategy.¹⁵ Clinical outcomes of the bifurcation 2-stent strategy might be different between the LMCA and non-LMCA bifurcation locations. Furthermore, clinical outcomes were comparable between the nonbifurcation stenting and the bifurcation

1-stent strategy in our study. The bifurcation 1-stent strategy is a preferred approach with better clinical outcomes in patients with LMCA bifurcation lesions.^{6,16} Our findings confirmed favorable clinical outcomes after stenting for LMCA bifurcation lesions comparable to those after stenting for LMCA nonbifurcation lesions if we could finish the procedure with the bifurcation 1-stent strategy.

In contrast to the favorable outcomes after the bifurcation 1-stent strategy, the bifurcation 2-stent strategy was associated with twofold increased risk for TLR and 3.5-fold increased risk for ST. We should pay more attention to the prevention of ST after the bifurcation 2-stent strategy by developing the optimal bifurcation stenting techniques and more potent antiplatelet therapy. However, the bifurcation 2-stent strategy was not associated with increased risk for all-cause and cardiac death compared with the bifurcation 1-stent strategy, although the 3-year follow-up from the j-Cypher registry suggested significantly higher risk for cardiac death with the bifurcation 2-stent strategy.⁷ It has been widely recognized that the bifurcation 2-stent strategy was associated with worse outcomes than the bifurcation 1-stent strategy. It is very likely that many patients treated with the bifurcation 2-stent strategy in our study could not be treated with the bifurcation 1-stent strategy. Therefore, it might not be clinically relevant to compare the bifurcation 2-stent strategy with the bifurcation 1-stent strategy. The clinical outcomes should be compared between patients treated with the bifurcation 2-stent strategy and those treated with CABG.¹⁷

It was remarkable that our study had no definite or probable very late ST up to 5 years. Low rates of ST after stent implantation for LMCA lesions have been reported,^{18,19} and our study also provided a reassuring evidence for it. The high flow milieu and low shear rate of the LMCA might be protective against very late ST.^{20,21} We should revisit the prolonged or even life-long dual antiplatelet therapy often implemented in patients who underwent LMCA stenting in the real-world settings.

There are several important limitations in the present study. First, this registry was conducted as a retrospective observational study. Selection bias was potentially present, especially in the comparison between the stenting strategies for bifurcation lesions because they were not randomized and could reflect each physician's preference, which was applied to intravascular imaging guidance as well. Therefore, we included the periods of treatment in addition to the potential confounders in the multivariate models. Second, we did not have a control group of patients treated with CABG. Third, the sample size was still too small to evaluate low frequency events such as ST and MI despite being one of the largest registries of patients undergoing LMCA stenting. Fourth, qualitative and quantitative coronary angiographic analyses were not performed in a central angiographic core laboratory. Fifth, we could not address the optimal bifurcation 2-stent strategy due to the relatively small number of patients treated with the bifurcation 2-stent strategy.²² Finally, various types of stent were used throughout the study period. The use of G2-DES for LMCA lesions might improve the long-term clinical outcomes.²³ The Evaluation of Xience Everolimus-Eluting Stent vs Coronary Artery Bypass Surgery for Effectiveness of Left

Main Revascularization trial, the largest trial comparing the LMCA PCI using everolimus-eluting stent with CABG, is currently ongoing.²⁴

Disclosures

Dr. Kimura serves as an advisory board member for Abbott Vascular. The other authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.amjcard.2016.10.033>.

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