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ORIGINAL RESEARCH

Differential Prognosis of True Bifurcation Lesions According to Left Main Versus Non–Left Main Location and Treatment Strategy

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BACKGROUND: Although true bifurcation lesions are associated with a high risk of procedural complications, the differential prognostic implications of percutaneous coronary intervention for true bifurcations according to lesion location are unclear. This study aimed to identify whether clinical outcomes of true bifurcation lesions differed between left main coronary artery (LM) and non-LM bifurcations and to determine the optimal treatment strategy for subtypes of bifurcation lesions in the current-generation drug-eluting stent era.

METHODS: The ULTRA-BIFURCAT (Combined Insights From the Unified COBIS III, RAIN, and ULTRA Registries) was created by merging 3 bifurcation-dedicated registries from Korea and Italy. For this, 6548 patients treated with bifurcation lesions were stratified by lesion location and subtype. The primary end point was major adverse cardiac events (MACEs; composite of all-cause death, myocardial infarction, target lesion revascularization, and stent thrombosis) at 800 days.

RESULTS: In patients with an LM bifurcation, those with a true bifurcation had a significantly higher risk of a MACE than those with a nontrue bifurcation (20.2% versus 13.4%, adjusted hazard ratio [HR], 1.44 [95% CI, 1.11–1.86]; *P*=0.006). Conversely, there was no significant difference in the risk of a MACE according to true versus nontrue bifurcation in patients with non-LM bifurcation lesions (9.0% versus 8.8%; adjusted HR, 1.02 [95% CI, 0.82–1.27]; *P*=0.849). For LM true bifurcations, MACE rates were comparable between 1-stent and 2-stent strategies, whereas for LM nontrue bifurcations, the 2-stent strategy was associated with a significantly higher risk of MACEs than the 1-stent strategy. No significant differences in the risk of MACEs were observed in non-LM bifurcation lesions according to lesion subtype or treatment strategy.

CONCLUSIONS: Clinical outcomes were worse for LM true bifurcation lesions than non-LM true bifurcation lesions. A provisional 1-stent strategy should be the preferred approach for treating LM nontrue bifurcation lesions.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03068494, NCT03544294, and NCT05205148.

Key Words: Medina classification ■ outcomes ■ percutaneous coronary intervention ■ stent technique ■ true bifurcation

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CLINICAL PERSPECTIVE

What Is New?

- Although the prognostic impact of true bifurcations appears to be attenuated in the second-generation drug-eluting stent era, patients with left main coronary artery (LM) true bifurcation lesions had a significantly higher risk of major adverse cardiac events than those with LM nontrue bifurcation lesions.
- The risk of a major adverse cardiac event was comparable between the 1-stent and 2-stent strategies in LM true bifurcation lesions, but the risk of a major adverse cardiac event was significantly higher when a 2-stent strategy versus a 1-stent strategy was used to treat patients with an LM nontrue bifurcation.

What Are the Clinical Implications?

- In line with current guidelines, the provisional 1-stent strategy should initially be considered, especially for LM nonbifurcation lesions.

Nonstandard Abbreviations and Acronyms

COBIS	Coronary Bifurcation Stenting
DES	drug-eluting stent
DK-CRUSH V	Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions
EBC MAIN	European Bifurcation Club Left Main Coronary Stent
EXCEL	Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
LM	left main coronary artery
MACE	major adverse cardiac event
MV	main vessel
POT	proximal optimization technique
RAIN	Very Thin Stents for Patients With Left Main or Bifurcation in Real Life
SB	side branch
ST	stent thrombosis
ULTRA	Ultrathin DES in Complex PCI Scenarios
ULTRA-BIFURCAT	Combined Insights From the Unified COBIS III, RAIN, and ULTRA Registries

Bifurcation lesions of the coronary arteries have a complex lesion profile that complicates percutaneous coronary intervention (PCI) and also have higher recurrence rates than nonbifurcation lesions.[1,2] Bifurcation lesions are broadly classified as true (Medina classification 1.1.1.; 1.0.1; and 0.1.1) or nontrue (Medina classification 1.0.0; 0.1.0; 1.1.0. and 0.0.1) depending on the presence of stenosis in both the main vessel (MV) and side branch (SB) ("true" bifurcations) or only in the MV or SB.[3] The majority of previous randomized trials comparing the provisional SB approach with an elective 2-stent strategy focused on true bifurcation lesions because lesions without SB involvement could be considered relatively simple.[4–9] This means that the optimal stent strategy in nontrue bifurcation lesions has yet to be established.

There are substantial differences in several anatomical characteristics and territory at jeopardy of SBs between left main coronary artery (LM) and non-LM bifurcation lesions. In this regard, we previously found that the stent strategies for LM and non-LM bifurcation lesions had differential prognostic effects based on analyses of the COBIS (Coronary Bifurcation Stenting) III registry.[10] Although a previous study of the COBIS II registry reported that true bifurcation lesions were associated with higher risks of cardiovascular events than nontrue bifurcation lesions, that study was performed in the era of first-generation drug-eluting stents (DESs) and does not reflect contemporary practice.[11] In particular, limited data are available regarding the differential prognostic impact of true bifurcation, which significantly affects the selection of treatment strategy, according to lesion location (LM versus non-LM bifurcations) on treatment outcomes.

Therefore, we sought to identify whether clinical outcomes of PCI for true bifurcation lesions differed between LM and non-LM bifurcations. Additionally, we sought to identify the optimal treatment strategy for each subtype of bifurcation lesion in the current era of DES.

METHODS

Anonymized patient-level data will be made available by the corresponding author in response to reasonable requests. Consent was not obtained for data sharing, but the presented data are anonymized, and the risk of identification is minimal.

Study Population

Patient-level pooled data of the ULTRA-BIFURCAT (Combined Insights From the Unified COBIS III, RAIN, and ULTRA Registries) registry included 6830 patients with bifurcation lesions who underwent PCI with second-generation DES and who were registered in the COBIS III (NCT03068494),[10] RAIN (Very Thin Stents for Patients With Left Main or Bifurcation in Real Life; NCT03544294),[12] and ULTRA (Ultrathin DES in Complex PCI Scenarios; NCT05205148) registries.[13] The COBIS III registry includes 2648 patients treated with second-generation DES from January 2010 to December 2014, while the RAIN registry includes 2889 patients treated with very-thin-strut DES (strut thickness <100 μm) from June 2015 to December 2017, and the ULTRA registry includes 1293 patients treated with ultra-thin-strut DES (strut thickness ≤70 μm) for bifurcation lesions from September 2016 to August 2021. A total of 6548 patients were included in the current analysis after exclusion of those patients with an unknown Medina classification (n=60) or unknown bifurcation location (n=222). The study population was stratified according to lesion location (LM versus non-LM bifurcation) and anatomical subtype (true or nontrue bifurcation) (Figure 1). The study protocols for these registries received approval from the institutional review board of each study center. Given the retrospective nature of the study, the requirement for written informed consent was waived. This study adhered to the principles outlined in the Declaration of Helsinki.

Intervention and Adjunctive Pharmacotherapy

The PCI procedures adhered to the relevant practice guidelines.[14,15] Access site selection, stenting technique (1-stent with provisional approach versus 2-stent technique), type of DES used, and use of ancillary techniques like intravascular imaging or physiology were at the discretion of the operator. Loading doses of aspirin (300 mg) and $P2Y_{12}$ inhibitors (clopidogrel 300–600 mg, prasugrel 60 mg, or ticagrelor 180 mg) were administered before PCI, unless the patient had prior exposure to these antiplatelet medications. Following PCI, all patients received a standard dose of antiplatelet drugs (75–100 mg aspirin once daily +75 mg clopidogrel once daily, 10 mg prasugrel once daily, or 90 mg ticagrelor twice daily). The duration of dual antiplatelet therapy was also left to the discretion of the individual operators.

Definitions, End Points, and Data Collection

Bifurcation lesions were classified according to the Medina classification by angiographic evaluation, in which the proximal MV, distal MV, and SB components of the bifurcation were allocated a score of 1 or 0 depending on the presence or absence of >50% diameter stenosis.[3] True coronary bifurcations were defined as Medina 1.1.1, 1.0.1, or 0.1.1 lesions. The primary end point was major adverse cardiac events (MACEs), a composite of cardiac all-cause death,

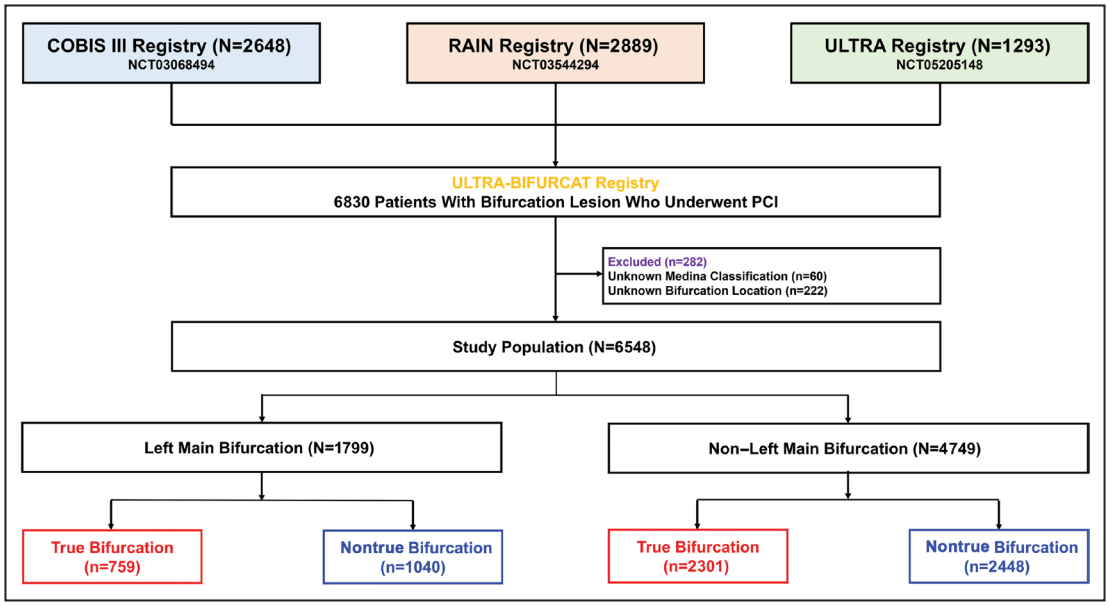

Figure 1. Study flow.
ULTRA-BIFURCAT indicates Combined Insights From the Unified COBIS III, RAIN, and ULTRA Registries; COBIS, Coronary Bifurcation Stenting; PCI, percutaneous coronary intervention; and RAIN, Very Thin Stents for Patients With Left Main or Bifurcation in Real Life.

myocardial infarction (MI), target-lesion revascularization, and definite or probable stent thrombosis (ST), at 800 days. Secondary end points were a composite of all-cause death or MI, target-lesion revascularization, and ST. All clinical events were defined on the basis of the recommendations from the Academic Research Consortium.[16] Clinical, angiographic, and procedural data were collected using a web-based reporting system for each registry. Follow-up data were obtained from electronic medical records of each participating center, clinical visits, telephone contact, or formal query to primary care physicians, if necessary.

Statistical Analysis

Continuous variables are reported as mean±SD and were compared using Welch's *t* test. Categorical data are reported as number and relative frequency and were compared using the χ^2 test. Cumulative incidence of clinical events was estimated by the Kaplan–Meier method and compared using the log-rank test. Patients were censored at 800 days or when any event occurred. To compare clinical outcomes, Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% CI between true and nontrue bifurcation in populations with LM or non-LM bifurcation lesions, using interaction terms. Covariates that were clinically relevant were included in the multivariable analysis: age, sex, diabetes, previous history of MI, acute coronary syndrome, transradial intervention, use of intravascular imaging, final kissing ballooning, and proximal optimization technique (POT). Interaction assessment of lesion location (LM versus non-LM bifurcation) and presence of true bifurcation lesions was also performed. Additionally, we compared the risk of cardiovascular events according to treatment strategy (1-stent versus 2-stent) for each type and location of bifurcation lesion to identify optimal treatment strategies for each lesion subset. Furthermore, subgroup analysis according to use of intravascular imaging for each type and location of bifurcation lesion was performed. Proportional hazards assumptions of the HRs in the Cox proportional hazards models were graphically inspected in "log–log" plots and also tested by Schoenfeld residuals; these were satisfied in all models without violation.

A 2-sided *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using R Statistical Software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Among the study population, 1799 patients (27.5%) had an LM bifurcation lesion, and the remaining 4749 patients (72.5%) had a non-LM bifurcation lesion. The mean age of the study population was 66.0±11.3 years; 5024 patients (76.7%) were men, and 2857 patients (43.6%) presented with acute coronary syndrome. Baseline clinical, lesion, and procedural characteristics of true and nontrue bifurcation lesions according to lesion location are described in Tables 1 and 2.

In patients with LM bifurcation lesions, those with true bifurcation lesions (n=759 [42.2%]) were older and more likely to have hypertension, chronic kidney disease, a previous history of PCI, a previous history of MI, and lower left ventricular ejection fraction than those with nontrue bifurcation lesions (Table 1). In patients with non-LM bifurcation lesions, those with true bifurcation lesions (n=2301 [48.5%]) were more likely to have hypertension, diabetes, hyperlipidemia, and a previous history of MI and to present with ST-segment–elevation MI at index admission (Table 1). Irrespective of true bifurcation lesions, the most common bifurcation location in non-LM bifurcation lesions was the left anterior descending artery and diagonal branch bifurcation lesions (Table 2).

With regard to procedural characteristics, patients with true bifurcation lesions were more likely to receive up-front 2-stent strategy and final kissing ballooning, but less likely to receive POT or re-POT, than those with nontrue bifurcation lesions, regardless of bifurcation location (Figure 2). Among patients who were treated using an up-front 2-stent strategy, the most commonly used technique was crush in true bifurcation lesions and T-stenting or T and protrusion in LM nontrue bifurcation lesions (Table 2). Transradial intervention was less commonly used in patients with LM true bifurcation lesions than in those with LM nontrue bifurcation lesions (50.1% versus 56.5%; *P*=0.008).

Clinical Outcomes in True Versus Nontrue Bifurcation Lesions

The median follow-up duration of the pooled cohort was 800 days (interquartile range, 384–800 days). Among the total population, no significant difference in rates of MACE were observed between true versus nontrue bifurcation lesions (true versus nontrue bifurcation, 11.8% versus 10.2%; adjusted HR, 1.13 [95% CI, 0.96–1.34]; *P*=0.132). There was a significant interaction between lesion subtype (true or nontrue bifurcation) and lesion location (LM versus non-LM) for the risk of MACEs (interaction *P*=0.009). In the population with LM bifurcation, true bifurcation was associated with a significantly higher risk of MACEs at 800 days than nontrue bifurcation (true versus nontrue bifurcation, 20.2% versus 13.4%; adjusted HR, 1.44 [95% CI, 1.11–1.86]; *P*=0.006; Figure 3A). Death or MI (11.9% versus 9.4%; *P*=0.044) and target-lesion revascularization (8.0% versus 4.6%; *P*=0.005) were also significantly

Table 1. Baseline Clinical Characteristics

Variables	LM bifurcation (N=1799)			Non-LM bifurcation (N=4749)			Overall *P* value
	True bifurcation (N=759)	Nontrue bifurcation (N=1040)	*P* value	True bifurcation (N=2301)	Nontrue bifurcation (N=2448)	*P* value	
Demographics							
Age, y	69.4±10.5	66.5±11.2	<0.001	65.6±11.5	65.1±11.2	0.110	<0.001
Male sex	583 (76.8)	811 (78.0)	0.597	1744 (75.8)	1886 (77.0)	0.327	0.536
Cardiovascular risk factors							
Hypertension	543 (71.5)	682 (65.6)	0.009	1508 (65.5)	1488 (60.8)	0.001	<0.001
Diabetes	270 (35.6)	360 (34.6)	0.711	739 (32.1)	684 (27.9)	0.002	<0.001
Chronic kidney disease	124 (16.3)	129 (12.4)	0.021	267 (11.6)	294 (12.0)	0.698	0.006
Former smoker	173 (22.8)	220 (21.2)	0.439	687 (29.9)	699 (28.5)	0.340	<0.001
Hyperlipidemia	390 (51.4)	517 (49.7)	0.514	1174 (51.0)	1152 (47.1)	0.007	0.029
Previous PCI	230 (30.3)	253 (24.3)	0.006	490 (21.3)	500 (20.4)	0.483	<0.001
Previous MI	172 (22.7)	153 (14.7)	<0.001	421 (18.3)	382 (15.6)	0.015	<0.001
Initial presentation							
Clinical presentation			0.260			<0.001	<0.001
Chronic coronary syndrome	409 (53.9)	576 (55.3)		1251 (54.4)	1455 (59.4)		
Unstable angina or NSTEMI	166 (21.9)	194 (18.7)		521 (22.6)	544 (22.2)		
STEMI	184 (24.2)	270 (26.0)		529 (23.0)	449 (18.4)		
LVEF (%)*	55.0±11.4	57.6±10.4	<0.001	56.0±9.5	55.5±9.0	0.113	<0.001
Medications at discharge							
DAPT type			<0.001			0.047	<0.001
Aspirin+clopidogrel	576 (77.0)	867 (84.2)		1629 (71.3)	1708 (70.1)		
Aspirin+ticagrelor or prasugrel	172 (23.0)	163 (15.8)		656 (28.7)	729 (29.9)		

Data are presented as mean±SD or n (%). DAPT indicates dual antiplatelet therapy; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Echocardiography data were available in 1658/1799 patients (92.2%) for left main bifurcation and 4782/4971 (96.2%) for non–left main bifurcation.

higher in the true bifurcation group than in the nontrue bifurcation group (Table 3). In contrast to LM bifurcation, there were no significant differences in the rates of MACEs (9.0% versus 8.8%; adjusted HR, 1.02 [95% CI, 0.82–1.27]; *P*=0.849), death or MI (5.6% versus 5.7%; *P*=0.992), or target-lesion revascularization (2.7% versus 2.4%; *P*=0.577) according to lesion subtype (true versus nontrue bifurcation) for patients with non-LM bifurcation lesions (Table 3, Figure 3B).

Clinical Outcomes According to Treatment Strategy in Each Lesion Subset

In exploratory subgroup analysis, the incidence of MACEs was comparable between 1-stent and 2-stent strategies (2-stent versus 1-stent, 20.7% versus 19.6%; adjusted HR, 1.14 [95% CI, 0.79–1.63]; *P*=0.484) for LM true bifurcation lesions (Figure 4A), after adjusting for age, sex, diabetes, previous history of MI, acute coronary syndrome, transradial intervention, and use of intravascular imaging. Conversely, the 2-stent strategy was associated with a significantly higher risk of MACEs than the 1-stent strategy (19.8% versus 12.7%; adjusted HR, 1.74 [95% CI, 1.04–2.91]; *P*=0.036) in LM nontrue bifurcation lesions (Figure 4B). In patients with non-LM bifurcation lesions, the risk of MACEs did not differ significantly according to stent strategy regardless of lesion subtype (true bifurcation or not; Figure 5).

Subgroup Analysis According to the Use of Intravascular Imaging

Figure 6 presents subgroup analysis according to the use of intravascular imaging. The use of intravascular imaging was associated with lower risk of MACEs in patients treated with LM bifurcation lesions (adjusted HR, 0.73 [95% CI, 0.56–0.94]; *P*=0.014) but not in those treated with non-LM bifurcation lesions (adjusted HR, 1.26 [95% CI, 0.97–1.62]; *P*=0.073). The clinical benefits of intravascular imaging usage were consistently

Table 2. Lesion and Procedural Characteristics

Variables	LM bifurcation (N=1799)			Non-LM bifurcation (N=4749)			Overall *P* value
	True bifurcation (N=759)	Nontrue bifurcation (N=1040)	*P* value	True bifurcation (N=2301)	Nontrue bifurcation (N=2448)	*P* value	
Lesion characteristics							
Bifurcation location			NA			<0.001	<0.001
LM (LAD/LCX)	759 (100)	1040 (100)					
LAD/diagonal				1637 (71.1)	1556 (63.6)		
LCX/OM				541 (23.5)	671 (27.4)		
RCA (PL/PDA)				123 (5.3)	221 (9.0)		
Medina classification			<0.001			<0.001	<0.001
1.1.1	527 (69.4)	0 (0)		1612 (70.1)	0 (0)		
1.0.1	120 (15.8)	0 (0)		388 (16.9)	0 (0)		
0.1.1	112 (14.8)	0 (0)		301 (13.1)	0 (0)		
1.0.0	0 (0)	114 (11.0)		0 (0)	443 (18.1)		
1.1.0	0 (0)	514 (49.4)		0 (0)	1228 (50.2)		
0.1.0	0 (0)	344 (33.1)		0 (0)	581 (23.7)		
0.0.1	0 (0)	68 (6.5)		0 (0)	196 (8.0)		
Procedural characteristics							
Treatment strategy			<0.001			<0.001	<0.001
Provisional 1-stent strategy	363 (47.8)	947 (91.1)		1763 (76.6)	2350 (96.0)		
Conversion to 2-stent strategy	12/363 (3.3)	1/947 (0.1)		47/1763 (2.7)	6/2350 (0.3)		
Up-front 2-stent strategy	396 (52.2)	93 (8.9)		538 (23.4)	98 (4.0)		
Crush	159/408 (39.0)	31/94 (33.0)		231/585 (39.5)	40/104 (38.4)		
T-stenting or TAP	126/408 (30.9)	36/94 (38.3)		222/585 (37.9)	34/104 (32.7)		
Culottes	38/408 (9.3)	9/94 (9.6)		45/585 (7.7)	14 (13.5)		
Others	85/408 (20.8)	18/94 (19.1)		87/585 (14.9)	16 (15.4)		
Stent type			<0.001			<0.001	<0.001
Everolimus-eluting stents	348 (45.8)	533 (51.2)		1052 (45.7)	958 (39.1)		
Zotarolimus-eluting stents	206 (27.1)	265 (25.5)		566 (24.6)	471 (19.2)		
Sirolimus-eluting stents	112 (14.8)	96 (9.2)		464 (20.2)	734 (30.0)		
Biolimus-eluting stents	50 (6.6)	122 (11.7)		148 (6.4)	198 (8.1)		
Mixed or other stents	43 (5.7)	24 (2.3)		71 (3.1)	87 (3.6)		
Transradial intervention	380 (50.1)	588 (56.5)	0.008	1549 (67.3)	1685 (68.8)	0.277	<0.001
Intravascular imaging guidance	368 (48.5)	581 (55.9)	0.002	499 (21.7)	588 (24.0)	0.060	<0.001
Use of rotablation	32 (4.2)	24 (2.3)	0.030	57 (2.5)	73 (3.0)	0.329	0.056
Final kissing ballooning	621 (81.8)	751 (72.2)	<0.001	1588 (69.0)	1427 (58.3)	<0.001	<0.001
POT	162 (21.3)	278 (26.7)	0.010	644 (28.0)	707 (28.9)	0.516	0.001
Re-POT	62 (8.2)	28 (2.7)	<0.001	199 (8.6)	237 (9.7)	0.237	<0.001

Data are presented as means±SD or n (%). LAD indicates left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; NA, not applicable; OM, obtuse marginal; PDA, posterior descending artery; PL, posterolateral artery; POT, proximal optimization technique; RCA, right coronary artery; and TAP, T and protrusion.

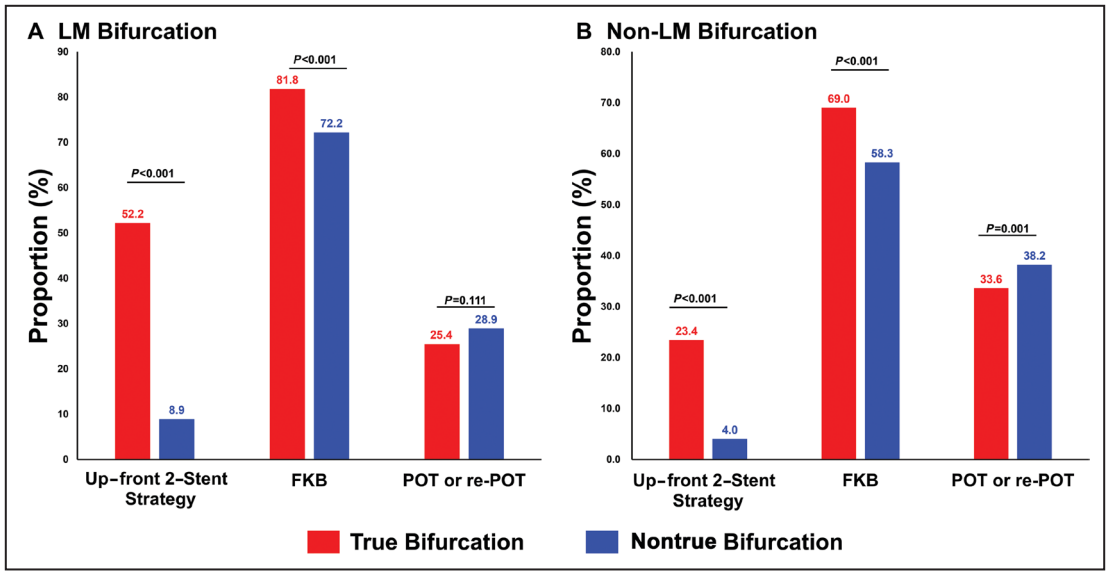

Figure 2. Treatment strategy for bifurcation lesions according to location and type.
Bar graphs show the proportion of up-front 2-stent strategy, FKB, and POT or re-POT in LM (**A**) and non-LM (**B**) lesions according to type of bifurcation (true vs nontrue). FKB indicates final kissing ballooning; LM, left main coronary artery; and POT, proximal optimization technique.

observed when treating LM bifurcation lesions, regardless of true or nontrue bifurcation lesions (interaction *P*=0.415). In patients with non-LM bifurcation lesions, there was no significant difference in the risk of MACEs according to the use of intravascular imaging in both lesion subtypes (true bifurcation or not; interaction *P*=0.792).

DISCUSSION

In the current study, we performed a patient-level pooled analysis of 3 large, dedicated bifurcation registries to compare the prognostic impacts of true bifurcation according to lesion location and to determine optimal treatment strategies. The principal findings of

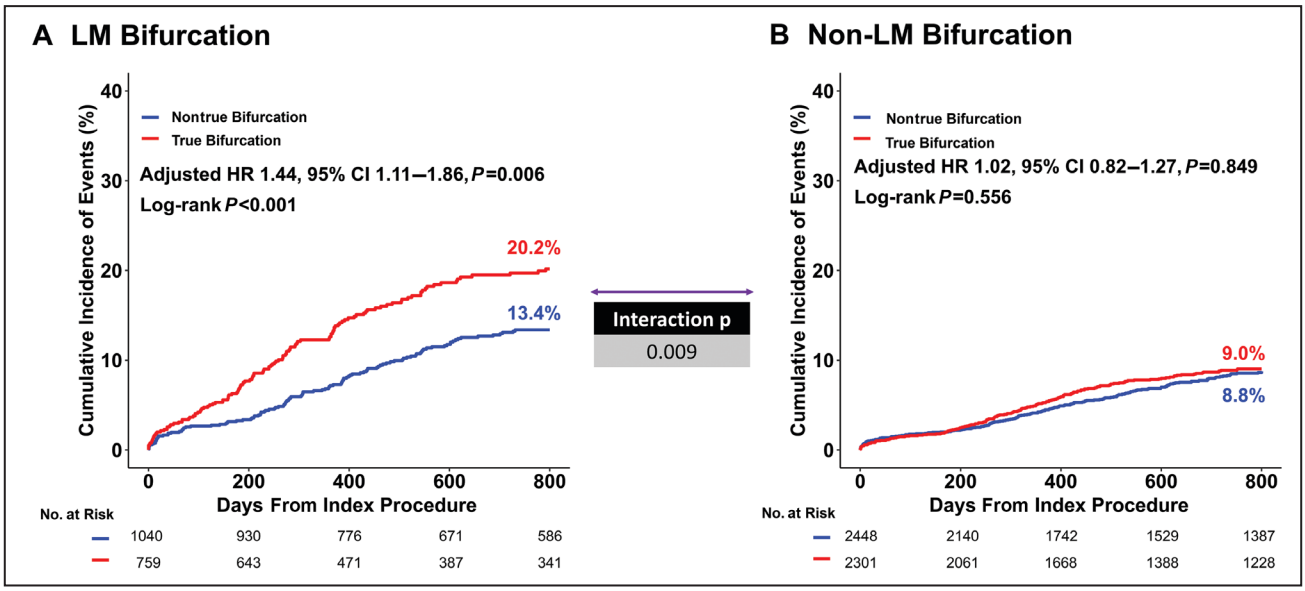

Figure 3. Comparison of MACEs according to bifurcation lesion location and type.
Kaplan–Meier curves comparing the risk of MACEs between true and nontrue bifurcation in LM (**A**) and non-LM (**B**) bifurcation lesions. Multivariable models included age, sex, diabetes, previous history of myocardial infarction, acute coronary syndrome, transradial intervention, use of intravascular imaging, final kissing ballooning, and proximal optimization technique. HR indicates hazard ratio; LM, left main coronary artery; and MACE, major adverse cardiac event.

Table 3. Cumulative Incidence of Adverse Events at 800 Days

Variables	LM bifurcation (N=1799)			Non-LM bifurcation (N=4749)			Overall *P* value
	True bifurcation (N=759)	Nontrue bifurcation (N=1040)	*P* value	True bifurcation (N=2301)	Nontrue bifurcation (N=2448)	*P* value	
MACE*	127 (20.2)	118 (13.4)	<0.001	171 (9.0)	172 (8.8)	0.556	<0.001
Death or MI	75 (11.9)	82 (9.4)	0.044	106 (5.6)	112 (5.7)	0.992	<0.001
Target-lesion revascularization	45 (8.0)	38 (4.6)	0.005	48 (2.7)	45 (2.4)	0.577	<0.001
Stent thrombosis	14 (2.1)	13 (1.4)	0.243	18 (0.9)	18 (0.9)	0.889	0.022

Values are n (%). Cumulative incidence of events was presented as Kaplan–Meier estimates. LM indicates left main coronary artery; MACE, major adverse cardiac event; and MI, myocardial infarction.

*MACE was defined as a composite of all-cause death, MI, target-lesion revascularization, and stent thrombosis.

this study were as follows. First, compared with patients with nontrue bifurcation lesions, those with true bifurcation lesions were more likely to undergo an upfront 2-stent strategy and final kissing ballooning but less likely to undergo a POT, regardless of lesion location. Second, in overall, no significant differences in MACEs were found between true and nontrue bifurcation lesions. However, there was a significant interaction between lesion subtype and location for the risk of MACEs. In patients with LM bifurcation lesions, true bifurcation was associated with a significantly higher risk of MACEs; this was not the case for patients with non-LM bifurcation lesions. Third, the risk of MACEs was comparable between the 1-stent and 2-stent strategies in LM true bifurcations. In contrast, the risk of MACEs was significantly higher when the 2-stent strategy was used in patients with LM nontrue bifurcations than when the 1-stent strategy was used.

Despite the development of advanced techniques and devices in interventional cardiology, PCI for bifurcation lesions remains a challenging procedure.[17] This is due to the necessity of considering numerous factors to achieve optimal stent implantation for bifurcation lesions.[18,19] These factors include bifurcation angle, lesion morphology, severity, location, SB territory, and the potential for jailing the SB after MV stenting.[20] Numerous attempts have been made to determine predictors of SB jailing during bifurcation PCI.[21–23] The independent predictor of SB jailing common to all these studies is significant SB diameter stenosis. Therefore, a true bifurcation lesion, which is defined as the presence of >50% stenosis of both the MV and SB, is associated

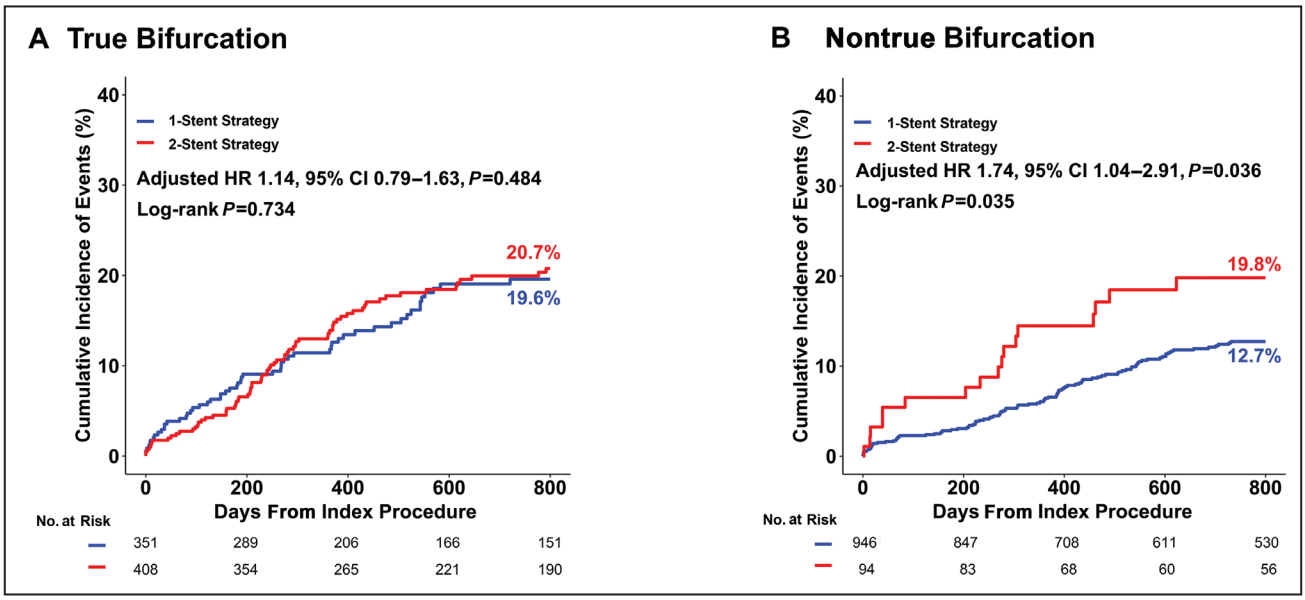

Figure 4. Comparison of MACEs in LM bifurcation lesions according to treatment strategy and true bifurcation.
Kaplan–Meier curves comparing the risk of MACEs between 1-stent and 2-stent strategies in LM true (**A**) and nontrue (**B**) bifurcation lesions. Multivariable models included age, sex, diabetes, previous history of MI, acute coronary syndrome, transradial intervention, and use of intravascular imaging. HR indicates hazard ratio; LM, left main coronary artery; MACE, major adverse cardiac event; and ULTRA-BIFURCAT, Combined Insights From the Unified COBIS III, RAIN, and ULTRA Registries.

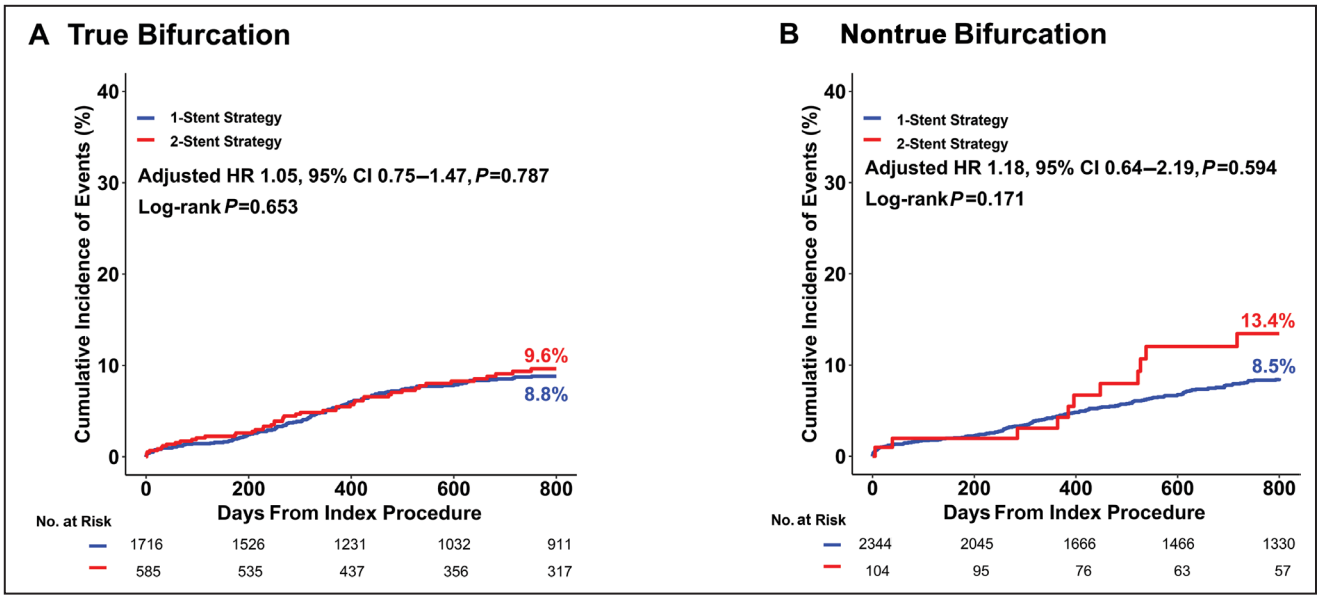

Figure 5. Comparison of MACEs in non-LM bifurcation lesions according to treatment strategy and true bifurcation.
Kaplan–Meier curves comparing the risk of MACEs between 1-stent and 2-stent strategies in non-LM true (**A**) and nontrue (**B**) bifurcation lesions. Multivariable models included age, sex, diabetes, previous history of myocardial infarction, acute coronary syndrome, transradial intervention, and use of intravascular imaging. HR indicates hazard ratio; LM, left main coronary artery; and MACE, major adverse cardiac event.

with a greater chance of SB jailing after MV stenting than a nontrue bifurcation lesion. In fact, in the current study, patients with true bifurcation lesions were more likely to receive an up-front 2-stent strategy and final kissing ballooning, which are used to treat or prevent a jailed SB. Park et al previously demonstrated that patients with true bifurcation lesions had a significantly higher risk of adverse cardiovascular events, including ST, than those with nontrue bifurcation lesions on the basis of analysis of a dedicated bifurcation registry (COBIS II).[11] However, given that >80% of patients in the previous study received PCI using first-generation DES and that second-generation DESs are associated with dramatically reduced cardiovascular event rates compared with first-generation DESs, new studies are needed to determine the prognostic impacts of true bifurcation lesions in the second-generation DES era. In contrast with a previous study, we found that the prognostic effects of true bifurcation were not significant in the overall population of a patient-level merged data set of 3 dedicated bifurcation registries. However, LM true bifurcation lesions were associated with a higher

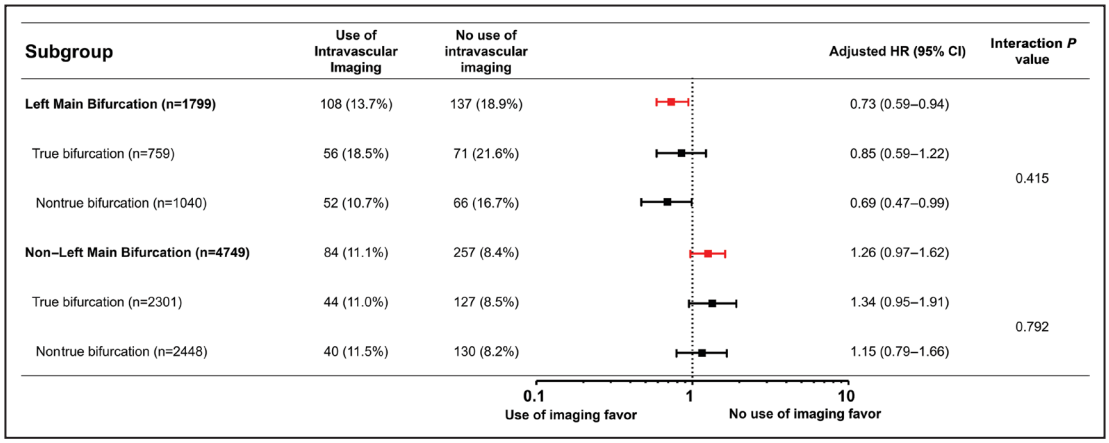

Figure 6. Comparison of MACEs according to use of intravascular imaging.
Forest plot comparing the risk of MACEs between use or no use of intravascular imaging according to bifurcation lesion location and type. Multivariable models included age, sex, diabetes, previous history of myocardial infarction, acute coronary syndrome, transradial intervention, final kissing ballooning, and proximal optimization technique. HR indicates hazard ratio; and MACE, major adverse cardiac event.

risk of cardiovascular events than LM nontrue bifurcation lesions. This result is consistent with the findings of Santucci et al.[24] In non-LM bifurcations, however, there was no significant difference in the risk of MACE between true and non-true bifurcations. This significant interaction between bifurcation type and location for the risk of MACE might be due to the differences in jeopardy of the SB territory between LM and non-LM bifurcation lesions.[25] Future large-scale long-term follow-up studies are needed to confirm whether the differential prognostic impacts of true bifurcation based on lesion location also apply to long-term outcomes.

The LM is the largest bifurcation of the coronary tree and has a number of unique characteristics that may require a different technical approach compared with other coronary bifurcations.[26] In this regard, the anatomical thresholds recommended by current guidelines that must be met to treat LM disease are lower than those for non-LM disease.[14,15] A previous study based on COBIS III registry data reported that patients with an LM bifurcation treated with PCI had a significantly higher risk of adverse cardiac events than those with a non-LM bifurcation.[10] Therefore, determining the optimal treatment strategy for LM bifurcation lesions is essential. The EBC MAIN (European Bifurcation Club Left Main Coronary Stent) study reported that fewer MACEs occurred with a stepwise layered provisional approach than with planned 2-stenting, although this difference was not statistically significant in patients with LM true bifurcation lesions.[6] By contrast, the DK-CRUSH V (Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions) trial demonstrated that provisional stenting for LM true bifurcation lesions was associated with significantly increased rates of target lesion failure and ST over 3 years of follow-up compared with DK crush stenting.[27] In agreement with the results from the EBC MAIN trial, we found no significant differences in the risk of MACEs between provisional 1-stenting and elective 2-stenting strategies for LM true bifurcation lesions, suggesting that the stepwise provisional strategy should remain the default for distal LM true bifurcation intervention. More importantly, it is not known which procedural strategy is the best option for LM nontrue bifurcation lesions because most randomized trials that have compared the outcomes of stenting strategies have exclusively enrolled true bifurcation lesions. In the current study, the risk of MACEs was significantly higher in patients who received an up-front 2-stenting strategy than in those who received a provisional 1-stenting strategy when treating LM nontrue bifurcation lesions. These results indicate that the choice of an elective 2-stent strategy should be made with caution, especially in LM nontrue bifurcations.

In the current large-sized real-world registry, we found that 16.2% of MACEs (20.2% in true bifurcations and 13.4% in nontrue bifurcations) at 800 days occurred in LM bifurcation PCI. This is similar to the event rates in the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (MACE 15.4% for PCI versus 14.7% for coronary artery bypass grafting). This finding is a strength of the study that in a real-world registry population LM complication rates are similar to potentially better than seen in prior randomized trials, supporting those prior conclusions that PCI in LM disease is noninferior to coronary artery bypass grafting regardless of true versus nontrue bifurcation or stent techniques.

Limitations

Several limitations of our study warrant acknowledgment. First, unmeasured confounding factors could have affected our study findings due to the observational nature of this registry. Notably, decisions regarding stenting strategy, application of intravascular imaging, vascular access, stent type, and concurrent medications were all at the discretion of the operators. In particular, this study did not have information on the operator's intentions regarding whether elective or bailout 2-stenting through a provisional approach was performed in patients who underwent PCI with a 2-stent strategy. Second, Medina classification relied on electronic case report data and was not based on quantitative coronary angiography analysis in a core laboratory with the exception of Medina classifications in the COBIS III registry. In addition, information on the SB size and angles were not available due to the absence of quantitative coronary angiography analysis in the RAIN and ULTRA registries. Third, despite leveraging the most extensive bifurcation-dedicated pooled registry assembled to date for our analysis, our sample sizes were insufficient to comprehensively examine differences in ST risk. Furthermore, the relatively short duration of follow-up might have hindered our ability to detect notable differences in hard end points. Fourth, it is possible that the underused 2-stent strategy in non-LM bifurcation lesions may have contributed to the lack of difference in outcomes. Fifth, the use rate of POT was low; therefore, it may not have reflected contemporary practice.

CONCLUSIONS

In this era of second-generation DESs, the prognostic impact of true bifurcations is attenuated. However, patients with LM true bifurcation lesions had a significantly higher risk of MACEs than those with LM nontrue bifurcation lesions. The provisional 1-stent strategy showed comparable clinical outcomes to the 2-stent strategy for the treatment of LM true bifurcation lesions. Furthermore, the 1-stent strategy was

associated with a lower risk of MACEs than the 2-stent strategy when treating LM nontrue bifurcation lesions. Therefore, in line with current guidelines, the provisional 1-stent strategy should initially be considered, especially for LM nonbifurcation lesions. However, this result should be interpreted cautiously because of the observational nature of the study design.

ARTICLE INFORMATION

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