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CORONARY

Impact of the Complexity of Bifurcation Lesions Treated With Drug-Eluting Stents

The DEFINITION Study (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts)

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ABSTRACT

OBJECTIVES The present study established criteria to differentiate simple from complex bifurcation lesions and compared 1-year outcomes stratified by lesion complexity after provisional stenting (PS) and 2-stent techniques using drug-eluting stents.

BACKGROUND Currently, no criterion can distinguish between simple and complex coronary bifurcation lesions. Comparisons of PS and 2-stent strategies stratified by lesion complexity have also not been reported previously.

METHODS Criteria of bifurcation complexity in 1,500 patients were externally tested in another 3,660 true bifurcation lesions after placement of drug-eluting stents. The primary endpoint was the occurrence of a major adverse cardiac event (MACE) at 12 months. The secondary endpoint was the rate of stent thrombosis (ST).

RESULTS Complex ($n = 1,108$) bifurcation lesions were associated with a higher 1-year rate of MACE (16.8%) compared with simple ($n = 2,552$) bifurcation lesions (8.9%) ($p < 0.001$). The in-hospital ST and 1-year target lesion revascularization rates after 2-stent techniques in the simple group (1.0% and 5.6%, respectively) were significantly different from those after PS (0.2% [$p = 0.007$] and 3.2% [$p = 0.009$], respectively); however, 1-year MACE rates were not significantly different between the 2 groups. For complex bifurcation lesions, 2-stent techniques had lower rates of 1-year cardiac death (2.8%) and in-hospital MACE (5.0%) compared with PS (5.3%, $p = 0.047$; 8.4%, $p = 0.031$).

CONCLUSIONS Complex bifurcation lesions had higher rates of 1-year MACE and ST. The 2-stent and PS techniques were overall equivalent in 1-year MACE. However, 2-stent techniques for complex lesions elicited a lower rate of cardiac death and in-hospital MACE but higher rates of in-hospital ST and revascularization at 1 year for simple lesions.
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Percutaneous coronary intervention of bifurcation lesions is technically challenging and is often associated with higher rates of in-stent restenosis. The ostial side branch (SB) is the most common site of in-stent restenosis (1,2) after placement of a drug-eluting stent. Patients with bifurcation lesions do not benefit from systematic 2-stent strategies, but provisional stenting (PS) using a jailed wire in the SB has been widely accepted as the gold standard in the majority of bifurcation lesions (1–6). This is based on several clinical trials (1–6); however, these trials have an important limitation of not being stratified according to the Medina classification (7). Inclusion of lesion complexity as a parameter in previous studies might have otherwise led to different stenting strategies, and consequently, the final clinical results might have been different (8–11).

Most importantly, current classifications do not provide more information about the complexity of bifurcation lesions (10). Therefore, it is too early to conclude that PS can be considered a final solution for coronary bifurcation lesions (10–12). Accordingly, the present DEFINITION (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts) study was designed to establish a practical, easy-to-use classification to differentiate simple from complex bifurcation lesions and analyze the effect of bifurcation complexity on clinical results after PS and 2-stent techniques.

METHODS

STUDY DESIGN AND PATIENT POPULATION. Between January 2004 and July 2012, 5,160 patients with at least 1 Medina 1,1,1 and 0,1,1 coronary bifurcation lesion (7) were prospectively registered. For 1,500 patients from January 2004 to June 2006 (training group), confounding factors for composite major adverse cardiac events (MACE) were selected by logistic regression analysis. The rate of MACE stratified by each confounding factor and combinations of several confounding factors were calculated. Definitions of complex and simple bifurcation lesions were then established according to the predictive value of the confounding factors.

Finally, these definitions were externally tested in 3,660 patients (study group) between July 2006 and July 2012. Patients in the study group were divided into 2 pre-specific subgroups according to the criteria established from the training group: the simple and complex groups. The ethics committee of each participating center approved the study protocol, and each patient provided written consent.

INCLUSION/EXCLUSION CRITERIA. Only Medina 1,1,1 and 0,1,1 coronary bifurcation lesions with an SB diameter ≥2.5 mm by visual estimation were included in the training and study groups. The following exclusion criteria were included: 1) SB diameter <2.5 mm; 2) ST-segment elevation myocardial infarction (MI) <1 week; 3) cardiogenic shock; 4) a history of coronary artery bypass grafting; 5) use of bare-metal stent; 6) in-stent restenotic lesions; 7) lesions being treated by classic crush stenting or the kissing stenting technique; and 8) patients who were already included in any other clinical study.

STENTING PROCEDURES. The selection of stenting techniques and of the transradial versus transfemoral approach was left to the physician's discretion. Stents for all implanted lesions were limus-eluting stents, including the Cypher (Cordis, Johnson & Johnson, Miami Lakes, Florida); Firebird or Firebird-2 (Microport Co., Shanghai, China); EXCEL, BIOMATRIX FLEX (Biosensor/Jiwei Co., Shandong, China); Partner (Lepu Med, Beijing, China); Xience or Xience Prime (Abbott Vascular, Santa Clara, California); and Endeavor or Endeavor Resolute (Medtronic, Minneapolis, Minnesota). Use of intravascular ultrasound was left to the physician's discretion. Stenting techniques have been described previously (3,4,12). Briefly, final kissing balloon inflation was recommended after all 2-stent strategies. Kissing balloon inflation was only used after PS if there were any of the following indications in the SB: Thrombolysis In

ABBREVIATIONS AND ACRONYMS

DK = double kissing
DS = diameter stenosis
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PS = provisional stenting
SB = side branch
ST = stent thrombosis
TLR = target lesion revascularization
TVR = target vessel revascularization

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TABLE 1 Baseline Clinical Characteristics in Training and Study Groups

		Study Group (n = 3,660)		
	Training Group (n = 1,550)	Simple (n = 2,552)	Complex (n = 1,108)	p Value*
Age, yrs	67 ± 9	65 ± 10	68 ± 9	<0.001
Male	1,162 (77.5)	1,911 (74.9)	873 (78.0)	0.011
Height, cm	165 ± 8	167 ± 7	167 ± 7	0.646
Weight, kg	67 ± 10	68 ± 11	68 ± 11	0.696
Hypertension	1,050 (70.0)	1,851 (72.5)	819 (74.0)	0.373
Diabetes	525 (35.0)	876 (34.3)	498 (45.0)	<0.001
Unstable angina	915 (61.0)	1,629 (63.8)	720 (65.0)	0.203
Acute myocardial infarction	135 (9.0)	237 (9.3)	135 (12.2)	0.009
Congestive heart failure	225 (15.0)	411 (16.1)	246 (22.2)	<0.001
Left ventricular ejection fraction <40%	135 (9.0)	144 (5.6)	199 (17.9)	<0.001
Current smoker	147 (9.8)	318 (12.5)	75 (6.8)	<0.001
Stroke	60 (4.0)	105 (4.1)	33 (3.0)	0.108
Gastrointestinal bleeding	3 (0.2)	6 (0.2)	3 (0.3)	1.000
Hyperlipidemia	720 (48.0)	1,242 (48.6)	513 (46.3)	0.207
White blood cells, × 10^9/l	7.25 ± 0.22	7.52 ± 0.39	7.21 ± 0.17	0.677
Red blood cells, × 10^9/l	4.25 ± 0.51	4.23 ± 0.61	4.23 ± 0.52	0.917
Platelet, × 10^9/l	188.45 ± 65.31	185.7 ± 66.54	202.82 ± 70.14	0.002
Hemoglobin, × 10^9/l	131.19 ± 16.58	131.49 ± 18.39	129.17 ± 17.66	0.114
Fasting glucose, mmol/l	6.27 ± 2.42	6.28 ± 2.46	6.29 ± 2.57	0.861
Cholesterol, mmol/l	4.03 ± 0.94	4.06 ± 0.97	4.05 ± 1.01	0.697
Low-density lipoprotein, mmol/l	2.51 ± 0.86	2.53 ± 0.81	2.56 ± 0.91	0.298
Creatinine, mmol/l	88.33 ± 42.9	85.41 ± 48.11	89.92 ± 49.8	0.015
eGFR <60 ml/min/1.73 m^2	5 (3.3)	84 (51.9)	45 (44.1)	0.256
High-sensitivity C-reactive protein, mg/dl	2.69 ± 0.68	2.67 ± 0.59	2.75 ± 0.68	0.024

Values are mean ± SD or n (%). *Indicates the comparison of simple and complex subgroups in the study group.
eGFR = estimated glomerular filtration rate.

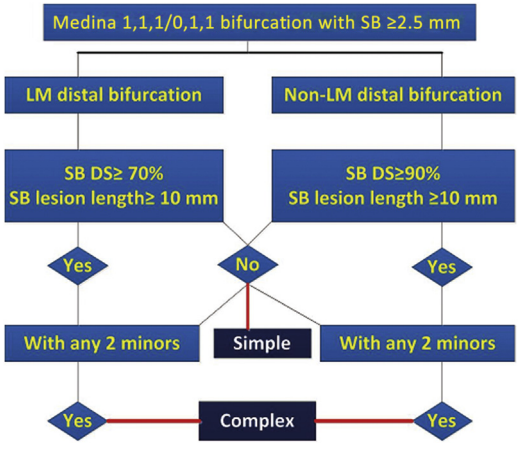

FIGURE 1 Description of Complex Bifurcation Lesion Definitions

For bifurcation lesions (Medina 1,1,1/0,1,1 with side branch diameter minimally 2.5 mm, major criteria (SB DS and SB lesion length) plus any 2 minor criteria are defined as complex bifurcation lesions. DS = diameter stenosis; LM = left main; SB = side branch.

Myocardial Infarction flow <3, type B dissection or greater, and residual diameter stenosis (DS) ≥70% by visual estimation. Stenting of the SB in the PS group was required if Thrombolysis In Myocardial Infarction flow was <3, the presence of type B dissection or greater, or residual DS was ≥70% after kissing balloon inflation. Finally, 2-stent techniques included double kissing (DK) crush, culotte, T and protrusion, and traditional T.

MEDICATIONS. All patients were pre-treated with aspirin and clopidogrel. A 300-mg loading dose of clopidogrel was administered before the index procedure if patients were not pre-treated. Intravenous unfractionated heparin was used to maintain an activated clotting time between 250 and 300 s throughout the entire procedure. Creatine kinase-myocardial band and troponin were dynamically measured until 72 h post-procedure. After discharge, aspirin therapy was continued indefinitely (100 mg/day for life), and clopidogrel (75 mg/day) was continued for at least 12 months.

FOLLOW-UP. Clinical follow-up was performed during visits or through telephone contact at 1, 6, 8, and 12 months. Adverse events were monitored throughout the entire study period. Follow-up coronary angiography was not recommended unless clinically indicated for earlier intervention.

STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint was the occurrence of MACE at 12 months, including cardiac death, MI, and target vessel revascularization (TVR). The secondary endpoint was the occurrence of stent thrombosis (ST). Academic Research Consortium definitions of MI, cardiac death, target lesion revascularization (TLR), TVR, angiographic and procedural success, and ST (13) were used. Lesion specificities were defined according to American Heart Association/American College of Cardiology criteria (14). Angiographic patterns of in-stent restenosis were defined by Mehran's classification (15) and classified as classes I through IV. Bifurcation angle and vessel angulation were defined according to previous studies (16). Calcification was identified as readily apparent radiopacity within the vascular wall at the site of the stenosis, and it was classified as none/mild, moderate (i.e., radiopacity noted only during the cardiac cycle before contrast injection), and severe (i.e., radiopacity noted without cardiac motion before contrast injection, generally compromising both sides of the arterial lumen [Figure 1A]). Multiple lesions (Figure 1B) included multiple-vessel disease (defined as ≥70% stenosis in at least 1 major

epicardial vessel and ≥50% stenosis in at least 1 other major vessel) or ≥2 lesions separated by at least a 5-mm normal segment in the target vessel. A thrombus-containing lesion was defined as a coronary strip, oval- or irregularly-shaped filling defect with retention of contrast medium or dye (Figure 1C). Estimated glomerular filtration rate was calculated according to the Modified Diet in Renal Disease formula (17).

STATISTICAL ANALYSIS. Multiple anatomic factors for MACE were analyzed in patients from the training group, and factors with a p value ≤0.001 with the highest sensitivity and specificity were considered major criteria. Otherwise, factors with a p value >0.001 were treated as minor criteria. The rates of MACE stratified by combinations of each major criterion with any 1 or more minor criteria were calculated. Sensitivity and specificity of this classification for MACE were calculated with the receiver-operating characteristic curve. The definitions of complex and simple bifurcation lesions were later established according to the predictive value of major plus minor criteria.

Comparability of baseline characteristics between the complex and simple groups or between PS and 2-stent subgroups (based on intention-to-treat) was assessed using a 2-sample *t* test for continuous variables or the Fisher exact test for categorical variables. Analyses of the adjudicated primary and secondary outcomes were conducted on data from all patients using Kaplan-Meier estimates and Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p values were calculated using models adjusted for the pre-specified baseline factors listed in Tables 1 and 2. Statistical significance was taken as a 2-sided p value <0.05. All analyses were performed using the statistical program SPSS version 16.0 (IBM, Chicago, Illinois).

TABLE 2 Lesions and Procedural Characteristics in Training and Study Groups

		Study Group (n = 3,660)		
	Training Group (n = 1,500)	Simple (n = 2,552)	Complex (n = 1,108)	p Value*
Lesion locations				<0.001
Distal left main	38 (2.5)	36 (1.4)	66 (6.0)	
LAD diagonal	1,035 (69.0)	1,944 (76.1)	675 (61.0)	
Left circumflex OM	285 (19.0)	432 (16.9)	327 (29.5)	
Distal right coronary artery	67 (4.5)	141 (5.5)	39 (3.5)	
Classifications				0.001
Medina 1,1,1	1,199 (80.0)	2,022 (79.2)	918 (83.0)	
Medina 0,1,1	301 (20.0)	531 (20.9)	189 (17.0)	
Main vessel				
Chronic total occlusion	113 (7.5)	186 (7.3)	117 (10.6)	0.001
Thrombus-containing	71 (4.6)	126 (4.9)	30 (2.7)	0.002
Reference vessel diameter <3.0 mm	173 (11.5)	297 (11.6)	294 (26.6)	<0.001
Reference vessel diameter <2.5 mm	345 (23.0)	555 (21.7)	396 (35.8)	<0.001
Side branch				
Chronic total occlusion	6 (4.0)	84 (3.3)	81 (7.3)	<0.001
Thrombus-containing	2 (1.3)	24 (0.9)	3 (0.3)	0.034
Lesion length ≥10 mm	525 (35.0)	1,002 (39.2)	786 (71.0)	<0.001
Severe tortuous	97 (6.5)	126 (4.9)	144 (13.0)	<0.001
Reference vessel diameter <3.0 mm	750 (50.0)	1,356 (53.1)	459 (41.5)	<0.001
Multivessel disease	1,095 (73.0)	1,668 (65.3)	1,068 (96.5)	<0.001
Transradial	1,215 (81.0)	2,248 (88.1)	774 (69.9)	<0.001
Pre-dilation				
Main vessel	915 (61.0)	1,452 (56.8)	711 (64.2)	<0.001
Side branch	450 (30.0)	720 (28.2)	453 (40.9)	<0.001
Kissing inflation	104 (6.9)	144 (5.6)	126 (11.4)	<0.001
Stents per patient	2.71 ± 1.35	2.45 ± 1.22	2.93 ± 1.37	<0.001
Stent diameter, mm	2.88 ± 0.41	2.93 ± 0.41	2.93 ± 0.49	0.676
Stent length, mm	75.0 ± 35.2	64.0 ± 34.8	78.0 ± 39.9	<0.001
Post-dilation in main vessel	1,494 (99.6)	2,544 (99.6)	1,104 (99.7)	1.000
Acute closure of side branch	113 (7.5)	213 (8.3)	69 (6.2)	0.031
Reopen	72 (4.8)	129 (60.6)	39 (56.5)	0.574
Complete revascularization	1,080 (72.0)	2,010 (78.7)	675 (61.0)	<0.001
IVUS assessment	451 (30.0)	681 (26.6)	468 (42.3)	<0.001
Angiographic success	14,333 (95.5)	2,434 (95.3)	1,052 (95.0)	0.875

Values are n (%) or mean ± SD. *Indicates the comparison of simple and complex subgroups in the study group.

LAD = left anterior descending artery; IVUS = intravascular ultrasound; OM = obtuse marginal.

TABLE 3 Independent Factors of Major Adverse Cardiac Events at 1 Year After Stenting by Regression Analysis of 1,500 Patients in the Training Group

	p Value	HR (95% CI)	Sensitivity, %	Specificity, %
Major 1: Distal LM bifurcation: SB-DS ≥70% and SB lesion length ≥10 mm	<0.001	55.2 (21.005–79.437)	80	72
Major 2: Non-LM bifurcation: SB-DS ≥90% and SB lesion length ≥10 mm	<0.001	66.3 (12.708–98.184)	80	74
Minor 1: Moderate to severe calcification	0.002	38.7 (24.516–72.695)	64	65
Minor 2: Multiple lesions	0.007	26.8 (4.322–57.004)	68	60
Minor 3: Bifurcation angle <45°	0.004	14.1 (9.245–18.018)	64	53
Minor 4: Main vessel RVD <2.5 mm	0.010	9.4 (7.556–14.814)	69	58
Minor 5: Thrombus-containing lesions	0.002	27.2 (4.662–78.301)	66	64
Minor 6: MV lesion length ≥25 mm	0.010	6.9 (3.879–12.398)	57	66
Major 1 + any 2 minor 1–6 = complex			87	83
Major 2 + any 2 minor 1–6 = complex			88	83

CI = confidence interval; DS = diameter stenosis; HR = hazard ratio; LM = left main; MV = multivessel; RVD = reference vessel diameter; SB = side branch.

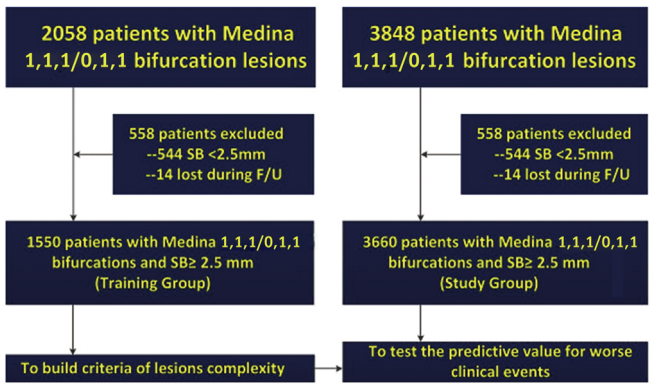

FIGURE 2 Study Flow Chart

The established criteria were tested externally in 3,660 patients with Medina 1,1,1/0,1,1 bifurcation lesions and a side branch (SB) ≥2.5 mm. F/U = follow-up.

RESULTS

BASELINE CHARACTERISTICS. A total of 1,500 patients were included in the training group. Baseline clinical (Table 1), lesions, and procedural (Table 2) characteristics in the training group were comparable to those in the study group. Of the 1,500 patients in the training group, 1-year MACE rate was 16.5%, with MI, cardiac death, and TVR in 3.8%, 1.3%, and 14.6% of patients, respectively.

TABLE 4 Clinical Outcomes in Complex and Simple Groups of 3,660 Patients

	Complex (n = 1,108)	Simple (n = 2,552)	Adjusted HR (95% CI)	p Value
In-hospital				
Myocardial infarction	75 (6.8)	96 (3.8)	0.62 (0.31-0.92)	<0.001
Cardiac death	9 (0.8)	9 (0.4)	2.32 (0.92-5.85)	0.076
Target lesion revascularization	0	9 (0.4)	–	0.066
Target vessel revascularization	0	12 (0.5)	–	0.052
Coronary artery bypass graft	0	3 (0.1)	0.40 (0.31-0.47)	0.560
Major adverse cardiac events	75 (6.8)	108 (4.1)	0.97 (0.58-1.06)	<0.001
Stent thrombosis	0	9 (0.4)		0.065
At 1 year				
Myocardial infarction	78 (7.0)	105 (4.1)	1.77 (1.31-2.39)	<0.001
Cardiac death	45 (4.1)	27 (1.1)	3.96 (2.45-6.42)	<0.001
Target lesion revascularization	66 (5.8)	96 (3.8)	0.35 (0.16-0.63)	0.003
Target vessel revascularization	87 (7.9)	126 (4.9)	0.46 (0.21-0.78)	0.001
Coronary artery bypass graft	9 (0.8)	3 (0.1)	1.88 (0.63-3.23)	0.004
Major adverse cardiac events	186 (16.8)	228 (8.9)	0.72 (0.51-0.93)	<0.001
Stent thrombosis	18 (1.6)	18 (0.7)	0.72 (0.56-0.84)	0.012
Definite and probable	12 (1.1)	18 (0.7)	1.54 (0.74-3.21)	0.246

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 3.

ESTABLISHMENT OF CRITERIA DIFFERENTIATING SIMPLEX FROM COMPLEX BIFURCATION LESIONS. Logistic regression of all lesion characteristics from patients in the training group listed in the Table 2 and entered into the model revealed 8 confounding factors that correlated with 1-year MACE ($p < 0.05$) (Table 3). Of these predictive factors, 2 parameters (for distal left main bifurcation: SB DS ≥70% and SB lesion length ≥10 mm; for nonleft main bifurcation: SB DS ≥90% and SB lesion length ≥10 mm) had the highest sensitivity (80%) and specificity (72% to 74%) for MACE (all p values <0.001), and these parameters were defined as major criteria; another 6 parameters with p values >0.001 were classified as minor criteria (Table 3). When each major criterion was combined with any 2 minor criteria, the sensitivity and specificity of this new stratification were ≥87% and 83%, respectively (Table 3).

According to our newly established criteria, 1,108 patients (30%) exhibited complex bifurcations, as shown in the study flowchart (Figure 2), and the remaining 2,552 patients (70%) were classified as having simple bifurcation lesions. Complex bifurcation lesions were more frequently observed in older male patients with more comorbidities (e.g., diabetes, acute MI, renal dysfunction, congestive heart failure), increased plasma platelet count, and severe inflammation.

CLINICAL OUTCOMES OF COMPLEX AND SIMPLE BIFURCATION LESIONS IN 3,660 PATIENTS IN THE STUDY GROUP. Generally, patients with complex bifurcation lesions had significantly higher in-hospital MACE rates compared with simple bifurcation lesions (6.8% vs. 4.2%, $p < 0.001$), which was mainly driven by increased MIs (6.8% vs. 3.8%, $p < 0.001$) (Table 4). The difference in MACE between the complex and simple subgroups became wider at the 1-year follow-up (16.8% vs. 8.9%; hazard ratio: 0.72; 95% confidence interval: 0.51 to 0.93; $p < 0.001$) (Figure 3A), and significant differences in all individual endpoints were observed between the 2 subgroups (Figures 3B to 3D). Notably, the incidence of overall ST in the complex group was 1.6%, which was significantly higher than 0.7% in the simple group ($p = 0.026$).

COMPARISON OF CLINICAL OUTCOMES BETWEEN THE 2-STENT AND THE PS SUBGROUPS. We first studied simple (n = 2,552) bifurcation lesions (as defined by our criteria) to examine the effect of PS (n = 1,961, 70%) versus 2-stent techniques (n = 591, 30%) and found that 2-stent techniques were associated with increased in-hospital ST (1.0% vs. 0.2%, $p = 0.007$) (Table 5). At 1-year follow-up, there were no significant differences in MACE, cardiac death, MI,

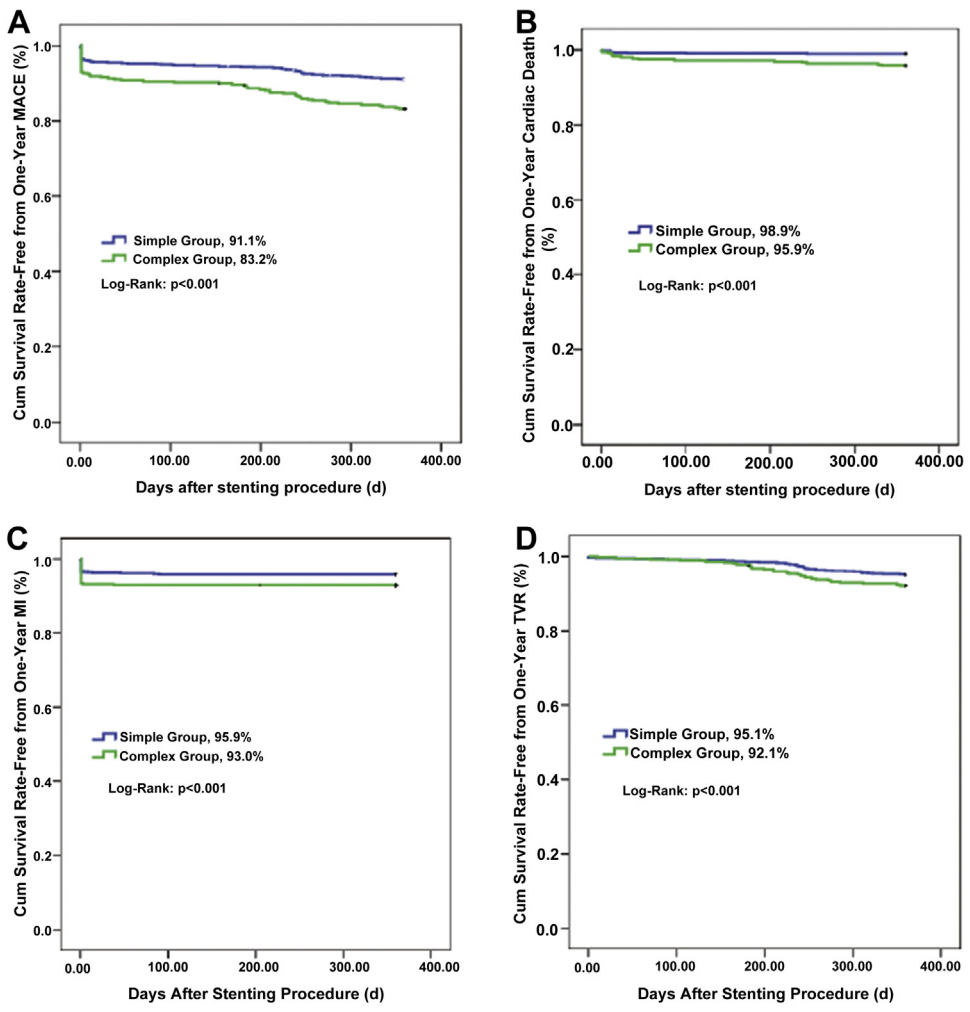

FIGURE 3 Comparison of the 3,660 Study Patients

Comparison of cumulative (Cum) 1-year survival rate free of major adverse cardiac events (MACE) **(A)**, cardiac death **(B)**, myocardial infarction (MI) **(C)**, and target vessel revascularization (TVR) **(D)** between the simple and complex groups.

and TVR between PS and 2-stent techniques in the simple group (Figure 4), although the TLR rate at 1 year (5.6%) in the 2-stent subgroup was significantly higher than that in the in PS subgroup (3.2%) ($p = 0.009$) (Table 5). Of 1,961 patients in the PS group, additional SB stenting was required in 3.0% ($n = 59$) of patients according to our angiographic criteria.

We examined complex bifurcation lesions in the second analysis ($n = 1,108$). We found a higher rate of in-hospital MACE (8.4%) in the PS subgroup ($n = 571$), which was significantly different from the 2-stent subgroup (5.0%, $p = 0.026$), mainly because of increased in-hospital MI rate in the PS group (Table 6). The rates of MACE, MI, and TVR at 1-year in the PS subgroup was not significantly different from that in 2-stent subgroup (Table 6, Figures 5A to 5D). However, PS was associated with a higher rate of 1-year cardiac death: 5.3% compared with 2.8% ($p = 0.041$) in the 2-stent subgroup (Table 6, Figure 5B). Of 571 patients in the PS subgroup, 18.1% ($n = 103$) crossed over to 2-stent techniques, and more final balloon kissing inflation was required ($n = 165$, 28.9%). These results were significantly different from the 14.7% in patients in the PS subgroup with simple bifurcation lesions (Tables 5 and 6).

DISCUSSION

We report newly established criteria for the differentiation of simple from complex coronary bifurcation lesions in a large patient cohort. The most important findings of the present study are the following: 1) the complex group after drug-eluting stent has more frequent composite MACE and ST than the simple group; and 2) 2-stent strategies for overall bifurcation lesions have 1-year MACE rates comparable to those with PS. However, patients with complex bifurcation lesions likely benefited from 2-stent techniques in terms of cardiac death.

LESSONS FROM PREVIOUS RANDOMIZED CLINICAL STUDIES ON BIFURCATION LESIONS. Previous studies have confirmed that systematically complex stenting strategies do not provide any advantage over PS for a given bifurcation lesion (1-7,18,19). As a result, PS of the SB has become the gold standard of care for bifurcation lesions. However, the DKCRUSH-II study (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) (8) showed reduced TLR rates after the administration of DK crush over PS for Medina 1,1,1 and 0,1,1 bifurcation lesions. The possible explanations for this different result between the DKCRUSH-II study and others are mainly discrepancies in the study design and lesion complexity, which were documented as SB size (from 2.0 to >2.5 mm), location (distal left main or nonleft main) and patterns (with or without Medina 1,0,1) of bifurcation lesions, plaque burden (SB DS varying from 40% to >60%), SB lesion length (5 to >10 mm), calcified lesions, chronic total occlusion, acute MI, and the use of 2-stent techniques. The CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study (5) reported severe plaque burdens (SB DS >60%) in SB, but classic crush stenting was the only 2-stent technique used, and this technique is inferior to culotte stenting (18) or DK crush stenting (3,8,20).

Based on the analyses mentioned above, there is an urgent need for a simple, comprehensive, and practical criteria that can differentiate simple from complex bifurcation lesions and guide the selection of an appropriate stenting approach (2-stent or PS), such as the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (6,21) and NERS (New Risk Stratification) score (22).

FEATURES OF THE PRESENT CRITERIA. An advantage of the current criteria was the successful implementation in a large external patient population with true bifurcation lesions (Medina 1,1,1 and 0,1,1) and SB ≥2.5 mm in diameter. The Medina 1,0,1 bifurcation lesion, 1 of the true bifurcation lesions, is commonly treated using PS from intention-to-treatment, and these lesions were excluded from our analysis.

Our new criteria include several factors that contribute to reliable risk stratification: 2 levels of stratifications (i.e., 2 major and 6 minor elements); relatively large SB (indicating the high risk of myocardium at jeopardy); severe SB plaque burden (not proposed in the Medina classification); moderate to severe calcification and multiple lesions (2 known factors attributing to poor outcome); renal and left ventricular dysfunction (2 known predictors of clinical events); and thrombus-containing lesions (commonly seen in acute coronary syndrome) and longer or diffuse main vessel lesions (a known factor of poor stent expansion). Accordingly, the combination of 1 major and any 2 minor criteria would likely indicate the complexity of a bifurcation lesion or the high-risk patients much better than the conventional Medina classification, which relies on only main vessel and SB involvement.

TABLE 5 Clinical Outcomes in 2-Stent and PS Subgroups in the Simple Group of 3,660 Patients

	Simple Group (n = 2,552)			
	2-Stent (n = 591)	PS (n = 1,961)	Adjusted HR (95% CI)	p Value
Final kissing inflation	509 (85.9)	288 (14.7)	–	<0.001
Side branch stenting	592 (100.0)	59 (3.0)	–	<0.001
In-hospital				
Myocardial infarction	18 (3.0)	78 (4.0)	0.76 (0.45-1.28)	0.295
Cardiac death	0	9 (0.5)	–	0.125
Target lesion revascularization	3 (0.5)	6 (0.3)	1.66 (0.41-1.66)	0.475
Target vessel revascularization	3 (0.5)	9 (0.5)	1.11 (0.29-4.09)	0.882
Coronary artery bypass graft	0	3 (0.2)	–	0.926
Major adverse cardiac events	18 (3.0)	90 (4.6)	0.68 (0.40-1.13)	0.136
Stent thrombosis	6 (1.0)	3 (0.2)	6.68 (1.67-26.80)	0.007
At 1 year				
Myocardial infarction	18 (3.0)	87 (4.4)	0.68 (0.40-1.13)	0.136
Cardiac death	6 (1.0)	21 (1.1)	0.95 (0.38-2.34)	0.905
Target lesion revascularization	33 (5.6)	63 (3.2)	1.78 (1.16-2.74)	0.009
Target vessel revascularization	33 (5.6)	93 (4.7)	1.19 (0.79-1.78)	0.413
Coronary artery bypass graft	0	3 (0.2)	–	1.000
Major adverse cardiac events	54 (9.1)	174 (8.9)	1.03 (0.75-1.42)	0.853
Stent thrombosis	6 (1.0)	12 (0.6)	1.66 (0.62-4.45)	0.311
Definite and probable	6 (1.0)	12 (0.6)	1.66 (0.62-4.45)	0.311

Values are n (%) unless otherwise indicated.
PS = provisional stenting; other abbreviations as in Table 4.

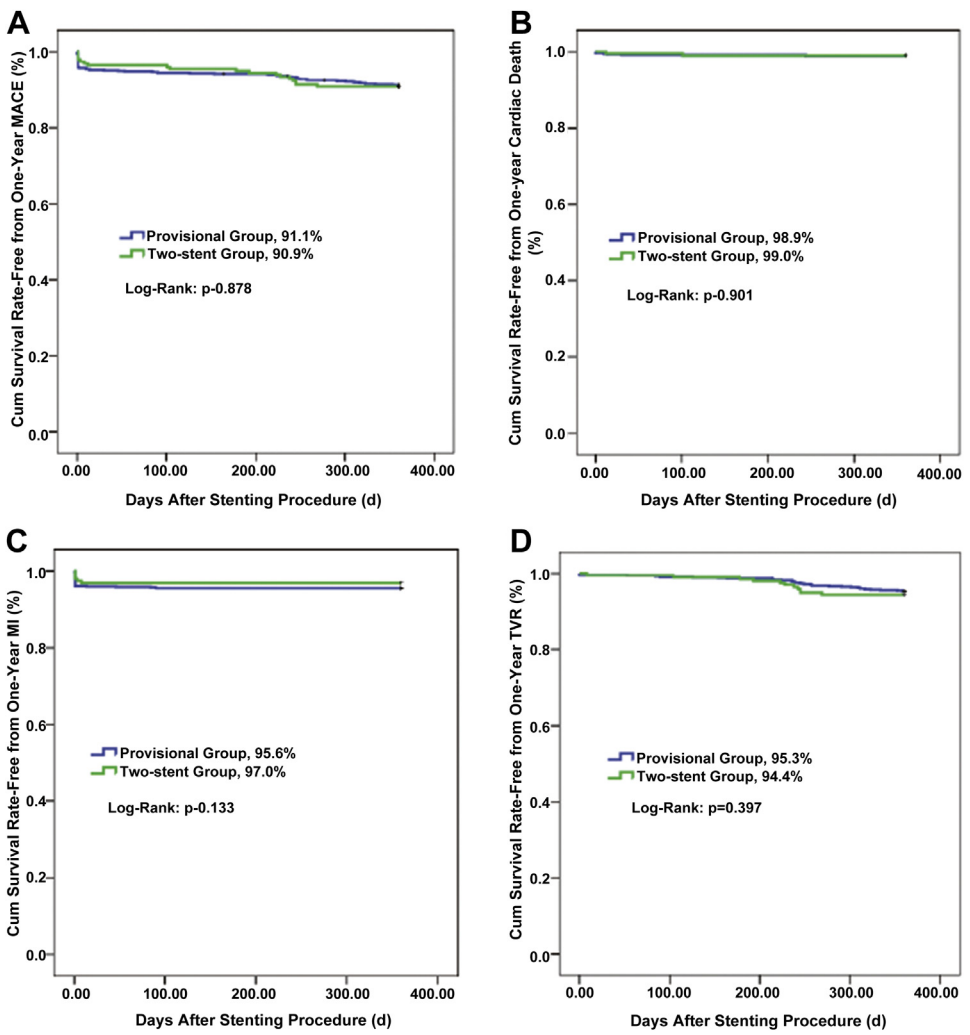

FIGURE 4 Comparison of Patients in the Simple Group

Comparison of cumulative 1-year survival rate free of MACE **(A)**, cardiac death **(B)**, MI **(C)**, and TVR **(D)** between provisional stenting and 2-stent approaches. Abbreviations as in Figure 3.

IMPACT OF BIFURCATION COMPLEXITY ON CLINICAL OUTCOMES. The most frequently used Medina classification (7) does not provide sufficient information about the real complexity of a given bifurcation lesion because of a lack of lesion specificities (10,11) and clinical variables. Moreover, several parameters (including relatively larger SB, long SB lesion, wide bifurcation angle, and high risk of hemodynamic deterioration associated with potential SB occlusion) have been introduced as indicators for ideal candidates for 2-stent techniques (9), but several questions are still debated. How large is larger? How long is longer? What are the accurate predictors of acute SB closure? Most importantly, these debated key points have not been systematically studied in a prospective clinical trial.

In general, our data clearly showed that complex bifurcation lesions were associated with more adverse events compared with simple bifurcation lesions in the entire cohort of bifurcation lesions, which indicates the enhanced predictive power of these newly established criteria. Our results support the concept that simpler is better for simple bifurcations, which account for 70% of bifurcation lesions from our

TABLE 6 Clinical Outcomes in 2-Stent and Provisional Stenting Subgroups in the Complex Group of 3,660 Patients

	Complex Group (n = 1,108)			
	2-Stent (n = 537)	PS (n = 571)	Adjusted HR (95% CI)	p Value
Final kissing inflation	473 (88.1)	165 (28.9)	–	<0.001
Side branch stenting	537 (100.0)	103 (18.1)	–	<0.001
In-hospital				
Myocardial infarction	27 (5.0)	48 (8.4)	0.58 (0.35–0.94)	0.026
Cardiac death	3 (0.6)	6 (1.1)	0.53 (0.13–2.12)	0.368
Target lesion revascularization	0	0	–	NS
Target vessel revascularization	0	0	–	NS
Coronary artery bypass graft	0	0	–	NS
Major adverse cardiac events	27 (5.0)	48 (8.4)	0.58 (0.35–0.94)	0.026
Stent thrombosis	0	0	–	NS
At 1 year				
Myocardial infarction	30 (5.6)	48 (8.4)	0.64 (0.40–1.03)	0.067
Cardiac death	15 (2.8)	30 (5.3)	0.52 (0.28–0.97)	0.041
Target lesion revascularization	33 (6.1)	33 (5.8)	1.07 (0.65–1.75)	0.803
Target vessel revascularization	45 (8.4)	42 (7.4)	1.12 (0.74–1.18)	0.532
Coronary artery bypass graft	6 (1.1)	3 (0.5)	2.14 (0.52–8.58)	0.285
Major adverse cardiac events	81 (15.1)	105 (18.4)	0.79 (0.57–1.08)	0.138
Stent thrombosis	9 (1.7)	9 (1.6)	1.06 (0.42–1.69)	0.899
Definite and probable	6 (1.1)	6 (1.1)	1.06 (0.34–3.13)	0.917
Possible	3 (0.6)	3 (0.5)	1.06 (0.21–5.28)	0.942

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 5.

data. Why is the 1-year rate of cardiac death after PS for complex bifurcation lesions double that of 2-stent techniques? We postulate that residual SB dissection (invisible on angiography) (23,24) and the progression of SB lesions (25) induced by kissing balloon inflation might be possible explanations, which is consistent with the DKCRUSH-II study (8) and intravascular ultrasound analysis (25,26). Otherwise, a well-defined PS technique (proximal optimized technique, imaging supported) would have likely shown improvements in clinical results (27–29), even for complex bifurcation lesions, as suggested by a consensus from the European Bifurcation Club (29).

CLINICAL IMPLICATIONS. Our newly established criteria provide a classification of the complexity of bifurcation lesions, demonstrated by more frequent MACE and individual endpoints after stenting complex bifurcation. Therefore, we are convinced that simpler is better for the treatment of simple bifurcation lesions. However, the benefits of 2-stent techniques for complex bifurcation lesions should be further evaluated in randomized studies.

STUDY LIMITATIONS. The major limitation of the present study was its nonrandomized design, which would likely reduce the power of the final conclusions. The second limitation was that we did not calculate how much of the use of the 2-stent techniques was based on lesion complexity. The third limitation was the exclusion of the classic crush technique from the current study due to more frequent malapposition, as documented by several intravascular ultrasound studies (27,28), more cases of MACE and ST based on a previous clinical study (20), and its common inclusion in our DKCRUSH-I study (20). Fourth, kissing stenting techniques (including V stenting and simultaneous kissing stenting) were only used in 6 patients using bare-metal stents, and these patients were excluded from our analysis. Finally, quantitative coronary analysis was not systematically performed. Regardless, our data from such a large patient sample provides clinically-driven outcomes (avoiding the "stenosis-reflex") in a real-world fashion.

CONCLUSIONS

The new criteria proposed in the present study can differentiate complex from simple bifurcation lesions: patients with complex bifurcation lesions had very poor clinical outcomes. Two-stent and PS techniques exhibited equivalent overall 1-year rates of MACE. A randomized clinical study is required to further elucidate the difference in clinical outcomes

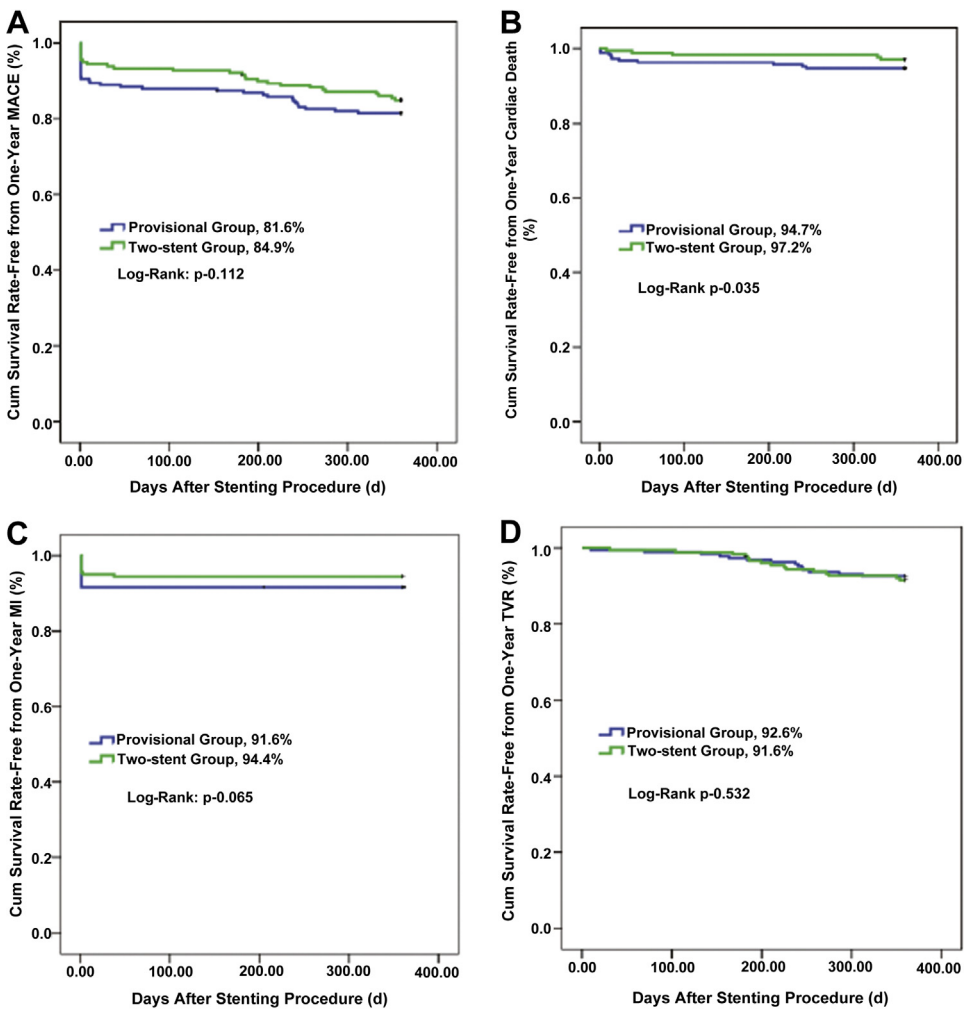

FIGURE 5 Comparison of Patients in the Complex Groups

Comparison of cumulative 1-year survival rate free of MACE **(A)**, cardiac death **(B)**, MI **(C)**, and TVR **(D)** between provisional stenting and 2-stent approaches. Abbreviations as in Figure 3.

between 2-stent and PS techniques for complex bifurcation lesions stratified using our new criteria.

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