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CORONARY

3-Year Outcomes After 2-Stent With Provisional Stenting for Complex Bifurcation Lesions Defined by DEFINITION Criteria

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ABSTRACT

BACKGROUND The multicenter and randomized DEFINITION II (Two-Stent vs Provisional Stenting Techniques for Patients With Complex Coronary Bifurcation Lesions) trial showed less 1-year target lesion failure (TLF) after a 2-stent approach for complex coronary bifurcation lesions compared with provisional stenting (PS). The authors report the 3-year clinical outcome of the DEFINITION II trial.

OBJECTIVES The aim of the present study was to investigate the difference in TLF at 3 years after a planned 2-stent approach vs PS for complex coronary bifurcation lesions stratified by DEFINITION (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) criteria.

METHODS A total of 653 patients with complex coronary bifurcation lesions were randomly assigned to either the 2-stent group or the PS group in the DEFINITION II trial and were followed for 3 years. The primary endpoint was the occurrence of TLF at 3 years. Stent thrombosis was the safety endpoint.

RESULTS At 3 years, TLF had occurred in 52 patients (16.0%) in the PS group and in 34 (10.4%) patients in the 2-stent group (HR: 0.63; 95% CI: 0.41-0.97; $P = 0.035$), driven mainly by increased target vessel myocardial infarction (8.0% vs 3.7%; HR: 0.45; 95% CI: 0.23-0.89; $P = 0.022$) and target lesion revascularization (8.3% vs 4.3%; HR: 0.50; 95% CI: 0.26-0.96; $P = 0.038$). There was no difference in TLF between the 2 groups between year 1 and year 3.

CONCLUSIONS For patients with complex coronary bifurcations who reach 1-year postprocedure without experiencing endpoint events, there is still a risk for future events. The type of procedure performed initially is no longer a future event risk determinant. (Two-Stent vs Provisional Stenting Techniques for Patients With Complex Coronary Bifurcation Lesions; NCT02284750) (J Am Coll Cardiol Intv 2022;15:1310–1320) © 2022 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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The prevalence of coronary bifurcation lesion is about 20% among patients who undergo percutaneous coronary intervention (PCI).[1] Given that provisional stenting (PS) is globally accepted as the mainstream stenting technique for most coronary bifurcation lesions, 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization[2] recommended that a systematic 2-stent approach may be preferable for complex bifurcation lesions defined as side branch (SB) lesion length >5 mm and SB reference vessel diameter ≥2.75 mm or anticipated difficulty accessing the SB after stenting the main vessel (MV), and distal left main true bifurcation lesions. This guideline points to the impact of the complexity of bifurcation lesions on the selection of stenting approaches[2] and clinical outcomes after PCI using drug-eluting stents.[2,3] However, there is lack of worldwide agreement as to how to define complex bifurcation lesions. In 2014, the DEFINITION (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After

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Percutaneous Coronary Intervention Using Drug-Eluting Stents) criteria for complex bifurcation lesions were developed from a large bifurcation cohort (n = 1,550) and subsequently validated in a 3,660-patient study.[4] Significant reductions in mortality and in-hospital adverse events were observed in patients with DEFINITION criteria-defined complex bifurcation lesions treated with routine 2-stent techniques. Furthermore, the prospective, multicenter, international, and randomized DEFINITION II (Two-Stent vs Provisional Stenting Techniques for Patients With Complex Coronary Bifurcation Lesions) trial[5] demonstrated a significant improvement in 1-year clinical outcomes after an upfront 2-stent approach among patients with complex coronary bifurcation disease stratified by DEFINITION criteria. There are no data showing the long-term benefits of an upfront 2-stent approach compared with PS for complex coronary lesion. Accordingly, the aim of this study was to evaluate the 3-year clinical outcomes after the 2-stent technique and PS for the patient population from DEFINITION II trial.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The DEFINITION II trial[5] was an international, multicenter, randomized study that was designed to compare the upfront 2-stent approach (double-kissing crush or culotte stenting) and PS among patients with complex coronary bifurcation lesions according to DEFINITION criteria.[4] The primary endpoint was target lesion failure (TLF) at 1-year follow-up, including cardiac death, target vessel myocardial infarction (TVMI) or clinically driven target lesion revascularization (TLR), whereas angiographic follow-up was performed 13 months after the indexed procedures. The study protocol was approved by the ethics committees of all participating centers, and written consent was obtained from all patients. Clinical follow-up was scheduled to be extended to 3 years, as shown in **Figure 1**. In brief, patients were eligible if they had ischemic symptoms or evidence of myocardial ischemia in the presence of Medina 1,1,1 or 0,1,1 de novo coronary bifurcation lesions.[6] For inclusion, all bifurcation lesions had reference vessel diameter in the SB ≥2.5 mm by visual estimation and had to meet DEFINITION criteria[4] for complex bifurcations. On the basis of DEFINITION criteria, complex bifurcation lesions were defined as any 1 major criterion (SB lesion length ≥10 mm with diameter stenosis of SB ≥70% for distal left main bifurcation lesions or ≥90% for nonleft main bifurcation lesions) plus any 2 minor criteria (moderate to severe calcification, multiple lesions, bifurcation angle <45° or >70°, MV reference vessel diameter ≤2.5 mm, thrombus-containing lesions, or MV lesion length ≥25 mm) by visual estimation. Patients were excluded if 3 or more stents were likely to be needed to treat the bifurcation, if they had an estimated life expectancy of <12 months, if they were scheduled for surgery requiring antiplatelet medication interruption within 6 months, if they required long-term oral anticoagulation, and if they had any clinical conditions that would interfere with medication compliance or long-term follow-up.[5] Pregnant or breastfeeding women were also excluded. Patients were randomly assigned to the study groups in a 1:1 ratio immediately after angiography. The main stenting techniques were described previously.[5] In the PS group, the recommendation was to not balloon-dilate or stent the SB unless the SB ostium was severely compromised or had a type B or C dissection or TIMI (Thrombolysis In Myocardial Infarction) flow grade <3. For both provisional and 2-stent approaches, the proximal optimization technique was used for all MV stents, and postdilatation of all stents was recommended with noncompliant balloons at ≥18 atm pressure.

ABBREVIATIONS AND ACRONYMS

DAPT = dual antiplatelet therapy

MI = myocardial infarction

MV = main vessel

PCI = percutaneous coronary intervention

PS = provisional stenting

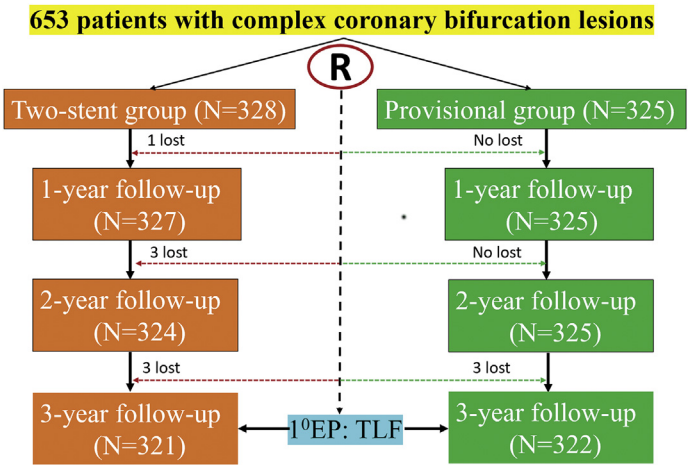
SB = side branch

TLF = target lesion failure

TLR = target lesion revascularization

TVMI = target vessel myocardial infarction

FIGURE 1 Study Flowchart



Of 653 patients included in the DEFINITION II (Two-Stent vs Provisional Stenting Techniques for Patients With Complex Coronary Bifurcation Lesions) trial, 321 in the 2-stent group and 322 in the provisional group completed 3-year follow- up. 1⁰EP = primary endpoint; R = randomization; TLF = target lesion failure.

TABLE 1 Clinical, Angiographic, and Procedural Characteristics

	2-Stent Approach (n = 328)	Provisional Stenting (n = 325)	*P* Value[a]
Clinical			
Age, y	63 ± 11	64 ± 10	0.289
Male	255 (77.7)	250 (76.9)	0.802
Hyperlipidemia	227 (69.2)	223 (68.6)	0.870
Hypertension	215 (66.2)	230 (70.1)	0.277
Diabetes	112 (34.1)	116 (35.7)	0.679
Prior MI	39 (11.9)	42 (12.9)	0.700
Congestive heart failure	28 (8.5)	39 (12.0)	0.145
Unstable angina	160 (48.8)	164 (50.5)	0.668
Acute MI (>24 h)	72 (22.0)	73 (22.5)	0.875
Angiographic			
Multivessel disease	194 (59.1)	199 (61.2)	0.586
Calcification	127 (38.7)	131 (40.3)	0.678
Chronic total occlusion			
Main vessel	15 (4.6)	16 (4.9)	0.833
Side branch	5 (1.5)	4 (1.2)	1.000
Procedural			
2-stent	302 (92.1)	73 (22.5)	<0.001
Final kissing inflation	287 (99.3)	70 (95.9)	0.392
POT performed	322 (98.2)	296 (99.0)	0.902
IVUS assessment	80 (24.4)	101 (31.1)	0.056
Complete revascularization	252 (76.8)	233 (71.7)	0.133
Angiographic success	306 (93.3)	304 (93.5)	0.899
Procedural success			
Main vessel	323 (98.5)	321 (98.8)	1.000
Side branch	324 (98.8)	319 (98.2)	0.357
Contrast volume, mL	223 ± 86	211 ± 90	0.085
Procedural time, min	84 ± 42	72 ± 39	<0.001

Values are mean ± SD or n (%). [a]*P* values are from chi-square tests.
IVUS = intravascular ultrasound; MI = myocardial infarction; POT = proximal optimization technique.

MEDICATIONS. All patients were treated with aspirin preprocedure and were administered a 300-mg loading dose of clopidogrel if not on long-term dual antiplatelet therapy (DAPT). After intervention, all patients received 100 mg/d aspirin indefinitely and clopidogrel 75 mg/d for at least 12 months. Additional medications for secondary prevention, including statins, β-blockers, and angiotensin-converting enzyme inhibitors, were prescribed according to current guidelines.

DEFINITION OF STUDY ENDPOINTS. The primary endpoint was TLF at 3 years, which included cardiac death, TVMI, and/or clinically driven TLR. ST defined by the Academic Research Consortium definite or probable criteria[7] was the major safety endpoint. Death of cardiac causes was defined as any death without a known reason. Protocol-defined periprocedural myocardial infarction (MI) was defined as within-48-hour creatine kinase-myocardial band >10 times the upper reference limit of the assay or >5 times the upper reference limit plus: 1) new pathologic Q waves in ≥2 contiguous leads or new left bundle branch block; 2) angiographically documented graft or coronary artery occlusion or new severe stenosis with thrombosis; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Spontaneous MI (after 48 hours) was defined as a clinical syndrome consistent with MI with creatine kinase-myocardial band or troponin >1 times the upper reference limit and new ST-segment elevation or depression or other findings as noted previously. All MIs were considered TVMIs unless there was clear evidence that they were attributable to nontarget vessels.[7] Clinically driven TLR was defined as angina or ischemia referable to the target lesion requiring repeat PCI or coronary artery bypass graft. All events were adjudicated by a central committee using original source documents blinded to treatment. For patients who were lost to follow-up at 3 years, the data at the last visit were used for analysis. Follow-up coronary angiography was scheduled at 13 months (after ascertainment of the primary clinical endpoint), unless performed earlier for clinical indications. The 13-month schedule for follow-up angiography meant that TVR of previously undetected restenoses found on follow-up angiography was not included in the previously reported 1-year endpoint but would be captured in this later follow-up.

STATISTICAL ANALYSIS. The calculation of sample size was described previously.[5] The chi-square test or Fisher exact test was used to compare categorical variables. Student's *t*-test or Wilcoxon rank sum

TABLE 2 Comparison of Clinical Events Between 2-Stent and Provisional Groups

	2-Stent Approach (n = 328)	Provisional Stenting (n = 325)	HR (95% CI)	*P* Value
Follow-up duration, d				
Median (IQR)	1,751 (1,481-1,924)	1,737 (1,473-1,927)		0.667
Mean ± SD	1,709 ± 276	1,703 ± 277		0.774
30-d follow-up				
Target lesion failure	10 (3.0)	24 (7.4)	0.41 (0.20-0.85)	0.017
Cardiac death	2 (0.6)	5 (1.5)	0.39 (0.08-2.03)	0.265
Target vessel MI	8 (2.4)	21 (6.5)	0.38 (0.17-0.85)	0.018
Clinically driven TLR	2 (0.6)	6 (1.8)	0.33 (0.07-1.62)	0.171
Stent thrombosis	3 (0.9)	6 (1.8)	2.04 (0.51-8.16)	0.313
31-d to 1-y follow-up				
Target lesion failure	10 (3.0)	13 (4.0)	0.77 (0.34-1.75)	0.525
Cardiac death	5 (1.5)	3 (0.9)	1.66 (0.39-6.93)	0.490
Target vessel MI	2 (0.6)	2 (0.6)	0.99 (0.14-7.08)	0.990
Clinically driven TLR	6 (1.8)	12 (3.7)	0.49 (0.19-1.32)	0.161
Stent thrombosis	1 (0.3)	2 (0.6)	0.49 (0.05-5.48)	0.567
1- to 3-y follow-up				
Target lesion failure	14 (4.3)	15 (4.6)	0.87 (0.41-1.82)	0.703
Cardiac death	10 (3.0)	7 (2.2)	1.43 (0.54-3.75)	0.469
Target vessel MI	2 (0.6)	3 (0.9)	0.66 (0.11-3.95)	0.649
Clinically driven TLR	6 (1.8)	9 (2.8)	0.54 (0.20-1.46)	0.226
Stent thrombosis	2 (0.6)	2 (0.6)	0.99 (0.14-7.01)	0.990
At 3-y follow-up				
Target lesion failure	34 (10.4)	52 (16.0)	0.63 (0.41-0.97)	0.034
Cardiac death	18 (5.5)	15 (4.6)	1.19 (0.60-2.36)	0.620
Target vessel MI	12 (3.7)	26 (8.0)	0.45 (0.23-0.89)	0.022
Clinically driven TLR	14 (4.3)	27 (8.3)	0.50 (0.26-0.96)	0.038
Stent thrombosis	6 (1.8)	10 (3.1)	0.59 (0.22-1.63)	0.308

Values are n (%) unless otherwise indicated.
MI = myocardial infarction; TLR = target lesion revascularization.

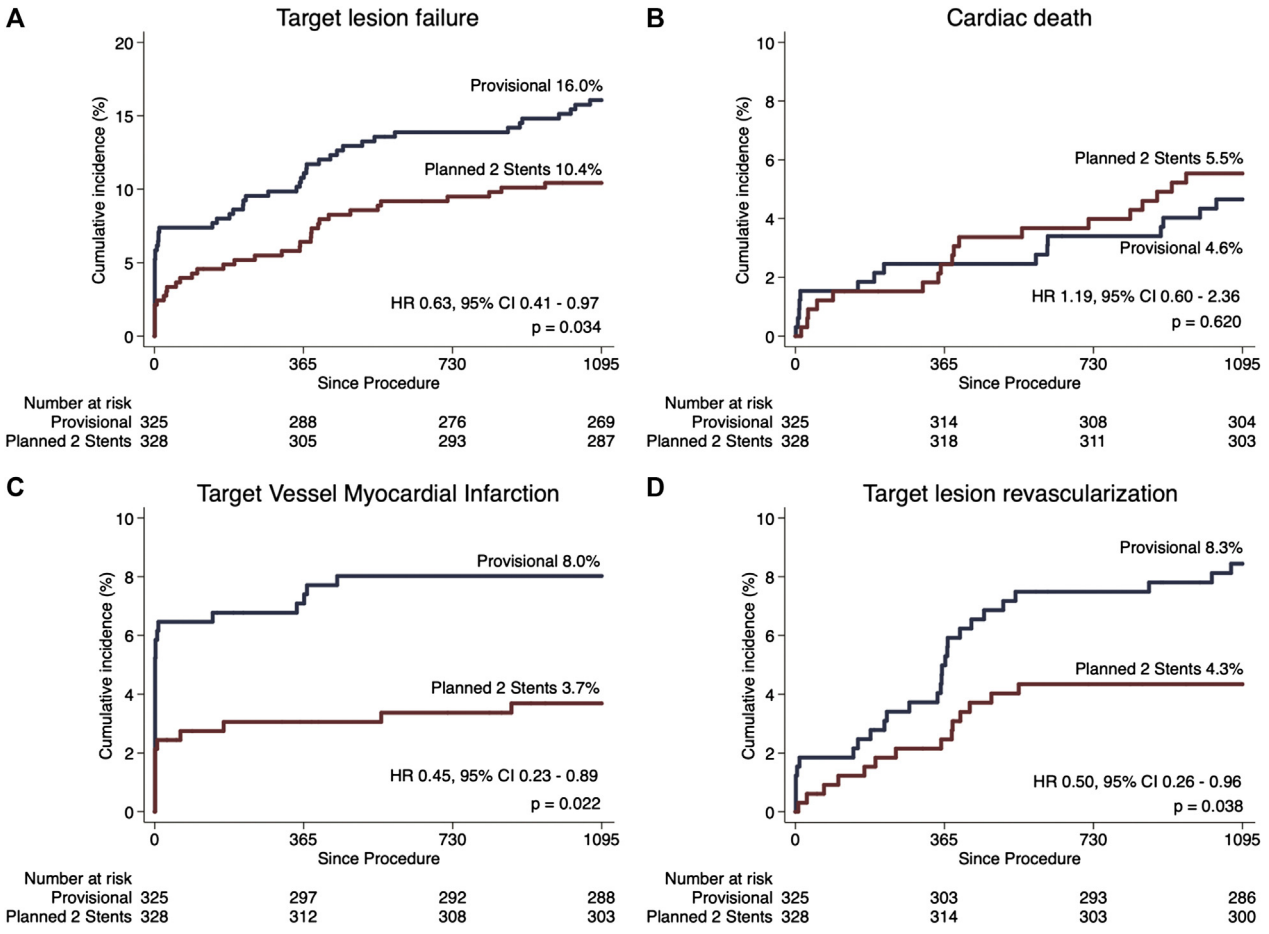
scores for non-normally distributed data were used to compare continuous variables. Time-to-first event curves were generated using Kaplan-Meier analysis and compared using the log-rank test. Cox regression was also used to compare the differences in both primary and secondary endpoints, with outputs of HR, 95% CI, and *P* value. All outcome analyses were performed in the intention-to-treat population, regardless of treatment received. Subgroup comparisons from 10 prespecified groups[5] were also performed. All statistical tests were 2-sided, and a *P* value of <0.05 was considered to indicate statistical significance. All analyses were performed with SAS version 9.4 (SAS Institute).

RESULTS

BASELINE CLINICAL, ANGIOGRAPHIC AND PROCEDURAL CHARACTERISTICS. Between December 23, 2015, and November 7, 2018, a total of 653 patients were enrolled (328 in the 2-stent group and 325 in the PS group). Baseline clinical, angiographic, and procedural characteristics (Table 1) were well matched between the 2 groups. At 3 years, 10 patients (1.5%) were lost to clinical follow-up, with 7 (2.1%) in the 2-stent group and 3 (0.9%) in the PS group (Figure 1). Diabetes was present in 34.9% of patients, and almost half of patients presented with unstable angina. Acute MI (>24 hours) was present in 22.2% of patients. A total of 73 patients (22.5%) in the PS group required additional SB stents for suboptimal results after MV stenting. SB pretreatment increased the intraprocedural requirement of an additional stent in the SB in the PS group (32.0% vs 14.3%; $P < 0.001$). The proximal optimization technique was performed equally frequently in both groups, and kissing balloon inflation was performed at similar rate between entire 2-stent group and the portion of the PS group that received SB stents. Intravascular ultrasound assessment was used in 27% of patients. Rates of angiographic success and complete revascularization were similar in the 2 groups, although procedural time was greater with the 2-stent technique than PS.

FOLLOW-UP AND CLINICAL OUTCOMES. DAPT at 3 years was prescribed in 53 patients (16.3%) in the PS group, nonsignificantly different from 73 patients

FIGURE 2 Kaplan-Meier Survival in the Provisional Stenting and 2-Stent Groups



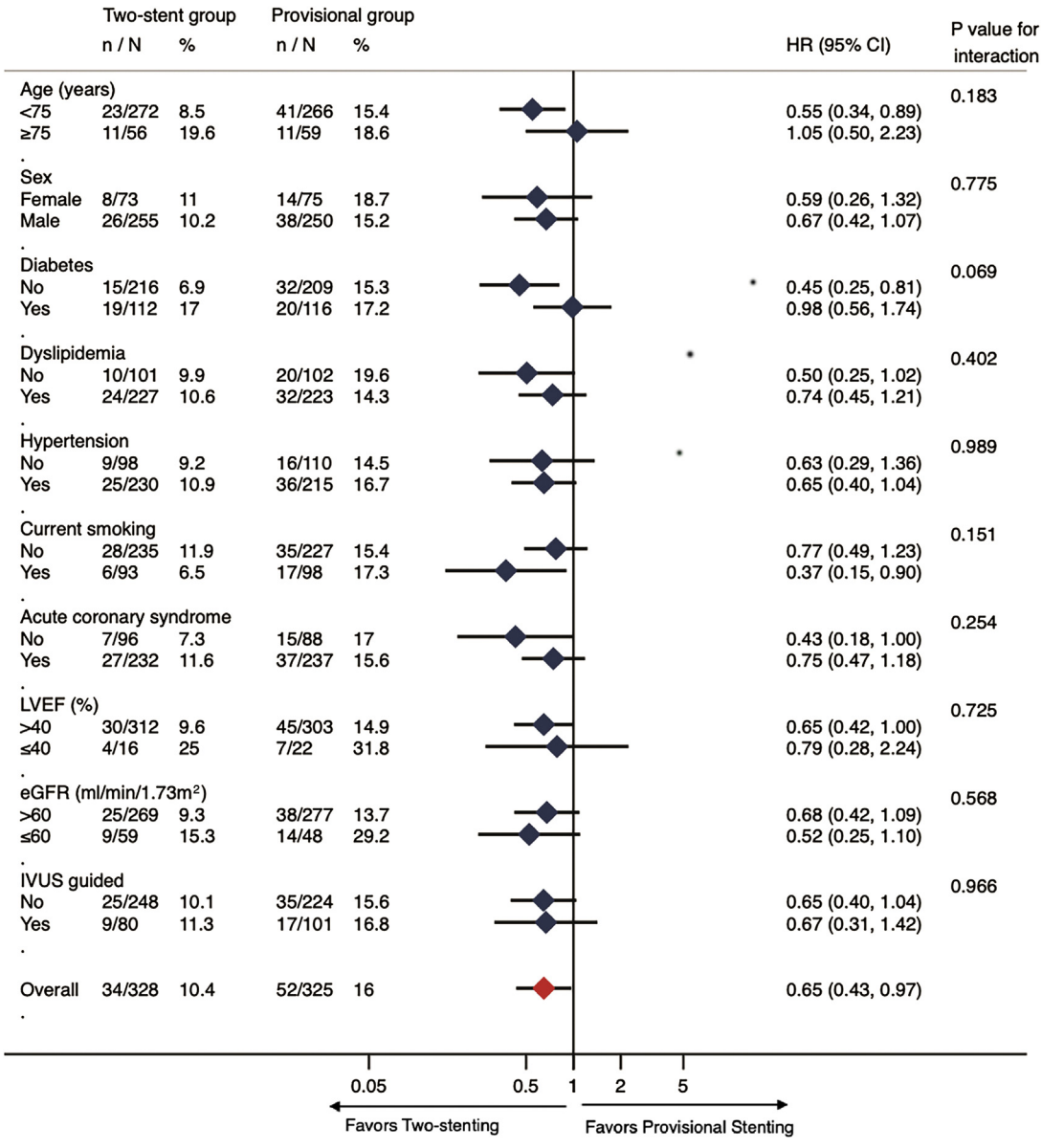
Survival rates of target lesion failure **(A)**, cardiac death **(B)**, target vessel myocardial infarction **(C)**, and target lesion revascularization **(D)**.

(22.3%) in the 2-stent group ($P = 0.060$). Angiographic follow-up was completed in 173 patients (53.2%) in the PS group and 183 patients (55.8%) in the 2-stent group at 13 months[5] and in 77 (23.7%) in the PS group and 78 (23.8%) in the 2-stent group ($P = 1.000$) between year 1 and year 3.

In the PS group, among 41 patients experiencing SB abrupt closure or SB type B or C dissection, TVMI within 48 hours occurred in 5 (12.2%), which was not significantly different from 16 patients (5.6%) ($P = 0.162$) without SB abrupt closure or dissection. Of patients who had intraprocedural complications (defined as type B or C dissection, TIMI flow grade <3, acute closure, perforation, or thrombus formation), TVMI was reported in 20.0% in the PS group and 13.6% in the 2-stent group, compared with 5.1% ($P = 0.008$ by log-rank test; HR: 4.023; 95% CI: 1.561-10.372) and 1.6% ($P = 0.016$ by log-rank test; HR: 8.427; 95% CI: 2.014-35.267) among patients without complications.

The rate of TLF at 30-day follow-up in the PS group was 7.4%, compared with 3.0% in the 2-stent group ($P = 0.017$ by log-rank test), driven largely by increased rate of TVMI (6.5% vs 2.4%; $P = 0.018$ by log-rank test) (Table 2). Although significant differences in cumulative TLF and TLR at 1-year follow-up between the PS (11.4% and 5.5%) and 2-stent (6.1% and 2.4%) ($P < 0.05$ for all) groups was achieved,[5] there were no differences in primary and secondary endpoints between year 1 and year 3 between the 2 groups (Table 2, Central Illustration). At 3-year follow-up, the cumulative incidence of TLF was 16.0% in the PS group and 10.4% in the 2-stent group (HR: 0.63; 95% CI: 0.41-0.97; $P = 0.035$) (Figure 2), mainly

FIGURE 3 Subgroup Analysis



Ten prespecified subgroup analysis showed a negative interaction *P* value. eGFR = estimated glomerular filtration rate; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction.

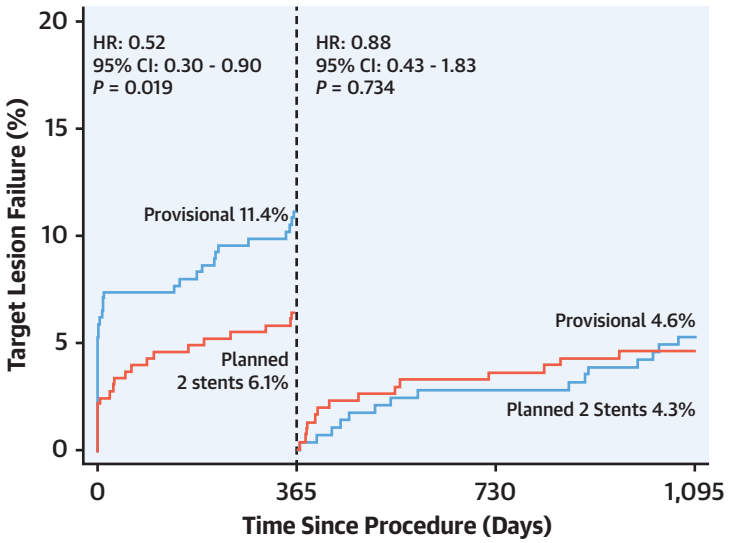
because of increased rates of TVMI (8.0% vs 3.7%; HR: 0.63; 95% CI: 0.41-0.97; $P = 0.035$) and TLR (HR: 0.50; 95% CI: 0.26-0.96; $P = 0.038$) in the PS group. The rate of definite and probable ST was 3.1% in the PS group and 1.8% in the 2-stent group ($P = 0.308$) (Table 2). Of 16 patients with definite or probable ST, only 2 patients (1 in each group) were receiving DAPT. A similar effect was seen across 10 specifically defined subgroups (Figure 3). However, landmark analysis (Central Illustration) demonstrated that TLF between year 1 and year 3 occurred in 15 patients (4.6%) in the PS group, nonsignificantly different from 14 (4.3%) in the 2-stent group (HR: 0.88; 95% CI: 0.43-1.83; $P = 0.734$). Notably, among patients in the PS group, 3-year TLF occurred in 18 patients (24.7%) with the 2-stent approach and 34 (13.5%) patients with 1 stent

CENTRAL ILLUSTRATION **Landmark Analysis of Target Lesion Failure**

3-Year Results From Definition II Trial (N = 653)

A

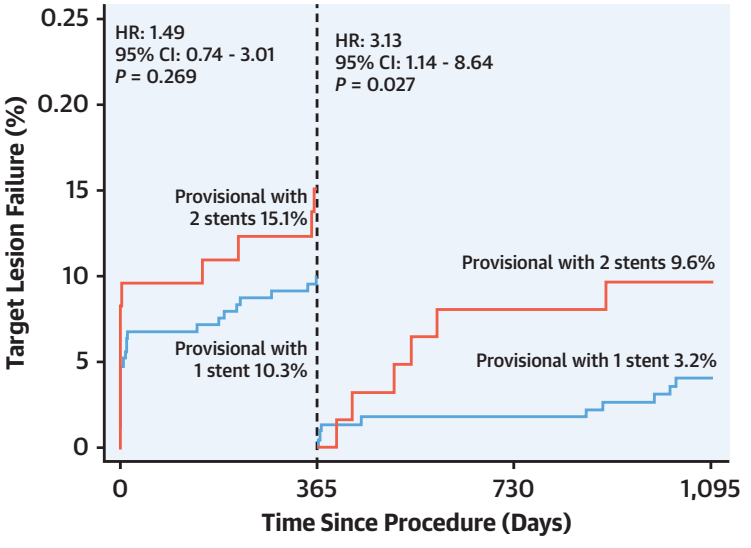
Provisional vs Planned 2 Stents



No. at risk:				
Provisional	325	287	276	269
Planned 2 Stents	328	306	293	287

B

Provisional With 1 or 2 Stents



No. at risk:				
Provisional with 1 Stent	252	226	220	215
Provisional with 2 Stents	73	62	57	56

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Landmark analysis showed a significant difference in 1-year target lesion failure between the provisional and planned 2-stent groups **(A)** or between patients with and without intraprocedural complications **(C).** In the provisional group, the 2-stent subgroup had a higher rate of target lesion failure after 1-year follow-up **(B).**

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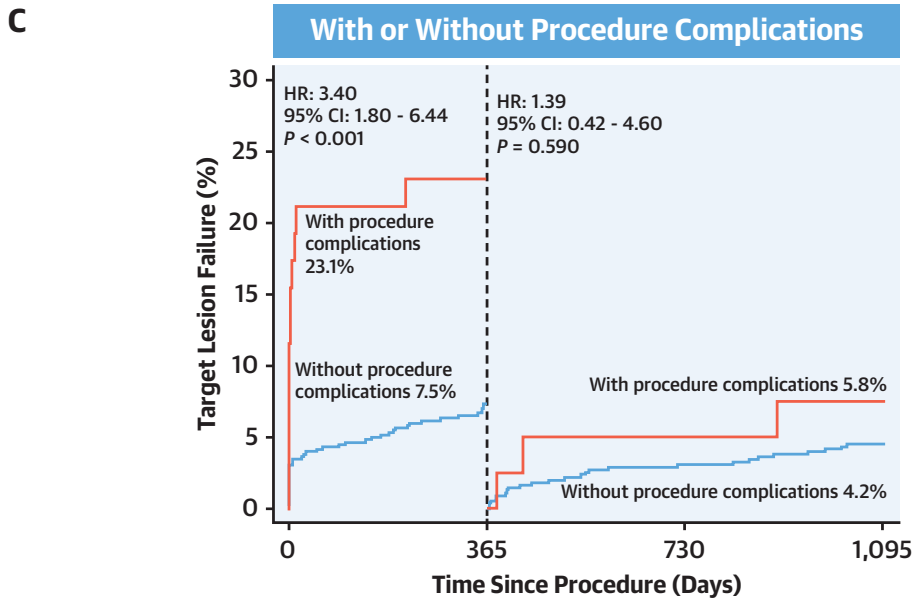
CENTRAL ILLUSTRATION Continued



($P = 0.029$), which was attributed to higher rate of TLR (6.8% vs 1.6%; HR: 4.45; 95% CI: 1.19-16.58; $P = 0.026$) between year 1 and year 3. For patients who experienced intraprocedural complications, there was a higher rate of 1-year TLF rather than 3-year TLF compared with patients who had no intraprocedural complications (Central Illustration).

DISCUSSION

The randomized, multicenter DEFINITION II trial for the first time evaluates long-term clinical outcomes after the 2-stent technique compared with a PS approach for treatment of complex coronary bifurcation lesions defined by DEFINITION criteria. Our findings demonstrate that although during the first year of follow-up, TLF, TVMI, and TLR occurred more frequently in the PS cohort, after 1 year, both cohorts had similar subsequent event rates. PS with the 2-stent approach is associated with frequent requirement of TLR.

Coronary bifurcation lesions vary with diameter stenosis and lesion length, as well as bifurcation angles, vessel diameters, and lesion specificities in both MV and SB. Medina classification[6] simply stratifies bifurcation lesions by false and true bifurcation lesions, dependent solely on the presence of MV and SB disease. The New Risk Stratification[8] and SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery)[9] scores were created to assess the complexity of left main disease and the degree of risk exposure to patients. Therefore, there is a lack of an internationally accepted standard to define a complex bifurcation lesion. The DEFINITION criteria[4] are established as identifying the most complex subset of all bifurcation lesions. On the basis of the validation group from the DEFINITION study,[4] the subsequent DEFINITION II trial[5] demonstrated a short-term (at 1 year) benefit in the reduction of TLF after a planned 2-stent approach for complex bifurcations. Obviously, serving as a risk stratification system, the DEFINITION criteria need to be further verified on 2 levels: Is the benefit of upfront 2-stent techniques for complex bifurcation lesions sustainable during long-term follow-up? What are the mechanisms underlying the increased rate of TLF after the PS approach?

Stenting selection is an old topic and is still a research hotspot. The global agreement that PS is noninferior to systematic 2-stent approaches came

TABLE 3 Comparison of Clinical Events Between PS With 1 Stent and PS With 2 Stents

	PS With 2 Stents (n = 73)	PS With 1 Stent (n = 252)	HR (95% CI)	*P* Value
30-d follow-up				
Target lesion failure	7 (9.6)	17 (6.7)	1.44 (0.59-3.47)	0.419
Cardiac death	1 (1.4)	4 (1.6)	0.87 (0.09-7.78)	0.900
Target vessel MI	7 (9.6)	14 (5.6)	1.74 (0.70-4.31)	0.232
Clinically driven TLR	2 (2.7)	4 (1.6)	1.73 (0.32-9.45)	0.526
Stent thrombosis	1 (1.4)	5 (2.0)	0.89 (0.08-5.98)	0.743
30-d to 1-y follow-up				
Target lesion failure	4 (5.5)	9 (3.6)	1.54 (0.47-4.99)	0.475
Cardiac death	1 (1.4)	2 (0.8)	1.74 (0.16-19.19)	0.651
Target vessel MI	0	2 (0.8)	0.03 (0.01-49.29)	0.639
Clinically driven TLR	4 (5.5)	8 (3.2)	1.72 (0.52-5.72)	0.375
Stent thrombosis	0	2 (0.8)	0.03 (0.01-48.34)	0.639
1- to 3-y follow-up				
Target lesion failure	7 (9.6)	8 (3.2)	3.13 (1.14-8.64)	0.027
Cardiac death	3 (4.1)	4 (1.6)	2.62 (0.59-11.69)	0.208
Target vessel MI	0	3 (1.2)	0.03 (0.01-35.90)	0.565
Clinically driven TLR	5 (6.8)	4 (1.6)	4.45 (1.19-16.52)	0.026
Stent thrombosis	0	2 (0.8)	0.03 (0.01-49.81)	0.639

Values are n (%) unless otherwise indicated.
MI = myocardial infarction; PS = provisional stenting; TLR = target lesion revascularization.

from prior studies[10-15] with more patients who had simplex bifurcation lesions with a view to 1-year clinical follow-up.

When clinical follow-up was extended to 3 to 5 years, patient-level pooled analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study[16] (both studies including patients mostly with simple lesions) showed that 5-year mortality was lower among patients who underwent a simple strategy rather than a complex strategy (3.8% vs 7.0%; $P = 0.04$), without a statistical difference in 3-year mortality. For patients with complex bifurcation lesions defined by DEFINITION criteria,[4] the 5-year TLR rate from DKCRUSH II (Randomized Study on Double Kissing Crush Technique Versus Provisional Stenting Technique for Coronary Artery Bifurcation Lesions) study[17] was much higher in patients with complex lesions who underwent the PS approach, mainly because of an increased 1-year TLR rate in the PS group, in line with findings from 1-year results of the DENIFITION II trial.[5] The correlation of bifurcation complexity with 1-year[18] and 3-year[19] clinical outcome was also confirmed in the DKCRUSH V study and an observational study[20] that compared PS with 2-stent techniques for left main distal bifurcation lesions. In the present 3-year analysis of the DEFINITION II trial, although difference in TLF was sustained through 3 years, we found that increased 1-year incidence of TLF was driven mainly by higher rates of TVMI at 30 days and cumulative TLR. Our findings also demonstrated that after 1-year follow-up, the occurrence of either TLF or secondary endpoints was nonsignificantly different between the PS and 2-stent groups. Conclusively, every effort should be made to reduce the 1-year rates of TVMI and TLR for patients with complex bifurcation lesions for whom a PS approach was selected. There may be bias when analyzing the chronological distribution of TLF because the sample size may be underpowered. However, our results and other findings have indicated the trend that there was no difference in the primary endpoint after 1-year follow-up between the PS and 2-stent techniques.

From the landmark analysis (**Table 3, Central Illustration**), after 1-year follow-up, PS with a 2-stent technique was associated with more frequent TLF, attributable mainly to increased TLR.

Taking into consideration the finding of a higher rate of 1-year TLF in patients with intraprocedural complications, our results underscore the importance of careful selection of stenting approaches for real complex bifurcations. An additional point is the requirement for clinical follow-up to >5 years to identify the durability of both PS and 2-stent techniques.

STUDY LIMITATIONS. First, our results cannot be applied to patients with simple bifurcation lesions, because all lesions in the DEFINITION II trial were classified by complex disease. Second, intravascular imaging was used in only one-fourth of patients. Whether intravascular ultrasound use in a higher proportion of patients in both groups would have influenced the observed outcomes in the present study is unclear.

Third, a direct comparison of double-kissing crush with other 2-stent techniques could not be performed because about 80% of lesions were treated using double-kissing crush in the 2-stent group. Finally, DAPT at 3 years was prescribed in 19.3% of all patients. The impact of shortened DAPT duration or SB pretreatment[21] on clinical outcome requires further study. Furthermore, the higher rate of 3-year TLR and TLF in patients who crossed over to the 2-stent approach in the PS group may indicate the importance of lesion classification and avoidance of stenting the SB.

CONCLUSIONS

In the present large-scale, multicenter, randomized trial, for patients with complex coronary bifurcations who reach 1-year postprocedure without experiencing endpoint events, there is still a risk for future

events. The type of procedure performed initially is no longer a determinant of future event risk.

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PERSPECTIVES

WHAT IS KNOWN? PS is still the main technique for simple coronary bifurcation lesions. In the randomized DEFINITION II trial, a 2-stent (mostly double-kissing crush) technique resulted in significant reductions in 1-year TLF, TVMI, and TLR compared with the PS approach in patients with complex bifurcation lesions defined by DEFINITION criteria.

WHAT IS NEW? The 2-stent approach was associated with less TLF, TVMI, and TLR through 3-year follow-up than PS for complex bifurcation lesions. However, there was no additional benefit from the 2-stent approach after 1 year.

WHAT IS NEXT? Further studies are warranted to evaluate whether clinical outcomes can be further improved with intravascular imaging guidance.

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