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Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: the DEFINITION II trial

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Aim	The present study aimed to assess the benefits of two-stent techniques for patients with DEFINITION criteria-defined complex coronary bifurcation lesions.
Methods and results	In total, 653 patients with complex bifurcation lesions at 49 international centres were randomly assigned to undergo the systematic two-stent technique (two-stent group) or provisional stenting (provisional group). The primary endpoint was the composite of target lesion failure (TLF) at the 1-year follow-up, including cardiac death, target vessel myocardial infarction (TVMI), and clinically driven target lesion revascularization (TLR). The safety endpoint was definite or probable stent thrombosis. At the 1-year follow-up, TLF occurred in 37 (11.4%) and 20 (6.1%) patients in the provisional and two-stent groups, respectively [77.8%: double-kissing crush; hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.30–0.90; $P = 0.019$], largely driven by increased TVMI (7.1%, HR 0.43, 95% CI 0.20–0.90; $P = 0.025$) and clinically driven TLR (5.5%, HR 0.43, 95% CI 0.19–1.00; $P = 0.049$) in the provisional group. At the 1 year after indexed procedures, the incidence of cardiac death was 2.5% in the provisional group, non-significant to 2.1% in the two-stent group (HR 0.86, 95% CI 0.31–2.37; $P = 0.772$).
Conclusion	For DEFINITION criteria-defined complex coronary bifurcation lesions, the systematic two-stent approach was associated with a significant improvement in clinical outcomes compared with the provisional stenting approach. Further study is urgently warranted to identify the mechanisms contributing to the increased rate of TVMI after provisional stenting.
Study registration	http://www.clinicaltrials.com; Identifier: NCT02284750.

Graphical Abstract
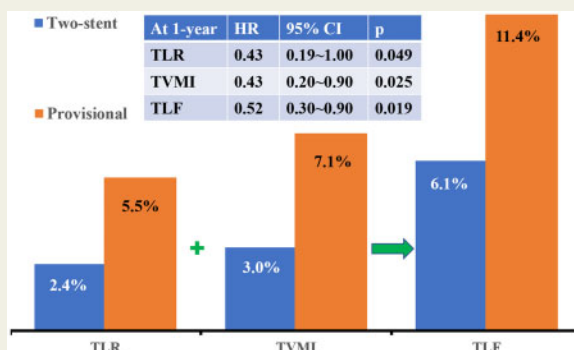
Introduction

Percutaneous coronary intervention (PCI) using drug-eluting stents has dramatically improved clinical outcomes in patients with coronary artery disease.[1] However, stenting of coronary bifurcation lesions is associated with suboptimal clinical results including more frequent stent thrombosis (ST) and unplanned repeat revascularizations compared with non-bifurcation lesions.[2] Although some studies have reported that the routine use of a two-stent technique[2–5] or dedicated bifurcation stent[6] is not advantageous in patients with bifurcation lesions, the double-kissing (DK) crush approach has demonstrated superiority to other approaches in bifurcations with increased complexity [e.g. side branch (SB) lesion length >10 mm][7] or distal left main (LM) lesions,[8,9] as reflected in

current guideline recommendations.[10] Widespread agreement is lacking, however, as to how to define complex bifurcation lesions. In 2014, the DEFINITION criteria of complex bifurcation lesions were developed from a large bifurcation cohort ($n = 1550$ patients) and subsequently validated in a 3660-patient study.[11] Significant reductions in mortality and in-hospital adverse events were observed in patients with complex bifurcation lesions so defined treated with routine two-stent techniques. However, the DEFINITION criteria have not been prospectively utilized in a randomized study. Accordingly, we designed the present international, multicentre, randomized DEFINITION II trial to examine the outcomes of routine two-stent compared with provisional stenting approaches in patients with bifurcation lesions defined by the DEFINITION criteria.

Methods

Study design

The design of the, multicentre, randomized DEFINITION II trial has been previously described.[12] The study organization, participating sites, and investigators are shown in the Supplementary material online, *Appendix*. The study was approved by the ethics committee at each participating centre and all patients provided written informed consent. The trial was mainly funded by the National Science Foundation of China (NSFC 91639303 and 81770441), who had no role in the site selection, study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to the data in the study, verified the accuracy of the data and analysis, and agreed with the decision to submit for publication.

Patient selection

Consecutive patients presenting with *de novo* coronary bifurcation lesions intended for PCI at participating centres were evaluated for enrolment in the trial. Patients were included if they were >18 years old, presented with silent ischaemia, stable or unstable angina, or myocardial infarction (MI) >24 h prior to treatment. For study inclusion, all bifurcation lesions were Medina 1, 1, 1 or 0, 1, 1 with reference vessel diameter (RVD) in the SB ≥2.5 mm by visual estimation and had to meet DEFINITION criteria[11] of complex bifurcations (*Figure 1*); briefly, complex bifurcation lesions were defined as any one major criterion (SB lesion length ≥10 mm with diameter stenosis of SB ≥70% for distal LM bifurcation lesions or diameter stenosis of SB ≥90% for non-LM bifurcation lesions) plus any two minor criteria [moderate-to-severe calcification, multiple lesions, bifurcation angle <45° or >70°, main vessel (MV) RVD <2.5 mm, thrombus-containing lesions, or MV lesion length ≥25 mm] by visual estimation. Patients were excluded if three or more stents were likely to be needed to treat the bifurcation, if they had an estimated life expectancy of <12 months, were scheduled for surgery requiring antiplatelet medication interruption within 6 months, required chronic oral anticoagulation, or had any clinical condition that would interfere with medication compliance or long-term follow-up. Pregnant or breastfeeding women were also excluded.

Study procedures

Eligible patients were randomly assigned in a 1:1 ratio to either provisional stenting or a routine two-stent approach using a central interactive web-based computerized system (*Figure 1*). The provisional stenting approach has been previously described.[7] In brief, the MV and SB are wired. Pre-dilation was left to the operator's discretion, although pre-dilating the SB is discouraged. A stent with the stent/artery ratio of 1.1:1 is implanted in the MV, and then proximal optimization technique (POT) using non-compliant balloons (1:1 of balloon/stent ratio, >18 atm) was performed. Ballooning or stenting the SB after MV stenting is performed only if the SB ostium was severely compromised or has a Type B/C dissection or Thrombolysis in Myocardial Infarction (TIMI) flow <3. If SB dilatation or stenting is required, the SB is rewired through a distal cell of the MV stent, followed by re-POT, kissing balloon inflation (KBI) and final POT using non-compliant balloons, with a suggested inflation pressure of >18 atm. The bailout strategy in the provisional group was left at operator's discretion and showed in Supplementary material online, *Figure S1*.

In the two-stent group, use of the DK crush or culotte stenting techniques was strongly recommended; other two-stent approaches (traditional T or TAP, classical crush or mini-crush, and kissing stenting) were discouraged. Details of the DK crush stenting technique have been described elsewhere.[8] In brief, the SB is stented with short (~2 mm) protrusion into the MV, followed by complete balloon crush, the first KBI,

MV stenting with post-dilation and POT, final KBI, and final POT. During the DK crush procedure, the SB stent is rewired (always from a proximal cell) twice. Alternating SB and MV inflations before each KBI are performed using a non-compliant balloon at ≥16 atm. The culotte stenting technique has been previously described in detail;[8] similar to provisional stenting, rewiring is also performed (always from the distal cell of the stent) twice, followed by alternative inflations, final KBI, and POT.

A stent with the stent/artery ratio of 1.1:1 implanted in the MV and SB was recommended in the two-stent group(s). Stents for all implanted lesions are listed in the Supplementary material online, *Appendix*. Stent selection was left at the operator's discretion, as was the use of intravascular ultrasound (IVUS). Complete revascularization for non-bifurcation lesions was encouraged, and it was left at operator's discretion.
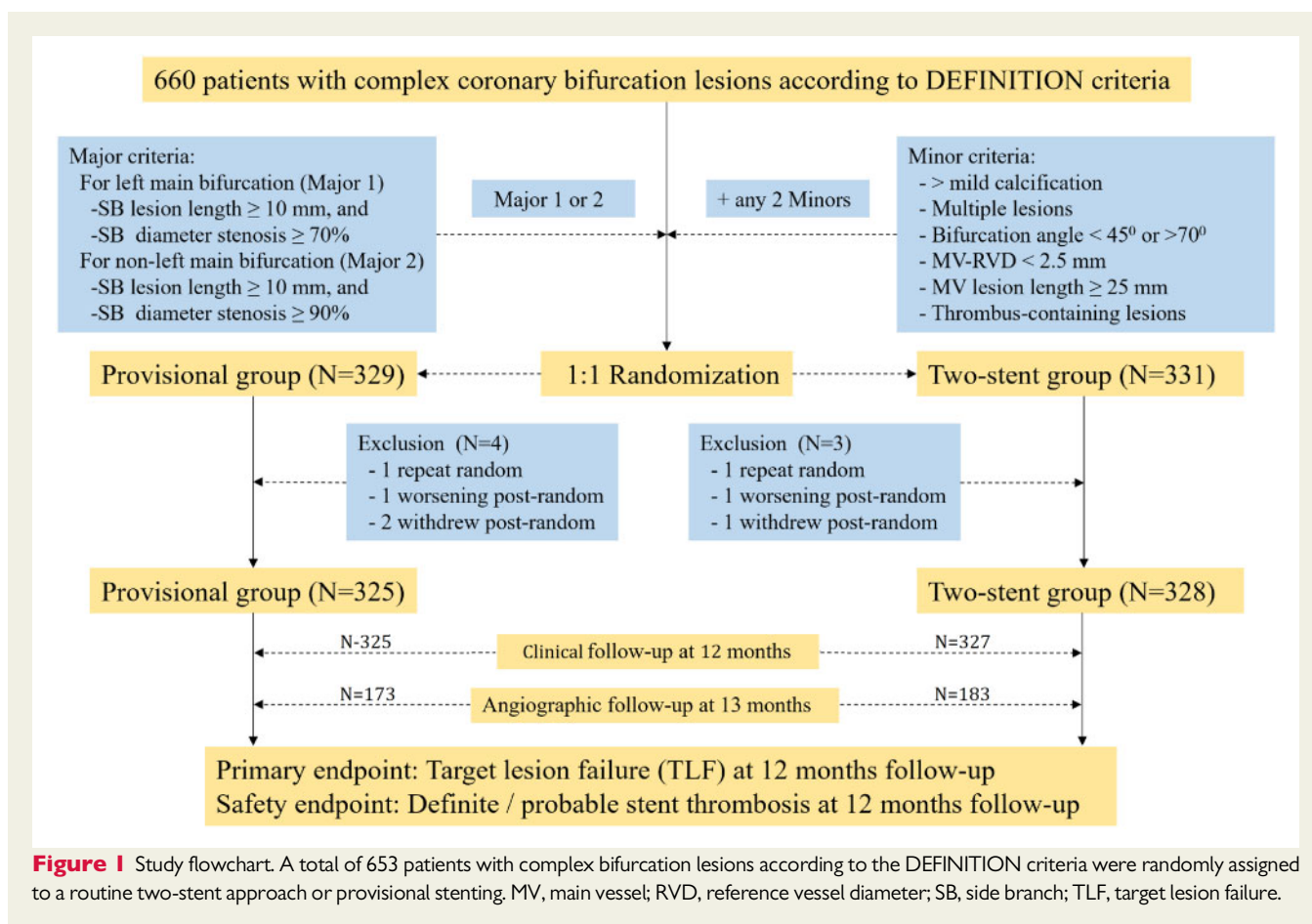
Follow-up

Clinical follow-up was performed through office visits or telephone interviews at 1, 6, and 12 months. Follow-up coronary angiography was scheduled at 13 months (after ascertainment of the primary clinical endpoint), unless performed earlier for clinical indications. Procedural and clinical data were entered into electronic case report forms, verified by independent on-site monitoring, and transmitted to a central database at Nanjing Medical University. Quantitative coronary analysis (QCA) was analysed at a central core laboratory using Cardiovascular Angiographic Analysis System (CAAS) II software (Pie Medical Imaging, the Netherlands), as previously described.[7–9] Restenosis was defined as a QCA DS >50% at follow-up.

Endpoints and definitions

The primary endpoint was target lesion failure (TLF) at 1 year, defined as the composite of cardiac death, target vessel MI (TVMI), or clinically driven target lesion revascularization (TLR). Death from cardiac causes was defined as any death without a clear non-cardiac cause. Protocol-defined peri-procedural MI (within 48 h) was defined as a CK-MB >10× the upper reference limit (URL) of the assay, or >5× URL plus either: (i) new pathological Q waves in ≥2 contiguous leads or new left bundle branch abnormality; (ii) angiographically documented graft or coronary artery occlusion or new severe stenosis with thrombosis; (iii) imaging evidence of new loss of viable myocardium; or (iv) new regional wall motion abnormality. Spontaneous MI (after 48 h) was defined as a clinical syndrome consistent with MI with a CK-MB or troponin >1× URL and new ST-segment elevation or depression or other findings as above. All MIs were considered TVMI unless there was clear evidence that they were attributable to a non-target vessel.[13] Clinically driven TLR was defined as angina or ischaemia (confirmed by symptoms, exercised EKG or nuclear medicine or coronary physiological assessment) referable to the target lesion requiring repeat PCI or coronary artery bypass graft.[14] Secondary endpoints included cardiac death, TVMI, clinically driven TLR, and all-cause death. Definite or probable ST according to the Academic Research Consortium[14] was the major safety endpoint. All events were adjudicated by a central committee using original source documents blinded to treatment. Procedural success in the MV was defined as residual stenosis <20%, TIMI grade flow 3, and no SB closure; it was defined as TIMI grade flow 3 for the SBs.

Statistical analysis

All analyses were performed in the intention-to-treat population, defined as all patients randomized, regardless of the treatment actually received (*Figure 1*). The primary analysis was the time from randomization to the first occurrence of any TLF event. Based on our previous studies, we hypothesized that the 1-year TLF rate would be 14% in the provisional group and 7% in the two-stent (please see the change in the modified

Figure 1 Study flowchart. A total of 653 patients with complex bifurcation lesions according to the DEFINITION criteria were randomly assigned to a routine two-stent approach or provisional stenting. MV, main vessel; RVD, reference vessel diameter; SB, side branch; TLF, target lesion failure.

version of protocol[12]) group.[7–9,11] Accordingly, a total sample size of 600 patients was needed for 80% power with a two-sided alpha of 0.05. A total of 660 patients (330 in each group) were planned for enrolment to conservatively account for 10% possible loss to follow-up.

Baseline characteristics are reported as counts and percentages or mean ± standard deviation. The χ^2 or Fisher's exact test was used to compare categorical variables. Student's *t*-test or Wilcoxon rank sum scores for non-normally distributed data were used to compare continuous variables. Time-to-first event curves were generated using the 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 hazard ratio (HR), 95% confidence interval (CI), and *P*-value. Potential interactions between the following subgroups and randomized treatment were examined for the primary outcome measure: age, sex, diabetes mellitus, hyperlipidaemia, hypertension, current smoking, acute coronary syndrome, cardiac dysfunction, renal insufficiency, and IVUS guidance vs. angiography guidance. All statistical tests were two-sided, and a *P*-value of <0.05 was considered statistically significant. All analyses were performed with SPSS version 24.0 (SPSS Institute Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics

We analysed 653 patients with complex bifurcation lesions between 23 December 2015 and 7 November 2018 (*Figure 1* and Supplementary material online, *Table S1*). Baseline clinical characteristics were well matched between the groups (*Table 1*). Diabetes and unstable angina were present in 35% and 50% of the patients, respectively. Moreover, 22% of the patients had an acute myocardial infarction (AMI) older than 24 h.

Lesion characteristics and procedures

Multivessel disease present in 60% of the patients, and the mean SYNTAX score was 24.5 (*Table 2*), with multivessel disease present in 60% of the patients. A total of 28.8% of the lesions localized in the distal LM.

The transradial approach was predominantly used (*Table 3*). In the provisional group, pre-dilation was used in 46.2% of SB lesions, mostly in response to severe SB compromise after MV pre-dilation. During provisional stenting, 28 (8.6%) SBs were occluded at some point, among which blood flow was restored in 25 SBs while 3 (10.7%) SBs remained permanently occluded (Supplementary material online, *Figure S1*). A total of 73 (22.5%) patients in the provisional group required an SB stent. In the two-stent group, SB stenting was not performed in 26 (7.9%) patients because of either SB diameter <2.5 mm by IVUS (*n* = 8), failure to wire the SB (*n* = 4), failure to advance a stent to the SB (*n* = 10), or MV pre-dilation resulting in TIMI flow <3 in the MV requiring urgent MV stenting (*n* = 4). DK crush was performed in 235 (77.8%) patients in the two-stent group, with Culotte stenting used in 54 (17.9%)

Table 1 Baseline clinical characteristics

	Two-stent group (N = 328)	Provisional group (N = 325)	P-value
Demographics			
Age (years)	63 ± 11	64 ± 10	0.289
Male sex	255 (77.7)	250 (76.9)	0.802
Physical measurements			
Height (cm)	166.88 ± 7.20	167.26 ± 7.49	0.506
Weight (kg)	69.13 ± 10.65	69.25 ± 10.76	0.887
Body mass index (kg/m^2)	24.77 ± 3.10	24.69 ± 3.10	0.753
Systolic blood pressure (mmHg)	136 ± 20	134 ± 18	0.251
Diastolic blood pressure (mmHg)	79 ± 11	79 ± 11	0.840
Mean arterial pressure (mmHg)	98 ± 12	97 ± 12	0.465
Heart rate (b.p.m.)	73 ± 10	73 ± 11	0.851
Risk factors			
Dyslipidaemia	227 (69.2)	223 (68.6)	0.870
Statin treatment	102 (44.9)	104 (46.6)	0.717
Hypertension	215 (66.2)	230 (70.1)	0.277
Current smoking	93 (28.4)	98 (30.2)	0.613
Diabetes	112 (34.1)	116 (35.7)	0.679
Diet treatment alone	3 (2.7)	8 (6.9)	0.137
Oral medications	67 (59.8)	68 (58.6)	0.854
Insulin	29 (25.9)	31 (26.7)	0.887
No treatment	13 (11.6)	9 (7.8)	0.325
Medical history			
Gastrointestinal bleeding	6 (1.8)	7 (2.2)	0.767
Nervous system disease	30 (9.1)	41 (12.6)	0.154
Peripheral artery stenosis	19 (5.8)	15 (4.6)	0.498
eGFR <60 mL/min/1.73 m^2	59 (18.0)	48 (14.8)	0.267
History of CVD			
Previous myocardial infarction	39 (11.9)	42 (12.9)	0.700
Prior coronary artery bypass graft	0	2 (0.6)	0.247
Prior PCI	65 (19.8)	54 (16.6)	0.289
Congestive heart failure	28 (8.5)	39 (12.0)	0.145
LVEF (%)	59 ± 10	60 ± 10	0.686
LVEF <30%	5 (1.5)	5 (1.5)	1.000
Presentation at admission			
Silent ischaemia	17 (5.2)	17 (5.2)	0.978
Stable angina	79 (24.1)	71 (21.8)	0.496
Unstable angina	160 (48.8)	164 (50.5)	0.668
Acute myocardial infarction	72 (22.0)	73 (22.5)	0.875
Laboratory measurements			
Red blood cell count (×10^{12})	4.42 ± 0.61	4.48 ± 0.69	0.268
White blood cell count (×10^9)	6.96 ± 2.06	7.02 ± 2.19	0.740
Haemoglobin (×10^9)	132.88 ± 17.00	134.01 ± 16.33	0.400
Platelet count (g/L)	204.84 ± 57.86	210.33 ± 65.54	0.267
Total cholesterol level (mmol/L)	4.07 ± 1.16	4.07 ± 1.20	0.984
LDL level (mmol/L)	2.40 ± 0.89	2.40 ± 0.89	0.959
HDL level (mmol/L)	1.00 ± 0.24	1.02 ± 0.25	0.464
Triglyceride level (mmol/L)	1.71 ± 1.36	1.73 ± 1.39	0.865

Values are n (%) or mean ± SD.
CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 2 Lesions characteristics

	Two-stent group (*N* = 328)	Provisional group (*N* = 325)	*P*-value
SYNTAX score	24.72 ± 9.46	24.24 ± 9.92	0.522
≤22, *n* (%)	147 (44.8)	158 (48.6)	0.331
23–32, *n* (%)	111 (33.8)	106 (32.6)	0.739
>32, *n* (%)	70 (21.3)	61 (18.8)	0.412
SYNTAX score II			
Percutaneous coronary intervention, scores	30.38 ± 9.21	30.21 ± 9.45	0.812
Coronary artery bypass graft, scores	24.99 ± 10.42	25.18 ± 9.16	0.809
Recommendation			0.743
Percutaneous coronary intervention, *n* (%)	6 (1.8)	4 (1.2)	
Coronary artery bypass graft, *n* (%)	89 (27.1)	84 (25.8)	
Either, *n* (%)	233 (71.0)	237 (72.9)	
NERS score II	11.07 ± 6.37	10.99 ± 6.21	0.860
Right coronary artery dominance, *n* (%)	271 (82.6)	264 (81.2)	0.644
Lesion length by QCA (mm)			
MV	40.97±13.23	42.15±15.43	0.306
SB	20.71±10.10	19.88±9.30	0.287
Multivessel disease, *n* (%)	194 (59.1)	199 (61.2)	0.586
Locations of bifurcation lesions, *n* (%)			0.552
Left anterior descending-diagonal	205 (62.5)	197 (60.6)	
Left circumflex-obtuse marginal	17 (5.2)	25 (7.7)	
Distal left main	94 (28.7)	94 (28.9)	
Distal right coronary artery	12 (3.7)	9 (2.8)	
Trifurcation lesions, *n* (%)	31 (9.5)	22 (6.8)	0.214
Complex bifurcation lesion, *n* (%)			
On-site assessment	328 (100.0)	325 (100.0)	1.000
Assessed by core lab	299 (91.2)	306 (94.2)	0.143
Complex bifurcations by core lab, *n* (%)			
Medina 1, 1, 1 bifurcation	283 (86.3)	268 (82.5)	0.179
Medina 0, 1, 1 bifurcation	41 (12.5)	47 (14.5)	0.463
SB reference vessel diameter ≥2.5 mm	313 (95.4)	317 (97.5)	0.143
SB diameter stenosis ≥70% or 90%	315 (96.0)	303 (93.2)	0.111
SB lesion length ≥10 mm	308 (93.9)	308 (94.8)	0.632
Moderate-to-severe calcification	127 (38.7)	131 (40.3)	0.678
Multiple lesions	278 (84.8)	275 (84.6)	0.960
Bifurcation angle <45° or >70°	213 (64.9)	218 (67.1)	0.564
MV reference vessel diameter <2.5 mm	16 (4.9)	13 (4.0)	0.586
Thrombus-containing lesions[a]	12 (3.7)	12 (3.7)	0.982
MV lesion length ≥25 mm	239 (72.9)	224 (68.9)	0.267
MV, *n* (%)			
TIMI flow grade <3	69 (21.0)	63 (19.4)	0.599
Chronic total occlusion	15 (4.6)	16 (4.9)	0.833
Thrombus-containing lesions	11 (3.4)	12 (3.7)	0.814
Moderate-to-severe calcification	127 (38.7)	128 (39.4)	0.862
SB, *n* (%)			
TIMI flow grade <3	44 (13.4)	31 (9.5)	0.120
Chronic total occlusion	5 (1.5)	4 (1.2)	1.000
Thrombus-containing lesions[a]	3 (0.9)	2 (0.6)	1.000
Moderate-to-severe calcification	58 (17.7)	59 (18.2)	0.875

[a]For patients with MI >24 h, all patients had a CK-MB value within normal range.
CK-MB, •••; MI, myocardial infarction; MV, main vessel; QCA, quantitative coronary analysis; SB, side branch; TIMI, Thrombolysis in Myocardial Infarction.

Table 3 Procedural characteristics

	Two-stent group (*N* = 328)	Provisional group (*N* = 325)	*P*-value
Transradial approach, *n* (%)	258 (78.7)	262 (80.6)	0.535
Use of GP IIb/IIIa inhibitor, *n* (%)	60 (18.3)	48 (14.8)	0.226
Main vessel pretreatment, *n* (%)	294 (89.6)	283 (87.1)	0.308
Thrombus aspiration	1 (0.3)	1 (0.3)	1.000
Rotational atherectomy	9 (2.7)	7 (2.2)	0.626
Cutting balloon pretreatment	16 (4.9)	11 (3.4)	0.338
Side branch pretreatment, *n* (%)	274 (83.5)	150 (46.2)	<0.001
Thrombus aspiration	1 (0.3)	0	1.000
Rotational atherectomy	1 (0.3)	0	1.000
Cutting balloon pretreatment	12 (3.7)	6 (1.8)	0.157
Main vessel stent	328 (100.00)	325 (100.00)	1.000
Stent number, *n*	1.75 ± 0.70	1.73 ± 0.67	0.698
Stent diameter (mm)	3.05 ± 0.32	3.02 ± 0.32	0.215
Stent length (mm)	46.29 ± 19.33	46.54 ± 19.65	0.871
Post-dilation, *n* (%)	315 (96.0)	312 (96.0)	1.000
Balloon diameter (mm)	3.35 ± 0.51	3.42 ± 0.54	0.092
Balloon length (mm)	12.32 ± 2.52	12.47 ± 3.01	0.486
Dilation pressure (atm)	17 ± 4	18 ± 4	0.071
Side branch stent	302 (92.1)	73 (22.5)	<0.001
Stent number, *n*	1.04 ± 0.46	0.27 ± 0.53	<0.001
Stent diameter (mm)	2.64 ± 0.30	2.76 ± 0.38	0.014
Stent length (mm)	25.62 ± 11.34	26.45 ± 12.28	0.580
Post-dilation, *n* (%)	274 (90.7)	56 (75.7)	<0.001
Balloon diameter (mm)	2.74 ± 0.37	2.86 ± 0.41	0.048
Balloon length (mm)	13.28 ± 2.75	14.38 ± 4.54	0.087
Dilation pressure (atm)	16 ± 4	16 ± 4	0.849
Technical sequences, *n* (%)			
Pre-dilation	304 (92.7)	293 (90.2)	0.266
Main vessel	293 (89.3)	280 (86.2)	0.216
Side branch	274 (83.5)	150 (46.2)	<0.001
First stent implantation[a]			
Main vessel	10 (3.3)	299 (92.0)	<0.001
First POT	10 (100.0)	296 (99.0)	1.000
Side branch dilation	10 (100.0)	83 (27.8)	<0.001
Kissing balloon inflation post-stent	10 (100.0)	83 (27.8)	<0.001
Second POT	9 (90.0)	80 (96.4)	0.402
Side branch	289 (88.1)	26 (8.0)[b]	<0.001
First POT for side branch stent	202 (69.9)	26 (100.0)	<0.001
Kissing balloon inflation	285 (98.6)	26 (100.0)	0.900
Second POT	54 (18.7)[c]	25 (96.1)	<0.001
Second stent implantation, *n* (%)[a]			
Main vessel	289 (88.1)	26 (8.0)	<0.001
Third POT	280 (96.9)	25 (96.2)	1.000
Side branch	10 (3.3)	47 (64.4)	<0.001
Techniques of two-stent	302 (92.1)	73 (22.5)	<0.001
T and protrusion	10 (3.3)	47 (64.4)	<0.001
Culotte/reverse culotte	54 (17.9)	12 (16.4)	0.446
Double-kissing crush	235 (77.8)	14 (19.2)	<0.001
Others (SKS, V stenting)	3 (1.0)	0	NS
Final kissing balloon inflation	287 (99.3)	70 (95.9)	0.392
Final POT	255 (88.9)	64 (91.4)	0.417

Continued

Table 3 *Continued*

	Two-stent group (N = 328)	Provisional group (N = 325)	*P*-value
Balloons for final kissing balloon inflation			
Main vessel			
Balloon diameter (mm)	3.24 ± 0.44	3.27 ± 0.40	0.529
Balloon length (mm)	13.07 ± 2.50	13.35 ± 3.42	0.327
Dilation pressure (atm)	12 ± 3	12 ± 3	0.556
Side branch			
Balloon diameter (mm)	2.67 ± 0.36	2.50 ± 0.56	0.001
Balloon length (mm)	13.35 ± 2.44	14.84 ± 3.97	<0.001
Dilation pressure (atm)	12 ± 3	11 ± 3	0.021
Balloons for final POT			
Balloon diameter (mm)	3.71 ± 0.52	3.91 ± 0.59	0.003
Balloon length (mm)	10.86 ± 2.66	10.54 ± 2.78	0.350
Dilation pressure (atm)	18 ± 4	18 ± 3	0.824
Staged PCI, *n* (%)	86 (26.2)	75 (23.1)	0.352
Intravascular ultrasound guidance, *n* (%)	80 (24.4)	101 (31.1)	0.056
Angiographic success, *n* (%)	306 (93.3)	304 (93.5)	0.899
Complete revascularization, *n* (%)	252 (76.8)	233 (71.7)	0.133
Intra-procedural complications, *n* (%)	22 (6.7)	30 (9.2)	0.234
Slow flow	2 (0.6)	6 (1.8)	0.175
Main vessel	2 (0.6)	3 (0.9)	0.685
Side branch	1 (0.3)	3 (0.9)	0.372
Type B/dissection	12 (3.6)	18 (5.5)	0.402
Main vessel	4 (1.2)	1 (0.3)	0.373
Side branch	8 (2.4)	17 (5.2)	0.069
Abrupt closure	3 (0.9)	6 (1.8)	0.338
Main vessel	2 (0.6)	0	0.499
Side branch	1 (0.3)	3 (0.9)	1.000
Perforation	2 (0.6)	0	0.499
Main vessel	1 (0.3)	0	1.000
Side branch	1 (0.3)	0	1.000
Thrombus formation	5 (1.5)	4 (1.2)	1.000
Main vessel	3 (0.9)	3 (0.9)	1.000
Side branch	2 (0.6)	1 (0.3)	1.000
Procedural success, *n* (%)			
Main vessel	323 (98.5)	321 (98.8)	1.000
Side branch	324 (98.8)	319 (98.2)	0.357
Resource utilization, *n*			
Number of guiding catheters used	1.13 ± 0.41	1.15 ± 0.48	0.634
Number of guidewires used	2.93 ± 1.19	2.93 ± 1.37	0.995
Number of balloons used	4.86 ± 1.89	3.89 ± 1.91	<0.001
Procedural time (min)	83.70 ± 42.33	71.74 ± 38.71	<0.001
Contrast volume (mL)	223 ± 86	211 ± 90	0.085

GP IIb/IIIa, glycoprotein IIb/IIIa; PCI, percutaneous coronary intervention; POT, proximal optimization technique; SKS, simultaneous kissing stenting.
[a]SKS and V stenting (*n* = 3) were not included.
[b]The inclusion of nine reverse culotte stenting.
[c]The rate of second POT after culotte stenting in the two-stent group.

and other two-stent techniques used in 13 (4.3%). Final KBI was more frequently used in the two-stent group than in the provisional group, although POT after final KBI was equally performed in both groups. Intravascular ultrasound guidance was only used in 27.7% of the patients, without a significant difference between the groups. The two-stent strategy was associated with longer procedural times, with no significant difference in contrast volume compared with the provisional approach.
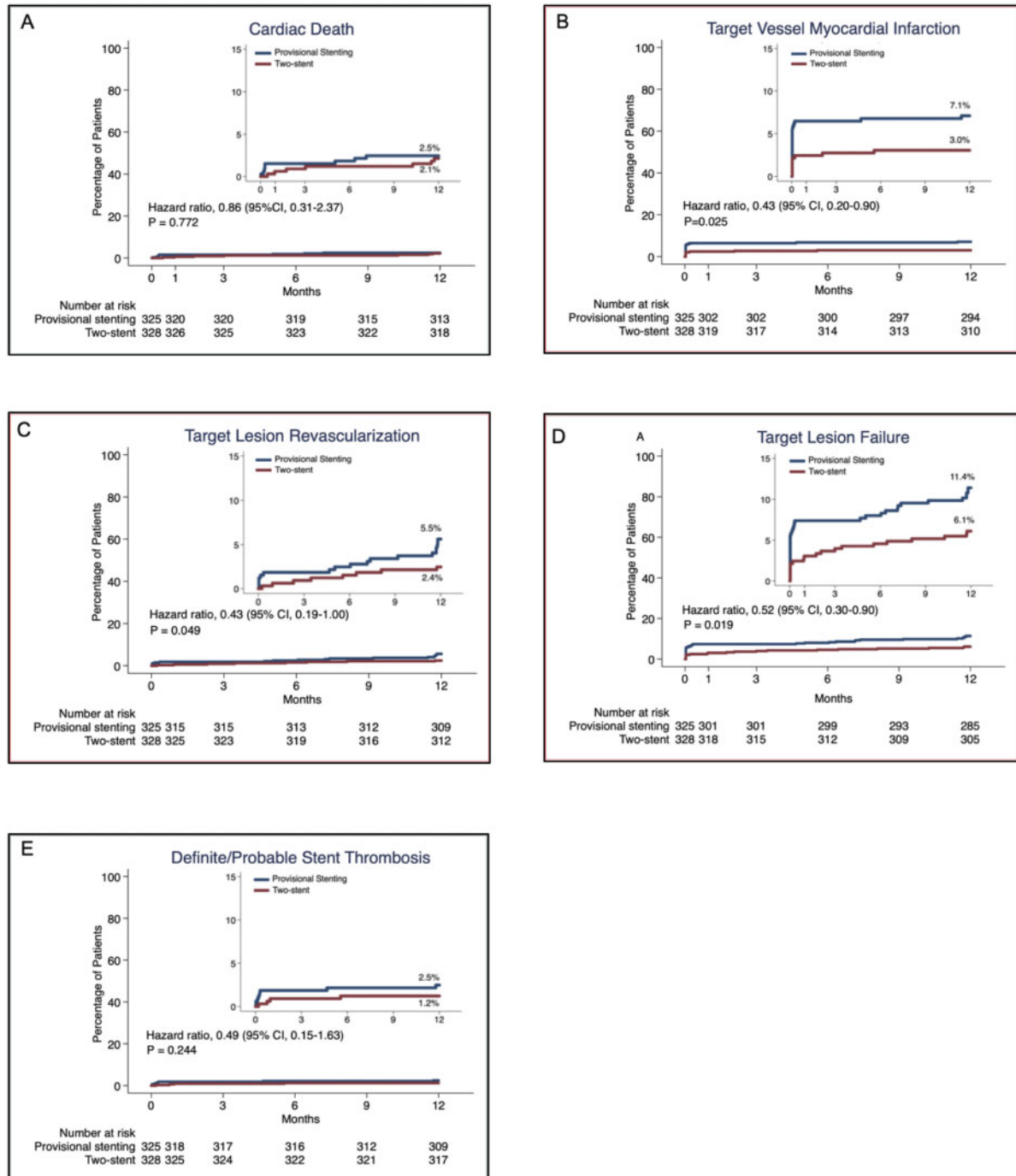
Figure 2 Kaplan–Meier survival curves. (*A*) Cardiac death; (*B*) target vessel myocardial infarction; (*C*) target lesion revascularization; and (*D*) target lesion failure (primary endpoint, target lesion failure). (*E*) definite/probable stent thrombosis. CI, confidence interval.

Clinical outcomes

One-year clinical follow-up was completed in all but one patient (in the two-stent group). At 30 days, the rates of TLF and peri-procedural MI were lower in the two-stent group compared with the provisional group (*Table 4*). The primary endpoint of TLF at 1 year occurred in 37 (11.4%) patients in the provisional group and 20 (6.1%) patients in the two-stent group (HR 0.52, 95% CI 0.30–0.90;

$P = 0.019$) (*Table 4* and *Figure 2*). This difference was driven by lower 1-year rates of TVMI (HR 0.43, 95% CI 0.20–0.90; $P = 0.025$) and clinically driven TLR (HR 0.43, 95% CI 0.19–1.00; $P = 0.049$) with the two-stent approach, without significant between-group differences in cardiac death. Nor were there differences in all-cause death or ST between the two strategies. A detailed description of the STs is shown in Supplementary material online, *Table S2*. The finding of
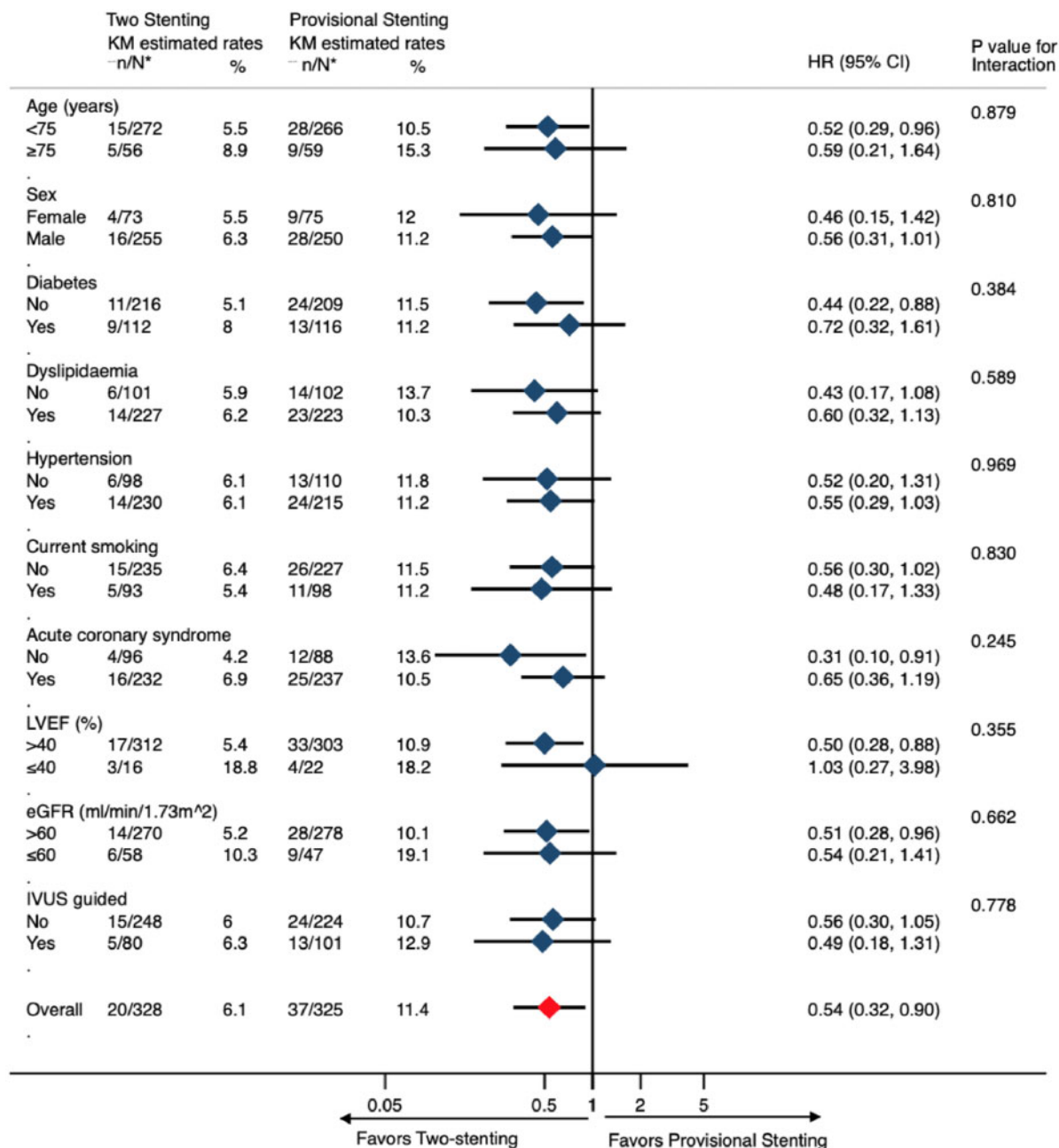
	Two Stenting KM estimated rates		Provisional Stenting KM estimated rates		HR (95% CI)	P value for Interaction
	⁻n/N*	%	⁻ n/N*	%		
Age (years)						0.879
<75	15/272	5.5	28/266	10.5	0.52 (0.29, 0.96)	
≥75	5/56	8.9	9/59	15.3	0.59 (0.21, 1.64)	
Sex						0.810
Female	4/73	5.5	9/75	12	0.46 (0.15, 1.42)	
Male	16/255	6.3	28/250	11.2	0.56 (0.31, 1.01)	
Diabetes						0.384
No	11/216	5.1	24/209	11.5	0.44 (0.22, 0.88)	
Yes	9/112	8	13/116	11.2	0.72 (0.32, 1.61)	
Dyslipidaemia						0.589
No	6/101	5.9	14/102	13.7	0.43 (0.17, 1.08)	
Yes	14/227	6.2	23/223	10.3	0.60 (0.32, 1.13)	
Hypertension						0.969
No	6/98	6.1	13/110	11.8	0.52 (0.20, 1.31)	
Yes	14/230	6.1	24/215	11.2	0.55 (0.29, 1.03)	
Current smoking						0.830
No	15/235	6.4	26/227	11.5	0.56 (0.30, 1.02)	
Yes	5/93	5.4	11/98	11.2	0.48 (0.17, 1.33)	
Acute coronary syndrome						0.245
No	4/96	4.2	12/88	13.6	0.31 (0.10, 0.91)	
Yes	16/232	6.9	25/237	10.5	0.65 (0.36, 1.19)	
LVEF (%)						0.355
>40	17/312	5.4	33/303	10.9	0.50 (0.28, 0.88)	
≤40	3/16	18.8	4/22	18.2	1.03 (0.27, 3.98)	
eGFR (ml/min/1.73m^2)						0.662
>60	14/270	5.2	28/278	10.1	0.51 (0.28, 0.96)	
≤60	6/58	10.3	9/47	19.1	0.54 (0.21, 1.41)	
IVUS guided						0.778
No	15/248	6	24/224	10.7	0.56 (0.30, 1.05)	
Yes	5/80	6.3	13/101	12.9	0.49 (0.18, 1.31)	
Overall	20/328	6.1	37/325	11.4	0.54 (0.32, 0.90)	

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        0.05          0.5   1   2     5
   <------------------------------------>
     Favors Two-stenting    Favors Provisional Stenting
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Figure 3 Subgroup analysis for the primary 1-year endpoint of target lesion failure. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction.

reduced 1-year TLF with the two-stent strategy was consistent in all examined subgroups (*Figure 3*).

Quantitative coronary analysis

Angiographic follow-up was completed in 173 patients (53.2%) at 382 ± 80 days in the provisional group and in 183 patients (55.8%) at 376 ± 102 days in the two-stent group (*P* = 0.511 and *P* = 0.537, respectively) (Supplementary material online, *Table S3*).

Discussion

The present multicentre randomized trial is the first to investigate clinical outcomes after a routine two-stent approach (mostly DK crush) compared with a provisional stenting approach for the treatment of complex bifurcation lesions according to the DEFINITION criteria. The major finding as shown in the *Take home figure* is that a planned two-stent strategy significantly reduced the incidence of 1-
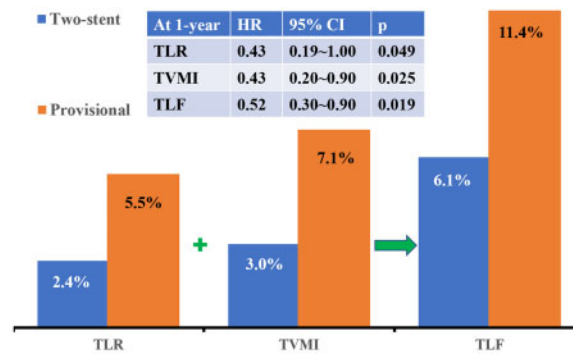
Take home figure For patients with complex bifurcation lesions defined by the DEFINITION criteria, systematic two-stent approaches were associated with a significant reduction of target lesion failure, compared with provisional stenting strategies. CI, confidence interval; HR, hazard ratio; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction.

Table 4 Clinical outcomes at the 1-year follow-up

	Two-stent group (n = 328)	Provisional group (n = 325)	HR (95% CI)	P-value
At 30 days				
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
Peri-procedural	7 (2.1)	19 (5.8)	0.37 (0.15–0.87)	0.022
Q-wave MI	1 (0.3)	2 (0.6)	0.47 (0.04–5.24)	0.544
Spontaneous	1 (0.3)	2 (0.6)	0.48 (0.04–5.25)	0.544
Clinically driven TLR	2 (0.6)	6 (1.8)	0.33 (0.07–1.62)	0.171
Stent thrombosis				
Definite	2 (0.6)	2 (0.6)	0.98 (0.14–6.98)	0.986
Probable	1 (0.3)	4 (1.2)	0.24 (0.03–2.19)	0.208
At 1 year				
Target lesion failure	20 (6.1)	37 (11.4)	0.52 (0.30–0.90)	0.019
Cardiac death	7 (2.1)	8 (2.5)	0.86 (0.31–2.37)	0.772
Target vessel MI	10 (3.0)	23 (7.1)	0.43 (0.20–0.90)	0.025
Q-wave MI	1 (0.3)	5 (1.5)	0.20 (0.02–1.67)	0.173
Clinically driven TLR	8 (2.4)	18 (5.5)	0.43 (0.19–1.00)	0.049
Stent thrombosis				
Definite	3 (0.9)	3 (0.9)	0.98 (0.20–4.86)	0.982
Probable	1 (0.3)	5 (1.5)	0.20 (0.02–1.68)	0.137
All-cause death	9 (2.7)	11 (3.4)	0.81 (0.33–1.94)	0.629

Values are n (%).
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TLR, target lesion revascularization.

year TLF compared with provisional stenting, driven by fewer TVMIs and clinically driven TLRs.

Coronary bifurcation lesions are diverse with wide variation in the bifurcation angles and vessel diameters of the MV and SB. The philosophy of 'making complex matters simple' has been supported by several clinical trials demonstrating that provisional stenting is associated with improved clinical outcomes compared with a routine two-stent approach.[2–4] Whether these findings apply to all two-stent techniques, especially in the treatment of truly complex bifurcation

lesions is controversial. In the DKCRUSH trials, the DK crush routine two-stent technique has consistently reduced the 1-year and later rates of adverse clinical events compared with provisional stenting in true coronary bifurcation lesions (Medina 1, 1, 1 or Medina 0, 1, 1).[7–9] In general, patients enrolled in the DKCRUSH trials had longer lesions and/or more severe disease in the SB compared with other studies.[2–9] As a result, the most recent guidelines[10] have emphasized the impact of the complexity of the bifurcation on clinical outcomes and recommended that the two-stent technique may be preferable

when the SB lesion length is >5 mm, the SB diameter is ≥2.75 mm, and/or the difficulty is anticipated in accessing the SB after MV stenting. Notwithstanding the NERS[15] and SYNTAX scores,[16] there is no general agreement as to what constitutes a complex bifurcation lesion. The DEFINITION study for the first time reported improvement in clinical results in 1550 patients with DEFINITION criteria-defined complex bifurcations with a routine two-stent technique, a finding that was validated in a subsequent large (*n* = 3660) group of paitents.[11] We thus prospectively utilized the definition criteria in the present trial and confirmed that indeed a routine two-stent technique strategy is superior to provisional stenting in complex coronary bifurcation lesions so defined. Of note, however, the present trial did not include more simple 'true' bifurcation lesions not meeting DEFINITION criteria, or bifurcation lesions without significant SB involvement. For many of these lesions, a provisional stenting approach may be appropriate.

In prior randomized trials, most planned two-stent techniques were inferior to provisional stenting in bifurcation lesions primarily because of greater peri-procedural myonecrosis, increased rates of repeat revascularization, and higher rates of ST with multiple stents.[2–5] In contrast, the DKCRUSH II trial first reported a reduced TLR rate by DK crush stenting in true bifurcation lesion (Medina 1, 1, 1 or Medina 0, 1, 1) compared with provisional stenting.[7] In the DKCRUSH V trial, the difference in clinically driven TLR between DK crush and provisional stenting in true distal LM bifurcation lesions was not statistically significant at 1-year follow-up but became significant at the 3-year follow-up.[9] Subgroup analysis from this trial demonstrated greater benefits from DK crush treatment in DEFINITION criteria-defined complex bifurcation lesions.[9,17] In the present randomized trial, DK crush was used in 77.8% of patients in the two-stent group, suggesting that the benefits of the two-stent approach observed in the present study may largely have relied on DK crush stenting (although the number of patients treated with other two-stent techniques was not large enough to make meaningful comparisons). Nonetheless, the present study has again confirmed the reliability of the DEFINITION criteria for dictating a (DK crush recommended) two-stent approach in complex bifurcation lesions.

Similar to that observed in the DKCRUSH V trial,[9] the present trial also demonstrated lower rates of TVMI with a routine two-stent approach compared with provisional stenting, using a similar definition as that used in the EXCEL trial and the Society of Cardiac Angiography and Interventions (SCAI), which has been correlated with subsequent mortality.[18,19] Given the absence of a difference in ST, the mechanism(s) underlying with the higher rate of TVMI after provisional stenting remain unclear. The higher rate of restenosis within the SB may in part explain a late increase in TVMI. Recently, Gonzalo *et al.*[20] reported that plaques with thin-cap fibroatheromas are more likely to localize at the proximal rim of the SB ostium, consistent with previous findings.[21] Thus, suboptimal stent coverage of unstable plaque may promote late TVMI, a hypothesis requiring validation in future studies. Furthermore, lower and oscillatory shear stress caused by MV stenting[22] initialize plaque progression and increase lesion's vulnerability via inducing inflammation and endothelial injury.[23] Innovations in modifying the geometry of bifurcated vessels are warranted.

The reduction in 1-year cardiac death after two-stent techniques of complex lesions that was observed in the prior DEFINITION study[11] was not duplicated in the present DEFINITION II trial. Similarly, in the DKCRUSH V trial, the 3-year cardiac death rate was similar after DK crush and provisional stenting for distal LM bifurcation lesions.[7] However, none of these studies were powered for cardiac death, and any such findings must be considered exploratory. Meta-analysis and individual patient data pooled studies may have a role in examining this issue. Longer-term follow-up is also required to see if the difference in TVMI with the two-stent approach will translate into improved late survival.

Limitations

The present trial suffers some limitations. First, all enrolled lesions were true complex bifurcation lesions, with greater SB lesion length and severity than included in some previous bifurcation trials.[2–4,24–27] Our results demonstrating that improved outcomes with a routine two-stent approach (mainly DK crush stenting) thus cannot be applied to patients with less complex bifurcation lesions. Second, intravascular imaging was only used in one-fourth of patients, significantly less than that in DKCRUSH V.[9] Whether IVUS use in a higher proportion of patients in both groups would have affected the observed outcomes in the present study is unknown. Furthermore, the POT technique was used in <100% of lesions (slightly less in the two-stent group) after final KBI in both groups. POT can repair distortion and improve apposition of the MV stent after KBI and is thus strongly recommended whatever the two-stent techniques were selected.[2–9,28] Indeed, some PIs in this study worried about the POT-induced proximal dissection and validated against study protocol using two balloons kissed in the MV to replace 'real' POT. This suggested the importance of training and continuous education by larger leading platforms. Finally, SB abrupt closure was seen in 28 (8.6%) patients in the provisional group. More recently, modified SB protections were introduced, such as jailed balloon or Corsair techniques,[29] which was not recommended by the present trial. Jailed balloon approach has the power to easily rescue the occluded SB.[30] Technically, after removing the jailed balloon (keeping its wire in the place, transferring to traditional provision stenting), a post-dilation is required to fully expand the MV stent. Thereafter, the risk of SB re-occlusion could be attenuated much more. Nevertheless, further study was warranted to compare the advantage of jailed balloon over jailed wire approach, particularly while early MI patients were included.

Conclusions

In the present large-scale multicentre randomized trial, a planned routine two-stent strategy reduced TLF at 1 year compared with a provisional strategy in patients with DEFINITION criteria-defined complex bifurcation lesions.

Supplementary material

Acknowledgements

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