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ORIGINAL INVESTIGATIONS

Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions

DKCRUSH-V Randomized Trial

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ABSTRACT

BACKGROUND Provisional stenting (PS) is the most common technique used to treat distal left main (LM) bifurcation lesions in patients with unprotected LM coronary artery disease undergoing percutaneous coronary intervention. The double kissing (DK) crush planned 2-stent technique has been shown to improve clinical outcomes in non-LM bifurcations compared with PS, and in LM bifurcations compared with culotte stenting, but has never been compared with PS in LM bifurcation lesions.

OBJECTIVES The authors sought to determine whether a planned DK crush 2-stent technique is superior to PS for patients with true distal LM bifurcation lesions.

METHODS The authors randomized 482 patients from 26 centers in 5 countries with true distal LM bifurcation lesions (Medina 1,1,1 or 0,1,1) to PS (n = 242) or DK crush stenting (n = 240). The primary endpoint was the 1-year composite rate of target lesion failure (TLF): cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization. Routine 13-month angiographic follow-up was scheduled after ascertainment of the primary endpoint.

RESULTS TLF within 1 year occurred in 26 patients (10.7%) assigned to PS, and in 12 patients (5.0%) assigned to DK crush (hazard ratio: 0.42; 95% confidence interval: 0.21 to 0.85; p = 0.02). Compared with PS, DK crush also resulted in lower rates of target vessel myocardial infarction I (2.9% vs. 0.4%; p = 0.03) and definite or probable stent thrombosis (3.3% vs. 0.4%; p = 0.02). Clinically driven target lesion revascularization (7.9% vs. 3.8%; p = 0.06) and angiographic restenosis within the LM complex (14.6% vs. 7.1%; p = 0.10) also tended to be less frequent with DK crush compared with PS. There was no significant difference in cardiac death between the groups.

CONCLUSIONS In the present multicenter randomized trial, percutaneous coronary intervention of true distal LM bifurcation lesions using a planned DK crush 2-stent strategy resulted in a lower rate of TLF at 1 year than a PS strategy. (Double Kissing and Double Crush Versus Provisional T Stenting Technique for the Treatment of Unprotected Distal Left Main True Bifurcation Lesions: A Randomized, International, Multi-Center Clinical Trial [DKCRUSH-V]; ChiCTR-TRC-11001213) (J Am Coll Cardiol 2017;70:2605–17) © 2017 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery

DES = drug-eluting stent(s)

DK = double kissing

DS = diameter stenosis

FFR = fractional flow reserve

ISR = in-stent restenosis

IVUS = intravascular ultrasound

KBI = kissing balloon inflation

LAD = left anterior descending coronary artery

LCx = left circumflex coronary artery

MI = myocardial infarction

MV = main vessel

PCI = percutaneous coronary intervention

POT = proximal optimization technique

PS = provisional stenting

QCA = quantitative coronary analysis

SB = side branch

ST = stent thrombosis

TLF = target lesion failure

TLR = target lesion revascularization

TVMI = target vessel myocardial infarction

ULMCAD = unprotected left main coronary artery disease

URL = upper reference limit

Patients with unprotected left main coronary artery disease (ULMCAD) are at high risk because of the large amount of jeopardized myocardium (1). In randomized trials, coronary artery bypass graft (CABG) surgery has been demonstrated to be more effective than percutaneous coronary intervention (PCI) with bare-metal or first-generation drug-eluting stents (DES) for treatment of ULMCAD, principally by reducing target lesion revascularization (TLR) (2–4). As a result, the 2014 U.S. guidelines favored CABG for most patients with ULMCAD (5). Registry studies (6,7) have reported that PCI with first-generation DES are effective for ostial and mid-shaft lesions of the LMCA, with clinical outcomes comparable to CABG. However, most patients with ULMCAD have involvement of the distal left main (LM) bifurcation, which is associated with inferior outcomes after PCI compared with isolated ostial/shaft treatment (6,7). In the recent EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, in which 1,905 patients with ULMCAD and low or intermediate SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores were randomized to PCI with second-generation everolimus-eluting stents versus CABG, ~80% of patients had disease of the distal LM bifurcation, most commonly treated with a provisional stenting (PS) approach (8). Although PCI provided comparable 3-year composite rates of death, myocardial infarction (MI), or stroke compared with CABG, repeat revascularization rates after 30 days were higher with PCI. In the recent NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trial, ~80% of patients also had distal LM involvement, again most often treated with PS. In the NOBLE trial, PCI with an earlier generation DES resulted in a higher composite rate of death, MI, stroke, or repeat revascularization at 5 years than CABG (9). Whether alternative approaches to the distal LM bifurcation might afford superior results is unknown.

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The PS approach to true bifurcation lesions consists of a DES to the main branch and balloon angioplasty of the side branch (SB), with stenting of the SB (usually with a T technique) reserved for a suboptimal balloon result. PS has been shown to be superior to a planned 2-stent approach in most randomized trials of non-LM bifurcation lesions (10–13). However, PS may require crossover to a second stent in more than one-third of cases (10–14), with failure to deliver the second stent in ~9% (15). PS may also result in higher rates of clinical recurrence compared to a 2-stent approach when treating complex coronary bifurcations (14,16). In prior multicenter randomized trials, the double kissing (DK) crush planned 2-stent technique resulted in lower rates of TLR compared with PS in non-LM coronary bifurcation lesions (14), and lower rates of target vessel revascularization), stent thrombosis (ST), and composite major adverse cardiac events compared with culotte stenting in

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distal LM bifurcation lesions (17,18). No trial, however, has directly compared DK crush to PS in ULMCAD bifurcation lesions. We therefore performed a large-scale, prospective, randomized, international, multicenter trial to evaluate the comparative outcomes of DK crush and PS in patients with true distal LM bifurcation lesions undergoing PCI.

METHODS

STUDY DESIGN. The design of the DKCRUSH-V trial (Double Kissing and Double Crush Versus Provisional T Stenting Technique for the Treatment of Unprotected Distal Left Main True Bifurcation Lesions: A Randomized, International, Multi-Center Clinical Trial) has been previously described (19). The study organization, participating sites, and investigators are listed in the Online Appendix. The protocol was designed by the steering committee and approved by the ethics committee at each participating center. The trial was funded by grants from the National Science Foundation of China (NSFC 91639303 and NSFC 81770441), and jointly supported by Nanjing Municipal Medical Development Project, Microport (Shanghai, China), Abbott Vascular (Santa Clara, CA, US), and Medtronic (Santa Rosa, California). The funding sources did not participate in the design or conduct of the study, analysis, or interpretation of the data, or the decision to submit the manuscript for publication. The authors had access to the complete database, vouch for the accuracy and integrity of the data and all analyses, prepared the manuscript, and controlled the decision to publish. The study is registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-11001213).

PATIENT POPULATION AND SITE SELECTION. Consecutive patients with ULMCAD presenting at participating centers were evaluated for enrollment in the trial. Inclusion criteria included patient presentation with silent ischemia, stable or unstable angina, or MI >24 h before treatment, and PCI intended in a true de novo distal LM bifurcation lesion (Medina 1,1,1 or 0,1,1) (20), with >50% diameter stenosis (DS) of both the ostial left anterior descending (LAD) and left circumflex (LCx) coronary arteries by visual estimation. Non-LM lesions in the LAD, LCx, or right coronary artery, if present, had to be treatable by no more than 2 additional stents. Patients were excluded if they had cardiogenic shock, severely calcified LM lesions requiring atherectomy, in-stent restenosis (ISR), need for oral anticoagulation, or any clinical condition that would interfere with medication compliance or long-term follow-up. Randomization was performed immediately after angiography and before LM PCI. However, if a chronic total occlusion was present in the LAD or LCx, the chronic total occlusion must have been successfully recanalized before randomization. All patients provided written informed consent.

Participating primary operators were required to have performed ≥300 PCIs/year for 5 years, including at least 20 LM PCIs per year. In addition, each operator performed 3 to 5 DK crush cases, which were reviewed by the steering committee to ensure appropriate technique before randomization commencing.

TABLE 1 Baseline Characteristics of the Randomized Groups

	Provisional Stent (n = 242)	DK Crush Stent (n = 240)	p Value
Demographics			
Age, yrs	64 ± 10	65 ± 9	0.15
Male	188 (77.7)	199 (82.9)	0.17
Height, cm	167 ± 7	168 ± 7	0.50
Weight, kg	70 ± 10	70 ± 10	0.94
Systolic blood pressure, mm Hg	132 ± 19	135 ± 18	0.07
Diastolic blood pressure, mm Hg	79 ± 10	79 ± 10	0.85
Heart rate, beats/min	73 ± 10	74 ± 12	0.34
Risk factors			
Hyperlipidemia	115 (47.5)	114 (47.5)	1.00
Hypertension	156 (64.5)	175 (72.9)	0.051
Diabetes	62 (25.6)	69 (28.8)	0.47
Insulin-treated	18 (29.0)	19 (27.5)	0.85
Current smoker	78 (32.2)	82 (34.2)	0.64
Prior stroke	4 (1.7)	3 (1.3)	1.00
Creatinine, μmol/l	78 ± 30	80 ± 25	0.40
eGFR, ml/min/1.73 m^2	81.1 ± 24.1	78.5 ± 23.0	0.22
<15 ml/min/1.73 m^2	1 (0.4)	0 (0.0)	
15–29 ml/min/1.73 m^2	3 (1.2)	2 (0.8)	
30–60 ml/min/1.73 m^2	31 (12.8)	39 (16.3)	
>60 ml/min/1.73 m^2	207 (85.5)	199 (82.9)	
Peripheral artery disease	16 (6.6)	18 (7.5)	0.73
Medical history			
Prior MI	51 (21.1)	52 (21.7)	0.91
Prior PCI	43 (17.8)	33 (13.8)	0.26
Prior CABG	2 (0.8)	2 (0.8)	1.00
LVEF, %	60 ± 9	59 ± 9	0.81
LVEF <30%	7 (2.9)	11 (4.6)	0.12
Symptomatic heat failure	33 (13.6)	37 (15.4)	0.58
Clinical presentation			0.49
Silent ischemia	10 (4.1)	7 (2.9)	
Stable angina	26 (10.4)	34 (14.2)	
Unstable angina	180 (74.4)	168 (70.0)	
Recent MI (>24 h)	26 (10.7)	31 (12.9)	
Laboratory			
Red blood cell, × 10^{12}/l	4.4 ± 0.6	4.4 ± 0.7	0.52
White blood cell, × 10^9/l	6.91 ± 2.1	6.9 ± 2.1	0.79
Hemoglobin, g/l	135 ± 15	134 ± 17	0.61
Platelet count, × 10^9/l	203 ± 63	194 ± 59	0.13
Total cholesterol, mmol/l	4.2 ± 1.2	4.0 ± 1.2	0.15

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; DK = double kissing; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Lesion Characteristics (Core Laboratory Assessment)

	Provisional Stent (n = 242)	DK Crush Stent (n = 240)	p Value
Multivessel disease	216 (88.8)	211 (87.9)	0.78
LAD lesion	145 (59.9)	141 (58.8)	0.85
LCx lesion	118 (48.8)	121 (50.4)	0.79
RCA lesion	156 (64.5)	150 (62.5)	0.71
SYNTAX score	30.1 ± 8.1	31.1 ± 7.9	0.23
0–22	33 (13.6)	28 (11.7)	
23–32	101 (41.7)	107 (44.5)	
>32	108 (44.6)	105 (43.8)	
NERS II score	27.6 ± 7.5	27.8 ± 8.1	0.60
≥19	97 (40.1)	95 (39.6)	0.86
LM lesion location			
Ostial	7 (2.9)	7 (2.9)	1.00
Body shaft	21 (8.7)	19 (7.9)	0.87
Distal LM	242 (100.0)	240 (100.0)	1.00
Medina 1,1,1 bifurcation	190 (78.5)	204 (85.0)	0.08
Medina 0,1,1 bifurcation	52 (21.5)	36 (15.0)	0.08
Trifurcation	43 (17.8)	43 (17.9)	1.00
Calcification*	96 (39.7)	89 (37.1)	0.58
Main vessel	88 (36.4)	83 (34.6)	0.70
Side branch	34 (14.0)	37 (15.4)	0.70
Chronic total occlusion	30 (12.4)	29 (12.1)	1.00
LM	1 (0.4)	1 (0.4)	1.00
LAD	14 (5.8)	14 (5.8)	1.00
LCx	5 (2.1)	8 (3.3)	0.42
RCA	12 (5.0)	8 (3.3)	0.49
TIMI flow grade <3			
Main vessel	48 (19.8)	49 (20.4)	0.27
Side branch	17 (7.0)	29 (12.1)	0.22
Pre-procedure IVUS use	70 (28.9)	68 (28.3)	0.92
Complex bifurcation	66 (27.3)	86 (35.8)	0.054

Values are n (%) or mean ± SD. *Defined as moderate calcification (radiopaque densities noted only during the cardiac cycle and typically involving only 1 side of the vascular wall) or severe calcification (radiopaque densities noted without cardiac motion before contrast injection and generally involving both sides of the arterial wall).

DK = double kissing; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main; NERS = New Risk Stratification; RCA = right coronary artery; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIMI = Thrombolysis In Myocardial Infarction.

STUDY PROCEDURES AND MEDICATIONS. Eligible patients were randomly assigned in a 1:1 ratio to either DK crush or PS using a central interactive web-based computerized system. Procedural anticoagulation was achieved with unfractionated heparin. Use of intravascular ultrasound (IVUS), intra-aortic balloon pump counterpulsation, and glycoprotein IIb/IIIa inhibitors were left to the operator's discretion. The PS and DK crush techniques have been previously described (14-18). For PS, the distal main vessel (MV) and SB were wired. Predilation was left to the operator's discretion, although pre-dilating the SB was discouraged. A stent with stent/artery ratio of 1.1:1 was implanted in the MV. The SB was rewired through a distal cell of the MV stent, followed by PCI of the SB (with kissing balloon inflation [KBI] performed if the residual DS of the SB was >75%, or dissection ≥ type B, or TIMI [Thrombolysis In Myocardial Infarction] flow grade <3 was present). An additional SB stent was implanted if suboptimal results (including a residual DS >75%, dissection ≥ type B, or TIMI flow grade <3) were still present after KBI. For DK crush stenting, following vessel wiring and pre-dilation a stent was implanted in the LCx protruding minimally (~2 mm) into the LM, after which it was crushed with a large noncompliant balloon. The LCx was then rewired through a proximal stent cell followed by the first KBI, after which the LM-LAD stent was implanted followed by an additional crush of the LCx stent with a noncompliant balloon inflation. The LCx stent was rewired for a second time (always from a proximal cell), and alternating LCx and LAD inflations were performed using a noncompliant balloon at ≥16 atm, followed by final KBI. For both PS and DK crush stenting, the proximal optimization technique (POT) was used for all LM stents, and post-dilation of all stents was recommended with noncompliant balloons at ≥18 atm pressure.

All patients were treated with aspirin pre-procedure and were administered a 300-mg loading dose of clopidogrel if not on chronic dual antiplatelet therapy. After intervention, all patients received 100 mg/day aspirin indefinitely and clopidogrel 75 mg/day 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.

FOLLOW-UP. Clinical follow-up was performed by office visit or telephone contact at 1, 7, and 12 months (Online Figure 1). Follow-up coronary angiography was scheduled at 13 months following the index procedure in all patients (after ascertainment of the primary clinical endpoint), unless it was performed earlier for clinical indications. Procedural and clinical data were entered into electronic case-report forms, verified by a central monitoring organization, and transmitted to a central database at Nanjing Medical University.

Quantitative coronary analysis (QCA) was analyzed at a central core laboratory using Cardiovascular Angiographic Analysis System (CAAS) II software version 5.0 (Pie Medical Imaging, Maastricht, the Netherlands), as previously described (14-18). Restenosis within implanted stents was defined as a QCA DS >50% at follow-up. For PS patients without a SB stent, restenosis in the SB was defined as a QCA DS >75%.

ENDPOINTS AND DEFINITIONS. The primary endpoint was target lesion failure (TLF): the composite of cardiac death, target-vessel MI (TVMI), or clinically

driven TLR at 1-year follow-up. Death from cardiac causes was defined as any death without a clear noncardiac cause. Protocol-defined periprocedural MI was defined as creatine kinase-myocardial band (CK-MB) >10× the upper reference limit (URL) of the assay, or >5× URL plus either: 1) new pathological Q waves in ≥2 contiguous leads or new left bundle branch block; or 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 72 h) was defined as a clinical syndrome consistent with MI with CK-MB or troponin >1× URL and new ST-segment elevation or depression or other findings as mentioned earlier in the text. All MIs were considered to be TVMI unless there was clear evidence that they were attributable to a non-target vessel (21). Clinically driven TLR was defined as angina or ischemia referable to the target lesion requiring repeat PCI or CABG (21). Secondary endpoints included all-cause death, all MI, periprocedural biomarker release (defined as a post-procedural increase in troponin I or T to >5× the upper limits of normal), all clinically driven revascularization, angina, and ISR. ST defined by the Academic Research Consortium definite or probable criteria (21) was the major safety endpoint. All events were adjudicated by a central committee using original source documents blinded to treatment.

The LM bifurcation lesion was categorized as being either simple or complex according to the DEFINITION (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) study (16), with complex defined as the presence of both major criteria (ostial SB lesion length ≥10 mm and DS ≥70%) plus any 2 minor criteria (distal bifurcation angle <45° or ≥70°, MV reference vessel diameter ≤2.5 mm, MV lesion length ≥25 mm, multiple bifurcations, thrombus-containing lesion, and severe calcification).

STATISTICAL ANALYSIS. The sample size for the trial was estimated on the basis of the findings from the DEFINITION (16) and DKCRUSH III (17) studies in which TLF at 1 year occurred in 5.0% of patients treated with DK crush and in 16.1% of patients treated with PS. Applying somewhat more conservative assumptions (6.0% for DK crush and 14.0% for PS), randomizing 220 patients per group would provide 80% power with a 2-sided alpha of 0.05 to demonstrate superiority for DK crush. To account for 10% possible lost to follow-up, a total of 484 patients (242 in each group) were planned for enrollment.

TABLE 3 Procedural Characteristics

	Provisional Stent (n = 242)	DK Crush Stent (n = 240)	p Value
Transradial approach	181 (74.8)	187 (77.9)	0.45
6-F guiding catheter used	129 (53.3)	129 (54.2)	0.58
Glycoprotein IIb/IIIa inhibitor used	46 (19.0)	52 (21.7)	0.70
Pre-dilation performed			
Main vessel	203 (83.9)	181 (75.4)	0.02
Side branch	96 (39.7)	164 (68.3)	<0.001
Main vessel stent	1.60 ± 0.64	1.58 ± 0.69	0.76
Total	373	374	0.99
Xience V	278	277	
Endeavor Resolute	29	31	
Firebird 2	66	66	
Diameter, mm	3.29 ± 0.38	3.32 ± 0.37	0.40
LM segment length, mm	28.8 ± 10.4	27.9 ± 9.9	0.50
Total main vessel length, mm	48.2 ± 18.4	49.3 ± 19.1	0.48
Covered ostial LM	135 (55.8)	152 (63.3)	0.70
Side branch stent	0.63 ± 0.76	1.19 ± 0.49	<0.001
1 or more stents implanted	114 (47.1)	240 (100.0)	<0.001
Total	140	347	<0.001
Xience V	106	267	
Endeavor Resolute	12	27	
Firebird 2	22	53	
Diameter, mm	2.97 ± 0.38	2.92 ± 0.35	0.25
LM segment length, mm	21.25 ± 7.44	21.00 ± 7.32	0.76
Total side branch length, mm	28.33 ± 9.10	32.44 ± 10.51	0.10
POT performed	239 (98.8)	238 (99.2)	0.39
Final kissing inflation			
Performed	191 (78.9)	239 (99.6)	<0.001
Main vessel			
Balloon diameter, mm	3.56 ± 0.47	3.49 ± 0.40	0.08
Inflation pressure, atm	14.1 ± 3.3	12.4 ± 3.1	0.84
Side branch			
Balloon diameter, mm	2.77 ± 0.47	2.97 ± 0.39	<0.001
Inflation pressure, atm	10.8 ± 3.2	13.5 ± 1.2	0.03
Procedural IVUS use	98 (40.5)	103 (42.9)	0.37
Final TIMI flow grade 3			
Main vessel	242 (100.0)	240 (100.0)	1.00
Side branch	239 (98.8)	240 (100.0)	0.39
Complete revascularization	168 (69.4)	174 (72.5)	0.48
PCI of non-LM lesions	83 (34.3)	72 (30.0)	0.18
Before randomization	41 (16.9)	33 (13.8)	
After randomization	42 (17.4)	39 (16.3)	
Angiographic success	235 (97.1)	236 (98.3)	0.54
Procedural time, min	66.1 ± 34.5	81.9 ± 37.6	<0.001
Contrast volume, ml	190.9 ± 73.8	226.7 ± 81.4	<0.001

Values are n (%), mean ± SD, or n.
POT = proximal optimization technique; other abbreviations as in Tables 1 and 2.

Baseline characteristics are reported as counts and percentages or mean ± SD. The chi-square test or Fisher exact test was used to compare categorical variables. The 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 by Kaplan-Meier analysis, and compared using the log-rank test. Potential

TABLE 4 Clinical Outcomes at 30 Days and 1 Year

	Provisional Stent (n = 242)	DK Crush Stent (n = 240)	p Value
30-day follow-up			
Target lesion failure	7 (2.9)	1 (0.4)	0.033
Cardiac death	4 (1.7)	0 (0.0)	0.046
Target vessel MI	4 (1.7)	1 (0.4)	0.10
Periprocedural	3 (1.2)	0 (0.0)	0.33
Non-periprocedural	2 (0.8)	1 (0.4)	0.50
Target lesion revascularization*	1 (0.4)	1 (0.4)	1.00
Stent thrombosis	6 (2.5)	1 (0.4)	0.06
Definite	1 (0.4)	1 (0.4)	1.00
Probable	5 (2.1)	0 (0.0)	0.04
1-yr follow-up			
Target lesion failure	26 (10.7)	12 (5.0)	0.02
Cardiac death	5 (2.1)	3 (1.2)	0.48
Target vessel MI	7 (2.9)	1 (0.4)	0.03
Target lesion revascularization*	19 (7.9)	9 (3.8)	0.06
PCI	17 (7.1)	8 (3.4)	0.67
CABG	2 (0.8)	1 (0.4)	0.56
Stent thrombosis	8 (3.3)	1 (0.4)	0.02
Definite	2 (0.8)	1 (0.4)	0.50
Probable	6 (2.5)	0 (0.0)	0.03
All-cause death	5 (2.1)	7 (2.9)	0.58
All revascularization†	19 (7.9)	13 (5.4)	0.32
Non-LM complex-related	0 (0.0)	4 (1.6)	0.09
Angina during follow-up‡	21 (9.3)	10 (4.5)	0.06

Values are number of events (Kaplan-Meier estimated event rate), compared by the log-rank test. *Clinically driven. Note: there were no nonclinically driven revascularizations during follow-up. †For LM and non-LM lesions. ‡Any recurrent stable or unstable angina.

Abbreviations as in Tables 1 and 2.

interactions between the following subgroups and randomized treatment were examined for the primary outcome measure: age (<70 vs. ≥70 years), sex, diabetes, distal LM bifurcation angle (<70° vs. ≥70°), simple versus complex bifurcation lesion, SYNTAX score (≤32 vs. >32), NERS (New Risk Stratification) score (<19 vs. ≥19 points) (22), and IVUS guidance versus angiography guidance. All outcome analyses were performed in the intention-to-treat population, regardless of treatment received. All statistical tests were 2-sided, and a p value of <0.05 was considered statistically significant. All analyses were performed with SPSS version 24.0 (SPSS Institute, Chicago, Illinois).

RESULTS

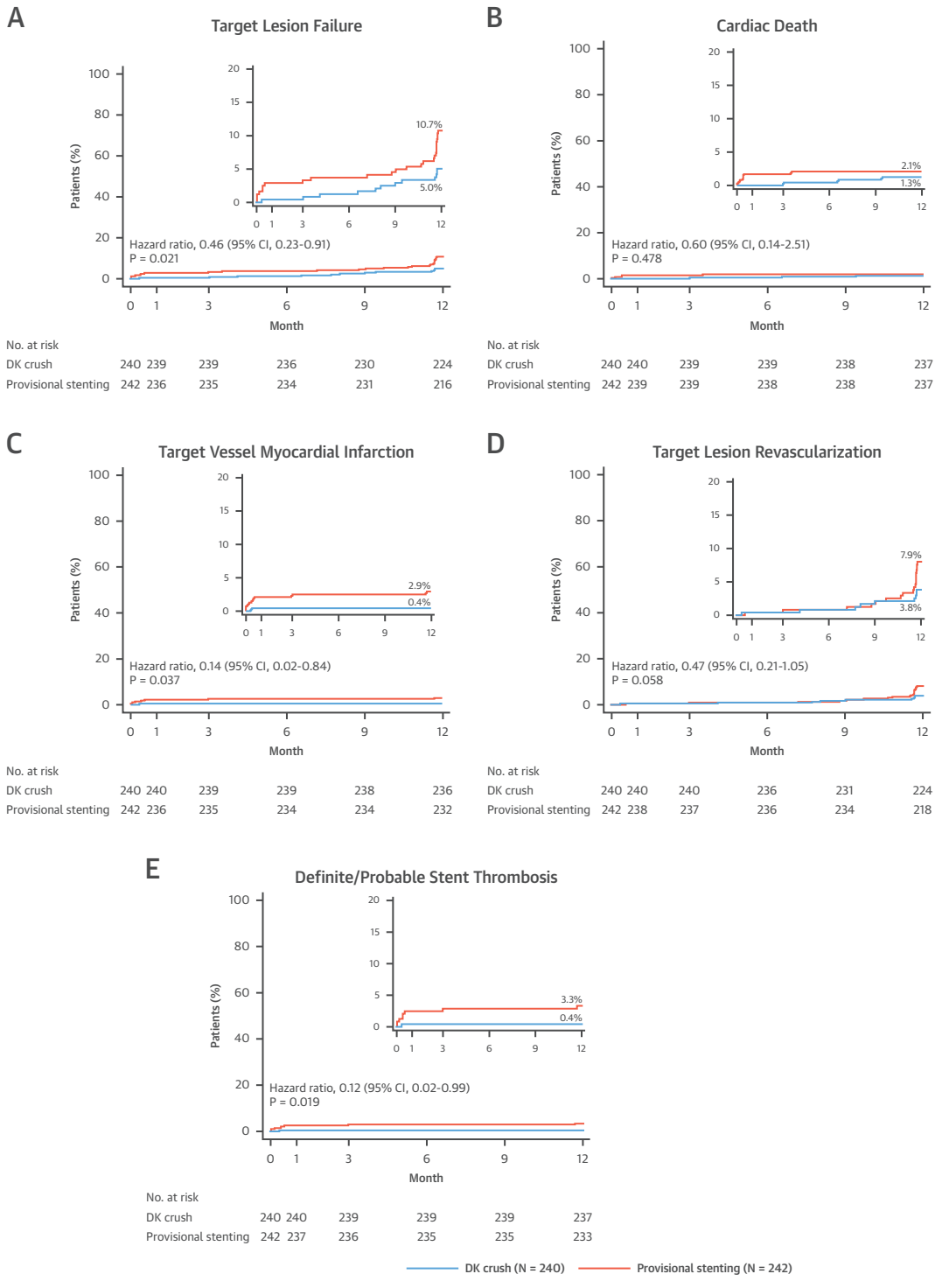
BASELINE CLINICAL, ANGIOGRAPHIC, AND PROCEDURAL CHARACTERISTICS. Between December 27, 2011, and February 21, 2016, 496 patients with ULMCAD and true distal bifurcation lesions met all the inclusion and exclusion criteria. Fourteen patients elected to undergo CABG. The remaining 482 patients were randomized at 26 centers in China, Indonesia, Thailand, Italy, and the United States to DK crush (n = 240) or PS (n = 242) (Online Figure 1). Baseline characteristics were well matched between the groups (Tables 1 and 2). Diabetes was present in 27.2% of patients, and most patients (72.2%) presented with unstable angina. The mean SYNTAX score was 30.6 ± 8.0 by angiographic core laboratory assessment, with multivessel disease present in 88.2% of patients. The distal LM bifurcation lesion was classified as Medina class 1,1,1 and 0,1,1 in 81.7% and 18.3% of cases, respectively; 17.8% of lesions were trifurcations.

Procedural characteristics are shown in Table 3. SB pre-dilation was performed in 39.7% of patients in the PS group, mostly in response to severe SB compromise after MV pre-dilation. A total of 114 (47.1%) patients in the PS group required an additional SB stent for suboptimal results after MV stenting, including 64 of 165 (38.8%) patients with simple LM bifurcation lesions and 50 of 77 (64.9%) patients with complex lesions (p = 0.001). A SB stent was successfully implanted in all DK crush patients. The POT and final KBI were more frequently used in the DK crush group than the PS group. Periprocedural biomarker release occurred in 27 (11.3%) DK crush patients versus 10 (4.1%) PS patients (p = 0.004), although there was no significant difference in the rates of the protocol definition of periprocedural MI (0 [0%] vs. 3 [1.2%] respectively; p =0.33). Rates of angiographic success and complete revascularization were similar in the 2 groups, although procedural time and contrast use were greater with DK crush stenting than PS.

CLINICAL OUTCOMES. Clinical follow-up was complete in all patients at 1 year. All study patients were treated with dual antiplatelet therapy throughout the 1-year follow-up period, except for a single patient in the DK crush group. At 30-day follow-up, TLF had occurred more frequently in the PS group than the DK crush group (2.9% vs. 0.4%; p = 0.03), in part due to more ST events with PS (2.5% vs. 0.4%; p = 0.09) (Table 4). Details of the ST cases occurring within 30 days are shown in Online Table 1. Among patients in the PS group in whom ST within 30 days did versus did not occur, the SB lesion length was longer (31.9 ± 13.3 mm vs. 12.4 ± 5.6 mm; p = 0.004) and the distal bifurcation angle was wider (110° ± 23° vs. 66.7° ± 2.5°; p = 0.01).

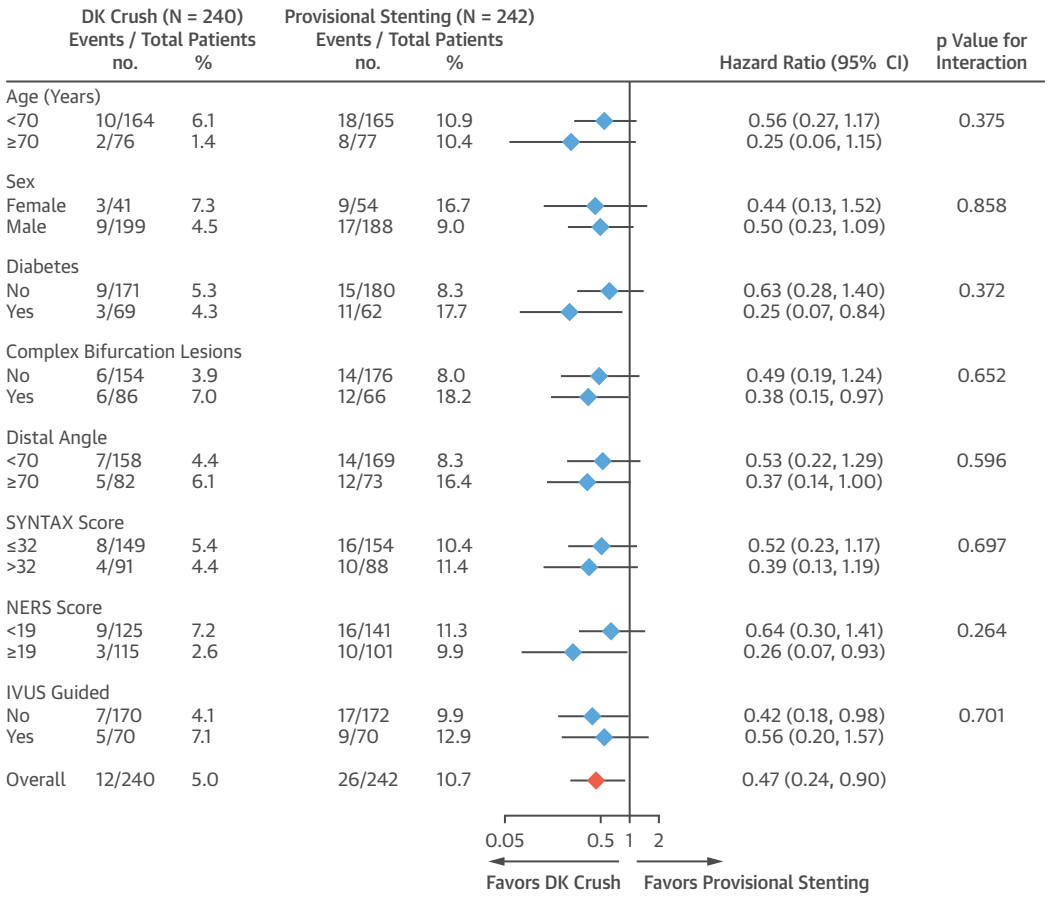
TLF at 1-year follow-up, the primary endpoint of the study, occurred in 26 patients assigned to PS versus 12 assigned to DK crush (Kaplan-Meier estimated rates 10.7% vs. 5.0%; p = 0.02) (Table 4, Figure 1, Online Figure 2). Compared with PS, patients treated with DK crush had lower 1-year rates of TVMI and ST, trends toward less clinically driven TLR and angina, and no significant differences in cardiac or

FIGURE 1 **Kaplan-Meier Time-to-First Event Curves**



(A) Target lesion failure; **(B)** cardiac death; **(C)** target-vessel myocardial infarction; **(D)** target lesion revascularization; **(E)** stent thrombosis (definite or probable). CI = confidence interval; DK = double kissing.

FIGURE 2 Subgroup Analysis

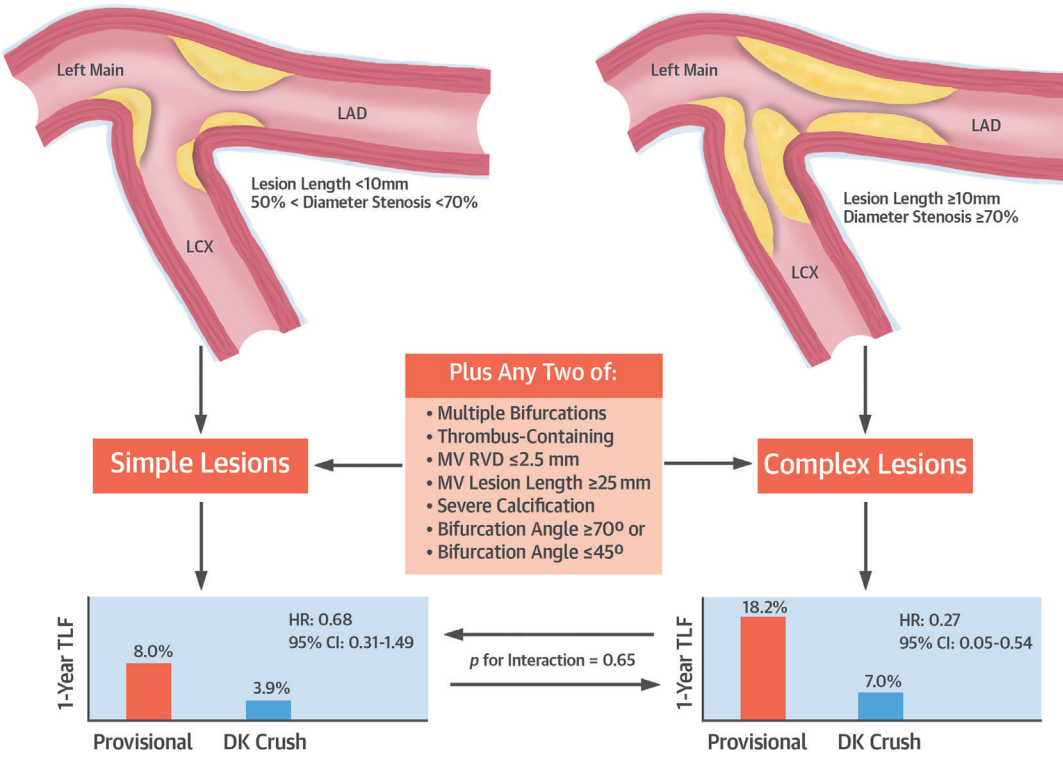


The reduction in target lesion failure at 1 year with the DK crush stent technique compared with provisional stenting was consistent across pre-specified subgroups. IVUS = intravascular ultrasound; NERS = New Risk Stratification; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; other abbreviations as in Figure 1.

all-cause mortality. The angiograms of the ST cases are shown in Online Figure 3. There were no significant interactions between any of the subgroups and technique randomization for the 1-year relative rates of TLF, although the absolute reduction in TLF was greater in complex compared with simple distal LM bifurcation lesions (**Figure 2, Central Illustration**). Comparing the 114 patients in the PS group who required a SB stent versus the 128 patients who did not, the 1-year rates of TLF were 13.2% versus 8.6%, respectively ($p = 0.30$), and the 1-year rates of ST were 6.1% versus 0.8%, respectively ($p = 0.03$).

QUANTITATIVE CORONARY ANALYSIS. Angiographic follow-up was completed in 158 patients (65.3%) in the PS group and 159 patients (66.3%) in the DK group at 367 ± 49 days and 371 ± 52 days, respectively ($p = 0.74$). These results included 32 PS and 15 DK patients who underwent elective repeat angiography before 12 months for recurrent chest pain, among whom TLR was performed in 15 PS and 8 DK patients. Baseline characteristics as assessed by QCA were comparable between the 2 groups (**Table 5**). Of note, the SB lesion length was ≥10 mm in nearly one-half of cases. At follow-up angiography, the minimal luminal diameter was larger and the DS smaller in the SB after DK crush stenting compared with PS; there were no significant QCA differences between the 2 techniques in the MV at follow-up. Angiographic restenosis at any location within the LM bifurcation complex occurred in 23 (14.6%) patients treated with PS versus 11 (7.1%) patients treated with DK crush ($p = 0.10$). ISR in both groups most commonly occurred at the ostium of the LCx (**Figure 3**).

CENTRAL ILLUSTRATION **Stenting for LM Bifurcations**



Chen, S.-L. et al. J Am Coll Cardiol. 2017;70(21):2605–17.

Patients with true distal left main (LM) coronary artery bifurcation lesions randomized to double kissing (DK) crush stenting compared to provisional stenting (PS) had similar relative reductions in the 1-year rates of target lesion failure (TLF) in both simple and complex lesions (interaction p value = 0.65), although the absolute benefit was greater for more complex lesions (11.2% vs. 4.1%). CI = confidence interval; DS = diameter stenosis; HR = hazard ratio; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LL = lesion length; MV = main vessel; RVD = reference vessel diameter.

DISCUSSION

The present randomized study has for the first time evaluated clinical and angiographic outcomes after treatment of true distal LM bifurcation lesions with the DK crush planned 2-stent technique versus a PS approach. The major findings are: 1) DK crush stenting significantly reduced the incidence of 1-year TLF compared with PS, driven by fewer TVMI and TLR events; 2) the reduction in TVMI with DK crush stenting compared with PS was driven by fewer definite and probable STs with DK crush; 3) trends were present for lower 1-year rates of clinically driven TLR and angiographic restenosis with DK crush stenting compared with PS, especially due to improved patency of the LCx ostium; and 4) the relative reduction in TLF at 1 year with DK crush compared with PS was consistent in pre-specified subgroups, including simple and complex distal LM bifurcation lesions, although the absolute benefits were greater in more complex lesions.

In prior randomized trials, most planned 2-stent techniques have been found to be inferior to PS in non-LM bifurcation lesions, primarily because of greater periprocedural myonecrosis with multiple stents (and higher rates of ST in some studies) (10–13). By contrast, in the present randomized trial of a routine planned 2-stent approach with DK crush versus PS in patients with true distal LM bifurcation lesions, DK crush resulted in greater freedom from ST, target vessel MI, and TLF through 1-year follow-up. The higher rate of early and late adverse events with PS compared with DK crush stenting in the present study may in part relate to the anatomy of the distal LM segment. Compared with non-LM bifurcation lesions, true distal LM bifurcation lesions involve larger caliber vessels, have a wider bifurcation angle, and have more frequent involvement of 3 vessel segments

TABLE 5 QCA at Baseline and Follow-Up

	Provisional Group (n = 158)	DK Crush Group (n = 159)	p Value
Lesion length, mm			
Main vessel	23.5 ± 12.8	22.37 ± 12.94	0.36
Proximal main vessel	6.9 ± 3.5	7.0 ± 3.4	0.94
Distal main vessel	6.7 ± 12.5	15.5 ± 12.8	0.30
Side branch	16.6 ± 11.9	16.2 ± 14.0	0.13
≥10 mm	104 (42.9)	120 (50.0)	0.14
Distal bifurcation angle, degrees			
Pre-PCI	79.7 ± 24.9	76.3 ± 22.3	0.13
Post-PCI	77.8 ± 20.9	74.4 ± 20.5	0.09
At follow-up	74.8 ± 22.2	70.2 ± 22.3	0.10
Angle reduction	−3.4 ± 20.8	−5.3 ± 22.2	0.48
Main vessel			
RVD, mm			
Pre-PCI	3.08 ± 0.45	3.12 ± 0.51	0.38
Post-PCI	3.09 ± 0.44	3.14 ± 0.51	0.28
At follow-up	3.05 ± 0.44	3.08 ± 0.49	0.58
MLD (in-stent), mm			
Pre-PCI	1.17 ± 0.51	1.22 ± 0.55	0.31
Post-PCI	2.65 ± 0.46	2.73 ± 0.49	0.09
Acute gain	1.49 ± 0.61	1.51 ± 0.60	0.78
At follow-up	2.40 ± 0.51	2.52 ± 0.64	0.16
Late loss	0.23 ± 0.35	0.20 ± 0.54	0.74
Diameter stenosis (in-stent), %			
Pre-PCI	61.8 ± 8.1	60.8 ± 7.2	0.51
Post-PCI	14.3 ± 8.2	13.0 ± 7.9	0.11
At follow-up	21.3 ± 11.8	17.8 ± 6.9	0.11
Restenosis (in-stent)	9 (5.7)	3 (1.9)	0.09
Side branch			
RVD, mm			
Pre-PCI	2.69 ± 0.44	2.68 ± 0.41	0.80
Post-PCI	2.74 ± 0.45	2.76 ± 0.48	0.23
At follow-up	2.56 ± 0.43	2.71 ± 0.50	0.04
MLD (in-stent), mm			
Pre-PCI	1.02 ± 0.43	1.03 ± 0.45	0.89
Post-PCI	2.01 ± 0.50	2.49 ± 0.48	<0.001
Acute gain	1.01 ± 0.46	1.47 ± 0.50	<0.001
At follow-up	1.72 ± 0.54	2.37 ± 0.48	<0.001
Late loss	0.28 ± 0.55	0.23 ± 0.44	0.10
Diameter stenosis (in-stent), %			
Pre-PCI	65.3 ± 8.3	65.8 ± 7.5	0.87
Post-PCI	25.2 ± 15.0	8.7 ± 2.1	<0.001
At follow-up	34.7 ± 21.2	13.5 ± 7.3	<0.001
Restenosis (in-stent)	19 (12.0)	8 (5.0)	0.09
Binary restenosis			
LM complex*	23 (14.6)	11 (7.1)	0.10
Non-LM lesions	12 (7.6)	9 (5.7)	0.41

Values are mean ± SD or n (%). *Any restenosis in the LM (body, bifurcation, or ostial main vessel and side branch).
MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RVD = reference vessel diameter; other abbreviations as in Tables 1 and 2.

(trifurcations) (3-7,8,9,23). In the DKCRUSH-III trial, DK crush stenting was superior to culotte stenting in treatment of distal LM bifurcation lesions (17). However, this result was driven by inferior results with culotte stenting in wide bifurcation lesions (angle ≥70°), in which a T-stent technique (either planned 2-stent or PS) is generally preferred (16,24,25). In the present study, the mean angle of the distal LM bifurcation was ~78°, which should have been favorable for PS. However, in the PS approach, the delivery of a "rescue" or bail-out SB stent through MV stent cells may be difficult or result in imprecise placement (14,15,26), incomplete expansion or asymmetry (14,27), or edge dissections (16,27), all of which may contribute to an increased rate of ST or clinically driven TLR during follow-up. Rescue stenting was required in ~47% of the PS cases in the present study, a relatively high rate reflecting the fact that we enrolled true bifurcation lesions of the distal LM, with SB lesion length ~16.4 mm and DS 65% by QCA. The challenges of bailout stenting in true bifurcation lesions of the distal LM, especially when complex, likely contributed to the relatively high rates of ST and TVMI with PS in our study. By contrast, although DK crush stenting is a more complex technique that entails more upfront procedural time and contrast, it offers a more controlled strategy to treat the entire LM complex, and affords more reliable lesion coverage and greater stent expansion of the ostial LCx (14,16,17), which in the present study resulted in improved clinical and angiographic outcomes compared with a PS approach. Although it is perhaps not surprising that the planned 2-stent approach was superior to PS in complex distal LM bifurcation lesions, the fact that the relative reduction in TLF at 1 year with DK crush compared with PS was also consistent in simple distal LM bifurcation lesions suggests that this technique may be preferable for most unprotected true LM bifurcation lesions.

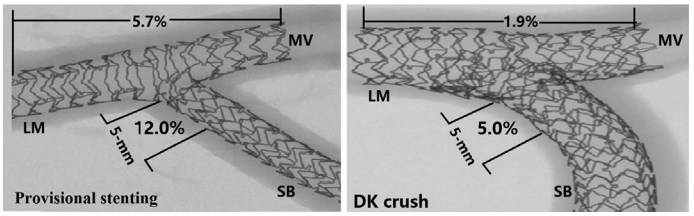
Of note, despite a higher rate of periprocedural myonecrosis with DK crush stenting compared with PS, there was no difference in the rate of large, clinically relevant periprocedural MI between the 2 techniques, using a similar definition as that used in the EXCEL trial (8) and recommended by the Society of Cardiac Angiography and Interventions, which has been correlated with subsequent mortality (28). By contrast, lower levels of periprocedural biomarker elevation do not appear to be prognostically relevant, although in this regard, more data are required in the setting of LM PCI.

Despite improved angiographic results with DK crush compared with PS (especially at the SB ostium), the difference in clinically driven TLR at 1 year did not reach statistical significance. This may represent type II error, because angiographic outcomes were improved with DK crush, and the observed TLR differences would have been significant had ~100 more patients been enrolled. Consistent with this

supposition, DK crush resulted in a lower rate of clinically driven TLR compared with PS in non-LM bifurcation lesions in the randomized DKCRUSH-II trial (14).

Learning the DK crush technique, although not overly complicated, requires training, experience, and attention to procedural detail, including carefully rewiring the SB, sequential post-dilation with noncompliant balloons at high pressure before each kissing inflation, and final POT after KBI. The operators participating in the DKCRUSH-V trial were relatively high-volume proceduralists, were familiar with the DK crush technique, and had to submit roll-in cases demonstrating their technical competence with this approach. The results of the present trial may not be replicated by less experienced operators.

FIGURE 3 Distribution of ISR



The rates of in-stent restenosis (ISR) in the main vessel (MV) at 13-month angiographic follow-up were comparable with DK crush stent and provisional stenting (PS). The rate of ISR at the ostium of side branch (SB) was 12.0% with PS versus 5.0% with DK crush ($p = 0.09$). LM = left main.

STUDY LIMITATIONS. First, intravascular imaging was not performed in more than one-half of all procedures. Intravascular imaging in LM bifurcations may be useful to guide stent diameter and length determinations, to ensure optimal stent expansion (especially of the ostial LCx), and to identify edge dissections and residual disease that may not be apparent by angiography. Nonetheless, the superiority of DK crush compared with PS was consistent with both IVUS guidance and angiography guidance. Second, fractional flow reserve (FFR) guidance of SB stenting in the PS group was not routinely performed. Because PS-assigned patients who received a SB stent had a higher rate of ST and TVMI, avoiding SB stenting if the FFR is >0.80 may be beneficial. However, FFR-guided SB stenting was not superior to angiographically guided SB stenting in non-LM bifurcation lesions in the DKCRUSH-VI trial (15). Third, as part of the procedural strategy, POT and KBI were performed more often with DK crush than PS. The extent to which these components of the DK crush technique contributed to its improved outcomes is uncertain. Fourth, adjustment for multiple comparisons in secondary endpoints and subgroups was not performed; all such hypothesis testing should thus be considered exploratory. However, the consistency of the study results across multiple subgroups suggests that the DK crush technique will result in superior outcomes in most true distal bifurcation lesions, although to a variable absolute extent depending on lesion complexity. Larger studies may identify patients or lesions that particularly benefit by DK crush or other stent techniques (29). Fifth, the visual-restenosis effect could not be excluded from the clustering of repeat TLR before 12 months. However, because all patients had symptoms (chest pain or angina) before repeat elective angiography, the rate of clinically driven LTR before 12 months of follow-up indicated the less durability of PS. Finally, all enrolled patients had true distal LM bifurcation lesions, with greater SB length and severity than studied in most prior bifurcation trials. Many of these, however, were noncomplex, with an ostial LCx length <10 mm and DS <70%. Nonetheless, our results suggest that DK crush stenting may benefit even these less severe true distal LM bifurcation lesions (**Central Illustration**). The findings from the present study do not apply, however, to LM lesions with <50% DS of the SB, for which PS should remain the standard approach.

CONCLUSIONS

In the present multicenter randomized trial, a planned DK crush 2-stent strategy reduced TLF at 1-year compared with a PS strategy in patients with true distal LM bifurcation lesions.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PS of distal LM coronary artery bifurcation lesions can be technically challenging and is associated with higher rates of MI and repeat revascularization than treatment of lesions involving the ostium or shaft of the LM artery. In a randomized trial, a 2-stent, DK crush technique was associated with better outcomes than the PS approach in patients with true distal LM bifurcation lesions.

TRANSLATIONAL OUTLOOK: Further studies using intravascular imaging and physiologic lesion assessment may help identify LM bifurcation lesions likely to respond most favorably to intervention using the 2-stent DK crush technique.

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KEY WORDS double kissing crush, left main bifurcation lesions, prognosis, provisional stenting

APPENDIX For a supplemental table and figures, and a complete list of the DKCRUSH-V participating sites and investigators, please see the online version of this article.