



Clinical Outcome After DK Crush Versus Culotte Stenting of Distal Left Main Bifurcation Lesions

The 3-Year Follow-Up Results of the DKCRUSH-III Study

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ABSTRACT

OBJECTIVES The present study aimed to investigate the difference in major adverse cardiac events (MACE) at 3 years after double-kissing (DK) crush versus culotte stenting for unprotected left main distal bifurcation lesions (LMDBLs).

BACKGROUND The multicenter and randomized DKCRUSH-III (Comparison of double kissing crush versus culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective study) showed that DK crush stenting was associated with fewer MACE at 1-year follow-up in patients with LMDBLs compared with culotte stenting. Here, we report the 3-year clinical outcome of the DKCRUSH-III study.

METHODS A total of 419 patients with LMDBLs who were randomly assigned to either the DK crush or culotte group in the DKCRUSH-III study were followed for 3 year. The primary endpoint was the occurrence of a MACE at 3 years. Stent thrombosis (ST) was the safety endpoint. Patients were classified by simple and complex LMDBLs according to the DEFINITION (Definition and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) study criteria.

RESULTS At 3 years, MACE occurred in 49 patients the culotte group and in 17 patients in the DK crush group (cumulative event rates of 23.7% and 8.2%, respectively; $p < 0.001$), mainly driven by increased myocardial infarction (8.2% vs. 3.4%, respectively; $p = 0.037$) and target-vessel revascularization (18.8% vs. 5.8%, respectively; $p < 0.001$) between groups. Definite ST rate was 3.4% in the culotte group and 0% in the DK crush group ($p = 0.007$). Complex LMDBLs were associated with a higher rate of MACE (35.3%) at 3 years compared with a rate of 8.1% in patients with simple LMDBLs ($p < 0.001$), with an extremely higher rate in the culotte group (51.5% vs. 15.1%, $p < 0.001$).

CONCLUSIONS Culotte stenting for LMDBLs was associated with significantly increased rates of MACE and ST. (Double Kissing [DK] Crush Versus Culotte Stenting for the Treatment of Unprotected Distal Left Main Bifurcation Lesions: DKCRUSH-III, a Multicenter Randomized Study Comparing Double-Stent Techniques; ChiCTR-TRC-11001877) (J Am Coll Cardiol Intv 2015;8:1335-42) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS**

CABG = coronary artery bypass grafting

DK = double-kissing

IVUS = intravascular ultrasound

LMDBL = left main distal bifurcation lesion

MACE = major adverse cardiac event(s)

MI = myocardial infarction

SB = side branch

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

A body of evidence has demonstrated that coronary artery bypass grafting (CABG) remains the standard treatment for patients with unprotected left main coronary artery disease (1-3), mainly driven by an increased rate of target lesion revascularization (TLR). Given the relatively simple stenting technique and comparable clinical results after percutaneous coronary intervention using drug-eluting stent placement for lesions that are ostial or body/shaft of the unprotected left main coronary artery (4,5), stenting left main distal bifurcation lesions (LMDBLs) remains a matter of debate. Furthermore, although provisional stenting is recommended for the great majority of coronary bifurcation lesions, a recent report showed a higher rate of cardiac death after

the single-stent technique for LMDBLs (6). On the other hand, LMDBLs often require 2-stent techniques, which results in less favorable long-term outcomes (7-9). Unfortunately, there is no consensus on the best option for elective stenting with systematic double-stent techniques. In the randomized DKCRUSH-III (Comparison of double kissing crush versus culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective study) study (10), we compared the DK crush and culotte stenting techniques for LMDBLs and observed fewer major adverse cardiac event (MACE) and TLR at 1-year follow-up in the DK crush group. There are no data showing the

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long-term clinical outcomes of 2-stent techniques for LMDBLs, particularly with regard to TLR and safety endpoint—stent thrombosis (ST). Accordingly, the aim of the current study was to evaluate the 3-year clinical outcome after DK crush and culotte stenting for the patient population from DKCRUSH-III study. The outcome in those patients was also compared in a subgroup stratified by DEFINITION (Definition and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) study criteria (11), a stratification system used to differentiate simple from complex LMDBLs.

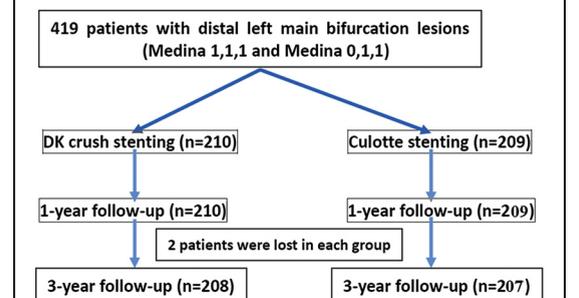
METHODS

STUDY DESIGN AND PATIENT POPULATION. The DKCRUSH-III study was an international (5 countries), multicenter (n = 18), randomized study that was designed to compare the DK crush and the

culotte stenting techniques for patients with LMDBLs. The primary endpoint of the primary publication (10) was the 12-month composite of MACE including cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR), whereas angiographic follow-up was performed 8 months after the indexed procedures. The study protocol was approved by the Ethics Committee of the 19 participating centers, and written consent was obtained from all patients or their legally authorized representative. The recruitment of participating centers was strictly according to our protocol (12). The clinical follow-up was scheduled to be performed as 3 years, as shown in Figure 1. Finally, between March 24, 2009 and October 22, 2011, a total of 419 patients were enrolled (210 in the DK crush and 209 in the culotte group). In brief, patients were eligible if they had ischemic symptoms or evidence of myocardial ischemia in the presence of a Medina (13) 1,1,1 or 0,1,1 de novo LMDBLs. For inclusion, the maximal treatable lesion length by visual estimation for each individual branch had to be completely covered by 2 drug-eluting stents. The exclusion criteria have been described in detail previously (10). Patients were randomly assigned to the study groups in a 1:1 ratio before undergoing balloon dilation. The recommended stents were Firebird-2 (balloon-expandable, cobalt chromium-based, sirolimus-eluting stent, Microport Co., Shanghai, China) and Xience V (Abbott Vascular, Irvine, California). The main stenting techniques were described previously (10). Final KB was recommended at the end of procedure for all lesions.

MEDICATIONS. A 300-mg loading dose of clopidogrel was administered before the index procedure if the patient was not pretreated. After the intervention, all

FIGURE 1 Study Flowchart



Four patients were lost to 3-year follow-up, with 2 patients in each group. Finally, 415 patients (208 in the DK and 207 in the Culotte group, respectively) formed the basis of the current study. DK = double kissing.

patients received 300 mg/day aspirin for 1 month; thereafter, they received 100 mg/day for life. Clopidogrel (75 mg/day) was continued for at least 12 months. After 1 year, clopidogrel was not routinely prescribed and left to the discretion of the patients' physician.

DEFINITION OF STUDY ENDPOINTS. The primary endpoint was the occurrence of a MACE at 3 years, which included MI, cardiac death, and/or TVR. The rate of definite and probable ST served as a safety endpoint. MI was diagnosed if the plasma level of creatine kinase-myocardial band and/or troponin I/T increased to more than 3 times the upper normal limit in no fewer than 2 blood samples. All deaths were considered cardiac in origin unless noncardiac reasons were indicated. TLR and TVR were defined as any repeat revascularization (percutaneous coronary intervention or CABG) for target lesions and target vessels, respectively, in the presence of symptoms or objective signs of ischemia. ST was defined according to the Academic Research Consortium definition (14).

STATISTICAL ANALYSIS. The calculation of patient sample size was described previously (10). The treatment group differences were evaluated with the *t* test or Wilcoxon rank sum scores for continuous variables as appropriate. The chi-square test or the Fisher exact test was used to analyze categorical variables. Survival rates free from events were generated by Kaplan-Meier analysis, and they were

compared using the log-rank test. Patients were classified by simple and complex subgroups according to DEFINITION study criteria (11). Briefly, a complex LMDBL was defined as a side branch (SB) diameter stenosis minimum of 90% and SB lesion length ≥10 mm, plus at least 2 minor criteria (including left main-left anterior descending artery lesions ≥25 mm, moderate or severe calcification, bifurcation angle ≤45°, multiple lesions, and thrombus-containing lesions). We also included center as a random effect in our analysis. Statistical significance was taken as a 2-sided *p* value <0.05. All analyses were performed with the statistical program SPSS version 16.0 (SPSS Institute Inc., Chicago, Illinois).

RESULTS

Baseline clinical and procedural characteristics (Table 1) were well matched in the 2 groups (10).

TABLE 1 Clinical, Angiographic and Procedural Characteristics

	DK Group (n = 210)	Culotte Group (n = 209)	p Value
Clinical			
Male	162 (77.1)	167 (79.9)	0.552
Age, yrs	64.3 ± 10.3	63.3 ± 9.2	0.296
Hypertension	148 (70.5)	128 (61.2)	0.055
Hyperlipidemia	87 (41.4)	88 (42.1)	0.921
Diabetes	67 (31.9)	63 (30.1)	0.298
Angiographic			
3-vessel disease	149 (71.3)	145 (69.5)	0.130
Patterns of bifurcation			0.896
Medina 1,1,1	207 (98.7)	198 (94.8)	
Medina 0,1,1	3 (1.3)	11 (5.2)	
IVUS assessment	145 (69.0)	154 (73.7)	0.331
Procedural			
Post-dilation			
Main vessel	205 (97.6)	200 (95.7)	0.293
Side branch	202 (96.2)	200 (95.7)	0.810
Final kissing balloon inflation	209 (99.5)	208 (99.5)	1.000
Angiographic success	204 (97.1)	208 (99.5)	0.122
Complete revascularization	180 (85.7)	171 (82.0)	0.351

Values are n (%) or mean ± SD.
 DK = double-kissing; IVUS = intravascular ultrasound.

TABLE 2 Clinical Outcomes After DK Crush and Culotte Stenting

	DK Crush (n = 208)	Culotte (n = 207)	p Value
1-year MACE*			
Cardiac death	2 (1.0)	2 (1.0)	1.000
MI	7 (3.3)	11 (5.3)	0.377
TLR	5 (2.4)	14 (6.7)	0.037
CABG	2 (1.0)	0	0.499
TVR	9 (4.3)	22 (10.5)	0.016
ST	1 (0.5)	2 (1.0)	0.623
Definite	0	2 (1.0)	0.248
Probable	0	0	NS
Possible	1 (0.5)	0	1.000
2-year MACE			
Cardiac death	3 (1.4)	6 (2.9)	0.338
MI	7 (3.4)	16 (7.7)	0.046
TLR	7 (3.4)	27 (13.0)	<0.001
CABG	2 (1.0)	1 (0.5)	0.623
TVR	10 (4.8)	37 (17.1)	<0.001
ST	1 (0.5)	8 (3.9)	0.020
Definite	0	7 (3.4)	0.007
Probable	0	1 (0.5)	0.499
Possible	1 (0.5)	0	0.318
3-year MACE			
Cardiac death	3 (1.4)	6 (2.9)	0.338
MI	7 (3.4)	17 (8.2)	0.037
TLR	8 (3.8)	29 (14.0)	<0.001
CABG	2 (1.0)	1 (0.5)	0.565
TVR	12 (5.8)	39 (18.8)	<0.001
ST	1 (0.5)	8 (3.9)	0.020
Definite	0	7 (3.4)	0.007
Probable	0	1 (0.5)	0.499
Possible	1 (0.5)	0	0.318

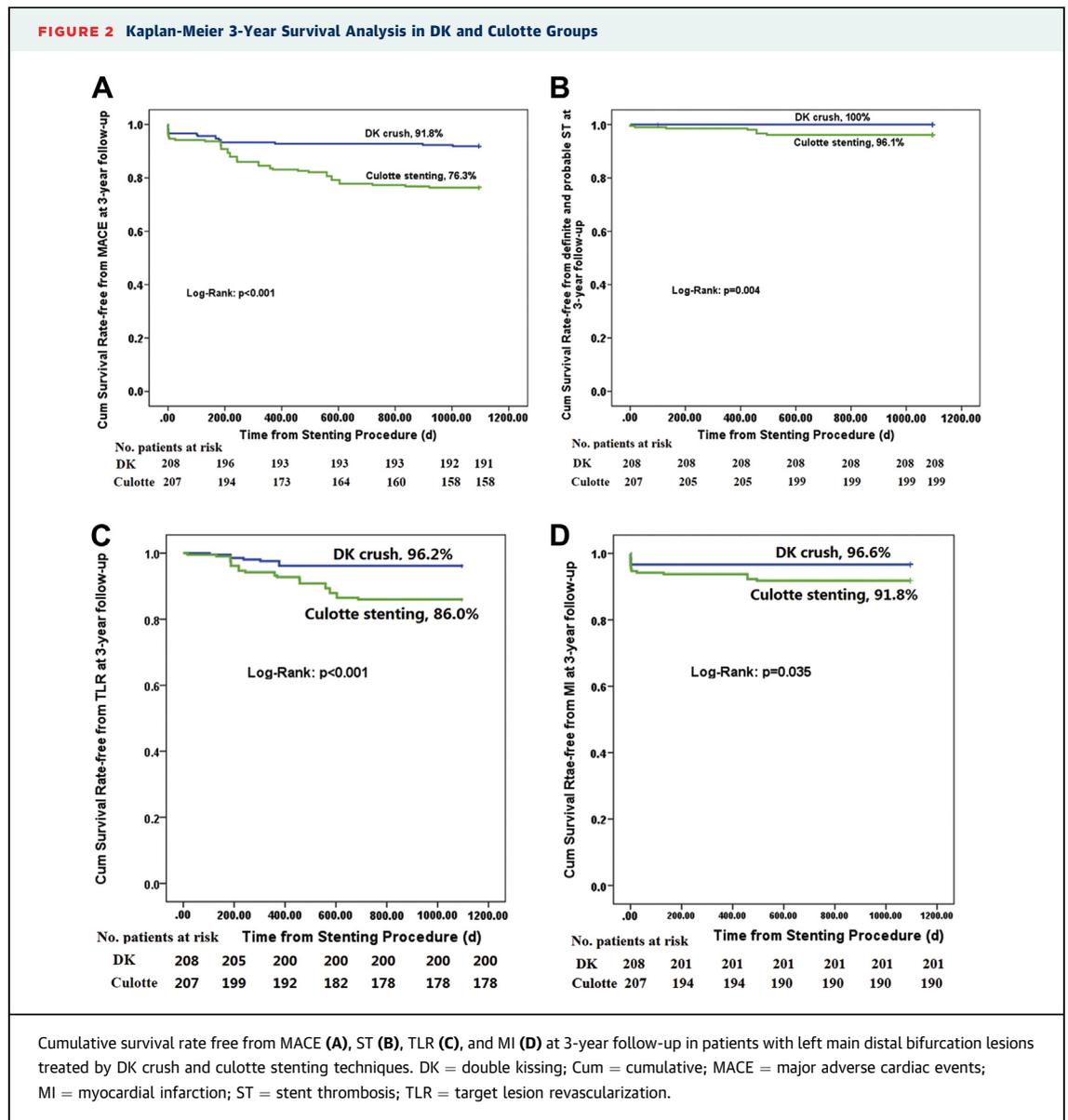
Values are n (%). *Indicates that patient number was 210 in the DK and 209 in the Culotte groups, respectively.
 DK = double-kissing; CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

There were 246 patients from centers in China and 173 patients from centers outside China, 7.2% of patients had recent MI (>2 weeks). Three-vessel diseases were seen in 70% of patients. The localization of lesions within the left main coronary artery was virtually the same. More than 96% of distal bifurcation lesions were stratified by Medina 1,1,1. Pre-procedural intravascular ultrasound (IVUS) assessment was used in >70% of patients. Post-dilation was performed in >95% of patients. Final kissing balloon inflation was not performed in 1 case in each group, respectively. Angiographic success was achieved in >98% of patients. Complete revascularization was achieved in 85.7% in the DK crush group

and 82.0% in the culotte group, respectively. Post-stent assessment using IVUS was performed in >85% of patients.

Four patients were lost to 3-year follow-up (Figure 1), 2 patients in each group. Finally, 415 patients (208 in the DK crush group and 207 in the culotte group, respectively) formed the basis of the current study. Aspirin was not taken by 2 patients in the DK crush group and by 1 patient in the culotte group. Dual-antiplatelet therapy was prescribed in 96 patients (46.2%) in the DK crush group, nonsignificant at 93 patients (44.9%) in the culotte group ($p > 0.05$).

Repeat angiography was performed in 176 patients in the DK crush group and 174 in the culotte group at

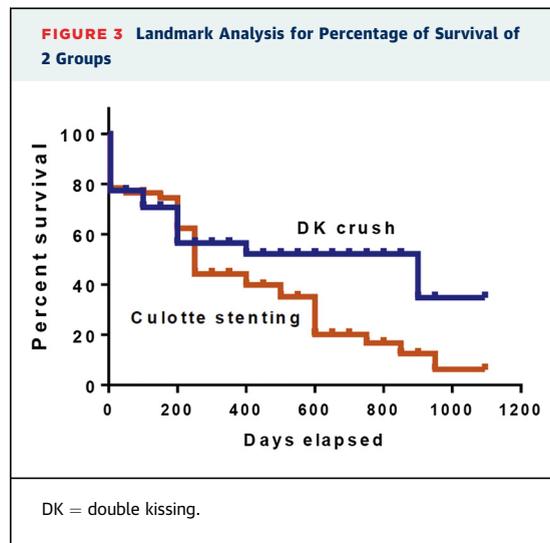


8 months after the index stenting procedure, and it was performed in additional 28 patients in the DK crush group and 31 in the culotte group at 2-year follow-up. At 3-year follow-up, angiography was performed in another 7 patients in the DK crush group and in 13 in the culotte group.

Clinical results are shown in **Table 2**. Based on angiography at 8 months after the index procedure, revascularization was performed in 3 patients (1 in the DK crush group and 2 in the culotte group) who had visual diameter stenosis $\geq 90\%$ without chest pain, but a treadmill test was positive for these 3 patients. At 1-year follow-up, there were more frequent MACE (16.4%) and TVR (11.1%) in the culotte group compared with the DK crush group (6.3%, $p = 0.001$ and 4.3%, $p = 0.010$). At 2- and 3-year follow-up, the cumulative incidences of MACE were 22.7% and 23.7%, respectively, in the culotte group and 7.2% and 8.2% in the DK crush group, respectively (all $p < 0.001$) (**Table 1**), mainly driven by increased rates of MI (7.7% vs. 3.4%, $p = 0.046$, and 8.2% vs. 3.4%, $p = 0.037$) and TVR (17.1% vs. 4.8%, $p < 0.001$, and 18.8% vs. 5.8%, $p < 0.001$) in the culotte group. Of patients who had MI, revascularization was performed in 3 in the DK crush group and in 5 in the culotte group, respectively. The rates of MACE-free survival are shown in **Figure 2A**. There was no significant difference in MACE or individual endpoint among centers or among countries.

By 3 years after the index procedures, the rate of definite and probable ST was 3.9% in the culotte group and 0% in the DK crush group ($p = 0.004$) (**Table 2**). The rates of event-free survival of definite and probable ST are shown in **Figure 2B**. In the culotte group, the rates of early (<30 days), late (within 1 year), and very late (>1 year) ST was 0.5%, 1.0%, and 2.4%, respectively. All patients having a definite or probable ST were taking DAPT. The rates of event-free survival of TLR and MI are shown in **Figures 2C and 2D**. Landmark analysis of the percentage of survival is shown in **Figure 3**.

According to the DEFINITION study criteria, 119 patients (28.7%) were classified by complex LMDBLs and 296 (71.3%) patients were included in the simple LMDBL subgroup. There were significant differences in the 3-year rates of MACE and definite and probable ST between simple (8.1% and 1.0%, respectively) and complex (35.3% and 5.0%, respectively) ($p < 0.001$ and $p = 0.047$, respectively) (**Table 3**, **Figure 4**), particularly in patients with complex LMDBLs treated by culotte stenting (51.5% and 7.6%, respectively) (**Table 4**) compared with DK crush stenting for complex LMDBLs (15.1% and 1.9%). DK crush stenting for



complex LMDBLs still tended to be associated with acceptable rates of MACE and ST at 3-year follow-up compared with simple LMDBLs after DK crush treatment.

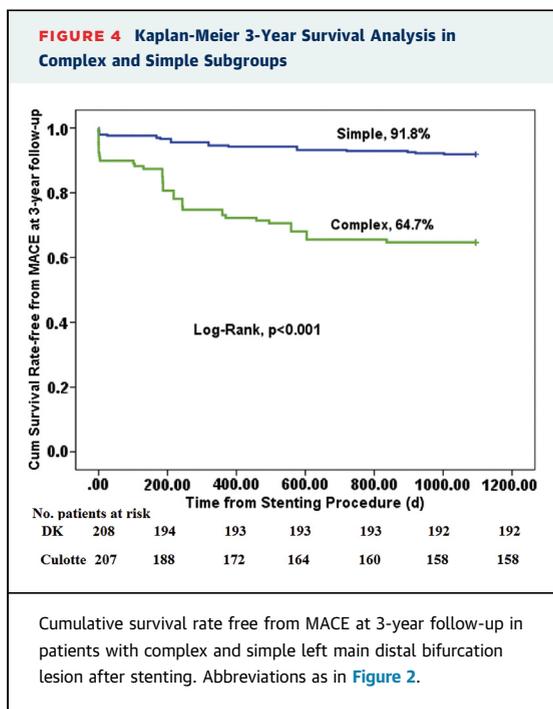
DISCUSSION

To our knowledge, the DKCRUSH-III study is the only multicenter and randomized study comparing DK crush with culotte stenting techniques for patients with LMDBLs. Our results showed that the difference in MACE between the 2 studied groups was sustained and became greater through 3-year follow-up. Another important finding was the increased 3-year rate of definite and probable ST in the culotte group, which translated into more frequent cardiac death and MI.

TABLE 3 The 3-Year Clinical Outcomes After Stenting in Patients With Complex and Simple Left Main Distal Bifurcation Lesions

	Complex (n = 119)	Simple (n = 296)	p Value
MACE	42 (35.3)	24 (8.1)	<0.001
Cardiac death	6 (5.0)	3 (1.0)	0.019
MI	16 (13.4)	8 (2.7)	<0.001
TLR	28 (23.5)	9 (3.0)	<0.001
CABG	3 (2.5)	0	0.023
TVR	33 (27.7)	18 (6.1)	<0.001
ST	6 (5.0)	3 (1.0)	0.019
Definite	4 (3.4)	3 (1.0)	0.108
Probable	1 (0.8)	0	0.287
Definite/probable	5 (4.2)	3 (1.0)	0.047
Possible	1 (0.8)	0	0.287

Values are n (%).
Abbreviations as in **Table 2**.



The 1-year clinical outcome after culotte stenting for coronary bifurcation lesions has been reported in 3 studies (10,12,15). In ISAR-LEFT MAIN (Paclitaxel-versus sirolimus-eluting stents for unprotected left main coronary artery disease) study (15), 384 patients with distal unprotected left main coronary artery lesions were treated by 2-stent techniques (98% received culotte stenting), the 1-year TLR and MACE rates in the Cypher group were 7.8% and 15.8%, respectively, and compared well with the culotte group from the DKCRUSH-III study (6.7% and 14.4%,

respectively) and the Nordic Stent Study (12). However, long-term clinical results after culotte stenting was only reported in the present study and the Nordic Stent Study (16). The latter study included 424 patients with overall bifurcation lesions (LMBLs in 41 patients) and reported lower rates of TLR (6.1%) and MACE (16.7%) at 3-year follow-up after culotte stenting, almost half of the rates in the present study (14.0% and 23.7%). These differences in TLR and MACE might be related to the discriminations in baseline characteristics between the Nordic Stent Study and the DKCRUSH-III study: less diabetes (15% vs. 30.1%), no acute MI (0% vs. 5.1%), fewer LMBLs (9.6% vs. 100%), and more false bifurcation lesions (18% vs. 0%). On the other hand, compared with classic crush in the Nordic Stent Study (16), classic crush stenting was associated lower rates of TLR (3.8% vs. 6.2%) and MACE (8.2% vs. 20.6%) at 3 years after the indexed procedures, which was even better than those in a recent study using a T-stent technique and sirolimus-eluting stent (TLR in 10%) (17), in line with previous DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) study (18), which only included true bifurcation lesions (Medina 1,1,1 and 0,1,1). Thus, DK crush seems to be a promising technique for true and complex bifurcation lesions.

For bifurcation lesions, a complex stenting approach has been an independent factor for ST (19-21), although there are no convincing data after stenting LMBLs. Similar to the 1-year ST rate (<1%) in the ISAR-LEFT MAIN (14) trial, the ST rate (1.0%) after culotte stenting in the DKCRUSH-III study is slightly lower than the 1.9% rate reported by Erglis et al. (12) and the 1.6% rate reported by Adriaenssens et al. (22). However, the long-term rate of ST was only reported by the present study and the Nordic Stent Study (16). We found that an overall rate of ST at 3-year follow-up was 3.9% after culotte stenting, nearly one-half the rate (7.1%) reported in the Nordic Stent Study (16). Less use of IVUS could not be excluded from the explanation of the higher ST rate after culotte stenting from that study. Previous studies have demonstrated the reduced rates of MI, cardiac death, and ST by IVUS-guided stenting procedure (23-25). Our previous study showed that even if DK crush was used for bifurcation lesions, IVUS-guided procedure could improve the procedural quality (less malapposition, edge dissection, and stent expansion) (25). Furthermore, Gao et al. (26) reported a trend of a reduced 1-year ST rate if stenting left main disease was guided by IVUS. Bench test reported that a “napkin” or a gap or a metallic ridge (27) is usually seen at the ostial SB after culotte stenting,

TABLE 4 The 3-Year Clinical Outcomes in Simple and Complex Left Main Distal Bifurcation Lesions After Either DK Crush or Culotte Stenting

	DK Crush (n = 208)		Culotte (n = 207)		p Value*
	Simple (n = 155)	Complex (n = 43)	Simple (n = 141)	Complex (n = 66)	
MACE	9 (5.8)	8 (15.1)	15 (10.6)	34 (51.5)	<0.001
Cardiac death	1 (0.6)	2 (3.8)	2 (1.4)	4 (6.1)	0.691
MI	3 (1.9)	4 (7.5)	5 (3.5)	12 (18.2)	0.110
TLR	4 (2.6)	4 (7.5)	5 (3.5)	24 (36.4)	<0.001
CABG	0	2 (3.8)	0	1 (1.5)	0.585
TVR	6 (3.9)	6 (11.3)	12 (8.5)	27 (40.9)	<0.001
ST	0	1 (1.9)	3 (2.1)	5 (7.6)	0.224
Definite	0	0	3 (2.1)	4 (6.1)	0.128
Probable	0	0	0	1 (1.5)	0.368
Definite/probable	0	0	3 (2.1)	5 (7.6)	0.041
Possible	0	1 (1.9)	0	0	0.445

Values are n (%). *Comparison of complex DK and complex culotte. Abbreviations as in Table 2.

leading to the failure to fully cover the ostial SB and resulting in increased in-stent restenosis, TLR, and ST. Our another important finding was the absence of definite and probable ST at 3-year follow-up after DK crush stenting, suggesting the importance of stenting techniques in improving the safety of stenting LMDBLs. Obviously, 1 advantage of the DK crush stenting technique is the introduction of first kissing inflation immediately after balloon crush, which may improve the stent expansion (10,12). Furthermore, alternative inflation using a noncompliant balloon with a minimal of 16 atm followed by kissing balloon inflation and proximal optimal technique during DK crush stenting (12) is another critical point to maintain a better stent apposition. Subsequently, less metal overlap, fully expanded stent at the ostial SB, and less distortion achieved by DK crush should be correlated with improved 3-year clinical results. Based on the strict criteria for recruitment of participating centers in our study, the difference in 3-year MACE was less likely related to the insufficient experience for operators.

In general, LMDBLs have intrinsic differences in terms of anatomic features. Our previous DEFINITION study (11) found that complex bifurcation lesions were roughly seen in one-third of overall bifurcation lesions, consistent with our current results (28%). From our serial analysis, the 3-year rates of TLR and MACE after stenting complex LMDBLs were extremely higher than those after stenting simple LMDBLs, particularly after culotte stenting. Stenting complex LMDBLs using DK crush still tends to be associated with increased rates of TLR, TVR, MACE, and ST, even though it did not achieve significance when compared with stenting simple LMDBLs using the DK crush approach. Taking previous studies (10,18) into consideration, we propose that LMDBLs should be stratified according to DEFINITION criteria (11) or scoring systems (2,3,19) before making decisions about the revascularization approach and the selection of stenting techniques.

STUDY LIMITATIONS. We did not include a CABG group to contrast with the stenting techniques. However, the promising results achieved by the DK crush

technique were comparable to those after CABG. Another limitation is that angiographic follow-up was scheduled for 8 months after indexed procedure, which might increase the rate of revascularization.

CONCLUSIONS

This randomized, multicenter study suggests that, compared with the DK crush technique, culotte stenting is associated with significantly increased MACE in patients with LMDBLs, especially in patients with complex lesions. Further studies are necessary to compare DK crush with provisional T-stenting in patients with complex LMDBLs.

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PERSPECTIVES

WHAT IS KNOWN? Stenting LMDBLs is technically challenging and associated with unfavorable results. DK crush stenting, a systematic 2-stent technique, was found in the previous study to be superior to culotte stenting for left main bifurcations.

WHAT IS NEW? We report less frequent ST and revascularization by DK crush during 3-year follow-up.

WHAT IS NEXT? Further study is required to compare DK crush stenting with provisional stenting for left main bifurcations.

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