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Original Article

Efficacy of one- vs. two-stent implantation for coronary bifurcation lesions in diabetic patients utilizing AIR2 as an endpoint

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Abstract: Objective: This study aimed to assess the long term outcomes (all-cause death, myocardial infarction, target vessel revascularization, and silent restenosis at 12 months) of one-stent vs. two-stent implantation due to coronary bifurcation lesionsin diabetic patients using AIR2 as a new endpoint. Methods and Results: A total of 178 diabetic patients with true coronary bifurcation lesions underwent percutaneous coronary intervention in the DK-Crush trials. All patients were stratified based on the stent placement strategy: one-stent group (n=76) and two-stent group (n=102). Results showed the primary endpoint, AIR2, in one-stent group was twice that in two-stent group (32.9% vs. 16.7%, *P*=0.013). The incidence of silent restenosis at 12 months was also significantly higher in one-stent group (19.7% versus 4.9%, *P*=0.003). Moreover, Kaplan-Meier analysis revealed the cumulative AIR2-free survival rate after a 12-month follow-up was markedly lower in one-stent group than in two-stent group. Interestingly, MACEs, including death, myocardial infarction and repeat revascularization, were not comparable between 2 groups (13.2% vs. 12.7%, *P*=0.935). Likewise, the incidence of definite or probable ST in one-stent group was also similar to that in two-stent group (2.6% vs. 4.9%, *P*=0.761). Conclusion: Our study indicates that, in terms of the AIR2 as a combined clinical and angiographic endpoint, two-stent implantation is superior to one-stent implantation for the treatment of coronary bifurcation intervention in diabetic patients.

Keywords: Coronary heart disease, bifurcation lesion, diabetes, percutaneous coronary intervention

Introduction

Percutaneous coronary intervention (PCI) of bifurcated coronary lesions remains technically challenging and is associated with lower procedural success rate and higher restenosis and thrombosis rates than that of non-bifurcated lesions [1-4]. Clinical trials have unanimously shown that the one-stent implantation, which involves implantation of one stent in the main vessel (MV) with or without balloon angioplasty of the side branch (SB), should be the first-line strategy for the therapy of the majority of lesions [5-10]. However, these trials have some limitations due to their study designs, including the enrollment of patients with false bifurcation lesions [11] and the use of improper endpoints.

When false bifurcation lesions are treated with-one-stent implantation, there is a low risk for occlusion ofthe SB because SB ismostly pinched by “carina shift”, rather than “plaque shift” [11]. Balloon angioplasty is adequate for carina shift, and stenting a SB has no additional advantage over balloon angioplasty alone. In contrast, the stenosis of residual SB after stenting MV in true bifurcation lesions is mainly attributed to the plaque redistribution, which worsens the SB ostial lesions. Thus, balloon angioplasty in the SB is almost inevitable. Intima damage caused by balloon inflation may inevitably cause hyperplasia, especially in patients with diabetes mellitus (DM). It is well known that neointimahyperplasia is a major cause of late restenosis. Drug-eluting stents (DES) are able to inhibit the proliferation of neo-

Table 1. Baseline characteristics ofpatients enrolled into present study

Variables	1-stent group (n=76)	2-stent group (n=102)	*P* value
Age (years)	63.2 ± 10.5	64.9 ± 8.9	0.245
Male, n (%)	48 (63.2)	63 (61.8)	0.877
Current smoker, n (%)	22 (28.9)	31 (30.4)	0.869
LDL-cholesterol (mg/dl)	145.5 ± 15.3	140.1 ± 14.6	0.018
Hypertension, n (%)	39 (51.3)	59 (57.8)	0.447
Stable angina pectoris, n (%)	25 (32.9)	32 (31.4)	0.872
Unstable angina, n (%)	40 (52.6)	55 (54.0)	0.880
Silent ischemia, n (%)	11 (14.5)	15 (14.7)	0.965
Previous MI, n (%)	4 (5.3)	5 (4.9)	0.913
Prior PCI, n (%)	6 (7.9)	9 (8.8)	0.825
Prior CABG, n (%)	1 (1.3)	3 (2.9)	0.637
Insulin-dependent DM, n (%)	11 (14.5)	17 (16.7)	0.836
LVEF (%)	57.1 ± 6.5	55.9 ± 6.2	0.213

Footnotes: LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; DM, diabetes mellitus; LVEF: left ventricular ejection fraction.

intima after the procedures and limit in-stent restenosis. Additionally, DES has been shown to be more effective than plain balloon angioplasty, even in DM patients [12-16]. Therefore, theoretically, the two-stent implantation of the SB with DES will improve the procedural success rate and consequently, the outcomes of true bifurcation lesions, when compared with one-stent implantation of the SB with balloon angioplasty alone, especially in the patients with DM and small vessel lesions. If this two-stent implantation will also avoid the deformation of stents and the insufficient coverage of SB ostium. On the contrary, the mechanism of branch involvement after one-stent implanted in true bifurcation lesions was the redistribution of plaque. Meanwhile, rates of simple balloon angioplasty induced endometriosis and restenosis would be significantly higher than branch stent implantation, especially in DM patients. Thus, when compared with simple balloon angioplasty, present DES angioplasty has been proved without exception to have incontrovertible advantages in patients with small vessel disease and DM [17-19]. Therefore, it can be concluded theologically that two-stent implantation is better than one-stent in improve the procedural success rate and prognosis in DM patients with true bifurcation lesions.

One of important limitations in these randomized trials on bifurcated coronary lesion is the lack of DM subgroup analysis. Revascularization procedures in DM patients are usually associated with poorer outcomes and increased rate of restenosis than in patients without DM [20-22]. Both DM and bifurcated coronary lesions may be potent determinants of adverse outcomes. Unfortunately, limited treatment information is available on the safety and efficacy of stentingin patients with DM and bifurcated coronary lesions.

Another main limitation in previous trials on bifurcated coronary lesionsis related to the inappropriate definitions of endpoints and outcomes. As patients with silent ischemia have the same adverse outcomes to those with symptomatic ischemia, they should also be treated. However, silent ischemia is difficult to identify definitively with available techniques. As a result, patients with significant angiographic stenosis but without symptoms and definitely need ingtarget vessel revascularization would not be included in the analysis of major adverse cardiac events (MACEs), especially in patients receiving one-stent implantation and without ischemic testing. On the contrary, variables related to angiographic anatomy, such as (re)stenosis, minimum lumen diameter (MLD), or late loss, were not always associated with vascular function. Accordingly, clinical events maybe absent, even the vascular stenosis is very severe, because not all of severe lesions by angiography cause hemodynamically significant consequences. To correct the biases in these clinical events and to compensate for the angiographic disadvantages, we evaluated the outcomes of DM patients with AIR2 as predefined composite endpoints, which include all-cause death, myocardial infarction (MI), target vessel revascularization (TVR), and silent restenosis (SR).

The present study aimed to compare the one-year AIR2 in a cohort of DM patients receiving one-stent and two-stent implantation due to bifurcated coronary lesions who were enrolled into the double-kissing (DK) - Crush trials [23-25].

Table 2. Baseline angiographic and procedural characteristics

	1-stent group (n=76)	2-stent group (n=102)	*P* value
Lesion locations, n (%)			0.979
LMT	13 (17.1)	19 (18.6)	
LAD-D1	37 (48.7)	51 (50.0)	
LCX-OM	15 (19.7)	18 (17.6)	
RCA	11 (14.5)	14 (13.7)	
Medina classification, n (%)			0.711
1.1.1	49 (64.5)	63 (61.8)	
0.1.1	27 (35.5)	39 (38.2)	
Lesion characteristics, n (%)			
Calcification	23 (30.3)	27 (26.5)	0.615
Thrombus	4 (5.3)	9 (8.8)	0.402
Restenosis	4 (5.3)	7 (6.9)	0.761
CTO	3 (3.9)	5 (4.9)	0.520
Mean lesion length (mm)			
Main vessel	21.25 ± 10.95	23.48 ± 12.38	0.214
Side branch	10.88 ± 6.09	12.01 ± 7.19	0.270
GPIIb/IIIa inhibitors, n (%)	14 (18.4)	19 (18.6)	0.972
IVUS guidance, n (%)	20 (26.3)	28 (27.5)	0.866
DES type, n (%)			0.299
SES	69 (54.8)	147 (62.8)	
PES	19 (15.1)	26 (11.1)	
EES	38 (30.2)	61 (26.1)	
Balloon diameter for KBI (mm)			
Main vessel	3.19 ± 0.29	3.12 ± 0.25	0.086
Side branch	2.24 ± 0.15	2.72 ± 0.20	<0.001
Maximal inflation pressure (atm)			
Main vessel	16.72 ± 2.64	16.08 ± 2.53	0.103
Side branch	7.49 ± 1.82	16.58 ± 1.69	<0.001
Final KBI, n (%)	76 (100%)	98 (96.1%)	0.137
Procedural time (minutes)	48.04 ± 22.26	65.11 ± 30.14	<0.001
Fluoroscopy time (minutes	14.09 ± 6.19	19.69 ± 7.12	<0.001
Contrast volume (ml)	116.7 ± 63.2	173.8 ± 80.06	<0.001
Angiographic success, n (%)			
Main vessel	76 (100%)	102 (100%)	1.000
Side branch	63 (82.9%)	96 (94.1%)	0.025

Footnotes: LMT, left main trunk; LAD-D1, left anterior descending artery and diagonal branch; LCX-OM, left circumflex artery and obtuse marginal branch; RCA, right coronary artery; CTO, chronic total occlusion; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stent; EES, everolimus-eluting stent; IVUS, intravascular ultrasound; KBI, kissing balloon inflation, defined as achievement of TIMI 3 flow with a final residual <30% stenosis of the main vessel and <50% stenosis of the side branch.

Methods

Patients

A total of 178 patients with DM were recruited into present study from DK-Crush trials [23-25], which compared the double-kissing technique with the provisional stenting, the culotte stenting, and the classical crush stenting techniques for the treatment of bifurcated coronary lesions. Of them, 76 received one-stent implantation (1-stent group), and 102 received two-stentim plantation (2-stent group). DM was diagnosed according to the World Health Organization Report [26].

All DK-Crush trials had similar inclusion and exclusion criteria [23-25]. Briefly, patients ≥18 years, having a diagnosed stable or unstable angina pectoris or silent is chemia and having a *de novo* true coronary bifurcationlesions were enrolled. Patients were excluded if one of following characteristics was present: MI within 24 h prior treatment, heavy calcification requiring rotational atherectomy, life expectancy of less than 1 year, serum creatinine greater than 3.0 mg/dl, liver dysfunction and allergy to any of drugs used, including aspirin, clopidogrel, sirolimus, and paclitaxel. An additional inclusion criterion was the presence of only one true coronary bifurcation lesionin a specific patient.

Definition of true coronarybifurcation lesions

A true coronary bifurcation lesion was defined as a >50% stenosis of both main branch and ostiumof the SB. This definition was adapted from the Medina classification (type 1.1.1 and type 0.1.1) [27], in which the reference vessel diameter (RVD) of MV and SB should be at least 2.5 mm and 2.2 mm, respectively, by visual estimate. The coronary bifurcation lesionshould be located in the anterior descending artery anda diagonal artery, the circumflex artery and an obtuse marginal artery, the right coronary artery and posterior descending artery/posterolateral artery,

Table 3. Quantitative angiographic analysis of the prebifurcation main vascular segment

	1-stent group (n=76)	2-stent group (n=102)	*P* value
Baseline			
RVD (mm)	2.91 ± 0.47	2.96 ± 0.52	0.510
MLD (mm)	0.98 ± 0.38	0.96 ± 0.32	0.704
SD (%)	64.5 ± 11.2	66.5 ± 13.3	0.291
Post-PCI			
RVD (mm)	3.02 ± 0.49	3.11 ± 0.43	0.195
MLD (mm)	2.74 ± 0.54	2.81 ± 0.69	0.465
SD (%)	10.3 ± 4.2	9.5 ± 3.8	0.186
Acute gain (mm)	1.71 ± 0.39	1.75 ± 0.45	0.536
12-month follow-up			
RVD (mm)	2.85 ± 0.45	2.89 ± 0.47	0.568
MLD (mm)	2.36 ± 0.49	2.47 ± 0.57	0.179
SD (%)	19.4 ± 11.5	17.6 ± 11.8	0.310
Late loss (mm)	0.40 ± 0.55	0.37 ± 0.46	0.693
Restenosis, n (%)	5 (6.6)	7 (6.9)	0.941

Footnotes: RVD, reference vessel diameter; MLD, minimum lumen diameter; SD, stenosis diameter; PCI, percutaneous coronary intervention.

Table 4. Quantitative angiographic analysis of the postbifurcation main vascular segment

	1-stent group (n=76)	2-stent group (n=102)	*P* value
Baseline			
RVD (mm)	2.81 ± 0.41	2.88 ± 0.46	0.295
MLD (mm)	0.89 ± 0.36	0.93 ± 0.39	0.485
SD (%)	60.5 ± 13.1	63.4 ± 16.3	0.204
Post-PCI			
RVD (mm)	2.89 ± 0.52	2.91 ± 0.48	0.791
MLD (mm)	2.65 ± 0.51	2.69 ± 0.57	0.629
SD (%)	12.3 ± 4.9	11.5 ± 4.2	0.243
Acute gain (mm)	1.64 ± 0.36	1.70 ± 0.41	0.311
12-month follow-up			
RVD (mm)	2.83 ± 0.42	2.90 ± 0.46	0.299
MLD (mm)	2.33 ± 0.37	2.40 ± 0.44	0.263
SD (%)	21.2 ± 12.3	18.9 ± 11.4	0.200
Late loss (mm)	0.34 ± 0.50	0.36 ± 0.59	0.812
Restenosis, n (%)	4 (5.3)	4 (3.9)	0.725

Footnotes: RVD, reference vessel diameter; MLD, minimum lumen diameter; SD, stenosis diameter; PCI, percutaneous coronary intervention.

or the left main stem/circumflex artery/left anterior descending artery in a right dominant system.

Stenting procedures

Patients were pretreated with aspirin (300 mg) and clopidogrel (300 mg). Activated clotting time (ACT) was maintained at >280 s using unfractionated heparin during the whole procedures. GP IIb/IIIa inhibitors were administered at the discretion of the operator. After PCI, clopidogrel at 75 mg/d was given for at least one year. Additionally, aspirinwas given at 300 mg/d for 1 month and the dose was subsequently reduced to 100 mg/d for long-term maintenance therapy.

Stents used in this cohort included sirolimus-eluting stents (Cypher™, CordisCorporation, USA; Excel™, Jiwei Corporation, China), paclitaxel-eluting stents (Taxus™, Boston Scientific, USA) and everolimus-eluting stents (XienceV, Abbott, USA). Different types of DES were not allowed in the same patient and the use of bare metal stents was prohibited in all DK-Crush trials.

Angiography/stenting was performed through a radial or femoral approach with a 6 F guiding catheter, according to a routine protocol. Either a 7 or 8 F catheter was used in the two-stent implantation. Pretreatment with conventional balloon or cutting balloon of segments not to be covered by stent was not carried out. In other words, the areas close to the MV segment in the 1-stent group and the MV plus SB segments in the 2-stent group were not subjected to intervention. The target lesion was predilated and/or postdilated at the discretion of the operator.

In the 1-stent group, the main treatment principles were as follows: (1) The MV was stented with wire protection of the SB. (2) Kissing balloon inflation (KBI) in both branches was under-

Table 5. Quantitative angiographic analysis of the side branch

	1-stent group (n=76)	2-stent group (n=102)	*P* value
Baseline			
RVD (mm)	2.31 ± 0.39	2.37 ± 0.43	0.340
MLD (mm)	0.83 ± 0.25	0.81 ± 0.30	0.638
SD (%)	62.1 ± 10.4	64.8 ± 13.1	0.140
Post-PCI			
RVD (mm)	2.50 ± 0.45	2.56 ± 0.51	0.416
MLD (mm)	1.35 ± 0.24	2.46 ± 0.32	<0.001
SD (%)	37.2 ± 15.6	12.5 ± 6.3	<0.001
Acute gain (mm)	0.51 ± 0.59	1.56 ± 0.64	<0.001
12-month follow-up			
RVD (mm)	2.41 ± 0.42	2.51 ± 0.39	0.103
MLD (mm)	1.26 ± 0.21	2.32 ± 0.20	<0.001
SD (%)	39.8 ± 18.3	20.6 ± 14.4	<0.001
Late loss (mm)	0.12 ± 0.16	0.18 ± 0.21	0.039
Restenosis, n (%)	19 (25.0)	14 (13.7)	0.078

Footnotes: RVD, reference vessel diameter; MLD, minimum lumen diameter; SD, stenosis diameter; PCI, percutaneous coronary intervention.

taken with anatomically appropriate sizing for each vessel. The SB was not treated further, unless at least 1 of the following conditions was present: residual ≥50% stenosis; dissection of type B or worse; thrombolysis in myocardial infarction flow ≤2. (3) If 1 of these situations applied, stenting of the SB was allowed with the T-stenting technique.

In the 2-stent group, the main treatment principles were the stenting of both the MV and SB with the DK-Crush technique [28], culotte technique [29], or T-stenting technique. In all cases of SB stenting, the operator was required to carry out a KBI at the end of procedures. Another key step in the procedures was the alternative inflation with a non-compliant balloon at a high pressure (≥16 atm) for SB before each kissing.

Follow-up

All the patients were followed up by telephone or hospital visit once monthly until June 2013. Adverse events were monitored throughout the study period. Coronary angiography for follow up was scheduled at 12 months after the indexed procedures, unless earlier follow-up was necessary due to clinical reasons.

Quantitative coronary angiographic measurements

Matched orthogonal views were used for quantitative coronary analysis (QCA) after intracoronary injection of nitroglycerine (100-200 μg). This was carried out before and after the procedures and at follow-up. The angiograms were analyzed off line with a validated automated edge-detection coronary bifurcation system (CAAS version 5.7.1, Pie Medical Imaging, Netherlands). Vascular segments involving coronary bifurcation lesions were divided into proximal MV, distal MV, and SB segments within 5-mm proximal or distal to the stent, and the polygon of confluence (POC) was obtained [30]. The QCA variables included RVD, minimal lumen diameter (MLD), acute gain, late lumen loss, and net gain. QCA analysis was performed by an independent core laboratory, China Cardiovascular Research Foundation (CCRF), Beijing, China.

Study endpoints and definitions

The composite endpoint, AIR2, at 12 months was used for the evaluation of long term outcomes. AIR2 included all-cause death, MI, target vessel revascularization (TVR) by PCI or coronary artery bypass surgery, and SR. The secondary variable for evaluation was the incidence of MACE, which was defined as the composite of cardiac death, MI and TVR. MI was diagnosed according to the type 1 definition in the universal definition of MI, and procedure-related MI was excluded [31]. Procedure-related MI was considered if CK-MB or troponin-I increased to more than three times the upper limit of normal (ULN).

TVR was recognized as an ischemia-driven repeat revascularization within the treated vessels. SR was defined as the non-revascularization with ≥75% stenosis diameter (SD) of the treated vessels at one-year follow-up angiography. Restenosis was defined as ≥50% SD of either the stented segment or the segment 5-mm proximal or distal to the stent. Stent thrombosis was assessed as definite, probable, or possible, according to the Academic Research Consortium (ARC) definition [32].

Angiographic success was defined as <30% residual stenosis for MV and 50% for SB, with

Table 6. AIR2 and MACE at 12months

	1-stent group (n=76)	2-stent group (n=102)	*P* value
Cumulative AIR2, n (%)	25 (32.9)	17 (16.7)	0.013
Cumulative MACE, n (%)	10 (13.2)	13 (12.7)	1.000
All-cause death, n (%)	2 (2.6)	3 (2.9)	0.902
Cardiac death	2 (2.6)	2 (2.0)	0.765
Myocardial infarction, n (%)	3 (3.9)	3 (2.9)	0.713
Target vessel revascularization, n (%)	6 (7.9)	8 (7.8)	0.990
Stent thrombosis, n (%)	3 (2.6)	5 (4.9)	0.761
Silent (re)stenosis, n (%)	15 (19.7)	5 (4.9)	0.003
(Re)stenosis, n (%)	22 (28.9)	17 (16.7)	0.067
MV	7 (9.2)	9 (8.8)	0.840
SB	19 (25.0)	14 (13.7)	0.078

Footnotes: MACE, major adverse cardiac events. AIR2 refers to the composite clinical and angiographic endpoints, including all-cause death, myocardial infarction, target vessel revascularization, and silent (re)stenosis. SR was defined as non-revascularization with ≥75% stenosis diameter (SD) within the treated vessels at one-year follow-up by angiography.

grade 3 TIMI flow in both branches. Procedural success was defined as the achievement of angiographic success in the absence of any in-hospital MACE. Lesion specificities were defined according to American Heart Association/American College of Cardiology (AHA/ACC) criteria [33].

Statistical analysis

Continuous variables were expressed as means ± standard deviations, and categorical variablesas percentages or frequencies. For continuous variables, comparisons between groups were done with an independent *t* test if they were normally distributed or with the Mann-Whitney *U* test if abnormal distribution was revealed. The Fisher's exact test or χ^2-test was used to compare the categorical variables between groups. Kaplan-Meier curves were generated to compare the long-term outcomes between 2 groups. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL).

Results

The mean age was 64.2 ± 9.4 years (range: 28 to 84 years), and there were 111 (62.4%) males among 178 patients. Additionally, 98 patients (55.1%) had hypertension, and 28 (15.7%) received glucose-lowering therapy with insulin. The indication for treatment (what treatment) was unstable angina pectoris in approximately 50% of the patients and stable angina pectoris in 1/3 of the patients. The demographics and clinical features of these patients are listed in **Table 1**. There were no significant differences between groups in terms of atherosclerotic risk factors, demographic and clinical characteristics. However, differencein serum low-density lipoprotein-cholesterol was observed betweengroups (145.5 ± 15.3 vs. 140.1 ± 14.6, $P=0.018$).

Details on the procedural and lesion characteristics of 2 groups are reported in **Table 2**. The index lesions in 2 groups were distributed in a similar manner in the left main trunk, left anterior descending artery, circumflex artery, and right coronary artery. There was also no significant difference between 2 groups inthe type of bifurcation, lesion length and lesion characteristics assessed by the operator. The use of GPIIb/IIIa inhibitors and IVUS was similar between groups. The procedure time, fluoroscopy time, and contrast volume used in 2-stent group increased significantly as compared to 1-stent group. In 2-stent group, DK-Crush technique was the mostfrequently used (65.7%), followed by culotte stenting (23.5%) and crush stenting (10.8%).

Angiographic success in the MV was achieved in all cases in both groups. However, angiographic success in the SB was significantly different between 1-stent and 2-stent groups (94.1% vs. 82.9%, $P=0.025$). More patients in 2-stent group (96.1%) successfully completed the procedure with final KBI. In 1-stent group, an additional stent was implanted on the SB in 25/76 (32.9%) patients, but successful KBI was achieved in 82.7%. The reasons for additional stenting included residual >50% stenosis in 19 patients (76.0%), and dissection of type B or worse in another 6 patients (24.0%).

Quantitative angiographic analysis

One-year angiographic data were available in 159 cases (89.3%), and the rate of follow-up by angiography was similar between 2 groups.

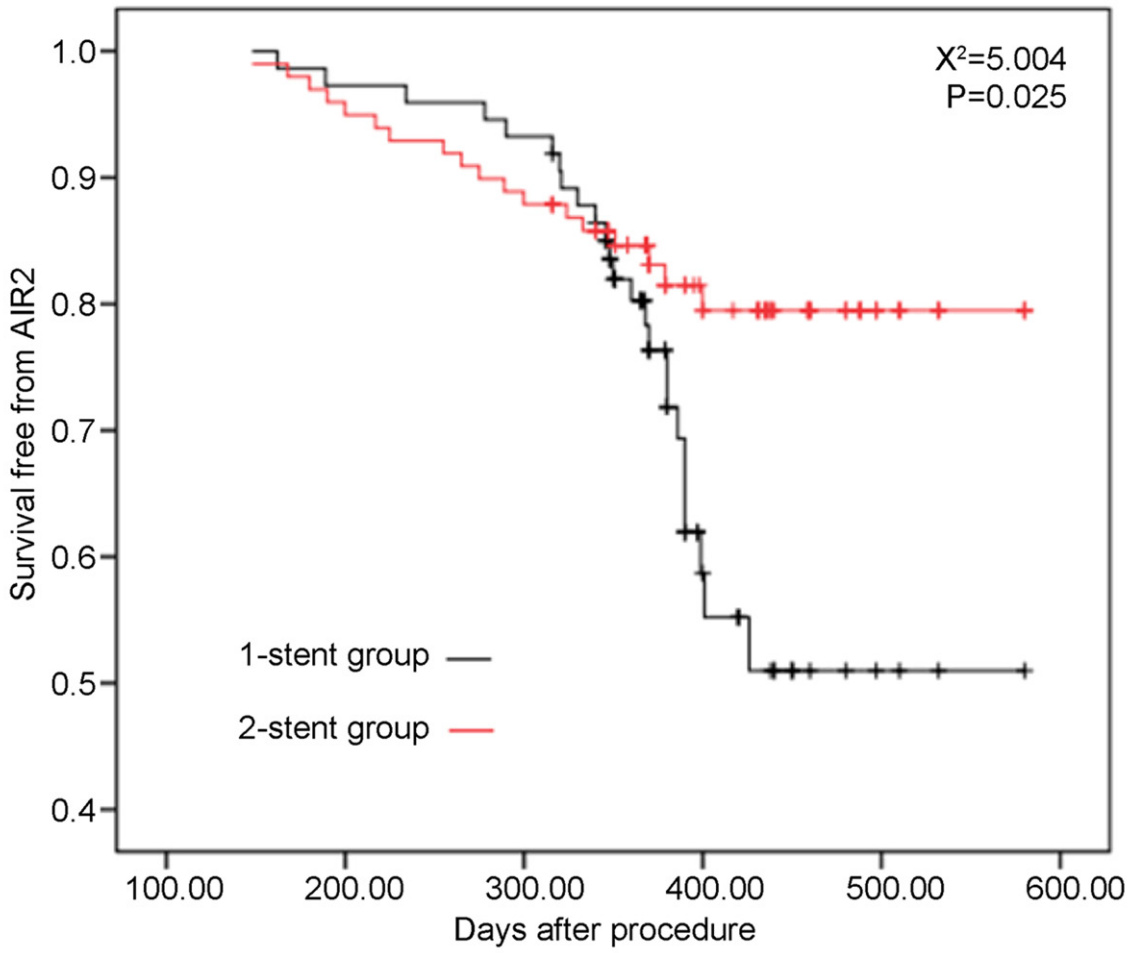

Figure 1. Kaplan-Meier curves for AIR2-free survival, defined by death, myocardial infarction, target vessel revascularization, and silent restenosis, in 1-stent group and 2-stent group during the 12-month follow-up period. *P*-values by log-rank test.

Results of pre-MV quantitative angiographic analysis are shown in **Table 3**. The baseline RVD was similar between groups, and the acute gain, MLD, late loss, and SD were also comparable between groups.

Results of post-MV are shown in **Table 4**. No difference in RVD was detected throughout the follow-up period, and acute gain, late loss and MLD were similar between two groups.

Data of SB analysis are depicted in **Table 5**. No differences were found in RVD, MLD and SD between two groups. However, at follow-up, MLD and SD in 2-stent group were significantly better than those in 1-stent group. Interestingly, the late loss in the SB was significantly lower in 1-stent group than in 2-stent group (0.12 ± 0.16 vs. 0.18 ± 0.21, *P*=0.039), with a trend towards a higher (re)stenosis rate in 1-stent group than in 2-stent group (25.0% vs. 13.7%, *P*=0.078).

Clinical outcome

Complete clinical follow-up was done for a mean of 402 ± 58 days (median: 382 days; Q1 321, Q3 446). In the whole cohort, complete 1-year outcomewas available in 167 (93.8%) cases. Intraprocedural complications occurred in very few patients, and procedure-related MI was not significantly different between groups (17.1% vs. 20.6%, *P*=0.700). During the one-year follow-up, 5 patients (2.8%) died. Cardiac death, MI, TVR and SR occurred in 2.2%, 3.4%, 7.9%, and 11.2% of patients, respectively, leading to a rate of 23.6% for AIR2 and 12.9% for MACE (**Table 6**). Angiographic (re)stenosis rates in the MV and SB were similar between 1-stent (9.2% and 25.0% no difference?) and 2-stent

groups (8.8% and 13.7%, both $P>0.05$). Similarly, the rate of MACEs was similar between 1-stent and 2-stent groups (13.2% vs. 12.7%, $P=0.935$). However, in 1-stent group, the cumulative AIR2 increased by about twice as compared to 2-stent group (32.9% vs. 16.7%, $P=0.013$), and patients in 1-stent group had a higher incidence of SR rate at 12 months (19.7% vs. 4.9%, $P=0.003$). Furthermore, Kaplan-Meier analysis showed the cumulative AIR2-free survival rate at 12 months was markedly lower in 1-stent group than in 2-stent group (**Figure 1**).

Stent thrombosis

The status of dual antiplatelet therapy 1 year after index procedure was available in 173 cases (97.2%). In bothgroups, only 5 patients had discontinued clopidogrel at the time of ST, and two patients assigned to 2-stent group died of sudden death. The incidence of definite or probable ST was similar between 1-stent and 2-stent groups during the follow-up period (2.6% vs. 4.9%, $P=0.761$; **Table 6**).

Discussion

There are some important differences between earlier studies and the present study. In the present study, silent restenosis was included as a part of composite endpoints, besides cardiac death, MI and TVR. Additionally, both the data from clinical and angiographic follow-up were analyzed in present studies. Our results showed treatment of true coronary bifurcation lesions with DES by 2-stent implantation in DM patients improved the long-term outcomes as compared to 1-stent implantation. The outcomes were assessed over a 12-month follow-up period, and the benefits were mainly attributed to the reduced restenosis of the SB.

Another major differenceis that we related the primary endpoint to definite outcomes. As mentioned above, severe stenosis may contribute to asymptomatic myocardial ischemia, especially in DM patients with damaged sensory nerves. Accordingly, this may influence the need for repeat revascularization and the incidence of MACEs. Thus, if the incidence of MACEs is used as the exclusive measure of outcomes, it would lead to an underestimation because silent ischemia, which more frequently occurred in 1-stent group, was not included. On the contrary, angiographic stenosis was not always associated with significant ischemia, as determined by vessel function tests [34]. This weak association suggests that anatomy is a poor predictor of the clinical impact of a stenosis, a fact that is particularly true for SB lesions. Therefore, the composite endpoint, AIR2, was used to correct for biases of clinical events and to compensate for angiographic disadvantages between groups. AIR2 included both clinical and angiographic outcomes and differed markedly from the MACE, which was routinely used in previous trials. The silent restenosis was defined as the lack of ischemic symptoms and ≥75% diameter stenosis within the treated vessels at one-year follow-up by angiography, which is a parameter related to myocardial ischemia. However, a previous study argued that lesions with angiographic <75% stenosis was not associated with a hemodynamically significant fractional flow reserve (FFR) [35].

Our study showed that the MACEs of 1-stent group and 2-stent group were 13.2% and 12.7%, respectively, showing no significant differences, which was in agreement with previous findings [5, 6, 9, 10, 24]. Despite the lack of significant difference, a trend was observed for a lower (re)stenosis rate in 2-stent groupas compared to 1-stent group (13.7% vs 25.0%, $P=0.078$). However, SR occurred more frequently in 1-stent group than in 2-stent group, and the ratio between 2 groups was approximate 4:1. Importantly, the frequency of composite endpoint, AIR2, was increased significantlyby about two times in 1-stent group than in 2-stent group, which was mainly due to restenosissecondary to TVR and asymptomatic restenosis. Accordingly, when evaluated by combined clinical and angiographic outcomes, the 2-stent implantation was better than the 1-stent implantation for the treatment of true coronary bifurcation lesions in DM patients. The improvement in the endpoint, AIR2, in 2-stent group was mainly due to the decreased SR as compared to 1-stent group. Based on the predefined SR, our results indicated that the ratio of AIR2 to SR in 1-stent group and 2-stent group was approximately 5:3 and 3.5:1, respectively.

Another main difference between earlier clinical trials and this study was the definition of

procedural successon the SB. To design an elegant trial on coronary bifurcation lesions, the identical criterion for judging procedural successor failure should be accentuated between 1-stent group and 2-stent group. Therefore, the acceptable cutoff value in the definition of SB procedural success should be identical between groups. In the present trial, the angiographic success was defined as residual <50% stenosis of the SB, which is unable to cause ischemia. Unfortunately, this was not employed in most of clinical trials involving coronary bifurcation lesions, and not a single publication can be found in this regard. For example, in the design of several randomized studies, the SB was not further treated in 1-stent group, unless there was TIMI flow <3 in the SB [5], or residual less than 70% [8] or 75% [9] stenosis. In contrast, in 2-stent group, the implantation of a stent was required for procedural success if the SB had more than 50% stenosis and less than 30% residual stenosis. In these trials, because of lack of an objective testof myocardial ischemia, it is unable to determine the procedural success of the SB even if the SB had ≥75% stenosis. A previous study also demonstrated that a hemodynamically significant SB stenosis, assessed by FFR, was present in 54.5% of severe lesions in angiography [34]. Accordingly, about half of patients with severe residual stenosis in previous trials failed to attain SB procedural success.

Nonetheless, as in other trials, all of the patients analyzed in our study were subjected to 100% of true bifurcations (had true coronary bifurcation lesions). After failure of plain balloon angioplasty in 1-stent group, as defined by the failure to achieve angiographic success, an additional stent on the SB was needed in 32.9% patients, which was similar to a previous trial on the true coronary bifurcation lesions [6, 24]. In the present study, the failure rate of stenting the SB in 1-stent group was 17.1%, mainly because of technical difficulties, such as rewiring the SB or the inability to advance the balloons through the stent struts. Procedures in patients without angiographic success were determined as unsuccessful because of residual ≥50% stenosisof the SB. In contrast, in 2-stent group, only 6 cases (5.9%) failed to attain angiographic success, of whom 4 received the classic crush technique and 2 received the culotte technique. Importantly, the stent thrombosis between 1- and 2-stent groups was similar in terms of any ARC. Overall, our results outlined that the 2-stent implantation represents a safe and effective technique for stenting of coronary bifurcation lesions in DM patients.

In present study, a key reason for the improvement ofprocedural success rate in 2-stent group was that the rate of successful KBI was 96.1%, which was markedly higher than previously reported (89% and 72% in the BBC ONE [8], 74% in the Nordic study [5], and 77.8% in the COBIS registry) [36]. Earlier studies have demonstrated that successful KBI is independently associated with better outcomes [6, 9, 10]. The rate of successful KBI in the present study was comparable to previously reported, possibly because most patients (65.7%) in 2-stent group received the DK-Crush technique. Our previous studies demonstrated that the DK-Crush technique improved the quality offinal KBI and resulted in a larger post procedural MLA of the SB, as compared to other dedicated techniques, including culotteand crush techniques [25, 37]. The sophistication of 2-stent techniques, such as high-pressure postdilation and mandatory kissing balloon inflation, is also related to the improvement of the short and long-term outcomes [38, 39]. These techniques have been demonstrated to reduce stent malposition and in-stent thrombosis.

Our results indicate that 2-stent implantation, mainly consisting of the DK-Crush technique, is associated with a significant reduction in the branch (re)stenosis and more favorable long-term outcomes for the treatment of coronary bifurcation lesions in DM patients, when compared with provisional stenting techniques. These results were also confirmed in our previous studies [24, 40].

Limitations

Like other retrospective studies, one of limitations of our study is the lack of random assignment. Only randomization can provide an unbiased estimation of the efficacy of a treatment. In this study, DM patients treated due to true coronary bifurcation lesions in DK-Crush trials were analyzed and assigned to two groups according to therapeutic strategies received. Clearly, this selection might be insufficient to avoid biases between groups. In addition,

DK-Crush trials were conducted nine years ago. In the present study, whether the SB was further treated was independent of vascular function test. As previously reported, the angiographic stenosis of the SB was not associated with significant ischemia determined by FFR. Ideally, a physiological assessment of the vascularstenosis, rather than the degree of stenosis, should be included into the composite primary endpoints.

Future large, randomized controlled trials are needed to confirm the efficacy of 1-stent vs. 2-stent implantation for treating coronary bifurcation lesions, as well as the feasibility of AIR2 as a composite primary endpoint.

In summary, our study suggests that the 2-stent implantationis better than the 1-stent strategy in the therapy of true coronary bifurcation lesionsin DM patients, as evaluated by combined clinical and angiographic outcomes.

Conclusion

The findings of present study suggest that therapy of coronary bifurcation lesions with two-stent implantation yields better outcomes as compared to one-stent implantationin DM patients, in terms of the combined clinical and angiographic outcomes.

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Disclosure of conflict of interest

None.

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