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Percutaneous Coronary Intervention

Comparison of Long-Term Safety and Efficacy of Bioresorbable Scaffolds between Patients with and without Diabetes Mellitus

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Introduction: Diabetes mellitus (DM) is a major risk of cardiovascular events. Bioresorbable stent frame materials capable of providing mechanical support and drug-delivery functions have been developed in an attempt to improve long-term outcomes. However, publications about the long-term outcomes of bioresorbable scaffolds (BRS) in DM patients are still limited. The aim of this study was to investigate the long-term safety and efficacy of BRS between patients with and without diabetes.

Methods: Data regarding BRS placement in consecutive patients receiving percutaneous coronary interventions were collected from the cardiovascular center of a single tertiary medical center from 2014 to 2017.

Results: A total of 138 cases were included and followed up for 4 years. The mortality rate was 1.1% in the non-diabetic group and 4.1% in the diabetic group (p = 0.2542). No cardiac mortality was observed. One patient had an acute myocardial infarction (0.7%) in the non-diabetic group. The rate of target lesion revascularization was 3.4% in the non-diabetic group and 4.08% in the diabetic group. The ratio of target vessel revascularization was 6.74% in the non-diabetic group and 4.1% in the diabetic group.

Conclusions: This study demonstrated no significant difference in long-term outcomes after BRS implantation between patients with and without diabetes in a single tertiary medical center.

Key Words: Acute myocardial infarction • Bioresorbable scaffolds • Coronary artery disease • Diabetes • Percutaneous coronary intervention

INTRODUCTION

Cardiovascular disease, especially ischemic heart disease, is one of the leading causes of mortality and morbidity worldwide.[1] Diabetes mellitus (DM) is one of the major risk factors for cardiovascular events, especially coronary artery disease and acute coronary syndrome.[2] Catheterization intervention with metallic drug-eluting stent placement for coronary artery stenosis is currently the mainstream treatment option. Moreover, the second generation of metallic drug-eluting stents has been proven to be safe and effective for coronary artery disease treatment.[3,4] However, late adverse events with permanent metallic stents may be caused by persistent inflammation, loss of normal vessel curvature, impaired vasomotor function, strut fracture, ongoing tissue growth within the stent frame, and neoatherosclerosis.[5] Consequently, fully bioresorbable material has been developed for the stent frame, which can provide both mechanical support and drug-delivery func-

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tions, in an attempt to improve long-term outcomes, especially in diabetic patients.

A previous randomized clinical trial revealed that everolimus-eluting bioresorbable scaffolds (BRS), as compared with everolimus-eluting cobalt-chromium stents (EES), were within the pre-specified margin for non-inferiority with respect to target-lesion failure at 1 year in patients with noncomplex obstructive coronary artery disease.[6] However, a subsequent trial revealed a higher rate of device-oriented composite endpoint due to target vessel myocardial infarction (MI), including peri-procedural MI in the BRS group.[7] The ABSORB III study reported a thrombosis rate of 2.3% with BRS versus 0.7% with EES at 3 years.[8] Furthermore, the non-US ABSORB II, ABSORB Japan, ABSORB China and US-based ABSORB III studies reported that the currently approved BRS is associated with higher rates of major adverse cardiac events and BRS thrombosis compared with metallic EES. These results led the U.S. Food and Drug Administration (FDA) to issue a safety alert for Absorb BRS, and the FDA has recommended a reference vessel diameter of $\geq$ 2.5 mm and $\leq$ 3.75 mm, with longer dual antiplatelet therapy in patients with small heart vessels.

Some studies have reported that diabetic and non-diabetic patients who received BRS placement had a similar incidence of device-related events at 1-year follow-up. Conversely, other studies have reported that patient-related adverse events were significantly higher in patients with DM than in controls without DM,[10] and that target lesion revascularization was also higher in patients with DM than in controls without DM.[11]

Currently, few publications have investigated the long-term outcomes with regards to the safety and efficacy of BRS in diabetic and non-diabetic patients. Therefore, the aim of this study was to investigate the long-term safety and efficacy of BRS between patients with and without diabetes.

METHODS

Data source

A total of 138 consecutive patients who had received BRS implantation were enrolled from the cardiovascular center of a tertiary medical center in Taiwan from 2014 to 2017. All patients met the diagnostic criteria for coronary artery disease with more than 70% stenosis compared with the reference vessel on coronary angiography. They also met the American Diabetes Association diagnostic criteria for diabetes.[12] This study was approved by the Human Research Committee of the hospital.

Study population

All patients were admitted for coronary artery disease and received complete basic laboratory tests, chest X-ray, and electrocardiography prior to percutaneous catheterization intervention. All patients were monitored at the hospital for at least 24 hours after the procedure.

Outcome analysis

The primary endpoint of the study was target lesion revascularization (TLR), and the secondary endpoints were target vessel revascularization (TVR), MI, and death. The definition of TLR in this study was clinically driven target lesion revascularization, and TVR was defined as any repeat percutaneous coronary intervention (PCI) in the target vessel. MI was defined as myocardial infarction of any coronary vessel, and death was defined as all-cause mortality.

All enrolled patients were followed until death or December 31st, 2019. Outcomes were recorded from both outpatient department and hospital admission medical records. The medical charts of the patients were reviewed by two independent physicians. Patients lost to follow-up, as identified from medical chart reviews, were contacted by telephone. Furthermore, a follow-up questionnaire was administered which included questions on medication compliance, complications, and mortality.

Statistical analysis

Categorical data were reported as percentages and evaluated using the chi-square test. Continuous variables were reported as means and standard deviations and compared using an independent t-test. The results of non-parametric statistical analysis for non-normal distribution were reported as median interquartile range (IQR) and compared using the Mann-Whitney U test. The Kaplan-Meier method was used to estimate cumulative survival. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Descriptive characteristics

A total of 138 patients with coronary artery disease receiving BRS were enrolled in this study. There were 89 patients in the non-diabetic group and 49 patients in the diabetic group. The clinical characteristics of the patients are shown in Table 1. Most patients were male in both groups (non-diabetic: diabetic = 93.3%: 89.9%, p = 0.4723) and the average age was higher in the diabetic group (non-diabetic: 56.8 ± 12.4 years; diabetic: 62.2 ± 11.0 years, p = 0.0095). There were no significant differences in average body height, body weight, and body mass index (non-diabetic: 26.0 ± 3.1 kg/m^2; diabetic: 27.3 ± 3.72 kg/m^2, p = 0.5832). In the diabetic group, the prevalence of hypertension was higher (non-diabetic: diabetic = 50.6%: 77.6%, p = 0.5832). In contrast, the prevalence of dyslipidemia was higher in the non-diabetic group (non-diabetic: diabetic = 46.1%: 26.5%, p = 0.0024). There were no other remarkable differences in other major comorbidities between the two groups, and the ratio of acute coronary syndrome in the patients who received BRS revascularization was similar in both groups (non-diabetic: diabetic = 43.8%: 44.9%, p = 0.9029) (Table 1).

The hemoglobin levels in the non-diabetic group was higher than that in the diabetic group (non-diabetic: 14.2 ± 1.1 g/dL; diabetic: 13.7 ± 2.0 g/dL, p = 0.0278). However, glycated hemoglobin (HbA1c) (non-diabetic: 6.0 ± 0.9%; diabetic: 7.6 ± 1.7%, p < 0.0001) and fasting blood sugar levels (non-diabetic: 115.3 ± 30.4 mg/dL; diabetic: 181.3 ± 85.5 mg/dL, p < 0.0001) were higher in the diabetic group. Serum creatinine was also higher in the diabetic group (non-diabetic: 1.1 ± 0.2 mg/dL; diabetic: 1.3 ± 0.6 mg/dL, p < 0.0042). Although the prevalence of dyslipidemia was higher in the non-diabetic group, there were no significant differences in the levels of low-density lipoprotein-cholesterol (LDL-C),

Table 1. Baseline characteristics of patients

Characteristics	Non-diabetic (n = 89)	Diabetic (n = 49)	p-value
Gender (male ratio)	N = 83 (93.3%)	N = 44 (89.9%)	0.4723
Age (years)	56.8 ± 12.4	62.2 ± 11.0	0.0095
BMI (kg/m^2)	26.0 ± 3.1	26.3 ± 3.72	0.5832
Height (cm)	167.7 ± 7.1	167.0 ± 7.4	0.5557
Weight (kg)	73.1 ± 10.2	73.3 ± 11.1	0.9312
Comorbidities			
Hypertension	n = 45 (50.6%)	n = 38 (77.6%)	0.0019
Dyslipidemia	n = 41 (46.1%)	n = 13 (26.5%)	0.0244
Family history of CAD	n = 51 (57.3%)	n = 26 (53.6%)	0.6311
Previous myocardial infarction	n = 13 (14.6%)	n = 6 (6.1%)	0.1363
Previous ischemia stroke	n = 0	n = 0	-
Peripheral artery disease	n = 1 (1.1%)	n = 0	0.4565
Coronary artery bypass grafting	n = 1 (1.1%)	n = 2 (4.1%)	0.2542
End stage renal disease	n = 0	n = 0	-
Heart failure	n = 1 (1.1%)	n = 0	0.4565
Acute coronary syndrome	n = 39 (43.8%)	n = 22 (44.9%)	0.9029
Cigarette smoking	n = 36 (40.5%)	n = 14 (28.6%)	0.1648
Lab Data			
Hemoglobin (g/dL)	14.2 ± 1.1	13.7 ± 2.0	0.0278
Creatinine (mg/dL)	1.1 ± 0.2	1.3 ± 0.6	0.0042
HbA1C (%)	6.0 ± 0.9	7.6 ± 1.7	< 0.0001
Blood sugar (mg/dL)	115.3 ± 30.4	181.3 ± 85.5	< 0.0001
Cholesterol (mg/dL)	168.8 ± 40.9	158.0 ± 42.1	0.1454
HDL (mg/dL)	40.4 ± 8.4	44.0 ± 16.6	0.0962
LDL (mg/dL)	97.9 ± 29.7	88.7 ± 26.5	0.0795
Triglyceride (mg/dL)	135.6 ± 93.5	148.3 ± 103.3	0.4746

BMI, body mass index; CAD, coronary artery disease; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

high-density lipoprotein (HDL-C), and triglycerides between the two groups (Table 1).

The percentages of the patients receiving antiplatelet therapy are shown in Table 2, including aspirin (98.8%), clopidogrel (47.2%) and ticagrelor (52.8%) in the non-diabetic group, and aspirin (95.5%), clopidogrel (67.35%) and ticagrelor (32.6%) in the diabetic group. The average duration of antiplatelet therapy was 1410.6 ± 299.0 days for aspirin, 329.4 ± 310.8 days for clopidogrel, and 485.8 ± 358.9 days for ticagrelor in the non-diabetic group, and 1416.5 ± 350.1 days for aspirin, 259.2 ± 257.3 days for clopidogrel, and 382.1 ± 292.7 days for ticagrelor in the diabetic group. The median (IQR) duration was 1331 (449.5) days for aspirin, 295 (425) days for clopidogrel and 433 (440) days for ticagrelor in the non-diabetic group, and 1374 (430) days for aspirin, 213 (284) days for clopidogrel, and 283.5 (427) days for ticagrelor in the diabetic group (Table 2).

Angiographic and procedural characteristics

Regarding lesion characteristics on coronary angiography, there were 15 type A lesions (16.9%), 29 type B1 lesions (32.6%), 25 type B2 lesions (28.1%), and 20 type C lesions (22.5%) in the non-diabetic group, and 13 type A lesions (26.5%), 16 type B1 lesions (32.7%), 11 type B2 lesions (22.5%), and 9 type C lesions (18.4%) in the diabetic group. The Syntax score was 12.27 ± 7.56 in the non-diabetic group and 14.3 ± 8.17 in the diabetic group. Furthermore, chronic total occlusion lesions accounted for 11.2% in the non-diabetic group (N = 10) and 10.2% in the diabetic group (N = 5). In addition, ostial lesions accounted for 15.7% in the non-diabetic group (n = 14) and 6.1% in the diabetic group (N = 3), and bifurcation lesions accounted for 24.7% in the non-diabetic group (N = 22) and 26.5% in the diabetic group (N = 13). Only 2 lesions were left main bifurcation lesions, both in the non-diabetic group (Table 3).

A total of 202 bioresorbable scaffolds were deployed. There were no statistically significant differences in BRS size and length between the non-diabetic and diabetic patients (Table 4). During the PCI procedure, 91.2% of the non-diabetic patients received balloon post-dilatation after BRS implantation compared to 95.5% in the diabetic patients. Intravascular image guidance, including optical coherence tomography (OCT) and intravascular ultrasound (IVUS), was performed equally in both groups (non-diabetic group: OCT, 34.6%; IVUS, 18.0%; non-diabetic group, OCT: 42.9%, IVUS: 24.5%) (Table 3).

Outcome analysis

A total of 138 patients were included during the 4-year follow-up period. The overall mortality rate was 2.2% (N = 3), and there was no significant difference between the two groups (non-diabetic: diabetic = 1.1%: 4.1%, p = 0.2542). The cause of mortality in these 3 patients was not directly related to cardiovascular disease. One patient had an acute MI in the non-diabetic group (1.1%). The rates of TLR (non-diabetic: diabetic = 3.4%: 4.1%, p = 0.8307) and TVR (non-diabetic: diabetic = 6.7%: 4.1%, p = 0.7118) were not significantly different

Table 2. Follow-up days and antiplatelet duration

	Non-diabetic (n = 89)	Diabetic (n = 49)	p-value[#]	p-value*
Follow up days				
Mean ± SD (days)	1422.1 ± 300	1420.6 ± 353.3	0.9793	-
Median (IQR) (days)	1351 (430)	1408 (427)	-	0.8800
Antiplatelet therapy				
Aspirin (percentage)	N = 88 (98.8%)	N = 47 (95.5%)	0.2542	-
Average duration (days)	1410.6 ± 299.0	1416.5 ± 350.1	0.9161	-
Median (IQR) (days)	1331 (449.5)	1374 (430)	-	0.8607
Clopidgrel (percentage)	N = 42 (47.2%)	N = 33 (67.35%)	0.0229	-
Average duration (days)	329.4 ± 310.8	259.2 ± 257.3	0.3107	-
Median (IQR) (days)	295 (425)	213 (284)	-	0.4634
Ticagrelor (percentage)	N = 47 (52.8%)	N = 16 (32.6%)	0.0229	-
Average duration (days)	485.8 ± 358.9	382.1 ± 292.7	0.3013	-
Median (IQR) (days)	433 (440)	283.5 (427)	-	0.2977

* Mann-Whitney U test ($p < 0.05$). [#] Independent t-test ($p < 0.05$). IQR, interquartile range.

Table 3. Angiographic and procedure characteristics

	Coronary angiography findings (N = 138)		
	Non-diabetic (N = 89)	Diabetic (N = 49)	p-value
Lesion type			
A	N = 15 (16.9%)	N = 13 (26.5%)	0.1762
B1	N = 29 (32.6%)	N = 16 (32.7%)	0.9934
B2	N = 25 (28.1%)	N = 11 (22.5%)	0.4702
C	N = 20 (22.5%)	N = 9 (18.4%)	0.5712
Left main bifurcation lesion	N = 2 (2.2%)	N = 0 (0%)	0.2905
Ostial lesion	N = 14 (15.7%)	N = 3 (6.1%)	0.1003
Bifurcation lesion	N = 22 (24.7%)	N = 13 (26.5%)	0.8149
Chronic total occlusion	N = 10 (11.2%)	N = 5 (10.2%)	0.8522
Syntax score	12.27 ± 7.56	14.30 ± 8.17	0.1438
Post-dilatation	N = 62 (91.2%)	N = 42 (95.5%)	0.3906
Intravascular image guide			
OCT	N = 34 (34.6%)	N = 21 (42.9%)	0.5930
IVUS	N = 16 (18.0%)	N = 12 (24.5%)	0.3627

IVUS, intravascular ultrasound; OCT, optical coherence tomography.

Table 4. Characteristics of stent size and length

	Bioresorbable Scaffolds (N = 202)		
	Non-diabetic (N = 132)	Diabetic (N = 70)	p-value
BRS size (mm)			
2.50	N = 18 (13.6%)	N = 14 (20.0%)	0.2385
3.00	N = 63 (47.7%)	N = 34 (48.57%)	0.9090
3.50	N = 51 (38.6%)	N = 22 (31.4%)	0.3102
BRS length (mm)			
12	N = 10 (7.6%)	N = 2 (2.9%)	0.1770
18	N = 25 (18.9%)	N = 12 (17.1%)	0.7534
23	N = 35 (26.6%)	N = 13 (18.6%)	0.2068
28	N = 62 (47.0%)	N = 43 (61.4%)	0.0503

BRS, bioresorbable scaffolds.

Table 5. Major event of BRS placement

	Non-diabetic (N = 89)	Diabetic (N = 49)	p-value
TLR	N = 3 (3.4%)	N = 2 (4.1%)	0.8307
TVR	N = 6 (6.74%)	N = 2 (4.1%)	0.7118
MI	N = 1 (1.1%)	N = 0	0.4565
Death	N = 1 (1.1%)	N = 2 (4.1%)	0.2542
Cardiac mortality	N = 0	N = 0	-

MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessels revascularization.

between the two groups (Table 5).

DISCUSSION

This study is the first long-term study to investigate the 4-year safety and efficacy of BRS in patients with and without diabetes. At 4 years of follow-up after BRS implantation, there were no significant differences in death, MI, TLR, and TVR (Figure 1) between the diabetic and non-diabetic groups.

Revascularization with BRS in daily practice

BRS was developed to dissolve fully within vessels within 3 years of implantation, with the intent of bypassing any negative side effects sustained from a metal stent. In the ABSORB III randomized trial, the Absorb BRS proved to be non-inferior to the Xience device with regards to the occurrence of target lesion failure (TLF), target vessel myocardial infarction (TVMI), and ischemia-driven TLR. The U.S. FDA approved Abbott's BRS device upon the release of these positive results, but recent reports from the Absorb III trial[8] have suggested increased instances of thrombosis and MI directly related to the dismantling process of the bioresorbable vascular scaffold. Around 2,000 cardiac patients took part in the ABSORB III study, all of whom underwent PCI. The Absorb BRS was deemed to be non-inferior to the Xience stent for the study's primary endpoint of 1-year TLF, with a risk difference of just 1.7% between the two devices. TLF was defined as a composite of ischemia-driven TLR,

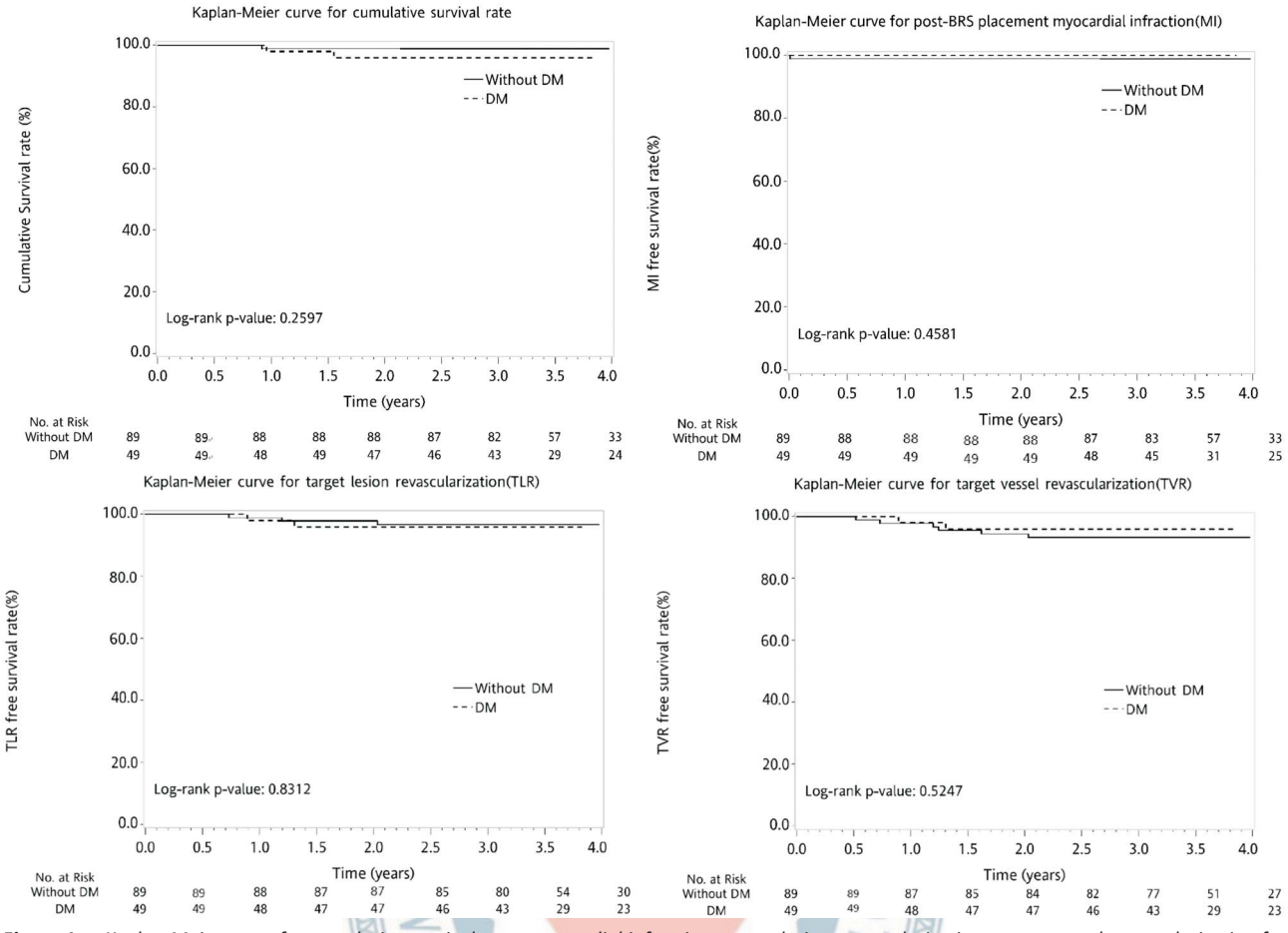

Figure 1. *Kaplan-Meier curve for cumulative survival rate, myocardial infarction, target lesion revascularization, target vessel revascularization for diabetic and non-diabetic patients after bioresorbable scaffolds (BRS) implantation.*

MI related to the target vessel, or cardiac death related to the target vessel. Device thrombosis was recorded in 1.5% of the BRS patients and 0.7% of the EES patients after the first 12 months. Three years into the study, the results varied more widely, and the device-oriented primary endpoint was observed in 13.4% of the BRS subjects compared to 10.4% of the EES patients. Between 1 and 3 years after treatment, TLF occurred in 7% and 6% of all BRS and EES patients, respectively. The BRS patients also had higher rates of target vessel failure, death, MI, and revascularization. Factors such as prior cardiovascular intervention, diabetes, and vessel size were all found to be independent predictors of adverse outcomes in the BRS-treated patients. Scaffold thrombosis events seemed to be clustered in very small vessels prior to the 1-year treatment mark, but later occurred in vessels more appropriately sized for the scaffold device.

Late thromboembolism events have been mainly associated with multifactorial origins, including the lesion, the device, the patient, antithrombotic, and procedural issues.[13,14] Attention to technical details may also improve results when PCI is performed with BRS. Because both the number of stents and the stent length can increase the the risk of thromboembolism events, refraining from excessive overall stent length and from stent overlap is important. Moreover, proper deployment of the BRS should be ensured, with care taken to fully expand it over its entire length, particularly in calcified lesions, and residual dissections should be avoided as when deploying drug-eluting stents (DES). Among patients with larger vessels, the TLF rate was 9.4% among the Absorb-treated patients and 7.0% among the Xience-treated patients, a difference that was not statistically significant (hazard ratio: 1.35; 95% confidence interval: 0.93-1.96).[8] Similarly, in those with a reference vessel diameter (RVD) $\geq$ 2.25 mm, the 2-year rates of definite/

probable stent thrombosis (ST) were 1.3% and 0.6% in the Absorb- and Xience-treated patients, respectively. Again, this difference was not statistically significant. An additional analysis of the data showed that when physicians followed the PSP protocol (i.e. predilatation, appropriate sizing, and post-dilatation), the rates of TLF and ST in the Absorb BRS arm were much closer to the rates observed with the Xience stent.

In the present study, none of the patients who received BRS implantation died due to cardiac causes, and there were few cases of TLR, TVR, and MI after 4 years. The main reason for the lack of major cardiac events in this study might be that most BRS used were more than 3 mm in size, and that we used an optimal technique with post-stent balloon dilatation. Moreover, intravascular images were used in more than half of the cases to assess the proper reference lumen size and lesion type and length. The appropriate use of intravascular images increases the accuracy of the chosen stent size and length. Dual antiplatelet therapy in most patients continued for at least 1 year after the procedure. Taken together, these factors may explain why there were relatively few major cardiac events in this study.

BRS in diabetes mellitus

Diabetes mellitus remains a major determinant of ischemia-driven TLR and TVR in the era of new-generation DES.[15] Therefore, the safety and efficacy of second-generation DES in patients with DM are constantly assessed, and currently the BRS for this subset remains to be established. Both diabetes and small vessel size are well-established risk factors for stent thrombosis.[8,17] A study showed no significant difference in 1-year TLF rate between patients with and without DM treated with BRS (3.7% vs. 5.1%).[16] Another subgroup analysis of ABSORB II, III, JAPAN studies reported that the rates of TLF and the TLF components of TVMI and ischemia-driven TLR were significantly increased among diabetic patients treated with insulin compared to those who were not using insulin, and also an increased smaller target vessel RVD ($\leq$ 2.25 mm).[16] TVMI was defined as a patient with MI with evidence of myocardial necrosis in the vascular territory of previously treated target vessels. In the ABSORB III trial, a smaller RVD (2.67 $\pm$ 0.45 mm) was found to be a significant independent predictor of 1-year TLF among the DM patients enrolled.[8] In this study, there were some characteristic significant differences between the non-diabetic and diabetic groups. The average age and prevalence of hypertension and renal function impairment were higher, and serum creatinine and hemoglobin levels were lower in the diabetic group. However, there was no statistically significant difference in major long-term outcomes, including TLR, TVR, and MI, after 4 years of follow-up between the non-diabetic and diabetic groups.

Limitations

This study was conducted at a single medical center, and the number of cases was relatively small. The lack of randomized assignment of patients with diabetes to treatment with either Absorb BRS or DES precludes direct comparisons of outcomes between the devices. In addition, the patients did not undergo regular follow-up imaging. However, this study provides relevant real-world data on the impact of DM on BRS performance. Further investigations are thus required with large-scale, comprehensive, randomized, and controlled trials for diabetic patients.

CONCLUSION

This study demonstrates that BRS implantation has similar long-term safety and efficacy outcomes, including TLR, TVR, MI, mortality, and major adverse cardiac events, between patients with and without diabetes.

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DISCLOSURES

All authors contributed equally to this work; both corresponding authors contributed equally to this work. The authors declare that there is no conflict of interest.

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