Everolimus-eluting bioresorbable vascular scaffolds implanted in coronary bifurcation lesions: Impact of polymeric wide struts on side-branch impairment

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ABSTRACT

Background

Limited data are available on bioresorbable vascular scaffolds (BVS) performance in bifurcations lesions and on the impact of BVS wider struts on side-branch impairment.

Methods

Patients with at least one coronary bifurcation lesion involving a side-branch ≥2 mm in diameter and treated with at least one BVS were examined. Procedural and angiographic data were collected and a dedicated methodology for off-line quantitative coronary angiography (QCA) in bifurcation was applied (eleven-segment model), to assess side-branch impairment occurring any time during the procedure. Two- and three- dimensional QCA were used. Optical coherence tomography (OCT) analysis was performed in a subgroup of patients and long-term clinical outcomes reported.

Results

A total of 102 patients with 107 lesions, were evaluated. Device- and procedural-successes were 99.1% and 94.3%, respectively. Side-branch impairment occurring any time during the procedure was reported in 13 bifurcations (12.1%) and at the end of the procedure in 6.5%. Side-branch minimal lumen diameter (Pre: 1.45 ± 0.41 mm vs Final: 1.48 ± 0.42 mm, p = 0.587) %diameter-stenosis (Pre: 26.93 ± 16.89% vs Final: 27.80 ± 15.57%, p = 0.904) and minimal lumen area (Pre: 1.97 ± 0.89 mm2 vs Final: 2.17 ± 1.09 mm2, p = 0.334), were not significantly affected by BVS implantation. Mean malapposed struts at the bifurcation polygon-of- confluence were 0.63 ± 1.11.

Conclusions

The results of the present investigation suggest feasibility and relative safety of BVS implantation in coronary bifurcations. BVS wide struts have a low impact on side-branch impairment when considering bifurcations with side-branch diameter ≥ 2 mm.

INTRODUCTION

Coronary artery bifurcation treatment is a frequent and challenging subset in interventional cardiology. The introduction of first generation drug eluting stents (DES) was associated with a reduction in main vessel restenosis rate compared with balloon angioplasty or bare metal stent implantation [1,2], but without a clear benefit in terms of side branch ostium impairment and restenosis regardless the technique used [3–5]. Data on second-generation DES, extrapolated from post-hoc analyses of randomized trials are encouraging, with similar long-term mortality after zotarolimus and everolimus DES implantation in bifurcation and non-bifurcation lesions [6]; On the other hand the presence of permanent metallic material at the side-branch ostia could be associated with delayed vascular healing and incomplete neointimal coverage [7] with a possible impact on late thrombotic events [8]. Given this background bioresorbable vascular scaffolds (BVS) could provide a novel paradigm for bifurcation treatment possibly overcoming some of the long-term limitation of metallic DES, avoiding after bioresorption sidebranch ostium caging and long-term malapposition. A possible drawback of the BVS usage in such lesions, could be represented by the theoretical risk of an increased acute side-branch impairment due to the wider BVS struts, as previously hypothesized and demonstrated for very small (b 0.5 mm) side-branches [9]. Despite the presence of recently reported analyses in relatively simple lesions, [10] at the current state of the art, very limited data are available on BVS performance in bi- furcation lesions [11,12] especially when evaluating the impact of BVS implantation on side-branch impairment in vessels with a visually estimated diameter ≥ 2.0 mm. Therefore, we sought to report feasibility, procedural performance and acute angiographic results after BVS implantation in this specific subgroup with a detailed evaluation of side- branch ostium at pre- and post-implantation and describing mid-term clinical outcomes.

Methods

The present report is an investigator initiated, single-arm, single-centre study to assess feasibility and performance of the second- generation everolimus-eluting BVS for the treatment of patients with coronary bifurcation lesions.

Patients eligible for the present analysis were ≥ 18 years of age, presenting with stable angina or acute coronary syndromes with at least one *de novo* bifurcation lesion (regardless of morphology, number, length and angulations), involving a side-branch (SB) ≥ 2 mm by visual estimation in diameter treated with at least one BVS implantation. Exclusion criteria were minimal comprising pregnancy, known intolerance to contrast medium and participation to another investigational drug or device study before reaching the primary endpoints. Procedural details, including materials and techniques were collected. Pre- and post-BVS implantation off-line two-dimensional quantitative

coronary angiography (QCA) and, if technically feasible, off-line three- dimensional-QCA were performed. Optical coherence tomography (OCT) analyses at post-BVS implantation in a subgroup of patients, and clinical long-term clinical outcomes were evaluated. All patients included in the present analyses were part of the bioresorbable vascular scaffold evaluation program at the Thoraxcenter Rotterdam, The Netherlands and were already included in the EXPAND or in the BVS STEMI FIRST study.

Survival status information was obtained from the national population registry. A questionnaire was sent to all living patients with specific queries on re-hospitalization and cardiovascular events. Patients received the questionnaire on planned follow-up (1-, 6-, 12-month follow-up).

For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed.

In case of death all possible events in that specific patient were investigated by reviewing our hospital records and referring hospitals or general practitioner were contacted to collect as much information as possible. In case patients did not send back the questionnaires, a second form was sent by post after one month. If this was not returned, patients were contacted by phone.

Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. The BVS received the CE mark for clinical use, indicated for improving coronary lumen diameter in patients with ischemic heart dis- ease due to *de novo* native coronary artery lesions with no restriction in terms of clinical presentation. Therefore, the BVS can be currently used routinely in Europe in different settings comprising the acute MI without a specific written informed consent in addition to the standard informed consent to the procedure. Given this background, a waiver from the hospital Ethical Committee was obtained for written informed consent, as according to Dutch law writ- ten consent is not required, if patients are not subject to acts other than as part of their regular treatment.

Study procedure

The procedures were performed according to standard practice. The device implantation was performed in accordance with the manufacturer's recommendations, at a rate of 2 atm per 5 s up to burst pressure. Pre- and post-dilatation were encouraged but not mandatory. Wiring of the side-branch before main vessel stenting was per- formed at the operator's discretion and mainly based on the extension of the disease and anatomical characteristics. A single scaffold approach was encouraged as preferred approach

for the majority of cases. Side- branch treatment was recommended only in cases with side-branch impairment or significant atherosclerotic disease. After the procedure, dual antiplatelet therapy was recommended for at least one year followed by aspirin indefinitely.

Definitions

Device success was defined as the attainment of a residual final stenosis b 30% in Main vessel (MV) or side-branch (SB) segment covered by BVS. Procedural success was defined as device success and no major peri-procedural complications (emergent CABG, coronary perforation requiring pericardial drainage, residual dissection impairing vessel flow with final TIMI-flow grade ≤ 2 in MV or SB). Clinical success was defined as procedural success and no in-hospital major adverse cardiac events (MACEs). All deaths were considered cardiac unless an undisputed non-cardiac cause was identified. Myocardial infarction (MI) and scaffold thrombosis were defined according to the Academic Research Consortium definition. Any target bifurcation revascularization was de- fined as clinically driven if at repeat angiography a diameter stenosis N 70% was observed, or if a diameter stenosis N 50% was present in the main vessel or in the daughter branches in association with 1) recurrent angina pectoris; 2) objective signs of ischemia (electrocardiogram changes) at rest or during exercise test, likely to be related to the target vessel; 3) abnormal results of any invasive functional diagnostic test. The target bifurcation failure was defined as the composite of cardiac death, target vessel myocardial infarction, or clinically-driven target bi- furcation revascularization. MACEs were defined as the composite of cardiac death, any re-infarction (Q or Non Q-Wave) or clinically- driven target bifurcation revascularization.

To investigate the BVS performance in MV/SB ostium, we adopted the following procedural and angiographic parameters already reported in de the literature [7]:

"Side-branch impairment", as previously described [7] and defined as a composite of 1) SB TIMI flow grade b 3 after MV stenting, 2) need of guidewire(s) different from the default wire to rewire SB after MV stenting, 3) failure to rewire the SB after MV stenting, or 4) failure to dilate the SB after MV stenting and SB rewiring; "SB acute angiographic result", defined as the comparison between the pre- and the post-procedure 2-dimensional QCA–estimated minimal lumen diameter of 3-mm ostial SB sub-segment, according to the modified eleven-segment model analysis [13–15].

Study device

The second-generation everolimus-eluting BVS (ABSORB; Abbott Vascular, Santa Clara, CA, USA) consist of a backbone of semi crystalline polymer of poly-L-lactide acid, an amorphous matrix of poly-DL-lactide acid which controls the everolimus release (100 micrograms/cm2) and two markers of platinum at proximal and distal edges of scaf-

fold which are radiopaque and facilitate the correct implantation of device. The entire polymer is degraded to carbon dioxide and water.

Quantitative coronary angiography analysis

Off-line quantitative coronary angiography (QCA) analysis was per- formed using the Cardiovascular Angiography Analysis System (CAAS; Version 5.10, Pie Medical Imaging, Maastricht, the Netherlands) soft- ware packages, according to methodological standards previously de- scribed and adopting the modified- eleven-segment model [13–15]. Only matched pre- and post-BVS implantation projections were considered for the analyses. Two-dimensional QCA (2DQCA) was performed using the angiographic image with the largest distal bifurcation angle. 3-dimensional QCA (3DQCA) was performed if at least two projections had been acquired at least 30° apart; The following parameters were included: reference vessel diameter (RVD), minimal lumen diameter (MLD) and percentage diameter stenosis (%DS) of MV, SB and 3-mm ostial SB sub-segment (segment 8 in the eleven segment model), bifurcation proximal angle (between proximal MV and SB) and bifurcation distal angle (between distal MV and SB). If 3DQCA was feasible, minimal lumen area and percentage area stenosis of MV, SB and 3-mm ostial SB sub-segment were added (Fig. 1). Bifurcation lesions were classified ac- cording to the Medina classification; AHA/ACC modified lesion criteria, extent of coronary disease, presence of calcification, lesion length, SB and main vessel (MV) thrombolysis in myocardial infarction (TIMI)- flow grade.

Optical coherence tomography image acquisition and analysis

Intravascular imaging was encouraged but not mandatory and left to the operator discretion. The Optical coherence tomography (OCT) ex- amination was performed with the Illumien or Illumien Optis systems and the corresponding Dragonfly or Dragonfly Duo intravascular imaging catheters (St. Jude Medical, St. Paul, MN, USA). The catheter was advanced into the MV distally to the treated segment and then automated pullback (20 mm/s) and simultaneous contrast injection (flush rate 3– 4 mL/s) were performed to acquire the images. Off-line analysis of the OCT images was performed using the QCU-CMS software (Medis Medical Imaging System, Leiden, The Netherlands) at 1-mm longitudinal intervals within the treated coronary segment, including proximal and distal 5-mm edge segments, after exclusion of frames with b 75% lumen contour visibility, using previously described methodology for the analysis of bioresorbable scaffolds [16]. Morphometric measurements were performed as previously described, using the abluminal strut points for the delineation of the scaffold contour. A scaffold strut was defined as incompletely apposed when there was no contact between the abluminal border of the strut and the vessel wall. This definition does not include struts located in front of SBs ostia which were defined as SB-related struts and were recorded

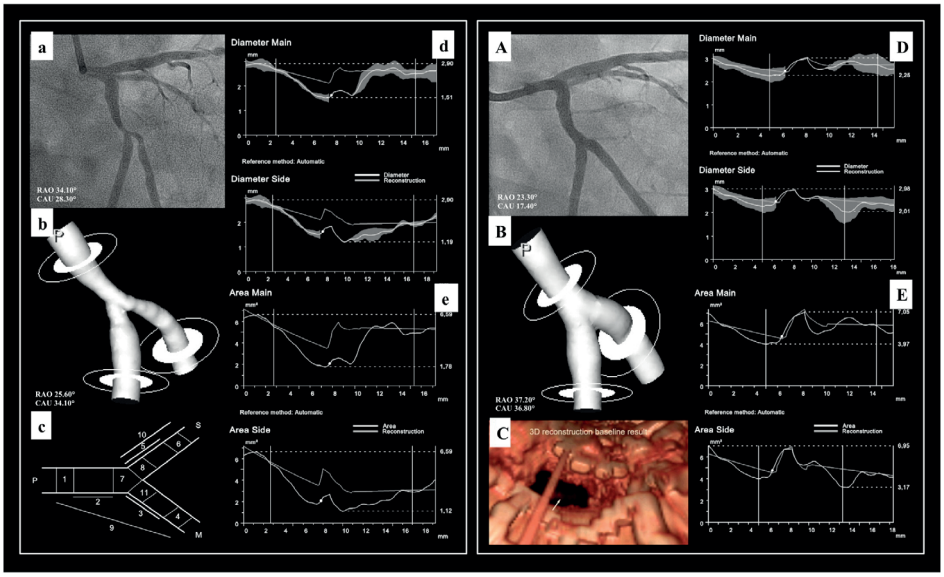

Figure 1 Quantitative coronary analysis and 3-dimensional reconstruction.
A. Pre-procedural angiogram of treated bifurcation was acquired at RAO34.10°CAU28.30° and LAO51.30°CAU29.70° (not shown). b. 3-dimensional reconstruction is shown in the optimal projection (P = proximal main vessel). c. 11-segment model in Cardiovascular Angiography Analysis System (CAAS); P, M and S = proximal main vessel, distal main vessel and side branch, respectively. d and e. Pre-procedural reference vessel diameter and area curve, respectively, for proximal main vessel into distal main vessel and side branch. A. Post-procedural angiogram. B and C. 3-dimensional reconstruction using 3dimensional-QCA and 3-dimensional OCT, respectively (white arrow indicates SB ostium). D and E. Post-procedural reference vessel diameter and area curve, for proximal main vessel into distal main vessel and side branch.

separately. The bifurcation of interest was identified in the OCT pullback and divided in 3 sub- segments: proximal, polygon of confluence and distal (Fig. 2). Strut apposition was calculated separately for each of the sub-segments.

Statistical analysis

Continuous variables were expressed as mean and standard deviation or as median and interquartile ranges if data were non-normally distributed. Dichotomous variables are presented as count and/or percentages. The paired *t*-test was used for comparison between pre and post-procedure QCA parameters. Statistical analysis was performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, US).

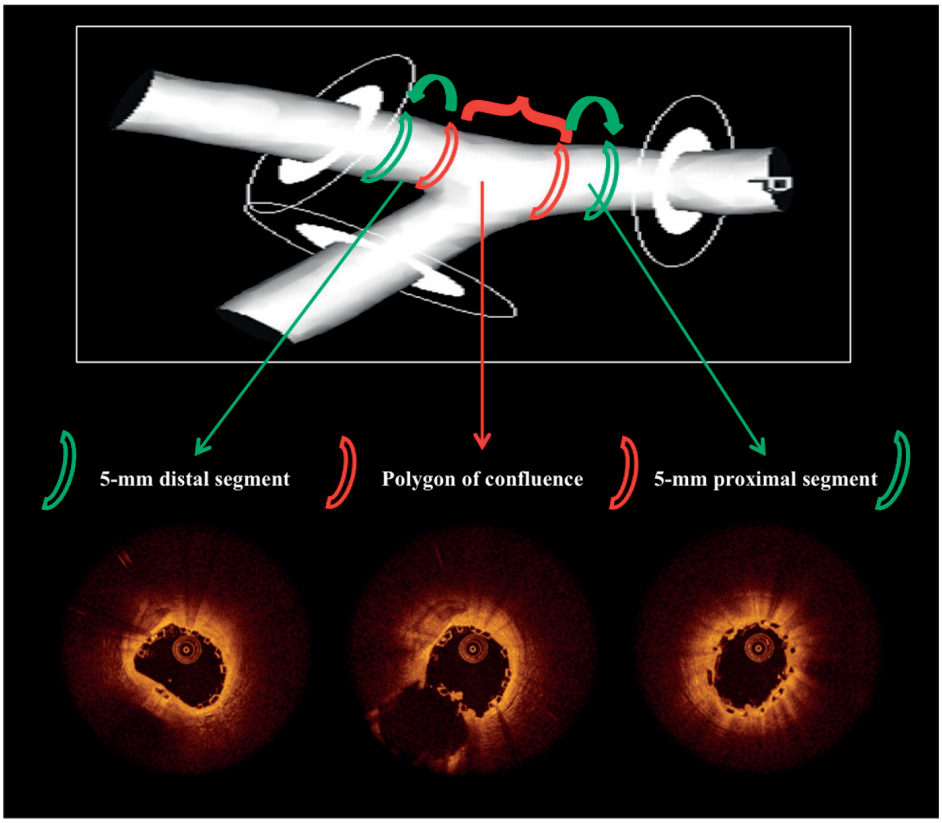

Figure 2 Subsegments location in the treated bifurcation lesion.
The bifurcation of interest was identified in the OCT pullback and divided in 3 sub-segments: we defined the polygon of confluence as the sub-segment between the last (distally) and the first (proximally) cross sections (red lines) in which the contort was not distorted by the side branch. The distal and proximal sub-segments (green lines) were defined as the 5-mm distal and the 5-mm proximal sub-segments from the last and the first cross sections of the polygon of confluence, respectively.

RESULTS

A total of 102 patients, with 107 bifurcation lesions, were included in this study. The baseline clinical characteristics are reported in Table 1. Briefly, the average age was 59.61 ± 10.79 years, 81.4% of the patients were male, 43.9% showed a multivessel disease, 57.8% were admitted with an acute coronary syndrome and approximately one third of these acute patients presented with ST-segment elevation myocardial infarction (Table 1).

Table 1. Baseline Clinical Characteristics

Patient characteristics	N = 102
Age, yrs	59.61 ± 10.79
Gender (male)	83 (81.4)
Risk factors	
Family History of CAD	30 (29.4)
Diabetes mellitus	16 (15.7)
Hypercholesterolemia	53 (52.0)
Hypertension	57 (55.9)
Active smoking	42 (41.2)
Kidney disease	6 (5.9)
Clinical history	
Previous MI	23 (22.5)
Previous PCI	15 (14.7)
Previous CABG	2 (2.0)
Previous TIA/stroke	4 (3.9)
Peripheral arterial disease	7 (6.9)
Chronic obstructive pulmonary disease	5 (4.9)
Extent of coronary artery disease	
Single vessel disease	60 (56.1)
2-vessel disease	40 (37.4)
3-vessel disease	6 (5.6)
Left main	1 (0.9)
Clinical presentation	
Acute coronary syndrome	59 (57.8)
STEMI	19 (18.6)
Acute heart failure	2 (2.0)
Out-hospital cardiac arrest	2 (2.0)

Values are expressed as mean ± standard deviation (SD) or count (n) and percentages (%). *CABG* = coronary artery by-pass; *CAD* = coronary artery disease; *MI* = myocardial infarction; *PCI* = percutaneous coronary intervention; *STEMI* = ST-segment elevation myocardial infarction; *TIA* = transient ischemic attack;

Angiographic and procedural characteristics

Angiographic characteristics of bifurcation lesions (N = 107) are listed in Table 2. The most frequently treated lesion was on left anterior descending/diagonal bifurcation (68.2%), a large part of the lesions involved both the main branch and the side-branch (true bifurcation lesions 42.0%), moderate or severe calcification was present in nearly one third of the lesions (28.9%) and long lesions were commonly observed (55.1%). In 10 cases (9.3%) the bifurcation was located in chronically occluded coronary segments.

Table 2 Angiographic Characteristics

Number of Bifurcations	N = 107
Target bifurcation	
Distal left main	2 (1.9)
Left anterior descending/Diagonal	73 (68.2)
Circumflex/Marginal	26 (24.3)
Right posterior descending/posterior lateral	6 (5.6)
ACC/AHA modified lesion classification	
Type B2	73 (68.2)
Type C	34 (31.8)
True bifurcations	45 (42.0)
Moderate or severe calcification	31 (28.9)
Length lesion > 20 mm	59 (55.1)
Chronic total occlusion	10 (9.3)
Medina bifurcation classification	
1.1.1	20 (18.7)
1.1.0	24 (22.4)
1.0.1	11 (10.3)
0.1.1	14 (13.1)
1.0.0	14 (13.1)
0.1.0	18 (16.8)
0.0.1	6 (5.6)
MV TIMI flow pre-procedure	
0	13 (12.1)
1	4 (3.7)
2	3 (2.8)
3	87 (81.3)
SB TIMI flow pre-procedure	
0	9 (8.4)
1	4 (3.7)
2	2 (1.9)
3	92 (85.9)

Values are expressed as count (n) and percentages (%).
ACC/AHA = American College of Cardiology/American Heart Association; MV = main vessel; SB = side branch; TIMI = thrombolysis in myocardial infarction.

Reflecting the presence of acute patients TIMI flow 0 or 1 pre- intervention was reported in 17 main vessel lesions (15.9%) and with a similar rate in the side-branch (Table 2).

The most commonly performed technique was the provisional one scaffold approach (93.4%). A crossover from a one-scaffold to two- scaffolds technique occurred in only one case.

Pre-dilation was highly recommended and performed in 84.1% of the main vessels and 23.4% of the side-branches before treatment.

Side-branch wire protection before provisional scaffolding was per- formed in 38.0% of the cases, in 41 cases (38.3%) a highly supportive wire (Hi-Torque Balance Heavy-weight or Hi-Torque Whisper ES) was the default for wiring the MV or the SB (MV 32.7%, SB 9.3%).

One-hundred and seventy-eight Absorb BVS were implanted, with a maximum scaffolded length of 102 mm (4 BVS). To achieve an optimal final angiographic result, the MV post-dilation was performed in 64 cases (59.8%), non-compliant balloons were frequently used (52/64, 81.2%) and a proximal optimization technique (POT) was performed in the 59.4% of overall post-dilations.

SB ostium dilation across MV scaffold struts was performed in 39 bifurcations (36.4%), using balloons with mean diameter of 2.03 mm ± 0.48 and semi-compliant in the 99% of cases (Table 3).

Table 3 Procedural Characteristics

Number of bifurcations	N = 107
Technique	
Provisional	100 (93.4)
T-stenting	5 (4.7)
Culotte	1 (0.9)
Mini-crush	1 (0.9)
MV direct stenting	14 (13.1)
MV pre-dilation	90 (84.1)
Semi-compliant balloon	82 (76.6)
Non-compliant balloon	17 (15.9)
SB wiring before MV provisional stenting	38 (38.0)*
Default supportive wire	41 (38.3)
MV supportive wire	35 (32.7)
SB supportive wire	10 (9.3)
Cutting balloon	1 (0.9)
Rotablator	2 (1.9)
SB ostium dilation before MV treatment	25 (23.4)
Total number of scaffolds	178
Mean scaffolds per-bifurcation	1.66 ± 0.84

Table 3 Procedural Characteristics (*continued*)

Number of bifurcations	N = 107
MV Scaffold	104 (97.2)
Scaffold diameter (mm)	3.03 ± 0.4
Scaffold length (mm)	19.95 ± 5.6
SB Scaffold	14 (13.1)
Scaffold diameter (mm)	2.8 ± 0.3
Scaffold length (mm)	16.21 ± 4.8
MV post-dilation	64 (59.8)
Semi-compliant balloon	17 (15.9)
Non-compliant balloon	52 (48.5)
POT	38 (35.5)
Final kissing balloon inflation	5 (4.6)
SB ostium dilation after MV stent	39 (36.4)
Balloon diameter (mm)	2.03 ± 0.48
Vascular access	
Radial	66 (61.7)
Femoral	42 (39.2)
Contrast media (ml)	208.15 ± 90.82

Values are expressed as mean ± standard deviation (SD) or count (n) and percentages (%). ∗ % calculated over all provisional approach.
MV = main vessel; POT = Proximal Optimization Technique; SB = side branch.

The device success was achieved in 99.1% of the cases (106/107), in one calcified lesion a residual final stenosis not inferior to 30% persisted at the end of the procedure. The procedural success was 94.3%, in one case, a distal edge dissection caused a post-procedure MV TIMI flow grade equal to 1 and in 4 cases the final SB TIMI flow grade was inferior to 3 (TIMI flow 0 in one case, after MV provisional approach without a previous SB wiring). The "SB impairments" occurred in 13 procedures (12.1%). The most frequently reported cause was a SB TIMI flow grade b 3 after MV scaffolding, reported in 10 cases. In 6 of those cases the final SB TIMI flow grade improved after SB ostium post-dilatation, with no need for SB treatment (Table 4).

Quantitative coronary angiography analysis

Two-dimensional and 3-dimensional QCA were performed in 103 patients and 40 patients, respectively (inadequate views either pre- or post- procedure were excluded).

At the end of the procedure, the side-branch was not significantly affected by the BVS implantation the main vessels. In the 2-dimensional and the 3-dimensional QCA analyses, there were no differences between the pre- and post-procedure reference vessel diameter (2D RVD: 1.98 ± 0.33 mm vs 2.03 ± 0.41 mm, p = 0.718 - 3D RVD: 2.00 ± 0.28

Table 4 Procedural results

Number of bifurcations	N = 107
Device success	106 (99.1)
Procedural succes	101 (94.3)
Final MV TIMI flow grade 3	106 (99.1)
Final SB TIMI flow grade 3	103 (96.3)
SB impairment	13 (12.1)
SB TIMI flow grade < 3 after MV stenting	10 (9.3)
SB TIMI flow grade =0 after MV stenting	4 (3.7)
SB TIMI flow grade =1 after MV stenting	2 (1.9)
SB TIMI flow grade =2 after MV stenting	4 (3.7)
Need to guidewire(s) different from the default wire to rewire SB after MV stenting	5 (4.7)
Failure to rewire the SB after MV stenting	1 (0.9)
Failure to dilate the SB after MV stenting	1 (0.9)

Values are expressed as count (n) and percentages (%).
MV = main vessel; SB = side branch; TIMI = thrombolysis in myocardial infarction.

mm vs 2.08 ± 0.34 mm, p = 0.28), minimal lumen diameter (2D MLD: 1.45 ± 0.41 mm vs 1.48 ± 0.42 mm, p= 0.587 - 3D MLD: 1.54 ± 0.37 mm vs 1.61 ± 0.41 mm, p = 0.363), and minimal lumen area (3D MLA 1.97 ± 0.89 mm2 vs 2.17 ± 1.09 mm2, p = 0.334). In true bifurcation lesions the (2D) diameter stenosis appeared significant- ly increased (%DS pre PCI 58.7% vs 31.9%, p = 0.0001) after treatment. Additionally, also in the 3-mm ostial SB sub-segment, no statistically significant pre- and post-procedural variations were reported in terms of reference vessel diameter (2D RVD: 1.99 ± 0.33 mm vs 2.06 ± 0.38 mm, p = 0.309 - 3D RVD: 2.03 ± 0.28 mm vs 2.10 ± 0.32 mm, p = 0.123), minimal lumen diameter (2D MLD: 1.51 ± 0.38 mm vs 1.53 ± 0.44 mm, p = 0.567 - 3D MLD: 1.59 ± 0.35 mm vs 1.62 ± 0.41 mm, p = 0.760) minimal lumen area (3D MLA 2.10 ± 0.86 mm2 vs 2.19 ± 1.10 mm2, p = 0.660) (Tables 5 and 6).

Optical coherence tomography findings

OCT imaging was performed in 20 bifurcations after BVS implantation (Table 7). Incomplete scaffold apposition (ISA) was observed in 15 patients, with a mean ISA area of 0.12 ± 0.14 mm2 and a mean percentage of malapposed struts per patient equal to 3.87 ± 4.12%.

The sub-segments analysis was available in 19 cases (one case was excluded owing to incomplete pullback of treated MV). The mean percentages of malapposed struts per patient in distal, polygon of confluence and proximal sub-segments were 1.50 ± 2.59%, 4.08 ± 9.45% and 6.41 ± 16.99% respectively.

Table 5 Pre- and post-procedural vessel diameters 2D-QCA-evaluation

Number of bifurcations	Pre-PCI (N=103)	Post-PCI (N=103)	p value
Main vessel			
Reference diameter (mm)	2.63 ± 0.61	2.77 ± 0.55	0.286
Minimal lumen diameter (mm)	1.30 ± 0.55	2.35 ± 0.52	<0.001
% diameter stenosis	50.13 ± 18.86	15.14 ± 8.40	<0.001
Side branch			
Reference diameter (mm)	1.98 ± 0.33	2.03 ± 0.41	0.718
Minimal lumen diameter (mm)	1.45 ± 0.41	1.48 ± 0.42	0.587
% diameter stenosis	26.93 ± 16.89	27.80 ± 15.57	0.904
3-mm ostial side branch sub-segment			
Reference diameter (mm)	1.99 ± 0.33	2.06 ± 0.38	0.309
Minimal lumen diameter (mm)	1.51 ± 0.38	1.53 ± 0.44	0.567
% diameter stenosis	23.97 ± 15.99	25.82 ± 16.15	0.697
Angle			
Proximal Main Vessel/Side Branch (°)	143.58 ± 17.44	143.53 ± 18.04	0.282
Distal Main Vessel/Side Branch (°)	53.47 ± 15.65	52.68 ± 17.95	0.764

Values are expressed as mean ± SD. PCI = percutaneous coronary intervention.

Table 6 Pre- and post-procedural vessels diameters and areas 3DQCA-evaluation

Number of bifurcations	Pre-PCI (N=40)	Post-PCI (N=40)	p value
Main vessel			
Reference diameter (mm)	2.60 ± 0.72	2.77 ± 0.48	0.128
Minimal lumen diameter (mm)	1.48 ± 0.59	2.43 ± 0.46	<0.001
Minimal lumen area (mm^2)	1.99 ± 1.52	4.81 ± 1.70	<0.001
Percentage area stenosis	63.47 ± 21.49	22.15 ± 12.27	<0.001
Side branch			
Reference diameter (mm)	2.00 ± 0.28	2.08 ± 0.34	0.280
Minimal lumen diameter (mm)	1.54 ± 0.37	1.61 ± 0.41	0.363
Minimal lumen area (mm^2)	1.97 ± 0.89	2.17 ± 1.09	0.334
Percentage area stenosis	42.25 ± 21.50	38.62 ± 21.33	0.305
3-mm ostial side branch sub-segment			
Reference diameter (mm)	2.03 ± 0.28	2.10 ± 0.32	0.123
Minimal lumen diameter (mm)	1.59 ± 0.35	1.62 ± 0.41	0.760
Minimal lumen area (mm^2)	2.10 ± 0.86	2.19 ± 1.10	0.660
Percentage area stenosis	34.98 ± 19.98	37.48 ± 20.28	0.798
Angle			
Proximal Main Vessel/Side Branch (°)	139.19 ± 15.94	140.86 ± 14.70	0.597
Distal Main Vessel/Side Branch (°)	59.02 ± 12.31	55.23 ± 13.34	0.189
Proximal Main Vessel/Distal Main Vessel (°)	152.40 ± 13.08	155.74 ± 10.27	0.128

Values are expressed as mean ± SD. PCI = percutaneous coronary intervention.

Table 7 Optical coherence tomography (OCT) analysis post-scaffold implantation in bifurcated coronary lesions

OCT variables	N = 20
In-segment analysis	
Minimum lumen area (mm^2)	5.05 ± 1.05
Mean lumen area (mm^2)	7.36 ± 1.37
Lumen volume (mm^3)	231.49 ± 97.72
Minimum scaffold area (mm^2)	5.68 ± 1.08
Mean scaffold area (mm^2)	7.61 ± 1.45
Scaffold volume (mm^3)	236.88 ± 99.71
Mean ISA area (mm^2)	0.12 ± 0.14
Max ISA area (mm^2)	1.64 ± 1.56
% ISA area	1.71 ± 2.22
Mean prolapse area (mm^2)	0.47 ± 0.27
Max prolapsed area (mm^2)	1.40 ± 0.75
% prolapse	6.27 ± 3.46
Distal dissection (N = 15)	5 (33.3)
Proximal dissection (N = 17)	4 (23.5)
Analyzed struts per patient	292 ± 117.52
Malapposed struts per patient	10.15 ± 8.37
% malapposed struts	3.87 ± 4.12
Side branch struts per bifurcation	3.20 ± 2.31
5-mm proximal MV sub-segment (N = 19)	
Malapposed struts	2.11 ± 4.53
% malapposed struts	6.41 ± 16.99
Polygon of confluence (POC) (N = 19)	
Malapposed struts	0.63 ± 1.11
% malapposed struts	4.08 ± 9.45
SB-related struts	2.0 ± 2.13
5-mm distal MV sub-segment (N = 19)	
Malapposed struts	0.61 ± 1.09
% malapposed struts	1.50 ± 2.59

Values are expressed as mean ± SD, median [IQR] or n (%). ISA = incomplete scaffold apposition. MV = main vessel. OCT = optical coherence tomography. POC = polygon of confluence.

Table 8 Clinical outcomes at 1-year follow-up.

Clinical events	N = 102
Major adverse cardiac events	5.5%
All cause death	2.2%
Cardiac death	1.1%
Myocardial infarction	4.4%
Target lesion revascularization	3.3%
Target vessel revascularization	6.6%
Non- target vessel revascularization	3.4%
Scaffold thrombosis	3.3%
Definite ST	2.2%
Probable ST	0.0%
Possible ST	1.1%

ST scaffold thrombosis

In the sub-group of patients in which a proximal optimization technique (POT) was performed, the percentages of malapposed struts in the polygon of confluence and in the proximal sub-segment were numerically lower compared with the sub-group in which POT was not performed (1.54 ± 3.42% vs 6.37 ± 12.49% and 3.31 ± 3.57% vs 8.33 ± 24.29% respectively).

Clinical outcomes

Survival status was available in 99.0% (101/102). The overall mortality at one year was 2.2% (2/101). Clinical follow-up rate was 91.1% (92/101) with a median follow up duration of 731 days (interquartile range, IQR: 644–762 days). 89 patients had a follow-up of at least one year (2 patients had a follow-up duration of 353 and 332 days respectively. One patient was lost to follow-up with follow-up duration of 202 days).

The remaining 9 out of 101 patients could not be approached for clinical follow-up the cause was refusal to participate and in one case emigration. A total of 5 patients were reported to have major adverse cardiac event (Fig. 4) including 1 cardiac death (and possible ST), 4 MI (2 ST-segment elevation MI, one peri-procedural MI caused by a distal scaffold dissection and one occurred after a staged procedure on a non-target vessel, and 2 non-ST elevation MI, both due to a late scaffold thrombosis(Table 8), 3 ischemia-driven target bifurcation revascularizations (due to an in-scaffold restenosis inducing angina). At one year, 2 cases of definite ST (at day 47 and at day 142) occurred. (See Table 9).

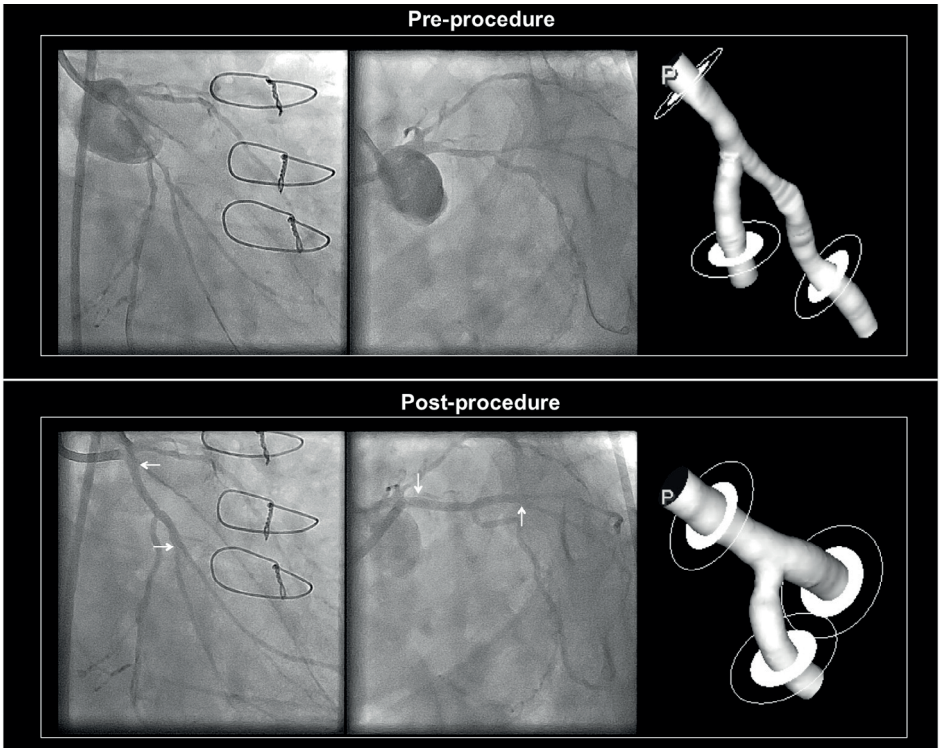

Figure 3 Treatment of a coronary bifurcation located in a diffusely disease vessel in a patient with previous coronary artery bypass graft.
In the upper panel angiographic appearance pre-intervention and 3-dimentional QCA reconstruction of the target bifurcation. In the lower panel post-procedure appearance and 3-dimentional QCA reconstruction with no side-branch impairment.

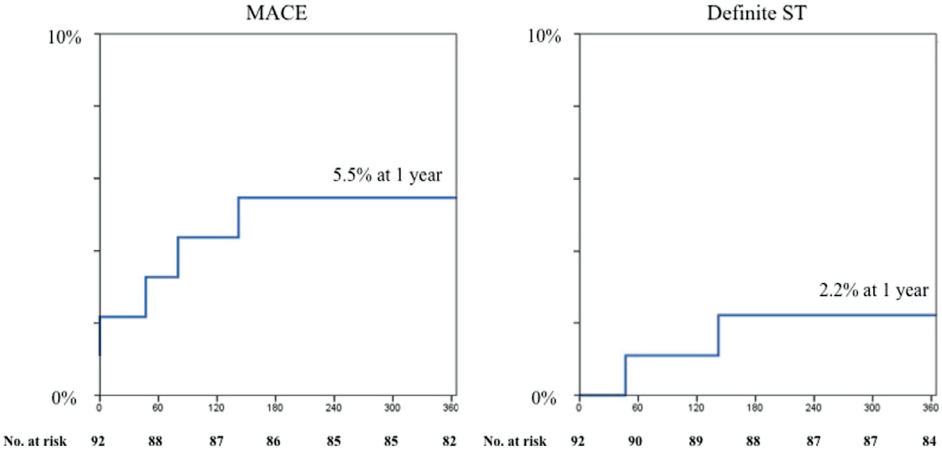

Figure 4 Kaplan–Meier curves for MACE and scaffold thrombosis.
MACE: major adverse cardiac events; ST: scaffold thrombosis

Table 9 Cases of definite scaffold thrombosis

Case #	Type of lesion	Technique	Device size (mm)	Timing (days from index procedure to scaffold thrombosis)	Dual antiplatelet therapy at the time of scaffold thrombosis
1	LAD/1°Diagonal Medina 1.1.1 Angulation 78°	"Provisional MV stenting"	3.0 x 18	142	ASA (80 mg) + PRASUGREL (10 mg)
2	LAD/1°Diagonal CTO	"Provisional MV stenting"	3.0 x 28 3.5 x 18 3.5 x 18 (2 overlap)	47	ASA (80 mg) + CLOPIDOGREL (75 mg)

ASA = aspirin; *CTO* = chronic total occlusion; *LAD* = left anterior descending; *MV* = main vessel.

DISCUSSION

Initial clinical experience with bioresorbable vascular scaffolds has been focused on simple lesions and relatively stable patients. Recent data, mainly derived from registry, provided additional information on safety, feasibility and performance of BVS in more complex lesions and patients [17,18], however specific challenging subsets such as bifurcation lesions remain poorly investigated.

In the present study we reported the BVS performance after implantation in bifurcation lesions in wide range clinical scenarios, including patients presenting with acute myocardial infarction or showing multivessel disease (Fig. 3) and coronary chronic total occlusions.

The approach adopted in the vast majority of the cases was a T-provisional scaffolding, a solid amount of evidence suggests this strategy as to be the preferable in most of the bifurcation cases [19,20]. Such evidences are provided from studies performed with metal stents but it is reasonable to apply the same principles to bioresorbable devices, especially considering the fact that a single scaffold technique reduce the amount of polymer at the bifurcation site, avoids overlap and the need for multiple layer of polymer.

The scaffold sizing in bifurcation lesions could be challenging in case of remarkable vessel tapering distally to the side-branch.

Recently Ishibashi et al. reported that oversizing the implanted scaffold compared to both the proximal and distal vascular maximal diameter (Dmax) could be associated with clinical events. On the other hand underexpansion was also shown to increase the risk of scaffold thrombosis [21]. Probably a reasonable approach could be to balance the proximal and distal Dmax, ensuring optimal apposition proximally after post-dilatation, without causing high vessel stretch and injury distally.

In the present series, the size of the BVS was usually chosen on the basis of the proximal maximal diameter (Dmax) [22] but also taking into account the distal Dmax, often performing low-pressure deployment and thereafter performing proximal optimization.

In our report we observed a trend toward a reduction in malapposition at the proximal segment and at the polygon of confluence in the cases with performed proximal optimization.

Taking into consideration the faith of the side-branches after BVS implantation, an initial concern associated with the larger BVS struts width and its possible impact on side-branch impairment has been raised [9]. Maramatsu et al. performed a post-hoc analysis of the ABSORB-EXTEND and SPIRIT First and II Trials [9] to assess the incidence of small SB occlusion (bifurcation lesions involving a SB b 2 mm) after either BVS or everolimus-eluting metal stents. BVS demonstrated a higher incidence of post-procedural side branch occlusion compared with EES but only in small side branches with a reference vessel diameter ≤ 0.5 mm.

To investigate the impact of BVS wider struts on side-branch impairment when treating what is most commonly considered a bifurcation lesion (with a side-branch of at least 2 mm in diameter) [20,23–27], we performed a detailed analysis taking into consideration both procedural and angiographic parameters.

We evaluated the composite parameter of "side-branch impairment" observing the TIMI flow, need for dedicated wires, or failure to re-cross or dilate the side-branch and we assessed the 2- and 3- dimensional QCA pre and post BVS implantation of the side-branch.

A side-branch impairment occurred in 13 cases (12.1%) after BVS deployment, the most frequently reported cause was a SB TIMI flow grade b 3 after MV scaffolding, (10 cases). Of note in 6 of those cases the final SB TIMI flow grade improved to grade TIMI flow 3 after SB ostium post-dilation, with no need for SB treatment and reducing the occurrence of final side-branch slow flow to only 4 bifurcations (3.7%). Such data are in line with previous investigations evaluating the impact of first- and second-generation drug eluting metal stents on side-branch impairment [7].

It would therefore appear that the concern of an increased side- branch damage or occlusion after BVS implantation may not be justified, when considering side-branches with a visually estimated diameter of 2 mm or more.

The OCT analysis although performed in a subgroup of patients showed a low amount of malapposition in the overall bifurcation segment probably also in association with a high rate of post-dilatation. Malapposition was distributed with a reduction from the proximal to the distal segment of the bifurcation, highlighting the possible need for proximal optimization.

Finally, although due to the small number of patients and events re- ported is not possible to reach firm conclusions in terms of clinical outcomes, the overall mortality and the MACE rate suggest a relative safety of BVS implantation in bifurcation lesions given a preferred single scaffold technique and a high rate of pre and post dilatation.

LIMITATIONS

The present report is an investigator initiated, single center, single arm study and is a retrospective analysis of the BVS evaluation program at Thoraxcenter Rotterdam, The Netherlands. The choice for BVS implantation was left to operator discretion; this could be source of selection bias. The absence of a comparator arm is limiting the interpretation of our data. In the present study side branch vessel with a visual estimated diameter ≥ 2.0 mm was evaluated, by QCA the mean RVD of the side branch was 1.98 mm highlighting the well-known underestimation of vessel size by QCA. Intravascular imaging was encouraged but not mandatory and left to the operator discretion, such approach could be associated with selection bias. The limited number of patients does not allow reaching firm conclusions in terms of clinical outcomes, therefore clinical data should be considered as purely descriptive and hypothesis generating.

CONCLUSION

The present investigation suggest the feasibility and good performance of everolimus-eluting BVS implantation in patients with a native bifurcated coronary lesion, involving a SB ≥ 2 mm in diameter. Further investigations in randomized clinical trials are required to provide the actual impact of this novel technology on safety, efficacy and long- term clinical outcomes, also compared to second-generation DESs.

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