http://hdl.handle.net/1765/116450

Erasmus MC
Universitair Medisch Centrum Rotterdam

Expanded clinical use of everolimus eluting bioresorbable vascular scaffolds for treatment of coronary artery disease.

R Diletti, Y Ishibashi, CM Felix, Y Onuma, S Nakatani, NM van Mieghem, ES Regar, M Valgimigli, PP de Jaegere, NS van Ditzhuijzen, JM Fam, JMR Ligthart, MJ Lenzen, PW Serruys, F Zijlstra, RJM van Geuns

Catheter Cardiovasc Interv. 2016 Nov 29

Erasmus University Rotterdam

ABSTRACT

Background

Limited data are currently available on the performance of everolimus-eluting bioresorbable vascular scaffold (BVS) for treatment of complex coronary lesions representative of daily practice.

Methods

This is a prospective, mono-center, single-arm study, reporting data after BVS implantation in patients presenting with stable, unstable angina, or non-ST segment elevation myocardial infarction caused by de novo stenotic lesions in native coronary arteries. No restrictions were applied to lesion complexity. Procedural results and 12-month clinical outcomes were reported.

Results

A total of 180 patients have been evaluated in the present study, with 249 treated coronary lesions. Device Success per-lesion was 99.2%. A total of 119 calcified lesions were treated. Comparable results were observed among severe, moderate and non-calcified lesions in term of %diameter stenosis (%DS) (20.3±10.5%, 17.8±7.7%, 16.8±8.6%; p=0.112) and acute gain (1.36±0.41mm, 1.48±0.44mm, 1.56±0.54 mm; p=0.109). In bifurcations (54 lesions), side-branch ballooning after main vessel treatment was often performed (33.3%) with low rate of side-branch impairment (9.3%). A total of 29 cases with coronary total occlusions were treated. After BVS implantation %DS was not different from other lesion types (17.2±9.4%, vs 17.7±8.6%; p=0.780). At one year, all-cause mortality was reported in 3 cases. A total of 5 target lesion revascularizations and 4 non-target vessel revascularisations were reported. Four cases of definite scaffold thrombosis occurred.

Conclusions

The implantation of the everolimus-eluting bioresorbable vascular scaffold in an expanded range of coronary lesion types and clinical presentations was observed to be feasible with promising angiographic results and mid-term clinical outcomes.

INTRODUCTION

The everolimus-eluting bioresorbable vascular scaffolds (BVS) represent a novel approach for treatment of coronary artery disease. Similarly to conventional metal stents the absorb BVS provide acute lumen gain, vessel scaffolding and drug elution to the vessel wall immediately after implantation.[1] However, at variance with standard stents, the polymeric structure of this device allows a gradual bioresorption of the implant over time.[2] Complete scaffold bioresorption is hypothesized to offer several advantages over permanent metal devices comprising re-acquirement of physiological vasomotion, late lumen enlargement, non-invasive imaging and future treatment with bypass grafting.[3-5] In addition the absence of a foreign body could avoid phenomena such as permanent side-branch jailing, late acquired malapposition and the occurrence of late and very late stent thrombosis.[5]

The absorb BVS has been initially tested in humans in two cohort studies, both showing promising results in terms of surrogate and clinical endpoints.[6-9] However, being those studies an early evaluation of this technology, they were characterized by a patient population showing stable coronary artery disease and relatively simple lesions. The first randomized data in selected patients (Absorb II, Absorb Japan) supported the further development of this technique.

At the current state of the art, very limited data are available on BVS performance in real-world patients, including those presenting with acute coronary syndromes and complex lesions. A lack of information is especially evident when considering important lesion subsets such as calcified plaques, long lesions, bifurcations, and total occlusions.

Given this background, the present study aims to report angiographic and clinical data after an expanded clinical use of the second generation BVS, implanted in patients admitted with different clinical presentations including acute coronary syndromes and having a broad range of coronary lesion types.

METHODS

This is an investigator initiated, prospective, single-centre, single-arm post market study, aiming to evaluate the feasibility safety and performance of the absorb BVS for treatment of patients with coronary artery disease in routine clinical practice. Enrolled patients were subjects presenting with stable, unstable angina, or non-ST segment elevation myocardial infarction caused by de novo stenotic lesions in native coronary arteries. No restrictions were applied to lesion complexity. Due to the absorb BVS size availability, a Dmax (proximal and distal mean lumen diameter) within the upper limit of 3.8 mm and the lower limit of 2.0 mm by online QCA was required. Exclusion criteria

were minimal and comprised allergies or contraindications to antiplatelet medication, female patient with childbearing potential or currently breastfeeding, acute ST segment elevation myocardial infarction and post CABG patients. As per hospital policy patients with a previously implanted metal DES in the intended target vessel were also excluded. Also, although old age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age. A hybrid approach combining BVS with small DES or large DES where necessary was also not recommended.

All patients were treated with DAPT according to current guidelines. DAPT was prescribed for one year after PCI. Prasugrel was standard therapy for ACS presenting patients while clopidogrel was initiated for stable angina patients only.

To assess clinical outcomes, a questionnaire was sent to all living patients with specific queries on re-hospitalization and cardiovascular events. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary.

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 disease 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 without a specific written informed consent in addition to the standard informed consent prior to the procedure. Therefore, a waiver from the hospital Ethical Committee was obtained for written informed consent, as according to Dutch law written consent is not required, if patients are not subject to acts other than as part of their regular treatment. Specific written informed consent post procedure was asked for a detailed follow-up program.

Study device

The device used in the present study is the second generation Absorb BVS (Abbott Vascular, Santa Clara, CA, USA); a balloon expandable scaffold with a polymer backbone of Poly-L lactide Acid (PLLA) coated with a thin layer of a 1:1 mixture of an amorphous matrix of Poly-D and L lactide acid (PDLLA) polymer, controlling the release of 100 micrograms/cm^2 of the anti-proliferative drug everolimus. Two platinum markers located at each Absorb BVS edge allowing for accurate visualization of the radiolucent Absorb BVS during angiography or other imaging modalities. Approximately 80% of the drug

is eluted within the first 30-days. Both PLLA and PDLLA are fully bioresorbable. The polymers are degraded mainly via hydrolysis resulting oligomers of lactate metabolized by Krebs cycle. Small particles, less than 2 µm in diameter, have also been shown to be phagocytised and degraded by macrophages.

Definitions

Device Success was defined as the attainment of <30% final in segment residual stenosis after absorb BVS implantation, by angiographic visual estimation. Procedure Success was defined as device success and no major peri-procedural complications (Emergent CABG, coronary perforation requiring pericardial drainage, residual dissection impairing vessel flow – TIMI-flow II or less -). Clinical success was defined as procedural success and no in-hospital major adverse cardiac events (MACE). 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 (ARC) definition. Any Target lesion revascularization (TLR) was defined as clinically driven if at repeat angiography a diameter stenosis >70% was observed, or if a diameter stenosis >50% was present in association with recurrent angina pectoris; objective signs of ischaemia (ECG changes) at rest or during exercise test, likely to be related to the target vessel; abnormal results of any invasive functional diagnostic test.

Target lesion failure was defined as the composite of cardiac death, target vessel myocardial infarction, or ischemia driven target lesion revascularization. Major adverse cardiac events (MACE), defined as the composite of cardiac death, any re-infarction (Q or Non Q-Wave), emergent bypass surgery (CABG), or clinically driven target lesion revascularization (TLR). Target vessel failure (TVF) was defined as cardiac death, target vessel myocardial infarction (MI), or clinically driven target vessel revascularization (TVR). Delivery failure was defined as opening of scaffold from its cover and insertion into the guiding-catheter without final implantation.

All potential events were adjudicated by a local independent Clinical Events Committee (CEC).

Quantitative coronary angiography

Quantitative coronary angiography (QCA) analyses were performed using the Coronary Angiography Analysis System (Pie Medical Imaging, Maastricht, Netherlands).

The QCA measurements we performed pre and post BVS implantation. The 37 µm platinum radio-markers located at each end of the Absorb BVS aided in the localisation of the non-radio-opaque scaffold for QCA. Analysed parameters included reference vessel diameter (RVD) - calculated with interpolate method - percentage diameter stenosis (%DS) and minimal lumen diameter (MLD). Acute gain was defined as post-procedural MLD minus pre-procedural MLD. The angiographic analysis were performed by three

investigators (YI, YO and RD) who were extensively trained in an experienced core-lab (Cardialysis BV, Rotterdam, The Netherlands)

A calcified coronary culprit lesion was defined as already reported[10] 'readily apparent densities noted within the apparent vascular wall at the site of the stenosis.' By qualitative assessment of the angiograms, target lesions were classified as severe ('radioopacities noted without cardiac motion prior to contrast injection generally involving both sides of the arterial wall'), moderate ('densities noted only during the cardiac cycle prior to contrast injection'), or none/mild (lesions other than severe and moderate calcified lesions). The Inter- and intra-observer variability in the qualitative analysis of coronary calcium on coronary angiograms have been already reported. [11]

To provide insights on the coronary bifurcation treatment with BVS we performed a full analysis of techniques and material used and we reported the occurrence of side-branch impairment, an end-point already reported in the literature as "side-branch trouble"[12] and defined as follow: at least 1 of the following procedural parameters: 1) Side-branch TIMI flow grade <3 after main vessel stenting; 2) need of guide-wire(s) different from the workhorse wire to rewire side-branch after main vessel scaffolding; 3) failure to rewire the side-branch after main vessel scaffolding; or 4) failure to dilate the side-branch after main vessel scaffolding and side-branch rewiring.

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation; p values were calculated with Fisher's Exact test for binary variables, Wilcoxon's Rank Sum test for continuous variables. Comparisons among multiple means were performed with analysis of variance (1-way ANOVA). A p value<0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 15.0 for windows (IL,US).

RESULTS

From September 2012 to July 2013 a total of 1529 percutaneous coronary interventions were performed in our center. A total of 180 patients have been enrolled in the present study, with 249 treated coronary lesions (Table 1). A total of 1157 patients were treated with standard second generation drug eluting stents. The remaining cases were treated with bare metal stents, dedicated bifurcation stents, balloon angioplasty only or thrombectomy only. Baseline clinical characteristics of the patients implanted with bioresorbable devices compared with those of the patients implanted with second generation drug eluting metal stents are reported in the supplement (Table 4). We observed that patients treated with bioresorbable devices were overall younger, more frequently

smokers, and had a lower rate of prior myocardial infarction, PCI and CABG. Therefore, this patient population is slightly different from the general population treated with percutaneous coronary intervention in everyday practice. However, the observed differences are in line with the predefined exclusion criteria.

Seventy-three patients (40.6%) showed multivessel disease. A total of 109 lesions (43.8%) were classified as type B2 or C, mean lesion length was 25.86 mm, bifurcation lesions with side-branch ≥ 2 mm were 54, a total of 119 lesions were defined with severe or moderate calcification and in 29 cases was present a total occlusion (Table 1).

Lesion preparation was performed in a large part of the cases mainly through balloon pre-dilatation (89.2%); rotational atherectomy was necessary in 4.8% of cases. Multiple scaffold implantations per lesion were allowed and often performed, (31.7%) up to the implantation of 5 scaffolds.

Table 1 Baseline clinical and lesion characteristics

Clinical characteristics	**N = 180**
Age	60.6 ± 10.6
Male n. (%)	134 (74.4%)
Hypertension n. (%)	94 (52.2%)
Hypercholesterolemia n. (%)	84 (46.7%)
Diabetes n. (%)	32 (17.8%)
Smoke n. (%)	99 (55.0%)
Peripheral vascular disease n. %	19 (10.6%)
CVA n. (%)	14 (7.8%)
Kidney disease n. (%)	11 (6.1%)
Prior MI n. (%)	30 (16.7%)
Prior PCI n. (%)	17 (9.4%)
Prior CABG n. (%)	0 (0.0%)
COPD n. (%)	11 (6.1%)
History of heart failure n. (%)	10 (5.6%)
Lesion characteristics	**L= 249**
One vessel disease	107 / 180 (59.4%)
Two vessel disease	61 / 180 (33.9%)
Three vessel disease	12 / 180 (6.7%)
Number of Treated Lesions per vessel (%)	
0 lesion	1/ 249 (0.4%)
1 lesion	189 / 249 (75.9%)
2 lesions	54 / 249 (21.7%)
3 lesions	4 / 249 (1.6%)
4 lesions	1 / 249 (0.4%)

Table 1 Baseline clinical and lesion characteristics (*continued*)

Lesion characteristics	L= 249
Lesion Location (%)	
LAD	120 / 249 (48.2%)
LCX	55 / 249 (22.1%)
RCA	66 / 249 (26.5%)
Diagonal	7 / 249 (2.8%)
LMCA	1 / 249 (0.4%)
AHA/ACC Lesion Classification (%)	
A	38 / 249 (15.3%)
B1	103 / 249 (41.4%)
B2	63 / 249 (25.3%)
C	46 / 249 (18.5%)
Lesion length (mm)	25.86 ± 13.64
Range min, max (mm)	5.32 - 80.01
Bifurcation lesion n. (%)	54 / 249 (21.7%)
Total occlusion (%)	29 / 249 (11.6%)
Calcification lesion (%)	119/ 249 (47.8%)

CVA= cerebrovascular accident; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease. Data are expressed as mean ± standard deviation or number and proportion

No scaffold dislodgment was reported. Bailout with drug eluting metal stents was performed in only 2 cases. Balloon post-dilatation was performed in a remarkable percentage of cases (45.0%) with often a balloon/scaffold ratio > 1.0 (41.8%). (Table 2) The overall device, procedure and clinical success rates per lesion, were respectively 99.2%, 98.8% and 98.8%

Table 2 Procedural data per-lesion analysis

Lesion characteristics	L= 249
Number of Scaffold or stent – per lesion (%)	
Average	1.41± 0.75
0 scaffold or stent	1 / 249 (0.4%)
1 scaffold or stent	169 / 249 (67.9%)
2 scaffolds or stents	61 / 249 (24.5%)
3 scaffolds or stents	10 / 249 (4.0%)
4 scaffolds or stents	7 / 249 (2.8%)
5 scaffolds or stents	1 / 249 (0.4%)
Overlapping	78
Overlapping BVS-BVS	76
Overlap scaffolds diameters 3.5mm-3.5mm,n (%)	20 (26.3%)
Overlap scaffolds diameters 3.5mm-3.0mm,n (%)	15 (19.7%)
Overlap scaffolds diameters 3.5mm-2.5mm,n (%)	3 (3.9%)

Table 2 Procedural data per-lesion analysis (*continued*)

Lesion characteristics	**L= 249**
Overlap scaffolds diameters 3.0mm-3.0mm,n (%)	15(19.7%)
Overlap scaffolds diameters 3.0mm-2.5mm,n (%)	15 (19.7%)
Overlap scaffolds diameters 2.5mm-2.5mm,n (%)	8 (10.5%)
Overlapping BVS-Metal	2 (2.6%)
Bailout scaffold/stent (%) – per lesion	
with BVS	8 / 249 (3.2%)
with Metallic stent	2 / 249 (0.8%)
Pre dilatation (%)	222 / 249 (89.2%)
Type of pre-dilatation balloon*	
Non-compliant	16 / 203 (7.9%)
Semi-compliant	187 / 203 (92.1%)
The usage of scoring (scoreflex or cutting)	9 / 219 (4.1%)
Average size of balloon	2.52 ± 0.36
Balloon / artery (pre-RVD) ratio < 1 (excluding total occlusion before procedure)	100 / 184 (54.3%)
Balloon / scaffold ratio ≤1	198 / 202 (98.0%)
Balloon 0.5mm smaller ≤ scaffold size	172/202 (85.1%)
Max pressure	13.95 ± 2.86
Use of other devices for lesion preparation	
Rotational atherectomy	12 / 249 (4.8%)
Manual thrombectomy	11 / 249 (4.4%)
Daughter catheter	5 / 249 (2.0%)
Buddy wire	18 / 249 (7.2%)
Post-dilatation (%)	112 / 249 (45.0%)
Type of post-dilatation balloon**	
Compliant	32 / 110 (29.1%)
Non-compliant	78 / 110 (70.9%)
Average size of balloon	3.27 ± 0.46 mm
Max pressure	15.58± 3.46
Balloon / Artery < 1	25 / 110 (22.7%)
Balloon > Scaffold size	46 / 110 (41.8%)
Balloon > Scaffold size+0.25mm	15 / 110 (13.6%)
Device success per lesion (%)	247 / 249 (99.2%)
Procedure success per lesion (%)	246 / 249 (98.8%)
Clinical success per lesion	246 / 249 (98.8%)
QCA pre-procedure	
RVD (mm)	2.63 ± 0.43
MLD (mm)	0.90 ± 0.35
% DS (%)	64.8 ± 14.5
Proximal Dmax (mm)	3.92 ± 8.28
Distal Dmax (mm)	2.89 ± 2.31

Table 2 Procedural data per-lesion analysis (*continued*)

Lesion characteristics	L= 249
QCA Post-procedure In-scaffold	
RVD (mm)	2.89 ± 0.42
DS (%)	17.6 ± 8.65
MLD (mm)	2.41 ± 0.41
Scaffold length	29.44± 15.71
Acute gain (mm)	1.51 ± 0.49
TIMI grade 2	2 / 249 (0.8%)
TIMI grade 3	247 / 249 (99.2%)

*Type of pre-dilatation balloon is reported in a subgroup of 203 patients. ** Type of post-dilatation balloon is reported in a subgroup of 110 patients. Data are expressed as mean ± standard deviation or number and proportion

QCA analysis

The mean pre-procedure reference vessel diameter (RVD) was 2.63 ± 0.43 mm, with a mean percentage diameter stenosis (%DS) of 64.8 ± 14.5% and a mean minimal lumen diameter (MLD) equal to 0.90 ± 0.35 mm. Post-procedure %DS was 17.60 ± 8.65 % with a mean MLD equal to 2.41 ± 0.41 mm reflecting a mean acute gain of 1.51 ± 0.49 mm. TIMI 3 flow was observed in 99.2% of the final angiograms. (Table 2, Figure 1)

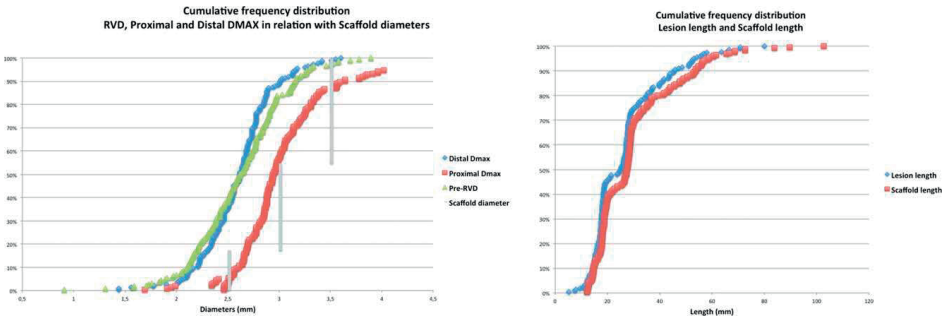

Figure 1 Vessel and scaffold diameters and lengths
Left panel, Cumulative frequency distribution of the reference vessel diameter the proximal end distal diameter in relation with the nominal size of the implanted scaffolds. Right panel, Cumulative frequency distribution of the lesion length in relation with the length of the implanted scaffolds

Bifurcation Lesions

A total of 54 lesions were located at the site of a bifurcation with a side-branch ≥ 2.0 mm. In 51 cases a provisional side branch technique was used, in addition 1 T-stenting, 1 culotte, 1 T-stenting with small protrusion (TAP) techniques were performed. In 18 cases side-branch wire protection was used, pre-dilatation and post-dilatation of the main vessel was often performed. Side-branch dilatation post MV stenting was necessary in

18 lesions. A final TIMI flow <3 in the main vessels (MV) was observed in only one case, in the side-branch this was reported in 3 lesions. Failure to re-wire the side-branch was never reported but in one case the operator was unable to re-cross the scaffold with a small balloon of 1.5 mm in diameter. (Table 5 Supplement) The overall rate of side-branch impairment was 9.3% (5/54)

Calcified lesions

A total of 119 calcified lesions were treated with BVS, 33 with severe calcification, 86 with moderate calcification, (Figure 2) and compared with non-calcified lesions. After treatment no differences were observed between calcified and non-calcified lesions in terms of MLD (Severe calcified 2.38 ± 0.38 mm, moderate calcified 2.41 ± 0.39 mm, non-calcified 2.42 ± 0.43 mm; p=0.889), %DS (Severe calcified 20.3 ± 10.5 %, moderate calcified 17.8 ± 7.7%, non-calcified 16.8 ± 8.6%; p=0.112) and acute gain (Severe calcified 1.36 ± 0.41mm, moderate calcified 1.48 ± 0.44 mm, non-calcified 1.56 ± 0.54 mm; p=0.109). These results were achieved with an overall higher use of buddy wires in calcified lesions (severe calcified 18.2%, moderate calcified 9.3%, non-calcified 3.0%; p=0.016)

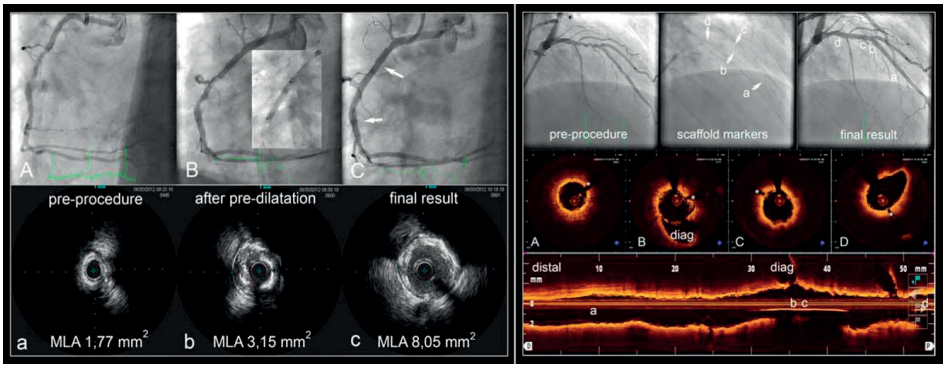

Figure 2 Calcified lesion and long lesions
Right panel. Calcified lesions. Angiogram showing a long lesion in the RCA (panel A). IVUS pre-procedure (Panel a) shows at the MLA more than 180 degrees superficial calcium (*). Panel B shows the angiogram after pre-dilatation (semi-compliant balloon 3.0 x 20mm). IVUS (panel b) shows clear "cracks" in the calcium (arrowheads), reducing the plaque resistance, thus sufficiently prepared for BVS implantation. Panels C and c show respectively the result on angiogram and on IVUS after implanting a BVS 3.5 x 28mm. Left panel. Long lesions. The angiogram top left shows the long lesion in the LAD. The mid-panel shows the markers of the two overlapping scaffolds (a & c distal BVS 3.0 x 28mm and b & d proximal BVS 3.5 x 18mm). The top right shows the final result with the OCT cross-section positions indicated by a to d). OCT (St.Jude Lightlab Dragonfly™) shows a well deployed scaffold. Panels B & C show the markers of respectively the proximal and distal scaffolds (*), indicating an overlap of approximately 1 mm.

Lesion preparation was more aggressive in calcified lesions with a higher use of rotational atherectomy (severe calcified 18.2%, moderate calcified 4.7%, non-calcified 1.5%; p<0.001) and scoring balloons (severe calcified 15 .2%, moderate calcified 3.5%, non-calcified 0.8%; p=0.001). Success rates were high in calcified vessels showing no significant differences when compare do non-calcified ones. Device success in severe calcified lesions was 97.0%, in moderate calcified 100% and in non-calcified 99.2%; p=0.251. (Table 3)

Total Occlusions

Vessels showing a total occlusion were 29. After vessel recanalization BVS implantation was performed achieving a final MLD and %DS not different from other lesion types (MLD: 2.51 ± 0.53 mm vs 2.40 ± 0.39; p=0.163; %DS: 17.2 ± 9.4% vs 17.7 ± 8.6%; p=0.780), with a high rate of final device success (96.6% vs 98.2%; p=0.465) and procedure success (96.6% vs 98.6%; p=0.393). To reach those results supportive wires were used much more frequently in occluded vessels (54.2% vs 2.1%; p<0.001). (Table 3, Figure 2)

Table 3 BVS implantation in calcified and total occluded lesions

Calcified lesions	Severe calcification (L = 33)	Moderate calcification (L =86)	No calcification (L =130)	P value
Lesion preparation				
Rotational atherectomy ,% (n)	18.2% (6/33)	4.7% (4/86)	1.5% (2/130)	<0.001
Scoring balloon ,% (n)	15.2% (5/33)	3.5% (3/86)	0.8% (1/130)	0.001
Daughter catheter ,% (n)	3.0% (1/33)	2.3% (2/86)	1.5% (2/130)	0.886
Buddy wire,% (n)	18.2% (6/33)	9.3% (8/86)	3.0% (4/130)	0.016
Average size of balloon	2.48 ± 0.38	2.55 ± 0.35	2.52 ± 0.36	0.702
Non-compliant balloon ,% (n)	13.3% (4/30)	9.5% (7/74)	5.1% (5/99)	0.276
QCA pre-procedure				
RVD (mm)	2.51 ± 0.35	2.66 ± 0.43	2.64 ± 0.46	0.256
MLD (mm)	0.97 ± 0.40	0.92 ± 0.36	0.87 ± 0.34	0.358
% DS (%)	62.3 ± 13.5	65.0 ± 12.6	65.3 ± 15.7	0.592
Lesion length	36.11 ± 2.34	27.99 ± 1.54	22.11 ± 1.16	<0.001
QCA post-procedure				
RVD (mm)	2.97 ± 0.38	2.93 ± 0.39	2.85 ± 0.46	0.244
MLD (mm)	2.38 ± 0.38	2.41 ± 0.39	2.42 ± 0.43	0.889
% DS	20.3 ± 10.5	17.8 ± 7.7	16.8 ± 8.6	0.112
Acute gain (mm)	1.36 ± 0.41	1.48 ± 0.44	1.56 ± 0.54	0.109
Device success per lesion, % (n)	97.0% (32/33)	100% (86/86)	99.2% (129/130)	0.251
Procedure success per lesion, % (n)	97.0% (32/33)	98.8% (85/86)	99.2% (129/130)	0.571
Clinical success (per lesion), % (n)	97.0% (32/33)	98.8% (85/86)	99.2% (129/130)	0.571

Table 3 BVS implantation in calcified and total occluded lesions *(continued)*

Occluded vs non-occluded	Occluded (L =29)	Non-occluded (L = 220)	P value
QCA post-procedure			
RVD (mm)	3.01 ± 0.47	2.88 ± 0.41	0.103
MLD (mm)	2.51 ± 0.53	2.40 ± 0.39	0.163
% DS (%)	17.2 ± 9.4	17.7 ± 8.6	0.780
Acute gain (mm)	-	1.51 ± 0.49	-
Procedural characteristics			
Daughter catheter, % (n)	3.4% (1/29)	1.8% (4/220)	0.465
Buddy wire, % (n)	10.3% (3/29)	6.8% (15/220)	0.449
Type of first wire (after recanalization)			
Supportive	54.2% (13/ 24)	2.1% (4/195)	<0.001
Non-supportive	45.8% (11/24)	97.9% (191/195)	<0.001
Device success after recanalization, % (n)	100% (29/29)	99.1% (218/220)	1.0
Procedure success after recanalization, % (n)	100% (29/29)	98.6% (217/220)	1.0
Clinical success after recanalization, % (n)	100% (29/29)	98.6% (217/220)	1.0

Data are expressed as mean ± standard deviation or number and proportion

Long Lesions

In a total of 79 lesions (31.7%) more than one device was implanted (Figure 1, Figure 3). The mean lesion length treated with BVS was 25.86 ± 13.64 mm. The maximum lesion length covered by BVS was 80.01 mm. Overlapping of BVS with BVS was often performed with a total of 76 overlapping scaffolds. The great majority (96%, 73/76) were performed using scaffold of the same diameter or with a maximum of 0.5 mm difference in nominal diameter. In 3 cases a 3.5 mm scaffold was placed in overlap with a 2.5 mm device.

Clinical outcomes

Survival data at 12 months after the procedure were available for 99.4 % of patients. At 12-month follow-up all cause-death was reported in 3 cases. A total of 5 target lesion revascularizations and 4 non-target vessel revascularisations were reported. Four definite, scaffold thrombosis (ST) occurred within one year after index procedure; none of them was acute or sub-acute. Of note, one of those cases was meeting the ARC criteria for ST but no clear thrombus was observed by optical coherence tomography (OCT). In the remaining 3 cases, severe calcification, bifurcation lesion and long overlap were observed but BVS underexpansion was the factor that was present in all of them.

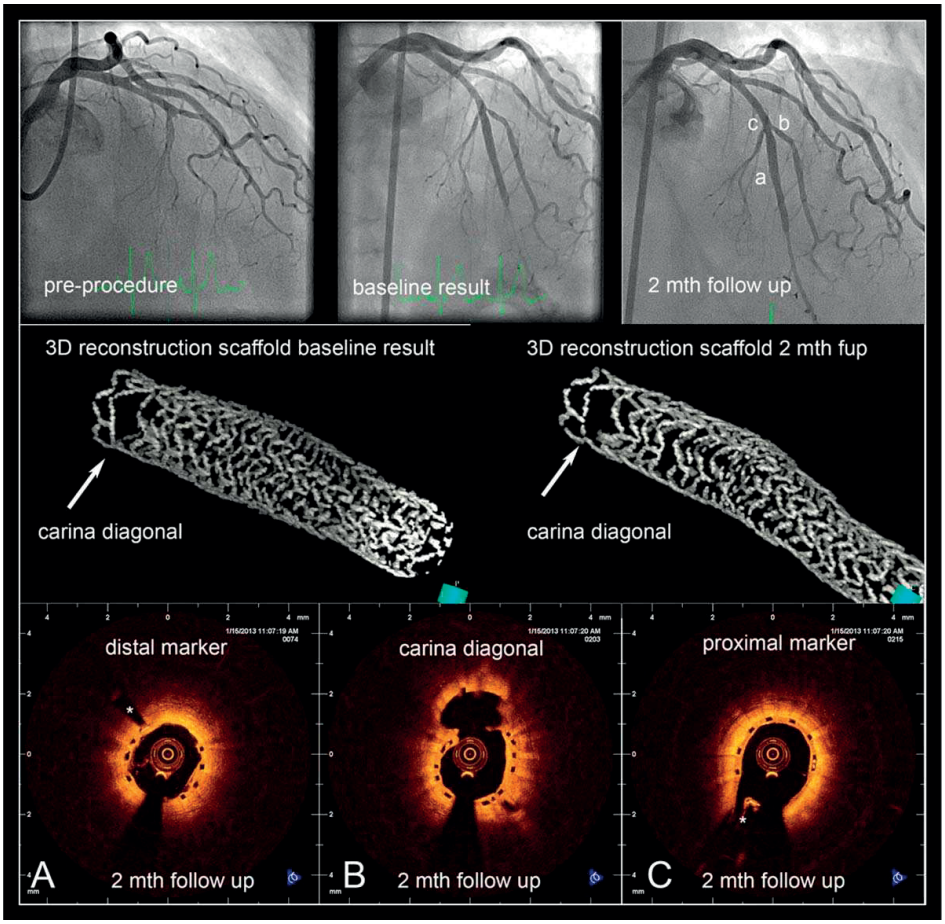

Figure 3 Chronic total occlusion and bifurcation

Top panels show from left to right the angiograms pre-procedure, after recanalization and scaffold implantation (BVS 3.0 x 28mm with the sequential post dilatation of the diagonal and the scaffold in the main branch) and 2-month follow-up with partial distal vessel positive remodelling. Characters a-c indicate the positions of the OCT cross-sections. OCT (St.Jude Lightlab Dragonfly™) post procedure show distal a well deployed scaffold (Panel A), a well opened carina with the diagonal branch (Panel B *) and the overlap of the proximal marker with the septal branch (Panel C *). The 3D reconstruction (Intage realia™, Cybersystems, Tokyo, Japan) shows the opening of the struts at the carina with the diagonal branch. (Arrowhead bottom panel).

DISCUSSION

The present investigation represents an evaluation of the feasibility of BVS implantation in everyday clinical practice reflected by in a wide range of coronary lesions subsets including bifurcations, calcified vessels, chronic total occlusions and long lesion in patients with stable coronary artery disease and acute coronary syndromes. At variance of

previous reports we also aimed to provide a detailed description of procedural data and techniques that were used to allow the use of this novel device in challenging subsets.

Bifurcation lesions

A common concern regarding this technology is the fact that implantation of the BVS in bifurcation lesions might result in side-branch compromise due to the thick strut nature of this device. In keeping with this concept, a recent study performed by our group showed that BVS deployment could be associated with an increased small (≤0.5 mm) side-branch occlusion and a consequent increase of enzymes release after procedure.[13]

However, in the present report the effect of BVS implantation in what is commonly considered a bifurcation lesion (with a side branch ≥ 2 mm) was specifically investigated.

Rewiring of the side-branch in those cases and consequent ballooning (mainly with small balloon 1.5-2 mm in diameter) of the SB ostium is feasible as we already reported[13] and safe also in terms of scaffold geometry and fracture.[14, 15] In the present study side-branch ballooning was performed in one third of the patients (33%, 18/54) with promising results. In majority of the cases this was done with sequential ballooning and proximal optimization technique (POT), kissing balloon only in 3 cases.

Taking into consideration the rates of TIMI flow < 3 in the main vessel or in the side-branch, the rate of failure to rewire the side-branch and failure to dilate the side-branch, the BVS performed at least as good as metallic if considering historical data. [12]

In addition the rate of the composite endpoint side-branch impairment (9.3%) was observed to be encouraging especially when compared with data recently reported by Burzotta et al. with rates of side-branch impairment in sirolimus- and everolimus-eluting stents respectively 16% and 11%. [12] These data are supportive of the concept that BVS could be used safely in bifurcation lesions with side-branch ≥ 2.0 mm with a single scaffold approach and could provide results similar to metallic stents.

Calcified lesions

A total of 119 calcified lesions with a considerable percentage of heavily calcified plaques, were treated with BVS. A large number of those lesions were located in diffusely diseased vessels with an overall mean treated lesion length of more than 36 mm (severe calcified group). QCA analysis showed a final MLD, %DS, acute gain and device, procedural and clinical success not different from non-calcified lesions. These results were obtained at the cost of a more aggressive lesion preparation with a considerable use of rotational atherectomy and scoring balloons.

Such approach is needed to facilitate the delivery of the scaffold given its slightly higher profile compared with second generation DES. In addition appropriate lesion preparation could avoid scaffold under-expansion or need for aggressive post-dilatation. This strategy could be relevant also when using metallic stents. [16] Our data might

suggest feasibility of BVS implantation in calcified vessels with optimal results given an adequate lesion preparation.

Although, many of the advantages proposed for BVS, namely the restoration of the vasomotion and vessel physiology could be minimized in calcified artery, patients with diffused calcified vessels have often also a multivessel disease;[17] in such scenario a temporary implant would allow future surgical treatments.

Total occlusions

Successful re-canalization of total occlusions has been previously associated with a significant improvement in angina symptoms [18, 19] and complete coronary revascularization was demonstrated to have an important impact on long-term clinical outcomes.[20]

Vessels with total occlusions have peculiar characteristics in terms of vascular remodelling; this is a dynamic process involving regulation of vascular cell migration and mitosis and apoptosis rates in response to several factors comprising blood flow and pressure, shear stress, circumferential stretch and wall tension.[21] Reduction or even more absence of blood flow in totally occluded vessels might promote negative remodelling and plaque growth; on the other hand restoration of flow could have an opposite effect.

Recently, Park J.J. and colleagues reported, at 6-month follow-up after successful total occlusion revascularization, a flow-dependent vascular remodelling process in human coronary arteries, associated with increases in lumen diameter, lumen area and external elastic membrane area.[22] This process was observed in a large part of treated vessels (69%) with a mean lumen diameter increase of 0.40 ± 0.34 mm. IVUS analysis of those vessels revealed that the amount of incomplete stent apposition increased significantly during 6 months in patients with positive remodelling and lumen area increase but not in those without lumen area increase.

In this scenario choosing a metal stent based on the vessel diameter at the index procedure might lead to stent under-sizing.

Given this background a theoretical advantage of BVS implantation in patients with total occlusion is the fact that it might allow at mid-term follow-up, after the loss of scaffold mechanical integrity, late lumen enlargement without late acquired malapposition, as at that time the remnants of the bioresorbable implant can follow the vessel remodelling.

Long lesions and overlap

In the present series several lesions were treated with more than one scaffold up to a maximum of 5 scaffolds for a maximum lesion length of 80 mm. Operators were advised to minimize the extension of overlapping segment using a marker-to-marker technique.

In the metal stent era, long segments treatment has been associated to an increased risk of stent thrombosis [23-25] and could results in prevention of future surgical revascularisations.

Both these issues could be overcome with the use of bioresorbable technologies and the introduction in the near future of bioresorbable scaffold with thinner struts could mitigate the effect of overlap on delayed vascular healing.

Clinical outcomes

The mid-term clinical outcomes of this study revealed a relatively reassuring safety profile of the BVS when used in a large range of lesion type and in patients with either stable symptoms or acute coronary syndromes. The event rate in this study is only minimally higher compared to the results in non-complex patients reported in the randomized Absorb II and Absorb Japan studies [26, 27]. In other European registries like GHOST-EU and AMC registries [28, 29] reporting early experience with BVS, the event rate was in slightly higher compared with more recent registries like the Milan registry [30] and ASSURE BVS [31] where more BVS specific implantation protocols where applied. Such observations suggest the relevance of a BVS dedicated implantation technique ensuring good lesion preparation and optimal scaffold deployment often facilitated by high pressure post-dilatation.

Regarding the occurrence of scaffold thrombosis (ST), at variance with previous reports no acute or sub-acute STs were observed in the present investigation. These findings could be related to procedural characteristics including a meticulous lesion preparation pre-BVS implantation and a reasonably high rate of post-dilatation.

The review of the cases with ST revealed that several factors might be associated with such events comprising severe lesion calcification, the presence of bifurcations, long overlap and antiplatelet therapy discontinuation. However, the factor that was particularly consistent was scaffold under-expansion. Previous investigations described stent underexpansion as an important predictor of ST with both bare metal stents and DES,[32-36] with an impact on the occurrence of ST that was hypostasized to be superior to stent malapposition.[37] The mechanisms behind these findings could be the fact that stent underexpansion translates into an abnormal shear stress. In particular increased radial transport of blood components and low wall shear stress, were described to promote platelet-dependent thrombosis.[38] In addition the impact of underexpansion on shear stress could be potentiated by the presence of the BVS thick struts.[39]

Although, given the small number of patients and events reported in the present study it is not possible to reach firm conclusions, our findings suggest that optimal BVS expansion, with lesion preparation and appropriate scaffold post-dilatation, should be pursued given the possible relevant clinical implications.

LIMITATIONS

The present report is an investigator initiated, single center, single arm study. 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. The limited number of patients does not allow reaching firm conclusions on clinical outcomes. The mid-term follow-up is preventing the availability of information on long-term safety and efficacy.

CONCLUSION

The implantation of the everolimus-eluting bioresorbable vascular scaffold in an expanded range of coronary lesion types and clinical presentations was observed to be viable with promising angiographic results and mid-term clinical outcomes. Larger studies with longer follow-up and a direct comparison with currently available metallic drug eluting stents are needed to fully evaluate the possible additional value of the bioresorbable technologies an all comers setting.

ACKNOWLEDGMENTS

This study was supported by an unrestricted grant from Abbott Vascular.

The authors want to thank Isabella Kardys, Johannes Schaar and Martijn Akkerhuis, for their contribution in the event adjudication.

REFERENCES

1. Serruys PW, Onuma Y, Ormiston JA, de Bruyne B, Regar E, Dudek D, Thuesen L, Smits PC, Chevalier B, McClean D, Koolen J, Windecker S, Whitbourn R, Meredith I, Dorange C, Veldhof S, Miquel-Hebert K, Rapoza R, Garcia-Garcia HM. Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of de novo coronary artery stenosis: six-month clinical and imaging outcomes. Circulation 2010;**122**(22):2301-12.
2. Onuma Y, Serruys PW, Perkins LE, Okamura T, Gonzalo N, Garcia-Garcia HM, Regar E, Kamberi M, Powers JC, Rapoza R, van Beusekom H, van der Giessen W, Virmani R. Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. Circulation 2010;**122**(22):2288-300.
3. Onuma Y, Serruys PW. Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? Circulation 2011;**123**(7):779-97.
4. Diletti R, Farooq V, Girasis C, Bourantas C, Onuma Y, Heo JH, Gogas BD, van Geuns RJ, Regar E, de Bruyne B, Dudek D, Thuesen L, Chevalier B, McClean D, Windecker S, Whitbourn RJ, Smits P, Koolen J, Meredith I, Li X, Miquel-Hebert K, Veldhof S, Garcia-Garcia HM, Ormiston JA, Serruys PW. Clinical and intravascular imaging outcomes at 1 and 2 years after implantation of absorb everolimus eluting bioresorbable vascular scaffolds in small vessels. Late lumen enlargement: does bioresorption matter with small vessel size? Insight from the ABSORB cohort B trial. Heart 2013;**99**(2):98-105.
5. Serruys PW, Garcia-Garcia HM, Onuma Y. From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? Eur Heart J 2012;**33**(1):16-25b.
6. Serruys PW, Ormiston JA, Onuma Y, Regar E, Gonzalo N, Garcia-Garcia HM, Nieman K, Bruining N, Dorange C, Miquel-Hebert K, Veldhof S, Webster M, Thuesen L, Dudek D. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;**373**(9667):897-910.
7. Onuma Y, Dudek D, Thuesen L, Webster M, Nieman K, Garcia-Garcia HM, Ormiston JA, Serruys PW. Five-year clinical and functional multislice computed tomography angiographic results after coronary implantation of the fully resorbable polymeric everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB cohort A trial. JACC Cardiovasc Interv 2013;**6**(10):999-1009.
8. Serruys PW, Onuma Y, Garcia-Garcia HM, Muramatsu T, van Geuns RJ, de Bruyne B, Dudek D, Thuesen L, Smits PC, Chevalier B, McClean D, Koolen J, Windecker S, Whitbourn R, Meredith I, Dorange C, Veldhof S, Hebert KM, Rapoza R, Ormiston JA. Dynamics of vessel wall changes following the implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. EuroIntervention 2014;**9**(11):1271-84.
9. Diletti R, Onuma Y, Farooq V, Gomez-Lara J, Brugaletta S, van Geuns RJ, Regar E, de Bruyne B, Dudek D, Thuesen L, Chevalier B, McClean D, Windecker S, Whitbourn R, Smits P, Koolen J, Meredith I, Li D, Veldhof S, Rapoza R, Garcia-Garcia HM, Ormiston JA, Serruys PW. 6-month clinical outcomes following implantation of the bioresorbable everolimus-eluting vascular scaffold in vessels smaller or larger than 2.5 mm. J Am Coll Cardiol 2011;**58**(3):258-64.
10. Onuma Y, Tanimoto S, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrie D, Thuesen L, Dorange C, Miquel-Hebert K, Veldhof S, Serruys PW. Efficacy of everolimus eluting

stent implantation in patients with calcified coronary culprit lesions: two-year angiographic and three-year clinical results from the SPIRIT II study. Catheter Cardiovasc Interv 2010;**76**(5):634-42.

11. Herrman JP, Azar A, Umans VA, Boersma E, von Es GA, Serruys PW. Inter- and intra-observer variability in the qualitative categorization of coronary angiograms. Int J Card Imaging 1996;**12**(1):21-30.
12. Burzotta F, Trani C, Todaro D, Mariani L, Talarico GP, Tommasino A, Giammarinaro M, Niccoli G, Porto I, Leone AM, Mongiardo R, Mazzari MA, Schiavoni G, Crea F. Prospective randomized comparison of sirolimus- or everolimus-eluting stent to treat bifurcated lesions by provisional approach. JACC Cardiovasc Interv 2011;**4**(3):327-35.
13. Muramatsu T, Onuma Y, Garcia-Garcia HM, Farooq V, Bourantas CV, Morel MA, Li X, Veldhof S, Bartorelli A, Whitbourn R, Abizaid A, Serruys PW, Investigators A-E. Incidence and short-term clinical outcomes of small side branch occlusion after implantation of an everolimus-eluting bioresorbable vascular scaffold: an interim report of 435 patients in the ABSORB-EXTEND single-arm trial in comparison with an everolimus-eluting metallic stent in the SPIRIT first and II trials. JACC Cardiovasc Interv 2013;**6**(3):247-57.
14. Dzavik V, Colombo A. The absorb bioresorbable vascular scaffold in coronary bifurcations: insights from bench testing. JACC Cardiovasc Interv 2014;**7**(1):81-8.
15. Ormiston JA, Webber B, Ubod B, Webster MW, White J. Absorb everolimus-eluting bioresorbable scaffolds in coronary bifurcations: a bench study of deployment, side branch dilatation and post-dilatation strategies. EuroIntervention 2014.
16. Abdel-Wahab M, Baev R, Dieker P, Kassner G, Khattab AA, Toelg R, Sulimov D, Geist V, Richardt G. Long-term clinical outcome of rotational atherectomy followed by drug-eluting stent implantation in complex calcified coronary lesions. Catheter Cardiovasc Interv 2013;**81**(2):285-91.
17. Genereux P, Madhavan MV, Mintz GS, Maehara A, Palmerini T, Lasalle L, Xu K, McAndrew T, Kirtane A, Lansky AJ, Brener SJ, Mehran R, Stone GW. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) TRIALS. J Am Coll Cardiol 2014;**63**(18):1845-54.
18. Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, Moussa I, Teirstein PS, Dangas G, Baim DS, Selmon M, Strauss BH, Tamai H, Suzuki T, Mitsudo K, Katoh O, Cox DA, Hoye A, Mintz GS, Grube E, Cannon LA, Reifart NJ, Reisman M, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation 2005;**112**(15):2364-72.
19. Stone GW, Reifart NJ, Moussa I, Hoye A, Cox DA, Colombo A, Baim DS, Teirstein PS, Strauss BH, Selmon M, Mintz GS, Katoh O, Mitsudo K, Suzuki T, Tamai H, Grube E, Cannon LA, Kandzari DE, Reisman M, Schwartz RS, Bailey S, Dangas G, Mehran R, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. Circulation 2005;**112**(16):2530-7.
20. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013;**61**(3):282-94.

21. Langille BL. Arterial remodeling: relation to hemodynamics. Can J Physiol Pharmacol 1996;**74**(7):834-41.
22. Park JJ, Chae IH, Cho YS, Kim SW, Yang HM, Seo JB, Kim SY, Oh IY, Yoon CH, Suh JW, Park KW, Chung WY, Youn TJ, Choi DJ, Kim HS. The recanalization of chronic total occlusion leads to lumen area increase in distal reference segments in selected patients: an intravascular ultrasound study. JACC Cardiovasc Interv 2012;**5**(8):827-36.
23. Park DW, Park SW, Park KH, Lee BK, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006;**98**(3):352-6.
24. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabate M, Escaned J, Banuelos C, Fernandez-Ortiz A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;**45**(6):954-9.
25. Suh J, Park DW, Lee JY, Jung IH, Lee SW, Kim YH, Lee CW, Cheong SS, Kim JJ, Park SW, Park SJ. The relationship and threshold of stent length with regard to risk of stent thrombosis after drug-eluting stent implantation. JACC Cardiovasc Interv 2010;**3**(4):383-9.
26. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrie D, Iniguez A, Dominici M, van der Schaaf RJ, Haude M, Wasungu L, Veldhof S, Peng L, Staehr P, Grundeken MJ, Ishibashi Y, Garcia-Garcia HM, Onuma Y. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet 2015;**385**(9962):43-54.
27. Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, Saito S, Yajima J, Hagiwara N, Mitsudo K, Popma JJ, Serruys PW, Onuma Y, Ying S, Cao S, Staehr P, Cheong WF, Kusano H, Stone GW, Investigators AJ. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. Eur Heart J 2015.
28. Capodanno D, Gori T, Nef H, Latib A, Mehilli J, Lesiak M, Caramanno G, Naber C, Di Mario C, Colombo A, Capranzano P, Wiebe J, Araszkiewicz A, Geraci S, Pyxaras S, Mattesini A, Naganuma T, Munzel T, Tamburino C. Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. EuroIntervention 2015;**10**(10):1144-53.
29. Kraak RP, Hassell ME, Grundeken MJ, Koch KT, Henriques JP, Piek JJ, Baan J, Jr., Vis MM, Arkenbout EK, Tijssen JG, de Winter RJ, Wykrzykowska JJ. Initial experience and clinical evaluation of the Absorb bioresorbable vascular scaffold (BVS) in real-world practice: the AMC Single Centre Real World PCI Registry. EuroIntervention 2015;**10**(10):1160-8.
30. Costopoulos C, Latib A, Naganuma T, Miyazaki T, Sato K, Figini F, Sticchi A, Carlino M, Chieffo A, Montorfano M, Colombo A. Comparison of early clinical outcomes between ABSORB bioresorbable vascular scaffold and everolimus-eluting stent implantation in a real-world population. Catheter Cardiovasc Interv 2015;**85**(1):E10-5.
31. Wohrle J, Naber C, Schmitz T, Schwencke C, Frey N, Butter C, Brachmann J, Ingwersen M, Drabik A, Markovic S, Mathey DG. Beyond the early stages: insights from the ASSURE registry on bioresorbable vascular scaffolds. EuroIntervention 2015;**11**(2):149-56.
32. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 2005;**45**(7):995-8.

33. Cheneau E, Leborgne L, Mintz GS, Kotani J, Pichard AD, Satler LF, Canos D, Castagna M, Weissman NJ, Waksman R. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation 2003;**108**(1):43-7.
34. Kasaoka S, Tobis JM, Akiyama T, Reimers B, Di Mario C, Wong ND, Colombo A. Angiographic and intravascular ultrasound predictors of in-stent restenosis. J Am Coll Cardiol 1998;**32**(6):1630-5.
35. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y, Kuntz RE, Fitzgerald PJ, Investigators S. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. J Am Coll Cardiol 2004;**43**(11):1959-63.
36. Uren NG, Schwarzacher SP, Metz JA, Lee DP, Honda Y, Yeung AC, Fitzgerald PJ, Yock PG, Investigators PR. Predictors and outcomes of stent thrombosis: an intravascular ultrasound registry. Eur Heart J 2002;**23**(2):124-32.
37. Liu X, Doi H, Maehara A, Mintz GS, Costa Jde R, Jr., Sano K, Weisz G, Dangas GD, Lansky AJ, Kreps EM, Collins M, Fahy M, Stone GW, Moses JW, Leon MB, Mehran R. A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. JACC Cardiovasc Interv 2009;**2**(5):428-34.
38. Sukavaneshvar S, Rosa GM, Solen KA. Enhancement of stent-induced thromboembolism by residual stenoses: contribution of hemodynamics. Ann Biomed Eng 2000;**28**(2):182-93.
39. Bourantas CV, Papafaklis MI, Kotsia A, Farooq V, Muramatsu T, Gomez-Lara J, Zhang YJ, Iqbal J, Kalatzis FG, Naka KK, Fotiadis DI, Dorange C, Wang J, Rapoza R, Garcia-Garcia HM, Onuma Y, Michalis LK, Serruys PW. Effect of the endothelial shear stress patterns on neointimal proliferation following drug-eluting bioresorbable vascular scaffold implantation: an optical coherence tomography study. JACC Cardiovasc Interv 2014;**7**(3):315-24.

SUPPLEMENTAL MATERIAL

Description of the Scaffold thrombosis cases

Case 1: A 59-year old male patient, smoker, with history of cerebrovascular accident and stable angina pectoris, was treated after pre-dilatation of a long lesion involving the ostial left anterior descending (LAD) and the bifurcation with the first diagonal (D1), using a BVS 3.5 x 28mm. Despite a post-dilatation was performed with a 3.5 non-complaint (NC) balloon at high pressure, the BVS remained under-expanded with an impaired flow in the first diagonal. At day 111 post PCI the patient was re-admitted with NSTEMI, while being on DAPT, and angiographically was observed a total re-occlusion of the LAD beginning from the ostium. After pre-dilatation a DES 3.5 x32mm was implanted. Of note, at day 81 after the second PCI the patients was again re-admitted for instable angina pectoris caused by a re-occlusion also of the metal stent in the proximal LAD. The patient was treated with CABG.

Lesion key characteristics: Ostial lesion, long lesion, bifurcation, impaired side-branch TIMI flow and BVS underexpansion

Case 2: A 69-year old male with history of dyslipidaemia and hypertension was admitted with NSTEMI. Angiographically was observed a long, severely calcified, chronic total occlusion (CTO) of the proximal and mid LAD with severe calcification and involvement of D1. After Pre-dilatation, 2x 3.5 x 18mm BVS were implanted. The procedure was complicated by pinching of D1 and thrombus formation. Additional ballooning of the ostium of the side-branch was performed, but at the end of the procedure remained BVS underexpansion and haziness in the mid LAD. Despite continued DAPT usage the patient developed on day 47 a non-Q wave MI due to definite scaffold thrombosis in the proximal LAD, which was treated with thrombectomy and DES implantation.

Lesion key characteristics: CTO, long lesion, bifurcation, severe calcification, thrombus formation and BVS underexpansion

Case 3: A 65-year old male patient, smoker, with history of hypertension was admitted with NSTEMI, due to a sub-occlusive lesion in the LAD located at the site of a tortuous trifurcation with the first and second diagonal. The initial TIMI flow was 1. After pre-dilatation, a 3.0 x 18mm BVS was implanted and after post-dilatation a TIMI III flow was achieved. At day 142 on DAPT the patient was re-admitted with NSTEMI. Angiographically a proximal BVS edge sub-total restenosis was observed with a distal TIMI flow 1. A DES stent 3.5 x38mm was deployed covering the BVS and a large proximal segment. Of note, this case was meeting the ARC criteria for stent thrombosis and was adjudicated as such by the CEC, but should be mentioned that an OCT performed before pre-dilatation did not showed any clear intraluminal thrombus.

Lesion key characteristics: tortuous trifurcation (no thrombus by OCT)

Case 4: A 70-year old male, with severe peripheral vascular disease, diabetes mellitus, dyslipidaemia, hypertension, and reduced left ventricular function was admitted with stable angina pectoris. Angiography revealed, a long and severely calcified lesion mid LAD involving two bifurcations (D1 and D2). Aggressive preparation was performed with rotational atherectomy and high-pressure dilatations with NC and cutting balloons. Two overlapping BVS were placed with a quite long segment of overlap (5 mm). Despite extensive post-dilatation under-expansion remained at the end of the procedure. Five months after index PCI, the patient underwent non-cardiac surgery. The antiplatelet therapy was interrupted (both aspirin and clopidogrel) and the patient developed a NSTEMI due to a scaffold thrombosis that was treated with balloon dilatation and eptifibatide. Unfortunately, the patient died few days later because of heart failure.

Lesion key characteristics: Severe calcification, bifurcation, long overlap, no antiplatelet therapy and BVS underexpansion