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ORIGINAL PAPER

Morphological and functional evaluation of the bioresorption of the bioresorbable everolimus-eluting vascular scaffold using IVUS, echogenicity and vasomotion testing at two year follow-up: a patient level insight into the ABSORB A clinical trial

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Abstract The aim of this study was to describe vasoreactivity (by Acetylcholine and Methergine tests) at 2 year follow-up in parallel with the individual changes in the echogenicity characteristics of the polymer struts of the everolimus eluting bioresorbable vascular scaffold (BVS), from post-treatment to 2 year follow-up, in patients enrolled in the ABSORB Cohort A study. Intravascular ultrasound assessment was performed with a phased array catheter (EagleEye, Volcano Corporation, Cordova, CA, USA) with automated pullback at 0.5 mm per second. The % ratio at 6 months and 2 years [(Scaffold Area post PCI- Lumen Area)/Scaffold Area post PCI] was calculated as a measure of scaffold shrinkage. The % change of hyperechogenicity was defined as: ([post-procedural hyperechogenicity] − [2 year follow up hyperechogenicity])/[post-procedural hyperechogenicity]) × 100. The vasomotion test with intracoronary acetylcholine (10^{-6} M) or intravenous methergine (0.4 mg) was performed at 2 years. Overall nine patients received all these analyses and were enrolled in the present analysis. A 50–96% reduction in hyperechogenicity was observed between baseline and 2 years, which corresponded to a change in vasoreactivity between 2 and 22%. A vasoconstriction of the scaffolded segment was observed in the 5 patients, who underwent the methergine test, with a mean decrease in lumen diameter after methergine of $9 \pm 7\%$ ($P = 0.06$), while vasodilatation occurred in the 4 patients who underwent the acetylcholine test with a mean increase in lumen diameter after acetylcholine of $8 \pm 5\%$ ($P = 0.125$). Bioresorption of the BVS is accompanied by re-establishment of both endothelial and non-endothelial dependent vasomotion.

Keywords Stents · PCI · CAD

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Introduction

The everolimus eluting Bioresorbable Vascular Scaffold (BVS) (Abbott Vascular, Santa Clara, CA, USA) is expected to perform similar to a metal stent post implantation by preventing acute recoil, providing a scaffold to the vessel during healing, and then being completely bioresorbed within 2–3 years [1]. The advantages of using bioresorbable scaffolds are the potential for the restoration of normal vascular function once the bioresorption process has been completed such that vessels can once again react to pulsatile flow, positively remodel and respond normally to endothelial factors.

In the ABSORB A clinical study echogenicity assessment, with grey-scale intra-vascular ultrasound (IVUS) computer aided analysis, has shown a significant reduction in percent hyperechogenic tissue between post-procedure and 6 month follow-up, with a further reduction observed between 6 months and 2 year follow-up [2]. The same study also demonstrated the restoration of vasomotion within the scaffolded and peri-scaffolded segments in response to acetylcholine and methergine at 2 year follow-up [2].

Amongst those patients enrolled in the ABSORB A study there has been no detailed comparison as yet on an individual patient level of the vasomotion and echogenicity changes from post-procedure to 2 year follow-up. The aim of this study was to describe vasoreactivity at 2 years (by Acetylcholine and Methergine tests) in parallel with the individual changes in the echogenicity characteristics of the polymer struts of the BVS, from post-treatment to 2 year follow-up, using a computer aided grey scale value analysis program, in patients enrolled in the ABSORB A study.

Methods

Patient population

The ABSORB Cohort A study design has been already described previously [1]. Briefly, in this single-arm, prospective study 30 patients, with a diagnosis of stable or unstable angina or silent ischemia, were enrolled in four participating centres between March and July 2006. All treated lesions were single, de novo lesions in a native coronary artery of 3.0 mm, shorter than 8 mm for the 12 mm device and shorter than 14 mm for the 18 mm device, with a diameter stenosis greater than 50% and less than 100%, and with a thrombolysis in myocardial infarction (TIMI) flow grade more than 1. Major exclusion criteria were patients with an acute myocardial infarction or unstable arrhythmias, those who had a left ventricular ejection fraction less than 30%, restenotic lesions, lesions located in the left main coronary artery, lesions involving a side branch more than 2 mm in diameter, and the presence of thrombus or another clinically significant stenosis in the target vessel. The protocol was approved by the ethics committee at the four participating centres. All enrolled patients signed a written informed consent. Angiography, IVUS and derived IVUS parameters (virtual histology, palpography and echogenicity) were assessed at 6 month and 2 year follow-up. Vasomotion testing with acetylcholine or methergine was performed at 2 years.

Study device

The BVS revision 1.0 has a polymer backbone of Poly-L (racemic)-lactic acid (PLLA) coated a thin layer of a 1:1 mixture of an amorphous matrix of Poly-D,L (racemic)-lactic acid (PDLLA) polymer, and 100 micrograms/cm^2 of the anti-proliferative drug everolimus. Both PLLA and PDLLA are fully absorbable. The polymer degrades via a bulk erosion process through hydrolysis of the ester bonds in the backbone. The resulting lactic acid oligomers eventually leave the polymer matrix and are metabolized in surrounding tissues and blood into the pyruvate and Kreb's energy cycles. Small particles <2 microns in diameter are phagocytosed by macrophages. The time for complete absorption of the polymer backbone is predicted from preclinical studies to be about 2 years whereas the polymer coating is absorbed in a faster timeframe. The implant is radiolucent, but has two platinum markers at each end that allow easy visualization on angiography and with other imaging modalities.

Quantitative coronary angiography (QCA) and vasomotion test

QCA was performed with the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands)

by an independent central research organization (Cardialysis B.V., Rotterdam, The Netherlands). The following QCA parameters were computed for the scaffolded segments and the proximal and distal references: minimal lumen diameter, reference vessel diameter, percent diameter stenosis, and lesion length. The accuracy of this method has been reported in detail previously [3]. The scaffolded segment was defined as the segment between the 2 radio-opaque platinum markers on both ends of the BVS.

To study vasomotion at 2 years, either the endothelium independent vasoconstrictor methylergometrine maleate (methergine, Novartis, Basel, Switzerland), or the endothelium dependent acetylcholine (Ovisot, Daiichi-Sankyo, Tokyo, Japan) was given, dependent on local practice. Calcium channel blockers and nitrates were withheld at least 48 h before the coronary angiogram. Mean lumen diameter in the scaffolded segment was measured by QCA after a baseline infusion of saline, and a sub-selective intracoronary administration of acetylcholine infused through a microcatheter at increasing dose up to 10^{-6} M. For the methergine test, QCA was measured 5 min after an intravenous bolus injection of methergine (0.4 mg). Both tests were terminated by intracoronary administration of 200 μg of nitroglycerin (nitronal, Pohl-Boskamp GmbH, Hohenlockstedt, Germany).

The two vasomotion tests produce two different responses in normal coronaries: vasodilation by Acetylcholine, vasoconstriction by Methergine. Methergine stimulates both alpha-adrenergic and serotonergic receptors and therefore exerts a direct constrictive effect on vascular smooth cells [4]. Acetylcholine infusion in the coronary artery causes the release of NO through activation of the muscarinic receptor on the surface of the endothelial cell with consequent relaxation of the smooth muscle cell and therefore vasodilation. This mechanism is disturbed in case of endothelial dysfunction, where a paradox vasoconstriction may be observed [5, 6], due to the direct activation of muscarinic receptors on the surface of smooth muscle cells.

Intravascular ultrasound

Intravascular ultrasound (IVUS) assessment was performed with a phased array catheter (EagleEye, Volcano Corporation, Cordova, CA, USA) with automated pullback at 0.5 mm per second. The region beginning 5 mm distal to and extending 5 mm proximal to the scaffolded segment was examined. The following parameters were measured with a computer-based contour detection software (Curad, version 3.1): [7, 8] vessel area, scaffold area, lumen area, neointimal area and luminal area stenosis. The appearance of the BVS struts on IVUS has been clearly defined previously [7]. The percentage ratio at 6 months [(Scaffold Area post PCI- Lumen Area at 6 months)/(Scaffold Area post PCI)] was calculated as a measure of scaffold shrinkage [9].

At 2 year follow up as a consequence of bioresorption the majority of struts were not visible on IVUS grey-scale imaging; thus the scaffold area at this time was assumed to be equal to the luminal area.

Automated echogenicity

A computer-aided grey-scale value analysis programme [9, 10] was used to assess the echogenicity of the polymeric struts after treatment, at 6 month and at 2 year follow up. The applied algorithms of this software have been previously published [10]. The mean grey-value of the adventitia is used to classify tissue components as either hypechogenic (e.g., grey-values lower than the mean adventitia level) or as hyperechogenic (e.g., grey-values at higher levels than that of the adventitia). The final automated echogenicity quantification was measured at each cross-section and hyper- and hypo-echogenicity tissues were colour coded in green and red, respectively. The difference (Δ) between the 2 year follow up and the post-procedural hyperechogenicity percentage was assessed in the treated segment. The percentage change of hyperechogenicity was defined as: {([post-procedural hyperechogenicity] − [2 year follow up hyper-echogenicity])/[post-procedural hyperechogenicity]} × 100.

Statistics

Binary variables are presented as percentages. Continuous variables are presented as mean ± SD. Paired comparisons between the post-procedure, 6 month and the 2 year follow-up of IVUS parameters were done by Friedman's test and Dunn's post-test for multiple comparisons of all pairs.

Paired comparisons between hyperechogenicity and vasomotion data were done by a Wilcoxon matched pairs test. Taking into account the small sample size, P values presented in this paper are exploratory and should therefore be interpreted with caution.

Results

The patient demographics are shown in Table 1. All patients were on secondary prevention with statins. At 2 year clinical follow-up all patients were asymptomatic and there were no reported major adverse cardiac events (MACE). Table 2 shows IVUS results on a patient level from post-procedure, 6 month and 2 year follow-up. The mean vessel area was 12.64 ± 3.72 mm^2 post-procedure, 13.22 ± 3.47 mm^2 at 6 months; and 12.32 ± 3.74 mm^2 at 2 years; P = NS. The mean lumen area was 6.17 ± 1.01 mm^2 post-procedure, 5.45 ± 1.28 mm^2 at 6 months, and 6.05 ± 1.73 mm^2 at 2 years; P = NS.

The complete dataset of vasomotion and echogenicity was available in 9 patients enrolled in the ABSORB A trial (Table 3).

Four patients showed no significant intimal hyperplasia ranging from 0.42 to 0.71 mm^2 at 6 month follow-up.

Seven patients showed an enlargement of the mean lumen area ranging from 0.64 to 1.85 mm^2 at 2 years, without significant changes in the mean vessel area.

The percentage ratio at 6 months [(Scaffold Area post PCI − Lumen Area at 6 months)/(Scaffold Area post PCI)] ranged between −7.42 and 28; whilst the percentage ratio at 2 years [{(scaffold area post-PCI) − (lumen area at 2 years)}/(scaffold area post-PCI)] was in the range of −27–50%, $P = 0.31$.

Of note, two patients (pt 8, 9) showed a percentage ratio at 6 months [(Scaffold Area post PCI − Lumen Area at 6 months)/(Scaffold Area post PCI)] of 26 and 28%, respectively. At 2 year follow-up the ratio in patient 8 decreased from 26 to 5%, whilst in patient 9 the ratio increased from 28 to 50%. There was no evidence of intimal hyperplasia in either of these 2 patients at 6 months.

The IVUS echogenicity and vasomotion findings on a patient level are shown in Table 3.

The mean hyperechogenicity percentage in all patients was $21 \pm 12\%$ (range: 5–38) post-procedure and $6 \pm 6\%$ (range: 0–19) at 2 year follow up, with a mean percentage change of $77 \pm 17\%$ (range: 50–96, $P = 0.004$). The residual level of hyperechogenicity at 2 years was similar to the natural hyperchogenicity of plaque pre-procedure ($6 \pm 6\%$ vs. $6 \pm 5\%$).

The vasomotion test at 2 years showed vasoconstriction of the scaffolded segment in the 5 patients who underwent the methergine test, with a mean decrease in lumen diameter after methergine of $-9 \pm 7\%$ ($P = 0.06$), while vasodilatation occurred in the 4 patients who underwent the acetylcholine test with a mean increase in lumen diameter after acetylcholine of $8 \pm 5\%$ ($P = 0.125$). Patient 9, who had a ratio [((scaffold area post-procedure) − (lumen area at 2 years))/(scaffold area post-procedure)] of 50% at 2 year follow-up showed the smallest response to acetylcholine with a change of only 2%, and a difference in mean lumen diameter of 0.03 mm between baseline and after infusion

Table 1 Clinical characteristics

	Sex	Age	Hypercholesterolemia	Hypertension	Smoker	Diabetes	Prior MI	Prior PCI	SA	UA
Pt 1	Female	69	Yes	Yes	No	No	No	No	No	Yes
Pt 2	Male	58	No	Yes	No	No	No	No	No	Yes
Pt 3	Male	72	No	No	No	No	No	No	Yes	No
Pt 4	Male	60	Yes	Yes	No	No	No	No	Yes	No
Pt 5	Female	47	Yes	Yes	No	No	No	No	Yes	No
Pt 6	Male	70	No	No	No	No	No	No	No	Yes
Pt 7	Female	61	Yes	Yes	No	No	Yes	No	No	Yes
Pt 8	Male	66	Yes	Yes	No	No	No	No	Yes	No
Pt 9	Male	78	No	No	No	No	No	No	No	Yes

MI myocardial infarction, *PCI* percutaneous coronary intervention, *Pt* patient, *SA* stable angina, *UA* unstable angina

Table 2 IVUS findings post-BVS implantation, at 6 month and 2 year follow-up

	Post-BVS implantation				6 Month follow-up					2 Year follow-up			
	VA (mm^2)	SA (mm^2)	PA (mm^2)	VA* (mm^2)	SAŦ (mm^2)	LA* (mm^2)	IH (mm^2)	PA (mm^2)	(SA post PCI-LA 6mo)/SA post PCI (%)	VA$^{\S\delta}$ (mm^2)	LA$^{\S\delta}$ (mm^2)	PA$^{\&}$ (mm^2)	(SA post PCI-LA 2 y)/SA post PCI (%)
Pt 1	16.93	7.80	9.13	16.99	7.64	7.11	0.54	9.88	2	15.91	7.75	8.16	1
Pt 2	19.40	7.23	12.17	17.67	6.66	6.16	0.5	11.51	8	16.02	7.05	8.97	2
Pt 3	11.01	5.66	5.35	14.26	6.08	6.08	0	8.18	−7	13.62	5.75	7.87	−1
Pt 4	14.64	6.57	8.07	16.17	6.70	6.70	0	9.47	−2	15.74	6.85	8.89	−4
Pt 5	12.34	6.15	6.19	13.03	5.96	5.96	0	7.07	3	13.64	7.81	5.83	−27
Pt 6	10.47	5.73	4.74	11.04	4.84	4.75	0.42	6.29	15	10.04	5.17	4.87	10
Pt 7	10.53	6.21	4.32	11.50	5.54	4.84	0.71	6.66	11	7.72	6.28	1.44	−1
Pt 8	11.15	5.98	5.17	11.64	4.43	4.43	0	7.21	26	12.45	5.7	6.75	5
Pt 9	7.30	4.24	3.06	6.70	3.05	3.05	0	3.65	28	5.71	2.13	3.58	50

Dunn's post-test multiple comparison for all pairs: * *P* value 6 Month Follow-up versus post-implantation = NS; § *P* value 2 year Follow-up versus post-implantation = NS; δ *P* value 2 year versus 6 Month follow-up = NS; Ŧ *P* value versus post-implantation < 0.05; & *P* value 2 year versus 6 Month follow-up < 0.05

IH intimal hyperplasia, *LA* lumen area, *PA* plaque area, *SA* scaffold area

Table 3 Post-implantation and 2 year follow-up IVUS based hyperechogenicity and vasomotion test at 2 years

	Hyperechogenicity (%)			Angiographic mean lumen diameter (mm) of the scaffolded segment after methergine or acetylcholine* test		
	Post-implantation	§2 years follow-up	% change	Baseline	δMeth/Ach*	% change after Meth/Ach
Patient 1	16	6	65	2.61	2.52	−3
Patient 2	5	0	96	2.64	2.08	−21
Patient 3	35	7	80	2.31	2.10	−9
Patient 4	11	5	59	2.57	2.35	−9
Patient 5	12	0	93	2.98	2.84	−5
Patient 6	16	1	92	1.90*	2.16*	14
Patient 7	33	11	67	1.81*	1.96*	8
Patient 8	38	19	50	2.47*	2.70*	9
Patient 9	25	2	93	1.29*	1.32*	2

* Acetylcholine test, § *P* value < 0.05, post-implantation versus 2 year follow-up

δ *P* value < 0.05, Meth/Ach versus baseline

Ach acetylcholine, *Meth* methergine

of acetylcholine. In this patient a decrease in the mean lumen diameter after nitrates was also observed in the scaffolded segment, and in the 5 mm segments proximal and distal to the scaffold (Fig. 1).

A 50–96% reduction in hyperechogenicity was observed between baseline and 2 years and this corresponded to a change in vasomotion of between 2 and 21%.

Discussion

The main finding of this study is that the bioresorption of the BVS is accompanied by the re-establishment of endothelial and non-endothelial dependent vasomotion. The bioresorption of the implant, as assessed by echogeniticity, is concomitant with lumen area enlargement at 2 years, and occurs without significant

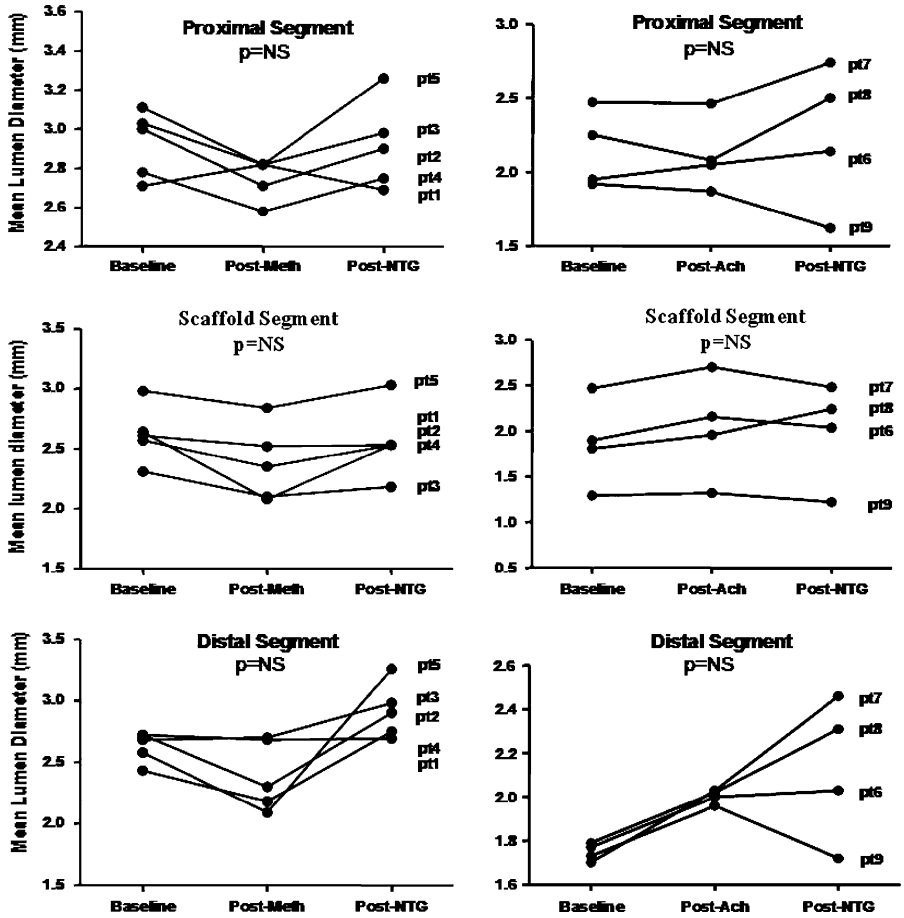

Fig. 1 Mean Lumen individual changes after Methergine or Acetylcholine and after final nitrates administration at 2 year follow-up

changes in the vessel area between 6 months and 2 years.

Despite this, it is unclear if the plaque reduction that occurs between 6 months and 2 years after the device implantation is the result of the mass loss due to the bioresorption process, and/or an actual decrease in the pre-scaffolding atherosclerotic plaque. Both situations could potentially explain the plaque shrinkage that was observed in these patients. Preclinical studies in the atherosclerotic rabbit model have shown that the implantation of metallic everolimus eluting scaffold results in a reduction of macrophages that is resulting from the triggering of an autophagic process through the mTor pathway inhibition by everolimus [11, 12]. Porcine histological studies 3 years after BVS device implantation have shown that the voids in the vessel wall that were previously occupied by the polymeric struts were still preserved but filled by proteoglycan material and a mineralization process was observed around them [2]. A further evaluation of these observations in relation to the pre-scaffolding atherosclerotic plaque would be useful to clarify the exact mechanism underlying the plaque shrinkage.

Our observations support the hypothesis that in the future the introduction of bioresorbable scaffolds could potentially overcome the three main mechanisms leading to the in-scaffold/vessel restenosis: acute recoil, constrictive vessel remodelling and neointimal hyperplasia.

In vivo acute recoil of the first generation BVS was slightly larger ($6.9 \pm 7.0\%$ vs. $4.3 \pm 7.1\%$, $P = 0.25$) but insignificantly different from that of the metallic everolimus eluting stent (EES), implying the radial strength of the BVS was similar to that of a metallic stent [13].

At 2 year follow-up the vasoreactivity to endothelial dependant and non-endothelial dependant agents was restored in eight of the nine patients. Patient 9 was the only subject who did not sufficiently

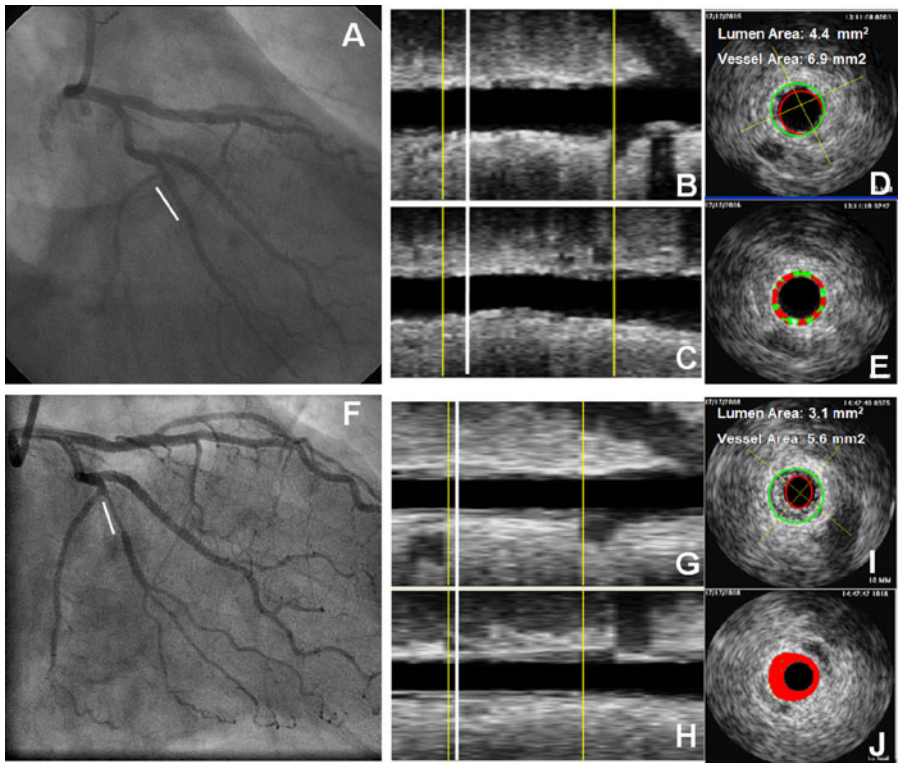

Fig. 2 *Panel* **a** presents a RAO Caudal angiographic image after ABSORB device (3.0 × 12 mm, *white line*) implantation on the Obtuse Marginal of the LCX; the post-procedural Intravascular Ultrasound longitudinal pullbacks (**b**, **c**) show the scaffold (*yellow lines*) and the frame (*white line*) corresponding to the cross-sectional image (**d**) on the top right with the color-coded hyperchogenicity on the bottom (**e**). The BVS struts are color coded as green. On the *bottom left* (**f**) the 2 year follow-up angiographic image shows a decreased lumen diameter of the scaffolded region (*white line*). This finding is confirmed on the intravascular ultrasound longitudinal pullbacks (**g**, **h**). The IVUS cross-sectional image (**i**) on the *bottom right* shows a reduced lumen area, the bioresorption of the BVS device struts is almost completed and no hyperechogenic tissue components are identified (**j**)

vasodilate (<3%) after an infusion of acetylcholine. This may have been anticipated considering the angiographic and IVUS findings in this patient (Fig. 2), which demonstrated a reduction in vessel and lumen area, and the presence of calcium within the treated segment.

The re-establishment of vasoreactivity after bioresorption of the scaffold could potentially lead to a decreased risk of stent thrombosis. The restoration of the vessel wall reactivity may ensure a normal response to shear stress in the scaffolded and peri-scaffold segments. This could facilitate a risk free discontinuation of dual anti-platelet therapy, and could prevent plaque progression.

The main limitation of this study is the small sample size. In the ABSORB Cohort A study the sample size was not defined on the basis of an endpoint hypothesis, but rather to provide information about the feasibility of the study and device safety. Therefore this sub-study should be seen as hypothesis-generating. The potential advantages of this drug-eluting bioresorbable implant are currently being assessed with a second-generation device in the ABSORB Cohort B study. This device, BVS revision 1.1, has a polymer that is processed differently so that its integrity and radial force can be retained for a longer time. The improved design- zigzag hoops linked by straight bridges- should provide a more uniform vessel support and drug application. The study will enrol 80 patients, with an acetylcholine test in all patients at 2 year follow-up. Therefore we expect to clarify the correlation between scaffold bioresorption and the restoration of vasoreactivity in the near future.

Conclusions

The bioresorption of the BVS is accompanied by re-establishment of both endothelial and non-endothelial dependent vasomotion. This is concomitant with lumen area enlargement without significant changes in the vessel area.

The ABSORB Cohort A study has proved the safety and feasibility of the everolimus eluting BVS. Our results support the hypothesis that in the near future the introduction into clinical practice of bioresorbable scaffolds could represent a real breakthrough in the field of interventional cardiology.

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