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IVUS Radiofrequency Analysis in the Evaluation of the Polymeric Struts of the Bioabsorbable Everolimus-Eluting Device During the Bioabsorption Process

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Background: In the ABSORB study cohort A the changes in the amount of dense calcium and necrotic core have not been reported in comparison to the prestenting phase; this evaluation could be useful to better clarify the bioabsorption process. Aim of this study was therefore to evaluate the dynamic changes in plaque size and plaque tissue composition observed between 6 months and 2 years follow-up, and to compare these findings to the prestenting phase. Methods: Angiography, intravascular ultrasound and derived parameters (virtual histology, palpography, and echogenicity) were serially assessed postprocedure, at 6 months and at 2 years in 20 patients. In a subset of 8 patients the same measurements were also recorded in the prestenting phase. Results: In the total population a reduction of 18% in the plaque area was observed between 6 month and 2 year follow-up (7.56 ± 2.32 mm^2 at 6 months vs. 6.16 ± 2.10 mm^2 at 2 year follow-up; $P < 0.01$). In the subgroup of eight patients who underwent IVUS during the pre-stenting phase, the plaque area at 2 year follow-up was not significantly different when compared to the prestenting plaque area (7.29 ± 2.29 mm^2 at prestenting vs. 7.48 ± 1.45 mm^2 at 2 year follow-up, P = NS). Necrotic core area was reduced by 24% between the 6 month and 2 year follow-up (0.97 ± 0.66 mm^2 at 6 months vs. 0.74 ± 0.53 mm^2 at 2 year follow-up; P = NS), whilst dense calcium was reduced by 14% from 6 month to 2 year follow-up (0.83 ± 0.50 mm^2 at 6 months vs 0.72 ± 0.64 mm^2 at 2 year follow-up; P = NS). Whilst the necrotic core at 2 years follow-up was not significantly different when compared to the pre-stenting phase (0.62 ± 0.42 mm^2 prestenting vs 1.07 ± 0.56 mm^2 at 2 year follow-up; P = NS), the area of dense calcium was significantly higher at follow-up compared to prestenting (0.35 ± 0.35 mm^2 pre-stenting vs. 0.84 ± 0.66 mm^2 at 2 year follow-up; $P < 0.05$). Conclusions: The reduction in the necrotic core component between 6 month and two year follow-up could be related to a synergistic effect of the bio-absorption process and the anti-inflammatory action of everolimus.

Key words: PCI—percutaneous coronary intervention; CATH—diagnostic cardiac catheterization; IVUS—intravascular ultrasound

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Conflict of interest: Susan Veldhof and Cécile Dorange are employees of Abbott Vascular.

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TABLE I. Patients Demographics

N pts	20
Age, years	63.5 ± 8.8 (20)
Male	55% (11/20)
Hypertension	70% (14/20)
Diabetes	5% (1/20)
Smoking	15% (3/20)
Dyslipidaemia	73.7% (14/19)
CAD familiarity	65% (13/20)
Clinical presentation	
Stable Angina	60% (12/20)
Unstable Angina	40% (8/20)

BACKGROUND

Bioabsorbable polymer drug-eluting stents may be a safe and feasible alternative to metallic stents, by providing a short-term vessel scaffolding combined with a drug delivery capability, and avoiding the long-term restrictions of metallic stents.

In the ABSORB study [1] the bioabsorption process of the BVS Revision 1.0, bioabsorbable drug eluting stent (BVS poly-lactide everolimus-eluting coronary stent, Abbott vascular, Santa Clara) has been indirectly evaluated with the use of IVUS echogenity with computer aided analysis software, and IVUS derived radiofrequency analysis of the apparent dense calcium and necrotic core components. Cohort A of the ABSORB study has previously reported a reduction in the amount of dense calcium and necrotic core between six months and two years, together with a decrease in the plaque area, and no significant change in the vessel area [1].

These data are in keeping with animal data which has demonstrated that the bioabsorption process occurs mainly between the six months and two years after stent implantation. The in vivo serial changes in the structural conformation of the BVS device during the bioabsorption process were established in a porcine coronary artery model. Mass loss was ~30% at 12 months, with a further reduction to 60% mass loss at 18 months after the implantation [2].

However, these changes in the amount of dense calcium and necrotic core have not been reported in comparison to the pre-stenting phase; an evaluation of this may serve to better clarify the bioabsorption process.

The aim of this study was therefore to evaluate the dynamic changes in plaque size and plaque tissue composition observed between 6 months and 2 years follow-up, and to compare these findings to the pre-stenting phase.

METHODS

The ABSORB study design has been already described previously [2]. 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 centers between March and July 2006. All treated lesions were single and *de-novo,* in a native coronary artery of 3.0 mm diameter, shorter than 8 mm for the 12 mm stent and shorter than 14 mm for the 18 mm stent, with a diameter stenosis greater than 50% and less than 100%, and with a thrombolysis in myocardial infarction (TIMI) flow grade more than 1.

Angiography and intravascular ultrasound (IVUS) derived radiofrequency parameters were acquired post-procedure, at 6 months and at 2 years in 20 patients. In a subset of 8 patients the same measurements were also recorded in the pre-stenting phase.

STUDY DEVICE

The BVS bioresorbable everolimus eluting device has a polymer backbone of Poly-L (racemic)-lactic acid (PLLA), coated with a Poly-D (racemic), L-lactic acid (PDLLA) polymer that contains and controls the release of the antiproliferative drug everolimus. Both PLLA and PDLLA are fully absorbable. The absorption process occurs via hydrolysis of the long chains of PLLA/PDLLA that become shorter as the bonds between the repeating units are hydrolysed, producing lactic acid which is metabolized via the Krebs cycle, and small particles $<2\mu$ in diameter that are phagocytosed by macrophages.

IVUS DERIVED RADIOFREQUENCY ANALYSIS

IVUS assessment was performed with a phased array catheter (EagleEye, Volcano Corporation, Cordova, CA) with automated pullback at 0.5 mm per second. The region beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. The IVUS derived radiofrequency (IVUS-RF) analysis was performed offline using pcVH 2.1 (Volcano Corporation, Rancho Cordova, CA) by an independent clinical research organization (Cardialysis, Rotterdam, The Netherlands). Four tissue components (necrotic core-red; dense calcium-white; fibrous-green; fibro-fatty-light green) were identified with autoregressive classification systems. The sensitivity and specificity of the technique for each tissue component has been previously validated in a postmortem study. The kappa statistics between histopathology and IVUS-RF derived plaque composition has been calculated at 0.845 indicating very high agreement [3,4].

From each cross section the polymeric stent struts were detected as areas of apparent dense calcium and necrotic core. As previously described [5], the changes

in quantitative analysis of these tissue components between implantation and follow-up have been used as a surrogate marker of the polymeric strut bioabsorption.

STATISTICS

Binary variables are presented as percentages. Continuous variables are presented as mean ± SD. Paired comparisons between the pre-stenting phase, postprocedure, 6 month and the 2 year follow-up of IVUS parameters were achieved using the ANOVA test for repeated measurements and Tukey's post-test for multiple comparisons of all pairs.

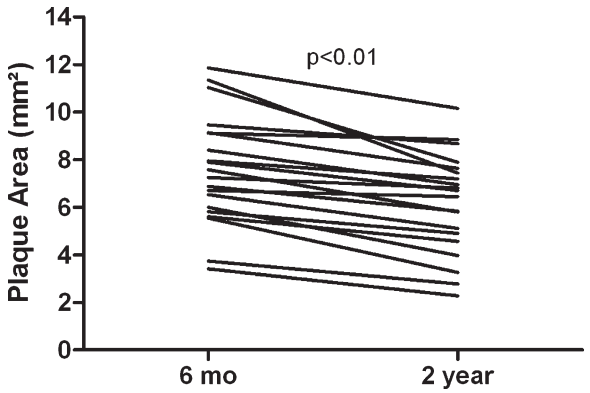

Fig. 1. Plaque area changes between 6 months and 2 year follow-up.

RESULTS

The patient demographics are shown in Table I. The total population consisted of 20 patients.

In the total population a reduction of 18% in the plaque area was observed between 6 month and 2 year follow-up (7.56 ± 2.32 mm^2 at 6 months vs. 6.16 ± 2.10 mm^2 at 2 year follow-up; $P < 0.01$) (Fig. 1).

There was a 24% reduction in necrotic core area between 6 month and 2 year follow-up (0.97 ± 0.66 mm^2 at 6 months vs. 0.74 ± 0.53 mm^2 at 2 year follow-up; P = NS), whilst during the same period a 14% reduction was noted in the dense calcium area (0.83 ± 0.50 mm^2 at 6 months vs. 0.72 ± 0.64 mm^2 at 2 year follow-up; P = NS).

In the subgroup of 8 patients who underwent IVUS during the pre-stenting phase, the plaque area at 2 year follow-up was not significantly different when compared to the pre-stenting plaque area (7.29 ± 2.29 mm^2 at preprocedure vs. 7.48 ± 1.45 mm^2 at 2 year follow-up, P = NS). In these patients an increase in the plaque area was observed between the pre- and post-stenting phase (Fig. 2). The plaque composition changes in this subset of patients are shown in Fig. 3.

Of note, the necrotic core area at 2 years was not significantly different when compared to the pre-stenting phase (0.62 ± 0.42 mm^2 at prestenting vs 1.07 ± 0.56 mm^2 at 2 year follow-up; P = NS), whilst the dense calcium was significantly higher than at prestenting (0.35 ± 0.35 mm^2 at prestenting vs. 0.84 ± 0.66 mm^2 at 2 year follow-up; $P < 0.05$).

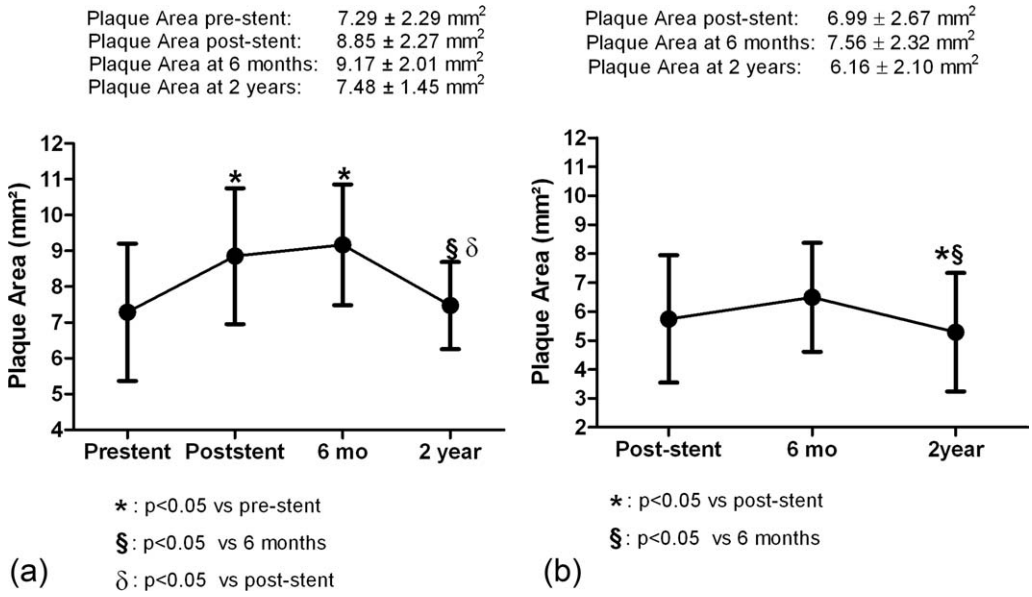

Fig. 2. Average plaque area (black dot) and its standard deviation (vertical bar) in the subset of patients with prestenting, post-stenting, 6 months, 2 year follow-up (Fig. 2a), and in the whole population at post-stenting, 6 months and 2 year follow-up (Fig. 2b).

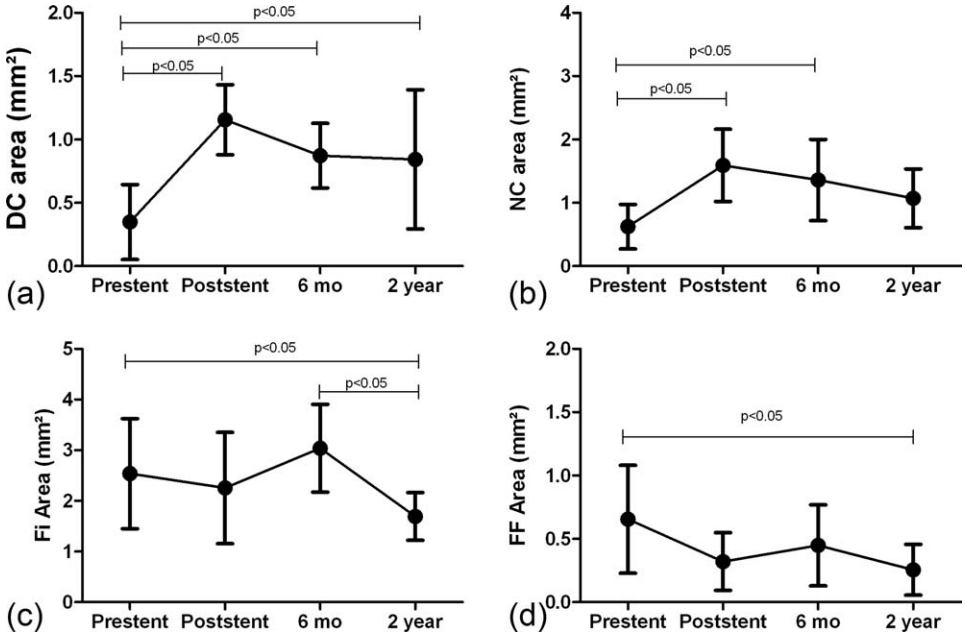

Fig. 3. Average area (black dot) of plaque tissue components [Dense calcium, (a); Necrotic Core, (b); Fibrous tissue, (c); Fibro-fatty tissue, (d)] and standard deviation at pre-stenting, post-stenting, 6 months, 2 year follow-up.

DISCUSSION

The present study demonstrates that the plaque shrinkage observed between the immediate post-stenting phase, and 2 year follow-up is most likely to be due to the bioabsorption of the stent struts, which leads to plaque area values at 2 years which are similar to the pre-stenting phase. Similarly, the plaque composition changes that have been observed at 2 year follow-up are related to the process of hydrolysis of the stent struts and mass loss, with consequent alteration of the IVUS radiofrequency signal.

Although IVUS radiofrequency analysis has not been validated to assess polymeric struts, the acute changes that occur after BVS device implantation, and the subsequent dynamic alteration in the amount of plaque components, suggest it can be a useful tool for a greater understanding of the bioabsorption process.

The 24% reduction in necrotic core area between 6 month and 2 year follow-up has to be interpreted with caution. It is likely that the reduction of this tissue component at 2 years is not merely due to the decrease of dense calcium as a result of the stent bioabsorption, but also a consequence to the decrease in the backscattering radiofrequency signal.

Of note, the reduction of necrotic core is 9% higher than the decrease in dense calcium seen at 2 years. Therefore, it is likely that other factors could influence this change in the plaque tissue composition.

Histological validation studies [3] have shown that necrotic core is a mainly highly lipid necrotic region with remnants of foam cells and dead lymphocytes, no collagen fibers, and poor mechanical integrity. This tissue is a source of metalloproteinases, a group of proteolytic enzymes that have an important function in inflammatory processes and vascular remodeling.

One of the factors that could contribute to the reduction of the necrotic core component seen in this cohort of patients is the effects of the released antiproliferative drug, everolimus. Oral everolimus has been shown to protect against transplant vasculopathy and limit coronary artery intimal thickening in cardiac transplant recipients [6–8]. Moreover, data obtained in transplant vasculopathy, and in-stent restenosis animal models has shown the ability of systemic treatment with everolimus to reduce intimal thickening of aortic orthotopic transplants in rats, to prevent neointima formation of carotid allografts in apolipoprotein E-deficient mice, and to prevent the development of atherosclerotic plaques at the aortic root and at the brachiocephalic artery in LDLR(_/_) mice [9–11]. Preclinical studies in an atherosclerotic rabbit model have shown that the implantation of metallic everolimus eluting stents results in a reduction of macrophages consequent to the triggering of an autophagic process through the mTor pathway inhibition by everolimus [12,13].

Regarding the dynamic changes in the dense calcium component, it is understandable that the larger decrease was observed 6 months after stent implantation as a consequence of device hydrolysis. The absence of a significant change between the 6 month and 2 year follow-up may support the porcine histological findings 3 years after the BVS stent implantation that have shown that the voids in the vessel wall, previously occupied by the polymeric struts, were still preserved but filled by proteoglycan material and a mineralization process was observed around them [1].

LIMITATIONS

It is important to acknowledge that IVUS radiofrequency analysis characterizes polymeric stent struts as dense calcium and necrotic core. Fortunately awareness of this misclassification makes it possible to evaluate the BVS bioabsorption process using these two tissue components as surrogate markers of the polymeric strut bioabsorption. Moreover, the IVUS radiofrequency findings have been consistent with the results obtained using other techniques such as optical coherence tomography, IVUS and echogenicity. In the ABSORB study all these techniques have been utilized to follow the bioabsorption process, even though none of them have been validated for this specific purpose.

CONCLUSIONS

IVUS radiofrequency analysis represents an important tool for the understanding of the bioabsorption process of the BVS stent. The reduction of the necrotic core component at two years could be related to a synergistic effect of the bioabsorption process and the anti-inflammatory action of everolimus.

Further trials with larger sample sizes and clinical follow-up are required before the impact of these observations are fully understood.

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