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ORIGINAL PAPER

# Implications of a bioresorbable vascular scaffold implantation on vessel wall strain of the treated and the adjacent segments

**Christos V. Bourantas · Hector M. Garcia-Garcia · Carlos A. M. Campos · Yao-Jun Zhang · Takashi Muramatsu · Marie-Angèle Morel · Shimpei Nakatani · Xingyu Gao · Yun-Kyeong Cho · Yuki Isibashi · Frank J. H. Gijsen · Yoshinobu Onuma · Patrick W. Serruys**

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**Abstract** *Background* Metallic stents change permanently the mechanical properties of the vessel wall. However little is known about the implications of bioresorbable vascular scaffolds (BVS) on the vessel wall strain. *Methods* Patients (n = 53) implanted with an Absorb BVS that had palpographic evaluation at any time point [before device implantation, immediate after treatment, at short-term (6–12 months) or mid-term follow-up (24–36 months)] were included in the current analysis. The palpographic data were used to estimate the mean of the maximum strain values and the obtained measurements were classified using the Rotterdam classification (ROC) score and expressed as ROC/mm. *Results* Scaffold implantation led to a significant decrease of the vessel wall strain in the treated segment [0.35 (0.20, 0.38) vs. 0.19 (0.09, 0.29); $P = 0.005$] but it did not affect the proximal and distal edge. In patients who had serial palpographic examination the vessel wall strain continued to decrease in the scaffolded segment at short-term [0.20 (0.12, 0.29) vs. 0.14 (0.08, 0.20); $P = 0.048$] and mid-term follow-up [0.20 (0.12, 0.29) vs. 0.15 (0.10, 0.19), $P = 0.024$]. No changes were noted with time in the mechanical properties of the vessel wall at the proximal and distal edge. *Conclusions* Absorb BVS implantation results in a permanent alteration of the mechanical properties of the vessel wall in the treated segment. Long term follow-up data are needed in order to examine the clinical implications of these findings.

**Keywords** Bioresorbable vascular scaffold · Palpography · Vessel wall strain

## Introduction

Vessel wall mechanical behavior appears to be associated with the compositional characteristics of the plaque and predict future cardiovascular events [1–4]. Several studies have shown that pharmaceutical or an interventional treatment can influence the mechanical properties of the vessel wall by altering its constituents [5–9]. Following an endoluminal device implantation (i.e., a metallic stent or a bioresorbable scaffold) the local vessel wall strain of the implanted segment is reduced and this has been attributed to the increased stiffness of the deployed device [5, 6, 9].

Recently we have reported the results of the palpographic analysis performed in segments implanted with the updated revision of the Absorb bioresorbable vascular scaffold (BVS) 1.1 [6]. We found that the vessel wall strain is reduced in the scaffolded segments immediately after device deployment but there are no further changes in the mechanical properties of the vessel wall between post-scaffold implantation and at short-term follow-up (i.e., at 6–12 months). The present analysis aims to investigate the mid-term implications (i.e., at 24–36 months) of the Absorb BVS 1.1 on the vessel wall strain.

On behalf of the Absorb Cohort B Investigators.

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C. V. Bourantas · H. M. Garcia-Garcia · C. A. M. Campos · Y.-J. Zhang · T. Muramatsu · M.-A. Morel · S. Nakatani · Y.-K. Cho · Y. Isibashi · F. J. H. Gijsen · Y. Onuma · P. W. Serruys (✉)
Interventional Cardiology Department, Thoraxcenter, Erasmus Medical Center, 's-Gravendijkwal 230, 3015, CE, Rotterdam, The Netherlands
e-mail: p.w.j.c.serruys@erasmusmc.nl

X. Gao
Abbott Vascular, Santa Clara, CA, USA

## Methods

### Included patients and study design

The ABSORB Cohort B trial (A Clinical Evaluation of the Bioabsorbable Everolimus Eluting Coronary Stent System the Treatment of Patients with de Novo Native Coronary Artery Lesions) was a prospective multicenter single-arm study designed to investigate the safety and efficacy of the Absorb BVS 1.1 (Abbott Vascular, Santa Clara, CA, USA) [10]. One hundred one patients were included in this study and were divided in two groups (B1 and B2). The first group had invasive imaging evaluation [i.e., coronary angiography, grayscale intravascular ultrasound (IVUS), IVUS virtual histology, palpographic and optical coherence tomographic imaging] at baseline, 6 months and 2 years follow-up; while the second group had the abovementioned invasive tests at baseline, 1 year and at 3 years follow-up. Optical coherence tomographic (OCT) examination was optional and was not performed in all the studied patients. The current analysis included only the patients who had a palpographic assessment at least at one time point. The Absorb Cohort B study was sponsored and financially supported by Abbott Vascular.

The Absorb BVS 1.1 used in the ABSORB Cohort B trial, is a fully bioresorbable device with dimensions 3.0 × 18 mm. The composition of the device consists of poly-L-lactide (PLLA) that is covered by an thin layer of an amorphous matrix of poly-D,L-lactide (PDLLA) which contains and controls the release of the anti-proliferative drug everolimus (concentration: 100 μg/cm$^2$). The Absorb BVS 1.1 has an in-phase zigzag hoops linked with bridges design that provides the device increased radial strength and eliminates the risk of late scaffold recoil, while the polymer of this revision has been processed in such a way so as to have a delayed degradation (by approximately 18 months comparing to the 1st revision).

The palpographic sub-study of the ABSORB Cohort B trial had pre-specified hypotheses. In particular the investigators expected that the delayed degradation in Absorb BVS 1.1 would result: either (1) in a delayed restoration of the normal, pre-scaffold implantation, strain, or (2) it would allow the built up of neointima tissue that would permanently alter the mechanical properties of the vessel wall.

### IVUS acquisition and analysis

Intravascular ultrasound imaging was performed in the treated artery using an Eagle Eye 20 MHz imaging catheter (acquisition frame rate 30 frames/s, Volcano Corp, Rancho Cordova, CA, USA) that was withdrawn with the use of an automated pull-back device at a speed of 0.5 mm/s. During IVUS examination the electrocardiogram and the aortic pressure were recorded.

The radiofrequency IVUS imaging data were acquired using a custom design workstation and were transferred to an independent clinical research organization (Cardialysis, Rotterdam, the Netherlands) for offline analysis. For each studied artery the IVUS images portraying the 5 mm proximal, the scaffolded, and the 5 mm distal segment were analyzed. The local strain was estimated from the radiofrequency IVUS data using cross correlation analysis according to a previously described methodology [11]. The measured strain values were displayed in spread-out vessel plots using a color coded map with the blue indicating low strain values and the red/yellow a high strain (range 0–2 %) [11].

The strain values were classified according to the Rotterdam classification (ROC) score to four classes (ROC I: 0–0.5 %, ROC II: 0.6–<0.9 %, ROC III: 0.9–<1.2 % and ROC IV: >1.2 %). A cross section was considered to have high strain when the measured strain was classified as ROC III–IV in an arc of >12°. For each cross section the highest strain value was recorded and considered as the strain of this section. The mean of the maximum strain values measured in each segment was determined and used to characterize the strain of the segment. Results are presented as ROC/mm (Fig. 1).

### Statistics

Continuous variables depending on their distribution are presented as mean ± standard deviation or as median with 25th and 75th percentiles, as indicated in the tables. Categorical variables are presented as absolute values and percentages. Because of the small number of patients who had palpographic evaluation at different time points we merged the data from Cohort B1 and B2 and present our results at 4 time points: at baseline pre-scaffold implantation, immediately after scaffold implantation, at short-term (6–12 months), and at mid-term follow-up (24–36 months). Comparison between the two cohorts was done by *t* test and Chi square test, or Fisher's exact test when Cochran's rule is not met.

Changes in the strain values between two different time points were evaluated by means of paired Wilcoxon singed rank test. A P value <0.05 (two-tailed) was considered statistically significant. Data analysis was performed using the SAS statistical computer package (SAS 9.2, SAS Institute Inc., Cary, NC, USA).

## Results

### Studied population

Fifty-three from the 101 patients who were enrolled in the Absorb Cohort B study had palpographic evaluation at

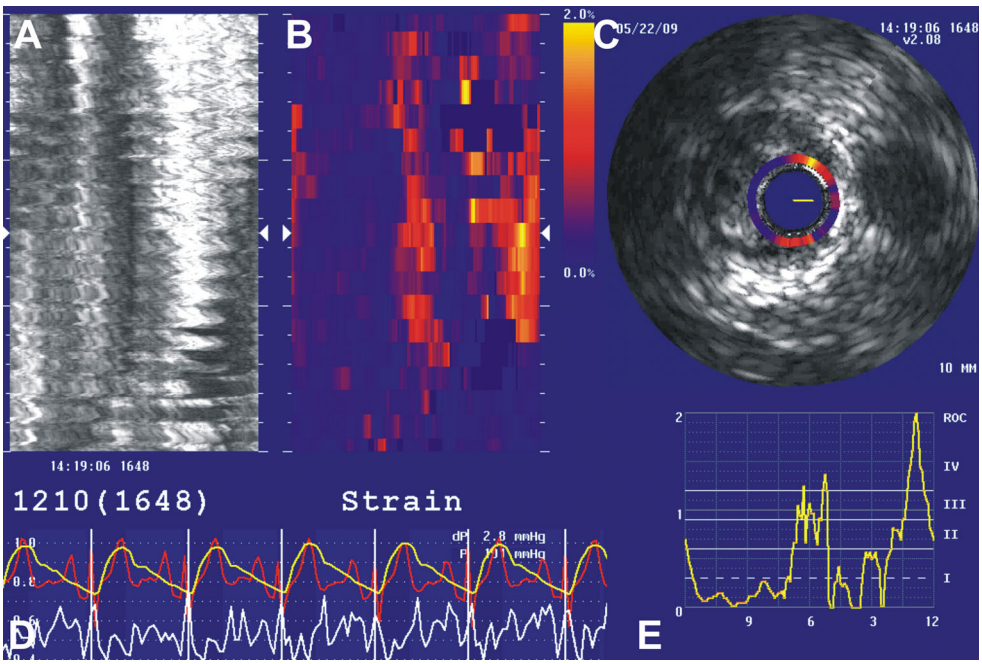


**Fig. 1** Snapshot showing the palpographic evaluation of a lesion before scaffold implantation. Panel *A* shows a longitudinal IVUS cross-section of the studied segment while panel *B* a spread out plot of the measured vessel wall strain (the *blue color* indicates low strain and the *red/yellow* high strain values). An IVUS cross section with the estimated strain at the superficial plaque shown in color coding is portrayed in panel *C*. Panel *D* shows the electrocardiogram, the measured strain, and the blood pressure changes during the cardiac circle throughout the pull-back of the catheter, whereas panel *E* displays the strain values measured in the cross-section shown in panel *C*. High strain was noted at 1 and 6 o'clock

least at one time point and included in this analysis. The baseline characteristics of the studied population are shown in Table 1. The patients that were enrolled in the Absorb Cohort B1 group did not smoke and were more likely to suffer from hypercholesterolemia and be admitted with stable angina symptoms comparing to the subjects included in the Absorb Cohort B2 group but otherwise there were not significant differences in the baseline demographics and angiographic characteristics between the two groups.

### Palpographic evaluation

Only 14 patients had palpographic evaluation before scaffold implantation, 44 patients had this investigation immediate after device deployment, 41 at short-term, and 36 at mid-term follow-up. Twenty patients had serial palpographic examination at the three time points (i.e., at baseline immediate after scaffold deployment, at short-term and mid-term follow-up).

For the entire study population (n = 53 patients) the strain values did not change immediate after scaffold deployment at the proximal and distal edge (Table 2). On the other hand in the treated segment the strain decreased significantly after device deployment. The vessel wall strain estimated at the proximal edge at the two follow-up time points was not different from the vessel wall strain before scaffold deployment ($P = 0.814$ for the short-term follow-up and $P = 0.162$ for the mid-term follow-up). However, when we compared the follow-up values at the proximal edge with the strain measured immediately after scaffold deployment we found statistical significant differences (Table 2). At the distal edge the strain values did not change with time.

The strain values in the scaffolded segment at the two follow-up time points were considerably lower comparing to baseline before device implantation ($P = 0.002$ for the short-term and $P = 0.001$ for the mid-term follow-up) but they were not different from these measured immediately after scaffold deployment.

When we included in our analysis only the segments (n = 20 patients) that had serial palpographic examination (i.e., at baseline immediate after device deployment, at short-term, and at mid-term follow-up) we found that the strain of the proximal edge and distal edge did not change with time (Table 3; Fig. 2). On the other hand in the scaffolded segment the strain values were significantly decreased at short- and mid-term follow-up comparing to baseline.

## Discussion

In this study we examined for the first time the implications of the second revision Absorb BVS on the mechanical

**Table 1** Baseline demographics, angiographic characteristics and medications of the studied population

| Patients' demographics | Absorb Cohort B N = 53 | Absorb Cohort B1 N = 20 | Absorb Cohort B2 N = 33 | *P* |
|---|---|---|---|---|
| Age (years) | 61.28 ± 8.41 | 63.84 ± 8.87 | 59.72 ± 7.85 | 0.096 |
| Male | 71.7 % (38/53) | 75.0 % (15/20) | 69.7 % (23/33) | 0.678 |
| Hypertension | 67.3 % (35/52) | 60.0 % (12/20) | 71.9 % (23/32) | 0.374 |
| Hypercholesterolemia | 83.0 % (44/53) | 100.0 % (20/20) | 72.7 % (24/33) | 0.010 |
| Diabetes | 18.9 % (10/53) | 15.0 % (3/20) | 21.2 % (7/33) | 0.725 |
| Current smoking | 15.1 % (8/53) | 0.0 % (0/20) | 24.2 % (8/33) | 0.019 |
| Prior PCI | 22.6 % (12/53) | 25.0 % (5/20) | 21.2 % (7/33) | 0.748 |
| Stable angina | 73.6 % (39/53) | 90.0 % (18/20) | 63.6 % (21/33) | 0.035 |
| Unstable angina | 9.4 % (5/53) | 5.0 % (1/20) | 12.1 % (4/33) | 0.639 |
| Silent ischemia | 1.9 % (1/53) | 0.0 % (0/20) | 3.0 % (1/33) | 1.000 |
| *Treated vessel* | | | | |
| Left anterior descending | 47.2 % (25/53) | 45.0 % (9/20) | 48.5 % (16/33) | 0.805 |
| Left circumflex | 24.5 % (13/53) | 25.0 % (5/20) | 24.2 % (8/33) | 1.000 |
| Right coronary artery | 28.3 % (15/53) | 30.0 % (6/20) | 27.3 % (9/33) | 0.831 |
| *QCA analysis pre-treatment* | | | | |
| RVD (mm) | 2.61 ± 0.34 | 2.60 ± 0.44 | 2.61 ± 0.28 | 0.949 |
| MLD (mm) | 1.04 ± 0.27 | 0.99 ± 0.31 | 1.07 ± 0.23 | 0.365 |
| Diameter stenosis (%) | 59.80 ± 9.96 | 61.25 ± 12.74 | 58.94 ± 7.98 | 0.482 |
| *Medications* | | | | |
| β-blockers | 73.6 % (39) | 65.0 % (13) | 78.8 % (26) | 0.270 |
| RAAS inhibitors | 69.8 % (37) | 65.0 % (13) | 72.7 % (24) | 0.443 |
| Statins | 94.3 % (50) | 100.0 % (20) | 90.9 % (30) | 0.165 |

*PCI* percutaneous coronary intervention, *QCA* quantitative coronary angiography, *RVD* reference vessel diameter, *MLD* minimum luminal diameter, *RAAS* renin angiotensin aldosterone system

**Table 2** Strain values at the proximal edge, the scaffolded segment and the distal edge before device implantation, immediately after device deployment, at short-term follow-up and at mid-term follow-up

| | Pre-scaffold implantation (n = 14) | Post-scaffold implantation (n = 44) | $P_1$ | Short term follow-up (n = 41) | Mid-term follow-up (n = 36) | $P_2$ | $P_3$ | $P_4$ |
|---|---|---|---|---|---|---|---|---|
| Proximal edge | 0.19 (0.13, 0.36) (12) | 0.23 (0.10, 0.35) (29) | 0.793 | 0.17 (0.12, 0.31) (28) | 0.15 (0.07, 0.20) (19) | 0.989 | 0.022 | 0.043 |
| Scaffolded segment | 0.35 (0.20, 0.38) (14) | 0.19 (0.09, 0.29) (44) | 0.001 | 0.16 (0.12, 0.22) (41) | 0.15 (0.10, 0.20) (36) | 0.391 | 0.064 | 0.410 |
| Distal edge | 0.14 (0.08, 0.31) (9) | 0.15 (0.06, 0.28) (28) | 0.739 | 0.10 (0.04, 0.26) (29) | 0.19 (0.11, 0.26) (25) | 0.675 | 0.771 | 0.445 |

$P_1$ denotes the significance of difference between the strain values estimated before and immediate after device implantation; $P_2$ the significance of difference between the strain values at post-scaffold implantation and at short-term follow-up; $P_3$ the significance of difference between the strain values at post-scaffold implantation and at mid-term follow-up; and $P_4$ the significance of differences of the strain values at the two follow-up time points

The number in the parenthesis at the left side of each column indicates the number of segments analyzed at each time point

properties of the vessel wall. We found that in contrast to the first generation which has a transient effect on vessel wall strain, the updated revision Absorb BVS 1.1 causes a permanent decrease of the strain values at the treated segment without affecting the mechanical properties of the proximal and distal edge [5, 6].

The reduction of the vessel wall strain noted immediately after Absorb BVS 1.0 or after Absorb BVS 1.1 deployment has been attributed to the shielding effect of the device, and to fact that the foreign material is likely to interfere with the palpographic estimations due to the artifactual acoustic properties of the struts [5, 6, 12]. In the first revision Absorb BVS the change in the strain values at the treated vessel was temporary as at 6 months and 24 months follow-up the measured strain was increased and approached the strain estimated before device

**Table 3** Strain values at the proximal edge, the scaffolded segment and the distal edge before device implantation, immediately after device deployment, at short-term and at mid-term follow-up in patients who had serial palpographic examination immediate after scaffold implantation and at the two follow-up time points

| | Post-scaffold implantation (n = 20) | Short term follow-up (n = 20) | Mid-term follow-up (n = 20) | $P_1$ | $P_2$ | $P_3$ |
|---|---|---|---|---|---|---|
| Proximal edge | 0.25 (0.13, 0.33) (12) | 0.15 (0.07, 0.23) (12) | 0.16 (0.09, 0.22) (12) | 0.278 | 0.135 | 0.817 |
| Scaffolded segment | 0.20 (0.12, 0.29) (20) | 0.14 (0.08, 0.20) (20) | 0.15 (0.10, 0.19) (20) | 0.048 | 0.024 | 0.922 |
| Distal edge | 0.11 (0.04, 0.23) (12) | 0.11 (0.06, 0.31) (12) | 0.20 (0.11, 0.24) (12) | 0.880 | 0.874 | 0.692 |

$P_1$ denotes the significance of difference between the strain values at post-scaffold implantation and at short-term follow-up; $P_2$ the significance of difference between the strain values at post-scaffold implantation and at mid-term follow-up; and $P_3$ the significance of differences of the strain values at the two follow-up time points

The number in the parenthesis at the left side of each column indicates the number of segments analyzed at each time point

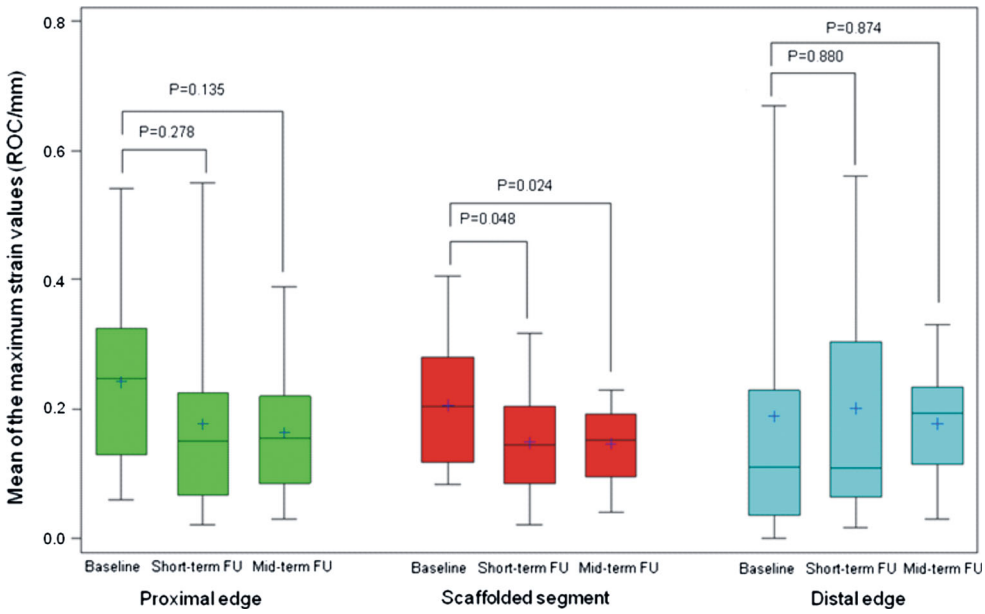


**Fig. 2** Changes in vessel wall strain (ROC/mm) at the proximal edge the scaffolded segment and the distal edge in patients who had serial palpographic examination immediately after scaffold implantation at short-term and mid-term follow-up. *ROC* Rotterdam classification

implantation [5, 6]. These findings were attributed to the resorption process which was completed at 2 years follow-up but also to the late recoil noted in the first revision [13, 14]. The latter argument is highlighted by the findings of Tanimoto et al. [13] who showed that late scaffold recoil is more intense at 6 months follow-up in the high-strain fibro-necrotic plaques; thus it can be speculated that the late recoil of the scaffold over these plaques may allow restoration of their mechanical properties contributing to the increased strain values noted at 6 and 24 months follow-up.

On the other hand in the second revision Absorb BVS the polymer has been processed in such a way so as its degradation to delay by approximately 18 months comparing to the first revision and the scaffold has a different design which provides the device with a better radial support [14]. These modifications prolong the mechanical integrity of the scaffold resulting in a delayed restoration of vessel vasomotion at 12 months follow-up, and eliminate the risk of late recoil [15].

Furthermore, we have recently demonstrated that in Absorb BVS 1.1 a thick layer of neointimal tissue develops (mean thickness 210–220 μm at short-term follow-up) that covers the entire circumference of the vessel shielding the underlying plaque [16]. Histology studies in porcine models have shown that the neointima tissue consists of smooth muscles cells and fibrous tissue and thus the superficial plaque is anticipated to exhibit low strain values in a palpographic examination [2, 3, 17]. Indeed the strain values reported in our analysis at short- and mid-term follow-up are close to the strain measured in fibrotic plaques by Korte et al. [3] using elastography in pig models. It appears that the second revision Absorb BVS 1.1 modifies permanent the mechanical properties of the superficial plaque by altering its phenotype to a more stable form (Fig. 3). Our findings indicate that in contrast to the metallic stents, which are anticipated to have a similar effect on the mechanical properties of the vessel wall, in bioresorbable scaffolds minor changes in their design are

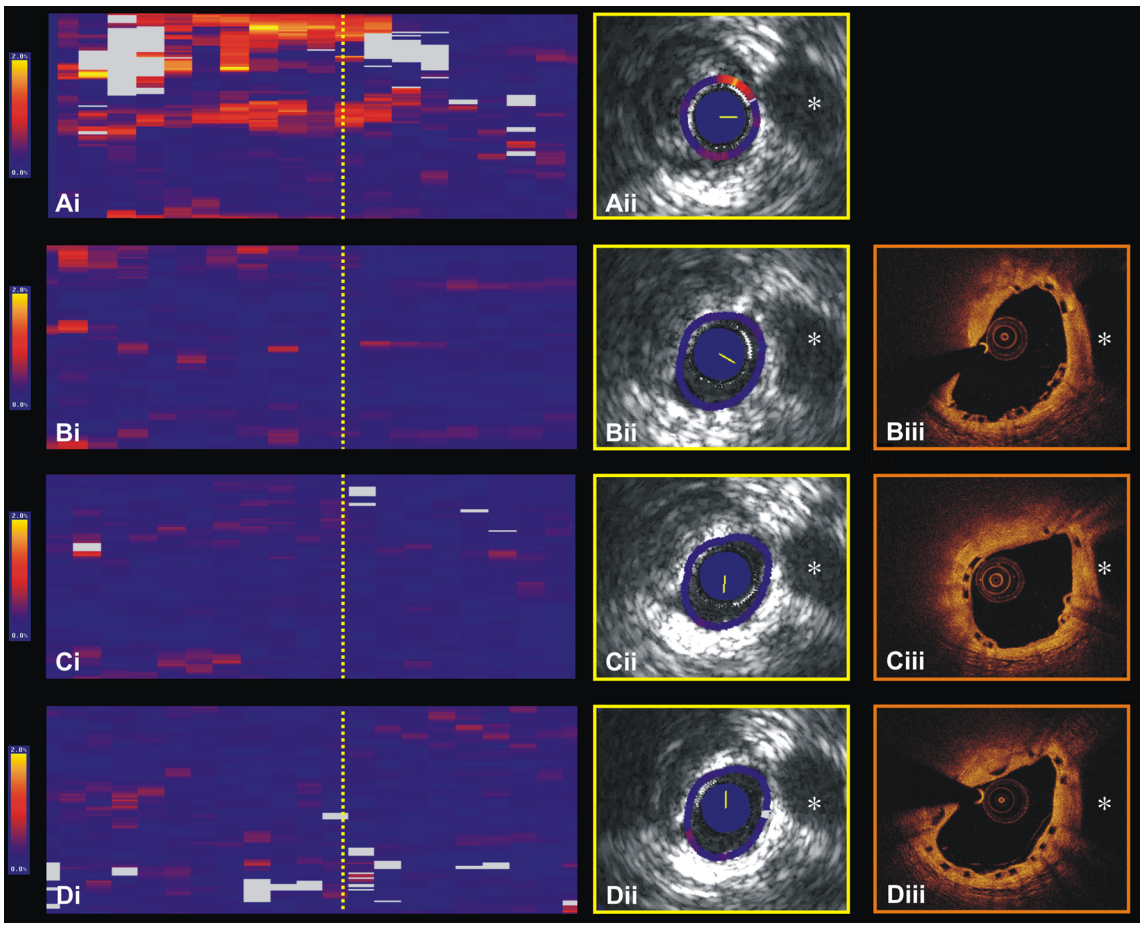


**Fig. 3** Spread out plot of the vessel wall strain at baseline before Absorb BVS implantation (Ai), immediate after scaffold deployment (Bi), at short-term (Ci), and mid-term follow-up (Di). The *blue color* indicates low strain values where the *red/yellow* a high strain. It is apparent that the incidence of the high strain values decreased immediate after scaffold deployment and it is even lower at short-and mid-term follow-up. Panels Aii, Bii, Cii and Dii portray corresponding IVUS cross-sections acquired at baseline before and immediate after scaffold deployment, at short-term, and at mid-term follow-up respectively. The position of these frames in the spread-out vessel plots is indicated with a *yellow line*. High strain values are noted at the shoulders of an echolucent plaque before scaffold implantation (Aii), however immediate after device deployment the strain values are low in the entire circumference of the lumen (Bii). OCT imaging performed after scaffold deployment this time point (Biii) indicates the presence of a lipid rich plaque (the correspondence between IVUS and OCT is shown with an *asterisk*). The strain values remain low at short- and mid-term follow-up in the IVUS cross-section (panels Cii and Dii respectively). OCT performed at the follow-up time points shows that neointima tissue has been developed that sealed the underlying plaque. The mean thickness of the neointima tissue is measured 150 μm at short-term and 220 μm at mid-term follow-up (Supplementary figure)

likely to have detrimental implications on vessel wall strain. Thus the results of this analysis cannot be extrapolated to other scaffolds even to these with a similar design and composition.

The effect of the decreased strain on vessel wall pathophysiology is yet unknown. Several studies have demonstrated that the ability of the vessel wall to expand as a response to a pulsatile cyclic strain has an athero-protective role as it stimulates eNOS gene regulation, promotes prostacyclin synthesis and maintains the contractile phenotype of the smoothes muscles cells [18–20]. However, plaques exhibiting low strain such as the pathological intimal thickening appear stable and rarely cause future events, while the plaques that demonstrate a high strain are associated with increased vulnerability [1, 4, 21]. Therefore it can be argued that the low strain estimated in stable plaques is sufficient for the stimulation of the pulsatile cyclic strain-dependent athero-protective mechanisms and for triggering the necessary mechanotransduction and pathophysiogical pathways that prevent plaque progression. In Absorb BVS this argument is supported by histology studies showing that in scaffolded segments the smooth muscles cells maintain their benign contractile phenotype, and by clinical reports demonstrating

restoration of the endothelial dependent vasomotion at 1 year follow-up, suggesting a functionally normal endothelium that is capable to respond to chemical and mechanical stimuli [15, 22].

Although palpography appears unable to predict the natural history of a high risk plaque there is robust evidence to support that the mechanical properties of the vessel wall provide useful prognostic information since patients with high strain plaques are more likely to experience acute coronary events comparing to those with low strain lesions [1, 4]. Furthermore, the Integrated Biomarkers and Imaging Studies I and II have shown that an aggressive pharmaceutical treatment reduces local strain values, whereas the vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT) trial that implemented a self-expanding stent to seal high risk plaques have demonstrated a significant decrease of the strain values immediate after device deployment [7–9]. Our results are similar to what has been reported to metallic stents, showing that Absorb BVS 1.1 implantation changes permanently the mechanical properties of the vessel wall and stabilizes the plaque. However, further palpographic data after the full resorption of the BVS are needed to confirm this statement and further research and robust data from randomized control trials are required before advocating the use of these devices for the invasive sealing of vulnerable, prone-to-rupture plaques [16, 23, 24].

### Limitations

A major limitation of the current study is the fact that a considerable number of patients did not have serial palpographic examination. Thus, we included all the data that were available from each patient acknowledging the fact that missing examinations can affect the reported results. To confirm the findings of our initial analysis we also performed a sub-analysis including the patients who had truly serial examinations. Although the number of patients in the sub-analysis was small the agreement noted between the results of the initial analysis and the sub-analysis with regards the scaffolded segment allows us to report these findings with some certainty. Another limitation of our analysis was the lack of a control group with serial palpographic examination that would allow us to compare the reported changes in the vessel wall stain in the scaffolded segments with these in native untreated arteries.

Unfortunately OCT was an optional examination in the ABSORB Cohort B study and thus only very few patients ($n = 4$) had serial palpographic and OCT assessment. Thus we were unable to combine these data and examine the association between the changes in the measured strain at follow-up and the neointimal thickness as well as the effect of the different plaque characteristics (i.e., composition of the plaque, thickness of the fibrous tissue over calcific and lipid tissue, extent of the lipid and calcific tissue, plaque burden and eccentricity) on this relation [25, 26].

## Conclusions

This study for the first time investigated the mid-term implications of the second revision Absorb BVS on the mechanical properties of the plaque. We found that in contrast to the first revision where the strain values of the treated segment change temporarily, in the second revision the strain of the vessel wall gradually decreases with time. Long-term clinical follow-up data and evidence from randomized studies are required in order to examine the clinical implications of these findings.

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**Conflict of interest** Xingyu Gao is employee of Abbott Vascular. None of the other authors have any conflict of interest to declare.

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