Evaluation of the Second Generation of a Bioresorbable Everolimus-Eluting Vascular Scaffold for the Treatment of De Novo Coronary Artery Stenosis

12-Month Clinical and Imaging Outcomes

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Objectives
The aim of this study was to demonstrate that the prevention of early scaffold area shrinkage of the ABSORB BVS (Rev.1.1, Abbott Vascular, Santa Clara, California) was sustained and not simply delayed by a few months.

Background
With improved scaffold design and modified manufacturing process of its polymer, the second iteration of ABSORB (BVS 1.1) has improved performance to prevent a scaffold area reduction at 6 months.

Methods
Fifty-six patients were enrolled and received 57 ABSORB scaffolds. Quantitative coronary angiography, intravascular ultrasound (IVUS), analysis of radiofrequency backscattering, echogenicity and optical coherence tomography (OCT) were performed at baseline and at 12-month follow-up.

Results
Overall the scaffold area remained unchanged with IVUS as well as with OCT, whereas the radiofrequency backscattering and the echogenicity of the struts decreased by 16.8% (p < 0.001) and 20% (p < 0.001), respectively; more specifically, the strut core area on OCT decreased by 11.4% (p < 0.003). Despite the absence of scaffold area loss, pharmacological vasomotion was restored. On an intention-to-treat basis, the angiographic late lumen loss amounted to 0.27 ± 0.32 mm with an IVUS relative decrease in minimal lumen area of 1.94% (p = 0.12), without significant changes in mean lumen area. The OCT at follow-up showed that 96.69% of the struts were covered and that malapposition, initially observed in 18 scaffolds was only detected at follow-up in 4 scaffolds. Two patients experienced peri-procedural and iatrogenic myocardial infarction, respectively, whereas 2 underwent repeat intervention, resulting in the major adverse cardiac event rate of 7.1% (4 of 56).

Conclusions

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In 2000, Tamai et al. (1) reported the first coronary clinical experience with a bioabsorbable poly lactide stent. The stent was mounted on a standard angioplasty balloon and was both thermal self-expanding and balloon expandable. The initial self-expansion occurred after the inflation of the delivery balloon with heated angiographic contrast medium (up to 70°C), whereas the final self-expansion of the stent occurred at 37°C in the 20 to 30 min after the initial stent deployment. The 6-month follow-up did not reveal any safety concerns, but the neointimal growth was comparable to that with a bare-metal stent. The failure of the stent to reach the clinical arena was primarily related to the use of heat to induce self-expansion; there were concerns that it could cause necrosis of the arterial wall leading to excessive intimal hyperplasia or increased platelet adhesion leading to stent thrombosis.

In 2007, Erbel et al. (2) described their first experiences with an absorbable metallic stent made of magnesium. The rate of restenosis was unacceptable at 6 months as well as at 1 year. However, when restenosis was not observed, the long-term results showed full resorption of the struts and return of vasomotion in the scaffolded area (3,4). In 2008, Ormiston et al. (5) published the 6-month results of 30 patients who received an ABSORB everolimus-eluting biore sorbable scaffold (Abbott Vascular, Santa Clara, California); the extent of neointima was comparable to that observed with a metallic everolimus-eluting stent, but intravascular ultrasound (IVUS) and optical coherence tomography (OCT) clearly documented a loss in scaffold area that resulted in an angiographic late loss of 0.44 mm. However, at 2-year follow-up, IVUS and OCT demonstrated full resorption of the polymeric struts, with retention of vasomotion in the scaffolded area (6). Furthermore, OCT and IVUS demonstrated 3 intriguing phenomena: 1) late luminal enlargement; 2) thinning of the vessel wall; and 3) absence of constrictive or expansive remodeling. In 2010, a second generation of the ABSORB (Abbott Vascular) everolimus-eluting biore sorbable scaffold was tested. The design of the platform and a different manufacturing process of the polymer ensured a longer and stronger mechanical integrity of the device that was confirmed at 6-month follow-up by the near elimination of late scaffold area loss together with limited signs of resorption, documented by OCT, radiofrequency back scattering, and echogenicity (7). Concomitantly in 2010, the publication of the 4-year follow-up of a porcine model shed light on the entire resorption process of the scaffold (8).

In humans, however, it remained uncertain whether the favorable result seen at 6 months would persist or whether a delayed inflammatory response accompanied by (very) late recoil and neointimal hyperplasia would occur mid-term at 12 months. Therefore, 2 cohorts of approximately 50 patients are being alternatively investigated either at 6 and 24 months or at 12 and 36 months. The present report concerns the cohort scheduled to undergo follow-up at 1 year.

### Methods

#### Study population.

The ABSORB Cohort B trial (A Clinical Evaluation of the Bioabsorbable Everolimus Eluting Coronary Stent System [BVS EECSS] in the Treatment of Patients With de Novo Native Coronary Artery Lesions) is a multicenter single-arm trial assessing the safety and performance of the ABSORB BVS (Rev.1.1, Abbott Vascular) in the treatment of patients with a maximum of 2 de novo native coronary artery lesions with a maximum diameter of 3.0 mm and a length of ≤14 mm, with a percentage diameter stenosis ≥50% and <100%, and a Thrombolysis In Myocardial Infarction flow grade of >1 (9).

For patients, major exclusion criteria were presenting with an acute myocardial infarction (MI), unstable arrhythmias, left ventricular ejection fraction <30%, restenotic lesions, lesions located in the left main coronary artery, lesions involving an epicardial side branch ≥2 mm in diameter by visual assessment, and the presence of thrombus or another clinically significant stenosis in the target vessel. The ethics committee at each participating institution approved the protocol, and each patient gave written informed consent before inclusion.

In total, 101 patients were enrolled in the ABSORB Cohort B trial. The current article reports the 12-month...
clinical and imaging results from the second group (B2) of 56 patients who were randomized to invasive imaging at 12 and 36 months. The remaining 45 patients (B1) have been randomized to 6- and 24-month follow-up.

**Study device.** The ABSORB BVS (Abbott Vascular) consists of a polymer backbone of Poly-L lactide coated with a thin layer of a 1:1 mixture of Poly-D, L-lactide polymer and the anti-proliferative drug everolimus to form an amorphous drug-eluting coating matrix containing 100 μg of everolimus/cm² of scaffold. The details of the device have been previously described (7,10). On the basis of pre-clinical studies, the time for complete absorption of the polymer backbone in patients is assumed to be approximately 2 years, whereas the polymer coating is absorbed in a faster timeframe (8).

**Study procedure.** Target lesions were treated with standard interventional techniques, with mandatory predilation. Post-dilation with a balloon shorter than the implanted stent was allowed at the discretion of the operator. Bail-out stenting with Xience V (Abbott Vascular) for edge dissection or insufficient coverage of the lesion occurred in 3 patients. A loading dose of 300 mg of clopidogrel was administered before the procedure, followed by 75 mg daily for a minimum of 6 months, whereas aspirin was continued lifelong according to the guidelines of the European Society of Cardiology/American Heart Association/American College of Cardiology.

**Definitions.** Clinical device success was defined as successful delivery and deployment of the clinical investigation scaffold at the intended target lesion with attainment of a final residual stenosis of <50% by quantitative coronary angiography (QCA) (by visual estimation, if QCA unavailable). Bail-out stenting was not considered a device failure. Clinical procedure success was defined as in the preceding text, using any adjunctive device without the occurrence of ischemia-driven major adverse cardiac events (MACE) during the hospital stay with a maximum of first 7 days after index procedure. The composite endpoint was cardiac death, any MI, and ischemia-driven target lesion revascularization for a QCA diameter stenosis of ≥50% with either symptoms or ischemia or diameter stenosis ≥70% at the time of scheduled or unscheduled angiography. For non-Q-wave MI, elevation of creatine kinase (CK) levels ≥2 times the upper limit of normal (ULN) with elevated creatine kinase-myocardial band (CK-MB) was required. All events were adjudicated by an independent clinical event committee, and all imaging procedures (QCA, IVUS grayscale, IVUS-virtual histology (VH), echogenicity, and OCT) were analyzed by an independent core laboratory (Cardialysis B.V., Rotterdam, the Netherlands). Results were reported on an intention-to-treat basis; however, the protocol predetermines a per-treatment analysis that excludes, for example, bail-out edge stenting and specific treatment protocol violations.

**Angiographic assessment.** In each patient, the treated segment and the peri-scaffold segments (defined by a length of 5 mm proximal and distal to the scaffold edge) were analyzed by quantitative coronary angiography (QCA), in paired matched angiographic views after procedure and at follow-up. All patients (n = 56, lesions = 57) had 12-month angiographic follow-up (100%); 1 lesion had no matched angiographic views at follow-up. The following QCA parameters were computed: minimal lumen diameter (MLD), reference vessel diameter obtained by an interpolated method, late loss, and binary restenosis, ascertained in scaffold, in peri-scaffold segment, and in segment (scaffold + peri-scaffold segments) (6).

**Vasomotion test.** At 1 year, vasomotion was studied with either methylergonovine or acetylcholine (Ach) according to local practice of vasomotion testing.

Vasomotion was assessed by measuring changes in mean lumen diameter in the scaffolded segment and in the 5-mm proximal and 5-mm distal adjacent segments (11). Vasodilatation was defined as a 3% change of the mean vessel diameter between baseline and vasomotor tone, measured after the infusion of the maximal dose of Ach (10⁻⁶ mmol/l) (11).

**IVUS gray-scale analysis.** Treated vessels after procedure and at follow-up were examined with phased array IVUS catheters (EagleEye, Volcano Corporation, Rancho Cordova, California) with a pullback speed of 0.5 mm/s. The region of interest beginning 5 mm distal to and extending 5 mm proximal to the treated segment was examined. The vessel area, mean and minimum scaffold area, mean and minimum lumen area, as well as intra-scaffold neointimal area and lumen area stenosis were measured with a computer-based contour detection program. Incomplete apposition was defined as 1 or more scaffold struts separated from the vessel wall, whereas acquired late incomplete apposition was defined as incomplete apposition at follow-up that was not present after procedure.

For echogenicity assessment of polymeric struts at baseline and follow-up, we used a computer-aided grayscale value analysis program for strut characterization (12,13).

**IVUS radiofrequency analysis.** Backscattering of radiofrequency signals provides information on vessel wall tissue composition (IVUS-VH) (14). Four tissue components (necrotic core [NC]: red; dense calcium [DC]: white; fibrous: green; and fibrofatty: light green) were identified with autoregressive classification systems and expressed as percentages (per cross section, NC + DC + fibrofatty + fibrous = 100%) (14,15). On each cross section, polymeric scaffold struts were detected as areas of apparent DC and NC with Shin’s methods (16). We used the change in quantitative analyses of these areas between implantation and follow-up as a surrogate assessment of the chemical and structural alteration of the polymeric struts (5,6,17).

**OCT analysis.** As an optional investigation, intravascular OCT imaging with either time domain OCT (M3 system, LightLab Imaging, Westford, Massachusetts) or frequency domain OCT (C7XR system, LightLab Imaging) was...
performed at baseline and at follow-up (10,18–20). The OCT measurements were performed with proprietary software for offline analysis (LightLab Imaging). Adjusting for the pullback speed, the analysis of continuous cross-sections was performed at each 1-mm longitudinal interval within the treated segment.

The ABSORB (Abbott Vascular) scaffold presents important differences from metallic stents when imaged by OCT. The optically translucent polymeric struts appear as a black central core framed by light-scattering borders that do not shadow the vessel wall and allow complete imaging of the strut thickness and the vessel behind the struts. The main quantitative measurements (strut core area, strut area, lumen area, scaffold area, incomplete scaffold apposition [ISA] area, and neointimal area) require different analysis rules than for metallic stents (7). Qualitatively, the diagnosis of late structural strut discontinuity due to bioresorption can be established: 1) if 2 struts overhang each other in the same angular sector of the lumen perimeter, with or without malapposition, covered or uncovered; or 2) if there is an isolated, covered or uncovered, strut(s) located more or less at the center of the vessel without obvious connection with other surrounding struts in 2-dimensional (2D) OCT. Three-dimensional (3D) OCT analysis might be helpful in imaging the 3D connection of this apparently isolated strut with the global structure of the scaffold (7).

The thickness of coverage was measured for every strut between the abluminal side of the strut core and the lumen. Because the strut thickness is 150 μm, the strut was considered as covered whenever the thickness of the coverage was above this threshold value (7). More detailed information on the OCT methodology for the tissue coverage assessment is available in the Online Appendix.

Statistical analysis. This was a feasibility study designed to provide preliminary information on the performance improvements of the ABSORB (BVS 1.1, Abbott Vascular) and to generate hypotheses for future pivotal randomized studies. The sample size was not defined on the basis of an endpoint hypothesis but rather to provide information on device performance. The sample size requirement was determined by assessing the minimal number of patients required to provide reliable comparison with the first ABSORB Cohort A clinical trial (n = 30) and the metallic everolimus eluting stent of the SPIRIT FIRST trial (A Clinical Evaluation of the Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) (21). For binary variables, percentages were calculated. Kolmogorov–Smirnov distribution was used to test normality of distribution. Values with normal distribution are expressed as mean ± SD, whereas the others are presented as median with interquartile range. Paired comparisons between post-procedure and follow-up were done by a Wilcoxon signed rank test for continuous variables and with McNemar’s test for binary variables. Survival curves with all available follow-up data were constructed for time-to-event variables with Kaplan-Meier estimates. Data on patients who were lost to follow-up were censored at the time of the last contact (Online Appendix). Because no formal hypothesis testing was planned for assessing the success of the study, no statistical adjustment was applied. The p values presented in this paper are exploratory analyses only and therefore should be interpreted cautiously.

Results

Fifty-six patients were enrolled, and the ABSORB (Abbott Vascular) investigational device (n = 57) was successfully implanted in all patients (Table 1). Bailout stents (Xience V, Abbott Vascular) were implanted in 3 lesions.

There were no deaths, either peri-procedurally or at 12 months. Two patients sustained an MI. The first was peri-procedural: a dissection visible on angiography occurred after pre-dilation, which was covered by the ABSORB (Abbott Vascular) implantation. Thrombolysis In Myocardial Infarction grade 3 flow was restored, despite the presence of a persisting angiographic dissection distal to the ABSORB (Abbott Vascular) scaffold. On day 1 after the procedure, the patient experienced further pain. The electrocardiogram was unremarkable. Troponin peaked to 0.81 μg/l (ULN <0.03 μg/l), CK value was 667 U/l (ULN <150 U/l), and CK-MB value was 97.2 ng/ml (ULN <4 ng/ml). The symptoms of the patient resolved with medical
therapy, and at follow-up the vessel was widely patent (late loss: 0.19 mm).

The second patient initially experienced angina (Canadian Cardiovascular Society Angina Classification class III) on day 18 after the procedure, but a stress test revealed no ischemia. On day 43, the patient experienced chest pain during the pre-planned diagnostic angiography, which did not disclose any angiographic restenosis; without anticoagulation adjustment, the diagnostic procedure was unduly prolonged by IVUS and OCT examinations. After a failed attempt at imaging the vessel with OCT, angiography showed the presence of thrombus surrounding the OCT catheter in the proximal, mid, and distal vessel. This intravascular thrombus was treated with the use of an aspiration extraction device and by multiple doses of intravenous heparin given to ensure appropriate anticoagulation. The intra-scaffold thrombosis and ensuing non–Q-wave MI was retained in the MACE count. Nevertheless, the non–Q-wave MI was not disclose any angiographic restenosis; without anticoagulation adjustment, the diagnostic procedure was unduly prolonged by IVUS and OCT examinations. After a failed attempt at imaging the vessel with OCT, angiography showed the presence of thrombus surrounding the OCT catheter in the proximal, mid, and distal vessel. This intravascular thrombus was treated with the use of an aspiration extraction device and by multiple doses of intravenous heparin given to ensure appropriate anticoagulation.

Table 2 summarizes the results of QCA data at baseline and at follow-up. A typical example of baseline and follow-up angiography is shown in Figure 1. At follow-up the intrascaffold MLD decreased from 2.27 ± 0.24 mm to 2.00 ± 0.32 mm (p < 0.001) with a late loss of 0.27 ± 0.32 mm. There were small but significant changes in MLD at the proximal (0.12 mm) and distal edges (0.07 mm) of the scaffold. Figure 2 shows the cumulative frequency distribution curve of the data. The in-scaffold and in-segment binary restenosis was 2 of 57 (3.5%).

Vasomotion. Thirty patients received an intravenous bolus infusion of 0.3 mg of methylergonovine, and all of them except 1 showed some degree of vasoconstriction of the scaffolded segments, with a significant change in mean lumen diameter of 0.16 mm (Fig. 3). Of the 24 patients who had an intracoronary infusion of a maximal dose of Ach (10⁻⁶ mmol/l), 5 were excluded from analysis because of unavailability of the matched view. Ten patients showed signs of vasoconstriction in the scaffolded segment, after administration of Ach, whereas 8 patients exhibited some degree of vasodilation. One patient did not show any vasomotion.

Gray-scale IVUS, radiofrequency backscattering, and echogenicity of struts. Over a period of 12 months, the mean and minimum lumen and scaffold areas remained unchanged. The amount of neointimal tissue growth was minimal, with an average area/scaffold of 0.09 ± 0.17 mm². Accordingly, the percentage of in-scaffold area obstruction was minimal (1.43 ± 3.09%)
but significant increase in total plaque area with a concomitant increase in vessel area (Table 3). The radiofrequency backscattering analysis revealed a significant decrease (17.7%, p \( < \) 0.001) in pseudo-calcium/calcium, and that ultrasonic alteration was confirmed by a significant decrease in echogenicity of the struts (baseline: 23.51 ± 8.57% vs. 12-month: 18.25 ± 7.19%, relative reduction: 19.7%, p \( < \) 0.001). The 2 other histological components (fibrotic and fibrofatty) increased significantly in relative and absolute terms (Table 3).

**OCT analysis.** Twenty-one patients with 22 lesions underwent OCT at baseline and at follow-up. An additional 9 patients had only follow-up OCT. The OCT results with paired analysis (n = 22) confirmed the IVUS data: 1) the mean and minimal scaffold area did not change at follow-up; and 2) the mean and minimal flow area decreased significantly by 18.1% and 23.4%, respectively, as a result of neointimal growth between and over the struts (1.34 ± 0.67 mm\(^2\)). The lumen area stenosis increased significantly from 20.2% after procedure to 26.9% at 12 months. After procedure, 18 patients showed ISA, whereas at follow-up only 4 patients showed ISA. There was no late-acquired ISA observed. At follow-up ISA area on average for the patient population with paired analysis was 2.94 ± 1.43 mm\(^2\). Among 22 patients with paired OCT at baseline and at follow-up, 7 patients presented with suspected structural strut discontinuities, 6 with apposed and covered struts, and 1 with malapposed and uncovered struts. In the case with malapposed struts suspected to show structural discontinuities in 2D OCT, a 3D OCT reconstruction revealed the connection of these apparently loose struts (in 2D), with the surrounding body of the scaffold. As indicated in the Methods section (and in the Online Appendix), the strut coverage was analyzed according to 2 different types of analysis (abliminal black core-lumen, or endoluminal black core-lumen) and 3 different thresholds of thickness (150 μm, or 0 and 30 μm). The respective percentages of coverage were 96.9%, 99.8%, and 95.5%.
The main findings of the current investigation are the following: 1) despite early signs of bioresorption, the polymeric struts are still easily detectable by ultrasound and OCT; 2) detection of persisting struts allowed accurate measurement of scaffold areas over time and confirms the absence of late or very late recoil; 3) the late lumen loss and the neointimal growth are slightly larger than the loss measured in the previous cohort that had (B1) 6-month follow-up but remain comparable to the loss and neointimal growth observed in a historical series of metallic everolimus-eluting stents analyzed at the same time point (12 months) (consequently, the restenosis rate is as low as 3.5%); 4) the mechanical integrity and radial force of the scaffold must have substantially subsided, because the scaffolded segments exhibit clear signs of pharmacologically induced vasoemotion; 5) the coverage of the polymeric struts as measured by OCT does not seem to differ from the observations made with metallic drug-eluting stents; 6) at 1 year, structural discontinuity of malapposed struts was detected in a patient among those having 2D OCT; and 7) the MACE rate at 1 year (7.1%) is comparable to that observed in a historical series of metallic everolimus-eluting stents.

Early signs of resorption and absence of late recoil.

Three different intravascular imaging techniques used for monitoring bioresorption concurred in demonstrating that the process of bioresorption has been initiated and is in progress: the measurement by OCT of the black core of the struts, the radio-frequency backscattering analysis, and the echogenicity assessment of the strut do not reflect the molecular dissolution of the polylactide but rather correspond to the filling by connective tissue of the void initially occupied by the polymeric struts (8). In the preclinical porcine model, when analyzing the explanted treated segments by gel permeation chromatography, we have established that molecular weight of the polylactide is reduced by 40% at 6 months, 70% at 12 months, and approximately 100% at 24 months (8). Therefore, it is not surprising to see that the radial force of the scaffold has partially subsided, as demonstrated by the vasoconstriction and vasodilation induced by vaso-active drugs. Although the scaffold has lost a great deal of its mechanical integrity and radial force, it is important to realize that between baseline and 12 months there has been no radial displacement of the struts toward the center of the vessel lumen. In other words, these observations confirm that the so-called constrictive remodeling is an early and short-term phenomenon, which is no longer operational 6 months after the scaffold implantation, because the scaffold at that stage is unable to oppose any mechanical resistance to the vasoconstrictive action of drugs and thus has lost its mechanical scaffolding function. These observations sub-

Figure 2 Cumulative Frequency Distribution Curves of Angiographic Late Loss: BVS 1.1 (Cohort B) Versus Xience V (Spirit FIRST)

Cumulative frequency distribution curves of late loss at 6 and 12 months, BVS 1.1 of the ABSORB (A Clinical Evaluation of the Bioabsorbable Everolimus Eluting Coronary Stent System [BVS EECSS] in the Treatment of Patients With de Novo Native Coronary Artery Lesions) Cohort B1 and B2 trials versus loss of metallic everolimus-eluting stent of the SPIRIT FIRST trial (A Clinical Evaluation of the Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) (22 patients with a serial follow-up at 6 months and 1 year). Two patients with myocardial bridge showed high late losses as well as 1 patient with intra-scaffold neointimal hyperplasia documented with intravascular ultrasound-virtual histology. Two patients underwent ischemia-driven target lesion revascularization (TLR). Online Figure 1 shows 1 of these cases with myocardial bridge. EES = everolimus-eluting stent.
stinate the concept of restenosis as a time-limited process and thereby validate the principle of a transient need for a scaffold. Previous published reports have already demonstrated that the restenotic process involving constrictive remodeling ceased to be active 4 months after balloon angioplasty (23–25).

**Table 3** IVUS Results

<table>
<thead>
<tr>
<th>IVUS grayscale, paired intent-to-treat (n = 54)</th>
<th>Post-PCI</th>
<th>365 Days</th>
<th>Difference %, Median (IQR), on the Basis of Individual Data</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean vessel area</td>
<td>13.52 (12.18 to 15.09)</td>
<td>14.63 ± 3.06</td>
<td>4.82 ± 11.53</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean scaffold area</td>
<td>6.29 ± 0.92</td>
<td>6.33 ± 0.98</td>
<td>0.90 ± 8.58</td>
<td>0.66</td>
</tr>
<tr>
<td>Neointimal hyperplasia area</td>
<td>—</td>
<td>0.01 (0.00 to 0.10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean lumen area</td>
<td>6.31 ± 0.95</td>
<td>6.33 ± 1.17</td>
<td>0.52 ± 13.18</td>
<td>0.20</td>
</tr>
<tr>
<td>Minimum lumen area</td>
<td>5.11 ± 0.96</td>
<td>4.98 ± 0.97</td>
<td>−1.94 ± 12.58</td>
<td>0.12</td>
</tr>
<tr>
<td>ISA area*</td>
<td>1.86 ± 1.33</td>
<td>4.48 ± 0.74</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patients with ISA</td>
<td>5 (9%)</td>
<td>4 (7%)</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque area</td>
<td>7.23 (6.33 to 8.87)</td>
<td>8.30 ± 2.35</td>
<td>8.94 ± 15.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen area stenosis, %</td>
<td>19.24 ± 6.85</td>
<td>21.25 ± 7.54</td>
<td>26.09 ± 77.11</td>
<td>0.30</td>
</tr>
<tr>
<td>In-scaffold area obstruction, %</td>
<td>—</td>
<td>0.20 (0.00 to 1.58)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Minimum scaffold area</td>
<td>5.11 ± 0.96</td>
<td>5.07 ± 0.92</td>
<td>−0.18 ± 11.21</td>
<td>0.38</td>
</tr>
</tbody>
</table>

IVUS VH, paired intent-to-treat (n = 48)

| Fibrous tissue area                              | 1.4 (0.8 to 1.9) | 1.9 (1.2 to 2.6) | 36.2 (−1.0 to 66.7) | <0.001 |
| Fibrous tissue area, %                           | 32.1 (25.7 to 38.8) | 40.94 ± 9.50 | 26.6 (0.0 to 46.3) | <0.001 |
| Fibrofatty tissue area                           | 0.1 (0.0 to 0.2) | 0.2 (0.1 to 0.3) | 103.5 (9.5 to 303.7) | <0.001 |
| Fibrofatty tissue area, %                        | 2.5 (1.0 to 4.0) | 4.0 (2.8 to 6.3) | 75.0 (7.4 to 292.4) | <0.001 |
| Dense calcium area                               | 1.32 ± 0.64 | 1.16 ± 0.50 | −16.8 (−32.1 to 22.3) | 0.022 |
| Dense calcium area, %                            | 30.17 ± 10.22 | 24.37 ± 7.73 | −17.7 (−35.6 to −3.2) | <0.001 |
| Necrotic core area                               | 1.4 (1.0 to 2.0) | 1.4 (1.0 to 1.9) | 5.2 (−17.4 to 23.1) | 0.992 |

Paired intravascular ultrasound (IVUS) measurements/lesion. Values given are millimeters squared, unless otherwise indicated. Values are mean ± SD or median (interquartile range [IQR]). Difference is consistently expressed as median with IQR. *Mean incomplete strut apposition (ISA) area was calculated as an average of ISA area in the frames having ISA.
Prevention of neointimal hyperplasia. We observed a possible increase in loss from $0.19 \pm 0.18$ mm at 6 months to $0.27 \pm 0.32$ mm at 12 months in the present series, when compared with the previous series analyzed at 6 months, and a parallel increment in neointimal growth as assessed by OCT from $1.25 \pm 0.36$ mm$^2$ at 6 months to $1.34 \pm 0.67$ mm$^2$ at 12 months. These comparisons are only descriptive and have no statistical basis, because the observations are not serial but only chronologically related. Without formal statistical comparison, we have to underline that serial analysis of loss in the SPIRIT FIRST trial showed an increase in angiographic late luminal loss from $0.10 \pm 0.23$ mm at 6 months to $0.23 \pm 0.29$ mm at 12 months (Fig. 2). Similarly, in the SPIRIT II trial with serial assessment at 6 and 24 months, the loss increased from $0.17 \pm 0.32$ mm to $0.33 \pm 0.37$ mm (26).

We also noticed a slight but significant increase in plaque media and vessel wall area, with an increase in fibrotic component from 1.4 to 1.9 mm$^2$ and fibro-fatty from 0.1 to 0.2 mm$^2$ without increase in necrotic core over a period of 12 months. Noteworthy, the preclinical porcine model treated with ABSORB BVS (Abbott Vascular) exhibits histologically at 1 year some remnant inflammatory reaction with granuloma that completely disappeared at 2 years. Therefore, in our patients we surmise that some late regression of plaque media is likely to occur at later follow-up, as previously documented with the first generation of ABSORB BVS (1.0) (Abbott Vascular) (6).

Vasomotion. Two types of vasomotor drugs have been optionally used in the present study: 1) methylergonovine, which is not endothelial dependent and potentiates contraction of smooth muscle cells by changing the action potential pattern so that almost all of our patients who submitted to this test showed some degree of vasoconstriction; and 2) Ach, which lowers the capillary resistance, thereby increasing flow and shear stress with stimulation of endothelial receptors with release of nitric oxide through endothelial nitric oxide synthesis activation. Anatomic and functional integrity of coalescent endothelial cells is a sine qua non condition for a vasodilatory reaction. In our series, 8

![Figure 4 OCT, IVUS Gray-Scale, and IVUS-VH at Baseline and 12 Months](image_url)
patients showed vasodilation of the scaffolded segment, 1 had unchanged luminal dimension, and 10 patients showed vasoconstriction of the scaffolded segment (Fig. 3). This suggests that full coverage by endothelial cells and complete return of functional capacity of these cells is not yet achieved in the majority of the patients. In the previous series with 2 years of follow-up, 4 of 9 patients undergoing the test responded by appropriate vasodilation of the scaffolded segment (6).

OCT findings. In general, the same OCT methodology as applied in the 6-month cohort was used in the present series for reasons of comparability. Nonparametric comparison of the coverage and neointimal hyperplasia between 6 months and 12 months did not show significant difference. However, we documented—at variance with the 6-month analysis—a significant reduction in strut cross-sectional area (black core), which methodologically makes the coverage and neointimal assessment more elusive, because the changing boundaries of the black core is used as fiducial boundaries for scaffold area and neointimal area assessment (Fig. 4) (7). The progressive OCT disappearance of the struts will further compound these assessments at 2 and 3 years (6,8) (Table 4).

The incidence of suspected structural discontinuity of apposed and covered struts (4 of 31, 13%) or malapposed and uncovered struts (3 of 31, 10%), as defined in Methods, might seem worrisome at first sight. The detection of this phenomenon, frequently not detectable by IVUS, exemplified the exceptional high resolution of OCT (8). Furthermore, the biological fate of the struts is a programmed biodegradation and loss of mechanical integrity of the scaffold, considered as 1 of the basic tenets of this new technology (24,27). Although rare, the presence of malapposed and uncovered struts potentially disconnected from the otherwise embedded scaffold might raise concerns and justifies further serial analysis of these cohorts at 2 and 3 years. In the ABSORB Cohort A trial, with the first ABSORB BVS (Abbott Vascular) generation, we retrospectively made a similar observation (28). However, imaging follow-up at 2 years showed complete incorporation and disappearance of all struts, including isolated and malapposed struts.

Review of clinical events. At 12 months in this series, we had 3 clinical events that could have been either anticipated or prevented. Two patients with obvious myocardial bridges were included in the trial; 1 underwent repeat intervention at 12 months, and the other, asymptomatic, was still under clinical surveillance after his 12-month angiographic follow-up. Myocardial bridges generate compressive pressure (up to 300 mm Hg) capable of fully closing the vessel in systole. This systolic external compression occurs at least 100,000 times/day and, as expected, a bioresorbable transient scaffold yields to such a mechanical stress. An increased incidence of in-stent restenosis, enhanced neointimal hyperplasia, and stent fracture has also been reported after placement of metallic drug-eluting stent in myocardial bridges (29). Second, the case of iatrogenic thrombosis could have been prevented by proper anticoagulation during unduly prolonged intravascular investigations.

Future prospect. When the clinical results of the Cohort B1 and B2 trials are pooled, the hierarchical MACE rate of the 101 patients at 12 months is 7% (7 of 101), even if we include the iatrogenic events described in the preceding text. Without performing a formal comparative analysis with adjustment, which in this simple population seems to be superfluous, it seems that the MACE rate at 12 months is similar to the rate observed in the historical series of the Xience V (Abbott Vascular) metallic everolimus-eluting stent (Online Fig. 2). These results constitute the foundation for the upcoming pivotal trial that plans to compare, at 1 year, the ABSORB (Abbott Vascular) bioresorbable everolimus-eluting scaffold with the metallic stent eluting the same drug (Xience Prime, Abbott Vascular). Ideally, in a trial, analysis of endothelial dysfunction by Ach should be recommended in a large proportion of patients, because the time course of reversal endothelial dysfunction could be

<table>
<thead>
<tr>
<th>Table 4 Optical Coherence Tomography Results</th>
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<tbody>
<tr>
<td>Mean scaffold area</td>
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<td>Mean prolapse area</td>
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<td>Mean strut core area</td>
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<tr>
<td>Lumen area stenosis, %</td>
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<td>ISA area (for patients with ISA)</td>
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**n = 22 lesions (21 patients). Values given are millimeters squared, unless otherwise indicated. Values are mean ± SD or median (interquartile range). Difference is consistently expressed as median with interquartile range.**

ISA = incomplete strut apposition.


Key Words: angiography • biodegradable scaffold • coronary artery disease • intravascular ultrasound • optical coherence tomography.