Evaluation of the Second Generation of a Bioresorbable Everolimus Drug-Eluting Vascular Scaffold for Treatment of De Novo Coronary Artery Stenosis
Six-Month Clinical and Imaging Outcomes

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Background—The first generation of the bioresorbable everolimus drug-eluting vascular scaffold showed signs of shrinkage at 6 months, which largely contributed to late luminal loss. Nevertheless, late luminal loss was less than that observed with bare metal stents. To maintain the mechanical integrity of the device up to 6 months, the scaffold design and manufacturing process of its polymer were modified.

Methods and Results—Quantitative coronary angiography, intravascular ultrasound with analysis of radiofrequency backscattering, and as an optional assessment, optical coherence tomography (OCT) were performed at baseline and at a 6-month follow-up. Forty-five patients successfully received a single bioresorbable everolimus drug-eluting vascular scaffold. One patient had postprocedural release of myocardial enzyme without Q-wave occurrence; 1 patient with OCT-diagnosed disruption of the scaffold caused by excessive postdilatation was treated 1 month later with a metallic drug-eluting stent. At follow-up, 3 patients declined recatheterization, 42 patients had quantitative coronary angiography, 37 had quantitative intravascular ultrasound, and 25 had OCT. Quantitative coronary angiography disclosed 1 edge restenosis (1 of 42; in-segment binary restenosis, 2.4%). At variance with the ultrasonic changes seen with the first generation of bioresorbable everolimus drug-eluting vascular scaffold at 6 months, the backscattering of the polymeric struts did not decrease over time, the scaffold area was reduced by only 2.0% with intravascular ultrasound, and no change was noted with OCT. On an intention-to-treat basis, the late lumen loss amounted to 0.19 ± 0.18 mm with a limited relative decrease in minimal luminal area of 5.4% on intravascular ultrasound. OCT showed at follow-up that 96.8% of the struts were covered and that malapposition of at least 1 strut, initially observed in 12 scaffolds, was detected at follow-up in only 3 scaffolds. Mean neointimal growth measured by OCT between and on top of the polymeric struts equaled 1.25 mm², or 16.6% of the scaffold area.

Conclusion—Modified manufacturing process of the polymer and geometric changes in the polymeric platform have substantially improved the medium-term performance of this new generation of drug-eluting scaffold to become comparable to those of current drug eluting stents.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00856856. (Circulation. 2010;122:2301-2312.)

Key Words: angiography ■ coronary disease ■ ultrasound ■ tomography, optical coherence

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2301
Bioresorbable drug-eluting vascular scaffolds (BVS; Abbott Vascular, Santa Clara, Calif) are a novel approach that provide transient vessel support with drug delivery capability without the long-term limitations of metallic drug-eluting stents such as permanent caging with or without malapposition.1–7 Permanent metallic stenting also may preclude surgical revascularization, prevent late lumen enlargement, result in jailing of side branches, and hamper noninvasive imaging of coronary arteries with multislice computed tomography and MRE.8–11

Clinical Perspective on p 2236

The fully resorbable BVS has been tested in the first-in-humans ABSORB cohort A study with a series of 30 patients and demonstrated excellent long-term clinical results up to 3 years with a major adverse cardiac event rate of 3.4%.12–14 The scaffold consists of a backbone of poly-L-lactide (PLLA) coated with poly-D,L-lactide (PDLLA) that contains and controls the release of the antiproliferative drug everolimus (Novartis, Basel, Switzerland). The first generation of BVS showed a slightly higher acute recoil than conventional metallic platform stents,15 and at 6 months, an 11.8% reduction in scaffold area and a 24.3% decrease in minimal luminal area were documented and dubbed “late recoil.”13,16,17 Although the short- and long-term results of the ABSORB cohort A trial were favorable, reinforcement of the mechanical performance of the device and prolongation of its mechanical integrity up to 6 months were regarded as potential improvements of this technology.

To enhance the mechanical strength of the struts and to reduce immediate and late recoil,17 the strut design and the manufacturing process of the polymer were modified in the revised version, BVS 1.1. First, the new design has in-phase zigzag hoops linked by bridges that allow a more uniform strut distribution, reduce maximum circular unsupported surface area, and provide more uniform vessel wall support and drug transfer (Figure 1).18 Second, a modified manufacturing process has resulted in a lower hydrolysis (in vivo degradation) rate of the polymer, thus preserving its mechanical integrity for a longer period of time.19

The BVS revision 1.1 was tested in 101 patients of the ABSORB cohort B study. This cohort was subdivided into 2 subgroups of patients: the first group (B1) had to undergo invasive imaging at 12 and 36 months. The purpose of the present report is to describe the improved performance of this second iteration, the BVS 1.1, at 6 months.

Methods

Study Population

The ABSORB cohort B trial is a multicenter single-arm trial assessing the safety and performance of the BVS revision 1.1 in the treatment of patients with a maximum of 2 de novo native coronary artery lesions. In this study, patients >18 years of age who had either stable or unstable angina pectoris or silent ischemia were suitable for inclusion. All treated lesions were de novo lesions in a native coronary artery with a maximum diameter of 3.0 mm, a length of <14 mm, a percentage diameter stenosis (DS) ≥50% and <100%, and a thrombolysis in Myocardial Infarction flow grade of >1.

Patients with acute myocardial infarction, 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 thrombus or another clinically significant stenosis in the target vessel were excluded. 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. This article reports the 6-month clinical and imaging results from the first group (B1) of 45 patients who were allocated to invasive imaging at 6 and 24 months. The remaining 56 patients (B2) have been allocated to 12- and 36-month follow-up (NCT00856856).

Study Device

BVS 1.1 balloon-expandable device consists of a polymer backbone of PLLA coated with a thin layer of a 1:1 mixture of PDLLA polymer and the antiproliferative drug everolimus to form an amorphous drug-eluting coating matrix containing 100 μg everolimus/cm² scaffold (Figure 1). The implant is radiolucent but has 2 platinum markers at each end that allow easy visualization on angiography and other imaging modalities. PDLLA allows controlled release of the everolimus so that 80% has eluted by 30 days; the elution rate, tissue concentration, and dose density of everolimus for the BVS device are similar to the XIENCE V everolimus-eluting stent. Both PLLA and PDLLA are fully resorbable. The polymer degrades via a bulk erosion process through hydrolysis of the ester bonds in the backbone. The resulting lactic acid monomer and oligomers eventually leave the polymer matrix once they reach high enough diffusivity and water solubility. They are rapidly metabolized in surrounding tissues and blood by entering the pyruvate and Kreb energy cycles. In this second iteration of the scaffold device, the hydrolysis of the polymer has been slowed through a proprietary manufacturing process. According to preclinical studies, the time for complete absorption of the polymer backbone is assumed to be 2 years, whereas the polymer coating is absorbed faster.19

Study Procedure

Target lesions were treated using standard interventional techniques with mandatory predilatation. Postdilatation with a balloon shorter than the implanted stent was allowed at the operator’s discretion (if an optimal angiographic result was not obtained immediately after scaffold deployment). Bailout stenting with Xience-V for edge dissection and insufficient coverage of the lesion was recommended if needed and occurred in 3 patients. Treatment with aspirin was started at least 24 hours before the procedure and continued throughout the length of the clinical investigation (5 years), followed by lifelong aspirin treatment according to guidelines of the European Society of Cardiology/American Heart Association/American College of Cardiology.20 A loading dose of 300 mg clopidogrel was administered before the procedure, followed by 75 mg daily for a minimum of 6 months.

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% of the target lesion by QCA (by visual estimation if QCA unavailable). Bailout stenting was not considered a device failure. Clinical procedure success was defined as above using any adjunctive device without the occurrence of ischemia-driven major adverse cardiac events up to 7 days after the index procedure. The composite end point was cardiac death, any myocardial infarction, or ischemia-driven target lesion revascularization for a QCA DS of ≥50% either with symptoms or ischemia or with DS ≥70% at the time of scheduled (180±14 days) or unscheduled angiography. For non-Q-wave myocardial infarction, elevation of creatine kinase (CK) levels ≥2 times the upper limit of normal with elevated CK-MB was required. Results were reported on an intention-to-treat basis; however, the protocol predetermines a per-treatment analysis that excludes, for instance, bailout edge stenting and specific treatment protocol violation (NCT00856856).
Angiographic Assessment

In each patient, the treated segment and the periscaffold segments (defined by a length of 5 mm proximal and distal to the scaffold edge) were analyzed by QCA in paired matched angiographic views after the procedure and at follow-up. The following QCA parameters were computed: minimal luminal diameter (MLD), reference vessel diameter obtained by an interpolated method, late loss, and binary restenosis, ascertained in scaffold, in periscaffold segment, and in segment (scaffold plus periscaffold segments). Information on the type of the largest balloon used during procedure was also collected. The predicted balloon diameter was obtained from the chart of postdilation balloon provided by the manufacturer using the balloon diameter and the pressure during the procedure. In addition, the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score was calculated to quantify the complexity of coronary anatomy using dedicated software available at the Website (www.syntaxscore.com) that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion and the morphological features of each single lesion.

IVUS Gray-Scale Analysis

Treated vessels after the procedure and at follow-up were examined with phased-array IVUS catheters (EagleEye, Volcano Corp, Rancho Cordova, Calif) using an automated pullback at 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, scaffold area, lumen area, intrascaffold neointimal area, and luminal area stenosis were measured with a computer-based contour detection program. The percentage of lumen area stenosis was calculated as 100 times minimal lumen area within scaffold divided by mean lumen cross-sectional area within the scaffold minus the minimal lumen area within scaffold divided by mean lumen cross-sectional area. Incomplete apposition was defined as 1 or more scaffold struts separated from the vessel wall; acquired late incomplete apposition was defined as incomplete apposition at follow-up that was not present after the procedure.

IVUS Radiofrequency Analysis

Backscattering of radiofrequency signals provides information on vessel wall tissue composition (IVUS-VH). Four tissue components (necrotic core, red; dense calcium, white; fibrous, green; and fibrofatty, light green) were identified with autoregressive classification systems and expressed as percentages (per cross section, necrotic core + dense calcium + fibrofatty + fibrous = 100%). On each cross section, polymeric scaffold struts (Figure 2) were detected as areas of apparent dense calcium and necrotic core resulting from the strong backscattering properties of the polymer. We used the change in quantitative analyses of these areas between implantation and follow-up as a surrogate assessment of the chemical and structural alterations of the polymeric struts.

Optical Coherence Tomography

As an optional investigation, intravascular OCT imaging using either time-domain OCT (M3 System, LightLab Imaging, Westford, Mass) or frequency-domain OCT (C7XR system, LightLab Imaging) was performed at baseline and at follow-up. The OCT measurements were performed with proprietary software for offline analysis (LightLab Imaging) by the core laboratory (Cardialysis, Rotterdam, the Netherlands). With adjustment for the pullback speed, the analysis of continuous cross-sections was performed at each 1-mm longitudinal interval within the treated segment.

The BVS presents important differences with respect to the 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 (Figure 3). 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 with the metallic stents (see the online-only Data Supplement). Qualitatively, the diagnosis of procedural strut fracture resulting from balloon overexpansion or late structural strut discontinuity can be established if 2 struts overhang each other in the same angular sector of the lumen perimeter, with or without malapposition, or if isolated struts are located more or less at the center of the vessel without obvious connection with other surrounding struts in 2-dimensional OCT. To confirm the diagnosis, it is helpful to perform 3-dimensional OCT reconstruction of the disrupted strut (Figure 4).

Statistical Analysis

This was a feasibility study designed to provide preliminary information on the performance improvements of the BVS 1.1 and to generate hypotheses for future pivotal randomized studies. The sample size was not defined on the basis of an end-point hypothesis but rather to provide information on device perfor-
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). For binary variables, percentages were calculated. When provided, the 95% confidence intervals were computed with the gaussian approximation, taking into account the paired analysis.

Paired comparisons between postprocedural and follow-up results were done by a Wilcoxon signed-rank test. Because no formal hypothesis testing was planned for assessing the success of the study, no statistical adjustment was applied. P values presented here are exploratory analyses only and should therefore be interpreted cautiously.

Figure 2. Gray-scale appearance (A) and radiofrequency analysis (B) after implantation and at follow-up. The echogenicity of the polymeric struts is detected as dense calcium (white) by the virtual histology program; compared with after implantation, there is no dense calcium decrease at follow-up.

Figure 3. A, Apposed or not, the optically translucent polymeric struts appear as black box-shaped cores framed by light-scattering borders that do not shadow the vessel wall. The contours of the lumen area (white line) and the contours of the scaffold area (green) are superimposed. B, At follow-up, the luminal area is delimited by the endoluminal contour of the neointima (red) growing between and on the top of the apposed struts (green); the abluminal side of the black box-shaped core is used to delineate the scaffold area (yellow); neointima hyperplasia is defined as scaffold area minus lumen area plus strut core area if all struts are apposed. See the online-only Data Supplement for instances when all struts are not apposed.
Forty-five patients were enrolled (Figure 5), and the investigational device was successfully implanted in all patients (Table 1). However, bailout stents were implanted in 3 lesions either to seal an edge dissection induced by predilatation (1 case) or by scaffold implantation (1 case) or to treat a stenotic lesion located <5 mm distal to the BVS (1 case). Myocardial enzyme release 2 times above the upper limit of normal (CK, 521 U/L with CK-MB 48 U/L) was documented in 1 patient with a transient occlusion of the treated vessel resulting from incomplete coverage of a dissection caused by predilatation.

Results

Forty-five patients were enrolled (Figure 5), and the investigational device was successfully implanted in all patients (Table 1). However, bailout stents were implanted in 3 lesions either to seal an edge dissection induced by predilatation (1 case) or by scaffold implantation (1 case) or to treat a stenotic lesion located <5 mm distal to the BVS (1 case). Myocardial enzyme release 2 times above the upper limit of normal (CK, 521 U/L with CK-MB 48 U/L) was documented in 1 patient with a transient occlusion of the treated vessel resulting from incomplete coverage of a dissection caused by predilatation.

Figure 4. A, IVUS cross section showing a small intraluminal defect at 6 o’clock that was not detected by the IVUS core laboratory. B and C, Two consecutive OCT cross sections. In panel B, at 6 o’clock, radiopaque markers with shadowing (arrow) are elongated and a covered strut reaches out from the center of the lumen. D, Three-dimensional OCT reconstruction showing the protruding strut in the lumen.
At 1 month, 1 patient presented with chest pain, sometimes at rest. Exercise-induced ischemia was documented. A recatheterization with OCT confirmed multiple signs of strut discontinuities that were previously documented after balloon postdilatation of the scaffold at implantation (nominal balloon size of 3.5 mm inflated to 16 atm with a predicted diameter of 3.96 mm). The treated lesion was then stented with a metallic everolimus-eluting stent (Xience V) despite a DS of 23%. The MLD before the reintervention was imputed as a 6-month QCA MLD.

At 6 months, 3 patients declined the angiographic follow-up. The remaining 41 patients underwent their 6-month angiographic follow-up (183 days). In 1 symptomatic (Canadian Cardiovascular Society class I) patient, control coronary angiography revealed a proximal edge stenosis (DS, 64%) that was treated with a metallic drug-eluting stent (Xience V).

**Angiographic Results**

Table 2 summarizes the results of QCA data at baseline and at follow-up. At follow-up, the intrascaffold MLD decreased from 2.32±0.28 to 2.13±0.29 mm (P<0.001). There were no significant changes in MLD at the proximal and distal edges of the scaffold. The angiographic late loss was 0.19±0.18 mm. Figure 6 shows the cumulative frequency-distribution curve of the data. In-scaffold binary restenosis was 0%, whereas 1 proximal edge restenosis was documented by angiography in a symptomatic patient (1 of 42; 2.4% in-segment binary restenosis).

**Gray-Scale IVUS**

The results of gray-scale IVUS and IVUS-VH are presented in Tables 3 and 4. At follow-up, IVUS was obtained in 37 patients. There was no significant change in vessel area, but decreases in mean scaffold area, minimal scaffold area, mean lumen area, and minimum lumen area attained significance, although the relative decreases at follow-up of these parameters were small, 2.0%, 4.6%, 3.1%, and 5.4%, respectively. On baseline IVUS, 4 patients showed ISA with respective volumes of 27.7, 2.6, 5.7, and 1.1 mm³. One ISA persisted at

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intention to Treat, n=45</th>
</tr>
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<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>65±9</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>33 (73)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (13)</td>
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<tr>
<td>Hypertension requiring medication, n (%)</td>
<td>27 (60)</td>
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<tr>
<td>Hyperlipidemia requiring medication, n (%)</td>
<td>42 (93)</td>
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<tr>
<td>Prior target vessel intervention, n (%)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>16 (36)</td>
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<tr>
<td>SYNTAX score (mean±SD)</td>
<td>2.98±2.27</td>
</tr>
<tr>
<td>Target vessel, n (%)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>17 (38)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>16 (36)</td>
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<tr>
<td>AHA/ACC lesion classification, n (%)</td>
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<tr>
<td>A</td>
<td>1 (2)</td>
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<tr>
<td>B1</td>
<td>20 (45)</td>
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<tr>
<td>B2</td>
<td>22 (50)</td>
</tr>
<tr>
<td>C</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mean reference vessel diameter, mean±SD, mm</td>
<td>2.65±0.46</td>
</tr>
<tr>
<td>MLD, mean±SD, mm</td>
<td>1.06±0.32</td>
</tr>
<tr>
<td>DS, mean±SD, %</td>
<td>60±12</td>
</tr>
<tr>
<td>Lesion length, mean±SD, mm</td>
<td>10.2±3.9</td>
</tr>
</tbody>
</table>

ACC indicates American College of Cardiology.
follow-up, and 3 ISAs resolved. At follow-up, 3 patients developed a late acquired ISA with respective volumes of 3.0, 1.7, and 1.5 mm³.

All percentage areas corresponding to the 4 tissue compositions of VH remained unchanged. In particular, the dense calcium that had been used as a surrogate marker of ultrasonic alteration of the polymeric strut did not decrease as with the first generation of BVS 1.0 (Figure 2).27,33,34

**OCT Analysis**

The representative OCT images at baseline and follow-up are presented in Figure 7. Overall, the OCT quantitative measurements confirm the absence of shrinkage of the scaffold, even at the site of minimum scaffold area (Table 5 and Figure 3). In 12 cases at baseline, the scaffold was not perfectly apposed to the vessel wall, resulting in areas of malapposition, but on average, these areas were very small. The luminal area was somewhat smaller than the scaffold area because of tissue prolapsing into the lumen. The flow area (ie, the effective lumen filled by circulating blood) is designated as the lumen area minus the strut area. This flow area has a minimal value that is the limiting factor for the blood flow. At follow-up, the neointima located between and over the struts represents a surface area of 1.25 mm². As a result, the mean luminal area, mean flow area, and minimal flow area decreased at follow-up by 16.7%, 10.3%, and 15.4%, respectively. Conversely, the luminal area stenosis increased significantly from after the procedure (19%) to the 6-month follow-up (24%). At baseline, ISA was detected in 12 of 25 investigated scaffolds with an average area of 0.19 ± 0.28 mm² (n = 12); at follow-up, it was detected in only 3 scaffolds with an average ISA area of 0.31 ± 0.26 mm² (n = 3). At follow-up, only 3.23% of struts were found uncovered.

At baseline, 3 scaffolds were suspected to present signs of strut structural discontinuity. In these patients, the predicted balloon diameter (see Methods) was 3.29, 3.4, and 3.96 mm, respectively.

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**Table 2. Paired QCA Analysis (n=42)**

<table>
<thead>
<tr>
<th></th>
<th>Proximal</th>
<th>In-Scaffold</th>
<th>Distal</th>
<th>In-Segment</th>
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<tr>
<td>Reference vessel diameter, mean±SD, mm</td>
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<td></td>
<td></td>
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<tr>
<td>After the procedure</td>
<td>2.87±0.40</td>
<td>2.76±0.38</td>
<td>2.64±0.36</td>
<td>2.72±0.40</td>
</tr>
<tr>
<td>At 180 d</td>
<td>2.72±0.36</td>
<td>2.65±0.37</td>
<td>2.53±0.38</td>
<td>2.60±0.40</td>
</tr>
<tr>
<td>P between after the procedure and follow-up</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0014</td>
</tr>
<tr>
<td>MLD, mean±SD, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After the procedure</td>
<td>2.46±0.52</td>
<td>2.32±0.28</td>
<td>2.24±0.45</td>
<td>2.09±0.37</td>
</tr>
<tr>
<td>At 180 d</td>
<td>2.38±0.49</td>
<td>2.13±0.29</td>
<td>2.15±0.38</td>
<td>1.97±0.35</td>
</tr>
<tr>
<td>P between after the procedure and follow-up</td>
<td>0.1</td>
<td>&lt;0.0001</td>
<td>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Immediate gain, mean±SD, mm</td>
<td>1.26±0.36</td>
<td></td>
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<tr>
<td>Late loss, mean±SD, mm</td>
<td>0.07±0.27</td>
<td>0.19±0.18</td>
<td>0.07±0.30</td>
<td>0.11±0.28</td>
</tr>
<tr>
<td>DS, mean±SD, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After the procedure</td>
<td>14.5±10.8</td>
<td>15.5±6.1</td>
<td>15.3±9.8</td>
<td>22.9±8.1</td>
</tr>
<tr>
<td>At 180 d</td>
<td>12.7±11.5</td>
<td>19.2±7.6</td>
<td>14.8±9.40</td>
<td>24.0±9.6</td>
</tr>
<tr>
<td>P between after the procedure and follow-up</td>
<td>0.086</td>
<td>0.0005</td>
<td>0.36</td>
<td>0.74</td>
</tr>
</tbody>
</table>

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**Figure 6.** Cumulative frequency distribution curves for late loss of BVS 1.1 (ABSORB cohort B), BVS 1.0 (ABSORB cohort A), SPÍRIT FIRST drug-eluting stent (Xience V) and SPÍRIT FIRST BMS (Multilink Vision) These data were directly compared considering the great similitude of baseline and procedural characteristics of these patients and lesions, rendering any statistical adjustments with or without propensity matching unnecessary.
patients received a metallic drug-eluting stent 33 days after the procedure. At the 6-month follow-up, structural discontinuity persisted in 2 scaffolds, and 2 new instances were diagnosed. One additional patient presented with strut discontinuity at follow-up, but baseline OCT investigation was not analyzable and the acquired or persistence of strut discontinuity could not be determined.

**Discussion**

The main findings of the study are the following: (1) the late luminal loss of 0.19 mm documented at 6 months is in the range observed with current metallic drug-eluting stents; (2) the phenomenon of stent area shrinkage previously observed with the first generation of BVS has been reduced drastically if not eliminated and, in conjunction with the growth of a small amount of neointima, results in a very modest reduction in lumen area over 6-month period; (3) the backscattering of radiofrequency signals stemming from the polymeric struts remained basically unchanged over 6 months, in contrast to the previously documented reduction of 24% in the backscattering signal with the first generation (this finding is likely related to the novel stent platform design and modified manufacturing process of the polymer that may have imparted longer-lasting mechanical integrity to the device); and (4) the observation of constancy of ultrasonic properties is largely confirmed by the absence of qualitative alterations of the appearance of the polymeric struts with OCT (strut core area). They uniformly kept their “preserved box” appearance. Strut appearance such as an open box, a dissolved bright box, or a black box was not observed at 6 months, at variance with that observed in the first-generation BVS 1.0. Quantitatively, the strut core area remained unchanged at 6 months. These observations suggest that the mechanical integrity of this new generation is longer lasting, thereby able to prevent any substantial scaffold shrinkage in the first 6 months of its implantation.

**Clinical Assessment**

The first-in-human ABSORB cohort A study was conducted in early 2006, before the publication of the Academic Research Consortium definitions, and the protocol definitions in this first trial were also applied in the ABSORB cohort B. In keeping with this, it must be emphasized that the enzyme release and reintervention of the patient with scaffold disruption after postdilatation would nowadays be adjudicated, according to the Academic Research Consortium definition, as non-Q-wave myocardial infarction (positive troponin in the absence of CK-MB) and ischemic-driven target lesion revascularization (nonscheduled angiography followed by target lesion revascularization). In the future, randomized trials will have to adopt contemporary event definitions.

**Angiographic Analysis of In-Scaffold Late Loss**

The late loss analysis has been performed on an intention-to-treat basis. It includes 3 cases of metallic bailout stenting at the edge of the scaffold, for which the analysis reports only the segment of the scaffold not overlapping with the metallic stent. Also included in the analysis are 2 patients who underwent reintervention, 1 at 1 month because of chest pain

### Table 3. IVUS Results: Paired Gray-Scale IVUS Measurements per Lesion, Intention to Treat (n=37)

<table>
<thead>
<tr>
<th></th>
<th>Post PCI (Mean±SD)</th>
<th>At 180 d (Mean±SD)</th>
<th>Difference (95% CI) Based on Individual Data, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel area, mm²</td>
<td>14.22±3.75</td>
<td>14.49±3.67</td>
<td>2.4±7.4 (–0.08–4.87)</td>
<td>0.06</td>
</tr>
<tr>
<td>Scaffold area, mm²</td>
<td>6.58±1.17</td>
<td>6.44±1.11</td>
<td>−2.0±4.8 (–3.56–0.34)</td>
<td>0.015</td>
</tr>
<tr>
<td>Minimum scaffold area, mm²</td>
<td>5.51±1.02</td>
<td>5.24±0.93</td>
<td>−4.6±7.4 (–7.05–2.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neointimal hyperplasia area, mm²</td>
<td>...</td>
<td>0.08±0.13</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean lumen area, mm²</td>
<td>6.60±1.22</td>
<td>6.37±1.12</td>
<td>−3.1±7.0 (–5.45–0.75)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Minimum lumen area, mm²</td>
<td>5.49±1.03</td>
<td>5.17±0.97</td>
<td>−5.4±8.7 (–8.29–2.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen area stenosis, %</td>
<td>16.8±4.8</td>
<td>18.7±7.5</td>
<td>14.6±40.4 (1.09–28.04)</td>
<td>0.24</td>
</tr>
<tr>
<td>In-scaffold area obstruction, %</td>
<td>...</td>
<td>1.2±2.1</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

### Table 4. IVUS Results: Paired Virtual-Histology IVUS Measurements per Lesion, Intention to Treat (n=32)

<table>
<thead>
<tr>
<th>IVUS virtual histology*</th>
<th>Median, IQR</th>
<th>Median IQR</th>
<th>Difference, Median (95% CI), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense calcium area, %</td>
<td>30.8 (22.3–36.9)</td>
<td>29.7 (22.3–36.1)</td>
<td>−5.8 (–14.5–23.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Necrotic core area, %</td>
<td>30.8 (25.9–35.7)</td>
<td>32.3 (24.4–34.9)</td>
<td>−2.1 (–5.7–14.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Fibrous area, %</td>
<td>33.2 (54.7–47.1)</td>
<td>36.6 (28.1–43.1)</td>
<td>5.6 (–8.5–38.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Fibrofatty area, %</td>
<td>2.1 (0.6–3.6)</td>
<td>2.5 (1.8–4.7)</td>
<td>73.4 (–12.6–146.1)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Because values are not normally distributed, data on percentage tissue composition (VH) are shown as median with interquartile range.
associated with scaffold structural discontinuity diagnosed by OCT. Noteworthy, the decision to reintervene in that case was not made on angiography (DS, 23%; late loss, 0.23 mm) but on OCT, possibly heralding a new era of oculo-OCT reflex. The other reintervention at 6 months was performed to treat a proximal edge restenosis (DS, 64%; proximal segment late loss, 1.06 mm) possibly caused by the acute mechanical trauma of an Amplatz left guiding catheter engaged half-way in the midsegment of the right coronary artery during an attempt to perform postprocedural IVUS. In the per-treatment analysis (n=36), the in-stent late loss was 0.19±0.17 mm.

**IVUS Analysis of Late Recoil**

The 20-MHz IVUS catheter is not a sheath-based pullback system, and the mechanical pullback of the IVUS catheter itself (0.5 mm/s) can be impeded by calcium or tortuosity, so the measurement of the scaffold length is not always reliable. Therefore, we reported our IVUS measurements in area units and not in volume (area times length) units.

Conversely, the OCT device is a sheath-based technology with a high pullback speed (20 mm/s), providing extremely reliable measurements of device length. Both extremities of the scaffold are made visible on OCT by two 37-μm-diameter platinum markers at each end. However, for reasons of comparability, we also reported the OCT measurements in area units.

Although the term late recoil has been used frequently in interventional cardiology to describe the constrictive remodeling of the external elastic membrane area, in the present case, it relates more specifically to the area reduction of the
treated segment, a phenomenon not previously observed in metallic stents. Attributed to the early alteration of the mechanical integrity of the scaffold, this phenomenon can be controlled by polymer processing. Late loss measurement by QCA, scaffold area assessment by gray-scale IVUS, and OCT all confirm the almost complete disappearance of this phenomenon. The VH examination of the BVS 1.0 over 6 months showed a reduction of 24% in percentage dense calcium and necrotic core, whereas these imaging variables remained unchanged over the same period of time with the BVS 1.1. The absence of change in radiofrequency backscattering, the uniform persistence of the preserved box appearance on OCT, and the unchanged surface area of the strut core area are imaging testimony to the low level of alteration of polymeric struts that could explain the new resilient mechanical integrity of the BVS 1.1 at 6 months.

On gray-scale IVUS, the intrascaffold neointima is conventionally measured from endoluminal leading edges of echogenic struts and is minimal (0.07 mm²) in the present analysis. In comparison, the intrascaffold neointima area of the first generation of BVS 1.0 was 0.3 mm² at 6 months. An increase in echogenic brightness of BVS 1.1 versus BVS 1.0 has been documented (data not shown), and this overblooming effect may interfere with the measurement of intrascaffold neointima, underestimating its amount.

The microscopic measurement (20-μm lateral resolution) of the intrascaffold neointima with OCT is based on a totally different methodological approach (see the online-only Data Supplement) that used the abluminal side of the translucent struts as the boundary for the scaffold area. The intrascaffold neointima measured between and on top of the struts has an area of 1.25 mm². This measurement method has been validated in a porcine model by comparing OCT and histomorphometric measurement at 2 years after implantation.

OCT Findings
At follow-up, 3 new instances of structural discontinuity of struts were detected by the OCT core laboratory, whereas the IVUS core laboratory did not report any abnormalities (Figure 4). The discordance between the IVUS and OCT observations emphasizes the fact that we have entered a new era of microscopic (20 μm with OCT versus 200 μm with IVUS) scrutiny in clinical trials. The morphological appearance of the polymeric struts on OCT (preserved black box) remained remarkably unchanged at 6 months, whereas with the BVS 1.0, we saw at 6 months only 3% of preserved box versus 30% of open box, 50% of dissolved bright box, and 18% of dissolved black box. Coronary OCT in vivo in Yorkshire swine euthanized 28 days after implantation has shown that 82% of struts showed a preserved box appearance, but at that time point, histology and gel permeation chromatography demonstrated preserved scaffold integrity with a moderate loss of molecular weight of the polymer. In vivo coronary OCT in Yukatan miniswine euthanized 2 years after implantation continued to show 80.4% of preserved box appearance. However, at that point, gel permeation chromatography barely detected PLLA in the strut voids, now filled with hyaline material as demonstrated by Alcian Blue staining. Not only did the OCT appearance of the struts not change qualitatively, but the strut core area also remained quantitatively unchanged. The 1- and 2-year assessments of the patients included in ABSORB cohort B will further elucidate the optical and ultrasonic long-term outcome of the polymeric struts.

Limitations
This first-in-humans trial provides a seminal observation on a small number of patients with a short duration of follow-up. One of the clinical investigations (OCT) was optional and performed only by centers selected for their expertise in intravascular imaging. However, the OCT results confirm the results obtained with IVUS (mandatory investigation) in this trial.

Conclusions
The promising results at 6 months of this second-generation bioresorbable drug-eluting scaffold (BVS 1.1) constitute...
proof of concept that this device can adequately revascularize coronary vessels and prevent restenosis. Considering the favorable outcomes of the first generation (BVS 1.0) at 2 years, it is deemed appropriate and timely to initiate a randomized pivotal trial comparing a metallic drug-eluting stent with this drug-eluting bioabsorbable vascular scaffold.

Source of Funding

This study was sponsored by Abbott Vascular.

Disclosures

C. Dorange, S. Veldhod, Dr Miquel Hebert, and Dr Rapoza are employees of Abbott Vascular. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE

The first generation of the bioresorbable everolimus drug-eluting vascular scaffold showed signs of shrinkage at 6 months, which largely contributed to late luminal loss. To maintain the mechanical integrity of the device up to 6 months, the scaffold design and manufacturing process of its polymer were modified. Forty-five patients successfully received a second-generation bioresorbable everolimus drug-eluting vascular scaffold. One patient had postprocedural release of myocardial enzyme without Q-wave occurrence; 1 patient was treated 1 month later with a metallic drug-eluting stent. At the 6-month follow-up, quantitative coronary angiography disclosed 1 edge restenosis (in-segment binary restenosis, 2.4%). The backscattering of the polymeric struts did not decrease over time; the scaffold area was reduced by only 2.0% with intravascular ultrasound, and no change was noted with optical coherence tomography. The late lumen loss amounted to 0.19±0.18 mm with a limited relative decrease in minimal luminal area of 5.4% on intravascular ultrasound. Optical coherence tomography showed at follow-up that 96.8% of the struts were covered and that malapposition was detected at follow-up in only 3 scaffolds. Mean neointimal growth measured by optical coherence tomography between and on top of the polymeric struts equaled 1.25 mm², or 16.6% of the scaffold area. A modified manufacturing process of the polymer and geometric changes in the polymeric platform have substantially improved the medium-term performance of the new generation of drug-eluting scaffold, making it comparable to that of current drug-eluting stents. The results constitute proof of concept that this device can adequately revascularize coronary vessels and prevent restenosis.
Evaluation of the Second Generation of a Bioresorbable Everolimus Drug-Eluting Vascular Scaffold for Treatment of De Novo Coronary Artery Stenosis: Six-Month Clinical and Imaging Outcomes


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Supplemental Material

Supplemental Methods

OCT analysis

At baseline, the strut area is imaged as a central black core and a light-scattering frame border. However, at follow-up, embedding, coverage and thickening of the frame borders, with apparent reduction of the central core render the analysis of the struts more complex. In this case, the strut (core) area is defined only by its black core, since the light-scattering frame is no longer distinguishable from surrounding tissue (figure 1 panel B).

The lumen and scaffold contours are obtained with a semi-automated detection algorithm available in the LightLab proprietary software and additional manual corrections are performed if necessary. At baseline, since the polymeric struts are translucent, the vessel wall lumen area can be imaged and delineated at the back (abluminal) side of the struts (figure 1, panel A). At follow-up, the luminal area is drawn by semi-automatic detection, following the endoluminal contour of the neointima between and on top of the apposed struts (Figure 1 Panel B). In case of malapposed struts, the analyst uses the endoluminal contour of the vessel wall behind the malapposed struts. (Figure 2)

At baseline, the scaffold area is measured by joining the middle point of the black core abluminal side of the apposed struts, or the abluminal edge of the frame borders of malapposed struts (Figure 1 panel A). The scaffold area is identical to the lumen area in the absence of ISA and prolapse. At follow-up, the back (abluminal) side of the central black core has been used to delimit the scaffold area. An alternative method of drawing the contour of the scaffold area by joining central points of the
strut cores yielded, in a subset of 12 patients studied with C7, similar changes in scaffold area from baseline to 6 months (data not shown).

Moreover, three different situations deserve special consideration. First, incomplete strut apposition is defined as a clear separation between the back (abluminal) side of the strut and the vessel wall. In case of malaposed struts, incomplete strut apposition (ISA) area is delineated by the abluminal-side of the frame border of the malapposed strut (covered or uncovered) and the endoluminal contour of the vessel wall (Figure 2 panel A). Second, in a case of prolapse protruding between struts into the lumen at baseline, the prolapse area can be estimated between the prolapsed contour (lumen contour) and the scaffold area. Third, an intraluminal defect free from the vessel wall (e.g. thrombus) is also quantified as an area.

According to these findings the flow area was defined as: (Scaffold area + ISA area) – (intraluminal strut areas + prolapse area + intraluminal defect) (Figure 2 panel C).

At follow-up when the struts are apposed, neointima grew between and on the top of the struts as demonstrated in our porcine model. To mimic these histomorphometric changes seen in the preclinical model, we attempted to measure these areas in our patients. Neointimal hyperplasia area was defined as (Scaffold area – [Lumen area + Black box area]) if all struts were apposed (Figure 1 Panel B), while it was calculated as ([(Scaffold area +ISA area + Malapposed strut with surrounding tissues) – [Lumen area + strut area]]) in case of malapposed struts (Figure 2 Panel C).

The thickness of the coverage was measured in every strut between the abluminal site of the strut core and the lumen. Since the strut thickness is 150 µm, the strut was considered as covered whenever the thickness of the coverage was above this threshold value. This method may slightly underestimate the thickness of the
coverage since it does not take into account changes in the size of the strut core over time. Consequently the percentage of uncovered struts may be slightly overestimated.
**Supplementary figure legends**

**Figure 1.** Panel A: Apposed or not, the optically translucent polymeric struts appear as black box-shaped cores framed by light-scattering borders that do not shadow the vessel wall. The contours of the lumen area (white line) and the contour of the scaffold area (green) are superimposed. Panel B: At follow-up, the luminal area is delimited by the endoluminal contour of the neointima (red) growing between and on the top of the apposed struts (green); the abluminal side of the black box-shaped core is used to delineate the scaffold area (yellow); neointima hyperplasia is defined as scaffold area- (lumen area + strut core area) if all struts are apposed.

**Figure 2** An OCT crosssection at follow-up showing one malapposed but covered strut at 8’oclock (A). In Panel B, the line A delineates the scaffold area, whereas the line B the luminal area. Strut core contours are superimposed on the illustration. In panel C, the red area depicts the neointimal growth between and around the struts apposed or non-apposed, and the blue area is the so-called flow area. On the consecutive frames (panel D), the malapposed strut seen on panel A becomes incorporated in the vessel wall and is surrounded by neointima.