A Polylactide Bioresorbable Scaffold Eluting Everolimus for Treatment of Coronary Stenosis
5-Year Follow-Up

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ABSTRACT

BACKGROUND Long-term benefits of coronary stenosis treatment with an everolimus-eluting bioresorbable scaffold are unknown.

OBJECTIVES This study sought to evaluate clinical and imaging outcomes 5 years after bioresorbable scaffold implantation.

METHODS In the ABSORB multicenter, single-arm trial, 45 (B1) and 56 patients (B2) underwent coronary angiography, intravascular ultrasound (IVUS), and optical coherence tomography (OCT) at different times. At 5 years, 53 patients without target lesion revascularization underwent final imaging.

RESULTS Between 6 months/1 year and 5 years, angiographic luminal late loss remained unchanged (B1: 0.14 ± 0.19 mm vs. 0.13 ± 0.33 mm; p = 0.7953; B2: 0.23 ± 0.28 mm vs. 0.18 ± 0.32 mm; p = 0.5685). When patients with a target lesion revascularization were included, luminal late loss was 0.15 ± 0.20 mm versus 0.15 ± 0.24 mm (p = 0.8275) for B1 and 0.30 ± 0.37 mm versus 0.32 ± 0.48 mm (p = 0.8204) for B2. At 5 years, in-scaffold and segment binary restenosis was 7.8% (5 of 64) and 12.5% (8 of 64). On IVUS, the minimum lumen area of B1 decreased from 5.23 ± 0.97 mm² at 6 months to 4.89 ± 1.81 mm² at 5 years (p = 0.04), but remained unchanged in B2 (4.95 ± 0.91 mm² at 1 year to 4.84 ± 1.28 mm² at 5 years; p = 0.5). At 5 years, struts were no longer discernable by OCT and IVUS. On OCT, the minimum lumen area in B1 decreased from 4.51 ± 1.28 mm² at 6 months to 3.65 ± 1.39 mm² at 5 years (p = 0.01), but remained unchanged in B2, 4.35 ± 1.09 mm² at 1 year and 4.12 ± 1.38 mm² at 5 years (p = 0.24). Overall, the 5-year major adverse cardiac event rate was 11.0%, without any scaffold thrombosis.

CONCLUSIONS At 5 years, bioresorbable scaffold implantation in a simple stenotic lesion resulted in stable lumen dimensions and low restenosis and major adverse cardiac event rates. (ABSORB Clinical Investigation, Cohort B [ABSORB B]; NCT00856856) (J Am Coll Cardiol 2016;67:766–76) © 2016 by the American College of Cardiology Foundation.
Bioresorbable scaffolds are novel treatments for coronary stenosis that provide transient vessel support with drug-delivery capability, but without the long-term limitations of metallic drug-eluting stents. By liberating the coronary artery from the metallic caging, the vessel is able to recover pulsatility and to remodel in response to shear and wall stress, physiological cyclic strain, and pharmacological agents (1,2).

Nevertheless, biosorbable scaffolds face multiple potential challenges that justify careful and long-term evaluation of this novel technology. First, the polymeric scaffolds have to match the mechanical properties of metallic stents. It has been demonstrated that the acute recoil of the novel scaffold was not inferior to that observed with an equivalent metallic device (3,4). Second, it has been established that mechanical integrity and the absence of recoil were maintained over a 6-month period (4). During that time, the biological process of restenosis, consisting of neointimal formation and constrictive remodeling, ceases, and therefore, the implantation of a permanent metallic prosthesis seems unjustified (5,6). In the following months, physiological and pharmacological vasomotion reappear, confirming that the scaffold has lost its mechanical integrity (7). The polymer is then progressively replaced by a malleable provisional matrix of proteoglycan, which does not impart any loss in scaffold area (8). On the contrary, at that stage, the malleable and dismantling scaffold can enlarge to accommodate the neointimal growth observed in the first 3 years. The ultimate integration of the scaffold into the vessel wall results from the de novo ingrowth of connective tissue into the proteoglycan matrix (9,10).

Rarely has a novel revascularization technique been so intensively scrutinized during the early days of its development, and the sequential assessment over 5 years provides new observations that have paved the way to large randomized trials (11). The ultimate expectation of this novel technology is the maintenance of the lumen area, or even occurrence of late lumen enlargement, associated with wall thinning and adaptive remodeling (2).

METHODS

The Absorb biosorbable vascular scaffold (BVS) device (Abbott Vascular, Santa Clara, California) was tested in 101 patients of the ABSORB Cohort B study, which was subdivided into 2 subgroups of patients: the first group (B1) underwent invasive imaging with quantitative coronary angiography, intravascular ultrasound (IVUS) grayscale, and optical coherence tomography (OCT) at 6, 24, and 60 months, whereas the second group (B2) underwent invasive imaging at 12, 36, and 60 months. The purpose of the present report is to describe the multimodality imaging performed post-procedure and at 6, 12, 24, 36, and 60 months, and to report the clinical follow-up of the entire cohort of patients at 60 months, in an attempt to anticipate the long-term results of the recently-started large randomized investigation device exemption trials of the Food and Drug Administration, which are conducted for commercial approval in the United States.

STUDY POPULATION AND IMAGING ANALYSIS. The study population, device, procedure, and definitions were previously described (4,9,10) (Online Tables 1 and 2). An independent core laboratory analyzed angiographic assessment, vasomotion test, IVUS grayscale, echogenicity, IVUS-based radiofrequency backscattering, and OCT, and their methodology has been extensively described (12). OCT, in the early days of its clinical use, was not available in each investigating center. A protocol amendment was planned to allow an imaging follow-up to take place at 60 months. All patients were requested to sign this additional informed consent. However, the national regulatory bodies in France and Germany did not agree with the implementation of this amendment.

STATISTICAL ANALYSIS. For binary variables, counts and percentages are presented. For continuous variables, mean ± SD are presented unless otherwise specified. For comparisons, the Student t
test was used as appropriate. Overall, the Friedman test was applied for comparison of serial imaging measurements. Pairwise comparisons between post-procedure and follow-up were performed by a Wilcoxon signed rank test, adjusted by the Bonferroni method. For imaging assessment, serial analysis, including pre-target lesion revascularization (TLR) assessment, is presented in the figures and in Online Table 3. To assess changes of imaging variables over time, the 2 cohorts (B1 and B2) were pooled for analysis of longitudinal repeated measurements with 6 time points (post-procedure and at 6, 12, 24, 36, and 60 months), using a linear mixed-effect model. The results are presented in Online Table 4.

No formal hypothesis testing was planned. The p values presented are exploratory analyses only, and should therefore be interpreted cautiously. The analysis was performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

CLINICAL OUTCOMES. A total of 101 patients were enrolled in this study from March 19, 2009, to November 6, 2009. Baseline characteristics are

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**TABLE 1** Nonhierarchical and Hierarchical Count of Clinical Events Over 5 Years (n = 101)

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<thead>
<tr>
<th>Event Type</th>
<th>30 Days (n = 101)</th>
<th>1 Yr (n = 101)</th>
<th>2 Yrs (n = 100)</th>
<th>3 Yrs (n = 100)</th>
<th>4 Yrs (n = 99)</th>
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Hierarchical

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</table>

Values are % (n). *1 patient lost to follow-up at 2-year follow-up (permanently missed); 11 patient missed the 4-year follow-up, but returned for the 5-year follow-up. †1 patient experienced 2 non-TVRs on days 52 and 1,014. CABG = coronary artery bypass graft; ID = ischemia driven; MACE = major adverse cardiac event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization.

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**FIGURE 1** Flow Chart of 5-Year Angiographic Follow-Up

- n=101, L=102
- 6M/12M angio (n=96/L=97)
- 24M/36M angio** (n=77, L=78)
- 60M angio*** (n=50, L=51)

*Including one patient who experienced TLR at 13 months.

**Additionally one patient (without TLR) who missed the first and 5-year follow-up but underwent 24/36 month angiography was included for the angiographic report.

***Additionally 3 patients (without TLR) who missed one earlier follow-up but underwent 5 year angio were included for the report.

angio = angiography; FUP = follow-up; ID = Ischemia driven; L = lesions; M = months; TLR = target lesion revascularization.
presented in Online Tables 1 and 2. The investigational device (Absorb BVS) was successfully implanted in all patients. Additional metallic drug-eluting stents were implanted in 3 lesions to treat a suboptimal result distal to the target lesion. Clinical follow-up at 5 years was available in all but 1 patient with Alzheimer disease, who withdrew consent after the 2-year follow-up. However, the vital status of
this patient was available through the referring physician, who confirmed the patient’s death 3 years after implantation. During the 5-year follow-up period, there were no cardiac deaths or probable or definite scaffold thromboses (13). By 5 years, there were 3 noncardiac deaths, all due to cancer. There were 2 periprocedural non-Q-wave myocardial infarctions, 1 non-Q-wave myocardial infarction related to a follow-up imaging procedure, and 8 ischemia-driven (ID) TLR events, which resulted in a 5-year major adverse cardiac event (MACE) rate of 11%. At 5 years, there were a total of 12 TLR events in 11 patients. Four TLRs were adjudicated as non-ID and were reported in previous publications (4,9,10,14). A total of 8 patients had ID-TLR, 7 within the first 3 years of follow-up. Between 3 and 5 years follow-up, there were no ID-TLR events. However, at the time of the planned 5-year follow-up, 1 symptomatic patient with an in-scaffold 56% diameter stenosis and a fractional flow reserve of 0.71 underwent a revascularization that was adjudicated as ID-TLR (Table 1). Dual antiplatelet therapy was maintained in 98% (99 of 101), 81% (82 of 101), 23% (23 of 100), 11% (11 of 97) and 7% (7 of 95) of the patients at 6, 12, 24, 36, and 60 months, respectively (Online Figure 1).

**QCA AT 6, 12, 24, 36, AND 60 MONTHS.** The flow chart in Figure 1 indicates at which time point the patients either refused the invasive follow-up or underwent TLR for clinical reasons.

There were no differences between the group of patients with serial angiography (n = 53) and the other group (n = 48) in baseline demographic or lesion characteristics, with the exception of a lower incidence of patients presenting initially with unstable angina in the group with serial angiographic follow-up (7.5% vs. 22.9%, p = 0.03; Online Table 2).
Figures 2A and 2B describe sequential changes in in-scaffold minimum lumen diameter (MLD) and late lumen loss (LLL) in B1 and B2 (panel A includes pre-TLR measurements, panel B excludes pre-TLR measurements). When all available angiographic data at 5 years were pooled, the LLL was 0.26 ± 0.42 mm (n = 63) and the MLD was 2.02 ± 0.45 mm (n = 64). The in-scaffold and in-segment binary restenosis rates were 7.8% (5 of 64) and 12.5% (8 of 64), respectively.

**VASOMOTION REACTION TO NITRATE.** The vasomotion test, using either ergonovine or acetylcholine, was performed at 6 and 12 months. Subsequently, at 2, 3, and 5 years, the vasomotion test was performed using intracoronary injection of nitrate. Figure 2F shows the relative changes of mean lumen diameter in the scaffold and in the 5-mm segments proximal and distal to the device. In 52 patients with 53 lesions without TLR that were analyzable for vasomotion, the scaffold MLD measured prior to and following intracoronary injection of nitrate showed, on average, a significant increase from 2.49 ± 0.37 mm to 2.56 ± 0.35 mm (p < 0.001).

**IVUS POST-PROCEDURE AT 6, 12, 24, 36, AND 60 MONTHS.** Between 6 and 60 months of follow-up, there were 21 (B1) and 30 (B2) serial IVUS measurements, including 3 cases in which IVUS was performed prior to a TLR event. These values were carried forward to the later follow-up time points (Figure 2C).

Because the polymeric struts are no longer discernable at 60 months, strut-level analyses, such as malapposition and assessment of the scaffold area, were no longer possible. Between post-procedure and the first 6 and 12 months of observation, the minimum lumen area decreased (−6.16%; p = 0.015, and −1.36%; p = 0.6021) and the plaque media increased significantly in both B1 and B2 (+9.66%; p = 0.014 and +8.51%; p = 0.0095).

In cohort B1, after 6 months, there was an increase in mean lumen area that became significant between 6 and 24 months (+9.66%; p = 0.015), as well as between 6 and 60 months for the entire cohort (+11.51%; p = 0.02). Despite this increase in mean lumen area, there was a modest but significant decrease in the minimum lumen area between 6 and 60 months for B1 (−7.56%; p = 0.044) and between 24 and 60 months for B2 (−9.90%; p = 0.036). In terms of total plaque area, there was a highly significant decrease between 24 and 60 months (−9.86%; p = 0.0005), accompanied by a decrease (p = NS) in mean vessel area (−4.51%) (Figure 3).

In Cohort B2, the minimum lumen area remained stable after 12 months. The mean lumen area increased significantly between 12 and 36 months (+5.56%; p = 0.003), and the total plaque area decreased between 12 and 36 months (−1.69%; p = 0.051) and between 36 and 60 months (−10.01%; p = 0.0001), which was accompanied by a significant decrease in mean vessel area (−7.00%; p = 0.0003) (Figure 2C).

**IVUS ECHOCENICITY AT 6, 12, 24, 36, AND 60 MONTHS.** Changes in hyper- and upper-echogenicity area over time, as a surrogate of biodegradation of the polymeric weight, are presented in Figure 2E.
5-Year Imaging Outcomes of Bioresorbable Scaffold: Long-Term Vessel Healing After Implantation of a BVS Scaffold in a Stenosed Coronary Artery


Continued on the next page
Approximately 50% of the reduction in hyper- and upper-echogenicity area was observed at 36 months, followed by a further 25% reduction between 36 and 60 months. The remaining 25% must correspond to permanent native dense calcium.

**OCT Post-Procedural at 6, 12, 24, 36, and 60 Months.** At the onset of the trial, the OCT investigation was not available in every investigational center. Between 6 and 60 months follow-up, there were 13 (B1) and 16 (B2) serial OCT measurements. On OCT, the struts were no longer discernable at 60 months (Figure 3); thus, eventually only lumen area could be measured.

In Cohort B1, there were significant decreases in mean and minimum lumen area from baseline to 24 months (−15.01%; p = 0.008, and −26.98%; p = 0.001, respectively), but there were no further changes in mean and minimum lumen area between 24 and 60 months (+3.97%; p = 0.305, and −9.89%; p = 0.339). Similarly, in Cohort B2, the mean and minimum lumen area decreased significantly in the first 12 months of follow-up by −20.78% (p = 0.001) and −28.09% (p < 0.0001), respectively. Changes from 12 to 60 months were minimal and nonsignificant (−0.30%; p = 1.00, and −5.60%; p = 0.244) (Figure 2D).

**Discussion**

The main findings of the study are the following:

1. The MACE rate at 60 months was 11.0%, with no definite/probable scaffold thrombosis.
2. Angiographic LLL remained unchanged between 6 to 12 months and 60 months, with in-scaffold and segment rates of binary restenosis of 7.8% and 12.5%, respectively. During the vasomotion test, 85% of the scaffold segments showed vasodilatation, with values ranging from 0.07% to 9.49%.
3. On IVUS, the total plaque media decreased in both groups from 6 to 12 months to 60 months (p = 0.023 and p < 0.0001). The struts were no longer visible at 60 months. The decrease in plaque media was accompanied by a decrease in the mean vessel area as a result of adaptive constrictive remodeling. The mean lumen area tended to increase from 6 to 12 months to 60 months for the entire cohort, whereas the minimum lumen area tended to decrease between 24 and 36 months and 60 months (p = 0.036 [B1] and p = 0.129 [B2]).
4. In quantitative OCT analysis, both the mean and the minimum lumen area remained unchanged after the first 12 or 24 months.
5. Echogenicity showed a 50% decrease over the first 36 months, and an additional 25% reduction between 36 and 60 months of follow-up.

This first-in-man study was not designed to detect any differences in clinical outcomes. However, a flattening of the Kaplan-Meier curve was noticed between 36 and 60 months. A previous post hoc comparison with 227 patients selected from the First (A Clinical Evaluation of an Investigational Device, The Abbott XIENCE V® Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions), II (A Clinical Evaluation of the XIENCE V® Everolimus Eluting Coronary Stent System), and III (A Clinical Evaluation of the Investigational Device XIENCE V® Everolimus Eluting Coronary Stent System (EECSS) in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) trials on the basis of a single implanted device with identical length and diameter (3.0 × 18 mm) has shown MACE rates of 11.4% (XIENCE [Abbott®]) and 9.9% (Absorb) at 3-year follow-up (14). The 60-month follow-up of this population showed MACE rates of 14.3% and 11.0%, respectively (Figure 4), a difference that we could not anticipate or predict at the time of the study.
the 36-month follow-up. Formal propensity analysis was attempted, including more complex patients and lesions from the SPIRIT trials (IV and V), but the statistical matching appears to not be statistically sound.

In terms of angiographic follow-up, it must be emphasized that the overall loss at 60 months, including the patients with TLR, amounts to 0.26 ± 0.42 mm in 63 of 101 patients recruited; it is tempting to compare that value to the 0.33 ± 0.37 mm LL of XIENCE at 24 months in 83 patients in the SPIRIT II trial, which recruited 227 patients (15).

The fact that the vasomotion observed at 5 years is comparable, or even slightly superior, to the vasomotion observed at 3 years indicates that the scaffolded vessel has maintained its vasomotoric capacity in more than 80% of cases (14,16). The return of vasomotion, restoration of physiological shear stress distribution, and cyclic strain associated with vasomotoric capacity should contribute to the mechanotransduction phenomenon that is responsible for the vessel wall metabolism of the metalloproteinase that play a major role in progression and regression of coronary plaque (17). In contrast, metallic caging of the vessel dramatically interferes with cyclic strain and shear stress of the vessel, and seems to be implicated in the neointimal tissue observed in first-, second-, and even third-generation drug-eluting stents (18).

On IVUS, the most striking observations are the decrease in plaque media together with adaptive, constrictive remodeling of the vessel area (Central Illustration). In the absence of local detection of any inflammatory biomarkers (such as metalloproteinases or cytokines) that would account for positive or negative biological remodeling, it is difficult to allude to atherosclerotic progression and/or regression. The stability of the lumen dimensions over a 5-year period may presage better clinical long-term follow-up (19). In this context, plaque media reduction has been documented, mainly over 3 and 5 years. Currently, it is unknown whether this plaque reduction is a true regression phenomenon or pseudoregression due to disappearance of the polymeric material, which is ultimately replaced by connective tissues affected in the long term by shrinking, or even breakdown, of neointimal tissue. However, the most plausible explanation for these changes is the implantation of the polymeric material followed by its mass loss (20).

The second observation is related to the difference in behavior of the mean and the minimum lumen areas. The minimum lumen area is in the most diseased part of the vessel (maximal plaque burden, presence of calcium, eccentricity, negative remodeling, among others) and would benefit most from additional preparation of the stenotic lesion (e.g., dilation by noncompliant balloon at high pressure, Rotablator, or cutting balloon at the time of implantation). In contrast, the surrounding, less-diseased vessel wall could be more prone to pharmacological and physiological interactions favoring late lumen enlargement. In the OCT measurements, both the mean and the minimum lumen areas showed no significant changes after the first 12 or 24 months. This absence of change over time (3 or 4 years) is extremely reassuring, considering the high resolution of this imaging technology (10 to 20 microns). Of note, the core laboratory did not detect any struts or vessel wall abnormalities.

There are some differences in the sequential and temporal changes in the IVUS and OCT area measurements between cohorts B1 and B2, which may raise questions about potential heterogeneity of the 2 patient groups. The small number of patients precludes formal multivariable analysis, but, in a univariable approach, it appears that cohort B1 was, on average, 5 years younger, had less hyperlipidemia requiring medication, and had fewer prior myocardial infarctions. In terms of quantitative angiography, there was no difference between the 2 groups, but in the American Heart Association/American College of Cardiology lesion classification, there was a trend for less complex lesions in cohort B2 (Online Appendix).

In 2013 and 2014, worldwide recruitment of numerous patients to large randomized trials comparing metallic drug-eluting stents and the Absorb bioresorbable scaffold was completed. Initial 1-year results of the ABSORB II trial confirmed that superiority cannot be demonstrated in the short term, and that the time needed to observe superior additional advantages of this new technology necessitates longer periods of clinical observation. In the meantime, it was of paramount importance to continue to use invasive imaging to investigate the patients included in the seminal observations 5 years ago. This represents the key safety and efficacy findings provided by the present study. The reassuring data observed over these 5 years of follow-up, albeit in simple lesions, allows us to have confidence in the long-term results of the ongoing randomized trials.

**STUDY LIMITATIONS.** The fact that the bioresorption process was still visible at 3 years using multimodality imaging prompted a protocol amendment for an additional invasive imaging follow-up at 60 months. As mentioned previously, in France and Germany, Ethics Committee and Competent Authority approvals for this amendment were not granted. In addition, patients were required to give a new informed consent. Nonavailability of invasive imaging in approximately 50% of patients may have had
an effect on our findings, although we have incorporated the quantitative measurements obtained prior to any TLR into our statistical analysis. The absence of symptoms and events in the population without further invasive investigation suggests maintenance of the early benefits of the treatment. In the angiographic analysis, however, pre-TLR minimum lumen diameter (therefore, the worst MLD) was measured in all event cases, and these values were carried forward to the later time points. Therefore, the MLD data derived from the current analysis may represent the worst-case scenario. Last, the current study, with a small number of patients, was, by design, unpowered to detect changes in the imaging endpoints from baselines to follow-up.

CONCLUSIONS

Five years ago, this first-in-man study aimed to demonstrate feasibility and safety as well as to understand, with multimodality imaging, the biological reaction of the vessel wall following the implantation of a bioresorbable scaffold. The current study confirms the long-term safety of the Absorb scaffold for treatment of relatively simple coronary artery stenosis, with demonstration of stable lumen dimensions from the mid- to long-term by invasive imaging. The results of this first-in-man study, although limited in the number of clinical observations, set an encouraging precedent for the long-term results of the ABSORB III and other ongoing trials.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a relatively small initial series, implantation of everolimus-eluting bioresorbable scaffolds in patients with morphologically simple stenotic coronary lesions yielded low rates of restenosis and MACE at 5 years.

TRANSLATIONAL OUTLOOK: Large-scale randomized trials are needed to confirm whether bioresorbable scaffolds offer clinical advantages compared with conventional stent devices in patients with stenotic coronary atherosclerotic lesions.

REFERENCES


**KEY WORDS** angiography, coronary artery disease, follow-up studies, intravascular imaging, long-term, tomography, optical coherence

**APPENDIX** For supplemental tables and figure, please see the online version of this article.