

Coronary Artery Vessel Healing Pattern, Short and Long Term, After Implantation of the Everolimus-Eluting Bioresorbable Vascular Scaffold

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Background—Although the Absorb bioresorbable vascular scaffold is increasingly used in daily clinical practice for the treatment of coronary artery disease, the exact vascular healing pattern and the resorption process in humans is unknown because histological data are derived only from animal studies.

Methods and Results—We have obtained 4 autopsies (5 scaffolds) since August 2013. Duration of bioresorbable vascular scaffold implantation ranged from 3 to 501 days. All autopsies and histological assessments were performed by dedicated cardiovascular pathologists. At 1 week after bioresorbable vascular scaffold implantation, struts were covered with a fine layer of fibrin and platelets. At 113 days, the scaffold struts were fully covered with smooth muscle cells. Hyaline eosinophilic and proteoglycan material infiltrating the scaffold struts was observed at 501 days after implantation. At all time points, we observed the presence of multinuclear foreign body giant cells adjacent to the scaffold struts.

Conclusions—Resorption and healing processes after bioresorbable vascular scaffold implantation in human patients mirror those observed in porcine models. The presence of multinucleated foreign body giant cells at both short- and long-term follow-up needs further investigation and may be related to a low-grade absorptive inflammatory response to the polymer. (*J Am Heart Assoc.* 2015;4:e002551 doi: 10.1161/JAHA.115.002551)

Key Words: absorb • bioresorbable scaffold • pathology

Bioresorbable scaffolds provide a novel approach to the treatment of coronary artery lesions. Numerous scaffolds are being evaluated in preclinical and clinical trials. The Absorb bioresorbable vascular scaffold (BVS; Abbott Vascular) is the most widely used, with >16 000 patients treated worldwide, and the most intensively investigated.¹ The device consists of a crystalline backbone of poly-L-lactide coated with a matrix composed of poly-D-L-lactide and the antiproliferative drug everolimus. The Absorb BVS now meets European Union quality standards (ie, CE-marked), and the prospect of treating

coronary lesions without leaving a permanent metal cage behind is attractive to both physicians and patients.

The use of the Absorb BVS in highly selected patients and relatively simple coronary artery lesions has been shown to be safe and feasible.^{2–4} More recent data derived from clinical registries with little or no selection of patient characteristics, and thus more comparable with daily clinical practice, have confirmed feasibility with good 6-month clinical outcomes. These registries, however, raised some concern about the risk of scaffold thrombosis, with reports of a somewhat higher rate (1.4% to 3.0%) at 6-month follow-up^{5–7} compared with second- and third-generation metallic drug-eluting stents (DESs; stent thrombosis rate of 0.2% to 1.0% at 2-year follow-up).⁸

The biodegradation process of the Absorb BVS has been evaluated in humans with the use of multiple invasive imaging modalities, such as optical coherence tomography, and complete strut resorption has been observed 5 years after scaffold implantation.⁹ Animal studies performed in porcine coronary arteries have provided a correlation between strut appearance on optical coherence tomography and histological findings. At 28 days, histology showed complete strut coverage with fibromuscular neointima, whereas at 2 years after

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implantation, the scaffold had open acellular regions that had well-defined calcified borders and were filled with hyaline and proteoglycan material. At 3-year follow-up, the struts were replaced by connective tissue, whereas at 4 years, smooth muscle cells started to infiltrate the connective tissue.¹⁰ Implants made of polylactic acid are known to trigger inflammatory responses of varying severity.^{11–13} Histology of animal data on the BVS demonstrated minimal to mild inflammation around BVS struts, consisting mostly of macrophages and a few lymphocytes at 12 to 36 months after implantation. Even so, multinuclear giant cells were occasionally observed adjacent to the struts at 1 month but were uncommon 3 to 6 months after implantation.^{10,14,15}

The exact resorption process of the Absorb BVS in human patients is unknown because histological data in humans are absent. In this report, we describe the first histology findings from implanted Absorb BVS in deceased patients after percutaneous coronary intervention. Our aim is to provide some insights into the resorption and vascular healing process of the Absorb BVS in human patients.

Methods

Between August 2013 and January 2015, the pathology department of the University of Amsterdam Academic Medical Center received a total of 4 lesions treated with 5 Absorb BVS, with duration of implantation ranging from 3 to 501 days. All available clinical records were reviewed for patient history, duration of implantation, risk factors, medications, and cause of death. The necessity to obtain informed consent was waived by the institutional review committee.

All autopsies and histological assessments were performed by dedicated cardiovascular pathologists. The treated arteries were dissected from the heart and submitted for plastic embedding in methyl methacrylate. Histological sections were cut at 6 μ m and stained with Hematoxylin (Klinipath, Duiven, the Netherlands) and Eosin (Merck, Darmstadt, Germany) for overall histomorphology, elastic van Gieson stain (Klinipath, Duiven, the Netherlands) for elastin and collagen fibers, and Alcian blue stain (Sigma, St. Louis, USA) for proteoglycans. Additional immunohistochemical stains with anti-smooth muscle actin antibody and an anti-CD31 antibody (DAKO, Heverlee, Belgium) were applied in all cases for visualization of smooth muscle cells and endothelial cells, respectively.

Results

Case 1: 3 Days After Scaffold Implantation

A man aged 59 years who was a current smoker with no prior cardiovascular history presented with an anterior ST-segment

elevation myocardial infarction. Diagnostic emergency coronary angiography showed a totally occluded left anterior descending artery (LAD). After thrombus aspiration and predilatation with two Sprinter semi-compliant balloons (2.0×20 mm at 14 atm and 2.5×20 mm at 20 atm), two overlapping BVSs (3.0×18 mm at 16 atm and 2.5×28 mm at 16 atm) were implanted in the proximal and middle LAD (Figure 1A and 1B). A few hours later, probably due to large infarct size and poor residual left ventricular function, the patient developed cardiogenic shock; despite optimal hemodynamic support, with a 2.5-L Impella device (Abiomed), the patient died 3 days after scaffold implantation.

Postmortem angiography showed no occlusion of the LAD and a patent scaffold. Histology of the scaffolded segment demonstrated an atherosclerotic coronary artery wall with a unilateral compressed intimal fibrotic plaque. The scaffold struts were identifiable by their impression of the lamina interna and by their contour in the intraluminal aggregate of blood cells. There was no evidence of scaffold thrombosis. Some of the struts, especially the struts located at the plaque-free wall, were covered by a thin layer of fibrin and platelets admixed with granulocytes and a few multinucleated giant cells (19% of the struts had giant cells adjacent) (Figure 1C and 1D).

Case 2: 8 Days After Scaffold Implantation

A man aged 48 years with a history of hypertension presented with ST-segment elevation in the precordial leads. Diagnostic emergency coronary angiography showed significant stenosis of the proximal left circumflex and the first obtuse marginal branch. The proximal LAD was suspected for a plaque rupture; after thrombus aspiration and predilatation with a 3.0×15-mm Sprinter semi-compliant balloon at 10 atm, a BVS (3.5×12 mm at 14 atm) was implanted in the proximal LAD. The procedure was finalized with postdilatation using a 3.5×9 mm Sprinter non-compliant balloon at 16 atm (Figure 2A and 2B). The patient was scheduled to undergo complete revascularization within 6 weeks after discharge; however, the patient presented 8 days later at our hospital in the setting of out-of-hospital cardiac arrest. Despite optimal cardiopulmonary resuscitation for >1.5 hours, the patient died.

Postmortem angiography showed a patent scaffold, and macroscopic inspection of the LAD showed no thrombus. Histological examination of the coronary artery at the scaffolded segment showed a unilateral lipid-rich atherosclerotic plaque. The contours of the scaffold were readily visible by their impression in the internal elastic lamina of the plaque-free wall. The struts were (partially) covered by a small layer of fibrin and platelets, with some lytic/condensed changes. The fibrin and platelet clot was

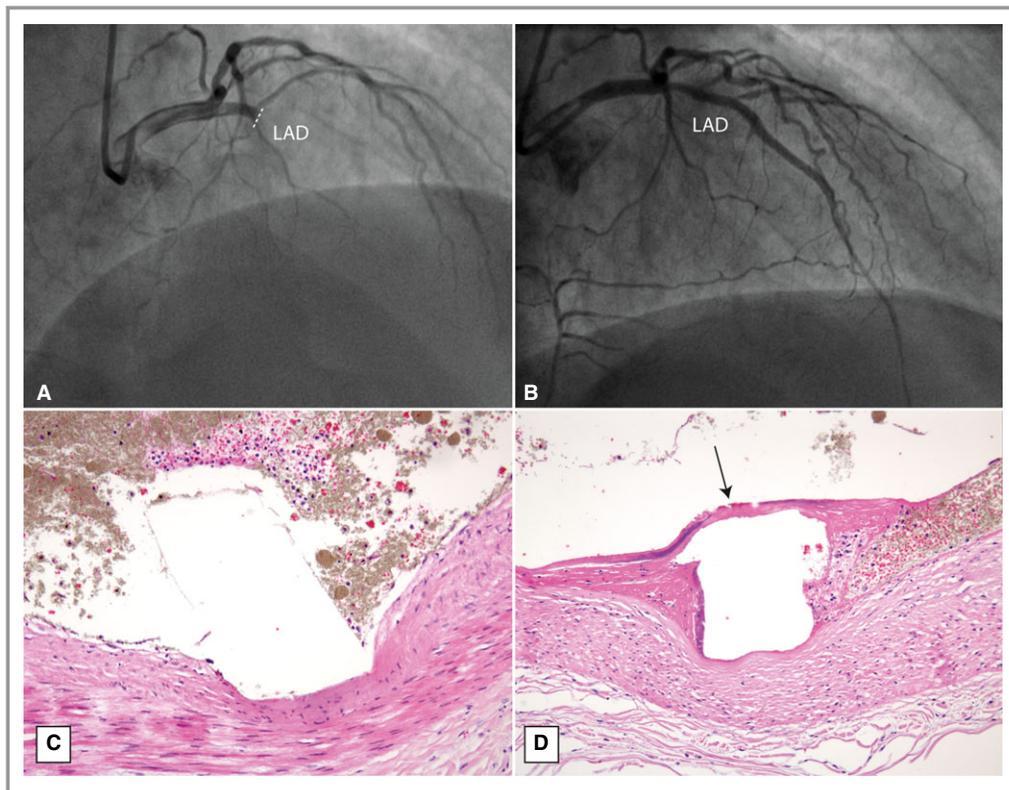


Figure 1. 3 days after scaffold implantation. Panel A shows a thrombotic total occlusion of the proximal LAD. After implantation of 2 overlapping Absorb bioresorbable vascular scaffolds (3.0×18 mm at 16 atm and 2.5×28 mm at 16 atm), Thrombolysis in Myocardial Infarction grade 3 flow was restored (B). At 3 days after scaffold implantation, the patient died due to cardiogenic shock. Histology (Hematoxylin and Eosin staining) of the scaffold showed scaffold struts compressing the intimal fibrotic plaque; the scaffold struts are identifiable by their impression of lamina interna and by their contour in the intraluminal aggregate of blood cells (C). Panel D shows a strut covered by a thin layer of fibrin (marked by the black arrow) and platelets, admixed with granulocytes. LAD, left anterior descending artery.

admixed with mononuclear inflammatory cells and low numbers of multinuclear foreign body giant cells. These giant cells were found adjacent to 68% of the BVS struts (Figure 2C and 2D).

Case 3: 113 Days After Scaffold Implantation

A man aged 70 years with a history of diabetes mellitus, peripheral artery disease, and transient ischemic attacks was referred to our hospital to undergo percutaneous coronary intervention of the left circumflex due to stable angina pectoris. The lesion was predilated with a TREK semi-compliant balloon (3.0×15 mm at 10 atm); thereafter, a 3.5×28 -mm BVS was implanted at 12 atm followed by postdilatation with a 3.5×15 -mm TREK non-compliant balloon at 16 atm (Figure 3A and 3B). At 3 months after implantation, the patient presented at our center with a scaffold thrombosis after stopping his dual antiplatelet therapy due to gastrointestinal bleeding. After multiple balloon dilatation, Thrombol-

ysis in Myocardial Infarction grade 3 flow returned, and optical coherence tomography imaging confirmed complete expansion and apposition of the scaffold (Figure 3C and 3D). The patient then developed (cardiogenic) shock, and emergency angiography showed a patent scaffold. Despite optimal medical hemodynamic support, the patient died in the intensive care unit.

Histology of the scaffolded segment of the coronary artery showed a unilateral lipid-rich plaque with calcifications. Some of the scaffold struts, especially those at the plaque-free wall, were covered with a thin layer of multilayered smooth muscle cells (Figure 3E). Adjacent to the struts located at the plaque-free wall, there was condensed fibrin, multinuclear foreign body giant cells (75% of the struts) and a few mononuclear inflammatory cells (Figure 3F). The stent struts at the side of the vessel wall with the plaque were surrounded by fibrin and blood cells that was admixed with a massive infiltrate of neutrophils and that also infiltrated the intima and media (Figure 3H and 3I). Full-body autopsy further identified

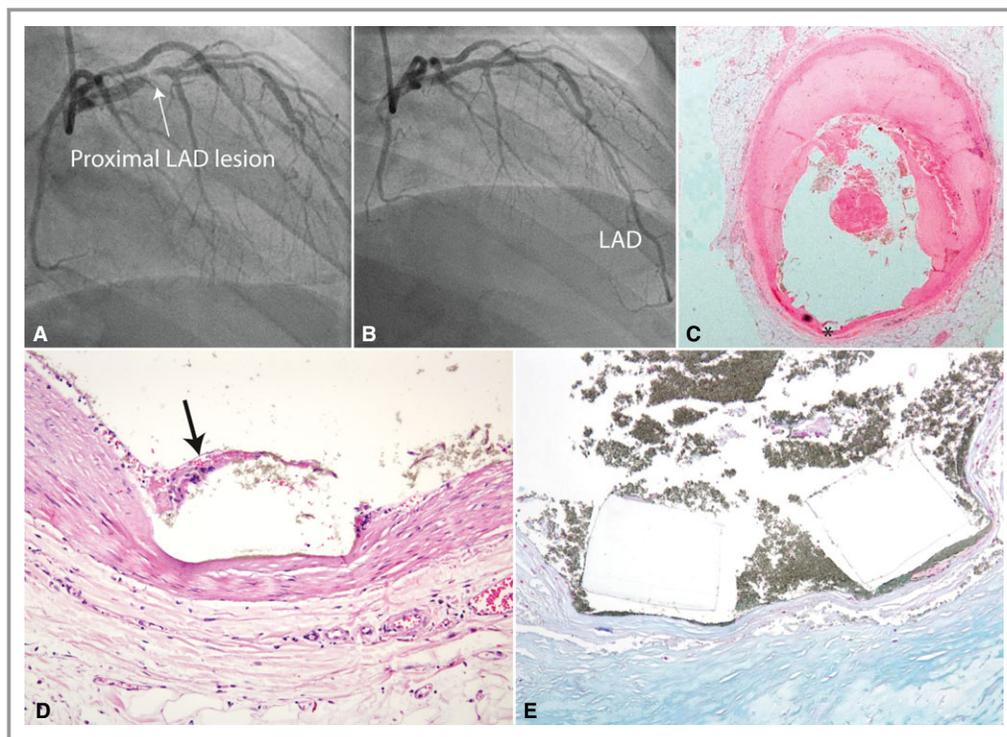


Figure 2. 8 days after scaffold implantation. The proximal LAD showed haziness, suspected to be a plaque rupture; after thrombus aspiration and predilatation, a bioresorbable vascular scaffold (3.5×12 mm at 14 atm) was implanted in the proximal LAD (A and B). At 8 days after scaffold implantation, the patient presented at our hospital in the setting of out-of-hospital cardiac arrest and died despite optimal cardiopulmonary resuscitation. Hematoxylin and eosin staining demonstrates the histological contours of the scaffold, readily visible by their impression in the lamina interna of the plaque free wall. *Histological contours of the scaffold (C). The struts are (partially) covered by a small layer of fibrin and platelets (black arrow). The fibrin and platelet clot is admixed with mononuclear inflammatory cells and multiple multinuclear foreign body giant cells (D). No material positive for Alcian blue staining infiltrated the scaffold strut (E). LAD, left anterior descending artery.

infectious pneumonia causing severe sepsis as the cause of death; therefore, the massive infiltration of neutrophils in the stented coronary artery was interpreted as a local septic complication, likely related to the presence of foreign body material.

Case 4: 501 Days After Scaffold Implantation

A man aged 81 years with a history of diabetes mellitus, hypertension, hypercholesterolemia, and multiple transient ischemic attacks was admitted at our hospital with unstable angina pectoris and underwent emergency percutaneous coronary intervention. Angiography showed a significant lesion (fractional flow reserve of 0.78) in the LAD, which was initially predilated with a semi-compliant balloon (2.5×15 mm at 10 atm), and a 3.0×18 -mm Absorb BVS was implanted at 12 atm (Figure 4A and 4B). At 3 months after implantation, the patient presented at our center with scaffold thrombosis after stopping his dual antiplatelet

therapy. The patient was treated initially with multiple balloon dilatations, but due to recurrent angina, the patient underwent a second percutaneous coronary intervention with implantation of 2 everolimus-eluting Xience DESs (Abbott Vascular) within the previously implanted scaffold (Figure 4C and 4D). At 1 year after the initial procedure, the patient developed an oropharynx carcinoma and died 6 months later of respiratory failure due to aspiration pneumonia.

Histology of the scaffolded segment of the coronary artery showed a unilateral lipid-rich atherosclerotic plaque with calcification. The intimal layer of the vessel contained a double row of stents (DES and BVS). The DES struts were smaller and rounder and sometimes contained iron mesh. All BVS struts were totally surrounded by intima with multilayered smooth muscle cells (Figure 4E). A few multinuclear foreign body giant cells and macrophages were seen adjacent to 67% of the struts. No T lymphocytes, B lymphocytes, or eosinophilic granulocytes were observed,

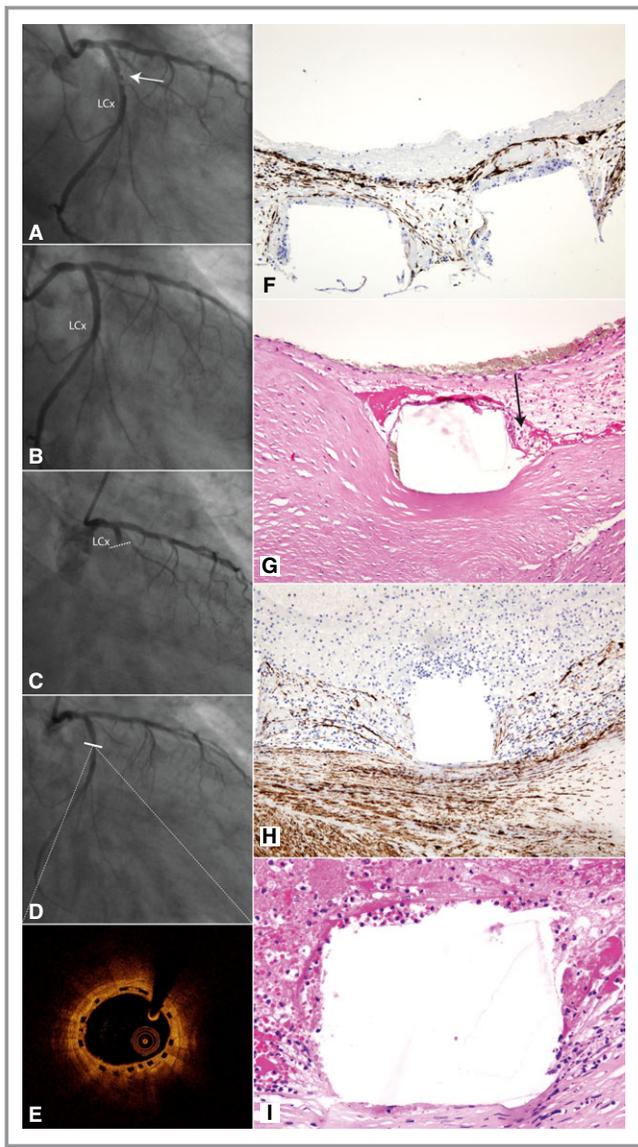


Figure 3. 113 days after scaffold implantation. Initially, the patient underwent percutaneous coronary intervention of the LCx due to stable angina pectoris with implantation of a 3.5×28-mm BVS at 12 atm (A and B). At 3 months after BVS implantation, the patient presented at our center with a scaffold thrombosis after stopping dual antiplatelet therapy due to gastrointestinal bleeding (C). Multiple-balloon dilatations were needed to obtain Thrombolysis in Myocardial Infarction grade 3 flow, and optical coherence tomography imaging confirmed complete expansion and apposition of the scaffold (D and E). Thereafter, the patient developed shock and, despite optimal medical hemodynamic support, died at the intensive care unit. Histology demonstrated coverage of some of the scaffold struts, especially those at the plaque free wall, with a thin layer of multilayered smooth muscle cells, demonstrated with smooth muscle actin staining (F). Hematoxylin and eosin staining demonstrated condensed fibrin, multinuclear foreign body giant cells (black arrow) and a few mononuclear inflammatory cells adjacent to the struts (G). The stent struts at the side of the vessel wall with the plaque were surrounded by fibrin and blood cells admixed with a massive infiltrate of granulocytes that also infiltrated the intima and media (H and I). BVS indicates bioresorbable vascular scaffolds; LCx, left circumflexus.

indicating no active immune response. Some of the BVS struts showed infiltration with fibrillary eosinophilic material (Figure 4F) that also stained with Alcian blue (Figure 4G), indicating degenerative change. The intraluminal site of the coronary artery was lined by a continuous layer of endothelium (Figure 4H).

Discussion

This report is the first to describe histological observations of implanted bioresorbable scaffolds in human patients during short- and long-term follow-up.

We observed strut coverage with a thin, fibrin-rich clot within 1 week after implantation. At 113 days after BVS implantation, we demonstrated that the scaffold struts were covered with smooth muscle cells. This finding is in accor-

dance with previously published animal data, which showed a fibromuscular layer over the scaffold at 28 days after implantation in a porcine coronary artery model. Furthermore, we noted the presence of low numbers of foreign body multinucleated giant cells in the vicinity of the struts at all time points (19%, 68%, 75%, 67% at 3, 8, 113, and 501 days, respectively). In only 1 case was there also a fulminant active inflammatory response of granulocytes infiltrating the intima and media and the overlying thrombus. At autopsy, this patient also showed severe bilateral bacterial pneumonia complicated by sepsis. As may occur with all implanted foreign materials in the human body during sepsis, this purulent reaction at the site of the stent can likely be interpreted as a local septic complication. Moreover, it is notably distinct from the eosinophilic hypersensitivity reaction (showing infiltration of eosinophilic granulocytes around the struts) described in first-generation DESs.¹⁶ Table summarizes our histological findings.

The observed multinuclear foreign body giant cell infiltration at 3, 8, 113, and 501 days plays a facilitating role in the resorption process of the scaffold. Multinucleated giant cell formation is known to be linked to chronic immune responses, particularly to indigestible materials or chronic infections such as tuberculosis.¹⁷ It has been demonstrated previously, in vitro and in vivo, that a strong inverse relationship exists between the rate of material degradation and the degree of inflammatory response to implanted material: A fast resorption process is accompanied by a high degree of inflammation.¹³ Furthermore, it has been demonstrated that polylactic acid-based devices implanted subcutaneously in rats triggered an inflammatory response, including multinu-

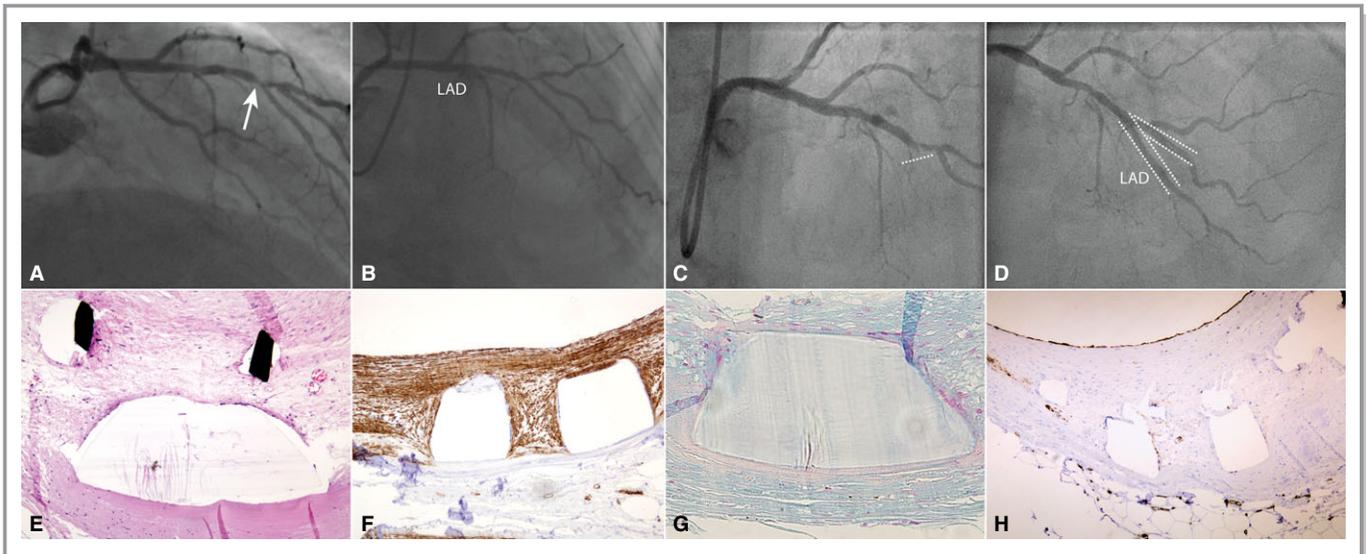


Figure 4. 501 days after scaffold implantation. Angiography showed a significant lesion (fractional flow reserve of 0.78) in the LAD, which was treated with a 3.0×18-mm Absorb BVS at 12 atm (A and B). At 3 months after implantation, the patient presented at our center with scaffold thrombosis after stopping dual antiplatelet therapy (C), and the patient underwent a second percutaneous coronary intervention with implantation of 2 everolimus-eluting Xience DESs (T-stenting technique) within the previously implanted scaffold and toward the side branch (D). At 1.5 years after the initial procedure, the patient died due to aspiration pneumonia. Histology of the scaffolded segment demonstrated the intimal layer of the vessel containing both the Absorb BVS and the Xience DES. All BVS struts were totally surrounded by intima with multilayered smooth muscle actin cells (E). Multinuclear foreign body giant cells and few mononuclear inflammatory cells were seen adjacent to the scaffold struts. The DES struts were smaller and sometimes clearly visible as iron mesh; some of the BVS struts show infiltration with fibrillary eosinophilic material (F). Furthermore, Alcian blue staining presented a blue hue in the scaffold strut, suggesting proteoglycan-containing material infiltrating the struts (G). CD31 staining demonstrated that the intraluminal coronary wall was lined by a continuous layer of endothelium (H). BVS indicates bioresorbable vascular scaffolds; DES, drug-eluting stent; LAD, left anterior descending artery.

cleated giant cells and macrophages, after coming in contact with the bones.¹⁸ In addition, we know from animal studies performed on first-generation DESs, such as the CYPHER (Cordis Corp) and TAXUS (Boston Scientific Corp), that the inflammatory response gradually increases after implantation, leading to a peak inflammatory response between 90 and 180 days.¹⁹

All of these previous findings support our hypothesis that the presence of multinuclear foreign body cells is linked to the resorption process, with peak intensity at 113 days. In animal studies, however, multinuclear giant cells were uncommon at 3 to 6 months after implantation of the Absorb BVS, with a peak intensity at 1 month (present in 34.8% to 37.0% of the struts).

At 6 months after scaffold implantation, Otsuka et al demonstrated almost no giant cells (0% to 0.6%), whereas others observed giant cells in 14.7±18.9% and 2.2% of the struts.^{10,14,15} Furthermore, all studies demonstrated peak intensity in the presence of multinucleated giant cells at 1 month. These results contrast with our findings, which showed peak numbers of multinucleated giant cells at 113 days (adjacent to 75% of the struts).

Our last case demonstrated that at >1.5 years after scaffold implantation, the polymer struts of the Absorb BVS were still present. Infiltration of the scaffold struts with hyaline eosinophilic and proteoglycan material, suggestive for resorption of the scaffold, is in accordance with the porcine

Table. Case Descriptions and Histological Findings

| Case | Time of Implantation, days | Comorbidities | Cause of Death | Fibrin Coverage | Smooth Muscle Cell Coverage | Endothelial Coverage | Struts With Giant Cells (%) |
|------|----------------------------|----------------------|----------------------|-----------------|-----------------------------|----------------------|-----------------------------|
| 1 | 3 | | Cardiogenic shock | + | — | — | 19 |
| 2 | 8 | | Cardiac arrhythmia | + | — | — | 68 |
| 3 | 113 | | Severe sepsis | + | + | — | 75 |
| 4 | 501 | Oropharynx carcinoma | Aspiration pneumonia | — | + | + | 67 |

animal model, which demonstrated this phenomenon 2 years after scaffold implantation.¹⁰ Despite the extra antiproliferative and immunosuppressive effects of the everolimus released from the Xience DES, implanted 3 months after implantation of the Absorb BVS, an active chronic inflammatory response was observed 501 days after BVS implantation with the presence of multinuclear foreign body cells and mononuclear cells adjacent to the scaffold struts.

Limitations

This study is a small case series. In 2 of the cases, the bioresorption process and the histology results could have been influenced partially by contributing factors such as systemic inflammation or additional DES implantation.

Conclusion

The observations in this histological case series mirror, to a large extent, the observations made in the porcine model. The presence of low numbers of the foreign body giant cells and macrophages in the vicinity of the struts observed was not seen in the porcine model at long-term follow-up and suggests a low-grade absorption process of the scaffold materials over a long time.

Disclosures

Wykrzykowska receives consultancy fees from Abbott Vascular. The AMC Heartcenter received a restricted research grant from Abbott Vascular. The others declare that they have no conflicts of interest.

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