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EDITORIAL COMMENT

Coronary Angioplasticity*

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"Change is the only constant"
—Heraclitus of Ephesos (1)

Proponents of bioresorbable scaffolds (BRS) define them as a transformative technology suggesting that coronary repair will improve long-term clinical outcomes. Skeptics have questioned the early safety, and overall merit of BRS in the era of second- and third-generation drug-eluting metallic stents (DES). Nevertheless, BRS have sparked enormous interest and debate. Indeed, over the last decade a plethora of short- and long-term translational observations have been generated from over six hundred in vivo deployments of the Absorb bioresorbable vascular scaffold (Absorb BVS, Abbott Vascular, Santa Clara, California) in healthy porcine coronary arteries (**Figure 1**).

The Absorb BVS is made of semicrystalline poly-L-lactic acid. Polylactides are relatively hydrophilic and polymer chains are gradually hydrolyzed to short lengths until they are converted to lactic acid monomers. Preclinical observations at 28 days reveal that only 75% of overlapped Absorb BVS demonstrate cellular coverage compared with complete coverage in second-generation DES. Interestingly, by 90 days cellular coverage of Absorb BVS appears to be complete (**Figures 1A and 1B**) (2). Vasomotor function within scaffolded segments and their adjacent edges appear to be repaired with restored pulsatility at 1 year. This physiologic vascular repair reflects the efficacious endothelial repopulation and gradual recovery of local fluid mechanical conditions in scaffolded segments, over the first year (3). Additional observations during this time point were lumen gain and vessel enlargement, attributed to compensatory remodeling augmented by the early loss (~6 months) of scaffold's mechanical integrity through hydrolytic degradation (4).

At 2 years, the strut material of poly-L-lactic acid is mostly resorbed, with resorption sites visualized as "preserved box" shapes by optical coherence tomographic (OCT) imaging. These sites are replaced by proteoglycan-rich matrix (**Figure 1D**) (5-7). Ex vivo assessment of smooth muscle cell phenotypic expression indicates upregulated connexin 43 gene levels at this time point. This observation addresses the continual smooth muscle cell shift toward a contractile "neomedia," enabling improved cell-to-cell communication with optimal functional reactivity (3). At 3 years, the Absorb BVS is degraded and resorption sites are gradually cellularized with connective tissue. Any scaffold remnants are visualized as "dissolved box" shapes with OCT imaging (**Figure 1E**). Finally, by 4 years resorption sites are mostly occupied with collagen-rich connective tissue enabling complete functional and anatomic restoration of the vessel's architecture (**Figure 1F**) (8). Indeed, the richness of translational observations collected thus far provides a detailed understanding of the interplay among bioresorption, physiologic vessel repair, and underlying biologic mechanisms. However, the relationship between strut resorption and late lumen enlargement remains unclear. Furthermore, whether in vivo imaging using OCT and intravascular ultrasound (IVUS) can identify the various stages of strut integration remains to be elucidated.

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In this issue of *JACC: Cardiovascular Interventions*, Nakatani et al. (9) present a porcine study providing additional insights into the Absorb BVS resorption process as well as to whether in vivo imaging can identify the stages of strut integration with the adjacent tissue. The authors used OCT-based light

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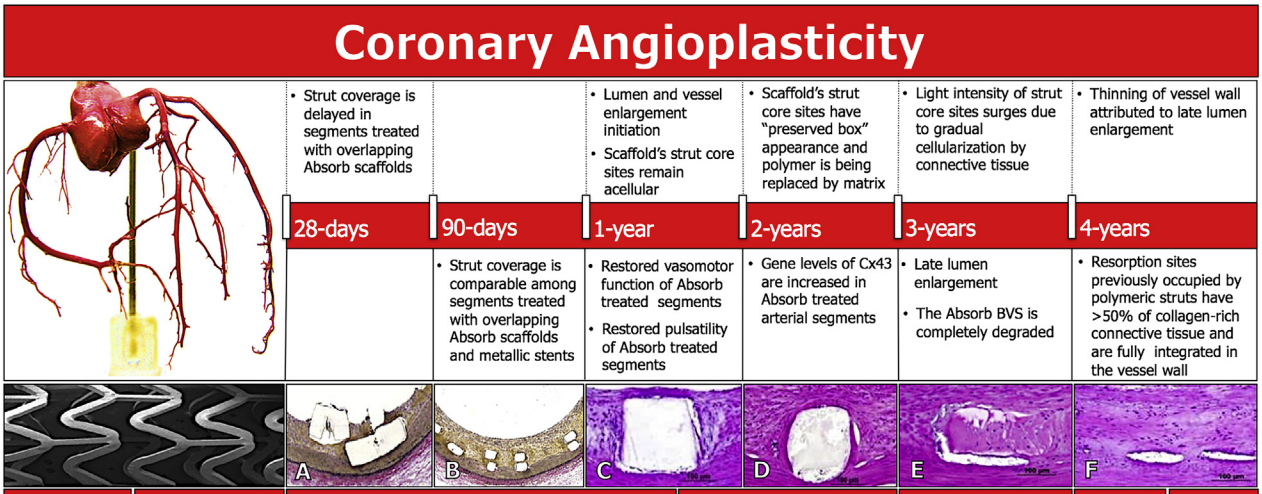
FIGURE 1 **Chronologic Insights From the Absorb BVS Translational Assessment in Healthy Porcine Coronary Arteries Up to 4 Years**



Year	Author	In vivo & Ex vivo Assessment		Aims	Non-atherosclerotic swine (n)	Absorb BVS (n)	Xience V (n)
2016	Nakatani et al.[9]	Angiography	GS-IVUS Echogenicity/OCT/Histology	Bioresorption process, Arterial Responses/ Remodeling	73	112	(-)
2016	Gogas & Benham et al.[3]		Tissue chamber/Gene analysis/Histology	Vasomotor function, Phenotypic expression	12	15	14
2015	Campos et al.[7]		GS-IVUS Echogenicity/GPC	Bioresorption process	40	97	(-)
2014	Otsuka et al.[8]		Histology/GPC	Histopathological variables, Arterial Responses/ Remodeling	136	263	72
2013	Lane et al.[4]		GS-IVUS/Histology	Arterial pulsatility, Arterial Responses/ Remodeling	70	109	70
2013	Farooq et al.[2]		OCT/Histology (overlapping segments)	Histopathological variables, Arterial Responses	17	22	15
2010	Onuma et al.[5] Gogas & Radu et al.[6]		OCT/Histology/GPC (single deployments)	Histopathological variables, Arterial Responses	17	35	(-)
Total					365	653	171

(A to F) Selected cross-sectional views of Absorb bioresorbable vascular scaffold (BVS) strut cores over the course of a 4-year follow-up, stained with elastic van Gieson **(A,B)** and hematoxylin and eosin **(C to F)**. GPC = gel permeation chromatography; GS-IVUS = grayscale intravascular ultrasound; OCT = optical coherence tomography.

intensity analysis, IVUS-based echogenicity assessment as well as ex vivo histology at numerous time points up to 4 years. They found: 1) Biphasic lumen enlargement at 1 and 3 years. The early phase is attributed to the scaffold's loss of mechanical integrity augmented by the natural growth of the juvenile porcine coronaries. The latter phase is governed by proteoglycan matrix replacement with connective tissue, leading to strut integration in the surrounding neointima (**Figures 1E and 1F**). 2) Vessel wall thinning due to both lumen and vessel enlargement. Interestingly, neointimal tissue and plaque/media areas remain unchanged. The authors acknowledge that the timing of strut wall integration and the changes in polymer molecular weight may differ in humans.

Cardiac *plasticity*, introduced by Hill and Olson in 2008 (10), describes the dynamic change of cardiac muscle in an effort to accommodate any underlying demand. This changing myocyte phenotype leads to physiologic compensation, pathologic hypertrophic remodeling, or atrophic phenotypic switch. Applying a similar concept to the coronary artery, coronary *angioplasticity* can be described as the vasculature's dynamic response after BRS deployment. The journey from Gruentzig's angioplasty to angioplasticity has been remarkable and fascinating. The question is whether this novel translational concept of vascular reparative therapy can be safely transitioned to clinical practice.

The plastic property of the vessel wall attempting to restore a more physiologic vascular milieu, has been thoroughly investigated in the ABSORB Cohort B registry at regular intervals up to 5 years (11). There was no scaffold thrombosis and struts were not discernable by OCT at 5 years. Interestingly, unlike observations from the present porcine study, lumen

area within the scaffolded segments did not enlarge between 1 and 5 years. In addition, a number of randomized clinical trials have generated additional evidence regarding the efficacy and clinical safety of the Absorb BVS.

In a recent meta-analysis including the ABSORB II and III, China, Japan (A Clinical Evaluation of Absorb BVS System), EVRBIO II (Everolimus- Versus Biolimus-Eluting Stents in All-Comers), and TROFI II randomized trials, the Absorb BVS was compared with a best-in-class cobalt-chromium DES in 3,738 patients (12). The average follow-up was 1 year. Both devices had similar efficacy outcomes. However, the primary safety outcome of early (<30 days) definite/probable thrombosis was higher in Absorb BVS compared to DES: 1.3% versus 0.5% with an odds ratio of 1.99 (95% confidence interval: 1.00 to 3.98; $p = 0.05$).

In addition to these early events, selected case reports have indicated very late scaffold thrombosis (up to 4 years) due to intraluminal scaffold dismantling suggesting that in humans atherosclerotic coronary arteries may not fully mirror the integrated bioresorption observed in the healthy porcine models (13).

Although most of these clinical trials did not have intravascular imaging cohorts, the ABSORB III randomized trial does have OCT and IVUS imaging arms post BVS deployment with 3-year imaging follow-up. Strut and vessel level wall shear stress conditions affected by the Absorb BVS reparative process will be carefully investigated in this detailed biomechanical analysis of the ABSORB III imaging substudy.

How can one explain the discrepancy between the experimental observations of adequately healed vessels with strut integration and the slightly higher rates of scaffold thrombosis compared with metallic DES? Two obvious possibilities come to mind. First, is the complexity of human atherosclerosis compared with the normal porcine coronary arteries. Second, is the learning curve associated with vessel preparation prior to scaffold deployment. With lower radial strength compared to DES, BRS deployed in fibrotic and fibrocalcific vessels require meticulous lesion preparation to achieve optimal expansion. Indeed, a recent meta-analysis demonstrates that implementing a specific protocol for Absorb BVS deployment results in significantly lower rates of scaffold thrombosis (14). A similar learning curve for first-generation DES deployment, which had similar strut thickness of 150 μm as first-generation BRS had to be overcome (15). This suggests that once a scaffold is carefully deployed in an atherosclerotic substrate, the subsequent healing and bioresorption process may mirror more closely the favorable observations of angioplasticity in experimental models.

As clinical experience with BRS accumulates with newer generations identifying the sweet spot between thinner struts with retention of radial strength, it is anticipated that the limitations of current technologies will be overcome. Detailed intravascular imaging and biomechanical studies will likely inform translation of experimental observations of coronary angioplasticity into clinical care. Indeed, "change is the only constant" as Heraclitus of Ephesos pointed out, however, we have to make sure that change is given time to mature.

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