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EDITORIAL COMMENT

Can the Vanishing Stent Reappear?

Fix the Technique, or Fix the Device?*

Spencer B. King III, MD, Bill D. Gogas, MD, PhD

The bioresorbable vascular scaffold (BVS) (Absorb, Abbott Vascular, Santa Clara, California), which is designed to biologically dissolve, has now commercially disappeared as well. In light of less than encouraging evidence, the manufacturer has decided to suspend sales. This concept of a stent that provides temporary scaffolding and then gradually dissolves, leaving a healed and functional unstented arterial wall, is a long-running movie. I first was made aware of the possibility in 1986 when Jack Whitehead, the founder of the Whitehead Institute at Massachusetts Institute of Technology, suggested to me alternative materials to the stainless-steel alloys we were investigating at the time. A visit to the polymer chemist Robert Langer at the Massachusetts Institute of Technology and later to Joachim Kohn at Rutgers led to some polymeric prototypes for translational testing.

The preliminary observations of others who were using degradable biomaterials in porcine coronary arteries convinced most of us that low-molecular-weight polymers induce significant inflammatory and hyperproliferative reactions that would probably doom this method of coronary revascularization (1,2). Now, more than 30 years later, we have finally had the chance to implant these devices in hopes of improving the results of our coronary interventions. If we had compared the current drug-eluting scaffolds to the stent methods we had 20 years ago, they would have been hailed as a major advance. But, with continued iterations of metal drug-eluting stents (DES), involving more biocompatible open-cell and thin-strut designs, novel antiproliferative agents, and thromboresistant biodegradable coatings, the competitive bar has been raised to new heights. Indeed, real-world randomized trials, observational registries, and meta-analysis suggest an approximate 3-fold incremental increase in scaffold thrombosis (ScT) rates beyond 1 year after implantation of the Absorb BVS compared with the benchmark metal drug-eluting model (3). Those results instilled a note of caution in lesion selection and resulted in warnings from the U.S. Food and Drug Administration as to which vessels should be avoided when BVS is considered a treatment option for coronary revascularization.

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In this issue of the *Journal*, the 3-year follow-up of the ABSORB III trial results has not changed this somewhat pessimistic outlook for the device in the intermediate follow-up (4). In an attempt to further recognize the variables leading to these outcomes, the results from this trial as well as 4 other prospective ABSORB trials were combined to evaluate the critical roles of both appropriate vessel sizing and implantation technique optimization (5).

The observations of the pivotal ABSORB III trial suggested that first-generation (gen) BVS is noninferior to metal DES after meeting the primary endpoint of target lesion failure (TLF) within a large noninferiority margin at 1 year. Although device thrombosis rates were comparable among the treated cohorts, thrombotic rates significantly increased by 4.6% in the BVS arm versus 1.55% in the metal DES arm when deployments occurred in vessels with quantitative coronary angiography (QCA)-derived reference diameter (RVD) of <2.25 mm (6). In the current work, Kereiakes et al. (4) present the 3-year clinical follow-up of ABSORB III trial, indicating that patients who received a degradable scaffold demonstrate significantly higher adverse event rates compared with those

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From the Andreas Gruentzig Cardiovascular Center, Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

treated with a metal DES. The device-oriented composite endpoint of TLF in this analysis occurred in 13.4% of BVS treated patients versus 10.4% of those treated with a metal DES (hazard ratio: 1.31; 95% confidence interval: 0.99 to 1.73; p = 0.056) driven by higher rates of target vessel myocardial infarction due to device thrombosis, which was 1.9% in the BVS arm versus 0.6% in the metal DES arm (p = 0.02). The overall thrombotic rate through 3 years reached 2.3% in the BVS arm versus 0.7% in the metal DES arm (hazard ratio: 3.12; 95% confidence interval: 1.21 to 8.05; p = 0.01). Despite more than 50% of treated subjects being on dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist after 1 year, BVS-treated patients experienced significantly more thrombotic events than the comparator cohort during this time frame. Interestingly, the majority of these events occurred in appropriately sized vessels (QCA-RVD ≥2.25 mm).

Because the sample size of the ABSORB III trial was inadequate to evaluate the effect of vessel size and procedural technique, in another paper in this issue of the *Journal*, Stone et al. (5) provide a broad overview of the combined effect of aggressive lesion predilation, appropriate vessel sizing, and optimal post-dilation (PSP) after analyzing 3,149 BVS-treated lesions from 4 other prospective ABSORB studies. PSP individual components across the ABSORB II, ABSORB III, ABSORB China, ABSORB Japan, and ABSORB Extend studies were pooled demonstrating that: 1) limitation of Absorb BVS deployment to arterial segments with QCA-RVD >2.25 mm would result in a 28% lower hazard of TLF through 3 years compared with the total group; 2) BVS implantation in QCA-RVD <2.25 mm was associated with a 3-fold increase in the rates of ScT within the first year, whereas beyond this time point, ScT tended to cluster in lesions with QCA-RVD >2.25 mm; 3) aggressive pre-dilation had a neutral effect in long-term outcomes; and 4) optimal post-dilation in general had beneficial effects by reducing numerically ScT rates and significantly TLF rates between 1 and 3 years.

Amid the turmoil generated by the AIDA (Amsterdam Investigator-initiated Absorb Strategy All-comers Trial) (7) indicating the 4-fold increase in the risk of ScT after BVS deployment over a 2-year time frame, the 3-year findings from the ABSORB III trial are similarly disappointing. Although vascular restoration with biodegradable scaffolds leads to restored plasticity (8) with mechanobiological recovery of the arterial wall, the first-gen Absorb BVS has been associated with significant safety concerns leading to increased rates of scaffold failure. In the absence of high-resolution optical coherence tomographic imaging in the ABSORB randomized trials, which might facilitate a broader understanding of the mechanism of ScT, we can only speculate on changes to guide clinical implantation and design iteration for second-gen bioresorbable platforms.

Early and late thrombotic events after BVS deployment likely occurred due to the rectangular strut geometry and bulky crossing profile in association with suboptimal PSP techniques that produced only modest strut embedment and strut underexpansion or malapposition, which triggers significant hemodynamic alterations. These rheological implications are currently being investigated with computational modeling techniques by our group in patients enrolled in the randomized ABSORB III imaging substudy (9), and preliminary observations indicate that strut profiles similar to the first-gen BVS in underexpanded segments are prone to flow separation and recirculation inducing lower wall shear stress, associated with platelet activation and higher thrombogenicity. Also, the ABSORB IV trial, which incorporates the PSP implantation techniques, will help clarify whether these methods will substantially improve clinical outcomes.

Although experimental observations using gel permeation chromatography from scaffolded porcine coronary arteries have indicated that poly-L-lactic acid is completely resorbed by 3 years, with more than 50% of resorption sites previously occupied by polymeric struts replaced by functional connective tissue (10), selective optical coherence tomographic reports have shown persisting struts even 4 years after BVS deployment with the potential to precipitate very late ScT events. Mechanisms similar to DES failure cannot be excluded after discontinuation of dual antiplatelet therapy; meanwhile, a novel mechanism of scaffold failure has been recently proposed called intraluminal scaffold dismantling in the absence of homogeneous neointimal strut coverage. Although neoatherosclerotic transformation is a prevalent etiology of very late stent failure even with newer-gen DES (11), it is premature to hypothetically associate neoatherosclerosis with vascular restoration therapy. Experimental studies performed by our group have indicated in healthy porcine coronary arteries that Absorb BVS-treated vessels have their functional capacity restored by 2 years, and complete mechanobiological reparation occurs with expressed pathways of cytoskeletal remodeling and endothelial to mesenchymal transitioning over the course of 4 years (12). In contrast, metal DES-treated arteries demonstrate heavily proatherogenic genotype through the lymphotoxin-β receptor-dependent pathway promoting the expression of vascular cell adhesion molecule 1 and

interleukin-2 and -8, enabling neointimal infiltrations with foamy macrophages.

Although the manufacturer halted commercial production of the scaffold, a second-gen BVS with a thinner strut profile of 99 μm and expansion limit of >0.75 mm over nominal diameter has been experimentally tested and will undergo first-in-man studies soon. Other manufacturers who develop polymer-based scaffolds have also implemented thinner strut profiles in their second-gen scaffolds such as the: 1) DESolve novolimus-eluting scaffold (Elixir Medical Corporation, Sunnyvale, California) with strut thickness of 120 μm; 2) MeRES 100 sirolimus-eluting hybrid cell design scaffold with strut thickness of 100 μm (Meril Life Sciences, Vapi, India); and 3) FANTOM scaffold with strut thickness of 125 μm (REVA Medical, San Diego, California). Obviously, these new-generation scaffolds will need to be tested against the best metallic stents. The speculation about whether these improvements will rival the very high bar set by the best metal DES will determine how many resources industry will allocate to evaluate the long-term promise of the "vanishing stent."

Whether the emphasis on improving the technique with the PSP protocol will prove effective or cost-effective remains to be seen. However, with the current generations of bioresorbable scaffolds, it is clearly necessary to precisely size the vessel. We tend to believe that improved platforms to make scaffold implantation as user friendly as metal stent implantation, as applied not only by the most highly experienced operators but also the average operator, will be required to match the very high bar already established by metal DES. The reason to persevere is not because of any expectation that scaffolds can beat metal stents in the intermediate term, but the concern that metal stents will begin to produce significant adverse events many years after implantation. That will have to become a demonstrated reality rather than a hypothetical speculation for bioresorbable scaffolds to replace metal stents. For the time being, although the ABSORBing scaffold has vanished, we believe that improved disappearing technologies will eventually reappear; whether they will be competitive with current and future coronary stents remains questionable.

ADDRESS FOR CORRESPONDENCE: Dr. Spencer B. King III, MD, Department of Medicine, Division of Cardiology, Emory University School of Medicine, The Andreas Gruentzig Cardiovascular Center, Saint Joseph's Heart and Vascular Institute, 5665 Peachtree Dunwoody Road NE, Atlanta, Georgia 30342. E-mail: spencer.king@emoryhealthcare.org.

REFERENCES

1. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996;94:1690–7.

2. King SB 3rd. Vascular stents and atherosclerosis. Circulation 1989;79:460–2.

3. Sorrentino S, Giustino G, Mehran R, et al. Everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents. J Am Coll Cardiol 2017;69:3055–66.

4. Kereiakes DJ, Ellis SG, Metzger C, et al., for the ABSORB III Investigators. 3-year clinical outcomes with everolimus-eluting bioresorbable coronary scaffolds: the ABSORB III trial. J Am Coll Cardiol 2017;70:2852–62.

5. Stone GW, Abizaid A, Onuma Y, et al. Effect of technique on outcomes following bioresorbable vascular scaffold implantation: analysis from the ABSORB trials. J Am Coll Cardiol 2017;70:2863–74.

6. Ellis SG, Kereiakes DJ, Metzger DC, et al. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. N Engl J Med 2015;373:1905–15.

7. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable scaffolds versus metallic stents in routine PCI. N Engl J Med 2017;376:2319–28.

8. Gogas BD, Samady H. Coronary angioplasticity. J Am Coll Cardiol Intv 2016;9:852–5.

9. Gogas BD, Yang B, Piccinelli M, et al. Novel 3-dimensional vessel and scaffold reconstruction methodology for the assessment of strut-level wall shear stress after deployment of bioresorbable vascular scaffolds from the ABSORB III imaging substudy. J Am Coll Cardiol Intv 2016;9:501–3.

10. Otsuka F, Vorpahl M, Nakano M, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211–23.

11. Lee SY, Hur SH, Lee SG, et al. Optical coherence tomographic observation of in-stent neoatherosclerosis in lesions with more than 50% neointimal area stenosis after second-generation drug-eluting stent implantation. Circ Cardiovasc Interv 2015;8:e001878.

12. Gogas BD, Kumar S, Benham JJ, et al. Very late vasomotor responses and gene expression profiles of porcine coronary arteries at 4 years after deployment of the everolimus-eluting bioresorbable vascular scaffold and the everolimus-eluting metallic Xience V stent. J Am Coll Cardiol 2016;68:B334–5.

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