ASK THE EXPERTS

Will Bioresorbable Scaffolds Ultimately Have a Role?

Experts discuss the outcomes of the ABSORB trials and what the future may hold for bioresorbable scaffolds.

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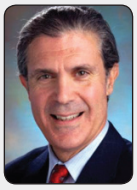

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The evolution of metallic coronary stent designs from bare metal to first- and second-generation drug-eluting stents (DESs) was associated with a progressive reduction in major adverse cardiovascular events, including stent thrombosis, with the greatest portion of risk difference between devices present during the first year after deployment.[1] Beyond 1 year, there is a 2% to 4% per year incidence of device-related events (ie, target lesion failure [TLF]) regardless of device.[2] Because permanent polymers have been associated with inflammation, neoatherosclerosis, and thrombosis, bioresorbable polymers that disappear after drug elution (third-generation DESs) have been developed. Limited late follow-up suggests that third-generation DESs have not altered the ≥ 2% per year TLF event rates beyond 1 year,[3] the pathogenesis of which relates to the common presence of a metallic prosthesis that physically distorts and constrains the vessel, prevents vasomotion and adaptive coronary remodeling, and serves as nidus for chronic inflammation, neoatherosclerosis, strut fracture, and thrombosis.

In this context, fully bioresorbable scaffolds (BRSs) composed of naturally occurring and synthetic polymers, salicylic acid, or magnesium-metal alloy have been developed to provide early mechanical support and drug delivery similar to metallic DESs followed by bioresorption with restoration of more normal vascular structure and function.[4] To compensate for reduced mechanical strength of polymer relative to metal, stent strut thickness and width dimensions were increased with consequent disruption in coronary flow dynamics/shear distribution and increased thrombogenicity. The greater space-occupying effect of the thicker and wider struts of the Absorb bioresorbable vascular scaffold (BVS; Abbott Vascular) was particularly problematic in smaller-caliber vessels (< 2.5 mm by visual estimate) and significantly increased the thrombosis risk. Randomized controlled trials comparing the Absorb BVS with a thin-strut metallic second-generation DES (Xience, Abbott Vascular) demonstrated higher rates of adverse clinical events, including device thrombosis through 3 years of follow-up.[5]

Furthermore, ischemic event rates continued to accrue beyond 1 year (particularly target vessel myocardial infarction [TVMI] and scaffold thrombosis [ScT]) due to uncovered and/or underexpanded struts,

neoatherosclerosis, and scaffold discontinuities with intraluminal scaffold dismantling—a novel cause of very late ScT not seen with metallic DESs. Late scaffold discontinuities are part of the polymeric bulk erosion resorption process, and when scaffold segments are not confined by endothelial/neointimal tissue coverage, they may translocate to the vessel lumen and precipitate thrombosis and/or restenosis. Studies suggesting that optimized scaffold deployment technique may mitigate differences in thrombosis rates between Absorb and Xience were post hoc, with few patients (< 15%) treated optimally, used variable definitions for optimal technique, and were not adjusted for baseline patient/lesion factors.[6-8] Additional studies are required to define the roles of optimal technique and extended dual antiplatelet therapy duration in improving BRS outcomes.

The relative hazard of Absorb BVS versus Xience is largely mediated by strut dimensions and resorption profile (ie, time course and mechanism). Improved scaffold outcomes will hopefully accompany thinner struts, more rapid resorption (device-related events require device presence), and either less fragmentation (discontinuity) during resorption or better fragment coverage to prevent intraluminal translocation. Second- and third-generation scaffolds with thinner struts, different polymer blends and/or processing techniques, and shorter times to complete resorption (1–2 years) are in clinical trials.[4] Novel third-generation polymeric and/or magnesium-based scaffolds have demonstrated low rates of adverse clinical outcomes and rare ScT events.[4] These studies have confirmed shorter resorption profiles with intravascular imaging and suggest that earlier vessel restoration with complete bioresorption may reduce very late ScT.

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BRSs were pulled from the market in the United States and worldwide in September 2017. The official reasoning was a business decision driven by low sales. But there is no doubt that this decision was also driven by safety concerns, such as late ScT and underperformance when comparing the first-generation Absorb to the best-in-class DES, Xience, in pivotal randomized clinical trials.

Some of these safety issues were addressed with implementation technique and refining the technology with a reduction in strut thickness. The BRS field suffered from a major setback and nearly permanent halt with industry pulling programs due to lack of commercial viability. Furthermore, the interventional cardiology community is questioning the future role of BRS technology. To address this important question, one needs to revisit the unmet needs and the utility of the technology from the patient/physician, industry, and regulatory perspectives.

PATIENT/PHYSICIAN PERSPECTIVE

Avoiding permanent metallic implants and removing a nidus for late events remain desirable among patients and physicians globally. Despite using the best-in-class DES, we continue to see reports of stent failure rates of 1% to 3% per year. The presentation of metallic DES in-stent restenosis is often devastating, leading to acute coronary syndrome, including myocardial infarction.

Despite treatment using the latest modalities of drug-coated balloons, repeat DES, and brachytherapy, the recurrence rate of in-stent restenosis remains high. If the hurdles of the first generation of BRSs can be overcome with improved BRS technology, it will be a matter of a number of years to demonstrate superiority of BRSs over metallic DES. Furthermore, the BRS technology continues to be appealing to the younger population, who would potentially be the biggest beneficiaries, and patients' desire to leave nothing behind after coronary intervention remains a priority. Physicians' enthusiasm about the technology can be renewed if the safety concerns are resolved and, for the short term, the device can truly perform equally to DES.

INDUSTRY PERSPECTIVE

The question of whether the technology gap between a first-generation BRS and best-in-class DES can be bridged by refining the technology, and at what cost, is unknown. Recently, there have been four important concepts that have been addressed with second-generation poly-L lactic acid–based platforms and with metallic resorbable platforms (magnesium- and iron-based alloys). These include: (1) thin struts in the range of 100 µm; (2) improvement of techniques with meticulous vessel preparation, adequate sizing, and postdilatation; (3) imaging guidance; and (4) eliminating implantation of the BRS in small vessels. These methods can result in better embedment of the struts in the vessel wall and enhanced healing of the adventitia, which should result in better performance.

Observations from the ABSORB IV study and other registries support that these concepts are improving outcomes, but the question of whether this will be enough is unclear. With respect to metallic resorbable alloys, it has been shown that platelets would be repelled from the magnesium scaffold, with no thrombosis demonstrated in feasibility studies, and the first-in-man study with iron-based resorbable scaffolds has recently been initiated in China.

With the erosion of pricing and commoditizing of DES technology, industry must look for the next stent technology that will add value to patients and physicians and increase revenues to propel commercial viability. The BRS still carries the potential to differentiate among vendors based on the availability of a successful BRS program, which is now within reach with a reasonable investment. The question remains whether the large corporate stakeholders will be willing to fund these developments, as well as a large randomized clinical trial, which will be critical to resurrect the technology.

REGULATORY PERSPECTIVE

The regulatory agencies initially embraced the technology and approved it for marketing. The US Food and Drug Administration carefully monitored the overseas data and long-term follow-up of the pivotal trials and issued advisory reports. Nevertheless, with experienced gained so far, it would be easier to set bench testing and future clinical trials to facilitate a path to approval for the next-generation DES. If, over the long run, the BRS technology shows superiority with a reduction in events, it would be justified to boost the reimbursement of this technology over latest generation of DES.

Although there is a light at the end of the tunnel with respect to the role of BRSs, enthusiasm is somewhat curbed. It would take a motivated group of scientists and physicians, as well as industry commitment, to solidify the role and the technology of BRSs for coronary intervention and to bring it back to the market.

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Over the past decade, we have witnessed the development, commercialization, and then recall of the Absorb BVS, the first approved BRS. Despite the seductive notion of a stent "doing its job and then disappearing,"[1] and despite randomized trials recruiting thousands of patients, the future role of BRSs after the Absorb BVS experience remains uncertain. DESs continue to be the mainstay of mechanical therapy. Nevertheless, limitations of permanent DESs cannot be ignored, including the risks of target lesion revascularization, neoatherosclerosis, exclusion of adaptive vessel enlargement, and the lack of vasomotion. Furthermore, there is a persistent (although low) risk of very late stent thrombosis. Will BRSs ultimately either supplement or supplant current metallic stent platforms, or will they go the way of the coronary perfusion balloon?

THE FIRST-GENERATION ABSORB EXPERIENCE

The pivotal randomized trials include ABSORB II, ABSORB III, and ABSORB IV, and the respective 4-year, 3-year, and 30-day outcomes of these studies were recently presented at the Transcatheter Cardiovascular Therapeutics 2017 scientific symposium. These trials compared the everolimus-eluting Absorb BVS with the Xience everolimus-eluting DES.[2-4]

In ABSORB II, 501 patients were randomized 2:1 to receive either Absorb or Xience. Three-year data were presented in 2016, and the two mechanistic coprimary endpoints of superior vasomotion and noninferior angiographic late luminal loss were not met. There was no significant difference in vasomotor reactivity for Absorb versus Xience ($P_{superiority}$ = .49). The late luminal loss was larger in the Absorb arm (0.37 mm [standard deviation (SD), 0.45] vs 0.25 mm [SD, 0.25]; $P < .0001$), and this difference did not meet the threshold for noninferiority ($P_{noninferiority}$ = .78). Of the secondary endpoints, the Absorb group had a higher rate of the composite clinical endpoint of cardiac death, TVMI, and clinically indicated target vessel revascularization (10% vs 5%; $P = .043$). This was primarily driven by an increase in TVMI in the Absorb group (6% vs 1%; $P = .011$). Furthermore, in the Absorb arm, nine of 320 (3%) patients had definite or probable ScT compared with 0% in the Xience group ($P = .033$). Of these thromboses, six were very late (≥ 365 days) and thought to be potentially related to late device dismantling. The 4-year follow-up revealed no events after year 3, the point after which there is complete bioscaffold resorption, which was reassuring.

Like ABSORB II, the ABSORB III trial randomized patients 2:1 to either Absorb (n = 1,322) or Xience (n = 686). In addition to eligibility criteria mimicking the earlier trials, ABSORB III also required simple lesions no longer than 24 mm with a reference vessel diameter visually estimated to be 2.5 to 3.75 mm. At 3 years, the primary outcome of TLF (cardiac death, TVMI, and ischemia-driven target vessel revascularization) for Absorb versus Xience was 13.4% and 10.4%, respectively, and was noninferior. Of the secondary outcomes, the procedural endpoints of acute success and immediate postprocedure angiography were significantly lower in the Absorb arm compared with the Xience arm: acute success, 94.3% versus 99.3% ($P < .0001$); in-device minimum lumen diameter, 2.37 versus 2.49 mm ($P < .0001$); and acute gain, 1.45 versus 1.59 mm ($P < .0001$), respectively. At 3 years, ScT was greater in the Absorb arm (2.3% vs 0.7%; $P = .01$). In the first year, higher ScT was found particularly in small vessels (defined as < 2.25 mm). Very late ScT, between 1 and 3 years, was also greater: 0.8% versus 0% ($P = .02$) and was more likely in larger vessels.

The ABSORB IV trial randomized patients in 1:1 to either Absorb (n = 1,296) or Xience (n = 1,308). This study included higher-risk patients with troponin-positive acute coronary syndrome, along with stable coronary artery disease patients. Compared with ABSORB III, better technique (ie, avoiding very small vessels) was used. At 30 days, there was a strong trend of higher device thrombosis with Absorb compared with Xience (0.6% vs 0.2%; $P = .06$).

As a result of the disappointing results from these randomized ABSORB studies, the device was taken off the market in September 2017.

CAN TECHNIQUE OVERCOME FIRST-GENERATION LIMITATIONS?

A retrospective review of the ABSORB III and ABSORB IV data revealed the impact of optimal implantation technique, which included *PSP*, defined as optimal preparation of the lesion, optimal sizing, and high-pressure postdilatation. Even in ABSORB IV, optimal PSP was infrequently implemented.[4] To understand the impact of optimal implantation technique, TLF and ScT rates were determined in 2,973 patients, with 3,149 Absorb-treated coronary artery lesions from five prospective studies (ABSORB II, ABSORB China, ABSORB Japan, ABSORB III, and ABSORB Extend). BRS implantation in properly sized vessels was an independent predictor of freedom from ScT through 1 year (hazard ratio [HR], 0.36; $P = .004$). Aggressive predilation was an independent predictor of freedom from ScT between 1 and 3 years (HR, 0.44; $P = .03$), and optimal postdilation was an independent predictor of freedom from TLF between 1 and 3 years (HR, 0.55; $P = .05$). These results suggest that operator technique was strongly associated with BRS-related outcomes during 3-year follow-up.

BEYOND ABSORB: WHERE DO WE GO FROM HERE?

At this stage, we are left with the results of a first-generation, thick-strutted device.[5-7] The 150-µm thick struts of Absorb BVS have been shown to perturb and disrupt coronary flow in the vicinity of the struts, inducing stagnation zones with lower shear stress leading to thrombus deposition. In addition, thick struts delay and/or prevent endothelial coverage. Unlike a metallic stent, the dismantled scaffold and associated cellular elements can fall into the lumen if not embedded under a tissue layer, leading to very late thrombosis. In this context, next-generation devices will have thinner struts and potentially faster absorption characteristics, a design feature that may be the key to solving the limitations associated with the

TABLE 1. NEXT-GENERATION BRSs WITH STRUTS ≤ 150 µM

Device	Strut Thickness (µm)	Backbone	Coating	Drug	Time Course of Scaffold Erosion
Magmaris (Biotronik)	150	93% magnesium	PLLA	Sirolimus	> 3–6 months
DESolve Cx (Elixir Medical)	120	PLLA	Biodegradable polymer	Novolimus	Uncages the vessel within 6 months, degrades within 1 year, and resorbs within 2 years
Fantom (Reva Medical, Inc.)	125	Desaminotyrosine polycarbonate with iodine atoms	Same as backbone	Sirolimus	> 80% within 1 year; complete resorption within approximately 3 years
Mirage (Manli Cardiology)	125	PLLA: d(dextrorotary)-isomer is < 5% of the total PLA	PLLA	Sirolimus	Approximately 14 months
MeRes 100 (Meril Life Sciences)	100	PLLA	PDLLA	Sirolimus	50% at 4–6 months; complete resorption by 2 years
Firesorb (MicroPort Scientific Corporation)	100–125	PLLA	PDLLA	Sirolimus	3 years

Abbreviations: PDLLA, poly-DL-lactic acid; PLA, polylactic acid; PLLA, poly-L-lactic acid.
Adapted from Sotomi Y, Onuma Y, Collet C, et al. Bioresorbable scaffold: the emerging reality and future directions. Circ Res. 2017;120:1341–1352.

Absorb BVS. These thinner-strut devices will improve scaffold delivery and ease of use but must preserve or enhance radial strength, a substantial obstacle with bioresorbable platforms.

Despite the setbacks with the Absorb BVS, the potential of BRSs continues to drive the field forward.[7] There is still much promise to BRSs, and the dream of performing an intervention with no permanent implant and lower late sequelae seems worth pursuing. These late-term benefits could perhaps include a reduction in late TLF from permanent materials, restoration of physiological flow, noninvasive imaging of the scaffold with CTA or MRA, and maintaining suitability for future percutaneous or surgical treatment options. The enthusiasm for the BRS concept has led to multiple platforms under experimental or clinical investigation. Table 1 outlines several next-generation devices under study.[7]

Finally, before the field broadly moves forward, the ABSORB trials late outcomes, beyond when the device has been completely resorbed, will need to confirm the promise that TLF has leveled off and is superior to a contemporary metallic DES comparator. If the TLF event curves after 3 years favor BRS, the BRS revolution will have only paused, not ended. ■

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