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A new generation of drug-eluting stents: Indications and outcomes of bioresorbable vascular scaffolds

ABSTRACT

Drug-eluting stents (DES) are increasingly being used as a less invasive alternative to coronary artery bypass grafting. Early generation DES had durable polymers that provided acceptable efficacy outcomes but had high rates of stent thrombosis leading to myocardial infarction and death. Second-generation DES have improved outcomes by reducing stent thrombosis and recurrent stenosis. Newer DES with biodegradable polymers have similar efficacy as second-generation DES, but have higher rates of stent thrombosis. This review compares outcomes of bioresorbable scaffolds and looks at stent technology developments that may improve outcomes.

KEY POINTS

Complications with first-generation durable polymer DES—stent thrombosis and restenosis with target lesion revascularization—led to the development of bioresorbable stents.

Bioresorbable and durable polymer metallic DES have similar rates of efficacy and of stent thrombosis.

Bioresorbable DES should be placed in appropriate patient populations and lesion subsets, and limited to arteries larger than 2.25 mm.

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The development of a new generation of drug-eluting stents (DES) has had a dramatic impact on the number of stents used for percutaneous transluminal coronary angioplasty for the treatment of coronary artery disease (CAD). But even second- and third-generation DES fall short when compared with coronary artery bypass grafting (CABG) with regards to the need for repeat reavascularization. CABG is advantageous because it bypasses the entire disease segment of the vessel. Thus for multivessel complex CAD, it is still considered the best choice. Nevertheless, most patients prefer the less-invasive option of stents, so practitioners need to provide the best stent available.

There are 3 primary criteria for DES selection:

- Efficacy for a broad range of patients and lesion complexities that primarily provides consistency in improving measures of angiographic and clinical efficacy
- Safety as determined by the following:
  - Enable healing and promote endothelialization
  - Permit functional endothelium
  - Obtaining complete apposition
  - Reduction or elimination of late and very late stent thrombosis
  - Minimizing the need for long-term dual antiplatelet therapy
- Performance provided by reliable delivery capabilities to the lesion site.

GREAT EXPECTATIONS

New DES must be shown to be superior to previous generation stents. Although preclinical endothelialization and other mechanistic surrogates are good enough to claim an improvement, the traditional method is to compare clinical outcomes with the new stent versus the existing stent in a randomized clinical trial.

The first-generation DES demonstrated superiority

over bare-metal stents and became the default stent of choice for revascularization. But complications of first-generation stents such as stent thrombosis and late restenosis led to the development of second-generation DES, which demonstrated superiority over the first-generation DES. Although third-generation DES have been introduced with bioresorbable polymers, these have not improved clinical outcomes when compared with second-generation DES. Overall, the outcomes of second-generation DES are good, with low event rates that challenge the ability to demonstrate further improvement or superiority with third-generation DES. Nevertheless, there is an ongoing effort to continue to improve the current stents with thinner struts and more biocompatible polymer, biodegradable polymer, or polymer-free stents. **Table 1** shows the evolution of DES from the nonbiodegradable polymer-based stents to the bioresorbable scaffolds, which are completely eliminated from the body.

TABLE 1
Evolution of drug-eluting stents

First generation

Nonbiodegradable (ie, durable) polymer-based thick strut
Sirolimus- or paclitaxel-eluting stents

Second generation

Nonbiodegradable (ie, durable) polymer-based thin strut
"Limus"-eluting stent (eliminated paclitaxel)

Third generation

Biodegradable polymer-based thick or thin strut
"Limus"-eluting stent

Third generation "B"

Polymer-free strut
"Limus"-eluting stents

Fourth generation

Bioresorbable, thick/thin strut
"Limus"-eluting vascular scaffolds (PLLA or magnesium)

"Limus" drugs: biolimus, everolimus, myolimus, novolimus, sirolimus, zotarolimus.
PLLA = poly-L-lactic acid

PROBLEMS WITH DURABLE POLYMER STENTS

Complications with durable polymer DES have included increased local inflammation and neoatherosclerosis. There are reports of subacute stent thrombosis due to lack of adequate expansion and stent apposition. Also reported was late thrombosis, resulting in increased rates of myocardial infarction and death.

These issues motivated engineers to improve and iterate the DES technology. One important technological change is the decrease in strut thickness from 140 µm to as low as 60 µm. The thickness of the polymer coating also has been reduced. The polymer became thinner, more biocompatible, and in some stents, only abluminal. Further developments were to substitute the durable polymer with a biodegradable polymer and perhaps even design a polymer-free stent.

BIORESORBABLE POLYMERS EMERGE

The time course for resorption of bioresorbable polymers ranges from 2 to 15 months, but they all degrade, which should improve long-term outcomes. A meta-analysis of data from the LEADERS trial and ISAR-TEST 3 and 4 found that the bioresorbable polymer stents were associated with significantly lower rates of target-lesion revascularization (P = .029) and stent thrombosis (P = .015) than durable polymer DES at 4 years after implantation.[1] Those results led to the notion that stents with a biodegradable polymer would result in lower rates of stent thrombosis than durable polymer stents; however, that was not the case when stents with biodegradable polymers were compared with second-generation DES.

In the COMPARE II trial,[2] the rates of stent thrombosis and target-lesion revascularization were not statistically different for the thick-strut biodegradable polymer biolimus-eluting stent (Nobori) compared with the second-generation thin-strut permanent-polymer stents (Xience). In the CENTURY II trial,[3] a third-generation biodegradable sirolimus-eluting stent (Ultimaster) had stent thrombosis rates similar to those of a durable polymer everolimus-eluting stent (Xience) 300 days after insertion (4.36% vs 5.27%, respectively). Target-lesion revascularization rates were also about the same for the stents. In the EVOLVE II trial comparing the thin-strut biodegradable everolimus-eluting stent (Synergy) vs the thin-strut permanent-polymer everolimus-eluting stent (Promus), the 12-month target lesion failure rates for the stents were essentially the same.[4]

THE RATIONALE FOR BIORESORBABLE STENTS

Another approach was to use biodegradable scaffolds that will be eliminating from the vessel wall once it "completes the job." The main bioresorbable materials used were polylactic acid or biodegradable metal-

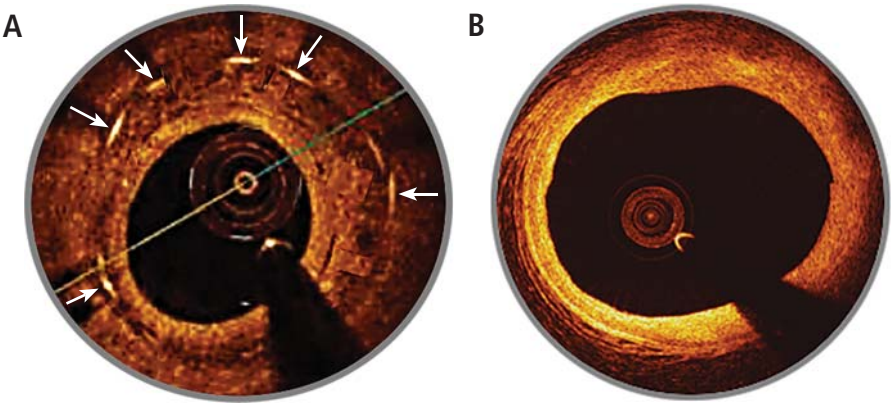

Figure 1. Optical coherence tomographic images show difference in arteries 5 years after implantation of metallic drug-eluting stent (A) and bioresorbable drug-eluting stent (B). Arrows (A) point to remaining stent. In contrast, the bioresorbable stent (B) was completely absorbed.

(A) Reprinted from Atherosclerosis (Kuramitsu S, et al. Long-term coronary arterial response to biodegradable polymer biolimus-eluting stents in comparison with durable polymer sirolimus-eluting stents and bare-metal stents: five-year follow-up optical coherence tomography study. Atherosclerosis 2014; 237:23–29). © 2014 with permission from Elsevier. (B) Courtsey of S. Windecker.

like magnesium. These materials pose a technological challenge. While the biodegradable scaffolds are completely eliminated overtime, they still need to equate the performance of best-in-class drug-eluting stent with respect to efficacy and safety. After the Absorb everolimus-eluting BVS system (Absorb BVS) was launched in Europe, initial studies showed scaffold-related thrombosis rates as high as 3.4%.[5–7] That compares with 0.4% for second-generation DES—a troubling result for a new technology.

Rates of restenosis and stent thrombosis are similar for bioresorbable stents and standard durable polymer stents. But what are the potential added benefits of bioresorbable stents? And will they improve patient outcomes?

Bioresorbable stents certainly appeal to patients who do not want a permanent, rigid, metallic implant. Also appealing are the proposed benefits of restoration of vasomotion, late luminal enlargement, preservation of CABG targets, and relief of angina. Whether bioresorbable stents improve these outcomes has not been established. Currently, there is no long-term evidence of reduced rates of adverse events, although in 1 study, optical coherence tomography images recorded 10 years after implantation of the first bioresorbable stents showed a pristine vessel with no signs of the struts.[8]

Several facts are known about the Absorb BVS:

- Preclinical evidence shows complete resorption and return of vascular function, but this takes 3 to 4 years.
- Imaging data at 5 years from the Absorb cohort B trial show complete resorption of struts, lumen preservation, return of function, and plaque regression.[9]
- In ABSORB III, the pivotal US trial, the stent was within the primary end point showing noninferiority in safety and effectiveness compared with Xience in the first year.[10]
- Absorb clinical trials in Japan and China confirmed ABSORB III results.
- Meta-analysis (> 3,300 patients) confirmed safety and effectiveness of Absorb.[11]
- Real-world Absorb clinical evidence continues to show improving outcomes with optimized implant techniques.
- Absorb stent was approved by the US Food and Drug Administration (FDA) in July 2016; more than 150,000 have been implanted worldwide.

In a 5-year follow-up study, optical coherence tomographic images showed encouraging results (**Figure 1**)[12]: the treated artery healed well, with a large lumen diameter and no remnants of metal. A meta-analysis of 1-year results showed no statistical differences in the patient-oriented composite end point for death, myocardial infarction, or target-lesion revascularization for Absorb vs the durable polymer Xience DES.[11] Stent thrombosis events also were not statistically different, although the numbers numerically were double for Absorb. Numbers also were higher for target-lesion failures, cardiac death, target-lesion myocardial infarction, and ischemic-driven target-lesion revascularization, but, again, they were not statistically significant.

The increased rates of target-lesion revascularization and stent thrombosis were likely attributable to inserting the stents into small-diameter vessels that are probably too small for the Absorb BVS. When small vessels (< 2.25 mm) are eliminated from the analysis, the rates were as follows.

Results for vessels > 2.25 mm:

- Target-lesion revascularization: 6.7 % vs 5.5%
- Stent thrombosis: 0.9% vs 0.6%.

Results for small vessels (< 2.25 mm):

- Target-lesion revascularization: 12.9% vs 8.3%
- Stent thrombosis: 4.6% vs 1.5%.

The lesson is that the Absorb BVS should not be

placed in arteries smaller than 2.25 mm in diameter.

ABSORB II STUDY RESULTS RAISE QUESTIONS

Another concern was uncovered in July 2016 when results were published from the ABSORB II trial on vasomotor reactivity at 3 years.[13] This clinical trial randomized 501 patients in a 2:1 ratio to the Absorb BVS or the Xience DES at 46 sites outside the United States. Assessment for changes in mean lumen diameter between pre- and post-nitrate administration showed no differences between the groups; thus, the Absorb BVS did not achieve a level of superior vasomotor reactivity. There was vasomotor reactivity probably because the surrogate marker was angiographic follow-up and not intravascular ultrasound or tomography.

Further, the coprimary end point of angiographic late luminal loss at 3 years did not meet its noninferiority standard. The Absorb BVS was expected to have lower rates of late lumen loss because the struts are gone and there is less new intimal formation; however, at 3 years, that was not the case.

The rate of acute stent thrombosis also was alarming: 8 cases for Absorb BVS versus none for Xience. This caused alarm, raising the question of why it was happening in these patients 2 to 3 years after implantation.

Animal studies investigating the association of thicker struts and increased thrombogenicity have reported that the 157-µm BVS had much more platelet buildup and thrombogenicity than a 120-µm biomatrix stent. The 74-µm Synergy stent had even lower rates of thrombosis. The reason for increased thrombogenicity with thicker struts requires further study.

Also, an analysis of the secondary cardiac end points at 3 years in ABSORB II found no clinical patient-oriented differences between the Absorb BVS and the Xience stent (20.8% vs 24.0%, respectively; $P = .44$). However, rates of device-oriented clinical end points were significantly higher for Absorb BVS (10.4% vs 4.9%; $P = .043$).[13]

Clearly, the results for Absorb BVS in this study were not positive. One explanation is suboptimal implantation techniques that did not appose the polymer to the wall. A few years ago, focus shifted to an optimal technique for scaffold deployment, which included predilation, appropriate sizing of the scaffold to the size of the vessel, and postdilation with the intention of embedding the polymer in the vessel wall. Multiple studies have reported fewer incidents of stent thrombosis with the implementation of this protocol.[14]

Further studies have continued to report increased rates of late scaffold thrombosis in follow-ups of 30 days to 3 years. This resulted in an advisory letter from the FDA focused on appropriate clinical use of the device and withdrawal of ABSORB from commercial use in Europe and Australia.

TABLE 2
Bioresorbable vascular scaffolds

Name (Marketer)	Strut thickness (µm)	Scaffold	Drug
First generation			
ReZolve (REVA)	228	PolyCarb	SES
ART 18AZ (ART)	170	PDLLA	None
Absorb BVS 1.1 (Abbott)	156	PLLA	EES
Fortitude (Amaranth)	150	PLLA	SES
DeSolve (ELIXIR)	150	PLLA	NES
Magmaris (Biotronik)	150, 120	Mg, PLLA	SES
Second generation			
Fantom (REVA)	125	PolyCarb	SES
Mirage (Manli Cardiology)	125	PLLA	SES
Aptitude (Amaranth Medical)	120	PLLA	SES
DESolve Cx (ELIXIR)	120	PLLA	NES
RENUVIA (Boston Scientific)	≤99		

ART = Arterial Remodeling Technologies; EES = everolimus-eluting stent; NES = novolimus-eluting stent; PDLLA = poly-DL-lactic acid; PLLA = poly-L-lactic acid; PolyCarb = poly-tyrosine-derived polycarbonate; SES = sirolimus-eluting stent

BIORESORBABLE SCAFFOLDS PIPELINE

The field of bioresorbable stents has expanded dramatically (**Table 2**). The first-generation devices range from 228 µm to 120 µm. The hypothesis is that over time, the smaller, resorbable stent scaffold will result in fewer adverse events because no stent or polymer will remain.

This is questionable because one has to believe in the vulnerable plaque theory, which assumes potential eruption of plaques. The Absorb can actually seal a thin cap atheroma and necrotic core over time. It seems that this technology can cause some late lumen enlargement and seal an existing plaque, which may have implications for the future.

SUMMARY

This is the current state of the Absorb BVS:

- More than 150,000 implanted globally
- Received FDA approval in July 2016
- Should not be used in small vessels (ie, lumen diameter < 2.25 mm)
- Thrombosis rates 2 to 3 years after implantation are of concern
- Focusing on appropriate surgical implantation technique can improve outcomes.

Overall, use of bioresorbable stent technology is intriguing. While there is ongoing patient preference for bioresorbable technology, clinical trial results raise the question of whether bioresorbable scaffolds are inferior to best-in-class DES. Improving the scaffold technology and the implantation techniques may equate the short-term outcome of the bioresorbable scaffolds with metallic stents with the hope that over time (when the scaffold is gone), the advantage will be with the bioresorbable scaffolds. Meanwhile, the technology is still seeking its best clinical utility, and a matching performance to the best-in-class DES.

Time will tell whether 5 to 10 years after implantation, BRS technology will outperform durable metallic stents.

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