A review of bioresorbable scaffolds: hype or hope?

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INTRODUCTION
Bioresorbable scaffolds (BRSs) are considered a major advance in the field of percutaneous coronary intervention. They are designed to overcome the drawbacks of metallic drug-eluting stents (DESs), which include chronic local inflammatory reaction, absence of physiological coronary vasomotion, late stent thrombosis and the prevention of future coronary artery bypass surgery at the same site. The Absorb Bioresorbable Vascular Scaffold (BVS; Abbott Vascular, Santa Clara, CA, USA), one of the most extensively evaluated BRSs, has been subjected to numerous studies. This review will critically analyse the potential safety, efficacy and complications of BRSs.

POTENTIAL BENEFITS OF BIORESORBABLE SCAFFOLDS
The BRS system works in three phases to achieve vascular reperative therapy: revascularisation, restoration and resorption. In the revascularisation phase, the BRS is intended to mimic the characteristics of the metallic DES (i.e. scaffold deployment with minimum recoil, provision of high radial strength and controlled release of an antiproliferative drug). Subsequently, in the restoration phase, vasomotion of the vessel is re-established, and there is a transition from active to more passive support. The resorption phase is characterised by the degradation and metabolism of the scaffold.

The BRS offers unique advantages that are not found in a metallic DES: (a) The restoration of coronary vasomotion is one of the main benefits. The BRS allows recovery of the endothelial function and a significant increase in the luminal diameter of the scaffold segment in response to vasoactive agents. The vessel recovers the ability to respond to physiological stimuli, which may translate into reduced anginal episodes and a better functional capacity than when the metallic DES is used. (b) In contrast to the metallic DES, the BRS has the potential for late lumen enlargement, starting at the resorption phase. Multimodality imaging has documented late lumen enlargement among patients in the ABSORB Cohort A and Cohort B trials. (c) Following the resorption phase, BRS struts are replaced by neointima, which resembles the thick fibrous cap of a de novo atherosclerotic lesion. The BRS may offer security in terms of stabilisation of a vulnerable plaque and possibly also prevent acute coronary syndrome, although further studies are necessary to determine whether this potential effect can be achieved. (d) After complete resorption, no foreign body is left in the vessel. Hence, the risks of very late stent thrombosis are potentially eliminated. (e) The BRS is relatively more transparent than the metallic DES and facilitates serial noninvasive imaging (coronary computed tomography and magnetic resonance imaging). (f) In patients needing repeat revascularisation, the BRS may permit surgeons to carry out an anastomosis of bypass grafts at distal segments.

USE IN CLINICAL PRACTICE
The first BRS used in humans was the Igaki-Tamai stent (Kyoto Medical Planning Co Ltd, Kyoto, Japan). Made from poly-L-lactide monofilament, the Igaki-Tamai stent is a coil stent that has a zigzag helical design and is self-expandable when heated. The stent struts disappear within three years. Immediate and six-month results suggested the safety and efficacy of the novel Igaki-Tamai stent. Its main drawbacks are the need for an 8-French guiding catheter for stent delivery, the absence of antiproliferative drug elution, and the use of a heated contrast dye that may result in vessel wall injury. Further research and development of this stent was interrupted by the evolution of the DES. However, the long-term clinical outcomes of the Igaki-Tamai stent are reassuring and lay the foundation for studies on various BRSs.

The most extensively studied BRS to date is the BVS. It is composed of a balloon-expandable poly-L-lactide scaffold (150-µm thick), which degrades completely in 2–3 years, and a thin, bioabsorbable poly-D, L-lactide coating for controlled release of everolimus. Radiopaque platinum markers at each end of the scaffold enable clear visualisation on imaging. The BVS was first evaluated in the ABSORB clinical trials (Cohorts 1, 2, 3 and 4).

Keywords: bioresorbable scaffold, coronary artery disease

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A and B) and showed encouraging results.\textsuperscript{(14,15)} Subsequently, a number of single-arm studies and a few randomised controlled studies were published.

The other BRS that has been evaluated in clinical studies is the DESolve\textsuperscript{®} Scaffold (Elixir Medical Corporation, Sunnyvale, CA, USA).\textsuperscript{(26)} Similar to the BVS, it is composed of a poly-L-lactide scaffold and elutes either anti-proliferative myolimus (first-generation) or novolimus (second-generation). In comparison to other BRSs, the DESolve Scaffold is believed to have a wider range of expansion, with reduced risk of strut fracture and self-correction of minor malapposition.

**CURRENT SUPPORTIVE EVIDENCE**

The vast majority of data that supports the use of the BRS in humans comes from studies using the BVS. The first-generation BVS (BVS 1.0) was tested in a series of 30 patients from the ABSORB Cohort A study.\textsuperscript{(14)} Although the cohort demonstrated encouraging long-term outcomes,\textsuperscript{(15,16)} the first-generation BVS demonstrated a slightly higher rate of acute and late recoil.\textsuperscript{(18,19)} To overcome this limitation, the strut design and the polymer’s manufacturing process was modified in the revised version (BVS 1.1). This was tested in 101 patients from the ABSORB Cohort B study. Alteration of the scaffold design led to a significant improvement in the medium and immediate-term outcomes of this novel second-generation BVS.\textsuperscript{(15)} This paved the way for the conduct of a randomised controlled trial comparing the BVS with the metallic DES. A five-year follow-up study on the same cohort of patients (i.e. Cohort B) yielded low rates of restenosis and major adverse cardiac events.\textsuperscript{(20)} To date, there have been six randomised trials that compared the BVS with the DES. The various studies are illustrated in Table I.

**Table I. Randomised trials of the Absorb Bioresorbable Vascular Scaffold (BVS).**

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Primary endpoint</th>
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<tbody>
<tr>
<td>ABSORB II\textsuperscript{(21)}</td>
<td>Compare BVS vs. CoCr-EES</td>
<td>Angiographic vasomotion at 3 yr, and difference in minimum lumen diameter after the index procedure and at 3 yr</td>
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<tr>
<td>ABSORB III\textsuperscript{(22)}</td>
<td>Compare the safety and efficacy of BVS vs. CoCr-EES</td>
<td>Target lesion failure at 1 yr</td>
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<tr>
<td>ABSORB Japan\textsuperscript{(23)}</td>
<td>Compare the safety and efficacy of BVS vs. CoCr-EES prior to complete bioreabsorption</td>
<td>Target lesion failure at 1 yr</td>
</tr>
<tr>
<td>ABSORB China\textsuperscript{(24)}</td>
<td>Assess the clinical and angiographic efficacy of BVS vs. CoCr-EES</td>
<td>Angiographic in-segment late loss at 1 yr</td>
</tr>
<tr>
<td>EVERBIO II\textsuperscript{(25)}</td>
<td>Compare the performance of BVS vs. CoCr-EES and biolimus-eluting stents in all-comer patients</td>
<td>Angiographic late lumen loss at 9 mth</td>
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<tr>
<td>TROFI II\textsuperscript{(26)}</td>
<td>Compare the arterial healing response at 6 mth following the use of BVS vs. CoCr-EES in patients with STEMI</td>
<td>Optical frequency domain imaging-derived healing score assessed at 6 mth</td>
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CoCr-EES: cobalt-chromium everolimus-eluting stent; STEMI: ST-segment elevation myocardial infarction

Follow-up data from this trial was reported at the Transcatheter Cardiovascular Therapeutics 2015 conference. Although the patient-oriented composite endpoint did not differ between the two groups, target lesion failure (a composite of cardiac death, target-vessel myocardial infarction and clinically indicated target-lesion revascularisation) was significantly higher in the BVS group (BVS 7.0% vs. CoCr-EES 3.0%; p = 0.07).

**ABSORB III**\textsuperscript{(22)} evaluated the relative safety and efficacy of the Absorb BVS versus the CoCr-EES in patients with coronary artery disease. The primary endpoint was target lesion failure (a composite of cardiac death, target-vessel myocardial infarction or ischaemia-driven target-lesion revascularisation) at one year. Target lesion failure occurred in 7.8% of patients in the Absorb group and 6.1% of patients in the CoCr-EES group (p = 0.007 for non-inferiority; p = 0.16 for superiority).\textsuperscript{(22)} Despite the performance of the Absorb BVS being comparable to that of the CoCr-EES, there were some concerns. The overall device thrombosis rate was reported to be higher in the Absorb group than in the CoCr-EES group (1.5% vs. 0.7%), although the difference was not significant. In comparison to the CoCr-EES group, the rate of subacute device thrombosis was significantly greater in the Absorb group.\textsuperscript{(22)} One of the important limitations of the ABSORB III study was its inability to examine low-frequency events such as cardiac death and device thrombosis. Clinical follow-up in this trial will be performed for five years and the results are awaited.

An overview of all trials on BVS showed no significant difference in one-year outcomes between the BVS and CoCr-EES for most endpoints. A pooled meta-analysis of four randomised trials showed similar results for both the BVS and CoCr-EES in patient- and device-oriented composite endpoints at one year.\textsuperscript{(27)} The BVS was developed to circumvent the limitations of the metallic DES, which are evident after one year of implantation. Imaging evidence supports the novel attributes of the BVS,\textsuperscript{(28)} but improved late clinical outcomes are required to definitively show the superior benefit of the BVS, as compared to the metallic DES. Hence, the results are not expected to become obvious until 3–5 years after implantation, and there is a need to wait for the clinical outcomes of ongoing large-scale randomised trials (e.g. ABSORB IV).
Data from multiple single-arm trials have provided reassurance of the safety and efficacy of the BVS. Interim analysis of the ABSORB EXTEND study revealed low rates of major adverse cardiac events and scaffold thrombosis at one year. Although the majority of studies on the BVS have been on stable patients and simple lesions, with better understanding of the BVS and improved operator expertise, it is now being used in complex lesion subsets. There is data on the application of the BVS in acute coronary syndrome, bifurcation lesions, left main disease, chronic total occlusion, calcific lesions, in-stent restenosis and multi-vessel disease.

**Implantation Technique**

The design and properties of the BVS are different from that of the metallic DES. Hence, appropriate technique for BVS implantation is vital for procedural success and clinical outcomes. A consensus has been reached on the optimal implantation procedure, and the key points are listed as follows:

**Preparation of lesion**

Predilatation of the lesion should be accomplished with a suitably sized balloon that matches the reference vessel diameter (sized 1:1). The BVS should not be implanted into lesions that have suboptimal results after predilatation (i.e., residual stenosis > 40%). If the predilatation results are unsatisfactory, BVS deployment will result in underexpansion and a predisposition to scaffold thrombosis and restenosis.

**Proper sizing of vessel**

Accurate vessel sizing before scaffold deployment is crucial for a favourable procedural outcome. Imaging with intravascular ultrasonography or optical coherence tomography is ideal for analysis of the vessel and selection of the scaffold size. It may not be practical to perform intravascular imaging in all cases; an assessment of the angiogram comparing the vessel lumen with the dimensions of the guiding catheter is reasonable. In addition, the balloon that is used for predilatation (sized 1:1) can be useful for scaffold sizing. The scaffold should cover at least 2 mm of the healthy vessel at either edge of the lesion.

**Consideration of expansion limit**

The BVS expansion limit is 0.5 mm above the nominal size. A 3.0-mm BVS should not be diluted beyond 3.5 mm, above which the struts are likely to fracture.

**Post-dilatation with noncompliant balloon**

Routine post-dilatation with a noncompliant balloon at high pressure is recommended for optimal outcome.

**Prescription of dual antiplatelet therapy**

Dual antiplatelet therapy should be prescribed as per the guidelines.

In contrast to metal stents, the deployment of the BVS must occur gradually (balloon inflation of 2 atm at every fifth second) until complete expansion. The deployed pressure should be maintained for at least 30 seconds. A successful procedure should result in no significant residual stenosis (<10%), total scaffold expansion and optimal strut apposition without complications. Many interventional cardiologists are still not familiar with the appropriate techniques of BVS implantation. The procedure is not straightforward and requires a learning period for operators to be familiar with the technique. Ideally, new users of the BVS should gradually build up their expertise, starting with stable patients and simple lesions, and as experience is gained, they may attempt the procedure on more complex lesions.

**Drawbacks and Concerns**

The drawbacks of the BRS are related to the mechanical properties of the scaffold structure and the technique of stent implantation. The higher strut thickness limits deliverability and increases nonlaminar flow, and the higher crossing profile restricts its use in difficult anatomical settings. The strut thickness of the BRS may result in more frequent side-branch occlusions and contribute to periprocedural myocardial infarction. Early causes of BRS failure include scaffold dislodgement, acute recoil and scaffold thrombosis. Scaffold dislodgement has principally been reported in lesions that are not adequately predilated and on the second insertion of the same scaffold. Early scaffold thrombosis reported in the GHOST-EU registry suggests that there is scope for improvement in terms of lesion selection and optimisation of BRS implantation. Acute recoil of the BRS is another important drawback related to improper stent implantation technique.

Very late stent thrombosis events are not expected in view of complete resorption of the BRS. However, such events have been documented in the literature and may indicate delayed healing, with the need to continue dual antiplatelet therapy beyond the first year. There is no convincing data or evidence in favour of shortening the duration of dual antiplatelet therapy in BRS-implanted individuals. Neoatherosclerosis, scaffold restenosis and acquired coronary aneurysm are the other late causes of BRS failure.

**Conclusion**

The concept of the BRS is logical and attractive. The short- and medium-term results are encouraging, but its long-term safety remains unknown. Therefore, more randomised long-term clinical data will be required to determine whether the theoretical advantage of the BRS can translate into routine practice. The superiority of the BRS over the second-generation DES has not been proven. Use of the BRS can be considered in a carefully selected group of individuals (e.g., young patients, lesions without significant calcification and tortuosity, long lesions, multi-vessel disease and lesions with spontaneous coronary artery dissection), with strict adherence to an optimal implantation technique.

**References**