Review

Update on coronary artery bioresorbable vascular scaffolds in percutaneous coronary revascularization

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Coronary angioplasty was first introduced in 1977. From plain old balloon angioplasty to the introduction of bare metal stents in 1986 and dual antiplatelet therapy in 1992 to much more later on. Due to the unacceptable rate of stent restenosis, drug eluting stents (DES) were introduced in 2000. The first generation showed an increase in late stent thrombosis which led to the introduction of the second generation DES with biocompatible or biodegradable polymers and thinner platforms. However very late stent thrombosis and late restenosis might still pose problems in the latter. Furthermore, there has been major debate regarding the impact of long-term vessel caging on normal vasomotricity and long-term positive remodeling. To resolve these issues, the bioresorbable vascular scaffolds (BVS) were launched into the real world in 2011, showing promising initial results. Multiple randomized trials, meta-analyses, and registries were performed, mainly with the Absorb Bioresorbable Vascular Scaffold System (Abbott Vascular, Chicago, IL, USA). This new technology is hindered by certain features, such as the BVS radial strength, its strut thickness, and the inflammatory process related to scaffold degradation. Moreover, there is known data indicating higher thrombosis rate with the Absorb BVS compared with the new generation of DES, despite similar cardiovascular death. In this review, we discuss the clinical procedural and technical evidence on BVS, with emphasis on their clinical impact. We finally tackle the future directions on device and procedural improvement while asking: is the bioresorbable technology still the way to the future?

Keywords

Percutaneous interventions; Bioresorbable vascular scaffolds; Outcomes

1. Introduction

Drug-eluting stents (DES) caused a remarkable reduction in the restenosis rate [1], but led to a progressive increase in late stent thrombosis (ST) [2]. The latter was reduced with the development of second-generation DES which provided thinner struts with a biocompatible or biodegradable polymer. Despite that, there still remains cases where ST - especially very late ST (VLST) - and late restenosis occur [3]. ST remains an issue due to the permanent metallic struts, possible inflammation caused by polymer degeneration, and/or negative effects of antiproliferative drugs on endothelial regeneration. Furthermore, long-term vessel caging impairs arterial physiology impeding normal vasomotricity while promoting long-term positive remodeling. With all that, DES still conferred excellent outcomes with very low restenosis rates and even much lower VLST (occurring more than 1 year).

In 2000, the first in man use of the self-degrading Igaki-Tamai coronary stent [4] -the first bioresorbable vascular scaffold (BVS or BRS)- showed favorable outcomes. BVS necessarily had to be compared to DES which already conferred very low rates of adverse events. In 2011, BVS were finally introduced into clinical practice, showing good initial short term outcomes [5]. It was thought they conferred multiple advantages over metallic stents including: reduction in long-term adverse effects of permanent materials, restoration of vasoreactivity in the long term, maintaining the applicability of future treatment options for multivessel disease and long lesions, use in STEMI patients who might have less extensive disease, pediatric applications and the relevance to perform noninvasive imaging, such as computed tomographic angiography or magnetic resonance imaging [5, 6].

Several studies were conducted, mainly with the Absorb BVS System (Abbott Vascular, USA), with nearly 200,000 devices implanted worldwide by June 2017 [7]. The Absorb BVS consists of a 150-μm-thick bioresorbablepoly(l-lactide) scaffold with a 7-μm thick everolimus eluting bioresorbable poly(d,l-lactide) coating.

Intracoronary imaging (ICI) studies highlighted the potential advantage of BVS showing recovery of pulsatility at 12 months, and late lumen gain with plaque regression between 2 and 5 years [5, 6]. However, multiple studies showed that those scaffolds still had multiple limitations like low radial strength while having thick struts. This made BVS less ideal for complicated and calcified lesions where deliverability and stent expansion would be problematic. Furthermore, there was concern regarding higher episodes of stent thrombosis that was seen in the Absorb BVS as compared to DES. This was postulated to be due to scaffold degeneration causing local inflammation and consequently thrombosis.

Table 1. Main prototypes of bioresorbable vascular scaffolds

Scaffold	Manufacturer	Polymer	Eluted drug	Strut thickness (μm)	Radial Strength (kPa)	Resorption time (months)	Development status
Igaki-Tamai	Kyoto Medical	PLLA	None	170	73	24-36	CE mark
Absorb 1.1	Abbott Vascular	PLLA	Everolimus	156	250	24-48	CE mark - FDA
DESolve	Elixir Medical	PLLA	Novolimus	150	218	12-24	CE mark
Magmaris	Biotronik	BIOlute coating	Sirolimus	150	313	12	CE mark
ART 18Z	Terumo	PDLLA	drug free	170	NA	18-24	CE Mark

CE, Conformité Européenne; NA, not available; PDLLA, poly dl lactic acid; PLGA, poly lactic-co glycolic acid; PLLA, poly l lactic acid; PTD-PC, poly-tyrosine-derived polycarbonate.

In this review, current data regarding technical and clinical evidence on BVS will be discussed while considering future directions.

2. Clinical data on bioresorbable vascular scaffolds

Several BVS with variable resorption from 1 to 3 years have been examined in clinical trials. All are impregnated with an antiproliferative limus family drug. The characteristics of the main promoted BVS are summarized in Table 1. The clinical/historical data are outlined as follows:

2.1 First in man experience: the Igaki-Tamai stent

It's made from non-drug-eluting, high-molecular-weight poly-l-lactic acid (PLLA) monofilaments [4] with a helical coil pattern and a strut thickness of 170 μm. It is the first fully BVS tested in humans (Kyoto Medical Planning, Japan). In 2012, an observational, nonrandomized clinical trial of 50 patients showed that survival rates free of cardiac death and major adverse cardiovascular events (MACE) were 98% and 50% respectively. Imaging also showed positive vessel remodeling and lumen enlargement. This experience paved the way for future development of BVS.

2.2 The absorb BVS

2.2.1 Absorb BVS in randomized clinical trials (RCTs) (Table 2)

○ In the **ABSORB II trial**, BVS was compared to the Xience metallic EES (Abbott Vascular, USA). At 1 year, use of BVS conferred lower rates of unstable angina as compared to EES use (20% vs. 30%; P = 0.04), while non-significant difference was seen for the device-oriented composite end point (DOCE). At 3-year follow-up, the Xience group had a significantly lower vasomotor reactivity with a non-inferior late luminal loss (LLL); while the Absorb group showed a higher rate of DOCE due to target vessel MI, including periprocedural MI. The patient-oriented composite endpoint, angina status, and exercise testing were not statistically different among both devices [8].

○ In **ABSORB Japan**, a single-blind, multicenter and randomized trial, the rate of TLF was non-significantly higher in the BVS than in the EES arm. Only the BVS arm had VLST and this was seen at a rate of 1.6% between one and two years [9]. Authors concluded that under-expansion of BVS was associated with greater negative remodeling and LLL which might explain the worse outcomes of BVS compared to EES [10].

○ The **EVERBIO II trial** showed that the use of BVS was associated with a non-significant increase in device related adverse events at 2 years as compared to EES and a significant increase in device related events as compared to Biolimus Eluting Stent [11].

○ The **ABSORB-STEMI TROFI II** randomized trial studied the use of Absorb vs. Xience stents in patients presenting with STsegment elevation MI (STEMI). The Absorb group showed a lower optical coherence tomography (OCT)-based healing score at 6 months than the EES group (1.74 vs. 2.80; $P < 0.001$ for noninferiority). The DOCE was similarly low in the two groups [12]. BVS resulted in more evidentendothelium-dependent and -independent vasomotion of the infarct related artery, compared with EES at 3 years. Also, BVS and EES had mostly adequate and similar functional microcirculatory parameters. Remaining strut footprints and larger number of intraluminal scaffold dismantling (26.3% vs. 0%; P = 0.049) were seen on OCT in the BVS group. Clinical significance and implications of these findings are discussed further [13].

○ In the **ABSORB III** randomized **trial**, the primary end point of TLF at 1-year follow-up was non inferior in the BVS group relative to the EES group. Cardiac death (0.6% vs. 0.1%; P = 0.29), target-vessel MI (TVMI; 6.0% vs. 4.6%; P = 0.18), and ischemia-driven TLR (3.0% vs. 2.5%; P = 0.50) were not significantly different. However, device thrombosis (DT) occurred in 1.5% of patients with BVS compared to 0.7% with EES (P = 0.13) [14]. However, patients with stable symptoms and noncomplex lesions were excluded, limiting the generalizability of this data. At 25 months, Absorb had higher MACE compared to Xience (TLF 10.9% vs. 7.8%; P = 0.03) which were mainly seen in the smallest-caliber treated vessels with a reference vessel diameter (RVD) of < 2.25 mm by quantitative coronary angiography (QCA) [14].

Based on the above data, the Food and Drug Administration released a safety alert in March 2017 recommending the adherence to dual antiplatelet therapy (DAPT) during BVS use while avoiding their use in small vessels to help decrease MACE [15].Three-year data for the ABSORB III trial then came out with the BVS group having higher event rates than EES, particularly TVMI and DT. Finally, a recent 5-year Follow-Up of the ABSORB III Trial, showed a higher rate

Table 2. Randomized clinical trials comparing BVS and DES

Clinical trial (year)	Number of patients (BVS : DES)	Primary end point	Primary outcome	DOCE rate (%; BVS vs. DES)	Scaffold thrombosis rate (%; BVS vs. DES)
ABSORB II (2015)	501 (2 : 1)	Vasomotion/minimal lumen diameter (3 years)	Ongoing (3-year follow-up)	5 vs. 3 (P = 0.35)	0.9 vs. 0 (P = 0.55)
ABSORB China (2015)	480 (1 : 1)	In-segment lumen loss (1 year)	0.19 ± 0.38 mm vs. 0.13 ± 0.38 mm (P = 0.01)	3.4 vs. 4.2 (P = 0.62)	0.4 vs. 0 (P = 1.00)
ABSORB Japan (2015)	400 (2 : 1)	Target-lesion failure (1 year)	4.2% vs. 3.8% (P_{ni} < 0.0001)	NA*	1.5 vs. 1.5 (P = 1.00)
EVERBIO II (2015)	240 (1 : 2)‡	Late lumen loss (9 months)	0.28 ± 0.39 vs. 0.25 ± 0.36 (P = 0.30)	12 vs. 9 (P = 0.6)	1.3 vs. 0
STEMI-TROFI II (2015)	191 (1 : 1)	Healing score§ (6 months)	1.74 vs. 2.80 (P_{ni} < 0.001)	1.1 vs. 0	1.1 vs. 0
ABSORB III (2015)	2,008 (2 : 1)	Target-lesion failure (1 year)	7.8% vs. 6.1% (P = 0.16, P_{ni} = 0.007)	10.9 vs. 7.8% (P = 0.03)	1.5 vs. 0.7 (P = 0.13)
AIDA-2015	1,845	24-month TVF	11.7% vs. 10.7% (P = 0.43)	NA*	3.5% vs. 0.9% (hazard ratio, 3.87; P < 0.001)

BVS, bioresorbable vascular scaffold; DES, drug-eluting stent; DOCE, device-oriented composite end point; NA, not available; P_{ni}, P value for noninferiority. *DOCE corresponds to the primary end point. ‡Patients with DES were treated 1 : 1 with either everolimus-eluting stents or biolimus-eluting stents. §Score based on optical coherence tomography imaging.

of cumulative adverse event after BVS compared with EES which mainly ended at 3 years, coincident with complete scaffold resorption [16].

○ The **AIDA trial** (Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial) randomly allocated 1845 patients undergoing percutaneous coronary intervention (PCI) to receive either a BVS or a DES [17]. Target-vessel failure (TVF, a composite of cardiac death, target-vessel MI, or target-vessel revascularization) was the primary end point. Because of safety concerns, the data and safety monitoring board advocated early disclosure of the study results. In the 2-year follow-up, definite or probable DT occurred in 3.5% vs. 0.9% (hazard ratio, 3.87; $P < 0.001$) with cardiac death occurring in 2.0% and 2.7%, respectively [8]. In the majority of patients (98.6% and 74%, respectively), pre and post-dilation were performed in the BVS group, however the 2-year rate of definite or probable ScT remained unacceptably high.

2.2.2 Absorb BVS in registries and retrospective analyses

Registries included a large number of patients with different plaque morphologies and clinical presentations allowing us to detect both common and uncommon features of using BVS. Stent thrombosis remained to raise a lot of concern which led to the design of randomized studies targeting that issue.

Initial registries were single centered and/or had 12 months' short term follow up. For example, the **ABSORB Extend study** (first 512 patients enrolled; 12-month MACE 4.3) [18] showed that minor routine oversizing of the BVS followed by high pressure post-dilatation was safe with a low rate of MACE and no reported ScT. In the **Polish National registry** (591 patients) [19], in patients with acute coronary syndrome (ACS) and those with complex lesions, early in-hospital results showed no significant differences between BVS and EES in the primary composite MACE endpoint. More recently, in the RAI Registry, a total of 1,505 patients were enrolled with predilatation and post-dilatation performed in practically all the cases. At one-year follow-up, TLR and ScT rates were 3.3% and 1.3%, respectively. TLR was significantly higher in the off-label group (4.0% vs. 2.2%; P = 0.05) while a trend towards a higher ScT rate was observed in the off-label group (1.7% vs. 0.6%; P = 0.06). At multivariate analysis, treatment of in-stent restenosis, chronic total occlusion and BVS diameter were independent predictors of TLR [20].

In the large multicenter **Ghost-EU registry,** authors looked at 1189 patients who underwent angioplasty with the Absorb BVS [21]. The only independent predictor of TLF was diabetes (HR 2.41, P = 0.006) and TLF occurred at a rate of 4.4% at 6 months. The cumulative incidence for definite or probable ScT was concerning with 1.5% at 30 days and 2.1% at 6 months. Independent predictors in this registry included ostial lesions (P = 0.049) and impaired left ventricular ejection fraction (P = 0.019). In both this registry and the **BVS registry Gottingen,** the rates of device-related complications with BVS were not negligible and did not decline over time [22].

Finally, the **ISAR-ABSORB registry** included 419 patients (39% with ACS) undergoing PCI with BVS [23]. The incidence of TLR and definite ST at 12 months were 13.1% and 2.6% respectively. At 2 years, there was a 21.6% MACE rate and a 4.2% rate of proven or probable ST [23].

2.2.3 Absorb BVS in meta-analyses

Lipinski et al. looked at 10510 patients treated with BVS where post-dilatation was performed in 52% of lesions. Compared to DES, there were higher rates of MI (OR 2.06, P = 0.002) and definite or probable ScT (OR 2.06, P = 0.03) in the BVS group [24]. No significant difference was found for all-cause and cardiovascular mortality.

Collet C. *et al.* looked at 16,830 patients treated with ABSORB. There was 1.8% overall rate of definite or probable ScT, and the residual diameter stenosis percentage was the only factor associated with ScT [25]. A similar meta-analysis of 1730 patients was conducted by the same authors with 24 months follow-up [26]. There was a higher incidence of DT in patients treated with Absorb BVS compared to those treated with EES, with 92% of the very late ScT occuring in the absence of DAPT. They also had a higher tendency for TLF (OR 1.48; P = 0.09) driven by a greater risk of TVMI and ischemia-driven TLR. No difference was found for cardiovascular mortality.

Polimeni *et al.* looked at 5219 patients and had similar findings for BVS with higher rates of TLF (9.4% vs 7.2%; OR = 1.33; P = 0.008) and DT (2.3% vs 0.7%; OR = 3.22; $P <$ 0.0001) compared with EES. BVS were associated with worse clinical outcomes at two-years and higher incidence of both early (within 30 days after implantation) and very-late ($>$ 1 year) DT [27].

Elias *et al.* looked at 3258 patients treated with BVS and 2319 with EES. The BVS group had higher rates of TLF (OR 1.34; P = 0.003), definite/probable DT (OR 2.86; $P < 0.001$) extending beyond 1 year of follow-up (OR 4.13; $P < 0.001$), clinically indicated or ischemia driven TLR, and all-cause MI. There was no significant difference with respect to cardiac death [28].

Sorrentino S *et al.* looked at 5,583 patients undergoing Absorb vs. metallic EES with a mean follow-up of 2 years. There was a higher incidence of TLF (9.6% vs. 7.2% with number needed to harm: 41; $P < 0.003$) and ST (2.4% vs. 0.7% with number needed to harm: 60; $P <$0.0001) in the BVS group. The increased risk for ScT was consistent across early ($<$ 30 days), late (30 days to 1 year), and very late ($>$ 1 year) periods [29].

A meta-analysis by Cassese S *et al.* compared BVS vs. EES in 5583 patients for mid-term clinical outcomes. BVS displayed a higher risk of TLF (odds ratio = 1.35; P = 0.0028) and ScT (OR 3.24; $P < 0.0001$) compared to EES particularly after 1 year from implantation [30].

De Rosa *et al.* recent meta-analysis on 2,318 patients aimed to assess the safety and efficacy of everolimus eluting-BVS vs. EES in ACS patients undergoing PCI. There was a higher risk of definite ST/ScT in patients treated with BVS compared to EES (2.3% vs. 1.08%, P = 0.03) and an increased risk of TLR at mid-term (9.5 months) follow-up [31]. Finally, two recent meta-analyses done on 10 and 6 randomized controlled trials respectively with 3 years follow-up found that BVS was inferior to second-generation DES in both safety and efficacy [32, 33].

2.3 Special situations where BVS has been studied

2.3.1 Acute coronary syndromes (ACS)

Mid-term outcome data for BVS and 2nd generation DES were compared in a recent systematic review and meta-analysis on a total of 1758 patients in the setting of ACS. BVS had higher risk of TLR and ScT at follow-up than the 2nd generation DES. ScT was the key factor determining the decreased safety and effectiveness of BVS relative to DES [34]. Other studies cited in this article (like AIDA and TROFI II trials) have also included patients with ACS and shown comparable results.

2.3.2 In-stent restenosis (ISR)

The prospective multicenter study RIBS VI included 141 patients treated with BVS for either BMS-ISR or DES-ISR. The study suggested that the use of BVS in patients with ISR was effective and safe. In this challenging anatomic scenario, BVS obtained late angiographic and clinical results similar to DEB but inferior to EES [35].

2.4 Actual CE-mark approved BVS

2.4.1 DESolve

Like Absorb, the DESolve (Elixir Medical) BVS, has a PLLA backbone with a biodegradable polylactide-based polymer coating that elutes the antiproliferative drug novolimus. The unique features of the DESolve scaffold include (1) intrinsic self-correcting deployment that becomes operative in the event of minor strut malapposition, and (2) relative elasticity/ductility which provides a wide range of expansion without risk of stent fracture [36].

The first series of the DESolve showed a LLL at 6 months of 0.19 $\pm$ 0.19 mm, which was similar to that seen with contemporary DES. The second series of the DESolve was assessed in the DESolve Nx trial. LLL at 6 months was 0.20 $\pm$ 0.32 mm; MACE rate at 24 months was 7.4%. No definite ScT were observed [36].

2.4.2 ART pure

This BVS has a 170 μm PDLLA or poly (l-lactide-co-d, l-lactide) backbone with no antiproliferative drug. The ART-DIVA trial (Arterial Remodeling Transient Dismantling Vascular Angioplasty), the first-in-man trial enrolled 30 patients, demonstrated 1 case of ischemic-driven TLR at 6 months. No other clinical result is available to date [37].

2.4.3 Resorbable magnesium scaffold (RMS)

It was developed in parallel to the PLLA polymeric scaffold [38]. However, RMS has a good radial strength with minor early elastic recoil and a superior compliance to vascular anatomy. They are electropolished which helps with trackability. Their implantation is more practical because of single step inflation. The safety and performance of the DREAMS 2G scaffold (i.e. 2^{nd} generation; Magmaris®, Biotronik AG) was assessed in a pooled outcomes study of BIOSOLVE-II and BIOSOLVE-III with 184 patients assessed respectively. At 24 months, the TLF, TVMI, and TLR rates were 5.9%, 0.9%, and 3.4% respectively with no definite or probable ScT. The BIOSOLVE-IV was a single-arm, multicenter registry that included data of 400 patients with a 12-month follow up. RMS showed similar performance to second-generation DES [39].

However, available evidence is currently limited to small observational studies. Positive outcomes have been reported for up to 3 years after second-generation drug-eluting RMS implantation in clinical trials. However, evidence is still lacking for this novel device, and more long-term clinical outcomes from the BIOSOLVE trials and further randomized trials involving other clinical and lesion subsets are needed in the future [39].

3. Characteristics and procedural aspects of the "vascular restoration"

3.1 Biodegradation and vascular restoration

The main theoretical advantage for BVS was thought to be restoration of vasomotricity [6, 40]. Data from randomized trials showed that the restoration of vasoreactivity/vasomotion was directly proportional to the degree of BVS reabsorption -12 and 24 months after implantation- and was influenced by plaque composition and endothelial function [6, 40]. Furthermore, it was noted that the resorption process of the scaffold was variable depending on scaffold design and thickness along with certain patient characteristics [40]. For example, if the scaffold was overexpanded, it was associated with faster degradation and consequently high rates of restenosis [41]. With a similar restenosis rate as compared to everolimus-eluting stent (EES), the minimal lumen diameter (MLD) at 2 years was similar.

3.2 Procedural aspects of BVS deployment

It was established that to obtain better outcomes with BVS and decrease the rates of ST [6], operators had to follow specific steps different from the routine steps for DES implantation. Oversizing Absorb BVS in small vessels was associated with a higher rate of (MACE) as compared to DES [42].

The key steps in BVS implantation, known as PSP (predilatation, sizing, postdilatation) are:

Step 1: Lesion preparation with predilatation

Operators are expected to use an appropriate size balloon to obtain a stent-like result before scaffolding with a theoretical benefit of decreasing ST.

Step 2: Sizing, stepwise deployment, and balloon inflation

Severe underexpansion was demonstrated in all reported cases of acute or subacute BVS thrombosis [43], which underlines the importance of careful BVS sizing. ICI might be used to accurately choose the right size BVS. Next, deployment should be done gradually (2 atm every 5 seconds) up to 12 atm to avoid proximal and distal injury [44]. Finally, balloon inflation should be maintained for $\geq$30 s to achieve optimal expansion.

Step 3: Postdilatation with a non-compliant balloon

It was shown that the lower the postdilatation rate the higher the rate of scaffold thrombosis (ScT). Deployment is completed with high pressure inflation of a non-compliant balloon with a nominal diameter up to 0.25-0.50 mm larger than the nominal scaffold diameter. The choice of balloon can also be guided by ICI that can detect insufficient expansion vs. scaffold undersizing. Differentiating between the two can help prevent rupture or stent fracture [6, 44].

3.3 Procedural optimization

The first issue is whether the clinical outcomes could be modified by improving the implantation technique. Studies have looked at the impact of device sizing and implantation techniques on acute device performance indices, including acute gain, expansion index, asymmetry index, eccentricity index, and strut embedment [45].

Optimal predilatation and postdilatation were expected to improve performance and reduce the rate of ScT from 3.3% to 1.0%, which still remained significant even after multivariate adjustment (hazard ratio, 0.19; $P = 0.012$) [43, 46]. However, this has not been proven by randomized studies.

3.4 Duration of DAPT after BVS implantation

The latest American guidelines advocate DAPT following DES for at least 6 months in patients with stable ischemic heart and for at least 12 months in patients with ACS [47]. However, the interruption of DAPT accounted for around 1/3 of BVS thromboses, and also VLScT. Stone G suggested that if intraluminal scaffold dismantling (ILSD) is visualized on OCT, prolonged DAPT has to be considered, especially in patients with low bleeding risk. Re-stenting with a metallic DES may also be appropriate in severe cases of ILSD [48].

Therefore, the increased risk of ScT up to 2 years provides a good rationale for continuation of DAPT for that period [47].

4. Current limitations of BVS

4.1 Mechanical Integrity

BVS differ from their metallic counterparts when it comes to their intrinsic mechanical properties [49]. They have suboptimal ductility, which effects scaffold retention on balloon catheter and limits the range of scaffold expansion during deployment. Second, they have thick struts to offset their low radial strength and help prevent recoil during vessel remodeling. Finally, they have limited elongation-to-break, which defines the opening range of the BVS. This makes BVS less practical options for difficult lesions whether in tortuous vessels or calcified lesions, among others.

4.2 Clinical and imaging concerns

Imaging is crucial in assessing ScT, restenosis, and TVR in patients undergoing BVS implantation.

4.2.1 Scaffold thrombosis: modifiable and non-modifiable features

A systematic analysis of all reported ScT cases evaluated by ICI was conducted [49]. Malapposition (24%), incomplete lesion coverage (18%) and under-deployment (12%) were most frequently observed. In late/very late cases, malapposition (35%), late discontinuity (31%), and peri-strut low-intensity areas (indicating the presence of neointima [19%]) were the predominant features.

Table 3. Next Generation BRS with Thinner Struts (≤ 150 μm)

Scaffold	Manufacturer	Backbone	Coating	Eluted drug	Strut thickness (μm)	Resorption time (months)	Development status
DESolve Cx	Elixir	PLLA	Biodegradable polymer	Novolimus	120	2 years	CE mark
Absorb BVS gen 2	Abbott Vascular	PLLA	poly-lactic-co-glycolic acid	Everolimus	≤ 99	36 months	CE mark
MeRes 100	Meril life Sciences	PLLA	PDLLA	Sirolimus	100	50% at 4-6 mo; complete resorption ≈2 y	CE mark
FORTITUDE	Amaranth Medical	Ultra-high molecular-weight PLLA	PDLLA	Sirolimus	150	10 mo	CE mark
Mirage	Manli Cardiology, Siingapore	PLLA	PLLA	Sirolimus	125	≈ 14 mo	CE mark
Firesorb	Shanghai MicroPort Medical	PLLA	PDLLA	Sirolimus	100-125	3 years	CE mark

DOCE indicates device-oriented composite end point; MACE, major adverse cardiac event; NA, data not available; PLLA, poly-l-lactide; PDLLA, poly(l-lactide-co-d, llactide); POCE, patient-oriented composite end point; RCT, randomized controlled trial; ScT, scaffold thrombosis; and TVF, target vessel failure.

This provides evidence that optimizing stent sizing and deployment might help to decrease the potential risk of ScT [42, 49]. This, however, does not address late discontinuity and peri-strut low-intensity areas.

Late discontinuity is a benign change during the bioresorption process and doesn't cause any complications if the scaffold struts are well covered by neointima. However, during bioresorption, struts might not be fully covered by neointima which brings thrombogenic proteoglycan into contact with blood; then, late discontinuity could be a malignant potential cause of VLScT [49].

That late discontinuity relative to ILSD was often observed by OCT imaging at the time of BVS VLST and was considered to be causally related to the thrombotic event [50].

Moreover, thick stent struts may lead to turbulence in flow and areas of **oscillatory shear stress** that could promote platelet activation or thrombogenicity especially when struts are left malapposed [51].

The first generation of BVS was limited by a high rate of **scaffold restenosis** and TVR, which was similar to that reported for BMS [52]. Such event could be related to either a suboptimal elution of antiproliferative drug or the complex implantation technique required and the subsequent injury. ICI including 3D OCT in symptomatic BVS restenosis showed extensive neointimal thickening [53].

5. Future directions of BVS

5.1 Device development

Newer BVS with better characteristics were reported, with promising results (Table 3):

- The DESolve Cx novolimus-eluting BVS, Elixir
- The Absorb BVS 2nd generation, Abbott Vascular
- The MeRes100 sirolimus-eluting BVS, Meril Life Sciences
- The Fortitude, Magnitude, and Aptitude sirolimus eluting BVSs, Amaranth Medical
- The MIRAGE sirolimus-eluting bioresorbable microfiber scaffold (Manli Cardiology, Singapore)
- The Firesorb sirolimus-eluting BVS, Shanghai MicroPort Medical

Therefore, thinner struts, lower crossing profile, and fast resorption characteristics could be the way to go. Also, obtaining strong radial force because of new post-processing of the polymer looks encouraging and might help improve outcomes.

6. Summary and conclusions

The added value of this "vascular restoration therapy" is still waiting for a proof of evidence, while safety concerns are already known, together with the challenging device implantation, the worse trackability, the longer procedural times, and the larger amounts of contrast used [52]. Furthermore, the PLLA based BVS have lower tensile strength ranging from 45 to 70 MPa compared with 1449 MPa for cobalt-chromium based stents. The elongation at break for polymers is 2% to 6% compared with 40% for metallic stents [52, 54]. These gaps in mechanical properties are a challenge to overcome, and despite the progress in improving the polymer composition, structure, and production process, the performance of the currently available polymer-based BVS technology appears to remain inferior to the second-generation metallic DES. Late dismantling of the polymer can also occur at the final stages of resorption, with the risk of ScT [50]. To overcome the tensile strength and stiffness deficiency, the first-generation BVS structure consisted of thick struts (150 μm) which made them unsuitable for small vessels and at higher risk for ScT. In addition, the polymeric BVS requires a meticulous implantation technique (PSP) [6].

To address that issue, ABSORB IV was a prospective, randomized study, a continuation of ABSORB III. However, two new criteria were implemented: all treated vessels had to have a RVD of > 2.25 mm, and a PSP technique of pre- and post-dilation and appropriate sizing were followed routinely. Results in both the BVS and EES arm improved as compared to prior studies, but BVS remained to have worse outcomes compared to EES (30 day TLF was 5.0% vs. 3.7%, *P* for non-inferiority = 0.02, *P* for superiority = 0.11) [55].

The Resorbable Magnesium scaffold appears to have better mechanical properties compared with PLLA-based polymers, with tensile strength ranging from 220 to 330 MPa and elongation at break of 40%. The RMS may become the way to go especially that it combines the physical properties of the metallic stents while being the fastest-dissolving device currently available, over just a 12-month period [38, 54]. Up to 3 years post implantation, RMS had good outcomes with only 2 ScT reported so far having strut malapposition as their underlying cause [39]. More data are still needed to prove their non-inferiority as compared to DES.

In summary, and to date, BVS have failed to demonstrate a clinical benefit over the conventional metallic stent. Further development of the bioresorbable technology is needed to overcome the limitations of first-generation BVS [56].

To conclude, this review article aimed to be broad, comprehensive and updated concerning the actual knowledge on BVS. Thinner struts, newer design characteristics, appropriate patient selection, and standardized techniques of implantation may lead to better outcomes and improve the care of our patients. In EuroPCR 2018 [57], Gregg Stone said that "we've learned a tremendous amount", and with the ongoing developments "we can get very close, if not equivalent, to metallic DES. And then the promise comes after 3 years".

Author contributions

NA designed and drafted this work. WS critically revised this work. All authors gave final approval.

Ethics approval and consent to participate

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References

[1] Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbæk H, *et al.* Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. New England Journal of Medicine. 2007; 356: 1030-1039.

[2] Holmes DR, Kereiakes DJ, Laskey WK, Colombo A, Ellis SG, Henry TD, *et al.* Thrombosis and drug-eluting stents: an objective appraisal. Journal of the American College of Cardiology. 2007; 50: 109-118.

[3] Martín-Reyes R, Moreno R, Sánchez-Recalde A, Navarro F, Franco J, Piñero A, *et al.* Comparison of the safety between first- and second-generation drug eluting stents. International Journal of Cardiology. 2012; 160: 181-186.

[4] Nishio S, Kosuga K, Igaki K, Okada M, Kyo E, Tsuji T,*et al.* Long-term (> 10 years) clinical outcomes of first in humans biodegradable poly-*l*-lactic acid coronary stents Igaki-Tamai stents. Circulation. 2012; 125 : 2343-2352.

[5] Tarantini G, Saia F, Capranzano P, Cortese B, Mojoli M, Boccuzzi G, *et al.* SICI-GISE Position paper: use of Absorb BVS in clinical practice. Giornale Italiano di Cardiologia. 2016; 17: 28S-44S. (In Italian)

[6] Indolfi C, De Rosa S, Colombo A. Bioresorbable vascular scaffolds - basic concepts and clinical outcome. Nature Reviews Cardiology. 2016; 13: 719-729.

[7] Serruys PW, Onuma Y, Garcia-Garcia HM, Muramatsu T, van Geuns R, de Bruyne B, *et al.* Dynamics of vessel wall changes following the implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. EuroIntervention. 2014; 9: 1271-1284.

[8] Serruys PW, Chevalier B, Sotomi Y, Cequier A, Carrié D, Piek JJ, *et al.* Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomized, controlled, single-blind, multicentre clinical trial. The Lancet. 2016; 388: 2479-2491.

[9] Onuma Y, Sotomi Y, Shiomi H, Ozaki Y, Namiki A, Yasuda S, *et al.* Two-year clinical, angiographic, and serial optical coherence tomographic follow-up after implantation of an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent: insights from the randomised ABSORB Japan trial. EuroIntervention. 2016; 12: 1090-1101.

[10] Okada K, Honda Y, Kitahara H, Ikutomi M, Kameda R, Brooke Hollak M, *et al.* Scaffold underexpansion and late lumen loss after bioresorbable scaffold implantation: insights from ABSORB JAPAN trial. IJC Heart & Vasculature. 2020; 31: 100623.

[11] Arroyo D, Gendre G, Schukraft S, Kallinikou Z, Müller O, Baeriswyl G, *et al.* Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds: two-year clinical outcomes of the EVERBIO II trial. International Journal of Cardiology. 2017; 243: 121-125.

[12] Sabaté M, Windecker S, Iñiguez A, Okkels-Jensen L, Cequier A, Brugaletta S, *et al.* Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST segment elevation myocardial infarction: results of the randomized ABSORB ST segment elevation myocardial infarction-TROFI II trial. European Heart Journal. 2016; 37: 229-240.

[13] Gomez-Lara J, Brugaletta S, Ortega-Paz L, Vandeloo B, Moscarella E, Salas M, *et al.* Long-term coronary functional assessment of the infarct-related artery treated with everolimus-eluting bioresorbable scaffolds or everolimus-eluting metallic stents: insights of the TROFI II trial. JACC. Cardiovascular Interventions. 2018; 11: 1559-1571.

[14] Kereiakes DJ, Ellis SG, Metzger C, Caputo RP, Rizik DG, Teirstein PS, *et al.* 3-year clinical outcomes with everolimus-eluting bioresorbable coronary scaffolds. Journal of the American College of Cardiology. 2017; 70: 2852-2862.

[15] Lou N, Writer S. FDA Probing Absorb Stent - higher risk of stent thrombosis and MI under Investigation. MedPage Today. 2017.

[16] Kereiakes DJ, Ellis SG, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, *et al.* Clinical outcomes before and after complete everolimus-eluting bioresorbable scaffold resorption. Circulation. 2019; 140: 1895-1903.

[17] Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, IJsselmuiden AJ, *et al.* Bioresorbable scaffolds vs. metallic stents in routine PCI. The New England Journal of Medicine. 2017; 376: 2319-2328.
[18] Abizaid A, Ribamar Costa J, Bartorelli AL, Whitbourn R, van Geuns RJ, Chevalier B, *et al.* The ABSORB EXTEND study: preliminary report of the twelve-month clinical outcomes in the first 512 patients enrolled. EuroIntervention. 2015; 10: 1396-1401.
[19] Rzeszutko Ł, Siudak Z, Włodarczak A, Lekston A, Depukat R, Ochała A, *et al.* Contemporary use of bioresorbable vascular scaffolds (BVS) in patients with stable angina and acute coronary syndromes. Polish National Registry. Kardiologia Polska. 2014; 72: 1394-1399.
[20] Ielasi A, Cortese B, Moscarella E, Loi B, Tarantini G, Varricchio A, *et al.* One-year clinical outcomes after unrestricted implantation of the Absorb bioresorbable scaffold (RAI registry). EuroIntervention. 2018; 14: e546-e553.
[21] Capodanno D, Gori T, Nef H, Latib A, Mehilli J, Lesiak M, *et al.* Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. EuroIntervention. 2015; 10: 1144-1153.
[22] Hellenkamp K, Becker A, Gabriel YD, Hasenfuß G, Hünlich M, Jacobshagen C, *et al.* Mid- to long-term outcome of patients treated with everolimus-eluting bioresorbable vascular scaffolds: data of the BVS registry Göttingen predominantly from ACS patients. International Journal of Cardiology. 2017; 234: 58-63.
[23] Wiebe J, Hoppmann P, Colleran R, Kufner S, Valeskini M, Cassese S, *et al.* Long-term clinical outcomes of patients treated with everolimus-eluting bioresorbable stents in routine practice: 2-year results of the ISAR-ABSORB Registry. JACC: Cardiovascular Interventions. 2017; 10: 1222-1229.
[24] Lipinski MJ, Escarcega RO, Baker NC, Benn HA, Gaglia MA, Torguson R, *et al.* Scaffold thrombosis after percutaneous coronary intervention with absorb bioresorbable vascular scaffold: a systematic review and meta-analysis. JACC: Cardiovascular Interventions. 2016; 9: 12-24.
[25] Collet C, Asano T, Sotomi Y, Cavalcante R, Miyazaki Y, Zeng Y, *et al.* Early, late and very late incidence of bioresorbable scaffold thrombosis: a systematic review and meta-analysis of randomized clinical trials and observational studies. Minerva Cardioangiologica. 2017; 65: 32-51.
[26] Collet C, Asano T, Miyazaki Y, Tenekecioglu E, Katagiri Y, Sotomi Y, *et al.* Late thrombotic events after bioresorbable scaffold implantation: a systematic review and meta-analysis of randomized clinical trials. European Heart Journal. 2017; 38: 2559-2566.
[27] Polimeni A, Anadol R, Münzel T, Indolfi C, De Rosa S, Gori T. Long-term outcome of bioresorbable vascular scaffolds for the treatment of coronary artery disease: a meta-analysis of RCTs. BMC Cardiovascular Disorders. 2017; 17: 147.
[28] Elias J, van Dongen IM, Kraak RP, Tijssen RYG, Claessen BEPM, Tijssen JGP, *et al.* Mid-term and long-term safety and efficacy of bioresorbable vascular scaffolds vs. metallic everolimus-eluting stents in coronary artery disease: a weighted meta-analysis of seven randomised controlled trials including 5577 patients. Netherlands Heart Journal. 2017; 25: 429-438.
[29] Sorrentino S, Giustino G, Mehran R, Kini AS, Sharma SK, Faggioni M, *et al.* Everolimus-eluting bioresorbable scaffolds vs. everolimus-eluting metallic stents. Journal of the American College of Cardiology. 2017; 69: 3055-3066.
[30] Elias J, van Dongen IM, Kraak RP, Tijssen RYG, Claessen BEPM, Tijssen JGP, *et al.* Mid-term clinical outcomes with everolimus-eluting bioresorbable scaffolds vs. everolimus-eluting metallic stents for percutaneous coronary interventions: a meta-analysis of randomized trials. EuroIntervention. 2017; 25: 429-438.
[31] De Rosa R, Silverio A, Varricchio A, De Luca G, Di Maio M, Radano I, *et al.* Meta-analysis comparing outcomes after everolimus-eluting bioresorbable vascular scaffolds vs. everolimus-eluting metallic stents in patients with acute coronary syndromes. The American Journal of Cardiology. 2018; 122: 61-68.
[32] Ni L, Chen H, Luo Z, Yu Y. Bioresorbable vascular stents and drug-eluting stents in treatment of coronary heart disease: a meta-analysis. Journal of Cardiothoracic Surgery. 2020; 15: 26.
[33] Ke J, Zhang H, Huang J, Lv P, Chen Y, Xu K, *et al.* Three-year outcomes of bioresorbable vascular scaffolds vs. second-generation drug-eluting stents. Medicine. 2020; 99: e21554.
[34] Ke J, Zhang H, Huang J, Lv P, Yan J. Mid-term outcomes of bioresorbable vascular scaffolds vs second-generation drug-eluting stents in patients with acute coronary syndromes. Medicine. 2020; 99: e19458.
[35] Alfonso F, Cuesta J, Pérez-Vizcayno MJ, García Del Blanco B, Rumoroso JR, Bosa F, *et al.* Bioresorbable vascular scaffolds for patients with in-stent restenosis: the RIBS VI study. JACC: Cardiovascular Interventions. 2017; 10: 1841-1851.
[36] Abizaid A, Costa RA, Schofer J, Ormiston J, Maeng M, Witzenbichler B, *et al.* Serial multimodality imaging and 2-year clinical outcomes of the novel desolve novolimus-eluting bioresorbable coronary scaffold system for the treatment of single de novo coronary lesions. JACC: Cardiovascular Interventions. 2016; 9: 565-574.
[37] Lafont A. ARTDIVA. Presented at BRS. 2014.
[38] Haude M, Ince H, Kische S, Abizaid A, Tölg R, Alves Lemos P, *et al.* Sustained safety and clinical performance of a drug-eluting absorbable metal scaffold up to 24 months: pooled outcomes of BIOSOLVE-II and BIOSOLVE-III. EuroIntervention. 2017; 13: 432-439.
[39] Ozaki Y, Garcia-Garcia HM, Shlofmitz E, Hideo-Kajita A, Waksman R. Second-generation drug-eluting resorbable magnesium scaffold: review of the clinical evidence. Cardiovascular Revascularization Medicine. 2020; 21: 127-136.
[40] Brugaletta S, Heo JH, Garcia-Garcia HM, Farooq V, van Geuns RJ, de Bruyne B, *et al.* Endothelial-dependent vasomotion in a coronary segment treated by ABSORB everolimus-eluting bioresorbable vascular scaffold system is related to plaque composition at the time of bioresorption of the polymer: indirect finding of vascular reparative therapy? European Heart Journal. 2012; 33: 1325-1333.
[41] Ishida K, Giacchi G, Brugaletta S, García-Álvarez A, Sabaté M. Unfavorable bioresorbable vascular scaffold resorption, a cause of restenosis? Cardiovascular Revascularization Medicine. 2016; 17: 571-573.
[42] Kawamoto H, Jabbour RJ, Tanaka A, Latib A, Colombo A. The bioresorbable scaffold: will oversizing affect outcomes? JACC: Cardiovascular Interventions. 2016; 9: 299-300.
[43] Puricel S, Cuculi F, Weissner M, Schmermund A, Jamshidi P, Nyffenegger T, *et al.* Bioresorbable coronary scaffold thrombosis: multicenter comprehensive analysis of clinical presentation, mechanisms, and predictors. Journal of the American College of Cardiology. 2016; 67: 921-931.
[44] Sorrentino S, De Rosa S, Ambrosio G, Mongiardo A, Spaccarotella C, Polimeni A, *et al.* The duration of balloon inflation affects the luminal diameter of coronary segments after bioresorbable vascular scaffolds deployment. BMC Cardiovascular Disorders. 2015; 15: 169.
[45] Suwannasom P, Sotomi Y, Ishibashi Y, Cavalcante R, Albuquerque FN, Macaya C, *et al.* The impact of post-procedural asymmetry, expansion, and eccentricity of bioresorbable everolimus-eluting scaffold and metallic everolimus-eluting stent on clinical outcomes in the ABSORB II trial. JACC. Cardiovascular Interventions. 2016; 9: 1231-1242.
[46] Tanaka A, Latib A, Kawamoto H, Jabbour RJ, Sato K, Miyazaki T, *et al.* Clinical outcomes of a real world cohort following bioresorbable vascular scaffold implantation utilizing an optimized implantation strategy. EuroIntervention. 2017; 12: 1730-1737.
[47] Capodanno D, Angiolillo DJ. Antiplatelet therapy after implantation of bioresorbable vascular scaffolds. JACC: Cardiovascular Interventions. 2017; 10: 425-437.

[48] Stone GW, Granada JF. Very Late Thrombosis after bioresorbable scaffolds: cause for concern? Journal of the American College of Cardiology. 2015; 66: 1915-1917.
[49] Sotomi Y, Suwannasom P, Serruys PW, Onuma Y. Possible mechanical causes of scaffold thrombosis: insights from case reports with intracoronary imaging. EuroIntervention. 2017; 12: 1747-1756.
[50] Chan CY, Wu EB, Yan BP. Very late bioresorbable scaffold thrombosis caused by intraluminal scaffold dismantling. JACC: Cardiovascular Interventions. 2016; 9: 1844-1847.
[51] Bourantas CV, Papafaklis MI, Kotsia A, Farooq V, Muramatsu T, Gomez-Lara J, *et al.* Effect of the endothelial shear stress patterns on neointimal proliferation following drug-eluting bioresorbable vascular scaffold implantation: an optical coherence tomography study. JACC: Cardiovascular Interventions. 2014; 7: 315-324.
[52] Waksman R. Bioresorbable scaffolds polymer troubleshooting or simply not good enough?. JACC: Cardiovascular Interventions. 2017; 10: 1131-1133.
[53] Indolfi C, Mongiardo A, Spaccarotella C, Caiazzo G, Torella D, De Rosa S. Neointimal proliferation is associated with clinical restenosis 2 years after fully bioresorbable vascular scaffold implantation. Circulation Cardiovascular Imaging. 2014; 7: 755-757.
[54] Sotomi Y, Onuma Y, Collet C, Tenekecioglu E, Virmani R, Kleiman NS, *et al.* Bioresorbable scaffold: the emerging reality and future directions. Circulation Research. 2017; 120: 1341-1352.
[55] Stone GW. A bioresorbable everolimus-eluting scaffold vs. a metallic everolimus-eluting stent IV - ABSORB IV. 2018. Available at: http://www.acc.org/latest-in-cardiology/clinical-trials/2017/10/30/16/03/absorb-iv (Accessed: 24 October 2020).
[56] Kawashima H, Zocca P, Buiten RA, Smits PC, Onuma Y, Wykrzykowska JJ, *et al.* The 2010s in clinical drug-eluting stent and bioresorbable scaffold research: a Dutch perspective. Netherlands Heart Journal. 2020; 28: 78-87.
[57] O'Riordan M. New bioresorbable scaffold, magmaris, delivers positive early outcomes. 2018. Available at: https://www.tctmd.com/news/new-bioresorbable-scaffold-magmaris-delivers-positive-early-outcomes (Accessed: 24 October 2020).