Review Article

Occurrence and management of bioresorbable vascular scaffold failure in real-life studies

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Abstract: Bioresorbable vascular scaffold (BVS) has emerged as a new technology aiming at overcoming some drawbacks of the conventional metallic stent. In spite of the initial promising results, this technology stumbled upon numerous challenges, which were revealed in the real world studies. Thanks to real world trials and registries findings, our knowledge about the BVS has grown over time, thus we have understood on BVS behavior in various settings and formulated better implantation techniques. In this article, we will review the incidence of BVS failure in real world studies, its different etiologies and management strategies.

Keywords: Bioresorbable vascular scaffold (BVS); scaffold failure

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Introduction

The clinical introduction of bioresorbable vascular scaffolds (BVS) was announced as the fourth revolution in interventional cardiology due to a paradigm shift (1). In this light, BVS have emerged as an interesting alternative to drug-eluting stents (DES), since the presence of the prosthesis in the coronary artery is transient. This technology enables to restore the normal vasomotor tone and allows positive remodeling, simultaneously reducing the trigger for persistent inflammation and facilitating further interventions by percutaneous or surgical means. Also, theoretically this technology should offer a reduced or even abolished very late thrombotic risk. Several BVS are meanwhile under development, but currently only four of them have the Conformité Européenne (CE) mark approval for coronary angioplasty: Absorb BVS™ (Abbott Vascular, Santa Clara, USA), Magmaris™ (Biotronik, Berlin, Germany), DESolve™ (Elixir Medical Corporation, Milpitas, USA) and Fantom™ (Reva Medical, San Diego, USA). The best studied and the most used one is the former, with several registries/trials published and more than 100,000 patients treated.

Preliminary clinical data from prospective registries showed an adequate efficacy and safety profile of the first two versions of the Absorb BVS (namely BVS 1.0 and 1.1), that entered the European market in 2012 (2). Thereafter, several randomized clinical trials compared it to the best-in-class everolimus-eluting stent (EES), namely Xience (Abbott Vascular, Santa Clara, USA). These trials confirmed the preliminary results from the prospective registries by showing comparable clinical outcome between the BVS and the EES at short term follow up (2,3). With the extended follow up and real world implantation of the scaffold, we started to face a new entity, which is "BVS failure". This article aims at reviewing the literature to assess the incidence and actual management of BVS failure in real world studies.

Clinical data

The first study that shed light on this complication was GHOST-EU which was a large real-world retrospective registry (n=1,189) that included more complex clinical and angiographic characteristics than those represented in previous studies; here the rate of target lesion failure (TLF) was 4.4% at 6 months. The cumulative incidence of definite/probable scaffold thrombosis was 1.5% at 30 days and 2.1% at 6 months (4). This was the first study that underlined for the first time this item. Similar results were also shown in the small single center AMC registry, where the rate of early BVS thrombosis was 2.2%: in two cases it was attributable to technical issues and in one to premature dual antiplatelet therapy (DAPT) interruption (5). In this view, we recently proposed that DAPT administration should continue up to 3 years after BVS administration (6) following recent laboratoristic and clinical data on the matter (7,8).

The ABSORB EXTEND, which was a prospective, single-arm, open-label clinical study, showed that at 1 year, for the first 512 patients enrolled in the study, the composite endpoints of ischemia-driven major adverse cardiac events (MACE), which is a composite of cardiac death, nonfatal recurrent myocardial infarction, ischemic stroke and ischemia-driven TLF were 4.3% and 4.9%, respectively. The cumulative rate of Academic Research Consortium (ARC) defined definite and probable scaffold thrombosis for this population was 0.8% at 1 year (9).

In a meta-analysis that included six trials, comprising data for 3,738 patients randomized to receive percutaneous coronary intervention (PCI) with either BVS (n=2,337) or EES (n=1,401), patients treated with BVS had a similar risk of TLR (OR 0.97, 95% CI: 0.66–1.43; P=0.87), TLF (OR 1.20, 95% CI: 0.90–1.60; P=0.21), MI (OR 1.36, 95% CI: 0.98–1.89; P=0.06), and death (OR 0.95, 95% CI: 0.45–2.00; P=0.89) as those treated with metallic stents after a median follow-up of 12 months. However, BVS showed a higher risk of definite or probable scaffold thrombosis (OR 1.99, 95% CI: 1.00–3.98; P=0.05), with the highest risk occurring between 1 and 30 days after implantation (OR 3.11, 95% CI: 1.24–7.82; P=0.02). Moreover, lesions treated with BVS had greater in-device late lumen loss than those treated with EES [weighted mean difference 0.08 (0.05–0.12); P<0.0001] (10).

Recently, the US Food and Drug Administration (FDA) have issued a safety alert for the Absorb BVS due to an increased rate of MACE observed in patients receiving the device. The alert came after the FDA's initial review of two-year data from the ABSORB III trial that showed an 11% rate of major cardiac events (cardiac death, myocardial infarction or TLR) in patients treated with the scaffold at 2 years, compared with 7.9% in patients treated with EES. Specifically, the 2 year results for ABSORB III trial have shown that EES had a lower incidence of TLF (11.0% *vs.* 7.9%, P=0.03), and target vessel myocardial infarction (7.3% *vs.* 4.9%, P=0.04), whereas cardiac death (1.1% *vs.* 0.6%, P>0.05) and device thrombosis (1.9% *vs.* 0.8%, P>0.05) were similar. Among the reasons for the increased incidence in adverse events in this study, the enrollment of patients with very small vessels (<2.25 mm) was considered one of the most important (11).

From the real world trials and registries, it is clear that thrombosis was the main player in BVS failure. This was also evident in the Absorb II trial, where the 3-year rate of probable/definite scaffold thrombosis was 1.5% *vs.* 0% in EES, P=0.17. Specifically, six events occurred beyond the first year. An accurate analysis of the six cases of very late scaffold thrombosis showed that in four cases the scaffold was probably undersized and in three cases it was not postdilated (12).

In a later meta-analysis to assess the actual incidence of very late scaffold thrombosis, the risk between 1 and 2 years was numerically higher in BVS than in EES-treated patients (OR 2.03, 95% CI: 0.62–6.71). The excess risk of BVS over the EES for device thrombosis through 2 years was instead significant (OR 2.08, 95% CI: 1.02–4.26). The risk for TLF was neutral between BVS and EES. In the 24 studies pooled, the estimated incidence rates of VLST, and ST through 2 years were higher in BVS than in EES (13).

Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial (AIDA), a single-blind, multicenter, investigator-initiated, non-inferiority trial compared the Absorb BVS with the EES in a broad study population of 1,845 patients and recently the preliminary data were reported. There was no significant difference in the rate of TVF, however BVS was associated with higher device thrombosis throughout 2 years (3.5% *vs.* 0.9%; HR 3.87; 95% CI: 1.78–8.42; P<0.001) [Wykrzykowska *et al.*, *New Engl J Med* 2017. (In Press)].

There are also several European all-comer registries that are investigating the efficacy and safety of BVS in the real world (RAI, IT-DISAPPEARS, GABI-R, UK REGISTRY, FRENCH REGISTRY, REPARA). To this day, only short term data are available. There is only one available publication (the Italian RAI registry), that showed a 30-day

occurrence of scaffold thrombosis of 0.8%. The authors, considering the lack of exclusion criteria in the registry, concluded that the short-term data of the registry were good overall [Cortese *et al.*, *Am J Cardiol* 2017, (In Press)].

In-scaffold restenosis (IScaR) has emerged as a new entity after the real world use of this technology. Limited data are available in the literature on this topic (14,15). IScaR may be attributed to multiple factors which include: geographical miss (edge effect) defined as failure of the device to appropriately scaffold a balloon-injured vessel or to fully cover the lesion, scaffold underexpansion, scaffold gap (missing overlap of several mm), uneven scaffold implantation in tight stenosis, small target vessel diameter (<2 mm) (strut overcrowding), delayed scaffold resorption, excessive neointimal proliferation, neoatherosclerosis and resistance to antiproliferative drugs (16,17). Some authors have found that early restenosis (<6 months) tended to be focal, mostly affecting the BVS edges, and showed a homogeneous appearance tissue. In contrast, late restenosis had a more diffuse angiographic pattern and showed heterogeneous tissue, often with clear features of neoatherosclerosis.

Potential causes for scaffold thrombosis

Various factors contribute to scaffold thrombosis. Firstly, strut thickness may play a role: it is well known thick-strut stents, when compared with thin-strut, are associated with higher rates of angiographic restenosis and are considered to be more thrombogenic. The same theory can be translated for BVS, at least for the time the struts are not totally reabsorbed. Due to the inherent limitations of current generation PLLA scaffolds, where thick struts seem thrombogenic and limit the deliverability of the device, the reduction of the thickness of clinically available BVS has been challenged with several attempts to develop scaffolds with thinner struts that can maintain their integrity for suitable duration, like the novel ultra-high molecular weight amorphous PLLA BVS (Amaranth Medical, Mountain View, California, USA) (18).

Another crucial factor for the occurrence of scaffold thrombosis includes the implantation technique. Data from the GHOST EU (4) and the real world European registries have clearly shown how the rate of early scaffold thrombosis is reduced if a correct implantation technique is achieved [Cortese *et al.*, *Am J Cardiol* 2017, (In Press)].

In order to reduce the incidence of BVS failure recommendations underscored by a "Dear Doctor" letter were issued by the FDA this year at the time of the ABSORB III presentation at the ACC meeting. That letter reminds operators using the BVS to follow instructions in FDA labeling by avoiding its use in small vessels, where BVS is indicated to be used for vessels with a reference vessel diameter of ≥2.5 and ≤3.75 mm, and adhering to the label's recommended implantation methods.

Currently, a "PSP implantation technique" is recommended. This technique includes three steps: firstly, operators have to achieve aggressive lesion preparation where predilatation is done using a 1:1 balloon-to-artery ratio (some operators prefer the use of non-compliant, other semi-compliant balloons). Here it is possible to use also scoring balloons or atherectomy if deemed necessary. At this time, it is still possible to switch to a DES-strategy. The second step of the PSP technique is **s**izing the vessel appropriately with the use of intravascular imaging or quantitative coronary angiography. The third step of the above mentioned technique is **p**ostdilatation of the scaffold to high pressure with a non-compliant balloon, which must be sized up to 0.5 mm above the nominal scaffold diameter. Although the CE Mark approval remains in place, only centers participating in formal registries will be able to use BVS since May 2017 (19).

As scaffold thrombosis has been the main concern with the BVS, a prolonged dual antiplatelet therapy duration is also recommended, in those patients at low hemorrhagic risk. Its length is not clear yet, but is suggested for a minimum of 2–3 years [Buccheri *et al.*, *J Thorac Dis* 2017, (In Press)].

As a final remark for the prevention of scaffold thrombosis, the use of intravascular imaging (OCT/IVUS) guidance for vessel sizing and implant optimization is recommended for currently available BVS in case of complex lesion management or low operator experience. To this day, this practice is still low. In a recent multicenter study involving 1,305 patients, the rate of ST with BVS was as high as 3%, but this complication was significantly reduced (by 70%) when optimal implantation strategy was employed (20).

Treatment of BVS failure

Regarding scaffold thrombosis, the optimal management should focus on a fast restoration of blood flow (like in any other case of primary PCI), including, if indicated, thrombus aspiration and direct stenting. Importantly, we believe that after vessel patency is obtained, intracoronary

imaging should be used to better understand the underlying cause, in order to treat it in the most accurate way. In this regard, in 2016 an expert-users survey on BVS thrombosis was published, in which the best treatment strategy identified was thrombus aspiration followed by DES implantation (21).

The use of adjunctive devices after BVS failure in real life is still a matter of debate. Different coronary devices were used in the management of this issue. In a case series from the GHOST-EU trial where BVS failure was caused by scaffold restenosis, percutaneous balloon angioplasty, drug-coated balloons (DCB), DES and BVS implantation were used in 2 (14%), 6 (43%), 5 (36%), and 1 (7%) case, respectively (16).

In a case series that aimed at investigating the clinical outcome following TLR for BVS failure in a real world population, 18 patients (20 lesions) which underwent TLR for BVS failure were identified at two high-volume centers. The type of scaffold failure at TLR was classified into focal pattern in 15 lesions, diffuse pattern in two lesions, restenosis at side branch ostium in one lesion and scaffold thrombosis in two cases. TLR was treated with POBA in two lesions, with DCB in three lesions, DES in 11 lesions and further BVS implantation in four lesions. During the follow-up (median: 345 days after TLR) there was one sudden cardiac death and three repeat TLRs. The authors concluded that the optimal treatment option for these patients remains to be determined (22). In another case series published by our group that aimed to evaluate the role of DCB for the management of IScaR, DCB was used as a primary therapeutic tool in nine patients. Follow-up coronary angiography at 12 months revealed failure in two patients which experienced type III restenosis. Both patients were treated with DES implantation (14).

Conclusions

In conclusion, our knowledge about this interesting new technology is growing. However, as it occurred with the first generation DES, we are still learning how to correctly manage BVS. Until this learning curve is not totally smooth out, we recommend a careful patient selection and the use of a dedicated and slavish implantation technique, in order to reduce the risk of scaffold failure.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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