Perspective

Bioresorbable vascular scaffolds—time to vanish?

Diego Arroyo, Stéphane Cook, Serban Puricel

Department of Cardiology, University and Hospital Fribourg, Fribourg, Switzerland

Correspondence to: Serban Puricel, MD. Department of Cardiology, University and Hospital Fribourg, CH-1708 Fribourg, Switzerland. Email: serbanpuricel@icloud.com.

Submitted Mar 25, 2016. Accepted for publication Apr 07, 2016.
doi: 10.21037/jtd.2016.04.50
View this article at: http://dx.doi.org/10.21037/jtd.2016.04.50

Why bioresorbable vascular scaffolds (BVS)?

Percutaneous coronary interventions have undergone a stepwise evolution with some tops and some flops since their inception by Andreas Grüntzig in 1977 (1). Bare metal stents (BMS), who suppressed the risk of occlusive dissection and lowered the risk of restenosis (2), dual antiplatelet therapy which decreased the risk of thrombosis, and drug-eluting stents (DES) which minimized the risk of restenosis were all significant advances. Other novelties, such as laser revascularisation and endobrachytherapy were nipped in the bud. Even the latest generation of metallic DES, despite continuous and significant improvements, may impair coronary vasomotion (3), trigger neoatherosclerosis and hamper surgical attempts to treat failed stented segments.

The studies on DES thrombosis in the years 2005 triggered a somewhat artificial emulation amongst stent-makers. From this, rose the concept and development of vanishing stents. Such temporary devices were thought to potentially restore lumen size and flow while disappearing over time and restoring vasomotor tone and normal coronary physiology. The first of these devices to receive CE-approval was the ABSORB (Abbot Vascular, Santa Clara, California, USA) BVS. Its technology relies on a polylactic acid polymer that serves as scaffold platform. It is coated with the antiproliferative drug everolimus, which is almost entirely eluted during the first 3 months after scaffold placement. Polylactic acid has been used in other medical specialities for quite a while as it induces minimal inflammation during bioresorption. The degradation of the polymer starts as early as 6 months after implantation, and full bioresorption may be reached after several years. Polylactic acid is transformed via the cycle of Krebs into carbon dioxide and hydrogen.

Putative advantages over conventional DES are early restoration of physiological processes, superior conformability, beneficial edge-vascular response, and suppression of late stent-related complications (i.e., in-stent restenosis and stent thrombosis).

From excitement to uncertainty

The initial reports from single-arm studies in highly selected patients with simple coronary lesions were very reassuring (4). However, an increasing body of evidence from "real-life" registries reported concerning rates of stent thrombosis as high as 3% at 1 year (5-7). Although several randomised-controlled trials have shown equivalent safety and efficiency outcomes at mid-term between BVS and other newer generation DES (8-10), all were of relatively small size and underpowered to assess differences in clinically relevant but rare events such stent thrombosis. To date, 3 meta-analyses have assessed the performance of the device compared to metallic DES (*Table 1*). There seems to be a definite trend towards higher rates of myocardial infarction and device thrombosis with the use of BVS.

There are several limitations to the unrestricted use of BVS that may explain these observations. First, accurate sizing is necessary when using the device in order to achieve optimal strut apposition (14). Choosing too small a scaffold diameter results in the need for overstretch dilation. Overstretching the BVS is limited to <1.0 mm above the nominal scaffold diameter. As the largest BVS is 3.5 mm and the maximal post-expansion recommended is 0.5 mm over the nominal diameter, major bifurcations and large vessels (≥4 mm) need best be avoided, including the left main coronary artery. There have been reports of polymer fracture after post-dilatation, triggered by overstretching

Table 1 Meta-analyses comparing BVS to metallic DES

Meta-analysis	Target lesion revascularization	Acute myocardial infarction	Thrombosis (definite and probable)	Cardiac death
Stone *et al*. [2016] (11)	1.14 (0.73–1.79)	1.45 (1.02–2.07)	2.09 (0.92–4.75)	1.26 (0.33–4.82)
	P=0.56	P=0.04	P=0.08	P=0.74
Cassese *et al*. [2016] (12)	0.97 (0.66–1.43)	1.36 (0.98–1.89)	1.99 (1.0–3.98)	0.95 (0.42–2.00)
	P=0.87	P=0.06	P=0.05	P=0.89
Lipinski *et al*. [2016] (13)	0.77 (0.48–1.25)	2.06 (1.31–3.22)	2.06 (1.07–3.98)	0.81 (0.42–1.58)
	P=0.36	P=0.002	P=0.03	P=0.54

Results are provided as odds or risk ratios with 95% confidence interval. Values >1 reflect increased risk or odds with the use of BVS. BVS, bioresorbable vascular scaffold; DES, drug-eluting stent.

of the device (15). Furthermore, local overexpansion might induce edge dissection. On the other hand, the use of an inappropriately large BVS results in oversizing and underexpansion, which has been linked to scaffold thrombosis (16). The use of the device in small vessels, particularly in vessels <2.25 mm, may augment the footprint of the device, i.e., the % of the vascular circumference occupied by the relatively thick BVS struts (150 µm) (17). The performance of the device is poor in small vessels and a high footprint has been identified as a predictor for scaffold thrombosis (7).

Secondly, the polymer platform is not as strong and has less radial strength than metallic stents (18), which is an issue in highly calcific lesions. As bioresorption progresses, radial strength further declines harbouring the risk for scaffold collapse.

The duration of dual antiplatelet therapy (DAPT) after BVS is an unresolved, important issue. Extended and efficient DAPT is indeed indicated. DAPT interruption results in high rates of scaffold thrombosis. In the acute phase after BVS placement, inflammation and the formation of micro-thrombi can be observed by histopathological examination (19). As time advances, struts are covered—a phenomenon, which can be visualised by optical coherence tomography (OCT) and is referred to as 'capping'. In metallic stents this 'capping' represents vascular healing and the visualized tissue is mainly composed of neointima. It might be that 'capping' of BVS-struts does not represent vascular healing but rather a correlate of thrombin apposition. The micro-thrombi visualized in the acute phase eventually grow and evolve into chronic organized thrombi visible on OCT imaging and undistinguishable from neointima. This mechanism possibly explains the deleterious effects of insufficient DAPT prescription, whether in efficacy or in duration.

The rate of thombosis has also been higher for BVS-treated ostial lesions compared to metallic stents where the abrasion of the catheter is thought to provoke more BVS strut distorsion (20). Another concern is the risk of side-branch occlusion, again, due to the bulky device with a higher scaffold to artery ratio (21). Interestingly, when the above issues are known and anticipated, a dedicated protocol for BVS implantation seems to be efficient in reducing the risk of thrombosis (7). Ultimately, and according to evidence gathered in the late 1960s by Charles Dotter, it is no surprise that contrary to the initial belief, BVS are not devoid of device thrombosis (22).

It is likely that, much like first-generation DES, the technical and bio-chemical limitations of first-generation BVS will be overcome. A new treatment standard for coronary artery disease (CAD) could be set if the industry manages to increase stretchability while creating stronger yet thinner backbones with less biodegradation-related inflammation. Several BVS devices are currently being tested clinically and many trials are ongoing, some of which will include patients with acute coronary syndrome (ACS) (4).

BVS in ST-elevated myocardial infarction

Percutaneous coronary intervention with a reperfusion strategy and stenting are all class I recommendations for the treatment of ST-elevation myocardial infarction (STEMI) (23). There is a of course a strong incentive to demonstrate clinical efficiency and safety of BVS in those who have the strongest indication for percutaneous coronary intervention.

And although BVS may have some limitations, their use

Table 2 Reported adverse events in patients presenting with ACS/STEMI treated by BVS

First author and year of publication	Subset	No. of STEMI patients	Comparator	Timing of primary end point/mean follow-up	Device-related adverse events (%)	Patient-related adverse events (%)	Definite scaffold thrombosis (%)
Single arm or unadjusted studies							
STEMI							
Kajiya *et al*. [2013] (24)	STEMI	11	None	53.0±45.9 days	9.1	9.1	0.0
Wiebe *et al*. [2014] (25)	STEMI	25	None	132.7±68.7 days	4.2	4.2	0.0
Diletti *et al*. [2014] (26)	STEMI	49	XIENCE	30 days	0.0	2.6	0.0
Kočka *et al*. [2014] (27)	STEMI	40	DES and BMS	n/a	2.5	2.5	2.5
ACS							
Dudek *et al*. [2014] (28)	ACS	16	None	1 year	4.0	n/a	1.0
Gori *et al*. [2015] (29)	ACS	51	None	1 year	n/a	13.5	2.3
RCT or PS-matched							
Brugaletta *et al*. [2015] (30)	STEMI	290	XIENCE/BMS	1 year	4.1	n/a	1.7
Sabaté *et al*. [2016] (31)	STEMI	95	XIENCE	6 months	1.1	1.1	1.1

n/a, unavailable; ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug-eluting stent; PS, propensity score; RCT, randomized controlled trials; STEMI, ST-elevation myocardial infarction; BVS, bioresorbable vascular scaffold.

in STEMI patients is particularly appealing. The lesions are indeed more often focal and less calcified. Moreover, patients tend to be younger than NSTEMI and other CAD-patients, and the advantages of BVS, such as a restoration of vasomotion or late lumen enlargement would be of greatest benefit on the long-term. However, STEMI-patients are also a high-risk patient subset, which present with higher rates of adverse events than patients with stable CAD.

The first reports of BVS-treated STEMI patients

The first reports of short to mid-term clinical outcome in BVS-treated STEMI patients were rather encouraging. However, the data stemmed from single-arm or unadjusted comparative studies (*Table 2*). Device related adverse events as defined by the academic research consortium ranged from 0% to 9.1% in the 192 reported patients.

The BVS-EXAMINATION Study

Brugaletta *et al*. made an important contribution to our understanding of the application of BVS in STEMI patients by reporting the outcomes of 290 consecutive patients treated at 6 institutions across the globe (30). The study was published in the January issue of the JACC Cardiovascular Interventions in 2015. The BVS-treated patients were compared to 290 propensity score (PS) matched everolimus-eluting stents (EES) and 290 PS matched BMS treated patients enrolled in the EXAMINATION Trial. The investigators assessed the occurrence of device-oriented adverse events, as well as stent or scaffold thrombosis at 1 month and 1 year. There were no significant differences in individual end points but they observed a numerically higher rate of early definite scaffold/stent thrombosis in the BVS group.

The information provided on short and mid-term outcome in BVS treated STEMI patients is of utmost clinical relevance and raises the question whether the unrestricted use of the device in a subgroup with an increased baseline risk for stent thrombosis is reasonable. Indeed, owing to the novelty of the technique and the distinct physical properties of the device, treatment of STEMI patients may be accompanied by unforeseen complications. Even though not statistically significant, the numerically higher rate of early stent thrombosis is concerning and likely the result of an implantation technique that was not tailored to the decreased radial strength, the increased acute recoil, and the need for optimal lesion preparation to avoid mechanistic complications such as underexpansion or incomplete stent apposition. Relevant information on target lesion revascularization and target-vessel related MI rates suggested an acceptable hazard with

BVS. However, the patient sample was relatively small and the data was observational in nature with residual differences in baseline characteristics between treatment arms.

The ABSORB-stemi TROFI II trial

Sabaté *et al*. made another important contribution by publishing the primary outcome of the multicentric, randomised, single-blinded TROFI II trial (31). They reported BVS to be non-inferior to EES in STEMI patients at six months for arterial healing based on a multimodal imaging score. Clinical outcomes were not different between the treatment groups. Clinical follow-up is still ongoing and will explore the mid- and long-term outcomes. It is important to point out, however, that patients with cardiogenic shock and significant vessel tortuosity or calcifications were not included in this trial.

Conclusions

Is BVS better than the other DES in our cathlabs? No, and the evidence shows that it is, at best and for specific patients and lesions, non-inferior with a trend toward being inferior. The evidence for BVS implantation in STEMI patients is very limited. While it appears to be safe in the hands of experienced operators who are well aware of the technical limitations, the ABSORB BVS does show a trend towards a higher rate of myocardial infarction compared to other metallic DES. The major safety concerns from the initial European experience have led to more careful lesion selection and preparation thus reducing the risk of stent thrombosis. Is ABSORB BVS a step toward a paradigm shift? Maybe.

There is no convincing evidence that the hypothetical advantages of BVS are or will be of any benefit to patients. More definitive evidence will only be available in about 5 to 7 years. Until then, the "optimistic" will continue to use it and the "sceptic" will wait. In March 2016, the advisory panel of the Food and Drug Administration has given near-unanimous support for approval of the ABSORB BVS, while its use has drastically decreased in Europe. One can only hope that the fruit will continue to ripen, and for our patients to benefit from further technological enhancements.

Acknowledgements

None.

Footnote

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

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Cite this article as: Arroyo D, Cook S, Puricel S. Bioresorbable vascular scaffolds—time to vanish? J Thorac Dis 2016. doi: 10.21037/jtd.2016.04.50