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Review

Bioresorbable scaffold — A magic bullet for the treatment of coronary artery disease?

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ABSTRACT

Today, drug-eluting metal stents are considered *the gold standard* for interventional treatment of coronary artery disease. While providing inhibition of neointimal hyperplasia, drug-eluting metal stents have many limitations such as the risk of late and very late stent thrombosis, restriction of vascular vasomotion and chronic local inflammatory reaction due to permanent implantation of a 'metallic cage', recognized as a foreign body. Bioresorbable scaffold stents (BRS) are a new solution, which is trying to overcome the limitation of the 'metallic cage'. This structure provides short-term scaffolding of the vessel and then disappears, leaving nothing behind. The purpose of this review is to present the theoretical rationale for the use of BRS and to outline the clinical outcomes associated with their use in terms of data obtained from RCTs, clinical trials, registries and real life use. We have also tried to answer all questions on this intervention based on available data, with a focus on ABSORB BVS (Abbott Vascular, Santa Clara, USA). We consider that this new technology can be the "*magic bullet*" to treat coronary artery disease.

1. Introduction

BioResorbable scaffolds (BRS) are novel devices designed to overcome the long-term limitations of the permanent stent implantation [1]. The first balloon angioplasty, performed in September 1977 by Andreas Grüntzig, a German physician, revolutionized the treatment of coronary artery disease (CAD) [2]. This was considered *the first revolution* in interventional cardiology and his method came to be known as plain old balloon angioplasty (POBA). The term and the procedure are still used today [2]. The patient treated then underwent coronary angiography on April 10, 2000, 23 years later and this revealed normal patency of coronary artery which had undergone angioplasty [3]. Despite this initial promise, the POBA technique has numerous disadvantages, including restenosis (due to elastic recoil, constrictive remodeling, and neointimal hyperplasia) and the risk of acute vessel closure (due to uncovered dissection) [4–6].

In March 1986, Jacques Puel implanted the first metal coronary stent (a self-expanding coronary stent called Wallstent) in a 63 years old male suffering from restenosis after POBA [7]. This new technology was introduced to treat restenosis after POBA and provided a solution to acute vessel occlusion by sealing the dissection flaps and preventing recoil [8,9]. Bare metal stents (BMS) are considered *the second revolution* in interventional cardiology. The presence of the metal stent prevents late luminal enlargement and advantageous vascular remodeling. However, the restenosis rate is reduced compared with POBA, but is not eliminated due to neointimal hyperplasia [8]. Drug eluting stents (DES), of which a sirolimus-eluting Bx velocity stent (Cordis, Johnson & Johnson, Warren, NJ) was the first example, are considered *the third revolution* in interventional cardiology. DES were developed in an attempt to reduce the restenosis rate [10]. The first generation of DES consisted of stent platform (stainless steel), a durable polymer coating, and an antiproliferative drug (sirolimus or paclitaxel). This structure was improved in the second generation of DES, which consisted of a platform (made of stainless steel, cobalt–chrome, or platinum–chrome), a biocompatible durable or biodegradable polymer and an antiproliferative drug (everolimus or zotarolimus) [11]. Drug-eluting

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stents have significantly reduced in-stent restenosis and target lesion revascularization (TLR) rates compared with BMS [12–14]. However, acute, late or very late stent thrombosis is still a problem, especially in first generation DES [15,16]. This can be due to a number of mechanisms, including strut fracture, late strut malapposition, loss of intimal coverage of the strut due to erosion, neo-atherosclerosis, or chronic inflammatory reaction to one of the stent components, such as the polymer coating. The problem of chronic inflammatory reactions to the polymer has improved with 2nd DES generation that have better polymers or bioresorbable polymers [17–19].

A meta-analysis of available RCTs which compared outcomes after DES and BMS implantation showed no detectable differences in death or MI, but a significant reduction in target vessel revascularization (TVR) when DES were used [20]. While providing inhibition of neointimal hyperplasia, drug-eluting stents have some limitations: the risk of late and very late stent thrombosis, restriction of vascular vasomotion and chronic local inflammatory reaction due to permanent implantation of a 'metallic cage', which is recognized as a foreign body [21–23].

The fourth revolution in interventional cardiology resulted from the attempt to overcome the limitation of the 'metallic cage' by replacing it with a bioresorbable scaffold. This structure provides short-term scaffolding of the vessel and then disappears, leaving nothing behind. The majority of bioresorbable scaffolds are made from poly-L-lactic acid (PLLA), but they can also be manufactured from metals (especially magnesium), tyrosine polycarbonate and poly (anhydride ester) salicylic acid [24,25]. Recently, the European Society of Cardiology (ESC)/European Association of Percutaneous Coronary Interventions (EAPCI) task force on the evaluation of coronary stents in Europe agreed that bioresorbable stents (BRS) is a more suitable term for bioresorbable vascular scaffold (BVS), since a scaffold might indicate a need for a temporary arterial support [26]. Only two BRS have received approval in Europe and received the CE Mark — the everolimus-eluting ABSORB BVS (Abbott Vascular, CA, USA) and the novolimus-eluting DESolve (Elixir Medical, CA, USA) (Table 1).

Taking into account the fact that bioresorbable stents disappear after about 2 years leaving healthy coronary artery, preventive cardiologists have also started to take an interest in this intervention, as it resembles the most effective pharmacological methods of atheroma plaque reduction (atherosclerosis regression) with statins [27]. However, there are still many questions from the view of preventive cardiologists. These include the risk of neo-atherosclerosis in the place of stent implementation, as well as how to treat these patients concerning their cardiovascular risk, and what should be the optimal therapy after stent resorption. Therefore, the purpose of this review is to present the theoretical rationale for the use of BRS and to outline the clinical outcomes associated with their use in terms of data obtained from RCTs, clinical trials, registries and real life use. We have also tried to answer all questions on this intervention based on available data. In particular, we will focus on ABSORB BVS. We think that this technology can be the "*magic bullet*" to treat coronary artery disease.

2. Search strategy

We searched using electronic databases [MEDLINE (1966 – 21st February 2016), EMBASE and SCOPUS (1965 – 21st February 2016), DARE (1966 – 21st February 2016)], and Web of Science Core Collection (up to 21st February 2016). Additionally, abstracts from national and international meetings were searched. Where necessary, the relevant authors were contacted to obtain further data. The main search terms were: bioresorbable scaffold, BVS, bioresorbable vascular stents, bioresorbable stents, BRS, ABSORB, drug-eluting stents.

3. Advantages of BRS over DES?

Ideal scaffolding must have a good radial strength and deliverability. It must remain present for an adequate time and then dissolve to prevent late side effect. Bioresorbable scaffolds offer potential advantages over current metallic stents [28]. After a period of time, the scaffold undergoes a process called 'bioresorption' and then totally disappears from the vessels. The PLLA scaffolds, such as the ABSORB BRS, degrade purely by hydrolysis, and neither require nor induce any tissue reaction for resorption. Finally the small individual lactic acid molecules undergo natural cellular metabolism to CO_2 and water [29,30]. The fact that the coronary artery is not "caged" allows for the restoration of physiological vasomotion, adaptive shear stress, late luminal gain (as opposed to late luminal loss with permanent stents), and late expansive remodeling [30]. This new technology has been developed to reduce adverse event of DES treatment such as late and very late stent thrombosis. Once bioresorption of the scaffold has occurred and the healing process is complete, long-term dual anti-platelet therapy is no-longer necessary (however the optimal duration of such therapy is still a topic for discussion) [31–34] and statins might be reduced (or even discontinued?). However, we still have had no data on this, especially it rises some doubts taking into account that atherosclerotic changes usually coexist in different arteries [35]. This approach might also reduce long-term bleeding complications and cost. Bioresorbable scaffolds can reduce the problem of jailing (obstructing) the ostium of side branches, which occurs with metallic stents and these patients can undergo further percutaneous or surgical revascularization after the scaffold has disappeared [36]. BRS allows the use of non-invasive imaging techniques such as computer tomography (CT) or magnetic resonance imaging (MRI) for follow-up studies [37]. The porous poly (L-lactide) (PLLA) scaffolds are radiolucent and do not cause blooming, an effect seen with metallic stents [37]. Bioresorbable stents also have a potential

Table 1
Comparison of CE mark bioresorbable scaffold.

	ABSORB BVS 1.1, Abbott, USA	ABSORB GT1, Abbott, USA	DESolve, Elixir Medical, USA
Backbone	PLLA	PLLA	PLLA
Polymer coating	PDLLA	PDLLA	PDLLA
Delivery system	Multi-Link SDS[a]	Glide Track[b]	DESyne catheter
Design	In-phase zigzag hoops, cross-linked by bridges	In-phase zigzag hoops, cross-linked by bridges	Tubularly arranged hoops, linked by bridges
Crossing profile	1.43 mm	1.43 mm	1.44 mm
Strut thickness	150 μm	150 μm	150 μm
Drug eluting	Everolimus[c]	Everolimus[c]	Novolimus[d]
Visualization	Two small platinum markers at scaffold edge	Two small platinum markers at scaffold edge	Two small platinum markers at scaffold edge
Dissolution	24–36 months	24–36 months	12–24 months
Diameter	2.5/3.0/3.5 mm	2.5/3.0/3.5 mm	2.5/3.0/3.25/3.5 mm
Length	8, 12, 18, 23, 28 mm	8, 12, 18, 23, 28 mm	14, 18, 28 mm

Abbreviations: PLLA—poly L-lactic acid; PDLLA—poly (D,L)-lactic acid.
[a] The same delivery system use in Xience V (Abbott, Santa Clara, USA).
[b] Catheter specially design and built for ABSORB GT1 with improve ease to use, improve push transmission.
[c] Similar dose density and release rate to Xience V (Abbott, Santa Clara, USA).
[d] Similar dose density and release rate to DESyne (Elixir Medical Corporation, USA).