

# **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.

**Key words:** atherosclerosis, bioresorbable stents, coronary artery disease, drug-eluting stents.

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## 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 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 2<sup>nd</sup> 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.

## **SEARCH STRATEGY**

We searched using electronic databases [MEDLINE (1966 – 21<sup>st</sup> February 2016), EMBASE and SCOPUS (1965 – 21<sup>st</sup> February 2016), DARE (1966 – 21<sup>st</sup> February 2016)], and Web of Science Core Collection (up to 21<sup>st</sup> 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.

## **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<sub>2</sub> 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 role in pediatric intervention because they disappear in time and after vessel growth can allow further surgical intervention. A successful treatment of preterm baby born at 26 weeks of gestation with a magnesium bioresorbable stent implanted in left pulmonary artery was reported, amongst other cases (38). BRS can also allay the concerns experienced by some patients about having a permanent implant in their body for the rest of their lives.

The two examples of BRS, which have been granted the CE mark (ABSORB BVS, Abbott Vascular, Santa Clara, USA and DESolve, Elixir Medical, CA, USA), have a similar profile to the Cypher stent (Cordis, a Johnson & Johnson Company, Miami, USA), with a strut thickness of 150 $\mu$ m and a crossing profile of 1.4 mm (**Table 1**). The ABSORB BVS (Abbott Vascular, Santa Clara, USA) is radiolucent with two additional platinum radio-opaque markers on the two ends of the scaffold. It has similar radial strength as Abbott MULTI-LINK metallic stent and drug release profile from is comparable to XIENCE™ V everolimus drug-eluting stent (Abbott Vascular, Santa Clara, USA), 80% at 30 days (36).

## **BIORESORPTION**

The term ‘bioresorption’ describes the total elimination of polymers by dissolution, assimilation, and excretion (39). The lifecycle of the bioresorbable scaffold is divided into three phases: revascularisation, restoration; and resorption. These have been described extensively in another paper (40). Intracoronary imaging techniques such as intravascular ultrasound (IVUS),

virtual histology intravascular ultrasound (VH-IVUS), and optical coherence tomography (OCT) have been used to analyze the process of bioresorption. In a IVUS trial on a first generation of ABSORB BVS Cohort A a polymeric stent strut was recognized as hyperechogenic tissue and a significant reduction in the percentage hyperechogenicity postprocedural and 6, 12 month follow-up was observed (41). Another study, using the second generation of everolimus eluting scaffold ABSORB BVS Cohort B did not reproduce this finding and reported a smaller reduction in hyperechogenicity at 6 and 12 months of follow-up, suggesting a slower degradation rate of the scaffold (42). On VH-IVUS necrotic core, dense calcium, fibro-fatty tissue, and fibrous tissue are represented as red, white, yellow-green, and green areas, respectively, on ultrasonic cross-sections and are expressed as percentages (with each area totaling 100%). On each cross-section, polymeric struts are detected as areas of apparent dense calcium surrounded by necrotic core due to the strong backscattering properties of the polymer. The change in quantitative analyses of these areas between implantation and follow-up as a surrogate assessment of the polymer bioabsorption process was used in Serruys multiple imaging study (41). In the first 6 months a decrease in percentage of dense calcium and percentage of necrotic core and an increase in fibro-fatty and fibrous tissue was observed in terms of relative percentages and absolute values. This was previously interpreted as a reduction of radiofrequency backscattering from the polymeric struts. VH-IVUS assessments showed that the percentage of each plaque component did not differ significantly between 6 months and 2 years (41). The same study observed a reduction of the apparent strut, at 6 and 24 months after implantation using OCT (39). This data was reported for the first generation of ABSORB Cohort A scaffold. In the second generation of everolimus eluting scaffold, ABSORB Cohort B scaffold, the radiofrequency backscattering analysis revealed a significant decrease (17.7%,  $p < 0.001$ ) in pseudo-calcium and that ultrasonic



alteration, confirmed by a significant decrease in echogenicity of the struts (baseline:  $23.51 \pm 8.57\%$  vs. 12-month:  $18.25 \pm 7.19\%$ , relative reduction: 19.7%,  $p < 0.001$ ) (43). In a porcine model, the struts were still discernible through OCT at 2 years, whereas at 3 and 4 years, both OCT and histology confirmed complete integration of the struts into the arterial wall (25, 44). The data obtained from IVUS suggest that the process of bioresorption is gradual, and ABSORB BRS can be expected to be fully resorbed by approximately 3 years after implantation, whereas OCT illustrates that, while resorbed, the pre-existing struts may still be apparent beyond 3 years until cellularized tissue has fully integrated into these sites.

## **HEALING PROCESS AFTER BRS IMPLANTATION**

Stent implant in coronary arteries initiates a cascade of complex physiological responses leading to sequentially to platelet and fibrin deposition, leukocyte recruitment, smooth muscle cell proliferation, deposition of cellular matrix, and, hopefully, re-endothelialisation of the treated portion of the vessel (40). Coronary plaque rupture and erosion with local thrombosis are the cornerstones of acute coronary syndrome (ACS). Pathological studies have documented that vulnerable plaques prone to rupture and erosion present as thin-cap fibroatheromas (TCFA), which consist of lipid core plaques covered by a thin fibrous cap ( $<65 \mu\text{m}$ ) (45). The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study showed that TCFA are independent predictors of coronary events in patients evaluated after ACS. (46) Attempts have been made to stabilize TCFA using both pharmacological and mechanical approaches. With respect to pharmacological treatment, a study conducted by Takarada *et al.* showed that statins have the ability to increase fibrous-cap thickness of coronary plaques, these effects are much more prominent in cases with thinner fibrous caps at baseline

(47). Mechanical treatment of TCFA consists of stent implantation. Bare-metal stents in particular, trigger the formation of a fibrotic layer (of varying thickness) on the top of the thin cap covering the lipid pool, potentially reducing the probability of plaque rupture or erosion (48).

The persistence of a metallic cage and/or non-degradable polymers into the vessel leads to chronic inflammation and can result in complications (neo-atherosclerosis with intra-stent restenosis and late and very late stent thrombosis) (17, 49-52). In first generation of DES some studies reported hypersensitivity vasculitis characterized by the presence of eosinophils and T-lymphocytes, with a focal giant cell reaction around stent strut and surrounding polymer infiltrating within all layers of the vessel wall without any extension into non-stented segment.

The first report evaluating the use of implanted BRS in porcine coronary artery model by OCT or histology was made by Onuma *et al.* (44). They evaluated BRS immediately after implantation, at 28 day, 2, 3 and 4 years. Using OCT, the strut appear like a preserved box (100%-82%-80.4%-5.4%-0%), open box (0%-18%-2.4%-16.1%-0%), dissolved bright box (0%-0%-0%-34.8%-51.2%) and dissolved black box (0%-0%-17.2%-43.7%-48.8%)(44). On OCT, all struts had a preserved box appearance immediately after implantation but at 4 years only dissolved bright and black boxes were seen. At 2, 3, and 4 years, all visible struts were fully apposed and covered by tissue (44). On histology evaluation, the struts were completely sequestered from the lumen by a thin, fibromuscular neointima and had well-defined and squared edges at 28 days, and no hyaline material positive for Alcian blue staining (44). At 2 years, it appeared as open acellular regions with well-defined borders, borders composed of faintly hyaline material that stained positively with Alcian Blue. Minimal calcification was present around all struts. Preexisting struts were completely sequestered within a fibromuscular neointima, with no or minimal inflammatory cells (macrophages, multinucleated giant cells)

being immediately associated with the struts (44). At 3 years, the majority of regions previously occupied with struts was replaced with hyaline material (identified as nonfibrillar glycoprotein by transmission electron microscopy) separated by extracellular matrix and cells (56.9%), with only a minority of cells integrated into the region of the preexisting strut stain positively with SMA, indicating that these cells are likely of alternative cellular origin (e.g., fibroblasts)) and remaining areas (43.1%) were recognized as regions without hyaline material but with connective tissue with low to moderately cellular density, which indicated complete, benign involution of the struts into the arterial wall (44). Macrophages and multinucleated giant cells were noted only occasionally meaning inflammation was minimal (44). At 4 years, the majority of strut region were circumscribed regions of dense connective tissue with low cellularity (67.8%), 30.1% were areas poorly circumscribed of dense connective tissue with moderate to low cellularity in which cells were not regularly arranged. Only a minority (2.1%) were regions with hyaline material separated by extracellular matrix and cells (44). With respect to inflammatory responses, the percentages of struts with granuloma were  $13.8 \pm 25.1\%$ ,  $3.96 \pm 6.93\%$ , and  $0.37 \pm 1.11\%$  at 1, 6, and 24 months, respectively; the percentages of struts with giant cells were  $34.8 \pm 20.5\%$ ,  $14.7 \pm 18.9\%$ , and  $1.6 \pm 2.9\%$ , respectively (44). At 3 and 4 years, no granuloma/giant cells were observed in the area previously occupied with polymeric struts – meaning that there was no significant inflammatory response (44). The authors concluded that BRS struts are first covered by a fibromuscular neointima, and then are replaced by a provisional matrix, which corresponds to resorption demonstrated by gel permeation chromatography (GPC) analysis (44). Thereafter, inspissations of the provisional matrix occurs and connective tissue cells infiltrate the region of the preexisting struts, and finally the areas of preexisting struts become fully integrated into the arterial wall and are difficult to discern (44).

Vorphal *et al.* compared vascular healing between ABSORB BVS Cohort A and Cypher sirolimus-eluting stent (first generation DES) in rabbit iliac arteries (53). They reported that inflammation scores for both implants were low, but cellular inflammation (which consisted predominantly of macrophages and peri-strut giant cells) was infrequently observed in BVS Cohort A implanted arteries at six and 36 months as compared to those with SES. Re-endothelialisation was complete in BVS implanted arteries at six and 36 months, whereas SES implanted arteries showed incomplete re-endothelialisation at all time points (53). Both studies reported limited ability to generalize the findings of this study directly to clinical outcomes in humans, because difference between healthy pig coronary, rabbit iliac and disease human coronary arteries. OCT and histology evaluations of BRS ABSORB in a porcine coronary artery model are described in **Figure 1**.

More relevant to current generation is the work of Otsuka *et al.* (54). They compared long-term safety of ABSORB second generation (ABSORB BVS 1.1) with a second generation DES (Xience) in a porcine coronary artery model (54). The results from this study showed a mild to moderate inflammation at 1 month, with minimal or absent inflammation at 42 months for both devices. In ABSORB group, there was greater neointimal thickening, along with the unique response of late lumen and vessel enlargement seen at  $\geq 12$  months (54).

Pharmacokinetic studies showed that the release of everolimus was similar between ABSORB and Xience and this was associated with fibrin deposition in both at 1 month. A scanning electron microscopic (SEM) examination showed that at 6 months more than 90% of struts from Xience and ABSORB BRS are covered suggesting similar endothelialisation process (**Figure 2**).

Degradation in Absorb was completed within 36 months in GPC analysis (54). Recently, the first histology findings from BRS implanted in human were reported (55). The data from autopsies of 4 patients with duration of implantation ranging from 3 to 501 days were described (55). At 3 days (case 1) the struts located at the plaque-free wall were covered by a thin layer of fibrin and platelets admixed with granulocytes and a few multinucleated giant cells (19% of the struts had giant cells adjacent). At 8 days (case 2) the struts were (partially) covered by a small layer of fibrin and platelets admixed with mononuclear inflammatory cells and multiple multinuclear foreign body giant cells. At 113 days (case 3) histology demonstrated coverage of some of the scaffold struts with a thin layer of multilayered smooth muscle cells, condensed fibrin, multinuclear foreign body giant cells and a few mononuclear inflammatory cells adjacent to the struts. At 501 days (case 4), all BVS struts were totally surrounded by intima with multilayered smooth muscle cells, minimal inflammation with a few multinuclear foreign body giant cells and macrophages without no T lymphocytes, B lymphocytes, or eosinophilic granulocytes were observed (55). Some of the BVS struts showed infiltration with fibrillary eosinophilic material that also stained with Alcian blue, indicating degenerative change (55). They concluded that after a week, the strut is cover with a thin, fibrin-rich clot, at 113 days with smooth muscle cells similar data with previously published animal data. Also at 501 days the BRS features progressive healing with minimal inflammation in accordance with porcine model (53, 55, 56).

BRS implantation leads to the formation of a symmetrical neo-tissue with a mean thickness of 220  $\mu\text{m}$  without remnants of polymeric struts, when the device is completely bioresorbed (57). The healing process following an ABSORB BVS 1.1 implantation is almost completed 6 months after the device implantation, without further increase of neointima overtime (25, 54, 58). The

formation of a thick neointimal layer, without remnants of polymeric struts, creates a “*de novo*” cap, which may be used to seal a thin-cap fibroatheroma (48). The number of patients included in this study was relatively small, but the results are very promising and we might think of BRS as being like an “intracoronary magic bullet” for CAD treatment.

## **ACUTE AND LATE RECOIL**

An *in vivo* study reported that acute recoil, as assessed by quantitative coronary angiography in bioabsorbable everolimus-eluting coronary stent recoil was slightly larger, but not significantly different to everolimus-eluting cobalt chromium stent (6.9 % vs 4.3 %) implying good radial strength in BRS (59, 60). Measurement of late lumen loss (LLL) is a common method to examine the long-term efficacy of DES and to evaluate restenosis (61). It has been reported that LLL is a predictor of future CV events and provided indirect evaluation of vessel response to different endovascular device (62). The first generation of ABSORB BVS 1.0 has a shorter duration of resorption than the second generation, and in this generation a lumen loss of 0.44 mm at 6 months and 0.46 mm at 2 years was reported (probably due to device shrinkage) (63, 64). This problem was corrected in the second generation ABSORB BVS 1.1 (which employed a better stent design to provide greater vessel wall support, a more consistent drug delivery and to allow device storage at room temperature). This resulted in a smaller lumen loss of 0.19 mm at 6 months and 0.27 mm at 2 years, comparable with DES (65). A recent study reported that in-stent/scaffold LLL at two-year follow-up in the Absorb BVS 1.1 group ( $0.26 \pm 0.19$  mm) was similar in terms of outcomes as compared to EES group ( $0.22 \pm 0.22$  mm,  $p=0.29$ ) (66).

## **RESTORING VASOMOTION**

Data from clinical trials suggested that after implantation of first generation of DES (sirolimus and paclitaxel), endothelium-dependent vasorelaxation is impaired (evaluated by intracoronary infusion of acetylcholine followed by bolus injection of nitrate and angiographic assessment of the artery segments adjacent to the implanted stent) (67-70). More recent data suggested that second generation DES (everolimus-eluting, biolimus-eluting, zotarolimus eluting) do not cause this effect (71-73). Bioresorbable scaffolds disappear over time, thus it is presumed that in BVS-implanted arteries, the initial resistance to vasomotion induced by vasoactive drugs decreases gradually, thereby allowing the potential recovery of normal vasomotor tone (74). Lane *et al.* study using IVUS to assess ABSORB BVS-implanted in a porcine model reported a restoration of the pulsatility (progressively increasing differences between end-diastolic and end-systolic lumen areas) occurring in arteries from 12 to 42 months (75). The first trial, which reported a recovery of vasoreactivity in a coronary segment scaffold after 2 years was ABSORB Cohort A trial (76). This result was further confirmed at 12 months in ABSORB Cohort B trial, where an improved scaffold was used (ABSORB 1.1) (77). A recent study reported that endothelial dysfunction in a coronary segment scaffold by an ABSORB BVS device is correlated with plaque burden and necrotic core (74). The restoration of vasomotion after implantation of BRS allow for a return of more normalized arterial flow, shear stress, and cyclical forces, and this essentially distinguishes BRS from metallic stents.

## **LATE LUMEN LOSS OR ENLARGEMENT?**

The ABSORB cohort A study showed a significant increase in minimal luminal area and average luminal area/volume, together with a significant decrease in plaque area/volume between

6 months and 2 years (78). The vessel areas/volumes remained constant during follow-up, suggesting the absence of significant remodeling with late enlargement of the lumen in the OCT subanalysis group (79). Serial quantitative multislice computed tomography (MSCT) assessment in the same study population showed no significant difference at 18 months and 5 years respectively in minimal lumen area (3.10 vs 3.25 mm<sup>2</sup>,  $p = 0.21$ ), mean lumen area (4.47 vs 4.29 mm<sup>2</sup>,  $p = 0.11$ ), mean vessel area (13.17 vs 11.93 mm<sup>2</sup>,  $p = 0.26$ ), mean plaque area (8.23 vs 7.10 mm<sup>2</sup>,  $p = 0.23$ ), with all scaffolds being patent. This serial assessment of lumen by MSCT of scaffold segment showed a trend towards decreased plaque area but with the persistence of lumen area up to 5 years (79). In the OCT evaluated subgroup a late luminal enlargement was noted together with complete strut bioresorption and development of a ‘sealing layer’ covering underlying thrombogenic plaque components (79). These results are promising and again allow qualify BRS therapy to be “new intracoronary magic bullet” for significant atherosclerotic disease treatment.

## **CLINICAL TRIALS**

The ABSORB Cohort A was the first-in-man trial to investigate an everolimus eluting biovascular scaffold. In this prospective, multicentre, single-arm, open-label trial, 30 patients with stable, unstable or silent ischemia were implanted with ABSORB BVS Cohort A (51). Complex lesion-like significant stenosis in the left main coronary artery, bifurcation lesions (lesions involving a side branch > 2 mm in diameter) and lesions with the presence of thrombus or more than one clinically significant stenosis in the target vessel were excluded. The procedural success was 100% with a rate of major adverse cardiac events of 3.3%, no acute or late stent thrombosis (57). The study reported no cardiac death, no ischemia-driven target lesion



revascularizations, nor any stent thrombosis at 2 years (41). No new MACE events were observed between 6 month and 5 years. At 5 years, the ischemia-driven major adverse cardiac event rate of 3.4% remained unchanged, without any scaffold thrombosis early, late or very late (79).

The ABSORB Cohort B study evaluated the second-generation BVS in a study which enrolled a total of 101 patients (102 lesions were treated) (80). The study was divided into 2 groups (Cohort B1 and B2) and reported a rate of major adverse cardiac events of 4.4% at 6 months, 6.8% at two years, 10.1% at 4 years, without any scaffold thrombosis (81, 82). The lesions treated with PCI were predominantly B class (B1 45%, B2 50%), with only 2% type C lesion according to the American College of Cardiology (ACC) /American Heart Association (AHA) coronary lesion classification (78). ABSORB EXTEND was a prospective single-arm study which included patients with lesion  $\leq$ 28 mm in length and reference vessel diameter 2.0-3.8 mm: more complex lesions than in other two studies (83). A preliminary report at twelve months in the first 512 patients enrolled, showed a composite rate of ischemia driven (ID)-MACE and ID- target vessel failure (TVF) were both 2.1% at 30 days, composite rate of ID-MACE and ID-TVF were 2.9% and 3.3% respectively at six months. At one year composite rate of ID-MACE and ID-TVF remained very low at 4.3% and 4.9%, respectively (83). Acute, subacute and late thrombosis rates were 0%, 0.4% and 0.4%, respectively. In this study, 41% of lesions treated were B2 and C according to the ACC/AHA classification (83). Some preliminary results published at 24 months of clinical follow-up of 250 patients, demonstrated a MACE rate of 7.3%, an ID-TLR rate of 6.9%, and a stent thrombosis rate of 0.8% (according to the Academic Research Consortium possible/definitive definition). At 36 months, a MACE rate of

9.3%, ID-TLR rate of 8.9% and rate of definite/probable scaffold thrombosis of 1.2% were reported (83).

The ABSORB II randomized controlled trial was designed to compare an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent (Xience) - considered to be a gold standard in interventional cardiology (84). The primary endpoint of the study was lumen area by IVUS and vasomotion at 3 years follow-up. Given only 501 patients were enrolled, it was underpowered for clinical endpoints. There was no significant difference in coronary lesion class between two groups, most patients had B type lesion (B1 53% in BRS arm and 50% in DES arm; B2 44% in BRS arm and 48% in DES arm). Only 2% in BRS arm and 1% in DES arm had C type lesion according to the ACC/AHA classification. At one year of follow-up, device oriented endpoint and MACE were similar between two groups (5% in BRS group and 3% in DES group). In the BRS group, 3 cases of stent thrombosis (0.9%) were reported (one acute, one subacute and one late). The implantation rate was similar in two groups despite differences in crossing profile (1.4 mm for Absorb with strut thickness of 150µm compared with 1.1 mm with 80µm strut thickness for Xience). This study reported a better conformability to coronary arteries for BRS compare with DES. The authors concluded that despite the significant but modest difference in acute performance of two stents, clinical outcomes at one year were similar between BRS and DES (84).

ABSORB III included 2008 patients with stable and unstable angina randomized to receive an everolimus-eluting bioresorbable scaffold (ABSORB) or an everolimus-eluting cobalt-chromium stent (Xience) (85). The primary end point was tested for both noninferiority and superiority and measured TLF at 1 year (85). The lesions treated were more complex than in previous study with 68.7% type B2 or C according to the ACC/AHA coronary lesion

classification (85). There was no significant difference between the procedural success rates for the two devices. The primary end point of TLF (predicted to be about 7% in this type of population) was 7.8% in ABSORB group vs 6.1% in Xience group with statistical significance for noninferiority ( $p=0.007$ ), but not for superiority ( $p = 0.16$ ) (85). Device thrombosis was a little more common in the ABSORB group (1.5% vs 0.7%,  $p = 0.13$ ), due to subacute thrombosis (between 1 day and 30 days after the procedure). The authors concluded that everolimus-eluting bioresorbable stent was noninferior to everolimus-eluting metallic stent regarding TLF at 1 year (85). Taken together, the ABSORB II and ABSORB III studies showed that everolimus-eluting bioresorbable stent is noninferior to Xience stent in term of TLF, but experts think that it is probably too early to show any advantage of ABSORB stents. The potential benefit is expected to appear after full absorption of the device, 3 years after the procedure and beyond (25, 86). The rate of TLF at 5 years is high with conventional stents, reaching 17% in some studies. The majority of these events have been attributed to the stent (87, 88).

Two interesting studies have reported recently: ABSORB Japan and ABSORB China (89, 90). The studies were designed to enable approval of the BRS in Japan and China. The ABSORB Japan study was a prospective, multicenter, randomized clinical trial, which included 400 patients undergoing everolimus-eluting bioresorbable stent (ABSORB) or everolimus-eluting metallic stent (Xience) implantation in 38 investigational site in Japan (89). The ABSORB arm included 56% type B2 and 20% type C coronary lesions according ACC/AHA classification. Primary endpoint (TLF) occurred in 4.2% of cases in ABSORB arm compared with 3.8% in DES arm, demonstrating noninferiority of BRS vs DES ( $p_{\text{non-inferiority}} < 0.0001$ ). The investigators reported a similar rate of stent thrombosis (1.5%) in both groups (89). In ABSORB China a total of 480 patients were randomized to be implanted with everolimus-eluting

bioresorbable stent (ABSORB) or everolimus-eluting metallic stent (Xience) at 24 sites (90). The primary endpoint was angiographic in-segment late loss (LL), powered for noninferiority with a margin of 0.15 mm. The primary endpoint of in-segment LL at 1 year was  $0.19 \pm 0.38$  mm for ABSORB group versus  $0.13 \pm 0.38$  mm, demonstrating noninferiority of BRS compared with DES ( $p_{\text{noninferiority}} = 0.01$ ), with similar 1-year rates of TLF (cardiac death, target vessel myocardial infarction [TVMI], or ID-TLR; 3.4% vs. 4.2%, respectively;  $p = 0.62$ ) and definite/probable scaffold/stent thrombosis (0.4% vs. 0%, respectively;  $p = 1.00$ ) in both groups (90).

Recently, results have been published from a single-center, assessor-blinded, randomized study of 240 patients randomly assigned in a 1:1:1 ratio to receive everolimus-eluting metallic stent (Promus Element, Boston Scientific), biolimus-eluting stent (Biomatrix Flex stent, Biosensors Europe) or everolimus-eluting bioresorbable scaffold (Absorb)-EVERBIO II (91). The lesions treated were predominantly B1 type (51% in BRS arm) according to ACC/AHA lesion classification. In-segment LLL was slightly but significantly higher in BRS group compared with the EES/BES group ( $0.30 \pm 0.44$  mm vs.  $0.19 \pm 0.42$  mm;  $p = 0.03$ ), but with similar clinical outcomes at 9 months. Stratified analysis results indicated that diabetes status or the presence of ACS did not affect in-stent late lumen loss rates. The patient-oriented MACE rate was 27% in the BRS group compared with 26% in the EES/BES group ( $p = 0.83$ ), and device-oriented MACE rate was 12% in the BRS group compared with 9% in the EES/BES group ( $p = 0.6$ ) (91).

An interesting study compared BRS (ABSORB) with second-generation metal drug eluting stent in 100 complex lesions treated under OCT guidance (92). The BRS group included more complex lesions than in other studies with moderate to heavy calcification, bifurcation lesion,

ostial lesion (different from aorto-ostial RCA and LM) and some case of chronic total occlusion (64% type C lesion according to ACC/AHA lesion classification; 34% bifurcation lesion, with 4% chronic total occlusion) (92). The authors concluded that the BRS showed similar post-procedure area stenosis, minimal lumen area, and eccentricity index as second-generation DES. Routine use of OCT guidance during BVS expansion may have contributed to these results (92).

## **REAL WORLD BRS USE**

The recently published GHOST-EU retrospective registry ( $n = 1,189$ ) presented the early and midterm experience with the ABSORB BRS in real world patients undergoing percutaneous coronary intervention (PCI) (93). Diabetes mellitus was present in 24.8% of participants (8.9% were on insulin therapy). Multivessel disease was present in 34.8% of patients with a total of 51% of lesions were of class B2 or C lesion type (93). The cumulative incidence of TLF was 2.2% at 30 days and 4.4% at 6 months, similar to that reported in DES. According to the available results, the authors showed that diabetes was the only independent risk factor for this outcome - patients with diabetes carried a 2.4-fold increased risk of TLF compared to those without. The cumulative incidence of definite/probable scaffold thrombosis was 1.5% at 30 days and 2.1% at six months, with 16 of 23 cases occurring within 30 days (70% of the cases occurred in the first month after PCI). This is seemed higher than results reported in clinical trials, but of course in this study there was no control group and outcomes were only site-reported and not independently adjudicated (93). Analysis of stent thrombosis cases showed that 20 of 23 patients were on dual antiplatelet therapy at the time of thrombosis. Early events are mostly attributable to procedural issues (i.e., dissection, incomplete stent apposition, incomplete stent expansion) and late events are more likely linked to stent factors and vascular responses. To reduce stent

thrombosis, the authors recommended scrupulous lesion selection and PCI techniques when using BRS, and the opportunity for systematic post-implantation assessment (i.e., intravascular imaging may result in additional post-dilation; this was performed in only nine of 23 patients who experienced stent thrombosis) (93).

More recently, the GHOST EU authors have published a more relevant study (94), in which they took the ABSORB patients in the GHOST EU retrospective registry and matched them to nearly identical Xience CoCr EES patients using propensity score matching methodology. They were able to match 905 ABSORB patients to 905 Xience patients, and then compared one-year clinical outcomes. In the matched cohort, there was no significant difference between ABSORB BRS and XIENCE EES in the risk of device-oriented composite endpoint (DOCE) at 1 year (5.8% *vs.* 7.6%, 95%CI: -4.1 to 0.5;  $p = 0.12$ ). Cardiac death was less likely to occur in the ABSORB BRS group (0.7% *vs.* 1.9%, 95%CI: -2.2 to 0.2;  $p = 0.03$ , and a trend toward a reduction in MI was noted with ABSORB BRS compared with XIENCE EES (2.4% *vs.* 4.0%, 95%CI: -3.2 to 0.0;  $p = 0.07$ ). Conversely, no differences in ID-TLR (4.6% *vs.* 3.5%, 95%CI: -0.7 to 2.9;  $p = 0.22$ ) and definite or probable device thrombosis (1.8% *vs.* 1.1%, 95%CI: -0.4 to 1.8;  $p = 0.23$ ) were detected between ABSORB BRS and XIENCE EES. Given that ABSORB goes away over time, this was considered a success for this new technology to compete so closely in real-world patients to the best-in-class Xience DES (94).

The AMC Single Centre Real World PCI registry reports procedural and midterm clinical outcomes after the use of the second-generation ABSORB everolimus-eluting BRS implanted in the Academic Medical Center, Amsterdam between August 2012 and August 2013 (95). In this registry 39% of patients had ACS and 62% had B2 or C lesion type (15% bifurcation lesion; 8% CTO). They reported that the 6-month cumulative TVF (composite of all-cause mortality, any-

MI and TLR) rate was 8.5%. The registry data showed a higher incidence of stent thrombosis compared with clinical trials (3% - three sub-acute and one late thrombosis). The explanation for this was cessation of dual antiplatelet therapy (DAPT) in two cases and peri-procedural complication in two cases (edge dissection and under-expansion of BRS). They concluded that implantation of ABSORB in daily practice is feasible with good procedural and clinical outcomes (95). Another source of information regarding the use of BRS in the real world is the ABSORB post-marketing surveillance registry designed to monitor the everolimus-eluting bioresorbable vascular scaffold in patients with coronary artery disease (ASSURE), which includes data from six German centers (96). Included patients had 64.7% of B2 or C lesions type. They reported an incidence of MACE at 12 months of 5%, similar to that reported in clinical trials. They concluded that BRS for *de novo* CAD were safe and effective in a real-world setting with a relatively high amount of complex lesions and without obligatory use of IVUS or OCT. They recommend high BRS expansion pressure, slight BRS oversizing, and careful selection of the BRS size (96). If this is done, BRS seems to be safe and effective and may become a useful alternative to DES in many patients undergoing coronary stent implantation.

Registro Absorb Italiano (BVS-RAI) is a prospective registry with 5-year follow-up of all consecutive patients who have undergone successful implantation of 1 or more coronary BRS following the indications, techniques and protocols used in each of the participating institutions (97). This registry is still recruiting, but some preliminary data showed that during the first year, the BRS have been used in a wide spectrum of clinical and angiographic conditions, often off-label with good clinical outcome (97).

Katsumasa S. *et al* compared the BRS ABSORB with new generation of drug eluting stent in real-world patients with complex lesions (98). More than 80% of lesions in both groups were

type B2 and C with 44% bifurcation lesion, 7.5% chronic total occlusion and 7.5% for in-stent restenosis in BRS group (98). The authors concluded that BRS implantation in a real-world population is associated with longer procedure and fluoroscopy time and larger amounts of contrast compared with DES but with similar clinical outcome between the two groups (98). They also report that BRS had better conformability compared with metallic stents and can be used in coronary segment with increased tortuosity (98). Costopoulos *et al.* compared early clinical outcome between ABSORB and everolimus-eluting metallic stent in real world patients (99). The lesions treated were more severe than that reported in other studies (most lesions were classified as either B2 or C types: 83.9% vs. 77.4%,  $p=0.19$ ). They reported that clinical outcomes at 6-months were similar between the two groups with respect to both TLR (3.3% vs. 5.4%,  $p=0.41$ ) and MACE (defined as the composite of target vessel revascularization, follow-up myocardial infarction and all-cause death - 3.3% vs. 7.6%,  $p=0.19$ ) (99). The number of patients treated with ABSORB was small but despite this fact the authors suggested that the use of BRS in all-corner population with mostly complex lesion is associated with good procedural and clinical outcome. No thrombotic event was reported in either group (99).

More recent large, national prospective registries in Germany/Austria (GABI-R) (100) and Iberia (Spain, Portugal) REPARA (101), as well as a more recent large international prospective registry, ABSORB FIRST (102), from patients treated in 2014 and 2015, have been presented at the Euro-PCR International Congress in May 2015 and TCT Congress in San Francisco in October 2015. These more organized, centralized prospective registries with core lab adjudication and during a time period that incorporated more physician learnings on ABSORB implant techniques, in general show declining 30-day and 1 year event rates. GABI-R presented their 30-day outcomes in 1536 showing TLF of 1.2% and stent thrombosis of 1.0%, outcomes



similar to that expected with 2<sup>nd</sup> generation DES (100). REPARA also presented 30-day rates in 1627 showing TLF of 2.4% and ST of 0.9% (101). ABSORB FIRST, with a total population of 1801 patients followed to 1 year, showed TLF of 2.2% and ST of 0.8%, again lower than rates from the early experience in the GHOST EU and other early registries and studies (102). This is consistent with physician learning from experience, which has been seen historically with each of the prior first generation “revolutionary” technologies (POBA, BMS, DES).

## **BRS USE IN STEMI PATIENTS**

The everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction (BVS STEMI) study was the first that evaluated BRS use in STEMI (103). The study included 49 participants and reported a procedural success of 97.9% and clinical success of 97.9%. At the 30-day follow-up, the rate of the device-oriented endpoint, TLF was 0% and no cases of stent thrombosis were reported (103). In the recent BVS-EXAMINATION study - Brugaletta *et al.* compared the 1-year outcome between BRS or everolimus-eluting metallic stent and bare metal stent in STEMI (104). The results showed that the cumulative incidence of device-oriented endpoint did not differ between the BRS and EES or BMS groups either at 30 days (3.1% vs. 2.4%, hazard ratio [HR]: 1.31, 95% confidence interval (CI): 0.48 to 3.52,  $p = 0.593$ ; vs. 2.8%, HR: 1.15, 95%CI: 0.44 to 2.30,  $p = 0.776$ , respectively) or at 1 year (4.1% vs. 4.1%, HR: 0.99, 95%CI: 0.23 to 4.32,  $p = 0.994$ ; vs. 5.9%, HR: 0.50, 95%CI: 0.13 to 1.88,  $p = 0.306$ , respectively), but the rate of stent thrombosis was higher in BRS group at 30 day (2.1% vs. 0.3%,  $p = 0.059$ ; vs. 1.0%,  $p = 0.324$ , respectively) with a small reduction in the difference at one year (2.4% vs. 1.4%,  $p = 0.948$ ; vs.

1.7%,  $p = 0.825$ , respectively). Possible contributory factors include the learning curve in BRS implantation and higher use of new antiplatelet agents with DES than in the BMS arm (104).

Another study, which compared BRS with everolimus-eluting metallic stent in STEMI patients, was published by Cortese *et al.* (105). At a median of 220-days (interquartile range 178 to 369) follow-up, no significant differences were observed in terms of patient-oriented composite end point (BRS 4.9% *vs* EES 7.0%,  $p = 0.4$ ); death (BRS 0.8% *vs* EES 2.0%,  $p = 0.4$ ), MI (BRS 4.1% *vs* EES 2.0%,  $p = 0.2$ ), TLR (BRS 4.1% *vs* EES 4.5%,  $p = 0.8$ ), device thrombosis (BRS 2.5% *vs* EES 1.4%,  $p = 0.4$ ). The incidence of stent thrombosis was slightly higher in BRS group (2.5% *vs* 1.3%,  $p = 0.399$ ) (105). The exact mechanism of stent thrombosis is not fully understood and the authors concluded that it might be related partially to implantation technique (105). The PRAGUE 19 study involved BRS implantation in STEMI patients (106). The investigators reported good procedural and clinical outcome in these patients, but with stent thrombosis rate of 2.4%, higher than that seen in clinical trials (106). An excellent review of BRS use in STEMI has been published elsewhere (107) and the authors stated that the unique properties of the BRS make STEMI the ideal scenario for BRS implantation. However we still only have a small amount of data from registries and trials (which are characterized by relatively small sample size and short-term follow-up). The possible increased incidence of in-stent thrombosis is an issue of concern and debate, and needs further investigations (107).

Recently published, were the result from ABSORB-STEMI TROFI II trial, a multicentre, single-blind, non-inferiority, randomized controlled trial with STEMI patients who underwent primary percutaneous coronary intervention treatment with the Absorb or EES (108). The primary endpoint was the 6-month optical frequency domain imaging healing score (HS), HS was lower in the Absorb arm when compared with EES arm [1.74 (2.39) *vs* 2.80 (4.44);

difference (90% CI)  $-1.06$  ( $-1.96$ ,  $-0.16$ );  $p_{\text{non-inferiority}} < 0.001$ ]. The DOCE rates were low (Absorb: 1.1% vs. Xience: 0%) at 6 months and one case of definite subacute stent thrombosis was reported in Absorb arm (1.1% vs. 0% EES;  $p = \text{ns}$ ).<sup>(108)</sup> The authors concluded that Absorb can deliver the same acute and mid-term results as second-generation DES when using an appropriate implantation technique in STEMI patients, with complete arterial healing at 6 month in both arms (108).

Data from “Registro ABSORB Italiano” (RAI registry) in STEMI patients was recent published (109). At six-month follow-up, two non-fatal MI (2.7%), three target lesion revascularizations (4.1%), and one subacute BRS thrombosis were reported in 74 treated with BRS patients. They concluded that BRS implantation in STEMI patients could be successfully performed with a high procedural success rate and encouraging midterm outcomes (109).

## **BRS USE IN COMPLEX LESIONS**

Case reports and *in vitro* testing have demonstrated good procedural outcomes when BRS are used in bifurcation lesions (110). Capranzano *et al.* reported bifurcation treatment with BRS in a small number of patients was associated with good procedural and clinical outcomes (111). A sub-analysis of the GHOST-EU registry reported the use of BRS in bifurcation lesions (112). In 27% of patients an Absorb BRS was implanted at a bifurcation lesion. Over 80% of bifurcations were treated with a provisional approach of only the main branch, with crossover to stenting of the side branch in about 5% of cases. The T-stenting and small protrusion (TAP) technique was the preferred strategy for crossover from provisional when the side branch needed to be stented (112). When the double stenting technique was employed the culotte and crush techniques should be avoided to prevent excessive overlapping of the thick struts and structural

deformation of the scaffold (112). In cases of true bifurcation with significant and diffuse side branch disease, the authors recommended a hybrid strategy. This consists of implanting a DES in the side branch, crushing the DES with a balloon, followed by implanting a BRS in the main branch (112). Data from GHOST-EU registry also showed that bifurcations can be treated with BRS and metallic stents in a similar way, with the provisional approach remains the default strategy, but certain rules with regard to SB dilatation and kissing balloon inflation which need to be respected when implanting BRS in bifurcations in order not to damage their structural integrity (112). A recent study investigated clinical outcomes of patients treated with the provisional stenting approach versus a double stenting strategy for coronary bifurcation lesions with BRS (113). They reported TLR rates of 5.5% in provisional stenting group and 11.2% in double stenting strategy ( $p=0.49$ ) at 1-year follow-up. No scaffold thrombosis cases were reported. This study suggests that BRS implantation for bifurcation lesions is technically feasible with lower TLR for the provisional strategy than double-stenting (113).

Another sub-analysis of GHOST-EU registry published data of BRS use in ostial lesions (114). There were 90 ostial lesions (5.8%) in 84 patients (6.4%) treated with BRS (114). Use of BRS in the treatment of ostial lesions was associated with an increased rate of all events compared with non-ostial lesions (12.6% vs 4.6% at 12 months,  $p = 0.001$ ), including scaffold thrombosis (4.9% vs 2.0%) and in multivariable analysis, treatment of coronary ostial lesions was an independent predictor of clinical events in a cohort of patients treated with BRS (114).

For chronic total occlusion (CTO) treated with BRS we have still had very limited data. These data are mainly derived from case reports and small studies. The CTO-ABSORB pilot study (115) result showed that use of BRS in CTO is feasible with at one-month follow-up no major adverse events were observed. These results were achieved thanks to an appropriate lesion

preparation assuring adequate expansion of fully bioresorbable scaffolds in this setting. It was also reported that IVUS guidance could be useful in some complex and calcified CTO cases, to size the vessel appropriately and avoid unexpected scaffold underexpansion (110). Good procedural outcome of BRS use in CTO lesion was reported in small study published by Wiebe *et al.* (116).

## **BRS IN META-ANALYSES**

Few meta-analyses regarding BRS have been published to date. A meta-analysis of randomized controlled trials was recent published by Cassese *et al.* (117). They included 6 trials comprising data from 3738 patients (117). Patients treated with bioresorbable vascular scaffolds had a similar risk of TLR (OR 0.97 [95%CI 0.66–1.43];  $p = 0.87$ ), TLF (1.20 [0.90–1.60];  $p = 0.21$ ), MI (1.36 [0.98–1.89];  $p = 0.06$ ), and death (0.95 [0.45–2.00];  $p = 0.89$ ) but with higher risk of stent thrombosis (OR 1.99 [95%CI 1.00–3.98];  $p = 0.05$ ), especially between 1 and 30 days after implantation (3.11 [1.24–7.82];  $p = 0.02$ ) (117). The meta-analysis has, however, also important limitations. The authors did not evaluate an important outcome - currently widely discussed – TVMI, which in our meta-analysis (see below) was significantly higher for BRS in comparison to conventional stents. They did not also discuss the numerically higher prevalence of any cause MI in BRS patients (5.2% vs 3.5%) with a trend to statistical significance ( $p = 0.06$ ). The concern of increased definite/probable stent thrombosis in BRS patients was also presented in Lipinski *et al.* meta-analysis (118). They reported that patients who received a BVS were at a higher risk of MI (OR: 2.06, 95% CI: 1.31 to 3.22,  $p = 0.002$ ) and definite/probable ST (OR: 2.06, 95% CI: 1.07 to 3.98,  $p = 0.03$ ) compared with patients who received DES, whereas there was a trend toward decreased all-cause mortality with a BVS (OR: 0.40, 95% CI: 0.15 to

1.06,  $p = 0.06$ ) (118). This meta-analysis was limited by methodology that mixed stable patients and STEMI, single arm registries and randomized trials, and included unpublished, non-peer reviewed registries. Also data from our (Lipid and Blood Pressure Meta-analysis Collaboration [LBPMC] Group) meta-analysis was not able to detect statistically significant differences in one-year outcomes between BRS and conventional stents. The results of 10 studies with 5773 subjects showed statistically significant increase in risk of TVMI between BRS and conventional stents (OR: 1.45, 95%CI: 1.03, 2.05,  $p = 0.032$ ). None of the other differences between BRS and conventional stents reached statistical significance: all-cause mortality (odds ratio [OR]: 0.46, 95% confidence interval [CI]: 0.18, 1.18,  $p = 0.105$ ), cardiac death (OR: 0.86, 95%CI: 0.37, 1.97,  $p = 0.715$ ), POCE (OR: 0.94, 95%CI: 0.68, 1.31,  $p = 0.736$ ), DOCE (OR: 1.00, 95%CI: 0.67, 1.51,  $p = 0.981$ ), all MI (OR: 1.34, 95%CI: 0.98, 1.82,  $p = 0.064$ ; but became statistically significant when analyzed using the Mantel-Haenszel method: OR 1.36, 95%CI 1.00, 1.85,  $p = 0.049$ ), TVR (OR: 0.79, 95%CI: 0.51, 1.23,  $p = 0.298$ ) and TLR (OR: 0.78, 95%CI: 0.50, 1.20,  $p = 0.258$ ) and the percentage of total variance due to heterogeneity was negligible. This data will be presented at ACC Annual Congress in Chicago (April 2016).

## **FUTURE PERSPECTIVE**

Important future randomized trials on ABSORB, including the ABSORB IV clinical trial in over 3000 patients, which will be pooled with the ABSORB III trial 2000 patients (total of 5000 patients), will examine whether Absorb is superior to Xience DES at a 5 year endpoint of TLF (85). It is a different kind of trial than we have seen previously. Incidence of angina recurrence at 1 year after PCI is high, as demonstrated in several studies, including the Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes (FREEDOM)

trial (119), the Clinical Evaluation of the XIENCE V® Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions (SPIRIT IV) trial (120), the Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization (SYNTAX) trial (121) and the Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) (122). Data from a propensity-matched analysis (ABSORB EXTEND (83) vs. SPIRIT IV (120), still unpublished data) showed that over time, patients with BRS reported less angina (16%) than patients with Xience (28%) ( $p = 0001$ ).

ABSORB IV will be the first randomized heart stent trial to prospectively measure angina as a primary endpoint at one year (123). The other primary endpoint of ABSORB IV assesses long-term clinical safety and performance based on the change in TLF from 1 to 5 years. Measuring angina is significant because of its impact on quality of life and healthcare costs (123). Taking into account some data suggesting the increased risk of MI and TVMI, we need to wait for the ABSORB IV trial, in which only experienced centers are included (lack of learning curve), and which results will have critical impact on the future implementation of BRS. Some possible benefits of BRS are hypothetical or only demonstrated in animal testing or small human cohorts. There are still also some doubts concerning the healing process after full resorption of stent. Despite we might observe the all strata of endothelium based on OCT, and VH-IVUS imaging, we cannot be sure, whether the inflammation process/oxidative stress is not present in the place of healed stenosis, and whether it is not a something like “*locus minoris resistentiae*” for neo-atherosclerosis process. Therefore, it would be still highly interesting to observe all patients for next several years, using available imaging methods, and to evaluate early markers of atherosclerosis, including sensitive markers of inflammation and stress oxidation (dysfunctional

HDL (124), subfractions and subpopulations of LDL-C/HDL-C (125), endocan (126), GlycA, GlycB, endothelium function - (NO, O<sub>2</sub>- and ONOO- measurements) (127), miRNA: miR-221, miR-155, miR-100 and hsa-miR-1273 (128)). Thus far, the optimal duration of dual-antiplatelet therapy after BRS implant is unclear and has not been investigated. There is also a great deal of discussion as to how patients should be treated during the resorption and after complete BRS resorption. Differences of opinion exist concerning both antiplatelet and antithrombotic therapy, as well as lipid lowering therapy. Should we really stop them after resorption? We do not know yet. In the majority of studies the median duration of dual antiplatelet therapy was 12 months, but further studies defining the duration are necessary (129). Finally, how should the patient's risk be stratified once there is no stenosis in the coronary artery? Should they be treated similarly to patients after ACS? Maybe there is no necessity to use the most potent statins and other drugs typical for the CV highest risk patients.

There are also still attempts to improve existing bioresorbable stents, and the next generation of BRS called ABSORB GT1 to improve the deliverability of past generation of BRS will soon be available. In Absorb GT1 bioresorbable vascular scaffold system is delivered *via* the matching GlideTrack catheter, Abbott's flagship delivery catheter designed with better pushability and tactile response, better scaffold control for optimal access through difficult anatomy, allowing its use in wide range of patients (**Table 1**). Also Abbott has been working on new generation of BRS with thinner struts, broader family of dimension (diameter 2.25, 4.0 mm and length 33, 38 mm), larger functional expansion limit and shorter resorption time.

## CONCLUSIONS



Evidence suggested that BRS represents the fourth revolution in interventional cardiology. This new technology provides transient vessel support and drug delivery capability without holding the vessel in a “permanent” metallic cage. Once the scaffold has lost sufficient radial strength, effectively no longer “caging” the artery, restoration of vasomotion can occur. This is one of the indicators on the path towards complete vessel healing, but the exact clinical advantage is still not known. Return of normal vascular function has opened a new horizon aimed at promoting “vascular reparative therapy” or VRT (130). We go further and say that, despite still existing questions and doubts, BRS might be “the new magic bullet” for treating coronary arteries disease. Implantation of a BRS offers a ‘sealing layer’ that covers underlying thrombogenic plaque components and seals thin-cap fibroatheroma.

The clinical and procedural outcome was similar in BRS use with that in second generation of DES in the majority of studies and we can say that BRS is not inferior to DES. We do not yet have evidence of superiority over DES, but this would not be expected to become apparent until after full resorption of BRS. Further study and a longer duration of follow-up will elucidate this issue. BRS achieve successful acute revascularization of coronary artery lesions and show reasonably low rates of TLR and MACE during early follow-up, compared with new generation of DES.

After PCI the vessel is injured and requires scaffolding but there is no consensus on how long this scaffolding is required (to avoid negative remodeling). Some studies suggest a minimum of three (131) to six months (25,132); however the optimal time for resorption together with progressive reduction in radial strength is not known. A longer resorption period may lead to chronic inflammation and is associated with risk of stent thrombosis and intra-stent restenosis.

The second generation of ABSORB BVS 1.1 had a better radial strength compare with first generation but needed longer period of time to fully disappear.

The main limitations of the BRS are the thickness of struts, which makes the whole device bulky, and the potential for stent fracture. Aggressive post-dilatation is not recommended and a balloon diameter more than 0.25-0.5 mm bigger than the scaffold diameter should be employed, in order to avoid strut fracture with subsequent loss of radial strength and possible vessel collapse. The other limitations are: the limited sizes and diameters currently available, the need for slow and prolonged dilatations (with the possibility of ischemia), lack of visibility on X-ray imaging (only two metallic markers visible at the end). It seems that next BRS generation might be free of these limitations.

One of the early concerns raised by BRS implantation was that of stent thrombosis. This rate was higher than for DES in early real world registries (2.1% in GHOST-EU registry (93); 3.0% in AMC registry (95), 1.3% in the Registro Absorb Italiano registry (97)-preliminary data). However, the rate of thrombosis has not been seen to be higher in the largest, most recent randomized controlled clinical trial (ABSORB III) or in the more recent large, prospective national registries (GABI-R, REPARA, ABSORB FIRST, propensity matched analysis of GHOST EU). It has been suggested that the thicker struts of BRS might explain these finding. Ensuring adequate lesion preparation and post implantation optimization of BRS with IVUS or OCT has been recommended to reduce this rate. Stent thrombosis in BRS appeared more often in the first 30 days after implantation, similar to the frequency distribution for metallic stents, and it is clear that resistance to DAPT therapy was involved in small number of cases. Adequate lesion preparation, no aggressive post dilatation and optimization with and imagistic technique can reduce the incidence of stent thrombosis in BRS. Late resorption of the scaffold (up to 2-3 years)

raises also the issue of optimal duration of DAPT as well as lipid-lowering management. No data are available yet. No economic evaluation of BRS use compare with DES is also currently available. Five years after BRS implantation, intravascular imaging reveals late luminal enlargement, complete strut bioresorption and development of “sealing layer” cover atherosclerotic plaque. Taking these all into account we believe that BRS might be the “new magic bullet” for treating coronary disease enabling natural healing of the endothelium. It is not yet ideal, but is a perfectible technology. The quest to find the ideal stent continues but we believe the first generation of BRS opens the door to the future possibility that our patients may someday never require a permanent implant to relieve their symptomatic and life-threatening coronary stenoses.

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	<b>ABSORB BVS 1.1, Abbott, USA</b>	<b>ABSORB GT1, Abbott, USA</b>	<b>DESolve, Elixir Medical, USA</b>
<b>Backbone</b>	PLLA	PLLA	PLLA
<b>Polymer coating</b>	PDLLA	PDLLA	PDLLA
<b>Delivery System</b>	Multi-Link SDS*	Glide Track <sup>¥</sup>	DESyne catheter
<b>Design</b>	In-phase zigzag hoops, cross-linked by bridges	In-phase zigzag hoops, cross-linked by bridges	Tubularly arranged hoops, linked by bridges
<b>Crossing profile</b>	1.43 mm	1.43 mm	1.44 mm
<b>Strut thickness</b>	150µm	150 µm	150µm
<b>Drug eluting</b>	Everolimus <sup>€</sup>	Everolimus <sup>€</sup>	Novolimus <sup>£</sup>
<b>Visualization</b>	Two small	Two small platinum	Two small platinum markers

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**Table 1.** Comparison of CE mark bioresorbable scaffold.

	platinum markers at scaffold edge	markers at scaffold edge	at scaffold edge
<b>Dissolution</b>	24-36 month	24-36 month	12-24 month
<b>Diameter</b>	2.5/3.0/3.5 mm	2.5/3.0/3.5 mm	2.5/3.0/3.25/3.5 mm
<b>Length</b>	8, 12, 18, 23, 28 mm	8, 12, 18, 23, 28 mm	14, 18, 28 mm

Abbreviations: PLLA-poly L- lactic acid; PDLA-Poly (D,L)-lactic acid;

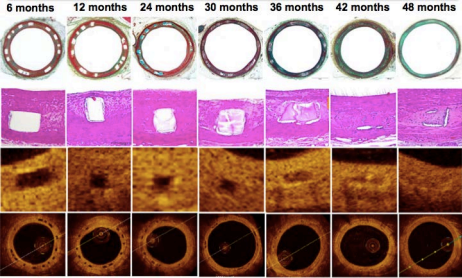
\*the same delivery system use in Xience V (Abbott, Santa Clara, USA); ¥ Catheter specially design and built for ABSORB GT1 with improve ease to use, improve push transmission; € Similar dose density and release rate to Xience V (Abbott, Santa Clara, USA); £ Similar dose density and release rate to DESyne (Elixir Medical Corporation, USA)

## FIGURES LEGENDS:

**Figure 1.** Histology and OCT of ABSORB BVS in a porcine coronary arteries model. Movat's pentachrome (MP), 2x objective (top row) and hematoxylin and eosin (HE), 20x objective, top center row. On histology, struts appear like acellular regions with well-defined borders at 6, 12, and 24 months. At 30 and 36 months, due to the minimal (30) to no (36) residual polymer content, struts are replaced by a largely acellular provisional matrix, which stains by both MP and HE. At 42 and 48 months, footprints of pre-existing struts are coalesced with surrounding tissue, being hardly discernible at 48 months. Histological images at the depicted time points show minimal to mild inflammation, no fibrin deposition, and no to scant calcification around struts/resorption sites. On OCT struts appear like a preserved box (6-12-24-30 months), open box (36 months), dissolved black box (42 months) and either dissolved bright box or were

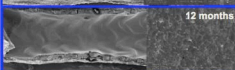
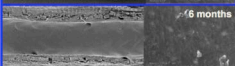
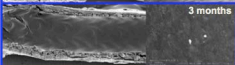
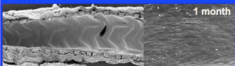
indiscernible (48 months). Image provide by courtesy of Abbott Vascular (Santa Clara, California).

**Figure 2.** Scanning electron microscopy (SEM) after implant of Xience (everolimus eluting metallic stent) and ABSORB BVS (everolimus eluting bioresorbable scaffold). At 1 month, struts of both Xience and Absorb were largely covered by endothelialized neointima (> 90% by visual estimate). Thereafter, both Xience and Absorb demonstrate complete and stable endothelialization. Image provided by courtesy of Abbot Vascular (Santa Clara, California).





## Absorb



## Xience

