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Review Article

Internal Medicine Section

Bioresorbable Scaffolds: Current Evidences in the Treatment of Coronary Artery Disease

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ABSTRACT

Percutaneous coronary revascularization strategies have gradually progressed over a period of last few decades. The advent of newer generation drug-eluting stents has significantly improved the outcomes of Percutaneous Coronary Intervention (PCI) by substantially reducing in-stent restenosis and stent thrombosis. However, vascular inflammation, restenosis, thrombosis, and neoatherosclerosis due to the permanent presence of a metallic foreign body within the artery limit their usage in complex Coronary Artery Disease (CAD). Bioresorbable Scaffolds (BRS) represent a novel approach in coronary stent technology. Complete resorption of the scaffold liberates the treated vessel from its cage and restores pulsatility, cyclical strain, physiological shear stress, and mechanotransduction. In this review article, we describe the advances in this rapidly evolving technology, present the evidence from the pre-clinical and clinical evaluation of these devices, and provide an overview of the ongoing clinical trials that were designed to examine the effectiveness of BRS in the clinical setting.

Keywords: Bioabsorbable vascular scaffold, Coronary stents, Percutaneous coronary intervention

INTRODUCTION

Percutaneous Transluminal Coronary Angioplasty (PTCA) by Andreas Roland Grüntzig in 1977, is a technique now known as Plain Old Balloon Angioplasty (POBA), arises new horizons in the treatment of Coronary Artery Disease (CAD) [1]. Undoubtedly, POBA has been considered as the first revolution in percutaneous treatment of CAD owing to its ability to dilate and restore coronary flow in diseased coronary vessels. However, initial enthusiasm was tampered due to the risk of acute vessel closure and restenosis attributed by elastic recoil, constrictive remodelling or neointimal hyperplasia [2-4].

Bare Metal Stents (BMS) were introduced to overcome these limitations of balloon angioplasty. Two landmark studies, Belgian-Netherland Stent Study (BENESTENT) and Stent Restenosis Study (STRESS), demonstrated superiority of BMS over POBA and established BMS as the second revolution in coronary intervention [5,6]. This technology resolved many issues of POBA i.e., elastic recoil and constrictive remodelling [7,8]. However, high incidence of in-stent restenosis (which was more prominent than with POBA) as a consequence of neointimal hyperplasia led to repeat intervention in numerous patients. Hence, the use of BMS in complex CAD was precluded [9,10].

The advent of Drug-Eluting Stent (DES) significantly reduced the risk of in-stent restenosis and subsequently reduced the rate of Target Lesion Revascularization (TLR) [11,12]. Thereby, metallic DES is dubbed as third revolution in interventional cardiology. Though the coated anti-proliferative drug prolongs vessel wall healing and reduces neointimal hyperplasia, there is still the risk of "late-catch up" phenomenon of neoinitimal proliferation [13]. Other safety concerns are stent fracture, mal-appositions, delayed endothelization, hypersensitivity reaction of the vessel wall to durable polymer, mal-appositions and abnormal vasomotion due to vessel caging. These limitations of earlier-generation DES questioned long-term safety of DES especially the occurrence of late adverse clinical events [13,14]. Hence, newer-generation of DES with thinner struts and biodegradable polymers were developed. However, the risk of late adverse clinical events was not completely eliminated with newer generation DES. Moreover, the existence of metal stents is associated with potential risk of neoartherosclerosis, impairment of vessel geometry and preclusion of the stented segment from other revascularization options, such as coronary artery bypass surgery [14-16]. It should be noted that unlike POBA, metallic stents in the vessel does not allow late luminal enlargement and advantageous vascular remodelling.

Bioresorbable Scaffolds (BRS), the next advancement in interventional cardiology, seems to resolve the shortcomings of DES. Apart from preventing acute vessel closure or recoil by transient scaffolding the vessel, these fully biodegradable scaffolds elute anti-proliferative drugs which counteract constrictive remodelling and neointimal hyperplasia. BRS subsequently resorbes, which allows vasomotor response in the vessel. Hence, it is potentially an ideal therapy for CAD and therefore, it is truly heralded as fourth revolution in interventional cardiology. Evidences of clinical benefits of this new technology accelerated the development of fully bioresorbable devices over the last 5-10 years. Currently, numerous devices are available which undergo pre-clinical and clinical testing. In this review article, we discussed theoretical advantages of this emerging technology over current generation metallic DES and provided brief overview of currently available BRS.

Potential Advantages: Successful acute revascularization of coronary artery stenosis has been achieved with BRS and is associated with low rates of repeat revascularization or Major Adverse Cardiac Events (MACE) (short-term outcomes) in preliminary studies. There are several advantages of PCI with BRS over current metallic DES technology. The occurrence of late or very late Stent Thrombosis (ST) will decrease after PCI with BRS as there is complete bioresorption without any foreign body remnant in the vessel wall. An important factor in the pathophysiology of ST is incomplete endothelization of the stent (uncovered struts) which is unlikely to be associated with BRS. Owing to its transient nature, BRS also mitigate the issue of 'late catch-up phenomenon' of in-stent restenosis secondary to low-grade inflammatory response to the polymer or device. In contrast to conventional stent, complete

bioabsorption of the scaffolds results into "liberation of the vessel from metallic cage" and thereby eliminate risk of adaptive shear stress, late luminal enlargement and late expansive remodelling [17].

Superior conformability and flexibility of BRS reduces altered distribution of tissue biomechanics and preserves vessel geometry. Additionally, minor mal-apposition can be resolved by BRS self-correction [18]. Moreover, BRS do not cause artifacts and therefore allows improved non-invasive imaging of the target site using computed tomography or magnetic resonance during post-intervention follow-up. Administration of dual anti-platelet therapy can be shortened which reduces incidences of bleeding complications [19]. As the presence of these scaffolds is not persistent, they may overcome many issues associated with permanent nature of metallic stents i.e., jailing of the side branches, overhang at ostial lesion and lack of revascularization option of stented segment [18].

Material Composition and Properties of BRS: Ideal BRS should have adequate radial support for a period of 3–6 months to limit recoil and constrictive remodelling and they should incorporate anti-proliferative drug that control neointimal formation and prevent restenosis. They should have as low crossing profile as possible and be flexible enough to allow delivery in more challenging anatomical disease together with thin struts to limit the healing response. But, at the end, BRS should completely corrode and be absorbed as soon as possible after its therapeutic period is over.

Various types of polymers have been used in BRS development. The most common polymer used in the development of BRS is Poly-L-Lactic Acid (PLLA) which provides sufficient radial strength to the scaffold (comparable to that of current DES). The radial strength is approximately 1200mmHg directly after the implantation of the scaffold and it is as much as 800mmHg after 1 year [15]. The degradation of PLLA occurs through hydrolysis of the ester bonds into small particles that are phagocytosed by macrophages and finally metabolized through the Kreb's cycle into carbon dioxide and water [20]. Several limitations of PLLA need to be addressed. For example, PLLA is limited in expansion and optimal scaffold apposition, overexpansion of the scaffold may result in strut fractures which may lead to target vessel failure. Moreover, the behaviour of PLLA scaffolds in bifurcations, calcified, long or diffusely diseased lesions is not extensively studied. Owing to these inherent limitations, its use is limited in complex lesions or narrowed indications [21,22]. Another polymer used in BRS technology is tyrosine polycarbonate. The catabolism of the polymer produces carbon dioxide and iodinated-disaminotyrosyl-tyrosine ethyl esters which ultimately hydrolyse to ethanol and iodinated-disaminotyrosyl-tyrosine [23].

Till date, two metal alloys, iron and magnesium (Mg), have been identified and evaluated as candidates for metallic BRS. Mg-based scaffolds have been widely investigated and now it is the metal candidate in BRS technology. Owing to high mechanical strength, it is possible to form a scaffold with thinner strut. However, Mg needs to be mixed with several elements such as zirconium, yittrium and other rare earth metals due to its fragile nature. The degradation products of scaffold dissolution are inorganic salts which triggers only a minor inflammatory response and produce electronegative charge having antithrombotic effect [24,25]. Absorbable Metal Stent (AMS-1) (Biotronik, Berlin, Germany) was the first Mg-based BRS which was uncoated and lacked anti-proliferative drug elution. In addition, too rapid degradation of the scaffold, before the end of the healing process led to early vessel recoil and restenosis. Hence, newer generation of AMS were designed to elute anti-proliferative drug with slower degradation rate.

Another metal for BRS is iron and its alloys. Iron and its alloys have good mechanical performance and biocompatibility. Experimental studies demonstrated that iron ions (released from bioresorbable iron stents) influence growth-related gene expression and thereby reduce vascular smooth muscle cell proliferation rate resulting into impedance of restenosis in-vivo [26]. Hence, research has been focused to shorten corrosion period of iron-based scaffold by accelerating the material corrosion (by alloy composition design, material structure design, material modification and introducing corrosion-promoting substances or mechanisms) [21].

Currently Available BRS: Several BRS are under development, either under pre-clinical evaluation or being examined in clinical setting. Only two scaffolds have acquired Conformité Européenne (CE) mark approval and are used in clinical practice for the treatment of CAD: Absorb bioresorbable vascular scaffold (Abbot Vascular) and the DEsolve scaffold (Elixir Medical Corporation). Of note, the Igaki-Tamai stent (Kyoto Medical Planning Co., Ltd., Japan) has also received CE mark but only for the treatment of peripheral vascular disease. [Table/Fig-1] summarises the technical aspects of currently available or investigated BRS.

1. Igaki-Tamai BRS: The Igaki-Tamai scaffold, the first fully bioresorbable stent to be evaluated in humans, was made of PLLA without any drug coating. The first revision of scaffold had a helical zigzag design and it was both thermal self-expanding and balloon expandable. Self-expansion of the device occurred in response to heated contrast (up to 70°C) which was applied through the delivery balloon. The device continued to expand at body temperature after its implantation over a 20–30 minute period, until it reached its final dimensions. In-vivo complete biodegradation of the device took 18-24 months. To aid visualization, there were two radiopaque cylindrical gold markers at either end of the scaffold.

The First-In-Man (FIM) study of the Igaki-Tamai scaffold enrolled 15 patients (19 lesions) treated with 25 scaffolds. The results demonstrated no MACE or ST within 30 days and 1 TLR (repeat PCI) at the 6-month follow-up. Angiographic follow-up at 3-months showed reduction in Minimal Lumen Diameter (MLD) as compared to post-procedural values (1.88±0.59mm vs. 2.59±0.35mm. There was no significant stent recoil at day-1. Intravascular Ultrasound (IVUS) imaging confirmed continued stent expansion in first three months. There was gradual increase in scaffold cross-sectional area [from 7.42±1.51mm^2 at baseline to 8.18±2.42 mm^2 ($p<0.1$) at 3 months and 8.13±2.52 mm^2 at 6 months ($p<0.1$)] [27].

Nishio et al. reported long term follow-up (>10years) of an observational prospective study which enrolled 50 elective patients (63 lesions, 84 Igaki-Tamai scaffolds). Angiographic analysis demonstrated a mean diameter stenosis of 25% compared with 38%, 29%, and 26% at 6, 12, and 24 months, respectively. The 10-year cumulative event-free survival rates of all-cause death, cardiac death and MACE were 87%, 98% and 48%, respectively. Serial angiographic follow-up demonstrated no change in minimum lumen diameter (2.01mm at 1 year vs. 2.06mm at 10 years). There were only two ST events at 10-year follow-up [28].

Despite of encouraging short- and long-term follow-up results, device failed to progress, mainly due to the concern about use of the heated contrast in coronary arteries which may cause arterial wall necrosis leading to an exaggerated neointimal hyperplastic response or increased risk of ST as a consequence of platelet adhesion [29]. Requirement of large guide catheter (8-French) was another drawback of the device. The new generation Igaki-Tamai scaffold potentially overcomes these pitfalls, as it can be implanted through a 6-French guide catheter without the need for a heated contrast agent. The device is currently undergoing pre-clinical evaluation in Germany [16]. However, the results of the PERSEUS study lead this device to be used in Europe for peripheral artery disease [30].

2. ABSORB Bioresorbable Vascular Scaffold (BVS): ABSORB BVS is the first drug-eluting BRS which is composed of PLLA. The scaffold is coated with Poly-D,L-Lactide (PDLA) polymer which controls the release of everolimus, 80% of which is eluted at the

Scaffold	Strut material	Coating material	Eluted drug	Strut thickness	Radio-opacity	Radial support duration (days)	Resorption (months)	Crossing profile	Current status
Polymeric scaffold									
Igaki-Tamai BRS[1] (Kyoto Medical Planning Co., Ltd., Kyoto, Japan)	PLLA[2]	None	None	170	Gold markers	180	24-36	-	CE[3] Mark for peripheral use
ABSORB BVS 1.0 (Abbott Vascular, Santa Clara, CA, USA)	PLLA	PDLLA[4]	Everolimus	156	Platinum markers	Weeks	18-24	1.4 mm	Discontinued
ABSORB BVS 1.1 (Abbott Vascular, Santa Clara, CA, USA)	PLLA	PDLLA	Everolimus	156	Platinum markers	180 days	24-48	1.4 mm	CE Mark
ABSORB BVS[5] new generation (Abbott Vascular, Santa Clara, CA, USA)	PLLA	PDLLA	Everolimus	<100	-	-	-	-	-
DESolve (Elixir Medical Corp., Sunnyvale, CA, USA)	PLLA	None	Myolimus	150	Metallic markers	-	12-24	1.5 mm	CE Mark
DESolve 100 (Elixir Medical Corp., Sunnyvale, CA, USA)	PLLA	PLLA	Novolimus	100	-	-	24	-	CE Mark
REVA scaffold (REVA Medical, Inc., San Diego, CA, USA)	PTD-PC[6]	None	None	200	Radioopaque scaffold	90-180 days	24	1.8 mm	Discontinued
ReZolve scaffold (REVA Medical, Inc., San Diego, CA, USA)	PTD-PC	None	Sirolimus	115-230	Radioopaque scaffold	90-180 days	4-6	1.8 mm	Clinical Trials
ReZolve[2] scaffold (REVA Medical, Inc., San Diego, CA, USA)	PTD-PC	None	Sirolimus	100	Radioopaque scaffold		48	1.5 mm	Clinical Trials
Fantom (REVA Medical, Inc., San Diego, CA, USA)	PTD-PC	-	Sirolimus	125	-	-	36	-	Clinical trials
IDEAL Biostent (Xenogenics Corp., Canton, MA, USA)	Polymer salicylate	Salicylate	Sirolimus	175	None	90 days	>12	1.5-1.7 mm	Clinical Trials
ART18Z BRS (Arterial Remodeling Tech., France)	PDLLA	None	None	170	None	90-180 days	3-6	6-Fr compatible	Clinical Trials
AMARANTH (Amaranth Medical Inc., CA, USA)	Semicrystalline polylactide		None	90-150	None	90-180 days	3-6	6-Fr compatible	Clinical Trials
Xinsorb BRS (Shandong HuaAn Biotech., Co. Ltd., China)	PLLA	PDLLA	Sirolimus	160	-	-	24-36	-	Clinical Trials
Acute BRS (Orbus Neich, Fort Lauderdale FL, USA)	PLCL7, PDLA, PLLA	-	Sirolimus, CD34+ antibody	150	-	-	-	-	
MeRes (Meril Life Sciences, Vapi, Gujarat, India)	PLLA	PDLLA	Merilimus	100	-	-	24	-	Clinical Trials
FADES (Zorion Medical, Indianapolis, IN, USA)	PLGA[8] and Magnesium	-	-	-	-	-	6	-	
Mirage Bioresorbable Micro-fiber scaffold (Mirage BRMS, Manli Cardiology, Singapore)	PLLA	-	Sirolimus	125-150	-	-	14	0.44"-0.058"	Clinical Trials
Metallic scaffold									
AMS-1 (Biotronik, Berlin, Germany)	Magnesium alloy	None	None	165	None	Weeks	<4	-	Discontinued
DREAMS[9] 1.0 (Biotronik, Berlin, Germany)	Magnesium with rare metals	PLGA	Paclitaxel	125	None	90-180 days	9	-	Clinical Trials
DREAMS 2.0 (Biotronik, Berlin, Germany)	Magnesium with rare metals	PLLA	Sirolimus	100	Metallic markers	90-180 days	9	-	Clinical Trials

[Table/Fig-1]: Technical aspects of currently available/ investigated bioresorbable scaffolds.
1 Bioresorbable scaffold
2 poly-L-lactic acid
3 Conformité Européenne
4 poly-D, L-lactide acid
5 bioresorbable vascular scaffold
6 Poly-tyrosine-derived polycarbonate
7 poly-L-lactide-co-ε-caprolactone
8 poly-lactide-co-glycolide
9 drug-eluting absorbable metallic stents

end of the first month following implantation and full hydrolytic degradation takes as long as 3 years [31].

BVS 1.0, the first version of ABSORB BVS, had a strut thickness of 150μm with crossing profile of 1.4mm. The device was constituted of circumferential out-of-phase zigzag hoops and the struts were linked directly together by thin and straight connections. ABSORB Cohort-A Trial (A Clinical Evaluation of the Bioresorbable Everolimus Eluting Coronary Stent System in the Treatment of Patients with de Novo Native Coronary Lesions), a prospective and open-label study, evaluated feasibility and safety of the scaffold in 30 patients with single de novo coronary artery lesion [20]. The cumulative estimated incidence of MACE was 3.3%, with only one patient having a non-Q wave Myocardial Infarction (MI) and no TLR at 1-year follow-up. No further events occurred between 1 and 5 years follow-up [32]. In-scaffold Late Lumen Loss (LLL) did not differ between the 6-month and 2-year follow-up (0.44 ±0.35mm, 0.48±0.28mm). A reduction in the lumen area between baseline and follow-up was observed by IVUS which was partially attributed to the scaffold shrinkage [33]. Hence, the scaffold was redesigned (BVS 1.1) and the redesigned scaffold had in-phase hoops and

straight links to provide additional radial support, and an updated polymer to provide additional mechanical strength to the scaffold [34].

The second generation ABSORB BVS was examined in ABSORB Cohort-B trial which enrolled a total of 101 patients (102 lesions) [35,36]. The studied population was divided into two groups; the first group (Cohort B1) had Quantitative Coronary Arteriography (QCA), IVUS, IVUS palpography, IVUS-VH, IVUS echogenicity, and Optical Coherence Tomography (OCT) at 6 months and 2 years. The second group (B2) had the same follow-up imaging processes at 1 and at 3 years. The rate of MACE in 101 patients was 9.0% (three non-Q-wave MI, six ischemia-driven TLR) at 2 year follow-up [37]. In the Cohort B1 group, QCA analysis demonstrated an LLL of 0.19±0.18mm at the 6-month, and 0.27±0.20mm at 2 year follow-up [38]. IVUS examinations demonstrated the minimum lumen area to be reduced at 6 months (from 5.45±1.08mm^2 post-procedure to 5.12±1.01mm^2), with no changes at 2 years (5.13±1.25mm^2) whereas the mean lumen area and mean scaffold area decreased at 6 months (from 6.53±1.24mm^2 post-procedure to 6.36±1.18mm^2 and from 6.53 ±1.23 mm^2 post-procedure to 6.42±1.17mm^2, respectively), and then increased at 2 years (6.85±1.78mm^2, 7.08±1.73mm^2, respectively). One-year follow-up results of Cohort B2 group demonstrated the LLL to be 0.27±0.3mm. The mean scaffold area and mean lumen area were similar between post-procedure and 1 year follow-up (6.29±0.92mm versus 6.33±0.98mm and 6.31±0.95mm versus 6.33±1.17mm, respectively). The vessel vasomotion was evaluated with the application of acetylcholine or methylergonovine which confirmed restoration of the vasomotion at 12 months after scaffold implantation [36]. At three years, intracoronary administration of nitrate showed a significant improvement of vasodilatation [39].

Other clinical trials which assess the performance of the scaffold are ABSORB II, ABSORB EXTEND and ABSORB Physiology. ABSORB II, the first randomized controlled trial, compares the efficacy and safety of a second generation BRS (Absorb, Abbott Vascular, Santa Clara, CA, USA) with a contemporary DES (Xience, Abbott Vascular, Santa Clara, CA, USA) in 501 patients. One-year clinical follow-up demonstrated no difference in MACE (defined as death, MI or TLR) between patients treated with a BRS or a contemporary metallic DES (5% vs. 3%, p=0.35). There was reduction of cumulative rates of first new or worsening angina in BRS group (22% vs. 30%, p=0.04) [40]. Post-procedure acute gain in minimum lumen diameter was significantly larger in metallic stent group than in BRS group (1.46±0.38mm vs. 1.15±0.38mm, respectively; p<0.001). Post-procedure in-stent/in-scaffold diameter stenosis was larger in BRS group than in metallic stent group (16±7% vs. 10±5%, respectively; p<0.001). The incidence of definite scaffold thrombosis was 0.6% in BRS and 0% in metallic stent group (p=1.0). One-year clinical follow-up showed higher incidence of MI in BRS group (4%) than in metallic stent group (1%) although it was statistically insignificant (p=0.06). There were two incidences of scaffold thrombosis.

Preliminary results from the international, multi-center ABSORB EXTEND single arm study demonstrated an incidence of MACE of 7.3%, ischemia driven TLR of 4.0%, and stent thrombosis of 0.8%, in 250 patients (including those with long lesions and small vessels) with 24 months of clinical follow-up [13]. The ABSORB Physiology study aims to estimate the short and long term effects of an ABSORB BVS and a Xience-V (Abbott Vascular, Santa Clara, USA) stent on the physiology of the vessel wall, and will include the following metrics: vascular compliance, distensibility, endothelial responsiveness and shear stress distribution [13].

3. DESolve: The DESolve Bioresorbable Coronary Scaffold System has a PLLA backbone and is coated with novolimus (5µg/mm) - a major metabolite of sirolimus. The device has strut thickness of 150µm and self-correction property. The scaffold with sinusoidal ring patterns has open cell body which provides high flexibility and ease of side branch access. It exhibits good radial strength. The reabsorption process of the scaffold takes approximately 2 years [41]. Next generation DESolve devices, DESolveNx (strut thickness of 120µm) and DESolve100 (strut thickness of 120µm), DESolve+ have been developed to address general BRS design limitations and expand clinical indications.

DESolve-I FIM is a multicentre feasibility trial which recruited 16 patients with single de novo native coronary artery lesions. QCA analysis at 6-month follow-up demonstrated LLL to be 0.19±0.19mm. OCT-results at 6-month follow-up demonstrated that 98.68±2.44% of the struts to be covered by neointima (mean neointimal hyperplasia obstruction was 13.16±5.59%) [41]. One-year clinical follow-up demonstrated three MACE (1 cardiac death, 1 target vessel MI and 1 TLR). However, there was no incidence of scaffold thrombosis [41]. Multi-center, prospective DESolve Nx trial recruited 126 patients to evaluate safety and efficacy of the scaffold. DESolve Nx trial was successful in demonstrating the safety and efficacy of the DESolve scaffold, with a low 6-month LLL by QCA (0.20±0.32mm), low 6-month IVUS% volume obstruction (5%) and evidence of early vascular restoration through lumen and scaffold growth, low 6-month Neointimal Hyperplasia (NIH) thickness by OCT (0.10mm), no reported late acquired incomplete strut apposition by IVUS / OCT at 6 months and high percentage of strut coverage by OCT at 6 months (98.8%) [42,43]. Three-year OCT imaging reveals the “golden tube” with maintenance of lumen area. There was no incidence of acute or late definite scaffold thrombosis at 3 year follow-up [44].

4. REVA: The REVA scaffold (REVA Medical, Inc., San Diego, CA, USA) is composed of tyrosine derived polycarbonate polymer. The device has no anti-proliferative drug coating and the bioresorption time is nearly 36 months. The slide and locking design, distinctive feature of the device, prevent deformation and weakening of the polymer during scaffold deployment.

The REVA endovascular study of a bioresorbable study (RESORB study) recruited 27 patients with de novo coronary artery lesions. The results of the study showed satisfactory acute gain in lumen diameter and vessel shrinkage following implantation of the device. The mean diameter stenosis pre- and post- implantation was 70% and 5.9% respectively. QCA analysis demonstrated increase in Mean Lumen Diameter (MLD) from 0.88 ±0.39mm to 2.76±0.36 mm. However, high incidence of TLR (66.7%) was noted at 6-month follow-up predominantly due to focal mechanical failure [45]. Hence, the scaffold has been redesigned.

The second generation ReZolve stent has strong and resilient radiopaque polymer, a spiral slide and lock design (rachet design) and is coated with the antiproliferative drug sirolimus (80µg). The ReZolve sirolimus-eluting bioresorbable coronary scaffold (RESTORE) aim to evaluate safety and efficacy of ReZolve. The trial enrolled 50 patients. At 12 months follow-up, acute recoil was 3.8±6.7%, and LLL was 0.29±0.33mm. Six-month clinical follow-up reported two incidences of MACE [46]. ReZolve 2 is being tested in the Safety and Performance Study of the ReZolve2 Sirolimus-Eluting Bioresorbable Coronary Scaffold study (RESTORE-II) (n= 112) [47]. The company has presented a new bioresorbable scaffold with thinner strut thickness and advancement of polymer, FANTOM.

5. Fantom: The Fantom (REVA Medical, Inc., San Diego, CA, USA) is a sirolimus-eluting scaffold. The device is composed of desaminotyrosine-derived polycarbonate material. The characteristic features of the device include complete scaffold visibility under x-ray (reduces need for IVUS or OCT), single-step continuous inflation, clinically significant expansion range, lower crossing profile, radial strength at 125µm strut thickness and vasomotion restoration < 1 year [47,48]. A pilot clinical trial, FANTOM-I, enrolled 7 patients to verify acute performance of

the device [49]. Another clinical trial (FANTOM-II) was designed to study the safety and performance of the device which was expected to enrol up to 220 patients across 30 different clinical centres (enrolment has been initiated in March 2015).

6. IDEAL Biostent: The IDEAL BioStent (Xenogenics Corp, Canton, Massachusetts, USA), a balloon expandable scaffold, is synthesised entirely from salicylic acid bioabsorbable polymer derivates. The backbone which provides mechanical support is comprised of polylactide anhydride mixed and a trimer of two salicylic acid molecules joined by a sebacic acid as a linker molecule. The backbone is coated with salicylate (a trimer of two salicylic acid molecules joined by adipic acid as a linker molecule) which controls release of anti-proliferative drug, sirolimus (8.3µg/mm) [50]. The stent elutes approximately 10µg of salicylic acid. Thus, the scaffold has both anti-inflammatory and anti-proliferative properties. It takes 30-days for complete drug-elution and 9-12 months for complete biodegradation of the scaffold [50]. The stent is radiopaque and 8-French guiding catheter compatible.

WHISPER study, a prospective FIM trial of IDEAL Biostent, enrolled 11 patients. Coronary angiography and IVUS analysis showed absence of scaffold recoil [51]. However, IVUS and OCT showed negligible neointimal suppression and a significant reduction in lumen area, which were attributed to the inadequate drug dose and fast drug elution. Hence, the new-generation IDEAL BioStent with higher drug dose, slower drug release kinetics, improved stent design with thin struts and a 6-French compatible delivery system has been designed which is currently undergoing pre-clinical evaluation.

7. ART: The ART (Arterial Remodeling Technologies; Noisy le Roi, France), a fully bioresorbable non-drug eluting scaffold, is made from amorphous semicrystalline PDLLA polymer and hence, reabsorption is rapid. The reabsorption process of the scaffold starts at 3 months and expected to be completed between 18 to 24 months. ART18Z is the new revision of the device.

Pre-clinical studies reported late lumen enlargement and positive arterial remodelling in ART18Z group at 9 month follow-up as evident by decreased LLL [13]. Based on these promising Pre-clinical results, the Arterial Remodeling Transient Dismantling Vascular Angioplasty (ARTDIVA) FIM trial has been initiated to evaluate the safety and efficacy of the ART18Z bioresorbable scaffold in the treatment of patients with CAD. ARTDIVA FIM is a multicentre trial (5 medical centre of France) which enrolled 30 patients with a single de novo lesion [13,52]. During 6 month follow-up period, there was 1 ischemia driven TLR and 2 non-ischemia driven TLR, no MI and stroke/TIA [53].

8. AMARANTH: The Amaranth (Amaranth Medical Inc, Mountain View, CA, USA) is made with proprietary tube fabrication. Multiple layers of polymers provide flexibility and strength to the scaffold. The structural integrity of the Amaranth scaffold lasts 3–6 months.

Preliminary experimental studies (Bare BRS 150µm) have demonstrated biocompatibility of the polymer and sustained biomechanical properties of the scaffold. The findings of BARE FIH study confirmed no evidence of scaffold thrombosis or restenosis at 2 year follow-up in 13-patients [54]. The sirolimus-eluting AMARANTH FORTITUDE BRS 150µm is being investigated in MEND II (n=42 patients) and RENASCENT-I (n=21 patients) studies [55]. Nine-month follow-up in 45 patients showed 2.2% Target Vessel Failure (TVF) (1 peri-procedural MI). RENASCENT-II, a prospective, multicentre trial, was expected to start in 2015 with the aim of evaluate safety and performance of AMARANTH FORTITUDE bioresorbable scaffold (BRS) 120µm. is currently being evaluated in two multi-center trials in centers in Colombia, South America (MEND-II trial) and Italy (RENASCENT trial) [55]. Next generation of AMARANTH FORTITUDE BRS is designed with reduced strut thickness (90µm) and albuminal sirolimus coating.

9. Xinosorb: The Xinsorb BRS (Huaan Biotechnology Co., Ltd., Hangzhou, Zhejiang, People's Republic of China) is a fully balloon expandable bioresorbable sirolimus-eluting scaffold. The device is composed of poly (aspartic acid-colactide), poly (ε-caprolactone), and polyglycolide. The device has radiopaque markers to facilitate its deployment. A total of 30 patients (with single de novo lesion) were enrolled in prospective FIM trial of Xinsorb. QCA was performed in 27 patients which demonstrated effectiveness of the scaffold in suppressing neointimal hyperplasia (In-scaffold LLL was 0.17±0.12mm and peri-scaffold LLL was 0.13±0.24mm) [56]. OCT and IVUS showed excellent intimal healing without apparent scaffold structure remodelling at 6 month follow-up. Clinical follow-up at 18 month demonstrated one confirmed ST [56].

10. Acute: The Acute BRS (OrbusNeich, Fort Lauderdale, FL, USA) is a tube-shaped lockable and balloon-expandable BRS. The absorbable stent platform incorporates a partitioned coating technology which combines the pro-healing endothelial progenitor cell capture antibodies (anti-CD34 antibodies) on luminal surface for rapidly achieving endothelial coverage and improved functionality along with a luminal low dose sirolimus drug elution for control of neointimal proliferation [57]. Preliminary Pre-clinical evaluation demonstrated an optimal device implantation without evidence of fracture [16].

11. MeRes: MeRes BRS (Meril Life Sciences, Vapi, Gujarat, India) is a merilimus eluting bioresorbable coronary scaffold. The backbone of the device is comprised of PLLA polymer with a top coat of PDLLA which controls release of the drug. Hybrid scaffold geometry structure of the device provides high radial strength and tri-axial radiopaque markers facilitate ease of procedure. Another characteristic feature of the device is thinner struts. Preliminary animal studies demonstrate favourable healing response at 30 and 60 days in porcine model [58]. Pre-clinical studies also confirmed the absence of thrombogenicity of the material and stability of the biomechanical properties. MeRes FIM multicentre study is recently enrolling patients (108 patients) across 16 medical centres of India [58].

12. Mirage BRMS: Mirage Bioresorbable Micro-fiber Scaffold (Manli Cardiology Singapore) is a PLLA-based sirolimus-eluting scaffold. The device incorporates a helix coil design that provides high flexibility. The strut thickness of scaffold is 125µm in scaffolds with diameter ≤ 3mm and 150µm in scaffolds with diameter ≥3.5mm. The scaffold has a low crossing profile (0.044"–0.058") and relatively short bioresorption time. Furthermore, the device exhibits high scaffold dislodging force and high radial strength. Pre-clinical studies showed promising results in porcine coronary arteries. To evaluate performance of the device in humans, a prospective, multi-center, single blinded, randomized clinical investigation has been initiated which enrolled 60 patients with de novo coronary lesions. The patients were randomized to receive the study stent (31 patients; 34 lesions) or BVS (Abbott vascular, Santa Clara, USA) (29 patients; 33 lesions). The study is ongoing.

Other polymeric BRS which are in their infancy are: 1) Avatar BRS (S3V Vascular Technologies, Bengaluru, Karnataka, India); 2) Sahajanand BRS (Sahajanand Medical Technologies, Surat, Gujarat, India); 3) Sanza BRS (480 Biomedical, Boston, Massachusetts, USA) and 4) Microport BRS (Microport, China).

Metallic Scaffolds

1. AMS: Absorbable Metal Stent (AMS-1) (Biotronik, Berlin, Germany) was the first metallic bioresorbable scaffold. First generation AMS (non-drug eluting) is composed of WE43 magnesium alloy. The scaffold has 4 crown/4 link (no markers) with 165µm strut thickness [59]. The radial strength of scaffold is similar to that of metallic stent with low elastic recoil (<8%), a high collapse pressure (0.8bar) and minimal shortening after inflation (<5%) [60]. Pre-clinical studies reported degradation into inorganic salts within 60 days [61,62].

The safety and feasibility of the scaffold (first generation AMS) was evaluated in the PROGRESS AMS which was a prospective, multicentre and non-randomized trial. A total of 63 patients with de novo native coronary artery lesions (with 71 implanted AMS) were recruited in PROGRESS AMS. During a follow-up at 4 month, the incidence of clinically driven TLR was 23.8% along with high LLL (1.08±0.49mm). A cumulative incidence of MACE at 12 month follow-up was 26.7% which was attributed to neointimal proliferation and vessel recoil (due to inadequate radial force) [60]. The study identified need of modifications of scaffold characteristics with prolonged degradation and drug elution. Hence, the device was redesigned predominantly to slow down the bioresorption process, so as to retain its mechanical strength for longer time-period in order to prevent early vessel recoil.

Drug Eluting Absorbable Metal Scaffold (DREAMS-1) was composed of refined Mg alloy (slower absorption rate). DREAMS-1 has 6-crown/3-link design (no markers) and reduced strut thickness [59]. The PLGA polymer carrier of the device elute paclitaxel drug. The DREAMS-1 device provides vessel scaffolding and paclitaxel drug elution for a period of 3 months. DREAMS-1 was evaluated in BIOSOLVE-I study, a prospective, multi-center and non-randomised trial. BIOSOLVE-I study recruited 46 patients with single de novo coronary lesions (47 implanted DREAMS) [63]. At 6-months, the TLR rate was 4.3% and the LLL was 0.64±0.50mm. At this same time point, improvements in the scaffolded segment angulation were evident, from 14.9±12.0° post-procedurally, to 26.1±15.9° at follow-up [63]. BIOSOLVE-I study confirms that vascular restoration was achieved at 6-month follow-up. Second generation DREAMS were designed for higher bending flexibility, slower dismantling rate, slower absorption rate, increased deployment diameter and higher acute radial force. DREAMS-2 has 6-crown/2-link design, reduced strut thickness (120/150μm-depending on nominal diameter) and tantalum radiopaque markers at both ends [59]. Duration of absorption of Mg-alloy of the scaffold is approximately 12-months. Based on promising pre-clinical results in porcine coronary arteries, DREAMS-2 is being evaluated in BIOSOLVE-II multicentre study. Clinical follow-up showed 3.3% TLF (a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG) and 1.7% TLR at 6-month in 120 enrolled patients of BIOSOLVE-II study. Six-month angiography follow-up of BIOSOLVE-II study showed 0.27±0.37mm LLL. IVUS results in a sub-group of 30 subjects demonstrate a preservation of the scaffold area with a low neo-intimal area at 6-month. Similarly, OCT-imaging in a sub-group of 30 subjects showed no intra-luminal masses [64].

2. FADES: The FADES scaffold (Zorion Medical, Indianapolis, IN, USA) is a fully bioresorbable drug-eluting scaffold. The polymer of the scaffold involves a hybrid material of magnesium alloy that includes rare earth elements and PLGA. Pre-clinical studies showed that the device was completely absorbed with little to no inflammatory tissue response within 90 days [16].

Other Mg-based BRS are currently in the Pre-clinical status and they are Medtronic Mg Absorbable Scaffold; BSCI Mg Absorbable Scaffold and QualiMed Mg Absorbable Scaffold.

CONCLUSION

BRS have improved significantly over the last few years with multiple devices in clinical trials at the moment. There are several limitations of this technology i.e., bulky nature of the device, risk of scaffold fracture and limited extensibility. However, further technological refinements would extend their applications in current clinical practice.

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