Indian Heart Journal 69 (2017) 107–111

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Editorial

A fresh look at bioresorbable scaffold technology: Intuition pumps

ARTICLE INFO

Keywords:
BRS
Radial strength
Strut thickness
Absorb
Fantom
AMS-1
DREAMS
DESolve
Acute BRS
Mirage
MeRes
ART BRS
XINSORB
FORTITUDE
Ideal biostent
FADES

ABSTRACT

Bioresorbable scaffolds (BRS) are a new enticing treatment option in coronary interventions. Absorb BVS™ Is the most widely used and researched polymer based BRS, eluting everolimus. However currently it has several technical limitations; low radial support, larger strut size, poor visualization, poor deliverability and complex implantation technique. Magnesium based BRS are an alternate but they are also limited not only by lower radial support and poor visualization but also earlier bio-absorption. Material processing: blow-molding, annealing, polymer orientation, change in composition and use of higher molecular weight polymer, as well new polymers like tyrosine or salicyclate analogs and even hybrid (polymer and metallic) combined with intelligent cell design has led to evolution of BRS technology. Newer BRS has higher radial strength, lower strut thickness, improved visualization, ease of scaffold implantation as also optimal bio-resorption time.

1. Introduction

Since the time immemorial humanity has been searching for therapies that increase life-span but at the same time are least invasive and toxic to the body. Coronary artery disease (CAD) due to coronary atherosclerosis has become the leading cause of mortality and morbidity world-wide. Ever since the first successful coronary artery bypass procedure was performed by Rene Favaloro in 1968, it has become a standard of care in patients with significant coronary atherosclerosis. However, this being a major surgery and a highly invasive procedure, angioplasty was developed as a relatively non-invasive substitute. Earlier, plain balloon angioplasty while less invasive was also less efficacious; limited by immediate vascular recoil and long term re-stenosis. Stents were developed in an attempt to provide temporary scaffold to tide over the problem of acute recoil. However, since the development of stents physicians and patients have been concerned at the prospect of a metal prosthesis left permanently in the body. Philosophically, "*The scaffolding must be removed once the house is built*." Indeed, there is a persisting risk of late and very late stent thrombosis after drug eluting stents (DES) implantation, which can result from delayed stent endothelialization, or hypersensitivity reactions to one of the stent components leading to poor intimal healing and providing a substrate for eventual stent thrombosis.[1] In this context the perfect human scaffold is one that is easily put in, does its job, and then disappears with no residual effects. This simple disappearing act may have several potential benefits in long term; restoration of physiologic vasomotion, late expansive remodeling, reduced risk of stent thrombosis, avoidance of long term jailing of side branches in bifurcation lesions, avoidance of long-term dual-antiplatelet use, improved availability of graftable (previously scaffolded) segments of coronary artery and improved imaging with computed tomography or magnetic resonance imaging. Thus bio-resorbable scaffolds seem ideal prosthesis to be implanted in the coronaries, however, the reality is that they still have a long way to go before they become the ideal 'disappearing' lscenery, a proposition that is aesthetically irresistible. While good in concept the major limitation of current generation scaffolds is that they are no-where close to technical characteristics of current generation DES.[2]

2. Challenges with current generation of scaffolds

2.1. Polymer scaffolds

With the evolution of DES technology several mechanical characteristics were determined which had an impact not only on the technical aspects of device delivery but even more importantly on long and short term outcomes.

http://dx.doi.org/10.1016/j.ihj.2017.01.006

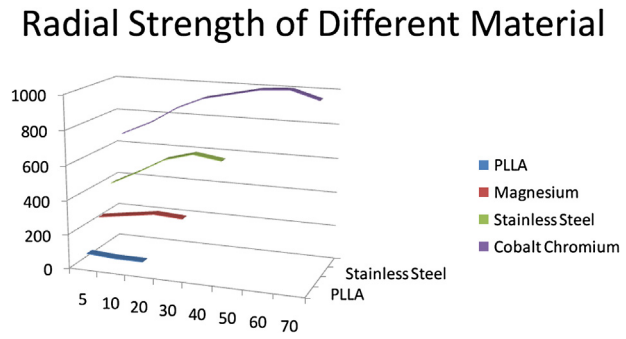

Fig. 1. Radial Strength of BRS and DES.

2.2. Visualization of the scaffold for implantation

Polymeric scaffolds are radiolucent, and thus it may be very difficult to visualize them accurately during fluoroscopy or angiography. Radio-opaque markers embedded near both edges of the angioplasty balloon on which scaffold is mounted help in localizing but they are generally small and still difficult to visualize under X-ray or even enhanced angiography such as stent boost. Thus for really optimal assessment of procedural result, PCI with BRS requires additional visualization technique. Optical coherence tomography (OCT) has a far greater surface resolution than both angiography and intra-vascular ultrasound (IVUS) and can be superior in post-deployment assessment.

2.3. Deliverability of scaffold

Larger strut size and plastic physical properties contribute to limited maneuverability of polymer based scaffolds so much so that there may be crossing issues especially in distal lesions, tortuous lesions or side-branches.

2.4. Scaffold implantation

Classic metallic stent can directly dilate a stenosed artery and expand significantly beyond its rated expansion diameter. Thus if metallic stent is under-sized it can be further dilated (upto 1.5 mm more) to reach full expansion enabling perfect apposition to the vessel wall. Polymeric scaffolds have a larger strut size and an plastic nature which prevent proper expansion (maximum 0.5 mm), limiting its ability to appose to the vessel wall. Furthermore, their technique of implantation is also different; optimal bed preparation (using 1:1 NC balloon, cutting balloon, rotablation or even laser), use of imaging (IVUS or OCT) for appropriate sizing, proper positioning of device, gradual inflation of device to achieve the target expansion, and finally, confirmation of full apposition by OCT.

2.5. Radial strength

The process of stenting involves compression of atherosclerosis plaques and sealing of dissections. This requires a sufficient radial force, the more the better. Poly-L-lactic acid (PLLA) is the most commonly used polymer in BRS is broken down via depolymerization and hydrolysis. The smaller chains are then metabolized by phagocytes into soluble monomers that are metabolized into pyruvate (a bio-chemical substance metabolized by body). Unfortunately, though completely bio-resorbable the radial strength of PLLA is much lower than the metallic prosthesis.[3] Fig. 1 Further, not only radial strength but tendency to elastic recoil is also higher. In practice this translates into higher strut thickness to compensate for inherent radial weakness in the basic material. Thus practically all bio-resorbable stents which use this technology have higher strut thickness.[4] Fig. 2 Finally, the physical characteristics of PLLA scaffold are such that there are higher chances of acute mal-apposition requiring more aggressive optimization but despite this the procedure success rate is somewhat lower.[5]

2.6. Strut thickness

Increased strut thickness provides increased radial support and prevents elastic recoil but reduces deliverability as also acutely decreasing neo-intimal area and causing flow disturbances, PLLA based BRS have a higher strut thickness which is responsible not only for poor deliverability but also higher neo-intimal volumes, leading possibly to flow limitations. Higher strut thickness is also co-relative of poor long term outcomes: restenosis and stent thrombosis. Thus the challenge is to have adequate radial support but still a low strut thickness.

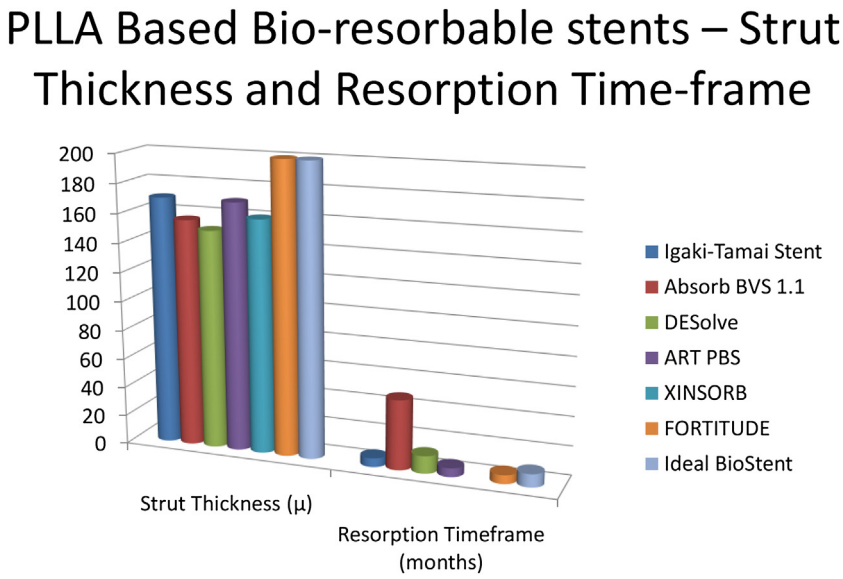

Fig. 2. PLLA based BRS – Strut thickness and resorption time-frame.

The **Absorb BVS**™ has a backbone composed of PLLA, which is coated with a poly-D,L-lactide (PDLA) polymer that contains everolimus. First generation BVS, Absorb 1.0 was prone to scaffold shrinkage on long term follow-up. The second generation BVS1.1 was designed to have an in-phase hoop, with straight links arrangements to provide an increased radial support and low scaffold shrinkage. In addition, the polymer in this version underwent blow-molding to give the scaffold additional mechanical strength and longer resorption. The third generation Absorb GT1 has an improved deliverability apparatus.[6]

XINSORB™ scaffold is a BRS system composed of poly(aspartic acid-*co*-lactide), poly(ε-caprolactone), and polyglycolide as its backbone, with a coating of PDLA and PLLA eluting sirolimus (80% eluted in 28 days). The strut thickness is 160 μ and the device is stored at 4 °C.[7]

The **ART BRS**™ is a BRS composed of PLLA amorphous polymer, without any anti-proliferative drug.[8]

3. Metallic BRS

3.1. Magnesium

Technically, metallic BRS is likely to score over polymer BRS because they may do away with some of their limitations, having: lower profile, better deliverability, and higher radial strength which allows for thinner struts Fig. 1. Magnesium alloys have enhanced bio-compatibility and low thrombogenicity. Furthermore, it an essential trace element with low systemic toxicity. However, magnesium based scaffolds have physical properties intermediate between classical metallic (stainless steel – 316 L) stents and polymeric scaffolds; lower yield strength, lower tensile strength and lesser elongation compared to stainless steel stents Fig. 3. They also suffer from very low radio-opacity and very low ductility (unlike other metallic stents). This leads to difficulty in forming mesh-like tubular scaffolds as also easy strut fracture when over-expanded. On longer term, accelerated degradation of magnesium scaffold may result not only in tissue overload with magnesium degradation products with a possibility of enhanced neointimal formation but on a more serious note early loss of mechanical integrity leading to premature loss in scaffold support. It is also prone to localized corrosion (in contradistinction to uniform corrosion) which may contribute to stent fractures, stent particle embolizations, thrombosis, excess inflammation, or fibrin deposition. While these concerns have not been confirmed clinically, restenosis was indeed higher due to larger neointimal growth and negative remodeling.[9,10]

3.2. Iron BRS

Iron is an interesting medium for BRS because of its mechanical properties; high radial strength (allowing for lower strut thickness) and high ductility (low strut fracture when the stent is expanded). However, the major limitation of iron based scaffolds is its slow degradation rate so that they do not corrode completely during prolonged follow up period.

4. Evolution in BRS technology

4.1. Improvement in radial strength and low strut thickness

Currently low radial strength is the most important limitation of polymeric BRS. Higher radial strength will allow for lower strut thickness, lower crossing profile (improving deliverability) as also reduce scaffold strut protrusion into vascular lumen minimizing blood flow perturbations in the index coronary artery and thus contribute to decreased thrombogenicity, ultimately improving both procedural and long-term outcomes. Several strategies can be employed to improve radial strength and consequently decrease strut thickness of the scaffold; polymer blending, annealing (heat treatment), polymer orientation and extraction of higher molecular weight components.

1. Polymer treatment

Blow-molding – Abbott Vascular uses stretch blowmolding to enhance the physical properties and impart increased radial strength to its PLLA. Next Gen Absorb™ is likely to have a strut thickness of around 100 μ.

Heat treatment – In the solid-state, polymers fall into two categories - Amorphous: random orientation of polymer chains and Semi-Crystalline: highly ordered crystal structures in an amorphous matrix.

• The relative balance of amorphous and crystalline phases affects strength, hardness, ductility, stiffness polymers. Crystalline structures have greater radial strength but also faster degradation time. Elixir DESolve™ employs tube and stent annealing to increase crystallinity without substantially increasing the biodegradation time. Its top-coat contains two novel antiproliferative drugs (novolimus and myolimus).[11]

Polymer orientation – The Acute BRS™ is a tube-shaped lockable BRS composed of three polymeric materials (poly-L-lactide-*co*-ε-caprolactone, PDLA, and PLLA) and employs a partitioned coating technology; abluminal sirolimus and luminal endothelial progenitor cell capture (+CD34) antibodies.

2. Change in polymer composition

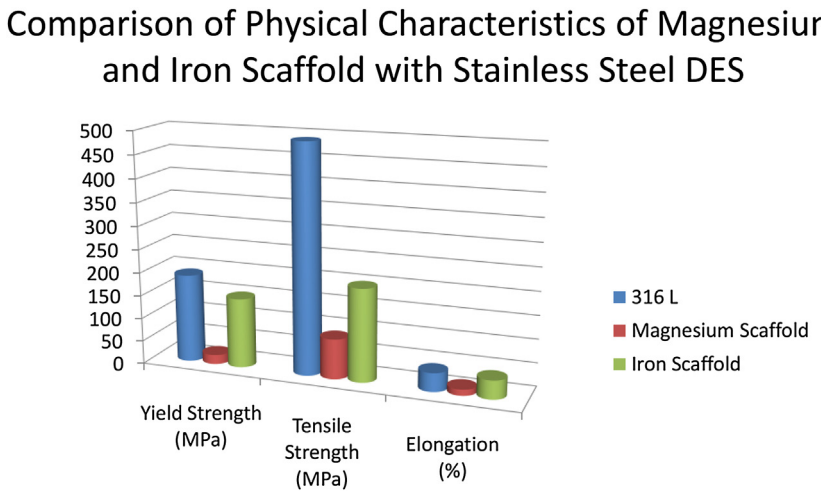

Fig. 3. Comparison of physical characteristics of metallic BRS with stainless steel DES.

Mirage™ is a PLLA based scaffold with higher L-isomer composition.

• MeRes100™ backbone is primarily comprised of semi-crystalline PLLA which allows for high radial strength during early months (0 – 3 months), after which it starts getting cleaved but scaffold support still provided by interspersed amorphous links (which cleave later). MeRes100™ is manufactured using high molecular weight (275–300 kDa) PLLA backbone with PDLLA coating eluting sirolimus, proprietary manufacturing process, novel hybrid design concept (closed cells at the edges and open cells throughout the scaffold) incorporating strut width variability which contributes to high radial strength and allows for metallic DES like strut thickness.

FORTITUDE™ (Amaranth) is a novel BRS which utilizes a special PLLA processing technology that yields high molecular weight semi-crystalline PLLA. The overall product has tailored amount of crystalline and amorphous domains locked in. The combination of high molecular weight and crystalline polylactide delivers superior strength, ductility, toughness and resistance to fracture. At the same time, the amorphous domain is specifically engineered to ensure that the scaffold undergoes a gradual and predictable hydrolytic degradation while maintaining its structural integrity during the clinically relevant healing period. This structural integrity results in a tailored, high-performance scaffold for each clinical application. the scaffold has a high radial strength, prolonged mechanical stability, and exhibits minimal recoil.[8]

3. Newer polymers

Reva polymer family (Fantom™ scaffold) employs phenyl ring structure comprised of tyrosine based polycarbonate material and other natural metabolites for enhanced radial support and reduced strut thickness. Furthermore it allows the device to maintain a greater level of its physical properties during expansion (deformation) and does not fracture in the same manner as a pure PLLA device when subject to continuous uniform expansion. Consequently by using the tyrosine analog polymer rather than a pure PLLA polymer the Fantom™ scaffold is able to achieve a clinically significant expansion range of 0.75–1.0 mm from the nominal size depending upon the scaffold diameter. .Furthermore, there is vasomotor restoration by 1 year and this scaffold requires no special storage or handling.[8]

The Ideal BioStent™ is a BRS having its core backbone synthesized from polylactide anhydride, and a trimer of two salicylic acid molecules joined by a sebacic acid. Its top coat is comprised of salicylate and sirolimus. The salicylate is more than a passive polymer, not only storing the anti-restontic drug and allowing its graduated release but has active anti-inflammatory and antiplatelet properties which may reduce restenosis and promote vessel healing during the polymer's degradation.[8]

4. Metallic BRS

Magnesium Scaffold – Since one of the limitations of early magnesium BRS (AMS-1™) was accelerated degradation contributing to early loss of mechanical integrity (2 months) and thus premature loss of scaffold support. The next generation BRS (DREAMS™) uses a refined, slower-resorbable WE43 alloy (93% Mg and 7% zirconium, yttrium and other rare earth elements) which is square shaped (unlike rectangular shape of AMS-1), with 6-crown, 3-link design and with a higher radial strength than AMS-1 (collapse pressure 1.5 vs.0.8 bar), reduced device shrinkage and also allowing for reduced strut thickness (AMS-1 160 μ, DREAMS™ 120 μ).[10] The DREAMS™ is coated with a 1 μ bioresorbable poly (lactide-*co*-glycolide) polymer matrix (PLGA) containing the paclitaxel (0.07 μg/mm2). A further design modification which is made of same alloy and design but with a strut thickness of 150 μ and radiopaque markers at both ends (made from tantalum) resulting in not only slower dismantling and resorption rate but improved visibility. For anti-restenotic drug paclitaxel has been substituted with sirolimus.

The FADES™ scaffold is a BRS composed of hybrid of polymer and a special magnesium alloy that includes rare earth elements and PLGA.[8]

5. Intelligent cell design

DESolve™ scaffold has an interesting design – closed-cell (with connectors for strength) and open-cell (with fewer connectors for flexibility) modules and increasing cell size from the centre to the edges: The smaller cells at the centre provide the greatest radial support and higher drug delivery, while the larger cells provide greater flexibility for ease of implantation. The radial strength of the device is comparable with metallic stent which allows for a lower strut thickness, and among polymer BRS it has a unique expansion capabilities which ensures minimal strut mal-apposition and ability to expand without strut fracture.

Mirage™ BRS has a helix cell design which contributes to flexibility and combined with its composition (D-isomer is <5%) it has a good balance of flexibility and radial strength. It has a low crossing profile (1.12–1.47 mm).

MeRes™ has an intelligent hybrid cell design (close cells at the edges and open cells along the length, ensuring optimal vessel wall conformability) which along with higher radial strength imparted by its higher molecular weight which enables it to achieve a strut thickness of 100 μ and 1.2 mm crossing profile.

Fig. 4 Strut thickness of current BRS.

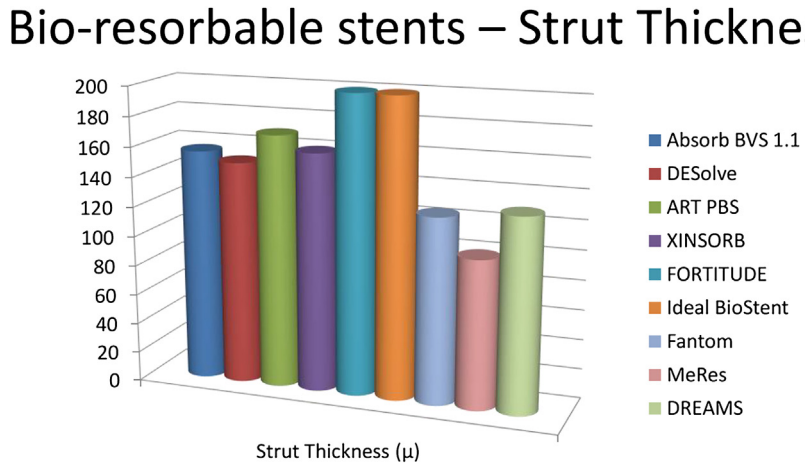

Fig. 4. Strut thickness of current BRS.

Table 1
Physical characteristics of BRS and DES.

Name of Stent	Material	Radial Strength	Strut Thickness (μ)	Elongation without fracture	Implantation Technique	Visibility	Bio-resorption (months)	Drug
Cypher™	Stainless Steel	+++	150	+++	One Step	+++	Nil	Sirolimus
Xience V™	Cobalt Chromium	++++	81	++++	One Step	++	Nil	Everolimus
Absorb GT1™	PLLA	+	156	+	Step by Step	0	48	Everolimus
Xinsorb™	PLLA	+	160	+	Step by Step	0		Sirolimus
ART BRS™	PLLA (Amorphous)	+	170	+	Step by Step	0	18–24	Nil
DESolve™	Heat treated PLLA	++	150	+	Step by Step	0	24–36	Novolimus & myolimus
Acute BRS™	Tube shaped – PLGA, PDLA, and PLLA	++		+	Step by Step	0		Abluminal sirolimus and luminal EPC (+CD34) antibodies
Mirage™	PLLA (↑ L-isomer)	++		+	Step by Step	0	14	
MeRes 100™	↑ mol. wt PLLA, balance of crystalline and amorphous material	++	100	+	Step by Step	0		Sirolimus
FORTITUDE ™ (Amaranth)	↑ mol. wt PLLA, balance of crystalline and amorphous material	++	200	+	One Step	0	12–24	Sirolimus
Fantom ™ (Reva)	Tyrosine analog	++	125	++	One Step	+	12	Sirolimus
Ideal BioStent™	Polylactide anhydride+ 2 ASA molecules	+	200	+	Step by Step	0	9	Salicylate & sirolimus
DREAMS™	Magnesium Alloy	++	120	++	One Step	0	9	Paclitaxel
FADES™	Hybrid of PLGA & magnesium alloy							

4.2. Improved visualization

1. Incorporation of radio-opaque material.

The Fantom™ scaffold has iodine is incorporated into the polymer backbone which allows the device to be visualized using conventional angiography allowing for precise scaffold placement, complete lesion coverage, confirmation of apposition to vessel wall thus reducing the need for additional imaging modality.

2. Intelligent placement of radio-opaque markers

Mirage™ BRS has 3 radio-opaque markers

MeRes™ BRS has couplets of Tri-axial RO marker discs at each end

4.3. Ease of scaffold implantation

Phantom™ scaffold is resistant to strut fracture so that it can be deployed in one smooth and continuous inflation step, similar to traditional metallic stents. Since it has large expansion range it can be safely post-dilated. The Absorb GT1™ upgrade consists of an updated delivery catheter.

4.4. Optimal resorption time-frame

Resorption time of BRS is another important parameter. After stent implantation the treated arterial segment requires support for around 6 months, anything beyond that is not necessary. Absorb™ BRS has a relatively higher resorption time of 4 years. Magnesium alloy has the fastest absorption rate: AMS-1™ was bio-absorbed by 2 moths and thus could not offer vascular support for long enough duration., the next generation BRS (DREAMS™) uses a refined, slower-resorbable WE43 alloy (93% Mg and 7% zirconium, yttrium and other rare earth elements) which allows it to be resorbed over 9 month period. Other newer BRS, DESolve™ (2–3 years), ART PBS™ (18–24 month), XINSORB™, FORTITUDE™ (1–2 year), Ideal Biostent™ (9 month), Mirage™ (14 month), Fantom™ (12 month), typically resorb within 1–2 year Fig. 2.

Some newer BRS in their infancy include the Sahajanand, Avatar™ BRS (S3V Vascular Technologies, Bangalore, Karnataka, India), and Stanza™ BRS (480 Biomedical, Boston, Massachusetts, USA).[8]

Various characteristics of BRS are shown in Table 1.

5. Conclusions

BRS is an attractive therapeutic option but is limited by low radial support, larger strut size, poor visualization, poor deliverability and complex implantation technique. Advances in BRS processing and material have led to improvement in this technology.

References

[1]. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol.* 2006;47:175–181.

[2]. Mishra S. Are all stents equal–need for scoring system to evaluate stents? *Indian Heart J.* 2016;68:589–591.

[3]. Foin N. *BRS Bench Testing: Expansion Capacity, Radial Strength*. http://www.bifurc.net/files/medtool/webmedtool/icpstool01/botm0800/pdf00001.pdf.

[4]. Ng V, Lansky A. *Bioresorbable Scaffolds: The New Tool in PCI*. file:///D:/IHJ%20Assignments/My%20Editorials/BVS/Bioresorbable%20Scaffolds_%20The%20New%20Tool%20in%20PCI%20-%20American%20College%20of%20Cardiology.html.

[5]. Bil J, Gil RJ. Bioresorbable vascular scaffolds—what does the future bring? *J Thorac Dis.* 2016;8(August (8)):E741–E745.

[6]. Campos CAM, Zhang Y, Bourantas CV, et al. *Bioresorbable Vascular Scaffolds in the Clinical Setting*. http://www.openaccessjournals.com/articles/bioresorbable-vascular-scaffolds-in-the-clinical-setting.pdf.

[7]. Chen J-H, Wu Y-Z, Shen L, et al. First-in-man implantation of the XINSORB bioresorbable sirolimus-eluting scaffold in China. *Chin Med J (Engl).* 2015;128(9):1275–127610.4103/0366-6999.156155.

[8]. Zhang Y, Bourantas CV, Farooq V, et al. Bioresorbable scaffolds in the treatment of coronary artery disease. *MedDev (Auckland, NZ).* 2013;6:37–48.

[9]. Moravez M, Mantovani D. Biodegradable metals for cardiovascular stent application: interests and new opportunities. *Int J Mol Sci.* 2011;12(7):4250–4270.

[10]. Campos CM, Muramatsu T, Iqbal J, et al. Bioresorbable drug-eluting magnesium-alloy scaffold for treatment of coronary artery disease. *Int J Mol Sci.* 2013;14:24492–24500.

Sundeep Mishra
AIIMS, New Delhi, India
E-mail address: sundeepmishraihj@gmail.com (S. Mishra).

Available online 31 January 2017