MINERVA CARDIOANGIOL 2015;63:441-8

Innovative DES technologies from Meril

S. BHATT [1], S. GUJARATHI [1], M. DE BENEDICTIS [2]

[1]Meril Life Sciences, Gujarat, India
[2]Unit of Cardiology, Presidio Umberto I Azienda Ospedaliera Ordine Mauriziano Turin, Italy

Technological advances and rise in global urbanity have paradoxically led to an increase in the incidence of metabolic syndrome and thankfully also in diagnosis and treatment of coronary artery disease. "Necessity is the mother of invention" – remarked Plato and this statement could not have had a better place than in the field of angioplasty and stenting. Interventional cardiology still continues to remain a busy place for smart, iterative changes leading to better treatment options. This article sketches contemporary trends in coronary stent engineering borne out of unmet clinical needs ranging from novel ultra-thin strut designs marrying biodegradable polymeric drug eluting platforms to anatomically tapered stents and finally the intuitive bioresorbable vascular scaffolds which promise freedom from full metal jacket.

KEY WORDS: Stents - Hybrid cells - Tissue scaffolds.

Since the advent of cardiac catheterization in the late 1920s and the development of coronary angiographic technology during 1950s, clinical limitations of balloon angioplasty (BA) quickly made way for metal stents which led the path for drug eluting stents. Currently DES are now clinically acknowledged and globally accepted treatment options for coronary artery disease. Since their first launch in 2002 (Figures 1), the first generation DES incorporated stainless steel stents with thick struts and close cell designs,[1-11] these DES had a permanent polymeric coating which was also linked to inflammation and to thrombosis,[12] further the stent systems were generally found to be difficult to deliver in tough anatomical situations.[13] Development of second generation of DES, employed cobalt chromium (L605 or MP35N alloys) sporting lower strut thickness and changed cell design (open cell configuration).[14, 15] Here again the emphasis was to use permanent polymeric coatings for drug delivery.[14, 15] Third generation of DES saw the intuitive migration of drug delivery technology towards biodegradable polymeric base and the use of poly-lactic acid was successfully seen on metal backed stents.[16] Inspired from the inefficiencies of the earlier generation of designs, the third generation stents now utilize the hybrid cell design allowing strut thicknesses to be reduced further without compromising on structural integrity of the stent.[17] The fourth generation of DES [18] is anticipated to challenge historical stent design concepts, innovate on drug delivery technologies and will compensate for the clinical and economical need for an ideal stent.

Corresponding author: M. De Benedictis, Unit of Cardiology, Presidio Umberto I, Azienda Ospedaliera Ordine Mauriziano, Corso Re Umberto 109, Turin, Italy.
E-mail: maurodebenedictis@yahoo.it

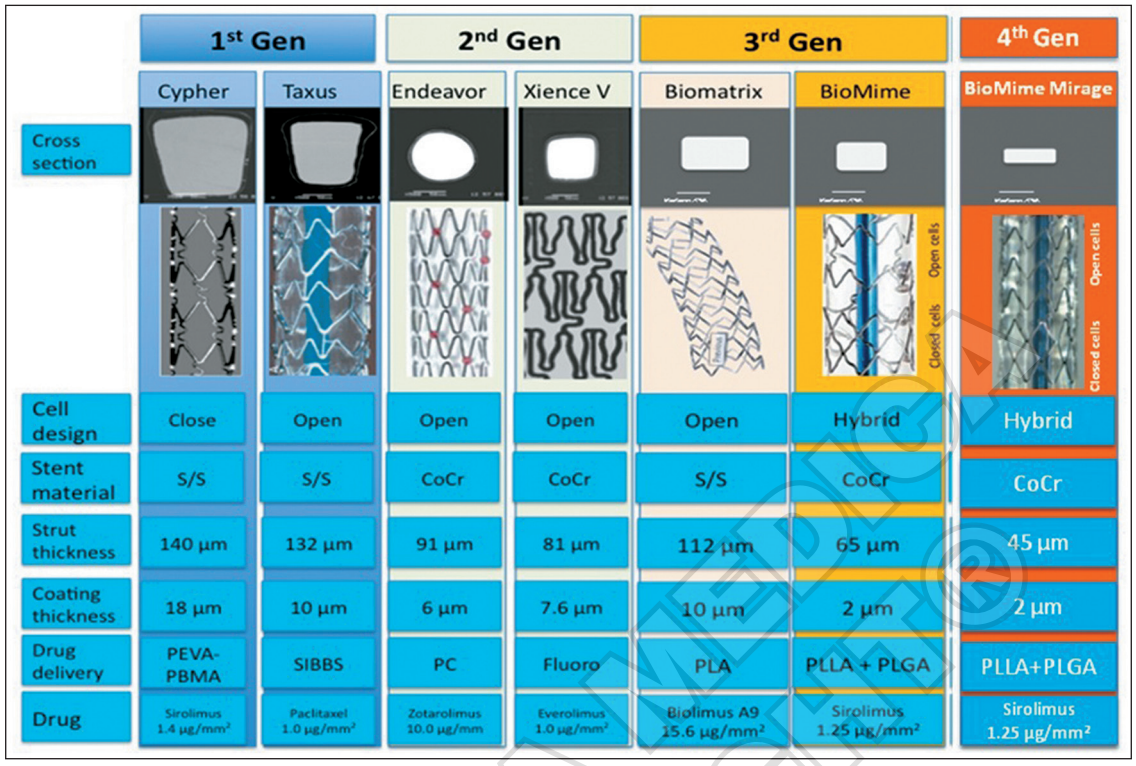

Figure 1.—A decade of DES design and its evolution.[19]

Paving the way for the future – From substance to sublime

The Penrose's triad [17] of ideal DES design comprising of – the ideal stent, the ideal drug and the ideal drug delivery method, have been previously cited. The ideal DES should eventually ensure safety, freedom from MACE and early cessation from DAPT while ensuring restoration of vascular function.

The features that an ideal DES may possess can be summarized as follows:

1. A thin strut stent design platform:
   i. that has to propensity to minimize vascular injury;
   ii. ensures optimal vessel wall apposition;
   iii. ensures early endothelialization due to ease of conformability;
2. A drug that ensures antiproliferative/anti-inflammatory effect:
   i. is predominantly cytostatic and anti-inflammatory;
   ii. is lipophilic for better bioavailability;
   iii. has a broad therapeutic window to allow for low drug dosage;
3. A drug delivery system which:
   i. is non-inflammatory and non-thrombogenic;
   ii. is biodegradable and bio-compatible;
   iii. allows for uniform and fatigue resistant coating.

Following algorithm (Figure 2) can be created based on the above philosophy to create an ideal DES.

Based on the above philosophy, following novel DES technologies have been discussed which cater to the current unmet clinical needs.

BioMime™ – Sirolimus eluting coronary stent system

The BioMime™ SES (Figure 3) is a novel DES design concept built on an ultra-low strut thickness (65 µm) cobalt chromium

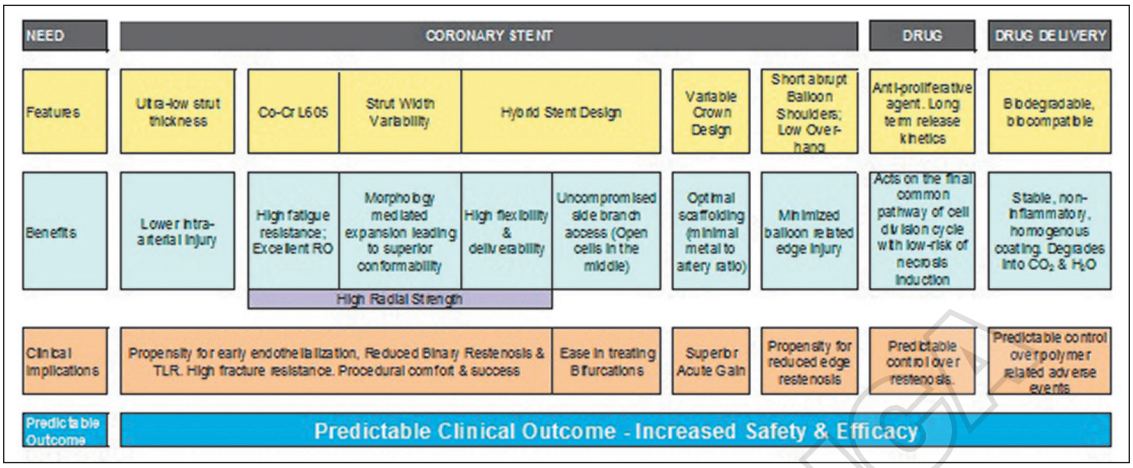

Figure 2.—Predictable outcome based ideal DES development philosophy.

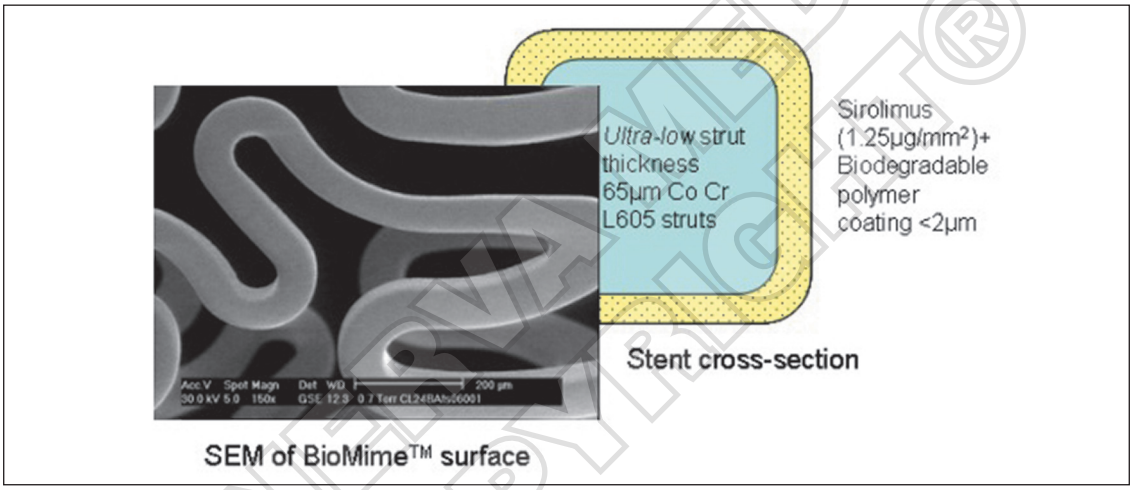

Figure 3.—BioMime™ SES cross section.

(L605) stent platform. Cobalt Chromium is denser than stainless steel (SS) and more MRI compatible. It is stronger than SS, allowing thin struts with yield strength higher than SS. The resultant stent system has a predictable low injury profile. Its hybrid design incorporates an intelligent mix of open and closed cells allowing for morphology-mediated expansion [17] (Figure 4).

This unique method of expansion eliminates the classical dog-boning seen in conventional designs and also ensures minimal edge injury.[18-27] This hybrid stent demonstrates high radial strength combined with flexibility. Bench testing demonstrates 3% recoil and 0.29% foreshortening. The delivery system maintains short-abrupt-balloon-shoulders to minimize balloon related edge injuries. The stent surface is coated with a formulation of biodegradable polymers – PLLA+PLGA and sirolimus (1.25 µg/mm^2), which elutes over 30 days. The resultant stent system has a predictably low injury profile. Clinical safety and efficacy of BioMime™ has been established *via* meriT-1 and meriT-2 studies. Table I summarizes the baseline demographics and clinical characteristics of the overall study population. Table II summarizes the clinical trial outcomes.

In simple, *de-novo* lesions, meriT-1 tri-

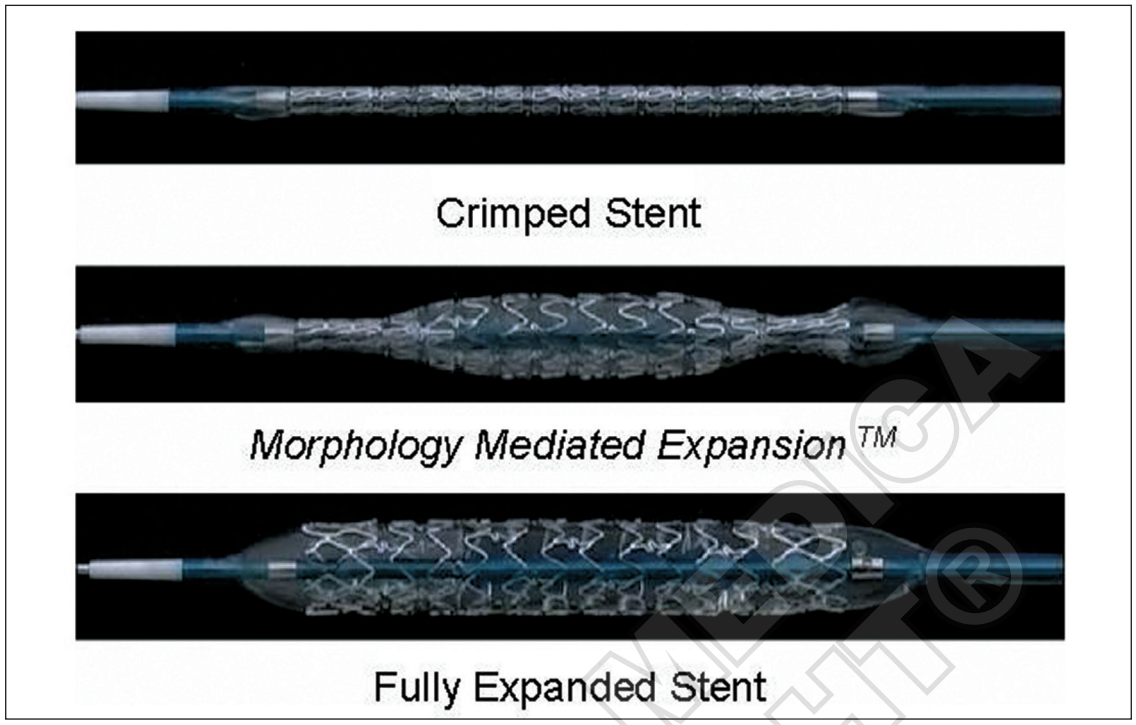

Figure 4.—Morphology mediated expansion of BioMime™ SES.

TABLE I.—*Clinical trial outcomes.*

Key demographics	meriT-1 (N.=30)	meriT-2 (N.=250)	meriT-3 (N.=1110)
Mean age, years	50.5±8	56.72±10.55	56.3±10.3
Gender, M	25 (83%)	208 (83%)	883 (79.5%)
Diabetes	9 (30%)	91 (36%)	454 (40.9%)
Hypertension	17 (57%)	123 (49%)	589 (53.1%)
Smokers	7 (23%)	66 (28%)	178 (16%)
Hyperlipidemia	3 (10%)	26 (11%)	64 (5.8%)
Previous MI	13 (43%)	80 (32%)	156 (14.1%)

TABLE II.—*Potential advantages of bioresorbable scaffolds (BRS) over bare-metal stents (BMS) and drug eluting stents (DES).*[33]

Results	meriT-1 (N.=28) 2-year follow-up	meriT-2 (N.=249) 3-year follow-up	meriT-3 (N.=1110) 1-year follow-up
MACE	0 (0%)	15 (6.2%)	24 (2.20%)
Cardiac deaths	0 (0%)	2 (0.80%)	10 (0.90%)
Non-fatal MI	0 (0%)	0 (0%)	2 (0.20%)
Clinical TLR	0 (0%)	13 (5.2%)	7 (0.63%)
Stent thrombosis	0 (0%)	1 (0.4%)	1 (0.1%)
Acute (<24 h)	0 (0%)	1 (0.4%)	0 (0%)
Sub-acute (2-30 days)	0 (0%)	0 (0%)	0 (0%)
Late (>30 days)			
Late loss (8m QCA)	26	218,309 lesions	Only clinical follow-up
In-segment	0.17	0.11	
In-stent	0.15	0.13	
Binary restenosis	0 (0%)	19 (6.2%)	

al [20] (N.=30), BioMime™ demonstrated zero percent MACE upto 24 months. Eight-month angiographic follow-up reveals a median late lumen loss of 0.15 mm demonstrating efficacy. Real world, complex patients studied in meriT-2 trial [20] (N.=250), demonstrates 3-year MACE of 6.2% and 0.4% ST. 8-month QCA of 250 lesions reveals a median in-stent late loss of 0.12 mm. In a prospective, phase IV, multicentric, non-randomized meriT-3 real world registry N.=1110, BioMime™ demonstrated 2.20% MACE and 0.1% stent thrombosis at one-year follow-up. The BioMime™ SES is CE marked and widely commercialized currently.

BioMime™ Morph – Sirolimus eluting coronary stent system

Coronary artery disease patients are seen to have a high coexisting diabetic condition.[21] Diabetic patients often represent with lesions, which are long and diffused.[22] It is well understood now that bare metal stenting in these patients brings about poor clinical outcomes with increased risk of restenosis and higher MACE.[23] Thus that lesions need to be treated with a DES is quite established.[23] Interestingly overlapping of stents required to treat long lesions is known to be a potential site for restenosis [24] and stent thrombosis (due to malapposed struts) and also potentially jail important side branches. Moreover, the natural shape of coronary arteries tapers from proximal to distal [25] and this becomes more pronounced as the artery throws up branches (Figure 5).

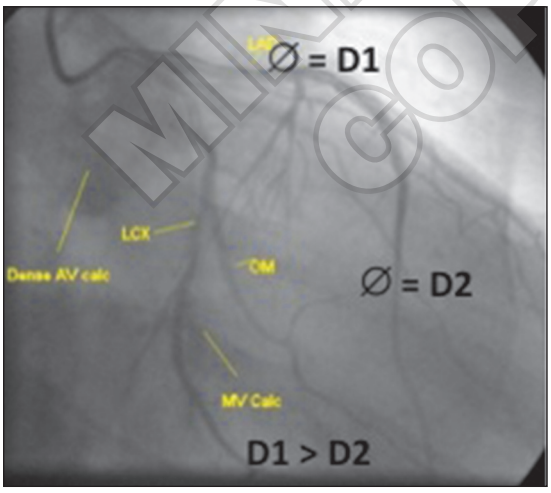

Figure 5.—Angiographic example of tapering LAD. D1: proximal LAD; D2: distal LAD.

While conventional stents are available only in cylindrical shapes and these alter the vessel anatomy rendering the vessel less flexible. Importantly, procedurally single long stent implantation is also technically convenient with reduced exposure to X-radiation (to the operator) and less contrast injection (to the patient). Finally multiple stenting in long lesion segment is also associated concerns of drug overload resulting in aneurysms with increased costs, whereas, one single long stent dramatically brings about the cost reduction.[26] BioMime Morph – long and tapered sirolimus eluting coronary stent system is designed to address precisely the issues and to cater to the currently unmet clinical needs. The stent tapers from proximal to distal with a ½ size taper in a range of diameter configurations 4.00, 3.50, 3.00, 2.75 mm (proximal) tapering to 3.50, 3.00, 2.50, 2.25 mm (distal) respectively. The stent is designed to have four lengths of 30, 40, 50 and 60mm (Figure 6). The stent surface is coated with a formulation of biodegradable polymers – PLLA+PLGA and Sirolimus (1.25 μg/mm^2), which elutes over 30days.

The unique hybrid design geometry of the BioMime family of design allows for reduction of strut thickness (without compromising radial force) and has a propensity to minimize vessel injury. The hybrid design allows for easy access to side branches without any threat of jailing. The stent thus created, is a low profile flexible stent meant for superior deliverability and has a uniform conformability across lesion site. The stent is mounted on a tapered rapid exchange PTCA balloon catheter specially designed to suit the anatomically tapering artery. The catheter shaft has been reinforced and strengthened, in order to minimize forces generated during delivering the stent system. The BioMime Morph is currently available in India and non-CE countries.

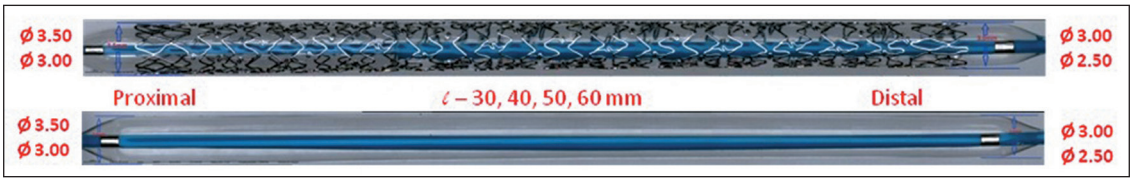

Figure 6.—BioMime™ Morph – Long and tapered sirolimus eluting coronary stent system.

BioMime Mirage™ – Sirolimus eluting coronary stent system

BioMime™ Mirage – Sirolimus eluting coronary stent system is slotted to be the world's thinnest drug eluting stent with ultra-low strut thickness stent (45 µm) cobalt chromium (Figure 7), incorporating a hybrid cell design concept, which allows for treatment during primary PCI for thrombus containing lesions. The stent surface is coated with a formulation of biodegradable polymers – PLLA+PLGA and sirolimus (1.25 µg/mm^2), which elutes over 30 days.

The Mirage is currently under pre-clinical testing and will soon enter human clinical trials, which will establish its usefulness in AMI cases.

MeRes100 sirolimus eluting bioresorbable vascular scaffold system

The concept of *cameo* appearance (implantation) of a stent for acute benefits and its eventual disappearance in order to free the vessel of a metal constriction is not just enticing; it appears to be the ultimate goal in achieving biomimicry in development of coronary or vascular endoprosthesis. Nonetheless, the research on bioresorbable scaffolds (BRS) has been agonizing and long drawn over the past two decades. Technological barriers and limitations into our insight regarding biomaterial science have further slowed down the progress. While several technologies in BRS are under development, the results driven by Absorb bioresorbable everolimus-eluting PLLA scaffold (Abbott Vascular, Santa Clara, CA, USA) are both encouraging and path breaking. Low long-term MACE, lumen enlargement, restoration of vasomotion in scaffolded segment [1] are some of the currently understood benefits of such technology.

Several technologies currently use the primary scaffold backbone as poly-L-lactide (PLLA) which insitu undergoes hydrolysis resulting into a mass loss and further cleavage of the long chains into easily metabolized lactic acid. The resultant conversion to CO_2 and H_2O *via* Kreb's cycle is now well catalogued. The process is completed in a range of 20-24 months. An anti-proliferative coating optimally ensures minimization of restenosis.

Today, while the proof of concept is established, penetration of BRS still remains under 10% of the global DES market. While finally, what will dictate the penetration of completely resorbable scaffolds within the coronary stent space; will depend on several factors that are both technological and economical. Anticipated ideal BRS characteristics can be elaborated as follows – novel scaffold architecture, low strut thickness, low profile delivery system, high radial strength, high flexibility and deliverability, good radiopacity, convenient side branch access, large size matrix and allows conventional storage methods.

MeRes100 – Sirolimus eluting bioresorb-

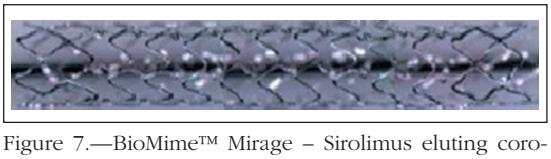

Figure 7.—BioMime™ Mirage – Sirolimus eluting coronary stent system.

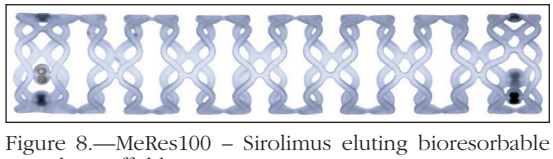

Figure 8.—MeRes100 – Sirolimus eluting bioresorbable vascular scaffold.

able vascular scaffold system comprises of the following components:

a. a balloon expandable bioresorbable scaffold made from polymer poly-L-lactide (PLLA);

b. a top coat comprising of an anti proliferative agent – Sirolimus (1.25 μgm/mm^2) eluting from PDLLA polymer base;

c. A rapid exchange PTCA balloon catheter which acts as the scaffold delivery system.

To indicate the total elimination of polymers by dissolution, assimilation and excretion, the concept of bioresorption was introduced.[28-32] Poly-L-lactide (PLLA) is one of the common commercially available aliphatic polyester that possess excellent biocompatibility, biodegradability, a high mechanical strength and good shaping and molding properties. The key mechanical traits for candidate material in coronary indications include high-elastic moduli to impart radial stiffness, large-break strains to impart the ability to withstand deformations from the crimped to expanded states, and low-yield strains to reduce the amount of recoil and over-inflation necessary to achieve a target deployment.[32] PLLA used in MeRes100 construction is a semi-crystalline polymer with the glass transition temperature of around 55-60 °C and the melting temperature of around 180°C. MeRes100 BRS is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to *de novo* lesion in native coronary arteries in patients eligible for PTCA and scaffolding procedures. The scaffold will eventually resorb and potentially facilitate normalization of vessel function in patients.

Bioresorption process of PLLA

Several technologies currently use the primary scaffold backbone as poly-L-lactide (PLLA) which *in vivo* undergoes hydrolysis resulting into a mass loss and further cleavage of the long chains into easily metabolized lactic acid. The resultant conversion to CO_2 and H_2O via Kreb's cycle is now well documented. The process is completed in over a period of 2-3 years.

Regulatory update and human clinical trial

MeRes100 is currently an investigational device and not available for sale in humans.

MeRes-1 is a prospective, multicenter, single arm, open label, pilot clinical study of MeRes100 Sirolimus Eluting Bioresorbable Vascular Scaffold System in the treatment of de-novo native coronary artery lesions. Ashok Seth *et al.* will be recruiting 108 patients in at least 14 centers across India and primary safety end point will be ischemia driven major adverse cardiac event (ID MACE) at 30 days, 6 months, 1, 2 and 3 years. A subset of population will undergo angiographic, IVUS, OCT and MSCT follow-up at 6 and 24 months. A subset of population will also undergo PK to measure time taken to reach maximum concentration (T_{max}) level in the blood after implantation of the scaffold, maximum concentration of the drug obtained in peripheral venous blood (C_{max}), mean initial ($T_{½i}$) and terminal ($T_{½T}$) half life period of the drug in venous blood, area under the curve (AUC) of the blood drug concentration.

Potential advantages of bioresorbable scaffold

In the light of data available, it may be postulated that BRS have certain advantages over currently available metal DES:

1. uncaging of vessel to allow for future interventions;
2. CT, MRI friendly device;
3. ponential to discontinue DAPT earlier without risk of stent thrombosis.

Conclusions

Progress in PCI in past two decades has been remarkable. In case of drug eluting stent continual improvements in drug delivery profile, polymer and reduction in strut thickness can serve the changing scenario of PCI. Gradual reduction in cost will make DES a mainstay of therapy for coronary artery disease.[33-36] BRS have been named as the fourth revolution in inter-

ventional cardiology. BRS are known to restore vascular integrity and function. This area looks exciting and promising where further improvements will change the PCI practices.

References

1. World Health Organization estimates. [cited 2015 May 19]. Available at: www.who.int/cardiovascular_diseases/resources/atlas/en/
2. Industry estimates. [cited 2015 May 19]. Available at: www.bccresearch.com/report/coronay-stent-devices-global-market-hlc111a.html
3. World Health Organization estimates. [cited 2015 May 19]. Available at: www.who.int/countryfocus/cooperation_strategy/ccsbrief_ind_en.pdf
4. Oldridge NB. Economic burden of physical inactivity: healthcare costs associated with cardiovascular disease. Eur J Cardiovasc Prev Rehabil 2008;15:130-9.
5. World Bank report. [cited 2015 May 19]. Available at: www.worldbank.org/depweb/beyond/beyondco/beg_04.pdf
6. Taking advantage of the Medtech market potential in India: Success will hinge on operating model innovation. Indian Medical Technology Report – 2012. [cited 2015 May 19]. Available at: www.pwc.com/medtech
7. Cardiovascular devices industry: market research reports, statistics and analysis. [cited 2015 May 19]. Available at: www.reportlinker.com/ci02250/cardiovascular-devices.html
8. Eeckhout E, Serruys PW. Bioresorbable scaffolds. In: The PCR-EAPCI Textbook. PCR Publishing 2012. Chapter 4/Part 3/Intervention 1/Volume 2.
9. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M *et al*. A randomized comparison of a Sirolimus eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.
10. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM *et al*. Lack of neointimal proliferation after implantation of Sirolimus coated stents in human coronary arteries: a quantitative coronary angiography and three dimensional intravascular ultrasound study. Circulation 2001;103:192-5.
11. Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF *et al*. Sustained suppression of neointimal proliferation by Sirolimus eluting stents: one year angiographic and intravascular ultrasound follow-up. Circulation 2001;104:2007-11.
12. Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O *et al*.; Intracoronary Stenting and Angiographic Restenosis Investigators--Test Efficacy of Rapamycin-eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3). Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. Eur Heart J 2008:29;1975-82.
13. Guidant and Cordis to copromote Cypher stent in the USA. [cited 2015 May 19]. Available at: http://www.medscape.com/viewarticle/784849
14. Xience Everolimus Eluting Coronary Stent System IFU. [cited 2015 May 19]. Available at: www.abbottvascular.com
15. Endeavor Sprint Zotarolimus Eluting Coronary Stent System. IFU. [cited 2015 May 19]. Available at: www.medtronic.com
16. Biomatrix Biolimus A9 Eluting Coronary Stent system. IFU. [cited 2015 May 19]. Available at: www.biosensors.com
17. Upendra K, Sanjeev B. Advantages of novel BioMime Sirolimus Eluting Coronary Stent System. Moving towards biomimicry. Minerva Cardioangiol 2012;60:23-31.
18. Evolutionary DES technologies – The creation of Mitsu. Dr. Martin Leon. Presented during TCT 2011.
19. Evolutions of DES and its technologies. Data on file with Meril Life Sciences Pvt. Ltd.
20. meriT-1 and meriT-2 data presented during TCT 2012. Dr. Ashok Seth.
21. Tan MH. Diabetes and Coronary Heart Disease. Diabetes Spectrum 1999;12:80-3. [cited 2015 May 19]. Available at: http://journal.diabetes.org/diabetesspectrum/99v12n2/pg81.htm
22. Aronson D, Edelman ER. Revascularization for coronary artery disease in diabetes mellitus: Angioplasty, stents and coronary artery bypass grafting. Rev Endocr Metab Disord 2010;11:75-86.
23. Garg P, Normand SL, Silbaugh TS, Wolf RE, Zelevinsky K, Lovett A *et al*. Drug eluting or bare metal stenting in patients with diabetes mellitus. Results from the Massachusetts Data Analysis Center Registry. Circulation 2008;118:2277-85.
24. Minutello RM Bhagan S, Feldman D, Sharma A, Hong MK, Wong SC. Angiographic pattern of restenosis following implantation of overlapping Sirolimus eluting (Cypher) stents. Am J Cardiol 2006;97:499-501.
25. Timmins LH, Meyer CA, Moreno MR, Moore JE Jr. Mechanical modeling of stents deployed in tapered arteries. Ann Biomed Eng 2008;36:2042-50.
26. Hoffmann R, Herrmann G, Silber S, Braun P, Werner GS, Hennen B *et al*. Randomized comparison of success and adverse event rates and cost effectiveness of one long versus two short stents for treatment of long coronary narrowings. Am J Cardiol 2002;90:460-4.
27. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;56;S43-78.
28. Bauters C, Meurice T, Hamon M, McFadden E, Lablanche JM, Bertrand ME. Mechanisms and prevention of restenosis: from experimental models to clinical practice. Cardiovasc Res 1996;31:835-46.
29. Data on File, Meril Life Sciences.
30. Bangalore S, Toklu B, Amoroso N, Fusaro M, Kumar S, Hannan EL *et al*. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. BMJ 2013;347:f6625.
31. Ormiston JA, Serruys PW. Bioabsorbable Coronary Stents. Circ Cardiovasc Interv 2009;2:255-60.
32. Gonzalo N, Macaya C. Absorbable stent: focus on clinical applications and benefits. Vasc Health Risk Manag 2012;8:125-32.
33. Iqbal J, Gunn J, Serruys PW. Coronary stents: historical development, current status and future directions. Br Med Bull 2013;106:193-211.
34. Htay T, Liu MW. Drug eluting stent: a review and update. Vasc Health Risk Manag 2005;1:263-76.
35. Cutlip D, Abbott JD. Drug-eluting compared to bare metal intracoronary stents. [cited 2015 May 19]. Available at: http://www.uptodate.com/contents/drug-eluting-compared-to-bare-metal-intracoronary-stents

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on April 29, 2015.