Editorial

Bioresorbable scaffold -fourth revolution or failed revolution: Is low scaffold strut thickness the wrong target?

1. Background

The prospect of leaving a metallic prosthesis in the body, especially when it is no longer required has always been a matter of concern to both physicians and patients alike. In case of metallic stents for coronary or peripheral interventions this is of particular worry because they don’t remain innocuous, rather interfere with vascular remodeling and flow and serve as a nidus for accumulation of platelets (stent thrombosis) as also interfere with future interventions in the area. Bioresorbable scaffolds (BRS) were developed with a view to address some of these philosophical and practical issues particularly that of late stent thrombosis with metallic drug eluting stents (DES) and were purported to represent “Fourth Revolution” in stent technology. The trick was to match physical performance of the metallic stent but at the same time making the scaffold disappear at a variable period of 6 months to 3 years after implantation. The initial results with this technology, in simple lesions with a careful application of technique, seemed equivalent to any metallic stent with the advantage of melting away in due course of time and possible favorable remodeling of artery and a better flow. However, soon problems of late scaffold thrombosis and post-procedural myocardial infarctions started cropping up, the very reasons BRS was developed in the first instance. Thus suddenly medical opinion moved from “Fourth Revolution” to possible “Failed Revolution.” This whole fiasco demands explanation and possible learning for future.

2. What are the reasons?

The reasons for this negative evolution could be numerous and encompass histo-pathological, mechanical and behavioral explanations. Table 1

2.1. Histo-pathological co-relates

1. Dense distribution of incompletely embedded, thick protruding struts (which are incompletely endothelized) may disrupt the laminar flow and induce endothelial shear stress, a precursor for adherent thrombosis.

2. Early structural disruption and late scaffold discontinuity, as a part of property of polymer used, with elongation and break at resorption points- an inherent component of resorption process (which in any case appears delayed in humans) could also make the site vulnerable to thrombotic events for a prolonged period of time.

3. Peri-strut, low intensity area (PSLA) in absence of classical mechanical triggers has been correlated with peri-strut inflammation, mal-apposition, evagination, strut fracture, and un-endothelialized struts in metallic DES and could serve as additional patho-physiological correlates with BRS as well.

2.2. Mechanical factors

The mechanical limitations of current BVS are:

1. Low tensile and radial strength of scaffold material. Typically bio-resorbable polymers, polylactide (PLLA) and poly(ε-caprolactone) have tensile strengths ranging between 45 and 70 MPa (<200 times) compared with nearly 1500 MPa with cobalt-chromium. The radial strength is also around 10 times lower.

Thus to improve the tensile and radial strengths, typically a greater strut thickness (≥150 μ) may be required but this
modifications can still remain inadequate to overcome the vast differences in radials and tensile strengths. Consequently, the embedding force during the deployment of scaffold may still remain deficient resulting in only partly embedded and largely exposed scaffold struts (a focal point for thrombus formation), despite high-pressure post dilatation.

2. Insufficient ductility is another mechanical aspect which affects not only the crimping ability of scaffold on the delivery balloon but also limits the range of device expansion because the polymer may easily snap during the process of deployment. The break-point for polymers occurs at only 2% to 6% of elongation compared with 40% for metallic stents.\textsuperscript{10,11}

3. Improper design of scaffold could be another factor. The rectangular shape and excessive height compared with current generation DES, increases its foot-print within the lumen, a large part protruding from the vessel wall, contributing to blood flow disturbances with consequent at least two-fold risk of scaffold thrombosis.\textsuperscript{12}

4. Strut thickness has been a correlate of metallic stent thrombosis and re-stenosis. However, this factor seems to play a lesser important role in context of BRS.\textsuperscript{13}

2.3. Physician factors

Several research and operator factors are also responsible for the current scenario.

1. Research questions may not have been properly framed and device trials pushed through without properly understanding how to use the device.

2. Inappropriate procedural technique; improper choice of lesions (small vessel, diffuse disease, calcific lesions), inability to prepare proper bed, sub-optimal vessel sizing and inability to achieve optimal deployment (non use of imaging techniques like OCT and IVUS, mal-apposed struts and inadequate post-dilation — with balloon sized ≥1.1:1 compared with scaffold diameter) all contribute to scaffold thrombosis.\textsuperscript{10−12,14,15}

3. Dual anti-platelet therapy discontinuation by physician or patients themselves also remains a risk factor for scaffold thrombosis.\textsuperscript{15}

3. What lies in future?

The current crisis is certainly not end-game for BRS technology; however innovations in material science will have to be made to overcome the deficiencies. The current attempts to tinker with complex composition of polymers, mixing PLLA, poly-glycolide, and poly-caprolactone to improve radial and tensile strength and improve ductility have yielded slightly superior mechanical characteristics. Improved strength has also been attempted to be imparted by altering the polymer orientation (melt extrusion, drawing) and polymer treatment (heat annealing and blow molding to achieve a proper mix of crystalline with amorphous polymer), even using newer polymers; tyrosine based polycarbonates and poly-lactide anhydrides. Currently, the main focus of innovation from structural stand-point has been to try achieve a lower strut thickness, which was a correlate of DES outcomes. However, it is possible that all this while, this may have been a step in wrong direction because for BRS the most important predictor of thrombosis is a low tensile and radial strengths contributing to un-embedded scaffold struts, a precursor for future events. Thus lower strut thickness could actually lead to even lower tensile/radial strength, and thus even less properly embedded scaffold struts, a potential recipe for paradoxically increased scaffold thrombosis. On the other hand it is possible that while these minor modifications in polymer technology may improve the tensile strength of device it may still be still difficult to bridge the 100 fold gap in tensile strength and 10 fold gap in radial strength. Thus unless a landmark innovation happens in polymer technology it will remain a dream unfulfilled. In this context magnesium, based BRS which have a tensile strength of 220–330 MPa and elongation at break-point like cobalt chromium (of 40%) may be more useful in immediate future.\textsuperscript{8} However, it has to be remembered that tensile strength is still 1/5th and radial strength 1/3rd of cobalt chromium, so there is still some work to do. Meanwhile the nattiness of BRS can still be utilized in suitable low risk younger patients with proper vessel preparation and application of technique utilizing some newer generation devices.

References

1. Mishra S. A fresh look at bioresorbable scaffold technology: intuition pumps. Ind Heart J. 2017;69:107–111.

2. Lipinski Michael Jcal, Escarcega Ricardo Ocro, Baker Nevin CvnC, et al. Scaﬀold Thrombosis After Percutaneous Coronary Intervention With ABSORB Bioresorbable Vascular Scaffold. JACC Cardiovasc Interventions. 2013;6(1):12−24.

3. Räber L, Brugaletta S, Yamaji K, et al. Very late scaffold thrombosis: intracoronary imaging and histopathological and spectroscopic findings. J Am Coll Cardiol. 2015;66:1901−1914.

4. Otsuka F, Pacheco E, Perkins LE, et al. Long-term safety of an everolimus-eluting bioresorbable vascular scaffold and the cobalt-chromium XIENCE V stent in a porcine coronary artery model. Circ Cardiovasc Interventions. 2014;7:330−342.

5. Cuculi F, Puricel S,Jamshidi P, et al. Optical Coherence tomography findings in bioresorbable vascular scaffolds thrombosis. Circ Cardiovasc Interventions. 2015;8:e002518.
6. Tellez A, Afari ME, Buszman PP, et al. Peri-strut low-intensity areas in optical coherence tomography correlate with peri-strut inflammation and neointimal proliferation: an in-vivo correlation study in the familial hypercholesterolemic coronary swine model of in-stent restenosis. Coron Artery Dis. 2014;25:595–601.
7. Arroyo D, Cook S, Puricel S. Mechanisms of late and very late bioresorbable vascular scaffold thrombosis: is it only about flow? J Am Coll Cardiol. 2016;67:1259–1260.
8. Waksman R. Bioresorbable scaffolds: polymer troubleshooting or simply not good enough? JACC Cardiovasc Interventions. 2017;10(June (11)):1131–1133.
9. Tenekecioglu E, Serruys PW, Onuma Y, et al. Randomized comparison of absorb bioresorbable vascular scaffold and mirage microfiber sirolimus-eluting scaffold using multimodality imaging. J Am Coll Cardiol Intv. 2017;10:1115–1130.
10. Gori T, Schulz E, Muñzel T. Immediate, acute and subacute thrombosis due to incomplete expansion of bioresorbable scaffolds. J Am Coll Cardiol Interventions. 2014;7:1194–1195.
11. Ortega-Paz I, Capodanno D, Gori T, et al. Predilation, sizing and post-dilation scoring in patients undergoing everolimus-eluting bioresorbable scaffold implantation for prediction of cardiac adverse events: development and internal validation of the PSP score. EuroIntervention. 2017;12:2110–2117.
12. Ellis SG. Fantom bioresorbable scaffold: verse, but not yet chorus (an incomplete composition). JACC Cardiovasc Interventions. 2017;10(September (18)):1839–1840.
13. Mishra S. Are all stents equal—need for scoring system to evaluate stents? Indian Heart J. 2016;68:589–591.
14. Capodanno D, Gori T, Nef H, et al. Percutaneous coronary intervention with everolimus- eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. EuroIntervention. 2015;10:1144–1153.
15. Ellis SG, Steffenino G, Kereiakes DJ, et al. Clinical, angiographic, and procedural correlates of acute, subacute, and late Absorb scaffold thrombosis. J Am Coll Cardiol Interventions. 2017;10:1809–1815.

Sundeep Mishra*
AIIMS, New Delhi, India
*Corresponding author.
E-mail address: sundeepmishraihj@gmail.com
Available online 6 October 2017