Drug-Eluting Resorbable Scaffolds Below the Knee – Old Dog, New Tricks

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The introduction of concept of bioresorbable scaffolds (BRS) to the world of percutaneous interventions first occurred roughly two decades ago and was heralded as the solution to several issues related to bare-metal stents (BMS) and the then recently approved coronary drug-eluting stents (DES). The development of BRS would have the benefit of mechanical support to prevent early vessel recoil and treat dissection similar to BMS and DES, without the permanent metallic struts that would lead to medium- and long-term complications such as hampered vasomotion, neo-intimal hyperplasia, and in-stent restenosis/thrombosis. Additionally, it could reduce the difficulty of performing repeat interventions on a patient compared to those with permanent metallic struts.

In this issue of the *Journal of Critical Limb Ischemia*, Miladinovic and colleagues briefly review the current state-of-affairs with regards to bioresorbable technologies for below the knee applications.[1] Their article gives compelling reasons for an optimistic outlook on BRS for below-the-knee applications given that the BRS of today differ from those in the initial below the knee investigation conducted in 2009 with the AMS INSIGHT trial, and certainly differ from Drs Tamai and Igaki et al original poly-L-lactic acid (PLLA) scaffolds in 2000.

For one, strut thickness has been substantially reduced. First generation BRS were typically measured between 150 to 170 µm while the newest generation is approaching that of DES in the sub-100 µm arena with the R3 Vascular Magnitude and Reva Medical Motiv leading the race at 98 µm and 95 µm, respectively. Although little formal comparative data exist, reduced strut thickness theoretically results in improved deliverability, faster stent endothelial coverage, and reduced side-branch flow disturbance, the result of lower crossing profiles, improved trackability, and flexibility.

Optimistically, reduction in at least early stent thrombosis similar to what has been seen in DES for coronary interventions could also be expected with reductions in strut thickness[2] given that in ex vivo flow loops and porcine coronary models, increased strut thickness results in platelet activation via non-laminar flow and thus increased early thrombus burden.[3] Other mechanisms of early stent thrombosis in BRS have also been found to be relatively consistent with those found for metallic DES. Those are principally related to procedural factors including malapposition, device underexpansion, and incomplete lesion coverage as seen in two small optical coherence tomography based studies.[4,5] However, DES strut thickness was not independently associated with 5 year target lesion revascularization (TLR), late stent thrombosis (LST), and very late stent thrombosis (VLST),[2] since both LST and VLST are thought to predominantly be related to stent malapposition, including late acquired related to positive vessel remodeling and late persistent, and rupture of neoatherosclerosis,[6] although uncovered struts and stent underexpansion may also play a lesser role.[7] In all, most lesions have more than one of the above qualities on optical coherence tomography (OCT) evaluation of patients with VLST.[7] Theoretically, LST and VLST thrombosis should be substantially reduced in patients receiving BRS given the lack of permanent metallic struts to contribute to malapposition and uncovered struts, however this has not panned out in randomized trials. This is suspected to be primarily related to inconsistent resorption of the BRS resulting in scaffold discontinuity, although malapposition, neoatherosclerosis, under expansion/scaffold recoil, and uncovered struts were also contributing factors. Multiple mechanisms were not uncommon and were found to be similar to what has been seen in DES.[8] Further research should be conducted to evaluate whether the newer thinner BRS struts are less susceptible to thrombus formation given the balancing act between deliverability, scaffolding strength, and risk of discontinuity.

One of the stated promises/advantages of BRS is that it can return the normal vasomotion to the vessel, whereas a metallic stent implant cannot. However, it is noteworthy that the demonstration of this promise has been sparse, the time period in which it might occur vague, and the promise of such a benefit to infrapopliteal vessels which are frequently involved with medial calcinosis may make this aspect of BRS likely less relevant.

New materials, such as ultra-high molecular weight amorphous PLLA, have resulted in higher radial strength which has allowed for the reduction in strut thickness. More importantly,

the material is better able to resist fracture in the setting of overexpansion.[9] Early adaptations of PLLA BRS were limited by poor ductility with minimal ability to post dilate without concern for strut fracture. This led to lengthy protocols to ensure adequate vessel preparation using non-compliant balloons for aggressive pre-dilation, resulting in longer procedures, requiring more radiation, and contrast. In addition, the lack of IVUS or OCT imaging guidance in many of the trials may confound the assessment of adequacy of device expansion which may lead to sub-optimal outcomes such as early target vessel revascularization and reduced primary patency.

Although imaging guidance is not the standard of care in below the knee intervention, intravascular imaging in endovascular procedures has continued to increase, albeit slowly, in coronary intervention, and recently has been gaining traction in the femoral-popliteal territory. Hopefully, the future will involve more frequent use of imaging even for infrapopliteal disease, given the suggestive emerging data on outcome improvements, and would likely benefit BRS implantation. For instance, a retrospective analysis of 234 propensity matched pairs of TASC II A-C femoropopliteal lesions compared 5-year outcome data between IVUS guided stenting and angiographically guided stenting revealing significantly higher primary patency (65% vs 35%), secondary patency, freedom from any reintervention, freedom from an adverse limb event, and event-free survival.10 Randomized control trial data is extremely limited in this area despite support from consensus guidelines. The sole high quality randomized control trial to evaluate the use of IVUS in the femoropopliteal arteries was recently performed by Allan et al.[11] The study randomized 150 patients in 1:1 fashion to angiographic or angiographic and IVUS guidance. Primary outcome data at 12 months showed a significantly higher freedom from binary restenosis by ultrasound (72.4% vs 55.4%) in the angiography and IVUS guided group. There was no significant difference in clinically directed target lesion revascularization between groups, however the trial was not powered to detect a difference in this endpoint. A change in treatment occurred as a result on IVUS guidance in 79% of cases. Treatment modality (balloon angioplasty, drug coated balloon, BMS, DES, atherectomy) was left to the discretion of the operator.

Reva Medical has been working towards approval in the US for their new dedicated below the knee BRS called Motiv, using a novel material called Tyrocore. Tyrocore is a compound containing iodinated desamino-tyrosine polycarbonate and polylatic acid which is ultimately degraded into iodinated diphenol, and water, carbon dioxide, respectively. Given the presence of iodine in the compound the stent has a similar radio-opacity to traditional DES. Reva Medical reports improved radial strength and acute recoil according to bench testing when compared to the Biotronik Magmaris BRS. Additionally, Tyrocore appears to have better biocompatibility compared in traditional PLLA in rabbit and porcine models, with fewer adherent platelets to scaffold struts in the early phase after deployment and less calcification at the scaffold-endothelial junction in the 4-12 month phase. Despite the use of polylactic acid, computational models reported low concentration levels of arterial wall lactic acid. The degradation to lactic acid has been reported as a concern given the potential to induce inflammation and thus a possible contributor to clinical events. Preliminary data in the MOTIV BTK trial were presented at the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) last fall. The trial focuses on the application of the new BRS in infrapopliteal lesions with lengths less than 100 mm, and with less than a quarter of the prespecified enrollment, the 12-month data that were presented revealed a primary patency rate of 88% with a freedom from clinically driven target lesion revascularization rate of 98.3%. Technical success rates were 99%. Data from the PTA comparator was not presented however the overall preliminary outcomes appear promising for the novel scaffold, and it will be interesting to review the final data when the trial is completed.

It is useful to review the effectiveness of drug-eluting metallic stents given that all anticipated future BRS data will incorporate similar sirolimus analogues. Many of these trials focused on below the knee intervention concentrate on more shorter lesion lengths in the range of 20-30 mm however in clinical practice it is not uncommon to be met with longer, diffuse disease in this territory. Patency rates for such diffuse disease is poor and treatment options are limited largely to PTA. Although coronary stents now reach lengths of 48 mm rendering treatment of longer lesions possible with permanent mechanical supports, generally DES are not employed past the proximal 1/3 of the infrapopliteal vessels due to concerns of possible external deformation. Accordingly, randomized controlled trials evaluating DES in the crural arteries have generally included shorter, proximal lesions. Trials such as YUKON-BTK12 and ACHILLES[13] revealed significantly improved primary patency rates for focal lesions at 12 months vs PTA or BMS, (respectively), however clinically driven target vessel revascularization in both YUKON-BTK and ACHILLES failed to show an improvement compared to bare metal stents and PTA, respectively. The IDEAS trial was one of the few trials that compared DES to DCB while focusing on longer lesions (>70 mm). This trial DES showed statistical reduction in immediate postprocedural stenosis and binary (>50%) angiographic restenosis rates without a difference in target lesion revascularization (TLR) over a 6-month trial period.[14]

The PADI trial[15] may have the longest-term available data comparing DES to PTA with bail-out BMS. This investigator-initiated trial enrolled patients with critical limb ischemia and lesions < 90 mm in length, with an average of 22 mm. Results agree with previous trials with improved patency according to CT angiography in the DES group in the per protocol group but no difference and in fact a trend towards increased revascularization in the DES group. At five year trial data there was statistically different event and amputation free survival, defined as major amputation and reintervention, favoring DES. Overall survival rates were

comparable and poor (37% vs 37.7%, PTA and DES respectively) at 5 years and dismal at 10-year outcome data (19.2% vs 21.9%, PTA and DES respectively). Despite critical limb ischemia these patients most often succumb to other cardiovascular disease, which suggests that the value of long-term patency in the critical limb patient may be diminished by the high rates of mortality. DES, BRS, and DCB devices, which all aim to improve vessel outcomes, are affected by this unfortunate math.

While all of these trials suffer from their own limitations, each is certainly limited by small study populations. This was addressed with the meta-analysis of randomized controlled trials (RCTs) conducted by Varcoe et al[16] which included seven RCTs and a total of 801 patients. With combined numbers able to power outcomes, at 12 months DES had improved rates of primary patency, freedom from TLR, major amputation, and Rutherford class without improvement in survival.

Given the limited but available data in infrapopliteal arteries in regard to the use of DES, the benefits of mechanical support in the prevention of vessel recoil and restenosis are clearly important, however it is not clear how the duration of BRS scaffolding strength aligns with the duration of mechanical support required to produce a benefit. Alternate non-polymeric materials used in BRS, such as magnesium, have much higher radial strength but typically have a longer time to resorption and may also cause greater inflammation upon resorption. Additionally, diffuse lesions in the infrapopliteal region would be difficult to treat with BRS given the currently available length for approved scaffolds which are even shorter than currently approved coronary DES. This would require numerous scaffolds and scaffold overlap has been suggested as a possible risk factor for stent thrombosis and restenosis, although this may be less of a concern as thinner strut devices become available. However, the potential utility of BRS in below the knee applications has been noted by medical device companies such as Abbott, Reva Medical, and R3 Vascular who are currently designing infrapopliteal specific BRS.

Bioresorbable scaffolds for infra-popliteal use are still relatively early in their development despite the more than 20-year journey that started in the coronaries. BRS ultimately had to compete against permanent metallic drug eluting stents which led to rapid design and material advances, ultimately culminating in superb clinical performance which was difficult to displace in the coronary territory. Current bioresorbable scaffold technology represent meaningful advances that will hopefully lead to positive infra-popliteal clinical data results. Studies such as LIFE BTK (Abbott) and MOTIV BTK (Reva Medical) will attempt to fill these voids. Given the poor life expectancies of infrapopliteal critical limb ischemia patients, who predominantly expire from non-peripheral artery disease comorbidities, perfection may not be needed. Improved clinical endpoints such as reduction in amputation and repeat interventions with improved ambulatory parameters and quality of life metrics within at least an intermediate time period of follow up is a reasonable target. Here's hoping...

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