

Bioresorbable Stent Technology for Femoropopliteal Disease Treatment: Where Do We Stand?

Appraising the current literature on bioresorbable technology use in the SFA, what can be learned from the coronary experience, and the future of bioresorbable stents in this anatomy.

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In more complex femoropopliteal disease, immediate technical failure of balloon angioplasty is frequently observed due to elastic recoil, flow-limiting dissection, or hemodynamically relevant residual stenosis, requiring stent implantation to achieve primary success. Mechanical support improved high 1-year restenosis rates between 60% to 70% after balloon angioplasty alone,¹ and the development of modern self-expanding nitinol bare-metal stents with enhanced flexibility and superior fracture resistance was associated with increased long-term patency rates of approximately 70% after 1 year.² Although better results were described with drug-eluting and high compression-resistant interwoven nitinol stents,^{3,4} the drawbacks of permanent implants have not been completely eradicated, including the risk of stent fracture in high motion regions and induction of chronic inflammation by stent struts. Importantly, restenosis after stent implantation is still a major concern, as disease progression within stents is typically aggressive and difficult to treat.

The concept of bioresorbable vascular scaffolds (BVSs) with additional antiproliferative drug delivery has attracted great interest in the past few years. These devices unify the advantages of metallic stents and drug-coated balloons by offering acute vessel support

and limiting neointimal hyperplasia and late lumen loss over time, and then they ultimately disappear and allow the return of physiologic vasomotion. Full BVS resorption over the course of 2 to 3 years would subsequently facilitate future endovascular procedures and the previously stented segment could even serve as a suitable landing zone for bypass surgery later.

Although BVS technologies were greeted with great enthusiasm in the cardiovascular community, increasing data from the coronary vessels lowered expectations that BVSs could substitute permanent implants in the near future. Importantly, biomaterials for BVS technologies should fulfill various requirements to rival metal stents, including optimal mechanical properties with good flexibility for delivery and biosafety without toxic intermediate products during the degradation process. Most BVSs tested in human studies were designed from synthetic polymers (mainly α -hydroxy acids such as poly-L-lactic acid [PLLA]). As an alternative, absorbable metallic stents made with magnesium or iron are being researched, as both materials naturally exist in the body.

PREVIOUS STUDIES OF BVSs IN THE SFA

So far, most BVSs used in peripheral artery disease, including femoropopliteal interventions, were adapted

from those used in the coronary setting. Thus, long complex femoropopliteal lesions with a high degree of calcification were not suitable for the currently available technologies. Stringent angiographic inclusion criteria were also typically required with online quantitative vascular angiographic evaluation to assess vessel diameter and lesion length.

The balloon-expandable, non-drug-eluting Igaki-Tamai stent (Kyoto Medical Planning Co., Ltd.) was the first BVS to be evaluated for femoropopliteal interventions. The GAIA study, the most informative series testing this device, evaluated 30 femoropopliteal lesions with a mean length of 5.9 cm.⁵ Although immediate technical success was comparable to metal stents, binary restenosis rates were high at 39.3% and 67.9% at 6 and 12 months, respectively. Histopathologic analysis of restenosis from eight specimens retrieved by atherectomy showed a mixed picture with hyperplastic tissue and remnants of stent struts (37.5%), inflammatory cells (50%), and thrombus (50%).

A single-center study combining drug-coated balloon treatment with subsequent Igaki-Tamai BVS implantation in 20 superficial femoral artery (SFA) lesions reported similarly disappointing results, with 11 patients exhibiting restenosis after 1 year.⁶ A randomized study of 80 patients who underwent treatment for common femoral stenosis compared the Igaki-Tamai BVS versus surgical carotid endarterectomy and showed inferiority of the endovascular arm (primary patency, 80% for BVS vs 100% for carotid endarterectomy at 1 year).⁷ A prospective, multicenter, observational registry from Belgium composed of 99 patients who received the Igaki-Tamai BVS (renamed the Remedy stent) reported lower patency rates (58% at 12 months), when compared with contemporary studies using modern nitinol stents in the SFA.⁸

The ESPRIT I study was a multicenter, prospective, single-arm trial evaluating the Esprit BVS system (Abbott Vascular) in 35 iliac (11.4%) or SFA (88.6%) atherosclerotic lesions that were ≤ 5 cm in length.⁹ The Esprit BVS consists of an everolimus-eluting PLLA scaffold. Procedural success was 100% and the binary restenosis rates were 12.1% and 16.1% at 1 and 2 years, respectively. No further events were reported between 2 and 3 years.¹⁰ The Stanza BVS (480 Biomedical, Inc.), a fully self-expanding polymeric poly(lactic-co-glycolic acid) scaffold, was tested without drug-eluting properties in the unpublished STANCE trial (NCT01403077) in 46 femoropopliteal lesions. In a first cohort of 25 patients, late lumen loss was a major issue due to a combination of vessel recoil and neointimal hyperplasia. After device modification, minimal vessel recoil was

reported in the second cohort of 21 patients.¹¹ The SPRINT trial (NCT02097082) was launched to test an updated stent with a paclitaxel coating in 28 femoropopliteal lesions. The DESappear study (NCT02869087) was initiated to study the balloon-expandable Prava sirolimus-eluting bioresorbable scaffold (Akesys Medical and Elixir Medical Corporation) in 60 patients with short SFA lesions (< 54 mm) but recruitment is currently stopped.

LESSONS FROM THE CORONARY FIELD

The Absorb BVS (Abbott Vascular), consisting of a poly-L-lactide backbone coated with a mixture of poly-D,L-lactide and an everolimus-eluting drug, received CE Mark approval in 2010 and FDA approval in 2016 and was considered a breakthrough technology for the treatment of coronary artery disease. The BVS was implanted in an estimated 200,000 patients worldwide and initial studies performed in relatively simple coronary lesions showed promising short- to midterm results.¹² However, a higher risk of target lesion failure was recently identified compared with the best-in-class drug-eluting stent (Xience, Abbott Vascular). The poorer outcome has been partly attributed to suboptimal implantation technique (ie, optimal vessel preparation, sizing, postdilatation) and vessel selection, as there were higher event rates in smaller-diameter vessels < 2.5 mm. Furthermore, the degradation and resorption process seems to be longer than anticipated, and heterogeneous reendothelialization of scaffold struts with incomplete integration into the vessel wall could also be a trigger for the observed late scaffold thrombosis risk.¹³

In addition to higher costs, several clinical disadvantages of the Absorb BVS were identified, including the need for increased imaging for optimal deployment, which is associated with longer procedure time, increased radiation exposure, and greater amounts of contrast dye. Accurate sizing is critical because overexpansion easily causes stent fractures. The normal commercial sale of Absorb BVS was discontinued in Europe and its use has been limited to clinical registries. Although this first-generation coronary BVS had a relatively bulky structure with a strut thickness of approximately 150 μ m, newer second-generation stents are being developed with a thinner profile and more flexibility, which could make them easier to deliver and potentially provide better outcomes.

THE FUTURE OF BVSs IN THE SFA

With rather disappointing data identified, such as high restenosis rates in the SFA and the limitation of BVSs in the coronary field, it raises the question, what

does an optimal BVS for femoropopliteal interventions look like? A major challenge seems to be the maintenance of the mechanical integrity in areas with high biomechanical stress, which is typical for the (distal) SFA and popliteal segment. To rival modern nitinol stents with enhanced fracture resistance and flexibility aiming to adapt to the vessel wall, a self-expanding BVS for the SFA should have similar mechanical properties to nitinol stents. Ideally, BVSs should provide mechanical integrity until the vessel has fully remodeled before the resorption process starts. Optimal resorption as well as antiproliferative drug delivery properties of drug-eluting BVSs have to be identified for the SFA, as they are likely different from the coronary arteries.

Interestingly, a novel bioresorbable, self-expanding composite polymeric scaffold was recently tested in preclinical studies and exhibited promising mechanical strength in terms of compression, expansion, and elasticity; however, no human studies have been reported.¹⁴ Future trials in the field should integrate the use of optical coherence tomography/intravascular ultrasound follow-up to analyze the time course of arterial remodeling, the resorption process, and the promised restoration of vasomotion. Histopathologic analysis of restenotic specimens retrieved by atherectomy could provide further insights into biocompatibility and inflammatory reactions triggered by the scaffolds.

CONCLUSION

Although the theoretical concept of BVSs holds great promise, especially because restoration of vasomotion could be particularly essential in the femoropopliteal segment, several questions remain. It is unclear if and when the technology will advance so that it becomes a workhorse device, replacing modern metallic permanent implants for coronary and peripheral artery disease. BVSs will have to compete with other continuously refined and advanced metal stents with respect to cost issues, deliverability, and clinical outcomes. ■

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