What Will Dominate the Next Era in SFA Therapy?

Experts discuss the current era of drug-eluting technologies and what might come next.

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Antirestenotic drug-eluting technologies are currently dominating the treatment of femoropopliteal disease. Their ease of use, excellent mid- and longer-term technical and clinical outcomes, and positive results on cost-effectiveness analyses make drug-coated balloons (DCBs) and drug-eluting stents (DESs) the winners at the moment. Even for the more challenging lesions, such as long lesions, occlusions, and in-stent restenosis, promising mid-term results have been described.

Some DCBs showed their efficacy in several proof-of-concept studies, multicenter randomized trials, and global registries. Perfectly responding to the "no metallic implant" concept, they are used worldwide. However, the often low drug transfer efficiency, their dubious role in heavily calcified vessels, need for perfect (but sometimes expensive) vessel preparation, undefined correct sizing, high(er) need for bailout stenting (and leaving metal) in more complex lesions, and lack of head-to-head DCB comparisons still leave questions to answer in the coming years. In addition, the selection of better excipients, coating mechanisms, and potentially other even more efficient drugs will influence their use and outcomes in the near future.

The two DESs on the market showed effectiveness in well-controlled randomized studies. One DES showed excellent clinical outcomes out to 5 years as well as consistency over several studies worldwide in different types of lesions and patient groups. The absence of head-to-head comparisons (IMPERIAL trial), the unclear role of polymer, and the lack of availability of longer device lengths are still unresolved.

Drug-eluting bioresorbable scaffolds are also very promising in the femoropopliteal area, but with the exception of one study involving short, focal lesions (Esprit BVS, Abbott Vascular), their role remains unclear. Although the idea of having a scaffold that returns the vessel to a normal state of vasomotion without definitive vessel caging is exciting, we need to see clinical data in real-world lesions showing that scaffolds help mid- and long-term clinical outcomes. Right now, the costs, more demanding implantation techniques, increased requirements of imaging, and longer dual-antiplatelet therapy are major drawbacks for their routine clinical use.

Other devices such as the Bullfrog Micro-Infusion Device (Mercator MedSystems, Inc.), which injects anti-inflammatory or antiproliferative agents subintimally, and drug-filled metallic stents that elute drugs through microscopic holes (Medtronic) might be an option for the near future.

I expect a lot from the nanostructure systems in development, which are designed for drug delivery. Antirestenotic drugs encapsulated in a nanocarrier (nanoparticles of 70 nm have shown high vessel wall uptake in vivo) coated on a balloon or fixed by a cationic electrodeposition technique on a metallic/bioresorbable scaffold might be the solution in the coming years.

Finally, I believe that genomics will affect the atherosclerotic field in the next 10 years. Genetically identifying (young) patients at risk and treating them medically so that they never progress to severe femoropopliteal disease makes sense. Today with drugs, we block inflammation, platelet aggregation, and smooth muscle cell hyperplasia—in the future, drugs will suppress many of the proteins involved in the initial severe plaque formation.

Even in 2016, treating complex femoropopliteal pathology remains exciting but challenging. We are on a good track with good vessel preparation and antirestenotic drugs, but there is still room for improvement. Thanks to newer drugs, innovative coating techniques, adapted bioresorbable technologies, new developments in nanocarrier science, and finally genomics, the future looks bright for our vascular patient with femoropopliteal disease.

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The superficial femoral artery (SFA) is one of the most commonly diseased arteries in humans. The most common symptomatic manifestation of SFA disease is claudication, but SFA pathology is commonly involved in critical limb ischemia (CLI) with concomitant infrapopliteal arterial involvement. Successful restoration of adequate flow is crucial in treating CLI as well as disabling claudication. Initially, balloon angioplasty was the primary interventional treatment, but this was associated with high rates of restenosis. Nitinol stents replaced percutaneous transluminal angioplasty (PTA) and became the standard of care, but they were associated with fractures and episodes of in-stent restenosis, which was difficult to manage clinically.[1-4] Many clinicians tried atherectomy (removing the plaque and leaving nothing behind), but this also had significant rates of restenosis, occasional complications such as embolization and perforation, and occasionally required concomitant stenting for flow-limiting dissections.[5-7] The most recent era of SFA therapy has been dominated by DCB therapy with or without concomitant atherectomy.[8-11] DCBs have been clinically effective, but they have been primarily studied in selective subsets of patients and have improved but not solved the restenosis problem. Initial results with atherectomy followed by DCBs have shown modest improvement over DCBs alone. Restenosis and reocclusion continue to challenge interventional therapy of SFA disease.

SFA disease varies widely from patient to patient. Factors such as lesion length, runoff, degree and location of dystrophic calcification, vessel size and mobility, associated thrombus, as well as nonlesion-associated factors such as smoking, hypertension, diabetes and lipid control, and adherence to therapeutic medical regimens all affect outcomes. How can we get to a threshold of 90% long-term patency?

I think that SFA therapy is likely to follow one of two paths. The MAJESTIC data demonstrating > 90% patency at 1 year utilizing a newer-generation, paclitaxel-eluting stent delivered via a polymer are encouraging, but these data are only for 1 year and the study was clearly not an "all-comer" study.[12] The Zilver PTX data utilizing a newer-generation nitinol stent has shown efficacy out to 5 years with low rates of stent fracture.[13] If the data from DES trials remain durable, this will continue to be one of the treatment paths. Of course, this would include other newer-generation DESs in the future, including some to address profound dystrophic calcification with marked elastic recoil, as well as potentially covered stents with modifications to limit edge stenosis. I think that the other treatment path will possibly be vessel preparation via atherectomy or ultrasonic modulation[14,15] to achieve a minimal acceptable lumen, followed by measured drug delivery to limit subsequent intimal ingrowth.

Treatment of the SFA has been far more challenging than most of us initially imagined. Strides have been made, but I suspect we will continue to require adaptive changes to achieve acceptable patency. I am closely following reports on the results of image-guided atherectomy with the Pantheris device (Avinger, Inc.) to determine if accurately guided atherectomy will result in improved long-term outcomes.

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When we consider the future of SFA intervention, it's important to study technology that has gone before it, and specifically, which technologies have been most and least effective. In doing so, it becomes possible to predict the likely combination of attributes that will enable us to address current unmet needs.

There seems to be little doubt that antiproliferative drugs, particularly paclitaxel, are effective at reducing neointimal hyperplasia, late lumen loss, and restenosis in the SFA. This has been demonstrated in a number of randomized trials, which have compared DCBs and stents to uncoated comparators. It follows that any technology that provides maximal durability in the SFA should incorporate an antiproliferative drug coating.

Intervention in the SFA is challenged by myriad extreme biomechanical forces, and it is common to encounter heavy calcification, which may lead to elastic recoil and flow-limiting dissection after angioplasty alone. Early-generation metal stents were designed to overcome recoil and dissection but often fatigued and fractured within the hostile environment of the adductor canal. A more recent generation of nitinol stents has proven more durable but not immune to fracture.

Even when stent integrity remains intact, devices exert a chronic outward force on the vessel wall, which can act as an irritant and be a barrier to future reintervention. There is no doubt that in-stent restenosis poses a greater technical challenge when attempting revascularization than restenosis after PTA. Because of this, many interventionists prefer to use a stand-alone PTA or DCB strategy. However, this ignores the fact that some form of scaffolding is required in a significant proportion of SFA disease, making it an important part of any discussion about the future. Current stents are imperfect, and in the future, it is suggested that whatever scaffold is developed should be resistant to fracture and kink, move with the artery, not against it, maintain its radial strength, and at the same time, produce little force against the native vessel to cause irritation.

An important lesson learned from the generation of mimetic nitinol stents is that the way they interact with the vessel wall and modify hemodynamic flow has the potential to reduce restenosis and extend durability. The relative success of the BioMimics 3D helical (Veryan Medical) and Supera interwoven nitinol stents (Abbott Vascular) suggests that the design and physical properties will play a greater role in future scaffold technology than what has been considered in the past.

The treatment of lower extremity arterial disease is often led by experiences in coronary artery disease, which provide insight into future technology applications. In the coronary arteries, drug-eluting bioresorbable scaffolds have demonstrated efficacy in large randomized trials. This generation of scaffold has clinical outcomes similar to the best metal DESs with several advantages related to their dissolution properties. Once resorbed, they stabilize the blood vessel wall and facilitate a return of normal contractile function. Moreover, they minimize artefact on cross-sectional imaging (CT and MRI), permit future reintervention or surgery when required, and may reduce late thrombotic events. Early drug-eluting bioresorbable scaffold trials in the SFA have shown promise, and this is likely to be an area for future development.

The ideal device for use in the SFA would include a combination of the features that have led to improvement and success with current devices. It would incorporate an antiproliferative drug coating and provide scaffolding to treat recoil and dissection, before being gently reabsorbed back into the body to leave behind an arterial wall resistant to neoatherosclerosis, and have the ability to contract. The concept of a drug-eluting bioresorbable vascular scaffold with high resistive radial strength and swirling flow characteristics may provide a future for the SFA that addresses all of its unmet needs. ■