

What SFA Trials Would You Most Like to See?

Experts discuss key questions to answer, potential trial designs, and the likelihood that the trials will be undertaken.



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I would plan a trial to evaluate the management of TASC C and D lesions. Trial design would be relatively open, including both claudicants and patients with critical limb ischemia. It would also include all anatomic morphologies, such as concomitant common femoral disease, long-segment popliteal lesions extending to the tibial arteries, and severe calcification. Treatment would be the choice of the operator—bypass or any endovascular option that the clinician believed would be successful.

The challenge in this patient group is that there is no single correct answer, even among the endovascular options. Treatment could include drug-coated balloons (DCBs), drug-eluting stents (DESs), atherectomy, and stent grafts. Does long-segment stenting work over the long term or not? If it does, which patients should be considered? Is there a lesion length at which one should consider using DESs exclusively and abandoning bare-metal stents? A randomized trial of these competing technologies would likely be too complex and probably out of date when it concluded. Clinical experience indicates that the long-term patency of some complex endovascular reconstructions is poor. Among these disease morphologies, it would be a major advance if we could identify one that could be treated successfully with a specific endovascular technique or combination of techniques. Even if every question were not specifically answered, we would have a strong sense of which approaches were a complete waste of time compared with others. Why not randomize against bypass? The challenge here is in finding patients who are well qualified for open surgery and also willing to accept randomization.

The exact anatomic detail present in each patient would be indexed to the procedures performed to treat that disease. It is likely data would emerge on which group of patients would be better treated with one technique over another. Once these data became available, they would immediately influence practice. If there is a group of patients whose anatomy had uniformly poor results with all endovascular techniques, these patients could be considered for initial bypass. In summary, this would be a simple, real-world, readily applicable approach to a common clinical problem.



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There are three trial designs that might be of major interest:

- A randomized comparison between the United States–approved DCBs, In.Pact Admiral (Medtronic), and Lutonix (Bard Peripheral Vascular, Inc.), that evaluates femoropopliteal lesions including Rutherford classes 2 to 5. The two major endpoints of interest include efficacy expressed as primary patency and a combined safety endpoint that assesses rates of amputation, time to wound healing, and death in the Rutherford class 5 subcohort to gain insight into whether downstream paclitaxel particles affect patient outcome. This subcohort must be adequately powered.
- A randomized comparison between the Supera stent (Abbott Vascular), best-in-class DES (Zilver PTX [Cook Medical] or Eluvia [Boston Scientific Corporation]), which is not yet approved in the

United States), and In.Pact Admiral DCB in order to show potential equivalency in terms of patency and potentially identify lesion characteristics that fit best for each of the treatment modalities.

- For those who believe in a stentless approach to treatment of the superficial femoral artery (SFA): a randomized controlled trial comparing DCB versus spot treatment of residual stenosis/dissection with atherectomy, followed by DCB after predilatation of the entire target lesion with an appropriately sized plain balloon. The two endpoints of interest would be primary patency as an efficacy marker and rate of bailout stenting.



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I would like to see a study on the impact of intravascular ultrasound (IVUS) on clinical outcomes after endovascular treatment for symptomatic peripheral artery disease presenting as femoropopliteal lesions. Femoropopliteal revascularization using endovascular treatment is not yet standardized. Despite today's widespread use of stents in clinical practice, some practice guidelines still advise against primary stenting in patients with intermittent claudication due to femoropopliteal lesions. The patency rate after stenting has varied from report to report, and this variation is also seen with other treatment approaches, such as drug treatment and debulking. Variation in procedural quality is believed to be a major cause of these interreport differences. Incomplete assessment of lesion characteristics and selection of devices that are inappropriate in type and size would worsen clinical outcomes. Now that an increased number of patients are undergoing femoropopliteal endovascular treatment, standardization of therapeutic procedures is urgently needed.

IVUS, already clinically covered by insurance in Japan, enables detailed assessment of vessel characteristics. We previously performed a retrospective multicenter study that included 1,000 femoropopliteal lesions, which showed that use of IVUS was associated with improved clinical outcomes.¹ We would now like to prospectively investigate whether improvement in procedural quality with the use of IVUS would subsequently improve clinical outcomes after endovascular treatment for symptomatic peripheral artery disease presenting as femoropopliteal lesions.

1. Iida O, Takahara M, Soga Y, et al. Efficacy of intravascular ultrasound in femoropopliteal stenting for peripheral artery disease with TASC II class A to C lesions. *J Endovasc Ther.* 2014;21:485-492.



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Unfortunately, some elements of what I would consider to be the ideal future SFA trial are impractical and unlikely to be accomplished. But, it is worthwhile to discuss what future trials should include regardless of their practicality, as well as focus on what might be more realistic possibilities.

Overall, I would like to see more studies address real-world lesions but with the same type of rigor that we typically see in randomized trials (eg, core lab–adjudicated rather than self-reported lesion characteristics and outcomes). Right now, we are stuck primarily with data from approval trials that involve easy lesions and short-term follow-up using different points in the Kaplan-Meier analyses, which makes it difficult to compare the various strategies. Future studies should include lesions with moderate lengths of up to 20 cm. There should also be longer-term (2- and 3-year) follow-up—and not just standard Kaplan-Meier analyses wherein cases are counted as successful even if they haven't completed follow-up evaluation.

Finally, I would like to see a study include true, modern comparative arms so that we can attempt to compare different therapies in the SFA. The ideal trial would allow operators to select from different strategies based on their preference and experience. Although not randomized, it would include propensity score matching, use the same core lab adjudication for all cases, and have clearly defined duplex parameters and office visits. It is essential that all therapies be evaluated by duplex ultrasonography to define patency in addition to clinical performance. I believe freedom from target lesion revascularization is a poor way to evaluate outcomes.

The technologic approaches included in the ideal, current multiarm study would be vascular mimetic stents, covered stent grafts, DCBs (both alone and with atherectomy), DESs, and nitinol stents. Because of the large number of patients required to yield comparable results, it would be virtually impossible to conduct this trial in a randomized fashion. Another challenge of randomization in a study like this is that operators cannot be equally proficient in each therapy, which would

challenge both enrollment and optimally comparable results. However, even without randomization, if the patient groups are sufficiently similar, the operators are free to choose what they feel is optimal therapy, and each group has the same long-term, objective evaluation, such a study would give us very valuable information from which we could make some meaningful comparisons.



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Recent randomized controlled regulatory trials have studied the use of DCBs versus a control arm of balloon angioplasty for the treatment of SFA disease. These regulatory trial designs include strict inclusion/exclusion criteria that seek to maximize the odds of a successful outcome and subsequent regulatory approval. Although such trials have been successful in achieving regulatory approval, market access, and payer approval, they do not address the essential questions for clinicians: When should we use a specific treatment/device strategy in a particular patient/angiographic cohort, and what are the cost implications of one treatment strategy over another? Most clinicians no longer consider plain old balloon angioplasty a worthy comparator in these device trials.

Moreover, there has been a recent evolution in thinking regarding appropriate “vessel preparation” prior to DCB use. The use of atherectomy, rather than plain old balloon angioplasty, in combination with DCB is an attractive treatment algorithm, as suggested by the results of the DEFINITIVE AR trial, a small, randomized controlled investigation of DCB alone versus directional atherectomy plus DCB in long, calcified SFA lesions. However, the durability and cost implications of combining atherectomy (with or without distal protection) and DCB use in the treatment of complex lesions have not been evaluated. Furthermore, recent data from the Medtronic global registry of adjudicated DCB outcomes through 1 year suggest that treatment of complex, long, calcified lesions is associated with the approximate 25% requirement for provisional stent use.

As such, the SFA trial that I would like to see is a head-to-head comparison of two device treatment strategies: atherectomy plus DCB versus primary DES implantation

(ie, Zilver PTX). As the field matures, it is essential that all stakeholders including physicians, industry, the US Food and Drug Administration, and the Centers for Medicare & Medicaid Services be provided with data on both safety and clinical effectiveness, as well as cost-effectiveness signals for appropriate device use in specific clinical and angiographic cohorts. Importantly, the cost implication to patients, payers, and hospitals should be an essential element of all trials moving forward. Furthermore, it is important that the cost implication be tied to the durability of a device. Durability should be measured by the rate of clinically driven target lesion revascularization through at least 2 years and the angiographic pattern of restenosis that may further drive subsequent device use (ie, stent grafts, atherectomy devices). Evaluating these important factors is essential in moving our field forward.



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In our daily practice, we face complex real-world patients who are more frequently presenting with heavily calcified SFAs. It is not uncommon to see calcium starting at the bifurcation and going down to the knee joint. We see combinations of high-grade stenosis but also all lengths of chronic total occlusions. We know that we have to remove the calcium, so that DCBs can be effective.

I would like to see a randomized controlled trial comparing atherectomy and DCBs with lithoplasty and DCBs, so that a direct comparison would be available to give us an insight into the discussion about how best to treat heavily calcified arteries—removal or cracking.

The disadvantage of atherectomy is that with the current devices, we don't know how far we are going into the vessel wall and what additional injury we might cause. Lithoplasty does not cause vessel wall injury, but critics note that because the calcium remains in the vessel, the technology is not sufficient enough to warrant subsequent DCB treatment.

Regardless, I would like to see the results of this type of trial, as I am concerned about the high overall complication rate of atherectomy, especially if performed by inexperienced physicians. Lithoplasty has proven to be safe and is easy to perform, but additional research needs to show that it is better than atherectomy for DCB usage. ■