PANEL DISCUSSION

# Peripheral Drug Delivery Devices: Where Do We Stand?

Surveying the landscape of paclitaxel and sirolimus/everolimus devices for peripheral artery disease revascularization, with commentary on advantages and disadvantages and when each might be used, treatment algorithms for above the knee, the next wave of below-the-knee trial data, and the role of bioresorbables.

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**What do you see as the advantages and disadvantages of paclitaxel-based devices in peripheral artery disease (PAD) revascularization? And of sirolimus-based devices?**

**Dr. Holden:** We have clear, high-quality evidence that paclitaxel-coated devices are associated with superior and relatively durable patency compared to plain balloons and bare-metal stents (BMSs), and societal guidelines support a drug-eluting treatment strategy as definitive therapy for femoropopliteal disease. The potential additional benefit of vessel preparation devices is yet to be fully proven, and this is particularly relevant in complex disease, including chronic total occlusions and severe calcification. It is also yet to be proven if sirolimus-

coated devices will provide similar, durable results in the femoropopliteal segment; however, the primary endpoint results of the SIRONA trial are promising in that regard.[1]

The major disadvantage of paclitaxel-coated devices is the failure to prove a patency or clinical benefit in below-the-knee (BTK) disease. The same is true to date for sirolimus-coated devices outside of coronary metal and bioresorbable stents.

**Dr. Schneider:** We don't have anything in the infrainguinal arteries that comes close to the success of limus-based coronary drug-eluting stent (DES). Twenty years of work have been dedicated to demonstrate the value of paclitaxel; when delivered by balloon or stent to the femoropopliteal segment, it results in significant reductions in reinterventions. This is a track record of success earned by our entire field, and it sets a relatively high bar for patency in the femoropopliteal arteries that will be challenging to compete with. The paradigm of improved patency that can occur when pharmacologic agents are combined with our long-standing methods of mechanical treatment is one that we would like to repeat. However, this endeavor has not been straightforward. There is no evidence of increased mortality with paclitaxel, but there is still some doubt about whether there are local issues at the site of paclitaxel delivery. My own opinion is that if this occurs, it is in a very small number of patients.

The BTK space remains wide open to inventive solutions. Paclitaxel and sirolimus drug-coated balloons (DCBs) have not yet been proven in the tibial arteries, but the LIFE-BTK trial showed a benefit to everolimus (an analogue of sirolimus) delivery using an absorbable scaffold.[2] Paclitaxel is readily delivered to the arterial wall by transfer from a balloon, whereas sirolimus and analogues seem to work best when there is an implanted delivery vehicle, such as a stent or drug-eluting resorbable scaffold (DRS).

**Dr. Choke:** Paclitaxel-based devices have been consistently proven by large multicenter, randomized trials to be very effective in maintaining the patency of superficial femoral artery (SFA). It has potent antiproliferative properties, which means it is able to effectively inhibit the process of neointimal hyperplasia after the barotrauma of plain old balloon angioplasty (POBA). Its properties lend itself to being relatively easy to coat onto balloon catheters, and it can be readily transferred to diseased vessel wall.

However, the reason for its potent antiproliferative effect lies in its ability to induce apoptosis of cells (cytotoxic properties). Although the controversy regarding the paclitaxel mortality signal has largely been negated, some physicians may still harbor the lingering concern regarding the cytotoxicity of paclitaxel. The apoptotic action may also lead to the unwanted side effect of wall thinning and aneurysmal degeneration of the treated vessel. Paclitaxel-coated balloons (PCBs) have the potential to cause the slow-flow phenomenon as a result of particulate distal embolization, which can lead to thrombosis of distal vessels or distal tissue necrosis. Although effective for SFA, paclitaxel devices have had poor results for BTK lesions and are not currently approved by the FDA for BTK lesions.

Sirolimus, like paclitaxel, is also an effective antiproliferative agent. In addition, it also has potent antimigratory and anti-inflammatory properties. In the coronary arena, it is accepted that sirolimus-based stents are more effective than paclitaxel-based stents. Unlike paclitaxel, sirolimus is cytostatic rather than cytotoxic, and in the coronary arena, sirolimus devices have been proven to be safe. Sirolimus-coated balloons (SCBs) are known to have very little, if any, slow-flow phenomenon. As far as I am aware, there have been no reports of distal embolization from SCBs.

The disadvantage of sirolimus is that it is difficult to coat onto balloons, and it is challenging to effectively deliver it to the vessel wall. The available SCBs on the market are currently limited to MagicTouch percutaneous transluminal angioplasty (Concept Medical) and Selution (Cordis).

**Dr. Steiner:** Paclitaxel-based devices have demonstrated proven efficacy in femoropopliteal interventions, supported by a strong track record across multiple randomized controlled trials (RCTs) and registries. Due to rapid tissue uptake and a sustained antiproliferative effect, these devices effectively inhibit neointimal hyperplasia, particularly in fibrotic and in-stent restenotic (ISR) lesions. However, drug penetration may be limited in heavily calcified plaques. The clinical relevance of downstream distal embolization and positive vascular remodeling, which is occasionally associated with ectatic changes, remains under debate.

Sirolimus-based devices currently have limited long-term data in the peripheral vascular field. Hypothetical advantages include a more favorable safety profile, additional anti-inflammatory properties, and potentially greater efficacy in lipid-rich lesions. However, slower tissue uptake could pose a challenge, particularly in fibrotic or calcified lesions that have not been adequately prepared.

**Dr. DeRubertis:** There are potential advantages and disadvantages for both of these device classes, although

the benefits of each are yet unproven in the tibial vasculature, and data are still sparse for sirolimus-based devices in the femoropopliteal circulation.

With paclitaxel, one advantage is the long track record of good results. This is true in the multiple clinical trials that have demonstrated a clear class effect in the femoropopliteal circulation and in clinical day-to-day use in the hands of many interventionalists. There is little doubt that these devices are beneficial in terms of reducing reintervention in the femoropopliteal vessels. On the other hand, sirolimus-based devices may have the added benefit of anti-inflammatory properties and may have less downstream embolic material, which has implications for both reintervention and preservation of distal runoff.

Regarding disadvantages, the biggest failure of paclitaxel has been the numerous failed BTK paclitaxel DCB trials and the fact that there remains no FDA-approved BTK DCB, despite multiple attempts at proving their efficacy. With sirolimus, there are above-the-knee (ATK) and BTK data to support its use, but little of these data are from large RCTs. Another disadvantage of sirolimus-based DCBs is the fact that the hydrophobic nature of the drug requires more complicated delivery methods to advance the drug into the vessel wall, serving as a technical barrier to the development of an effective product.

## If both paclitaxel- and sirolimus-based devices are available on your shelves, are there patient or lesion factors that will make you lean one way or the other?

**Dr. Schneider:** It is very unlikely that a single drug will be the right one for each application, for different vascular beds, and with a variety of underlying pathologies. I would also not eliminate the possibility that additional different drugs should be considered, whether that is a different analogue of sirolimus (we already have everolimus in the BTK vasculature), a different antineoplastic or anti-inflammatory or anti-thrombotic, or a combination of these. The venous system will likely require a different approach because thrombosis, inflammation, and scar formation are so different from the arterial system.

At present, we are focused primarily on paclitaxel and sirolimus, and I believe that each will have a role. In-stent occlusion or ISR will likely be best treated with paclitaxel. Likewise, the inflammation and intimal hyperplastic response in dialysis applications will likely remain best treated with paclitaxel. Perhaps sirolimus will be more successful in the small BTK arteries where paclitaxel has so far failed. This remains to be seen. We may find that different types of plaque respond better to a different drug. We are treating a variety of pathologies, from calcified plaque to soft plaque, focal versus diffuse, bulky plaque in the intima versus thin plaque in the media, and everything in between.

**Dr. DeRubertis:** If both prove equally effective in eventual trials, the decision regarding which to use will likely be based on cost in many centers. However, there are probably some important lesion or patient characteristics that would influence this decision. One scenario that immediately comes to mind is patients with limited distal runoff where any distal embolic debris could severely impact outcome. While we never accept distal embolization recognized on completion angiograms without performing maneuvers to correct this situation, some embolization is difficult to appreciate, and there is evidence that microscopic embolization occurs with currently available DCBs and that this embolization can lead to muscle necrosis or other downstream effects.

**Dr. Steiner:** My treatment selection is generally guided by plaque morphology, lesion preparation, and patient-specific factors. PCBs remain a strong option in most cases due to their well-established and potent antiproliferative efficacy.

Emerging data support the use of SCBs in BTK disease, but comprehensive evidence, especially long-term outcome data, is still lacking. In cases of prior paclitaxel failure or suboptimal response, switching to an SCB-based strategy is a reasonable consideration, although the clinical rationale for doing so remains to be firmly validated.

**Dr. Choke:** In general, for the following reasons, my preference is SCBs over PCBs for both SFA and BTK lesions.

First, due to its different properties, sirolimus requires different technology (nanotechnology) compared to paclitaxel to achieve effective balloon coating and subsequent transference to the vessel wall. This means that it is more difficult to develop an effective SCB; however, a positive that has emerged from this technology is the lack of distal embolization and slow-flow phenomenon. The MagicTouch SCB uses the phospholipid carrier to deliver sirolimus, with a very noticeable absence of slow-flow phenomenon. This means that it is safe even when used in small, distal BTK arteries.

Secondly, sirolimus is cytostatic rather than cytotoxic (paclitaxel), and it has additional desirable biological properties, such as antimigratory effects on smooth muscle cells and anti-inflammatory effects.

For SFA, the SIRONA randomized trial has shown that SCBs are noninferior compared to PCBs.[1] It is fair to

say that use of PCBs BTK has been equivocal, with large RCTs showing negative results in the past. On the other hand, although still early, single-arm trials have reported promising results in BTK lesions for SCBs. Large RCT data of SCBs versus POBA for BTK should be available in the next few years and are eagerly awaited.

To summarize, I would use SCBs as first choice in all patients and lesions and reserve PCBs for recurrent lesions (SFA) that have failed to respond to SCBs.

When using PCBs for SFA lesions, I would be cautious in cases of highly calcific lesions. This is because drug transference across the calcium barrier is likely to be poor, with higher chance of distal embolization. I would also be cautious if the outflow is limited to only one BTK vessel, as thrombosis of this single outflow vessel may lead to a catastrophic situation.

**Dr. Holden:** In our current clinical practice, there are almost no patient or lesion factors that would deter us from using paclitaxel-coated devices in ATK intervention. Until we have a significant volume of quality clinical trial data with at least 2 years of follow-up (preferably randomized between paclitaxel-coated devices and sirolimus-coated devices), we will not replace the safe and effective therapy that paclitaxel-coated devices provide. I mention 2 years, and even longer, because the lipophilic properties of paclitaxel mean it is more bioavailable than sirolimus. Subsequently, SCBs require more complex technology to deliver and retain the drug in the vessel wall.

Of course, we are participating in some of those trials, so we do have the opportunity to use sirolimus-coated devices in that setting. In time, and with more data, efficacy, safety and cost will influence decision-making, although there may be patient and lesion factors that become apparent.

## With the controversy surrounding the paclitaxel early mortality association having been resolved, do you have any other safety concerns with either drug?

**Dr. DeRubertis:** The primary concern about currently available DCBs is probably the above-referenced issue regarding particulate matter and the potential for distal embolization. It is worth noting that recent paclitaxel investigational device exemption (IDE) DCB trials included only claudicants, and these devices have not been as well-studied in chronic limb-threatening ischemia (CLTI) patients, whose distal runoff is generally more severely diseased and more susceptible to catastrophic embolic events. However, in routine clinical practice, we use them regularly on CLTI patients, and there has been no signal in any large data set nor significant anecdotal experience regarding increased rates of tissue loss or amputation. With sirolimus, the safety concerns are probably less, considering the large therapeutic window of this drug and the fact that the next-generation excipients and microspheres used for drug transfer seems to have lower embolic risk. The biggest problem for sirolimus-based devices remains their largely unproven efficacy, not safety concerns.

**Dr. Holden:** I am delighted that the paclitaxel safety controversy has been resolved. Although there were some important lessons learned, particularly around trial design, the controversy came at a huge financial cost, delayed research, and exposed patients to the increased morbidity of reintervention.

In terms of any ongoing safety concerns with paclitaxel-coated devices, there have been concerns reported around distal particulate embolization and potential small vessel effects, such as fibrinoid necrosis. Although I have seen the slow-flow phenomenon in distal circulation after DCB angioplasty of long femoropopliteal lesions, this has fortunately not been associated in our experience with serious clinical sequelae. That said, if I have CLTI patients with limited BTK runoff and long femoropopliteal lesions, I consider alternate strategies to PCBs, including SCBs and DESs.

## In the SFA, how do you decide between using a DES and a DCB? Has this decision changed much over time?

**Dr. Steiner:** Treatment strategies—whether to deploy DES or pursue a DCB-first approach—must carefully weigh patient characteristics, lesion morphology, and angiographic results after lesion preparation and debulking using various devices. Short, focal lesions without significant vessel recoil after angioplasty are ideally managed with DCBs to preserve future treatment options. In contrast, longer lesions, post-PTA dissections, suboptimal immediate results, or heavily calcified segments often require definitive scaffolding using newer-generation DES or dedicated interwoven/biomimetic stents after adequate plaque modification.

Clinical presentation further guides device selection. In patients with lifestyle-limiting claudication, concerns about progression to CLTI have made the "leave-nothing-behind" philosophy especially attractive. Avoiding stent implantation whenever technically feasible could mitigate this risk, although it remains unclear whether adverse outcomes stem from stenting or from angioplasty-induced vascular injury. At the same time, improving walking capacity to promote physical activ-

ity is vital not only for symptom relief but also for overall cardiovascular health.

In patients with CLTI, the threshold for choosing a stent-based strategy is lower. Complex or heavily diseased segments in this cohort carry a high likelihood of recoil or flow-limiting dissection, making mechanical support with DES an often fast and reliable option.

**Dr. DeRubertis:** I have never been a large proponent of permanent scaffolds, especially when used to line long segments of the lower extremity peripheral circulation; so for me, I almost always prefer DCB over DES, and this has not changed much over time. When the need for stenting arises due to dissection or recoil following my use of a DCB, then I will either use DES or, more commonly, an interwoven stent as a bailout, with the goal of limiting the permanent implant length as much as possible. The use of intravascular ultrasound (IVUS) can help with the latter issue of minimizing stent usage to the areas that absolutely require it.

**Dr. Choke:** My approach with SFA is to leave nothing behind where possible. The issue with putting stents in SFA is that there will be a proportion of such patients who will return with ISR or occlusions. While not a technically challenging problem to treat, ISR is an expensive problem, frequently requiring atherectomy devices to fully treat it. It is also fraught with low patency rates and thus high recurrence rates once ISR sets in.

I will therefore use a DCB for SFA lesions and stop at that if the results are satisfactory. I will use DES if there is a flow-limiting dissection requiring a mechanical solution with a scaffold or if IVUS shows unsatisfactory luminal gain after POBA. Another indication to use DES is for returning patients who present with restenosis after using DCB.

**Dr. Holden:** Our ATK treatment algorithm has not changed greatly over the last decade. We use POBA as vessel preparation, dilated to nominal diameter, and assess the result to decide on which drug-eluting strategy to use. In cases where there is no significant recoil, residual stenosis, or dissection, we use DCB. For cases with significant residual stenosis, we use DCB. Outside of clinical trials, we reserve other vessel preparation devices to calcified lesions (where we mainly use intravascular lithotripsy) and eccentric lesions with recoil (where we may use directional atherectomy).

Recently, I was able to present a soon-to-be published meta-analysis of proportions reviewing a large number of patients in clinical trials who underwent SFA stenting.[3] Excellent results were shown for the polymer-based paclitaxel-coated stent at both 1 and 2 years, and these data may alter my threshold for DES in cases with equivocal results after POBA.

**Dr. Schneider:** In general, I have been in favor of scaffold avoidance where possible. One of the outstanding features about paclitaxel is its ability to be readily delivered by balloon. My general approach is to perform aggressive vessel preparation and reevaluate the lesion and the lumen. If after vessel preparation these are satisfactory, I generally support use of a DCB. On the other hand, if the lesion and lumen are unsatisfactory and there is extensive residual stenosis, dissection, or other factors requiring a scaffold, I would proceed with DES. Of note, recent data have shown further benefits for DES in comparison to DCB. This was a little bit of a surprise for me, as we have had DES now for many years. Nevertheless, the Sports trial and a recent DCB/DES/BMS/percutaneous transluminal angioplasty meta-analysis showed superior patency for a paclitaxel stent at 2 years.[4,5]

## BTK disease so far has proven to be beyond the reach of the DCB effectiveness observed in the SFA and popliteal segments, with several trials and technologies coming up short. How likely do you think it is that the next wave of trials using new formulations and device designs show better results?

**Dr. DeRubertis:** These prior failures of BTK DCB trials have been disappointing and are concerning for future device trials. However, designing a clinical trial for the BTK space is challenging, and some of these failures may have had less to do with a device's biologic efficacy and more to do with trial design and the need to develop trial endpoints that reflect both clinical success and device effects. I believe that we have learned a considerable amount from recent successful trials and am hopeful that we can use these lessons to help demonstrate the biologic efficacy of some of these devices.

**Dr. Schneider:** The BTK population is complex enough that showing the benefit of a single device will remain complex. In general, a population that is healthy enough for proper inclusion in a BTK trial tends to be only a subset of those we see with CLTI. I think we are slowly developing a formula for this challenge, which will help pave the way for additional device approvals. The development and regulatory timelines are many years in length, and iteration seems painstakingly slow at times; we are also facing what feels like an increasing clinical challenge posed by large numbers of patients with very

aggressive disease. We currently have several trials using drug delivery in the BTK space with SCBs and PCBs as well as limus-based DRS. I am optimistic that what we have learned about devices and trial design from the first generation of studies will help us navigate with greater success in the current wave of development.

**Dr. Steiner:** BTK disease remains particularly challenging due to pronounced patient and plaque heterogeneity, with various forms of intimal and medial calcification frequently limiting the effectiveness of drug-eluting technologies. In this setting, vessel recoil—rather than neointimal hyperplasia—often plays a dominant role in restenosis, diminishing the standalone efficacy of drug-based therapies. These complexities must be carefully considered in the design and interpretation of clinical trials.

Despite these challenges, there is meaningful potential for progress in BTK revascularization. Advances in drug delivery platforms, such as microreservoirs and sustained-release coatings, may help overcome limitations like short drug-tissue contact and rapid washout. Additionally, combination strategies, including incorporating dedicated lesion preparation, BTK-specific DCBs, and spot stenting with DRS, may be necessary to achieve optimal clinical outcomes.

Although a definitive shift in clinical practice is still likely several years away, the outlook is far more promising than it was just 5 years ago. However, it is essential to recognize that these advanced technologies come at a high cost, and ensuring equitable access to care will be just as critical as the technologic innovation itself, especially for this often-underserved and socioeconomically disadvantaged patient population.

**Dr. Holden:** The failure of DCB technology (and a number of other devices) in BTK disease is, at least in part, due to two things: limitations in trial design and in device design. In terms of trial design, the LIFE-BTK trial has provided some important lessons, including the careful design of safety and effectiveness endpoints, having the control arm being a "real-world" comparator, use of objective wound photography, and use of imaging to better characterize vessel patency. The adoption of these and other learnings will increase the likelihood of positive future trials.

In addition, there are exciting ongoing developments in DCBs and other devices to address some of the unique challenges in BTK disease, including late recoil, intimal and medial calcification, and optimized antirestenotic therapies. I believe more positive results are in the pipeline!

**Dr. Choke:** For BTK disease, RCTs of PCBs have mostly reported disappointing results in patency rates. Paclitaxel, when used for BTK lesions, may even be harmful in terms of tendency toward higher rates of amputation compared to POBA.[6,7] Distal embolization of paclitaxel particulate has been suggested as a possible reason for the poor outcomes in BTK lesions.

Early single-arm trials have reported promising results for SCBs in BTK lesions, but this remains to be confirmed by randomized trials. There are currently multiple ongoing randomized trials comparing SCBs versus POBA in BTK lesions.

In my opinion, there is a good chance that SCBs will be proven effective in BTK lesions by these randomized trials because of the following reasons:

- In addition to its antiproliferative properties, sirolimus also has anti-inflammatory properties, as it was initially developed as an immunosuppressive drug. This may give it an additional potency for BTK lesions compared to paclitaxel. BTK lesions are associated with diabetes and CLTI, whereas the SFA lesions previously investigated in PCB trials were associated with smoking and claudication; thus, the biology of BTK and SFA lesions may be different. Although purely hypothetical, this may be a possible reason for the differential effectiveness of PCBs for SFA lesion but not BTK lesions. Hopefully, sirolimus can overcome the BTK challenges with its additional anti-inflammatory actions.
- Additionally, use of SCBs does not confer a significant risk of distal embolization, thereby making it a safe option for BTK lesions. BTK lesions are more unforgiving compared to SFA lesions, with a lower threshold for thrombosis, and they do not respond well to distal embolization.

## What role do you see bioresorbables with antiproliferatives playing both BTK and ATK? Will they disrupt the current paradigm of permanent stents and balloons, and if so, what will drive wider adoption?

**Dr. Holden:** The positive primary endpoint results reported in the LIFE-BTK trial with subsequent FDA approval of Esprit (Abbott) stimulated a great deal of interest in DRSs in BTK disease, and several further randomized trials are now currently recruiting. It is also encouraging that promising cost-effectiveness data have been presented.[8] There are outstanding questions, such as whether the trial results can be replicated in clinical practice and where DRS fits into a BTK endovascular algorithm. One often-raised question is whether primary DRS is superior to the prior standard strategy of POBA with provisional DES.

The recent success of DRS in BTK disease has also renewed interest in ATK disease. There is no doubt that the combination of an acute scaffold and drug for restenosis and ultimately leaving nothing behind is at least as attractive in the mobile femoropopliteal segment as it is BTK. Recently, the first clinical results from the Efemoral DRS (Efemoral Medical) used in ATK disease were presented.[5] I hope these positive results will stimulate more research activity in this important space.

**Dr. DeRubertis:** While there are some interesting technologies being investigated for the ATK space, the BTK area is where these devices have clearly been shown to be effective. With the success of the LIFE-BTK trial, we now have a device that has been shown to be superior to the dominant percutaneous modality over the last 40 years: balloon angioplasty. This fact alone makes these devices game-changing in the BTK space, where they have the potential to improve patency, reduce reintervention rates, and increase wound healing and limb salvage. At least BTK, I believe they should become the dominant treatment paradigm, provided the patient has appropriate anatomy. Going forward, one of the primary drivers of increased adoption will likely be the demonstrated results of these devices when used in patients with more complex anatomy than those included in the RCTs.

**Dr. Choke:** Everolimus-eluting resorbable scaffolds have been proven to be effective for BTK lesions.[2] Esprit is not yet widely available in many countries, so experience is still limited. As such, we have not yet seen a disruption of the current paradigm of treatment algorithms. Nevertheless, with the positive data, it is likely that with increased availability and real-world experience, new treatment algorithms incorporating DRS will be developed. As most BTK lesions are long, I believe a longer DRS would be advantageous in driving a wider adoption.

## Outside of the drugs and devices themselves, what kind of impact might new BTK trial designs, endpoints, and follow-up protocols have compared to the trials of the previous decade?

**Dr. Choke:** The endpoint of any BTK trial should be focused on what the device is intended to achieve. Endovascular devices mostly have one objective, and that is to keep the treated BTK artery patent for as long as possible. The endpoint should therefore be primary patency alone, defined as angiographic- or duplex-defined absence of stenosis or occlusion, in the absence of any target lesion revascularization. Composite endpoints should be avoided, as this introduces other variables that are not related to the device being investigated.

For example, SCBs are hypothesized to improve patency rates of BTK lesions compared to POBA, but it would be a step too far to also expect SCBs to reduce major limb amputations or improve wound healing.

It is understandable that regulatory bodies may want a translation into clinical benefits, but in reality, there are "compensatory events" that can lead to equivalent amputation and wound healing between SCB and POBA. To compensate for reduced patency rates in the POBA group, the physician will normally reintervene with repeated angioplasty procedures to save the limb, and so limb outcomes may still be the same between SCBs and POBA.

**Dr. Schneider:** The idea that we would have a similar paradigm as for the SFA (eg, a comparative trial around a single lesion in a patient with reasonable life expectancy) is clearly a thing of the past. We have learned, mostly the hard way, that it will not be simple to study patients with BTK disease.

There are a few notable developments in the current thinking about BTK trials. We are a lot more focused on wound healing rather than limb salvage alone. A wound core lab is typically included in any sophisticated study. There is more focus on hemodynamics. There is wide recognition that ankle-brachial index is not adequate and other types of hemodynamic measurements, such as toe-brachial index, are being employed. Having said that, there is still widespread dissatisfaction with our ability to get immediate, reproducible, point-of-care assessment of hemodynamics. The use of follow-up duplex ultrasound has evolved toward an assessment of peak systolic velocity (PSV), rather than just an evaluation of whether the artery remains open or has occluded. Not long ago, we could not recruit sites that were willing and able to deliver PSV. Now, many sites are collecting PSV as a more accurate method of assessing the patency of the vessel. Patient quality of life has taken on new emphasis, as well as an increased interest in patient-reported outcomes. Dialysis patients have not typically been included in IDE trials in the past, but a concerted effort is being made to include them. In every trial, numerous secondary endpoints are being included, and this is very appropriate for understanding this complicated group of patients. The FDA has also been helpful in recognizing the challenges and in introducing some flexibility to the process.

**Dr. Steiner:** One of the most pressing needs in BTK research is the adoption of more pragmatic trial designs that truly reflect the broad spectrum of patients encoun-

tered in clinical practice. Many current trials continue to exclude individuals with end-stage renal disease (ESRD), despite this group comprising a substantial and clinically relevant segment of the BTK/CLTI population. Excluding such high-risk patients limits our ability to evaluate how therapies perform where they are often most needed.

Equally important is a more thorough and systematic characterization of patients enrolled in trials. Key comorbidities, such as heart failure, ESRD, frailty, and advanced age, must be better captured to allow for more accurate subgroup analyses, risk stratification, and a deeper understanding of treatment effects in heterogeneous patient populations. Without this granularity, the generalizability and clinical relevance of study findings remain constrained.

In parallel, modern imaging and diagnostic technologies should be incorporated into study protocols. Innovations such as photon-counting CT may significantly enhance the assessment of vessel wall structure and plaque composition. Likewise, the development and use of quantitative flow and perfusion metrics can help move beyond purely anatomic endpoints (like binary restenosis) toward more meaningful physiologic and functional outcome measures.

Taken together, broader inclusion criteria, improved patient characterization, longer and adaptive follow-up, and integration of advanced imaging technologies have the potential to reshape the clinical evidence base for BTK therapies and bring more relevant, real-world solutions to the patients who need them most.

### Whether ATK or BTK, balloons versus stents, or any other combination, what is the head-to-head trial you most want to see?

**Dr. DeRubertis:** I think an intriguing study would be a three-arm BTK trial involving DCB alone, DCB plus atherectomy, and DRS. Most of our large trials are aimed at device approval; very few actually help us define actual therapeutic strategy. A trial like this might be able to solve that.

### Looking down the road 5 years or so, what does this market look like? What new options might be available, either BTK or ATK?

**Dr. Steiner:** In my opinion, the next 5 years will bring several key developments that will reshape the treatment of PAD. I expect SCBs to gain expanded indications in both ATK and BTK territories, supported by growing clinical evidence. Therapy will likely become more individualized, with imaging-based plaque characterization guiding the choice of device and strategy based on lesion- and patient-specific factors.

I also foresee broader adoption of DRS and hybrid approaches—such as combining DCBs with temporary scaffolding—to balance mechanical support with long-term vessel preservation. Enhanced lesion preparation with technologies such as intravascular lithotripsy and atherectomy is likely to become even more routine than it is today, particularly prior to DCB use in heavily calcified lesions, where optimal vessel modification is essential for effective drug uptake and long-term patency.

Additionally, I believe artificial intelligence will increasingly support procedural planning, especially in complex and multilevel PAD cases, helping to optimize device selection, treatment strategy, and procedural efficiency. Overall, I hope to see a continued shift toward durable outcomes, minimal use of permanent implants, and enhanced vessel healing—all aimed at improving long-term patient benefit and reducing the risk of disease progression.

Equally important, in my view, is a stronger focus on early identification and aggressive risk factor modification in patients at highest risk of progressing to CLTI. Medical intervention, including optimized management of diabetes, hypertension, lipid profiles, smoking cessation, and antithrombotic therapy, must play a central role alongside endovascular strategies to meaningfully improve outcomes across the full spectrum of PAD.

**Dr. DeRubertis:** I would be surprised to see major technology-driven changes to our current ATK treatment paradigms, as there are currently many options for femoropopliteal disease, and our treatment strategies have matured over the last decade. This is not true BTK, and the dominant treatment strategies are still POBA and atherectomy. I believe that over the next 5 years, we will see a considerable uptake of DRSs. However, I think the combination of DRS and DCB will ultimately prove to be the optimal BTK strategy, and only when some of these BTK DCBs become available will DRS adoption become maximized.

**Dr. Holden:** In terms of the next 5 and even 10 years, it is likely that angioplasty balloon-based therapies, stents, or scaffolds and antirestenotic drugs are likely to dominate the ATK and BTK space. What we will see in that period is clarity on the relative value of paclitaxel-coated devices, limus-coated devices, or even a combination or both for ATK and BTK disease. We're also likely to get more clarity on the value of vessel preparation devices, including the management of vessel calcification. For BTK disease, I hope we make strides in management of patients with small vessel disease, including the benefit or otherwise of deep venous arterialization.

In the longer term, I believe the treatment options are likely to be very different, assisted by artificial intelligence and including a range of disease-modifying therapies. ■

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*Disclosures*

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