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DRUG-ELUTING TECHNOLOGIES

Choosing the Best Option Through Data-Informed Decision Making



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BY MICHAEL R. JAFF, DO



When comparing the myriad options available for the treatment of patients with peripheral artery disease (PAD) today compared to just 1 decade ago, it is a testimony to physicians who have advocated for their patients and to innovators dedicated to advancing the field. Although these technological advances provide hope for the rapidly expanding population of patients with claudication or critical limb ischemia,¹ the selection of optimal strategies by physicians has become challenging. With the publication of important comparative trials of one technology versus another, we are finally gaining prospective, multicenter, and, in some cases, randomized data to help us make better choices.

The major classes of endovascular technologies, including percutaneous transluminal angioplasty (PTA), bare-metal balloon-expandable and self-expanding stents, fabric-covered stents, and atherectomy (directional, rotational, and laser), have all demonstrated various degrees of efficacy and acceptable safety for patients. However, it has been the advent of drug-eluting technologies, including drug-eluting stents (DESs) and drug-coated balloons (DCBs), that has rapidly influenced the decisions of endovascular specialists.

DCBs have demonstrated significant improvements in primary patency and target lesion revascularization (TLR) rates when compared to uncoated PTA catheters in high-quality, multicenter, prospective randomized controlled trials.^{2,3} In addition, recently published 5-year data comparing DESs to PTA or uncoated self-expanding stents have given specialists confidence in drug-eluting technology due to durable superiority in patency and TLR.⁴

There remains confusion, however, regarding the role of DESs versus DCBs in the management of PAD. Some advocate for initial therapy with a DCB, promoting the “leave nothing behind” concept and allowing for simpler revascularization options should restenosis occur. Others believe that for longer lesions or more complex, heavily calcified atherosclerotic plaques, DESs will offer superior primary patency. Until prospective randomized trials comparing these two classes of devices are reported, we are left with best efforts at clinical decision making for individual patients.

Scientists have studied mechanisms and dosing of drug-delivery in order to determine optimal device development.

It does appear that strategies to prolong exposure of therapeutic antirestenosis drug levels may offer clinical advantages, at least in animal models.⁵ These data may advance the development of next generations of drug-eluting technologies.

Although we are moving closer to understanding which device strategies to use in which patients, there remains a significant knowledge gap that, until closed, will promote expert opinions, consensus, and individual patient assessments for the selection of treatment strategies. There is no doubt that in addition to patency and TLR reduction data, cost effectiveness will play an impactful role in decision making at the provider and system levels. As the cost-effectiveness data arise, TLR appears as the major driver of added costs.⁶ However, the ultimate algorithm for the treatment of PAD remains elusive.⁷ ■

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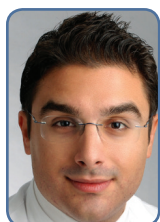
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Interim Results From the Muenster Postmarket All-Comers Registry

A look at the latest data on use of the Eluvia drug-eluting stent in challenging SFA lesions.

BY THEODOSIOS BISDAS, MD, PhD



The atherosclerotic superficial femoral artery (SFA) remains one of the best investigated vascular territories in the human body. However, the vessel's characteristics and its exposure to external forces, especially near the knee joint, compromise the effectiveness of the currently available treatment strategies.¹ Traditional plain balloon angioplasty has shown a high restenosis rate (up to 60% at 12 months), and it cannot be further legitimized as standalone therapy for treating the SFA.² Similarly, the midterm outcomes of bare-metal stents did not confirm the initial enthusiasm for this approach due to considerably low patency rates, especially in long lesions.³

The introduction of drug-coated balloons (DCBs) with the concept of paclitaxel delivery into the arterial wall led to an effective prevention of intimal hyperplasia and restenosis.² However, the pharmacokinetic effect is highly variable between devices, which may influence the durability of this strategy. Still, any effort to leave nothing behind remains the recommended first-line approach in the SFA.

Nonetheless, two issues continue to limit the applicability of this strategy: (1) the lower penetration rate of paclitaxel through calcified lesions (severely calcified lesions are a barrier for the delivery of paclitaxel into the adventitial layer) and (2) the increased need of bailout stenting in chronic total occlusions and long lesions (> 15 cm). Fanelli et al confirmed the lower patency rate of DCB angioplasty in areas with a greater calcium burden.⁴ In such cases, removal of the calcium by atherectomy or the use of primary stenting to address recoil remain mandatory.⁵ In addition, DCB registries, which included all-comers and more challenging lesions, revealed a higher bailout stenting rate (up to 50%) when the length and severity of the lesions were greater.⁶ It should be noted that all randomized controlled trials studying DCBs have excluded patients with suboptimal

angioplasty, and thus the true rate of bailout stenting in these trials is unclear. Hence, the question is: if the approach of leaving nothing behind is not feasible, which is the best device to leave in the SFA?

DRUG-COATED STENTS

Based on the currently available evidence, drug-coated stents (eg, Zilver PTX, Cook Medical) are a good alternative to leave behind.⁷ Drug-coated stents combine the antiproliferative role of paclitaxel and the mechanical support of a bare-metal stent, with the drug directly coating the stent metal. Drug-coated stents showed promising long-term outcomes in short lesions,⁷ but a high restenosis rate in real-world and more challenging lesions.⁸ A possible explanation for this finding is that the release of the drug with drug-coated stents is completed within 1 month, while it is well known that the peak time of restenosis in the SFA reaches 12 months.⁹

Eluvia Stent

In contrast to drug-coated stents, the Eluvia stent (Boston Scientific Corporation) is the first drug-eluting stent that aims to follow the course of SFA restenosis and to increase vessel patency with controlled and prolonged release of paclitaxel for more than 12 months. The unique technology of the stent includes a dual-layer coating, which utilizes a primer n-butyl methacrylate (PBMA) layer that promotes adhesion of an active layer of paclitaxel and polyvinylidene fluoride-hexafluoropropylene (PVDF-HFP) onto the stent.¹⁰ This combination enables controlled and sustained elution of the drug over time. PBMA+ PVDF-HFP is a biocompatible and stable polymer that is currently used in the coronary everolimus-eluting stents (Xience V, Abbott Vascular; Promus, Boston Scientific Corporation), with well-established and proven safety and effectiveness results.

In regard to the stent design, the Eluvia stent is built on Boston Scientific's commercially available Innova self-expanding nitinol stent platform. A 6-F, low-profile, triaxial delivery system enables easy and accurate stent implantation. The stent architecture combines a closed-cell design at each end of the stent for precise deployment and an open-cell design for increased flexibility and fracture resistance.

Eluvia Versus Zilver PTX

The Eluvia stent is designed to provide the following advantages compared to the Zilver PTX stent:

- It includes a unique technology of drug-elution that sustains drug release in order to match the restenotic process in the SFA.
- The polymer is highly biocompatible with proven clinical safety.
- The Eluvia stent is built on the Innova stent platform, which was designed for the SFA with greater strength, flexibility, and fracture resistance.

However, the head-to-head comparison between drug-coated and drug-eluting stents in the framework of the prospective randomized controlled IMPERIAL trial will highlight the impact of polymer and will confirm or disprove the aforementioned advantages.

MAJESTIC TRIAL

At present, the effectiveness of the new concept and the safety of the Eluvia stent in humans are being studied in the prospective, core lab–adjudicated MAJESTIC trial.¹¹ In this multicenter, single-arm study, 57 patients (Rutherford category 2–4) underwent implantation of the Eluvia DES at 14 vascular centers. The mean lesion length was 71 ± 28 mm, with involvement of the distal SFA and proximal popliteal artery in 86% of the patients. Of note, 65% of the lesions were determined by the core lab to be severely calcified, and 46% of the lesions were total occlusions. Freedom from target lesion revascularization (TLR) at 2 and 3 years was 93% and 85%, respectively. Moreover, no stent fractures were reported, and clinical improvement was observed in 91% of the patients at 2 years.

PRELIMINARY RESULTS OF THE MUENSTER POSTMARKET REGISTRY

The MAJESTIC trial demonstrated the efficacy of the stent in relatively short lesions, but the performance of the device in real-world patients has not yet been investigated. For this reason, we analyzed our prospectively collected data between March 2016 (when the stent first became available

TABLE 1. PATIENT SYMPTOMATOLOGY AND LESION CHARACTERISTICS IN THE MUENSTER POSTMARKET REGISTRY

CHARACTERISTICS	NO. OF PATIENTS
Symptoms	
Rutherford stage 3	32 (52%)
Rutherford stage 4	14 (23%)
Rutherford stage 5	10 (16%)
Rutherford stage 6	6 (10%)
Lesion	
Mean length (in mm)	199 ± 107
Minimum lumen diameter (mean, in mm)	0.06 ± 0.17
Occlusion	49 (79%)
Moderate/severe Ca ²⁺	26 (42%)
Location	
Proximal SFA	33 (53%)
Middle SFA	43 (69%)
Distal SFA	47 (76%)
P1 segment	27 (44%)
P2 segment	2 (3%)
Run-Off Status	
0 vessels	1 (2%)
1 vessel	11 (18%)
≥ 2 vessels	50 (80%)

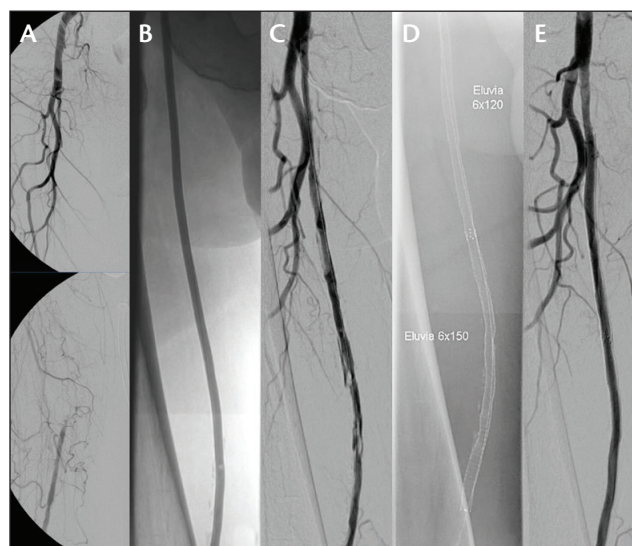


Figure 1. Case presentation of an occlusion of the right SFA (26 cm) in a man with Rutherford stage 5 disease (A). Predilatation with a 5-X 250-mm balloon catheter resulted in a flow-limiting dissection across the SFA (B, C). Implantation of two Eluvia stents (6 X 150 mm and 6 X 120 mm) (D) and completion angiography (E).

on the market) and April 2017. The study was a single-center, single-arm study that included 62 consecutive patients (39 men, 23 diabetics) undergoing implantation of the Eluvia stent. The indication for stent implantation was any subop-

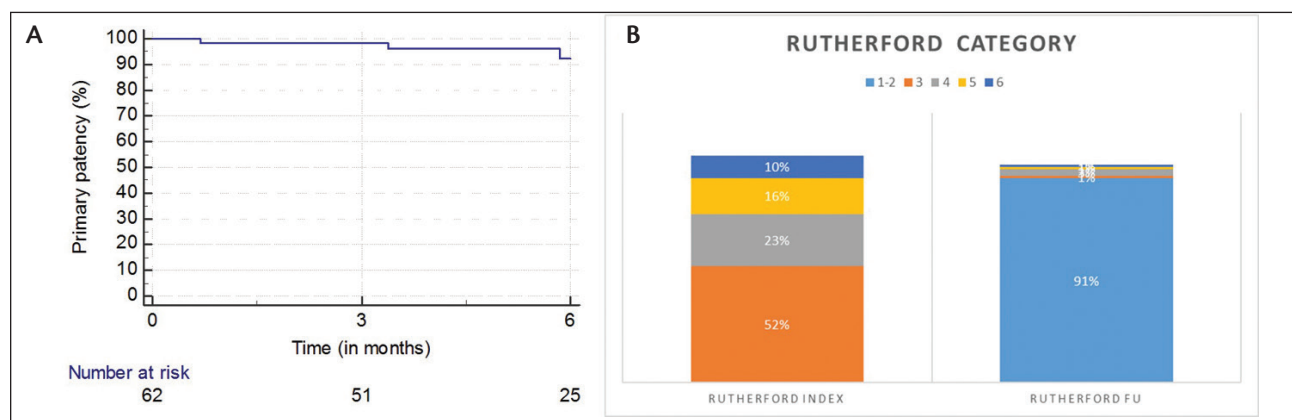


Figure 2. Primary patency at 6 months (A) and improvement of Rutherford clinical category at index and at 6 months follow-up in the Muenster postmarket registry (B).

timal angioplasty (flow-limiting dissection or recoil > 50%) after plain balloon angioplasty in 1 cm less than the nominal vessel diameter (Figure 1). Patients with in-stent or bypass stenosis, as well as those with acute limb ischemia (< 4 weeks), were excluded from this study. All patients underwent clinical examination and duplex ultrasound at 6 months, with repeat assessments planned at 12 months.

The primary endpoint of the study was primary patency, defined as freedom from significant restenosis (peak systolic velocity ratio > 2) or occlusion without any reintervention based on duplex ultrasound evaluation. A total of 104 stents were implanted in 62 patients. Table 1 provides the symptomatology of the patients and relevant angiographic characteristics of the included lesions. The average lesion length was nearly 20 cm, 79% of the lesions were total occlusions, and 42% of the lesions were severely calcified. The preliminary results showed a primary patency rate of 93% at 6 months (Figure 2), and 91% of the patients returned to Rutherford stages 1 or 2. Three occlusions were observed. No stent fractures were found on x-ray at 6 months. Secondary patency at 6 months was 96% (number at risk, 25), and freedom from TLR was 93% (number at risk, 28). Two patients, one with severe Rutherford stage 6 disease and a skin infection and another with Rutherford stage 6 disease and a traumatic injury underwent major amputations despite having patent stents.

CONCLUSION

Despite the efforts to leave nothing behind after endovascular treatment of the SFA, there is still a considerable

number of lesions that require bailout stenting. Due to the proven efficacy of paclitaxel, use of the Eluvia stent could be the most effective solution for treating the SFA. In this context, the first test of the Eluvia stent in our all-comers registry, and with the very challenging nature of SFA lesions, showed encouraging 6-month performance. ■

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Twelve-Month Results From the RANGER-SFA Trial

What these findings tell us about the safety and efficacy of the Ranger drug-coated balloon.

WITH DIERK SCHEINERT, MD

Twelve-month results from the RANGER-SFA trial were presented by Professor Dierk Scheinert, MD, at the 2017 Charing Cross Symposium in London, United Kingdom. Prof. Scheinert serves as Principal Investigator of the RANGER-SFA trial. The first-in-human RANGER-SFA trial is a multicenter randomized controlled trial evaluating the Ranger paclitaxel-coated percutaneous transluminal angioplasty (PTA) balloon catheter (Boston Scientific Corporation) for the treatment of lesions in the superficial femoral artery (SFA) and popliteal artery. The trial was designed to prove that the Ranger drug-coated balloon (DCB) is superior to uncoated PTA balloons as assessed by duplex ultrasound at 12 months postprocedure.

METHODS

The investigators enrolled 105 patients with femoro-popliteal artery lesions at 10 sites in Germany, France, and Austria. Patients were randomized 2:1 to treatment with the Ranger DCB (n = 71) or to the control therapy (n = 34). Follow-up will be conducted through 3 years.

TWELVE-MONTH RESULTS

In the Ranger DCB group, 59 patients returned for 12-month follow-up. In the control group, the 12-month follow-up visit was completed for 28 of 34 patients. Patient and lesion characteristics were similar between the Ranger DCB and control groups. Technical and procedural success rates were also similar between the two groups.

At the Charing Cross Symposium, Prof. Scheinert reported superior 12-month primary patency and freedom from target lesion revascularization (TLR) rates for the Ranger DCB group as compared with the control group. The Kaplan-Meier estimate of the 12-month primary patency rate for patients treated with the Ranger DCB was 86%, which is significantly greater than that observed for patients treated with control balloons (56%). Likewise, freedom from TLR was greater for the Ranger DCB group than the control group at 12 months (Kaplan-Meier estimate, 91% vs 70%). Prof. Scheinert has previously reported that Ranger met its 6-month primary endpoint with significantly



"The rates of primary patency and freedom from target lesion revascularization are amongst the highest observed in this type of first-in-man trials

at 1 year. As a clinician, it is important to have a treatment option like the Ranger drug-coated balloon that exhibits consistent performance and outcomes; for patients, these attributes impact their quality of life, such as alleviating pain and discomfort, as well as reducing the probability of repeat procedures."

—Dierk Scheinert, MD
Professor of Angiology
Head, Department of Angiology
University Hospital Leipzig, Germany
Principal Investigator of the RANGER-SFA trial

cantly less late lumen loss (LLL) for the Ranger DCB group as compared with the control group.¹ LLL of +0.76 mm was observed at 6 months for the control group compared with -0.16 mm for the Ranger DCB group ($P = .0017$).

The rates of adverse events and serious adverse events were similar in the two groups, with no target limb amputations and no deaths related to the device or procedure by 12 months. The investigators concluded that patients treated with the Ranger DCB demonstrated significantly higher rates of primary patency and freedom from TLR at 12 months versus patients in the control group. ■

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Economic Analysis Supporting the Use of Drug-Eluting Technologies in the Femoropopliteal Artery

These evolving modern therapies are showing promise in reducing health care costs while offering better outcomes.

BY KONSTANTINOS KATSANOS, MSc, MD, PhD, EBIR



Drug-eluting stents (DESs) and drug-coated balloons (DCBs) are increasingly being used in the femoropopliteal artery based on solid evidence from several large-scale, multicenter, randomized studies investigating local delivery of paclitaxel to inhibit neointimal hyperplasia and improve clinical outcomes of infrainguinal interventions.^{1,2} Contrary to the sirolimus family of drugs and its analogues that have dominated percutaneous coronary interventions, paclitaxel has become the mainstay drug for inhibition of postangioplasty vascular restenosis in the above-the-knee arteries.^{2,3} DESs combine drug delivery with a metal scaffold that eliminates vessel recoil and maximizes immediate lumen gain and are best suited for the treatment of complex occlusive disease, whereas DCBs offer a balloon-based drug delivery option for the treatment of simpler disease without leaving any permanent implants behind.³

CLINICAL AND COST-EFFECTIVENESS ANALYSES

Some analyses have recently been published exploring the impact of wider adoption of drug-eluting technologies on the budgets of government-funded health care systems. For the case of the National Health System in the United Kingdom, one model involved pooling of 28 clinical studies encompassing 5,167 femoropopliteal artery lesions (mostly claudicants; critical limb ischemia in 15%–20%) with a time horizon of 2 years.⁴ As expected, a significant reduction in the rate of target lesion revascularization (TLR) up to 24 months was noted with the use of drug-eluting technologies, driving TLR rates

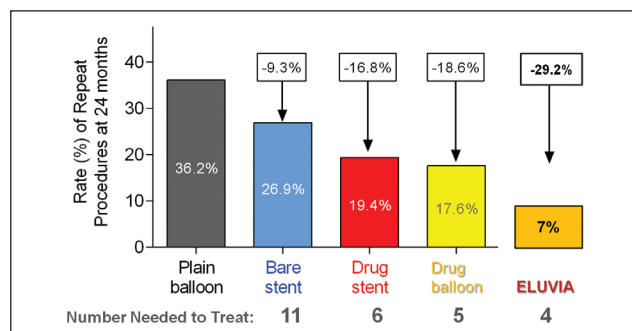


Figure 1. Comparing reduction of repeat limb procedures with DESs versus DCBs. TLR rate reduction calculated according to 24-month aggregate data.⁴ Eluvia results at 2 years from cumulative TLR events reported (4 of 57 cases). Number needed to treat to avoid one TLR event up to 2 years.

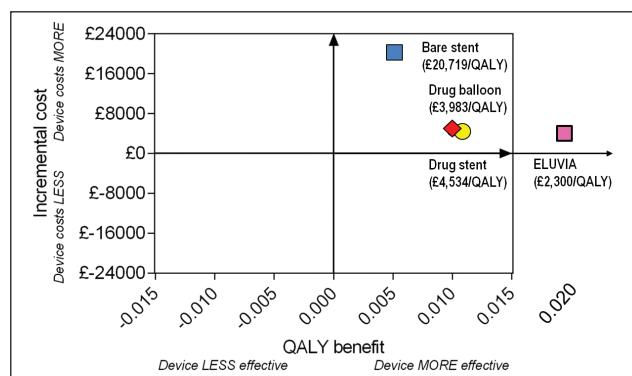


Figure 2. Incremental cost effectiveness of DESs compared to DCBs. Eluvia results calculated according to an approximate 10% TLR rate at 2 years to allow for sampling uncertainty.

from 36.2% with plain old balloon angioplasty (POBA), down to 26.9% with bare-metal stents (BMSs) (-9.3%), and further down to 19.4% with DESs (-16.8%) and 17.6% with DCBs (-18.6%). Consequently, the number needed to treat (NNT) to avoid one TLR in 24 months were 10.8, 6.0, and 5.4 with BMS, DES and DCB use (Figure 1), respectively, at an average cost premium per-patient of £112, £44, and £43 (economic comparison included the index procedure and any applicable reinterventions costs up to 2 years).⁴ Furthermore, the incremental cost-effectiveness ratio (ICER) was projected to be £4,534 per quality-adjusted life-year (QALY) gained for DESs and £3,983 per QALY for DCBs compared to more than £20,700 per QALY with nitinol BMSs (Figure 2).⁴

A similar budget impact model has been also released for the United States and German health care systems, reporting very similar clinical benefits in terms of reducing the rate of TLR and marginal cost savings for the health care system.⁵ Up to 24 months, aggregate patient costs were significantly reduced following a primary DES or DCB treatment strategy for both the United States (DCB: \$10,214; DES: \$12,904; POBA: \$13,114; BMS: \$13,802) and the German public health care system (DCB: €3,619; DES: €3,632; POBA: €4,290; BMS: €4,026).⁵

THE ELUVIA STENT SYSTEM

Eluvia (Boston Scientific Corporation) is a new-generation, polymer-based, sustained-release, paclitaxel-eluting stent with promising results seen in early clinical studies. The MAJESTIC single-arm study in the superficial femoral artery (n = 57 patients) has recently released a compelling 92.5% freedom from TLR rate at 24 months, with only four patients out of 53 requiring a reintervention.⁶ Hence, the relevant economic analysis of Eluvia (assuming a nearly 10% rate of TLR at 24 months, which is nearly half of the DES rates reported in the aforementioned published budget impact models) would calculate an NNT of only 3.8 cases needed to

be treated to avoid one TLR event and a projected ICER of £2,300 per QALY. This makes the Eluvia stent a very favorable investment for improved clinical outcomes in the femoral artery.

CONCLUSION

Clearly, modern drug-eluting technologies are not only associated with a very favorable cost-utility profile but may even produce some cost savings for the taxpayers at up to 2 years, depending on individual government reimbursement policies. ■

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Clinical Benefit of Long-Length Drug-Coated Balloons

The anatomic factors that make longer DCBs the ideal choice for treating longer, more difficult lesions.

BY GUNNAR TEPE, MD



The use of drug-coated balloons (DCBs) to prevent restenosis has increasingly become the standard therapy in femoropopliteal artery disease.¹ This shift in preference toward DCBs has been driven by positive data from both randomized controlled trials, which have included primarily TASC A and B lesions, as well as all-comer, single-arm studies that have shown excellent results in long lesions, total occlusions, and even in in-stent restenosis.² These studies also showed excellent results for DCBs in long lesions, total occlusions, and even in in-stent restenosis. Nevertheless, there is no class effect of DCBs; some are simply more effective than others.

TREATING THE ENTIRE LESION

Although different types of lesions have been extensively studied to understand their susceptibility to restenosis after 1, 2, and 3 years, little is known about the variables encountered during the intervention. It seems to be that even though predilation is recommended when DCBs are used, patients who did not receive predilation have similar outcomes compared with those who received vessel preparation. Nevertheless, several modes of failure are possible for the intervention. Undersizing has been identified as one factor related to the inferior outcome of the Lutonix DCB (Bard Peripheral Vascular, Inc.) in the LEVANT I study.³ Besides undersizing the DCB, a mismatch of DCB therapy following predilation was found to create a so-called edge phenomenon. If the length of the DCB does not reach the length of predilation, those areas without DCB coverage will have the same results as if plain balloon angioplasty alone were used. In the areas that do not receive drug delivery, the restenosis rate is much higher compared to the vessel areas where there is DCB coverage.

The problem of drug coverage is an even greater issue in longer lesions. DCBs can only be used once, since most of the drug is gone from the surface of the balloon after the first inflation. This means that multiple short DCBs must be used to treat longer lesions, which results in multiple device exchanges. Because DCBs leave no marker behind to indicate where the lesion has been treated, in a scenario in which multiple DCBs are used, it becomes more likely that the edges of the lesion are undertreated and/or portions of the lesion are treated multiple times with drug due to overlapping of the DCBs. This limitation has recently been overcome by the development of longer-length DCBs. For example, the Ranger DCB (Boston Scientific Corporation) is now available in lengths up to 200 mm. With the use of these balloons in longer lesions, the problem of mismatch within the lesion has been solved, and the treatment is also quicker and easier.

CONCLUSION

In summary, longer-length DCBs have a more predictable outcome. In addition, they save on time and costs during the endovascular procedure. Therefore, the addition of such longer-length devices are quite a beneficial tool. ■

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Experience With Atherectomy and DCBs

The merits of a two-part approach in the SFA and popliteal artery.

BY ULRICH SUNDERDIEK, MD, PhD



In patients with chronic peripheral artery disease (PAD), the options for interventional therapy have tremendously increased within the last few years. Traditional percutaneous transluminal angioplasty (PTA) with drug-coated balloons (DCBs), with or without adjunctive stenting, is the current endovascular option of choice for treatment of severe PAD. The development of next-generation peripheral stents and drug-coated stents have led to the improved treatment of more complex superficial femoral artery (SFA) lesions.¹ Technical success and short-term results have been excellent with these endovascular interventions, as successful percutaneous revascularization significantly improves amputation rates, survival in patients with intermittent claudication and critical limb ischemia, as well as quality of life.

However, in complex femoropopliteal lesions, long-term patency and restenosis rates have generally been more disappointing regardless of the technique employed. Late results have been limited by high restenosis rates and

recurrent symptoms. Atherosclerotic disease progression in the femoropopliteal arterial segment is often diffuse, with complex morphologies including soft and fibrous tissue, thrombus, and superficial and deep calcium. These factors have limited the utility of PTA with DCBs alone for sustainable, favorable results. The rate of bailout stenting after DCB angioplasty has been reported to be as high as 40% in long lesions and as high as 46% in chronic total occlusions (CTOs).² So far, the femoropopliteal arterial segment remains a challenge to manage, with no evidence-based standard treatment defined.

How can the results after DCB be optimized? The negative predictors that significantly influence the outcome of treatment in patients with PAD are as follows: cardiovascular comorbidities, long lesion lengths, total occlusions, and the presence of calcification. Due to these reasons, the concept of atherectomy is becoming attractive, as it allows ablation of the plaque material, straightens eccentric lesions, and creates a lumen or widens the vessel lumen prior to PTA. Therefore, overstretching of the vessel wall can be avoided. As demonstrated in various

TABLE 1. COMPARISON OF DIFFERENT PROPERTIES OF ATHERECTOMY DEVICES

Device	Jetstream (Boston Scientific Corporation)	Phoenix (Philips Volcano)	HawkOne (Medtronic)	Pantheris (Avinger, Inc.)	Turbo-Elite Laser (Spectranetics Corporation)
Atherectomy Type	Rotational	Rotational	Directional	Directional	Photoablative
Eccentric lesion	X	X	XX	XX	
Soft/fibrotic plaque	XX	XX	XX	XX	XX
Thrombotic lesion	XX				X
Highly calcific lesion	XX	X	X		X
Chronic total occlusion	XX	XX	X	X	XX
In-stent restenosis	X	X		XX	XX
In-stent occlusion with thrombus	XX			X	XX
X indicates good applicability; XX indicates perfect applicability.					

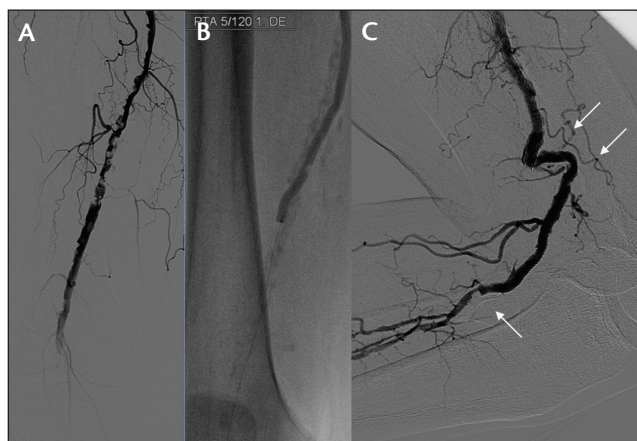


Figure 1. A 76-year-old woman (Rutherford class 5) with a heavily calcified distal SFA and popliteal artery (A, B). After placement of two stents, the vessel segment shows severe kinking (double arrows) and luminal mismatch (one arrow) in the distal popliteal artery (C).

atherectomy studies, the dissection and bailout stenting rates are low (Table 1).

CLINICAL EXPERIENCES

In daily endovascular treatment of PAD, we are often confronted with severely calcified lesions in the distal femoropopliteal segment. Our routine angiographic control of the femoropopliteal segment with $> 90^\circ$ bended knee often demonstrates the failure of important stent properties, such as flexibility and adaptability to the vessel, in the distal SFA or popliteal artery, especially with older-generation nitinol stents. In this particular segment, we see a number of reocclusions and severe restenosis, even with the latest-generation stents (Figure 1). To avoid these negative aspects, using atherectomy for vessel preparation in the femoropopliteal artery is an important step before PTA. This is particularly true in occlusions where we recanalize the vessel with an 0.014-inch system, which allows the operator to use a variety of different CTO wires, without the risk of severe vessel injury. With a 0.014-inch system, we are able to more successfully cross these occlusions intraluminally compared to larger wire sizes. After placing a distal protection system in almost all procedures, the rotational Jetstream atherectomy system (Boston Scientific Corporation) is used to create a channel and gain a larger vessel lumen prior to adjunctive therapy with a DCB (Figure 2).

Moreover, in-stent restenosis or reocclusion can effectively be treated with Jetstream, which gained CE Mark approval for treating in-stent restenosis in 2016. In Figure 3, reocclusion of a stented segment in the distal SFA is shown. After recanalization and placement of a distal protection system, we used the larger Jetstream atherectomy system (2.4 X 3.4 mm) to debulk before DCB therapy. A severe

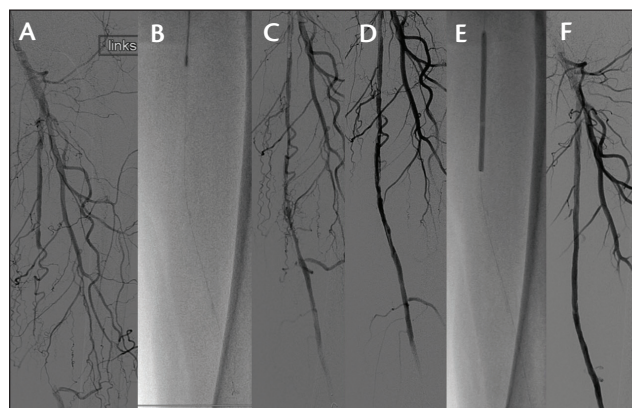


Figure 2. A 69-year-old woman (Rutherford class 3) with a longer occlusion of the SFA (A). After crossing the occlusion with a 0.014-inch CTO wire (Sion Blue, Asahi Inc.), a filter wire (Emboshield Nav6, Abbott Vascular) is placed (B) and Jetstream atherectomy is performed using a 2.4- X 3.4-mm device, with two passes with blades down (C) and two passes with blades up (D). A low-pressure (4-atm) DCB is then used (E, F).

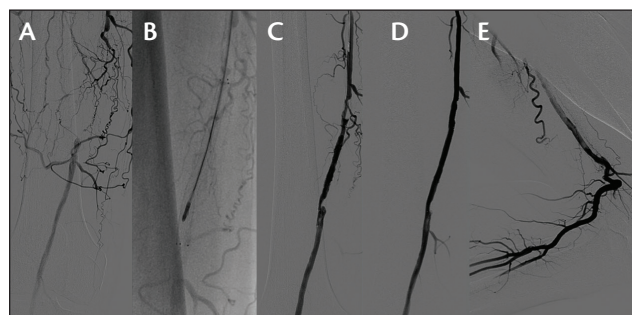


Figure 3. A 58-year-old man (Rutherford class 3) presents with in-stent restenosis in the distal SFA (A). After recanalization with a 0.014-inch CTO wire, several passes using the 2.4- X 3.4-mm device Jetstream atherectomy system are performed (B, C) followed by a 6- X 120-mm DCB. A good result is achieved, revealing a stenosis in the distal portion of the stent and the lateral angiographic series showing the stent compromising the movement of the distal SFA when bending the knees $> 90^\circ$ (D, E).

stenosis in the distal end of the stent was revealed, again, showing the injury of the stent to the vessel in the movement segment of the femoropopliteal artery. Thus, an important aim of this experience is to avoid placing a stent in this particular complex vessel segment.

RATIONALE FOR ATHERECTOMY

Early elastic recoil, frequent dissections, and poor primary and secondary patency rates for long lesions limit balloon angioplasty of complex vessel lesions, despite the high procedural success rates. The use of latest-generation self-expanding nitinol stents may be an effective treatment for focal lesions. However, restenosis can be as high as 10% to

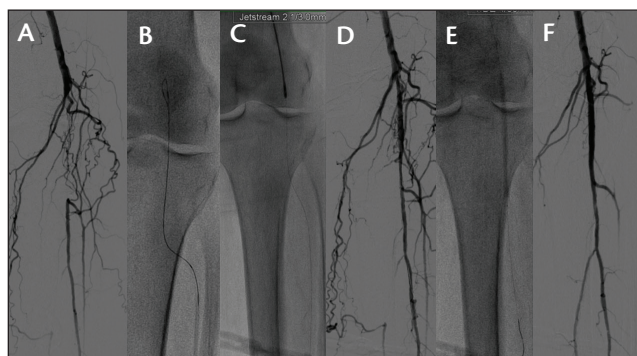


Figure 4. A 73-year-old woman (Rutherford class 5) with an occlusion of the distal popliteal artery (A). Due to numerous collaterals, it was impossible to recanalize this segment antegrade. Therefore, retrograde recanalization (via the anterior tibial artery) is performed for intraluminal recanalization (B) and Jetstream atherectomy is done (C, D). After adjunctive DCB therapy, restoration of the distal popliteal artery is achieved (E, F).

40% at 12 to 24 months. Furthermore, the presence of rigid calcified plaques may result in incomplete stent expansion and significant residual stenosis.³

There are a variety of different atherectomy devices available on the market. They are all designed to cut, shave, or vaporize atherosclerotic or calcified lesions, as summarized in Table 1. It has been shown in a number of atherectomy studies (mostly CE Mark approval studies without DCB ballooning) that the rate of flow-limiting dissections remained low (< 10%), and therefore the bailout stent rate was almost below 10% as well.⁴⁻⁷ However, with laser atherectomy, the bailout stent rate was higher at 23.3%.⁸ These data demonstrate that atherectomy is safe and effective within 12 months in most atherosclerotic lesions.

The first data for the Jetstream system were published in 2009 by Zeller and colleagues in the Pathway PVD trial.⁷ In 172 patients with relatively short lesions (approximately 27 mm), they demonstrated the safety and effectiveness of the first-generation rotational atherectomy device, formerly called the Pathway Medical system (2.1 mm with blades down and 3 mm with blades up). The patency rate (peak systolic velocity ratio < 2.4 by duplex ultrasound) was 61.8% with a target lesion revascularization (TLR) rate of 26% after 12 months.

In the Jetstream Calcium Study,⁹ IVUS analysis showed that after Jetstream atherectomy, the lumen area increased from $6.6 \pm 3.7 \text{ mm}^2$ to $10 \pm 3.6 \text{ mm}^2$ ($P = .001$), and calcium reduction was responsible for $86\% \pm 23\%$ of the lumen increase. In this study, the Jetstream atherectomy system increased lumen dimensions in moderately or severely calcified femoropopliteal lesions by removing superficial calcium without major complications. This study, which had severe calcium in 63.6% of lesions, concluded that the Jetstream atherectomy system removed and modified

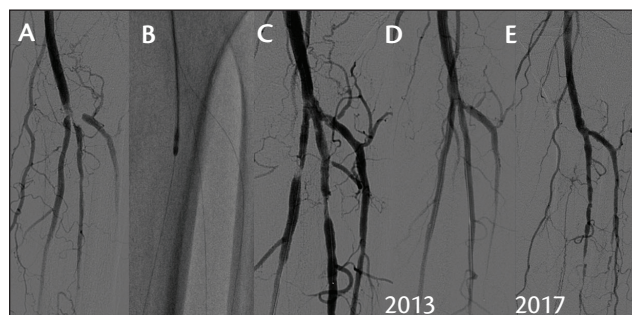


Figure 5. A 72-year-old man (Rutherford class 5) with diabetes mellitus type I presented in March 2013 with a nonhealing ulcer on his first digit. A subtotal occlusion of the trifurcation below the knee on the left leg is observed (A). After placing three 0.014-inch bare wires into each vessel, Jetstream atherectomy with the 2.1- X 3-mm system is performed (B). After adjunctive DCB therapy, restoration of the trifurcation is nicely achieved (C, D). In February 2017, angiography showed a new ulceration of the foot, revealing a good long-term result of the treated lesion. However, progression of atherosclerotic disease in the distal vessels is obvious (E).

superficial calcium to achieve significant lumen gain. In early 2017, data presented from the JET Registry demonstrated a 77.2% patency rate and 81.7% freedom from TLR at 12 months when Jetstream was combined with PTA, with an average lesion length of 16.4 cm. The subgroup analysis showed that with the use of the current generation of the Jetstream system in nonstent lesions (157 patients), there was a patency rate of 79.5%, and in-stent lesions (84 patients) a rate of 72.2% was achieved.¹⁰

At our institution, we performed 228 procedures with the Jetstream atherectomy system between 2014 and 2015. Lesions lengths were between 2 to 28 cm, with an occlusion rate of 68%. The procedural success rate was high at 96.5%. DCB therapy was used 100% of the time, with a bailout stent rate of 7.9%. Freedom from TLR after 1 year was 86%; however, there are clear limitations, as the follow-up was achieved via routine patient control and additional data were collected via the electronic data system of our institution.

To obtain a more reliable data set, we started a single-center registry in February 2017. The dissection rate and bailout stent rate was low, even in complex lesions, like below-the-knee (BTK) and bifurcation lesions (Figures 4 and 5). In these lesions especially, we do not have a lot of endovascular options to achieve a longer lasting patency, as it is known from a number of BTK studies. To obtain a more reliable data set, we started a single-center registry in February 2017. In this registry, patients with femoropopliteal lesions (up to 25 cm in length) are included to compare endovascular treatment with Jetstream atherectomy plus a DCB versus a DCB and stenting.

POTENTIAL BENEFIT FOR ATHERECTOMY BEFORE DCB USE

Today, based on a meta-analysis of 11 trials with 1,838 participants, there is clear evidence of an advantage for DCBs compared with plain old balloon angioplasty (POBA) in several anatomic endpoints such as primary vessel patency, binary restenosis, and target lesion revascularization for up to 12 months.¹¹ It is also remarkable that after 24, and even 36 months, DCB results show improved patency compared to POBA in treating femoropopliteal lesions.¹²⁻¹⁴

However, limitations are recognized in these studies, and it is clearly demonstrated in the study from Fanelli and colleagues¹⁵ with 60 patients enrolled, that in heavily calcified SFA lesions, stand-alone DCB therapy yielded only 50% primary patency rates with significantly higher late lumen loss, regardless of lesion length after 1 year. This study concluded that to achieve a durable antiproliferative effect, deep penetration of the drug into the media layers with maximum uptake is required, but calcified lesions may act as a physical barrier to optimal drug penetration and adequate distribution. Therefore, vessel preparation via atherectomy to reduce the calcium burden plays an important role. Atherectomy may remove the potential barrier, and the integrity of the DCB will be protected, especially in CTOs, by creating a larger vessel lumen before placing the balloon. On the other side, DCB therapy may inhibit the inflammatory response caused by mechanical trauma of plaque excision.

In the DEFINITIVE AR study,¹⁶ Zeller and his group first described the combination of directional atherectomy with a DCB compared to stand-alone DCB use. In this small pilot study, a trend toward an added benefit for directional atherectomy with a DCB over DCB use alone in challenging lesions was described. However, no significant differences exist between the two groups, thus further investigation in larger, prospective, randomized, statistically powered trials is necessary. Last year, the REALITY study began evaluating patient outcomes with adjunctive use of the HawkOne or TurboHawk atherectomy systems (Medtronic) with the In.Pact Admiral DCB (Medtronic) in significantly calcified and symptomatic femoropopliteal PAD (NCT 02850107). In addition, Stavroulakis¹⁷ reported on a single-center study comparing DCB angioplasty versus directional atherectomy with antirestenotic therapy (DAART) for isolated lesions of the popliteal artery. These data revealed that the use of DAART was associated with a higher primary patency rate compared with DCB angioplasty (82% vs 65%) for isolated popliteal lesions.

Very recently, Shammass et al showed the advantage of DCB versus POBA after Jetstream atherectomy in a core lab–adjudicated analysis.¹⁸ Eighty-one patients (49.4% men; mean age, 68.3 years; 53.1% with diabetes) with de novo or restenotic femoropopliteal lesions (Rutherford

category 1–5) were enrolled in the JET-SCE single-center experience. At 18 months follow-up, the TLR rate was significantly reduced with atherectomy and adjunctive DCB use compared to atherectomy with adjunctive POBA alone (91.1% vs 63.7%; $P = .03$). Furthermore, Drs. Shammass and Garcia plan to begin enrollment this year in a much larger multicenter study evaluating the combination therapy of Jetstream plus the Ranger DCB (Boston Scientific Corporation) in complex lesions.

As previously discussed, our experiences support these data, and a very interesting case of a complex trifurcation lesion nicely demonstrated long-lasting patency (Figure 5). In 2013, when we started using this combination therapy, we performed Jetstream atherectomy with adjunctive DCB therapy and observed a good interventional result, avoiding any stent implantation. Four years later, reintervention was necessary due to the progressive vessel disease and showed a nice long-term result of the former trifurcation lesion.

In addition, a more detailed description of the Jetstream atherectomy system, along with tips and tricks for its use, can be found in a recent article by Shammass in *The International Journal of Angiology*.¹⁹

SUMMARY: ATHERECTOMY AND DCBs

Atherectomy, specifically with the Jetstream atherectomy system, offers an effective tool for endoluminal, mechanical debulking of plaque and thrombotic materials, even in severely calcified lesions. We have seen that treatment even in critical vessel segments is safe and possible. Due to preservation of the native vessel by avoiding the placement of stents, future interventions might be possible.

After creating a larger vessel lumen of the diseased femoropopliteal segment via atherectomy, an important detail might be to consider low pressure angioplasty (3–6 atm) to avoid overstretch of the vessel wall.

With DCB use as a well-established treatment for PAD, atherectomy can remove the potential barriers for drug uptake, allowing increased drug penetration/application into the vessel wall. Therefore, the combination of endovascular atherectomy prior to DCB use is an important option in the treatment of long lesions, total occlusions, and calcified vessels. ■

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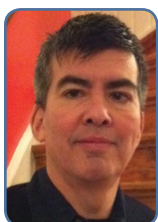
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Experience With Drug-Eluting Technologies in BTK Interventions

Promising results for drug-eluting stent use in CLI patients with lesions below the knee.

BY HANS VAN OVERHAGEN, MD, PhD, EBIR



Critical limb ischemia (CLI) is the end stage of peripheral artery disease and represents a substantial burden for patients and health care systems due to its poor prognosis for both limbs and lives. Recanalization of occluded leg vessels remains the most effective therapy, since

medical treatment is not very effective and new cell therapies have been disappointing thus far. In the last decade, endovascular therapy has replaced vascular surgery as the recommended recanalization strategy. For lesions below the knee (BTK), the combination of percutaneous transluminal angioplasty (PTA) and bailout bare-metal stenting (BMS) is the standard endovascular treatment.¹ Although the initial technical success rate of PTA and bailout BMS is reported to be relatively high, long-term results are negatively affected by restenosis due to intimal hyperplasia.²

FINDINGS FROM RECENT STUDIES

Drug-eluting technologies have been used in BTK lesions in order to reduce restenosis rates after endovascular treatment. After an initial optimistic report, the results of drug-coated balloons (DCBs) BTK have been disappointing. In the IN.PACT DEEP trial, a randomized postmarket trial designed to assess the safety and efficacy of the paclitaxel-eluting In.Pact Amphirion DCB (Medtronic) compared with PTA within the CLI population, all lesion-specific primary and secondary endpoints showed insignificant differences between the two study arms. In addition, the DCB showed “a trend towards an increased major amputation rate through 12 months compared to PTA,” as noted by Zeller et al.³ The authors state that it can be hypothesized that potential disease, device, and/or procedural factors may have contributed to the observed lack of drug treatment effect; that the 2.4-fold higher major amputation rate is perplexing; and that these negative results are contrary

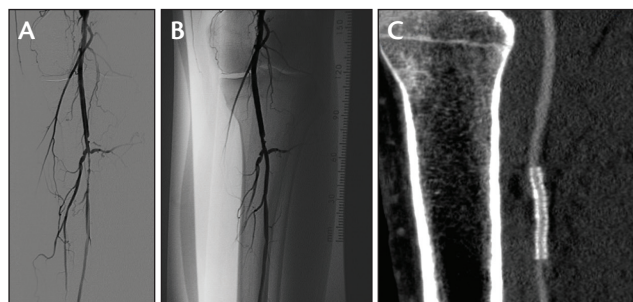


Figure 1. Stenosis of peroneal artery in a patient with CLI (A). Results after DES implantation (B). CTA at 6-month follow-up (C).

to the results of the In.Pact DCB and others in the femoropopliteal arteries.³

Regarding the morphology of stenotic and occluded BTK arteries in CLI, one may hypothesize that the drug is rubbed off the balloons during passage through the long, narrow, and calcified tract toward the crural arteries, and thus diminished local effectiveness and distal embolization result. Mounting polymer and drug to a stent may result in a more fixed coating with better-controlled release of the drug without particle embolization. In the IDEAS randomized controlled trial that compared paclitaxel-coated DCBs with drug-eluting stents (DESs) in long (≥ 70 mm) infrapopliteal lesions, DESs demonstrated significantly lower residual postprocedure stenosis and significantly reduced restenosis at 6 months.⁴ Results of DES BTK in general have been more encouraging morphologically regarding restenosis rates, but until recently, clinical data were lacking.⁵ This may be at least partially caused by the fact that many DES BTK studies have included patients with intermittent claudication who are unlikely to reach hard clinical endpoints, such as amputation or death, as well as the limited numbers of patients in the studies.

In the PTA and DES for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) trial, patients with CLI (Rutherford

category ≥ 4) were randomized to undergo treatment with either PTA \pm BMS or a paclitaxel DES (Taxus Liberté, Boston Scientific Corporation). The primary endpoint was 6-month primary binary patency of the treated lesions, defined as $\leq 50\%$ stenosis on CTA (Figure 1). Stenosis $> 50\%$, retreatment, major amputation, and CLI-related death were regarded as treatment failure. The severity of failure was assessed with an ordinal score, ranging from vessel stenosis through occlusion to clinical failures.⁶

Six-month patency rates were 48% for the DES arm and 35.1% for the PTA \pm BMS arm ($P = .096$) in the modified intention-to-treat population and 51.9% and 35.1% ($P = .037$), respectively, in the per-protocol analysis. The ordinal score showed significantly worse treatment failure for PTA \pm BMS versus DES ($P = .041$). The observed major amputation rate remained lower in the DES group until 2 years posttreatment, with a trend toward significance ($P = .066$). Fewer minor amputations occurred in the DES arm through 6 months posttreatment ($P = .03$).⁷

Long-term follow-up of the PADI trial consisted of annual assessments up to 5 years posttreatment or until a clinical endpoint was reached. Preserved primary patency ($\leq 50\%$ restenosis) of treated lesions was an additional morphological endpoint assessed by duplex ultrasound. The estimated 5-year major amputation rate was lower in the DES arm (DES, 19.3% vs PTA \pm BMS, 34%; $P = .091$). The 5-year amputation-free survival and event-free survival (survival free from major amputation and reintervention) rates were significantly higher in the DES arm (DES, 31.8% vs PTA \pm BMS, 20.4%; $P = .043$; and DES, 26.2% vs PTA \pm BMS, 15.3%; $P = .041$, respectively). Survival at 5 years (52%–56%) was comparable for both groups. The limited available morphologic results showed higher preserved patency rates with the DES than after PTA \pm BMS at 1, 3, and 4 years of follow-up.⁸

CONCLUSION

Currently available data on DCBs BTK are disappointing, whereas the results of DESs BTK in those with CLI seem promising. The long-term follow-up results from PADI show that survival rates at 5 years in patients with CLI are around 50%, which suggests that the “leave nothing behind” approach may not be the only treatment pathway to be followed in CLI patients who require BTK treatment. Because DESs, at present, are of limited length and patients with CLI are known to have long lesions, the development of a long, self-expandable DES seems warranted. ■

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New Technologies to Solve the Challenges of CLI

The unique features of this disease are finally being addressed with new devices.

BY J.A. MUSTAPHA, MD, AND FADI SAAB, MD



Over the last 30 years, revascularization specialists have used the same techniques over and over, expecting different outcomes but continuing to have the same results. In

some situations, worse results have been experienced. Infrapopliteal plain old balloon angioplasty (POBA) has failed to show sustainable results in patients with critical limb ischemia (CLI), with 1-year primary patency rates reported as low as 63% and major amputation rates as high as 15% in a recent meta-analysis.¹ Yet, in some instances, POBA continues to be considered the gold standard of endovascular therapy for infrapopliteal disease.

LIMITATIONS OF CURRENT TREATMENTS

In a recent study on infrapopliteal calcification patterns in CLI, the nature of atherosclerotic disease in popliteal and tibial vessels was examined. The results were surprising, as calcification involving tibial vessels extended through multiple layers across the vessel from the intima to the adventia.² Findings such as this could certainly contribute to the suboptimal results noted with balloon angioplasty and, in theory, limit the success of drug-coated balloons (DCBs).

Results from bare-metal self-expanding stent trials have been disappointing, such as the XCELL trial, which showed a high rate of

restenosis, a high rate of clinically driven target lesion revascularization, and a low rate of wound healing.³ We believe that the distal tibial vessels through the plantar circulation behave differently on multiple levels, including mechanically and pathologically (Figure 1). Most treatment modalities have failed in these segments, and in some trials, these segments were excluded.

Although DCB technology in the infrapopliteal regions was met with enthusiasm, current data evaluating DCB use in the tibial segments do not support its long-term benefit. Reasons behind the lack of efficacy are complex and poorly under-

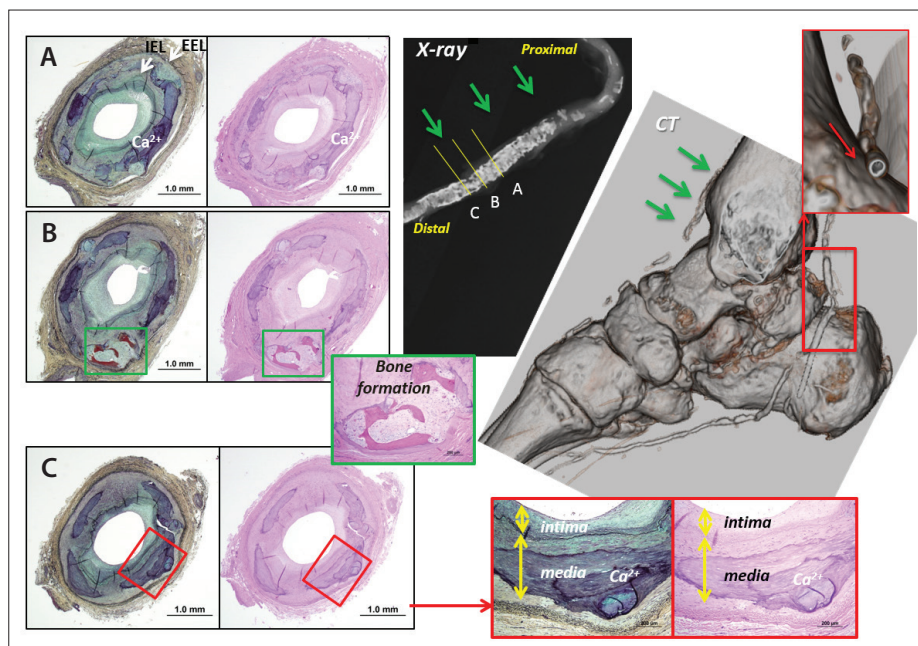


Figure 1. Monckeberg's calcification in the pedal arteries of a patient with end-stage renal disease. Calcium deposits are seen (Ca^{2+}), as well as the disruptions of the IEL and EEL (A); inset shows bone formation (osseous metaplasia) (B); inset shows a calcium deposit (C). High-resolution x-ray and high-resolution CT depicting medial arteriosclerosis. Abbreviations: EEL, external elastic lamina; IEL, internal elastic lamina. Reprinted with permission from Mustapha JA, Diaz-Sandoval LJ, Saab F. Infrapopliteal calcification patterns in critical limb ischemia: diagnostic, pathologic and therapeutic implications in the search for the endovascular holy grail. *J Cardiovasc Surg (Torino)*. 2017;58:383–401.

stood.⁴⁻⁶ Again, we believe that calcification and undersizing of tibial balloons most likely played a significant role in the suboptimal results.

In a substudy of 356 patients enrolled in the Peripheral Registry of Endovascular Clinical Outcomes (PRIME) registry,⁷ the rate of tibial vessel recoil and late lumen lost after angioplasty was examined via duplex ultrasound. The substudy found that patients who required reintervention had a recoil rate of 32% at 1-month postintervention.⁸ In our opinion, this is a reflection of the complexity of tibial calcification and occlusions.

Trials examining the benefit of balloon-expandable drug-eluting stents in the tibial vessels showed significant promise. However, the lesion length evaluated falls short of real-world tibial lesions and chronic total occlusions, with average treated lesion length of 4 to 6 cm. In the PRIME registry, the treated lesion length ranged from 200 to 260 mm.⁹⁻¹¹

ADDRESSING THE CHALLENGES OF CLI

Given the previously mentioned challenges in treating infrapopliteal disease, a scaffold-based drug-eluting technology may provide a better treatment solution. Boston Scientific Corporation is developing a new, purpose-built, below-the-knee drug-eluting stent designed to resolve two critical challenges to CLI pathophysiology: (1) poor uptake of the antiproliferative agent through calcified vessels, and (2) the elastic vessel recoil frequently seen following balloon dilatation in infrapopliteal arteries. This new technology (currently an investigational device) is designed to optimize drug delivery in calcified lesions through the use of a highly biocompatible polymer that maintains a reservoir of antiproliferative agent adjacent to the lesion for an extended period of time. This sustained drug release is intended to improve clinical outcomes by facilitating a more efficient drug uptake in the vessel. The technology is designed to address the challenge of elastic recoil in infrapopliteal lesions by providing a self-expanding scaffolding in long lengths with adequate radial force.

In recognition of the unmet clinical need for better solutions to treat infrapopliteal disease and the unique solution provided by this technology, the US Food and Drug Administration has granted Boston Scientific an Expedited Access Pathway designation for this product. This accelerated pathway allows the device to be clinically tested in the United States and in other sites around the world with a goal of speeding innovation to patients.

CONCLUSION

In conclusion, CLI involving tibial and plantar disease remains a very challenging space to treat. Balloon angioplasty as the main revascularization modality has not been shown to be effective in achieving adequate short- and long-term outcomes. The pathological and mechanical properties of tibial vessels are certainly different and will require new tech-

nology to address the stark differences from other vascular conduits. We remain cautiously optimistic as newer technologies designed specifically for this space evolve. ■

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