CLI Compendium

CLIC: THE VOICE OF CRITICAL LIMB ISCHEMIA

Turning the Key to Critical Limb Ischemia Therapy

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From Metro Health Hospital, Wyoming, Michigan.

Welcome to the Critical Limb Ischemia Compendium, or CLIC, which was born out of the need to provide more information to health care providers treating patients with critical limb ischemia (CLI), who are often left with minimal to no options for care. It is time to turn the key that opens the door to CLI therapy and just treat CLI.

The time has come for vascular specialists to create a movement in the implementation of therapeutic plans for CLI patients that includes promising alternatives to amputation. The time has come to ask for more resources, tools, data, medications, and systems of care for the sick CLI patient.

The spectrum of presentation of CLI has changed and therefore it is time for CLI therapy goals to change. CLI used to be the disease of elderly and debilitated patients. This is no longer true. CLI is claiming younger patients every day and is reaching epidemic proportions.

Given the predicted morbidity and mortality associated with CLI, vascular specialists, family physicians, podiatrists, and wound care specialists have to turn the key by using each of their educational backgrounds and clinical experience to provide the level and spectrum of appropriate care these patients need. As the impact of this disease continues to broaden, so do the skills, tools, and medicines available to counter the progressive stages of the disease. Each member of the team with his or her unique and varied skill set has

something to contribute to the therapeutic algorithm of the CLI patient. So let's put our hands together, unify directed efforts and "Just treat it!"

The CLI Continuum of Care Model: A Multidisciplinary Approach to Improve Outcomes

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Treatment of Critical Limb Ischemia

The contemporary treatment of patients with critical limb ischemia (CLI) is complex due to the inherent disease process (which is multifaceted in nature) and the apparently invisible fragilities of our current practice workflow, whereby different specialists treat a patient in an isolated fashion. Each expert takes care of one aspect of the patient's disease process, but this tends to lead the team to miss the big picture, represented by the need for a simultaneous, transitionless, passionate, and dedicated multidisciplinary approach.

It must be emphasized that the extant management of CLI should include a combination of endovascular or surgical revascularization as the mainstay of therapy, complemented by a host of non-interventional therapies. This newly proposed, combined approach should be delivered as a CLI continuum of care model, which can be envisioned as a chain whereby the patient's care is carried by each one of its links or team members. One of the greatest weaknesses of our current approach to

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Editor's note: Articles in this supplement to Cath Lab Digest *did not undergo peer review.*

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Vascular Effects of Drug-Coated Balloons for Peripheral Vascular Disease

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More than 185,000 amputations are performed annually in the United States[1] and the vast majority of these are related to complications resulting from critical limb ischemia (CLI),[2] with more than 50% affecting diabetic patients.[3,4] Treatment options in advanced PAD comprise surgical as well as interventional strategies. Currently, the main limitation of endovascular therapies (balloon angioplasty [BA] and bare metal stents [BMS]) for femoropopliteal arterial lesions is the high rate of early restenosis requiring repeat revascularization.[5]

Achieving Patency in Arterial Disease

The 1-year patency rates following BA alone are reported to be as high as 20% to 50%,6 although improved results have been reported with stent implantation.[7] However, depending on the lesion length, in-stent restenosis rates at 1 year are still in the range of 30% to 45%, lacking clear superiority when compared to BA alone.[8-11] Also, BA and BMS have not demonstrated favorable long-term patency outcomes.[12] Drug-eluting stents (DES) for coronary artery disease have shown excellent early and late patency with low rates of restenosis.[13] However, although 6-month results with sirolimus or everolimus on self-expanding stents in the femoropopliteal location showed early promising results, longer term results were sobering.[10] This is thought to be at least partially due to the increased incidence of stent strut fractures in the SFA, which is related to the high biomechanical stress to which these devices are subjected in this particular area of the anatomy, leading to justified skepticism about the use of DES technology in PAD.[14] Nevertheless, recent results with the Zilver PTX polymer-free, paclitaxel-coated nitinol DES have been promising, with higher long-term patency than BMS.[15]

As a novel approach to the treatment of long lesions, drug-coated balloons (DCB) have shown promising effects in simple lesions.[16,17] This technology allows delivery of the antiproliferative drug while avoiding hazardous vascular reactions from polymers and stents.[18,19] Some of the inevitable advantages of this concept pertain to the absence of foreign body reactions arising from permanent scaffolds with an early complete restoration of the vessel wall integrity, including accelerated endothelial healing and the potential for adaptive vessel remodeling.[20] Another potential superiority of DCB over DES might be its even and uniform drug delivery to the vessel wall, as opposed to the focal gradients of drug concentration created by the nonuniform coating of stent struts, which may potentially trigger inflammation and neointimal regrowth in DES.[21]

Drug-Coated Balloons in Femoropopliteal Lesions

To date, clinical evidence for the efficacy of DCBs has been established in patients with in-stent restenosis and femoropopliteal atherosclerotic disease,[16,22,23] and is likely the result of effective drug retention within the neointimal tissue and within the atherosclerotic plaque,[24] thanks to the use of excipients (i.e., carriers) and by increase in the drug payload.[25]

Paclitaxel has been the primary drug of choice used to coat balloons because of its long-lasting effects even after short single-dose applications.[26,27] It is a cytotoxic drug that arrests cell cycle and induces cell death by interfering with microtubule disassembly during cell division.[28] Paclitaxel suppresses smooth muscle cell (SMC) as well as endothelial cell proliferation and migration when applied in adequate concentrations.[29-31] After transfer into the vessel wall, the resulting reduction of neointimal growth is accompanied by delayed healing, with fibrin deposition and decreased leukocyte transmigration and inflammation resulting in overall decrease in SMC within the medial layer.[25]

Coating Strategies for Optimal Drug Delivery

However, due to its insufficient solubility in water and the need for crystalline physical properties required for the drug to persist, specific solvents are necessary for an angioplasty-based application of this drug. Preclinical studies using a porcine stented coronary artery model with DCB demonstrated that paclitaxel alone was less effective in the inhibition of neointimal proliferation as compared to DCB coated with excipients in combination with crystalline paclitaxel.[18,24] In this context, a number of different coating strategies were tested to establish sufficient retention and efficacy to inhibiting neointimal growth, supporting the pivotal role for the use of excipients in the success of DCB technology.[25]

Paclitaxel-coated balloons have been well characterized to date regarding vascular reactions that are observed following usage of different excipients.[25] These effects observed following DCB deployment heavily depend on the extent of successful drug transfer and persistence of the drug in the vessel wall in sufficient quantities for a minimum of 3 to 4 weeks.[26]

Studies focusing on pharmacokinetics also observed long-term drug persistence, with biological effects on the medial layer of the vessel wall showing SMC loss even up to 180 days in preclinical animal studies.[32] One of the drawbacks of the technology in preclinical studies has been that 5% to 10% of the histologic sections of the skeletal muscles exhibit pathologic changes in small arteries either from embolization of coating or from toxic effects of paclitaxel released from DCB. Fortunately, effects on the skeletal muscle such as necrosis have been a rare phenomenon.

The biggest intrinsic problems regarding DCBs are acute recoil and excessive dissections of the treated vascular segment. In addition, the relatively high index dose of drug (up to 3.5µg/mm^2) on contemporary DCBs is associated with drug loss into the bloodstream during transition to the lesion, and the biggest loss occurs during delivery of the balloon to the target lesion site. In an experimental model, it has been reported that at least 25% to 35% of the paclitaxel loaded on the balloon with urea-matrix or iopromide coating is lost into the blood stream.[27] Similar loss also occurs during inflation of the balloon. However, novel paclitaxel-coated balloons have shown reduced loss during passage as well as inflation.[32]

Improvements for the Future of Drug-Coated Balloon Technology

Current efforts in refining DCB technology concentrate on reduction of drug loss in transition by either decreasing overall drug load or improving coating integrity to restrict acute wash-out effects. While focal accumulation of crystalline paclitaxel on the endoluminal surface seems to be associated with sustained

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CLI Continuum

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Larry J. Diaz-Sandoval, MD

CLI is the reigning disconnectedness of the pieces that should conform the CLI continuum of care team. In this proposed multidisciplinary approach (Figure 1), the patient first enters "the chain" through any of its constituent links. The first member of the team sees and evaluates the patient, then proceeds with a simultaneous referral to the remainder of the team. The patient is evaluated by a series of providers, including a primary care physician (sometimes an endocrinologist), an infectious disease specialist, a wound care specialist, a podiatrist, occasionally an orthotics specialist and vascular rehabilitation specialist, and last but definitely not least, the vascular specialist (either a vascular surgeon, an interventional cardiologist, an interventional radiologist, or, in Europe, an angiologist). The patient then undergoes a series of appropriate noninvasive vascular tests in order to do the following:

1. Diagnose the extent of disease;
2. Plan the therapeutic revascularization strategy;
3. Serve as baseline for future surveillance studies.

Once the patient undergoes complete revascularization, the CLI continuum of care team moves forward. The patient should continue to be followed by all members of the team to ensure complete healing and post-healing surveillance. One commonly unrecognized link in the continuum of care is long-term care facilities. The care provided in this setting can cause a break in the chain of care. Often patients are transferred to a rehab facility either permanently or to finalize their care prior to transitioning back to home, and due to lack of awareness, knowledge, staff, and equipment, the appropriate care is not delivered, jeopardizing the effort previously put forth by the rest of the team. A high index of suspicion and an aggressive approach should be maintained, with prompt referral for repeat revascularization to minimize potential complications and increase the likelihood of permanent positive outcomes. This is of paramount importance because of the delicate balance of perfusion in these patients, which can become insufficient if there is additional insult to the skin barrier. Unfortunately, currently followed protocols in clinical practice are not designed to function in this manner. Generally the patient is only referred to the vascular specialist after months of failed wound therapy or repetitive visits to the podiatrist for serial debridements without improvement.

Another weakness of this approach has been the traditional referral to specialists who are not trained in the latest revascularization techniques, leading to frequent amputations without an angiographic evaluation. In the best of scenarios, referral to a vascular specialist is appropriate and timely, and patients undergo appropriate noninvasive and invasive testing and finally receive adequate revascularization therapy. In reality, only a very small fraction of these patients returns for follow-up with the vascular specialist or with any of the other members of the team. Many times they do follow up with a wound clinic that is not affiliated with the system where the vascular specialist performed the intervention, and therefore is not familiar with the latest techniques. Overall, there is a widespread lack of knowledge and an attachment to old ways that needs to be overcome. Unfortunately, data-driven clinical studies do not exist that evaluate strategies for surveillance; use and duration of antiplatelet therapy, anticoagulants, and other risk-factor-modifying therapies; noninvasive testing; and indications for repeat revascularization in these patients. Current data has been derived from retrospective studies, with inconsistent reporting standards leading to a paucity of evidence, especially following endovascular revascularization in CLI.

Non-interventional therapies have a role as primary treatment in patients who have failed to improve despite revascularization, and in patients who are unsuitable or unfit for revascularization. Their role is adjuvant after revascularization procedures and when used to reduce the incidence of cardiovascular events.

Three pillars constitute the foundation of adequate CLI treatment, and each one encompasses different goals:

1. *Medical:* Goals include pain control, reduction of major adverse cardiovascular events, and improvement in quality of life.
2. *Interventional:* Goals include limb salvage, wound healing, and maintenance of ambulatory status.
3. *Surveillance:* Goals include close follow-up and monitoring after treatment delivery and even after healing. The first sign of stalled progress, clinical decline, or recurrence should prompt an immediate referral to the CLI continuum of care team.

The medical goals are tasks that should be led by the primary care physician and endocrinologists. The interventional goals require the active participation of podiatrists, wound care and infectious disease specialists, vascular specialists, vascular rehabilitation specialists, and orthotics specialists. The surveillance goals should be a task carried by all the members of the team.

Non-interventional therapies for the management of CLI comprise the use of preventive measures, wound care, pharmacotherapy (primary: to treat CLI, and adjuvant: to reduce major adverse cardiovascular events and to improve post interventional outcomes), biotherapies (cell and gene therapy), and mechanical therapies designed to achieve the aforementioned goals.

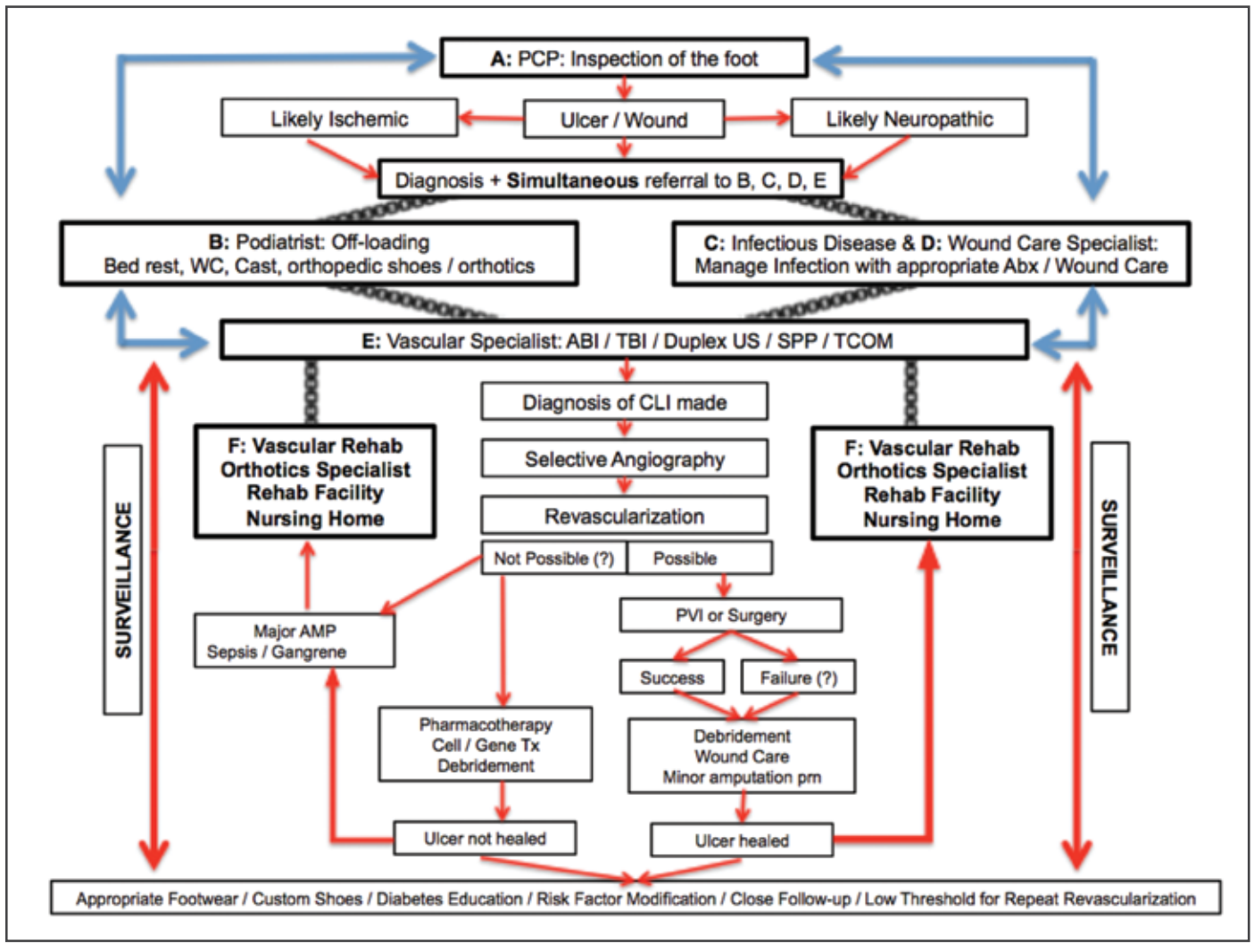

Figure 1. Continuum of care model

Prevention

Preventive measures should constitute the cornerstone of managing patients with CLI, especially among patients without tissue loss. Primary prevention efforts should be directed at measures to avoid skin breakdowns. These include skin moisture, adequate footwear or orthotics, adequate toenail care, and education on preventing foot trauma and falls. Patients need to be educated on being proactive and inspecting their feet daily and to contact the team if there is evidence of any new skin breakdown or any change in pre-existing wounds. In patients who have already undergone revascularization procedures, the team should expand to include physical therapy and rehabilitation

specialists to help patients get back to a functional status that improves their quality of life. In those patients who have had to undergo some form of amputation despite the best efforts at revascularization, the addition of the orthotics specialist is of paramount importance. Secondary prevention should address smoking cessation, blood pressure and glycemic control, lipid lowering, and antiplatelet agents. Unfortunately, many patients with CLI do not receive counseling for or do not follow intensive risk factor modification.

Wound Care

Meticulous wound care is critical for patients with CLI and tissue loss. Underlying infection should be treated and necrotic tissue debrided. Topical therapies with recombinant growth factors and hyperbaric oxygen are being investigated.[1] Repetitive debridement and application of topical therapies without urgently involving the vascular specialist is the norm in the United States and Latin America. Once again, the simultaneous participation of the CLI continuum of care team should be one of the cornerstones of a successful strategy to manage the patient with CLI, from the time of diagnosis, until complete wound healing has occurred (median time from revascularization to complete wound healing is approximately 190 days)[2,3], taking into consideration that female patients tend to have poorer wound healing compared to their male counterparts.[4]

Hyperbaric Oxygen

There is no proven benefit of hyperbaric oxygen in CLI as primary therapy. A Cochrane review of the effect of hyperbaric oxygen on ulcer healing in patients with diabetes concluded that the therapy increased the rate of ulcer healing at 6 weeks, but not at 1 year, and there was no significant difference in the risk of major amputation.[5] However, these studies were performed in patients who had not undergone revascularization. Studies directed at analyzing the adjuvant role of hyperbaric oxygen combined with aggressive wound care and revascularization would likely show faster healing times and improved outcomes. As well as with the latest drug-coated balloons, 1-year outcomes appear not to be the most adequate endpoint for studies looking at effectiveness of CLI therapies, since the critical time to heal is during the first 3 to 6 months after revascularization. Prospective data is much needed in this field, which is plagued by retrospective, single-center studies.

Mechanical Therapies

Spinal cord stimulation (SCS) and intermittent pneumatic compression (IPC) have been evaluated as adjuvant treatment options for CLI patients who are deemed poor candidates for revascularization. SCS improves microcirculatory blood flow, relieves ischemic pain, and reduces amputation rates in patients with CLI. In a retrospective study of 150 patients with CLI who failed conservative and surgical management, SCS increased blood flow and was associated with significant pain relief, improved quality of life, and increase in the transcutaneous pressure of oxygen.[6] A more recent study of 101 consecutive patients with no revascularization options found that reducing the delay between the ulcer onset and implantation of a SCS resulted in improved quality of life and walking distance.[7] Further studies should be conducted in the role of these therapies in patients who have undergone revascularization procedures and are felt to no longer have any more endovascular or surgical options, as the number of patients deemed "poor candidates for revascularization" will continue to decrease, thanks to advances in revascularization therapies.

In CLI patients with no revascularization options who underwent treatment with IPC, this therapy has shown to be a cost effective and clinically effective solution, providing adequate limb salvage rates and relief of rest pain without revascularization.[8]

Summary

The pathophysiology of CLI is complex and involves both microvascular and macrovascular pathology. Therefore it is not surprising that therapeutic modalities are multifold, spanning many health care specialties and requiring substantial institutional infrastructure to provide optimal patient care. Though challenging, the future of CLI treatment is exciting with increasing focus on optimal wound care and prevention, adherence to proven medical therapies, improving revascularization results with novel endovascular and surgical techniques and devices, and ongoing investigation into promising therapies like therapeutic angiogenesis. The creation of the CLIC team will provide aggressive referral upon identification of skin breakdowns or any other factors that can predispose the patient to a rapid decline and compromised prognosis. Patients with CLI often have chronic wounds, and newer cell-based therapies for chronic wounds show interesting parallels to stem cell therapy for CLI. Several human-derived wound care products and therapies, including human neonatal fibroblast-derived dermis, bilayered bioengineered skin substitute, recombinant human platelet-derived growth factor, and autologous platelet-rich plasma, may provide insight into the mechanisms through which differentiated cells could be used as therapy for chronic wounds, and by which stem cells might have a therapeutic role in the management of patients with CLI.

References

1. Zhang L, Chen J, Han C. A multicenter clinical trial of recombinant human GM-CSF hydrogel for the treatment of deep second degree burns. *Wound Repair Regen*. 2009;17(5):685-689.
2. Soderstrom M, Aho PS, Lepantalo M, Alback A. The influence of the characteristics of ischemic tissue lesions on ulcer healing time after infrainguinal bypass for critical leg ischemia. *J Vasc Surg*. 2009:49(4):932-937.
3. Soderstrom M, Arvela E, Alback A, Aho PS, Lepantalo M. Healing of ischaemic tissue lesions after infrainguinal bypass surgery for critical limb ischaemia. *Eur J Vasc Endovasc Surg*. 2008;36(1):90-95.
4. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel vs aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-1339.
5. Kranke P, Bennett M, Martyn-St James M, Schnabel A, Debus SE. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2012;4:CD004123.
6. Petrakis IE, Sciacca V. Spinal cord stimulation in critical limb ischemia of the lower extremities: our experience. *J Neurosurg Sci*. 1999;43(4):285-293.
7. Tshomba Y, Psacharopulo D, Frezza S, Marone EM, Astore D, Chiesa R. Predictors of improved quality of life and claudication in patients undergoing spinal cord stimulation for critical lower limb ischemia. *Ann Vasc Surg*. 2014;28(3):628-632.
8. Tawfick WA, Hamada N, Soylu E, Fahy A, Hynes N, Sultan S. Sequential compression biomechanical device versus primary amputation in patients with critical limb ischemia. *Vasc Endovascular Surg*. 2013 Oct;47(7):532-539.

Drug-Coated Balloons in Long Femoropopliteal Lesions

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The femoropopliteal (FP) segment is the most commonly involved compartment in atherosclerotic peripheral arterial disease (PAD).[1] As many as 60% of lesions are located in this territory,[2,3] are usually long, and have varying degrees of calcification, which renders most of them as TransAtlantic Inter-Society Consensus (TASC) C and TASC D categories.[4,5] Endovascular techniques and strategies have rapidly evolved over the past decade, and as such have become the initial strategy for most FP lesions, including those in patients with critical limb ischemia (CLI). Despite these advances, the long-term patency rates of FP interventions are not as good as those achieved in iliac interventions.[6,7]

Percutaneous transluminal angioplasty (PTA) of the superficial femoral artery (SFA) has a high rate of technical success, but target lesion revascularization (TLR) and target vessel revascularization (TVR) remains high; it ranges from 30% to 80% at 6 months,[8] especially in total occlusions and long diseased segments. Failure rates can be as high as 70% at 1 year in long lesions.[9,10] This is likely the result of neointimal hyperplasia, intimal dissection, and elastic recoil of the arterial wall. Metallic stents with good radial strength obliterate recoil and manage dissections, but in-stent restenosis remains the Achilles' heel, especially in patients with CLI and those with poor infrapopliteal arterial run-off.[11,12] The 12-month primary patency rates of bare-metal stents in the SFA range between 50% to 65%.[13,14] Other factors contributing to poor patency include stent fracture and vessel kinking at the adductor canal and popliteal segment. The former is due to competing and coexisting biomechanical forces such as internal and external rotation, as well as compression and expansion; while the latter is secondary to high flexion forces. With the advent of drug-eluting stents (DES), the panorama appears to be changing. The Zilver PTX study demonstrated appreciable clinical efficacy in symptomatic FP disease patients.[15] However, the trial was criticized for treating only short lesions, thus not representing real-world experience. Moreover, CLI patients often present with extensive FP disease.

Principles of Drug-Coated Balloons

Drug-coated balloons (DCBs) are an attractive alternative to DES because they can deliver the antiproliferative agent to the vessel wall without leaving any stent behind. There are three key features to the use of DCBs.[16] First is vessel preparation (PTA utilizing a noncoated undersized balloon), followed by a DCB to facilitate even distribution of the drug. Second, the preferred antiproliferative agent is paclitaxel, as it tends to stay in the local microenvironment, thus increasing its inhibitory effects on intimal cell proliferation. Finally, the preferred carrier is a hydrophilic spacer, which can deliver the drug in a very short time frame with minimal loss into the systemic circulation. Prolonged drug elution is not necessary to obtain sustained inhibition of intimal hyperplasia.[17] Nonetheless, persistence of the antiproliferative drug in the vessel wall, with its release occurring during the most active phase of neointimal proliferation, should be enough to decrease restenosis.

Clinical Trials

Most of the evidence for the use of DCBs in peripheral arteries is based on trials involving FP lesions. The following trials paved the way for the use of DCB in PAD. The THUNDER trial (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) was the first human trial of DCBs in non-coronary arteries.[18] It was a multicenter study with a 3-way randomization protocol consisting of 154 patients with severe disease or total occlusion of the FP segment. The first group was treated with a paclitaxel-DCB, the second group was treated with a standard uncoated balloon, and the third group was treated with an uncoated balloon with paclitaxel dissolved in iopromide contrast medium. The mean lesion length was 7.4 cm. The primary endpoint was 6-month angiographic late lumen loss (LLL). The paclitaxel-DCB group had a marked reduction in LLL when compared to the other two groups. TLR at 6 months was reduced in the DCB group (4% vs 29%; P=0.001). These favorable DCB effects were sustained at 24-month follow-up. Also, at 5 years, the decrease in LLL persisted.[19] However, TLR rates were not statistically different between the standard balloon and the uncoated balloon with paclitaxel dissolved in contrast medium. The FEMPAC (femoral paclitaxel) trial randomized 87 patients in a 1:1 fashion between a standard uncoated balloon and paclitaxel DCB.[20] Femoropopliteal lesions were short in length (5.7 cm vs 6.1 cm). Results were similar to the THUNDER trial. At 6-month follow-up, LLL was significantly lower in the DCB group. Similarly, TLR rates were lower in the DCB group (6.7% vs 33%; P=0.002). These results were sustained at 18 months. There was significant improvement in Rutherford class, but there was no significant difference in ankle brachial index (ABI). These multicenter trials were limited to relatively short, noncomplex FP lesions, heterogeneous study subjects, unconventional endpoints, angiographic follow-up limited to only 6 months, and small sample sizes. The LEVANT 1 trial (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) was a prospective, multicenter, randomized study that evaluated the safety of the paclitaxel-coated MOXY balloon (Bard).[21] A total of 101 patients with de novo and restenotic FP lesions with CLI were randomized to paclitaxel-DCB (49 patients) and standard uncoated balloon (52 patients). The mean lesion lengths were 80.8 mm vs 80.2 mm. The primary endpoint of LLL at 6 months was significantly lower in the DCB group. Also, the DCB group continued to demonstrate a reduction in LLL when compared to those patients who underwent bailout stenting (26 patients) due to failed PTA (however, the trial was underpowered to conclude that there is a statistical difference between the stent and DCB groups). Composite 24-month major adverse events were lower in the DCB group than the non-DCB group (39% vs 46%). These trials demonstrated that incomplete balloon expansion and geographic miss resulted in a significant decrease in primary patency and an increase in TLR rates at 12 months.[22] The LEVANT 2 trial was a prospective, randomized, controlled multicenter study that randomized 476 patients with stenotic or occlusive FP lesions to standard uncoated balloon and MOXY DCB. This was the first clinical trial in the United States to study the use of DCB for FP artery disease.[23] The primary safety endpoints were composite freedom from all-cause mortality and freedom of amputation and/or reintervention at 12 months. The primary efficacy endpoints were primary patency rates at 12 months and freedom from TLR. The PACIFIER trial[24] (Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis) was a prospective, multicenter randomized controlled single-blinded study that studied 91 FP lesions treated with either the In.Pact Pacific DCB (Medtronic), or an uncoated balloon. The mean lesion length was 68 mm ± 2 mm. The DCB group exhibited a significant reduction in LLL and had better TLR rates at 6 months. In a subgroup analysis, the benefits of DCB with regard to LLL were seen irrespective of the lesion type or its length. At 12 months, the DCB group had fewer adverse events (death, amputation, or TLR) than the standard uncoated balloon group. A meta-analysis of the THUNDER, FEMPAC, LEVANT I, and PACIFIER trials showed improved results with DCBs at a median follow-up of 10.3 months, with significant reduction in TLR, LLL, and angiographic restenosis

The concept of biodegradable stents is promising and enticing. The fact that we can achieve antiproliferative drug delivery and prevent acute recoil and negative remodeling, coupled with the disappearance of the stent when the process of neointimal proliferation has ended, is an attractive concept.

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Drug-Coated

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without an increase in adverse events.[25]

Some of the more recent trials, such as IN.PACT SFA I (European arm) and II (US arm), are ongoing multicenter randomized studies.[26] These trials intend to assess the safety and efficacy of the Admiral DCB in FP lesions. Preliminary 12-month results of 331 patients randomized in a 2:1 fashion (220 in the DCB group and 111 in the standard balloon PTA group) across Europe (150 patients) and the United States (181 patients) showed that the DCB group had better primary patency rates (82.2% vs 52.4%), clinically driven TLR (2.4% vs 20.6%), primary sustained clinical improvement, freedom from 30-day device- and procedure-related death, target limb major amputation, clinically driven target vessel revascularization, and thrombosis. The DEBELLUM study (Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment) was a prospective, randomized, single-center study that enrolled 50 patients with FP (75.4%) and below-the-knee lesions.[27] Twenty-five patients were randomized to be treated with the In.Pact Admiral DCB and 25 patients to be treated with a standard uncoated balloon. At 6 months, LLL was better in the DCB group. BIOLUX P-I was an international, multicenter, randomized controlled trial that evaluated the safety and efficacy of the Passeo-18 Lux paclitaxel-coated balloon (Biotronik) in 30 patients compared to the standard uncoated balloon (30 patients).[28] The DCB group showed a significant reduction in LLL at 6 months. The overall major adverse event rate did not differ in both groups. The DCB group showed a slightly better outcome in regard to Rutherford class. The DEFINITIVE AR study was a European multicenter, prospective, randomized trial that evaluated the effectiveness of DCBs in heavily calcified lesions. Patients were randomized to directional atherectomy followed by paclitaxel-coated Cotavance balloon (Bayer HealthCare) vs paclitaxel-coated Cotavance balloon alone. The 30-day preliminary results showed significantly higher technical success in the atherectomy + paclitaxel DCB arm.[29]

New-Generation Drug-Coated Balloons

The new generation of DCBs (Legflow and PRIMUS, both by Cardionovum) has paclitaxel nanoparticles embedded in an innovative stable shelloic acid coating. This helps to prevent embolization and wipe-off when introducing the DCBs through the valve of the sheath. Preliminary studies involving these new generation DCBs have shown promising results with regards to efficacy and safety endpoints.[30] In a similar fashion, the ILLUMENATE study is a prospective, controlled, multicenter trial evaluating safety and efficacy of a new DCB that utilizes a rapid-release drug delivery mechanism to infuse paclitaxel (Stellarex; Covidien).[31] Fifty-eight FP lesions were treated with the Stellarex DCB achieving a 12-month primary patency of 87%. Regarding safety endpoints, there were no amputations or deaths.

Finally, the DANCE study (Dexamethasone Infusion to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization) is an open-label, nonrandomized, single-arm, single-center pilot trial evaluating the safety and efficacy of a new balloon drug delivery catheter, which deploys a microneedle into the adventitia, delivering dexamethasone (an anti-inflammatory drug).[32] A total of 20 patients were enrolled in the study, which demonstrated an improvement in ABI at discharge, 6 months, and 12 months, along with Rutherford class. The 6-month patency rates were comparable to that of DES and DCBs.

Benefits

The main advantages of DCBs are as follows:

- Ability to deliver the antiproliferative drug homogeneously and at a greater dose per square millimeter.
- Ability to treat bypass landing zones.
- No permanent implant, which can be a source of physical and chemical irritation, in addition to being an immunologic trigger.
- Preservation of the original anatomy of the vessel.
- Ability to use the DCBs in segments where the use of stents is not advised (common femoral and popliteal arteries).
- Ability to reduce the occurrence of delayed healing, which is seen in the presence of a polymer matrix.
- Ability to reduce the duration of dual antiplatelet therapy, as the controlled alteration of the vessel wall is short lived.
- Delivery of the antiproliferative drug during the critical phase of neointimal proliferation.
- Cost effectiveness, given that DCBs can prolong patency and avoid TLR. A recent study showed that drug-eluting strategies had a lower projected budget impact (over 2 years) when compared to standard balloon PTA and bare-metal stents.[33]

Pitfalls of Drug-Coated Balloons

DCBs fail to overcome elastic recoil and negative remodeling of the vessel wall, especially in calcified lesions. Also, in long calcified vessels, they fail to deliver the drug homogeneously. Hence, the DEFINITIVE AR study was undertaken with the intention of excising plaque and improving perfusion to the vessel wall, which would (at least theoretically) translate into homogeneous drug delivery. Finally, there always remains concern about drug loss before the balloon reaches the target segment. Using long guiding catheters or sheaths can potentially prevent drug loss. It is usually in the first 10 seconds of balloon inflation that transfer of paclitaxel into the vessel wall occurs.[34] However, when the inflation is performed for 30 seconds to 60 seconds, only 20% of the paclitaxel is transferred into the vessel wall.[35] Some of the concerns regarding drug loss before deploying the balloon are the local and systemic toxic effects of this antiproliferative agent. Newer generation DCBs have paclitaxel nanoparticles embedded. Finally, meticulous handling of the DCB equipment is of utmost importance, in order to prevent contamination from other laboratory equipment. All measures should be taken to avoid the staff from drug exposure through inhalation.

Future

The concept of biodegradable stents is promising and enticing. The fact that we can achieve antiproliferative drug delivery and prevent acute recoil and negative remodeling, coupled with the disappearance of the stent when the process of neointimal proliferation has ended, is an attractive concept. Recently, a multicenter, nonrandomized registry evaluating the efficacy and safety of a biodegradable (REMEDY) stent demonstrated a primary patency of 71% and TLR of 22%.[36]

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References

1. Brodmann M. Prime time for drug eluting balloons in SFA interventions? *J Cardiovasc Surg (Torino)*. 2014;55(4):461-464.
2. Kasapis C, et al. Current approach to the diagnosis and treatment of femoral-popliteal arterial disease. A systematic review. *Curr Cardiol Rev*. 2009;5(4):296-311.
3. Zeller T, et al. Drug-coated balloons in the lower limb. *J Cardiovasc Surg (Torino)*. 2011;52(2):235-243.
4. Dormandy JA, et al. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg*. 2000;31:S1-S296.
5. Norgren L, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33:S1-S75.
6. Schillinger M, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med*. 2006;354(18):1879-1888.
7. Krankenberg H, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the Femoral Artery Stenting Trial (FAST). *Circulation*. 2007;116(3):285-292.
8. Matsi PJ, et al. Femoropopliteal angioplasty in patients with claudication: primary and secondary patency in 140 limbs with 1–3-year follow-up. *Radiology*. 1994;191(3):727-733.
9. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty. Factors influencing long-term success. *Circulation*. 1991;83:I70-I80.
10. Laird JR. Limitations of percutaneous transluminal angioplasty and stenting for the treatment of disease of the superficial femoral and popliteal arteries. *J Endovasc Ther*. 2006;13:(Suppl 2):II30-II40.
11. Muradin GS, et al. Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. *Radiology*. 2001;221(1):137-145.
12. Grimm J, et al. Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. *J Vasc Interv Radiol*. 2001;12(8):935-942.
13. Moses JW, et al. Perspectives of drug-eluting stents: the next revolution. *Am J Cardiovasc Drugs*. 2002;2(3):163-172.
14. Stettler C, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370(9591):937-948.
16. Dake MD, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol*. 2013;61(24):2417-2427.
17. De Vries JP et al. First- and second-generation drug-eluting balloons for femoro-popliteal arterial obstructions: update of technique and results. *J Cardiovasc Surg*. 2013;54(3):327-332.
18. Deloose K, et al. Drug eluting technologies in femoral artery lesions. *J Cardiovasc Surg (Torino)*. 2013;54(2):217-224.
19. Tepe G, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358(7):689-699.
20. Minar E, et al. Innovative technologies for SFA occlusions: drug coated balloons in SFA lesions. *J Cardiovasc Surg* (Torino). 2012;53(4):481-486.
21. Werk M, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118(13):1358-1365.
    Scheinert D, et al. The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization. *JACC Cardiovasc Interv*. 2014;7(1):10-19.
22. Scheinert D. Lessons learned from LEVANT 1 First-in-man study: 12 month analysis. Presented at: Leipzig Interventional Course, Leipzig, Germany, 2012.
23. 6-month data of the LEVANT 2 trial presented at TCT 2013 [news release]. Cardiovascular Research Foundation. August 24, 2014. http://www.eurekalert.org/pub_releases/2013-10/crf-smd103013.php.
24. Werk M, et al. Paclitaxel-coated balloons reduce restenosis after femoropopliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv*. 2012;5(6):831-840.
25. Cassese S, et al. Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoro-popliteal arterial disease. A meta-analysis of randomized trials. *Circ Cardiovasc Interv*. 2012;5(4):582-589.
26. IN.PACT Admiral Drug-Eluting Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery (SFA) and Proximal Popliteal Artery (PPA) (INPACT SFA II). ClinicalTrials.gov [database online]. Bethesda, MD: National Library of Medicine. http://clinicaltrials.gov/show/NCT01566461.
27. Fanelli F, et al. Lower limb multilevel treatment with drug eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther*. 2012;19(5):571-580.
28. Scheinert D, et al. TCT-585 six month results of the BIOLUX P-I first in man study comparing a paclitaxel releasing balloon catheter versus an uncoated balloon catheter in femoropopliteal lesions. *J Am Coll Cardiol*. 2012;60 (17_S).
29. DEFINITIVE AR 30-day results presented on directional atherectomy plus DCB [news release]. October 10, 2013. http://evtoday.com/2013/09/definitive-ar-30-day-results-presented-on-directional-atherectomy-plus-dcb
30. Briguori C, et al. From bench to bedside: initial experience with the PRIMUS drug-coated balloon catheter. *Minerva Cardioangiol*. 2012;60(5):507-515.
31. ILLUMENATE first-in-man study shows promising results with Covidien's new drug-eluting balloon [news release]. May 29, 2013. http://www.cxvascular.com/vn-latest-news/vascular-news---latest-news/illumenate-first-in-man-study-shows-promising-results-with-covidiens-new-drug-eluting-balloon.
32. Balloon with microneedle creates drug-eluting reservoir to prevent restenosis [news release]. August 29, 2013. http://www.cxvascular.com/vn-latest-news/vascular-news---latest-news/balloon-with-microneedle-creates-drug-eluting-reservoir-to-prevent-restenosis-.
33. Pietzsch JB, et al. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. *Catheter Cardiovasc Interv*. 2014;84(4):546-554.
34. Dake MD, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv*. 2011;4(5):495-504.
35. Scheller B, et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation*. 2004;110(7):810-814.
36. Vermassen F, et al. Role of bioresorbable stents in the superficial femoral artery. *J Cardiovasc Surg (Torino)*. 2013;54(2):225-234.

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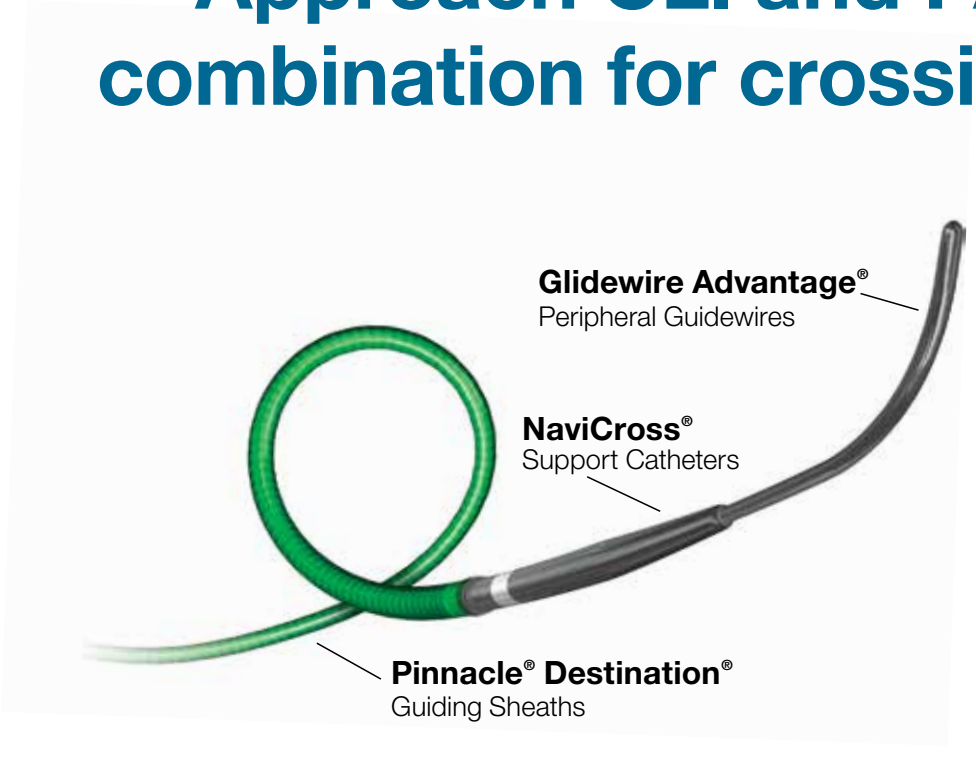

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Early Experience With DCBs in a Single Center

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Andrej Schmidt, MD

Since the first studies of paclitaxel-coated balloons (THUNDER and FemPac trials) showed a reduction in the restenosis rate after angioplasty of femoropopliteal lesions, drug-coated balloons (DCBs) became one of the most promising technologies for endovascular peripheral arterial occlusive disease therapy.[1,2] Recently, several different DCBs have been tested in proof-of-concept studies, mainly in the femoropopliteal segment, whereas only a few below-the-knee (BTK) trials have been initiated. In fact, restenosis after endovascular treatment of infrapopliteal arteries in patients with critical limb ischemia (CLI) using standard, non-coated balloons has not been studied to a sufficient extent until recently. Furthermore, our knowledge about the impact of restenosis on the clinical course of CLI patients is still nearly exclusively derived from retrospective studies, and therefore incomplete.

Prospective studies testing drug-eluting stents (DES) in infrapopliteal arteries have shown that restenosis can be reduced by this technology.[3-5] Clinical endpoints such as target lesion revascularization (TLR) could be reduced by the use of DES, and in one study, even major amputation was lower after DES implantation compared to bare-metal stents after 3 years of follow-up.[5] However, DES are only applicable in relatively short lesions and CLI patients mainly present with long BTK occlusions. In a recent "real-life" registry of CLI patients, DES implantation was used as an endovascular recanalization strategy in only 5% of patients.[6] Long, low-profile drug-eluting balloons might therefore be the solution for these typically long infrapopliteal lesions in CLI patients.

First Experience With DCB in Infrapopliteal Arteries

The first DCB approved in Europe was the In.Pact Amphirion (Medtronic). Before this approval, the standard treatment for CLI patients with long infrapopliteal lesions at our center was plain old balloon angioplasty (POBA) with long low-profile balloons like the Amphirion Deep (Medtronic). In a registry of 58 CLI patients, we demonstrated that clinical results can be very satisfying using this approach, but restenosis occurs very early and in a high proportion of patients. Angiography performed 3 months after POBA revealed a nearly 70% restenosis rate in BTK lesions with a mean length of 183 mm (Figure 1).[7] Therefore our policy became to perform control angiography at 3 months whenever the patient was still in a Rutherford class IV to VI. Using this strategy, the TLR rate approached 50% within 15 months (most procedures performed at 3 months), but the limb salvage rate was 100%, supporting the invasive protocol. After introducing the In.Pact Amphirion PTX-coated balloon, we continued this approach and were able to compare the 3-month DCB restenosis rates to our historical registry. In 104 patients, we found a 3-month restenosis rate of only 27% for lesions with a mean length of 173 mm. The TLR rate at 1 year was 17%, which was significantly lower than in our previous series using POBA.[8]

Considering the good results (in terms of limb salvage) that can be achieved by POBA according to our own experience and from the literature (e.g., Ferraresi et al achieved a limb-salvage rate of 93% at nearly 3 years in diabetic CLI patients with isolated BTK lesions with a mean length of 213 mm[9]), the goal of treatment with DCB cannot be to improve this endpoint. However, TLR reduction can indeed represent a clinically meaningful outcome for these typically very fragile CLI patients, as well as resulting in cost savings.

Other DCB Trials Below the Knee

The first randomized study using a DCB in the BTK segment was the IN.PACT DEEP: an investigator-initiated, single-center trial without industry support.[10] The primary endpoint was the restenosis rate at 1 year, assessed mainly by angiography. In 132 diabetic CLI patients, 158 BTK lesions in 143 limbs were randomized in a 1:1 fashion. Lesion length was 129 mm (DCB) and 131 mm (POBA). Restenosis at 1 year was significantly lower in the DCB group (27% vs 75%). Moreover, the 12-month

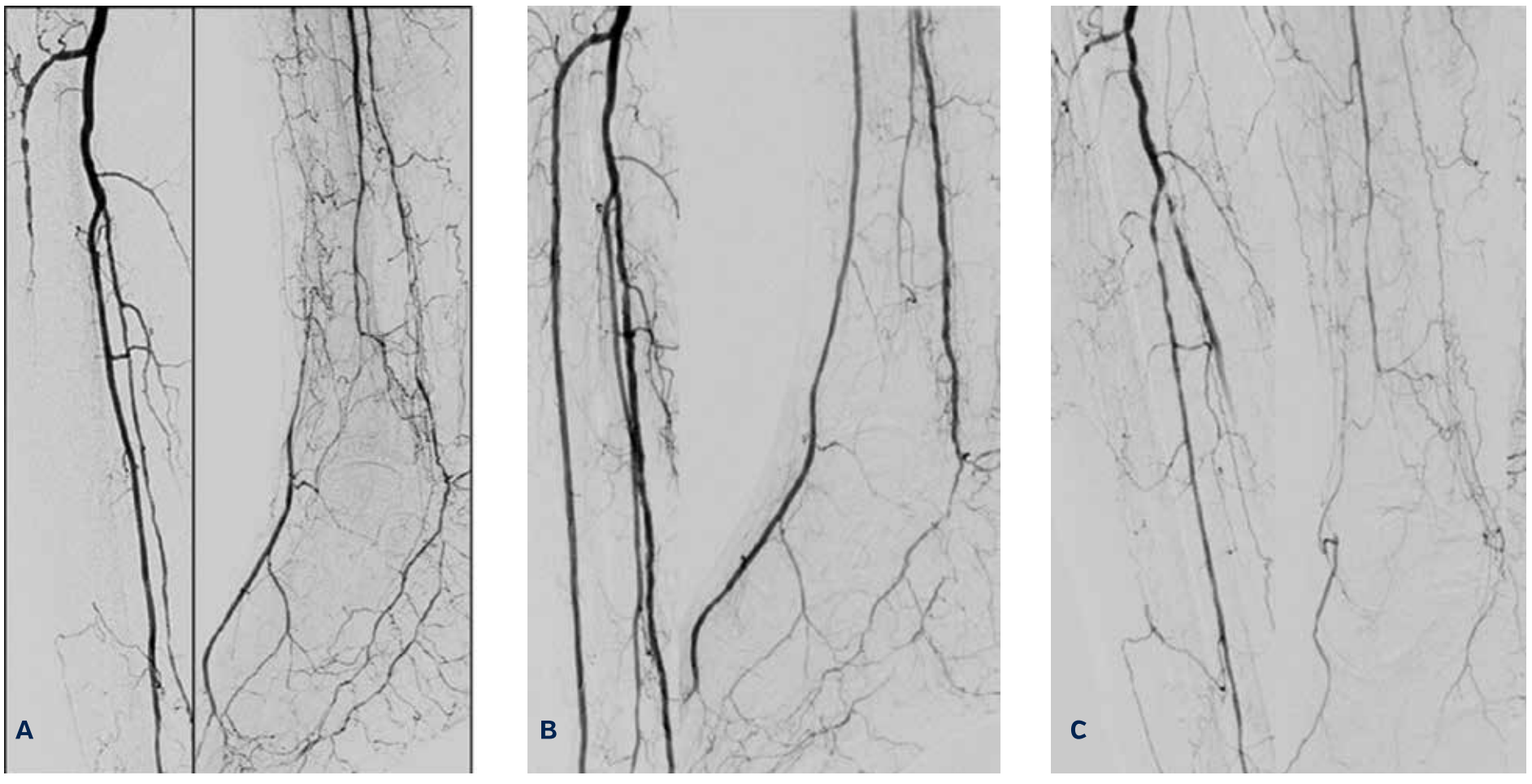

Figure 1. Diabetes patient with critical limb ischemia in the right forefoot and long BKT lesions. Total occlusion of the anterior tibial artery and diffuse disease of the posterior tibial artery (A). After treatment with noncoated low-profile balloon (B). Slow healing, angiography 2.5 months after PTA showed diffuse reocclusion (C).

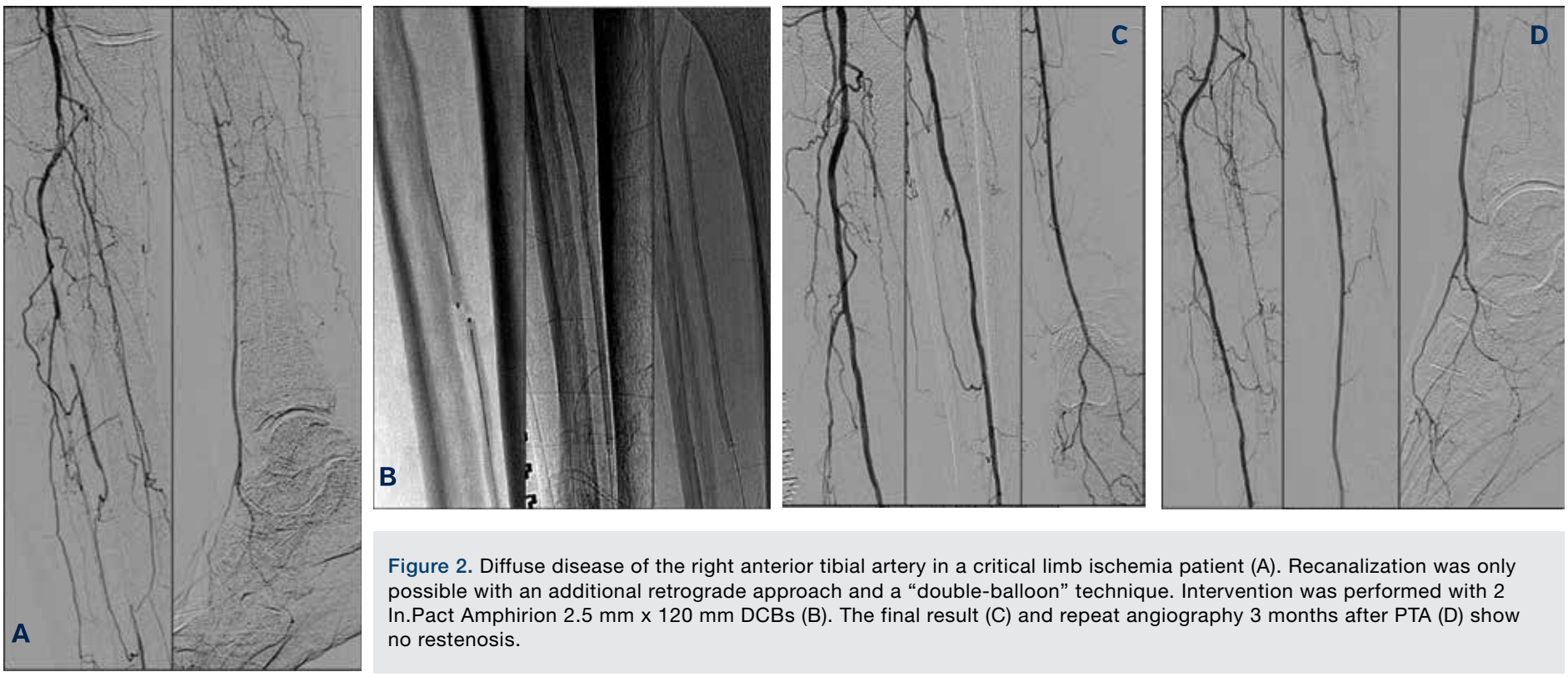

Figure 2. Diffuse disease of the right anterior tibial artery in a critical limb ischemia patient (A). Recanalization was only possible with an additional retrograde approach and a "double-balloon" technique. Intervention was performed with 2 In.Pact Amphirion 2.5 mm x 120 mm DCBs (B). The final result (C) and repeat angiography 3 months after PTA (D) show no restenosis.

major adverse event rate was significantly lower in the DCB group (31% vs 51%), mainly driven by a lower TLR rate. Healing time was shorter and the rate of complete ulcer healing was higher in the DCB arm.

Recently the results of the larger multicenter, randomized IN.PACT DEEP trial were published[11]: 358 CLI patients were randomized in a 2:1 fashion to either the DCB (In.Pact Amphirion) or POBA arms. Primary efficacy endpoints were late lumen loss (LLL) and TLR rates at 12 months. If the lesion was ≤100 mm in length, patients underwent mandatory angiography at 12 months to study the LLL, but all patients were followed clinically. Results were surprising: no difference was seen in LLL between both groups. Moreover, results showed a trend toward higher major amputations with 8.8% in the DCB arm vs 3.6% in the POBA arm at 12 months, and these results led to a voluntary recall of the In.Pact Amphirion DCB from the market, although causality between major amputations and the use of the In.Pact Amphirion could not be established.

An extensive discussion of the results is not possible until the full dataset is released, but some comments to explain these results (which are contrary to our own experience and that of Ferraresi et al), might be attempted here. The lesions in IN.PACT DEEP were relatively benign compared to those in DEBATE-BTK (IN.PACT DEEP reported lesion lengths of 59 mm with 46% chronic total occlusions, whereas DEBATE-BTK lesion length was 129 mm with 78% chronic total occlusions). Based on our experience, it appears fair to say that long and complex lesions should benefit from DCB treatment, as these lesions typically exhibit high restenosis rates after POBA. In addition to this, the POBA arm in IN.PACT DEEP had an unusually low restenosis rate compared to the literature, which might partially explain the endpoint similarity between the DCB and POBA groups.

Drug-coated balloons can become a valuable tool to treat long BTK lesions.

It is also worth considering that the attempt to demonstrate a reduction of LLL and restenosis at 12 months might be too ambitious. The difference between DCB and POBA we have seen at 3 months might indeed be lost over a longer time period. For the clinical course of the patient, this may have a low impact. For wound healing, the first months after recanalization are the most crucial, and DCBs keeping the arteries patent for this time period might help to bring more patients out of the critical ischemia stage before restenosis occurs.

Long-Term Clinical Results From Single-Center Studies

In light of the potential safety signal of the IN.PACT DEEP study, we analyzed long-term results from a larger patient group using the In.Pact Amphirion DCB. In 195 CLI patients, 205 limbs were treated, and the average lesion length of 214 BTK arteries was 142 mm. A median follow-up of 425 days and the fact that only 1 patient was lost to follow-up allows us to report some safety data even out to 3 years. The major amputation rate at 1 year was 3.9% and does not raise any safety concerns. At 3 years, the major amputation rate was 5.9%, which is promising compared to the literature. The rate of clinically driven TLR in our DCB cohort was 21%. This is comparable to our initial series of 104 patients with a TLR rate of 15% and to the TLR rate of 18% at 1 year in the DEBATE-BTK trial.

Nevertheless, due to the results of the IN.PACT DEEP trial, DCBs are currently only used within studies at our center using alternative paclitaxel-coated balloons approved in Europe, like Lutonix (Bard) or Passeo-18 Lux (Biotronik). If the results from these trials do not meet our expectations, the question will be left unanswered about whether the concept of DCB below the knee does not work or whether other DCBs are simply not as effective.

Conclusion

Our impression is that DCBs in infrapopliteal arteries are effectively lowering the high early restenosis rate and can become a valuable tool to treat long BTK lesions. We do not think that the goal of BTK DCBs should be the reduction of major amputations, as standard non-coated balloons have demonstrated excellent results in this regard. We do think that achieving TLR reductions as well as shorter clinical recovery times for the patients are endpoints worth considering in the design of future BTK DCBs trials, as they represent valuable goals for the patient.

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References

1. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Eng J Med*. 2008;358(7):689-699.
2. Werk M, Langer S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118(13):1358-1365.
3. Bosiers M, Scheinert D, Peeters P, et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg*. 2012;55(2):390-398.
4. Scheinert D, Katsanos K, Zeller T, et al. A prosepctive randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. *J Am Coll Cardiol*. 2012;60(22):2290-2295.
5. Rastan A, Brechtel K, Krankenberg H, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents. Long-term results from a randomized trial. *J Am Coll Cardiol*. 2012;60(7):587-591.
6. Baumann F, Bloesch S, Engelberger RP, et al. Clinically-driven need for secondary interventions after endovascular revascularization of tibial arteries in patients with critical limb ischemia. *J Endovasc Ther*. 2013;20(5):707-713.
7. Schmidt A, Ulrich M, Winkler B, et al. Angiographic patency and clinical outcome after balloon-angioplasty for extensive infrapopliteal arterial disease. *Catheter Cardiovasc Interv*. 2010;76(7):1047-1054.
8. Schmidt A, Piorkowski M, Werner M, et al. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol*. 2011;58(11):1105-1109.
9. Ferraresi R, Centola M, Ferlini M, et al. Long-term outcomes after angioplasty of isolated, below-the-knee arteries in diabetic patients with critical limb ischemia. *Eur J Vasc Endovasc Surg*. 2009;37(3):336-342.
10. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation*. 2013;128(6):615-621.
11. Zeller T, Baumgartner I, Scheinert D, et al; IN.PACT DEEP Trial Investigators. IN.PACT Amphirion paclitaxel eluting balloon versus standard percutaneous transluminal angioplasty for infrapopliteal revascularization of critical limb ischemia: rationale and protocol for an ongoing randomized controlled trial. *Trials*. 2014;15:63.

Drug-Eluting Balloon Technology in the Treatment of Peripheral Arterial Disease: Current Outcomes and Considerations for Use in Clinical Practice

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Treatment of atherosclerotic peripheral vascular disease is extremely challenging owing to multiple factors, including the wide range of vessel size seen in the periphery, complex and variable lesion histopathology and morphology including the frequent presences of chronic total occlusion and heavy calcification, as well as bilateral and multilevel disease. Recent years have seen an explosion of technologies to address these challenges, including multiple atherectomy devices, chronic total occlusion devices and wires, re-entry devices, distal protection devices, scoring and other focused-force balloons, stents and drug delivery devices.

Current Status of Peripheral Antirestenotic Therapy

Although improved stent technology has yielded progressively improved long-term patency rates, stenting in and of itself remains problematic in the periphery. Most current peripheral stent studies have enrolled patients with relatively short diseased segments, in contrast to the long stent treatment zones typically seen in real-world experience. Multiple long stents may be associated with stent fracture and increased restenosis rates and may also limit future surgical intervention. It therefore makes sense to pursue methods of achieving a "stent-like" result without a stent, as well as long-term patency rates more in line with those seen with drug-coated stents in the coronary arteries. Given the poor 12-month patency rates seen with balloon angioplasty alone, atherectomy has gained substantial traction as a means of getting stent-like luminal gain in the short term. Alternative methods of delivering antirestenotic therapy have been pursued in lieu of drug-eluting stents as a means of maintaining that initial luminal gain long term. Drug-eluting balloons (DEB) are one of those methods.

In addition to primary treatment of atherosclerotic peripheral vascular disease, restenosis remains the "Achilles' heel" of peripheral intervention and is likely to remain a major therapeutic dilemma for the foreseeable future. In spite of the aforementioned explosion of technology, balloon angioplasty and bare metal stenting alone or in combination still account for the primary modality used in over 80% of superficial femoral artery (SFA) interventions today.[1]

In contrast to what has been observed with coronary drug-eluting stents (DES), "limus" drugs used in peripheral studies such as the SIROCCO and STRIDES trials yielded disappointing results. In the SIROCCO trial, sirolimus-coated SMART nitinol self-expanding stents (Cordis Corporation) failed to demonstrate superiority over the bare metal version.[2] Results from the STRIDES trial using everolimus were equally unimpressive.[3] In contrast to the above-the-knee experience, "limus" drugs have shown promise when delivered via drug-coated stents below the knee.[4] Paclitaxel, on the other hand, has been demonstrated to be quite effective as an antirestenotic agent when applied to either stents or balloons for the treatment of femoropopliteal disease.

The Zilver PTX randomized controlled trial demonstrated superiority of the Zilver PTX paclitaxel-coated self-expanding stent (Cook Medical) over balloon percutaneous transluminal angioplasty (PTA). Compared with the PTA group, the Zilver DES exhibited superior 12-month event-free survival (90.4% vs 82.6%; P=.004) and primary patency (83.1% vs 32.8%; P<.001).[5]

Paclitaxel applied to balloon angioplasty catheters has yielded similar positive outcomes. Paclitaxel is a lipophilic drug bound to angioplasty balloons with a hydrophobic spacer or "excipient." The drug is released directly into the vessel wall upon balloon expansion (although the majority of drug is lost in transit to the treatment zone). Balloon surface concentration of drug has typically been 2 to 3 mcg/mm^2. Studies outside the United States confirming the effectiveness of DEB have included the THUNDER, FEMPAC, PACIFIER, and LEVANT 1 trials.[6-10]

The THUNDER trial randomized 154 patients to control (plain old balloon angioplasty [POBA] alone, 54 patients), POBA and intra-arterial paclitaxel (52 patients) and paclitaxel-coated balloon (40 patients). Late lumen loss was significantly less in the paclitaxel balloon group as compared to the other two groups (P<.01). Target revascularization at 12 months was 10% in the drug-eluting balloon group vs almost 50% in the POBA alone group and 39% in the uncoated balloon and intra-arterial paclitaxel group. Late lumen loss was also significantly reduced as compared to the other group (P<.01).[6,7] The FEMPAC trial demonstrated 6-month restenosis rates of 19% vs 47% (paclitaxel-coated vs uncoated balloon).[8] The PACIFIER study enrolled 450 patients at 55 European and US sites and reported a composite outcome of death, amputation, and TLR at 1 year of 7% vs 35% for paclitaxel-coated and uncoated balloon angioplasty respectively.[9] Finally, the LEVANT I trial reported late lumen loss of 0.18 and 1.09, TLR of 10% and 33.3%, and primary patency (freedom from TLR and restenosis, peak systolic velocity ratio >2.5) of 85.7% and 54.8% respectively for coated vs uncoated balloon angioplasty.[10] More recent trials include IN.PACT SFA 1 and 2 (Medtronic Endovascular; currently enrolling) and the LEVANT 2 study of the Lutonix drug-coated balloon (Bard). Twelve-month data for LEVANT 2 submitted to the FDA resulted in a unanimous panel vote to recommend approval of this DEB in the United States. At 6 months, primary patency was 92.3% for the DEB vs 82.7% for angioplasty alone (P=.003), and at 12 months, primary patency was 65.2% and 52.6%, respectively (P=.015). Unfortunately, the IN.PACT DEEP study (Medtronic Endovascular) using a paclitaxel DEB below the knee was terminated early due to poorer outcome in CLI patients treated with DEB as compared to balloon angioplasty alone. There are numerous theories as to why the DEB group had poorer outcomes, including flaking and embolization of the excipient or impairment of tissue healing distally due to the paclitaxel traveling downstream.

Practice Considerations

Once DEBs are approved in the United States, clearly they will rapidly become part of the "toolbox" used in peripheral vascular intervention, with their use in turn justified by the mounting data confirming their effectiveness. That being said, the peripheral interventional physician should keep several important points in mind when using these devices.

1. *Cost:* DEBs are expensive one-time-use devices. Addressing a long SFA lesion may require 3 or 4 balloons to adequately cover the entire treatment zone. In an environment of declining reimbursements, use of multiple DEBs may not be economically prudent or even feasible.
2. *Critical Limb Ischemia (CLI):* Given the adverse events observed in the IN.PACT DEEP trial upon treating below-the-knee disease with DEBs in CLI patients, caution is warranted when treating above-the-knee disease in those patients. The majority of DEB trials have involved the randomization and treatment of femoropopliteal disease in claudicants, not CLI patients. Whatever the reasons for the adverse outcomes seen in the IN.PACT DEEP trial, the same factors may come into play when treating above-the-knee disease in a CLI patient.
3. *Proper Balloon Technique:* Since the advent of coronary stenting, proper balloon angioplasty technique has largely become a lost art form. Even severe dissections or perforations of coronary vessels can rapidly be managed by stent placement. If the goal in the periphery is to avoid or limit the amount of stenting required, then the art of proper balloon technique must be rediscovered by many operators. In the days prior to coronary stenting, pristine angiographic results were frequently obtained by very prolonged balloon inflations, accompanied by very slow and controlled balloon inflation and deflation. Similar balloon technique, along with prolonged inflation times for drug delivery balloons, have been clearly specified as part of the protocol in all of the peripheral DEB studies. The usefulness of this technique to avoid dissection (and therefore stenting) can be demonstrated by comparing the dilatation process to stretching modeling clay or toffee. Stretch these substances quickly and they snap and break apart; pull them apart slowly

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Drug-Eluting

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and they stretch and can be molded. The same holds true when dilating a vessel. Dilating a vessel slowly and over a prolonged period of time will allow the internal elastic lumina and fibrotic material in the vessel to stretch and mold, rather than snap and dissect. Patience is the order of the day when performing balloon angioplasty in the periphery. Even if dissection doesn't occur, a rapid inflation and deflation will almost certainly result in early elastic recoil within 24 hours to 48 hours after the procedure.

4. *Vessel Preparation:* Given the diffuse vessel histopathology and morphology encountered in the periphery, uniform uptake of an antirestenotic drug may not always occur, particularly in heavily calcified lesions. The question then becomes whether a DEB can be a stand-alone device or can the effectiveness of a DEB be enhanced by more aggressive vessel preparation such as atherectomy? Though no large-scale studies have been carried out to answer this question, smaller studies are now being carried out that may support the concept. The DEFINITIVE LE study (Coviden) evaluated the effectiveness of directional atherectomy in claudicants and CLI patients.[11] Eight hundred patients were evaluated at 47 centers. At 12 months, primary patency in claudicants was 78% (77% in diabetic patients). Freedom from amputation in CLI patients was 95%. The combination of directional atherectomy plus drug delivery is now being evaluated in the DEFINITIVE AR study. The PHOTOPAC study (Photoablative Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis in Instent Femoropopliteal Obstructions) is currently enrolling at several European centers to evaluate the effectiveness of debulking in-stent restenosis with laser prior to delivery of antirestenotic therapy with DEBs. A small study, Registry Lugano, conducted by Jos van den Berg[12] and presented at the Leipzig Interventional Course in 2012, reported results from 14 patients with in-stent restenosis treated with laser atherectomy followed by DEB. Mean lesion length was 133 mm (range 10 mm to 38 mm). Mean clinical follow-up was 15.6 months with no TLR and no restenosis reported.

More data are required for balloon drug delivery in peripheral intervention and all peripheral interventional modalities and their long-term outcomes. Until such data become available and until formal guidelines are established, reasonable algorithms based on lesion morphology would be as follows:

1. Simple lesions (short/noncalcified):
   a. Balloon angioplasty or focused-force balloon angioplasty (with or without DEB)
   b. Provisional stenting
2. Complex lesions (long/calcified):
   a. Atherectomy followed by balloon angioplasty or focused force balloon angioplasty
   b. DEB
   c. Provisional stenting
3. Chronic total occlusions:
   a. Atherectomy (only if a true luminal crossing is assured)
   b. Balloon angioplasty or focused-force balloon angioplasty
   c. DEB
   d. Provisional stenting

Conclusion

Drug-eluting balloons hold great promise for impacting long-term outcomes in peripheral intervention. However, endoluminal drug delivery may not be the final answer for addressing neointimal hyperplasia and restenosis. Because restenosis starts in the media and adventitia with cellular proliferation and migration to the intimal layers, endoluminal delivery of drugs treats the symptom and not the disease. It would be more efficient and effective to stop restenosis at the source or before it starts. Investigational devices such as the Bullfrog Catheter (Mercator Med Systems), which uses a microinfusion needle to delivery therapeutic agents to the media and adventitia, may actually prove to be more effective than DEBs. The key for the peripheral interventional operator is therefore to keep each new device in perspective, understand fully the mechanism of actions, understand the clinical scenarios and vascular anatomy and pathology in which that device may or may not be effective, understand device limitations, and understand how and when to use that device to exploit its full potential benefit, while minimizing its potential adverse effects and complications. The importance of proper device technique, especially when using a balloon catheter, can also not be understated.

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References

1. Millenium Research Group. US Markets for Peripheral Vascular Devices 2012. http://www.mrg.net/Products-and-Services/Syndicated-Report.aspx?r=RPUS11PV11
2. Duda S, Mosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther.* 2006;13(6):701-710.
3. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of Nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. *J Vasc Surg.* 2011;54(2):394-401.
4. Bosiers M, Scheinert D, Peeters P, et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg.* 2012;55(2):390-398.
5. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease. Twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv.* 2011;4:495-504.
6. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med.* 2008;358(7):689-699.
7. Tepe G, Zeller T, Schnorr B, et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study. *J Endovasc Ther.* 2013;20(6):792-800.
8. Werk M, Langner S, Reinkensmeir B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation.* 2008;118(13):1358-1365.
9. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv.* 2012;5(6)831-840.
10. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv.* 2014;7(1):10-19.
11. McKinsey JF, Zeller T, Rocha-Singh KJ, Jaff M, Garcia L. Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. *JACC Cardiovasc Interv.* 2014;7(8):923-933.

Vascular Effects

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drug effect in preclinical models, a lack of biological threshold to predict clinical efficacy remains to be an important limitation and may become a key obstacle to widening the clinical applications of this technology. To overcome this hurdle, DCB technology has recently been extended to employ "limus" coatings, which might ultimately help to improve the risk profile of this emerging technology. However, vascular responses may vary between different coating strategies employing different drugs and carriers, and potentially affect intrinsic safety profiles. Efficacy and safety of each DCB should be independently supported by a high level of preclinical and clinical studies.

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References

1. Owings MF, Kozak LJ. Ambulatory and inpatient procedures in the United States, 1996. *Vital Health Stat 13.* 1998;(139):1-119.
2. Mozes G, Keresztury G, Kadar A, et al. Atherosclerosis in amputated legs of patients with and without diabetes mellitus. *Int Angiol.* 1998;17(4):282-286.
3. Suzuki K, Iida O, Yamauchi Y, et al. Impact of diabetes mellitus on critical limb ischemia with below the knee disease: Japan below-the-knee artery treatment subanalysis. *Angiology.* 2013.
4. Williams DT, Price P, Harding KG. The influence of diabetes and lower limb arterial disease on cutaneous foot perfusion. *J Vasc Surg.* 2006;44(4):770-775.
5. Scheinert D. Treatment paradigms for the superficial femoral artery: are they a-changin? *JACC Cardiovasc Interv.* 2012;5(3):339-340.
6. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G, Viva Physicians Inc. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. *Catheter Cardiovasc Interv.* 2007;69(6):910-919.
7. Krankenberg H, Schluter M, Steinkamp HJ, et al. Nitinol stent implantation versus percutaneous translumminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). *Circulation.* 2007;116(3):285-292.
8. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. *Circ Cardiovasc Interv.* 2010;3(3):267-276.
9. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med.* 2006;354(18):1879-1888.
10. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther.* 2006;13(6):701-710.
11. Bosiers M, Torsello G, Gissler HM, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of the DURABILITY I study. *J Endovasc Ther.* 2009;16(3):261-269.
12. Iida O, Nanto S, Uematsu M, et al. Long-term results of endovascular therapy with nitinol stent implantation for TASC II A/B femoro-popliteal artery lesions: 4 years' experience. *Circ J.* 2009;73(11):2143-2147.
13. King L, Byrne RA, Mehilli J, Schomig A, Kastrati A, Pache J. Five-year clinical outcomes of a polymer-free sirolimus-eluting stent versus a permanent polymer paclitaxel-eluting stent: final results of the intracoronary stenting and angiographic restenosis - test equivalence between two drug-eluting stents (ISAR-TEST) trial. *Catheter Cardiovasc Interv.* 2013;81(1):E23-E28.
14. Scheinert D, Scheinert S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. *J Am Coll Cardiol.* 2005;45(2):312-315.
15. Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol.* 2013;61(24):2417-2427.
16. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med.* 2008;358(7):689-699.
17. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation.* 2008;118(13):1358-1365.
18. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med.* 2006;355(20):2113-2124.
19. Waksman R, Pakala R. Drug-eluting balloon: the comeback kid? *Circ Cardiovasc Interv.* 2009;2(4):352-358.
20. Indermuehle A, Bahl R, Lansky AJ, et al. Drug-eluting balloon angioplasty for in-stent restenosis: a systematic review and meta-analysis of randomised controlled trials. *Heart.* 2013;99(5):327-333.
21. Posa A, Hemetsberger R, Petnehazy O, et al. Attainment of local drug delivery with paclitaxel-eluting balloon in porcine coronary arteries. *Coron Artery Dis.* 2008;19(4):243-247.
22. Micari A, Cioppa A, Vadala G, et al. Clinical evaluation of a paclitaxel-eluting balloon for treatment of femoropopliteal arterial disease: 12-month results from a multicenter Italian registry. *JACC Cardiovasc Interv.* 2012;5(3):331-338.
23. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv.* 2014;7(1):10-19.
24. Scheller B, Speck U, Abramjuk C, Bernhardt U, Bohm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation.* 2004;110(7):810-814.
25. Radke PW, Joner M, Joost A, et al. Vascular effects of paclitaxel following drug-eluting balloon angioplasty in a porcine coronary model: the importance of excipients. *EuroIntervention.* 2011;7(6):730-737.
26. Milewski K, Afari ME, Tellez A, et al. Evaluation of efficacy and dose response of different paclitaxel-coated balloon formulations in a novel swine model of iliofemoral in-stent restenosis. *JACC Cardiovascular interventions.* 2012;5(10):1081-1088.
27. Kelsch B, Scheller B, Biedermann M, et al. Dose response to Paclitaxel-coated balloon catheters in the porcine coronary overstretch and stent implantation model. *Invest Radiol.* 2011;46(4):255-263.
28. Fan W. Possible mechanisms of paclitaxel-induced apoptosis. *Biochem Pharmacol.* 1999;57(11):1215-1221.
29. Heller PF. Paclitaxel and arterial smooth muscle cell proliferation. *Circulation.* 1998;97(16):1651.
30. Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation.* 1997;96(2):636-645.
31. Hayashi S, Yamamoto A, You F, et al. The stent-eluting drugs sirolimus and paclitaxel suppress healing of the endothelium by induction of autophagy. *Am J Pathol.* 2009;175(5):2226-2234.
32. Yazdani SK, Pacheco E, Nakano M, et al. Vascular, downstream, and pharmacokinetic responses to treatment with a low dose drug-coated balloon in a swine femoral artery model. *Catheter Cardiovasc Interv.* 2014;83(1):132-140.

Drug-Coated Therapies for Infrapopliteal Disease: Did We Find the Holy Grail?

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From Metro Health Hospital, Wyoming, Michigan.

Critical limb ischemia (CLI) represents the terminal stage of PAD and the clinical findings correspond to those traditionally classified as Rutherford-Becker IV to VI (although the original classification was designed to exclude patients with diabetes, who represent a rather large subset of the CLI population).[1]

Treatment of Critical Limb Ischemia

Anatomically, CLI is characterized by multilevel and multivessel disease, including tibial artery stenoses and occlusions that create a severe imbalance between supply and demand of oxygen in the affected tissues, compromising viability and threatening limb loss. The treatment of CLI is complex. Its cornerstone is revascularization attained by either surgical or endovascular means, and it has traditionally been focused on restoration of in-line arterial flow to the foot.

Recently the angiosome-guided revascularization approach has challenged the status quo and current interventional strategies mandate that all attempts be made to revascularize the vessel that directly supplies the ischemic area. When this is not feasible, efforts should be made to establish direct blood flow to the pedal arch.[3,4]

Surgical revascularization is still the most current recommendation for infrapopliteal (IP) lesions classified as TransAtlantic Inter-Society Consensus (TASC) D, which represent the vast majority of patients with CLI.[5] Coexisting comorbidities, lack of adequate outflow vessels or "targets," and lack of suitable autologous conduits for bypass are some of the most

J.A. Mustapha, MD

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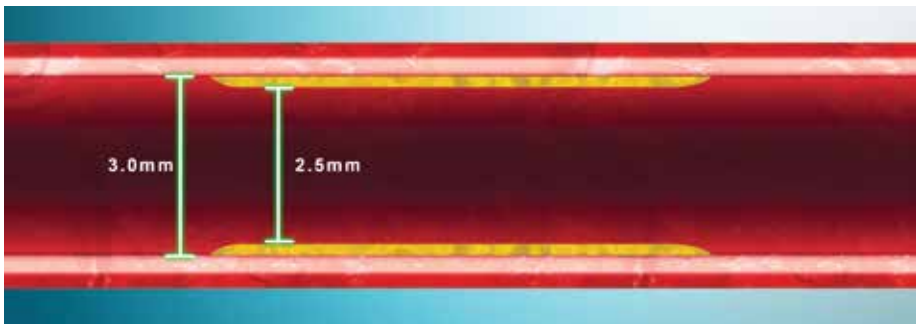

Figure 1. Schematic of sizing and measuring of both circumferential plaque (2.5 mm) as, well as circumferential vessel lumen (3.0 mm). The decision for balloon sizing should be made on the circumferential lumen diameter.

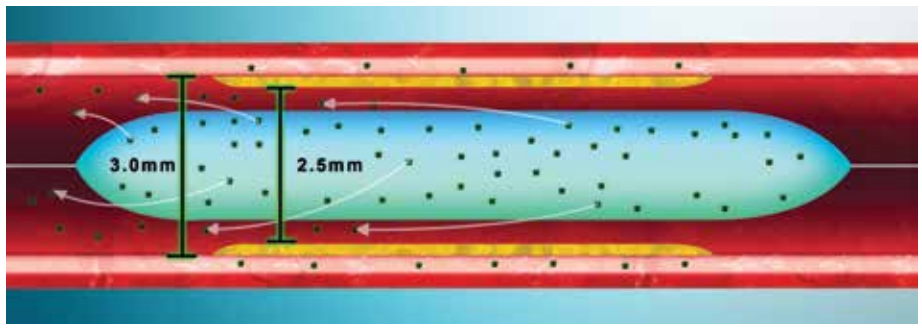

Figure 2. Appropriate sizing is crucial for the following reasons: an undersized DCB has many unfavorable implications including drug/excipient distal and local embolization and an undersized balloon with a large drug-coated surface area, in a hostile environment of high flow velocity coupled with turbulent flow, and irregular plaque morphology increases risk of distal embolization. To avoid such implications one should utilize fluoroscopy, intravascular ultrasound and extravascular ultrasound to insure proper sizing.

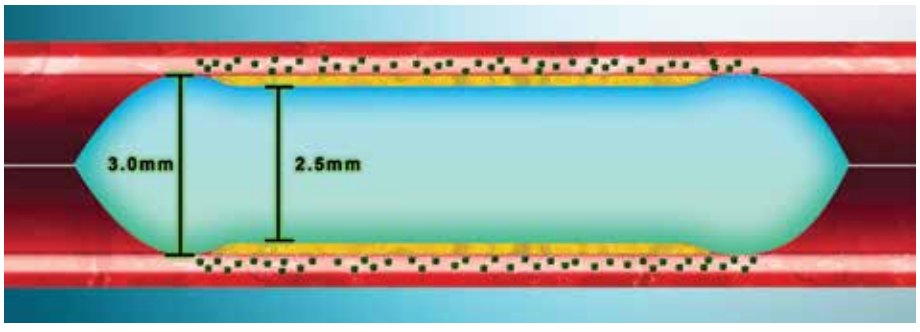

Figure 3. A properly sized balloon, with a 1:1 ratio, prevents the high flow velocity, turbulent flow, and exposure of the surface area of the balloon, securing a nonhostile environment for the balloon to transfer the drug to the surface area of the vessel.

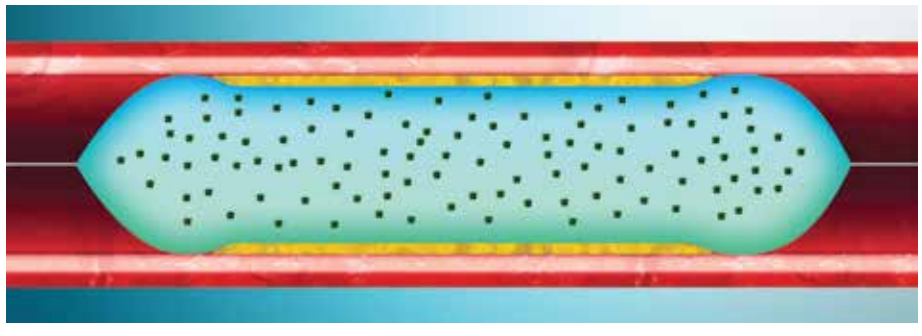

Figure 4. The result of proper sizing of a balloon to vessel leads to transfer of the majority of the drug to the vessel wall, which minimizes the chances of distal embolization.

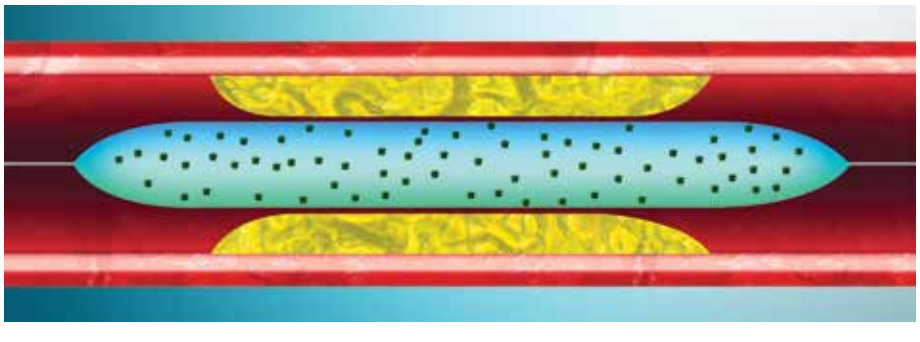

Figure 5. A drug-coated balloon delivered to a nonprepared vessel that contains a high plaque burden. The thickness of the plaque will most likely create an obstacle for the drug transfer from the surface of the balloon to the media of the vessel wall. If this is combined with an undersized balloon, it works as a double negative, which doubles the risk of embolization and lowers the likelihood of drug transfer to the vessel wall.

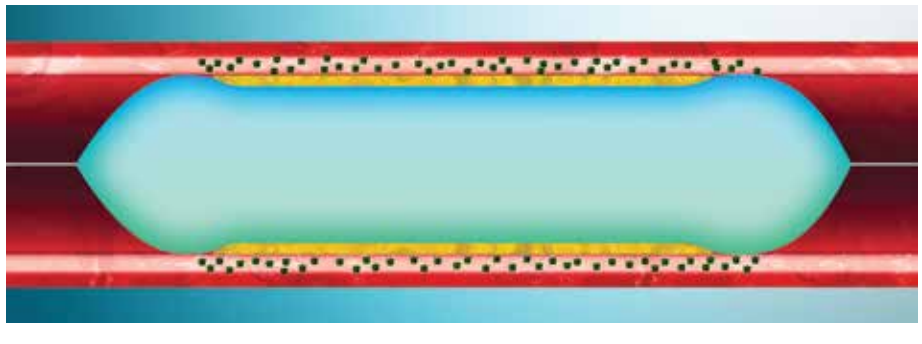

Figure 6. The value of a properly prepared vessel creates a suitable environment for the delivery of drug from the balloon to the vessel wall.

The Future of Drug-Coated Balloons in Europe

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Thomas Zeller, MD

Despite an initial technical success rate of more than 95% for percutaneous transluminal angioplasty to recanalize the femoropopliteal artery using dedicated crossing and re-entry devices,[1,2] recanalization procedures are limited by restenosis rates of 20% to 65% of the treated segments after 6 to 12 months.[3,4] Recently published and presented studies investigating drug-coated balloons (DCB) have shown a substantial improvement of durability of endovascular therapy.[5-8,9-12] However, DCBs basically have the same limitations as plain old balloon angioplasty (POBA), specifically acute recoil including undilatable calcified lesions and severe dissections requiring provisional bare metal stenting.[7,11]

Moreover, current drug coatings are still imperfect with regard to drug persistence on top of the balloon catheter during insertion of the balloon into the sheath and target lesion as well as during balloon expansion. As a result, the endovascular specialist is potentially exposed to the antiproliferative drug, currently exclusively paclitaxel, which potentially can be inhaled in an uncertain dose, and there is a downstream drug distribution into tissue distal to the lesion location with uncertain consequences to, for example, tissue wounds in particular in critical limb ischemia patients suffering from complex wounds as discussed in the IN.PACT DEEP trial. Currently, only 10% to 20% of the active drug is transferred into the vessel wall during DCB procedures.[9,13]

Study Results

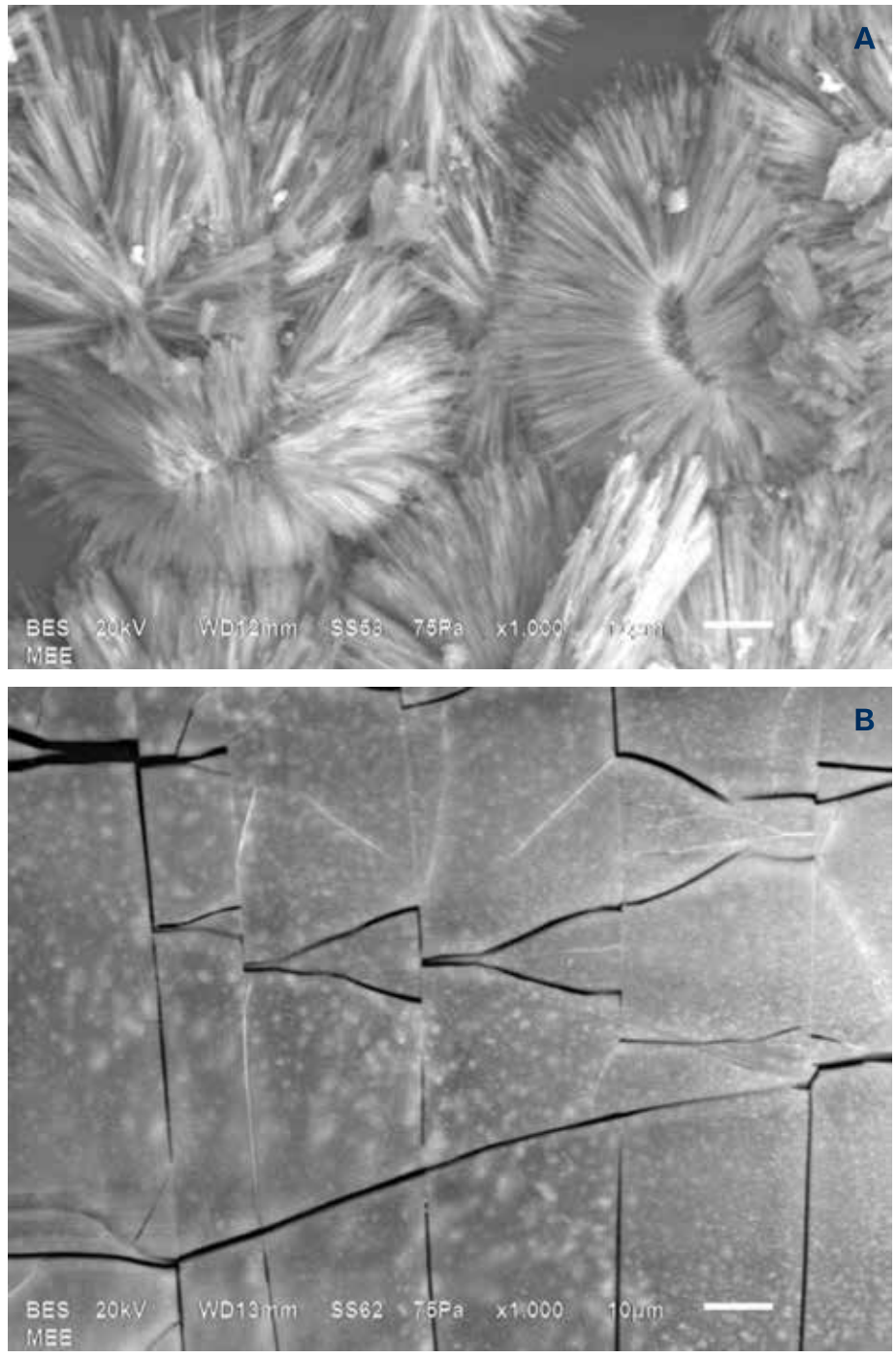
Nevertheless, 2 large pivotal randomized controlled trials (RCTs) – LEVANT 2 and IN.PACT SFA – have recently confirmed the initial positive results of pilot studies investigating different drug coatings in the treatment of femoropopliteal artery lesions.[5-8] However, the only larger scale RCT investigating DCB in tibial arteries, IN.PACT DEEP, turned out to be negative despite two initial successful single-center studies, including one RCT using the same DCB device.[10-12]

In IN.PACT DEEP, the technical outcome of the DCB cohort in terms of vessel patency was identical to the control cohort and by trend there was a higher major amputation rate found in the DCB cohort, suggesting a lack of biological efficacy of the drug and a potential negative impact of the lost antiproliferative drug on wound healing in critical limb ischemia (CLI) patients.

Two major reasons explain why the In.Pact Amphirion DCB (Medtronic), which was used in the IN.PACT DEEP trial, was not as efficient compared to the In.Pact Pacific DCB used in the PACIFIER trial[7] and the In.Pact Admiral DCB used in the IN.PACT SFA trial. First, there was a difference in the manufacturing process in that the Amphirion DCB is coated while deflated whereas the Pacific and Admiral balloons are coated while inflated. Thus, the majority of the drug is protected against washoff between the balloon folds after the coated balloon catheter is deflated and refolded. Second, the plastic materials of the balloon catheters are not alike, with different drug adherence properties.

Appropriate drug coating of a balloon catheter surface is not trivial. Due to its lipophilic nature, paclitaxel does not penetrate into the vessel wall sufficiently without a second drug, a so-called spacer or excipient. Also, both drugs have to be fixed effectively on the balloon surface in order to avoid significant drug loss prior to balloon expansion, and sufficient (ideally 100%) drug release into the vessel wall during balloon expansion has to be guaranteed.

In both of these facets, current DCB coatings are still imperfect. Whereas crystalline coatings result in higher vessel wall persistence and result in a more effective suppression of neointima proliferation, amorphous coatings are more stable on the surface of the balloon catheter with a significant lower loss of drug during balloon insertion into and through the sheath (Figure 1).



C	Crystalline	Amorphous
Particles released	+++	++
Uniform coating	++	+++
Drug transfer to vessel	+++	++
Drug retention vs time	+++	+
Biological effectiveness	+++	++

Figure 1. Crystalline coating (A) and amorphous coating (B); comparison of coating properties (according to J. Granada) (C).

Currently researchers are investigating hundreds of potential excipients to optimize drug transfer into the vessel wall as well as drug persistence in the vessel wall to optimize the biological efficacy of DCBs and to potentially reduce the dose of the antiproliferative drug. Under optimal conditions, systemic drug release should be reduced to serum levels below the level of detection even immediately after balloon inflation. For this purpose, encapsulation of the drug into microspheres is under investigation. In addition, polymer-like coatings that disrupt during balloon expansion could solve the problem of drug loss during balloon insertion into the lesion.

Tests with alternative antiproliferative drugs other than paclitaxel, such as sirolimus and everolimus, did not achieve biological efficacy due to insufficient drug persistence in the vessel wall.

Status of Use in Europe

Although the indication for DCB in femoropopliteal lesions, including instent restenosis is increasingly accepted in Europe, there is still a lack of data regarding the performance of DCB below

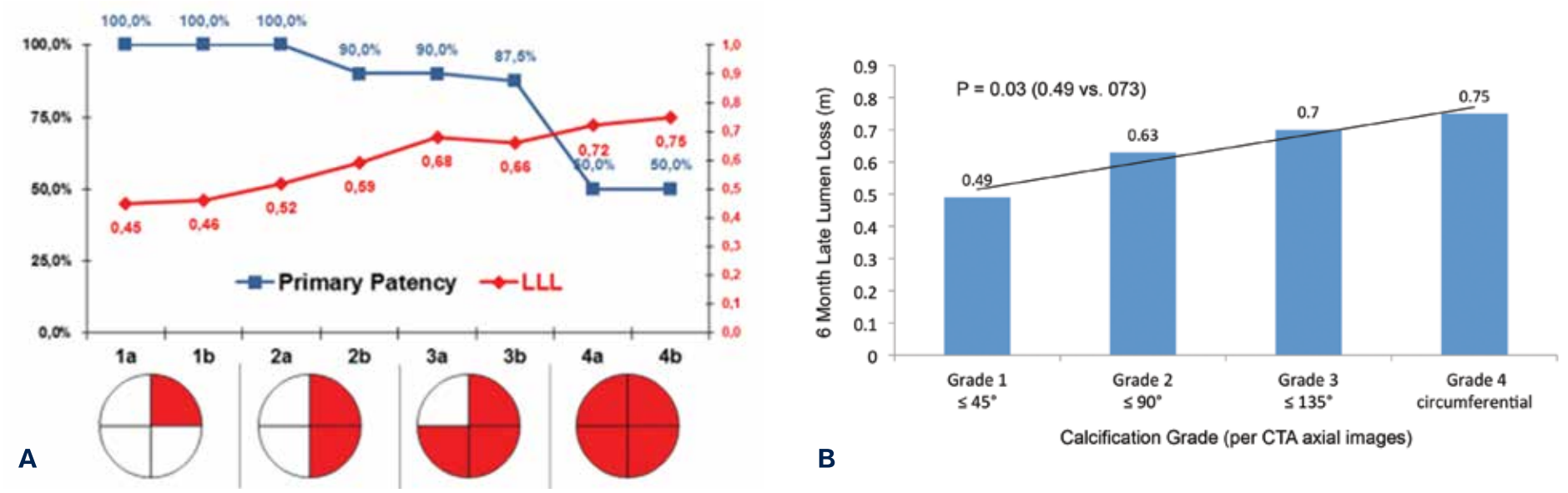


Figure 2. Drop in primary patency (A) and increase in late lumen loss at 6 months after drug-coated balloon angioplasty of femoropopliteal lesions with increasing degree of calcification (B).[17]

the knee. Currently, there is only one RCT (Lutonix BTK) investigating the performance of DCB in a CLI population using the CE-marked Lutonix 14 DCB compared to POBA; however, the enrollment has been slow due to strict inclusion criteria. The ADCAT trial is looking at an alternate approach to BTK disease by investigating the impact of upfront directional atherectomy prior to DCB angioplasty compared to DCB alone using the Lutonix 14 DCB.

The premise behind the study is the hypothesis that preparation of the vessel bed might improve the acute treatment outcome of DCB angioplasty and might, in addition, improve the biological efficacy of the antiproliferative drug. Intimal calcification can increase the loss of antiproliferative drug when advancing the DCB into the lesion (especially if the lesion is not properly predilated) and can impair uptake.[13] The role of Mönckeberg medial calcification (a common manifestation in patients with diabetes and end-stage renal insufficiency)[14] on the biological efficacy of DCB is still unknown.[15,16] Fanelli et al reported a significant drop in primary patency and increase in late lumen loss following DCB angioplasty of femoropopliteal lesions with concentric calcification (Figure 2).[17]

Atherectomy mechanically recanalizes the vessel without overstretch, removes the barrier for delivery of the antirestenotic therapy with a DCB, and reduces the likelihood of bail-out stenting even in calcified lesions and as a result preserves the native vessel. The DEFINITIVE Ca++ single-arm trial demonstrated calcified disease can be treated effectively with directional atherectomy using an embolic protection device.[18] The bail-out stent rate was as low as 4.1% and flow-limiting dissections were found in 1.5%. However, even after atherectomy, loss of patency ranges from 20% to 40% due to neointimal proliferation, in particular, if the external elastic lamina is damaged during the atherectomy procedure. Thus, supplementing atherectomy with DCB angioplasty is an attractive approach to preserve the acute lumen gain achieved by atherectomy.

There is still a lack of evidence regarding the beneficial performance of DCB in below-the-knee lesions in CLI patients. Moreover, there is a need for further optimization of the drug coatings in terms of reducing drug loss during balloon insertion to almost 0% and increasing drug penetration and persistence in the vessel wall.

Conclusion

Drug-coated balloons have proven effective in the treatment of femoropopliteal lesions in patients with claudication. However, there is still a lack of evidence regarding the beneficial performance of DCB in below-the-knee lesions in CLI patients. Moreover, there is a need for further optimization of the drug coatings in terms of reducing drug loss during balloon insertion to almost 0% and increasing drug penetration and persistence in the vessel wall with the goal of further optimization of biological drug efficacy despite reducing the effective drug dose on the balloon surface. It will be important to keep in mind that each combination of balloon, drug, and excipient will have to be independently studied in RCTs, as there is no "class effect."

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References

1. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease. *Int Angiol*. 2007;26(2):81-157.
2. Beschorner U, Sixt S, Schwarzwälder U, et al. Recanalization of chronic occlusions of the superficial femoral artery using the Outback re-entry catheter: a single centre experience. *Cath Cardiovasc Intervent*. 2009,74(6):934-938.
3. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. *Radiology*. 1992;183(3):767-771.
4. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med*. 2006;354(18):1879-1888.
5. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358(7):689-699.
6. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118(13):1358-1365.
7. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoropopliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv*. 2012;5(6):831-840.
8. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv*. 2014;7(1):10-19.
9. Schnorr B, Kelsch B, Cremers B, Clever YP, Speck U, Scheller B. Paclitaxel-coated balloons - survey of preclinical data. Minerva *Cardioangiol*. 2010;58(5):567-582.
10. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *JACC*. In press.
11. Schmidt A, Piorkowski M, Werner M, et al. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol*. 2011;58(11):1105-1109.
12. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation*. 2013;128(6):615–621.
13. Schnorr B, Albrecht T. Drug-coated balloons and their place in treating peripheral arterial disease. *Expert Rev Med Devices*. 2013;10(1):105-114.
14. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes--a review. *Diabet Med*. 2010;27(1):4-14.
15. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral Arterial Calcification: Prevalence, Detection and Clinical Implications. *Catheter Cardiovasc Interv*. 2014;83(6):E212-E220.
16. Lanzer P, Böhm M, Sorribas V, et al. Medial vascular calcification revisited: review and perspectives. *Eur Heart J*. 2014;35(23):1515-1525.
17. Fanelli F, Cannavale A, Boatta E, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther*. 2012;19(5):571-580.
18. Roberts D, Niazi K, Miller W, et al; DEFINITIVE Ca++ Investigators. Effective endovascular treatment of calcified femoropopliteal disease with directional atherectomy and distal embolic protection: final results of the DEFINITIVE Ca(++) trial. *Catheter Cardiovasc Interv*. 2014;84(2):236-244.

Drug-Coated Therapies

Continued from page 15

common limitations encountered by vascular surgeons. Therefore, endovascular revascularization has become an attractive therapeutic option, and even the TASC document acknowledges that "there is increasing evidence to support a recommendation for angioplasty in patients with CLI and infrapopliteal artery occlusion."[5] Arterial patency after percutaneous transluminal angioplasty (PTA) tends to be short lived due to elastic recoil, neointimal hyperplasia, and restenosis. However, limb salvage rates at 1 year were deemed equivalent to bypass surgery in a recent meta-analysis.[6]

Patients with CLI who undergo PTA are at risk for early restenosis and subsequent limb loss. Strict wound and hemodynamic surveillance, wound care, and timely reinterventions are crucial to achieve successful outcomes in this patient population.[7] Historically, concerns of restenosis after PTA have been successfully addressed by implantation of endovascular stents in the different arterial trees. The Comparing Angioplasty and DES in the Treatment of Subjects With Ischemic Infrapopliteal Arterial Disease (ACHILLES) trial was the first prospective, multicenter, randomized controlled trial of IP drug-eluting stents (DES) compared to PTA for treatment of IP lesions, and the results favored DES at 1 year.[8] The Drug Eluting Stents In The Critically Ischemic Lower Leg (DESTINY) study compared DES to BMS in patients with CLI, with results once again tipping the scales in favor of DES.[9]

Late lumen loss (LLL) appears to be more pronounced in the tibial vessels than in the coronaries and it is possible that drugs may be less effective at inhibiting neointimal proliferation in the tibial vessels, or that the pathophysiologic process that leads to restenosis in this particular vascular bed may be different from the coronaries. Another proposed mechanism leading to LLL in tibial vessels was proposed by Kashyap et al, who compared the angiographic vs histologic size of the popliteal and tibial arteries from patients with CLI who ultimately underwent amputation and determined that angiography (considered the "gold standard" imaging modality in the evaluation of PAD) severely underestimated both the extent of atherosclerosis (even in "normal appearing" segments) and the size of the popliteal and tibial vessels, which led to the use of undersized balloons.[10]

Mechanism of Drug-Coated Balloons

Drug-coated balloons (DCB) are covered with a drug-excipient combination. Paclitaxel, a cytotoxic agent with hydrophobic-lipophilic properties that facilitate drug cellular uptake and deliverability, has been the most frequently used drug. It has been shown to achieve high tissue concentrations after a single-dose delivery with 10% to 15% of the total dose remaining in the wall 40 minutes to 60 minutes after treatment.

Paclitaxel is considered very effective in providing the necessary antiproliferative therapy following an acute single-dose delivery with maintained long-term results due to its hydrophobicity and tight binding to intracellular microtubules, whereas drug toxicity is limited due to the small dose and local application. Paclitaxel appears to be optimal due to its lipophilic properties, short absorption time, and prolonged duration of antiproliferative effects.

Effective drug transfer and release requires an appropriate balloon coating (carrier or excipient: a hydrophilic spacer capable of delivering the hydrophobic molecules of paclitaxel). Various coating technologies are currently available, such as iopromide, urea, polymers, and nanoparticles, and none has proven superior. Given that some of the drug coating can be lost during introduction through hemostatic valves and sheaths and while crossing severely calcified or occluded arterial lesions, predilatation with a smaller standard balloon is recommended. In case of nonsatisfactory final angiographic result, postdilatation with a standard balloon may follow.

Drug-coated balloons clearly represent an exciting proposition, eliminating jailing of branches and allowing treatment without "leaving anything behind." However, there are limitations. Current DCBs are associated with significant downstream drug delivery, and their effect on ulcers or infected tissues needs evaluation. Tibial arteries characteristically display a very high prevalence of medial calcification, which could theoretically affect the diffusion of drug into the media and adventitia.

Clinical Data on Drug-Coated Balloons

Attempts to answer these questions are on their way. The IN.PACT DEEP, a prospective, multicenter, randomized controlled trial of patients with IP CLI, compared PTA with the IN.PACT Amphirion DCB (Medtronic), with FreePac hydrophilic balloon coating that uses urea as a carrier, vs standard balloon. The study failed to reach its primary efficacy endpoints, showing similar rates of clinically driven TLR and LLL compared to PTA. With regards to the primary safety endpoint, the DCB demonstrated noninferiority to conventional PTA.

The EURO CANAL study compares the Cotavance DCB (Medrad) to standard PTA. The Cotavance DCB uses the Paccocath coating technology, a dual matrix of paclitaxel and iopromide. Other DCBs suitable for below-the-knee (BTK) lesions are (1) DIOR (Eurocor), a paclitaxel-coated coronary balloon that uses a coating technology based on a 1:1 combination of a natural resin (shellac, composed of aleuritic and shellolic acid) and paclitaxel directly on the balloon surface;[11] (2) FREEWAY (Eurocor), a paclitaxel-coated ultra-low-profile IP peripheral balloon, which uses the same shellac coating as DIOR; and (3) The Genie balloon (Acrostak Corp.), which does not use coating but delivers paclitaxel through microporosities.

DEBATE-BTK is a prospective, randomized, open-label, single-center trial, which looked at IN.PACT Amphirion (Medtronic) vs PTA in 132 diabetic CLI patients with 158 IP long lesions. Binary restenosis by angiography was 27% (DCB) vs 74% (PTA). Target lesion revascularization was 18% vs 43%, and target vessel occlusion was 17% vs 55%.[12]

The results of IN.PACT DEEP have been released (not yet published) and have undoubtedly raised several flags, despite the remarkable results from DEBATE-BTK. As acknowledged by Liistro et al, their results may have been in part influenced by its single-center nature in a high-volume practice with a unique patient referral pattern, interventional technique, and integrated multidisciplinary approach, which may not be reproducible in other centers.[12]

Conclusion

As of today looking at all the data that has been published, including the interesting discrepancies between DEBATE BTK and IMPACT DEEP, one cannot

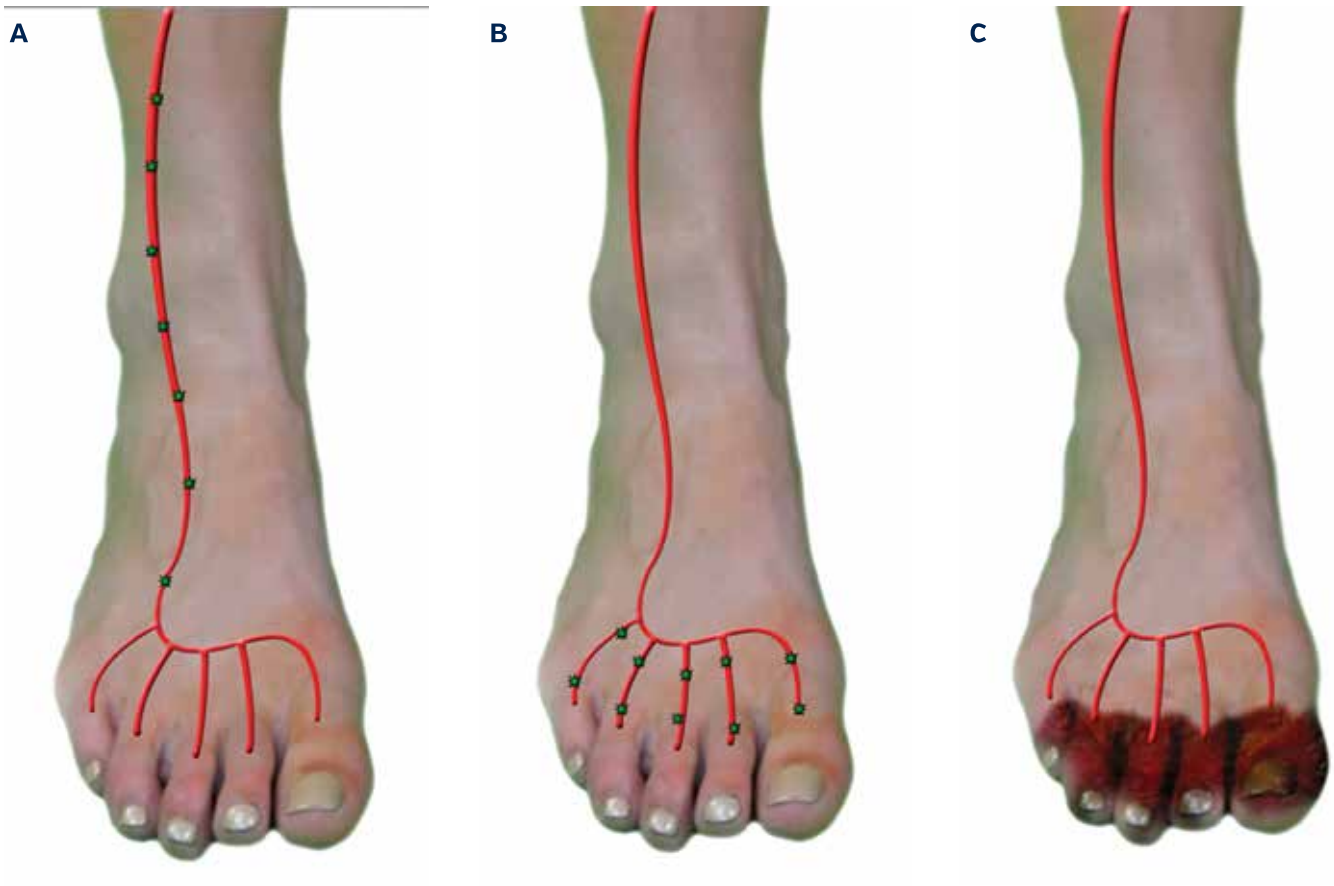

Figure 7. The focus on embolization in a CLI patient is of great concern because of the detrimental outcome as these patients already are at risk due to ischemic skin breakdown, malnourished tissue, and poor skin perfusion. Adding to that, embolization of a drug that inhibits proliferation, which is the tool required for the tissue to regenerate and heal. The sequential events seen in Figures 7A to 7C describe the stages of embolization to progression and worsening of skin breakdown.

help but wonder how close are we to the Holy Grail. DEBATE BTK showed excellent outcomes with tibial intervention utilizing drug coated balloons (DCB) in a setting of experienced operators. IMPACT DEEP showed different results when the DCB was utilized in the hands of many operators with variable experience and expertise. Could it be that the delivery of the DCB is not currently being performed appropriately to have the most valuable benefit of this device. The question remains to be answered, if the trend seen in IMPACT DEEP was a result of DCB worsening outcomes in CLI patients, what was the mechanism for this to occur? Hypothetically, one can speculate under-sizing plays a major role when a long DCB is inflated in a tibial vessel with significant under-sizing creating a source of embolization. The large surface area of exposed DCB, high pressure and flow velocity surrounding the large surface area of the balloon could be an excellent set up for embolization. The lengthy balloon would allow the flow velocity and high pressure of the arterial pulse to remove the drug from the balloon and move it downstream. If this were to occur, this is especially problematic for CLI patients with already compromised skin breakdown. Could it be that we need to revisit the sizing of the DCB used in IMPACT DEEP and DEBATE BTK and compare the average size of the balloon used in the average size of the tibial vessel? We may find a significant discrepancy between the two trials. It is possible we might find that the average size of the DCB used in IMPACT DEEP is smaller than the average size of the DCB used in DEBATE BTK. Also, it is possible that operators estimated the average diameter of the tibial vessels in IMPACT DEEP to be much smaller than the tibial vessels in DEBATE BTK.

The Holy Grail is not far from us. Further studies are needed to answer some of the remaining queries about safety and efficacy. Close attention to details such as the role of medial arterial calcification and appropriate balloon sizing (utilizing IVUS core lab adjudication) is of paramount importance to determine if DCBs will be good enough as stand-alone therapy in this group of patients or whether there will be a role for the combined use of atherectomy and DCBs, especially when it refers to the potential extension of the use of these technologies in below-the-ankle interventions. This is the next frontier in CLI therapy and the next door to be opened in the search for the holy grail of CLI interventions.

Further studies are needed to answer some of the remaining queries about safety and efficacy. Close attention to details such as the role of medial arterial calcification and appropriate balloon sizing is of paramount importance to determine if DCBs will be good enough as stand-alone therapy in this group of patients.

References

1. Bell PR F, Charlesworth D, dePalma R G, et al. The definition of critical ischemia of a limb. *Br J Surg.* 1982;69:S2.
2. European Working Group on Critical Limb Ischemia. Second European consensus document on chronic critical leg ischaemia. *Eur J Vasc Surg.* 1992;6(Suppl A):1-32.
3. Alexandrescu, V; Vincent, G; Azdad, K, et al. A reliable approach to diabetic neuroischemic foot wounds: Below-the-knee angiosome-oriented angioplasty. *J Endovasc Ther.* 2011;18:376-387.
4. Iida O, Nanto S, Uematsu M, et al. Importance of the angiosome concept for endovascular therapy in patients with critical limb ischemia. *Catheter Cardiovasc Interv.* 2010;75(6):830-836.
5. Norgren L, Hiatt WR, Dormandy JA, et al; for the TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33 Suppl 1:S1-75.
6. Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. *J Vasc Surg.* 2008;47(5):975-981.
7. Saqib NU, Domenick N, Cho JS, et al. Predictors and outcomes of restenosis following tibial artery endovascular interventions for critical limb ischemia. *J Vasc Surg* 2013;57(3):692-699.
8. Scheinert D, Katsanos K, Zeller T, et al; ACHILLES investigators. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. *J Am Coll Cardiol.* 2012;60(22):2290-2295.
9. Bosiers M, Scheinert D, Peeters P, et al. Randomized comparison of everolimus-eluting versus bare metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg.* 2012;55(2):390-399.
10. Kashyap VS, Pavkov ML, Bishop PD, et al. Angiography underestimates peripheral atherosclerosis: lumenography revisited. *J Endovasc Ther.* 2008;15(1):117-125.
11. Posa A, Nyolczas N, Hemetsberger R, et al. Optimization of drug-eluting balloon use for safety and efficacy: evaluation of the 2nd generation paclitaxel-eluting DIOR-balloon in porcine coronary arteries. *Catheter Cardiovasc Interv.* 2010;76(3):395-403.
12. Liistro F, Porto I, Angioli P, et al. Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK): A randomized trial in diabetic patients with critical limb ischemia. *Circulation.* 2013;128(6):615-621.

A Recap of the 2014 Amputation Prevention Symposium

The CLI Revolution was kicked off in August in Chicago at the 4th annual AMPutation Prevention Symposium. Esteemed faculty, attendees and industry from over 30 states and 6 countries joined together to send the message to CLI that a revolution has started, demonstrating the collective commitment and passion to use every skill and tool possible, provided by innovative minds and skilled physicians throughout the world to fight back against CLI.

The revolution is fueled by our passion and commitment to those that don't have a voice and are affected the most by this relentless disease. It is for the patient that we fight this battle. Attendees represented institutions performing over 100,000 procedures annually. Collectively we can make a difference. Collectively we will make a difference.

The pre-meeting Atherectomy Summit was again a success with lively discussion and hands-on workshops that included tibial access and intervention with cadaveric models, tibial ultrasound mapping with live models, atherectomy stations, and tibial access stations.

David Dilley, a professor Emeritus from Michigan State University and a support of CLI research was honored during the opening ceremony of AMP. Professor Dilley represents the reason that meetings like AMP are needed. He was destined for bilateral amputation and thanks to the advancement in CLI technologies, both of his legs were saved and he was able to walk into the general session to accept his honor.

William R. Hiatt, MD was the AMP 2014 Keynote Speaker. He addressed the fundamental value of noninvasive testing and physical examination of the CLI patient. Dr. Hiatt is an endowed professor for cardiovascular research at the University of Colorado, School of Medicine, with a clinical and research focus in vascular medicine.

Live cases were performed by George Adams, MD, and Ravish Sachar, MD, both from Rex Healthcare in Garner, NC; Christopher Metzger, MD, from Wellmont CVA Heart Institute in Kingsport, TN; and William Julient, MD, from South Florida Vascular Associates in Coconut Creek, FL.

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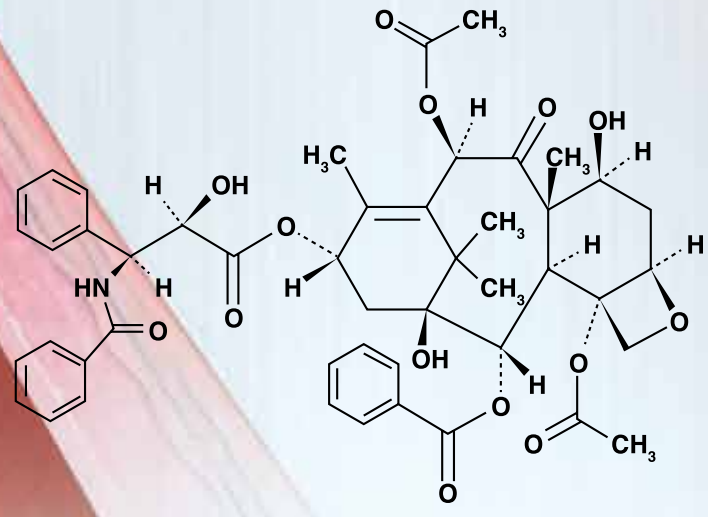

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1 LEVANT 2 clinical trial data on file. N=476. At 12 months, treatment with LUTONIX® 035 resulted in a primary patency rate of 73.5% versus 56.8% with PTA alone (p=0.001). Primary patency defined as absence of binary restenosis defined by DUS PSVR >2.5 and freedom from Target Lesion Revascularization (TLR). At 12 months, treatment with LUTONIX® 035 resulted in a freedom from primary safety event rate of 86.7% versus 81.5% with PTA alone. Percentages reported are derived from Kaplan-Meier analyses (not pre-specified).