Drug-Eluting Therapies for Infrapopliteal Lesions in Patients With CLI

Where do they stand, and where are they heading?

BY JIHAD A. MUSTAPHA, MD, AND LARRY J. DIAZ-SANDOVAL, MD

Critical limb ischemia (CLI) is the "terminal" or "end-stage" presentation of peripheral artery disease, defined by the presence of rest pain and/or tissue loss for at least 2 to 4 weeks that can be attributed to occlusive arterial disease. The diagnosis is clinical in nature. The presenting symptoms have been classified as Fontaine stages III and IV or Rutherford-Becker 4, 5, and 6, and the European Consensus Conference has also included the need for analgesia for more than 2 weeks or ischemic tissue loss with an ankle pressure of < 50 mm Hg as part of the definition.[1] Anatomically, CLI is characterized by multilevel and multivessel infrainguinal and tibial arterial stenoses and occlusions that create a severe imbalance between supply and demand of oxygen in the affected tissues, compromising their viability and threatening limb loss. It is estimated that 1.5 million patients in Europe and 2 million patients in the United States older than 50 years of age manifest symptoms of CLI. Although CLI encompasses < 5% of all cases of peripheral artery disease, its prognosis is poor: the 1-year mortality and major amputation rates range from 20% to 50%.[2-4]

CURRENT APPROACHES IN CLI

The treatment of CLI primarily consists of revascularization via surgical or endovascular interventions. Treatment has traditionally been focused on restoration of at least one "in-line" arterial conduit to the foot, but this notion is currently being challenged by the angiosome-guided revascularization approach, according to which it is not enough to re-establish flow through one vessel to the foot if this vessel is not supplying the area where the ulcer is located. The currently available data are limited but rather provocative, and at our institution, we base our revascularization strategies on this approach. All attempts should be made to revascularize the vessel that directly supplies the ischemic area, and when not possible, at least to ensure that the revascularization procedure allows direct blood flow to the pedal arch.[5,6]

The surgical approach to revascularization represents the most current recommendation for treating TASC D infrapopliteal lesions, which represent the vast majority of patients with CLI. Coexisting comorbidities, lack of adequate outflow vessels or "targets," and lack of suitable conduits for bypass represent some of the most common limitations encountered by vascular surgeons; endovascular revascularization has become an attractive therapeutic option, as successful interventions can be achieved in most cases, even in tibial arteries with complex disease. Arterial patency after percutaneous transluminal angioplasty (PTA) tends to be short lived due to elastic recoil, neointimal hyperplasia, and restenosis, with primary patency rates of 48% to 81% at 1 year and 40% to 78% at 2 years;[7] however, limb salvage rates at 1 year have been deemed equivalent to bypass surgery in a recent meta-analysis.[8]

TABLE 1. REGISTRY DATA FOR THE USE OF DES BELOW THE KNEE						
Author	**Year**	**DES**	**N**	**Design**	**Stents**	**PP/LS**
Siablis et al[7]	2005	S	29	Registry	66	96%/100% at 6 m
Commeau et al[9]	2006	S	30	Registry	106	97%/100% at 7 m
Bosiers et al[10]	2006	S	18	Registry	24	100%/94.1% at 6 m
Scheinert et al[11]	2006	S	30	S vs BMS	30	100% vs 82% at 6 m
Siablis et al[12]	2007	S	29	S vs BMS	66	86.4% vs 40.5% at 1 y
Siablis et al[4]	2007	P	29	Registry, SC	62	30 %/88.5% at 1 y
Grant et al[13]	2008	S/P	10	Registry, SC	17	10% TVR at 12 m
Rosales et al[14]	2008	S	24	Registry, SC	41	95 %/12 m
Siablis et al[15]	2009	S	62	Registry, SC	153	33%/82% at 3 y
Karnabatidis et al[16]	2009	S	103	S vs BMS	239	85% vs 35% at 2.5 y
Fischman et al[17]	2010	S	56	Registry	101	82% at 16 m
Rastan et al[18]	2010	S	104	Registry	180	84% at 12 m
Balzer et al[3]	2010	S	128	Registry MC	341	83% at 18 m
Feiring et al[19]	2010	S/P	106	Registry	228	12% TVR at 68% ± 5% at 36 m
Karnabatidis et al[16]	2011	E	81	E/BMS	332	81% vs 68% TLR free at 36 m
Werner et al[20]	2012	S	95	Retrospective	158	84% 5-y patency
Total			934		2,144	80% to 100% PP

Abbreviations: E, everolimus; LS, limb salvage; P, paclitaxel; PP, primary patency; S, sirolimus; BMS, bare metal stent; SC, single center; MC, multicenter; TLR, target lesion revascularization; TVR, target vessel revascularization.

Historically, long-term results of PTA have been improved by implanting endovascular stents in the different arterial trees. In the coronary arteries, drug-eluting stents (DES) have largely supplanted the use of bare-metal stents (BMS). Even now, after the "boom" of DES has passed, most coronary interventions employ these devices, as it is clear that the rates of restenosis are significantly lower, and the major limitation to their use has been the requirement for patients to take dual-antiplatelet therapy for a prolonged period of time. Therefore, it is no surprise that eventually, interventionists will desire to use these devices in the similarly sized and histologically comparable tibial arteries.

INFRAPOPLITEAL DES

In 2005, the first study with the use of sirolimus DES as a bailout in the treatment of infrapopliteal lesions in patients with CLI revealed a 0% rate of major amputation and a 4% rate of target lesion revascularization at 6 months.[7] Later, Commeau et al achieved similar results in a cohort of 30 patients with planned primary stenting (instead of bailout therapy),[9] and comparable results were achieved by Bosiers and Scheinert et al.[10,11] All of these reports have in common the small number of patients treated and the single-center, nonrandomized nature of the studies. One may conclude that the use of DES to treat infrapopliteal lesions in CLI should be the focus of larger studies, as the 6-month and 1-year outcomes of these small studies suggest an amazing benefit of the use of this therapeutic modality, with a 50% absolute risk reduction for major amputation.

Attempts to use different drug platforms have also been made (Table 1). In 2007, Siablis et al studied 29 consecutive patients with CLI who underwent placement of sirolimus DES, and 1-year outcomes were remarkable, with an 86.4% primary patency rate and 96% limb salvage.[12] The same group reported on a CLI cohort who received 62 paclitaxel DES to treat 50 infrapopliteal lesions. Outcomes at 1 year were disappointing from the primary patency standpoint, with an underwhelming 30%, despite achieving a comparable rate of limb salvage of 88.5%.[4] More prolonged follow-up studies have revealed some thought-provoking data on the 3-year outcomes of a 62-patient cohort who underwent placement of 153 sirolimus stents as a bailout treatment after failed angioplasty. A remarkable 82% rate of limb salvage shows that this parameter is not significantly changed from data published in 1-year outcomes; however, the primary patency rate was significantly decreased at 33%. Upon analyzing the data, there is a clear separation of

TABLE 2. MULTICENTER, RANDOMIZED DATA FOR DES USE BELOW THE KNEE					
Author/Study Name	**Year**	**DES**	**N**	**Design**	**Primary Patency/TLR Free**
Rastan[21] YUKON-BTK	2011	S	82	Multicenter, double-blind, randomized	81%/93% at 1 y
Scheinert[22] ACHILLES	2012	S	99	Multicenter, randomized	75%/90% at 1 y
Bosiers[2] DESTINY	2012	E	74	Multicenter, randomized	85%/91% at 1 y
Total			255		> 90% TLR free

the patency curves until approximately 30 months, at which point the patency curve from the DES group swiftly decreases, becoming parallel and almost equal to that of the BMS group.[15]

In 2010, Feiring et al added a remarkable set of data to the already available evidence. The PARADISE trial, which included more than 100 patients, revealed a 94% ± 2% rate of limb salvage at 3 years and a 93% rate of wound healing and relieved rest pain with only 12% binary restenosis. The results of this study contrast significantly with TASC II, which benchmarks a 1-year major amputation rate of 30% and a 20% rate of patients with unresolved symptoms. The PARADISE study patients had a 6% rate of major amputation at 3 years, with resolution of symptoms in 99% of patients.[19]

In 2011, Karnabatidis et al published the first study using two newer-generation DES: Xience (Abbott Vascular, Santa Clara, CA) and Promus (Boston Scientific Corporation, Natick, MA), both of which featured everolimus as the antiproliferative drug. Notable along with the everolimus-eluting stents for the first time were the inclusion criteria, which demanded a lesion length of at least 4.5 cm. Outcomes at 3 years revealed 81% freedom from target lesion revascularization and 87% amputation-free survival; however, the results of the study continue to suffer from the most common pitfall of all these reports, which is their single-center, nonrandomized nature.[16]

Rastan et al finally tackled this particular issue in YUKON-BTK, a prospective, multicenter, randomized, double-blind study that compared polymer-free sirolimus DES with placebo-coated BMS in patients with both CLI and claudication, including patients with Rutherford-Becker class 2 symptoms. The 1-year primary patency rate was 81%, and there was a significant improvement in symptoms, as evidenced by changes in the Rutherford-Becker classification.[21] This effort has been replicated in the multicenter, prospective, randomized ACHILLES study,[22] in which 200 patients were randomized to sirolimus DES versus angioplasty for the treatment of infrapopliteal lesions that were 27 ± 21 mm in length, comprising both patients with claudication and CLI. Results at 1 year revealed improved patency (75% vs 57.1%) among patients treated with DES.

Another recent addition to the data set is the DESTINY study, which compared everolimus DES versus BMS in patients with CLI. The primary patency rate at 1 year was 85% for DES versus 54% for BMS, and freedom from target lesion revascularization was 91% for DES vs 66% for BMS, once again tipping the scales in favor of drug-eluting devices.

Despite these data, the use of DES is not yet the standard of care for the treatment of patients with infrapopliteal disease. The numbers are good, yet somewhat disappointing when compared to data in the coronary arteries. What are we missing?

In coronary trials, late lumen loss correlated very well with restenosis and target lesion revascularization. In the DESTINY trial, it was shown that the Xience (everolimus DES) stent had significantly less late lumen loss than its BMS counterpart, the Vision stent (Abbott Vascular, Santa Clara, CA).[2] The authors note that late lumen loss appears to be more pronounced in the tibial vessels when compared to the coronaries; it is possible that the drug may be less effective at inhibiting the formation of tibial neointima, or that the process that governs the proliferation of neointima in the tibial vessels may be somewhat different from its coronary counterpart. A comparison of the trials described in this section is shown in Table 2.

So far, we have discussed the state of the art when it comes to stenting in the infrapopliteal vasculature. That is where we are, but more importantly, where are we going?

The development of drug-coated balloons (DCBs) has created significant interest in this technology. To gain an understanding of their potential in the infrapopliteal segment, let us review the science behind them. Currently, standard balloon catheters are covered with the drug/excipient combination. The theoretical goal would be to maintain the antiproliferative agent on the balloon until it is positioned at the lesion and then have the entire intended dose released from the balloon and be absorbed completely within the targeted tissue, with

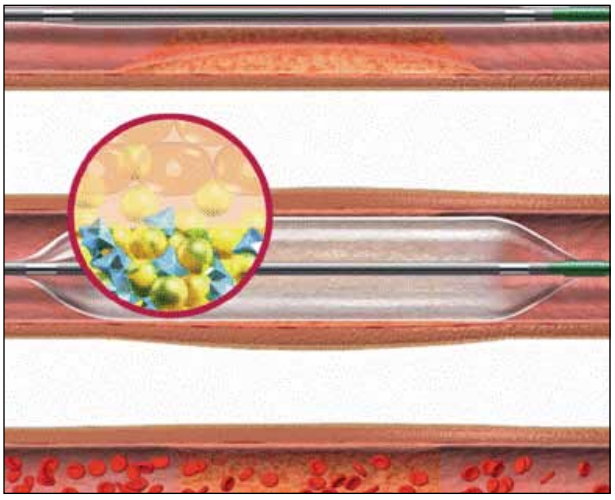

Figure 1. Composition of DEB coating with Paccocath technology. Reprinted with permission from *Indian Heart J*, Volume 62. Sundeep M, Bahl VK. Coronary hardware part 3—balloon angioplasty catheters, p. 340. Copyright Elsevier.

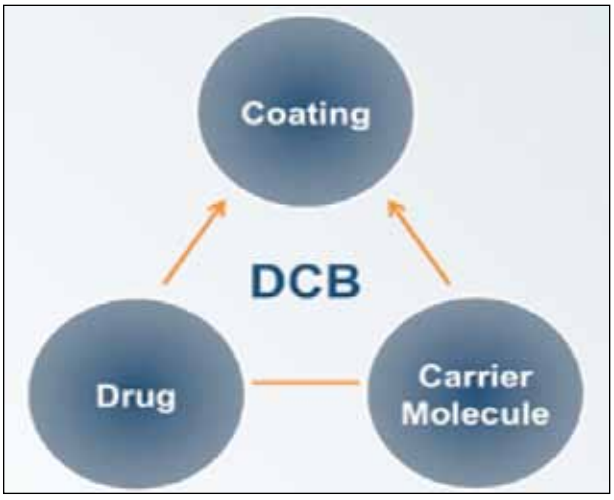

Image courtesy of C. R. Bard.

Figure 2. Mechanism of action for antiproliferative drugs. The carrier molecule plays a pivotal role in drug transfer and stabilization.

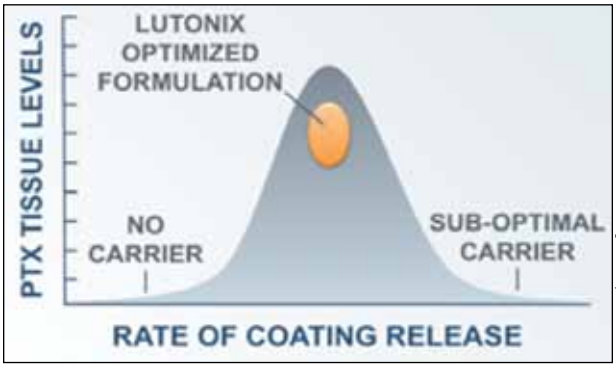

Image courtesy of C. R. Bard.

Figure 3. Mechanism of action for antiproliferative drugs. With no carrier, the release rate is too slow, leading to insufficient drug uptake. With a suboptimal carrier, the release rate is too fast, leading to excessive transit drug loss and insufficient drug uptake in the vessel wall.

minimal (if any) systemic loss. Current technology has fallen short on many of these goals.

The current approach uses a combination of an antiproliferative agent and an excipient in crystalline form that, once in the intima, maintains a "micro-depot" for the antiproliferative to diffuse into the tissue for a prolonged period of time. The currently used antiproliferative agent is paclitaxel in a dose ranging from 2 to 3 μg/mm^2. Early technology, such as Paccocath (Medrad, Inc., Warrendale, PA, a part of the Medical Care division of Bayer HealthCare, Leverkusen, Germany), utilized iopromide as a carrier for paclitaxel (Figure 1). The challenge will be to apply the drug mixture to the balloon surface and achieve uniform distribution with minimal loss during packing, sterilization, shipping, and handling. Considering the amount of variability a typical DCB transitions through, stabilizing the drug on the balloon surface and expediting the transition to the tissue is necessary (Figure 2), as the carrier molecule plays a pivotal role in drug transfer and stabilization.

Although most of the data for DCBs currently relate to paclitaxel, the "limus" family of agents may also be suitable. However, this family of drugs may not diffuse into media and adventitia and maintain tissue concentrations for as long as is necessary to treat this disease process (which would appear counterintuitive when analyzing the stent data, which clearly demonstrate "limus" agents to be superior to paclitaxel). Paclitaxel appears to be optimal due to its lipophilic properties, short absorption time, and prolonged duration of antiproliferative effects. With regard to the other part of the equation, a number of excipients have been used, such as iopromide, urea, polymers, and nanoparticles. After typical balloon inflations (30–60 seconds), the majority of the drug is released downstream, with 10% to 15% of the total dose remaining in the wall 40 to 60 minutes later. Approximately 10% (one-hundredth of the initial balloon dose) will still be present at the treatment site 24 hours later. Figure 3 demonstrates a good example of excipient coating. It is important to recognize the crystallized and noncrystallized forms of paclitaxel; paclitaxel in crystal formation makes it less attractive and less likely to traverse the endothelial lining of tibial vessels as well as in the media and adventitia. A carrier added to paclitaxel physically transforms the drug into a more suitable and transformable compound that is much easier to traverse the tibial layers. Other forms of drug delivery that currently have CE Mark include the catheter-based prolific device, which utilizes

Image courtesy of CardioProlific.

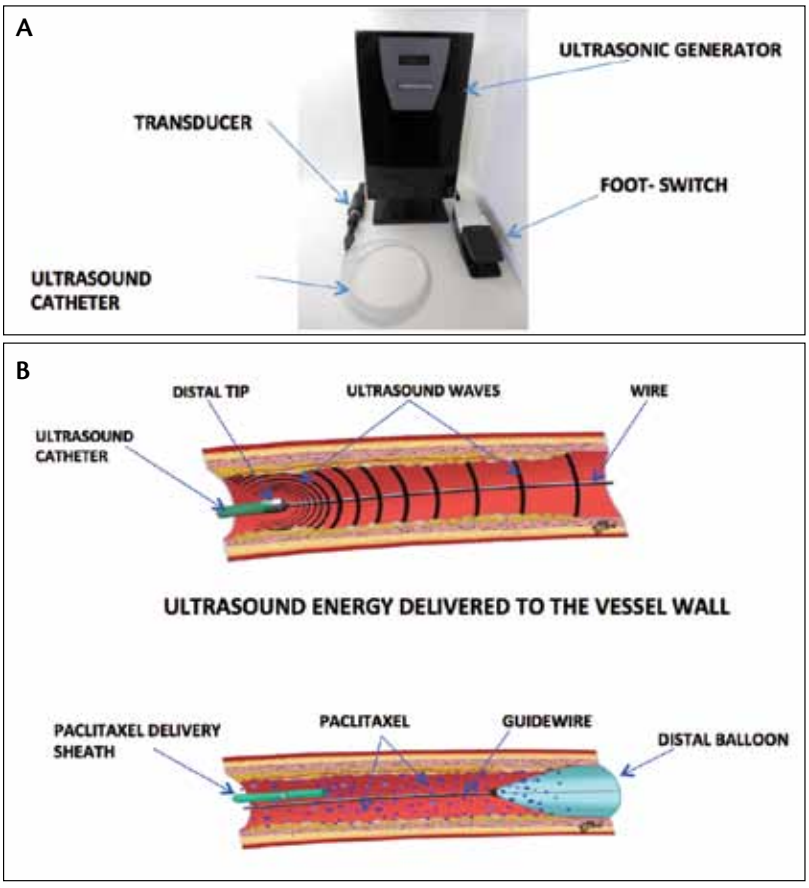

Figure 4. Ultrasound system (A). Mechanism of action (B).

ultrasonic vibration to augment the paclitaxel transitioning through the peripheral arterial walls (Figure 4).

Another form of drug delivery is via the Tapas catheter (Spectranetics Corporation, Colorado Springs, CO) (Figure 5). It contains two compliant balloons that enable targeted local delivery of any physician-specified agent. The adjustable treatment zone expands up to 300 mm, allowing for the treatment of long vessels with only one device. The medication can be aspirated out of the catheter after treatment, providing localized intravascular treatment without systemic runoff. One device can be used to treat multiple segments and vessels. The primary product features include treatment zone adjustments to lengths of up to 300 mm, dual-occlusive balloons to control delivery, posttreatment aspiration capability, and proprietary heparin and hydrophilic coating. The primary product benefits are its ability to locally deliver any therapeutic or diagnostic agent at any given dose, treat long vessel segments with only one device, and provide localized intravascular treatment without systemic runoff by aspirating the remaining agent before deflating the balloons that mark the limits of the treated segment.

The ClearWay RX liquid drug delivery balloon (Maquet Vascular Systems, Hudson, NH) is a microporous PTFE balloon catheter designed to achieve local delivery of various therapeutic agents directly into the coronary and peripheral arterial wall. It is a semicompliant low-pressure balloon with atraumatic tip, which supports its use in compromised vessels while reducing the potential for additional vessel trauma.

ClearWay's ability to optimize site-specific drug delivery is accomplished through its unique mechanism of action, which occludes flow and allows for selective local infusion of drug to the arterial wall through the micropores located in the PTFE coating. These actions combined allow the drug to be delivered with minimal dilution and help to increase drug residence time while the balloon is inflated. The ClearWay RX drug delivery balloon provides up to 500 X 1 the drug concentration (compared to IV drug delivery) at the point of delivery without increasing systemic load beyond the initial bolus delivered. The ClearWay RX is a rapid-exchange system compatible with a 0.014-inch guidewire platform, and is available in 1- to 4-mm balloon diameters with lengths ranging from 10 to 50 mm. This platform will allow the physician to use different kinds of drugs, including antiproliferative agents, which could evolve into an alternative form of drug delivery and potentially be considered an innovative "drug-eluting" balloon.

The use of DCBs is an exciting proposition, as it would allow for treatment of segments where stents could "jail" other branches, and it would provide the potentially perfect scenario of adequate treatment without leaving anything behind. However, there are some nuances to DCBs that make rigorous clinical evaluation important.

As previously noted, current DCBs are associated with a significant amount of downstream drug delivery. Any possible effect of this downstream cytotoxic agent dosing on ulcers or infected tissues will require evaluation. From a pathological point of view, tibial arterial disease characteristically affects the media of the vessel and is associated with a very high prevalence of calcification that could theoretically affect the diffusion of the drug into the media and adventitia. Currently, the only study of infrapopliteal DCB in CLI was reported by Schmidt et al.[23] They evaluated 104 patients with CLI (82.6%) or severe claudication (17.4%).

Image courtesy of The Spectranetics Corporation®.

Figure 5. The Tapas catheter.

The mean lesion length of the arteries treated was 176 ± 88 mm. The device used was a paclitaxel-eluting balloon (In.Pact Amphirion, Medtronic, Inc., Minneapolis, MN). This balloon is coated with FreePac, a proprietary formulation of 3 µg of paclitaxel/mm^2 and urea, which serves as a hydrophilic spacer to facilitate separation and release of paclitaxel into the vessel wall. During a follow-up period of 378 ± 65 days, the limb salvage rate was 95.6%. The restenosis rate at 3 months was 27.4%.

In the United States, trial design for infrapopliteal approval of DCBs will be complex. As noted in the BASIL trial and a recent large meta-analysis comparing plain PTA with surgery, patency was improved with bypass, but amputation-free survival was not significantly different up to 3 years later. This lack of differentiation may be due to the short period of time required to provide improved perfusion to heal wounds, as well as the high mortality rate in these patients. It may also be important to consider different clinical endpoints in this population, such as wound healing rates, time to healing, time to ambulation, and maintenance of independent living status. Patient selection may also be important, as illustrated in the PARADISE trial, which revealed that Rutherford-Becker category 4 and 5 patients survive longer and have higher limb salvage rates than Rutherford-Becker category 6 patients.

SUMMARY

We are still in the early stages of discovering the various paths of therapy for complex CLI disease. Drug-eluting therapy is another step forward in the struggle against CLI. As new data slowly emerge from trials examining the different types of drug-delivering technologies, we hope to be able to determine a best therapeutic approach for the variable complexities of CLI patients. As the search for a definitive answer continues, our patients benefit from the already available therapeutic remedies. Today, patients have many more options for limb salvage and revascularization than years ago, partly due to the significant advancements in therapy as well as from the efforts to increase awareness for this complex disease. ■

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