

Treating Femoropopliteal Lesions in Patients With CLI

Optimal use of DCBs in treating lesions of the superficial femoral and popliteal arteries.

BY VINAYAK SUBRAMANIAN, BS; ROXANA MARTINEZ, BA; AND GEORGE L. ADAMS, MD, MHS

Peripheral artery disease (PAD) continues to be a significant economic and public health burden, affecting 8 to 12 million people in the United States and approximately 204 million people worldwide.^{1,2} The increase in incidence of PAD can be attributed to the growing global epidemics of diabetes and kidney disease. At its worst, chronic PAD manifests as critical limb ischemia (CLI), which is characterized by nonhealing wounds on the extremities and significant rest pain.³ Patients with CLI often present for endovascular intervention as a last resort, often facing the morbid prospect of limb amputation, which itself is associated with increased morbidity and mortality.⁴

The CLI population has historically been underserved due to the numerous technical challenges an interventionist must overcome to treat lesions successfully. CLI patients present with long lesions extending both above and below the knee. Additionally, these lesions are often populated with multiple chronic total occlusions. When treating CLI, an interventionist must be prepared to treat a variety of plaque morphologies ranging from homogenous/thrombotic plaque to heterogeneous plaque to densely calcified plaque. Furthermore, poor patency of the target lesion after initial intervention has emerged as one of the most significant shortcomings in this era of endovascular interventions. Recent innovations in endovascular therapy, increased awareness of the disease state, and technical ingenuity of pioneering interventionists have all helped the endovascular approach become widely accepted as the first option for CLI patients.

Drug-coated balloons (DCBs) are among the latest innovations in the field of endovascular therapy, possibly being a much-needed solution to high restenosis rates after interventions. This article focuses on the optimal use of DCBs in treating lesions of the superficial femoral artery (SFA) and popliteal artery segments, illustrated with a case example using these devices.

CHALLENGES WITH TREATING SFA/ POPLITEAL LESIONS

The SFA and popliteal arteries are unlike any other artery in the body. These vessels are subject to triplanar intermittent mechanical stresses, which include extension, contraction, compression, torsion, and flexion. These dynamic stresses limit the efficacy of rigid mechanical prostheses, such as stents, which are only able to deform to a limited extent in response to the stresses exerted on the artery.⁵ This lack of flexibility and resistance to stress may induce stent fractures in the prosthesis, which may promote poorer patency. In the Femoral Stenting in Obstructions (FESTO) study, it was found that stent fractures were common in long lesions (52% stent fractures in > 16 cm stented length). Furthermore, significant restenosis (> 50%) was seen in 32.8% of cases, and complete stent reocclusion was noted in another 34.4% of cases. Overall, patients with stent fractures had poorer patency compared to those without stent fractures (41.1% vs 84.3% at 12 months; $P < .0001$).⁶

Next-generation stents have made significant improvements in terms of flexibility, and recent trials such as the RESILIENT study had a markedly reduced stent fracture rate of 4.1% at 18 months.⁷ However, the challenge of reduced patency of long lesions remains a ubiquitous challenge in treating patients with CLI. An additional challenge with stenting in general is that the vessel loses its ability to undulate naturally with the prosthesis; subsequently, the vessel behaves like a rigid structure. This rigidity may contribute to poor patency. For this reason, many interventionists advocate for a leave-nothing-behind strategy in order to keep the options of surgical and endovascular intervention open for the future.

PROMISING DATA BEHIND DCBs

DCBs utilize paclitaxel, an antiproliferative agent, to prevent inflammation that can lead to restenosis of lesions.

Currently, there are two DCBs approved for use in the United States: Lutonix 035 (Bard Peripheral Vascular, Inc.) and In.Pact Admiral (Medtronic). The initial randomized controlled trials evaluating both DCBs in treating SFA and popliteal lesions have shown promising results. Bard's LEVANT study found a significantly higher primary patency at 12 months with the Lutonix 035 DCB as compared with plain-old balloon angioplasty (73.5% vs 56.8%; $P < .001$).⁸ Similarly, Medtronic's IN.PACT SFA trial found a higher primary patency at 12 months in the In.Pact Admiral DCB group compared with the percutaneous transluminal angioplasty (PTA) group (89.8% vs 66.8%; $P < .001$), as well as a significantly lower rate of clinically driven revascularization (2.4% vs 20.6%, respectively; $P < .001$).⁹

UTILITY OF DCBs IN TREATING SFA AND POPLITEAL DISEASE

Unlike stenting, balloon angioplasty allows the vessel to retain its mechanical flexibility, in addition to leaving all future intervention options open. Furthermore, because a foreign body is not permanently left in the patient's body, balloon angioplasty has a much smaller risk period for inflammation than stenting, which provides a permanent risk of inflammation.

Using DCBs to treat in-stent restenosis (ISR) is preferred to placing additional stents, because placement of additional overlapping stents is associated with an increased rate of stent fracture and thus restenosis. Several studies have looked into the utility of DCBs in treating ISR. The FAIR trial, which compared ISR lesions in the SFA treated with plain-old balloon angioplasty or DCBs found that ultrasound-assessed recurrent ISR at 6 months was lower in the DCB group (15.4% vs 44.7%; $P = .002$). Target lesion revascularization rates showed a similar trend at both 6 and 12 months (96.4% vs 81.0%; $P = .0117$ and 90.8% vs 52.6%; $P < .0001$, respectively).¹⁰ The DEBATE-ISR study also found a lower recurrent restenosis rate in the DCB group than in the PTA group (66% vs 34%; $P < .001$).¹¹ Recently, Grotti et al reported that the 3-year follow-up results from the DEBATE ISR trial show that TLR rates between plain-old balloon angioplasty and DCBs are not significantly different (43% vs 40% at 3 years). However, it is important to realize that in treating patients with CLI, the goal of therapy is often wound healing and to this end, short-term patency that allows successful wound healing and amputation prevention in a patient with CLI is an important treatment consideration.¹²

Due to the high rate of restenosis in the CLI population, an interventionist should leave all options for future endovascular and surgical intervention open, something that is possible when using DCBs for treatment. To this end, DCBs can be used in certain no-stent zones such as the adductor

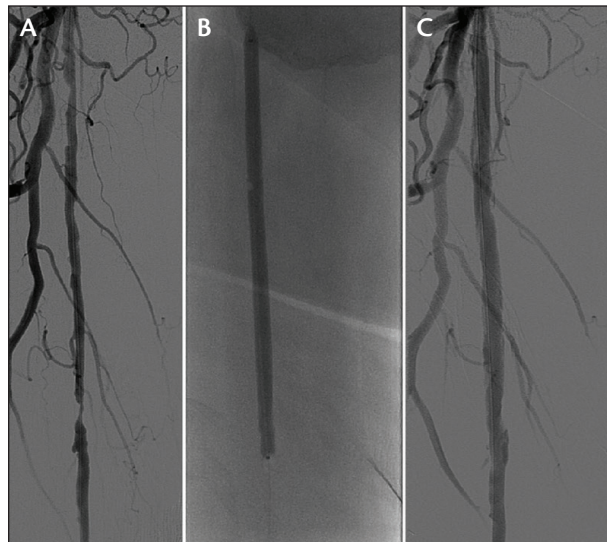


Figure 1. Angiogram of the right mid-SFA before intervention showing approximately 90% stenosis (A), during treatment with a 6- X 150-mm Lutonix 035 DCB (B), and after intervention showing approximately < 30% residual stenosis (C).

canal and popliteal artery. Additionally, DCBs may be the key to treating lengthy lesions that plague patients with CLI. Although DCBs seem to be a promising treatment option for CLI patients, the role of DCBs in cases of CLI should be further studied.

LIMITATIONS OF DCBs

One of the advantages of DCBs is also one of their limitations. Currently, DCBs only utilize paclitaxel as the active agent. The development of devices with a variety of antiproliferative drugs will allow the interventionist to customize therapy based on patient needs. For instance, patients with CLI are most in need of intervention that supports wound healing and, consequently, salvages limbs. The use of cytotoxic agents such as paclitaxel may adversely have an impact on wound-healing efforts.

Furthermore, patients with PAD, especially those with CLI, often present with calcified plaque. Calcific plaque has been challenging to treat and is often associated with poor procedural and long-term success. Unfortunately, DCBs have also had limited success in maintaining patency in calcific vessels. Fanelli et al found that patients with increased calcific plaque burden had limited therapeutic benefit from DCBs.¹³ This study showed that calcium, especially in the media, represents a barrier for drug uptake.¹³ Preparing the vessel with atherectomy prior to using DCBs is a strategy that may hold some promise in improving the therapeutic effect of DCBs in calcified lesions. Cioppa et al conducted a small pilot study to illustrate the safety and efficacy of utilizing a combination of directional atherectomy (DA)

with DCBs in treating calcific femoropopliteal disease. This small study considered 30 patients with life-limiting claudication and CLI who had calcific femoropopliteal disease as determined by duplex ultrasound. Primary patency at 12 months was reported as 90% (27/30) with a limb salvage rate of 100%.¹⁴ More recently, the DEFINITIVE AR study was designed to evaluate the effects of DA plus DCB therapy as compared to DCB therapy alone. This multicenter pilot study considered 121 patients enrolled at 10 sites. At 12 months, the DA plus DCB strategy illustrated a trend of improved patency (82.4% vs 71.8%). Patients with long lesions and severely calcified lesions derived the most benefit from this approach (90.9% vs 68.8% patency in lesions > 10 cm; 58.3% vs 42.9% patency in severe calcified lesions).¹⁵ Although additional multicenter randomized controlled studies are needed on the use of atherectomy prior to therapy with DCBs, these initial findings are promising for the treatment of CLI.

CASE STUDY

A 69-year-old woman with a history of hypercholesterolemia presented to the clinic with bilateral lower extremity claudication, which was worse in the right leg than the left. Duplex ultrasonography of her lower extremities revealed a > 70% stenosis of both her right and left SFAs. She was brought to the diagnostic angiography, which showed a 90% stenosis of her right mid-SFA (Figure 1A). The target lesion was successfully crossed with a run-through wire. After crossing the lesion, orbital atherectomy with a Diamondback 360° 2-mm classic crown device (Cardiovascular Systems, Inc.) was performed at low/medium and high revolutions. This was followed by DCB angioplasty with a 6- X 150-mm Lutonix 035 at nominal pressure (Figure 1B). The residual stenosis was < 20% (Figure 1C).

CONCLUSION

In this era of endovascular intervention, restenosis following interventional work represents one of the largest challenges facing the field. The goal of intervention, especially in the CLI population, is to not only open the vessel, but also to keep it open in order to enhance wound healing and prevent amputation. DCBs represent a significant innovation in the treatment of PAD. DCBs can be used to treat femoropopliteal lesions, including lesions that often provide a challenge to stenting (long lesions, ISR lesions, lesions in the mid-popliteal segment, etc).

Although the future of DCBs is promising, improvements are needed to expand its use for CLI patients. Development of DCBs with a variety of antiproliferative and anti-inflammatory agents is needed so that care can be customized for each patient, especially patients with nonhealing wounds and limbs at risk for amputation. Furthermore, DCBs are

currently only indicated for use of at-the-knee disease; this is not sufficient for CLI patients who often present with multilevel disease (eg, lesions above and below the knee). CLI patients often present with lesions composed of heterogeneous and calcific plaque. The efficacy of DCBs in these plaque morphologies is limited. Combination approaches to prepare the vessel with atherectomy prior to DCB therapy have shown promise, but additional data comparing different DCB and atherectomy combinations will allow interventionists to further personalize care based on patient needs. ■

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2-e220.
2. Fowkes FGR, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329-1340.
3. Lyden SP, Smouse HB. TASC II and the endovascular management of infrainguinal disease. *J Endovasc Ther*. 2009;16(2 suppl):5-18.
4. Barani J, Nilsson JA, Mattiasson I, et al. Inflammatory mediators are associated with 1-year mortality in critical limb ischemia. *J Vasc Surg*. 2005;42:75-80.
5. Jonker FS, Moll F, Muhs B. Dynamic forces in the SFA and popliteal artery during knee flexion. *Endovasc Today*. 2008;53(5):53-58.
6. Scheinert D, Duda S, Zeller T, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. *J Am Coll Cardiol*. 2005;45:312-315.
7. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. *J Endovasc Ther*. 2012;19:1-9.
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;7:10-19.
9. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and/or popliteal peripheral artery disease: 12-month results from the IN. PACT SFA randomized trial. *Circulation*. 2015;131:495-502.
10. Krankenberg H, Tübler T, Ingwersen M, et al. Drug-coated balloon versus standard balloon for superficial femoral artery in-stent restenosis: the Randomized Femoral Artery In-Stent Restenosis (FAIR) trial. *Circulation*. 2015;132:2230-2236.
11. Liistro F, Angioli P, Porto I, et al. Paclitaxel-eluting balloon vs. standard angioplasty to reduce recurrent restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: the DEBATE-ISR study. *J Endovasc Ther*. 2014;21:1-8.
12. Grotti S, Liistro F, Angioli P, et al. Paclitaxel-eluting balloon vs standard angioplasty to reduce restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: three-year results of the DEBATE-ISR study. *J Endovasc Ther*. 2016;23:52-57.
13. Fanelli F, Cannavale A, Gazzetti M, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. *Cardiovasc Intervent Radiol*. 2014;37:898-907.
14. Cioppa A, Stabile E, Popusoi G, et al. Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: one-year single centre clinical results. *Cardiovasc Revasc Med*. 2012;13:219-223.
15. Zeller T. DEFINITIVE AR: a pilot study of antirestenosis treatment. Presented at Vascular Interventional Advances (VIVA); November 4-7, 2014; Las Vegas, NV.

Vinayak Subramanian, BS

Department of Biomedical Engineering
North Carolina State University
Raleigh, North Carolina
Disclosures: None.

Roxana Martinez, BA

North Carolina Heart and Vascular Research
UNC Rex Healthcare
Raleigh, North Carolina
Disclosures: None.

George L. Adams, MD, MHS

University of North Carolina Health System
Chapel Hill, North Carolina
george.adams@unchealth.unc.edu
Disclosures: None.