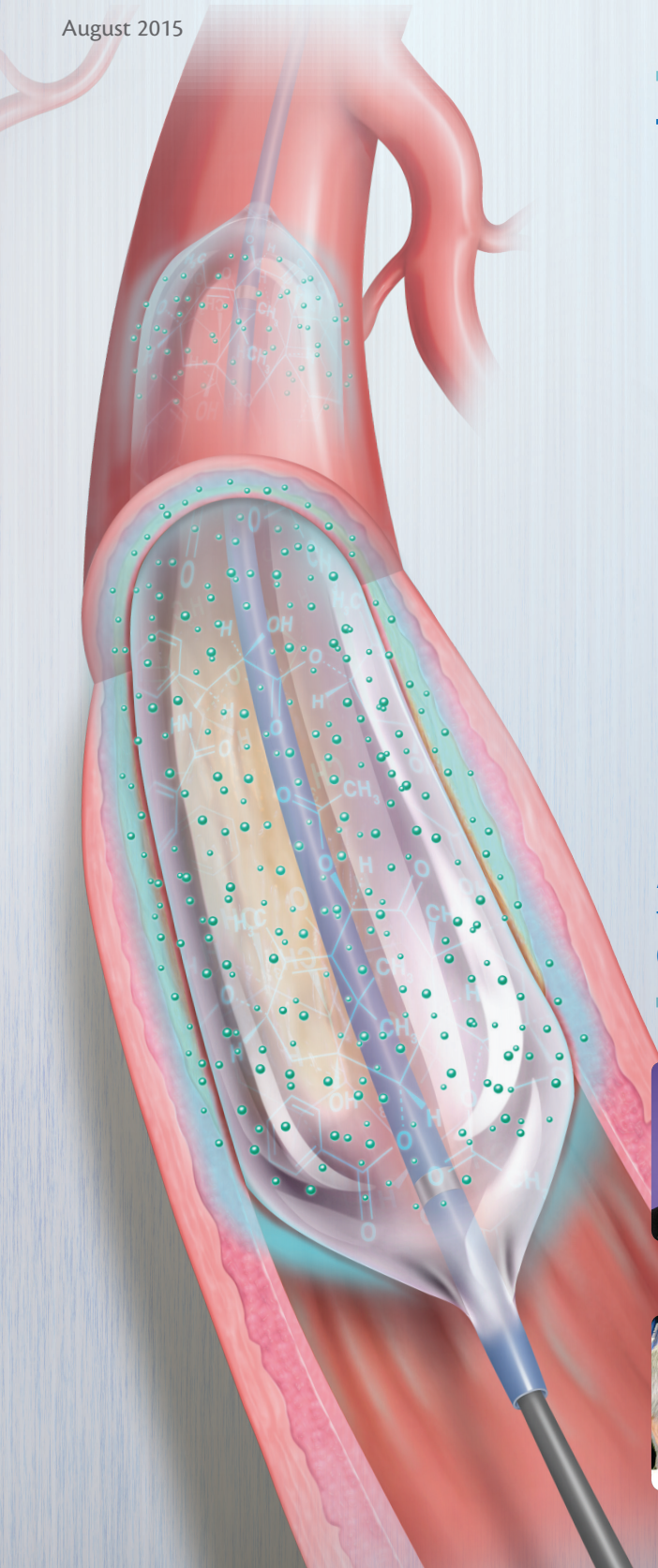
Supplement to

Sponsored by Bard Peripheral Vascular, Inc.

Endovascular TODAY

August 2015



THE EVOLUTION OF SFA CARE:

THE DCB PARADIGM SHIFT

An in-depth look at how the science and clinical use of the first FDA-approved drug-coated balloon, LUTONIX® 035, continues to advance the treatment of PAD.


J.A. Mustapha, MD


Chad R. Laurich, MD


Lawrence A. Garcia, MD


Patrick J. Geraghty, MD


Prakash Krishnan, MD


Renu Virmani, MD


Mark W. Burket, MD


Constantino S. Peña, MD


Carlos Mena, MD


Scott Trerotola, MD

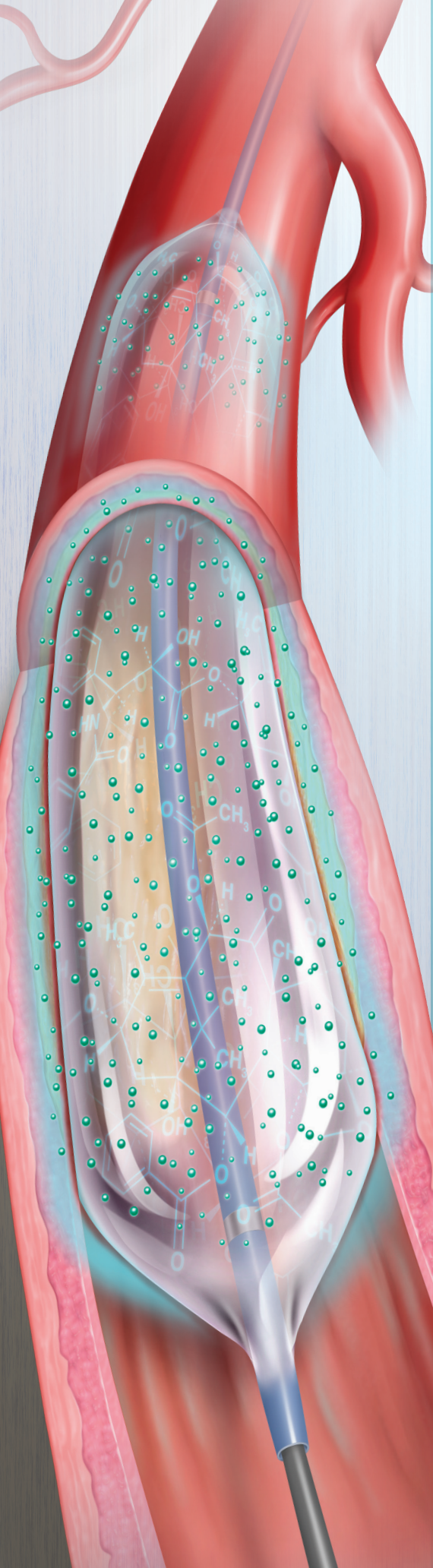


TABLE OF CONTENTS

THE EVOLUTION OF SFA CARE: THE DCB PARADIGM SHIFT

FEATURING


J.A. Mustapha, MD


Chad R. Laurich, MD


Lawrence A. Garcia, MD


Patrick J. Geraghty, MD


Prakash Krishnan, MD


Renu Virmani, MD


Mark W. Burket, MD


Constantino S. Peña, MD


Carlos Mena, MD


Scott Trerotola, MD

Drug-Coated Balloons: The Future Ahead

Experts weigh in on the ongoing trial data supporting the use of drug-coated balloons.

What is the significance of these investigational device exemption trials, and what does this mean for your future treatment algorithms for drug-coated balloons (DCBs)?

J.A. MUSTAPHA, MD

PI, LUTONIX BTK TRIAL

"Critical limb ischemia (CLI) has many associated comorbidities, which can make it extremely difficult to treat. Today, many of us struggle with what is the best therapy for our CLI patients. This type of below-the-knee (BTK) landmark trial will shed light on future therapeutic options for these patients while setting the stage and strengthening the foundation of additional studies and research."

PATRICK J. GERAGHTY, MD

PI, LUTONIX BTK TRIAL

"We know that treatment of CLI requires popliteal and/or tibial intervention in the majority of patients. Our current failure mode isn't so much found in the restoration of patency to these vessels—we're already quite good at that—but in our inability to maintain that newly restored lumen. Biologic modification of the injury response is critical to achieving durable success in this challenging territory, and the LUTONIX BTK trial is the first United States IDE to rigorous examine the ability of paclitaxel-coated angioplasty balloons to achieve that outcome. I'm excited that this trial will provide clinicians with superb data for clinical decision-making in CLI. That's been a rarity in the past, but going forward, savvy clinicians are going to demand that competing technologies provide a similar level of evidence for their treatment. Data-driven CLI therapy—the LUTONIX BTK trial gets us a big step closer to that goal."

CARLOS MENA, MD

PI, LUTONIX ISR TRIAL

"In-stent restenosis (ISR) is one of the most complex clinical issues we have, as the superficial femoral/popliteal arteries are subjected to multiple forces that result in restenosis. In addition to this, patients often have issues getting their risks factors for peripheral artery disease (PAD) under control. Over the last few years, there has been an increased usage of endovascular (i.e., stenting) procedures, and because of this, many patients will experience ISR. Currently, there are no randomized clinical trials that would help us to determine the role, if any, of the DCB technology in this specific clinical setting. There are few other options that have been explored. From the endovascular point of view, if we are able to determine the role of DCB technology in this vexing clinical problem, it will be a step forward in the treatment of patients with PAD.

This trial will clearly determine if there is a role for this technology in this clinical scenario. If positive, this trial will result in DCBs becoming the default strategy for patients with ISR. Given the ease of use, the additional reimbursement (at least in the United States), and the low risk of complications, physicians all over the world would likely endorse this approach. Patients themselves would also favor this approach."

SCOTT TREROTOLA, MD

PI, LUTONIX AV TRIAL

"Because of its large size and multicenter nature, this arteriovenous (AV) trial should determine the value of DCBs in hemodialysis fistulas. If a benefit of DCBs is shown over conventional percutaneous transluminal angioplasty, DCBs will become another key tool in our armamentarium against restenosis.

Further, by not leaving anything behind, as one does when placing a stent or stent graft, late concerns about stent integrity will be eliminated. Matching the natural longevity of fistulas with a means of recharging that longevity without a permanent footprint would be a major win for patients with hemodialysis fistulas."

Treatment Algorithms: This Is How I Use a DCB

An expert panel discusses the current role, data, and techniques for the use of drug-coated balloons in tackling PAD.

PARTICIPANTS

J.A. Mustapha, MD, is Director of Cardiovascular Catheterization Laboratories Metro Health Hospital in Wyoming, Michigan, and Clinical Assistant Professor of Medicine, Michigan State University CHM and COM in East Lansing, Michigan. He has disclosed that he is a consultant to Bard Peripheral Vascular, Inc. and Medtronic.

Chad R. Laurich, MD, is with Sanford Vascular Associates in Sioux Falls, South Dakota. He has disclosed that he is a consultant for Medtronic, Ekos Corporation, and Bard Peripheral Vascular, Inc.

Lawrence A. Garcia, MD, is with the Section of Interventional Cardiology and Peripheral Interventions, St. Elizabeth's Medical Center in Boston, Massachusetts. He has disclosed equity interests, which include CV Ingenuity, Primacea, Spirox, Essential Medical, Scion Cardiovascular, Tissue Gen, and Syntervention, and that he is involved in research for Abbott Vascular and Medtronic.

Patrick J. Geraghty, MD, is Professor of Surgery and Radiology, Vascular Surgery Section, Washington University School of Medicine in St. Louis, Missouri. He has disclosed that he is a consultant/trial PI for Bard Peripheral Vascular, Inc., Boston Scientific Corporation, Cook Medical, Intact Vascular, and Spectranetics Corporation (all revenue goes to Washington University).

Prakash Krishnan, MD, is Assistant Professor of Medicine, Director of Endovascular Intervention, Mount Sinai Heart in New York, New York. He has disclosed that he is a consultant for Bard Peripheral Vascular, Inc.

How do you think drug-coated balloons (DCBs) have changed the overall treatment of peripheral artery disease (PAD) in the superficial femoral artery (SFA)?

Dr. Mustapha: I believe DCBs have created a significant paradigm shift in treating claudicants. They allow us to treat more aggressively, especially lesions at the ostium of the SFA and those that involve the P2 and P3 segments of the popliteal artery.

Dr. Laurich: I think the biggest impact that DCBs have on changing the overall treatment, particularly in the SFA, is the decreased use of stenting as the primary therapy. We're going to see a shift away from stenting as first-line treatment, meaning that we'll try to minimize our stent usage. Stenting creates a more permanent change to the vessel, and shifting away from that is a good thing, because it leaves more treatment options open to the patient in the future. In vascular disease treatment, every therapy that we deliver has a lifespan, even bypass. If we can keep all options open for as long as possible, I think that greatly benefits patients.

Dr. Garcia: The SFA has been one of the most challenging areas to treat. We've bailed out to using stents for many years, with the understanding that stents can do reasonably well at 1 year, but don't have a great success rate out to 2 and 3 years. Additionally, there's been a movement that a lot of us have championed and is now becoming more mainstream, which is to leave nothing behind in the SFA. With DCBs, leaving nothing behind is really appealing because if you need further interventions in the future, you won't have to deal with the stent that was previously left in the vessel. Overall, I would say that they've changed our practice by affording us at least a bit of a pause in therapy, allowing us to treat various lesions without having to leave a stent behind in the SFA.

Dr. Geraghty: They've been a nice addition to the toolbox. Particularly for small-caliber arteries and for enthusiasts of the "no metal left behind" approach,

they're a real boon. We'd still like to see some longer-term data, particularly when we look at DCB use in claudication patients.

Dr. Krishnan: For the first time, we have level 1 evidence that compares a DCB to plain balloon angioplasty out to 1 year, with very good results. This gives us the confidence to treat SFA disease without leaving a prosthesis behind. Even though we previously saw that the Zilver drug-eluting stent (Cook Medical) provided great outcomes in this area, it has the downside of leaving a stent in the vessel.

In what ways does DCB use affect both the treated vessel segment and future treatment options?

Dr. Laurich: Recurrence is obviously the Achilles' heel of endovascular therapy. The long-term result is really the primary focus now. The problem that we struggle with most is recurrence via the intimal hyperplasia process, and until now, we haven't had a tool that directly focused on addressing this. There is a lot of excitement surrounding DCBs because this is the first medical therapy that we can deliver endovascularly, instead of relying solely on mechanical forces to treat the vessel. Everything we do mechanically affects the biology of the vessel, but this is the first therapy directed at the biological process itself, which is exciting because this is the number one issue we struggle with. There are no "silver bullets," but I believe this will certainly be an effective tool that could ultimately provide a longer-lasting solution for our patients.

Dr. Garcia: I think DCB treatment has the potential to address what I call the proverbial creep of disease associated with repeated stent treatments. This refers to a situation when you have a 10- or 12-cm-long lesion, and you place a 15-cm stent that fails, so then you start adding stents, which makes a 15-cm lesion now 20 cm. If the stents continue to fail, the treatment area keeps growing, and then you ultimately need to do a bypass. If a DCB fails, you can still retreat that same lesion length rather than progress to lengthier and lengthier areas of the vessel. With the DCB, you don't have to overcompensate for failure based on restenosis due to repeated stent treatments of increasing length. If you asked those who treat this disease on a daily basis whether we'd rather see in-stent restenosis or restenosis without a stent, I think it's safe to say that we'd all much prefer to treat restenosis without a stent. The "leaving nothing behind" strategy is really picking up steam in the SFA. It may not be ready for prime time in regard to all-comers, but I think it's really shifting the practice paradigm for many patients who have SFA disease and claudication.

Dr. Geraghty: One notable advantage is the theoretical ease of reintervention, in the sense of not having to deal with the metal scaffolding, which gives us more options for reintervention. I think as long as DCBs can maintain a favorable patency profile that will keep them competitive with other options in the SFA, the ease of reintervention certainly makes them very attractive.

Dr. Krishnan: We know that once the paclitaxel is in the vessel, it significantly inhibits restenosis compared to a non-coated balloon, at least up to 1 year. What we don't know is how these results will endure long-term. However, even if the vessel does restenose, we won't have to deal with a previously implanted prosthesis, which makes it a lot easier to go back and reintervene, if needed.

How do DCBs fit into your treatment algorithm?

Dr. Mustapha: It is becoming a primary choice of therapy in my algorithm, regardless of which vessel preparation I do first. As you know, at this point, it is not approved or available in the United States for below-the-knee disease. However, for the patients with multilevel critical limb ischemia (CLI), such as in the popliteal and SFA, DCBs play a major role in treating CLI patients in my practice.

Dr. Laurich: DCBs have become first-line therapy for claudicants and CLI patients. Using an antirestenotic therapy to reduce the likelihood of a repeat intervention decreases the risk for every patient. I strongly believe that vascular physicians should keep a life-long treatment algorithm in mind when delivering therapies. DCBs play a role in that by helping you keep as many options open for them as possible.

Dr. Geraghty: I've actually been using them more for CLI than claudication. The thought is that with smaller-caliber arteries and oftentimes more distal lesions in terms of the popliteal, I'm more reluctant to leave behind metal scaffolding. The caliber is not as well matched for some of the available drug-eluting stent products, so I prefer DCBs in these cases.

Considering that the two DCBs that are approved in the United States market are different in design and drug dose, how do you decide which DCB to use in a particular case?

Dr. Mustapha: Both are good DCB balloons. I tend to use the LUTONIX® DCB (Bard Peripheral Vascular,

Inc.) more because their 6-mm balloon goes through a 6-F sheath, and the 6-mm In.Pact balloon (Medtronic) requires a 7-F sheath.

Dr. Laurich: Well, there are issues of both efficacy and safety to be discussed. As far as efficacy, both have been proven effective. I don't think the drug concentration on the balloon is necessarily the important number; one has 2 μg/mm^2, and the other has 3.5 μg/mm^2. The issue is really the amount of drug you are able to deliver to the deep intimal and medial layers of the vessel wall.

Dr. Garcia: One factor we consider is the range of balloon lengths available, as we definitely need longer balloons to treat the longer lesions we're seeing. Overall, I don't think there's a huge difference between the two designs, even though the drug dosing on each is a bit different.

Dr. Geraghty: I personally don't care so much about the drug dose, I care more about the results. You can have different drug doses, and if different balloons have different washout rates and transfer rates to the wall, the drug dose matters very little. In the end, I look at the results that the balloon generates in terms of efficacy and safety. Thus far, at year 1, both competitors had very good efficacy and safety, and at year 2, I see the LUTONIX® DCB story, but I don't have the other balloon's data to look at yet.

Dr. Krishnan: I choose which DCB to use based on the balloon sizing options each provides and what I need in order to best treat the lesion in front of me.

How does lesion length and severity affect your decision on which DCB to select? When do you use a DCB, and when do you use a stent?

Dr. Geraghty: In the past, I favored stenting over atherectomy for complex SFA lesions. As part of that procedure, I would predilate, particularly when treating chronic total occlusions (CTOs). Once I crossed the lesion, I'd predilate a 3- or 4-mm channel, just to know that I could open the stent without difficulty and then postdilate within the stent. Now, I'm much more aggressive with my predilatation to see if I can achieve that good lumen and potentially use the DCB as a treatment option. This is how my practice has changed, particularly for short to mid-length lesions.

Dr. Garcia: When you have a long CTO, I think most interventionists would choose to stent based on the available data. But if you look at moderately long lesions, they all had fairly robust CTO numbers between 25% and 33% of enrolled patients in the THUNDER, LEVANT, and IN.PACT trials. I think the paradigm of, "If it's occluded, you have to put a stent in," may not actually be valid. We're all trying to decide how best to treat this disease, but I think most of us are leaning toward leaving nothing behind, even in the CTO.

Dr. Laurich: With CLI patients, I am more apt to stent, but I will use a DCB as first-line therapy. You often have multilevel disease to treat as well, so you want to be sure you've maximized your SFA and popliteal flow. In general, I will use DCBs in the SFA and popliteal and be a little more liberal with my stenting, and then treat their tibiopedal diseases with angioplasty or atherectomy/angioplasty.

Dr. Mustapha: Vessel preparation is key when it comes to complex calcified lesions. There aren't any specific data to support the superiority of one particular balloon over the other in calcified lesions. In that regard, I go back to my previous point that sizing determines balloon choice. Vessel preparation for calcified lesions has no specific tool that fixes all. So, I look at the vessel and make a decision based on what I see, as well as the location of the lesion in the vessel.

How do you typically predilate, and why is that important?

Dr. Garcia: I tend to believe that predilatation is very important for two reasons. One reason is you want to see the reaction of the artery to predilatation. Although we usually undersize the predilatation balloon, if this step creates a major catastrophe (i.e., dissection or perforation), then you know to stent it and perhaps skip the DCB altogether. Alternatively, the predilatation might look great, so do your definitive therapy with the DCB.

The second reason I predilate, and the way to get the best angioplasty result, is not only to go long in your duration of therapy, but also do multiple inflations. What happens is the artery finally releases and tends to dilate rather than tear, and the smooth muscles usually relax when you do multiple inflations. In terms of inflation time, we don't inflate for long during the predilatation, and then we use a DCB for a protracted period of time (3 to 4 minutes), with the goal to have the artery resist the recoil response to dilatation.

Dr. Mustapha: I personally prefer to predilate using a 1:1 ratio to create the most suitable environment for the DCB to deliver the drug to a vessel wall that no

longer requires any additional dilatation. Therefore, I use the DCB as a tool of drug delivery and not a tool to dilate.

Dr. Laurich: Predilatation was included as part of the United States trials, and we saw that there are two important reasons to predilate. Number one is that it allows good vessel prep. The second is to understand sizing. With DCBs, you definitely want to size your balloon to the vessel 1:1 or slightly oversize; it should never be undersized. There are a number of studies that show that you need 1:1 apposition of that balloon to the vessel wall in order to provide adequate drug transfer.

It is also important to use good angioplasty technique. I think interventionists are becoming more aware that this should be done slowly, and the balloon should be inflated for an appropriate amount of time. There has been some evidence that better angioplasty results can be achieved by inflating the balloon for 3 minutes instead of only 1 minute.

So, if possible, one should try to achieve the desired profile with slightly less pressure and leave the balloon inflated a little longer to allow the vessel more time to remodel, which may ultimately lead to better results.

Dr. Geraghty: In the trials, we saw that even plain balloon angioplasty did significantly better than we would have historically expected. I think part of that was the good angioplasty technique using predilation and appropriate balloon sizing. For me, that's changed the way that I approach the SFA with my first dilation; I try to get to nominal size so that I can really tell if the artery is going to be a good candidate for DCB application.

What steps do you take to ensure proper alignment between your predilatation balloon and the DCB?

Dr. Laurich: My method is that I always physically mark the vessel on the screen and map out the goal of treatment. I think it's important to have a standard method of marking the location of the lesion. Some will use a road map technique, which is fine, but patient shift can be a problem. I find that the screen-marking technique allows me to be more precise.

When I predilate, I prevent geographic miss by never using a predilatation balloon longer than my DCB. So, for example, if the lesion is 8 cm, I'll predilate with an 80-mm balloon, and I'll use a 100-mm DCB, just to be sure that I'm not ballooning beyond the region of where I intend to treat with the medicine.

Dr. Garcia: Geographic miss is critical. In the old days when you had a lesion, it was like throwing a grenade or playing horseshoes. You could get close with a stent, and it was fine in covering the lesion. If you had a 10-cm lesion and placed a 15-cm stent, you could miss it by 2 cm on either side and still cover the lesion.

When it comes to DCBs, you have to be a little better at not only visually assessing where the lesion lives, but also accurately treating it. When we predilate, we always have a ruler in view of the lesion to avoid geographic miss. For example, we'll use a 40- or 60-mm balloon to predilate in preparation for using an 80-mm DCB. You always want to go longer than the original predilatation. However, you have to be careful when you have multiple predilatations, because you want to be sure to clearly mark the front and back end of the lesion to avoid geographic miss.

Dr. Geraghty: We've always used the radiopaque markers on the leg. In the past, we tended to put those on the drape, but more and more, we are putting them directly on the patient because it gives you a more stable marker that you can refer to. Even a couple of millimeters of shift might throw you off and cause geographic miss. It's also important to record the predilation images so that we know exactly where our proximal and distal ends are, and then we can be sure that we have good overlap.

Dr. Krishnan: This is a very important technical aspect of DCB use. It is important to use glow or marker tape on the patient, and once you balloon the lesion, the reference needs to be marked on the side monitor. Once this is done, you should ensure that you cover 1 mm distal to where you predilate with the regular balloon; otherwise, you will see geographic miss and high restenosis rates.

What are the implications of misalignment between your predilatation balloon and the DCB?

Dr. Mustapha: Misalignment can lead to many potential untoward side effects. The most common is the lack of drug delivery to the vessel wall. Therefore, misalignment should be avoided as much as possible.

Dr. Laurich: You just want to be sure you're providing treatment to the desired area. This is a basic skill that we all need to make sure we pay attention to.

Dr. Garcia: One of the best ways to recreate restenosis is an overstretch model in any artery, particularly

a diseased artery. If you miss by predilating an area that you don't cover with medication (i.e., drug), then that area will have the simplest response to that injury, which would be a restenosis due to recoil and hyperplasia. Moreover, the edge between where the drug was placed and the nontreated area can cause the so-called candy wrapper effect. This was very common in the early days of drug-coated stents in the coronaries. Basically, this refers to when there's an inhibition to restenosis from the medication and then 2 to 4 mm from that area, a hyperplastic response makes the edges of the segments look like a candy wrapper.

Dr. Geraghty: We know that in the SFA trials, when they went back and looked at study images and could identify areas of geographic miss, they could track those treatment failures. This makes sense from the biology standpoint, as we're trying to get the drug onto every area that undergoes an angioplasty injury. If that doesn't happen, you haven't achieved the desired result with your intervention. The same thing holds for drug-eluting stenting, in that you don't want to angioplasty outside the confines of the stent. With DCBs, it takes a little more attention to detail because you don't have the metal markings of the stent, but I think for any experienced operator, it just takes a minute or two of attention to the predilation images to be precise and successful.

Dr. Krishnan: The implications of geographic miss are simple: higher restenosis rates.

Where do you foresee the future of DCBs going in the next few years? Bare-metal stents? Drug-eluting stents?

Dr. Mustapha: I see the future of DCBs to be part of our everyday practice in both claudicant and CLI patients. I don't see DCBs overtaking other therapeutic vascular interventions completely, as there is a good possibility that various combinations of DCBs with other therapies may in the future prove to be viable options. I am very optimistic about the future with DCBs, including their potential to treat more complex lesions than we are treating today.

Dr. Laurich: I think we can look to Europe for some sense of where our future is going with DCBs, as they've had them for a few years now, with multiple products on the market. I've had the pleasure of speaking with some of our European colleagues, and they saw that after the initial excitement for DCBs died down, and as the market matured, there was a shift back toward stent usage overall. If you look at the large trials and the real-world trials, what we find is that there's about a 20% to 25% stenting rate in all patients. So, I think there is always going to be a certain need for stents, but what I'm curious about is how far are we going to swing in that spectrum. This remains to be seen in the United States.

Dr. Garcia: One issue is that we'll need 200-mm balloons that have reasonably good inflation pressures in terms of volume and diameter and that deliver the drug to a longer swath of vessel to keep costs low. We also need head-to-head comparator trials between DCBs and drug-eluting stents and/or DCBs and bare-metal stents. If the dominoes fall in favor of the DCB across these types of trials, then I would only foresee that DCB use will go up. If at any time the DCB falters, and a different therapy is better suited, then that will become the default therapy. It's survival of the fittest when it comes to these head-to-head comparator trials.

Overall, I think DCBs have an exceedingly good chance of winning because the downstream failures of endoprotheses, whether it be bare metal or drug eluting, are critical. Once those failures occur, there's no taking it back—the damage is done. Those failures portend poor prognostic events over time, and if we see these failures, then DCBs will take off and become the default therapy.

Dr. Krishnan: The future of DCBs is bright; however, we still need longer-term data.

Dr. Geraghty: We're currently running the LUTONIX DCB below-the-knee trial, and we're very excited to see the results of that. CLI is an area in which we're in desperate need of better therapies. The DCB manufacturers have put a lot of effort and funding into doing this study right, and we hope to complete enrollment this year. If the results confirm that this DCB offers better results than traditional angioplasty in treating the distal popliteal and tibial disease that almost universally affects CLI patients, that would be a real step forward. ■

Disclaimer: The opinions and clinical experiences presented herein are for informational purposes only. The results may not be predictive for all patients. Individual results may vary depending on a variety of patient-specific attributes. Drs. Mustapha, Laurich, Geraghty, and Krishnan have been compensated by Bard Peripheral Vascular, Inc. for the time and effort in preparing this article for Bard's further use and distribution.

Safety of Drug-Coated Balloons: Insight from Preclinical Studies

Understanding the advantages and disadvantages that can result from different balloon technologies on the market.

BY KAZUYUKI YAHAGI, MD; FRANK D. KOLODGIE, PHD; AND RENU VIRMANI, MD

Atherosclerosis is the primary cause of peripheral artery disease (PAD), which continues to increase in the United States and Europe and affects more than 27 million people.[1,2] The symptoms of PAD widely vary from mild claudication to critical limb ischemia (CLI) with gangrene and limb loss, and it is associated with high morbidity, especially in the elderly.[3,4] Historically, treatment strategies for PAD have involved medical therapy and open surgical bypass procedures.[5] Over the last decade, endovascular treatment, including percutaneous transluminal angioplasty, stenting (with or without drug), stent grafts, and atherectomy, have become the standard of care.[4] However, treatment is complicated by the fact that the superficial femoral artery (SFA) is one of the longest and most dynamically active vessels in the body, undergoing torsion, compression, flexion, and extension relative to hip and knee motion. The lower limb vessels are also susceptible to atherosclerosis because of low shear stress and spiral flow, which is most evident in the long segment of the lesser curvature of the SFA.[6]

Endovascular interventions are currently the first-line strategy for treatment, as recommended by the TransAtlantic Inter-Society Consensus for type A and B lesions. Surgical revascularization is still advocated for type D lesions, and type C lesions may be treated by interventions or surgery.[7] Despite the changing paradigm for the treatment of PAD, the femoral and crural territories are still hampered by relatively high restenosis rates and lack of sustained benefit in CLI patients.[5,7]

More recently, drug-coated balloons (DCBs) are now considered novel alternatives to drug-eluting stents (DES), as they provide the same antiproliferative drug without leaving a permanent stent.[8,9] Potential benefits of DCBs over DES include the rapid delivery of drug, which is more diffusely distributed on the luminal surface without a polymer carrier or rigid metallic frame, avoiding the aforementioned unfavorable foreign body response that can contribute to in-stent restenosis.

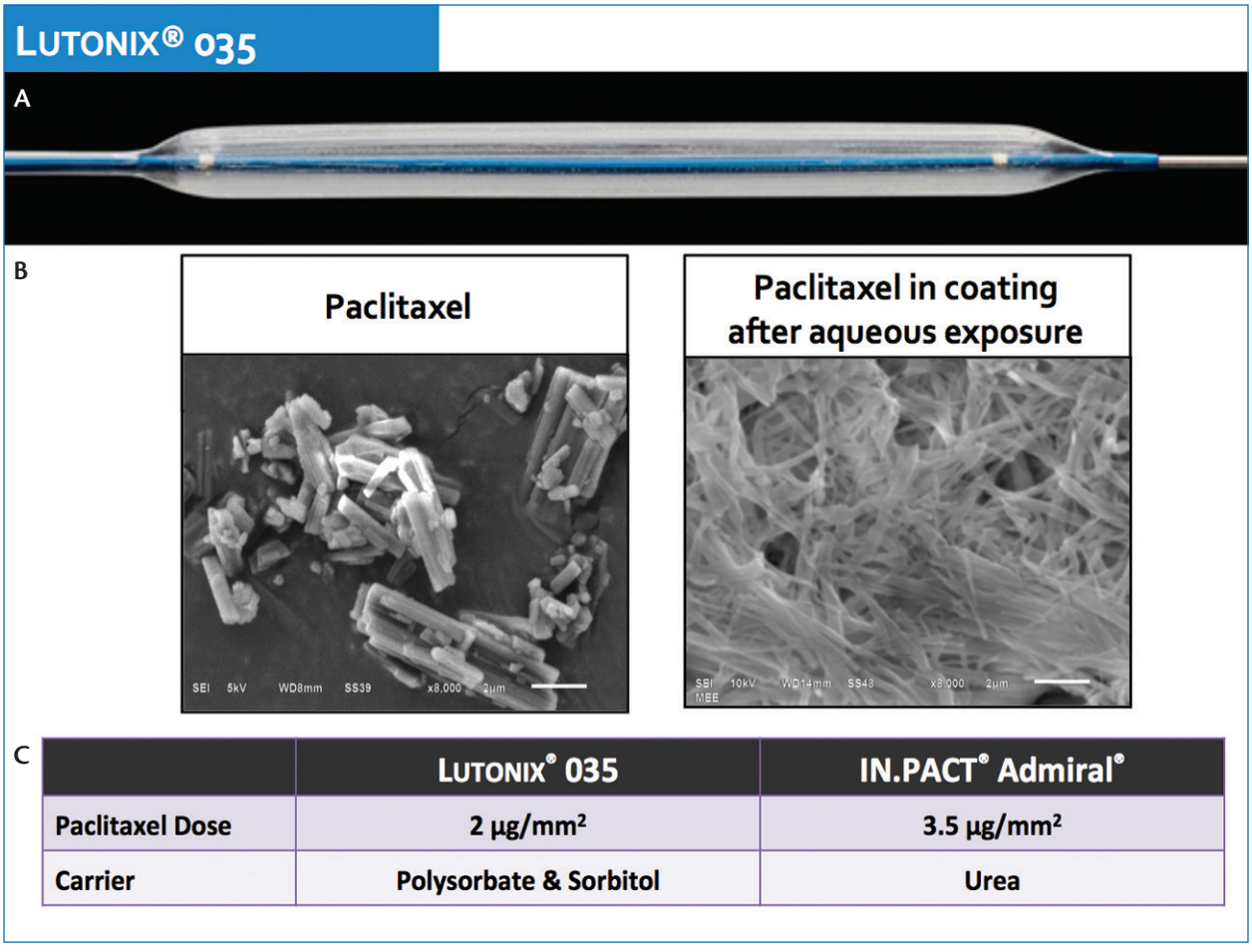
Drug delivery through adherence to the vessel wall is facilitated by carrier excipients, a revolutionary discovery that has led to the success of DCB technology.

To date, paclitaxel is the most commonly used drug for DCB technology, which has high lipophilic physiochemical properties, allowing passive absorption through the cell membrane and a sustained effect within the treated vessel wall. Drug delivery through adherence to the vessel wall is facilitated by carrier excipients, a revolutionary discovery that has led to the success of DCB technology.[8] Another potential advantage of DCBs is the uniform deliverability of drug to the vessel wall relative to DES, in which drug is delivered over the stent platform, potentially resulting in nonhomogeneous drug-tissue transfer dependent on the stent design and interstrut distances.[10]

PRECLINICAL DATA ON THE LUTONIX® DCB

The LUTONIX® DCB (Bard Peripheral Vascular, Inc.) is coated with low-dose (2 µg/mm^2) paclitaxel drug using a novel polysorbate/sorbital carrier (Figure 1). In a recent study, we reported the pathologic response

Courtesy of Bard Peripheral Vascular, Inc.



	LUTONIX® 035	IN.PACT® Admiral®
Paclitaxel Dose	2 µg/mm²	3.5 µg/mm²
Carrier	Polysorbate & Sorbitol	Urea

Figure 1. The LUTONIX® DCB. Gross micrograph of the inflated balloon (A). Transmission electron microscopy of the balloon surface with or without hydration (B). Relative comparison of dose and carrier for the LUTONIX® 035 balloon and the In.Pact Admiral balloon (Medtronic; C).

following DCB treatment of swine femoral arteries in animals survived for 28, 90, and 180 days,[11] with low-pressure balloon inflation either at one clinical dose (single inflation, 2 µg/mm^2 paclitaxel) or four clinical doses (two DCBs, each with 4 µg/mm^2 paclitaxel), with a standard uncoated balloon (SUB) serving as the control.

DCB treatment resulted in minimal endothelial loss, fibrin deposition, and minimal inflammation, with a sustained dose-dependent drug effect characterized by the loss of medial smooth muscle cell (SMC) peaking at 90 days for both groups. The SMC loss of the medial wall was graded from 1 to 4: grade 1 = < 25% of the inner surface medial wall showing loss of SMCs; grade 2 = > 25% but < 50%; grade 3 = > 50% but < 75%; and grade 4 = > 75% SMC loss. In arteries treated with the DCB, the transmural SMC loss score at one clinical dose was 1.1 ± 1.4 versus control SUB 0 ± 0 (P = .008), and at four clinical doses, the transmural SMC loss score was 2 ± 1.5 versus control SUB 0 ± 0 (P < .001). No inflammation was observed in the one-dose group at 180 days, and there was an absence of necrosis and/or aneurysmal dilatation at all time points for both doses.[11]

The loss of medial SMCs was accompanied by mild medial thinning, which is also consistent with drug effect. In parallel, arterial healing was observed at 90 days in both study arms, with significantly greater medial proteoglycan and collagen deposition peaking at 90 days in the one-dose group and at 180 days in the four-dose group (Figure 2).[11]

The arterial tissue paclitaxel concentration following treatment with one dose was high at 1 hour (58.8 ± 54.2 ng/mg), significantly decreased at 24 hours (4.4 ± 6.9 ng/mg), and was sustained at 30 days (0.3 ± 0.4 ng/mg). On the other hand, paclitaxel concentration in the plasma peaked at 3 minutes and could not be detected beyond 24 hours.[11]

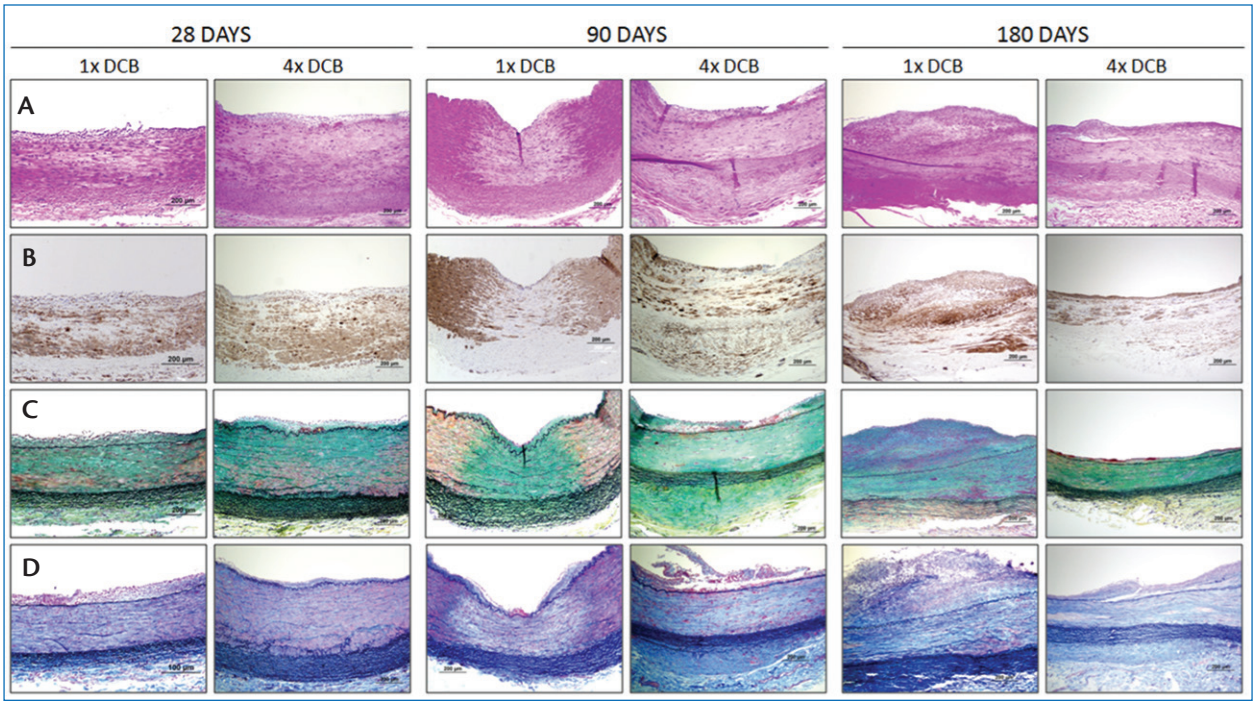


Figure 2. Representative images of the arterial response in swine SFA following one- and four-dose DCB treatment. Hematoxylin and eosin stain (A). Antibody staining against alpha-SMC actin shows peak loss of SMCs at 90 days in both the one- and four-dose DCB groups (B). In parallel, proteoglycan and collagen replacement can be observed at 90 and 180 days by the Movat (C) and Masson's trichrome (D). Reprinted with permission from Yazdani SK et al. Catheter Cardiovasc Interv. 2014;83:132–140.[11]

DOWNSTREAM EFFECTS FOLLOWING DCB DILATATION

Histologic examination of downstream skeletal muscle from the same preclinical study[11] demonstrated no evidence of ischemic changes, emboli, or systemic toxicity for both the one- and four-dose DCB groups. Overall, changes in skeletal muscle were few, with < 0.025% of arterioles showing mild fibrin deposits within the walls of the muscular arteries or arterioles. The main findings involved single or clusters of small vessels (predominately arterioles) with varying degrees of SMC apoptosis and loss and adventitial inflammation, and rarely was the fibrinoid change accompanied by lymphocytic inflammation. The percentage of arterioles with pathological findings in the four-dose–treated arteries was at its maximum at 28 days, but the overall involvement remained low at 0.24%. The vascular changes within the skeletal muscle were mostly resolved by 90 days, although three skeletal muscle sections from the four-dose animals did show rare pathological changes of focal fibrin and SMC loss.[11]

We recently performed an independent blinded analysis of two DCBs that have received United States and CE Mark approval in order to further understand the pathologic changes that occur in the downstream vascular bed following arterial dilatation. The purpose was to compare the LUTONIX® DCB (paclitaxel dosage 2 µg/mm^2 at three times the loading dose, with a total dose of 6 µg/mm^2) and the In.Pact Amphirion balloon (Medtronic; paclitaxel loading dose 3.5 µg/mm^2 at three times the loading dose, with a total dose of 10.5 µg/mm^2). To reach the three-times loading dose, each balloon had three balloon exchanges in the SFA in the 90-day swine model.

These studies were performed in two separate sets of animals. Different animals received either the LUTONIX® balloon or In.Pact balloon. The overall percentage of downstream vascular and skeletal muscle necrosis/fibrosis following DCB dilatation was lower for LUTONIX® DCB (8.9 %) as compared to the In.Pact Amphirion balloon (48.7%) (Figure 3). Moreover, there was no evidence of downstream skeletal muscle necrosis/fibrosis in the LUTONIX® DCB group, whereas In.Pact Amphirion showed 11.5% of histologic sections with necrosis/fibrosis, and crystalline materials were found in 5.1% of sections (Figure 3). Taken together, these data emphasize the critical aspect of the formulation for local paclitaxel delivery, and may be related to high drug load and coating integrity.[12]

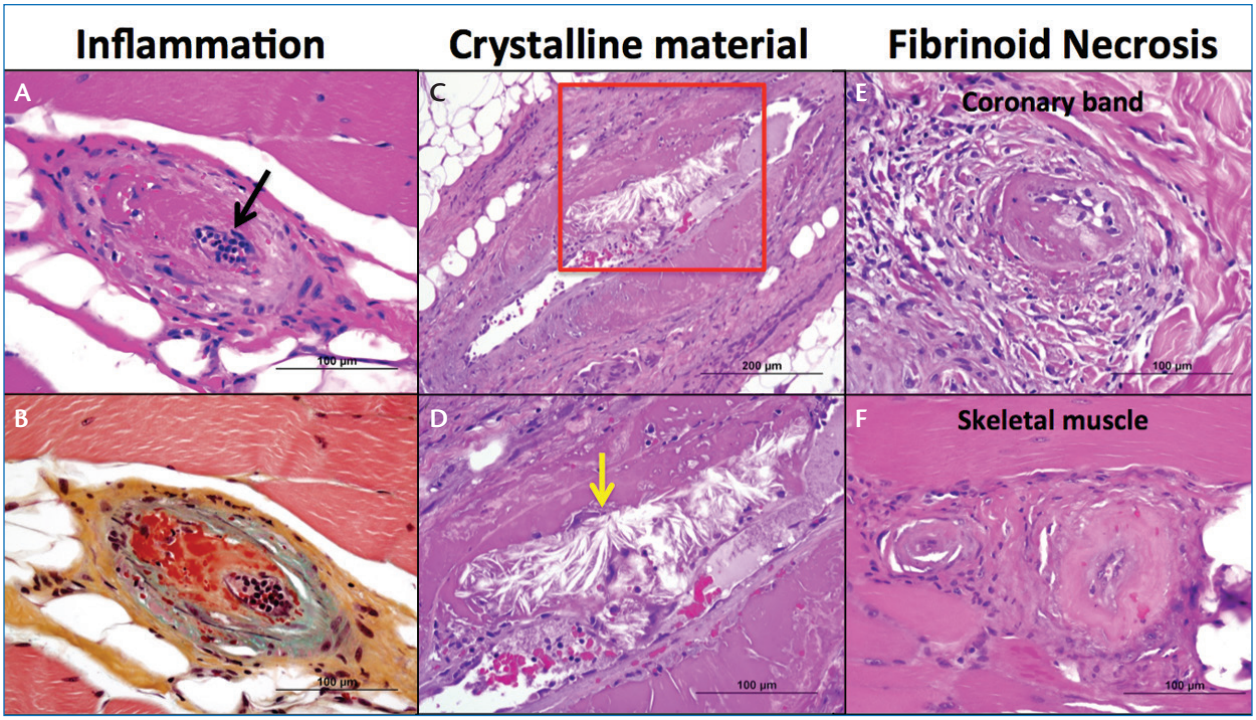


Figure 3. Representative images of embolic changes in skeletal muscle and coronary band territories mainly involving small arterioles following iliofemoral artery dilation with paclitaxel DCB in healthy swine. Hematoxylin and eosin (A) and Movat pentachrome (B) connective tissue stain, respectively showing fibrinoid necrosis of an arteriole in downstream skeletal muscle at 90 days following iliofemoral dilation using the LUTONIX® DCB (2 µg/mm²) with overlapping (three) dilatations. Low-power image shows embolic crystalline material in nontarget skeletal muscle at 90 days following femoral artery dilation with the In.Pact Amphirion (3.5 µg/mm²) with overlapping (three) balloons (C). High-power image (D) of the region represented by the red box in panel C shows fine needle-shaped crystalline material (yellow arrow) with acellular areas of fibrin. Similar findings of fibroid necrosis at 90 days after In.Pact Amphirion use were also observed in the coronary band (E) and other skeletal muscle beds (F) following use of three repeated overlapping dilations.

INTERPRETATION OF PRECLINICAL DATA

Although arterial repair after balloon injury occurs more rapidly in animals than in humans, preclinical models hold predictive value for biological effects attributed to drug delivery.[13] Transferring preclinical findings observed in healthy porcine arteries to diseased atherosclerotic arteries in humans is not entirely straightforward, as lesions are further complicated by necrosis and calcification. Nonetheless, preclinical studies in translational animal models should help to provide clues into drug-related biologic effects, as well as unfavorable results such as inflammation, excessive intimal growth, and embolic phenomenon.

In experimental models, it has been reported that at least 25% to 35% of the paclitaxel loaded on balloons with either urea matrix or iopromide coating is lost in the blood stream.[14] The presence of such phenomenon observed in the animal model may be of relevance in PAD, especially when DCBs are used in patients suffering from CLI. However, not all DCBs are created equal, and further clinical studies are needed to clarify the effect of downstream emboli on adverse clinical outcomes.

CONCLUSION

DCBs have emerged as an important therapeutic alternative in the treatment arsenal of peripheral vascular disease. However, the downstream effects observed in preclinical testing of skeletal muscle following DCB usage present one of the major concerns, which may help distinguish the available balloon technologies on the market. Clinicians should understand the potential advantages and disadvantages of the various products before selecting an appropriate DCB. ■

Kazuyuki Yahagi, MD, is with the CVPath Institute, Inc. in Gaithersburg, Maryland. He has stated that he has no financial interests related to this article.

Frank D. Kolodgie, PhD, is with the CVPath Institute, Inc. in Gaithersburg, Maryland. He has stated that he has no financial interests related to this article.

Renu Virmani, MD, is with the CVPath Institute, Inc. in Gaithersburg, Maryland. She has disclosed that she receives research support from Abbott Vascular, BioSensors International, Biotronik, Boston Scientific, Medtronic, MicroPort Medical, OrbusNeich Medical, SINO Medical Technology, and Terumo Corporation; has speaking engagements with Merck; receives honoraria from Abbott Vascular, Boston Scientific, Lutonix, Medtronic, and Terumo Corporation; and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore. Dr. Virmani may be reached at (301) 208-3570; rvirmani@cvpath.org.

Disclaimer: The opinions and clinical experiences presented herein are for informational purposes only. The results may not be predictive for all patients. Individual results may vary depending on a variety of patient-specific attributes. Dr. Virmani has been compensated by Bard Peripheral Vascular, Inc. for the time and effort in preparing this article for Bard's further use and distribution.

1. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45(suppl S):S5-67.
2. Owens CD, Conte MS. Medical management of peripheral arterial disease: bridging the "gap"? Circulation. 2012;126:1319-1321.
3. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet. 2005;366:1773-1783.
4. Spies JB, Burke DR, Husted JW, et al. Guidelines for percutaneous transluminal angioplasty. J Vasc Interv Radiol. In press.
5. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg. 2000;31:S1-S296.
6. Back LH, Back MR, Kwack EY, Crawford DW. Flow measurements in a human femoral artery model with reverse lumen curvature. J Biomech Eng. 1988;110:300-309.
7. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113:e463-654.
8. Gray WA, Granada JF. Drug-coated balloons for the prevention of vascular restenosis. Circulation. 2010;121:2672-2680.
9. 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.
10. Nakano M, Yazdani SK, Virmani R. The present state of drug-coated balloons. Cardiology Today's Intervention. 2012;1:10-11.
11. 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;83:132-140.
12. Virmani RV. Preclinical safety data and technology overview. Presented at Transcatheter Cardiovascular Therapeutics 2014; September 15, 2014; Washington, DC.
13. Schwartz RS, Edelman ER, Carter A, et al. Preclinical evaluation of drug-eluting stents for peripheral applications: recommendations from an expert consensus group. Circulation. 2004;110:2498-2505.
14. 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;46:255-263.

The Economic Impact of Drug-Coated Balloons in the SFA

From a financial standpoint, DCBs have become the most attractive endovascular option for treating atherosclerosis in the superficial femoral artery.

BY MARK W. BURKET, MD

It is well-recognized that peripheral artery disease (PAD) affects millions of individuals worldwide. In countries with an aging population, and with a growing prevalence of diabetes, there is an even greater growth of this malady. Although it has been common for PAD to be undiagnosed or misdiagnosed in the past, educational efforts by health care workers, professional societies, and industry have enhanced awareness in recent years.[1] Due to an increase in prevalence and awareness, greater numbers of patients with PAD are now being treated. This has led to an increase in financial expenditures related to PAD. In addition to this increase in patients being treated, new therapeutic options have become available, generally at a higher cost than older therapies. Thus, the overall expense associated with PAD is accelerating.

These increasing expenditures come at a time when scrutiny about funds spent on health care has become much more intense. Whereas "safety and efficacy" were the watchwords of the past, these terms are no longer good enough. In the current era, a proposed therapy must also impart value and cost effectiveness. Given the fact that disease of the superficial femoral artery (SFA) is the most common cause of claudication, it is of little wonder that there is now focused interest in determining the most cost-effective strategy for its treatment.

THE COSTLIEST OPTIONS

Although the focus of this discussion is cost effectiveness for endovascular treatment, it is vital to hold minimally invasive options within a broader perspective. Percutaneous therapy is often chosen as an alternative to surgical treatment, as the latter is typically associated with higher expenditures. For example, an uncomplicated femoropopliteal bypass operation produces hospital and physician fee costs of approximately $20,000.[2] Should the procedure be associated with infection or other perioperative complications, the expense would be dramatically higher.

Even worse than this is the option of amputation. Although in some ways this procedure may seem to be a simple and definitive solution to an intractable problem, it is not that at all. Patients have poor functional recovery, with many never achieving ambulatory status again. This is especially true after above-the-knee procedures. Dillingham et al reported that among patients undergoing amputation, 26% required an additional amputation, and 36% had died by 1 year.[3] Furthermore, the financial cost is comparatively high, with first-year costs of $40,000 to $45,000 and structured rehabilitation doubling that cost.[4]

OTHER STRATEGIES

Of course, the simplest strategy for managing PAD consists of smoking cessation, structured exercise, antiplatelet therapy, lipid-lowering therapy, and cilostazol.[5] As all three of the mentioned drug classes have become generic, the associated monthly expenditure has become reasonable for many patients. However, if drug side effects or lack of efficacy make conservative therapy untenable, then percutaneous treatment can be a more viable option. A hidden cost associated with medical therapy may lie in the associated physical disability. Patients suffering from intermittent claudication have a significant reduction in function and quality of life and may reduce the ability to sustain gainful employment.

When conservative therapy alone is abandoned, percutaneous options are typically pursued. In the 50 years since Dotter's use of a simple Teflon dilator to open a critical stenosis in the femoropopliteal segment of an elderly woman in 1964, there has been a deluge of devices designed to treat atherosclerotic peripheral arteries.[6]

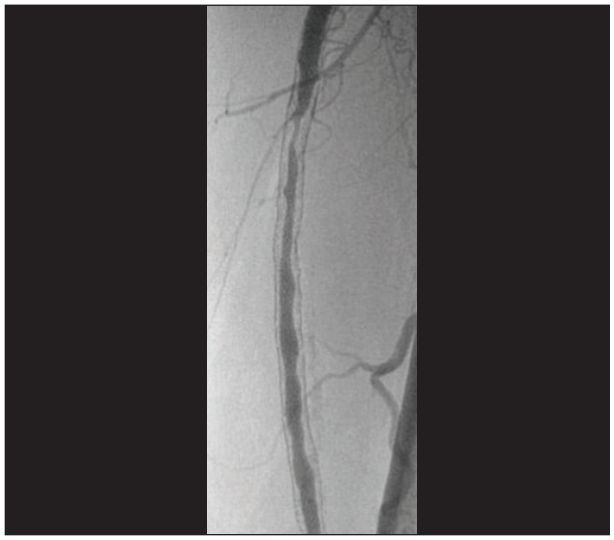


Figure 1. Nitinol in-stent restenosis.

As new equipment and techniques were introduced into clinical use, they were initially assessed only in terms of their ability to safely restore circulation. As experience grew in the femoropopliteal segment, it became apparent that durability, typically measured by primary patency and target lesion revascularization (TLR), was just as important. It has been less than a decade since intense interest has also been placed on the cost effectiveness of SFA intervention. In recent years, virtually any thorough discussion concerning PAD treatment has included consideration of the economic impact of various treatment options. Given the wide variability in price attached to percutaneous treatment devices, as well as differences in outcomes, it is logical to critically compare therapies when considering health care costs. In essence, the goal is to achieve adequate limb perfusion for as long as possible and as cost effectively as possible.

An important concept in understanding expenditures associated with femoropopliteal intervention is that of commoditization. When products come to market with higher efficacy or other unique features in comparison to existing devices, a competitive edge exists, which allows for higher pricing. In contrast, when multiple vendors offer equipment that is nearly identical, price competition invariably follows. Access sheaths, diagnostic catheters, access guidewires, and simple balloons are examples of products that have become commodities.

Largely because of commoditization, percutaneous transluminal angioplasty (PTA) is a procedure that can be provided at very modest equipment costs. A typical price for a balloon catheter is $100, a small fraction of what was charged in the 1990s. For straightforward lesions, ancillary equipment costs are negligible, giving

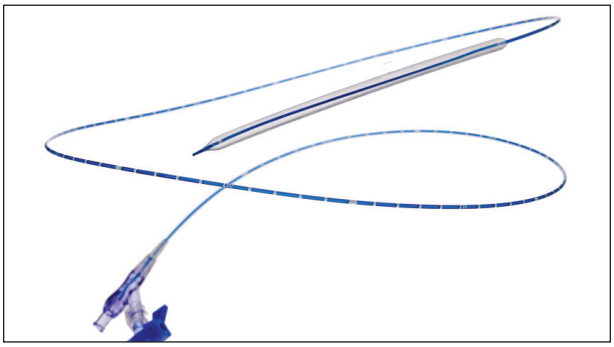


Figure 2. The LUTONIX® drug-coated balloon.

an initial impression that PTA may be an economically desirable option. The hidden cost of angioplasty comes during follow-up in the form of TLR. Studies of PTA outcomes have revealed disappointing primary patency rates, as low as 33% at 1 year and TLR rates in excess of 50% at 2 years.[7,8] An analysis performed at the University of Toledo Medical Center determined that the estimated 2-year follow-up cost after successful PTA is $3,915.[9]

The next step up in procedural complexity and expense is associated with placement of a bare-metal nitinol stent, a practice that is commonplace in the current era. Assuming that a "commodity-type" stent is used, which can provide a $48 higher physician Medicare reimbursement, there is an initial increase in procedural cost of $748 over PTA, as estimated by the University of Toledo model. The increased cost, however, was shown by the model to be offset by a lower rate of TLR.[10] Although there is no consensus about the optimal therapy to treat SFA in-stent restenosis (Figure 1), some form of ablative therapy, such as laser or atherectomy, is commonly employed, which could drive up the cost per TLR. Using the previously described model, and including the $748 initial excess, the resultant 2-year cost is estimated at $3,778, which is slightly less than balloon angioplasty. Thus, the higher procedural cost can be completely offset by downstream savings. This benefit, however, is lost if the stent cost increases by as little as $200.

With US Food and Drug Administration approval of the LUTONIX® paclitaxel-coated balloon (Bard Peripheral Vascular, Inc.) in October 2014 (Figure 2) and its subsequent commercial availability, as well as the In.Pact paclitaxel-coated balloon (Medtronic), the economic landscape for SFA treatment has notably changed. These devices come at a significant increase in price, yet due to a low rate of TLR and the fact that no in-stent treatment is required in this TLR algorithm, the 2-year total cost is much lower at $2,827, which is roughly $1,000 less than the aforementioned options.

The next option is that of paclitaxel-coated nitinol stent placement (Zilver PTX, Cook Medical), also a

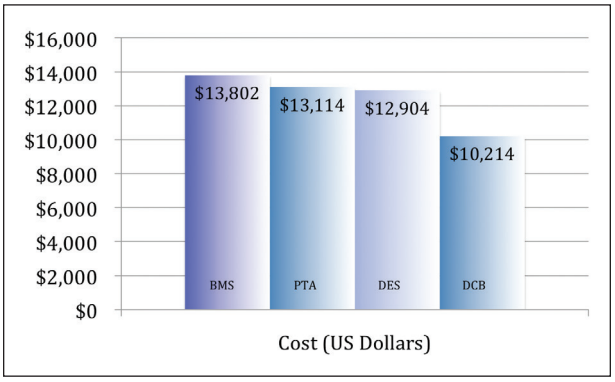


Figure 3. Two-year total cost for various treatment strategies for the SFA. Data derived from Pietzsch JB et al. Catheter Cardiovasc Interv. 2014;84:546–554.[10]

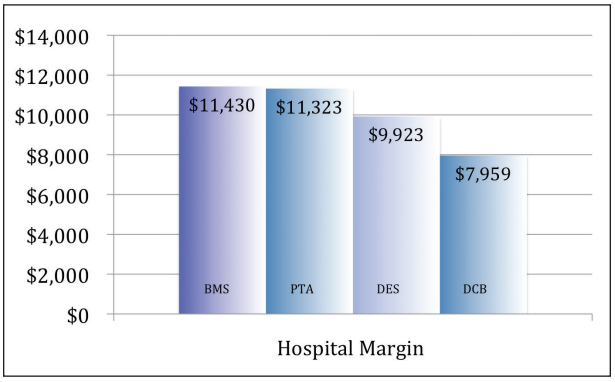


Figure 4. Two-year hospital profit for various treatment strategies for the SFA. Data derived from Pietzsch JB et al. Catheter Cardiovasc Interv. 2014;84:546–554.[10]

recent addition to United States health care practices after its US Food and Drug Administration approval in November 2012.[11] As with the drug-coated balloon (DCB), the addition of paclitaxel to a nitinol stent was associated with a dramatic reduction in TLR to 13.4% at 2 years. Given the higher TLR expense associated with in-stent restenosis as compared to treatment in the absence of a prosthetic device, the 2-year cost estimate in the University of Toledo model was $3,288, which is 16% higher than with a DCB.

Among the treatment options that are commonly employed in the SFA, atherectomy is estimated to be the costliest by a wide margin.[9] Using the average price of popular atherectomy devices and assuming the use of an embolic protection device, this procedure can cost up to $4,718 more than simple angioplasty. Even if the follow-up expense is moderate, the estimated 2-year cost is more than twice as much as that of a DCB. The initial outlay is so high, in fact, that even if TLR rates were reduced to zero, atherectomy would still be the most expensive treatment option.

MODELING THE EFFECT OF DCBs

Three recent publications have assessed the economic impact of DCBs in various health care systems.[10-13] Pietzsch and colleagues constructed a model to estimate the 2-year cost for four commonly employed SFA treatment strategies. As with any model, numerous assumptions had to be made about lesion complexity, device cost, patient mix, etc. Notably, the model allows for only one TLR during the entire 2-year period. TLR rates for each of the proposed therapies were derived from a literature review. Within this construct, the lowest total expenditure in the United States was found with DCB therapy, followed by drug-eluting stents (DES) and then simple balloon angioplasty (Figure 3). The most expensive option was treatment with a bare-metal stent (BMS). The same ranking was found in the German health care system. Ironically, hospital profit was exactly the opposite: lowest with DCBs and highest with BMS procedures (Figure 4). Thus, when considering financial incentives, payers (Medicare, private insurance, self-pay patients) benefit most from DCB treatment, whereas hospitals profit most from bare stents.

Diehm et al found that nearly identical forces come into play in Switzerland.[12] They constructed a model similar to Pietzsch et al, using a literature review to estimate TLR. A comparison of simple PTA to DCB therapy showed that the latter was associated with lower cost. As with the United States and German models, Swiss hospitals and physicians saw more financial benefit from PTA.

A British model confirmed these findings in yet another health care system.[13] In this study, a wide variety of treatment options was entertained: PTA, PTA with bailout DES, DCBs, DES alone, BMS, brachytherapy, and stent grafts. As with every other model discussed so far, the lowest cost was found with DCBs. The next best option was PTA with bailout DES.

THE PROBLEM OF INCENTIVES

Under ideal circumstances, the financial incentives of patients, health care providers, and payers would be identical. As the previous discussion has made clear, these incentives are not just poorly aligned; in some cases, they are polar opposites. Historically, hospitals have made the most money on the therapies that make the least financial sense. The same can be true for United States physicians, who are reimbursed more liberally for atherectomy (the costliest option) than for DCB use (the most economical). In addition, both hospitals and physicians profit from TLR, which payers and patients wish would never happen. Significant efforts have been made to correct this misalignment. A step in the right direction was made when

Medicare agreed to reimburse hospitals at a higher rate when DES were used on inpatients. The same practice for outpatient procedures would be logical, but has not yet been accomplished. This is especially important because most femoropopliteal interventions are performed as outpatient procedures. Medicare did, however, take a major step forward by approving a pass-through for outpatient DCB use effective April 1, 2015. Initially, this provided a limited incremental payment to the hospital for the first DCB, with full reimbursement for additional DCB use. In June 2015, the Medicare position was changed to an even more favorable one, in which the full cost of all DCBs was paid to hospitals, retroactive to April 1, 2015. This largely eliminates financial disincentives for DCB use and represents a huge benefit to patients. As of August 2015, and going into effect on October 1, 2015, Medicare approved an add-on payment for DCBs under the Medicare hospital inpatient prospective payment system to help cover additional costs incurred by hospitals treating Medicare beneficiaries with this product.

SUMMARY

Among the wide variety of options to treat atherosclerosis of the SFA, the lowest cost appears to be associated with DCBs. This observation applies across multiple health care systems. Adequate reimbursement from payers for DCBs (and DES) encourages providers in supplying optimum care. ■

Mark W. Burket, MD, is Chief, Division of Cardiovascular Medicine, University of Toledo Medical Center in Toledo, Ohio. He has disclosed that he has received research support from Cook Medical, Biotronik, and Bard Peripheral Vascular, Inc.; is a speaker for Cook Medical; and is a consultant to Biotronik, Covidien, and Cardinal Health. Dr. Burket may be reached at (419) 383-6095; mark.burket@utoledo.edu.

Disclaimer: The opinions and clinical experiences presented herein are for informational purposes only. The results may not be predictive for all patients. Individual results may vary depending on a variety of patient-specific attributes. Dr. Burket has been compensated by Bard Peripheral Vascular, Inc. for the time and effort in preparing this article for Bard's further use and distribution.

1. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286:1317-1324.
2. Burket MW. Why drug-eluting stents are cost effective in the superficial femoral artery. Endovasc Today. 2013;12:8-11.
3. Dillingham TR, Pezzin LE, Shore AD. Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations. Arch Phys Med Rehabil. 2005;86:480-486.
4. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-S67.
5. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease. J Am Coll Cardiol. 2006;47:1239-1312.
6. Dotter CT, Judkins MP. Transluminal treatment of atherosclerotic obstruction. description of a new technic and a preliminary report of its application. Circulation. 1964;30:654-670.
7. Rocha-Singh KJ, Jaff MR, Crabtree TR, et al. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv. 2007;69:910-919.
8. 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;358:689-699.
9. Burket, MW. SFA revascularization: what's the real cost? Presented at Vascular InterVentional Advances 2014; Las Vegas, Nevada; November 4–7, 2014.
10. Pietzsch JB, Geisler BP, Garner AM, et al. Economic analysis of endovascular interventions for femoropopliteal disease. Catheter Cardiovasc Interv. 2014;84:546-554.
11. Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: two-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol. 2013;61:2417-2427.
12. Diehm N, Schneider H. Cost-effectiveness analysis of paclitaxel-coated balloons for endovascular therapy of femoropopliteal arterial obstructions. J Endovasc Ther. 2013;20:819-825.
13. Kearns BC, Michaels JA, Stevenson MD, et al. Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease. Br J Surg. 2013;100:1180-1188.

The Role of SFA Stenting in the DCB Era

How will drug-coated balloons change the role of stenting in the SFA?

BY CONSTANTINO S. PEÑA, MD

Few endovascular technologies have been as anticipated as drug-coated balloons (DCBs). For at least 5 years, the endovascular community has been discussing the role of paclitaxel in the peripheral arterial system and its potential value, first on stents and now on angioplasty balloons. Do we finally have a solution for restenosis and intimal hyperplasia? Can we potentially eliminate the need to leave stents in patients? How will the long-term patency and, more importantly, the clinical efficacy of these technologies change our practice? These are all questions that we are just beginning to answer.

EVOLVING TREATMENT PARADIGMS AND TRIAL DATA

The treatment of patients with claudication has always been questioned. Should we treat a patient who has claudication if there is a 33% chance that he or she will require reintervention within the first 12 months with a plain old balloon angioplasty (POBA) and then likely have worse disease and symptoms, or at least harder-to-treat disease? More importantly, if an endovascular stent is placed as a first-line treatment option, are we limiting or making future treatments more difficult?

We welcomed DCB technology into our institution once it was made available. The inherent value of decreasing the restenosis rate without the need for a permanent implant was very appealing. The hope of increasing vessel patency and clinical outcomes after interventions made DCBs a natural replacement for POBA. Our initial experience included patients who would have traditionally undergone POBA treatment, as well as those in whom we traditionally would have utilized stents. Unfortunately, limitations, including the cost of the technology, were further magnified by a limited availability of balloon lengths. With the latest changes in outpatient reimbursement and the availability of longer balloon lengths for the LUTONIX® DCB (Bard Peripheral Vascular, Inc.), these initial limitations seem to have been addressed.

The LEVANT 2 trial led to the LUTONIX® DCB becoming the first DCB to receive US Food and Drug Administration approval to treat the femoral and popliteal arteries. This trial randomized 476 patients in a 2:1 ratio between DCBs and POBA in a blinded fashion. At 12 months, the primary patency (peak systolic velocity ratio > 2.5) was shown to be superior for the DCB compared to POBA (73.5% vs. 56.8%). Furthermore, although no head-to-head studies have been conducted, the reported target lesion revascularization rates for the DCB at 12 months were similar to previous superficial femoral artery (SFA) stenting trials (with only a 2.5% bailout stenting rate in the DCB arm). LEVANT 2 also demonstrated the safety of the LUTONIX® DCBs. The global registry trial (n = up to 1,000 patients) is evaluating the real-world use of the LUTONIX® DCB. This registry is expected to provide important results as it represents a realistic lesion mixture, including chronic total occlusions, calcified lesions, and popliteal lesions. There is likely little reason to use POBA when a DCB can be used.

The RESILIENT trial demonstrated improved patency and target lesion revascularization rates with LIFESTENT® vascular stent (Bard Peripheral Vascular, Inc.) compared to angioplasty in moderate-length lesions, and a number of less rigorous self-expanding stent trials that have followed demonstrated similar results in the short term. The role of DES was met with optimism, and the long-term data demonstrated significantly improved patency compared to angioplasty and supported paclitaxel for treating neointimal hyperplasia. However, DES use has been limited in terms of widespread use because routine lesion lengths can exceed 20 cm.

As we evaluate stent technology in the SFA, do we understand the long-term risk compared to the potential benefits of leaving a permanent implant in the vessel? The use of stents in the SFA developed due to the need to increase patency over POBA; however, there are certain factors that may affect stent placement and retreatment options following stent placement. The decision to place a stent, as compared to angioplasty alone, may be

based on a number of factors including the patient's age and symptoms along with the lesion's location, length, morphology, and native vessel diameter.

In patients with long-segment SFA disease, we are usually faced with the decision between DCB and primary stenting. The current DCB regulatory status, plus the lack of long lesion data for DCBs and lack of long DCB and DES lengths, makes the use of self-expanding stents more frequent, especially in older patients who may require more than 15 cm of coverage in order to treat the SFA. The 200-mm LIFESTENT® SOLO™ vascular stent has demonstrated favorable results in lesions between 150 and 180 mm.* Additionally, in patients with critical limb ischemia, multilevel disease is common. When these patients have long-segment SFA disease, the importance of maintaining SFA inflow becomes paramount to support tibial interventions. This is another situation in which self-expandable stents may be used to provide inflow for wound healing.

Is there value in treating all SFA lesion lengths up to 150 mm with a DCB and limiting the use of stents to areas that may demonstrate less-than-ideal results (> 30% residual or flow-limiting dissection)? Is it better for the patient if we place a focal stent in a long lesion instead of placing a stent throughout the treatment length?

*The LIFESTENT® vascular stent system is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions up to 240 mm in length in the native SFA and proximal popliteal artery with reference vessel diameters ranging from 4 to 6.5 mm.

CONCLUSION

In the DCB era, we will find out whether the push toward less stenting proves to be the best treatment paradigm and whether DCBs, such as the LUTONIX® DCB, effectively limit restenosis and allow patients to have more durable results while limiting the use of stents in the SFA. Without a doubt, drug elution has a true benefit. How we develop the best treatment algorithm will likely require further experience and evaluation of the outcomes. ■

Constantino S. Peña, MD, is an interventional radiologist with Miami Cardiac and Vascular Institute in Miami, Florida. He has disclosed that he serves on advisory boards for Bard Peripheral Vascular, Inc., Penumbra, Inc., and Boston Scientific Corporation. He has also been involved with teaching and speaking for Cook Medical. Dr. Peña may be reached at tinopena@msn.com.

Disclaimer: The opinions and clinical experiences presented herein are for informational purposes only. The results may not be predictive for all patients. Individual results may vary depending on a variety of patient-specific attributes. Dr. Peña has been compensated by Bard Peripheral Vascular, Inc. for the time and effort in preparing this article for Bard's further use and distribution.

FOR US AUDIENCES ONLY

LUTONIX® 035 Drug Coated Balloon PTA Catheter

Indications for Use:
The LUTONIX® 035 Drug Coated Balloon PTA catheter is indicated for percutaneous transluminal angioplasty, after pre-dilatation, of de novo or restenotic lesions up to 150 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6 mm.

Contraindications:
The LUTONIX® Catheter is contraindicated for use in:
· Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
· Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.
· Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

Warnings:
· Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use.
· Do not use if product damage is evident.
· The LUTONIX® Catheter is for use in one patient only; do not reuse in another patient, reprocess or resterilize. Risks of reuse in another patient, reprocessing, or resterilization include: – Compromising the structural integrity of the device and/or device failure which, in turn, may result in patient injury, illness or death. – Creating a risk of device contamination and/or patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to patient injury, illness or death.
· Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.
· Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.
· This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds.
· The safety and effectiveness of the LUTONIX® Catheter have not been established for treatment in cerebral, carotid, coronary, or renal vasculature.
· The safety and effectiveness of using more than two LUTONIX® drug coated balloons (i.e., a maximum drug coating quantity of approximately 7.6 mg paclitaxel) in a patient has not been clinically evaluated.

Precautions:
General Precautions:
· The LUTONIX® Catheter should only be used by physicians trained in percutaneous interventional procedures.
· Consideration should be given to the risks and benefits of use in patients with a history of non-controllable allergies to contrast agents.

Potential Adverse Events:
Potential adverse events which may be associated with a peripheral balloon dilatation procedure include:
· Additional intervention · Allergic reaction to drugs, excipients, or contrast medium · Amputation/loss of limb · Aneurysm or pseudoaneurysm · Arrythmias · Embolization · Hematoma · Hemorrhage, including bleeding at the puncture site · Hypotension/hypertension · Inflammation · Occlusion ·Pain or tenderness · Pneumothorax or hemothorax · Sepsis/infection · Shock · Stroke ·Thrombosis · Vessel dissection, perforation, rupture, or spasm
Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel. Potential adverse events, not described in the above source, which may be unique to the paclitaxel drug coating include:
· Allergic/immunologic reaction to the drug coating (paclitaxel) ·Alopecia · Anemia · Blood product transfusion · Gastrointestinal symptoms · Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia) · Hepatic enzyme changes · Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis ·Myalgia/Arthralgia · Myelosuppression · Peripheral neuropathy

Please consult product labels and instructions for use for indications, contraindications, hazards, warnings and precautions. ℞only

Endovascular TODAY

S120726 R0