Supplement to

Sponsored by Spectranetics Corporation

Endovascular TODAY

September 2017

Evidence From the Next-Generation DCB

Delivering top-tier clinical outcomes.

Table of Contents

Sponsored by Spectranetics Corporation

Comparative Analysis of Drug-Coated Balloons

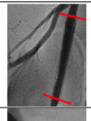
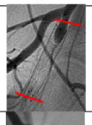
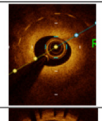
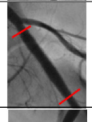
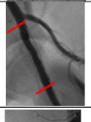
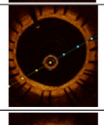
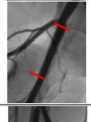
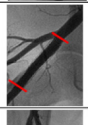
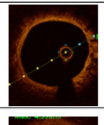
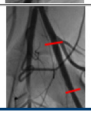
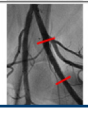
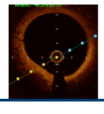
BY JUAN F. GRANADA, MD, FACC

Drug-coated balloons (DCBs) are rapidly becoming the leading strategy for the treatment of peripheral artery disease. Despite the fact that all clinically available DCB concepts are based on paclitaxel, important technological differences influence biological efficacy and clinical outcomes. Experimental validation of DCBs has been key to unveil the mechanism of action and efficacy and safety profiles of these technologies. Specifically, the impact of reduced-dose DCBs on biological efficacy and restenosis prevention is not fully understood. A comparative study of three clinically available DCBs (In.Pact Admiral [Medtronic], 3.5 µg/mm^2; Lutonix [Bard Peripheral Vascular, Inc.], 2 µg/mm^2; and Stellarex™ [Spectranetics Corporation], 2 µg/mm^2) versus percutaneous transluminal angioplasty (PTA) with the Armada PTA balloon (Abbott Vascular) was performed by the CRF Skirball Center for Innovation in a validated familial hypercholesterolemic swine model of in-stent stenosis to assess treatment efficacy at 28 days.[1] Two weeks after stent implantation, each in-stent stenotic lesion was randomly treated with a DCB or PTA. Quantitative vascular analysis (QVA) was performed on both the treatment day and at day 28 after treatment by blinded evaluators to the assigned treatment; optical coherence tomography (OCT) was performed on day 28 after treatment. The vessels treated with DCBs maintained a larger luminal diameter than the vessels treated with PTA (Table 1).

Comparing the percent stenosis on day 28 after treatment, all DCBs showed improvement over PTA; however, Stellarex had negligible luminal loss, similar to higher-dose DCB competitors, despite having a 43% lower drug dose. Variation in percent diameter stenosis was also lowest for the Stellarex DCB, as confirmed by the low standard deviation of ± 4% for Stellarex compared to a standard deviation of ± 17% for Lutonix.

This predictability in results may be due to the consistent integrity and durability of the Stellarex coating. This head-to-head comparison study, performed in a porcine lesion model, shows for the first time that the reduced-dose Stellarex balloon achieved a comparable biological efficacy to higher-dose DCB and has the potential to improve the safety profile of DCB technologies. ■

TABLE 1. VESSELS TREATED WITH DCBs VERSUS PTA AS ASSESSED BY QVA AND OCT

	Treatment	Termination	
		QVA	OCT
PTA n = 7			
Stellarex n = 8			
In.Pact Admiral n = 6			
Lutonix n = 7			

1. Granada JF, Milewski K, Zhao H, et al. Vascular response to zotarolimus-coated balloons in injured superficial femoral arteries of the familial hypercholesterolemic swine. Circ Cardiovasc Interv. 2011;4:447-455.

Juan F. Granada, MD, FACC
Executive Director and Chief Innovation Officer
Cardiovascular Research Foundation
Skirball Center for Innovation
Orangeburg, New York
jgranada@crf.org
Disclosures: The Skirball Center for Innovation has received research grants from Spectranetics Corporation.

Sponsored by Spectranetics Corporation

The Stellarex Difference: Critical Components of an Optimal DCB

BY MANASI RAMACHANDRAN, PHD, AND MICHAEL S. OWENS, PHD

Since the first prototype of a paclitaxel drug-coated balloon (DCB) was developed, we have learned that DCB performance is built on a critical balance of multiple factors that include the right coating morphology, the right excipient, and an optimal drug dose. Following in-vitro and preclinical tests, performance must ultimately be demonstrated by rigorous, well-designed, and well-conducted clinical trials.

The Stellarex™ DCB (Spectranetics Corporation) carefully balances these critical factors and has been demonstrated as safe and effective in common to complex patients by the durable and consistent clinical results of the ILLUMENATE trials (Figure 1).[1-4]

THE ACTIVE DRUG PACLITAXEL

Paclitaxel is lipophilic and characterized by high fat affinity, meaning it is naturally captured by the fatty tissue constituents. It is also hydrophobic, meaning it does not bind with aqueous media such as blood.

Due to its lipophilic properties, paclitaxel is captured by tissue after exposure to or direct contact with the vessel wall. In order to apply its antirestenotic action, paclitaxel must be in an available form so that it binds to and stabilizes arterial smooth muscle cell microtubules. Animal studies suggest that following transfer, paclitaxel must stay resident in the vessel, acting as a drug reservoir, to exert action through the critical 30-day restenosis window.[5,6]

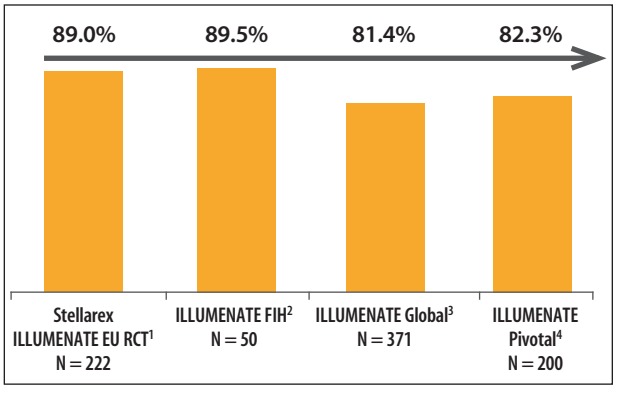


Figure 1. Consistent patency rates (based on Kaplan-Meier estimates) were observed across four separate studies with Stellarex at 12 months.

CRYSTALLINE VERSUS AMORPHOUS PACLITAXEL

There are different types of coating formulations and coating processes for a DCB; each brand of DCB has its own unique formulation and coating process. As a result, paclitaxel morphology on the balloon surface can range from amorphous to crystalline. Having an optimal mix of amorphous and crystalline paclitaxel along with the right excipient is necessary for an efficacious DCB.

Amorphous paclitaxel morphology is durable during tracking and it effectively transfers drug to the vessel wall. Research suggests an amorphous coating does not stay resident in the vessel at therapeutic levels as long as crystalline paclitaxel morphology.[7]

Crystalline paclitaxel morphology is more brittle than an amorphous morphology during tracking but also allows for effective drug transfer. Research indicates that it resides in the vessel at therapeutic levels out to the 30-day restenotic window. Research shows crystalline paclitaxel dissolves into the tissue slowly for sustained release over time.[7] Figure 2 demonstrates the different pharmacokinetic properties of the different paclitaxel morphologies. After being transferred to the vessel wall, crystalline paclitaxel may form "drug depots," which may help in sustained release (Figure 3).[8]

The Stellarex DCB has an optimal mix of amorphous and crystalline paclitaxel (Figure 4), merging the characteristics of both amorphous and crystalline paclitaxel morphologies. Research performed on animal studies

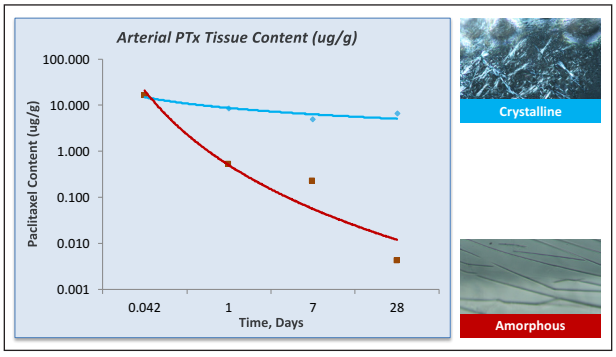


Figure 2. Pharmacokinetic properties by paclitaxel morphology. Porcine model data on file at Spectranetics (reference study).

Sponsored by Spectranetics Corporation

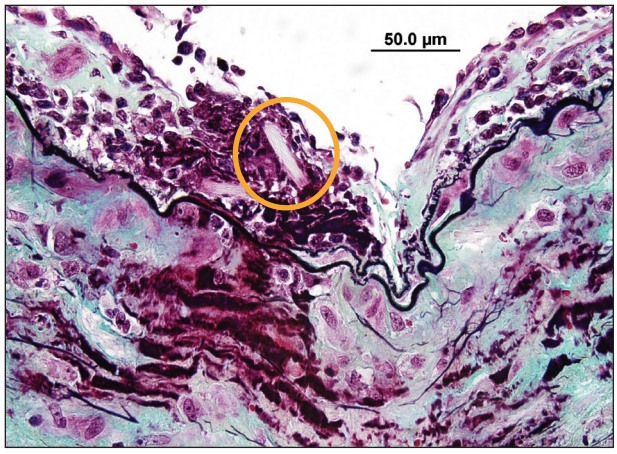


Figure 3. Histopathologic image of paclitaxel drug depot in a porcine model. Porcine model data on file at Spectranetics.

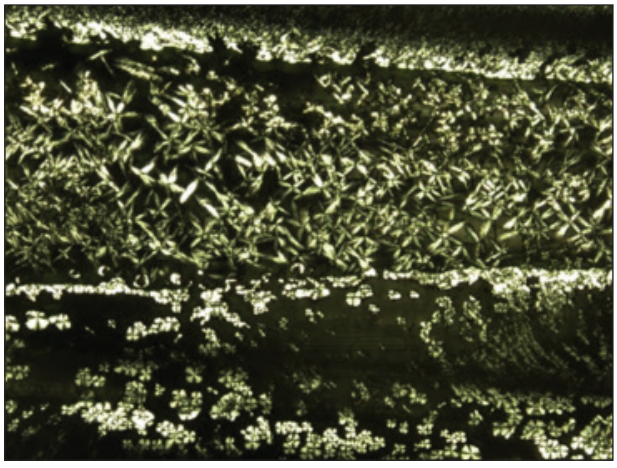


Figure 4. Stellarex EnduraCoat Technology under optical microscopy.

indicate that the Stellarex coating formulation creates a durable coating that helps prevent drug loss during handling and transit to the treatment site and provides uniform drug transfer with drug residency at a therapeutic dose throughout or passing the 30-day restenotic window.

THE EXCIPIENT

DCBs require paclitaxel to remain on the balloon surface during transit to the treatment site and be released when inflated and in contact with the vessel wall. An excipient is intended to help facilitate/maximize paclitaxel adherence to the balloon during transit and transfer from the balloon to the tissue once the balloon is inflated. The type and quantity of excipient are important design factors; this ensures that paclitaxel is not excessively and prematurely lost once in contact with the bloodstream before the balloon is inflated at the treatment site.

Stellarex uses polyethylene glycol (PEG) as the excipient. PEG is a hydrophilic polymer, meaning it has affinity for water. PEG has a large molecular weight of 8,000, which is designed to dissolve slowly, keeping the drug protected during use. This may allow Stellarex more time to track to the lesion without losing drug prematurely. The combination of PEG and water results in a plasticized coating with attractive mechanical properties (eg, adhesion, flexibility, elasticity, and elongation) for adaptability during balloon deformation such as flexion, torsion, and compression. This increases the durability of the coating, making it less likely to flake off during handling, tracking, and inflation. Additionally, PEG's hydrophilic properties render it durable to most chemical reactions. It is also a nontoxic excipient that has been used in topical, oral, and intravenous applications for decades. This nontoxic, durable excipient acts as a reliable carrier of paclitaxel. Therefore, a DCB with PEG, such as Stellarex, is designed to have a low drug dose and allow for a therapeutic dose to reach the target lesion.

Excipients exert their actions in different ways. Hydrophilic excipients such as PEG or urea are polar molecules that act as inert fillers; once hydrated, they swell and start a process of separating paclitaxel molecules to free them from each other, hence increasing their bioactive surface and augmenting absorption onto the arterial wall. Although urea is also water soluble, it doesn't exhibit the polymer mechanical properties that PEG exerts, possibly rendering it less durable. Polysorbate (the excipient for the Lutonix DCB [Bard Peripheral Vascular, Inc.]) has been claimed to act as an emulsifier. When emulsifiers are combined with a more amorphous paclitaxel morphology, paclitaxel dissolution can be accelerated, which may lead to less drug being available over time. Using PEG as an excipient allows the Stellarex DCB to balance coating durability and the transfer efficiency of paclitaxel.

The coating solution of paclitaxel and PEG, along with the proprietary manufacturing process for the Stellarex DCB, is the EnduraCoat™ Technology. The EnduraCoat Technology allows the Stellarex DCB to achieve durable and consistent clinical outcomes with a low-dose drug.

TREATMENT IN CALCIUM

Treatment success in calcium has been touted as the Achilles' heel of DCB therapy. However, Stellarex has shown clinical efficacy in a patient population with high rates of severe calcium.

In the ILLUMENATE Pivotal trial, Stellarex achieved primary patency of 82.3% in the most complex patient

Sponsored by Spectranetics Corporation

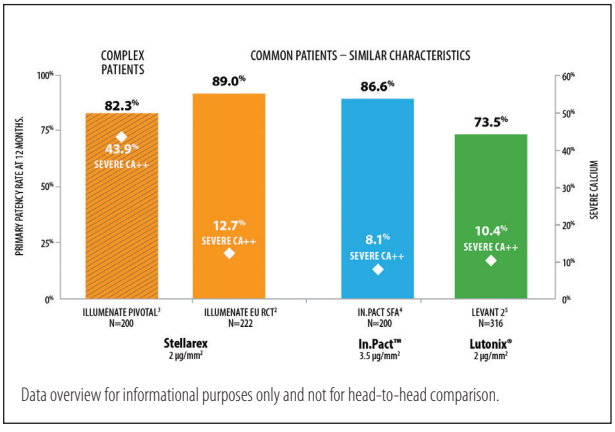


Figure 5. Reported patency rates from available DCB trials.

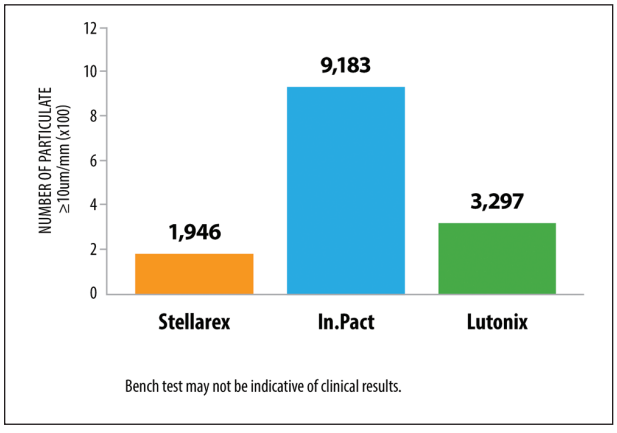


Figure 6. Particulates lost after tracking and inflation. Data on file at Spectranetics.*

population and the highest rates of severely calcified lesions ever reported in a published DCB randomized controlled trial (Figure 5).[4]

The success of Stellarex in calcified lesions may be attributed to the excipient PEG. PEG has a high affinity to hydroxylapaptite (HAp), the primary component of calcified atherosclerotic lesions.[11] PEG will form ionic bonds with HAp, which may limit the amount of paclitaxel washoff in calcified lesions.[11]

DISTAL EMBOLIZATION

The downstream effect of paclitaxel during DCB use must be clearly understood as it relates to safety concerns associated with DCBs. Specifically, the downstream effect of paclitaxel in the presence of foot ulcers may impede wound healing and ultimately affect limb salvage. Therefore, it is crucial for any given DCB to incorporate the smallest dose possible to achieve clinical efficacy in order to reduce the possible safety risks posed by downstream effects of paclitaxel. In order to prove the downstream safety effect of paclitaxel while using Stellarex, 5.5 times the particulate limit from the largest balloon was tested in animal studies to find no downstream safety issues as demonstrated by all gross pathology and histopathology safety outputs.

COATING DURABILITY

High coating durability is the result of extensive drug formulation coating process optimization to enhance performance on the Stellarex-specific balloon material. The ultimate objective was twofold: (1) to obtain excellent drug adherence during balloon preparation and handling, insertion through the introducer, and transit through the vasculature to the target lesion, and (2) to maximize drug release to the vessel wall once the balloon is inflated.

The coating durability of Stellarex is confirmed by quantitative particulate testing after tracking the DCB through an anatomical vascular model.[12] This testing supports that Stellarex limits drug particle loss compared to other DCB competitors with the same (and higher) drug dose. In a comparative assessment, Stellarex resulted in 79% fewer particles produced during tracking than the In.Pact Admiral DCB (Medtronic) and 41% fewer particles than the Lutonix DCB (Figure 6).

THE STELLAREX DIFFERENCE

DCB performance relies on the optimal mix of amorphous and crystalline paclitaxel, a durable excipient, and an optimal drug dose. The balance of these critical factors determines the clinical results and safety profile.

A DCB such as the Stellarex DCB, with an optimal mix of both amorphous and crystalline paclitaxel, maintains durability during tracking and is designed for effective drug transfer and provides drug residency through the 30-day restenosis window. The EnduraCoat Technology allows the Stellarex DCB to achieve durable and consistent clinical outcomes combined with a low drug dose.

The Stellarex DCB has shown a top-tier 12-month primary patency rate of 89% for common patients and a primary patency rate of 82.3% in complex patients with the highest rate of severely calcified lesions of 43.9% in core lab–adjudicated randomized controlled trials (Figure 5).[1,4] The ILLUMENATE first-in-human study demonstrated a primary patency rate of 80.3% at 2 years, suggesting durability of this treatment option.[2] ■

1. Schroeder H, Werner M, Meyer DR, et al. Low-dose paclitaxel-coated versus uncoated percutaneous transluminal balloon angioplasty for femoropopliteal peripheral artery disease: one-year results of the ILLUMENATE European randomized clinical trial (randomized trial of a novel paclitaxel-coated percutaneous angioplasty balloon). Circulation. 2017;135:2227–2236.
2. Schroeder H, Meyer DR, Lux B, et al. Two-year results of a low-dose drug-coated balloon for revascularization of the femoropopliteal artery: outcomes from the ILLUMENATE first-in-human study [published online February 23, 2015]. Catheter Cardiovasc Interv.

Sponsored by Spectranetics Corporation

3. Zeller T. LLUMENATE global study Stellarex DCB. Presented at LINC 2017; January 24–27, 2017; Leipzig, Germany.
4. Lyden S. ILLUMENATE pivotal Stellarex DCB IDE study 12-month results. Presented at TCT 2016; November 2, 2016; Washington, DC.
5. Ansel GM, Schneider PA. The role of drug-coated balloons in infrapopliteal interventions. Interv Cardiol. 2012;7:63-65.
6. Kamath KR, Barry JJ, Miller KM. The Taxus drug-eluting stent: a new paradigm in controlled drug delivery. Adv Drug Deliv Rev. 2006;58:412-436.
7. Granada JF. Future directions, clinical applications and local drug delivery technologies. Presented at the Transcatheter Cardiovascular Therapeutics (TCT) 25th annual scientific symposium; October 27–November 1, 2013; San Francisco, California.
8. Porcine model data on file at Spectranetics.
9. Jaff M. Drug-coated balloon treatment for patients with intermittent claudication: insights from the IN.PACT global full clinical cohort (Updated data from IN.PACT SFA presented on slide 12). Presented at VIVA 2016; September 19-22, 2016; Las Vegas, NV.
10. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373:145-153.
11. Venkatasubbu GD, Ramasamy S, Avadhani GS, et al. Surface modification and paclitaxel drug delivery of folic acid modified polyethylene glycol functionalized hydroxyapatite nanoparticles. Powder Technol. 2013;235:437-442.
12. Data on file at Spectranetics.

*Competitor studies are independent clinical trials with different protocols and definitions. Therefore, they are not head-to-head comparisons, and data presented cannot be directly compared. Calcium definitions may vary from study to study, and the rates presented herein are based on those used and reported in each respective study. Complex patients refers to high rates of severe calcium, diabetes, and renal insufficiency. Primary patency based on Kaplan-Meier estimates.

Manasi Ramachandran, PhD
Lead Engineer, Stellarex
Spectranetics Corporation
Maple Grove, Minnesota
manasi.ramachandran@spnc.com

Michael S. Owens, PhD
Vice President, Vascular Intervention, Research and Development
Spectranetics Corporation
Maple Grove, Minnesota
michael.owens@spnc.com

Sponsored by Spectranetics Corporation

The ILLUMENATE SFA Clinical Program

Data on the Stellarex DCB for treatment of femoropopliteal arterial disease.

BY HENRIK SCHRÖDER, MD, AND PRAKASH KRISHNAN, MD

Drug-coated balloons (DCBs) are becoming a more widely accepted and preferred first-line therapy for the treatment of peripheral artery disease. As such, there is a continued effort and investment by industry to evolve and improve on the efficacy of DCBs through optimization of the coating characteristics. Modern DCB goals are to maximize drug transfer to the target lesion while minimizing systemic drug loss. Due to differences in coatings and drug transfer capabilities, robust clinical evidence is required for each DCB; clinical data from one DCB cannot be generalized to another. The Stellarex DCB (Spectranetics Corporation) is the newest DCB on the market in the United States. The novel coating consists of paclitaxel and polyethylene glycol (PEG).

The ILLUMENATE SFA clinical program was designed to evaluate the safety and performance of the Stellarex DCB and includes five studies with more than 1,200 patients (Figure 1). All studies are being conducted with robust controls including angiographic and duplex ultrasound core laboratory oversight, clinical events committee adjudication, and 100% monitoring of source data to confirm accuracy of the databases. Importantly, this program includes two separately conducted randomized controlled trials, the ILLUMENATE European randomized clinical trial (EU RCT) and the ILLUMENATE Pivotal trial.

ILLUMENATE EU RCT

ILLUMENATE EU RCT was the first randomized study of the Stellarex DCB following the promising early results of the ILLUMENATE first-in-human study.[1] Recently, 12-month results from the ILLUMENATE EU RCT study were published in *Circulation*.[2] In total, 294 patients were randomized to treatment with the Stellarex DCB (n = 222 patients, 254 lesions) or percutaneous transluminal angioplasty (PTA) (n = 72 patients, 79 lesions). Key baseline data can be found in Table 1.

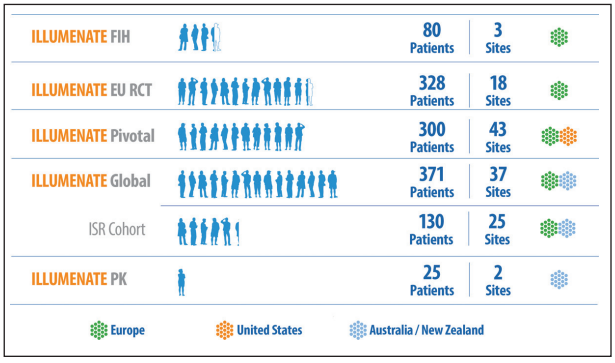


Figure 1. The ILLUMENATE clinical SFA program.

The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days postprocedure and freedom from major target limb amputation and clinically driven target lesion revascularization (CD-TLR) through 12 months postprocedure. The primary safety endpoint was met and superiority was demonstrated; freedom from a primary safety event was 94.1% (193/205) with DCB and 83.3% (50/60) with PTA, for a difference of 10.8% (95% confidence interval, 0.9%–23%). The primary effectiveness endpoint was primary patency at 12 months, which was met. Superiority of Stellarex over PTA was achieved (83.9% [188/224] vs 60.6% [40/66]; $P < 0.001$). The primary patency rate per Kaplan-Meier esti-

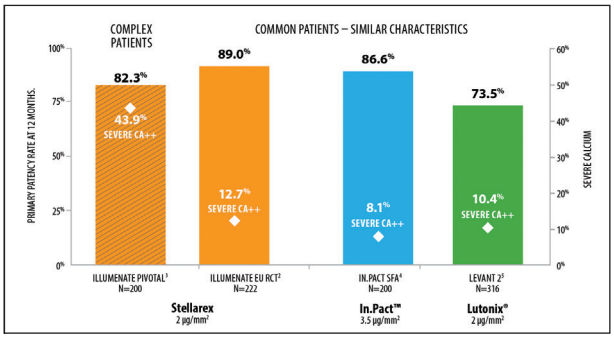


Figure 2. Twelve-month patency rates across similarly designed and conducted RCTs.*

Sponsored by Spectranetics Corporation

TABLE 1. ILLUMENATE EU RCT KEY BASELINE CHARACTERISTICS

Lesion (Per Core Lab)	Stellarex n = 254 Lesions	PTA n = 79 Lesions	*P* Value
Lesion length (cm)	7.2 ± 5.2 (250)	7.1 ± 5.3 (79)	0.878
Total occlusions	19.2 (48/250)	19 (15/79)	0.967
Severe calcification	12.7 (32/251)	10.1 (8/79)	0.533
Baseline diameter stenosis	78.7 ± 16 (250)	80.8 ± 15.7 (79)	0.297
Demographics	**Stellarex n = 222 Patients**	**PTA n = 72 Patients**	***P* Value**
Age (y)	66.8 ± 9.2 (222)	69 ± 8.6 (72)	0.079
Male	72.1 (160/222)	68.1 (49/72)	0.514
Rutherford clinical category ≥ 3	84.6 (187/221)	78.9 (56/71)	0.260
Diabetes	37.4 (83/222)	36.1 (26/72)	0.846
Previous or current smoker	89.2 (198/222)	83.3 (60/72)	0.188

Values are mean ± SD or % (n/N).

mate at day 365 was 89% for Stellarex versus 65% for PTA (log rank, $P < 0.001$), the highest published 1-year primary patency rate in any DCB RCT (Figure 2). As expected, the higher patency rate resulted in CD-TLR rates that were significantly lower in the Stellarex cohort (5.9% vs 16.7%; $P = 0.014$). At 12 months, a similar percentage of patients in both the DCB and PTA cohorts had improvements in ankle-brachial index (83.9% and 76.8%), Rutherford classification (89.2% and 86.2%), and walking distance (77.1% and 72.1%). Importantly, these similar outcomes were achieved with a significantly lower rate of CD-TLR in the DCB cohort. This has potential implications from both a cost-effectiveness and quality-of-life perspective.

Recently, the 24-month outcomes were reported and the significant treatment effect was sustained out to 2 years with no indication of late catch-up.[6] Patients treated with the Stellarex DCB maintained a significantly higher primary patency rate of 75.2% versus 61.2% (log-rank *P* value, 0.004) per Kaplan-Meier estimate at day 730. The exact patency rates, calculated as the ratio of event-free patients divided by evaluable patients, through the full 2-year follow-up window of 790 days was 75.9% (145/191) versus 61% (36/59) ($P = 0.025$). Similarly, the rate of CD-TLRs was significantly lower in the Stellarex group (12.1% vs 30.5%; $P < 0.001$) (Figure 3). These long-term results of the ILLUMENATE EU RCT trial validate the initial findings from the ILLUMENATE first-in-human study that demonstrated primary patency rates of 89.5% at 12 months and 80.3% at 24 months.[1]

ILLUMENATE PIVOTAL

The ILLUMENATE Pivotal study is an investigational device exemption study being conducted in the United States and supported approval of Stellarex DCB by the US Food and Drug Administration.[7] This study randomized 300 patients to treatment with Stellarex (n = 200) or standard PTA (n = 100). The primary safety endpoint was freedom from device- and procedure-related death through 30 days, as well as freedom from major target limb amputation and CD-TLR through 12 months. The primary effectiveness endpoint was primary patency through 12 months.

The two cohorts were well matched and included a high rate of diabetic patients (50%), women (41%), and

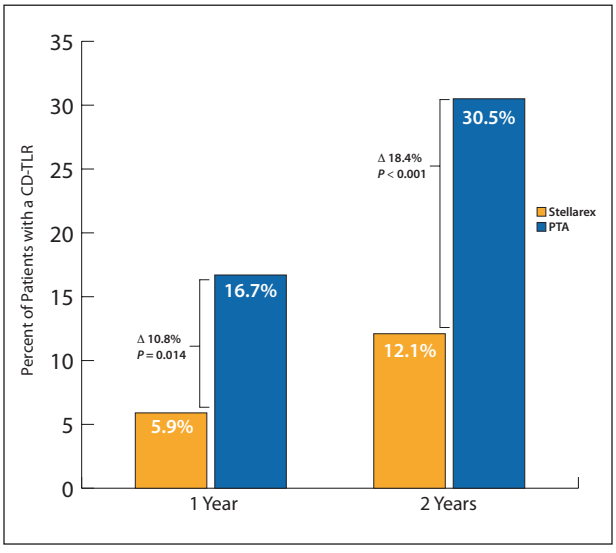


Figure 3. Rates of CD-TLR at 1 and 2 years in the ILLUMENATE EU RCT trial. A significantly lower rate of CD-TLRs was observed in the Stellarex group out to 2 years, with the treatment effect increasing from 1 to 2 years.

Sponsored by Spectranetics Corporation

TABLE 2. ILLUMENATE PIVOTAL STUDY KEY BASELINE CHARACTERISTICS

Lesion (Per Core Lab)	**Stellarex n = 200 Lesions**	**PTA n = 100 Lesions**	***P* Value**
Lesion length (cm)	8 ± 4.5 (199)	8.9 ± 4.6 (100)	0.105
Total occlusions	19 (38/200)	18 (18/100)	0.834
Severe calcification	43.9 (87/198)	43 (43/100)	0.877
Baseline diameter stenosis	73.9 ± 17 (200)	74.8 ± 17 (100)	0.673
Demographics	**Stellarex n = 200 Patients**	**PTA n = 100 Patients**	***P* Value**
Age (y)	68.3 ± 10.3 (200)	69.8 ± 9.8 (100)	0.225
Female	44 (88/200)	36 (36/100)	0.185
Rutherford clinical category ≥ 3	68.5 (137/200)	65 (65/100)	0.542
Diabetes	49.5 (99/200)	52 (52/100)	0.683
Previous or current smoker	84 (168/200)	75 (75/100)	0.061
Ankle-brachial index	0.75 ± 0.21 (193)	0.76 ± 0.2 (100)	0.508
Renal insufficiency	18 (36/200)	16 (16/100)	0.666
Body mass index ≥ 30 kg/m^2	39.5 (79/200)	30 (30/100)	0.107

Values are mean ± SD or % (n/N).

those with calcified lesions (43.9%); the mean lesion length was 8.3 cm (data by group in Table 2). This patient population presented with more comorbidities than the ILLUMENATE EU RCT cohort. When comparing the DCB cohorts from both trials, more pivotal patients were reported to have renal insufficiency (18% vs 9%), diabetes (50% vs 37%), previous coronary revascularization (45% vs 21%), and a body mass index ≥ 30 kg/m^2 (40% vs 26%).

The primary safety endpoint was met and superiority was achieved (92.1% vs 83.2%; superiority, $P = 0.246$). The primary effectiveness endpoint was also met and superiority was demonstrated (76.3% for DCB vs 57.6% for PTA; $P = 0.003$). Primary patency per the Kaplan-Meier estimate was significantly higher for Stellarex versus PTA (82.3% vs 70.9%; $P = 0.002$). Likewise, the rate of CD-TLR was significantly lower in the DCB cohort (7.9% vs 16.8%; $P = 0.023$).

Similar to what was observed in the ILLUMENATE EU RCT study, the improvements in clinical/functional assessments were comparable between cohorts, but this was achieved in the DCB cohort with half as many revascularizations. In total, 73% of patients in both cohorts had an improvement in walking distance as assessed by the 6-minute walk test at 12 months as compared to baseline, and the walking impairment question composite scores were improved in 78% of patients in both cohorts.

There has been a lot of discussion around the potential mechanisms that contributed to the success of the Stellarex DCB despite the high preponderance of female patients, diabetics, and patients with calcified lesions enrolled. We know several features such as drug dose, coating formulation (crystalline or amorphous), and type of excipient affect the pharmacokinetic profile and potentially have an impact on the amount of drug that is transferred to the wall of the artery.[8] The Stellarex DCB incorporates a low dose (2 µg/mm^2) of paclitaxel in a hybrid formulation made of both amorphous and crystalline paclitaxel molecules, combined with PEG (the excipient). The hybrid formulation likely helps maintain coating integrity (an attribute of the amorphous state) while allowing for sustained drug tissue release (due to the more crystalline molecules).[8] PEG is a polymer

Sponsored by Spectranetics Corporation

with a high molecular weight, which means that it has some mechanical properties (eg, durability and adhesion) that allow the coating to maintain its integrity through typical balloon deformation such as flexion and elongation.[9] Additionally, PEG has been reported to have a high affinity to hydroxylapatite, which is a primary structural component in calcified atherosclerotic lesions.[10] The hybrid coating in combination with PEG's durability is a likely contributor to the drug transfer efficiency of the Stellarex DCB. The affinity of PEG to hydroxylapatite may maintain this transfer efficiency by limiting washout in the presence of calcified lesions; however, further studies are needed to evaluate the role of excipients in drug transfer efficiency in severely calcified lesions.

The results from this study were validated by the results of the ILLUMENATE Global study (n = 371, single-arm DCB), which reported an 81.4% primary patency rate at 12 months in a population that included complex lesions with 31.3% chronic total occlusions and 40.8% severe calcium.[11]

The ILLUMENATE series of studies are robust and are generating consistent and compelling data. The Stellarex DCB should be considered as a first-line treatment option for femoropopliteal lesions. ■

1. Schroeder H, Meyer DR, Lux B, et al. Two-year results of a low-dose drug-coated balloon for revascularization of the femoropopliteal artery: outcomes from the ILLUMENATE first-in-human study. Catheter Cardiovasc Interv. 2015;86:278–286.
2. Schroeder H, Werner M, Meyer DR, et al. Low-dose paclitaxel-coated versus uncoated percutaneous transluminal balloon angioplasty for femoropopliteal peripheral artery disease: one-year results of the ILLUMENATE European randomized clinical trial (randomized trial of a novel paclitaxel-coated percutaneous angioplasty balloon). Circulation. 2017;135:2227–2236.
3. Lyden S. ILLUMENATE pivotal Stellarex DCB IDE study 12-month results. Presented at TCT 2016; November 2, 2016; Washington, DC.
4. Tepe G et al. IN.PACT SFA Trial Investigators Circulation 2015 + G.Tepe, Charing Cross 2014 oral presentation + Jaff M. Drug-coated balloon treatment for patients with intermittent claudication: insights from the IN.PACT global full clinical cohort. (Updated data from IN.PACT SFA presented on slide 12) Oral Presentation, VIVA 2016.
5. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373:145–153.
6. Brodmann M. ILLUMENATE European randomized trial: 2-Year results. Presented at: VIVA; September 13, 2017; Las Vegas, Nevada.
7. Krishnan P, Faries P, Niazi K, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: 12-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies [published online July 20, 2017]. Circulation.
8. Granada JF, Stenoien M, Buszman PP, et al. Mechanisms of tissue uptake and retention of paclitaxel-coated balloons: impact on neointimal proliferation and healing. Open Heart. 2014;1:e000117.
9. Mark J, Graessley W, Mandelkern L, et al. Physical Properties of Polymers. 3rd ed. Cambridge, United Kingdom: Cambridge University Press; 2004.
10. Venkatasubba G SR, Avadhani GS, Ramakrishnan V, Kumar J. Surface modification and paclitaxel drug delivery of folic acid modified polyethylene glycol functionalized hydroxyapatite nanoparticles. Powder Technol. 2013:437-442.
11. Zeller T. ILLUMENATE global study. Presented at LINC 2017; January 24–27, 2017; Leipzig, Germany.

*Studies shown are not head-to-head comparisons, and data presented cannot be directly compared. Calcium definitions may vary from study to study, and the rates presented herein are based on those used and reported in each respective study. "Complex patients" refers to high rates of severe calcium, diabetes, and renal insufficiency estimates. Primary patency is based on Kaplan-Meier estimate.

Henrik Schröder, MD
Center for Diagnostic Radiology and Minimally Invasive Therapy
Jewish Hospital
Berlin, Germany
Disclosures: National Principal Investigator for ILLUMENATE EU RCT and ILLUMENATE first-in-human studies; received speaking honorarium from Spectranetics.

Prakash Krishnan, MD
Associate Professor of Medicine and Cardiology
Mount Sinai Hospital
New York, New York
Disclosures: Co-National Principal Investigator for ILLUMENATE pivotal study; consultant and has received speaking honorarium from Spectranetics.

Sponsored by Spectranetics Corporation

Vessel Preparation With Laser Atherectomy and Scoring Balloon Angioplasty Before Drug-Coated Balloon Angioplasty

BY EHRIN J. ARMSTRONG, MD

Drug-coated balloon (DCB) angioplasty has significantly advanced the treatment options for femoropopliteal artery disease. Clinical trials have demonstrated patency rates with DCB use similar to those of nitinol stents, with the advantage of not leaving behind a permanent metallic implant.[1,2] Initial registries have also suggested acceptable outcomes of DCB use for the treatment of longer and real-world lesions.[3] For these reasons, DCBs are increasingly used as first-line therapy for the treatment of femoropopliteal lesions.

Despite the promise of DCB angioplasty, limitations of this therapy still need to be addressed. All of the data from DCB trials are based on an adequate predilation without significant residual stenosis or flow-limiting dissection. In studies that included more complex and longer lesions, the rates of bailout stent placement have averaged 20% to 40%.[4] Additionally, treatment of more complex lesions such as femoropopliteal in-stent restenosis,* long-segment disease, or heavily calcified lesions may limit the efficacy of DCB angioplasty due to insufficient drug penetration or residual stenosis. For these reasons, vessel preparation before DCB insertion is crucial to optimizing the outcomes of endovascular intervention. A focus on adequate predilation (achieving a residual stenosis < 30%) and minimization of significant dissection (achieving dissection grade < C) before DCB angioplasty ensures optimal procedural and long-term outcomes.[5]

As part of vessel preparation, laser atherectomy and scoring balloon angioplasty can have important roles in optimizing outcomes of complex lesions. Laser atherectomy vaporizes plaque, thrombus, and other mixed morphology at the site of the lesion or in-stent restenosis. Scoring balloon angioplasty provides focal force dilation at the site of balloon angioplasty via interconnected nitinol scoring elements. This scoring ensures luminal gain at the site of plaque and minimizes the likelihood of significant dissection. These two modalities therefore have complementary roles in vessel preparation prior to DCB angioplasty. The following cases demonstrate the utility of laser atherectomy and scoring balloon angioplasty for optimization of DCB angioplasty in the treatment of complex femoropopliteal lesions.

CASE 1: LONG-SEGMENT SUPERFICIAL FEMORAL ARTERY OCCLUSION

Figure 1 demonstrates a case of a long-segment superficial femoral artery (SFA) occlusion. The patient was a 67-year-old man with a long-standing history of claudication that had recently worsened to the point that he could only walk 50 yards before reaching an absolute claudication distance (consistent with Rutherford class 3 claudication). Initial angiography demonstrated a long-segment occlusion of the SFA with reconstitution at the adductor canal (Figures 1A and 1B). The occlusion was successfully crossed with a straight stiff Glidewire (Terumo Interventional Systems), and the true lumen position was confirmed distally. The Glidewire was exchanged for a supportive 0.014-inch guidewire. Laser atherectomy was then performed with a 2-mm laser at a fluence of 60 mJ/mm^2 and a rate of 45 Hz, for a total of three passes (Figure 1C). Subsequent angiography before balloon angioplasty revealed impressive luminal gain with minimal residual stenosis (Figure 1D). Further vessel preparation was performed with a 6- X 200-mm AngioSculpt scoring balloon (Spectranetics Corporation) at 6 atm for 2 minutes (Figure 1E); follow-up angiography revealed < 30% residual stenosis and no flow-limiting dissections. DCB angioplasty was performed with overlapping 6- X 150-mm In.Pact Admiral DCB (Medtronic)

Sponsored by Spectranetics Corporation

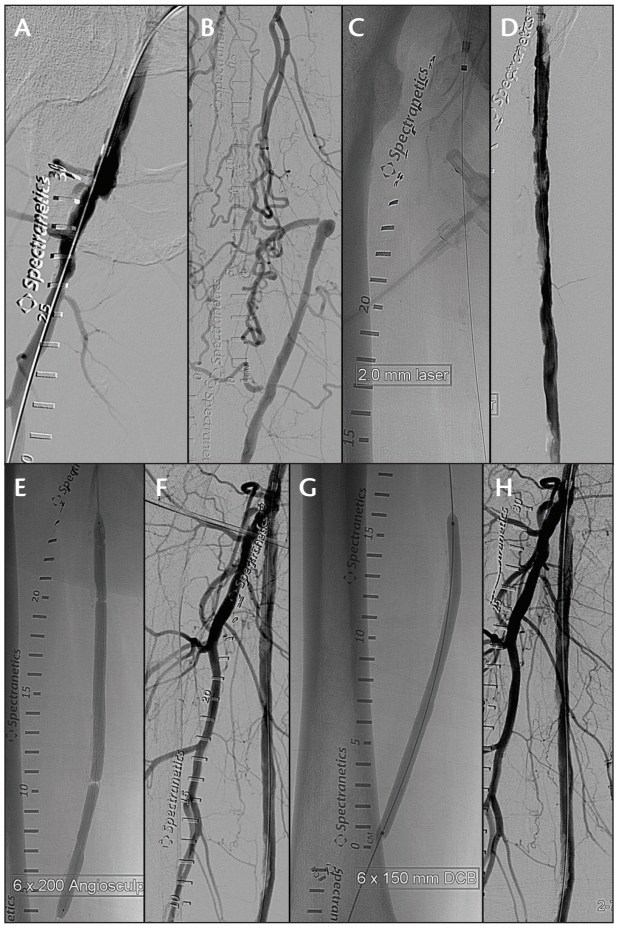


Figure 1. A long-segment SFA occlusion.

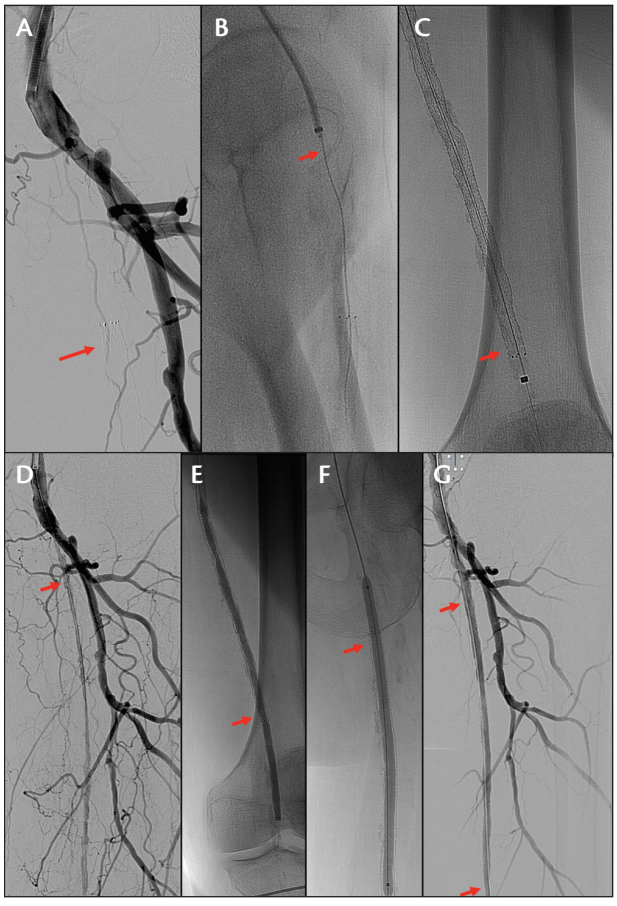


Figure 2. An in-stent occlusion.

(Figure 1F). Final angiography demonstrated minimal residual stenosis and no significant dissections. The patient had immediate relief of claudication, and follow-up duplex ultrasound at 1 year demonstrated continued patency without evidence of restenosis.

Previous studies have demonstrated the efficacy of laser atherectomy for the treatment of complex de novo femoropopliteal disease, including patients with long-segment occlusions and those with multilevel critical limb ischemia.[6,7] Overall, these studies demonstrated that laser atherectomy was associated with high rates of lesion crossing and procedural success, as well as lower rates of bailout stenting when compared to balloon angioplasty alone. Combining laser atherectomy with scoring balloon angioplasty as a technique for vessel preparation in complex femoropopliteal disease before DCB angioplasty may help minimize the need for bailout stent placement and potentially improve paclitaxel diffusion into the vessel by minimizing barriers to drug diffusion.

CASE 2: IN-STENT RESTENOSIS

Figure 2 demonstrates a case of SFA in-stent occlusion. The patient had a history of critical limb ischemia with a long-segment SFA occlusion that was treated 3 years earlier with overlapping nitinol stents. The patient's wound healed at that time, and he had done well until the last 6 months, when he developed severe claudication. Duplex ultrasound demonstrated occlusion of the left SFA stents, prompting referral for lower extremity angiography and endovascular intervention.

Baseline angiography (Figure 2A) demonstrated a flush occlusion of the SFA ostium with an occluded stent (arrow) that reconstituted in the mid-popliteal artery. A 7-F Flexor Ansel guiding sheath (Cook Medical) was placed and a 150-cm NaviCross support catheter (Terumo Interventional Systems) and a straight stiff Glidewire were used to access the occluded stent (Figure 2B). A 2.3-mm Turbo-Power laser atherectomy catheter (Spectranetics Corporation) was advanced to the occluded stent (Figure 2C) and was advanced at

Sponsored by Spectranetics Corporation

1 mm/sec at a fluence of 60 mJ/mm^2 and a rate of 60 Hz. A total of four passes were performed, with directional ablation utilized via rotation of the torque wire. Follow-up angiography after laser atherectomy (Figure 2D) demonstrated excellent luminal gain with antegrade flow and no flow-limiting dissections. A 5- X 200-mm AngioSculpt scoring balloon was inflated at 8 atm for 2 minutes to optimize the luminal gain (Figure 2E), increase stent expansion, and limit dissection. Overlapping 5- X 150-mm In.Pact paclitaxel-coated balloons were inflated at 8 atm for 3 minutes (Figure 2F). Final angiography (Figure 2G) demonstrated minimal residual stenosis, no significant dissection, and excellent antegrade flow through the previously occluded stent.

Laser atherectomy has demonstrated superiority over balloon angioplasty for the treatment of in-stent restenosis based on the EXCITE-ISR trial as well as real-world registry data.[8,9] More recently, clinical application of the Turbo-Power laser atherectomy catheter has allowed directional atherectomy, thereby increasing the luminal gain and vaporizing a greater percentage of neointima. A small study has also suggested that the combination of laser atherectomy with DCB angioplasty is superior to DCB angioplasty alone for the treatment of in-stent occlusions.[10] The mechanisms of this benefit are uncertain but may include better luminal gain and/or increased paclitaxel penetration after laser atherectomy. For this reason, the combination of laser atherectomy with DCB angioplasty is especially attractive for the treatment of femoropopliteal in-stent restenosis.

CASE 3: SEVERELY CALCIFIED SFA STENOSIS

Figure 3 demonstrates a case of a patient with severe claudication and a heavily calcified SFA. The patient had a history of coronary artery disease and previous myocardial infarction and was prescribed optimal medical therapy including an antiplatelet agent, statin, and angiotensin-converting enzyme inhibitor. The patient's subsequent cardiac rehabilitation was limited by severe left lower extremity claudication. Physiologic studies demonstrated a normal right ankle-brachial index but a left ankle-brachial index of 0.65. Based on the patient's symptoms, despite optimal medical therapy and attempts at an exercise program, he was referred for lower extremity angiography.

Baseline angiography demonstrated multifocal areas of severe stenosis in the proximal and mid-SFA (Figure 3A). Nonsubtracted angiography confirmed severe calcification in the areas of stenosis (Figure 3B). A 7-F Ansel sheath was placed and the lesion was crossed with a 0.014-inch guidewire. A 2.3-mm Turbo-Power laser atherectomy catheter was advanced to the lesion (Figure 3C)

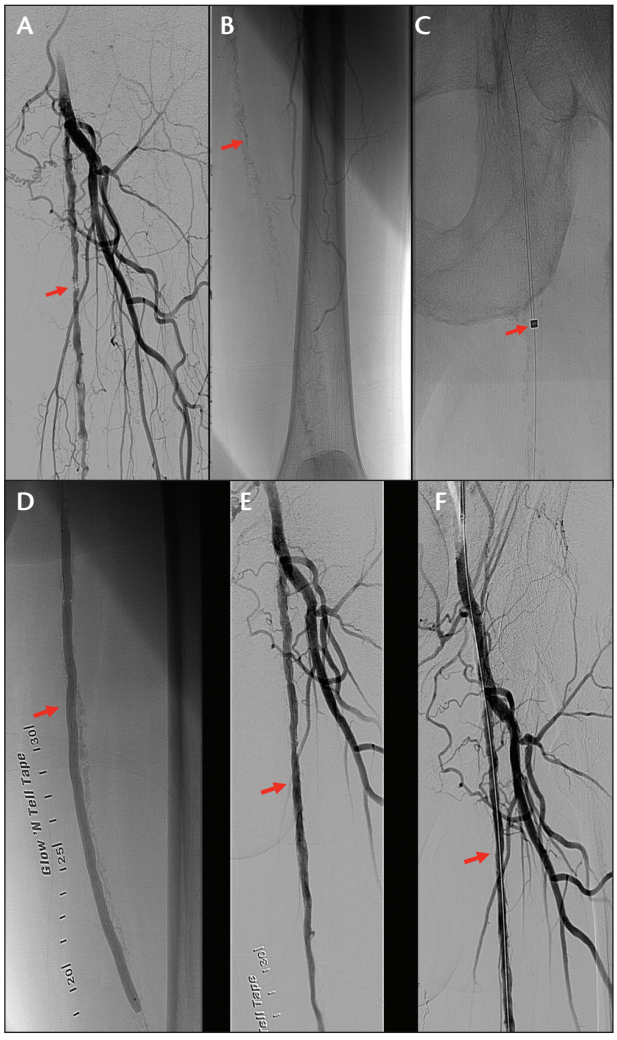


Figure 3. A heavily calcified SFA.

at 1 mm/sec using an initial fluence of 45 mJ/mm^2 and rate of 60 Hz. The torque wire of the laser catheter was used to direct the laser tip toward the areas of eccentric calcification, thereby maximizing lesion ablation and the kinetic energy of vapor bubble formation. A 5- X 200-mm AngioSculpt balloon was then inflated at low pressure (6 atm was sufficient to maximize scoring balloon inflation) (Figure 3D). Subsequent angiography demonstrated excellent luminal gain without evidence of dissection (Figure 3E). After subsequent DCB angioplasty with a 6- X 150-mm In.Pact Admiral DCB, the final angiographic result was excellent (Figure 3F). The patient had resolution of his claudication symptoms and was able to complete cardiac rehabilitation.

Although DCBs have demonstrated excellent patency in many femoropopliteal lesions, calcification remains a significant limitation on outcomes. Calcium is asso-

Sponsored by Spectranetics Corporation

ciated with increased rates of dissection, inadequate lumen expansion, and may also limit drug diffusion into the vessel. Consistent with this, initial studies have suggested the presence of severe calcification is associated with lower patency rates after DCB angioplasty.[11,12] The combined use of laser atherectomy and scoring balloon angioplasty ensured maximum lesion preparation before the delivery of paclitaxel and may therefore be associated with improved patency. Ongoing studies are further investigating the potential benefits of adjunctive atherectomy in the treatment of calcified lesions.

CONCLUSION

DCBs have significantly expanded the treatment options for patients with symptomatic femoropopliteal artery disease. Vessel preparation is crucial before DCB angioplasty, especially for complex lesions. Laser atherectomy can effectively vaporize plaque and create a pilot channel through complex lesion morphology, while scoring balloon angioplasty can maximize lesion expansion and minimize dissection. As we continue to advance endovascular options for patients with peripheral artery disease, the use of adjunctive technologies to maximize vessel preparation will become increasingly important in realizing the goal of long-term femoropopliteal patency after endovascular intervention. ■

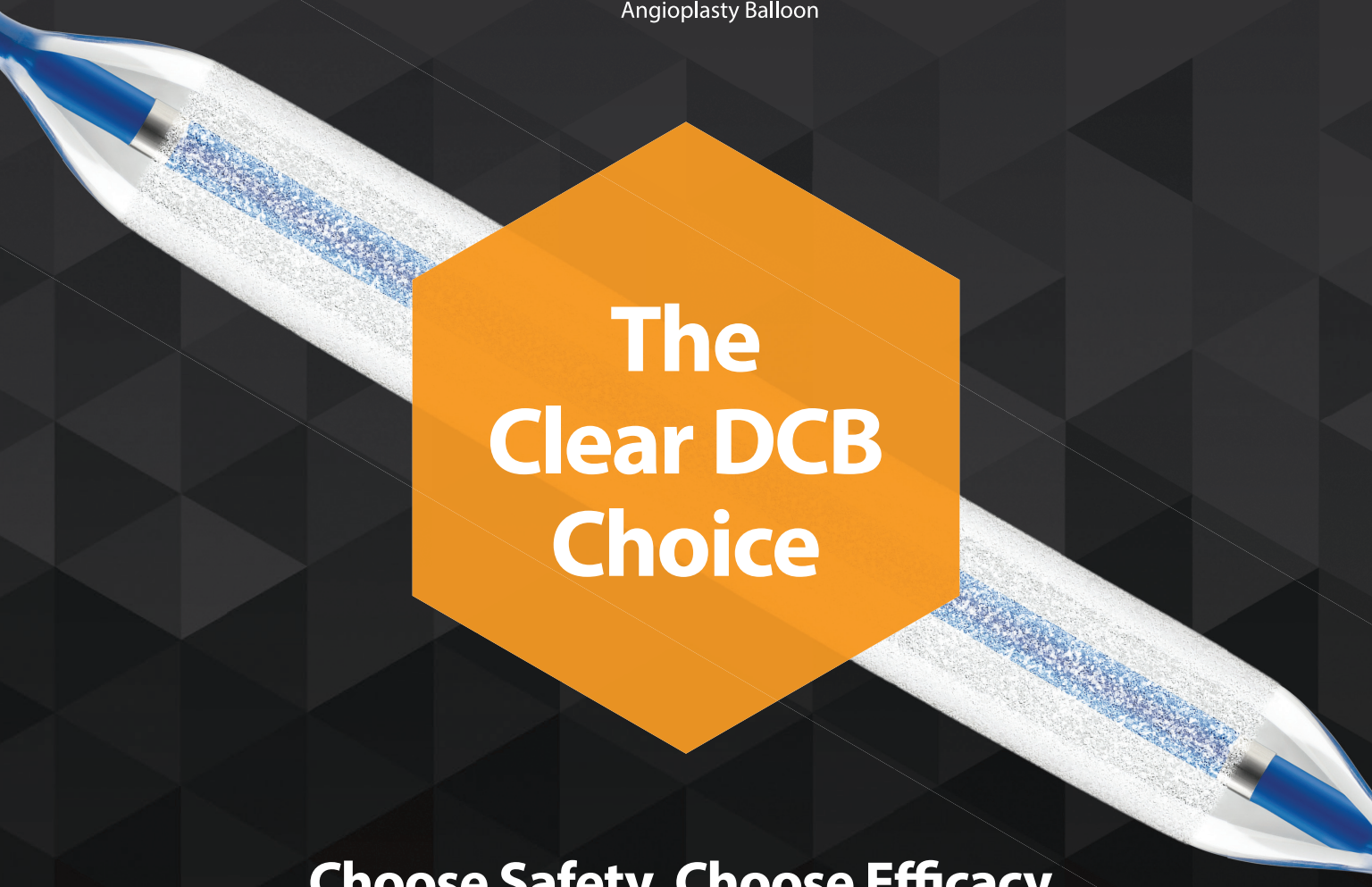
1. Krishnan P, Faries P, Niazi K, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: 12-month outcomes from the randomized ILLUMINATE pivotal and pharmacokinetic studies [published online July 20, 2017]. Circulation.
2. Laird JR, Schneider PA, Tepe G, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. J Am Coll Cardiol. 2015;66:2329-2338.
3. Micari A, Nerla R, Vadala G, et al. 2-year results of paclitaxel-coated balloons for long femoropopliteal artery disease: evidence from the SFA-Long study. J Am Coll Cardiol. 2017;10:728-734.
4. Foley TR, Cotter RP, Kokkinidis DG, et al. Mid-term outcomes of orbital atherectomy combined with drug-coated balloon angioplasty for the treatment of femoropopliteal disease. Catheter Cardiovasc Interv. 2017;89:1078-1085.
5. Fujihara M, Takahara M, Sasaki S, et al. Angiographic dissection patterns and patency outcomes after balloon angioplasty for superficial femoral artery disease. J Endovasc Ther. 2017;24:367-375.
6. Scheinert D, Laird JR, Schroder M, et al. Excimer laser-assisted recanalization of long, chronic superficial femoral artery occlusions. J Endovasc Ther. 2001;8:156-166.
7. Laird JR, Zeller T, Gray BH, et al. Limb salvage following laser-assisted angioplasty for critical limb ischemia: results of the LACI multicenter trial. J Endovasc Ther. 2006;12:1-11.
8. Dippel EJ, Makam P, Kovach R, et al. Randomized controlled study of excimer laser atherectomy for treatment of femoropopliteal in-stent restenosis: initial results from the EXCITE-ISR trial. J Am Coll Cardiol. 2015;8:92-101.
9. Armstrong EJ, Thiruvoipati T, Tanganyika K, et al. Laser atherectomy for treatment of femoropopliteal in-stent restenosis. J Endovasc Ther. 2015;22:506-513.
10. Gandini R, Del Giudice C, Merolla S, et al. Treatment of chronic SFA in-stent occlusion with combined laser atherectomy and drug-eluting balloon angioplasty in patients with critical limb ischemia: a single-center, prospective, randomized study. J Endovasc Ther. 2013;20:805-814.
11. 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.
12. Tepe G, Beschorner U, Ruether C, et al. Drug-eluting balloon angioplasty for femoropopliteal occlusive disease: predictors of outcome with a special emphasis on calcium. J Endovasc Ther. 2015;22:727-733.

*The Stellarex DCB is not currently indicated for use in femoropopliteal in-stent restenosis.

Ehrin J. Armstrong, MD
Associate Professor of Cardiology
University of Colorado
Aurora, Colorado
Disclosures: Consultant to Abbott Vascular, Boston Scientific Corporation, Cardiovascular Systems, Inc., Medtronic, and Spectranetics.

stellarex™

Drug-coated
Angioplasty Balloon



The Clear DCB Choice

Choose Safety. Choose Efficacy.

Only Stellarex™ delivers top-tier clinical outcomes with the lowest therapeutic drug dose in all patients—common to complex.

"THE STELLAREX TECHNOLOGY IN ONE WORD, PREDICTABILITY—PREDICTABLE RESULTS, CLINICAL EFFICACY THAT'S SUSTAINED OVER TIME AND NO SAFETY CONCERNS."

JUAN F. GRANADA, MD, FACC | CRF SKIRBALL CENTER FOR INNOVATION, ORANGEBURG, NY

STUDY RESULTS[1-2] SHOW STELLAREX DCB ACHIEVES:

89% PRIMARY PATENCY

41% LESS PARTICULATE LOSS THAN LUTONIX®

1. Schroeder H, et al. *Circulation.* 2017;135:2227-2236.
2. Based on bench or animal studies. Data on file.

Spectranetics®
Always Reaching Farther