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Evidence From the Next-Generation DCB

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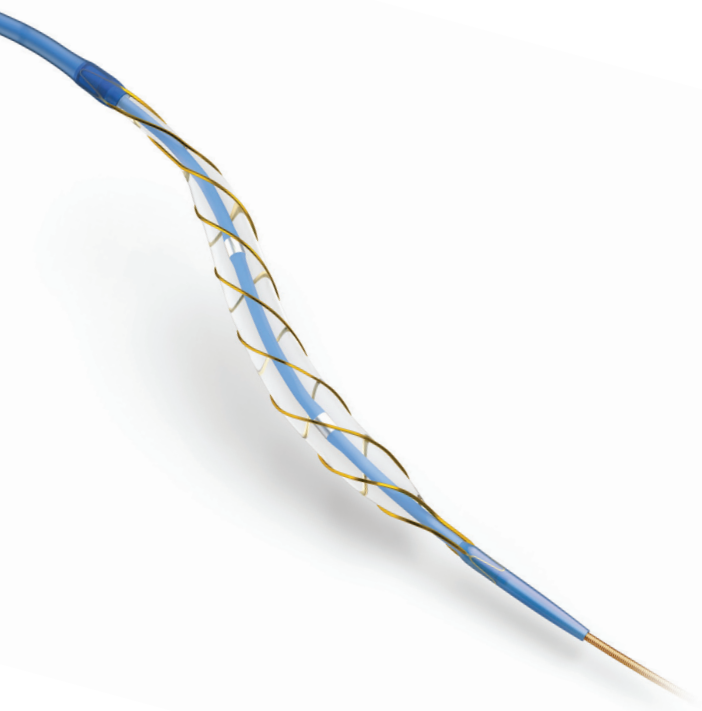

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The Latest in DCB Evidence

ILLUMENATE Global confirms findings of ILLUMENATE FIH

BY PROF. THOMAS ZELLER, MD

The advent and growth of drug-eluting technologies have raised the bar and expectations for clinical evidence requirements. This is forcing all stakeholders, from manufacturers to health care providers and payers, to collaborate toward meaningful trials to fully appreciate and justify the "why," "when," and "at what cost" so that modern combination technologies may best fit into the treatment of peripheral artery disease. Although there are currently more than 10 drug-coated balloon (DCB) technologies available in Europe, only a few manufacturers are conducting clinical trials of various sizes and levels of rigor.

Pharmacokinetic (PK) and proof-of-concept studies represent the appropriate first step of any research plan, and well-designed randomized controlled trials should follow. These types of trials should be powered on an objective primary patency endpoint and accompanied by a comprehensive array of secondary endpoints including clinical and functional metrics. These trials should be followed by real-world and real practice evidence from large-scale registries. Finally, health economic evidence should be an integral part of these trials, with the important mandate to understand the affordability of these technologies within various health care environments and across different geographical regions.

In this context, the ILLUMENATE trial series (composed of ILLUMENATE first-in-human [FIH][1]; ILLUMENATE Pivotal[2]; ILLUMENATE PK[3]; ILLUMENATE EU-RCT[4]; and ILLUMENATE Global[5]) represents an exemplary case of a clinical program with breadth and quality. Each DCB brand should commit to this same breadth and quality in order to reveal the full potential, best indications, and major limitations within the wide peripheral artery disease clinical and anatomical spectrums.

The ILLUMENATE series was designed to evaluate the safety and performance of the Stellarex DCB (Spectranetics Corporation). The Stellarex DCB is a 0.035-inch guidewire-compatible angioplasty catheter coated with paclitaxel (2 µg/mm^2 balloon surface) and polyethylene glycol, an excipient that facilitates the transfer of the paclitaxel into the vessel wall.

ILLUMENATE FIH

ILLUMENATE FIH,[1] the first completed and published study from the ILLUMENATE series, is a multicenter, single-arm study characterized by high scientific rigor as typical of pivotal randomized trials. Independent imaging evaluation was provided by external angiographic and duplex ultrasound core laboratories, adjudication of clinical events by a clinical events committee (CEC), and full source data verification conducted by external monitors. Eighty patients were enrolled and treated with the Stellarex DCB for stenosis or occlusion of femoropopliteal arteries in patients with symptoms of claudication or rest pain (Rutherford categories 2–4).

ILLUMENATE FIH was the first DCB trial to offer insight on the role of predilatation. Two patient cohorts were subsequently enrolled: one with predilatation (n = 50) and one without predilatation (n = 30). Primary patency and freedom from target lesion revascularization (TLR) for 12 and 24 months are illustrated in Figures 1 and 2. Although the outcomes through 2 years were similar between the two groups, it's notable that the rates of postdilatation (35.1% vs 12.1%) and stent placement (8.1% vs 5.2%) were higher in the direct cohort as compared with the predilatation cohort. While predilatation may be optional in simple lesions, these findings suggest predilatation reduces the need for postdilatation and stenting. Predilatation

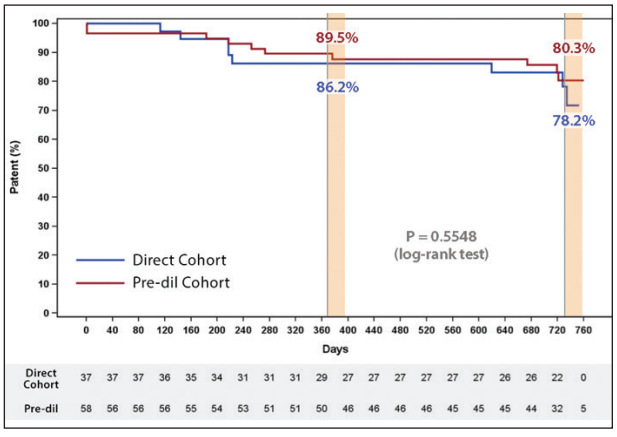

Figure 1. ILLUMENATE FIH outcomes: freedom from loss of primary patency through 24 months.[6]

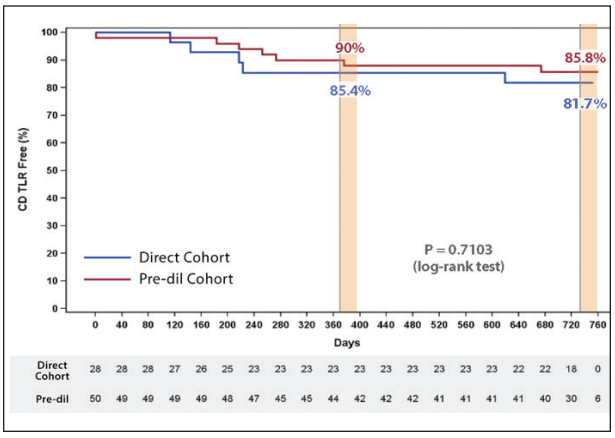

Figure 2. ILLUMENATE FIH outcomes: freedom from CD-TLR through 24 months.[6]

is still highly recommended in total occlusions and in the presence of calcification.

ILLUMENATE GLOBAL STUDY

Recently presented at the Charing Cross Symposium, interim results of the ILLUMENATE GLOBAL study add to the current evidence base of the Stellarex DCB and suggest consistency with the promising results in the ILLUMENATE FIH study.[1]

The ILLUMENATE Global study is a prospective, single-arm, multicenter study that enrolled 371 patients at 37 centers in Europe, Australia, and New Zealand. All subjects enrolled were treated with the Stellarex DCB and will be followed for up to 5 years. It is important to distinguish this single-arm study from other global registries. Unlike most global registries, this study is being conducted with the highest level of data collection rigor. The study includes an angiographic core laboratory (Beth Israel Deaconess Medical Center, Boston, MA), duplex ultrasound core laboratory (VasCore, Boston, MA), independent monitoring of all data, and oversight by a CEC and data safety monitoring board to ensure data are unbiased and accurate.

The primary safety endpoint is freedom from device and procedure-related death through 30 days postprocedure and freedom from target limb major amputation and clinically driven TLR (CD-TLR) through 12 months. The primary effectiveness endpoint is primary patency at 12 months. Primary patency is defined as the absence of restenosis per duplex ultrasound (peak systolic velocity ≤ 2.5) and freedom from CD-TLR.

Key inclusion criteria included the following: Rutherford category 2 to 4, target limb has at least one patent (< 50% stenosis) runoff vessel to the foot, and the patient has one or two target lesions with a cumulative length ≤ 20 cm. Key exclusion criteria included in-stent restenosis, severe calcification that precludes adequate percutaneous transluminal angioplasty treatment, and lesions that would require adjunctive therapies such as atherectomy catheters or scoring balloons. Follow-up assessments include a duplex ultrasound for patency assessment, functional outcome questionnaires (EQ-5D and Walking Impairment Questionnaire), an ankle-brachial index assessment, and adverse event evaluations.

The interim analysis included 153 patients with 174 lesions. Per angiographic core laboratory assessment, the mean lesion length was 7.3 cm, 25.6% were total occlusions, and 42.4% had severe calcification. Postdilatation was performed in 25.3% of lesions, and the provisional stent rate was 12.6%. The freedom from a composite primary safety event rate was 91% (Figure 3).

The primary patency rate, per core lab adjudication and Kaplan-Meier estimate, was 84.7% at day 365

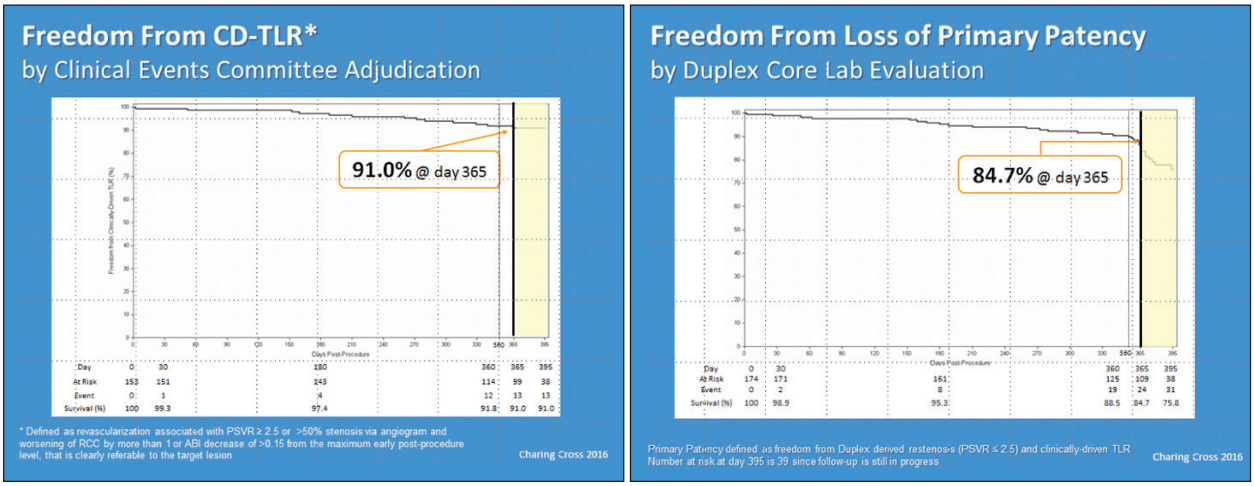

Figure 3. ILLUMENATE Global interim results released at the Charing Cross Symposium in London, UK.[7]

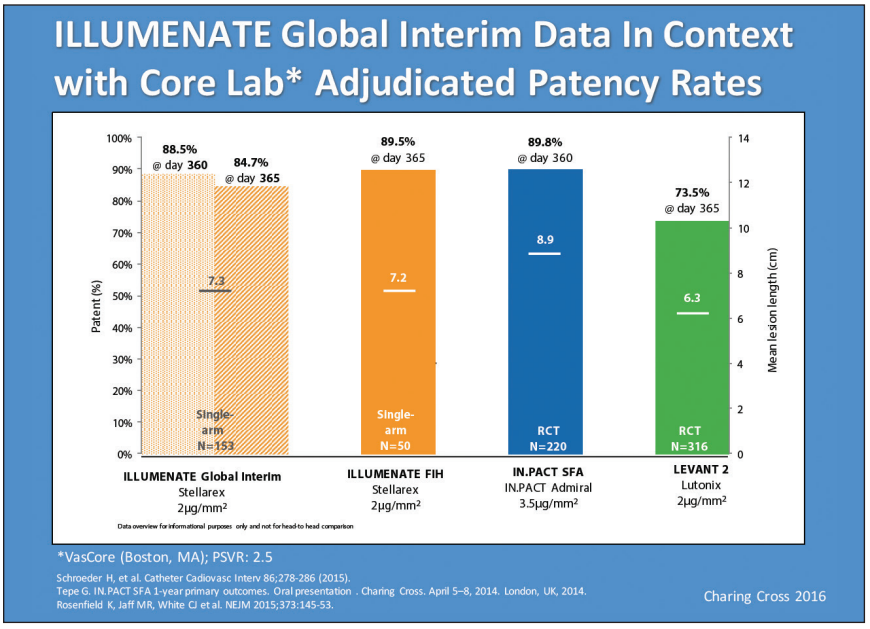

Figure 4. Core-lab adjudicated primary patency rates from DCB trials: the ILLUMENATE Global interim primary patency rate is consistent with the primary patency rate observed in the ILLUMENATE FIH study, which is comparable to the IN.PACT SFA study and favorable compared to the LEVANT 2 study.[7]

(Figure 3), which is in line with the 89.5% patency rate observed in ILLUMENATE FIH.[1] The freedom from CD-TLR rate, per CEC adjudication and Kaplan-Meier estimate, was 91% at day 365, also similar to the 90% rate observed in ILLUMENATE FIH.

While the data are still only interim, compared with other core laboratory-adjudicated patency data (Figure 4), 84.7% is favorable compared to the LEVANT 2 study[8] and comparable to the rate observed in the IN.PACT SFA study.[9,10]

The two randomized controlled trials, ILLUMENATE Pivotal and ILLUMENATE EU-RCT, are fully enrolled and currently in the follow-up phase. The data are highly anticipated and expected to be released later this year.

CONCLUSIONS

ILLUMENATE Global interim results suggest consistent outcomes with the final results observed in the ILLUMENATE FIH study and are comparable with the highest reported core lab–adjudicated DCB patency rates. Overall, the ILLUMENATE series of studies represents one of the broadest and highest-quality clinical evidence programs within the entire endovascular therapy landscape. Notably, the ILLUMENATE program includes two rigorously conducted randomized controlled trials with more than 600 patients, and results from these trials are expected to be released later this year. ■

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The DCB Technology Evolution

Future perspectives on DCB

BY JUAN F. GRANADA, MD, FACC

More than 10 years of progress in drug-coated balloon (DCB) research, development, and manufacturing have passed since the first paclitaxel-based DCB prototype was developed and tested.[1,2] During this decade, DCB design goals have been refined to match four clear targets: (1) limit drug dose, (2) minimize drug loss during balloon transit, (3) maximize drug transfer efficiency during inflation, and (4) maintain clinical efficacy over time.

Improving drug transfer efficiency so that more is delivered and less is lost builds upon the desire to have a reliably stable coating during all stages, from balloon preparation and handling to its final delivery to the target lesion. Ultimately, this improved efficiency is meant to secure sufficient and predictable drug levels to be transferred to the tissue wall and, just as important, to limit potential side effects related to drug distal embolization.

While the clinical relevance of distal embolization is still unclear, some concern exists about the potential for downstream effect of paclitaxel within specific clinical and anatomical situations. DCB use for the treatment of infrapopliteal arterial disease in the presence of foot ulcers due to critical limb ischemia has raised some questions in relation to possible reaction from paclitaxel embolization on wound healing and ultimately on limb loss. Moreover, besides the pharmacological side effect of paclitaxel, the risk of jeopardizing distal perfusion by drug mass embolization has been anecdotally raised in the treatment of very distal targets characterized by single-vessel run off and preexisting poor microcirculation, which is typical in patients with diabetes and end-stage renal disease. Although the particle burden of paclitaxel is normally negligible compared to the plaque debris dislodged by standard angioplasty of atherosclerotic lesions,[3] such a small amount of paclitaxel mass may turn out to be relevant in specific and challenging settings like those described previously. Therefore, more sophisticated and drug-efficient delivery technologies are needed to continue improving clinical outcomes as well as the safety profile of first-generation DCB technologies. ■

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Stellarex: The Next-Generation DCB

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

Newer-generation drug-coated balloons (DCBs) with a lower drug load of 2 µg/mm^2 balloon surface have been developed as alternatives to first-generation DCBs featuring up to 50% or 70% higher doses of 3 or 3.5 µg/mm^2.

The performance of a DCB relies on four design elements: drug dose; coating stability to survive handling, insertion, tracking, and lesion crossing; coating balloon adhesion or surface energy to control drug transfer to the arterial wall; and extent of paclitaxel crystallinity versus amorphous microstructure to control drug residency in the arterial tissue. The balance of these features determines the performance of a DCB, and whether any one feature is more important remains debatable and a matter of further research.

The Stellarex DCB (Spectranetics Corporation) is a next-generation DCB designed to match the aforementioned design goals.

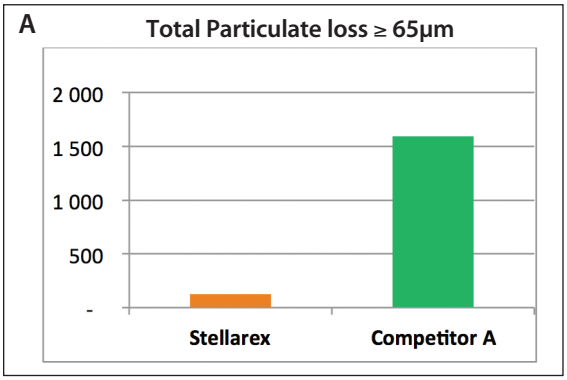

Figure 1. Total particulate loss after balloon inflation in a vessel of room temperature water (A). Photo display of the particulate generated after a balloon is submerged in a vessel of room temperature water, inflated to nominal pressure, and removed from the vessel (B).

THE STELLAREX DCB

Optimal Drug Dose

EnduraCoat technology is characterized by a low dose of 2 µg/mm^2 of paclitaxel and a polyethylene glycol excipient (an additive largely adopted in pharmaceutical and cosmetic applications). The balloon platform is coated in the unfolded state (partially inflated) and subsequently deflated and folded into the final balloon configuration. This allows most of the drug coating to be protected by the folds as the balloon is tracked to its final destination within the body, allowing for a lower coated dose. A lower drug dose is highly advantageous as it mitigates the downstream effect caused by paclitaxel, while still delivering a highly efficacious treatment to the target lesion.

Coating Stability

High coating stability is the result of extensive drug formulation 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.

Superior coating stability of Stellarex during preparation, handling, and manipulation appears evident through qualitative comparisons to competitor DCBs (Figure 1) and through quantitative drug content analysis after handling it in a variety of ways (Figure 2).

The coating stability of Stellarex is confirmed by quantitative particulate testing after tracking the DCB through a vasculature model.[1] This testing supports the notion that Stellarex limits drug particle loss compared to other DCB competitors with the same (and higher) drug dose. In a competitive assessment, Stellarex resulted in up to 50% fewer particles produced during tracking (Figure 3).

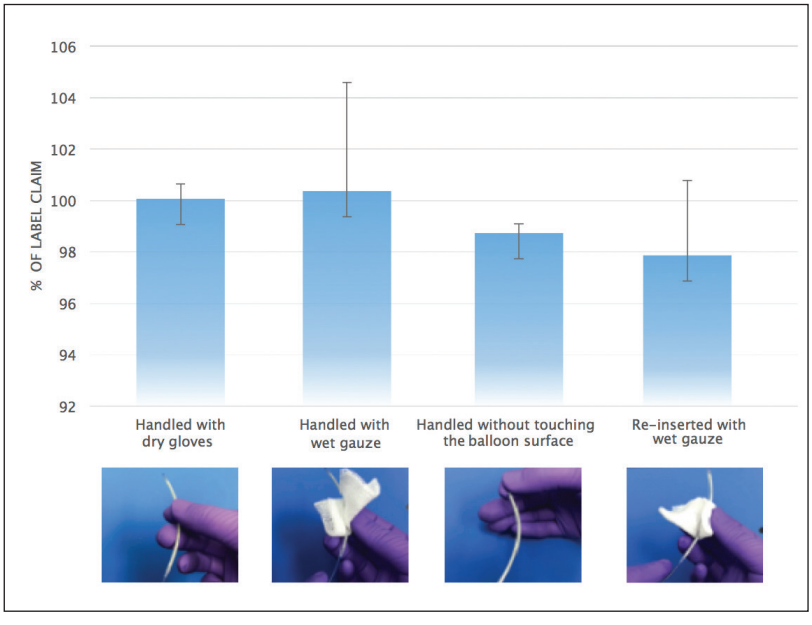

Figure 2. Quantitative drug content analysis after handling it in a variety of ways.

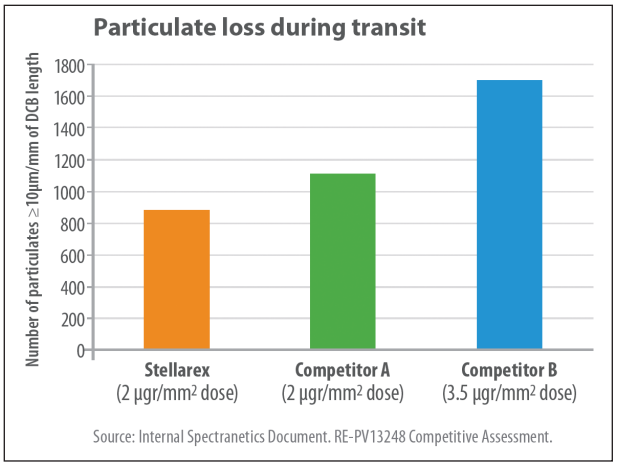

Figure 3. Particulate competitive assessment.

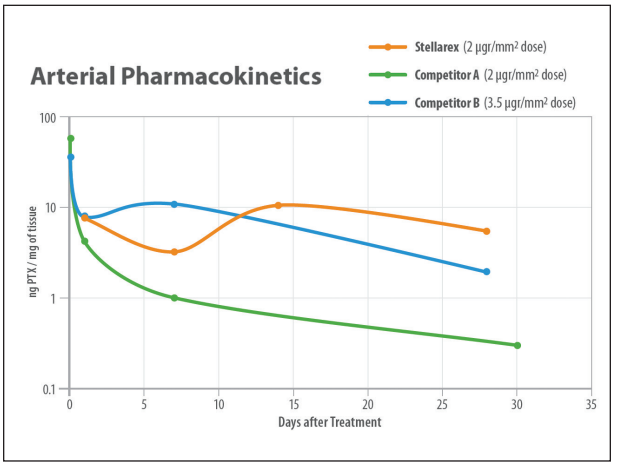

Figure 4. Sustained drug transfer and tissue residency at 28 days is similar to a DCB with ~75% higher dose (3.5 µg/mm²). Superimposed pharmacokinetics curve from different data sets.[3-5]

Drug Tissue Transfer and Residency

Stellarex achieves the optimal balance between coating stability and drug transfer to tissue by balancing the ratio of amorphous to crystalline paclitaxel on the balloon surface. In general, amorphous paclitaxel tends to be more durable, whereas crystalline paclitaxel delivers the best therapeutic effect.

The crystalline form of paclitaxel on the Stellarex DCB allows efficient transfer of the drug to vessel tissue. Entrenching paclitaxel into the vessel tissue is of utmost importance; the healing response of a vessel after injury caused during balloon expansion lasts up to 28 days. With Stellarex, a high dose of paclitaxel remains in the tissue for the duration of the healing process (Figure 4). This prevents scar tissue from forming in the vessel during this critical period, thereby preventing restenosis.

Clinical Performance

Initial results from the ILLUMENATE first-in-human trial (the first of a multitude of Stellarex trials) support the notion that a well-designed low-dose DCB can result in high clinical performance similar to, or better than, the best performing DCBs of higher dose and equal dose, as measured in primary patency rates of about 90% and 80% at 1 and 2 years, respectively, in patients with symptoms of claudication and rest pain due to femoropopliteal disease.[2]

CONCLUSION

DCB technologies are evolving toward an optimized balance between minimal drug load, minimal downstream loss, and maximal tissue transfer. Particulate loss may lead to potentially relevant clinical implications in specific clinical and anatomical settings, which justify continuous research efforts to enhance DCB process efficiency. Confirmed by a series of bench, preclinical, and clinical evidence, Stellarex represents an important step ahead toward this goal. ■

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The Role of Plaque Scoring

DCB therapy in complex settings: how to optimize treatment results

BY PROF. FABRIZIO FANELLI, MD, EBIR

Supported by a growing body of clinical evidence, drug-based endovascular technologies are increasingly adopted within a wide array of clinical and anatomical settings, including a variety of lesion complexities frequently observed in patients with peripheral artery disease. In addition to TASC A and B lesions, much more difficult anatomical challenges are often encountered, such as long lesions and occlusions, frequently with high plaque burden and severe calcium.

Determining how to obtain and maintain vessel patency, as well as the safest, most efficacious, and easiest way to do so is crucial. The achievement of satisfactory and stable lumen gain and flow improvement, while referred to as *acute success*, is likely also instrumental to long-term outcomes, especially in the current era of drug elution and, even more importantly, within these complex lesions.

TREATMENT OF CALCIFIED LESIONS

Calcium is a particularly well-known enemy of endovascular practice. Underdiagnosed and underestimated by angiography, it makes vessels resistant to dilatation, subject to recoil and embolism, and correlates with an increase in the incidence of dissections. Seventy-one percent of flow-limiting dissections occur with calcium. As a result, primary stenting is the preferred strategy in these settings. Nonetheless, once a stent is deployed, calcium continues to bring further challenges with a risk of malapposition, suboptimal expansion, and increased likelihood of stent fractures.[1,2] Moreover, calcium has been indicated as a potential barrier to optimal drug absorption after the use of drug-coated balloons (DCBs). Particularly, circumferential distribution seems to be a strong predictor for loss of patency versus longitudinal extension.[3,4]

Various solutions are being explored to improve the treatment of calcified lesions. Although directional atherectomy has shown promising results, tradeoffs may exist inherent to the length and complexity of the procedure and to the risk of potential complications such as plaque embolization mandating the use of a distal filter; all of which pose a big question concerning cost-effectiveness, especially in the lack of reimbursement.[5,6] Plaque scoring, on the other hand, represents a viable and simple process aimed at improving acute luminal gain while limiting the likelihood of severe dissections. In addition, plaque scoring holds the potential to optimize DCB effectiveness and associated long-term outcomes.

PLAQUE SCORING

The AngioSculpt plaque-scoring angioplasty balloon (Spectranetics Corporation) features three to five (depending on balloon size) rectangular cross-section nitinol wires (the "scoring elements") wrapped in a spiral fashion around the full length of the balloon. AngioSculpt's mechanism of action combines balloon dilatation with focal incision of the lesion to aim to break plaque continuity and relieve internal hoop stress (the internal tensions that exert circumferentially within a cylinder). Inducing predictable and controlled dissections that facilitate mechanical dilatation and luminal gain without flow-limiting downsides is the expected outcome.

Plaque scoring has been reported as highly effective in a broad range of complex peripheral and coronary lesions. It confers precision, predictability, and stability during dilatation with significant acute gains and the ability to achieve optimal stent expansion afterward.[7-9]

Tepe et al described the effect of dissections in the context of DCB utilization. They reported that non–flow-limiting dissections cannot only be left unstented while still bringing positive outcomes, but patients with severe dissections (grade C, D, E) seem to benefit the most from DCBs in terms of lower late lumen loss at 6 months and lower target lesion revascularization rates at 2 years (compared to those with less severe dissections [grade A, B]).[10] This observation supports the hypothesis that dissections may create a path for improved drug absorption, which may be beneficial in overcoming plaque burdens and calcium barriers.

Erwin Blessing recently reported the combination of AngioSculpt and DCBs for the treatment of calcified superficial femoral artery (SFA) lesions within a single-center registry.[11] The results supported the notion that plaque scoring can provide a benefit to both procedural and long-term success. Calcification was not a predictor

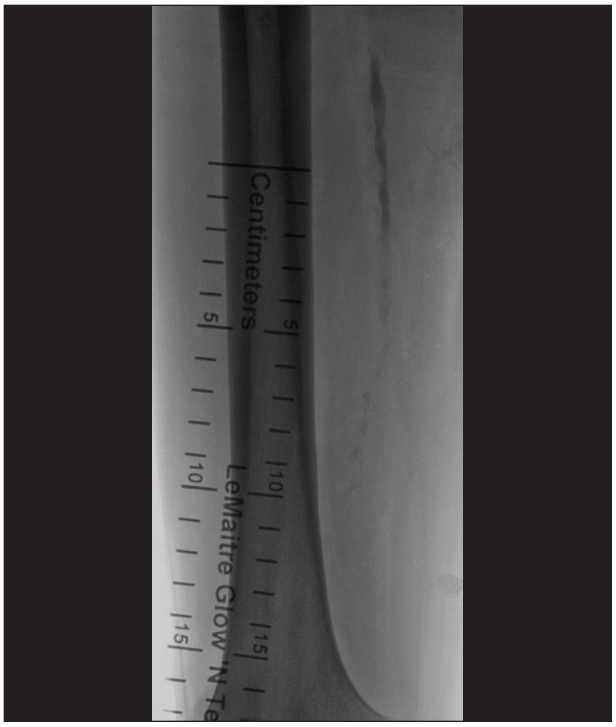

Figure 1. Left SFA with severe calcium.

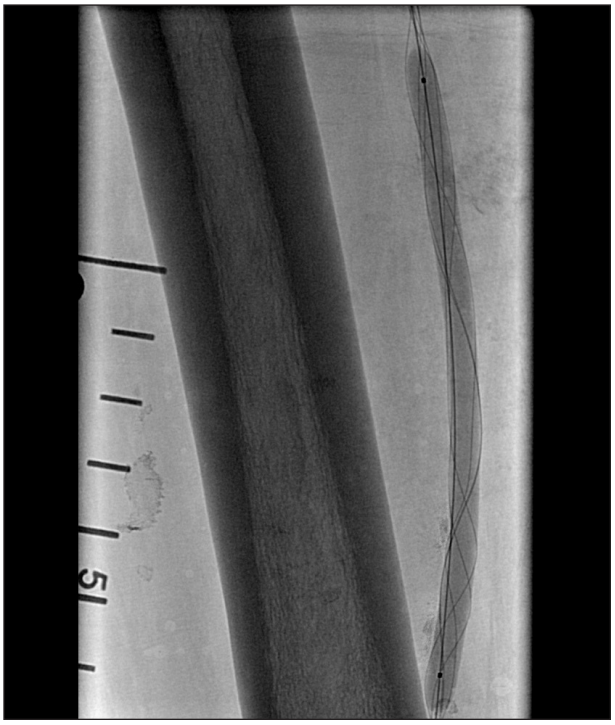

Figure 2. A 5-mm X 10-cm AngioSculpt in the SFA.

for loss of 12-month patency as long as lesion preparation was performed with AngioSculpt.

CASE STUDY

The following case describes the use and results of AngioSculpt for the treatment of severe calcification.

A 72-year-old man who was a heavy smoker with hypertension and diabetes presented with a small ulcer at the level of the forefoot and rest pain in the right leg. CT angiography showed obstruction of the left SFA with severe calcification (grade 3, according to our classification[3]) (Figure 1). The patient's ankle-brachial index was 0.35 (right) and 0.5 (left).

Retrograde contralateral access was achieved via the left common femoral artery using a 6-F, 45-cm braided introducer (Destination sheath, Terumo Europe). We were unable to cross the SFA occlusion endoluminally using an antegrade approach. Retrograde right popliteal access was then employed. Recanalization of the occluded segment was achieved with a 0.035-inch angled hydrophilic guidewire.

Dilatation of the obstructed segment was performed with a 4-mm X 4-cm AngioSculpt balloon in the P1 segment and a 5-mm X 10-cm balloon in the SFA (Figure 2). The inflation time was 3 minutes each to 10 atm.

Digital subtraction angiography showed recanalization of the vessel with dissection at the level of the distal portion of the SFA (not flow limiting). The P1 segment was dilated with a 4-mm X 8-cm Stellarex DCB (Spectranetics Corporation), and the SFA was dilated with three 5-mm

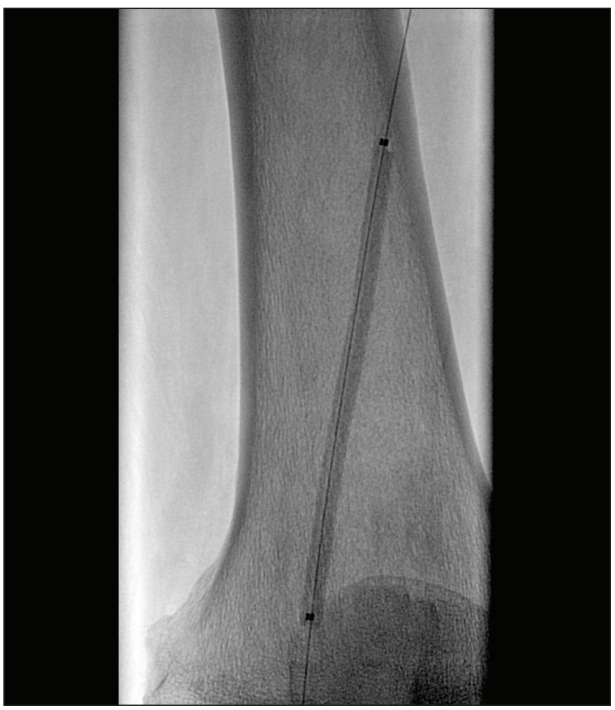

Figure 3. A 5-mm X 12-cm Stellarex in the SFA.

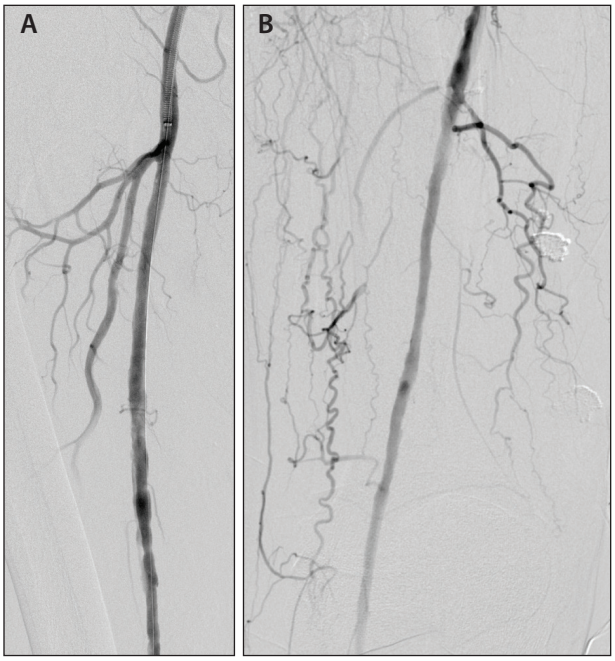

Figure 4. Left SFA final result. Proximal (A). Distal (B).

balloons (5 mm X 12 cm, 5 mm X 12 cm, 5 mm X 8 cm) up to its origin (Figure 3). The inflation time was 3 minutes for each balloon, overlapping 1 cm, to 10 atm.

Subsequent digital subtraction angiography showed good recanalization with persistence of the dissection flap at the level of the distal portion of the SFA, not limiting the flow. Postdilatation with a 5-mm noncoated Dorado balloon (Bard Peripheral Vascular, Inc.) was performed, with an inflation time of 5 minutes.

The final angiogram showed a complete resolution of the dissection with improvement of the distal flow in the below-the-knee region (Figure 4).

CONCLUSIONS

DCBs are more frequently used for the treatment of increasingly complex lesions. Although further research is warranted, plaque scoring represents a viable, user-friendly, and effective solution to improve acute success by achieving larger luminal gain and decreasing the likelihood of flow-limiting dissections. In addition, plaque scoring holds promise to facilitate optimal drug tissue absorption in settings where calcium may otherwise be a barrier. ■

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Treating In-Stent Restenosis

Is laser atherectomy plus DCB the answer to achieving superior results in ISR treatment?

BY MICHAEL LICHTENBERG, MD

Technologies and techniques such as direct stenting have been developed to provide physicians with more options for the endovascular treatment of occlusive disease affecting the superficial femoral artery and infrapopliteal arteries. Stents allow physicians to deal with common procedural complications (eg, flow-limiting dissections). As a result of the more favorable outcomes that have been achieved, femoropopliteal stents are liberally implanted (> 400,000 annually worldwide)[1]; however, in spite of the overall trend toward decreasing the use of stents, femoropopliteal in-stent restenosis (ISR) remains a frequent and recurrent problem. Between 30% to 40% of patients will present with ISR after initial stent implantation and, of those, 65% will return with recurrent ISR after treament.[2] Along with current ISR solutions such as laser atherectomy, the development of drug-coated balloons (DCBs) has expanded the available treatment modalities. Additionally, the ability to potentially combine these treatments provides a new opportunity to improve outcomes in ISR.

Endovascular procedures such as balloon percutaneous transluminal angioplasty (PTA; with or without stenting) can produce trauma including vessel stretching, removal of endothelium, rupture of the internal elastic lamina, and medial injury. Vessel injury results in vessel recoil, negative remodeling, and development of neointimal hyperplasia. All of these processes continue to develop over time and eventually lead to the formation of a complex restenotic lesion with an underlying morphology that is distinct from de novo lesions.[3] ISR lesions are heterogeneous, consist primarily of a hydrated collagen matrix (60% to 80% of the restenotic volume is aqueous), and present a higher restenosis burden (Figure 1). Angiographic characteristics of femoropopliteal ISR lesions are also an important predictor of subsequent outcomes. Tosaka et al described angiographic patterns of ISR specific to the femoropopliteal segment: short, focal lesions (class I: ≤ 50 mm) and diffuse lesions (class II: > 50 mm) are associated with reasonable patency after treatment; however, total in-stent occlusions (class III) often predict recurrent ISR when treated with PTA (85% recurrence at 2 years).[2] This confirms the inadequacy of simple balloon dilation and the need for more advanced endovascular techniques. Additionally, removing as much of the stenosis as possible during the initial treatment of ISR may be an important step toward improving patency and reducing the risk of recurrent ISR.

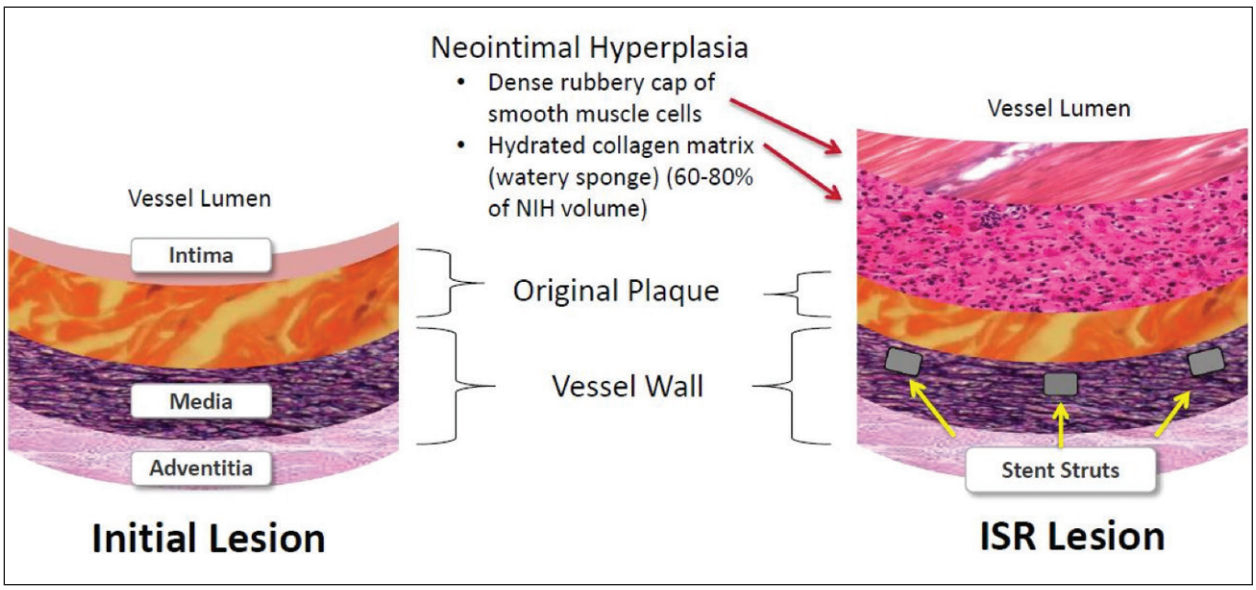

Figure 1. Morphology of ISR versus de novo lesions.

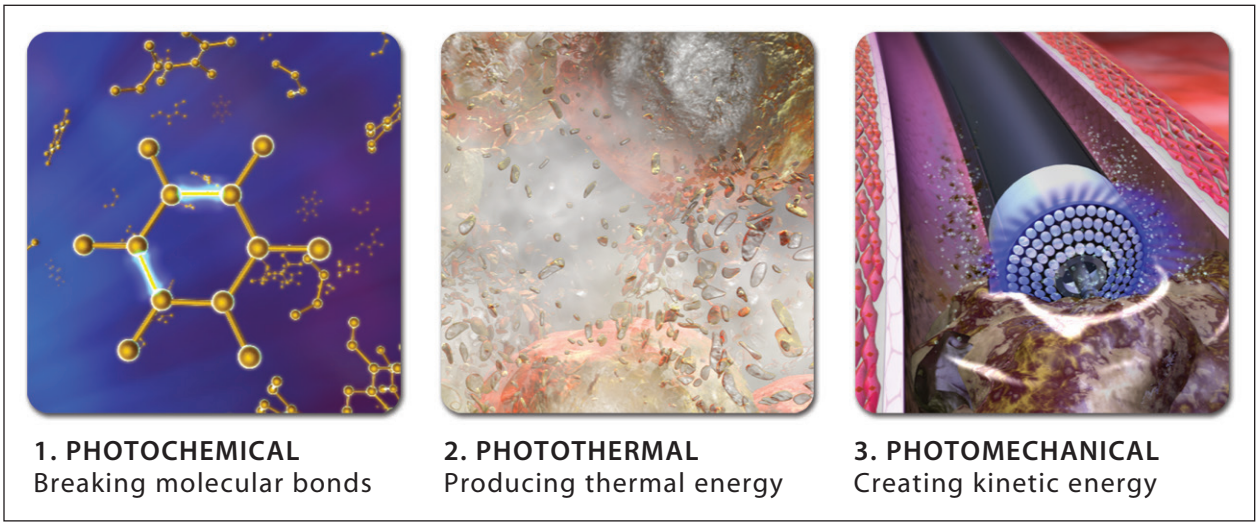

Figure 2. Excimer laser mechanisms of action.

USE OF LASER ATHERECTOMY IN TREATING ISR

Laser atherectomy works through photoablation, which is the use of light to break down and vaporize matter. Three distinct mechanisms of action contribute to laser photoablation (Figure 2) and the debulking/modification of plaque.

There are many unique benefits to the use of laser atherectomy in ISR, such as the ability to recanalize the vessel and debulk/modify plaque while avoiding interference with stent struts and reducing complications. Several studies support the safety and efficacy of the device in ISR, with results from the EXCITE ISR trial being the most recently published.

The EXCITE ISR trial was a prospective, multicenter, randomized study evaluating the effectiveness of an excimer laser with adjunctive PTA versus PTA alone for the treatment of femoropopliteal ISR.[4] The study enrolled 250 patients (169 laser plus PTA vs 81 PTA) with a mean lesion length of > 19 cm. Patients treated with laser plus PTA had superior procedural success (93.5% vs 81.7%), significantly fewer procedural complications including fewer dissections (7.7% vs 17.2%) and bailout stenting (5.3% vs 16%), greater freedom from target lesion revascularization (TLR) at 6 months (73.5% vs 51.8%), a 52% reduction in TLR (hazard ratio, 0.48; 95% confidence interval, 0.31–0.74), and a lower rate of major adverse events (5.8% vs 20.5%). Additionally, the benefits of laser plus PTA over PTA alone were proportionally better in longer lesions (> 25 cm). At 12 months, excimer laser atherectomy (ELA) and PTA was associated with a 43% reduction in TLR. Additionally, subanalysis of a subset of complex lesions (TASC C/D) revealed improved freedom from TLR at 12 months after treatment with ELA and PTA as compared with PTA alone (47% vs 24.5%; $P < .002$).[5] These data demonstrate that ELA and PTA is safer and more efficacious than PTA alone and highlights the ability of the excimer laser to improve outcomes in long, complex lesions. The ability of the laser to ablate and remove neointimal hyperplasia is ideally suited for the creation of a clean channel, which can accommodate subsequent complementary treatments as needed.

CASE STUDY

A 78-year-old man with in-stent occlusion of the right superficial femoral artery receives excimer laser debulking therapy with an adjunctive DCB (6 mm X 12 cm, Stellarex, Spectanetics Corporation) angioplasty (Figure 3).

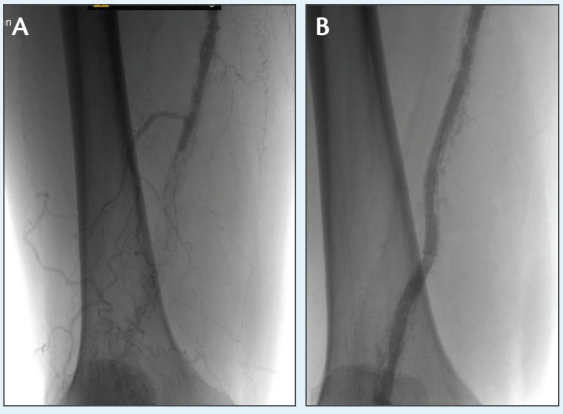

Figure 3. Prior to treatment (A). After laser and DCB treatment (B).

TABLE 1. OUTCOMES FOR LASER, DCBs, AND THE COMBINATION IN TREATING FEMOROPOPLITEAL ISR

Study (ordered by mean lesion length)	Treatment	Patients (n)	Lesions (n)	Lesion Length (cm)	Primary Patency			Freedom From TLR		
					6 months	12 months	24 months	6 months	12 months	24 months
FAIR[8]	PTA	57	57	8.1	55.3%	37.5%	–	81%	52.6%	–
	DCB	62	62	8.2	84.6%	70.5%	–	96.4%	90.8%	–
Virga/ Stabile[9,10]	DCB	39	39	8.3	–	92%	70.3%	–	92%	78.4%
DEBATE-ISR[11]	PTA	44	44	13.7	–	28%	–	–	69%	–
	DCB	42	42	13.2	–	81%	–	–	86%	–
van den Berg[12]	Laser + DCB	14	14	13.3	–	100%	91.7%	–	100%	92.9%
EXCITE ISR[4,5]	PTA	81	81	19.3	–	–	–	51.8%	41.7%	–
	Laser + PTA	169	169	19.6	–	–	–	73.5%	53.8%	–
Gandini[13]	DCB	24	24	23.3	58.3%	37.5%	–	–	50%	–
	Laser + DCB	24	24	20	91.7%	66.7%	–	–	83.3%	–

USE OF DCB IN TREATING ISR

DCBs have been well proven in short, femoropopliteal, de novo lesions with long-term patency.[6,7] Several studies have also evaluated the use of DCB in the treatment of superficial femoral artery ISR (Table 1).[4,5,8-13] However, not all ISR lesions are equal, and not all respond to treatment with DCBs evenly over the long-term. For example, a prospective noncontrolled study conducted by Virga et al[9] showed a 2-year patency rate of 70.3% and a 1-year patency rate of 92.1%, drawing into question the long-term effectiveness of DCB treatment in ISR. The DEBATE-ISR study is currently one of the only series to report safety and efficacy of DCBs in femoropopliteal ISR out to 3-year follow-up.[14] A benefit of DCB treatment in primary patency and freedom from TLR at 1- and 2-year follow-up was observed. However, a catch-up phenomenon was observed at 3 years, and the results demonstrated that treatment of more complex ISR lesions (Tosaka class III) was associated with an increased rate of TLR regardless of treatment with PTA or DCB. Although DCBs may provide an efficient treatment of short ISR lesions, they may lack long-term durability in more complex lesion subsets.

COMBINATION THERAPY (LASER PLUS DCB) IN TREATING ISR

Both DCB and laser show superiority to PTA at 1 year as stand-alone therapies; however, the benefit may be further improved overall, beyond 1 year and within complex subsets (occlusive/long ISR lesions). Recently, early results from a preclinical animal model of ISR chronic total occlusions demonstrated that laser debulking with adjunctive DCB produced overall better lumen quality compared to DCB alone.[15] The pilot study also showed that laser plus DCB resulted in a greater reduction in stenosis and intimal thickness, confirming the feasibility of successful DCB outcomes after revascularization with laser atherectomy. This interesting observation in animals is consistent with the available clinical data. For example, in a single-center, randomized trial of 48 patients, the combination of laser and DCB was compared to DCB alone in the treatment of complex ISR.[13] All of the patients had chronic limb ischemia and presented with long, occlusive, ISR lesions (> 20 mm; Tosaka class III). Along with improved primary patency in the laser plus DCB group (66.7%) versus DCBs alone (37.5%), the study demonstrated a significant reduction of TLR and major adverse events and improved wound healing at 12 months.

In a small case series of 14 patients (mean lesion length, 13.3 cm), van den Berg et al demonstrated the potential for the long-term durability of treatment with a laser in combination with DCB with patency rates of 100% and 91.7% at 1 and 2 years, respectively.[12] Additionally, the time to TLR after laser and DCB (one TLR event observed at 3 years) was significantly

better compared to initial treatment with PTA (mean time to TLR after PTA treatment was 8 months).

CONCLUSION

DCB angioplasty is an efficient treatment of short ISR lesions, but it may lack long-term durability in more complex lesion subsets. Early data suggest debulking and modifying the plaque before DCB treatment seems to be of key importance in more complex ISR lesions, such as Tosaka class II and III. Additionally, DCB application suffers from the same procedural limitations as PTA, including dissection and residual stenosis necessitating bailout stenting. As reported in EXCITE ISR, laser treatment provides a significant procedural advantage to PTA alone. Indeed, initial evidence suggests that laser plus DCBs is the right combination to achieve superior and more durable results in ISR treatment while avoiding additional stent layers, and the greatest benefits seem to be observed when the combination is applied in long, occlusive ISR lesions. ■

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