

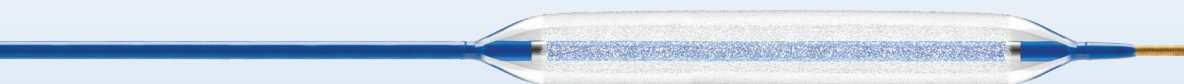
# Endovascular

## TODAY

**EUROPE**

Volume 3, No. 4

## The Next Generation of Drug-Coated Balloons



# MORE

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WHERE **COATING STABILITY** AND  
**TRANSFER EFFICIENCY** INTERSECT

# Not All DCBs Are Created Equal

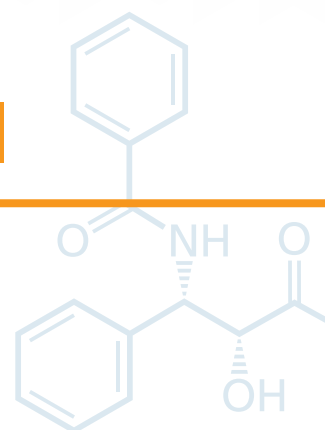
**stellarex**™  
Drug-coated  
Angioplasty Balloon

## ENDURACOAT™ TECHNOLOGY

Spectranetics' proprietary EnduraCoat™ Technology limits drug loss during transit and facilitates efficient drug delivery with a

low-dosage density of

$2 \mu\text{g}/\text{mm}^2$



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Clinicians want to have an effective drug-coated balloon (DCB) that is flexible and has good trackability and pushability to be delivered to the lesion. In addition, particulate embolization and loss of drug in transition are important factors that should be minimized. Arterial healing also plays a key role because in some patients, it may be necessary to shorten dual-antiplatelet therapy. If the same level of efficacy can be delivered with less drug, that would certainly be helpful, but this needs to be proven.

Not all DCBs are created equal. In general, paclitaxel-coated balloons offer the greatest efficacy so far, and there seems to be agreement that balloons with excipient coating technology offer greater efficacy. Within this group, however, there is tremendous variability with respect to efficacy in drug transfer, drug loss, and particulate.

The crystallinity of the coating plays a very important role in paclitaxel-coated balloons and the uniformity of drug coating. The higher the crystallinity, the greater the drug uptake for DCBs. Small- to medium-sized paclitaxel crystals stick to the injured vessel surface and continuously release paclitaxel over time into the underlying tissue.

With regard to how the coating technology affects durability, many factors are involved, such as the drying process, coating on a folded versus an inflated balloon, crystallinity, ultrastructure, etc.

To improve restenosis rates, the drug should remain resident in the tissue for at least 3 months, and the most important factors that seem to improve or worsen drug residency in the tissue are the level of crystallinity and the degree of injury. ■



# MORE

With Less

## 89.5%

primary patency at 12 months\*

## 80.3%

primary patency at 24 months\*

*“Not all DCBs are created equal. The final formulation on the surface of the balloon depends on many factors—not just the paclitaxel, but the way it is combined with the carriers, as well as processed to be put on the coating.*

*— Juan F. Granada, MD, FACC ”*

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*— Michael Joner, MD*



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Drug-coated balloons (DCBs) essentially function via the passive transfer of paclitaxel into the vessel wall by means of a carrier that helps the transportation of paclitaxel from the surface of the balloon to the vessel wall. Then, the paclitaxel particles that adhere to the vessel wall are responsible for the drug-tissue concentrations over time.

One challenge in the effectiveness of this approach is that although some of the drug goes into the vessel, there is an important degree of drug loss into the bloodstream. At present, the potential biological effect of the drug lost downstream is unknown. However, an important attribute for DCB technologies is having a consistent dose—that is, a coating that is stable on introduction into the human body that provides a precise percentage of transfer into the vessel wall and achieves a long-term pharmacokinetic profile to prevent restenosis.

### FORMULATIONS AND COATING CHARACTERISTICS

Not all DCBs are created equal. The final formulation on the surface of the balloon depends on many factors—not just the paclitaxel, but the way it is combined with the carriers, as well as processed to be put on the coating. Similarly, not all paclitaxel coatings are the same. Some are more soluble than others, and some are more crystalline. All of these important differences in coating characteristics provide specific pharmacokinetic and efficacy profiles in patients.

I believe coating characteristics are the most important aspect of DCBs. One big difference between DCBs and drug-eluting stents is that in the latter, the medication is encapsulated inside of a polymer, and its release is precisely titrated over time. In drug-eluting stents, the biological

effect relies on the principle of drug release that is known and predictable via the polymeric surface. The pharmacokinetics in DCBs depend on two things: (1) a proper amount of drug transfer at the time of balloon inflation, and (2) an appropriate distribution and retention of the drug over time. Characterization of the coated surface is essential in helping us determine which types of DCBs have the attributes that achieve the desired clinical effects.

The first DCB concepts were created with a combination of iopromide, which is a contrast agent, and paclitaxel. Iopromide was intended to help carry the drug into the vessel wall. But, we very quickly found out that although this combination produced a highly crystalline coating that was extremely effective in transferring the drug into the vessel surface, the coating was also brittle and fragile.

Industry has since attempted to balance the crystallinity such that the tissue penetration levels can be maintained over time while decreasing the potential for embolization and improving the consistency of the coating. I believe that a certain degree of crystallinity is important in achieving a biological effect. There are absolute differences in drug residency between the different DCBs, and the pharmacokinetic profiles of clinically available devices also appear to be different. But, acute transfer is more important than long-term drug retention.

## MEETING ANATOMY- AND LESION-SPECIFIC CHALLENGES

We now have a significant amount of clinical data gathered regarding local drug delivery technologies in both the coronary and peripheral vasculatures. For polymer-based coronary drug-eluting stent applications, industry typically designed technologies to maintain drug presence in the tissue for anywhere from 45 to 60 days; this is a curve that is reproduced for paclitaxel-based technologies in the peripheral territory. However, due to the unique biological differences encountered in each setting, we must be careful in designing peripheral vascular technologies based on knowledge gathered in the coronary field. I would still estimate that anywhere between 45 and 60 days of resi-

dency time—but perhaps longer—would be needed for a paclitaxel-coated balloon to work in the peripheral space.

At the experimental level, the absence of plaque, atherosclerosis, and calcium is the best-case scenario. It is difficult to extrapolate those lessons into the human clinical arena.

Although most research has been performed for above-the-knee arterial disease in claudicants, I believe there is even more of a need and role for DCBs in below-the-knee disease in patients with critical limb ischemia. The unmet clinical need is even higher, and the clinical impact would be greater for below-the-knee disease, in which the options are currently limited. However, this is a very different vascular territory: the disease behavior is very aggressive; there is often significant calcium; and there is a large burden of disease. Usually, these vessels are as small as coronary arteries, but they are much longer and slower in blood flow. Critical limb ischemia is a unique clinical scenario with a very different biological makeup, so, similar to the caution we must take in applying our coronary understanding in the periphery, we must be careful in extrapolating the knowledge we have obtained in the superficial femoral artery into below-the-knee therapy.

Accordingly, the technical approach will also be anatomy-specific. There may be more need for vessel preparation with ancillary devices, such as atherectomy and others, and the balloons used will likely need to be simultaneously longer and smaller in diameter. There is a significant potential for DCB use in below-the-knee disease, but it must be approached with the right technology and formulation. There is the potential risk of distal embolization, which is compounded in the presence of limited vessel runoff and tissue loss, so we must be careful in evaluating each technology with regard to the specific challenges of the below-the-knee vascular territory.

At present, this application requires significant clinical evaluation, but these are a few of the important considerations for companies developing these technologies. Efforts must be focused on addressing drug dosing, coating stability, and transfer efficiency in this challenging environment. ■

# Drug-Coated Balloons: The Road Ahead

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



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## Do the drug-coated balloon (DCB) clinical data to date lead you to believe that there are differences between DCB technologies, or do DCBs perform consistently as a class?

**Dr. Tepe:** I think there is a difference between DCBs; there is no class effect, and there are balloons that are going to perform better than others. There are also some balloons that don't seem to work at all. I think this is very important to note; it might be that some of the DCBs have good results at 6 months, or at least some effect, but in the long term, say 1 to 3 years, they are not doing any better than any control group. So, there is a difference.

**Dr. Rocha-Singh:** Given the available peer-reviewed data, and understanding that the inclusion and exclusion criteria in the two largest RCTs (LEVANT 2 and IN.PACT ADMIRAL) were fairly similar, I believe that there is no class effect, and additional data with longer-term follow-up on the durability of the DCB effect will bear this out. We need only look at the emerging additional data from the IN.PACT DEEP Amphirion CLI trial as an example. In the end, this trial failed due to the fundamental failure of the DCB used in the trial. The Amphirion balloon

(Medtronic plc), when compared to the same manufacturer's SFA platform, showed that differences in the coating methodology (ie, applying the paclitaxel to the balloon in its deflated configuration), although resulting in the same amount of total drug on the balloon, had a drug distribution that was nonuniform and dissimilar from the In.Pact Admiral coating process. Perhaps more importantly, the different balloon materials had very different balloon "surface energy," meaning the Amphirion balloon material retained paclitaxel with substantially more affinity than the In.Pact Admiral balloon material. These two differences resulted in the discrepant findings published from the two trials and underscore how a class effect cannot be assumed.

Additionally, I believe that when the two FDA-approved DCBs get into more general use, we will observe several things that will cause all of us to pause. First, the crossover rate to stenting is not going to be less than 5%. Physicians will use these products outside the inclusion criteria, may not predilate the lesion, and will use them in longer chronic total occlusions and de novo lesions; this will drive provisional stenting in these patients and affect the cost equation of device use.

Second, with regard to severe circumferential vascular

calcification, while such lesions were to be excluded in the two regulatory trials, I believe they were enrolled by investigators and, when analyzed further, their clinically driven target lesion revascularization (TLR) rates through 12 months will be higher than the clinically driven TLR rates in noncalcified lesions.

**Dr. Micari:** Oh, yes, definitely. I strongly agree that there is no class effect in the DCB technology because, while I think that the effects of paclitaxel are quite the same for all the balloons within the market, there is a great difference in the technology.

### What lessons have been learned from the studies of first-generation DCBs?

**Dr. Micari:** All we have learned from first-generation DCBs should be reappraised in the light of second-generation DCB technologies and clinical data. It is quite a similar story for drug-eluting stents in the coronary arena; if you consider the first-generation drug-eluting stents, of course, they are not comparable with the newer generation in that second-generation stents normally showed important improvement over their predecessors. Ultimately, all lessons build upon (originate from) robust clinical programs, which is what second-generation DCB manufacturers should continue to commit to.

I think this field of drug-combination devices progresses in step-by-step increments and, as much as first-generation DCBs showed very encouraging data (some backed by robust randomized trials), I expect new-generation DCBs to deliver the same or better clinical results while relying on refined coating technologies with lower drug load, higher coating stability, and improved drug transfer efficiency.

**Dr. Tepe:** DCBs are safe. I have not heard, at least in the SFA, of any side effects attributed to a DCB that caused major problems. Also, most of the studies have shown that DCBs are effective. It is also very important to note that if you compare studies, the patient cohorts are different; sometimes, there are longer lesions, sometimes shorter lesions, and sometimes more calcified lesions, so it's very difficult to compare. But, such a comparison does reveal that there are differences.

**Dr. Rocha-Singh:** I think there may have been a rush to market whereby specific clinical issues have not been adequately addressed in the preclinical animal models, and I am again referring to calcium. The FDA only requires you to look at safety and effectiveness and understand the preclinical science as it relates to safety. However, industry has not invested in the development

of a preclinical in vivo model of vascular calcification, and relies on cadaver models.

There is an evolving concern that higher grades of vascular calcium may impact the paclitaxel elution into the vessel wall and affect the clinical durability of DCBs. We have already seen preliminary, hypothesis-generating data from the DEFINITIVE AR trial, which in post hoc assessments presented by Prof. Thomas Zeller,<sup>1</sup> would lead one to consider the use of atherectomy prior to DCB use as a potential method to address this perplexing issue. Of course, we do not have clear signals that this is a validated method. Unfortunately, I suspect clinicians and industry marketing folks may not wait for such data before advocating its use.

But I can tell you that the problems of severe calcification, given the epidemic of diabetes, are not going away, and we need to start designing relevant trials to address this hypothesis.

### There has been an evolution of clinical endpoints associated with DCBs. Early studies focused on late lumen loss, and newer studies are focused on primary patency or TLR. What clinical outcomes do you look at to make informed treatment decisions?

**Dr. Tepe:** The first studies were done with a late lumen loss only to see if there was a treatment effect. The endpoints are restenosis, which is patency and TLR, and for claudicants, it's walking distance and TLR—especially because what we prevent with DCBs is restenosis, and restenosis then transforms into the TLR rate.

Nevertheless, it has to be stated that unlike late lumen loss, TLR is not such an independent point that it cannot be influenced based on patients' symptoms because (1) we do not perform PTA on a patient with no symptoms, and (2) some patients are fine with a walking distance of 150 meters, whereas others are not.

**Dr. Micari:** Endpoints in clinical trials should focus on the true clinical impact of any specific therapy on that specific disease. Particularly for claudication, metrics such as walking distance and quality of life, besides target lesion and target vessel revascularization, indeed describe what matters the most for patients. Critical limb ischemia is a totally different disease in which functional limb preservation is the most important goal. That said, vessel patency remains a similarly important revascularization metric that needs to be rigorously measured and reported in device trials of both claudication and critical limb ischemia. The correlation between patency and patient-relevant endpoints, in fact, can only be assessed when both variables are taken into account and rigor-



ously measured. Moreover, other “extravascular” variables, such as medical therapy or wound healing, should also be taken into account, controlled for, and carefully measured because they affect the final clinical outcome. If they are not properly assessed, they end up being confounding factors.

**Dr. Rocha-Singh:** I think these issues of surrogates of late lumen loss relate more to getting at an assessment of the adequacy of the therapy. I’m more interested in patient-centric endpoints. I think we have to start putting these claudicants on a 6-minute walk test, minimally. I believe we must also call into question binary restenosis and its correlation to clinically driven TLR. I would suspect that the peak systolic velocity may be a superior surrogate than simple binary restenosis. Finally, we MUST follow and publish longer-term clinical data in claudicants. The 1-year time frame is an established and accepted regulatory endpoint; if 2- and 3-year adjudicated data reflect a substantial loss of durability, that will be difficult to defend.

### Which data had the most impact on your use of DCBs?

**Dr. Rocha-Singh:** Understanding the established differences between the currently available drug-eluting platforms, I believe that there may be reasons to interpret the effectiveness of one balloon to be potentially superior to the other, appreciating the differences in trial inclusion/exclusion criteria. There are multiple variables that should be noted that may account for the prevailing opinion that no “class effect” was evident between platforms; these include the balloon-coating technologies and excipients and our understanding of the potential differences in balloon surface energy that allows the elution of the drug off of the balloon surface and into the arterial wall, etc.

In reviewing data presented at Bard’s FDA panel, which is available to the public, I am concerned by the drop-off in vessel primary patency when the 30-day window past the prespecified 365-day endpoint (ie, 13 months) is analyzed. When intervals are compared, the drop-off in patients extended out to 13 months comes close to that of angioplasty.

As such, we are left to question the durability of this therapy as we await the 2-year data, which will better assess the durability of this technology. Importantly, a similar decline, although not to the same extent, was observed in the ADMIRAL data. Documentation of the clinical durability of this new technology beyond 1 year will be very important in order to substantiate the added financial expenditures.

**Dr. Tepe:** I had the honor of using the first DCBs ever used in clinical practice. The first result of this balloon was very important to me because the follow-up angiograms at 6 months or 1 year looked even better compared to the postintervention results. There’s a kind of imprint of the DCB where the balloon was inflated. This was most impressive to me, and it translates into the current studies. What I’m currently looking at first is, of course, clinical results: the TLR rate and patency rate. I also look at how a study is done. But I also can look at the images, and if I see a 6-month angiogram with a positive remodeling effect compared to the postintervention imaging, I know that the DCB is going to work.

**Dr. Micari:** After the initial promising signals from proof-of-concept trials (THUNDER and FEMPAC), I led one of the very first large DCB multicenter registries on patients with claudication and rest pain due to SFA disease, characterized by a systematic and rigorous assessment of functional endpoints.<sup>2,3</sup> We demonstrated that the use of DCBs not only can translate into excellent patency rates at 1 and 2 years, but also showed that patency preservation was associated with a significant clinical benefit that was well-perceived by the patient, as measured by quality of life and absolute claudication distance improvements. These are the important lesion-based, and more importantly, patient-functional endpoints that matter to me.

### Have any predictors for restenosis been identified either in your experience or in clinical studies, and how do you treat patients with these predictors?

**Dr. Micari:** In our registry, predictors of restenosis were searched for but not identified, which is not surprising because this was still a relatively small population for that scope. In general, DCB-specific predictors have not been rigorously studied or found so far. However, we may expect diabetes, long lesions, and calcium to reduce the therapeutic effect of DCBs even though this technology may continue to be superior to plain balloons or bare-metal stents in these settings.

**Dr. Tepe:** There are some predictors of restenosis after DCB treatment that can be changed and others that cannot. In the retrospective study that I have done, I have seen that diabetes affects restenosis rates. Also, as compared to use in de novo stenoses, DCB use in restenosis has not met the same level of results.

In general, DCBs perform better than uncoated balloons, even in this difficult patient cohort. Nevertheless, these risk factors for restenosis cannot

be modified. In contrast, there are other circumstances that might be modified before DCB therapy, such as calcium, which is also a predictor of less favorable outcome. An artery that is heavily calcified is also something that cannot be easily treated with a DCB compared to other lesions. However, unlike other outcome predictors, calcium can be modified. You can use either atherectomy or a cutting balloon to prepare the vessel for drug uptake.

**Dr. Rocha-Singh:** My primary concern relates to the issue of vascular calcification and its severity and location (intimal, medial, or both). This was and continues to be a prespecified exclusion criterion in United States regulatory DCB trials. The CTA-based evaluation by Fanelli et al.<sup>4</sup> of the clinical impact of various degrees of circumferential SFA calcification on de novo lesions of various lengths was small ( $n = 60$ ) and unadjudicated, but it certainly defines a concern for a potential mode of failure of this new technology.

These findings will also, intentionally or unintentionally, drive the unproven hypothesis that “vessel preparation” with atherectomy prior to DCB use will favorably affect the clinical results in severely calcified SFAs. Unfortunately, as we proceed down this path of “vessel preparation,” I am uncertain as to whether there are sufficient data to guide physicians as to which of the five commercially available atherectomy devices is the most efficient and safe at debulking calcified atheroma. In this regard, I believe there is fertile ground for clinical research.

### Do known failure modes exist for DCBs? If so, what are those failure modes?

**Dr. Tepe:** The one major failure mode is when a DCB does not transfer enough drug into the vessel wall,

resulting in an effect similar to an uncoated balloon. What is important is not how much drug is on the surface of the balloon, but rather how much drug really gets into the vessel wall and stays there for some time. The use of a so-called spacer that makes the drug adherent to the balloon and then also allows for good delivery to the vessel wall is also very important. This differs from DCB to DCB. The major failure mode of a DCB is that, even if there is enough dose on the surface of a balloon, there is an underdosing in the vessel wall. This underdosing does not give a result that is any different from plain-old balloon angioplasty.

**Dr. Rocha-Singh:** Unfortunately, we are challenged by the simple fact that we do not have a unified, validated definition of calcium severity in the peripheral vasculature. However, work to establish such a calcium grading scale is actively ongoing.

Given this, we do know that patients with “severe” calcium have been enrolled in DCB trials; however, these numbers were small, and we have not been provided with any angiographic follow-up of this cohort to see if there are any adverse clinical trends associated with the presence of severe calcium.

**Dr. Micari:** Severe calcium probably represents a barrier to optimal drug elution into the media. Particularly in the presence of full circumferential calcium (360°), the expected biological effects of the drug may be reduced, as demonstrated by the small study by Fanelli et al.<sup>4</sup> ■

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# The ILLUMENATE Clinical Program

Demonstrating the efficacy of the Stellarex™ drug-coated balloon.

BY HENRIK SCHRÖDER, MD



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Recently published data from the ILLUMENATE first-in-human (FIH) study<sup>1</sup> are promising, and more and equally robust clinical trials are well underway to assess the safety and effectiveness of the Stellarex™ drug-coated balloon (DCB; Spectranetics Corporation).

## ILLUMENATE FIRST-IN-HUMAN STUDY

The purpose of the ILLUMENATE FIH study was to assess the safety and effectiveness of the Stellarex™ DCB to inhibit restenosis in the superficial femoral (SFA) and/or popliteal artery. ILLUMENATE FIH was a prospective, single-arm, multicenter study with independent adjudication by angiographic and duplex ultrasound core laboratories (VasCore). The study was composed of two sequentially enrolled patient cohorts. In the first 50-patient cohort, lesions were treated with traditional predilatation with an uncoated angioplasty balloon prior to inflation of the DCB. In the second 30-patient cohort, lesions were treated by direct DCB application without predilatation.

The primary efficacy endpoint was 6-month late lumen loss, as determined by the angiographic core laboratory. The major secondary endpoint was major adverse event rate at 6 months, which was defined as cardiovascular death, amputation, and/or clinically driven target lesion revascularization (TLR).

In the first cohort (the predilatation group, n = 58 lesions), the mean lesion length was 7.2 cm, and baseline stenosis was 75.1%. Calcification was present in 62.1% of lesions, and 12.1% were occluded. Both endpoints met their prespecified performance goals: At 6 months, the major adverse event rate was 4%, and the mean late lumen loss was 0.54 mm. The Kaplan-Meier estimate of primary patency, as determined by the duplex ultrasound core laboratory was 89.5%<sup>i</sup> at 12 months and 80.3% at 24 months, whereas freedom from clinically driven TLR was 90.0%<sup>ii</sup> at 12 months and 85.8% at 24 months. Additionally, there were

no amputations or cardiovascular deaths reported through 24 months (Figure 1).

These promising results instill high confidence in this second-generation DCB technology, which is set to further advance the treatment options for patients with peripheral artery disease. When these results are reviewed in context with other multicenter DCB trials reporting primary patency rates by duplex core lab adjudication, ILLUMENATE FIH compares favorably.<sup>2,3</sup> These promising long-term findings suggest that the Stellarex™ coating is the right formulation that balances deliverability with durability and transfers an effective amount of the antirestenotic drug to the treatment site.

## ECONOMIC IMPACT

The economic implications of durable results are at the forefront of everyone's minds as the prevalence of peripheral artery disease increases and medical costs rise.

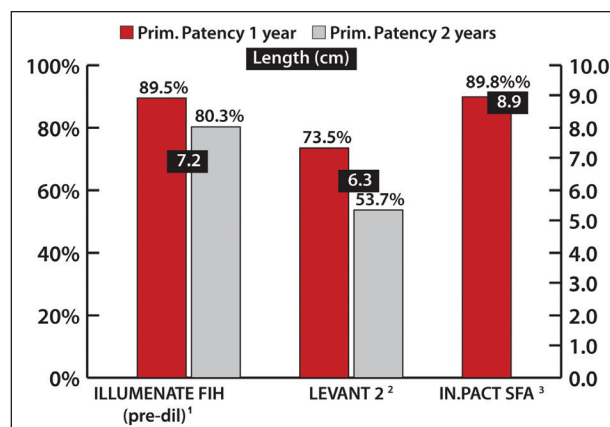


Figure 1. Primary patency rates at 1 and 2 years (when available) across three multicenter DCB studies with the same duplex ultrasound core lab and duplex-derived peak systolic velocity ratio threshold ( $\leq 2.5$ ).

<sup>i</sup>The primary patency rate was 89.5% at day 365 and 87.7% at day 395, the upper end of the follow-up window. The primary patency rate was 80.3% throughout the 24-month follow-up window (at day 730 and day 760).

<sup>ii</sup>The freedom from clinically driven TLR was 90.0% at day 365 and 87.9% at day 395, the upper end of the follow-up window. The rate was 85.8% throughout the 24-month follow-up window (at day 730 and day 760).



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It doesn't surprise me that the 2-year patency rate of 80.3% compares favorably to other drug-coated balloon (DCB) data. This shows that the amount of paclitaxel that is on the surface of the balloon does not play such a major role, and that the outcome depends on what is imbedded in the vessel wall. We know that with a lot of products, up to 20% of the drug at maximum is getting to the vessel wall; most of the drug is either washed off or stays on the balloon. The total drug dosage on the balloon is not the major driver. The amount of drug that reaches the vessel wall is the ultimate driver of success. The delivery is more precise and better if you can decrease the amount of drug coating on the balloon

compared to other balloons.

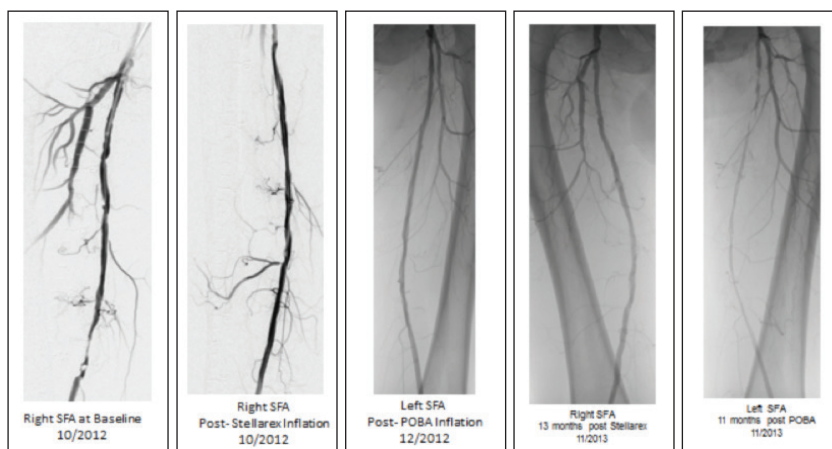
I think what is very important, and which might differentiate one DCB from another, is what the curve concerning target lesion revascularization and restenosis looks like compared to other products.

It is important to look at the long-term (12 month or 2 year) patency and target lesion revascularization rates in DCBs because, in a balloon that doesn't work as well, there might be good results in the short term but a falloff in the long term and no durable results. Therefore, it's very important to have that good long-term result and, if nothing happens between 12 and 24 months, that is really a good sign.

Data from the ILLUMENATE FIH and historical plain-old balloon angioplasty (POBA) data were used to construct a budget impact model through 2 years.<sup>1,2,4,5</sup> The model was based on the total cost of the baseline procedure plus revascularizations (determined by clinically driven TLR rates). Costs for the baseline procedure and clinically driven TLR were assigned to both groups using the 2013 German G-DRG reimbursement tariffs. The budget impact model demonstrated cost advantages for Stellarex™ through 24 months. At 12 months, a patient treated with Stellarex™ cost ~€450 less than with PTA (€3,575 vs €4,027); at 24 months, the difference increased to €741 (€3,668 vs €4,409). Extrapolated to 25,000 patients with peripheral artery disease, the use of Stellarex™ has the potential to save the health care system more than €11,000,000 at 12 months and more than €18,500,000 at 24 months. The number of patients treated with Stellarex™ (compared to PTA) to prevent one TLR was four at 12 months and three at 24 months.

An interesting element of the ILLUMENATE FIH study was the previously mentioned "direct cohort," in which lesions were treated without predilatation. Twenty-eight patients with 37 lesions were included in the direct DCB cohort analysis; two

patients were excluded because they were predilatated. The mean lesion length was 6.4 cm, and calcification was present in 48.6% of lesions. At 6 months, the mean late lumen loss was 0.08 mm, indicating a good drug effect. However, the primary patency rate was 77.5% at 12 months,<sup>iii</sup> which was lower than the 89.5% observed in the predilatation cohort. The freedom from the clinically driven TLR rate, per Kaplan-Meier estimate, was 85.4% at 12 months.<sup>iv</sup> The lower patency and freedom from TLR rates in the direct cohort can partially be explained by two TLRs



**Figure 2.** Angiograms of a 50-year-old male patient with claudication due to bilateral SFA disease. He had two lesions in the right SFA treated with the Stellarex™ DCB. The left SFA was subsequently treated with an uncoated angioplasty balloon. Approximately 1 year later, the lesions treated with Stellarex™ were patent, and the POBA-treated lesion was reoccluded.

<sup>iii</sup> The primary patency rate was 77.5% throughout the 12-month follow-up window (at day 365 and day 395).

<sup>iv</sup> The freedom from clinically driven TLR rate was 85.4% throughout the 12-month follow-up window (at day 365 and day 395).



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Regarding cost effectiveness of treatment using DCBs, it is essential to know that not every DCB performs the same. There are elementary differences in coating technologies, including drug dose and the presence or type of excipient that has an impact on the patients' clinical outcome in terms of freedom from target lesion revascularization. Thus, profound knowledge of the current literature is essential for the appropriate treatment choice.

From the payers' perspective, preserving the acute clinical benefit as long as possible reduces the overall health care costs of the individual patient. This cost effectiveness has been shown up to a 2-year period after the index procedure for the United States, Germany, Switzerland, and the United Kingdom. DCBs have been shown to be at least equally cost effective as drug-eluting stents for femoropopliteal TASC II A and B lesions and superior to bare-metal stents and plain-old balloon angioplasty. The gain in cost effectiveness is related to the reduced TLR rates but also to the more effective and less expensive treatment options in case of a re-intervention.

From the providers' perspective, the situation is different: Cost effectiveness means sufficient reimbursement for the use of a given technology. In the case of DCBs, this means that the price difference between a DCB and a conventional balloon catheter must be covered

by the payer; considering that this means that for an individual patient more than one single DCB might be necessary, and some lesions deserve up front predilatation. On the other hand, physicians are not responsible for reimbursement systems—that's a governmental, health care responsibility—but we are responsible for offering our patients the best possible care. Thus, the aim of the treating physician should be to use the best available technology, including the most effective DCB. Currently, this choice is difficult because no head-to-head comparisons yet exist. However, a valuable guide could be using only devices in clinical practice outside of study protocols that have solid published data or, at least, data from high-quality, multicenter, independently adjudicated trials.

The most relevant data for the payers is a stable clinical follow-up of the patient after the treatment of his or her underlying disease, in case of peripheral artery disease claudication or critical limb ischemia, without rehospitalization or target lesion revascularization. This is the main source of driving costs. Obviously, it would also be of interest if it could be shown that preserved vessel patency and ambulation would result in an extension of survival or a reduction of overall cardiovascular events, and if the patient benefits, in terms of quality of life and in the long term, could be improved.

that were thrombotic occlusions that occurred in two patients who were not compliant with their prescribed antiplatelet medications. It is noteworthy that the rates of postdilatation (35.1% vs 12.1%) and stent placement (8.1% vs 5.2%) were higher in the direct cohort versus the predilatation cohort. These findings suggest a role for predilatation in potentially improving outcomes and lowering the need for permanent implants, thus supporting the value proposition of DCBs.

## ONGOING STUDIES

The ILLUMENATE FIH study is the first in a series of five robust studies that will evaluate the safety and effectiveness of the Stellarex™ DCB in a broader population.

## ILLUMENATE EU-RCT

The ILLUMENATE European randomized, controlled

study will enroll up to 360 patients at approximately 24 sites in the European Union. Subjects with symptoms of claudication or rest pain are being randomized to treatment with the Stellarex™ DCB or a bare PTA balloon catheter for de novo or restenotic lesions in the SFA and/or popliteal arteries. Patients will be followed for 5 years.

## ILLUMENATE Pivotal

The ILLUMENATE Pivotal randomized clinical trial is being conducted at approximately 45 centers in the United States. It is a prospective, randomized, multicenter, single-blind study that will enroll up to 360 subjects with symptoms of claudication or rest pain, with follow-up through 5 years. The study is being led by Dr. Sean Lyden of the Cleveland Clinic in Cleveland, Ohio, and Dr. Prakash Krishnan of Mount Sinai Heart in New York City, New York.

### ILLUMENATE Global

ILLUMENATE Global is a prospective, single-arm, multicenter study that is enrolling patients in Europe, Australia, New Zealand, Canada, and Colombia. All subjects enrolled will undergo treatment with the Stellarex™ DCB and will be followed for 3 years. Prof. Thomas Zeller from Herz-Zentrum Bad Krozingen in Germany is the Global Principal Investigator. The International Principal Investigators are Dr. Yann Goueffic from the Hopital Nord Laennec in France, Dr. Andrew Holden from the Auckland City Hospital in New Zealand, and Dr. Carlos Mena of Yale University in the United States.

### ILLUMENATE PK

ILLUMENATE PK is a prospective, nonrandomized, single-arm, multicenter, pharmacokinetic study that is currently ongoing in New Zealand and is led by Dr. Andrew Holden. All subjects enrolled will undergo treatment with the Stellarex™ DCB and have periodic blood draws to measure the amount of paclitaxel in their blood. The study will enroll 25 subjects.

### CASE REPORT

The angiograms in Figure 2 show an interesting case of

a 50-year-old man with symptomatic (Rutherford class 3) bilateral SFA disease. Two lesions in the right SFA were treated with a direct DCB technique. The 7.9-cm lesion in the mid-SFA and the proximal 5.9-cm lesion were both treated with 5- X 80-mm Stellarex™ DCBs. The left SFA was treated with an uncoated angioplasty balloon. Approximately 1 year later, the artery treated with the Stellarex™ DCB is patent, whereas the artery treated with POBA is restenotic.

We are excited about the data published to date and clinical work that is currently underway. We have a dedicated group of physicians around the world participating in these trials, and we look forward the next wave of data. ■

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## The PANTHER Study

The real-world application of AngioSculpt in calcification. Can vessel preparation with a scoring balloon offset the detriment to patency caused by calcification?

BY ERWIN BLESSING, MD

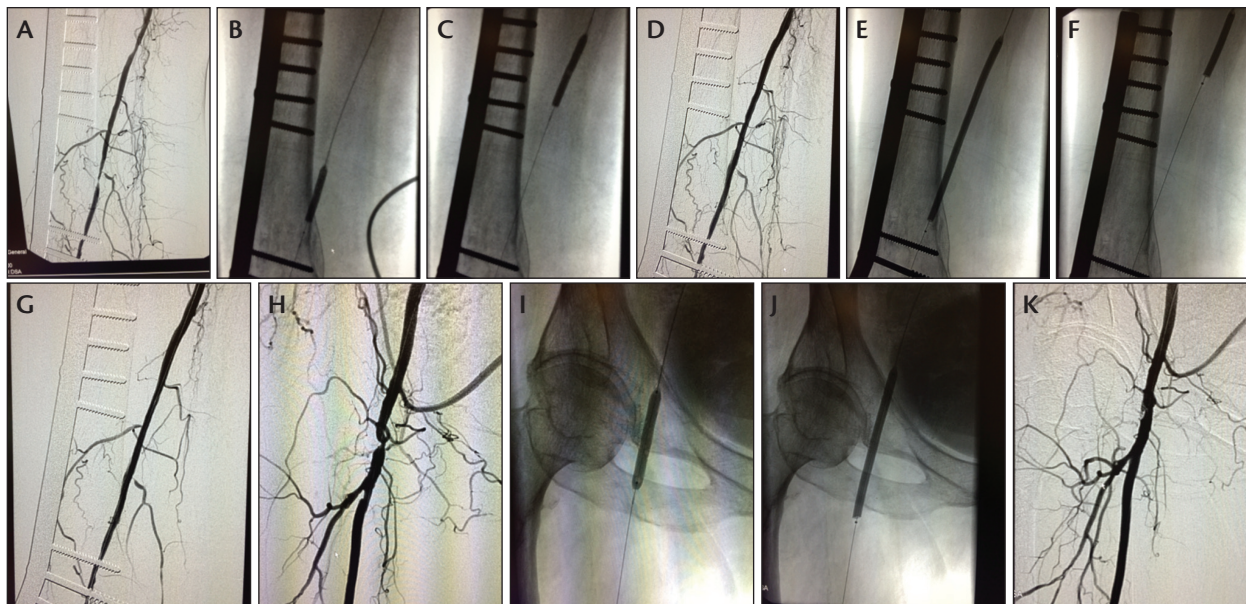


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The impact of arterial calcification has not been well described, but early work suggests that calcification may decrease the effectiveness of drug-coated balloons (DCBs).<sup>1</sup> Fanelli et al assessed 60 patients with de novo superficial femoral artery (SFA) lesions who underwent angioplasty with a DCB.<sup>1</sup> The patients were categorized

into groups based on the length and degree of circumferential calcification present in the treated lesion based on CT angiography axial images. In patients with circumferential (360°) calcification, the patency rate at 12 months was only 50%. Circumferential calcium distribution was a better predictor for loss of patency than longi-





**Figure 1.** Baseline right SFA (A). AngioSculpt® scoring balloon (5 X 40 mm) inflation (B, C). Result after use of AngioSculpt® (D). Stellarex™ DCB (5 X 120 mm and 5 X 40 mm) inflations (E, F). Final result in the SFA (G). Baseline common femoral artery (H). AngioSculpt® scoring balloon (5 X 40 mm) inflation (I). Stellarex™ DCB (5 X 80 mm) inflation (J). Final result in the common femoral artery (K).

tudinal extension of vascular calcification. Because there was no control group treated with standard angioplasty, it remains speculative whether calcification really limits the benefits of antiproliferative therapy or whether calcification generally results in poorer long-term patency.

Is there inadequate penetration of paclitaxel into the media and adventitia? Would preparation of the lesion improve the drug absorption and, therefore, patency in calcified lesions? The PANTHER study was designed in part to address these questions.<sup>2</sup>

## STUDY DESIGN

The PANTHER study enrolled 101 patients with 124 lesions. The majority of patients had hypertension (93.1%), and 34.7% presented with critical limb ischemia. The mean lesion length was  $7.4 \pm 5.9$  cm, and the mean percent diameter stenosis was 85.5%; 16.1% were total occlusions. Calcification was present in all lesions and categorized as mild (21.8%), moderate (34.7%), and severe (43.5%).

An AngioSculpt® scoring balloon (Spectranetics Corporation) was used in each case, but adjunctive use of a bare-metal stent or DCB was at the discretion of the interventionist. In 40 lesions (32.3%), AngioSculpt® use was followed by inflation of a DCB, and in 38 cases (30.6%), a bare-metal stent was placed (Supera™, Abbott Vascular). In 46 lesions (37.1%), stand-alone AngioSculpt®

use was the treatment of choice. At 12 months, the primary patency rate was 81.2%, and the secondary patency rate was 91.8%.

When stratified by calcification severity, there was no discernible difference between the patency rates (mild, 78.9%; moderate, 81.3%; and severe, 81.8%). Within the AngioSculpt® + DCB group, the mean lesion length was 5.9 cm, and 17.5% were chronic total occlusions. The primary patency rate was 83.9% at 12 months. Although limited in size, this study is encouraging for the use of scoring balloons in calcified lesions. Additional studies need to be conducted to define the role of scoring balloons and DCBs, but the future looks bright.

## CASE PRESENTATION

### Vessel Preparation With AngioSculpt® + Stellarex™ DCB

Recently, the Stellarex™ DCB became commercially available, and I have used it in conjunction with the AngioSculpt™ device with good acute outcomes. The patient was a 70-year-old woman with type 2 diabetes mellitus and hypertension. She presented with ischemic ulcers (Rutherford category 5) and a baseline ankle-brachial index of 0.46. Duplex ultrasound confirmed high-grade stenoses in the common femoral artery and distal SFA.

In this case, I used 5- X 40-mm AngioSculpt® scoring balloons to predilate the lesions prior to treatment

with the DCB. For predilatation before DCB use, I recommend undersizing by 1 mm whether using a plain angioplasty balloon or an AngioSculpt® scoring balloon. I followed-up with DCB treatment using the Stellarex™ DCB (Spectranetics Corporation).

During preparation, it is essential that contact with the DCB is avoided, in particular contact with fluid, which could lead to significant loss of the coating. I also believe it is crucial to minimize the time between insertion of the DCB into the sheath and final deployment. I try to keep this time to < 1 minute. It is important to use road mapping and radiopaque rulers to ensure that the final location of the DCB covers the length of the artery that was predilated, which is to say avoidance of “geographic miss.” As far as sizing is concerned, I try to match the DCB diameter to the reference vessel diameter.

In this case, I used two Stellarex™ DCBs (5 X 120 mm and 5 X 60 mm) in the SFA, being careful to adequately overlap the balloons by at least 1 cm. One Stellarex™ DCB (5 X 80 mm) was used in the common femoral artery. An inflation time of 1 minute is the minimum, but I tend to keep the balloon inflated for approximately 3 minutes to ensure good mechanical dilatation of the artery (Figure 1).

The early data that are currently available have excited the medical community about the potential of DCBs. As more complex lesions are included in clinical trials and real-world use data are reported, we will learn more about the limitations and when vessel preparation is necessary to ensure good drug uptake and durable results. ■

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## Expert Opinion on When to Use DCBs



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Percutaneous transluminal angioplasty (PTA) remains the standard of care of treatment in superficial femoral artery (SFA) and below-the-knee (BTK) lesions. It has been the only proven treatment modality but, with growing lesion length and new tools to improve our success and patency rate, the use of adjunctive therapy beyond stenting, such as drug-coated balloons (DCBs) and atherectomy is growing. Nowadays, primary stenting is a rare case in SFA and BTK lesions, but it is the primary approach in iliac arteries in our cath lab. Adjunctive treatment modalities, such as DCBs or atherectomy, do not yet play a role in the iliac arteries. In Germany, even though a lot of DCBs have CE Mark approval and our health care system is reimbursing the use of DCBs, we still have to justify their use.

### STRATEGIES OF TREATMENT

Strategies in the treatment algorithm of stenosis or occlusions in SFA lesions do not differ all that much—lesion length, grade of calcification, and location of the lesion strongly influence our modalities.

In cases of an ostial SFA lesion or a lesion of the common femoral artery, as well as in the popliteal artery, or the areas known as “no-stent zones,” we would primarily start with the atherectomy or scoring PTA in combination with DCBs. Twelve-month data presented at VIVA 2014 indicated that atherectomy in combination with DCBs may lead to better results in complex femoropopliteal lesions.

In these areas, we know that stenting with nitinol stents faces restrictions and requires special technolo-



gies. There are stents on the market that qualify (more for mechanical stress and their use in areas of flexion), but everybody would agree that the native artery without any mechanical implant inside is superior in terms of flexibility and behavior during motion.

Mostly, we try to achieve intraluminal wire passage followed by vessel preparation and plaque removal with atherectomy followed by a PTA with a DCB. If we run into a subintimal route, we probably would not opt for atherectomy.

In cases of flow-limiting dissection, we would not hesitate to use a dedicated stent in these areas, except in the common femoral artery, because we still believe that open surgery is a valid alternative with robust data in terms of patency and durability.

In noncalcified SFA lesions, if the wire passage is performed successfully, we currently would start with a gentle predilation by using an undersized balloon. If the primary result looks promising in terms of good flow and the absence of major dissections and thrombus, the next step would be a DCB sized properly to match the reference vessel diameter. Inflation time would be at least 3 to 5 minutes. If the lesion length exceeds the balloon length of a single DCB, several may be used. In such cases, we are careful to ensure that the entire length of the lesion and predilated area is treated with a DCB. If the result is good, the patient would be set on dual-antiplatelet therapy for at least 3 months, and an early follow-up by duplex ultrasound would be scheduled.

If the result does not look good, we would go for stenting of the dissected/subintimal area.

In stenoses or occlusions located within a stent, we use DCBs in 100% of cases.

In calcified lesions, we would use atherectomy or scoring technology as a primary treatment to prepare the vessel for a DCB or stenting. If atherectomy was not effective in reducing the calcified plaque burden, a DCB would play a limited role. In such cases, we would opt for PTA with a short, noncompliant balloon with high inflation pressure or for a scoring/cutting balloon to prepare the vessel for final stenting. DCBs are probably not as effective in severely calcified lesions as they are normally,<sup>1</sup> but further study and data are needed.

In BTK lesions, we still believe that the concept of local drug delivery is promising, although the IN.PACT DEEP trial brought significant drawbacks to the interventional community.<sup>2</sup> The data from the Biolux P-II trial showed safety data without any increase in amputation rates after 6 months. However, the same as for

IN.PACT DEEP, in this randomized trial of Biotronik DCB versus PTA, the primary efficacy endpoint was not met.<sup>3</sup> It seems as if the right choice of DCB for treatment below the knee is more crucial than in the SFA, and this is probably driven by the excipient used on the balloon and the coating technology.

To date, we do not treat CLI BTK cases with DCBs, and we are waiting for more robust data to help determine optimal therapy. In these cases, we opt for a long inflation time with a standard PTA balloon and, for spot stenting, a drug-eluting stent. The treatment of patients with severe claudication with concomitant BTK lesions is probably safe with use of a DCB, and we administer local drugs at ostial or bifurcation lesions in such cases.

The data supporting the use of DCBs for SFA de novo lesions are robust and a little less robust for in-stent restenosis. If we look for predictors of restenosis in general, the following were identified: long lesions (TASC C and D), small arteries and areas of flexion such as the common femoral artery, the popliteal artery, and the SFA proximally and distally.

These indications qualify more for DCB use with or without adjunctive therapy; however, there remain unanswered questions.

Dialysis access has the highest restenosis rate reported so far; these arterialized veins qualify for DCBs, as indicated by some preliminary small trials.

## SUMMARY

For clinical practice, we need DCB technology that addresses dialysis challenges, such as shunt veins, and safe DCB technology for BTK lesions. There is a lack of data for long SFA and popliteal lesions because in all trials presented so far, the lesion length is approximately 6 to 8 cm. Most clinical cases we treat to date exceed this lesion length.

Future trials and registries should primarily address long lesions and combination therapy with scoring technology and debulking devices. Data from the DEFINITIVE AR trial concerning the combination of atherectomy and DCBs are showing promising results, but the cohort of this pilot trial was too small to produce evidence. ■

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