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/mm²; Lutonix [Bard Peripheral Vascular], 2 μg/mm²; and Stellarex™ [Spectranetics Corporation], 2 μg/mm²) 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 restenosis to assess treatment efficacy at 28 days. Two weeks after stent implantation, each in-stent restenotic 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 stability of the Stellarex coating. This head-to-head comparison study shows for the first time that the reduced-dose Stellarex balloon achieved a comparable biological efficacy compared to higher dose DCB and has the potential to improve the safety profile of DCB technologies.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>QVA</th>
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<td>PTA</td>
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<tr>
<td>Stellarex</td>
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<td>In.Pact Admiral</td>
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<td>Lutonix</td>
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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 by the durable and consistent clinical results of the ILLUMENATE trials (Figures 1 and 2).

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 tissue. In order to apply its antirestenotic action, paclitaxel must be in a bioavailable form so that it binds to and stabilizes arterial smooth muscle cell microtubules. Once transferred to the tissue, paclitaxel must stay resident in the vessel, acting as a drug reservoir. This offers bioavailability to exert action through the critical 30-day restenosis window.

THE EXCIPIENT

DCBs require paclitaxel to remain on the balloon surface during transit to the treatment site and be released only 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 readily absorbs water. The combination of PEG and water results in a plasticized coating with attractive mechanical properties (eg, adhesion, flexibility, elasticity, and elongation). 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 stable to most chemical reactions. It is also a nontoxic excipient that has been used in topical, oral, and intravenous applications for decades. This nontoxic, stable excipient acts as a reliable carrier of paclitaxel from the balloon to the lesion wall. Therefore, a DCB with PEG, such as Stellarex, can have a low drug dose and allow for a therapeutic dose to reach the target lesion.

Figure 1. Consistent patency rates were observed across three separate studies with Stellarex.

Figure 2. The ILLUMENATE clinical program.
Once hydrated, 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 tissue-capturing power. Although urea is also water soluble, it doesn’t exhibit the polymer mechanical properties that PEG exerts, possibly rendering it less durable. Other excipients (such as polysorbate) act as emulsifiers—they may help dissolve paclitaxel. When these emulsifiers are combined with a more amorphous paclitaxel morphology, paclitaxel may not provide sustained bioavailability, thus allowing smooth muscle cell proliferation to continue. Using PEG as an excipient allows the Stellarex DCB to balance coating stability and the transfer efficiency of paclitaxel.

THE SURFACE ENERGY

The surface energy of a balloon plays a critical role in optimizing the balance of coating adhesion to the balloon during tracking to the lesion and drug transfer during balloon inflation.

In the case of DCBs, surface energy defines the relationship between the surface of the balloon and the drug coating. If the surface energy of a balloon is too low, the coating does not adhere well to the balloon surface and the coating flakes off and is lost systemically prior to reaching the treatment site. The EnduraCoat™ Technology of the Stellarex DCB achieves the optimal surface energy needed to provide appropriate coating adhesion.

It is important to note that the 12 commercially available DCBs in the European market all use paclitaxel as the active pharmaceutical ingredient. However, only three of these DCBs have data available from robust multicenter, randomized, core lab–adjudicated clinical trials; and of these three DCBs, only two show 12-month primary patency rates > 85%. Stellarex is the only DCB with a drug dose of 2 μg/mm² that shows patency rates of up to 89% at 1 year in core-lab–adjudicated, randomized controlled trials (Figure 3).

The coating solution of paclitaxel and PEG, along with the proprietary manufacturing process for the Stellarex DCB forms the EnduraCoat Technology. The EnduraCoat Technology allows the Stellarex DCB to achieve durable and consistent clinical outcomes combined with an optimized drug dosage.

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, the coating 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.9

Crystalline paclitaxel morphology is more brittle than an amorphous morphology during tracking but also allows for effective drug transfer. However, it resides in the vessel at therapeutic levels out to or past the 30-day restenotic window. Research shows crystalline paclitaxel dissolves into the tissue slowly for sustained release over time.9 Figure 4 demonstrates the different pharmacokinetic properties of the different coating morphologies. After being transferred to the vessel wall, crystalline paclitaxel may form “drug depots,” which may help in sustained release (Figure 5).10

The Stellarex DCB has an optimal mix of amorphous and crystalline paclitaxel (Figure 6), merging the characteristics of both amorphous and crystalline paclitaxel morphologies. The Stellarex coating formulation creates a stable 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 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 will determine 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 for effective drug transfer and provides drug residency through the 30-day restenosis window. The EnduraCoat Technology (Figure 6) allows the Stellarex DCB to achieve durable and consistent clinical outcomes combined with a low drug dose.

The Stellarex DCB has shown a best-in-class 12-month primary patency rate of 89%, a 24-month primary patency rate of 80.3%, and a clinically driven target lesion revascularization of 2.9% and 14.2% at 12 and 24 months, respectively.

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10. Porcine model data on file at Spectranetics.

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