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The Next Generation of Drug-Coated Balloons

The Ranger Paclitaxel-Coated PTA Balloon Catheter

One of the more exciting advancements in the field of endovascular interventions has been the addition of drug-eluting therapies. Since the first approved drug-coated balloon (DCB) in 2009 in Europe, important innovation and continued research have helped to further evolve this space. A next-generation DCB launched in July 2014 and was designed to provide efficient drug transfer and sustained retention into the vessel tissue, thus contributing to a consistent and predictable treatment.

TRANSPAX™ COATING TECHNOLOGY

Building upon nearly 20 years of research on the vascular use of paclitaxel, the proprietary TransPax™ coating technology used on the Ranger DCB (Boston Scientific Corporation) was developed to address the delicate and often unstable nature of the coat-

ing associated with contemporary DCBs. Unlike most technologies, which utilize hydrophilic carriers (eg, urea, sorbitol, etc.) that make the coating more fragile, the TransPax™ coating formula combines paclitaxel and a citrate ester excipient that is highly hydrophobic, to efficiently transfer drug to the lesion while maintaining proper coating stability throughout the delivery process (Figure 1).

Ranger DCB treatment with the TransPax™ coating technology achieves consistent and more predictable drug tissue levels in the days and weeks after the angioplasty.¹ Preclinical studies confirm the excipient/drug ratio allows for a sustained state of drug levels in the tissue during the restenotic cascade.² In addition, despite the lower drug loading dose of Ranger (2 µg/mm²) compared with In.Pact (Medtronic, Inc; 3 µg/mm²), Ranger provided a similar arterial paclitaxel concentration

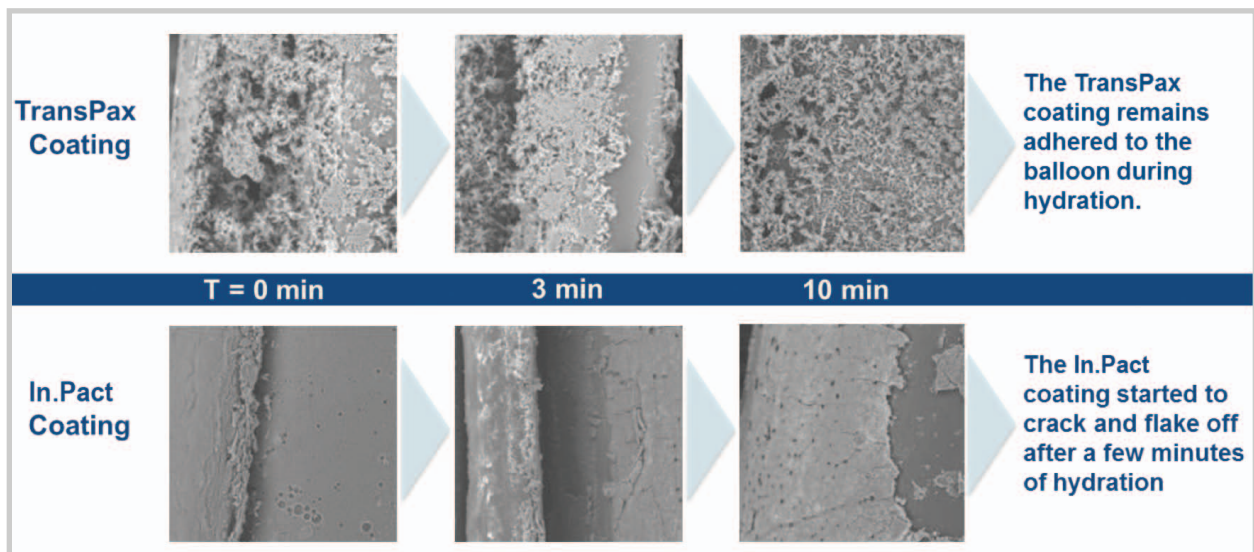


Figure 1. Enhanced coating integrity of TransPax™ technology.

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(Figure 2), suggesting that the formulation and processing of Ranger's coating provides a more efficient drug delivery. Conversely, Lutonix (Bard Peripheral Vascular, Inc.) drug tissue levels drop significantly within the first 24 hours, while Ranger maintains a higher drug tissue concentration through the restenotic cascade.³

PARTICULATE STUDY

First-generation paclitaxel-coated balloon technologies were limited by the amount of coating particulate produced after balloon inflation. At the present time, although the potential impact of coating particulate shedding on microvessel embolization remains a theoretical concern, one below-the-knee trial demonstrated an increased amputation rate.⁴ Improved coating stability upon balloon inflation may translate into lower particulate loss into the bloodstream. In a benchtop model, an inline 47-mm-diameter black polycarbonate filter (5- μ m pore size) was used to collect downstream particulates shed during use of Ranger, Lutonix, and In.Pact Pacific DCBs. In the quantitative analysis, the average number of large particles (< 300 μ m) for Ranger was approximately 6 to 8 times lower compared to both Lutonix and In.Pact Pacific. Large particles are important, as they have the potential to occlude larger vessels downstream following balloon inflation. However, although these findings are theoretically appealing, their clinical relevance is presently unknown.

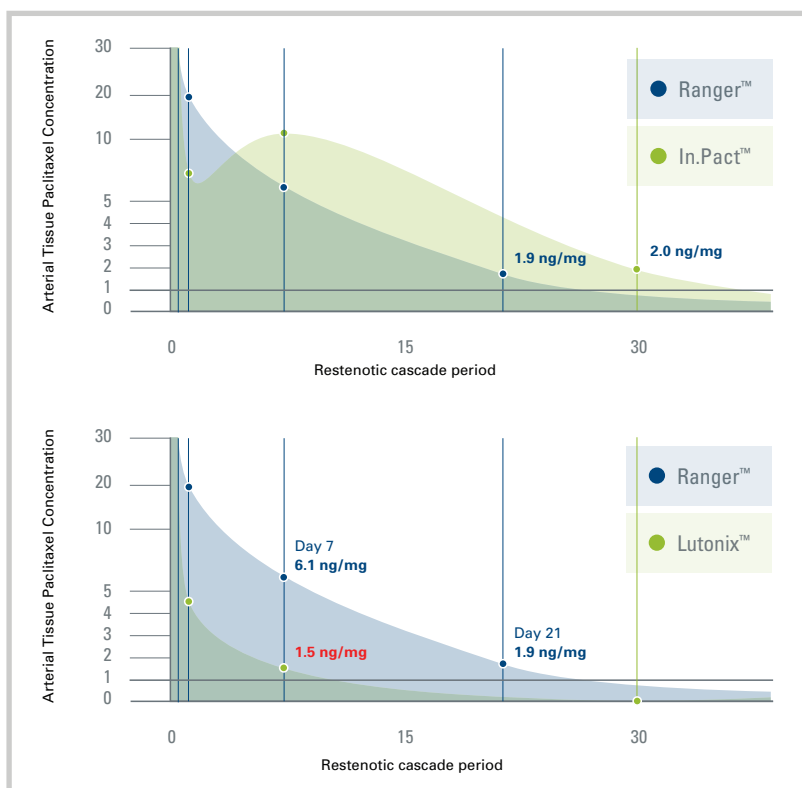


Figure 2. Arterial tissue paclitaxel concentrations over time of Ranger, In.Pact Pacific, and Lutonix.

LOADING AND DELIVERY

DCB coatings can become damaged upon insertion through the introducer valve and during tracking to the target site. Therefore, the Ranger DCB was designed with a loading tool to prevent damage to the coating upon insertion (Figure 3). In addition, Ranger leverages the Sterling balloon platform, which is the most commonly used 0.018-inch (0.46-mm) balloon globally with

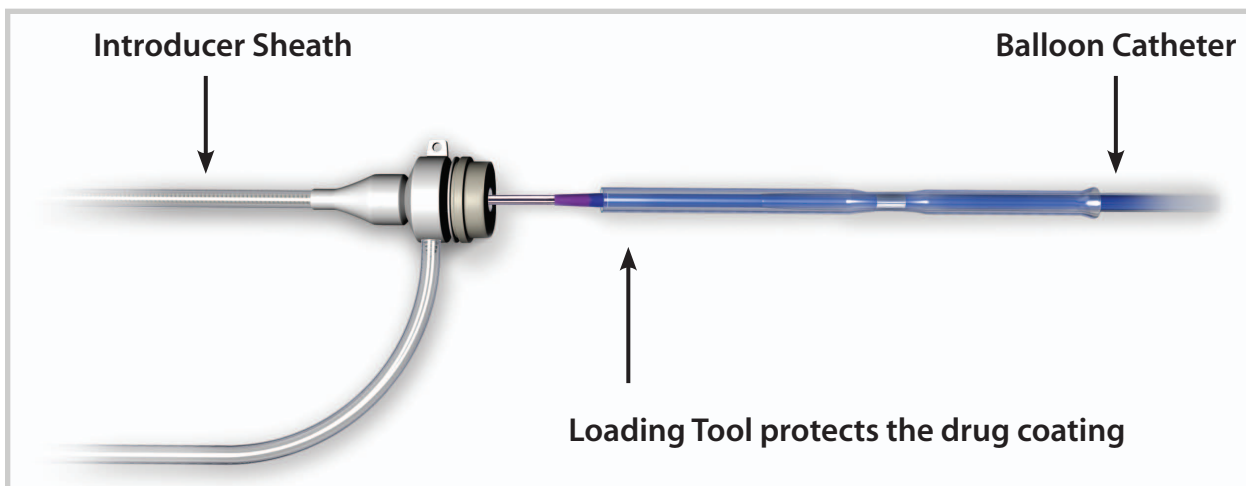


Figure 3. The Ranger DCB loading tool is designed to enhance ease of use and preserve drug coating integrity.

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The company expects to enroll more than 1,200 patients worldwide in their drug-eluting clinical program.

the ability to treat both superficial and below-the-knee arteries (2–8 mm, up to 150 cm in length). In recent market evaluations across 36 centers in Europe, the Ranger DCB balloon was rated as superior to currently used competitive brands, demonstrating recognition of a better coating stability maintained throughout the

procedure.⁵ Of the physicians surveyed, 70% rated the Ranger DCB more favorably for deliverability and ease of use over their currently used competitive brand.

CLINICAL COMMITMENT

Given the challenging biological environment posed by these vessel beds such as the superficial femoral artery (SFA), it is clear that multiple drug-eluting approaches should be explored as the treatment algorithm continues to evolve. Boston Scientific continues to collaborate with physicians and health care systems to advance the science of drug elution in the periphery, including clinical research on both DCBs and drug-eluting stent (DES) technologies.

TRANSLATIONAL FINDINGS

Bridging a pathway for clinical consideration of drug-coated balloons.

By Juan F. Granada, MD

With the inception of drug-coated balloons in the peripheral vasculature, researchers have further studied this technology to better solidify where the treatment fits in the current algorithm. Today, DCBs have proven to be the therapeutic option of choice in relatively short, noncalcified lesions in which the use of stents may be challenging. In the future, the technical drivers behind the technology—coating stability, acute drug transfer, and the durability of the biological effect related to paclitaxel tissue residency—will be critical to clinical success. DCBs employ different coating technologies to deliver the antirestenotic drug without the use of a permanent polymer carrier. The ideal coating formulation should maximize neointimal inhibition by maintaining therapeutic tissue levels over time, while ensuring adequate

healing and minimizing particulate loss.

Compared to first-generation DCB technologies, the Ranger DCB is designed with a reduced drug surface

density while maintaining a balanced degree of crystallinity to promote better adherence during hydration and reduce coating embolization upon

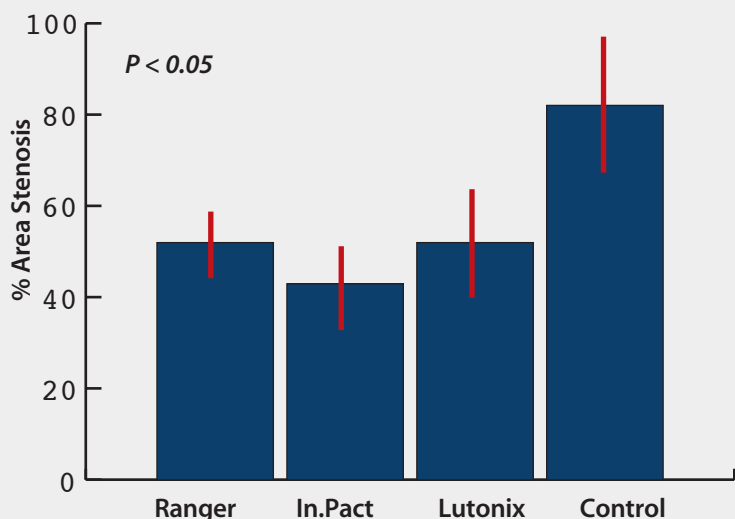


Figure 1. All drug-coated balloons demonstrated a significant reduction in percent stenosis versus control percutaneous transluminal angioplasty.

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The company expects to enroll more than 1,200 patients worldwide in their drug-eluting clinical program, including both large, randomized trials and investigator-initiated research on both DCBs and DESs. The Ranger SFA multi-center study is ongoing in Europe, randomizing the Ranger DCB to a standard, uncoated PTA balloon. Results from the MAJESTIC trial, which is evaluating the company's next-generation peripheral DES platform, are expected to be presented in the first half of 2015. Additional research is planned to explore both DESs and DCBs in a variety of applications, as well as the study of vessel preparation with atherectomy and thrombus removal before application of drug-eluting technologies. ■

1. Ranger DCB preclinical data on file at Boston Scientific.
2. Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. *J Am Coll Cardiol.* 1991;17:758-769.
3. Virmani R. Bard Lutonix DCB catheter technology. Presented at: Leipzig Interventional Course; January 2014; Leipzig, Germany.
4. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results From the IN.PACT DEEP randomized trial. *J Am Coll Cardiol.* 2014;64:1568-1576. doi:10.1016/j.jacc.2014.06.1198.
5. Market evaluations on file at Boston Scientific. The Ranger DCB evaluation phase took place from CE mark date (mid-July 2014) until September 2014 with 36 participating centers from across Europe including Germany, France, Italy, UK, Spain, and Belgium.

inflation. The efficacy of this technology was evaluated along with two other commercially available DCBs and an uncoated balloon control group in the familial hypercholesterolemic SFA in-stent restenosis swine model.¹ In this study, all DCBs showed significant inhibition of neointimal formation when compared to the uncoated balloon

control (Figure 1).

However, despite the fact that the In.Pact DCB provided the highest levels of neointimal inhibition, it also displayed the highest levels of immature neointima and peristrut fibrin deposits (Figure 2). The Ranger DCB provided comparable levels of neointimal inhibition but a more homogeneous healing

profile when compared to In.Pact.¹

In summary, the Ranger DCB technology demonstrated sustained tissue retention at lower loading doses with less particulate formation, but with an efficacy profile comparable to the already clinically proven first-generation DCB technologies. ■

1. Gongora CA, Shibuya M, Huijbregtse BA, et al. First in vivo evaluation of efficacy of a novel peripheral drug-coated balloon in a familial hypercholesterolemic swine model of in-stent restenosis. *J Am Coll Cardiol.* 2014;64. doi:10.1016/j.jacc.2014.07.332.

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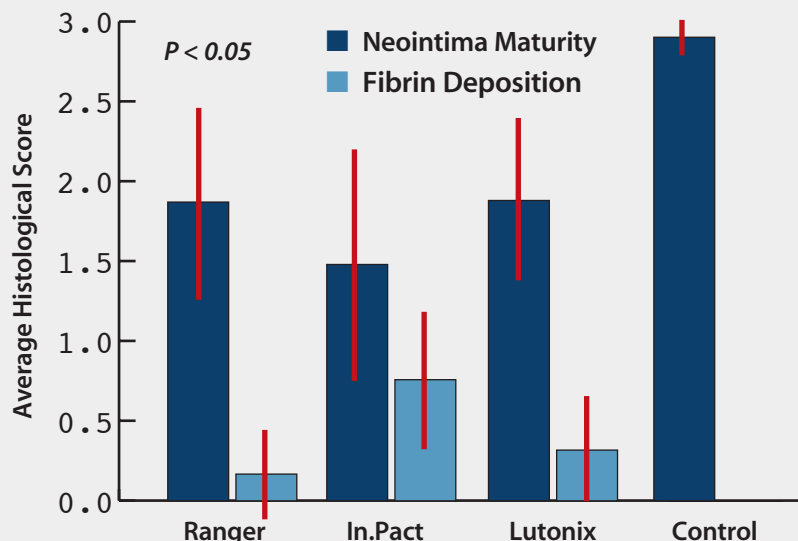


Figure 2. Ranger DCB provided more homogeneous healing profiles.

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 -Lutonix Moxy™ Drug Coated Balloon Catheter is a trademark of C.R. Bard Inc.