Innovations are created to solve the limitations of an existing technology or approach. In the endovascular arena, bare-metal stents were designed to combat the elastic recoil and restenosis that can limit the effectiveness of plain balloon angioplasty, antiplatelet therapy was modified to minimize the risk of stent thrombosis after stenting, and drug-eluting stents (DES) were developed to curtail the neointimal hyperplasia and late loss that are responsible for unacceptable restenosis rates with bare-metal stents. Most recently, drug-coated balloon (DCB) technology has been developed as an alternative to address the limitations of existing therapeutic approaches to coronary and peripheral arterial disease.

Compared with DES and other existing therapeutic approaches, DCBs offer several potential advantages, including targeted drug release without the use of a polymer, a degree of homogeneous drug delivery to the vessel wall that is not achieved with DES, and a shortened duration of antiplatelet therapy. In addition, DCBs may treat vascular lesions that are not well served by stents, such as high flexion sites, small vessels, long lesions, and bifurcation stenoses.

The use of stents for the percutaneous treatment of peripheral vascular disease can be limited by the occurrence of stent fracture, high restenosis rates, and anatomical challenges. Likewise, in coronary artery stenting, there remain significant clinical challenges, including in-stent restenosis, delivery of devices through calcified or tortuous anatomy, obstruction of side branches in bifurcation lesions, and management of small-vessel disease. Preclinical and clinical data suggest that DCBs may play an important role in addressing these challenges by delivering local antiproliferative agents to the vasculature without implantation of a foreign body (ie, a stent) or the need for long-term dual-antiplatelet therapy.

With DES, as in the early years of any new technology, extensive preclinical and clinical research and product development were undertaken to refine the first-generation technologies, weed out the poor performers, and, ultimately, develop the DES that are widely used today. Like those early stages of DES development, DCB technology is currently in its infancy and is just beginning its journey through the iterative scientific process that can yield a robust, clinically validated technology to address some of the remaining challenges in treating atherosclerotic disease.

THE HISTORY OF DCB DEVELOPMENT

Through a series of cell culture experiments, Scheller and colleagues determined that short-duration exposure (≤3 min) to paclitaxel admixed to the contrast medium, iopromide, produced long-term inhibition of cellular proliferation of vascular smooth muscle cells. In subsequent studies using the porcine coronary overstretch model, the same group demonstrated that short-duration exposure to paclitaxel, either dissolved in iopromide or coated onto a balloon catheter with iopromide, is sufficient to inhibit cell proliferation and neointimal hyperplasia.

In Europe, four DCB technologies have been introduced for coronary interventions, as well as three for peripheral interventions, although none have yet been approved by the US Food and Drug Administration. These innovative DCB technologies were introduced with great promise but thus far have been adopted cautiously. This is likely due to somewhat inconsistent clinical results, which may be related to important differences among the devices.

Initial coronary and peripheral outcomes have been largely positive, with a few exceptions. For example, randomized, controlled trials of the Paccocath DCB (B. Braun Interventional Systems Inc., Bethlehem, PA) for treating coronary in-stent stenosis have shown the superiority of DCBs over uncoated balloons, with signif-
icantly lower late lumen loss and fewer major adverse cardiac events. These beneficial effects were maintained 2 years after intervention, in spite of only 4 weeks of postprocedure antiplatelet therapy (as opposed to 12-month or lifelong therapy for DES). However, clinical and angiographic outcomes with some of the other DCB designs on the market have been less promising.

In peripheral vessels, the Paccocath DCB has been evaluated for treating stenosis or occlusion in the superficial femoral or popliteal arteries (THUNDER trial) and the femoropopliteal artery (FemPac trial). Compared with uncoated balloons, the use of DCBs in both studies resulted in a significant reduction in late lumen loss at 6 months and fewer target lesion revascularizations through 18 to 24 months postprocedure. These encouraging early data have generated hope that DCBs might provide a compelling therapeutic answer to the pervasive challenge of achieving exceptional clinical outcomes for infrainguinal disease.

The variability of performance among a new class of devices should not be disconcerting, or even surprising. In their recent editorial on DCBs, Gray and Granada point out that “not all DCBs are the same” and forecast that “their construct will have implications for their clinical effectiveness.” Although the current generation of DCBs all use the antiproliferative agent paclitaxel, their delivery mechanisms and coating characteristics may differ substantially from one another and from some of the newer DCBs in development.

CRITICAL ASPECTS OF DCB DESIGN

In the case of DES, the coating matrix turned out to be at least as important as the chosen drug. So too, the critical differences among DCBs relate to their formulations and, specifically, to the drug carrier used. In the early DCB experiments, Scheller noted that not all forms of a paclitaxel-coated balloons were similarly effective. Further preclinical research has confirmed Scheller’s initial observations. Although all of the marketed devices thus far have used paclitaxel, all use different drug carriers, each of which can vary widely in its transfer efficiency.

The drug carrier is of great importance because it governs several critical parameters affecting both safety and efficacy. These parameters include the total drug load required on the balloon, the durability and uniformity of the balloon coating drug dose, the relative uptake by the vessel wall, and the downstream drug dose. Drug retention during delivery to the therapeutic site is also an important variable. Figure 1A illustrates the impact that different carriers have on drug loss during balloon transit to the treatment site. For example, a carrier that allows a greater percentage of paclitaxel to be shed from the balloon during transit results in a
higher dose lost to downstream tissues and organs. Transfer efficiency of the carrier, another important parameter, determines the amount of drug actually delivered to the vessel wall. Figure 1B shows how a carrier with lower transfer efficiency results in less of the balloon’s paclitaxel load successfully diffusing into the arterial wall. When using carriers that have either low drug retention during transit or low transfer efficiency, more paclitaxel must be loaded on the balloon to reach the targeted therapeutic dose. Of note, the carrier molecule is a necessary feature of DCBs; without it, the hydrophobic paclitaxel is retained on the balloon during transit through the bloodstream, but it does not transfer efficiently into the arterial wall. The ideal carrier is one that optimizes retention during transit and transfer during inflation. Figure 2 demonstrates the optimization of drug carrier characteristics in terms of drug retention during transit, the optimal rate of drug release at the treatment site, and adequate tissue levels of paclitaxel.

Along with the drug carrier itself, the manufacturing process and resulting coating durability characteristics are critical factors in DCB design. For example, if coating particles flake off during balloon preparation or insertion into the valve, an undetermined amount of paclitaxel has been removed from the balloon, thereby making it difficult to ensure consistent dose levels to the arterial wall. It is also essential that the coating be robust enough to withstand intra-arterial conditions that can cause drug loss during transit, such as vessel tortuosity, heavy plaque burden, or calcification. These issues will be important for the developers of DCBs to investigate with rigorous bench and preclinical research. The uniformity and robustness of each balloon coating is dictated by both the specific formulation and the manufacturing methods, such as coating application. Some DCBs are coated while the balloon is deflated, whereas others, such as the Moxy™ Drug-Coated Balloon Catheter (Lutonix, Inc., Maple Grove, MN) (Figure 3), have the coating applied while the balloon is inflated, after which, the balloon is deflated and wrapped.

The ideal DCB should meet several criteria. Although the clinical impact of different coating methods is not yet clear, it is essential that the coating be robust enough to maintain the drug on the balloon during transit to the treatment site. The drug carrier should rapidly and efficiently deliver a therapeutic dose to the vessel wall with the lowest possible drug load on the balloon to minimize the downstream drug effect. Even coating distribution on the balloon and an efficient drug carrier will also be important to optimize the delivery dose to the vessel wall. Finally, the technology should be supported by extensive, rigorous preclinical science using the precise formulation and manufacturing processes as the clinically tested commercial product.

NEXT-GENERATION DCB TECHNOLOGY

The DCBs that have been introduced in Europe thus far share a number of characteristics in common—all use paclitaxel, most are loaded with 3 µg/mm² of paclitaxel on the balloon, and all but one employ a drug carrier, although the choice of drug carrier varies from one device to another. To date, the carriers used include iopromide, urea, butyryl-trihexyl citrate, and shellolic acid. Future development efforts may encompass alternative antiproliferative agents, drug carriers, or both.

One new DCB that aims to improve on the first-generation technologies is the Moxy balloon (Figure 4). Rather than model their drug carrier after the existing compounds, the Moxy development process began with exploring the universe of possible carrier molecules in an effort to screen and optimize the coating formulation. The final formulation is a result of assessing more than 225 possible carriers and more than 250 possible formulations through more than 40 preclinical animal studies spanning pharmacokinetics to arterial dose distribution. The resulting proprietary formulation of paclitaxel plus a highly efficient drug carrier from the
US Food and Drug Administration intravenous-approved list delivers the same therapeutic dose of paclitaxel to the vessel wall as the current DCBs on the European market, with a minimal amount of drug (2 µg/mm²) loaded on the balloon. This proprietary carrier is stable, nonreactive, hydrophilic, water soluble, and has an affinity for paclitaxel. The evenly distributed, stable coating (Figure 3) is specifically designed to deliver a uniform dose to the vessel wall while minimizing downstream drug delivery.

The mechanism by which a single application of antiproliferative drug inhibits restenosis for months to years remains uncertain,¹ and the rate of drug release and amount of tissue uptake will vary depending on the formulation used. Preclinical research and computational modeling show that the Moxy balloon lays down a paclitaxel reservoir from which the drug diffuses into the vessel wall over time. During balloon inflation, the paclitaxel and drug carrier are delivered to the endoluminal surface, where they remain after the balloon is deflated (Figure 5A). Paclitaxel gradually diffuses into the medial and adventitial layers from this reservoir. Over time, the paclitaxel dose levels become subtherapeutic at the endoluminal surface, but remain resident at therapeutic levels deeper in the arterial wall. Consequently, healthy endothelial cells are able to grow and reline the lumen while the deeper arterial layers continue to receive a sustained therapeutic dose (Figure 5B).

Lutonix has completed three first-in-man clinical studies, for which 6-month angiographic and clinical follow-up will be available later this year. In the peripheral arteries, the LEVANT I randomized trial (N = 101) is evaluating the Moxy balloon compared with an uncoated balloon for treating ischemic lesions in the superficial femoral and popliteal arteries. Angiograms from a patient in LEVANT I (Figure 6) show improvement from 80% stenosis in the proximal portion of the left superficial femoral artery at baseline to a residual stenosis of 25% postprocedure and a widely patent vessel during 6-month follow-up angiography. In the coronary arteries, the De Novo (N = 26) and PERVIDEO I (N = 41) single-arm studies are evaluating the Moxy balloon in de novo and in-stent restenosis lesions, respectively.
A BRIGHT FUTURE FOR DCB TECHNOLOGY

Appreciating the potential of DCB technology requires a closer look at several factors: the clinical efficacy of each individual device, the specific drug carrier and coating formulation, and the appropriate clinical indications and techniques employed. DCBs may offer a valuable therapeutic alternative in situations in which the current therapies have proven unfeasible. In the coronary arteries, DES are suboptimal for in-stent restenosis lesions, small-vessel disease, and bifurcation lesions in which the stent can obstruct side branches. In the peripheral arteries, in which restenosis and stent fracture are concerns, DCBs may offer a much needed therapeutic option for femoral, popliteal, and below-the-knee artery disease. Well-designed, randomized controlled clinical trials will be essential for elucidating the most appropriate clinical indications for DCBs.

Acknowledgements: The authors wish to thank Laurie LaRusso, MS, ELS, for her contribution to the writing of this article.

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