

Safety of Drug-Coated Balloons: Insight from Preclinical Studies

Understanding the advantages and disadvantages that can result from different balloon technologies on the market.

BY KAZUYUKI YAHAGI, MD; FRANK D. KOLODGIE, PhD; AND RENU VIRMANI, MD

Atherosclerosis is the primary cause of peripheral artery disease (PAD), which continues to increase in the United States and Europe and affects more than 27 million people.^{1,2} The symptoms of PAD widely vary from mild claudication to critical limb ischemia (CLI) with gangrene and limb loss, and it is associated with high morbidity, especially in the elderly.^{3,4} Historically, treatment strategies for PAD have involved medical therapy and open surgical bypass procedures.⁵ Over the last decade, endovascular treatment, including percutaneous transluminal angioplasty, stenting (with or without drug), stent grafts, and atherectomy, have become the standard of care.⁴ However, treatment is complicated by the fact that the superficial femoral artery (SFA) is one of the longest and most dynamically active vessels in the body, undergoing torsion, compression, flexion, and extension relative to hip and knee motion. The lower limb vessels are also susceptible to atherosclerosis because of low shear stress and spiral flow, which is most evident in the long segment of the lesser curvature of the SFA.⁶

Endovascular interventions are currently the first-line strategy for treatment, as recommended by the TransAtlantic Inter-Society Consensus for type A and B lesions. Surgical revascularization is still advocated for type D lesions, and type C lesions may be treated by interventions or surgery.⁷ Despite the changing paradigm for the treatment of PAD, the femoral and crural territories are still hampered by relatively high restenosis rates and lack of sustained benefit in CLI patients.^{5,7}

More recently, drug-coated balloons (DCBs) are now considered novel alternatives to drug-eluting stents (DES), as they provide the same antiproliferative drug without leaving a permanent stent.^{8,9} Potential benefits

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of DCBs over DES include the rapid delivery of drug, which is more diffusely distributed on the luminal surface without a polymer carrier or rigid metallic frame, avoiding the aforementioned unfavorable foreign body response that can contribute to in-stent restenosis.

To date, paclitaxel is the most commonly used drug for DCB technology, which has high lipophilic physiochemical properties, allowing passive absorption through the cell membrane and a sustained effect within the treated vessel wall. Drug delivery through adherence to the vessel wall is facilitated by carrier excipients, a revolutionary discovery that has led to the success of DCB technology.⁸ Another potential advantage of DCBs is the uniform deliverability of drug to the vessel wall relative to DES, in which drug is delivered over the stent platform, potentially resulting in nonhomogeneous drug-tissue transfer dependent on the stent design and interstrut distances.¹⁰

PRECLINICAL DATA ON THE LUTONIX® DCB

The LUTONIX® DCB (Bard Peripheral Vascular, Inc.) is coated with low-dose (2 µg/mm²) paclitaxel drug using a novel polysorbate/sorbital carrier (Figure 1). In a recent study, we reported the pathologic response

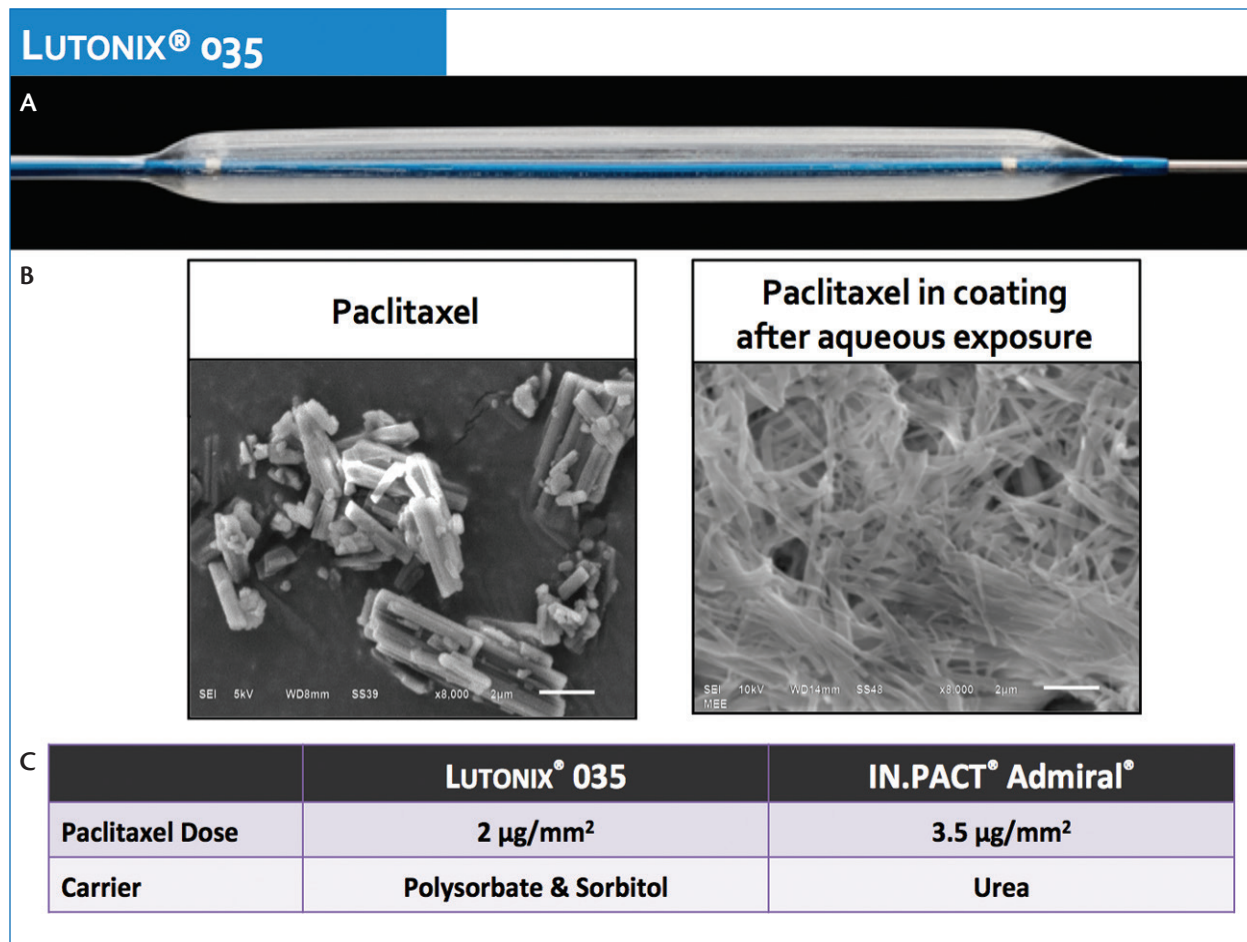


Figure 1. The LUTONIX® DCB. Gross micrograph of the inflated balloon (A). Transmission electron microscopy of the balloon surface with or without hydration (B). Relative comparison of dose and carrier for the LUTONIX® 035 balloon and the In.Pact Admiral balloon (Medtronic; C).

following DCB treatment of swine femoral arteries in animals survived for 28, 90, and 180 days,¹¹ with low-pressure balloon inflation either at one clinical dose (single inflation, 2 µg/mm² paclitaxel) or four clinical doses (two DCBs, each with 4 µg/mm² paclitaxel), with a standard uncoated balloon (SUB) serving as the control.

DCB treatment resulted in minimal endothelial loss, fibrin deposition, and minimal inflammation, with a sustained dose-dependent drug effect characterized by the loss of medial smooth muscle cell (SMC) peaking at 90 days for both groups. The SMC loss of the medial wall was graded from 1 to 4: grade 1 = < 25% of the inner surface medial wall showing loss of SMCs; grade 2 = > 25% but < 50%; grade 3 = > 50% but < 75%; and grade 4 = > 75% SMC loss. In arteries treated with the DCB, the transmural SMC loss score at one clinical dose was 1.1 ± 1.4 versus control SUB 0 ± 0 ($P = .008$), and at four clinical doses, the transmural SMC loss score was 2 ± 1.5 versus

control SUB 0 ± 0 ($P < .001$). No inflammation was observed in the one-dose group at 180 days, and there was an absence of necrosis and/or aneurysmal dilatation at all time points for both doses.¹¹

The loss of medial SMCs was accompanied by mild medial thinning, which is also consistent with drug effect. In parallel, arterial healing was observed at 90 days in both study arms, with significantly greater medial proteoglycan and collagen deposition peaking at 90 days in the one-dose group and at 180 days in the four-dose group (Figure 2).¹¹

The arterial tissue paclitaxel concentration following treatment with one dose was high at 1 hour (58.8 ± 54.2 ng/mg), significantly decreased at 24 hours (4.4 ± 6.9 ng/mg), and was sustained at 30 days (0.3 ± 0.4 ng/mg). On the other hand, paclitaxel concentration in the plasma peaked at 3 minutes and could not be detected beyond 24 hours.¹¹

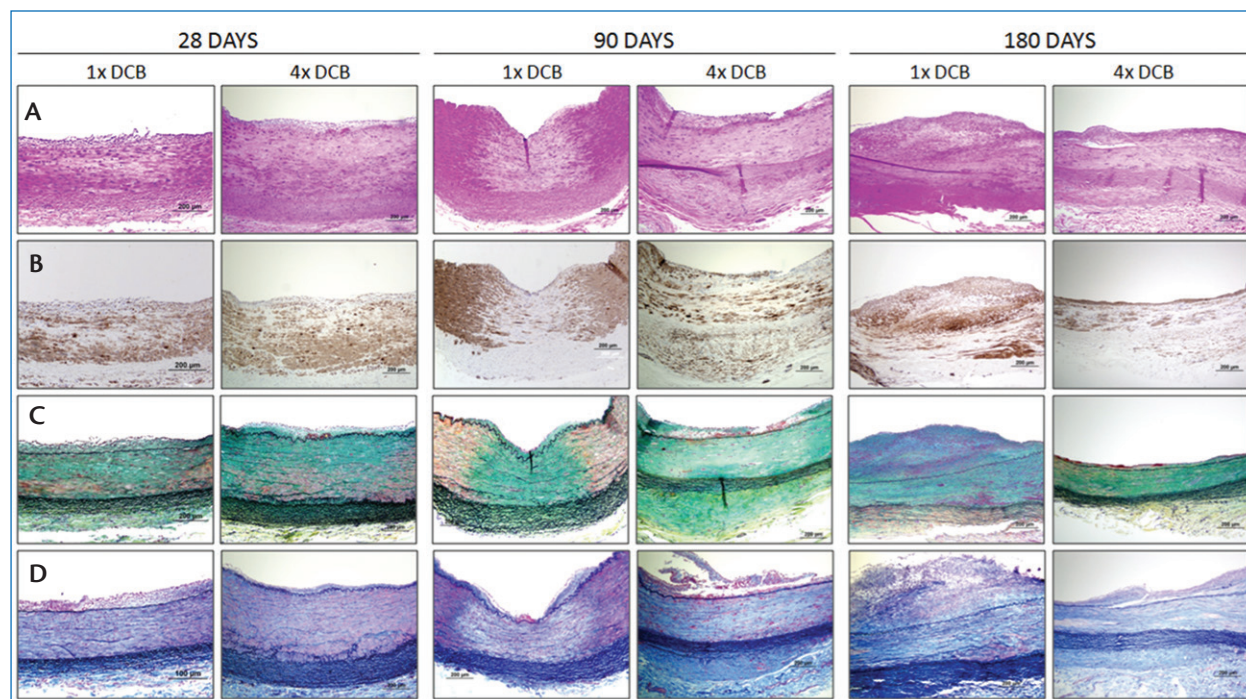


Figure 2. Representative images of the arterial response in swine SFA following one- and four-dose DCB treatment. Hematoxylin and eosin stain (A). Antibody staining against alpha-SMC actin shows peak loss of SMCs at 90 days in both the one- and four-dose DCB groups (B). In parallel, proteoglycan and collagen replacement can be observed at 90 and 180 days by the Movat (C) and Masson's trichrome (D). Reprinted with permission from Yazdani SK et al. *Catheter Cardiovasc Interv.* 2014;83:132–140.¹¹

DOWNSTREAM EFFECTS FOLLOWING DCB DILATATION

Histologic examination of downstream skeletal muscle from the same preclinical study¹¹ demonstrated no evidence of ischemic changes, emboli, or systemic toxicity for both the one- and four-dose DCB groups. Overall, changes in skeletal muscle were few, with < 0.025% of arterioles showing mild fibrin deposits within the walls of the muscular arteries or arterioles. The main findings involved single or clusters of small vessels (predominately arterioles) with varying degrees of SMC apoptosis and loss and adventitial inflammation, and rarely was the fibrinoid change accompanied by lymphocytic inflammation. The percentage of arterioles with pathological findings in the four-dose-treated arteries was at its maximum at 28 days, but the overall involvement remained low at 0.24%. The vascular changes within the skeletal muscle were mostly resolved by 90 days, although three skeletal muscle sections from the four-dose animals did show rare pathological changes of focal fibrin and SMC loss.¹¹

We recently performed an independent blinded analysis of two DCBs that have received United States and CE Mark approval in order to further understand the patho-

logic changes that occur in the downstream vascular bed following arterial dilatation. The purpose was to compare the LUTONIX® DCB (paclitaxel dosage 2 µg/mm² at three times the loading dose, with a total dose of 6 µg/mm²) and the In.Pact Amphirion balloon (Medtronic; paclitaxel loading dose 3.5 µg/mm² at three times the loading dose, with a total dose of 10.5 µg/mm²). To reach the three-times loading dose, each balloon had three balloon exchanges in the SFA in the 90-day swine model.

These studies were performed in two separate sets of animals. Different animals received either the LUTONIX® balloon or In.Pact balloon. The overall percentage of downstream vascular and skeletal muscle necrosis/fibrosis following DCB dilatation was lower for LUTONIX® DCB (8.9 %) as compared to the In.Pact Amphirion balloon (48.7%) (Figure 3). Moreover, there was no evidence of downstream skeletal muscle necrosis/fibrosis in the LUTONIX® DCB group, whereas In.Pact Amphirion showed 11.5% of histologic sections with necrosis/fibrosis, and crystalline materials were found in 5.1% of sections (Figure 3). Taken together, these data emphasize the critical aspect of the formulation for local paclitaxel delivery, and may be related to high drug load and coating integrity.¹²

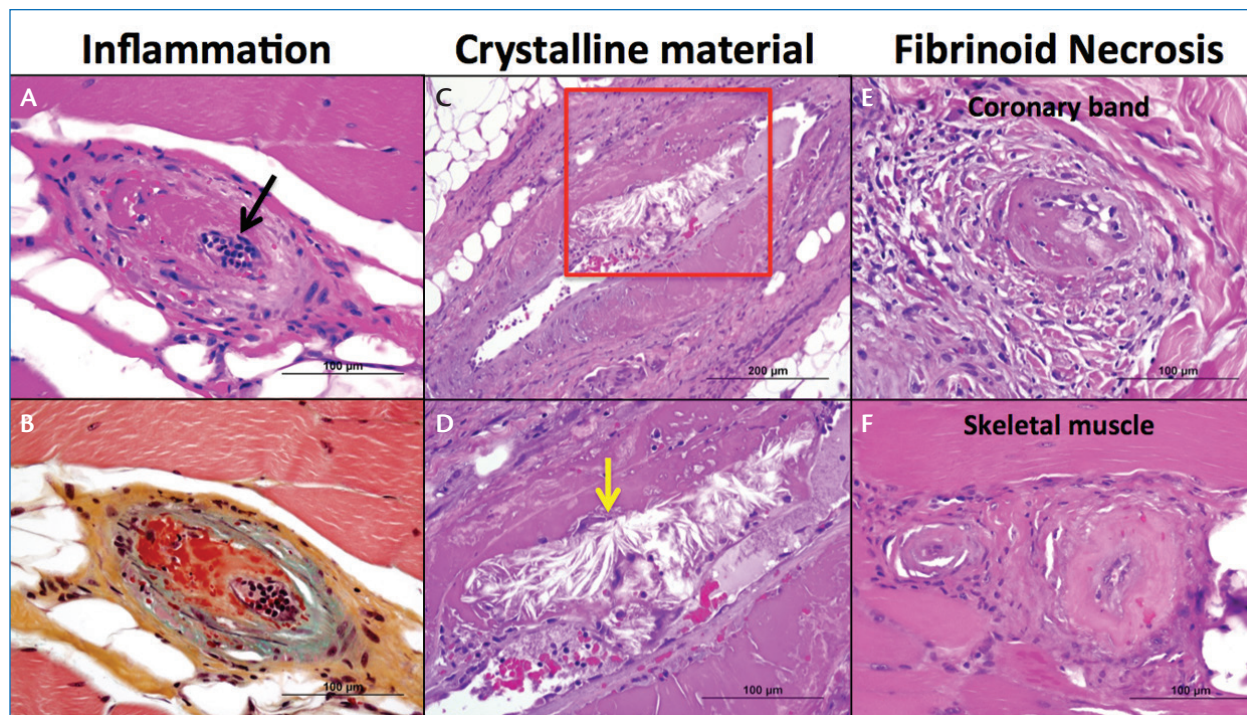


Figure 3. Representative images of embolic changes in skeletal muscle and coronary band territories mainly involving small arterioles following iliofemoral artery dilation with paclitaxel DCB in healthy swine. Hematoxylin and eosin (A) and Movat pentachrome (B) connective tissue stain, respectively showing fibrinoid necrosis of an arteriole in downstream skeletal muscle at 90 days following iliofemoral dilation using the LUTONIX® DCB (2 µg/mm²) with overlapping (three) dilations. Low-power image shows embolic crystalline material in nontarget skeletal muscle at 90 days following femoral artery dilation with the In.Pact Amphirion (3.5 µg/mm²) with overlapping (three) balloons (C). High-power image (D) of the region represented by the red box in panel C shows fine needle-shaped crystalline material (yellow arrow) with acellular areas of fibrin. Similar findings of fibrinoid necrosis at 90 days after In.Pact Amphirion use were also observed in the coronary band (E) and other skeletal muscle beds (F) following use of three repeated overlapping dilations.

INTERPRETATION OF PRECLINICAL DATA

Although arterial repair after balloon injury occurs more rapidly in animals than in humans, preclinical models hold predictive value for biological effects attributed to drug delivery.¹³ Transferring preclinical findings observed in healthy porcine arteries to diseased atherosclerotic arteries in humans is not entirely straightforward, as lesions are further complicated by necrosis and calcification. Nonetheless, preclinical studies in translational animal models should help to provide clues into drug-related biologic effects, as well as unfavorable results such as inflammation, excessive intimal growth, and embolic phenomenon.

In experimental models, it has been reported that at least 25% to 35% of the paclitaxel loaded on balloons with either urea matrix or iopromide coating is lost in the blood stream.¹⁴ The presence of such phenomenon observed in the animal model may be of relevance in PAD, especially when DCBs are used in patients suffer-

ing from CLI. However, not all DCBs are created equal, and further clinical studies are needed to clarify the effect of downstream emboli on adverse clinical outcomes.

CONCLUSION

DCBs have emerged as an important therapeutic alternative in the treatment arsenal of peripheral vascular disease. However, the downstream effects observed in preclinical testing of skeletal muscle following DCB usage present one of the major concerns, which may help distinguish the available balloon technologies on the market. Clinicians should understand the potential advantages and disadvantages of the various products before selecting an appropriate DCB. ■

Kazuyuki Yahagi, MD, is with the CVPPath Institute, Inc. in Gaithersburg, Maryland. He has stated that he has no financial interests related to this article.

Frank D. Kolodgie, PhD, is with the CVPath Institute, Inc. in Gaithersburg, Maryland. He has stated that he has no financial interests related to this article.

Renu Virmani, MD, is with the CVPath Institute, Inc. in Gaithersburg, Maryland. She has disclosed that she receives research support from Abbott Vascular, BioSensors International, Biotronik, Boston Scientific, Medtronic, MicroPort Medical, OrbusNeich Medical, SINO Medical Technology, and Terumo Corporation; has speaking engagements with Merck; receives honoraria from Abbott Vascular, Boston Scientific, Lutonix, Medtronic, and Terumo Corporation; and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore. Dr. Virmani may be reached at (301) 208-3570; rvirmani@cvpath.org.

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