

Drug-Coated Balloons for Coronary Artery Disease

A discussion on the current state of drug-coated balloons and their use for the prevention of in-stent restenosis.

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Since the introduction of coronary stents, restenosis has been the most important measure of clinical success, and a great deal of research has been undertaken to help understand the underlying biological mechanisms.^{1,2} In-stent restenosis, the result of the interaction of a variety of biological processes beginning immediately after device implantation, is characterized by an excessive proliferation of neointima.³ Drug-eluting stents (DES) reduced recurrent stenosis by effectively inhibiting neointimal proliferation and have become the therapy of choice for the interventional treatment of coronary artery disease.⁴ However, this demonstrated clinical efficacy of DES has been challenged by the rare and unpredictable risk of late stent thrombosis.⁵

During the past several years, drug-coated balloons (DCB) have emerged as a therapeutic alternative in treating coronary artery disease.⁶ It is believed that the short-term transfer of antiproliferative agents into the coronary wall can be achieved without requiring a permanently implanted drug delivery system. As a consequence, this technology may offer the potential to reduce the untoward effects associated with polymeric DES technologies. The original data regarding DCB technologies for use in the coronary territory have been derived from small clinical trials using paclitaxel-coated balloons (PCB) in the setting of in-stent restenosis.⁷ More recent data are emerging using DCB in de novo lesions and other specific coronary applications. In this article, we discuss the basic principles of DCB and the current preclinical and clinical data that are available today for its use in the coronary territory.

RATIONALE OF DCB TECHNOLOGY

The concept of delivering drugs into the vessel wall as a single-time dose treatment during balloon angioplasty has existed for several decades.^{8,9} However, in spite of extensive efforts using a variety of transfer methods, several studies have demonstrated a wide variability of drug uptake and clearance of the delivered compounds, thus limiting the technical viability of these methods.¹⁰ In addition, the successful introduction of DES technologies into clinical practice decreased the enthusiasm to develop any other balloon-based drug delivery technologies. Nevertheless, a very important step toward the successful development of the first DCB prototypes was the successful clinical applicability of paclitaxel and sirolimus in the prevention of restenosis after stent implantation.^{11,12}

Several technical features make DCB a viable alternative in interventional cardiology. First, by virtue of the large surface area on a balloon that is available for drug delivery, it is possible to achieve a greater and more homogeneous drug transfer profile than with a stent. Second, it is possible that by avoiding the ongoing presence of a polymer, increased biocompatibility (a lesser degree of inflammation related to any possible hypersensitivity reaction) could be achieved, thus resulting in a shorter time requirement for dual-antiplatelet therapy. Third, physician familiarity with balloon use predicts easier operator adoption and may be useful for situations in which DES use is problematic or less effective, such as in ostial disease, small vessels, bifurcations, diffuse disease, etc. A wide variety of DCB platforms are currently under development (Table 1). Although several coating tech-

TABLE 1. DCB TECHNOLOGIES CURRENTLY UNDER DEVELOPMENT FOR CORONARY APPLICATIONS

Technology	Company	Drug-Excipient	Dose (mg/mm ²)
Cotavance (Paccocath Technology)	Medrad Interventional/Possis (Indianola, PA)	Paclitaxel-iopromide	3
SeQuent Please	B. Braun Interventional Systems Inc. (Bethlehem, PA)	Paclitaxel-iopromide	3
Dior II	Eurocor GmbH (Bonn, Germany)	Paclitaxel-shellac	3
Elutax	Aachen Resonance GmbH (Aachen, Germany)	Paclitaxel	2
In.Pact Falcon	Medtronic, Inc. (Minneapolis, MN)	Paclitaxel-urea	3
Lutonix	Lutonix, Inc. (Maple Grove, MN)	Paclitaxel-unknown	2
Pantera Lux	Biotronik (Berlin, Germany)	Paclitaxel-BTHC	3
Abbott	Abbott Vascular (Santa Clara, CA)	Zotarolimus-unknown	Unknown

Abbreviations: BTHC, butyryl trihexyl citrate.

niques have been tested in small human clinical trials, it is still unknown which of the primary clinical applications (in-stent restenosis, de novo, etc) will be the primary niche for this technology.

DCB AND CORONARY APPLICATIONS

Although the concept of using balloon-based drug delivery in the coronary territory appears to be simple, there are several biological and technological issues that must be considered. The clinical success achieved with the original generation of DCB technologies relies on the single-time transfer of paclitaxel into the vessel wall, with the expectation of a durable biological effect. Therefore,

although it is a potentially elegant approach, this initial loading burst can be unpredictable and depend on both the amount of injury inflicted at the time of inflation and the characteristics of tissue receiving the drug. One of the key lessons learned early in the development of DCB was the need to use a carrier to enhance drug transfer to the vessel wall. Most of the carriers currently in use are non-polymeric in nature and appear to enhance the transfer and biological availability of paclitaxel (Figure 1). In particular, the use of the contrast agent iopromide creates a high molecular surface contact area between the lipophilic drug and the vessel wall, thus enhancing the bioavailability of the drug while remaining biologically inert (Figure 2).¹³

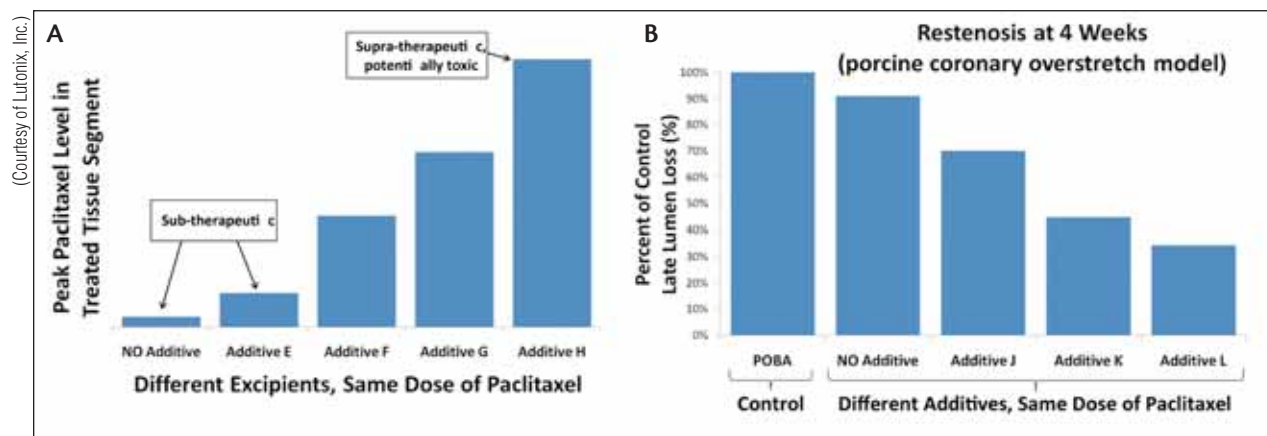


Figure 1. Biological effect of a carrier (excipients) on paclitaxel tissue levels (A) and biological activity (B, angiographic lumen loss in the porcine overstretch model).

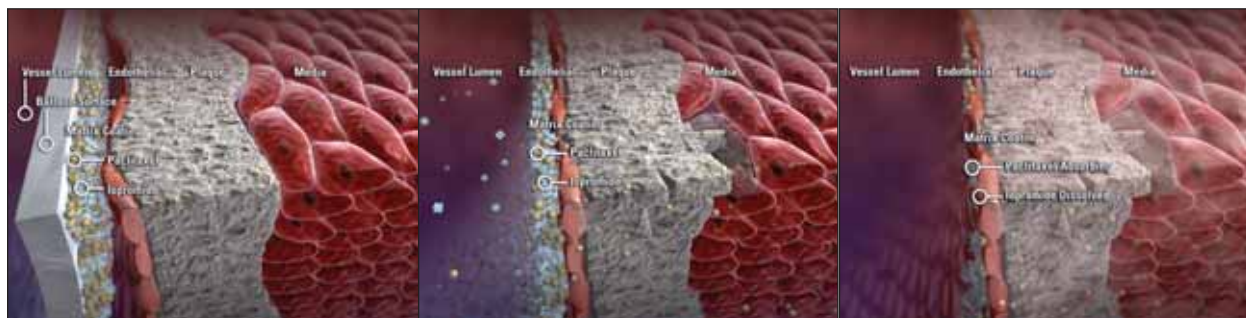


Figure 2. Figure describing the mechanism of drug transfer in DCB and the effect of hydrophilic spacers.

Most of the data currently available for antiproliferative agents in DCB technology involve paclitaxel.^{14,15} Paclitaxel exerts its potent antiproliferative effect by binding to the β subunit of tubulin, resulting in arrest of microtubule function. Paclitaxel is characterized by prolonged tissue retention rates,¹⁶ which is desirable in any DCB compound under consideration. Sirolimus and its analogues have also been tested and have been found, at least at the preclinical level, to have a profile that might allow for their consideration as alternatives to paclitaxel.¹⁷ Although small preclinical studies have shown that the short-term delivery of sirolimus may inhibit neointimal proliferation after balloon injury,¹⁷ it is believed that the biologic effect of sirolimus and its analogues may require more stable tissue levels over time and perhaps the development of more sophisticated carriers.¹⁸ Due to its lipophilic profile, zotarolimus appears to have the best profile among the sirolimus analogues for this particular application.¹⁹

PRECLINICAL DATA

The first available preclinical data on DCB used the relatively basic combination of iopromide-paclitaxel directly deposited within the folds of an angioplasty balloon. Using the porcine model of coronary restenosis, bare-metal stents crimped on iopromide-paclitaxel-coated balloons ($3 \mu\text{g}$ of drug per mm^2 of balloon surface) decreased in-stent restenosis compared to the bare-metal stents crimped on uncoated balloons.²⁰ Using a similar model, Cremers et al confirmed that drug transfer occurs very early after balloon inflation.²¹ In addition, in the same study, the safety profile of applying several balloon inflations within the same vascular segment (overlapping) was demonstrated.²¹ Interestingly, in contrast to the common late restenosis catch-up phenomenon seen in the porcine model with current DES technologies, the antiproliferative effect for DCB seems to be sustained over time.²⁰ The impact of the variation of coating composition on safety and effi-

cacy has been recently studied. Cremers et al compared the iopromide-paclitaxel DCB coating with a surface-modified balloon directly coated with paclitaxel alone²² and found that the iopromide-paclitaxel DCB system resulted in less neointimal formation. Preclinical data using sirolimus analogues delivered on DCB platforms are scarce, as several drug carriers tailored to deliver these compounds are currently under development. A recent report showed that a zotarolimus DCB decreased restenosis compared to balloon angioplasty in a coronary porcine model of restenosis.²³

CLINICAL DATA

Although most of the biological effects ascribed to DCB are still under investigation, several clinical studies using different DCB technologies in the coronary territory are in progress or have been completed (Table 2). The first report of DCB use in humans was published in 2006.⁷ In this study, 52 patients with coronary in-stent restenosis were randomized to conventional percutaneous transluminal coronary angioplasty or a $3\text{-mg}/\text{mm}^2$ iopromide-paclitaxel-coated balloon (Paccocath). At 6 months, angiographic follow-up demonstrated a significant difference in the primary endpoint of less in-segment late lumen loss (LLL) in the Paccocath group ($\text{LLL} = 0.76 \pm 0.86 \text{ mm}$ vs $0.09 \pm 0.49 \text{ mm}$; $P = .003$). In an extension of this study, an additional 56 patients with coronary in-stent restenosis were randomized, and the entire cohort of 108 patients was followed up to 2 years.²⁴ In this study, the findings were confirmed, and the in-segment LLL described was consistent with the original report (in-segment binary restenosis was 6% in the DCB group vs 51% in the uncoated balloon group). At 24 months, the net clinical effect of the Paccocath technology was maintained, with significant reductions in target lesion revascularization (37% vs 6%; $P = .001$).

Another group of investigators using a similar Paccocath technology platform (SeQuent Please) have initiated a series of studies (PEPCAD trials) to test this technology in the coronary territory. The PEPCAD I trial

was a nonrandomized study investigating the safety and efficacy of the SeQuent Please DCB in small vessel (mean reference vessel diameter = 2.36 mm) de novo lesions in 120 patients.²⁵ At 6 months, in-segment LLL was 0.28 mm in the intention-to-treat population. Most of the patients were treated with DCB alone; however, 28% of patients required BMS placement due to elastic recoil or severe dissection. In the as-treated subset of patients (treated only with DCB), late lumen loss was 0.18 mm. It is believed that most of the restenosis observed in patients requiring a stent, with late lumen loss of 0.73 mm, was due to geographic miss. In addition, the stent thrombosis rate was lower in the DCB alone group, in spite of a shorter duration of dual-antiplatelet therapy (3 vs 6 months).

PEPCAD II was a multicenter, randomized trial of the

SeQuent Please DCB versus the Taxus Liberté DES (Boston Scientific, Natick, MA) in 131 patients with coronary in-stent restenosis.²⁶ The primary endpoint (6-month in-segment LLL) was significantly lower in the DCB group compared with the DES group (0.17 ± 0.42 mm vs 0.38 ± 0.61 mm; $P = .03$). At 12 months, there was a trend toward maintaining the differences seen at 6 months (DCB = 6% vs DES = 15%; $P = .15$). The PEP-CAD III study randomized patients with single de novo atherosclerotic disease to either BMS crimped on the same paclitaxel balloon technology (SeQuent) or the Cypher sirolimus-eluting stent (Cordis Corporation, Bridgewater, NJ) in 637 patients (RVD = 2.5–3.5 mm in diameter and < 24 mm long).²⁷ At 9 months, the primary angiographic endpoint (in-stent LLL) was significantly lower for the DES group compared to the

TABLE 2. CURRENT CLINICAL TRIALS UNDER DEVELOPMENT INVOLVING PCB TECHNOLOGIES IN THE CORONARY TERRITORY

Trial Name	Technology	Indication	Patients (n)	Binary Restenosis
PEPCAD I	SeQuent Please	SVD	114	PCB, 5.5%; PCB + BMS, 41.3%
PEPCAD II	SeQuent Please	ISR	131	PCB, 7%; Taxus Liberté, 20.3%
PEPCAD III	SeQuent Please	De novo	637	PCB + BMS, 13.8%; Cypher, 4.9%
PEPCAD IV	SeQuent Please	De novo (DM)	160	9-month follow-up expected by fourth quarter of 2010
PEPCAD V	SeQuent Please	Bifurcations	56	PCB, 7.1% (SB)
PEPCAD CTO	SeQuent Please	CTO	50	9-month follow-up expected by fourth quarter of 2010
PICCOLETTTO	Dior II	SVD	57	PCB, 32.1%; Taxus Liberté, 10.3%
VALENTINES	Dior II	ISR	300	Data due August 2010
PERVIDEO I	Lutonix	ISR	40	Data due October 2010
Lutonix De Novo	Lutonix	De novo	24	Data due September 2010
PEPPER	Pantera Lux	ISR	80	Data due October 2010
IN.PACT CORO ISR	Invatec, Inc. (Bethlehem, PA; recently acquired by Medtronic, Inc.)	ISR	23	PCB, 4%
IN.PACT CORO I	Invatec, Inc.	De novo	30	Enrolling
BELLO	Invatec, Inc.	De novo SVD	182	Enrolling

Abbreviations: CTO, chronic total occlusion; DM, diabetes mellitus; ISR, in-stent restenosis; SB, side branch; SVD, small vessel disease.

DCB/BMS group (0.16 ± 0.39 mm vs 0.41 ± 0.51 mm; $P < .001$). In addition, 9-month clinically driven target lesion revascularization and target vessel revascularization favored the DES group, as did the safety endpoint of stent thrombosis. PEPCAD V was a small dual-center study enrolling patients with bifurcation lesions.²⁸ Both the main and side branches were ballooned with a paclitaxel DCB. The primary endpoint was procedural success, which was defined as residual in-segment stenosis $< 30\%$ in the main branch and $< 50\%$ along with TIMI grade 3 flow in the side branch. A total of 28 patients were enrolled, and four patients (14.3%) required a stent in the side branch. At 9 months, the stent thrombosis and significant restenosis of the side branch was similar (two patients, 7.1%). The mean LLL of the side branch at angiographic follow-up was 0.21 ± 0.47 mm. PEPCAD CTO was a 50-patient, single-center study (also in Germany), and follow-up data have not been presented to date.

The PICCOLETTI trial²⁹ employed a different paclitaxel-eluting balloon technology not involving a drug carrier (Dior). This single-center trial enrolled a total of 80 patients with de novo small vessel (< 2.75 mm) lesions and randomized the patients to either the Dior DCB or to the Taxus Liberté DES. Enrollment was halted before completion due to the significant differences in outcomes seen between the groups. For the 57 patients analyzed (6-month angiographic and clinical follow-up), the percent diameter stenosis (primary endpoint) was significantly worse in the DCB group ($43.6\% \pm 27.4\%$) compared to the control group ($24.3\% \pm 25.1\%$; $P = .029$). In addition, the VALENTINES trial is a multicenter, international, short-term registry designed to assess clinical success and efficacy of the Dior paclitaxel-eluting balloon treatment for in-stent restenosis at 6 to 9 months of follow-up. The total intended sample size is 300 patients, and the primary endpoint is clinical success at 6 to 9 months, which is defined as freedom from major adverse cardiac events (death, myocardial infarction, target lesion revascularization, target vessel revascularization, and stent thrombosis). A cohort of the registry will undergo angiographic follow-up at 6 or 9 months to assess in-stent and in-segment late loss and binary restenosis.

FUTURE PERSPECTIVE

Several small clinical studies using DCB have shown encouraging results for the application of this technology in the coronary territory. However, from this point forward, most of the efforts in DCB development will be focused on improving the potential technical limitations of the technology. The safety and efficacy of DCB

in certain applications, such as overlapping areas and in combination with other ancillary therapies such as atherectomy and stents, need to be further evaluated. Most importantly, the risk of distal embolization of the coating elements and its associated risk for tissue toxicity will need to be fully evaluated. In the future, improvements in various aspects of the technology, including alternative antiproliferative agents, carriers, and coatings, will hopefully result in higher tissue transfer and lower particulate embolization rates. However, as new clinical data emerge, the current clinical application of this technology must remain limited to in-stent restenosis, in which almost all platforms have been shown to be successful compared to other clinically approved coronary technologies. Larger randomized clinical trials have the potential to show expanded clinical applications of DCB and its role in coronary intervention. ■

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