New Drugs and Technologies

Drug-Coated Balloons for the Prevention of Vascular Restenosis

William A. Gray, MD; Juan F. Granada, MD

From early in the history of percutaneous cardiovascular intervention, restenosis has been one of the most important clinical and biological measures of success, and a great deal of effort has been put into understanding the mechanisms responsible.\(^1,2\) Restenosis is the result of the interaction of a variety of mechanical and biological processes that begin immediately after balloon injury, including early vessel recoil,\(^3,4\) negative vascular remodeling,\(^5\) and excessive neointimal proliferation.\(^6-7\) The most important limitations of balloon angioplasty, abrupt vessel closure resulting from elastic recoil and occlusive plaque dissection, were effectively solved by the introduction of balloon-expandable stents.\(^8\) However, in-stent restenosis (ISR), the result of the initial injury and the vascular response to the implanted metallic prosthesis leading to excessive neointimal proliferation, remained as the most important cause of failure of these devices.\(^9,10\) Drug-eluting stents (DES) effectively reduced ISR by addressing the biological mechanisms of neointimal proliferation and have become the mainstay of the interventional treatment of coronary atherosclerotic disease.\(^11\) However, the demonstrated efficacy of DES is balanced by the small but unpredictable risk of very late stent thrombosis thought to be due to delayed vascular healing resulting from either the initial antiproliferative effect (and associated late acquired incomplete stent apposition) or a hypersensitivity reaction to the drug, polymer coating, or their combination.\(^12,13\) Moreover, beyond the coronary vasculature, there has been a paucity of effective therapies to manage restenosis after intervention.

In recent years, drug-coated balloons (DCBs) have emerged as a therapeutic alternative in the interventional field.\(^14\) With this technology, short-term transfer of antiproliferative drugs to the arterial wall is achieved without the requirement of an implanted drug delivery system, thus potentially reducing the untoward effects associated with polymer-based stent technologies. In small clinical randomized trials, paclitaxel-coated balloons have been shown to be safe and effective in reducing restenosis among patients with coronary ISR\(^15\) and de novo femoropopliteal lesions.\(^16\) In this review, we discuss the basic principles of the DCB technology, pharmacokinetic profiles, and current preclinical and clinical data available today.

Balloon-Based Local Drug Delivery Revisited

The concept of delivering biologically active compounds into the vessel wall as a single-time dose treatment during an interventional procedure to prevent restenosis has been present for almost 20 years.\(^17-20\) However, despite extensive efforts to improve the efficiency of local arterial delivery through a variety of transfer methods, several studies showed a marked variability of the site-specific uptake and a rapid washout of the delivered compounds, thus limiting the enthusiasm for these technologies.\(^21,22\) In addition, the successful development of easy-to-use balloon-expandable coronary stents superseded advances in balloon-based drug delivery technologies; with the subsequent successful application of antiproliferative agents to the stent surface and a marked improvement in efficacy, there was further uncertainty around both the need for and feasibility of balloon-based drug delivery technology.

Several biological, technical, and clinical aspects make balloon-based local drug delivery an increasingly attractive alternative to current DES technologies for the treatment of atherosclerotic cardiovascular disease. First, in contrast to the challenge encountered by researchers in the past, several antiproliferative agents with a successful record of clinical safety and efficacy are now available.\(^23-25\) Second, there is the theoretical advantage of greater drug delivery per square millimeter of balloon surface with DCBs compared with surface doses on DES, which may translate to greater therapeutic efficacy. In addition, the lack of the ongoing presence of both drug and polymer may lead to more rapid vascular healing and/or a reduction in inflammation related to any hypersensitivity to those elements, possibly leading to a shorter time requirement for dual antiplatelet therapy. From a technical point of view, the ease of use and high deliverability of balloon-based drug delivery systems open an opportunity for their use in coronary territories in which DES can be problematic or have not proved to be particularly effective such as small vessels, bifurcations, long lesions, ostial lesions, and saphenous vein grafts. Finally, DCB technologies have the potential to improve outcomes in other noncoronary arterial territories in which DES have thus far proved to be ineffective such as the femoral-popliteal distribution or where restenosis has been particularly problematic as in
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These methods appear to be inadequate as standalone solutions to satisfy the aforementioned performance requirements. Most involved in the field believe that thin, homogeneous coatings consisting of both drug and adjunctive vehicles for both retention and release will be an integral component of successful drug delivery for DCB. Accordingly, a variety of methods have been identified for this purpose including polymer-based balloon coatings in which the drug diffuses through a matrix, resorbable polymers liberated during balloon inflation from which encapsulated drug is released into the vascular tissue, and balloon surface modifications that increase surface area and retention (eg, etchings) combined with amorphous coatings. However, the chief experience has been with the use of nonpolymeric carriers (contrast agents, fatty acids, urea, etc) that are able to provide a uniform coating while enhancing the transfer capabilities of lipophilic drugs into the vascular tissue. In particular, the use of hydrophilic spacers, specifically the contrast agent iopromide, aids in creating a high-contact molecular surface area between the lipophilic drug and the vessel wall, thus enhancing the bioavailability of the drug while remaining biologically inert.

The ideal antiproliferative agent for use on DCB would have both important biological and manufacturing qualities. Biological properties would include high lipophilicity that facilitates its retention in the vessel wall after drug transfer and therefore a longer-term antiproliferative action. Importantly, no local, downstream vascular bed or systemic toxicity at doses adequate to inhibit local restenosis can result from DCB use, so the agent must have a reasonably wide therapeutic window. The manufacturing qualities important to the application of the agent to the balloon surface include the ability to create a uniform distribution of a specific drug concentration along the balloon surface (ie, it mixes well with any potential carrier agent), minimal loss or disruption of coating with packing, sterilization and handling before use, a reasonable shelf life, and a minimal loss or disruption on transitioning the balloon through catheter/vasculature and on initial inflation until the balloon surface/drug reaches the vessel wall. In addition, although not discussed here in depth, balloon characteristics such as the method of wrapping and its inflation pattern are important adjuncts of drug retention and delivery.

Most of the data available today for antiproliferative agents in DCB technology relate to paclitaxel.29–31 This drug exerts its potent antiproliferative effect by binding to the β subunit of tubulin, resulting in arrest of microtubule function. Paclitaxel is also characterized by prolonged tissue retention rates,25,32 which is desirable in any DCB compound under consideration. Several studies have shown that after a short exposure to the drug, there is a sustainable structural modification of the cytoskeleton of human smooth muscle cells that alters their proliferation and migration over a period of at least 14 days without showing rebound or cytotoxic effects.25,31 Although different in their mechanism of action and biological response,34 compounds such as sirolimus and its analogs have been tested and found, at least in preclinical models, to have qualities that might allow their consideration as alternatives to paclitaxel.35 Compared with a dextran control, both sirolimus and paclitaxel exhibited similar tissue

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Table 1. Technical and Biological Considerations for the Development of DCB Technologies

<table>
<thead>
<tr>
<th>Drug features</th>
<th>Coating features</th>
<th>Delivery features</th>
<th>Catheter features</th>
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<tbody>
<tr>
<td>Chemical structure of the drug (lipophilic=&gt;hydrophilic)</td>
<td>Homogeneous coating thickness</td>
<td>Rapid drug transfer (&lt;60 s)</td>
<td>Minimal drug loss during catheter transit and inflation</td>
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<td>Sustained biological effect at nanomolar scale</td>
<td>Homogeneous drug concentration throughout the surface coated area</td>
<td>Homogeneous and precise drug transfer</td>
<td>Optimal vessel wall contact on delivery</td>
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<td>Controlled drug concentration within a predetermined nominal range</td>
<td>Efficient (high transfer, low loss ratio)</td>
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<td>Coating fragmentation into submicron particles on balloon inflation</td>
<td>Rapid dissolution of the coating on vessel contact</td>
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arterial-venous fistulas for dialysis access.27 As a result of both the technology advances and certain ongoing unsatisfied clinical needs, a wide variety of balloon-based local drug delivery devices have continued to evolve, along with the potential of working in combination with other established interventional devices (ie, atherectomy). Although several methods of balloon-based drug delivery have been developed (eg, weeping balloons, dual balloons creating a chamber for infusate to dwell), we focus this review primarily on current DCB technologies because the majority of the preclinical and clinical data concern these technologies.

Technical Considerations for DCB Development

Although the concept of balloon-based drug delivery appears straightforward on first reflection, several biological and methodological factors must be considered in the development of effective DCB technologies (Table 1). In contrast to DES technologies in which drug delivery is relatively controllable for several weeks and specific elution profiles can be achieved largely through the manipulation of the polymeric coating, the success of DCB devices relies on the rapid transfer of a single dose of an antiproliferative agent into the vessel wall with the expectation of a durable biological effect. Therefore, the dominant design challenge for the success of this technology is the development of a coating system with properties robust enough to physically maintain the agent on the surface of the balloon during transit of the device through the vascular system but still allow its rapid, uniform, efficient, and directed (ie, with limited downstream distribution) transference to the vessel wall during balloon inflation.

Before we examine the options available for antiproliferative agents, it is important to highlight the importance of adjunctive transfer agents and coating methods intended to optimize balloon delivery and vascular retention of the chosen therapeutic agent. Although initial concepts relied on balloon fold geometry to permit efficient drug transportation,
uptake kinetics and avid tissue binding that was significantly greater than dextran.\textsuperscript{36} In the same study, however, there appeared to be a differential in the vascular wall depth of drug transfer between the 2 agents, with paclitaxel demonstrating a significantly greater tissue levels in the adventitia. Although in vivo balloon transfer of pure drug (no carrier) appears to be more effective for paclitaxel compared with sirolimus (Figure 1), there seems to be a further enhanced effect of transference specifically for paclitaxel when the iopromide molecule is added as a carrier agent (Figure 2). Although small preclinical studies have shown that the short-term delivery of sirolimus may inhibit neointimal proliferation after balloon injury,\textsuperscript{35} it is believed that the biological mechanism of sirolimus and it analogs may necessitate constant tissue levels for a more prolonged period of time, and the development of more sophisticated carriers could be required for this class of drugs.\textsuperscript{37,38} Because of its lipophilicity and other pharmacological properties, early data suggest that zotarolimus may have the best profile among the sirolimus analogs for this particular application.\textsuperscript{39}

**Proposed Mechanism of Action**

The mechanism of action by which single application of a antiproliferative drug dose using paclitaxel-based DCB works to inhibit restenosis is still unknown but likely depends on the presence of a carrier and the resultant tissue kinetics, with several reports on the paclitaxel-iopromide DCB as contributing to this understanding.\textsuperscript{14,28} With this combination used in preclinical models, drug transfer occurred relatively quickly, possibly within the first 10 seconds of balloon inflation.\textsuperscript{40} In nonatherosclerotic porcine models, \( \approx 10\% \) to 15\% of the total dose loaded on the balloon is immediately transferred into normal coronary arteries, with tissue levels of paclitaxel declining rapidly thereafter; at 72 hours, the levels are < 75\% of the original tissue levels (Figure 3). However, after this initial washout, more prolonged tissue retention is suspected as an explanation for the sustained biological effect seen in human clinical studies. In addition, the amount of vessel uptake of paclitaxel appears to be influenced by both the presence of a stent and whether the delivery balloon was used as a predilatation or postdilatation device\textsuperscript{14}; however, current models do not account for the possible effects of atheromatous plaque on uptake or retention. In contrast to paclitaxel, the direct delivery (without a carrier) of sirolimus appears to be inefficient (Figure 2), and nanoparticle-based delivery of sirolimus may become an important and necessary adjunct for the delivery of this group of drugs.\textsuperscript{38} As a proof of concept, then, the short-term transfer of antiproliferative agents into vascular tissue by short-term balloon contact appears to be feasible and, at least in the case of the paclitaxel-iopromide combination, to be capable of maintaining tissue levels over time to induce a favorable clinical impact on clinical restenosis.

![Figure 1](image1.png)

**Figure 1.** In vivo transfer of rapamycin (Rapa) and paclitaxel (Ptx) to arterial tissue without a carrier molecule. Angioplasty balloons coated only with drug were deployed in normal swine arteries. Left, Rapamycin or paclitaxel tissue levels at 24 hours after drug delivery. There was a significant 3-fold difference in tissue levels at 24 hours among both groups. Right, Residual drug concentration remaining on the balloons after inflation. Figure courtesy of Caliber Therapeutics Inc, Monmouth, NJ.

![Figure 2](image2.png)

**Figure 2.** Effect of iopromide on sirolimus and paclitaxel (Ptx) transfer to the arterial tissue in vivo. Angioplasty balloons coated with both drugs formulated with iopromide were deployed in normal swine arteries. All arterial segments were analyzed for iopromide and either sirolimus or paclitaxel levels. Left, Tissue concentrations at 24 hours after balloon inflation. For each group, levels are given of the respective drug and iopromide extracted from the same samples. Right, Residual drug and iopromide levels found on the balloons after in vivo deployment. Rapa indicates rapamycin. Figure courtesy of Caliber Therapeutics Inc, Monmouth, NJ.
Preclinical Data on Safety and Efficacy
In several animal models of restenosis, the intramural delivery of paclitaxel has demonstrated high tissue retention rates and inhibition of neointimal proliferation after balloon injury.20–31,41,42 and like the preliminary in vivo work to date, most of the published preclinical data on balloon-based drug delivery concern paclitaxel. An important step forward in the field of local drug delivery occurred with the introduction of contrast agents (specifically iopromide) as a way to solubilize and promote delivery of crystalline paclitaxel to the arterial wall.28 Supported by early cell culture data demonstrating that the addition of iopromide to paclitaxel enhanced smooth muscle cell inhibition compared with paclitaxel alone, Scheller et al28 confirmed that the intracoronary injection of an iopromide-paclitaxel combination led to decreased restenosis rates after bare metal stent (BMS) implantation in a porcine model of restenosis. The first available preclinical data on DCB used the relatively crude combination of iopromide-paclitaxel directly deposited within the folds of an angioplasty balloon. With the normal porcine model of coronary restenosis, BMS crimped on iopromide-paclitaxel DCB system resulted in comparatively less neointimal formation.Thim et al44 tested several paclitaxel-iopromide formulations for short-term drug transfer and neointimal formation by using BMS crimped on uncoated balloons.14,43

Although some of the initial research in DCB technology was begun more than a decade ago, data on short-term drug transfer, its in vitro biological effects, and long-term pharmacokinetics are still emerging. In an early rabbit model, Herdeg et al30 demonstrated that although only 2% to 3% of paclitaxel was delivered to the vessel wall with a basic noncarrier formulation, the sustained presence of paclitaxel in the vessel wall was confirmed by microtubule staining at 1 week (Figure 3). In the same study, vessel recoil and remodeling were found to be substantially less with paclitaxel DCB compared with standard balloon angioplasty. Although much of the attention on efficacy of DCB has rightly been focused on neointimal suppression, these data on the effects of DCB on the mechanical elements of restenosis will also be important in the ultimate clinical efficacy of this approach. Subsequent study in a coronary porcine model has demonstrated a marked reduction in paclitaxel tissue levels as a percentage of the initial balloon load over the first 24 hours but an apparent stabilization of tissue levels at 72 hours (Figure 4) (internal data, Bayer Schering Pharma/MEDRAD Inc, Minneapolis, Minn). Again using the porcine model of coronary restenosis, Cremers et al40 confirmed that drug transfer occurs very early after balloon inflation. In a similar model, Thim et al44 showed that after an initial transfer dose of between 10% and 12%, paclitaxel tissue levels decrease by >80% 24 hours after balloon transfer. In addition, the safety profile of applying several balloon inflations within the same vascular segment using either the same or an additional DCB system has been demonstrated.40 Interestingly, in contrast to the common late restenosis “catchup” phenomenon seen in the porcine model with current DES technologies, the antiproliferative effect for DCB is maintained over time. Few published studies have addressed the impact of the variety of possible balloon coating formulations on safety and efficacy. Cremers et al45 compared the iopromide-paclitaxel DCB combination with a surface-modified (roughened) balloon passively coated with paclitaxel and found that the iopromide-paclitaxel DCB system resulted in comparatively less neointimal formation. Thim et al44 tested several paclitaxel-iopromide formulations for short-term drug transfer and neointimal formation by using BMS crimped on the coated balloons and deploying them in normal porcine coronary arteries. In this study, formulations displaying high-delivery efficiency (8.8±3.9% of the original loaded dose at 5 minutes) and prolonged presence in tissue (3.5±1.0% of the original loaded dose at 24 hours) reduced angiographic late lumen loss (LLL) by 70% and 50% and histological neointimal area by 60% and 53%, respectively, compared with control uncoated balloons.

There are fewer preclinical data on the safety, efficacy, and tissue pharmacokinetics of DCB in peripheral arteries where,
Milewski et al. recently tested predilatation with paclitaxel levels by 72 hours (J.F.G., unpublished data, 2009). There is less within the first 60 minutes, and a rapid decay occurring after initial balloon inflation, a decay that is potentially less effective. Second, DCBs used for noncoronary arteries are by necessity larger with a greater surface area and thus may result in higher drug losses during transit and inflation. The preclinical data that do exist on noncoronary arteries are by necessity larger with a greater potential for edge effect and geographic miss.

Figure 5. Synergistic effect of predilatation with a paclitaxel DCB (Cotavance, PACCOCATH Technology, Bayer Schering Pharma/ MEDRAD Inc) on BMS implantation in the SFA restenosis swine model. Right external iliac (REI) was predilated with a paclitaxel-coated balloon before stent implantation. The right SFA (RSFA) was predilated with an uncoated balloon of identical size. Peripheral angiography taken 2 days after stent implantation. Histological pictures courtesy of Dr Renu Virmani, CVPath Institute Inc, Gaithersburg, Md. Figure courtesy of Krzysztof Milewski, Skirball Center for Cardiovascular Research, Orangeburg, NY.

compared with their coronary application, 2 important differences exist. First, self-expanding (usually nitinol) stents typically used in some cases may actually promote neointimal formation over years, so a single application of an antiproliferative may be less effective. Second, DCBs used for noncoronary arteries are by necessity larger with a greater surface area and thus may result in higher drug losses during transit and inflation. The preclinical data that do exist on DCBs in peripheral arteries suggest tissue kinetics similar to those of coronary arteries, with an early small peak in tissue levels occurring after initial balloon inflation, a rapid decay within the first 60 minutes, and a >90% decrease in tissue levels by 72 hours (J.F.G., unpublished data, 2009). There is less similarity when self-expanding nitinol stents are applied. Milewski et al. recently tested predilatation with paclitaxel DCB versus control balloons followed by self-expanding nitinol stents using a novel model of restenosis in the porcine superficial femoral artery (SFA) territory; they noted a dose-dependent decrease in neointimal formation. However, although a single balloon application was marginally effective, the double use of a paclitaxel DCB resulted in 60% less neointimal area compared with control balloons (Figure 5). The findings of this study are interesting because they suggest that a higher dose may be required to inhibit the more prolonged proliferative response elicited by self-expanding stents.

Preclinical data using sirolimus analogs delivered on DCB platforms are scarce, with several drug carriers tailored to deliver these compounds under development. An early report, a rabbit iliac model of restenosis, demonstrated that the single application of sirolimus using a local drug delivery device (not DCB) decreased restenosis after balloon angioplasty. More recently, a zotarolimus DCB decreased restenosis compared with control balloon angioplasty in a coronary porcine model of restenosis.

In summary, although significant lessons have been learned as to the biology, safety, and efficacy of paclitaxel delivery via DCB technologies using the coronary model of restenosis, less is understood about their use in other vascular territories such as the SFA. Interestingly, based on the currently available data, this inhibition of neointimal hyperplasia is accomplished with relatively low tissue levels vis-à-vis the dose loaded on the balloon, leaving open the possibility lower balloon dosing if greater transfer mechanisms can be developed.

Clinical Data

In the United States, no DCB devices have been approved for human use. In Europe, regulatory approval currently exists for 4 coronary devices—SeQuent Please (B. Braun, Melsungen, Germany), In.Pact Falcon (Invatec, Roncadelle, Italy), Dior (Eurocor, Bonn, Germany), and Elutax (Aachen Resonance, Aachen, Germany)—and 3 peripheral devices—In.Pact Admiral for the SFA (Invatec), In.Pact Pacific for the SFA (Invatec), and In.Pact Amphirion for infrapopliteal vessels (Invatec). There is only now an emerging, and incomplete, body of data in the literature on the clinical safety and utility of DCBs as a standalone therapy. In addition, using DCB in combination with BMS raises questions of both safety and efficacy given the potential for edge effect and geographic miss.

Pharmacokinetics

In the current iteration, because the amount of drug delivered by the coated balloon to the vessel wall is a minor fraction of the total dose loaded, the majority of the drug is distributed into the bloodstream either before or during balloon inflation. Therefore, defining the systemic dose of drug delivered in this pulse is important, especially given the potential to use larger, longer, and possibly multiple coated balloons particularly in a peripheral vascular application. In a recent presentation (“An Open-Label, Multicenter Study to Investigate Plasma Levels and Catheter Tolerability Following Application of Paclitaxel Coated Balloon Catheter in Patients With Stenotic, or Occluded Femoro-Popliteal Arteries Due to Atherosclerosis” presented by T. Zeller at the Vascular Interventional Advances 2009; Las Vegas, Nev), 14 patients treated at 2 sites for femoropopliteal disease with DCBs had blood sampling at multiple time intervals before and after treatment with balloons ranging up to 5×100 mm, in addition to monitoring vital signs and ECG analysis. There were no untoward physical or ECG findings, and the immediate postintervention mean blood level of paclitaxel was roughly an order of magnitude less than the mean therapeutic levels sustained during chemotherapeutic use. Moreover, the blood levels dropped quickly so that at 2 hours more than half the
samples were below the lower limit of quantification. The investigators concluded that although the study was small with a considerable heterogeneity of both patients and balloon sizes, it suggested a reasonable safety margin of systemic paclitaxel in this setting. However, it is not yet known what, if any, systemic effects the use of longer or multiple balloons in more extensive SFA disease will have.

Coronary Application

Although DES have become the de facto standard for coronary intervention today, specific challenges remain to their use relative to both the stent prosthesis and the biological activity of the drug and polymer. Specifically, coronary territories such as bifurcations, small vessels, saphenous vein grafts, long lesions, and diabetic disease all have less robust outcomes with DES than do simpler lesions. In addition, although the incidence is small and appears to be dropping with more recent generations of DES, very late stent thrombosis continues to be a serious clinical event when it occurs. In addition, the current need for at least 6 months of dual antiplatelet therapy can be clinically challenging for some patients with medication intolerance and bleeding, and the possible consequences of nonresponders to antiplatelet therapy are still being elucidated. DCBs have the potential to improve outcomes in at least some of the vascular territories mentioned and to require a more limited duration of dual antiplatelet therapy. Although some of the mechanisms of DCB effects have not been clearly defined, several randomized clinical studies speak to the efficacy of the technology in at least 2 different vascular beds. Before reviewing these data, it is important to note that, as can be ascertained from the previous preclinical survey, not all DCB are formulated the same, and the specifics as to formulations (to the extent that they are known) are called out before the clinical trial results are discussed.

The first report of DCB use in humans was published in 2006. In this multicenter study, 52 patients with coronary ISR were randomized to angioplasty with standard uncoated balloon or a 3-μg/mm² iopromide-paclitaxel–coated balloon (PACCOCATH, licensed by Bayer Schering Pharma); aspirin and clopidogrel were given for 1 month followed by aspirin alone. Baseline demographics, angiography, and short-term procedural outcomes were not different between the 2 groups. At the 6-month angiography, the PACCOCATH group demonstrated a marked difference in the primary end point of less in-segment LLL (0.76±0.86 versus 0.09±0.49 mm; P=0.003). Secondary end points of minimal lumen diameter and binary restenosis at 6 months were also significantly better in the DCB group. In an extension of this study, an additional 56 patients with coronary ISR were similarly randomized, and the entire cohort of 108 patients were followed up for 2 years. The 6-month angiographic primary end point of in-segment LLL was consistent with the original report, plus in-segment binary restenosis of only 6% for the coated-balloon group compared with 51% for the uncoated-balloon group without findings of notable effects for gender or the presence of diabetes mellitus. A sustained clinical effect of PACCOCATH was noted at 24 months with significant reductions in target lesion revascularization (TLR; 37% versus 6%; P=0.001); no subacute thrombosis or other safety issues were noted in the DCB group.

Another group of investigators have initiated a series of studies (Paclitaxel-Eluting PTCA–Catheter In Coronary Disease [PEPCAD]) to test the same DCB PACCOCATH formulation (SeQuent Please, licensed by B. Braun) in a variety of coronary therapy comparisons. PEPCAD I was a nonrandomized study investigating the safety and efficacy of the SeQuent Please DCB with or without a cobalt chromium stent (Coroflex) in small-vessel (mean reference vessel diameter, 2.36 mm) de novo lesions in 120 patients (B. Scheller, presented at the 74th Meeting of German Cardiac Society; Mannheim, Germany; 2008). At the 6-month follow-up, in-segment LLL was significantly less with DCB alone compared with DCB plus stent (0.18 and 0.73 mm, respectively); most of the restenosis was noted at the stent edges, presumably where DCB contact was inadequate. Although underpowered for an assessment of stent thrombosis, it was nevertheless noted that vessel thrombosis occurred less frequently in the DCB alone group despite a shorter duration of dual antiplatelet therapy (3 versus 6 months).

PEPCAD II was a multicenter, randomized trial of the SeQuent Please DCB versus the TAXUS Liberté DES in 131 patients with coronary ISR. In 2 well-matched groups of patients with vessels averaging ~3.0 mm in diameter, the primary end point of 6-month in-segment LLL was significantly less with the DCB compared with the DES (0.17±0.42 versus 0.38±0.61 mm; P=0.03). At 12 months, TLR trended in favor of the DCB (6% versus 15%; P=0.15), leading the authors to conclude that DCB was at least as effective as DES for coronary ISR without the need for repeat stent implantation. Results from the PEPCAD III (C.W. Hamm, presented at the AHA Scientific Sessions; 2009; Orlando, Fla) were recently disclosed. This multicenter randomized study paired the same SeQuent Please DCB with a BMS and compared it with the Cypher sirolimus-eluting stent (Cordis/Johnson & Johnson, Miami Lakes, Fla) in 637 patients with single de novo coronary lesions between 2.5 and 3.5 mm in diameter and <24 mm long. The primary angiographic end point of 9-month in-stent LLL was significantly better for the DES compared with DCB/BMS (0.16±0.39 versus 0.41±0.51 mm; P<0.001), although there was less difference in in-segment LLL (0.11±0.40 versus 0.20±0.11 mm; P=0.06). In addition, the 9-month clinical efficacy end points of TLR and target vessel revascularization favored the DES approach, as did the safety end points of myocardial infarction and stent thrombosis. The investigators concluded that DCB efficacy at the stent margin had been achieved although noninferiority with Cypher DES was not achieved in the DCB/BMS arm and that LLL for the combination therapy was comparable to paclitaxel-eluting stent.

In the paclitaxel-eluting balloon versus paclitaxel-eluting stent in small coronary vessel disease (PICCOLETO) trial (B. Cortese, presented at EuroPCR09, Barcelona, Spain), a different paclitaxel-eluting balloon construction that did not involve a carrier molecule was used (Dior, Eurocor, Bonn, Germany). The single-center trial intended to enroll a total of 80 patients with de novo small-vessel (<2.75 mm) disease, randomizing them to either the Dior DCB or the TAXUS
Liberté DES. Enrollment was halted after two thirds of the originally intended number were enrolled because of marked outcome differences between the groups. For the 57 patients with complete 6-month angiographic and clinical follow-up, the primary end point of percent diameter stenosis appeared significantly worse in the DCB group (43.6±27.4% versus 24.3±25.1%; P=0.029). Corollary findings of significantly less minimal lumen diameter and more binary restenosis in the DCB arm were also noted. The investigators concluded that the Dior DCB failed to show equivalence to the TAXUS Liberté DES and hypothesized that adjunctive stenting in the DCB may be required to achieve DES-like results.

Next in the PEPCAD series of investigations, the results from PEPCAD V (D. Mathey, presented at Transcatheter Therapeutics 2009; San Francisco, Calif) were recently disclosed. This study was a single-arm feasibility and safety trial using DCBs (SeQuent Please) for the treatment of coronary bifurcation disease, specifically by using DCB in main and side branches, a BMS in the main branch, and a provisional BMS strategy in the side branch. Twenty-eight patients were treated in 2 sites in Germany with low side branch stenting rate (8%) and LLL of 0.38 mm in the main branch and 0.21 mm in the side branch at 9 months. Achievement of the primary end point (<30% stenosis in the main branch, <50% stenosis in the side branch) occurred in 97% and 89% of vessels, respectively. Although there were no deaths in the follow-up, 2 late stent thromboses occurred (1 definite, 1 probable) in the main branch stent. The investigators concluded that there was evidence of efficacy but that the late stent thrombosis noted raised the issue of the safety for DCBs used in combination with BMS.

**Peripheral Vascular Application**

Long-term patency after endovascular intervention is variable according to the vascular bed, but the most relevant vascular territory with the greatest demonstrated need for reduced restenosis rates is the contiguous SFA and popliteal artery (femoropopliteal), which today is responsible for most of the lifestyle-limiting claudication present in clinical practice. Taken together, these vessels are the longest nonaortic conduits in the body (at times >300 mm) and are often significantly calcified and chronically occluded throughout their length. Importantly, they are subject to not only the potential for external compression but also complex forces during hip and knee flexion, including bending, torsion, and axial elongation/shortening. Balloon angioplasty has proved to be inferior to stent implantation for moderate length lesions (≥13 cm), but 1-year patency rates even with stents was still only 63%. In the longer lesions commonly encountered in practice patency, it is even worse.

Unlike the coronary artery, DES have not proved to be effective in reducing restenosis in the femoropopliteal territory; at least 2 trials with self-expanding nitinol stents coated with either sirolimus or everolimus (F. Lammer, presented at CRSE Meeting; 2009) using a durable polymer failed to show efficacy. Results from a third trial using paclitaxel without a polymer to modulate its release are pending. Many involved in this field believe that among the explanations for the failure to date of DES in the femoropopliteal region is the tendency for stents to fracture (because of the forces listed), which appears to be associated with restenosis, the ongoing irritant of a rigid stent interacting with a vessel constantly in motion, and the lack of the correct “formula” of drug dose and duration when accounting for stent provocation of intimal hyperplasia in this unique vessel. Therefore, development of DCB technology holds the promise of improved outcomes without a permanent stent implant.

The first human examination of DCB in a noncoronary territory, the Local Taxane With Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) trial, was multicenter study involving a 3-way randomization of 154 patients with either stenosis or occlusion of a femoropopliteal segment to standard balloon angioplasty (control), to an iopromide-paclitaxel (3 μg/mm², PACCOCATH)–coated balloon, or to paclitaxel mixed with iopromide contrast (0.171 mg/cm³) and used for a standard balloon procedure up to a maximum dose of 17.1 mg. With a mean lesion length of ~7.5 cm, there was a marked reduction in the iopromide-paclitaxel balloon group for the primary end point of 6-month angiographic LLL compared with both the control balloon and paclitaxel in contrast groups (0.4±1.2 versus 1.7±1.8 versus 2.2±1.6 mm; P=0.001 for DCB versus control). Similarly, TLR at 6 months was reduced in the DCB group compared with control (4% versus 29%; P=<0.001) but with no effect seen with the paclitaxel and contrast groups (29%; P=0.41). The effects of the DCB were sustained to the 24-month follow-up.

A second study using the same coating technology produced strikingly similar results. Referred to as the Femoral Paclitaxel trial, 87 patients underwent 1:1 randomization between control balloon angioplasty and iopromide-paclitaxel–coated balloon angioplasty in relatively short (~6 cm) lesions in the femoropopliteal arteries. The coated balloon exhibited significantly less LLL (primary end point) at 6 months than the control balloon (0.5±1.1 versus 1.0±1.1 mm; P=0.031) and significantly fewer TLR events (6.7% versus 33%; P=0.002), and this difference in TLR was sustained beyond 18 months. Importantly, there were no safety issues related to the balloon coating in either study.

**Future Horizons for DCB Technologies**

Despite the generally encouraging results for DCB to date, there are still many questions to be answered and regulatory processes to be satisfied to gain a wider patient access. Going forward, most of the efforts in DCB development will be focused on addressing the potential limitations of the technology (Table 2). The safety and efficacy of these technologies in certain applications such as overlapping balloons and in combination with therapies, including atherectomy and stents, need to be addressed. Importantly, the risk of distal embolization of the coating elements and any related effects need to be more completely understood, especially in visceral applications. Additionally, as the understanding of the mechanism of action of DCB increases, so does the opportunity to improve various aspects of the technology, including alternative antiproliferative agents and different carrier molecules that could both further extend the tissue residence of the agents and result in more directed deposition of drug into the vessel with reduced wash-off and distal distribution.
Table 2. Development of DCB Technologies: Challenges and Unknown Effects

- Potential for systemic toxic effects
- Mainly peripheral applications (long balloon use)
- Large drug content in long balloons (<10 cm)
- Multiple balloon usage

Potential for local toxic effects
- Overlapping areas
- Heterogeneous drug uptake because of tissue type
- Use of ancillary devices (stents, atherectomy, etc)
- Delayed healing, potential for stent thrombosis

Potential for distal tissue damage
- In any contemplated visceral vessel application

Fragmentation of the coating (embolization)
- Nonvascular drug-carrier toxicity

Multiple clinical studies either are underway or are being planned in the near-term future in Europe and the United States using this technology. They range from coronary to femoropopliteal to infrapopliteal applications, are being performed by several manufacturers, and generally are comparing DCB and balloon angioplasty outcomes. The potential for positive outcomes of these studies could open the application of the technology to other fields such as renal arteries, dialysis fistulas, intracranial, venous, and even aortic valvuloplasty. However, all of these possibilities must be considered against the background of uncertainty as to the question of the essential paradox of DCB therapy: How does a single-dose, single-“elution” treatment deliver sufficient antiproliferative action given the alternate DES paradigm of elution kinetics lasting several weeks? Moreover, the need for stent implantation to maintain short-term vessel patency may limit the application of DCB in certain territories unless safety and efficacy can be shown in combination with permanent metal prostheses.

Summary

The concept that the balloon delivery of a short burst of an antiproliferative agent to a targeted vessel segment as feasible, safe, and effective has been validated in several preclinical and clinical studies with more in progress but has had some mixed results in selected coronary applications. There is still much to learn about the mechanisms and outcomes of the use of DCB, with the potential for improvements in what must be considered an early phase of the technology. Nevertheless, in a short time span, DCBs have demonstrated the capacity to have a significant impact on the practice of percutaneous cardiovascular intervention.

Disclosures

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References


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