

# Mechanisms of Action in Drug-Coated Balloons

Insights into the clinical safety and efficacy of this emerging technology.

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**D**rug-coated balloons (DCBs) have been shown to be efficacious in the prevention of restenosis in the settings of coronary in-stent restenosis<sup>1-3</sup> and peripheral vascular disease.<sup>4-6</sup> Although a significant amount of experimental and clinical data are available,<sup>7-9</sup> there is a paucity of data regarding the impact of the coating formulation on the mechanism of action and overall clinical efficacy. Theoretically, in contrast to drug-eluting stents (DES), DCBs provide the following potential advantages: (1) short-term, non-polymeric-based local drug delivery, (2) no permanent metallic scaffold left behind, and (3) enhanced vessel healing due to the relatively short-term permanence of the drug inside the vessel wall. These benefits are especially important because implantable, polymeric-based drug delivery systems have been associated with foreign body reaction and late stent thrombosis.<sup>10,11</sup>

If proven to be efficacious, DCBs have the potential to shorten the length of dual-antiplatelet agent use, especially when stents are not placed. In addition, compared to DES systems, DCBs have the potential for higher drug tissue bioavailability due to the higher drug surface area presented to the vessel wall.<sup>12</sup> Finally, in certain anatomical locations (ie, long, below-the-knee lesions) in which the use of stents may be difficult or impractical, DCBs are positioned to become the therapeutic tool of choice.

## PHARMACOKINETICS OF DCBS

All DCBs available today utilize paclitaxel in combination with different carriers and excipients. Therefore,

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the resulting pharmacokinetic profile of any given paclitaxel-coated balloon (PCB) relates to the coating type as a result of the interaction of paclitaxel with the carrier during the coating process. The presence of a drug carrier plays a central role in the transfer of paclitaxel into the vessel wall from the surface of a balloon. Pioneering work performed by Speck et al and Scheller et al demonstrated the effect of iopromide in paclitaxel transfer via balloon coating.<sup>7,13-15</sup> Subsequently, iopromide (Ultravist, Schering AG, Berlin, Germany) was the proprietary contrast media used for the first-generation DCB (Paccocath, Bavaria Medizin Technologie GmbH, Oberpfaffenhofen, Germany). This hydrophilic x-ray contrast, apart from serving as a coating matrix for the antiproliferative drug, has been shown to facilitate the rapid transfer of paclitaxel into the vessel wall (< 60 seconds).<sup>14,16</sup> This is likely achieved by enhancing the solubility and vessel adherence of the lipophilic antiproliferative drug.

It is believed that the coating process using this carrier produces a crystalline coating that provides a reproducible pharmacokinetic profile after balloon

delivery. After balloon inflation, approximately 10% to 12% of the drug loaded on this type of PCB is transferred to normal porcine arteries. Tissue levels decline by > 80% in 24 hours,<sup>17</sup> and at 72 hours, there is stabilization of tissue levels (Figure 1). Recent data suggest that tissue levels continue to decline but remain detectable up to 180 days in normal porcine arteries.<sup>18</sup> Another PCB concept using urea as a carrier has demonstrated a similar pharmacokinetic behavior suggesting the presence of similar chemical features within this coating formulation.<sup>19</sup> Other coating types display a faster and steeper decline in tissue levels, resulting in lower long-term tissue retention that is consistent with more amorphous features of the coatings.

Once paclitaxel is transferred to the media of the vessel, tissue clearance depends on well-described pharmacokinetic profiles. Creel et al demonstrated that after paclitaxel delivery, most of the drug is bound to fixed hydrophobic binding sites, and a smaller quantity is transported by diffusive and convective mechanisms.<sup>20,21</sup> The partitioning of paclitaxel into the tissues and drug binding slows transport, which explains the accumulation of drug in sites adjacent to drug delivery. It has been hypothesized that the uptake of drug could be accomplished directly through the lumen or the vasa vasorum and capillaries.<sup>15</sup> The transfer of drug and subsequent binding and long-term tissue levels are regulated by the inherent physico-chemical properties of paclitaxel.<sup>20</sup> Besides acute tissue transfer, the homogeneous distribution of the drug and occupancy of the binding receptor sites may play a central role in the overall efficacy of these technologies.

Considering that the vessel uptake is a minor fraction of the total loaded dose, there have been concerns about the possibility of distal tissue embolization and systemic drug effects. Freyhardt et al studied the bioavailability of paclitaxel in the plasma among 14

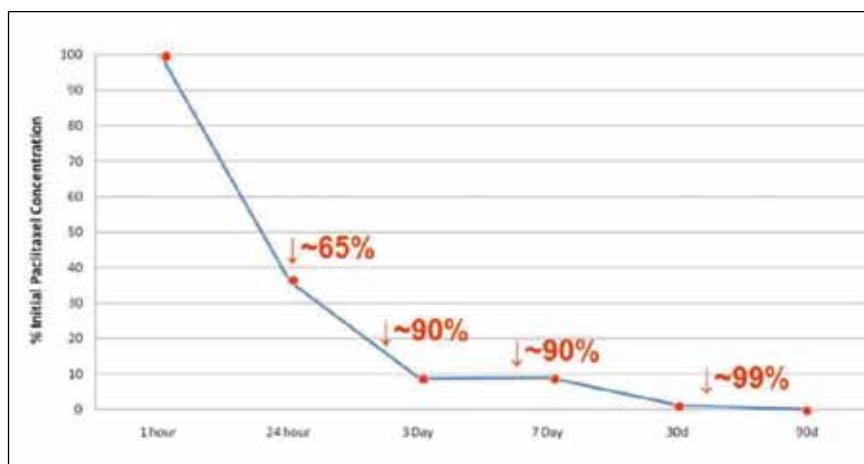


Figure 1. Typical pharmacokinetic profile of a PCB consisting of a crystalline coating.

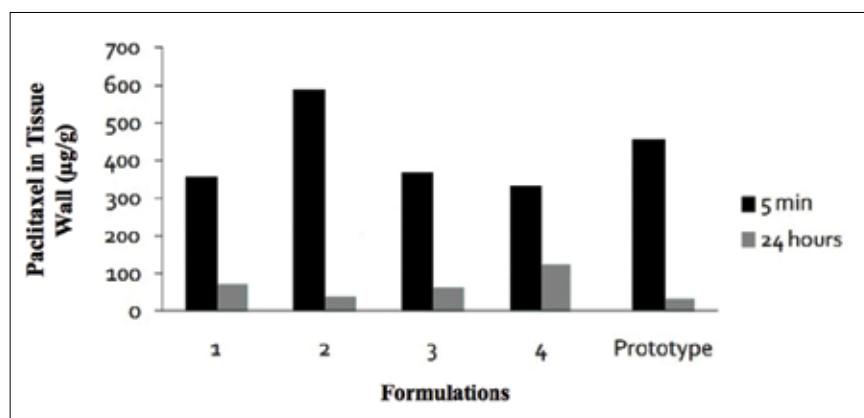


Figure 2. Acute drug transfer after PCB delivery of different paclitaxel-iopromide formulations containing identical concentrations but different solubility profiles. Data obtained from Bayer Pharma AG/Medrad, Inc.

patients with SFA disease who underwent PCB therapy (Cotavance, Bayer Pharma AG/Medrad, Inc., Indianola, PA). A maximum paclitaxel plasma concentration of  $40.1 \pm 76.6$  ng/mL was found immediately after intervention, and within 24 hours, the paclitaxel plasma level was below detectable levels in all patients.<sup>22</sup> Also, despite the majority of the coating dissolving into the peripheral circulation, there is no clinical evidence of acute vascular occlusions or ischemic events among patients undergoing clinical trials of DCBs to treat peripheral vascular disease.

## PHARMACOKINETICS AND COATING FEATURES

Coating characteristics directly influence acute drug transfer and long-tissue retention of paclitaxel after PCB use.<sup>14,16</sup> An earlier generation of PCB in which

paclitaxel was freely deposited to a modified balloon surface proved to be less efficacious in reducing neointima in both preclinical and clinical settings.<sup>16,23</sup> In addition, Cremers et al demonstrated that the percent residual drug on the balloon in which drug was freely deposited was higher (approximately 50%) compared to balloons in which a specific carrier was used (approximately 5%).<sup>16</sup> Subsequently, further changes in the technology, like adding a new carrier (shellac), showed a significant increase in acute drug transfer, highlighting the importance of drug transporters in tissue transfer.<sup>24</sup>

In another study, Kelsch et al compared PCB containing urea (Falcon Bravo, Medtronic Invatec, Frauenfeld, Switzerland) versus iopromide as carriers.<sup>19</sup> In this study, both technologies demonstrated comparable vessel uptake and efficacy by histology. Also, the urea matrix coating showed a dose-dependent neointimal inhibition for doses ranging from 1 to 9  $\mu\text{g}/\text{mm}^2$ . Tissue transfer is also influenced by the final characteristics of the coating that result from the manufacturing process. Figure 2 depicts the *in vivo* acute transfer rates of different coatings containing identical amounts of carrier and paclitaxel but different manufacturing methods.

Compared to the test control (original Paccocath formulation), different patterns of acute transfer rates and short-term retention are achieved. Some of these differences may be explained at least in part by the final solubility of the coating. It has been proposed that more crystalline coatings achieve higher tissue levels and biological efficacy. However, less crystalline coatings (amorphous) have been shown to result in better uniformity and less particulate formation. Therefore, different technological approaches have opted to develop hybrid solutions aiming to balance the safety and efficacy profiles (eg, microcrystalline coatings).<sup>25</sup>

## MECHANISM OF DRUG RETENTION

Although the pharmacokinetic profiles of short-term transfer and long-term tissue retention of paclitaxel have been shown in the experimental setting, little is known about the mechanism of action of PCB. Scheller et al demonstrated that one type of PCB lost approximately 6% of

the dose during transit and approximately 80% during balloon inflation, resulting in approximately 16% of the drug being transferred to the injured vessel.<sup>7</sup> This transfer appears to occur within 10 seconds of balloon inflation,<sup>26</sup> and the biological effects were sustained over time.<sup>23</sup>

Once paclitaxel is transferred into the vessel wall, it acts by altering cytoskeletons in cells and irreversibly inhibiting arterial smooth muscle cell proliferation.<sup>27</sup> Its unique mechanism of action, as well as its highly lipophilic profile, makes this drug ideal for this particular application inhibiting cell proliferation after a single-dose use.<sup>28</sup> This differs from DES, in which the stent is deployed with a fixed amount of drug per unit of metal surface area and a polymeric delivery system releasing a prespecified amount of drug over time (Figure 3). The sustained drug release in DES has been identified as a culprit of delayed healing, which increases the risk of late thrombosis.<sup>29,30</sup>

Contrary to DES, which elute drug primarily to the stented-dilated area, DCBs have the potential to deliver an identical amount of paclitaxel proximally and distally to the stented segments.<sup>14</sup> Cremers et al studied different doses of paclitaxel inflated at 10, 60, and 2 X 60 seconds using two different DCBs (inflating one for 60 seconds and then another for 60 seconds in the same position) in the porcine coronary overstretch and stent implantation model.<sup>26</sup> They found no difference between a 10- and 60-second inflation time, indicating that most of the drug is released immediately after inflation.

Another interesting observation is the fact that the degree of neointimal inhibition was not increased by

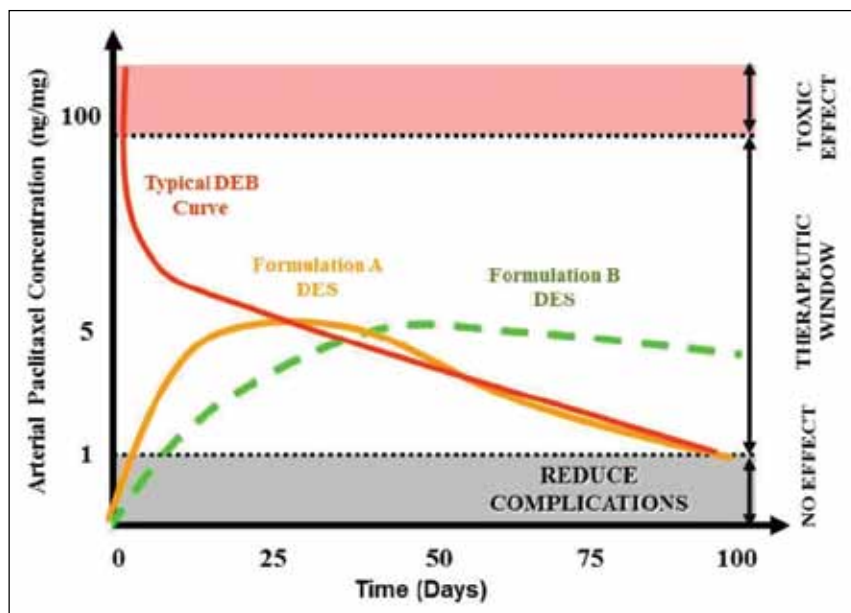


Figure 3. Schematic comparison of pharmacokinetic tissue profiles of PCBs and DES.

the use of multiple balloons inflated at the same site. Tissue tolerance and absence of toxicity (thrombosis, aneurysm, etc.) was demonstrated even at the maximum dose of 10  $\mu\text{g}/\text{mm}^2$  (mimicking two overlapping balloons or three times the therapeutic dose). Cremers' group also investigated the short- and long-term effects of bare-metal stents (BMS) crimped on PCBs compared to DES (Cypher [Cordis Corporation, Bridgewater, NJ] and Taxus [Boston Scientific Corporation, Natick, MA]). At 6 months, there was a comparable degree of neointimal proliferation in the PCB plus BMS group to commercially available DES technologies, confirming that despite a short transfer, the efficacy of PCBs extends to long-term follow-up.<sup>31</sup>

The method of drug delivery (with or without the presence of a stent) also causes variations in the amount of drug found in the tissue. In an experimental study, it was demonstrated that delivery was always more efficient when BMS were present (approximately 17% of the loaded dose on BMS crimped on PCBs and approximately 16% after BMS postdilation with PCBs) compared to PCB only (approximately 8%).<sup>7</sup>

Additional research has been presented in regard to the mechanism of drug transfer and retention of PCB technologies through the development of computational models and experimental studies. It has been proposed that after balloon PCB dilatation, paclitaxel is deposited on the vessel lumen and serving as a reservoir that allows paclitaxel to subsequently diffuse into the deeper vascular layers (medial and adventitial). Over time, therapeutic drug levels are attained in the deep layers while the drug level rapidly becomes subtherapeutic on the vessel surface (Figure 4A). As shown in Figure 4B, the mechanism of drug distribution in DES differs significantly, as the drug levels in the vessel lumen and deep tissue layers are constant due to sustained delivery of the drug.

## CONCLUSION

Despite the large amount of experimental and clinical data presented to date, the mechanism of drug reten-

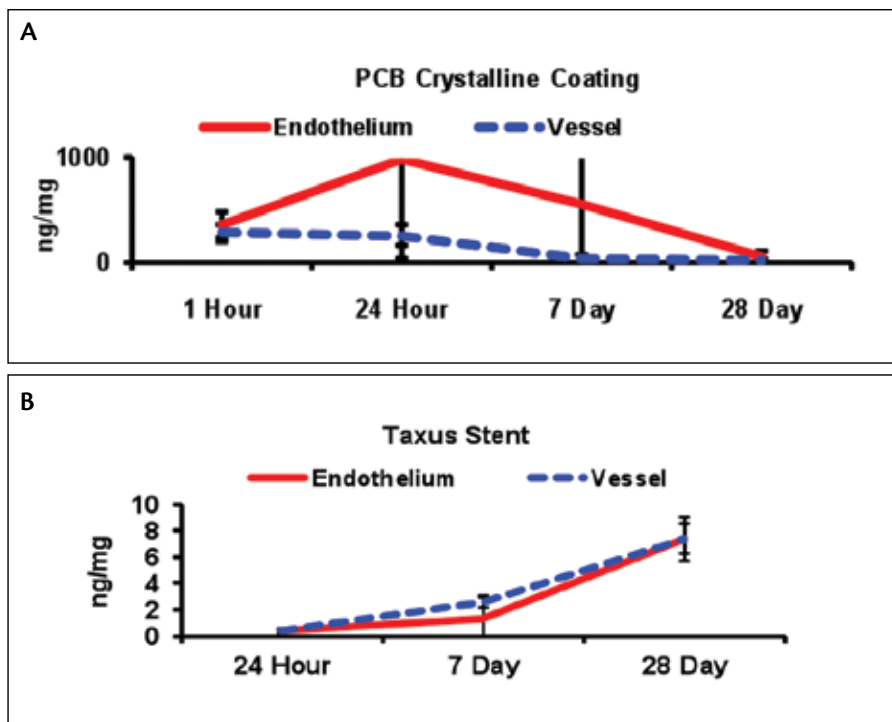


Figure 4. Comparison of tissue paclitaxel retention on the vessel surface versus the vessel wall of crystalline PCB (A) and the paclitaxel-eluting stent, Taxus (B). Data obtained from Bayer Pharma AG/Medrad, Inc.

tion following PCB use remains unknown. The need for drug carriers appears to be critical during the process of initial drug transfer. In addition, the coating characteristics (eg, degree of crystallinity) affect long-term tissue levels. These particular pharmacokinetic characteristics are important because they may have an impact on the overall vascular toxicity and patient safety. A more extensive understanding of the mechanism of action, pharmacokinetics, and alternative antiproliferative agents will be important in the improvement of the technology. Nevertheless, preliminary data suggest that local drug delivery via balloon platforms is feasible, and this technology has the potential to become an important player in the field of endovascular therapies. ■

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- Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355:2113-2124.
- Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol*. 2008;97:773-781.
- Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119:2986-2994.
- Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358:689-699.
- Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118:1358-1365.
- Micari A, Cioppa A, Vadala G, et al. A new paclitaxel-eluting balloon for angioplasty of femoropopliteal obstructions: acute and midterm results. *EuroIntervention*. 2011;7 (suppl K):K77-82.
- Scheller B, Speck U, Abramjuk C, et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation*. 2004;110:810-814.
- Speck U, Scheller B, Abramjuk C, et al. Neointima inhibition: comparison of effectiveness of non-stent-based local drug delivery and a drug-eluting stent in porcine coronary arteries. *Radiology*. 2006;240:411-418.
- Albrecht T, Speck U, Baier C, et al. Reduction of stenosis due to intimal hyperplasia after stent supported angioplasty of peripheral arteries by local administration of paclitaxel in swine. *Invest Radiol*. 2007;42:579-585.
- van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation*. 1996;94:1690-1697.
- Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701-705.
- Zeller T, Schmitzmeier S, Tepe G, Rastan A. Drug-coated balloons in the lower limb. *J Cardiovasc Surg (Torino)*. 2011;52:235-243.
- Scheller B, Speck U, Romeike B, et al. Contrast media as carriers for local drug delivery. Successful inhibition of neointimal proliferation in the porcine coronary stent model. *Euro Heart J*. 2003;24:1462-1467.
- Scheller B, Speck U, Schmitt A, et al. Addition of paclitaxel to contrast media prevents restenosis after coronary stent implantation. *J Am Coll Cardiol*. 2003;42:1415-1420.
- Speck U, Scheller B, Abramjuk C, et al. Inhibition of restenosis in stented porcine coronary arteries: uptake of paclitaxel from angiographic contrast media. *Invest Radiol*. 2004;39:182-186.
- Cremers B, Biedermann M, Mahnkopf D, et al. Comparison of two different paclitaxel-coated balloon catheters in the porcine coronary restenosis model. *Clin Res Cardiol*. 2009;98:325-330.
- Thim T, Milewski K, Tellez A, et al. Biological effect on coronary restenosis of bare metal stents crimped on paclitaxel coated balloons: preliminary animal data in the porcine overstretch model. *Am J Cardiol*. 2009;104:177.
- Cremers B, Milewski K, Clever YP, et al. Long-term effects on vascular healing of bare metal stents delivered via paclitaxel-coated balloons in the porcine model of restenosis. *Cathet Cardiovasc Interv*. In press.
- Kelsch B, Scheller B, Biedermann M, et al. Dose response to paclitaxel-coated balloon catheters in the porcine coronary overstretch and stent implantation model. *Invest Radiol*. 2011;46:255-263.
- Creel CJ, Lovich MA, Edelman ER. Arterial paclitaxel distribution and deposition. *Circ Res*. 2000;86:879-884.
- Lovich MA, Creel C, Hong K, et al. Carrier proteins determine local pharmacokinetics and arterial distribution of paclitaxel. *J Pharm Sci*. 2001;90:1324-1335.
- Freyhardt P, Zeller T, Kroncke TJ, et al. Plasma levels following application of paclitaxel-coated balloon catheters in patients with stenotic or occluded femoropopliteal arteries. *Rofo*. 2011;183:448-455.
- Cortese B. The PICCOLETO study and beyond. *EuroIntervention*. 2011;7 (suppl K):K53-56.
- Posa A, Nyolczas N, Hemetsberger R, et al. Optimization of drug-eluting balloon use for safety and efficacy: evaluation of the 2nd generation paclitaxel-eluting DIOR-balloon in porcine coronary arteries. *Cathet Cardiovasc Interv*. 2010;76:395-403.
- Hehrlein C, Richardt G, Wiemer M, et al. Description of Pantera Lux paclitaxel-releasing balloon and preliminary quantitative coronary angiography (QCA) results at six months in patients with coronary in-stent restenosis. *EuroIntervention*. 2011;7 (suppl K):K119-124.
- Cremers B, Speck U, Kaufels N, et al. Drug-eluting balloon: very short-term exposure and overlapping. *Thromb Haemost*. 2009;101:201-206.
- Herdeg C, Goehring-Frischholz K, Zuern C, et al. Local catheter-based delivery of antithrombotic or antiproliferative drugs: a new concept for prevention of restenosis. *Thromb Res*. 2008;123:236-243.
- Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation*. 1997;96:636-645.
- Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
- Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation*. 2008;118:1138-1145.
- Cremers B, Brautgam M, Kaufels N, et al. Early endothelialization and neointimal proliferation in pigs up to 6 months after implantation of BMS by paclitaxel-coated balloon catheters, Cypher- and Taxus-stents. *Eur Heart J*. 2008;29:335.