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Drug-eluting balloons and bifurcations, a new future?

Pieter R. Stella*, MD, PhD; Anouar Belkacemi, MD; Pierfrancesco Agostoni, MD, PhD

Department of Interventional Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

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Current perspective

In recent years, the drug-eluting balloon (DEB) technology has emerged as a potential alternative to drug-eluting stents (DES) to prevent restenosis. The DEB technology has demonstrated safety and efficacy in the porcine model of restenosis and in randomised clinical trials for patients with in-stent restenosis. Nevertheless, the technology carries challenges in release kinetics, ability to overcome elastic recoil, and concerns whether it can be coupled successfully to bare metal stents.

The active substance on a DEB should be lipophilic enough to have a high absorption rate through the vessel wall,[1] compensating for the short time of contact between the inflated balloon and the vessel wall itself, and to maintain sustained effect once released.[2] The drug of choice at this moment seems to be paclitaxel. Paclitaxel was identified as the primary drug for DEB with the ability to retain in the vessel wall for nearly a week. Paclitaxel is a broad-spectrum antimitotic agent that inhibits cell division in the G2/M phase, stabilising the polymerised microtubules, and thus inhibiting cell replication of the smooth muscle cells and by that reducing neointimal hyperplasia.[3]

Cells have been shown to contain effective doses of paclitaxel *in vivo* experiments for at least six days, even when plasma levels of paclitaxel were below the detection limit.[4]

Currently there are several commercially available DEB in Europe (all CE approved) which all use paclitaxel as an active drug. However the coating and release methods are quite different. It has been demonstrated that the coating method, next to the active substance paclitaxel, highly determines the efficacy of a DEB.[5]

Technical aspects

A high degree of similarity exist among DEB manufactures in terms of basic principles, however the Sequence Please™ (or its predecessor PACCOCATH) and the DIOR™ have been investigated extensively in accessible studies, giving us insight in certain important properties (e.g., delivery dose of paclitaxel in the vessel wall, and drug release properties).

Coating with matrix carrier

The SeQuent Please™ (B. Braun Melsungen AG, Melsungen, Germany), the Protégé™ (Blue Medical Devices BV, Helmond, The Netherlands), the Pantera Lux™ (Biotronik, Berlin, Germany), and the In Pact Falcon™ (Medtronic Inc., Minneapolis, MN, USA) are all catheters coated with paclitaxel (3 µg/mm^2). In general they are coated with a matrix composed of paclitaxel and a hydrophilic spacer (matrix carrier). This coating method should improve the solubility and transfer of paclitaxel to the vessel wall.[5] The hydrophilic character of the matrix carrier and the lipophilic properties of paclitaxel support the release of the drug from the balloon surface and its delivery into the vascular wall by preventing paclitaxel to lump on the balloon.

Different types of hydrophilic spacers have been introduced by the manufactures (Table 1), all relying on the same concept that was first developed in the SeQuent Please™ (its predecessor PACCOCATH™) DEB. Intra-coronary delivery of paclitaxel first simply diluted in hydrophilic contrast medium (iopromide)[6] and later loaded directly on a balloon catheter[5] resulted in concentrations of the drug in vascular tissue that were high enough to have antiproliferative effects. The SeQuent Please™ DEB currently used are coated with paclitaxel and a small amount of iopromide as spacer, using acetone as the main solvent.[5,7]

The Protégé™, the Pantera Lux™, and the In Pact Falcon™ have been introduced using the same coating principle; these three DEBs are the latest introduced devices. Next to the matrix carrier technology, both Protégé™ and Pantera Lux™ use a shielding technique. This is a dedicated folding of the balloon in its non-inflated status in order to prevent paclitaxel from an early wash-off

* *Corresponding author: University Medical Centre Utrecht, Heidelberglaan 100, room E.01.207, 3584 CX, Utrecht, The Netherlands*
E-mail: P.Stella@umcutrecht.nl

Table 1. Technical properties of CE marked drug-eluting balloons.

DEB	Coating with matrix carrier	Coating Without matrix carrier (hydrophilic spacer)	Drug load	Shielding technique	Release from balloon surface 30 s	Release from balloon surface 60 s	Vessel wall paclitaxel concentration after DEB treatment: concentration (µg) - time of inflation (s) - time after measuring vessel wall paclitaxel concentration (min)
Sequent please™	+ (PACCOCATH+ Paclitaxel)	–	3 µg/mm²	–	NA	93%	47-94 µg – 60 s – (40 – 60 min)
First-generation DIOR™	–	Rough balloon surface; Crystalline+ paclitaxel	3 µg/mm²	+ (3- fold)	20%	25%	1.6-6 µg – 60 s – 90 min
Second-generation DIOR™	–	Shellac+ paclitaxel	3 µg/mm²	+ (3- fold)	75%	85%	167 µg – 30 s – 45 min
Protégé™	+	–	3 µg/mm²	+ (3- fold) Wing-seal technology	NA	NA	NA at this time
Pantera Lux™ (BTHC+Paclitaxel)	+	–	3 µg/mm²	+	NA	NA	165 µg – 30 s – 30 min
In Pact Falcon™ (FREEPAC+Paclitaxel)	+	–	3 µg/mm²	–	NA	NA	NA

NA: not available; BTHC: Butyryl- tri- hexyl citrate; Min: minutes; s: seconds; µg:micrograms; –=No; +=Yes

effect. Whether the shielding technique is clinically useful or not, is not proven. It has been shown that, while using the SeQuent Please™, which does not use a shielding technique, at least 6% of the paclitaxel is released into the systemic circulation.[5] Most likely this amount has no harmful effect; during chemotherapy much higher doses of paclitaxel are reached (at least 1,000 times higher).

Coating without matrix carrier

The DIOR™ catheter (Eurocor GmbH, Bonn, Germany) is coated with paclitaxel (3 µg/mm²). The first generation DIOR-I™ (not in use anymore) had a roughened balloon surface, containing a crystalline coating. The currently available DIOR-II™ has a coating consisting of a 1:1 mixture of paclitaxel with shellac applied to the balloon by a micro-pipetting procedure. Shellac is a natural coating layer derived from a resin secreted by a bug and it is approved as coating for food. In the DIOR-II™ the hydrophilic shellac-network, once in contact with body tissues, swells and opens the structure for the pressure-induced fast release of paclitaxel on the inflated balloon. The advised inflation time in order to deliver the adequate amount of drug to the vessel tissue is 30-45 seconds.

The DIOR™ was the first DEB adopting the already mentioned shielding technique, by which the non-inflated DEB is 3-folded and protects the loaded drug from an early wash-off effect during insertion and tracking of the coronary lesions (Table 1). In contrast with SeQuent Please™, no plasma concentrations of paclitaxel can be detected after DIOR™ inflation, indicating no systemic circulation release with the use of a DIOR™.[2]

One of the drawbacks of DIOR-I™ was the low delivery dose of paclitaxel into the vessel wall (25% of the dose loaded on the balloon), the DIOR-II™ has a higher delivery dose (up to 85% of the dose loaded on the balloon), comparable to the Pantera Lux™. The DIOR-II™ showed significantly better properties of distribution into the vessel wall with an 5- to 20-fold higher tissue/drug concentrations in comparison to the DIOR-I™, resulting in shorter inflation times.[8] This reduction of inflation time results in less ischaemia and arterial injury combined with undetectable levels of paclitaxel in the systemic circulation.[8]

Clinical trials

Although several clinical studies have shown promising results in different patient groups, still little data on randomised trials is available with usually small numbers. Where most studies have focused on restenotic lesions in stented coronary arteries (PACOCATH ISR I and II, and PEPCAD II), only recently new data arrived on *de novo* coronary lesions (PEPCAD I and III, PICCOLETO and the Spanish multicentre registry Vaquerizo B, Barcelona, Spain, unpublished data AHA 2009 in Orlando), and just one on bifurcation lesions (DEBIUT trial).

In-stent restenosis

The PACOCATH ISR I and II[9,10] trials were the first benchmark studies which showed clinical superiority of SeQuent Please™ DEB in comparison with a regular balloon in the treatment of bare metal stent (BMS) or drug-eluting stent (DES) restenosis, with sustained results up to 24 months. Furthermore 6-month angiographic follow-up demonstrated significant reductions in late lumen loss and binary restenosis with DEB.

Similar positive results were found in the PEPCAD II[11] trial, comparing a SeQuent Please™ DEB with a paclitaxel-eluting stent also to treat bare metal stent restenosis. Superior angiographic results were found for the DEB at 12 month follow-up. Furthermore no significant trends towards reduced major adverse cardiac events (mainly driven by target lesion revascularisation) were found for the DEB group.

De novo lesions

Inconsistent data were found for *de novo* lesions. The PEPCAD I,[12] a prospective registry on the treatment of *de novo* small coronary arteries with a SeQuent Please™ DEB (and provisional bare metal stenting), demonstrated that DEB possibly yields the potential as a treatment alternative for these types of lesions. These results were not confirmed in the PICCOLETO[13] randomised trial, where a DIOR-I™ DEB (with provisional stenting) was compared with a paclitaxel-eluting stent (PES) in *de novo* lesions in small vessels. The trial was interrupted after enrolment of two-thirds of the patients due to clear superiority of the paclitaxel-eluting stent group over the DEB group. It should however be noticed that the both groups had significant differences at index procedure: 1) in the DEB arm only 25% pre-dilatation was performed; 2) considerably lower inflation pressures were used (maximal mean inflation pressure of 7.71 atmospheres); 3) a significant difference between both arms, with regard to residual stenosis after PCI, was seen (19% in DEB arm versus 9.9% in the PES arm). Clinical and angiographic results in the DEB group were considerably worse than in the PEPCAD I study. One explanation could be that the PICCOLETO study was performed with a DIOR-I™ where the SeQuent Please™ as used in PEPCAD I can probably be considered as superior to the DIOR-I™ in terms of tissue dosage.[14] A second explanation could be the occurrence of so called "geographical miss" which led to in-stent restenosis in lesion sites which were not adequately treated with DEB.

The PEPCAD III trial (Hamm C, Bad Nauheim, Germany, unpublished data AHA 2009 in Orlando) investigated a new hybrid drug-eluting balloon/stent system (Coroflex DEBlue®) as an alternative to drug-eluting stents. This study failed to show non-inferiority, angiographically and clinically at nine months, for the DEB group in comparison with the DES group (Cypher™). Although the study failed to show non-inferiority, outcome measures for DEB were very reasonable, with a late luminal loss of 0.41 mm and a target lesion revascularisation rate of 10.5% at nine months if compared to historical known BMS data.

The Spanish, prospective non-randomised, registry assessed the value of a DIOR-I™ DEB in; 1) in-stent restenosis (BMS and DES); 2) *de novo* small vessels (i.e., bifurcation lesions); 3) patients with contraindication to dual antiplatelet therapy. Only a 3.4% MACE rate in all three groups was found at three months follow-up. Results seem to be good, however cautious interpretation of these results, is warranted since all limitations of a non-randomised registry apply. Data on *de novo* small vessel lesions remain therefore inconclusive; larger randomised trials comparing latest DEB versus latest DES are warranted to define the value of DEB in this subgroup of patients.

Bifurcation lesions: would a DEB help?

Bifurcations, which account for 15-20% of all lesions treated percutaneously,[15] remain hampered by procedural difficulties, postprocedural complications and suboptimal long-term results.[16] As systematic stenting of both the main branch (MB) and the side branch (SB) has never been shown to improve outcomes when compared to MB stenting only,[17] the latter should be the treatment of choice, however it is still hampered by considerable SB restenosis rates.[18,19]

Given the provisional T-stenting technique as the favoured technique, the potential advantages of the use of DEB in bifurcations are: 1) homogeneous administration of the drug to the vessel wall (specifically at the ostium of the SB), whereas the DES only delivers the drug in the proximity of the struts; 2) delivery of high concentrations of drug into the vessel wall at the moment of highest injury; 3) no distortion of the original anatomy of the bifurcation; and 4) minimisation of strut deformation, of polymer crushing and of potential uncontrolled drug release (in case of multiple DES) and therefore; 5) potential decrease in dual antiplatelet therapy.

After successful completion of a pilot study,[20] a physician-initiated randomised, multicentre trial comparing the DIOR-I™ DEB in MB and SB and subsequent BMS implantation in the MB versus two control groups (1. balloon angioplasty instead of DEB and BMS in the MB or 2. balloon angioplasty and paclitaxel eluting stent in the MB), has been recently conducted: the DEBIUT trial (ClinicalTrials.gov number, NCT00857441). Enrolment was completed December 2009, and preliminary results presented during LBT, Euro-PCR 2010. Upcoming publication of this study will give us more insight in the value of a DEB in bifurcation lesions. Moreover it has the potential to serve as a benchmark for future trials with other DEBs.

Finally, as accounted for drug-eluting stents, we have to realise that a thorough validation of various DEBs has to be performed in order to exploit their full potential, and determine the different values of each individual DEB. Although the baseline conceptual characteristic seems to be the same, the technical aspects of the different DEBs remain unclear. Especially actual tissue delivery dosages as achieved and measured in animal testing should be reported, in order to provide more insights into the technical properties of the different DEBs.

At this point of development of DEBs, it is still difficult to understand if this new technique will remain a promise or become a real asset. However in certain niches where DES still fails to show good results – like bifurcations and ISR – the promise seems to hold. It will be interesting to see whether other drug based DEB (e.g., zotarolimus) will provide new insights in near future.

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