Drug-eluting Balloons in Coronary Artery Disease – Current and Future Perspectives

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Abstract

Percutaneous treatment of complex coronary lesions, such as small-vessel disease, diabetes and long diffuse disease, remain hampered by suboptimal results, even with the use of drug-eluting stents (DES). The paclitaxel drug-eluting balloon (DEB) is an interesting emerging device that optimises clinical outcomes in these specific lesions. The DEB may become a viable alternative treatment option for the inhibition of coronary restenosis and subsequent revascularisation, as it allows local release of a high-concentration antirestenotic drug, paclitaxel, into the coronary vessel without using a metal scaffold or durable polymers. Several studies have already shown promising and consistent results in the treatment of in-stent restenosis. The DEB has demonstrated its added value compared with certain DES. Inspired by these results, an increasing number of studies have been started in different coronary lesion subsets to explore the value of the DEB in a broader range of lesions. It will be interesting to see whether the DEB will find more indications beyond in-stent restenosis treatment. Moreover, will all DEBs offer the same added value, or will there be differences in efficacy among the DEBs produced by the various manufacturers? As was the case in the development of DES, now the puzzle pieces have to be put together for DEB.

Keywords

Complex coronary lesions, angioplasty, drug-eluting balloon, drug-eluting stent

Disclosure: Pieter Stella is member of a Scientific Advisory Board of Eurocor GmbH. The remaining authors have no conflicts of interest to declare.
Received: 5 June 2011 **Accepted:** 22 July 2011 **Citation:** *European Cardiology*, 2012;8(1):56–9
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In the past few decades, major progress has been made in the percutaneous treatment of coronary artery disease. Initially, the emergence of balloon angioplasty offered an alternative option for coronary revascularisation. However, abrupt closure and restenosis caused by elastic recoil, neointimal hyperplasia and late remodelling were major drawbacks of balloon angioplasty.[1] The use of drug-eluting stents (DES) majorly reduced in-stent restenosis, not only preventing recoil of the vessel wall and late negative remodelling, but also significantly inhibiting neointimal hyperplasia formation. However, concerns about in-stent thrombosis and the dependency on prolonged dual antiplatelet therapy, as well as persisting restenosis in complex lesion subsets, led to a search for alternative treatment devices that tackle restenosis rates without the drawbacks associated with DES.[2–5] Recently, a new technology – the drug-eluting balloon (DEB) – has begun to emerge as a potential alternative to combat restenosis.[6–12] DEB technology has demonstrated safety and efficacy in a porcine model of restenosis and in randomised clinical trials for patients with in-stent restenosis.[9,10,12] This article discusses technical aspects, studies performed and future perspectives of DEB.

Introduction to Drug-eluting Balloons

DEBs are conventional semi-compliant angioplasty balloons covered with an antirestenotic drug which is released into the vessel wall during inflation of the balloon, usually at nominal pressures with a specific minimal inflation time. The active substance on the DEB should be lipophilic enough to have a high absorption rate through the vessel wall[13] to compensate for the short period of contact between the inflated balloon and the vessel wall itself, and to maintain a sustained effect once released.[14] The drug of choice at the moment is paclitaxel. 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, thereby reducing neointimal hyperplasia.[15] Paclitaxel was identified as the primary drug for DEB owing to its pharmacological characteristics, such as its high lipophilic properties and its ability to remain in the vessel wall for nearly a week.[16] Thus, stent- and polymer-driven sustained drug release may not be necessary in all cases.[17]

Technical Aspects

The basic principles of DEBs are very similar among DEB manufacturers. The SeQuent Please (and its predecessor PACCOCATH; B Braun Melsungen AG, Melsungen, Germany) and the DIOR (Eurocor GmbH, Bonn, Germany) are the most extensively studied models, and the results with these devices provide an insight into certain important properties, such as the delivery dose of paclitaxel in the vessel wall and drug release properties.

Coating with Matrix Carrier

The SeQuent Please, Protégé (Blue Medical Devices BV, Helmond, The Netherlands), Pantera Lux (Biotronik, Berlin, Germany) and In.Pact Falcon (Medtronic Inc., Minnesota, US) catheters are all 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 improves the solubility of paclitaxel and its transfer to

the vessel wall.[10] 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. Without the matrix carrier paclitaxel exist as microcrystals, causing less vascular absorption. Different types of hydrophilic spacers have been introduced (see *Table 1*),[29] all relying on the same concept that was first developed for the SeQuent Please DEB. Paclitaxel, which in the beginning was delivered intracoronary by dilution in hydrophilic contrast medium (iopromide),[18] and later was directly loaded onto a balloon catheter,[10] resulted in high enough concentrations of the drug in vascular tissue to cause antiproliferative effects. The SeQuent Please DEB currently in use is coated with paclitaxel and a small amount of iopromide as the spacer, using acetone as the main solvent.[7,10]

Protégé, Pantera Lux and In.Pact Falcon were then introduced using the same coating principle; these three DEBs are the most recently introduced devices. In addition 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 to prevent paclitaxel from an early wash-off effect. The clinical value of the shielding technique has still not been proved. In fact, it has been shown that with the SeQuent Please, which does not use a shielding technique, at least 6 % of the paclitaxel is released into the systemic circulation.[10] Most likely this amount has no harmful effect, as much higher doses of paclitaxel are reached during chemotherapy (50–1,000 times higher).

Table 1: Overview of Conformité Européenne Approved Drug-eluting Balloons

DEB	Release from Balloon Surface (30 Seconds)	Release from Balloon Surface (60 Seconds)	Vessel Wall Paclitaxel Concentration after DEB Treatment:
			• concentration (µg) • time of inflation (seconds) • time after measuring vessel wall paclitaxel concentration (minutes)
SeQuent Please	NA	93 %	• ~45–95 µg • 60 seconds • 40–60 minutes
Protégé	NA	NA	NA
Pantera Lux	NA	NA	• 165 µg • 30 seconds • 30 minutes
In.Pact Falcon	NA	NA	NA
First-generation DIOR	20 %	25 %	• ~1.5–6 µg • 60 seconds • 90 minutes
Second-generation DIOR	75 %	85 %	• 167 µg • 30 seconds • 45 minutes

DEB = drug-eluting balloon; NA = not available.

Coating without a Matrix Carrier

The DIOR catheter is coated with paclitaxel (3 µg/mm^2). The first-generation DIOR-I (no longer produced) had a roughened balloon surface with 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 using a micro-pipetting procedure. Shellac is a natural coating layer derived from a resin secreted by the female lac bug and is approved as a coating for food. In the DIOR-II, the hydrophilic shellac network, once in contact with body tissues, swells and opens its structure for the pressure-induced fast release of paclitaxel on the inflated balloon. The advised inflation time to deliver an adequate amount of drug to the vessel tissue is 30–45 seconds.

DIOR was the first DEB to adopt the above-mentioned shielding technique, in which the non-inflated DEB is thrice folded and protects the loaded drug from an early wash-off effect during insertion into the vasculature and tracking to the lesions (see *Table 1*). In contrast to SeQuent Please, no plasma concentrations of paclitaxel can be detected after DIOR inflation, indicating no systemic release into the circulation with the use of DIOR.[14] 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 that achieved with SeQuent Please and Pantera Lux. The DIOR-II showed significantly better distribution properties into the vessel wall, with a five- to 20-fold higher tissue drug concentration compared with DIOR-I, resulting in shorter inflation times.[19]

Animal Studies

Neointimal hyperplasia (proliferation of smooth-muscle cells) is the pathophysiological cause of restenosis after stent placement. In the 2000s it was shown that paclitaxel is a potent inhibitor of this process.[17] Consequently, studies delivering paclitaxel locally to the coronary arteries were performed. The first pre-clinical study compared a combination of paclitaxel dissolved in a contrast agent (iopromide) with iopromide only (control group) after stent placement. The study showed that the combination of paclitaxel dissolved in iopromide inhibited the neointimal hyperplasia process to a greater extent than seen in the control group.[20] Sequentially, the same authors compared the delivery mode of paclitaxel and iopromide after stent placement. Intracoronary injection of paclitaxel and iopromide inhibited the neointimal hyperplasia process more profoundly than intravenous injection.[18] Hence, a local delivery platform was developed. An angioplasty balloon was coated with the combination of paclitaxel and iopromide to generate a DEB. After stent placement, DEB inflations (with an inflation time of 60 seconds to allow paclitaxel to 'impregnate' the vessel wall) were performed, showing a reduction of neointimal hyperplasia compared with inflations with conventional balloons.[10] There was still some uncertainty about the warranted inflation times and distribution rates of paclitaxel into the vessel wall. Cremers et al. showed that, even with shorter inflation times (10 seconds instead of the 60 seconds used in the previous studies), sufficient paclitaxel was absorbed by the vessel wall. Moreover, these authors found no increased safety risk after two overlapping DEB inflations (two times 5 µg/mm^2) in the same vascular segment.[7]

Clinical Studies

Several randomised clinical studies of DEBs have shown promising results; however, these trials were performed in small numbers of patients. While most studies have focused on in-stent restenotic lesions (the Paclitaxel-coated balloon catheter for in-stent restenosis [PACCOCATH ISR I and II] and the Paclitaxel-eluting percutaneous transluminal coronary angioplasty balloon catheter to treat small vessel [PEPCAD II]), only recently new data have been published on *de novo* coronary lesions (PEPCAD I and III, PICCOLETO and the Spanish multicentre registry), and just one on bifurcation lesions (the Drug eluting balloon in bifurcation Trial [DEBIUT] trial).

Table 2: Ongoing Trials of Drug-eluting Balloons in Various Subsets of Lesions

Trial	Device	Indication	n	Outcome
DEBIUT	DIOR-I versus BMS versus PES	Bifurcations	117	6-month LLL and 12-month MACE
DEB-AMI	DIOR-II versus BMS versus PES	Acute myocardial infarction	150	6-month LLL and 6-month MACE
Valentines-I	DIOR-II	Effect in BMS and DES ISR	276	8-month MACE
DEB-ISR	In.Pact Falcon and DIOR-II (non-randomised)	Effect in BMS and DES ISR	40	6-month angiographic, FFR and OCT results
BELLO	In.Pact Falcon versus PES	*De novo* small vessel	182	6-month LLL
Indicor	SeQuent Please followed by BMS versus BMS followed by SeQuent Please	*De novo*	125	6-month LLL
PEPCAD-BIF	SeQuent Please versus POBA	SB lesions (medina 0,0,1)	120	9-month LLL
PEPCAD DES	SeQuent Please	Effect in PES versus sirolimus ISR	120	6-month LLL
RIBS IV	SeQuent Please versus Xience V	Effect in DES ISR	310	6–9-month MLD
RIBS V	SeQuent Please versus Xience V	Effect in BMS ISR	190	6–9-month MLD
BABILON	SeQuent Please SB and PES MB	Bifurcations	190	9-month LLL
ISAR-DESIRE-3	SeQuent Please versus PES versus POBA	Limus ISR	375	6–8-month in-segment DS
PEPCAD IV	Sequent Please + BMS versus PES	*De novo* DM	128	9-month LLL
RESTENOZA ISR-II	SeQuent Please versus rapamycin DES	Effect in BMS ISR	200	9-month angiographic restenosis, OCT LLL, IVUS neointimal volume

Percutaneous treatment of coronary bifurcation lesions remains hampered by suboptimal results, mainly in the side branch, even with the use of drug-eluting stents.
BMS = bare-metal stent; DES = drug-eluting stent; DM = diabetes mellitus; DS = diameter stenosis; FFR = fractional flow reserve; ISR = in-stent restenosis; IVUS = intravenous ultrasound; LLL = late lumen loss; MACE = major adverse cardiac events; MB = main branch; MLD = minimum lumen diameter; OCT = optical coherence tomography; PES = paclitaxel-eluting stent; POBA = plain old balloon angioplasty; SB = side branch.

In-stent Restenosis

The PACCOCATH ISR I and II[8,9] trials were the first benchmark studies, which showed the clinical superiority of the SeQuent Please DEB in comparison with a conventional balloon in the treatment of bare-metal stent (BMS) restenosis, with sustained results up to 24 months. Furthermore, six-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 trial, which compared the SeQuent Please DEB with a paclitaxel-eluting stent (PES) to treat BMS restenosis. Superior angiographic results were found for the DEB at 12-month follow-up. Furthermore, non-significant trends towards reduced major adverse cardiac events (mainly driven by target lesion revascularisation [TLR]) were found for the DEB group.[12] Recently, in a randomised study with 50 patients, it was shown that the SeQuent Please DEB is more effective than a conventional angioplasty balloon in the treatment of DES (sirolimus) in-stent restenosis. At six months, late lumen loss was 0.18 mm and 0.72 mm in the DEB and conventional angioplasty arms, respectively.[21]

The prospective, non-randomised Spanish registry (Serra A, presented at the EuroPCR Congress 2011 in Paris, France) assessed the value of the DIOR-I DEB in: in-stent restenosis (BMS and DES); *de novo* small vessels (including also bifurcation lesions); and patients with contraindications to dual antiplatelet therapy. The results at 12-month follow-up showed a low TLR rate of 9.2 % in BMS in-stent restenosis and 14.8 % in DES in-stent restenosis. In very small vessels (1.98 mm mean vessel diameter), the TLR rate at 12 months was very low, at 2.9 %. These results seem to be very good; however, cautious interpretation is warranted since all limitations of a non-randomised registry apply. Finally, the Valentines Trial (Stella P, presented at the EuroPCR Congress 2011 in Paris, France) assessed the efficacy and safety of a second-generation DIOR DEB. In this all-comer registry, 276 patients underwent treatment for BMS and DES in-stent restenosis. At eight-month follow-up, a low clinically driven TLR rate of 7.4 % was found. Interestingly, patients with small-vessel disease were not excluded from the study.

De Novo Lesions

Inconsistent data were found for *de novo* lesions. PEPCAD I,[11] 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 has potential as a treatment alternative for these types of lesions. In the PICCOLETO[22] randomised trial, the DIOR-I DEB (with provisional stenting) was compared with PES in *de novo* lesions in small vessels. The trial was interrupted after enrolment of two-thirds of patients owing to the clear superiority of the PES group over the DEB group. However, it should be noted that both groups had significant differences in terms of index procedure: in the DEB arm, only 25 % pre-dilatation with conventional balloons was performed; and considerably lower inflation pressures were used in the DEB group (average maximal inflation pressure 7.7 atmospheres in the DEB group versus 13.4 atmospheres in the PES group). 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 DIOR-I whereas the SeQuent Please, which can probably be considered superior to the DIOR-I in terms of tissue dosage, was used in PEPCAD I.[23] A second explanation could be the occurrence of so-called 'geographical mismatch', which can lead to restenosis in stented lesion sites not adequately pre-treated with a DEB.

The PEPCAD III trial (Hamm C, presented at the American Heart Association Congress 2009 in Orlando, US) investigated a new hybrid DEB/stent system (Coroflex DEBlue; Braun Melsungen AG, Melsungen, Germany) as an alternative to DES. This study failed to show non-inferiority, both angiographically and clinically, at nine months for the DEB group in comparison with the DES group (Cypher sirolimus-eluting stent). Although the study failed to show non-inferiority, outcome measures for DEB were very reasonable, with late lumen loss of 0.41 mm and a TLR rate of 10.5 % at nine months, compared with historically known BMS data. Moreover, the results showed that a stand-alone procedure with a DEB yields superior results than a hybrid DEB/stent system.

Bifurcation Lesions

Two pilot studies and one randomised trial have been performed with DEBs in bifurcation lesions. In the first pilot study performed,[6] the DIOR DEB was used; among the 20 patients enrolled, no major adverse

cardiac events were reported at six-month clinical follow-up (Stella P, presented at the Transcatheter Cardiovascular Therapeutics congress 2008 in Washington DC, US). The second small non-randomised study, PEPCAD V, enrolled 28 patients with bifurcation lesions in two centres. Both the main and side branch were ballooned with a Sequent Please DEB, with BMS deployment in the main branch. The primary endpoint, procedural success, was met in all cases. At nine-month follow-up there were three binary restenosis recorded, of which in one a TLR was required. At nine-month angiographic follow-up, late lumen loss was 0.38 mm in the main branch and 0.21 mm in the side branch. Comparing these results with historical data for DES treatment, restenosis percentages were seemingly not higher in this pilot study. The third study, DEBIUT, an international multicentre randomised trial, enrolled 117 patients in total.[24] The aim of the study was to compare the default treatment strategy for coronary bifurcation lesions – the provisional T-stenting technique using DEB followed by BMS implantation – versus standard BMS implantation versus standard DES implantation. The main inclusion criteria were stable or unstable angina pectoris or silent ischaemia owing to *de novo* coronary artery lesions (stenosis >50 % and <100 %) at the level of a bifurcation. Eligible patients were assigned to one of the three treatment groups, with all three groups using a stent with the same design to exclude this being a confounding factor. Considering the primary endpoint, the DEB group showed a numerically similar late lumen loss to the BMS group. The values of late lumen loss in the DES group were numerically and statistically better than in the DEB and BMS groups. Regarding major adverse cardiac event rates at follow-up, the numbers for DEB and DES were similar; however, the BMS group had worse outcomes, although not statistically significant. At 12-month follow-up, the major adverse cardiac event rates were 20 %, 29.7 % and 17.5 % in the DEB, BMS and DES groups, respectively.

Future Perspectives

Aside from technical improvements (such as release kinetics), it will be interesting to see whether DEBs based on drugs other than paclitaxel will provide further improvements. Two pre-clinical studies using sirolimus and zotarolimus have shown encouraging results so far. In the first study, local administration of sirolimus during angioplasty showed inhibition of both smooth-muscle cells and the expression of extracellular matrix components.[24] In the second study, a porcine animal study, a zotarolimus-eluting balloon showed a marked reduction in neointimal proliferation with respect to conventional balloon angioplasty. Interestingly, even better angiographic results for the zotarolimus-eluting balloon were found compared with the established zotarolimus-eluting stent.[25] At this point in the development of DEBs, it is still difficult to understand whether this new technique will remain a promise or become a real asset. Various technical and safety aspects have yet to be clarified in studies large enough to address these factors. Moreover, studies have to address the effect of the latest-generation DEBs for various indications. For instance, DEB treatment for BMS in-stent restenosis can be considered as a good indication, with class IIa level B evidence (European Society of Cardiology guidelines for percutaneous coronary intervention, 2010) for clinically proven DEB (SeQuent Please and Dior). The efficacy of DEB in DES in-stent restenosis is less established, although a sub-study of the Valentines registry and the Spanish registry show good results, with TLR rates of approximately 11–14 %. Another recently published randomised study demonstrated the efficacy of a DEB over a conventional angioplasty balloon in sirolimus in-stent restenosis treatment.[21]

Currently, BMS in-stent restenosis treatment is the only guideline-approved indication for DEB use, next to non-coronary peripheral artery disease.[27] Nevertheless, the rationale is there for other complex subsets of lesions, such as small-vessel disease, as even DES treatment in the ISAR-SMART studies demonstrated high binary restenosis rates. Moreover, when using DES no improvement can be found with respect to BMS in vessels <2.8mm.[28,29] Hence, a new-generation DEB with a high delivery dose, or perhaps a zotarolimus/sirolimus-eluting DEB, may provide a solution to this ongoing problem and potentially overcome the high restenosis rates in small vessels. Forthcoming studies (see *Table 2*) will further address all the above-mentioned issues and provide more insight on the value of each DEB in different subsets of lesions. In conclusion, as was the case for DES, a thorough validation of the various DEBs has to be performed to allow us to exploit their full potential and determine the value of each individual DEB in different subsets of lesions. ■

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