Drug-eluting Balloons in Coronary Artery Disease: Past, Present and Future

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ABSTRACT

Percutaneous treatment of complex coronary lesions like small vessel disease, diabetics 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 to optimise the clinical outcomes in these specific lesions. In order to inhibit coronary restenosis, and revascularisation, the DEB may become a viable alternative treatment option by means of a high concentration, local release of an anti-restenotic 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. Even when compared to certain DES, the DEB has demonstrated its added value. Inspired by these results, an increasing number of studies have been started in different coronary lesion subsets, exploring 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, as several DEB produced by different manufacturers, are present on the market, specific investigations are needed to address whether these devices offer the same added value, or show relevant differences.

As accounted for DES development in the past, now the puzzle pieces have to be put together for DEB.

INTRODUCTION

In the past, major progresses have been made in the percutaneous treatment of coronary artery disease. Initially the emergence of balloon angioplasty offered an alternative coronary revascularisation option. However, abrupt closure and restenosis caused by elastic recoil, neo-intimal hyperplasia, and late remodelling became major drawbacks of balloon angioplasty.\textsuperscript{1}

The use of drug eluting stents (DES) majorly reduced in-stent restenosis though preventing not only recoil of the vessel wall and late negative remodelling, but also significantly inhibiting neo-intimal hyperplasia formation. However, concerns about in-stent thrombosis, and the dependency on prolonged dual antiplatelet therapy, and continued restenosis in complex lesion subsets, led to a search for alternative treatment devices that will tackle restenosis rates without the drawbacks associated with DES.\textsuperscript{2-5}

Recently, a new technology of drug eluting balloons (DEB) is emerging as a potential alternative to combat restenosis.\textsuperscript{6-12} The DEB technology demonstrated safety and efficacy in the porcine model of restenosis and in randomised clinical trials for patients with in-stent restenosis.\textsuperscript{9, 10, 12}

In the present article the technical aspects, studies performed up to day and future perspectives of drug-eluting balloons will be discussed.

Drug-eluting balloons

Drug eluting balloons are conventional semi-compliant angioplasty balloons covered with an anti-restenotic 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,\textsuperscript{13} compensating for the short time of contact between the inflated balloon and the vessel wall itself, and to maintain a sustained effect once released.\textsuperscript{14}
The drug of choice at this moment is paclitaxel. Paclitaxel is a broad-spectrum anti-mitotic agent that inhibits cell division in the G2/M phase, stabilising the polymerised microtubules, thus inhibiting cell replication of the smooth muscle cells, and by that reducing neo-intimal hyperplasia. Paclitaxel was identified as the primary drug for DEB due to its right pharmacological characteristics such as high lipophilic property and ability to remain in the vessel wall for nearly a week. Thus, a stent-driven sustained drug release may not be necessary in all cases.

**TECHNICAL ASPECTS**

A high degree of similarity exists among DEB manufacturers in terms of basic principles; however, the SeQuent Please (or its predecessor PACCOCATH) and the DIOR have been mostly studied, giving us insight into certain important properties (e.g. delivery dose of paclitaxel in the vessel wall, and drug release properties).

These catheters are all coated with paclitaxel (3 µg/mm2). 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. 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.

Different types of hydrophilic spacers have been introduced by the manufacturers (Table 1), all relying on the same concept that has been firstly developed in the SeQuent Please DEB.

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**Table 1: Overview of CE approved drug-eluting balloons.**

<table>
<thead>
<tr>
<th>DEB</th>
<th>Coating method</th>
<th>Release from balloon surface</th>
<th>Release from balloon surface</th>
<th>Vessel wall paclitaxel concentration after DEB treatment: concentration (µg) - time of inflation (s) – time after measuring vessel wall paclitaxel concentration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequent please</td>
<td>Paclitaxel + PACCOCATH (iopromide)</td>
<td>NA</td>
<td>93%</td>
<td>(~45–95 µg) – 60 s - (40 – 60 min)</td>
</tr>
<tr>
<td>Protégé</td>
<td>Unknown</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pantera Lux</td>
<td>Paclitaxel + BTHC</td>
<td>NA</td>
<td>NA</td>
<td>165 µg – 30 s - 30 min</td>
</tr>
<tr>
<td>In.Pact Falcon</td>
<td>Paclitaxel + FreePac</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>First-generation DIOR</td>
<td>paclitaxel + Crystalline</td>
<td>20 %</td>
<td>25%</td>
<td>(~1.5 – 6 µg) – 60 s - 90 min</td>
</tr>
<tr>
<td>Second-generation DIOR</td>
<td>paclitaxel + Shellac</td>
<td>75 %</td>
<td>85%</td>
<td>167 µg – 30 s - 45 min</td>
</tr>
</tbody>
</table>

NA = not available; Min = minutes; s = seconds; µg = microgram

Paclitaxel, in the beginning delivered intracoronary by dilution in hydrophilic contrast medium (iopromide) and later directly loaded on a balloon catheter, resulted in concentrations of the drug in vascular tissue that were high enough to have anti-proliferative effects. The SeQuent Please DEB currently used is coated with paclitaxel and a small amount of iopromide as spacer, using acetone as the main solvent.

**ANIMAL STUDIES**

Neo-intimal hyperplasia (i.e. proliferation of smooth muscle cells) is the patho-physiological cause of restenosis after stent placement. Already in the previous decade it was shown that paclitaxel is a potent inhibitor of this process. Consequently, studies delivering paclitaxel locally to the coronary arteries were performed. The first preclinical study compared a combination of paclitaxel solved in a contrast agent (iopromide) with a control group with iopromide only, after stent placement. The study showed that the combination of paclitaxel solved in iopromide inhibited the neo-intimal hyperplasia process better than the control group.

Sequentially, the same authors compared the delivery mode of paclitaxel and iopromide after stent placement. Intracoronary injection of paclitaxel and iopromide inhibited the neo-intimal hyperplasia process more profoundly than intravenous injection. 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 neo-intimal hyperplasia as compared to inflations with conventional balloons.
Still there was 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 60 seconds in the previous studies, sufficient paclitaxel was absorbed by the vessel wall. Moreover, they found no increased safety risk after two overlapping DEB inflations (2 times 5 μg/mm²) in the same vascular segment.⁷

Apart from efficacy testing, there is a growing interest for the patho-physiological effects of DEB (e.g. endothelial function). For instance, since studies have demonstrated that DES implantation causes local toxicity, inflammation, delayed healing and oxidative stress, causing an impaired vasomotor function. Nakamura et al. were investigating whether these effects would also occur when using a DEB. They demonstrated that akin to DES, DEB also causes an impaired vasodilatory response to acetylcholine. Since recent studies demonstrated efficacy with shorter inflation times, one issue is whether this impaired endothelial function would have been seen with shorter inflation times too.

**CLINICAL STUDIES WITH DEB**

The benchmark study is the PACCOCATH ISR I and II, which tested the angiographic efficacy of a DEB in comparison to a standard balloon in patients with in-stent restenosis. Of 52 randomised patients, 45 had angiographic follow-up. In the DEB group late-luminal loss was significantly better than for the standard balloon alone (0.03±0.48 mm vs. 0.74±0.86 mm, p=0.002). Consequently the number of re-interventions was lower for the DEB group (0% vs. 23% (p=0.02). The effect of DEB sustained up to 24-month follow-up. This highly promising result led to several clinical trials in various lesion subsets.

**In-stent restenosis:**

Similar positive results, as in the PACCOCATH ISR studies, were found in the Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat In-Stent Restenoses (PEPCAD) II trial, comparing the SeQuent Please DEB with paclitaxel eluting stent to treat BMS restenosis. Superior angiographic results were found for the DEB compared to DES at 6-month follow-up (0.17±0.42 mm vs. 0.38±0.61 mm, p=0.03). Furthermore no significant trends towards reduced major adverse cardiac events (mainly driven by target lesion revascularisation) were found for the DEB group compared to DES at 12-month clinical follow-up (9% vs. 22%, p=0.08).¹⁴

Recently in a randomised study with 50 patients, it has been shown that a SeQuent Please DEB is more effective than a conventional angioplasty balloon in patients with in-stent restenosis. At 6-month the late lumen loss was 0.18±0.45 mm and 0.72±0.55 mm (p=0.001) in the DEB and conventional angioplasty arm, respectively.²⁵

The Spanish, prospective nonrandomised, registry assessed the value of DIOR-I DEB in:

1) in-stent restenosis (BMS and DES);
2) de novo small vessels (including also bifurcation lesions);
3) patients with contraindication to DAPT.

The results at 12-months follow-up show a low target lesion revascularisation (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 with 2.9%.

Results seem to be promising, however cautious interpretation of these results is warranted since all limitations of a non randomised registry apply. Moreover, no angiographic follow-up was performed, making it difficult to compare this study to the PEPCAD I randomised trial.

Finally, the Valentines Trial assessed the efficacy and safety of a second generation DIOR DEB. In this all comer registry 276 patients underwent treatment for bare metal stent (BMS) and DES in-stent restenosis. At 8-month follow-up a low clinical driven target lesion revascularisation rate of 7.4% was found. The Valentines Trial was an interesting study, enrolling patients at over 100 centers worldwide, within a one week period. Instead of enrolling patients at high volume expertise centres, a real-world approach was applied. Hence, small centres were also involved in the enrolment of patients.

**De novo lesions**

Inconsistent data were found for de novo lesions. The PEPCAD I, 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 treatment alternative for these types of lesions. In 118 patients with a mean vessel diameter of 2.35±0.19, late lumen loss was 0.28±0.53 mm at 6-month angiographic follow-up.

However, in the PICCOLETO randomised trial, the first generation DIOR DEB (with provisional stenting) was compared with paclitaxel-eluting stents (PES) in de novo lesions in small vessels. The trial was interrupted after enrolment of two –thirds of patients due to clear superiority of the paclitaxel DES group over the DEB group. Restenosis rates were 32.1% and 10.3% (p=0.04), and major adverse cardiac events rates were 35.7% and 13.8% (p=0.05) in DEB and DES groups, respectively.

It should however be noticed that both groups had significant differences at index procedure:

1) in the DEB arm only 25% pre-dilatation with conventional balloons was performed;
2) considerably lower inflation pressures were used (on average, maximal inflation pressure of 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 where the SeQuent Please as used in PEPCAD I can probably be considered as superior to the DIOR-I in terms of tissue dosage. A second explanation could be the occurrence of so-called "geographical mismatch" which led to restenosis in stented lesion sites which were not adequately pre-treated with DEB.
The PEPCAD III trial (Hamm C, presented at the American Heart Association congress 2009 in Orlando, United States) investigated a new hybrid DEB/stent system (Coroflex DEBlue) as an alternative to DES. This study failed to show non-inferiority, angiographically and clinically at 9 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 a late luminal loss of 0.41 mm and a TLR rate of 10.5% at 9 months if compared to historically known BMS data. Moreover, they showed that a standalone procedure with a DEB yield superior results with respect to a hybrid DEB/stent system.

Bifurcation lesions

Currently two pilot studies and one randomised trial have been performed with DEB in bifurcation lesions. In the first pilot study performed,6 DIOR DEB was used and among the 20 patients enrolled, no major adverse cardiac events at 6-month clinical follow-up were reported.

The second small non randomised study, PEPCAD V, enrolled 28 patients with bifurcation lesions in two centres. Both main and side branch were ballooned with a SeQuent Please DEB, with BMS deployment in the main branch (MB). The primary endpoint, procedural success, was met in all cases. At 9-month follow-up there were 3 binary restenoses recorded, one in which a TLR was required. Furthermore, at 9-month angiographic follow-up late luminal loss was 0.38 mm in the MB and 0.21 mm in the side branch (SB). Comparing these results with historical data of DES treatment, restenosis percentages are seemingly not higher in this pilot study.

The third, the Drug-eluting Balloon in Bifurcations Trial (DEBIUT), an international multicentre randomised trial, enrolled 117 patients in total.30 The study aimed at comparing the default treatment strategy for coronary bifurcation lesions, 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 ischemia, due 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 having comparable success rates.31

At 9-month angiographic follow-up late luminal loss was 0.45±0.57 mm in the MB and 0.53±0.52 mm in the SB. Comparing these results with respect to a hybrid DEB/stent system.

FUTURE PERSPECTIVE

Apart from technical improvements (i.e. release kinetics), it will be interesting to see whether other drug-based DEB will provide further improvements. Two preclinical studies using the delivery of 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 as well as the expression of extracellular matrix components.31 In the second study, a porcine animal study, a zotarolimus eluting balloon showed a marked reduction in neo-intimal proliferation with respect to conventional balloon angioplasty.35

At this point of development of DEB it is still difficult to understand if this new technique will remain a promise or become a real asset. Different technical and safety aspects have yet to be clarified in studies large enough to address these aspects. For instance, recently it has been shown that there is no statistical difference between deploying a stent first followed by a DEB dilatation or a DEB dilatation first followed by a stent placement (0.45±0.57 vs. 0.53±0.52, p=0.83).32

Upcoming studies should also elucidate on the necessity of predilatation and the vessel to DEB sizing ratio.

Moreover, dedicated trials have to address the effect of latest generations DEB for various indications. For instance, DEB treatment for BMS in-stent restenosis can be considered as an established indication, with a class IIa level B evidence (European Society of Cardiology guidelines for percutaneous coronary intervention (2010)) for clinically proven DEB. The efficacy of DEB in DES in-stent restenosis is less established.25

Currently, BMS in-stent restenosis treatment is the only guideline-approved indication for DEB use, next to non-coronary peripheral artery disease.33 Nevertheless the rationale is there for other complex subset of lesions such as small vessel disease, as even DES treatment in this lesion subset demonstrated high restenosis rates.34,35 Hence, a new generation paclitaxel high delivery dose DEB, or perhaps zotarolimus/sirolimus eluting DEB in the future, may provide a solution to this ongoing problem and potentially can overcome the high restenosis rates in small vessels.

Upcoming studies (Table 2) will further address all above mentioned aspects, and will give us more insights into the value of each DEB in different subset of lesions.

Thus, as accounted for DES, we have to realise that a thorough validation of various company-manufactured DEB has to be performed in order to exploit their full potential, and determine the value of each individual DEB in different subset of lesions.
Table 2: Overview of running trials in various subsets of lesions using a drug-eluting balloon.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Indication</th>
<th>N=</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBIUT</td>
<td>DIOR-I vs BMS vs PES</td>
<td>Bifurcations</td>
<td>117</td>
<td>6-month LLL and 12-month MACE</td>
</tr>
<tr>
<td>DEB-AMI</td>
<td>DIOR-II vs BMS vs PES</td>
<td>Acute myocardial infarction</td>
<td>150</td>
<td>6-month LLL, OCT, acetylcholine testing, and MACE</td>
</tr>
<tr>
<td>DEB-ISR</td>
<td>In.Pact Falcon and DIOR-II (non-randomised)</td>
<td>Effect in BMS and DES ISR</td>
<td>40</td>
<td>6-month angiographic, FFR, and OCT results</td>
</tr>
<tr>
<td>BELLO</td>
<td>In.Pact Falcon vs PES</td>
<td>De novo small vessel</td>
<td>182</td>
<td>6-month LLL</td>
</tr>
<tr>
<td>Indicor</td>
<td>SeQuent Please followed by BMS vs BMS followed by Sequent Please</td>
<td>De novo DM</td>
<td>125</td>
<td>6-month LLL</td>
</tr>
<tr>
<td>PEPCAD-BIF</td>
<td>SeQuent Please vs POBA</td>
<td>Side branch lesions (medina 0,0,1)</td>
<td>120</td>
<td>9-month LLL</td>
</tr>
<tr>
<td>PEPCAD DES</td>
<td>SeQuent Please</td>
<td>Effect in PES vs Sirolimus ISR</td>
<td>120</td>
<td>6-month LLL</td>
</tr>
<tr>
<td>RIBS IV</td>
<td>SeQuent Please vs Xience V</td>
<td>Effect in DES ISR</td>
<td>310</td>
<td>6-9 month MLD</td>
</tr>
<tr>
<td>RIBS V</td>
<td>SeQuent Please vs Xience V</td>
<td>Effect in BMS ISR</td>
<td>190</td>
<td>6-9 month MLD</td>
</tr>
<tr>
<td>BABILON</td>
<td>SeQuent Please SB and PES MB</td>
<td>Bifurcations</td>
<td>190</td>
<td>9-month LLL</td>
</tr>
<tr>
<td>ISAR-DESIRE-3</td>
<td>SeQuent Please vs PES vs POBA</td>
<td>Limus ISR</td>
<td>375</td>
<td>6-8 month in segment DS</td>
</tr>
<tr>
<td>PEPCAD IV</td>
<td>SeQuent Please + BMS vs PES</td>
<td>De novo DM</td>
<td>128</td>
<td>9-month LLL</td>
</tr>
<tr>
<td>RESTENOZA ISR-II</td>
<td>SeQuent Please vs rapamycin DES</td>
<td>Effect in BMS ISR</td>
<td>200</td>
<td>9-month angiographic restenosis, OCT LLL, IVUS neo-intimal volume</td>
</tr>
<tr>
<td>Dare-trial</td>
<td>SeQuent Please vs Xience prime</td>
<td>ISR</td>
<td>270</td>
<td>9-month MLD</td>
</tr>
<tr>
<td>Seduce OCT study</td>
<td>SeQuent Please vs Xience V</td>
<td>Effect in BMS ISR</td>
<td>50</td>
<td>9-month OCT</td>
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REFERENCES
REFERENCES (Continued)


