



Drug elution without the need for stent struts and polymers: a promising technology?

“The theoretical advantages of DEBs over DESs appears tantalizing and the technology is currently trying to find its place for the management of coronary artery disease, especially in restenotic lesions and small vessel disease. With the currently available data, it could be concluded that DEBs are superior to POBA and first-generation DESs for the treatment of ISR.”

KEYWORDS: *de novo* lesion ■ drug-eluting balloon ■ in-stent restenosis ■ paclitaxel

Coronary stents were invented to combat high rates of dissection, restenosis and abrupt closure of the vessels that were common following plain old balloon angioplasty (POBA) [1,2]. Despite consistent improvements in stent technology, a small risk of unexpected stent thrombosis remains [3,4]. In addition, stents are not immune to restenosis (ISR) and certain patient and lesion subsets (e.g., diabetes, chronic kidney disease, lesions involving bifurcation and saphenous vein graft lesions) are more vulnerable for restenosis [5,6]. Recently however, we have readopted the strategy of balloon angioplasty, but the difference now includes the use of drug-eluting balloons (DEBs) [7]. The luxury of drug-elution without the need for stent struts and polymers makes this technology attractive. In this article, we take an overview of DEBs and the existing clinical data and discuss the current applicability of this technology in our clinical practice.

Advantages of DEBs over drug-eluting stents

Balloon-based drug delivery seems to offer several advantages over drug-eluting stents (DESs). The fundamental benefit lies in the absence of polymer, stent struts and ongoing presence of drugs that are known to hinder early vascular healing and pose the scare of late stent thrombosis. Secondly, drug-elution from the balloon surface results in homogenous distribution of the antiproliferative drug to the vessel wall, which may not be achievable with stents. High deliverability of DEBs offers an advantage in those lesions, where deliverability is an issue with stents. Finally, DEBs may be an ideal alternative to DESs, in patients who cannot

tolerate or safely assume dual antiplatelet therapy for an extended period of time.

Several DEBs are currently available, and several others are in varying stages of development. Some of the important ones that have been tested in clinical trials are provided in SUPPLEMENTARY TABLE S1 (see online: <http://www.futuremedicine.com/doi/suppl/10.2217/ica.12.26>). Although each DEB has unique properties with regards to drug-elution and utility of the carrier matrix, all the currently commercially available DEBs elute a common antiproliferative drug (paclitaxel at a dose of 3 µg/mm²). Paclitaxel facilitates easy transfer and retention in the vessel wall due to its high lipophilicity and therefore provides longer antiproliferative action [8]. It has demonstrated superiority over other drugs such as sirolimus for balloon-based delivery [9].

The concept of a DEB is based on a short-term drug elution (limited to the duration of the balloon inflation) and subsequent longer-term retention (up to 1 week) by the vessel wall, mainly by the endothelial and smooth muscle cells. This is predominantly achieved by coating the DEB with a carrier matrix or excipient that improves the solubility and transfer of paclitaxel onto the vessel wall (iopromide in SeQuent Please™ [B Braun Melsungen AG, Berlin, Germany], and PACCOCATH® [Bayer Schering Pharma, Berlin, Germany], butyryl-tri-hexyl citrate in Pantera Lux™ [Biotronik, Berlin, Germany] and FreePac in In Pact Falcon™ [Medtronic, CA, USA] and proprietary carrier molecule in Moxy™ [Lutonix, MN, USA]). Certain DEBs (Pantera Lux), in addition to the matrix, use a shielding technique as a result of a dedicated folding of the balloon in its noninflated status in order to prevent paclitaxel from early wash-off.



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The currently available second-generation DIOR II™ (Eurocor GmbH, Bonn, Germany) has no carrier matrix, but a coating consisting of a 1:1 mixture of paclitaxel with shellac applied to the balloon by a micropipetting procedure. 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.

Clinical evidence

Laboratory testing of DEBs on several animal models has demonstrated high tissue retention rates of paclitaxel and inhibition of neointimal proliferation [10,11]. These results provoked testing on humans. Details of the studies utilizing DEBs and their outcomes are provided in SUPPLEMENTARY TABLE S2. The following lesion subsets have been tested with DEB technology.

DEBs in ISR

DEBs may be particularly useful in ISR, as the underlying mechanism is usually due to a mechanical cause such as under-expansion or malapposition of the stent [5,6]. Implantation of another stent may be avoided if the mechanical issue is addressed. Use of adequate balloon dilatation and drug delivery may be sufficient, which can be attainable with conventional balloons and use of DEB technology. Moreover, outcomes with further stents in the treatment of ISR are disappointing with high rates of recurrence [12].

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The first-in-man study of DEB technology was performed in the PACCOCATH ISR I trial. This was a randomized study comparing a paclitaxel-coated balloon and POBA for treatment of bare-metal stent (BMS)-ISR in 52 patients. At 6-month follow-up, the DEB group had significantly better angiographic outcomes compared with the POBA group (late lumen loss of 0.03 vs 0.74 mm; $p = 0.002$) and significantly lower major adverse cardiac event rates (4 vs 31%; $p = 0.01$) [13]. These results were further strengthened in the PACCOCATH ISR II trial, which recruited more patients (108 patients) with longer follow-up [14]. Recently, the group reported their 5-year follow-up and the clinical event rate remains significantly reduced in patients treated with the DEB [15]. These studies confirmed the

superiority of DEBs over POBA for BMS-ISR. However, the accepted standard treatment for BMS-ISR is the implantation of a DES. Thus, in the PEPCAD II trial, DEBs were compared against DESs in patients with BMS restenosis. A total of 130 patients with BMS-ISR were randomized to receive either a DEB (SeQuent Please) or a paclitaxel-coated DES (TAXUS® Liberté®, Boston Scientific, MA, USA). At follow-up, clinical outcomes in the DEB group were at least as good as the DES group, but the angiographic late loss was significantly better in patients treated with DEBs (0.17 vs 0.38 mm; $p < 0.03$) [16].

The utility of DEBs in DES-ISR was assessed in two separate studies using the SeQuent Please DEB. The first study was by Habara *et al.*, where 50 patients with DES-ISR were randomized to receive either a DEB or POBA [17]. In the second study (PEPCAD-DES), a total of 110 patients with DES-ISR were randomized to angioplasty with a DEB or uncoated balloon angioplasty [18]. Both studies demonstrated superiority of DEBs over POBA in the treatment of DES-ISR with regards to both angiographic and clinical end points.

The Valentines Trial assessed the safety and efficacy of the second-generation DEB for ISR in real-world setting. The trial enrolled 250 patients with ISR (predominantly BMS-ISR, 63%) from 104 centers worldwide over a 1-week period. At 8 months clinical follow-up, the target lesion revascularization and major adverse cardiac event rates were low (7.4 and 11%, respectively) [19].

It is clear from the above studies that DEB is superior to POBA for BMS and DES restenosis and comparable to a first-generation DES in the treatment of BMS-ISR. However, there are no studies comparing DEBs with second-generation DESs in the treatment of ISR. In the current era, POBA and first-generation DESs have almost become obsolete for the treatment of both ISR and *de novo* lesions. Although the optimal treatment of ISR is not clear, most interventional cardiologists prefer using second-generation DESs. A study comparing DEBs versus second generation DESs for the treatment of ISR would be ideal and is currently underway.

DEBs in *de novo* lesions

The evidence for DEBs in *de novo* lesions is not as convincing as for ISR due to some inconsistent results. PEPCAD I was the first prospective registry of 120 patients with *de novo* lesions in small coronary arteries treated with

SeQuent Please DEBs (and provisional BMS, if required). A total of 32 (28%) patients required BMS due to suboptimal results or dissection. The mean in-segment late lumen loss was 0.28 mm. In patients treated with only a DEB, the in-segment late lumen loss was 0.16 mm compared with 0.73 mm in patients receiving a DEB + BMS [20]. Subsequent trials, PICCOLETO and PEPCAD-III, have failed to show any benefits. In the PICCOLETO trial, DIOR I™ DEB was compared with paclitaxel-DES in *de novo* lesions in small vessels. The trial was terminated early due to clear superiority of paclitaxel-eluting stents over the DEB. The DEB group demonstrated a higher percentage of diameter stenosis (44 vs 24%; $p = 0.03$) and angiographic restenosis (32 vs 10%; $p = 0.04$) [21]. The negative outcome was attributed to the use of a first-generation DIOR I, which had low delivery dose of paclitaxel into the vessel wall (25% of the dose loaded on the balloon) in comparison with other DEBs including second-generation DIOR II, which has a higher delivery dose (up to 85%). The PEPCAD III trial investigated a new hybrid DEB/stent system (Coroflex DEBlue®, B Braun Melsungen AG, Berlin, Germany) as an alternative to DESs (sirolimus) in relatively large vessels (2.5–3.5 mm). This study failed to demonstrate noninferiority of DEBs with regards to both angiographic and clinical end points [22]. Our center has conducted a multicenter, randomized trial (BELLO) in small vessel *de novo* lesions, comparing the In Pact Falcon DEB (with provisional stenting) versus paclitaxel-DES. The results are encouraging with significantly lower in-stent (in-balloon) late loss in the DEB group compared with the DES group (0.09 vs 0.30 mm; $p = 0.001$) [23]. There were no differences in the clinical end points, although it tended to favor DEBs.

The PEPCAD IV DM trial tested diabetic patients with *de novo* lesions, who were randomized to either a DEB (SeQuent Please) or a DES (Taxus Liberté). The study recruited only 65% of the intended sample size due to slow enrollment. Nevertheless, the clinical and angiographic outcomes between the two groups were similar [24].

The use of different DEBs, which have different matrix and release properties, could explain the conflicting results from the above studies. The data for *de novo* small vessel lesions are promising, with the positive results of the BELLO trial. Further

randomized trials comparing the latest DEBs and second-generation DESs are required to prove the value of DEBs in *de novo* lesions. Furthermore, the cross-over rates to address suboptimal results or dissection in the above studies ranged from 28 to 34% [20,21]. The operators are compelled to deploy BMSs in such scenarios, due to theoretical concerns that the use of DESs may augment the potential toxicity to the vessel wall from dual drug-elution. This infers that lesions, which would have benefited from a DES, might end up receiving a DEB + BMS combination, which may be inferior to second-generation DESs.

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■ DEBs in bifurcation lesions

The only study that has studied DEBs in bifurcation lesions was DEBUIIT, which was a randomized, international, multicenter study [25]. As a part of the study, 117 patients with bifurcation lesions were randomized into three groups:

- Group 1: DEB (DIOR I) in both the main branch and side branch with a BMS (Liberte) in the main branch;
- Group 2: conventional balloon in the main branch and side branch + BMS (Liberte) in the main branch;
- Group 3: conventional balloon in the main branch and side branch + DES (Taxus Liberté) in the main branch.

The 6-month angiographic follow-up demonstrated that there was no difference between group 1 and group 2 in terms of late luminal loss (main branch: 0.58 vs 0.60; side branch: 0.19 vs 0.21). However, group 3 had significantly less late luminal loss (main branch: 0.13; side branch: 0.11). There were no differences in the rate of major adverse cardiac events at 12 months between the 3 groups (20 vs 29.7 vs 17.5%; $p = 0.40$). The probable explanation for the failure could be due to the use of the first-generation DIOR I balloon, which delivers a low dose of paclitaxel onto the vessel wall. With the availability of second-generation DESs, it is difficult to substantiate the use of DEB + BMS in bifurcation lesions. The evidence from the DEBUIIT study does not support use of DEBs in bifurcation lesions.

Future of DEBs

The theoretical advantages of DEBs over DESs appears tantalizing and the technology is currently trying to find its place on the shelves of Interventional Cardiologists, especially in restenotic lesions and small vessel disease. With the currently available data, it could be concluded that DEBs are superior to POBA and first-generation DESs for the treatment of ISR. Given the complexity of ISR, the optimal treatment remains unknown. Deployment of additional stents in restenotic lesions may not be ideal with high rates of recurrence. The DEB technology that offers drug-elution in the absence of stent struts can be considered as the first choice. However, in the era of second-generation DESs it would be interesting to compare DEBs with second-generation DESs as a treatment for ISR. If DEBs are proven to be superior or even noninferior to second-generation DESs, it could become undisputedly the first choice for the treatment of ISR.

Trials in *de novo* lesions have yielded inconsistent results, which might be related

to use of different DEBs. However, DEBs can be considered in patients who cannot tolerate dual antiplatelet therapy for the recommended duration of 12 months post-DES implantation. In addition, they can be considered in small vessel coronary artery disease, where suitably sized stents are not available or stents in such lesions are considered inappropriate. With ongoing trials and new innovations, we can anticipate more compelling data on DEBs for wider applicability. DEB technology should not be considered as competition to DES technology, but can be used as an alternative or complementary to DES technology.

Financial & competing interests disclosure

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