◆COMMENTARY ———————————————————————————— ◆

Drug-Eluting Balloons for Carotid In-Stent Restenosis:

Can This Technology Deliver the Goods?

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Percutaneous transluminal treatment of coronary and peripheral artery diseases has revolutionized the field of interventional medicine. Over the years, progressive technological and pharmacological advances have improved clinical outcome and offered an effective alternative to surgical treatment of atherosclerotic disease in both coronary and peripheral districts. Relatively new to this field are drug-eluting balloons (DEBs), which represent an attractive and novel treatment modality that offers numerous theoretical advantages over standard angioplasty and stent technologies. Among these benefits are homogenous distribution of an antiproliferative drug to the vessel wall (not just to segments of the wall in direct contact with stent struts); immediate drug release without the use of a polymer that could trigger late thrombosis; no prolonged, direct drug contact with the arterial wall, allowing better re-endothelization of the vessel if a bare metal stent (BMS) is used in conjunction; no foreign object left in the body, which is especially important in peripheral applications where stents may be used for suboptimal results; maintenance of original vessel anatomy and flexibility, important during superficial femoral artery revascularization especially; and finally, lower restenosis rates in some indications.[1]

Recently, data from randomized clinical trials (RCT) showed that this technology is a viable alternative for the treatment of coronary in-stent restenosis (ISR) and of de novo and restenotic lesions in the peripheral arteries. Furthermore, treatment of bifurcation lesions, de novo lesions in small vessels, long lesions, and cerebrovascular interventions have been proposed.

In the setting of ISR, the first major impact of DEBs in the management of ISR was shown by the results of the Paccocath ISR I trial (Treatment of In-Stent Restenosis by Paclitaxel Coated PTCA Balloons) comparing the efficacy of the Paccocath drug-eluting balloon vs. an uncoated balloon.[2,3] The 6-month angiographic results showed binary restenosis and major adverse cardiovascular event (MACE) rates of 5% and 4%, respectively, in the DEB group compared with 43% and 31%, respectively, in the uncoated balloon group (p=0.002 and 0.02).[2] During a follow-up of 5.4 ± 1.2 years, the clinical event rate was significantly reduced in patients treated with the DEB (59.3% vs. 27.8% MACE, p=0.009), which was mainly driven by the reduction in target lesion revascularization (TLR) from 38.9% to 9.3% (p=0.004).

The PEPCAD II trial[4] enrolled 4131 patients after BMS complicated by ISR with a 1:1 randomization to either receive a DEB or a Taxus stent. The primary endpoint of the study was late lumen loss at 6 months, which was significantly smaller in the DEB group compared to the Taxus group (0.17 vs. 0.38 mm, respectively). In addition, MACE at 12 months was 9% in the DEB group and 22% in the Taxus group, mainly driven by a TLR of 6% in the DEB group vs. 15% in the Taxus group. These results suggest that the DEB was not only not inferior, but apparently even superior to a DES in the treatment of ISR.

Recently, the multicenter, randomized, single-blinded PEPCAD-DES study (Treatment of DES In-Stent Restenosis With SeQuent Please Paclitaxel Eluting PTCA Catheter)[5] found paclitaxel-coated balloon angioplasty superior to plain balloon angioplasty, with a late lumen loss of 0.43 vs. 1.03 mm (p<0.001), respectively, and a restenosis rate reduced from 58.1% to 17.2% (p<0.001). Based on these 3 pivotal trials, the European Society of Cardiology has given the DEB a class IIa and level B recommendation for the treatment of ISR after prior bare metal stenting.[6]

In the context of ISR in the peripheral district, only a few patients were enrolled in 2 RCTs comparing DEB vs. standard treatment (22 of 154 in the THUNDER trial[7] and 6 of 87 patients in the FemPac trial[8]), making it difficult to draw any conclusions about the efficacy of DEBs in the periphery. However, more information has come to light with the recent publication of the DEBELLUM (Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment) randomized trial comparing a DEB to a conventional angioplasty balloon in the treatment of multilevel lower limb occlusive disease.[9] Fifty consecutive patients with 92 femoropopliteal and 30 below-the-knee stenoses (n=96) or occlusions (n=26) were randomized to treatment with the DEB (25 patients with 57 lesions) or plain balloon (25 patients with 65 lesions). The DEB group had lower late lumen loss (0.5 vs. 1.6 mm, p<0.01), fewer TLRs (6.1% vs. 23.6%, p=0.02), and lower binary restenosis rates (9.1% vs. 28.9%, p=0.03).

In the cerebrovascular circulation, only one study[10] has until now been published on DEB treatment in patients affected by carotid ISR and that pertained to intracranial lesions. Now, in this issue of the *JEVT*, 2 articles describe for the first time the off-label utilization of DEB for treatment of extracranial carotid ISR. Liistro and co-investigators[11] reported 3 cases of ISR (mostly focal) after Carotid Wallstent placement. The patients were successfully treated by a 1-minute inflation of a peripheral drug-eluting balloon after standard balloon predilation. The optimal immediate angiographic results were durable over a follow-up that extended from 6 to 24 months.

In a subsequent article, Montorsi and co-authors[12] reported 10 cases of ISR at a mean 20.9±19.4 months after carotid artery stenting (CAS) among 830 consecutive CAS procedures. Seven of the 10 patients were treated with DEBs (1 common and 6 internal carotid arteries). The authors utilized intravascular ultrasound–guided predilation with distal cerebral protection followed by inflation of a DEB with a 1:1 stent-to-balloon size ratio. In all 7 patients, Doppler ultrasound performed at a median 13.7 months following DEB treatment showed a reduction in the average peak systolic velocity from 4.00±0.97 to 0.90±0.14 m/s (p=0.0001).

There are several issues that should be considered regarding these preliminary experiences with DEB treatment of carotid ISR. First, the ideal treatment has yet to be defined. While different strategies have been reported in the literature, such as medical treatment (especially if the patient is asymptomatic), re-stenting (with BMS or DES[13]), repeat balloon angioplasty (preferably with cutting balloon[14]), and surgical treatment [carotid endarterectomy with stent removal (eversion technique), carotid artery bypass, or interposition graft[15–17]], clinical and angiographic results are extremely variable. In this context, a strategy as simple as DEB inflation may represent an extremely attractive solution. However, it is worth keeping in mind that the DEB concept is still in development; early on, the technology was hampered by a lack of solid preclinical data, attainment of marketing approval in Europe without long-term animal studies, non-standardized coating methods with differences in drug stability and prema-

TABLE

Drug-Eluting Balloons (DEBs) and Bare Metal Stents (BMS) Mounted on DEBs
Currently on the Market or in Development

Devices (Manufacturer)	Features
Dior (EuroCOR GmbH)	First generation: Mixture of paclitaxel (3 $\mu g/mm^2$) with dimethylsulfoxide on a rough, tri-folded balloon that protects the loaded drug from early wash-off. Inflation of the DIOR DEB for 45–60 seconds distributes the full, clinically-effective dose of paclitaxel equally over 100% of the coronary lesion.
	Second generation: A 1:1 mixture of aleuritic and shellolic acid with paclitaxel (5 $\mu g/mm^2$). The ultra-thin film, which is not transferred to the body, holds and liberates paclitaxel much better. Inflation time reduced to 30–45 seconds.
Elutax I and II (Aachen Resonance GmbH; distributed by Biotronik AG)	Paclitaxel (2.0 $\mu g/mm^2$) applied on the balloon surface in 2 layers: the first is bound to the balloon while it is inflated, and the second is in the form of crystal powder. A final chemical treatment fixes the drug on the balloon. Twenty percent of the drug is released at each inflation, and several inflations are possible.
Sequent Please (B. Braun Melsungen)	Paclitaxel (3 $\mu g/mm^2$) with iopromide formulation (Paccocath technology).
Cotavance (Bayer AG; MEDRAD)	Paclitaxel with iopromide formulation (Paccocath technology).
Advance (Cook Inc.)	DEB for the treatment of peripheral vascular disease; paclitaxel with undisclosed additive-based formulation.
Coroflex DEBlue (B. Braun Melsungen)	The SeQuent Please DEB technology with a thin-strut cobalt-chromium stent.
Magical (EuroCOR GmbH)	System in which a BMS can be delivered using the Dior balloon catheter.
IN.PACT catheters (Medtronic-Invatec)	DEB (paclitaxel with FreePac hydrophilic formulation) for the treatment of peripheral artery disease, specifically below the knee.
Moxy (Lutonix USA)	Paclitaxel in an undisclosed matrix.
Pantera Lux (Biotronik)	Paclitaxel in a n-butyryl-tri-n-hexylcitrate matrix.
Wombat (Avidal)	Paclitaxel in a proprietary drug wrap.

ture in-transit loss, and variances in the reproducibility of results.

Today, several DEBs are on the market for both coronary and peripheral application (Table), with a typical paclitaxel dosage of 3 $\mu g/mm^2$ of balloon surface. Although DEBs are not equal, the DEB technology can usually be characterized by 3 main components: the balloon catheter, the drug, and the carrier (excipient). The balloon is usually a compliant or semicompliant angioplasty balloon covered with the antiproliferative drug. The mechanical action as the balloon crushes the plaque creates microchannels through which the paclitaxel can be absorbed by the vessel. Preliminary preparation of lesions using predilation, atherectomy, or cutting balloon can optimize drug transfer during DEB inflation. Compared to long inflation times, short inflations and nominal pressure cause less arterial injury, preserving the inhibitory effect of paclitaxel,[18] and make the procedure more tolerable to patients.

The ideal drug for local delivery should have pharmacological characteristics that permit high adsorption rates and sustained effects in a short contact time. Currently, paclitaxel is the drug of choice due to its lipophilic properties and long antiproliferative effects (up to 14 days after a single dose application[19]), but sirolimus can also be delivered by nanocarrier technology or amphiphilic formulations.

In the beginning, paclitaxel was delivered to the intracoronary lumen by dilution in a hydrophilic contrast medium (iopromide); later, the drug was directly loaded on a balloon catheter. Preclinical studies showed that short exposure to paclitaxel coated on a balloon (inflation time of 60 seconds) was sufficient to diffuse an adequate drug concentration to inhibit neointimal growth compared to conventional angioplasty.[18] Recently,

Cremers et al.[20] showed that only 10 seconds of inflation time are sufficient for paclitaxel uptake by the vessel wall. Moreover, they found no increased safety risk after 2 overlapping DEB inflations (2 times 5 $\mu g/mm^2$) in the same vascular segment.

Different coating strategies have been developed, ranging from standard contrast agents to newer additives (Table) that bestow different elution and retention characteristics to DEBs. Recently, Radke et al.[21] tested in a porcine model the capability of 4 different additives [iopromide, acetyltriethyl citrate (ATEC), n-butyryl-tri-n-hexylcitrate (BTHC), and lecithin excipient] and found no differences in efficacy endpoints using histomorphology or quantitative angiography. The maximum tissue concentration of paclitaxel was detected in the BTHC group followed by iopromide. However, the use of DEBs utilizing these excipients was associated with delayed intimal healing and significantly higher inflammation and fibrin scores compared to uncoated control balloons. At the other end of the spectrum, the deployment of DEBs utilizing lecithin as the excipient resulted in inflammation scores similar to the uncoated control balloon, with no fibrin deposition. DEBs with ATEC as the excipient produced moderately increased inflammation and fibrin scores, representing an intermediate potential in paclitaxel transfer.

A second issue relative to the experiences of Liistro[11] and Montorsi[12] is that predilation with a standard balloon, as correctly done by the authors, is mandatory in all cases (both for de novo and ISR lesions). Indeed, it is of paramount importance to follow the correct technique when applying this technology. For example, to avoid balloon slippage, it is advisable to first use a non- or semicompliant balloon with a diameter 0.5 mm smaller than the reference vessel diameter. Then, the use of a larger conventional balloon with a balloon-to-vessel ratio of 0.8 to 1.0 is strongly encouraged, particularly if incomplete stent expansion is still visible. Cutting balloons, scoring balloons, or noncompliant high-pressure balloons can also be considered.

After predilation, the operator has to decide whether to proceed with a DEB or implant a stent in case of significant residual stenosis or an extensive or flow-limiting dissection. If the angiographic result is satisfactory, a DEB can then be used. In this case, it is fundamental to extend balloon length by 2 to 3 mm beyond the predilated area on each side. The operator should also choose a balloon-to-vessel ratio of 0.8 to 1.0 and inflate the DEB for at least 45 to 60 seconds at nominal pressure to avoid dissection outside the stent.[4]

In general, it is accepted that DEBs should not be used for direct mechanical treatment of ISR, but rather as a device for drug delivery after optimal predilation. Moreover, in the setting of carotid ISR, utilization of distal or proximal protection devices is highly recommended due to the fact that there have been reports of the carrier/excipient being dislodged from the balloon.

A final consideration is related to the future of DEB technology. Several registries and RCTs have been completed or are underway[22–26] to test this technology in different clinical settings. Nonetheless, the currently available data on DEBs for coronary and peripheral ISR are still limited, though promising. The extension of endovascular therapy to more demanding lesions (such as carotid ISR) might also increase the demand for a technology that reduces restenosis without compromising the normal vascular anatomy. However, the combination of paclitaxel and an excipient to transport the drug is of paramount importance since some balloons coated with the same amount of paclitaxel failed to show efficacy in both animal and clinical settings. Therefore, there is an enormous need for robust preclinical data related to drug transfer capability, drug transfer amount in the vessel, residual drug concentration after inflation, and vessel tolerance to large drug amounts delivered in a short interval. Subsequently, this information must be translated to the clinical arena by RCTs to confirm DEB efficacy in patients affected by atherosclerotic disease in both coronary and peripheral districts. The pioneering application of DEB technology to carotid ISR by Liistro[11] and Montorsi[12] and their colleagues deserves our congratulations. However, only when RCTs are performed in this setting will we know if the DEB technology can deliver the goods in the battle against restenosis.

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