UPDATE ON DRUG-ELUTING BALLOONS FOR PERCUTANEOUS CORONARY INTERVENTIONS

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ABSTRACT

Restenosis prevention continues to be a challenge to the interventional cardiologist. The introduction of stents has virtually eliminated the problems of elastic recoil, late negative remodelling and scaffolds unpredictable dissections, leaving neointimal hyperplasia as the primary cause of restenosis. Drug-eluting stents (DES), using antiproliferative drugs added to stents, serve to prevent the development of neointima hyperplasia. However, they can be associated with an irregular endothelialisation, requiring prolonged double antiplatelet therapy to reduce the risk of late and very late stent thrombosis. Moreover, incomplete suppression of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DES, especially when they are used "off-label" in complex clinical and anatomic settings.

Drug-eluting balloons (DEBs) may represent a therapeutic alternative for the interventional treatment of coronary disease. With the use of this technology, the short-term transfer of antiproliferative drugs to the arterial wall appears feasible, thus potentially reducing the untoward effects of the prolonged drug release associated with polymer-based stent technologies, and avoiding the risk associated with having a permanent metallic cage. In the last few years, research in this field has been increasing, and several trials have already been published or are planned to determine the place in therapy of these devices. The present article will review the available *in vitro*, animal and human evidence regarding these devices at present, and discuss the emerging role and their future perspectives.

Keywords: Drug coated balloon, paclitaxel, in-stent restenosis, paclitaxel eluting balloon.

INTRODUCTION

With the aim to overcome the limitations of drug-eluting stents (DES), a new concept of coronary intervention has been introduced in the recent years: the use of drug-eluting balloons (DEB). Paclitaxel coated-balloon (PCB) angioplasty appeared with the objective to achieve a local and homogeneous high concentration of an antiproliferative agent at the site of endovascular interventions. Advantages of this approach over the use of DES include a more homogeneous drug distribution and the fact that this mode of local delivery does not require foreign material implantation. Moreover, the recently introduced concept of "combined treatment strategy" of bare metal stent followed by DEB has aroused the interest of interventional cardiologists. Therefore the information that has emerged in a short time has been incredible.

This review provides an update on drug-eluting balloons. We analyse in detail the DEB commercially available, including essential data about their physicochemical properties. Moreover, first clinical experiences with DEB in different scenarios are reviewed in detail.

CHARACTERISTICS OF PACLITAXEL-COATED BALLOONS

Since the initial research undertaken by Scheller et al.,[4] several companies started commercialising

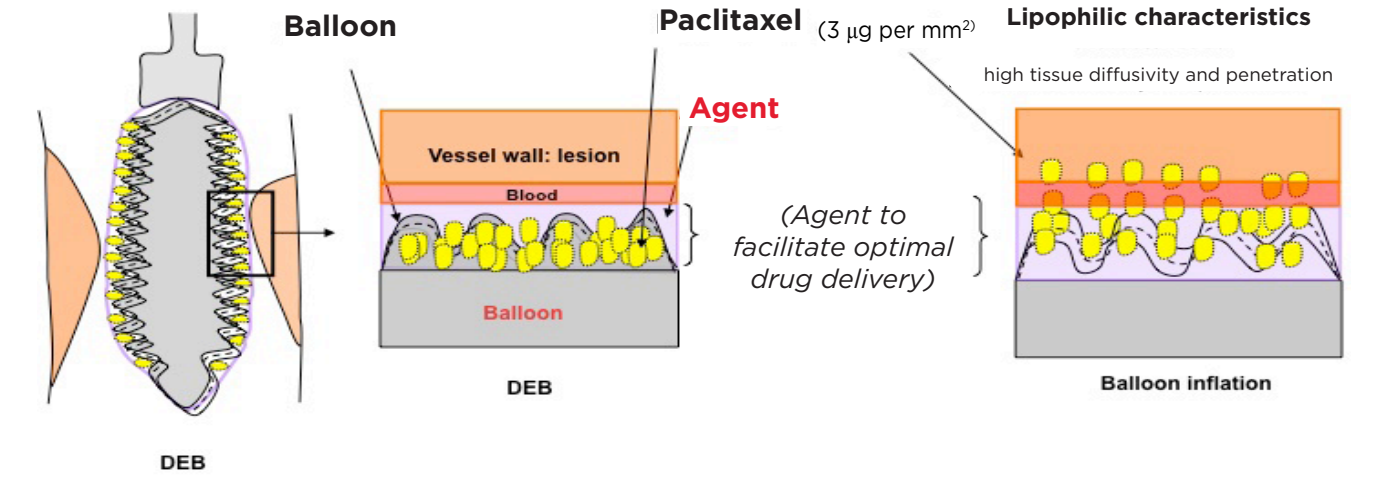

Figure 1. Drug-eluting balloon technology: the three components.

or developing drug-coated balloons (DCB). The best studied DEB, the SeQuent Please (B.Braun, Melsungen, Germany) and the Dior (Eurocor, GmbH, Germany), have given us insight into certain important properties of DCB (Figure 1). It has been proposed that the overall effectiveness of any DCB technology depends on the particular drug formulation and the coating method.[1]

Antiproliferative Agent

Paclitaxel was identified as the primary drug for DEB due to its high lipophilic property and ability to remain in the vessel wall for nearly a week.[2] The action of paclitaxel on vascular smooth muscle cells has been known since 1988. Paclitaxel is characterised by rapid intracellular uptake and irreversible binding to microtubules, inhibiting cell division and migration. The structural intracellular changes caused by paclitaxel explain its long-lasting effects.[3]

Compared with paclitaxel-eluting stents (PES), the concentration of paclitaxel on DEB is about three times higher with 3 µg/mm^2. This specific dose is the same for all DEB and this is based on *in vitro* studies that showed only about 10 to 20% of the paclitaxel is transferred from the balloon surface to the vessel wall.[4] 10% of the dose is lost while the catheter is advanced to the lesion through the haemostatic valve and the guiding catheter and most of the dose (70-80%) released at the target site is washed away in the blood stream during inflation. Thus, PCB delivers a dose to the target site in a very short time that is higher than the total dose released by stents over the course of the weeks. With this immediate drug release, there is no need for a polymer for drug administration, thus avoiding chronic inflammation and late thrombosis with first generation DES.

In the near future the lipophilic nature of the antiproliferative drug zotarolimus makes it a potential candidate for DCB applications. Zotarolimus-coated balloons were found to effectively reduce , proliferation in the porcine coronary overstretch model and showed profound anti-inflammatory effects.[5] Zotarolimus can be effectively formulated onto angioplasty balloons, ensuring delivery of high drug concentrations to the arterial target segments.[5]

Local Vascular Effects

It is well-known that restenosis due to neointimal hyperplasia is a slow process, suggesting the need for prolonged or repeated drug administration. Sustained drug release is considered to be essential for preventing restenosis by local drug delivery.[6] However, the concept of non-stent-based, local paclitaxel delivery was stimulated by the surprising observation that the short period of exposure of paclitaxel through the coronary arteries allows for taxane uptake sufficient to inhibit restenosis. A short incubation time (3 minutes) with paclitaxel almost completely inhibited vascular smooth muscle cell proliferation for up to 12 days.[7] The PCB releases the drug almost entirely in the first 48 hours, however, its biological effect has been discovered to persist for the first 14 days. This is very important because the process of restenosis is seen in the first days after the barotrauma induced by angioplasty, and paclitaxel primarily exerts its effect at that time.[7]

Formulation Used to Coat the Balloon. The Importance of Excipients

Current products range from those with no additive/

Name of PEB	Type of Coating	Formulation	Realease from balloon surface 30/60(s)	Vessel wall paclitaxel concentration & time of inflation	Company	Procedure
Paccocath™	Iopromide	3 µg paclitaxel/mm² balloon surface, admixed iopromide (Ultravist 370™)			Bavaria Medizin Technology	- BMS-ISR (RCT): PEB vs POBA (11)
SeQuent™ Please	Iopromide	3 µg paclitaxel/mm² balloon surface, modified Paccocath™	NA/93%	45-95 µg- 60 s	B. Braun, Melsungen, Germany	- BMS-ISR (RCT): PEB vs PES (14) - DES-ISR (RCT): PEB vs POBA (12, 13). PEB vs PES vs POBA(16) - *De novo* lesions (r) (16, 17)
Cotavance™	Iopromide	3 µg paclitaxel/ mm² balloon surface, modified Paccocath™	NA	NA	MEDRAD Inc, Warrendale, PA	NA
DIOR I	No carrier	Paclitaxel micro-crystals coated onto a 3-fold-microporous balloon surface structure	20/25%	1.5-6 µg – 60 s	Eurocor, GmbH, Germany	BMS/DES-ISR (r) (20) *De novo* lesions (RCT) (30)
DIOR II	Shellac	3 µg paclitaxel/mm² balloon surface, 1:1 mixture of paclitaxel and shellac	75/85%	167 µg – 30 s	Eurocor, GmbH, Germany	BMS/DES-ISR (r) (20, 21) *De novo* lesions (r) (31)
IN-PACT (FALCON)	Urea	FreePac™ paclitaxel-coated balloon catheters (Invatec, S.P.A., Italy)	NA	NA	Medtronic, Inc., Santa Rosa, California	BMS-ISR (r)(23) *De novo* lesions (RCT) (24)
Pantera Lux	Butyry trihexyl citrate (BTHC)	3 µg paclitaxel/ mm² balloon surface, matrix: BTHC	NA	165 µg – 30 s	Biotronik, Berlin, Germany	BMS/DES-ISR (r) (25, 26)
Elutax I	No carrier	2 µg paclitaxel/mm² balloon surface, formulated pure paclitaxel, coated on structured balloon surface	NA	NA	Aachen Resonance GmbH	ISR & *De novo* lesions: RCT: SeQuent™ Please vs Elutax I (8)
Protégé	No additive and very tight binding of the drug to the balloon membrane	Precise Paclitaxel volume administration at the precise location on the balloon surface between the wings prior to folding	NA	NA	Blue Medical, Helmond, the Netherlands	NA
Danubio	n-Butyryl tri-n-hexyl citrate (BTHC)	The SpeedPAX technology : BTHC and paclitaxel	NA	NA	Minvasys, Gennevilliers, France	NA

ISR: In-stent restenosis; NA = not available; s = seconds; µg = microgram; RCT= randomised clinical trial; (r) =registry.

Table 1. Paclitaxel-Eluting Balloons (PEB) commercially available.

carrier and very tight binding of the drug to the balloon membrane to those applied in conjunction with standard contrast agents or other additives. Different types of water-soluble matrix have been introduced by the manufactures, all relying on the same concept that has been firstly developed in the Paccocath DEB (Table 1). According to the initial investigation of comparative DEB performance in humans[8] and porcine model of coronary restenosis,[1,9,10] it seems that the most effective DEB in terms of antiproliferative effect could be related with the final tissue dosage, which depends on the formulation used to coat the balloon. It has been reported (Table 1) that the Pantera Lux DEB (drug concentration 165 μg) was more effective than SeQuent Please DEB (drug concentration 45-95 μg), and Elutax first generation (no data could be found in the literature concerning the delivery dose).[10] Moreover, SeQuent Please was more effective than Dior first generation (paclitaxel concentration 1.5-6 μg)[9] and Elutax first generation.[1] Thus, it seems that the highest drug retention in the vessel wall, the most effective DEB. Also it is important to note that evidence of delayed healing was observed in the most effective DEB groups.[10]

PACLITAXEL-ELUTING BALLOONS STUDIED IN CLINICAL TRIALS

The SeQuent Please (or its Predecessor Paccocath) (B. Braun, Melsungen, Germany)

The results of Scheller et al.[4] demonstrated that paclitaxel admixed to a small amount of the hydrophilic X-ray contrast medium, iopromide, emerged as a very effective coating matrix in numerous *in vitro* and *in vivo* experiments. The concentrations of paclitaxel achieved in iopromide-370 are about 20 times higher than in saline or other aqueous media because iopromide greatly enhances the solubility of paclitaxel. Scheller et al.[7] demonstrated that short exposure of the vessel wall to paclitaxel was sufficient to achieve an arterial wall concentration high enough for preventing restenosis. A very ambitious clinical study program investigating this balloon catheter was initiated in 2004; published results show good agreement with the Paccocath™ ISR study.[11] In randomised trials, PCB angioplasty (Paccocath, SeQuent Please) was superior to uncoated balloon angioplasty and PES for treatment of in-stent restenosis (ISR) in bare-metal stent (BMS)[11] and DES.[12,13,14,15] Moreover, for *de novo* lesions, PCB angioplasty resulted in good angiographic and clinical results.[16,17]

The Dior I and II (Eurocor, GmbH, Germany)

Both generations of Dior™ balloons share most general properties: the drug and the dose of paclitaxel, the same balloon designed with three-folds of microporous surface ensuring good contact with paclitaxel, and similar preparative process. However, the coating method was completely different. The first generation Dior balloon had a nanoporous surface containing microcrystals of pure paclitaxel that were then embedded on the vessel wall at the time of balloon inflation.[18] The second generation Dior balloon contains shellac as a paclitaxel carrier. Shellac is an inert substance that has already been approved by the FDA as a food additive. It is mostly composed of aleuritic acid, jalaric acid and shelloic acid. The microporous balloon surface contains a 1:1 mixture of paclitaxel and shellac. A balloon inflation time dependency study in the porcine model of coronary artery overstretch showed almost maximum tissue paclitaxel concentrations after shorter balloon inflation times of 30 seconds and release of 75% of the drug from the balloon surface, which resulted in an up to 100-fold higher drug concentration after 45 minutes when compared with the first generation Dior, and around the same delivery dose of the Sequent Please DEB. Moreover, tissue paclitaxel resulted in much lower concentration 12 hours after balloon inflation, a result comparable with other PCB in previous studies.[19] As it has been demonstrated the type of PCB coating had an impact on clinical results. In real life registries, second generation Dior DEB has shown low target lesion revascularization (TLR) and major adverse cardiac events (MACE) at mid term.[20,21]

In.Pact (Falcon) (Medtronic, Inc., Santa Rosa, California)

Various FreePac™ paclitaxel-coated balloon catheters (Invatec, S.P.A., Italy) have been introduced since early 2009. FreePac™ is a proprietary hydrophilic coating formulation with urea as matrix substance. Urea is a non-toxic, ubiquitous endogenous compound, commonly used in pharmacy and is supposed to enhance the release of paclitaxel during the short time of contact with the vessel wall. A comparison of the FreePac™ coating formulation on a balloon catheter with an uncoated balloon catheter (negative control) and the Paccocath™ coating (positive control) was performed in the coronary overstretch and stent implantation porcine model. In this study, similar mean residual drug content on the used balloons and similar amounts of paclitaxel were transferred to the vessel wall with

the Paccocath™ coating and the FreePac™ coating, 15-25 minutes after stent implantation.[22] The initial data from a registry of this novel paclitaxel urea coated angioplasty balloon in the treatment of coronary BMS in-stent restenosis showed promising results.[23] Moreover a randomised clinical trial with this DEB in small coronary vessels has revealed similar late loss at 6 months late loss compared to PES. Furthermore, DEB and PES were associated with similar rates of angiographic restenosis, MACE, and repeat revascularisation in small vessels.[24]

Pantera Lux (Biotronik, Berlin, Germany)

Pantera Lux™ (Biotronik AG, Germany) uses butyryltrihexyl citrate (BTHC) as a carrier for paclitaxel. BTHC is used in different medical devices and cosmetics and is approved for blood contact in blood bags. Preliminary clinical data have been published recently with promising results for the treatment of BMS restenosis.[25,26]

Elutax™ (Aachen Resonance, Germany)

This DCB uses pure paclitaxel without a matrix, coated on structured balloon surface. This balloon has a drug configuration with a concentration of 2 µg/mm^2 paclitaxel, without any excipient. To date, no data have been published in the literature concerning the delivery dose of this balloon. Comparative assessment of DCB (Pantera Lux, SeQuent Please and Elutax I) in an animal study with porcine model of coronary restenosis showed worse results in terms of antiproliferative effect of Elutax comparing with Pantera Lux and SeQuent Please DCB.[14]

EVIDENCE IN CLINICAL APPLICATIONS

In-Stent Restenosis (Table 2 & 3)

Paclitaxel-eluting balloon (PEB) is emerging as an effective treatment for in-stent restenosis in both BMS and DES.

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
BMS-ISR		**RCT**					
	PACCOCATH-ISR I (11) & II trials (27)	DEB vs POBA	I (n= 52) I & II (n=108)	Paccocath™	0.03±0.48 vs 0.74±0.86 mm*	6 mo: 0 vs 23%* 5y: 9.3 vs 38.9%*	5y: 27.8 vs 5.3%*
	PEPCAD II (14)	DEB vs PES	n=101	SeQuent™ Please	0.17±0.42 vs 0.38±0.61 mm*	12 mo: 9 vs 22%*	
BMS-ISR		**DEB Registries**					
	Spanish Multicenter Dior registry (20)		n=65	Dior I & II		12 mo: 9.2%	12 mo: 12.3%.
	Valentines I trial (21)		n=168	Dior II		7.5 mo: 5.1%	
	World Wide Registry (16)		n=743	SeQuent™ Please		9 mo: 3.6%	9 mo: 5.3 %
	IN-PACT (FALCON) (23)		n=43	IN-PACT (FALCON)	- In-stent 0.07±0.37mm	6mo restenosis: 4.3%	
	PEPPER trial (26)		n=43	Pantera Lux	0.05±0.28 mm		12 mo: 11.8%

The European Society of Cardiology Guidelines for Percutaneous Coronary Intervention (2010) recommended that DEB should be considered for the treatment of in-stent restenosis after prior bare-metal stent (class 2 IIa, evidence B) (28).

ISR: In-stent restenosis; mo=month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05

Table 2. Paclitaxel-Eluting balloons (PEB) for bare metal in-stent restenosis (BMS-ISR).

Bare metal stent restenosis:

In randomised trials, PCB angioplasty (Paccocath, SeQuent Please) was superior to uncoated balloon angioplasty (POBA) for treatment of ISR in BMS.[11] Similar positive results were found when comparing the SeQuent Please DEB with PES to treat BMS restenosis.[12] Superiority was demonstrated for angiographic and clinical endpoints and for the long term follow-up (Table 2).[27] Moreover, positive results have been reported in a "real, non-selected, population" in registries and for other DCB balloons.[16,20,21,23,26] Thus the European Society of Cardiology Guidelines for Percutaneous Coronary Intervention (2010) recommended that DEB should be considered for the treatment of in-stent restenosis after prior BMS (Class IIa, evidence B).[28]

Drug-eluting stent restenosis:

The optimal management strategy for patients with DES-ISR certainly remains unknown. Clinically, treatment of DES restenosis lesions seems to be associated with higher rates of adverse events and recurrent restenosis.[29] In randomised trials, PCB angioplasty (SeQuent Please) was superior to uncoated balloon angioplasty for treatment of in-stent restenosis (ISR) in DES.[12,13] Futhermore, the recently published ISAR-DESIRE 3 has revealed comparable results of DEB and PES in the treatment of DES restenosis. Both strategies showed to be superior to balloon angioplasty, (Table 3).[15] Despite DES restenosis is associated with adverse outcomes compared to BMS restenosis, four published multicentre and prospective registries using different DCB have reported promising results.[16,20,21,26]

De Novo Lesions (Table 4)

The efficacy of DEB in *de novo* lesions needs to be established. Potentially DEB may be particularly advantageous over DES in the treatment of *de novo* lesions by providing an immediate and homogenous drug uptake, avoiding inflammatory reaction to stent

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
BMS-ISR		**RCT**					
Sirolimus/ Everolimus/ Paclitaxel ISR	PEPCAD DES (12)	DEB vs POBA	n=110	SeQuent™ Please	0.43±0.61 vs 1.03±0.77 mm*	6 mo: 15.3 vs 36.8%*	6 mo: 16.7% vs 36.8%*
Sirolimus-ISR	Habara S et al. (13)	DEB vs POBA	n=50	SeQuent™ Please	0.18±0.45 vs 0.72±0.55 mm*	6 mo: 4.3% vs 41.7%*	
Limus-ISR	ISAR-DESIRE 3 (15)	DEB vs PES vs POBA	n=137/131 /134	SeQuent™ Please	DEB 0.37±0.59 vs PES 0.34±0.61 mm, p=NA DEB/PES vs POBA 0.70 ± 0.60 mm*.	DEB 22.1 vs PES13.5%* DEB/PES vs POBA 43.5%*	DEB 23.5 vs PES 19.2%* DEB/PES vs POBA 46.3%*
BMS-ISR		**DEB Registries**					
	Spanish Multicenter Dior registry (20)		n=61	Dior I & II		12 mo: 14.8%	12 mo: 21.3%.
	Valentines I trial (21)		n=86	Dior II		7.5 mo: 10.8%	
	World Wide Registry (16)		n=464	SeQuent™ Please		9 mo: 9.6%	9 mo: 11.6%
	PEPPER trial (26)		n=38	Pantera Lux	0.19±0.29 mm		12 mo: 11.8%

ISR: In-stent restenosis; mo=month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05

Table 3. Paclitaxel-Eluting balloons (PEB) for drug-eluting in-stent restenosis (DES-ISR).

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
Small Vessel				RCT			
MRD= 2.54±0.47 mm	PICOLETO trial (30)	DEB vs PES	n=60	Dior I	Bailout BMS DEB group: 35.7%. ISR: 32.2% vs 10.3%*		35.7 vs 13.8%*
MDR= 2.15±0.2 7mm	The BELLO trial (24)	DEB vs PES	n=182	In-Pact (FALCON)	Bailout BMS DEB group: 20.1%. 0.08±0.38 vs 0.29±0.44mm ISR: 8.9 vs 14.1% p=ns	6mo: 4.4 vs 7.6% p=ns.	7.8 vs 13.2% p=ns
		DEB Registries					
MDR= 1.9±0.34 mm	Spanish Multicenter Dior registry (31)		n=103	Dior II (46%)	Bailout BMS required: 7.5%. 0.34±0.23 mm ISR 19.6%.	12 mo: 2.9%	12 mo: 5.8%
MRD= 2.36±0.18 mm	PEDCAD I (17)		n=118	SeQuent™ Please	Bailout BMS required: 26.9%. 0.28±0.53 mm ISR 18%.	12 mo 11.9%	12 mo: 15.3%
MRD= 2.5±0.4 mm	World Wide Registry (16)		n=390	SeQuent™ Please	Bailout BMS required: 26.9%. 0.28±0.53 mm ISR 18%.	12 mo 11.9%	12 mo: 15.3%
Bifurcated lesion		RCT					
Provisional T stent strategy	Stella et al. (32)	(A) DEB MB & SB & BMS MB vs (B) BMS MB & POBA SB (C) DES MB & POBA SB	n=117	Dior II	(A) MB proximal 0.58±0.65 MB distal 0.41±0.60 / SB 0.19±0.66 (B) MB proximal 0.60±0.65 MB distal 0.49±0.89 / SB 0.21±0.57 (C) MB proximal 0.13±0.45 MB distal 0.16±0.64 /SB 0.11±0.43* ISR: (A) 24.2% (B) 28.6%. (C) 17.5% p=0.45. MACE : (A) 20%. (B) 29.7%. (C) 17.5%. p=0.40.		
		DEB Registries					
Provisional T stent strategy	PEDCAD V (33)	DEB MB & SB BMS MB	n=28	SeQuent™ Please	Bailout BMS require SB: 14.3%. MB 0.38±0.46mm and SB 0.21±0.48mm. ISR: MB 3.8% and SB 7.7%. 2 late stent thrombosis at 6 and 8 mo	9mo TLR MB 3.8%.	
Other		DEB Registries					
	Valentines II (*)		n=103	Dior II	Bailout BMS require: 11.9%	6-9 mo:2.9%	6-9 mo:8.7%

MRD= Mean Reference Diameter; ISR: In-stent restenosis; mo=month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05

(*) Angiographic results of the Dior Drug-coated Balloon fro the novo coronary lesions: Results from the Valentines II trial. Lob JP, Serra A, Malik F, et al. J Am Coll Cardiol Intv. (2013) 6.No2. Page S3.

Table 4. Paclitaxel-Eluting balloons (PEB) for *de novo* lesions.

struts or polymers, and preserving the normal vessel anatomy. DEB also provide a therapeutic option in very small vessels (<2.25 mm), for which DES sizes are not available. However, with this technology, flow limiting dissections and acute recoil may require the additional implantation of stents.

Small vessel disease:

There are few specific studies published in the literature that have assessed the role of DCB in small vessel coronary disease. The PEPCAD I was the first study (single-arm non-randomised trial) evaluating the safety and efficacy of the Sequent Please balloon for the treatment of small vessel disease, and showed good angiographic and clinical results, thus, demonstrating that DEB possibly yields the potential as treatment alternative for these types of lesions.[16] Moreover, this study reported a significantly higher late loss and restenosis rate in lesions treated with a combination of DEB and BMS, especially if geographic mismatch occurred (i.e. stent implanted in an area that was not treated with DEB).[16] Then, two randomised trials have reported different results. The recently published BELLO randomised trial reported that the In.Pact Falcon DEB was noninferior to PES in suppressing neointimal proliferation in small vessels. Furthermore, DEB and PES were associated with similar rates of angiographic restenosis, MACE, and repeat revascularisation.[24]

On the other hand, the PICCOLETO trial failed to demonstrate Dior I DEB equivalence to a PES for the treatment of small vessel disease, both in terms of angiographic and clinical restenosis.[30] It is important to note some procedural limitations of this study as plain balloon predilatation was done only in 25% of cases and bailout stent implantation in the DEB group was 35.6% with the occurrence of so-called "geographical mismatch", which led to restenosis in stented lesion sites that were not adequately pretreated with DEB. Another important fact that could explain the negative result of the PICCOLETO could be that this study was performed with Dior I while the SeQuent Please used in PEPCAD I and the In.Pact Falcon used in the BELLO Trial, probably could be considered superior to the Dior I in terms of tissue dosage (Table 1). The Spanish Dior Registry[31] used 49% Dior-II to treat really small vessel disease in a real-world population. The investigators in the Spanish Multicentre Registry study were particularly careful to use DCB as a delivery drug system, thus lesion predilatation was performed in all cases with a shorter plain balloon than Dior. Bailout stent implantation was only needed in 7.5% of cases, and in these cases investigators were particularly careful to ensure that any needed stent was implanted within the DEB-treated zone. This registry showed similar positive results to other published registries (Table 4).[16,17]

Bifurcated lesions:

To date, two approaches to treat bifurcated lesions with DEB have been described; i) sequential DEB treatment of the bifurcation branches followed by BMS implantation in the MB; ii) simple MV stenting followed by kissing DEB. Few results have been reported with inconsistent data.[32-34] In the first group, The PEPCAD V, a small prospective register, enrolled 38 patients with bifurcation lesions. SeQuent Please DCB, was used to dilate both main and side branch, with BMS deployment in the main branch (MB) by provisional T stent strategy. Only in case of more than 75% residual stenosis in the SB or reduced Thrombolysis in Myocardial Infarction (TIMI) flow, final kissing balloon dilation was performed. At 9-months, the percentage of restenosis was comparable to the historical data of DES treatment.[33] By contrast, the recently published Drug-eluting Balloon in Bifurcations Trial,[32] enrolled 117 patients in a multicentre randomised trial. The study aimed to compare three strategies based on the provisional T-stenting approach, firstly using Dior II DCB in both branches followed by BMS implantation in MB, versus standard BMS implantation versus standard DES implantation. Considering the primary endpoint, the DEB group showed similar late luminal loss as the BMS group, being both inferior to the DES group. No significant differences were found in MACE rate between the three groups (Table 4).

In the second group of strategy type, only one feasibility study of 14 patients reported procedural success of provisional stenting with an open-cell design BMS and final kissing balloon with second-generation DEB. At a mean follow-up of 234±81 days, no MACE was reported.[34] The German consensus group has recommended an approach of sequential regular balloon predilatation of the bifurcation branches, and if there is a good angiographic result, it is to be followed by DEB treatment in the MB and SB. Stent implantation was recommended as a bail-out strategy in case of major dissection or TIMI <III. Moreover if the SB has >75% residual stenosis or TIMI flow is reduced, a final kissing balloon dilatation with conventional balloons was recommended.[35]

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
Diabetes		RCT					
MRD= 2.87±0.34 mm	(37)	DEB + BMS vs PES	n=84	SeQuent™ Please	0.51±0.61 vs 0.53±0.67 mm, p=ns. 6 mo ISR: 8.7 vs 10.3%, p=ns.		13.3 vs 15.4%, p=ns
CTO		DEB Registries					
	PEDCAD-CTO (38)	DEB + BMS vs PES	n=48	SeQuent™ Please	0.64±0.69 vs 0.43±0.64 mm, p=0.14. 6 mo ISR: 27 vs 20.8%, p=0.44.		14.6 vs 18.8%, p=ns
STEMI		RCT					
	DEB-AMI (39)	(A) BMS vs (B) DEB+BMS vs (C) PES	n=150	Dior II	(A) 0.74±0.57 (B) 0.64±0.56 (C) 0.21±0.32* ISR: (A) 26.2 (B) 28.6 (C) 4.7%*		(A) 23.5 (B) 20.0 (C) 4. 1%

ISR: In-stent restenosis; mo= month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05.

Table 5 . Treatment strategy with Paclitaxel-Eluting balloons (PEB) plus bare metal stent (BMS) for the *de novo* lesions.

Drug-Coated Balloon Angioplasty Plus Bare-Metal Stent (Table 5)

For the *de novo* lesions, sequential application of DCB and not pre-mounted BMS for treatment of *de novo* coronary lesions resulted in efficient inhibition of neointimal hyperplasia. The sequence of application (DCB first vs. BMS first) did not seem to influence the outcome (6 months late loss 0.45±0.57 mm vs. 0.53±0.52 mm, p=0.83), except for better apposition in BMS first (p=0.013).[36]

In patients with diabetes, the treatment strategy with SeQuent Please DCB angioplasty plus BMS revealed similar results compared with PES.[37] In chronic patients, the use of PCBs in combination with BMS was tested in the Paclitaxel-Eluting Percutaneous Transluminal Coronary Angioplasty - Balloon Catheter in Coronary Artery Disease to Treat Chronic Total Occlusions (PEPCAD-CTO) trial. With 48 patients matched to a historical population with paclitaxel-eluting stents, the angiographic late loss, the need for TLR and MACE was similar between the two treatment strategies and there was no stent thrombosis within 12 months follow-up.[38] However, in the DEB-AMI randomised trial, (two-centre, single-blinded, three-arm study) STEMI patients were randomly assigned to group A: BMS; group B: Dior II DCB plus BMS; or group C: DES after successful thrombus aspiration. As is shown in Table 5, DCB followed by BMS implantation failed to show angiographic superiority to BMS only. Angiographic results of DES were superior to both BMS and DEB. Moreover, DEB before implantation induced more uncovered and malapposed stent struts than BMS, but less than after DES.[39] Therefore, what limited data exist to date do not suggest a clear role for this modality in the *de novo* lesions.

CONCLUSIONS

Preclinical and clinical investigation on the DEB performance in humans and in porcine models of coronary restenosis, suggest that efficacy of DEB in terms of antiproliferative effect and better clinical outcomes, relies on the achievement of sufficient bioavailability of paclitaxel at the vessel lesion site. Moreover, the final tissue dosage sufficient to result in successful angiographic results may depend on the formulation used to coat the balloon and on the type of the coronary lesion treated. Since there is no certain class effect, efficacy and safety have to be demonstrated for different types of DEB and in different subset of lesions.

Rigorous preclinical and clinical work is needed to establish safety and efficacy beyond the current stage. It has been demonstrated that to enhance the solubility of the lipophilic paclitaxel, DEB needs the use of a smaller amount of additives. In the second generation of DEB (SeQuent Please, Dior II, In-Pact Falcon and Pantera Lux) different types of water-soluble matrix (iopromide, shellac, BTHC, and urea) have been introduced by the manufacturers, all relying on the same concept that has been firstly developed in the Paccocath DEB. It has been reported for Dior II and Pantera Lux DEB a delivery dose similar to the SeQuent Please DEB. These promising preclinical results need to be better confirmed in clinical trials.

Despite clinical randomised trials and registries, DEB has demonstrated to be superior to uncoated balloon angioplasty and PES for the treatment of in-stent restenosis in BMS and DES. Currently, the treatment of BMS in-stent restenosis is the only guideline-approved indication for DEB use. For the *de novo* lesions the efficacy of DEB seems promising but needs to be established. However, DEB cannot overcome the mechanical limitation of acute recoil and flow-limiting dissections seen after post-balloon angioplasty. Furthermore, it is not clear whether DEB can avoid the late negative remodelling seen with noncoated balloons. The concept of "combined treatment strategy" of BMS followed by DEB has been recently challenged but further validation in appropriately designed trials is needed. Furthermore, the results of the DEB technology need to be compared in randomised trials against the second generation DES. Research in this field is active, and new trials are already planned to determine the place in therapy of these devices.

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