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Current Pharmaceutical Design, 2018, *24*, 381-396

REVIEW ARTICLE

Drug-coated Balloons: Technologies and Clinical Applications

Huiying Ang[a,#], Jinjie Lin[a,#], Ying Ying Huang[b], Tze Tec Chong[c], Salvatore Cassese[d], Michael Joner[d] and Nicolas Foin[a,e,*]

[a]*National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609, Singapore;* [b]*School of Materials Science and Engineering, Nanyang Technological University, Nanyang Avenue, Singapore 639798, Singapore;* [c]*Department of Vascular Surgery, Singapore General Hospital, 169608 Singapore, Singapore;* [d]*Deutsches Herzzentrum München, Technische Universität München, Munich 80636, Germany;* [e]*Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore*

ARTICLE HISTORY

Received: November 24, 2017
Accepted: December 22, 2017

DOI:
10.2174/1381612824666171227221305

Abstract: The progress and development of drug-coated balloons (DCBs) represents an emerging alternative treatment in peripheral and coronary artery diseases, particularly when a non-stent approach is necessary. Several studies and meta-analyses have evaluated the clinical outcomes of DCBs in different lesions and this review aims to compile the progress and updated clinical data of DCB strategy in both peripheral artery diseases (PAD) and coronary artery diseases (CAD). The review highlights that clinical data has encouraged the use of DCB for applications in PAD and in the treatment of coronary in-stent restenosis (ISR). The employment of DCB in side branch treatment of bifurcation lesions has been reported to be feasible and safe, with good angiographic and clinical outcome. The use of DCB for arteriovenous fistula and grafts stenoses is a promising strategy, but more clinical data is required to draw reliable conclusions. The limitations and impact of the current generation of DCBs will be discussed and the clinical development of newer generation of the device is also covered in this review.

Keywords: Drug-eluting balloon, drug-coated balloon, peripheral interventions, coronary artery disease, paclitaxel, restenosis.

1. INTRODUCTION

1.1. Development of Drug-coated Balloons (DCB)

The use of the balloon angioplasty in interventional cardiology, is associated with deficiencies such as acute vessel closure caused by dissection or elastic recoil, late vascular remodelling, and neointimal hyperplasia [1]. Elastic recoil typically occurs in 10-15% of patients within minutes or hours after the procedure, resulting in rebound occlusion of artery and in turn acute myocardial infarction [2]. The development and use of Bare Metal Stents (BMS) prevented acute vessel closure following dissection or elastic recoil after balloon angioplasty [2]. However, the use of BMS resulted in a high In-Stent Restenosis (ISR) rate (20-30%) and the issue of neointimal hyperplasia still persisted [2-4]. Drug-Eluting Stents (DES) were thus developed to overcome the limitations of BMS. DES have been the standard of care in percutaneous interventions due to their good mechanical support and stable drug eluting profile for the treatment of occluded vessels. However, the employment of DES is not always suitable in cases such as small vessels, bifurcations and challenging peripheral arterial segments [5, 6]. DES implantation has been associated with late stent thrombosis (LST), delayed healing and occurrence of ISR. Concerns about the safety of DES were raised, following the emergence of evidence from clinical case reports suggesting complications linked to stent thrombosis [2, 7, 8]. The use of metallic implants cages the vessels permanently and has led to a consistent of 2-4% per year incidence rate of Target Lesion Failure (TLF) events (*e.g.* composite of cardiac-related death, target vessel–related myocardial infarction or ischemia-driven target lesion) beyond the first year. This is similar to the very late rates seen in BMS and 1st generation DES implantation [9].

Thus, the use of a nonstent-based local drug delivery system was developed as an alternative treatment to DES, which has been the motivation behind the development of Bioresorbable Scaffolds (BRS) and Drug-coated Balloon (DCB) [3]. DCB may provide a non-stent strategy without the increased risk of late catch-up phenomenon or stent thrombosis that have been demonstrated with the current generation of DES and BRS. The potential benefits of DCB are: (i) a wider contact surface area and more uniform drug transfer; (ii) improved arterial healing due to absence of long-term inflammatory source; (iii) preservation or early restoration of normal vessel anatomy and function and (iv) application in scenarios where stent implantation is undesirable (ISR, bifurcation carina, superficial femoral artery and/or popliteal artery space) [10], or allowing access to territories that are hard to treat using DES [5, 6]. Early investigations revealed that single-dose exposure of paclitaxel (PTX) to smooth muscle cells led to an inhibition of proliferation and migration whether in monocultures or co-cultures group. Local PTX delivery using microporous or perfusion balloon catheters demonstrated effective neointimal inhibition [11].

1.2. Mechanisms of Actions

There are four key elements in DCB – (1) balloon platform, (2) drug, (3) excipient and (4) balloon coating process. Upon contact after inflation, acute drug transfer occurs almost immediately to deliver the anti-proliferative drug from the balloon's surface to the vessel wall, mostly binding to hydrophobic binding sites on the latter, with lesser amount being transported by diffusion and convection [12-14]. Factors influencing transfer efficiency include the inherent physicochemical properties of the drug, manufacturing and coating process, and the presence of excipients. Excipients increase drug transfer capability by counteracting the hydrophobicity of the drug which causes it to remain on the balloon's surface [13, 15]. Anti-proliferative drug applied onto commercial DCB has traditionally been Paclitaxel (PTX), although recent DCB development is seeing the use of sirolimus instead (Fig. **1**) due to cytotoxicity of PTX. PTX exerts its anti-proliferative behaviour by binding onto the tubulin subunits of microtubules of cell cytoskeleton, thus inhibiting microtubule disassembly and its dynamics [16]. Sirolimus, on the other hand, inhibits a serine/threonine protein kinase (mTOR) which prevents cell proliferation [17]. The effect of Si-

*Address correspondence to this author at the National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609, Singapore;
E-mail: nicolas.foin@gmail.com
[#]*These authors contributed equally.*

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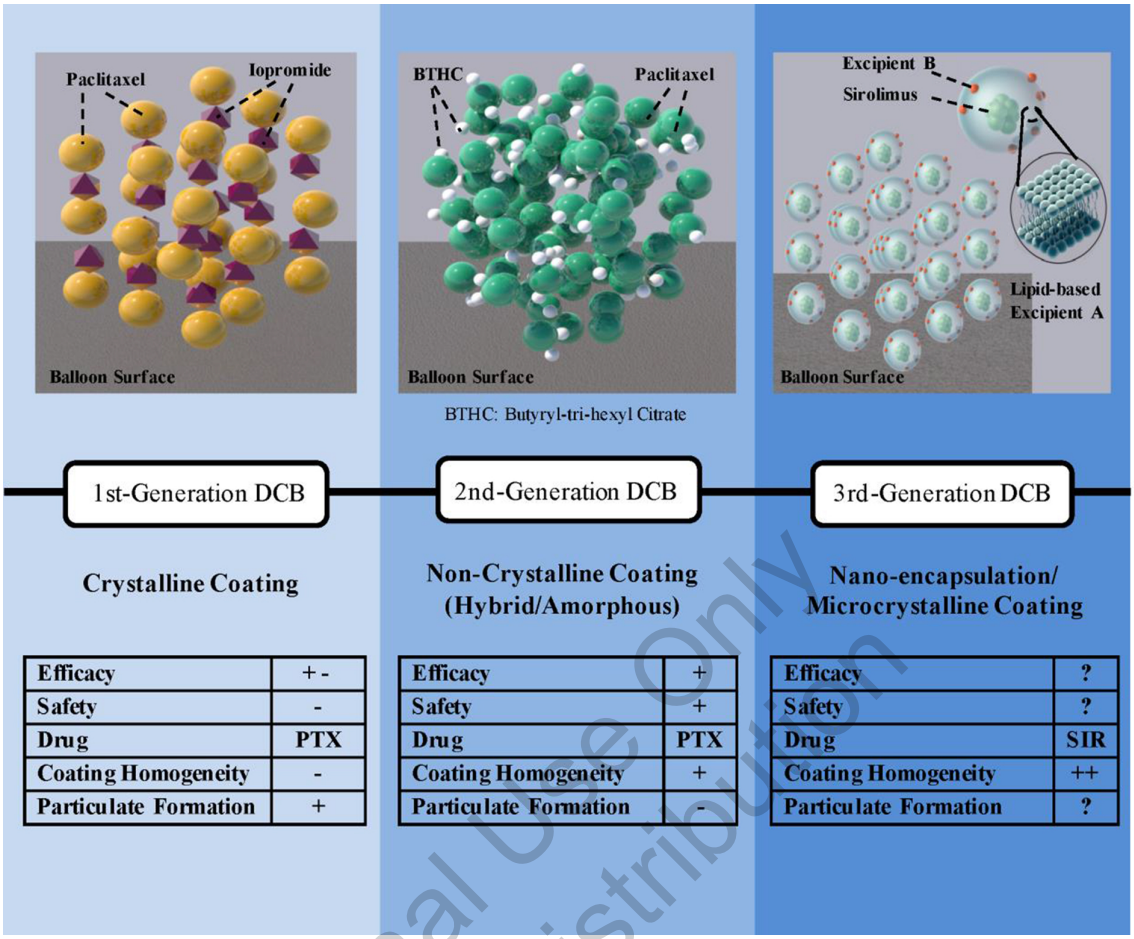

Fig. (1). Different generations of drug-coated balloons (DCBs). The 1st and 2nd generation of DCB employed paclitaxel as the anti-proliferative drug and the crystallinity of the coating played a role in the extent of particulate generation. The 3rd generation is moving towards the use of Sirolimus as it is less cytotoxic but the efficacy and safety of the newer DCB coating require further evaluation. BTHC = Butyryl Trihexyl Citrate; PTX = Paclitaxel SIR = Sirolimus.

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rolimus has been considered to be cytostatic at therapeutic doses used in the prevention of restenosis, whereas PTX is generally cytotoxic at therapeutic doses [18]. Table **1** is a comparison between the use of PTX and Sirolimus as anti-proliferative drugs [19-23].

1.3. Current and Upcoming DCB Platforms

The balloon coating should ideally exhibit the robustness to retain drugs on the surfaces as during tracking of the device while enabling efficient and homogeneous drug transfer to vessel walls. First generation DCB employed the original Paccocath formulation, which made use of the hydrophilic contrast agent iopromide as an excipient to coat PTX on the balloon [24]. The manual dipping coating process had led to a non-homogeneous coating [25]. Furthermore, the high coating crystallinity is believed to have resulted in the high amount of particulate loss observed, due to the coating matrices being brittle and fragile [26]. However, high drug transfer to tissue was reported as small- and medium-sized paclitaxel crystals continue to deliver the drug into the underlying tissue after adherence [26]. On the other hand, second generation DCB seek to reduce particulate formation by reducing the crystallinity of the coating matrices using a different coating method [25]. Hybrid and amorphous coatings, and coating through accurate microsyringe circumferential deposition were ultilized.

Other hydrophilic excipients (*e.g.* urea and shellac) and hydrophobic excipients (*e.g.* Butyryl Trihexyl Citrate (BTHC)) were explored. Hydrophilic excipients have the advantage of effective drug transfer due to polarity difference of the coating and balloon material but often have a high drug wash-off rate and particulate generation during tracking. In an experimental preclinical model, a minimum of 25 to 35% of PTX was found to have been shed from PTX-iopromide and PTX-urea DCB while in the vessel, presumably due to embolization of the coating [27].

Hydrophobic excipients improve coating integrity, reduce drug loss and increase retention of the drug in the tissue, but can have poor transfer rate due its affinity to the hydrophobic balloon material. Amphiphilic excipients (*e.g.* polysorbates) have the potential to ensure drug coating integrity with minimal particulate generation while facilitating effective drug transfer and retention during tissue contact.

The third generation DCB are moving into the use of encapsulation carriers in their coating. Encapsulating the drug improves its stability and solubility while achieving targeted delivery of the drug to tissue. Support C DCB (eucatech AG) and the Sirolimus-based Magic Touch DCB (Concept Medical) are examples of such DCB with microcrystalline and nano-sphere coatings, respectively, which reportedly have higher drug transfer and tissue levels, but also a higher amount of particulate loss [28]. A comparison between the three DCB generations and their potential benefits and drawbacks is shown in Fig. **1**.

Lastly, micro-porous balloon drug delivery systems in which perforated balloon catheters are used, present another strategy to deliver drugs without the use of an excipient. Such system utilize the perforated balloon as an infusion conduit to transport the drug to

Table 1. Characteristics of Paclitaxel and Sirolimus as anti-proliferative agents [18, 19, 21].

Characteristics	Paclitaxel	Sirolimus	Advantage
Lipophilicity	Higher	High	Paclitaxel
Water solubility	Insoluble	Insoluble	N.A
Toxicity (IV TD_{Lo})	1.54mg/kg (in human)	0.45mg/kg (in rat)	Sirolimus
Mode of action	Cytotoxic	Cytostatic	Sirolimus
Margin of safety	100 fold	10,000 fold	Sirolimus
Coating difficulty	Low	High	Paclitaxel
Tissue absorption	Longer	Shorter	Paclitaxel

the tissue while avoiding the issues of drug wash-off and particulate generation commonly associated with balloons coated with drug/excipient. One drawback of micro-porous balloons is the force produced by the fluid jet during the infusion which may cause vessel injury [29]. Table **2** is a list of current commercially available and upcoming DCBs for coronary and peripheral artery diseases. In this review, we discuss the use of DCBs to treat Peripheral Artery Disease (PAD), Coronary Artery Disease (CAD) and other applications. The technological progress and limitations of current DCBs will also be covered in this review.

2. USE OF DCB IN CLINICAL SETTING

This segment reviews the clinical data of DCB treatment in Coronary Artery Disease (CAD), Peripheral Artery Disease (PAD) and other applications.

2.1. DCB for Coronary Arteries

DCB therapy for Coronary Artery Diseases (CAD) can be categorized into two main applications: coronary In-stent Restenosis (ISR) and de novo coronary diseases [10]. DCB have also been used in the treatment of stenosis in small coronary arteries and bifurcations. Table **3** is a compiled list of clinical trials and registry studies conducted for CAD [10, 24, 30, 31].

2.1.1. In-stent Restenosis (ISR)

DCB has emerged as a treatment alternative in ISR due to its capacity to administer anti-proliferative drugs without adding another layer of stent. The meta-analysis by Lee *et al*. compared the efficacy and safety of DCB, DES and balloon angioplasty in the treatment for ISR. 11 RCTs with 2,059 patients were evaluated and the superiority of DCB or DES to balloon angioplasty was clearly demonstrated in terms of Target Lesion Revascularization (TLR) and Major Adverse Cardiac Events (MACE) outcomes, with a significantly lower risk of binary restenosis. Between DCB and DES, efficacy was comparable but the DCB arm displayed a lower risk of Myocardial Infarction (MI) or all-cause mortality than DES without statistical significance. Therefore, in this meta-analysis, DCB was ranked as the first treatment option for ISR, followed by DES [32]. The 2014 ESC/EACTS Guidelines on myocardial revascularization state with a class I level A that DCB are recommended for the treatment of ISR within BMS or DES [33].

However, in another meta-analysis published in 2016, involving 7 studies (3 multi-centre RCTs and 4 observational studies) and 1,065 patients, results of the efficacy of DCB achieved a different conclusion. The results demonstrated that using DCB to treat ISR led to similar clinical outcomes (TLR, MACE, MI, TVR) at intermediate follow-up when compared to the DES-arm. When only the RCTs were considered, a more inferior angiographic outcomes and significantly binary restenosis rate were observed in the DCB cohort, with an increased incidence of TLR and MACE [34]. The difference in these two meta-analyses could be due to the usage of first generation DES (in the first study) and the use of second generation DES in the 2016 study. The newer generation of DES with thinner struts, biocompatible polymers and different –limus drugs may improve performance of DES as the relationship between strut thickness and restenosis is more evident in small vessels [35]. This outcome was also evident in the meta-analysis by Siontis *et al*. published in 2015, which included 27 trials with 5,923 patients. The study revealed that Everolimus-eluting stents were the most effective strategy (best angiographic and clinical outcomes), followed by DCB but without significant differences from Sirolimus-eluting or Paclitaxel-eluting stents for any type of coronary ISR [36]. The use of DCB for ISR needs to be considered based on individual patient's clinical and anatomical specifications.

2.1.2. De Novo Coronary Diseases

DCB angioplasty in de novo coronary diseases can be classified into 2 categories: (1) DCB deployment complemented with default BMS implantation, or (2) DCB-only approach [10]. For DCB deployment with adjunct BMS implantation, a meta-analysis with 11 trials and 1,279 patients revealed that DCB with BMS might be better than BMS alone as the risk of Late Lumen Loss (LLL) and incidence of MACEs were significantly decreased with a comparable risk for binary restenosis, Stent Thrombosis (ST), death, MI, and TLR.

The study agreed that the DCB with BMS treatment should not be recommended for the treatment of de novo coronary lesions, except for patients who cannot receive DES [37]. However, it is important to understand that a plain BMS strategy is no longer considered an appropriate control. The only study that compared a DCB plus BMS strategy against DES was the PEPCAD III study, which revealed that the DCB/BMS treatment failed to demonstrate non-inferiority compared to Sirolimus-eluting stents at 9-months follow-up. Late in-stent lumen loss was significantly and markedly greater, and TLR and TVR rates were found to be twice in DCB/BMS arm compared to Sirolimus-eluting stents (reported at the American Heart Association 2009 Scientific Sessions). Unfortunately, this study has not been published to date.

Similarly, the DCB-only approach has not shown promising results in de novo coronary lesions. The use of DCB-only requires careful lesion preparation and is only adopted following acceptable angiographic result after pre-dilatation. The DCB-only approach aims to avoid unnecessary use of stents and shorten the duration of DAPT (approximately 4 weeks in DCB only approach *vs*. 6 - 12 months in DES approach) [38].

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Table 2. List of Commercial DCB, respective excipients, and drug uptake in arterial tissues.

Company	Product	Drug (Dose ($\mu g/mm^2$)	Excipient	Arterial Tissue Concentation	Indication	Development
University (Charité)	Paccocath	Paclitaxel	Iopromide	~15 ng/mg after 1 hour	CAD/PAD	Not Pursued
B.Braun Melsungen AG	SeQuent Please	Paclitaxel (3)	Iopromide	330 ng/mg after 1 hour	CAD	CE (2009)
	Coroflex DBlue	Paclitaxel (3)		N.A	CAD	CE
Bayer Healthcare	Cotavance	Paclitaxel (3)	Iopromide	~43 ng/mg after 1 hour	PAD	CE (2011)
Medtronic-Invatec	In.Pact Pacific	Paclitaxel (3.5)	Urea	60 ng/mg after 1 hour	PAD	CE
	In.Pact Amphirion			N.A	PAD	CE
	In.Pact Admiral			48.7 ng/mg after 4 hours	PAD	CE (2009), FDA (2014)
	In.Pact Falcon	Paclitaxel (3.0)		N.A	CAD	CE
Spectranetics	Stellarex	Paclitaxel (2)	Polyethylene glycol	58 ng/mg after 1 hour	PAD	CE (2014)
Bard PV	Lutonix	Paclitaxel (2)	Polysorbate/ Sorbitol	59 ng/mg after 1 hour	CAD/PAD	CE (2011), FDA (2014)
Eurocor GmbH	Dior I	Paclitaxel (3)	No Excipient (Nanoporous balloon surface)	~4 uM/L after 1 hour	CAD	CE (2007)
	Dior II		Shellac	196 mM/L after 45 minutes	CAD	CE (2007)
	Freeway		Shellac	N.A	PAD	CE (2010)
Biosensors International	Biopath 014	Paclitaxel (3)	Shellac	~145 mM/L after 45 minutes	PAD	CE
	Biopath 035	Paclitaxel (3)	Shellac	~140 mM/L after 45 minutes	PAD	CE
	Biostream	Paclitaxel (3)	Shellac	~200uM/L after 45 mins	CAD	CE
Biotronik AG	Pantera Lux	Paclitaxel (3)	BTHC	165 ng/mg after 30 minutes	CAD	CE (2010)
	Passeo-18 Lux			N.A	PAD	CE (2014)
Angioscore	Coated AngioSculpt	Paclitaxel (3)	N.A	N.A	CAD/PAD	Late-Stage Development
Cook Group, Inc	Advance 18 PTX	Paclitaxel (3)	N.A	N.A	PAD	CE (2011)
Minvasys	Danubio	Paclitaxel (2.5)	BTHC	N.A	PAD	CE
Boston Scientific	Ranger	Paclitaxel (2)	BTHC	49.6 ng/mg after 4 hours	PAD	CE (2014)
	Agent	Paclitaxel (2)	ATBC	~40ng/mg at 0 days	CAD	CE (2014)
Aachen Resonance GmbH	Elutax I	Paclitaxel (2)	No Excipient (Structured Balloon Surface)	1ng/mg after 1 hour	CAD	CE (2008)
	Elutax II		No Excipient (2 Layers of PTX)	70uM/L after 1 hour	CAD/PAD	CE (2008)
	Elutax SV		Dextran Sulfate	250 mM/L after 1 hour	CAD	CE
Blue Medical Devices B.V.	Protégé	Paclitaxel (3)	BTHC	N.A	CAD/PAD	CE (2010)
	Protégé NC	Paclitaxel (3)			CAD/PAD	CE (2012)

(Table 2) Contd....

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Company	Product	Drug (Dose (µg/mm^2)	Excipient	Arterial Tissue Concentation	Indication	Development
QT Vascular Ltd	Chocolate Touch	Paclitaxel (3)	N.A	N.A	PAD	CE (2015)
	Chocolate Heart	Paclitaxel (N.A)	N.A	N.A	CAD	CE (2016)
iVascular	Luminor	Paclitaxel (3)	Organic Ester	212 µg/g after 15-30 mins	PAD	CE
	Essential	Paclitaxel (3)	Organic Ester	212 µg/g after 15-30 mins	CAD	CE
Hexacath	Zonda	Paclitaxel (2.5)	BTHC	N.A	CAD	-
Cardionovum	LegFlow	Paclitaxel (3)	Shelloic Acid	200 ng/mg after 30mins	PAD	CE
	Restore	Paclitaxel (3)		200 ng/mg after 30mins	CAD	CE
	Aperto	Paclitaxel (3)		N.A	CAD/PAD	CE
Concept Medical Inc.	Magic Touch	Sirolimus (1.27)	Phospholipid Based Excipient	140.6 ng/mg after 1 day	CAD	CE (2016)
Eucatech	Support C	Paclitaxel (3)	BTHC	~60ng/mg at 0 days	CAD	CE
Nano Therapeutics	Curex	Paclitaxel (2.3)	N.A	N.A	CAD/PAD	-
SurModics	SurVeil	Paclitaxel (2)	N.A	N.A	PAD	-
Balton	mcPCB	Paclitaxel (3)	Micro-crystalline Coating	N.A	PAD	-
Meril Life Sciences	Mozec	Paclitaxel (3) / Sirolimus (N.A)	Nano-particles	N.A		-
Med Alliance	SELUTION	Sirolimus (1.0)	N.A	262 µg/g after 1 hour	CAD/PAD	-
Caliber Therapeutics	Virtue	Sirolimus (N.A)	No Excipient (Perforated Balloon Surface)	N.A	CAD	-

ATBC: Acetyl Tributyl Citrate, BTHC: Butyryl Trihexyl Citrate, CAD: Coronary Artery Disease, N.A: Not Available; PAD: Peripheral Artery Disease, PTX: Paclitaxel

Table 3. List of Clinical trials and Registry Studies conducted for CAD.

Study	DCB Model (Drug (Dose /ug/mm^2))	Control (Drug (Dose /ug/mm^2))	No. of Patients	Indications	Primary Endpoints	LLL / mm (Follow up, Months)	Binary Restenosis Rate (Follow up, Months)	TLR / % (Follow up, Months)	MACE / % (Follow up, Months)
Paccocath ISR (2006)	Original Paccocath formulation (PTX-Iopromide (3.0))	PTA	52	ISR	6 months LLL	In-Segment: 0.03 *vs* 0.74 (6)	-	-	4 *vs* 31 (12)
DEBIUT Trial (2008)	Dior I (MB+SB) (PTX-DMSO (3.0)), followed by BMS MB *vs* BMS MB *vs* DES MB	N.A	117	DNL	-	-	-	20 *vs* 27 *vs* 15 (18)	-
PEPCAD II (2009)	SeQuent.Please (PTX-Iopromide (3.0))	DES	131	ISR	6 months LLL	0.17 *vs* 0.38 (6)	7 *vs* 20.3 (6)	6.3 *vs* 15.4 (12)	7.6 *vs* 16.9 (12)
PEPCAD I (2010)	SeQuent.Please (PTX-Iopromide (3.0))	SeQuent.Please (PTX-Urea (3.0)) + BMS	114	DNL	6 months LLL	0.18 *vs* 0.73 (6)	5.5 *vs* 44.8 (6)	4.9 *vs* 27.1 (12) 2.4 *vs* 6.3 (36)	6.1 *vs* 37.5 (12) 7.3 *vs* 40.6 (36)

(Table 3) Contd....

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Study	DCB Model (Drug (Dose /ug/mm^2))	Control (Drug (Dose /ug/mm^2))	No. of Patients	Indications	Primary Endpoints	LLL / mm (Follow up, Months)	Binary Restenosis Rate (Follow up, Months)	TLR / % (Follow up, Months)	MACE / % (Follow up, Months)
PEDCAD III (2010)	Sequent.Please (PTX-Iopromide (3.0)) + BMS	BMS *vs* DES	637 (77 re-ported)	DNL	9 months LLL	0.36 *vs* 0.85 *vs* 0.25 (9)	-	-	-
PIC-COLETTO (2010)	Dior I (PTX-DMSO (3.0))	DES	57	DNL	6 months Diameter Stenosis (43.6 *vs* 24.3 (6))	-	32.1 *vs* 10.3 (6)	32.1 *vs* 10.3 (9)	35.7 *vs* 13.8 (9)
Spanish DIOR Registry (2010)	Dior I (PTX-DMSO (3.0)) Dior II (PTX-Shellac (3.0))	N.A	103	ISR + DNL	6 months LLL	0.34 (6)	-	3 (12)	-
DEBAMI (2011)	SeQuent.Please (PTX-Iopromide (3.0)) + BMS	N.A	30	DNL	12 months TLR rate	0.42 (9)	19 (9)	16.7 (12)	16.7 (12)
Habara *et al.* (2011)	SeQuent.Please (PTX-Iopromide (3.0))	PTA	47	ISR	6 month LLL	0.18 *vs* 0.72 (6)	8.7 *vs* 62.5 (6)	4.3 *vs* 41.7 (6)	4.3 *vs* 41.7 (6)
PAPPA (2011)	Pantera Lux (Pacli-taxel-BTHC (3.0))	NA	100	DNL	1 month MACE	-	-	2 (1)	3 (1)
PEPCAD IV (2011)	SeQuent.Please (PTX-Iopromide (3.0)) + BMS	DES	84	DNL	9 months LLL	0.37 *vs* 0.35 (9)	-	8.9 *vs* 10.3 (9)	13.3 *vs* 15.4 (9)
PEPCAD V (2011)	SeQuent.Please (PTX-Iopromide (3.0) (MB+ SB) + BMS (MB))	N.A	28	DNL	9 months LLL	0.38 (MB) (9) 0.21 (SB) (9)	-	3.8 (9)	0 (9)
Valentines Registry (2011)	Dior II (PTX-Shellac (3.0))	DES	250	ISR	8 months MACE	-	-	5.9 *vs* 9.8 (8)	9.8 *vs* 13.4 (8)
BELLO (2012)	In.Pact Falcon (PTX-Urea (3.0))	DES	182	DNL	6 months LLL	0.08 *vs* 0.29 (6)	-	-	-
DEB-AMI (2012)	Dior II (PTXl-Shellac (3.0)) + BMS	BMS *vs* DES	149	DNL	6 months LLL	0.64 *vs* 0.74 *vs* 0.21 (6)	28.6 *vs* 26.2 *vs* 4.7 (6)	20 *vs* 17.6 *vs* 2 (6)	20.0 *vs* 23.5 *vs* 4.1 (6)
INDICOR (2012)	SeQuent.Please (PTX-Iopromide (3.0)) + BMS	BMS + Se-Quent.Please (PTX-Urea (3.0))	97	DNL	6 month LLL	0.50 *vs* 0.49 (6)	-	4.1 *vs* 2.1 (12)	10.2 *vs* 4.2 (12)
ISAR-DESIRE 3 (2012)	Sequent Please (PTX-Iopromide (3.0))	DES *vs* PTA	402	ISR	6-8 months % diameter stenosis (38.0 *vs* 37.4 *vs* 54.1 (6-8))	0.37 *vs* 0.34 *vs* 0.70 (6-8)	27 *vs* 24 *vs* 57 (6-8)	-	-
Paccocath ISR-II (2012)	Original Paccocath formulation (PTX-Iopromide (3.0))	PTA	108	ISR	LLL	In-Segment: 0.11 *vs* 0.81 (6)	6.38 *vs* 51.0 (6)	4.25 *vs* 40.8 (12) 9.3 *vs* 38.9 (64.8)	-
PEPCAD DES (2012)	SeQuent.Please (PTX-Iopromide (3.0))	PTA	110	ISR	6 months LLL	0.43 *vs* 1.03 (6)	17.2 *vs* 61.3 (6)	15.3 *vs* 36.8 (6)	16.7 *vs* 50.0 (6)

(Table 3) Contd....

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Study	DCB Model (Drug (Dose /ug/mm^2))	Control (Drug (Dose /ug/mm^2))	No. of Patients	Indications	Primary Endpoints	LLL / mm (Follow up, Months)	Binary Restenosis Rate (Follow up, Months)	TLR / % (Follow up, Months)	MACE / % (Follow up, Months)
PEPCAD-CTO (2012)	SeQuent.Please (PTX-Iopromide (3.0)) + BMS	DES	48	ISR	-	0.33 *vs* 0.26 (6)	27.7 *vs* 20.8 (6)	14.6 *vs* 14.6 (12)	14.6 *vs* 18.8 (12)
PERfECT (2012)	EPS Stent + Se-Quent.Please (PTX-Iopromide (3.0))	EPC Stent	120	DNL	6 months LLL	0.34 *vs* 0.88 (6)	5.1 *vs* 23.2 (6)	4.8 *vs* 15.5 (6)	4.8 *vs* 17.2 (6)
PEPPER Registry (2012)	Pantera Lux (PTX-BTHC (3.0))	DES	81	ISR	6 months LLL	-0.05 *vs* 0.19 (6)	-	-	6.5 (6)
PEPPER (2012)	Pantera Lux (PTX-BTHC (3.0))	N.A	81	BMS-ISR/ DES-ISR	6 months LLL	Overall: 0.07 (6) BMS-ISR: -0.05 (6) DES-ISR: 0.19 (6)	-	-	Overall: 6.5 (6), 11.8 (12)
SEQUENT Worldwide Registry (2012)	Sequent Please (PTX-Iopromide (3.0))	Sequent Please DCB + BMS	572	ISR	10 months MACE	-	-	1 *vs* 2.4 (10)	2.6 *vs* 2.4 (10)
Valentines II (2012)	Dior II (PTX-Shellac (3.0))	NA	103	ISR	8 months MACE	-	-	2.9 (8)	8.7 (8)
Liistro *et al.* (2013)	Elutax II DCB (PTX (2.0)) + BMS	DES	125	DNL	9 months binary restenosis	1.14 *vs* 0.34 (9)	25 *vs* 4 (9)	-	29.0 *vs* 26.0 (9)
BABILON (2014)	SeQuent.Please (PTX-Iopromide (3.0)) (MB, followed by SB) + BMS (MB)	DES (MB)	108	DNL	9 months LLL	In-Segment MB: 0.31 *vs* 0.16 (9) In-stent MB: 0.35 *vs* 0.27 (9) SB: -0.04 *vs* -0.03 (9)	-	15.4 *vs* 3.6 (24)	17.3 *vs* 7.1 (24)
DELUX Registry (2014)	Pantera Lux (PTX-BTHC (3.0))	N.A	1064	BMS-ISR/ DES-ISR/ DNL	MACE	-	-	-	Overall: 8.5 (6) BMS-ISR: 6.0 (6) DES-ISR: 11.5 (6) DNL: 7.0 (6) Overall: 15.1 (12) BMS-ISR: 11.6 (12) DES-ISR: 20.6 (12) DNL: 9.4 (12)

(Table 3) Contd....

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Study	DCB Model (Drug (Dose /ug/mm^2))	Control (Drug (Dose /ug/mm^2))	No. of Patients	Indications	Primary Endpoints	LLL / mm (Follow up, Months)	Binary Restenosis Rate (Follow up, Months)	TLR / % (Follow up, Months)	MACE / % (Follow up, Months)
RIB IV (2014)	SeQuent.Please (PTX-Iopromide (3.0))	DES	309	ISR	6-9 months minimal lumen diameter (1.80 *vs* 2.03 (9))	-	19 *vs* 11 (9)	-	-
Chocolate Heart FIH Study (2015)	Chocolate Heart	PTA	19	DNL	6 months LLL	0.01 (6)	-	0 (30 days)	0 (30 days)
DEBSIDE (2015)	DES (MB), followed by Danubio (PTX-BTHC (2.5)) (SB)	NA	50	Bifurcation lesions	6 months LLL	SB: -0.04 (6) MB: 0.54 (6)	-	Non-clinically driven TLR: 2 (6)	-
ISAR-Desire 4 (2015)	Scoring Balloon + Pantera Lux (PTX-BTHC (3.0))	PTA + Pantera Lux (PTX-BTHC (3.0))	252	ISR	6-8 months % diameter stenosis	-	18.5 *vs* 32.0 (6-8)	16.8 *vs* 22.6 (12)	-
PEBSI RCT (2015)	BMS + Pantera Lux (PTX-BTHC (3.0))	BMS	223	STEMI	9 months LLL	0.32 *vs* 0.85 (9)	2.2 *vs* 29.8 (9)	-	-
SARPEDON (2015)	DES (MV (Main Vein)) + Pantera Lux (PTX-BTHC (3.0)) (SB (Side Branch))	N.A	58	SB Ostium	6 months restenosis	SB: 0.09 (6) MV: 0.21	-	-	19 (12)
AGENT ISR (2016)	Agent DCB (PTX-ATHC (2.0))	SeQuent.Please (PTX-Iopromide (3.0))	122	ISR	6 months LLL	0.397 *vs* 0.393 (6)	-	-	-
BIOLUX RCT (2016)	Pantera Lux (PTX-BTHC (3.0))	DES	229	BMS-ISR/ DES-ISR	6 months LLL	-0.01 *vs* 0.10 (6)	-	-	-
CONSE-QUENT (2016)	SeQuent.Please (PTX-Iopromide (3.0))	PTA	153	DNL	6 months LLL	0.49 *vs* 0.98 (6)	Binary Resteno-sis Rate >50%: 21.2 *vs* 47.2 (6)	11.6 *vs* 25.7 (6)	-
FALCON Registry (2016)	In.Pact Falcon (PTX-Urea (3.0))	N.A	753	DNL and ISR	12 months CD-TLR	-	-	DNL: 4.9 ISR: 7.3	DNL: 7.9 ISR: 12.1
Lee *et al.* (2016)	SeQuent.Please (PTX-Iopromide (3.0))	N.A	85	Ostial ISR lesions	NA	-	-	19.2 (12)	Major Adverse Cardiac Celebral Events: 24.4 (12
Nanolute Registry (2016)	Magic Touch (SIR-based (1.27))	N.A	337	Nanolute ISR/Nanolute DN small vessel disease	6 months MACE, Proce-dural Success	-	-	Overall: 4.43 (12) ISR: 6.11 (12) DN Small Vessel Disease: 2.73 (12)	Overall: 5.17 (12) ISR: 6.87 (12) DN Small Vessel Dis-ease: 3.64 (12)
Parikh *et al.* (2016)	Magic Touch (SIR-based (1.27))	N.A	119	Coronary lesions in small vessels (=<2.75mm)	MACE	-	-	-	4.30 (12)

(Table 3) Contd....

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Study	DCB Model (Drug (Dose /ug/mm^2))	Control (Drug (Dose /ug/mm^2))	No. of Patients	Indications	Primary Endpoints	LLL / mm (Follow up, Months)	Binary Restenosis Rate (Follow up, Months)	TLR / % (Follow up, Months)	MACE / % (Follow up, Months)
RIBS V (2016)	SeQuent.Please (PTX-Iopromide (3.0))	DES	189	ISR	9 months minimal lumen diameter (2.01 *vs* 2.36 (9))	0.14 *vs* 0.04 (9)	9.5 *vs* 4.7 (9)	8 *vs* 2 (36)	-
Rosenberg *et al.* (2016)	SeQuent.Please (PTX-Iopromide (3.0))	N.A	1025	DNL/ BMS-ISR/ DES-ISR	9 months TLR	-	-	Overall: 3.2 (9) DNL: 2.3 (9) BMS-ISR: 2.9 (9) DES-ISR: 5.2 (9)	Overall: 6.8 (9) DNL: 5.6 (9) BMS-ISR: 7.8 (9) DES-ISR: 9.6 (9)
TIS Study (2016)	SeQuent.Please (PTX-Iopromide (3.0))	Promus DES	136	ISR	12 months LLL	0.02 *vs* 0.19 (12)	8.7 *vs* 19.1 (12)	-	10.3 *vs* 19.1 (12)

BMS: Bare Metal Stent; BTHC: Butyryl Trihexyl Citrate; DES: Drug-eluting Stent; DNL: De Novo Lesion; EPS: Embolic Prevention System; EPC: Endothelial Progenital Cell; ISR: In-stent Restenosis; , LLL: Late Lumen Loss; MACE: Major Adverse Cardiac Events; MB: Main Branch; PTA: Percutaneous Transluminal Angioplasty; RCT: Randomized Controlled Trials; SB: Side Branch; SIR: Sirolimus; STEMI: ST Segment Elevation Myocardial Infarction; TLR: Target Lesion Revascularisation [10, 24, 30, 31].

The first meta-analysis (8 studies, 1,706 patients) to evaluate the use of DCB-only approach in de novo coronary diseases showed that DCB was not superior to standard treatment using BMS or DES, there was no significant difference between DCB and the control groups in terms of MACE or mortality. DES was considered to have the most superior clinical outcomes and it was suggested that patients who can receive DES should not be treated with a DCB [39]. In these meta-analyses, the use of DCB did not show better clinical performance compared to the use of DES, but was considered to be a better treatment option than BMS alone [37, 40]. Other registries have evaluated DCB for de novo lesion treatment. The NANOLUTE registry also sought to investigate the efficacy and safety of Magic Touch DCB against de novo coronary lesions and found that the 12 month TLR and MACE induced were 2.73% and 6.11%, respectively [41]. Hence, the use of DCB in de novo lesions is considered feasible with theoretical benefits, but should only be reserved for use in patients who are unable to receive a stent.

2.1.3. Other Potential Use in Small Vessel and Bifurcation Diseases

Myocardial revascularization of small vessels has an increased rate of technical failure in coronary bypass grafting and an increased risk of restenosis leading to repeat intervention [42]. Thus it remains a challenge to select an optimal strategy in the treatment of small-vessel CAD, which has been reported in 30% to 40% of patients undergoing percutaneous coronary intervention. In a recent meta-analysis conducted by Siontis *et al*. currently available treatment options in small-vessel CAD over 19 RCTs (including 5072 patients) were evaluated. The results revealed that implantation of early generation Sirolimus-eluting Stents (SES) and Paclitaxel-Eluting Stents (PES) were more effective treatments in terms of angiographic outcomes assessed by % diameter stenosis, (leading to a decrease in risk of TLR) as compared to DCB. BMS and plain balloon angioplasty ranked the lowest for all study outcomes and could not be considered effective alternatives in treating small vessel disease [36]. However, there was no study that investigated the outcome of newer generation of DES in small vessels.

Coronary bifurcation lesions remain a huge challenge for interventional cardiologists due to suboptimal results which occurs mainly in the Side Branch (SB). The use of DES has improved the outcome of the bifurcation (with mid-large side branch) lesion subset but issues such as stent thrombosis and ISR still remain. The current strategies for bifurcation lesions involve a simple approach (stenting only the main branch, MB) and a complex approach (stenting both MB and SB). The most widely adopted strategy is currently provisional stenting whereby only the MB receives a stent, and SB stenting is only carried out in case of unsatisfactory result. There are several trials and single studies dedicated to analysing the role of DCB in the treatment of coronary bifurcation lesions [43]. The DEBIUT trial examined the outcome of using DCB in the SB and MB with BMS/DES in the MB. The use of DCB revealed no angiographic and clinical superiority over BMS, with DES-only strategy achieving the best angiographic results [44]. The BABILON trial concluded with the same results whereby the DCB and BMS approach led to higher rates of TLR and MACE compared to the DES-only group [45].

In terms of DCB-only strategy in coronary bifurcation, the PECAD-BIF study compared the use of SeQuent Please DCB compared to plain balloon angioplasty in the MB and SB. The DCB group achieved lower TLR incidence, demonstrating potential benefit of this strategy. While evaluating the use of DCB in SB and DES in MB, several studies (DEBSIDE, BIOLUX-I and SARPEDON) examined the efficacy and feasibility of the DCB in SB option [43]. Cortese *et al*. reviewed various studies on DCB for bifurcation lesions treatment strategies and the authors reached the following conclusions [30]:

1. Main branch treatment with DES should be the preferred treatment strategy unless the patient is unable to receive stenting
2. The use of DCB/BMS should not be considered as first-choice option in main branch treatment
3. Side branch treatment with DCB is feasible and safe, with good angiographic and clinical outcome

The use of DCB for bifurcation restenosis was examined by two groups of investigators and their research findings suggested that DCB may be an acceptable treatment strategy especially in de novo bifurcation lesions [46]. However, the clinical data regarding the

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use of DCB in coronary bifurcation lesions remains scarce and more data from RCTs will be required to assess its clinical value.

2.2. DCB for Peripheral Arteries

Compared to coronary vascular interventions, where stent implantation has become the standard revascularization procedure, morphological and procedural peculiarities of peripheral vascular interventions make stent implantation less attractive. The implantation of early-generation nitinol stents in diseased femoropopliteal segments showed an increased risk of stent fracture, due to the physiological torsion of the artery, with subsequent vessel wall damage and restenosis [47]. In fact, vessel bending has a significant influence on the risk of stent failure due to the continuous deformation of metallic prostheses during the patient's daily walking cycle [48].

New-generation stents, with or without anti-proliferative substances, have somewhat reduced though not completely eliminated the incidence of stent failure in the femoral vasculature. Preclinical models of peripheral artery stenting have demonstrated that metallic implants permanently overstretch the arterial wall, leading to sustained inflammation and persistent neointimal growth, likely responsible for the exaggerated "catch-up" phenomenon observed in this vascular bed [49]. Hence, DCB therapy represents a viable treatment option to deliver anti-proliferative drugs following dilatation of stenotic peripheral arteries, by leaving no permanent implants behind. Table **4** is an overview of clinical trials and registries investigating the performance of DCB therapy in PAD [5, 10, 24, 50].

2.2.1. Femoropopliteal Arteries

As compared to balloon angioplasty (or Percutaneous Transluminal Angioplasty (PTA)), DCB therapy was proven to be effective both in terms of angiographic restenosis and Target Lesion Revascularization (TLR) [51]. In an updated meta-analysis by Giacoppo *et al*. including 8 randomized trials, the use of DCB compared to PTA resulted in: (1) reduced risk of TLR with similar mortality at 12 months; (2) sustained reduction in TLR without safety issues up to 2 years; (3) significant heterogeneity with respect to treatment effect due to the LEVANT I and II studies, which only showed a moderate reduction in TLR [52]. However, it is important to note that the device used in the LEVANT studies was the Lutonix balloon which appeared to result in lower efficacy compared to other DCB. The pharmacokinetic profile showed that Lutonix had a lower PTX tissue bioavailability compared to In.Pact and Stellarex DCB after 28 days. This translated into the clinical outcome where the LEVANT II study reported lower percentages of primary patency and freedom from target lesion revascularization at 1 year follow-up [53]. 5-years follow-up data from the THUNDER trial revealed sustained long-term efficacy of DCB over PTA, with significantly lower binary restenosis and TLR rates [54]. The recently published ILLUMENATE FIM, RCT and pharmacokinetics (PK) studies showed the safety and efficacy of the Stellarex DCB compared to uncoated PTA. Vessel patency rates of 89.5% and 80.3% were exhibited at 12 and 24 months follow-up respectively [55-57].

According to the international definitions, the employment of DCB in femoro-popliteal TASC IIA and B de novo and restenotic lesions is highly recommended [58]. Although meta-analyses have confirmed the superior performance of DCB versus PTA for de novo femoropopliteal lesions [50, 59-61], the long-term durability of DCB therapy, as well as the efficacy of DCB therapy in patients presenting with ISR of femoropopliteal arteries should be further investigated.

The drug dose density, formulation and the type of excipient used to coat the balloon will influence the uptake and retention of the drug into the vessel wall. This will in turn lead to various PTX pharmacokinetic profile and bioavailability, which may result in different treatment outcomes between the DCB devices. More randomized studies will be required for better understanding of the drug tissue bioavailability and the resulting clinical efficacy of different DCBs.

2.2.2. Below-the-Knee Arteries

The optimal percutaneous treatment of atherosclerotic disease of below-the-knee (BTK) arteries represents a matter of ongoing debate. On the one side, balloon-expandable coronary DES have been found superior to PTA and bare metal stents in the treatment of focal BTK lesions, though the diffuse nature of atherosclerotic disease in this vascular segment precludes the routine use of these devices [62].

In this manner, the performance of DCB for BTK disease has been less conclusive [63-66]. A single-centre observational study from Schmidt *et al*. reported favourable short-term restenosis rates and mid-term clinical outcomes when using the IN.PACT Amphirion DCB. Similarly, the single-centre randomized DEBATE-BTK trial showed superior results of using DCB compared with PTA at 1-year in terms of binary restenosis, target vessel occlusion and TLR [54]. Against this background, the multi-centre randomized IN.PACT Deep trial failed to prove the superiority of the IN.PACT Amphirion DCB compared to PTA in terms of TLR and LLL [67]. Notably, in this trial there was a higher incidence of amputation and a trend towards higher mortality in the DCB-arm, raising concerns regarding the clinical safety of this technology [67, 68]. In response to this, the manufacturer has withdrawn this device from the market.

Recently, an updated meta-analysis comparing the relative safety and efficacy of different percutaneous strategies for BTK disease found that DCB has similar clinical efficacy and superior angiographic performance when compared with PTA or DES at 1-year follow-up [69]. In particular, the authors reported that treatment with DCB led to relatively lower LLL, without improving clinical outcomes regarded as pivotal for patients suffering from BTK atherosclerotic disease, such as amputation and wound healing. The conclusion of this meta-analysis was two-fold: a dedicated wound care management should be implemented for all patients with advanced-stage atherosclerotic BTK disease in order to evaluate the net clinical benefit associated with different revascularization strategies in this field; the number of patients available so far does not allow definitive assumptions regarding DCB technology in this specific setting.

2.2.3. DCB in Combination with other Therapy

DCB has been used with percutaneous atherectomy to improve patency. Cioppa *et al*. reported the use of intravascular ultrasound-guided directional atherectomy following by application of a DCB, showing promising 1-year primary patency of 90% with no drug-related adverse event [70]. The DEFINITIVE AR trial was a multicentre RCT comparing upfront atherectomy and DCB approach versus a DCB-only approach in patients with superficial femoral and/or popliteal lesions. Angiographic patency was 82.4% in the atherectomy and DCB arm compared to 71.8% in DCB-only group, suggesting the potential benefit of performing debulking atherectomy before the use of DCB. The REALITY study has been launched to evaluate the adjuctive use of directional atherectomy and DCB strategy in patients with symptomatic PAD in long calcified SFA and/or popliteal artery lesions [71].

2.3. Other Applications of DCB

PTX-coated DCB have potential roles in treating stenoses of hemodialysis access, such as arteriovenous fistula and grafts (AVF/AVG). Although not as common as CAD and PAD, clinical results with the use of DCB in AVF/AVG venous stenosis and/or restenosis have reported promising primary outcomes with higher Circuit Patency (CP) and Targeted Lesion Patency (TLP) with 100% anatomical success [72, 73]. In two randomized trials for venous stenoses of the AVF/AVG, the 6-month and 1-year TLP of

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Table 4. List of Clinical trials and Registries investigating the performance of DCB therapy in patients with PAD.

Study	DCB Model (Drug (Dose /μg/mm^2))	Control (Drug (Dose /μg/mm^2))	No. of Patient	Arterial Segment of Inter-est	Primary Endpoint	Primary Patency / % (Follow up, Months)	LLL / mm (Follow up, Months)	Binary Restenosis Rate/ % (Follow up, Months)	TLR / % (Follow up, Months)
FemPac (2008)	PTA coated with PTX (PTX-Iopromide (3.0))	PTA	87	FP	6-month LLL	-	0.5 *vs* 1.0 (6)	-	13 *vs* 50 (24)
THUNDER (2008)	Paccocath (PTX-Iopromide (3.0))	PTA and PTA + Paclitaxel in contrast medium	154	FP	6-months LLL	-	0.4 *vs* 1.7 *vs* 2.2 (6)	-	15 *vs* 52 (24)
Schmidt *et al.* (2011)	In.Pact Amphirion (PTX-Urea (3.5))	N.A	104	BTK	3-month binary restenosis	-	-	27.4 (3)	17 (12)
Schmidt *et al.* (2011)	In.Pact Amphirion (PTX-Urea (3.5))	N.A	104	BTK	3-month binary restenosis	-	-	27.4 (3)	17 (12)
PACIFIER (2012)	In.Pact Pacific (FreePac PTX-Urea (3.5))	PTA	91	FP	6-month LLL	-	0.01 *vs* 0.7 (6)	-	7 *vs* 28 (12)
DEBATE-BTK (2013)	In.Pact Amphirion (PTX-Urea (3.5))	PTA	132	BTK	12-month binary restenosis	-	-	27 *vs* 74 (12)	18 *vs* 43 (12)
DEBATE-SFA (2013)	In.Pact Admiral (PTX-Urea (3.5)) + BMS	PTA + BMS	110	FP	12-month binary restenosis	-	1.3 *vs* 2.7 (12)	17 *vs* 47 (12)	17 *vs* 33 (12)
Micari *et al.* (2013)	In.Pact Admiral (PTX-Urea (3.5))	N.A	105	FP	27-month primary patency	72.4 (27)	-	-	14 (27)
BIOLUX P-II (2014)	Passeo-18 Lux (PTX-BTHC (3.0))	PTA	72	BTK	30-day MAE rate, 6-month target lesion primary patency	82.9 *vs* 73.9 (6)	-	-	-
DEBELLUM (2014)	In.Pact Admiral (PTX-Urea (3.5))	PTA	50	BTK, FP	6-month LLL	Overall: 0.5 *vs* 1.6 (6) Overall: 0.64 *vs* 1.81 (12) FP: 0.61 *vs* 1.84 (12) BTK: 0.66 *vs* 1.69 (12)	-	9.1 *vs* 28.9 (6)	Overall: 6.1 *vs* 23.6 (6) 12.2 *vs* 35.3 (12)
DEFINITIVE AR (2014)	Cotavance (PTX-Iopromide (3.0))	Atherectomy + Cotavance (PTX-Iopromide (3.0))	102	FP	12-month target lesion stenosis	85.9 *vs* 96.8 (12)	-	-	-
FAIR (2014)	In.Pact Admiral (PTXl-Urea (3.5))	PTA	119	FP	6-month binary restenosis	-	-	15.4 *vs* 44.7 (6)	9.2 *vs* 47.4 (12)
FREERIDE (2014)	Freeway (PTX-Shellac (3.0))	PTA	62	FP	6-month TLR	-	-	-	5.4 *vs* 20 (12)
IDEAS (2014)	In.Pact Amphirion (PTX-Urea (3.5))	DES	50	BTK	Target lesion restenosis >50% at 6 months	-	1.15 *vs* 1.35 (6)	Binary res-tenosis rate (>50%): 57.9 *vs* 28 (6)	13.6 *vs* 7.7 (6)

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Study	DCB Model (Drug (Dose /μg/mm^2))	Control (Drug (Dose /μg/mm^2))	No. of Patient	Arterial Segment of Interest	Primary Endpoint	Primary Patency / % (Follow up, Months)	LLL / mm (Follow up, Months)	Binary Restenosis Rate/ % (Follow up, Months)	TLR / % (Follow up, Months)
ILLUMENATE First-in-Humans Study (2014)	Stellarex (PTX-PEG (2.0))	N.A	50	FP	6-month LLL	89.5 (12) 80.3 (24)	0.54 (6)	-	Freedom from TLR: 90.0 (12) 85.8 (24)
IN.PACT DEEP (2014)	In.Pact Amphirion DCB (PTX-Urea (3.5))	PTA	358	BTK	12-month TLR and LLL	-	0.605 *vs* 0.616 (12)	41.0 *vs* 35.5 (12)	11.9 *vs* 13.5 (12)
IN.PACT Global (2014)	In.Pact Admiral (PTX-Urea (3.5))	N.A	655	FP	12-months freedom from CD-TLR, 12-month primary patency (imaging cohort)	-	-	-	CD-TLR: 8.7 (12) Overall TLR: 9.0 (12)
IN.PACT SFA (2014)	In.Pact Admiral (PTX-Urea (3.5))	PTA	331	FP	12-month primary patency	82.2 *vs* 52.4 (12) 78.9 *vs* 50.1 (24)	-	-	CD-TLR: 2.4 *vs* 20.6 (12) 9.1 *vs* 28.3 (24)
LEVANT 1 (2014)	Lutonix (PTX-Polysorbate/Sorbitol (2.0))	PTA	101	FP	6-month LLL	71.2 *vs* 41.5 (6) 66.7 *vs* 54.8 (12) 57.1 *vs* 39.5 (24)	0.46 *vs* 1.09 (6)	-	12.7 *vs* 22.2 (6) 28.9 *vs* 33.3 (12) 35.7 *vs* 48.8 (24)
BIOLUX P-I (2015)	Passeo-18 Lux (PTX-BTHC (3.0))	PTA	60	De Novo/ Restenotic FP Lesions	6-month LLL	-	0.51 *vs* 1.04 (6)	11.5 *vs* 34.6 (6)	16.0 *vs* 52.9 (12)
DEBAS Registry (2015)	DES + Passeo-18 Lux (PTX-BTHC (3.0))	N.A	65	FP	12- and 24-month primary patency	92.2 (12)	-	-	Freedom from CD-TLR: 94.1 (12)
ENDURE (2015)	Chocolate Touch (PTX-based DCB (3.0))	N.A	67	FP	-	90 (6)	0.16 (6)	-	1.7 (6)
Goverde *et al.* (2015)	Legflow (PTX-Shellac (3.0))	N.A	51	FP	-	92 (6)	-	8 (6) 24 (12)	6 (6) 23 (12)
LEVANT 2 (2015)	Lutonix (PTX-Polysorbate/Sorbitol (2.0))	PTA	476	FP	12-month primary patency	65.2 *vs* 52.6 (12)	-	-	12.3 *vs* 16.8 (12)
BIOLUX P-III All-Comers Registry (2016)	Passeo-18 Lux (PTX-BTHC (3.0))	N.A	204 (interim at 6 months)	BTK	6-months freedom from MAE, 12-month freedom from CD-TLR	-	-	-	Freedom from CD-TLR: 96.8 (6)
PACUBA 1 (2016)	Freeway (PTX-Shellac (3.0))	PTA	74	FP	12-month primary patency	40.7 *vs* 13.4 (12)	-	-	49 *vs* 22.1 (12)
ILLUMENATE European RCT (2016)	Stellarex (PTX-PEG (2.0))	PTA	222	FP	12-month primary patency	83.9 *vs* 60.6 (12)	-	-	Freedom from CD-TLR: 94.8 *vs* 85.3 (12)
ILLUMENATE Pivotal and PK Study (2016)	Stellarex (PTX-PEG (2.0))	PTA	300	FP	12 months freedom from device- and procedural-related deaths, TLR	82.3 *vs* 70.9 (12)	-	-	Freedom from CD-TLR: 92.1 *vs* 83.2 (12)

BMS: Bare Metal Stent; BTHC: Butyryl Trihexyl Citrate; BTK: Below The Knee; CD-TLR: Clinically-driven Target Lesion Revascularization; DES: Drug-eluting Stent; FP: Femoropopliteal; LLL: Late Lumen Loss; MAE: Major Adverse Events; PEG: Polyethylene Glycol; PTA: Percutaneous Transluminal Angioplasty; PTX: Paclitaxel; TLR: Target Lesion Revascularisation [5, 10, 23, 30]

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DCB were significantly higher than PTA ((70 *vs* 25%, p<0.001), (35 *vs* 5%, p<0.001), respectively) [72, 73]. Correspondingly, CP was also higher for DCB (65 *vs* 20%, p<0.002)) [72]. The requirement of a postprocedural high pressure dilation to achieve anatomical success was reported in some studies with the DCB (55% [72] and 65% [73] of DCB procedures). This has led to the development of a dedicated high-pressure DCB for AVF/AVG (PTX-APERTO OTW, Cardionovum) with promising preliminary data (95 % primary patency at 6 months, 150 patients) [74].

In a systematic review conducted by Khawaja *et al*. 6 studies with 254 patients were evaluated and reported the use of DCB being safe and may impart some benefit in terms of improved rate of restenosis when used to treat AV access disease. Nonetheless, more clinical data will have to be obtained for DCB usage in AVF/AVG settings before reliable judgement can be passed on their suitability in AVF/AVG stenosis therapy [75].

3. CURRENT LIMITATIONS OF DCB

3.1. Efficacy / Drug Loss and Transfer

Achieving an effective drug transfer from the DCB to the target tissue remains a major challenge in the use of DCB in clinical setting. The type of excipients plays an important role in influencing the drug distribution, drug loss from the DCB surface during tracking, and drug transfer into the arterial tissues. Hydrophilic excipients such as iopromide (SeQuent™ Please DCB) and urea (In.Pact DCB) rely on polarity differences with the hydrophobic PTX to spur the release of drug [76]. However, the hydrophilicity of these excipients causes high wash-off rates during tracking and resulted in low drug transfer rates. The use of iopromide as a coating excipient has achieved a transfer of approximately 13% and 16% PTX tissue concentration in the Contavance™ technology and SeQuent™ Please DCB [77-79]. Newer hydrophilic excipients such as PEG/PEO and dextran sulfate sodium (DSS) have been explored to minimize drug loss during tracking. *In vitro* studies have revealed that the a lower rate of drug loss (~20%) was achieved for DSS but the efficacy of these newer excipients remains to be determined [80].

Hydrophobic (*e.g*. BTHC) and amphiphilic (*e.g*. polysorbate/sorbitol) excipients improve the distribution of the hydrophobic drug during the coating process and decreases the solubility of the coating which can reduce drug loss during wash-off and tracking. However, strong affinity of the coating matrix to the balloon surface has led to mixed results in the drug transfer efficiency. Biotronik's Pantera Lux (BTHC) DCB reported a PTX tissue concentration of 165ng/mg after 30 minutes while Bard PV's Lutonix (polysorbate/sorbitol) DCB achieved 59ng/mg after 1 hour [81-83]. Current DCB still faced the issue of high drug loss (60-70%) due to tracking and relatively lower drug transfer to tissue (< 20%) [84]. Thus, it can be seen the DCB still requires a more robust drug coating system that is able to prevent drug loss during tracking and at the same time allows efficient release and acute uptake of the drug into the tissues.

3.2. Evidences of Particulate Generation and Embolization in DCB

Downstream particulate embolization has been identified as a safety concern of DCBs since the development of the first generation DCBs, due to separation of coating matrices from DCB surface during tracking and inflation in the vasculature. Ideal coating matrices do not crack, and therefore delaminate, upon inflation. Other reasons leading to delamination of coating matrices include improper storage conditions and manufacturing processes. While particulate embolization may theoretically cause slow flow or periprocedural mycardial infarction after DCB angioplasty [10], benchtop studies and clinical trials, examining particulate formation are scarce in number to facilitate comparison.

Iopromide and urea-based DCBs are effective but are also known to produce high amount of particulates, as a result of high coating matrix crystallinity [85]. In another *in vitro* study, Gongora *et al.* compared the amount of particulates (>300 μm) generated in a benchtop model, through which PTX-urea DCB (Medtronic, In.Pact (3μg/mm PTX), PTX-polysorbate/sorbitol DCB (Lutonix-Bard (2μg/mm PTX)), and PTX-BTHC DCB (Boston Scientific Ranger (2μg/mm PTX) were separately deployed [15]. The study showed that the BTHC-based DCB generated 12.5 times and 8.8 times less particulates than the PTX-urea DCB and PTX-polysorbate/sorbitol DCB, respectively [86].

3.2.1. Preclinical In vivo Studies

Downstream necrotic and fibrotic events are strongly attributed to particulate generation. A study conducted by Yahagi *et al.* compared the overall percentage downstream vascular and skeletal muscle necrosis or fibrosis upon deployment of polysorbate/sorbitol DCB (Lutonix®, Bard PV) and PTX-urea DCB (In.Pact Amphirion, Medtronic), at 3 times their loading dose, in swine models, and showed significantly better results for the Lutonix-arm (8.9% versus 48.7%) [87]. Additionally, while no downstream skeletal muscle necrosis or fibrosis was noted for the Lutonix-arm, 11.5% and 5.1% of histologic sections were found with necrosis or fibrosis, and crystalline materials, respectively for the In.Pact Amphirion-arm. This also hints at the possibility of much lower distal embolization and from the polysorbate/sorbital excipient.

The risk of thrombotic occlusions was amplified when high dose PTX-urea and PTX-iopromide coatings were used, albeit at an excessive dosage of 9 μg/mm^2 (3 times the usual dose). In this preclinical model, 20 % of high-dose treated animals developed thrombotic occlusions [88]. While direct clinical evidence linking embolic particles to vessel occlusion is still missing, one study of note was conducted by Siskin *et al* to evaluate the pathological effects of polymeric embolic particles in porcine models [89]. Acute inflammatory responses led by neutrophils were observed immediately after embolization and at 7 and 28 days after embolization, chronic inflammation characterized by the presence of macrophages and giant cells was observed at days 7 and 28 [89].

3.2.2. Clinical Impact of Embolization

Embolization as a result of particulate loss from DCB is a valid concern, with the likelihood in leading to micro-occlusion (Fig. **2**). Therefore, evidences of the clinical impact of particulate embolization are mostly indirect. Embolization has been suggested as one of the underlying mechanisms leading to the high amputation rate experienced in the DCB group in the IN.PACT Deep RCT. Larger RCTs are required to determine the efficacy and safety of DCB in cases with extensive plaque burden.

CONCLUSION - FUTURE DIRECTION

The progress of DCB is an important development in the treatment of stenotic artery diseases, particularly when a non-stent approach is mandated. As highlighted in this review, clinical data has encouraged the use of DCB for applications in PAD and in the treatment of coronary ISR. Although in the case of coronary ISR, recent studies have concluded that the second generation DES still performs better than most DCB and remains a first choice option if the patient is able to receive stenting. The employment of DCB in side branch treatment of bifurcation lesions has been reported to be feasible and safe, with good angiographic and clinical outcome. Similarly, the use of DCB for AVF/AVG stenoses is a promising strategy, but more clinical investigation is required in that territory before reliable conclusions can be drawn.

The current limitations of DCB include high drug loss and low tissue transfer, which still affects the efficacy of these devices in clinical setting. Furthermore, as PTX is considered to be cytotoxic, newer generations of DCB are turning to limus-based drug (such as Sirolimus) as a preferred choice of anti-proliferative drug. How-

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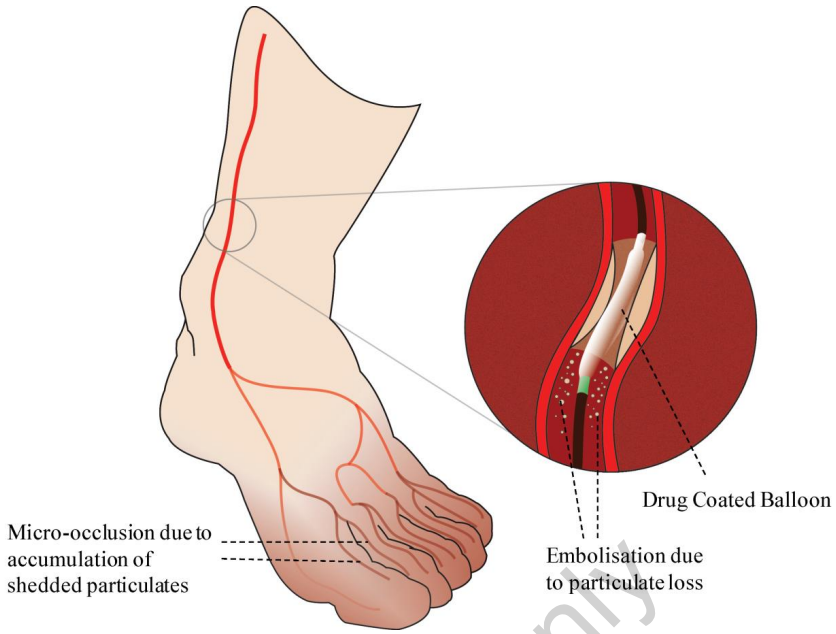

Fig. (2). The embolization of the balloon coating in an important limitation, in particular with first generation DCBs. The choice of excipient and the crystallinity of the coating are reported to influence particulate loss from the balloon.

ever, limus-based drugs as compared to PTX, do not transfer and remain easily into the arterial wall which lowers drug retention at the target site. Hence, new technologies play an important role in the development of novel, more efficient carriers, adapted for both low dose PTX and limus-based drugs. These 3rd generation of DCBs are now emerging and can potentially overcome the shortcomings of current DCBs, but more clinical studies are needed as the efficacy and safety of these novel technologies still remain unknown.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Dr N. Foin holds an appointment in Philips-Volcano, and is adjunct faculty in NHRIS/ Duke-NUS. Dr M. Joner is a consultant and receives speaker fees from Biotronik and OrbusNeich. None of the remaining authors has a conflict of interest related to the contents of this manuscript to disclose.

ACKNOWLEDGEMENTS

Declared none.

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