

Drug-Eluting Balloon Technology

This promising new technology represents what might be an alternative option for treating coronary and peripheral arterial disease.

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Balloon angioplasty revolutionized the field of cardiology. However, the early enthusiasm for this technology was tempered by postprocedural acute vessel closure due to coronary dissection or suboptimal results by elastic recoil and negative vascular remodeling leading to restenosis. The introduction of coronary stent implantation reduced the need for reintervention but increased a localized inflammatory response related to the occurrence of in-stent restenosis (ISR).

During the past decade, local intravascular drug delivery by drug-eluting stents (DES) has further reduced the incidence of ISR compared with bare-metal stents (BMS).¹⁻³ Nevertheless, recent data suggest an increase in the occurrence of late stent thrombosis after the use of first-generation DES⁴ caused by inhomogeneous drug distribution and incomplete endothelialization of the stent struts,⁴⁻⁶ particularly in high-risk patients or in those with complex lesions.⁷⁻⁹

To obviate the side effects of DES, multiple approaches have been proposed during the last 5 years for drug delivery to the vessel wall. Of those, second-generation DES, DES with bioabsorbable polymers, free-polymer DES, and ultimately, bioabsorbable DES represent the latest progress in the field of percutaneous coronary intervention (PCI). In addition, drug-eluting balloons (DEB) have recently been used in clinical practice with numerous theoretical advantages:

1. Compared to DES, with which approximately 15% of the stented surface is not covered by struts, DEB allow a homogenous distribution of the antiproliferative compound and not only on vessel segments that are directly covered by stent struts. In addition, this uniformity of deliverance could enhance the efficacy of the drug to the vessel wall.

2. The absence of drug in prolonged, direct contact to the arterial wall could help to better re-endothelialize the stent (if used) and potentially limit the risk for late stent thrombosis.
3. The absence of polymer could decrease the stimulus of chronic inflammation, which may be related to very late stent thrombosis.
4. In the absence of stent implantation, the original vessel anatomy could be preserved, decreasing abnormal flow patterns at the stent edge, as observed in cases of bifurcation or small vessel treatment.
5. Overdependence on antiplatelet therapy could be limited.
6. Local drug delivery could also be applied when stents are not used or when undesirable (eg, very small vessels, ISR, provisional stenting in bifurcation lesions).
7. If a stent should be used, there would be no limitation to a particular type of stent.

This article briefly explores the different characteristics of DEB devices that are currently present in the market and summarizes the results obtained both in animal models and clinical practice, giving an indication of the potential field of application for this new technology.

PACLITAXEL-ELUTING BALLOONS IN PRECLINICAL STUDIES

Paclitaxel is the ideal drug for local delivery because of its lipophilic properties, short absorption, and prolonged duration of antiproliferative effects.¹⁰ When compared with hydrophilic drugs, the efficacy of local drug delivery is 10 to 20 times higher, with an antiproliferative effect up to 14 days after single-dose application.¹¹ In a porcine

TABLE 1. PEB AND COMBINATION TECHNOLOGY WITH BMS MOUNTED ON PEB CURRENTLY AVAILABLE ON THE MARKET OR IN THE DEVELOPMENT PHASE

Company	Device Name	Technical Specifications and Features
Aachen Resonance GmbH (distributed by Biotronik AG, Bülach, Switzerland)	Elutax I	Paclitaxel is applied on the balloon surface in two layers: the first is “lacked” on the balloon surface while it is inflated, the second is in the form of crystal powder. A final chemical treatment fixes the drug on the balloon. Loaded paclitaxel concentration dosage = 2 µg/mm ² balloon surface area. Indicated for coronary disease.
	Elutax II	Two layers of paclitaxel (elastic and drug depot). Indicated for coronary and peripheral arterial disease. Loaded paclitaxel dosage = 3 µg/mm ² .
Acrostak Corporation (Winterthur, Switzerland)	Genie	Liquid drug delivery catheter. No excipient. Direct contact of drug with vessel wall by a chamber created between the proximal and distal edge of the balloon.
Avidal Vascular (Halle, Germany)	Wombat	Paclitaxel proprietary drug wrap. Indicated for coronary and peripheral arterial disease.
B. Braun Interventional Systems Inc. (Bethlehem, PA)	Coroflex DEBlue (PEB + BMS)	The SeQuent Please DEB technology with a thin-strut CoCr stent. Loaded paclitaxel dosage = 3 µg/mm ² .
	SeQuent Please	Improved Paccocath technology (paclitaxel with iopromide formulation).
Bavaria Medizin Technologie GmbH (Oberpfaffenhofen, Germany)	Paccocath	Drug-eluting balloon catheter that delivers drugs directly to the lesion during angioplasty. Paclitaxel is embedded in a hydrophilic spacer coating. Loaded paclitaxel dosage = 3 µg/mm ² .
Biotronik, Inc. (Lake Oswego, OR)	Pantera Lux	Paclitaxel with butyryl-trihexyl-citrate. Indicated for coronary disease.
	Paseo 18 Lux	Paclitaxel combined with butyryl-trihexyl-citrate for increased bioavailability and optimized antiproliferative effect. Indicated for femoropopliteal disease.
CID Vascular (Saluggia, Italy)	No information released yet.	Sirolimus-eluting balloon with amphiphilic carrier.
Cook Medical (Bloomington, IN)	Advance (in development phase)	DEB for the treatment of peripheral vascular disease. Paclitaxel with unknown additive-based formulation. Loaded paclitaxel dosage = 3 µg/mm ² .
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TABLE 1. PEB AND COMBINATION TECHNOLOGY WITH BMS MOUNTED ON PEB CURRENTLY AVAILABLE ON THE MARKET OR IN THE DEVELOPMENT PHASE (CONTINUED)

Company	Device Name	Technical Specifications and Features
Eurocor, GmbH (Bonn, Germany)	Dior	First generation: mixture of paclitaxel with dimethyl sulfoxide on rough balloon. Loaded paclitaxel dosage = 3 $\mu\text{g}/\text{mm}^2$. The three-folded balloon protects the loaded drug from early washout effect. Inflation of Dior DEB for 45–60 s distributes the full, clinically effective dose of paclitaxel. Second generation: 1:1 mixture of aleuritic and shellolic acid with paclitaxel. The ultra-thin film holds and liberates paclitaxel better. The film is not transferred to the body. Loaded paclitaxel dosage = 3 $\mu\text{g}/\text{mm}^2$. Inflation time is reduced at 30–45 s.
	Magical (PEB + BMS)	Dior balloon catheter in combination with stent. Loaded paclitaxel concentration dosage = 3 $\mu\text{g}/\text{mm}^2$.
Lutonix, Inc. (Maple Grove, MN)	Moxy	Paclitaxel-coated balloon with undisclosed transfer-efficient carrier molecule. Loaded paclitaxel dosage = 2 $\mu\text{g}/\text{mm}^2$.
Medrad Interventional/Possis (Indianola, PA)	Cotavance	Paclitaxel with iopromide formulation (Paccocath technology) for peripheral arterial disease. Loaded paclitaxel dosage = 3 $\mu\text{g}/\text{mm}^2$.
Medtronic Invatec (Frauenfeld, Switzerland)	In.Pact Admiral	DEB for the treatment of peripheral arterial disease, specifically, superficial femoral and proximal popliteal arterial disease. Paclitaxel with FreePac hydrophilic formulation.
	In.Pact Amphirion	DEB for the treatment of peripheral arterial disease, specifically, disease below the knee. Paclitaxel with FreePac hydrophilic formulation. Loaded paclitaxel dosage = 3 $\mu\text{g}/\text{mm}^2$.
	In.Pact Falcon	DEB for the treatment of coronary disease. Paclitaxel with FreePac hydrophilic formulation.
	In.Pact Pacific	DEB for the treatment of peripheral arterial disease, specifically, superficial femoral disease. Paclitaxel with FreePac hydrophilic formulation.

Abbreviations: CoCr, cobalt chromium; PEB, paclitaxel-eluting balloons.

model, Scheller et al¹² showed that after 60 seconds of dilatation, approximately 90% of the drug was released from the balloon within the arterial wall, and 40 to 90 minutes later, 10% to 15% of the drug could be detected within the vessel wall. Paclitaxel-coated balloon inflation led to a marked dose-dependent reduction in stent neointimal area (63% less compared to percutaneous-only balloon angioplasty [POBA]), with similar re-endothelialization of stent struts. In addition, a dose-dependent inhibitory effect was observed only when paclitaxel was dissolved in acetone, suggesting that it is important to use proper solubilizing agents to increase optimal drug delivery.

Compared to DES in porcine coronary arteries, paclitaxel-coated balloons inhibited neointimal formation by 54%, whereas sirolimus-eluting stents reduced in-stent neointimal area by only 26%.¹³

In another animal study, Albrecht and colleagues¹⁴ compared local intra-administration of paclitaxel using drug-coated balloons and/or a mixture of paclitaxel and contrast medium during angioplasty of peripheral arteries to balloon-only angioplasty. They concluded that both methods of paclitaxel delivery reduced restenosis if compared to balloon-only angioplasty and, specifically, balloon delivery allowed a 68% decrease in diameter stenosis and a 56% decrease in late lumen loss.

Recently, Cremers et al¹⁵ evaluated the influence of inflation time and increased dose due to overlapping balloon inflations before stainless steel stent implantation in domestic pigs. The results showed that the efficacy of paclitaxel-eluting balloons (PEB) in combination with BMS was independent of the inflation time. Angiographic and histological findings showed a marked reduction of morphometric parameters characterizing ISR in all animals treated with PEB. Treatment with DEB (5 µg paclitaxel/mm² balloon surface) for 10 seconds reduced the neointimal area (57% compared to control) to the same extent as contact with the vessel wall for 120 seconds (56%). Furthermore, neointimal proliferation could not be further decreased by inflating two DEB in the same vessel segment for 60 seconds each. These results suggest that DEB release most of the drug rapidly during the first seconds of inflation.

PEB TECHNOLOGY

The concept of using a balloon catheter to deliver an antirestenotic drug, such as paclitaxel, at the site of arterial disease was promoted by Scheller et al in 2003.¹² Today, several types of DEB have been introduced in the market (Table 1).

All DEB systems are characterized by three main components: (1) the balloon catheter, (2) the drug, and (3)

the excipient. Balloon catheters do not differ from a standard balloon, with the only addition that the balloon is folded to prevent drug washout after balloon insertion into the blood. The drug used with the different systems is always paclitaxel, and the typical dosage is 3 µg/mm² of balloon surface. What really differs between the competitors is the excipient. The excipient is necessary to separate paclitaxel molecules to increase drug solubility and balance hydrophobicity, which will enhance drug transportation within the wall.

As the balloon unwraps, the drug excipient coating is fully exposed and presented to the vessel wall. The drug excipient coating contacts the vessel wall, where the combination of paclitaxel's hydrophobicity and the increased solubility conferred by the excipient allows for rapid diffusion across the vessel wall. The majority of paclitaxel is cleared from the medial layer at 1 day, but the combination of paclitaxel's hydrophobicity and binding affinity lead to the retention of therapeutically relevant levels of drug in the media. In addition, it is very important to perform predilatation with POBA before applying a DEB. This will crack the plaque, creating microchannels through which the paclitaxel can absorb into the vessels due to its lipophilic properties, and form a homogenous surface to ensure full balloon contact with the vessel wall.

USE OF PEB IN CLINICAL PRACTICE

Several studies have been performed to test the efficacy and safety of PEB in various vascular diseases (Table 2).

ISR

The PACCOCATH ISR I trial was a controlled, randomized, blinded, first-in-man study that investigated paclitaxel-coated balloon catheters for treating ISR. Patients who were treated with the coated Paccocath balloon (Bavaria Medizin Technologie GmbH, Oberpfaffenhofen, Germany) had significantly better angiographic results compared with patients who were treated with POBA (in-segment lumen loss 0.03 ± 0.48 mm vs 0.74 ± 0.86 mm; $P = .002$) and concomitant 12-month clinical outcomes.¹⁶ The results of this trial were confirmed on longer follow-up and by the subsequent PACCOCATH ISR II trial.¹⁷ In contrast to DES, clopidogrel was given for only 1 month followed by treatment with aspirin alone in both the studies.

PEDCAD II was a randomized, prospective, multicenter trial studying the safety and efficacy of the SeQuent Please balloon (B. Braun Interventional Systems Inc.) versus the Taxus stent (Boston Scientific Corporation, Natick, MA) in 131 patients with coronary ISR. At 6-month follow-up, the use of DEB led to a significant reduction of

TABLE 2. PUBLISHED CLINICAL TRIALS WITH PEB

Study	Device Used	Lesions Treated	No. of Patients	Endpoint(s)	Outcome
DEBUT ²¹	Dior balloon	De novo coronary bifurcation	20	MACE at 4 mo	0% clinical TLR
FemPac Pilot trial ²²	Paccocath (A1) vs uncoated catheter (A2)	De novo femoropopliteal artery lesions	87	LLL at 6 mo	A1 = 0.3 mm; A2 = 0.8 mm
				BR at 6 mo	A1 = 19%; A2 = 47% ^a
				TLR at 6 mo	A1 = 7%; A2 = 33% ^a
				BR at 18–24 mo	A1 = 7%; A2 = 17% ^b
				TLR at 18–24 mo	A1 = 17%; A2 = 40% ^b
IN.PACT CORO ISR ²⁰	In.Pact Falcon	BMS ISR	23	In-stent LLL at 6 mo	0.07 ± 0.37 mm
				In-segment LLL at 6 mo	-0.02 ± 0.04 mm
				BR at 6 mo	4%
PACCOATH ISR I ¹⁶	Paccocath (A1) vs uncoated balloon (A2)	ISR	52	LLL at 6 mo	A1 = 0.03 ± 0.48 mm ^{2a} ; A2 = 0.74 ± 0.86 mm ²
				BR at 6 mo	A1 = 5% ^a ; A2 = 43%
				MACE at 1 y	A1 = 4% ^c ; A2 = 31%
PACCOATH ISR II ¹⁷	Paccocath (A1) vs uncoated balloon (A2)	ISR	108	LLL at 2 y	A1 = 0.11 ± 0.44 mm ^d ; A2 = 0.8 ± 0.79 mm
				BR at 2 y	A1 = 6% ^d ; A2 = 51%
				TLR at 2 y	A1 = 6% ^d ; A2 = 37%
				MACE at 2 y	A1 = 11% ^d ; A2 = 42%
PEDCAD I SVD ²³	SeQuent Please	De novo, small vessels	120	LLL at 6 mo	0.32 ± 0.56 mm
				BR at 6 mo	17.3%
				TLR at 6 mo	11.7%
PEDCAD II ISR ¹⁸	SeQuent Please (A1) vs Taxus (A2)	ISR	131	LLL at 6 mo	A1 = 0.45 ± 0.68 mm; A2 = 0.2 ± 0.45 mm ^c
				BR at 6 mo	A1 = 20.3%; A2 = 7% ^b
				TLR at 6 mo	A1 = 15.4; A2 = 6.3% ^b
				MACE at 6 mo	A1 = 16.9; A2 = 7.8 ^b

(Continues)

TABLE 2. PUBLISHED CLINICAL TRIALS WITH PEB (CONTINUED)

Study	Device Used	Lesions Treated	No. of Patients	Endpoint(s)	Outcome
PEPCAD III ²⁶	Coroflex DEBlue (A1) vs Cypher (Cordis Corporation, Bridgewater, NJ) (A2)	De novo coronary stenosis	637	In segment LLL at 9 mo	A1 = 0.2 ± 0.52 mm; A2 = 0.11 ± 0.4 mm ^b
				In-stent LLL at 9 mo	A1 = 0.41 ± 0.51 mm; A2 = 0.16 ± 0.39 mm ^d
				MACE at 9 mo	A1 = 18.5%; A2 = 15.4% ^b
PICCOLETO ²⁷	Dior (A1) vs Taxus Liberté stent (Boston Scientific Corporation) (A2)	Stable or unstable angina and small coronary vessels (≤ 2.75 mm)	57	% diameter stenosis	A1 = 0.34 ± 0.45 mm; A2 = 0.88 ± 0.48 mm ^d
				BR at 6 mo	A1 = 23.2%; A2 = 5.1% ^b
				MACE	A1 = 17.2%; A2 = 4.8% ^b
Prevention of Restenosis After Genous Stent Implantation Using a Paclitaxel-Eluting Balloon in Coronary Arteries ²⁸	CD34 antibody-coated Genous stent (OrbusNeich, Fort Lauderdale, FL) + SeQuent Please (A1) vs CD34 antibody-coated Genous stent (A2)	De novo coronary stenosis	120	LLL at 6 mo	A1 = 43.61%; A2 = 24.33% ^c
				BR at 6 mo	A1 = 32.1%; A2 = 10.3% ^d
				MACE at 6 mo	A1 = 35.7%; A2 = 13.8% ^d
THUNDER ²⁹	Paccocath (A1) vs uncoated balloon with paclitaxel dissolved in contrast medium (A2) vs uncoated balloon (A3)	De novo femoropopliteal artery lesions	154	LLL at 6 mo	A1 = 0.4 ± 1.2 mm ^d ; A2 = 2.2 ± 1.6 mm ^b ; A3 = 1.7 ± 1.8 mm
				TLR at 6 mo	A1 = 4% ^d ; A2 = 29% ^b ; A3 = 37%

^aP = .002; ^bP = NS; ^cP = .02; ^dP < .001.

Abbreviations: BR, binary restenosis; LLL, late lumen loss; TLR, target lesion revascularization.

angiographic in-segment late lumen loss (0.17 ± 0.42 mm vs 0.38 ± 0.61 mm; $P = .03$) and binary restenosis rate (7% vs 22%; $P = .06$). Moreover, event-free survival was improved with DEB compared to DES at 12-month follow-up.¹⁸

In this respect, the superiority of PEB was also recently confirmed in a randomized study of clinical and angiographic outcomes in treating sirolimus-eluting stent restenosis.¹⁹

IN.PACT CORO ISR was a first-in-man trial to evaluate the use of the In.Pact Falcon PEB (Medtronic Invatec) for the treatment of BMS ISR. At 6-month follow-up, in-stent late lumen loss was 0.07 ± 0.37 mm, and in-segment late lumen loss was 0.02 ± 0.5 mm, with a binary restenosis rate of 4%.²⁰

Finally, the VALENTINE registry, the largest registry

evaluating treatment of ISR with both BMS and DES was presented at the 2011 Cardiovascular Research Technologies meeting in Washington, DC. Two hundred fifty patients underwent predilatation with a regular balloon, with subsequent DEB inflation in the target lesion. Additional stenting of the target lesion was left to the operator's discretion in case of suboptimal angiographic success (thrombolysis in myocardial infarction flow grade < 3 and/or residual stenosis > 30%). The cumulative major adverse cardiovascular event (MACE) rate at 9-month follow-up was 11.1%, with three (1.2%) cardiac deaths, one (0.4%) noncardiac death, five (2%) myocardial infarctions (of which two [0.8%] were periprocedural), and 21 (8.6%) target vessel revascularizations (of which 18 [7.4%] were target lesion revascularizations and two [0.8%] were definite stent thrombosis).²⁴

Given this large burden of data, DEB treatment for ISR has been added to the European Society of Cardiology guidelines with a class IIa, evidence level B indication.²⁵

Bifurcation Lesions

In the DEBIUT registry, Fanggiday et al²¹ evaluated the clinical outcome of PCI with the Dior first-generation balloon (Eurocor GmbH, Bonn, Germany) in 20 coronary artery bifurcation lesions. Both the main branch and side branch were predilated with standard balloons and then with Dior at high atmosphere for more than 1 minute; a BMS was then deployed in the main branch, and final kissing-balloon dilatation with standard balloons was performed. Clinical follow-up was performed at 1 and 4 months after the procedure. During this period, no MACE or reintervention occurred, and all patients were symptom free. The authors concluded that the use of PEB in patients with bifurcation lesions was effective and safe up to 4 months after PCI.

De Novo Lesions

PEPCAD I was the first trial to investigate the safety and efficacy of the SeQuent Please PEB in native small coronary vessels of 120 patients with de novo lesions. At 6-month follow-up, the late lumen loss was significantly less in the group that was treated with PEB as compared to the group that was treated with PEB plus BMS ($0.18 \text{ mm} \pm 0.38 \text{ mm}$ vs $0.73 \pm 0.74 \text{ mm}$). In addition, the rate of restenosis was only 5.5% in the PEB only group. Interestingly, the PEB plus BMS group showed ISR, especially at both edges of the stents where there was no balloon contact.²³

A new device consisting of a cobalt chromium stent that is premounted on a paclitaxel-coated balloon was compared to the Cypher stent in 637 patients with native coronary stenosis in the multicenter PEPCAD III trial.²⁶ In-stent late lumen loss was significantly higher in the PEB plus BMS group compared to the DES group ($0.41 \pm 0.51 \text{ mm}$ vs $0.16 \pm 0.39 \text{ mm}$; $P = .001$); however, in-segment late loss was not significantly different ($0.2 \pm 0.52 \text{ mm}$ vs $0.11 \pm 0.4 \text{ mm}$; $P = .07$). The total MACE rate was 18.5% in the PEB plus BMS group and 15.4% in the DES group ($P = .16$).

Recently, Wöhrle et al²⁷ investigated a new approach using paclitaxel-coated balloon angioplasty plus endothelial progenitor cell (EPC) capture stent implantation in 120 patients with de novo lesions in native coronary artery disease. Patients were randomly assigned to undergo treatment with either a paclitaxel-coated balloon plus EPC stent or an EPC stent alone. Treatment with the paclitaxel-coated balloon plus EPC stent was superior to the EPC stent alone, with an in-stent late loss of $0.34 \pm 0.45 \text{ mm}$ versus $0.88 \pm 0.48 \text{ mm}$ ($P < .001$). The restenosis rate was reduced from 23.2% to 5.1% ($P = .006$), and the clinical endpoint was reduced from 17.2% to 4.8% ($P = .039$).

In the PICCOLETO trial, patients with stable or unstable angina undergoing PCI of small coronary vessels ($\leq 2.75 \text{ mm}$) were randomized to Dior (28 patients) or Taxus (29 patients) devices. Unfortunately, this study was interrupted due to a clear superiority of DES. In fact, on quantitative coronary angiographic analysis, the patients receiving the Dior DEB had a percent diameter stenosis (the primary endpoint) almost twice that of patients receiving the Taxus DES ($43.6\% \pm 27.4\%$ vs $24.3\% \pm 25.1\%$; $P = .029$), and other angiographic endpoints, such as binary restenosis, were significantly higher with DEB compared to DES.²⁸ However, predilatation with a standard balloon was not used during the study, which may explain the poor result associated with DEB.

Peripheral Arterial Disease

In the THUNDER multicenter trial, 154 patients with stenosis or occlusion of the femoropopliteal artery were randomly assigned to treatment with the Paccocath balloon, an uncoated balloon with paclitaxel dissolved into contrast medium, or an uncoated balloon. Despite the short follow-up of only 6 months, this trial suggests that the use of PEB for percutaneous treatment of femoropopliteal disease is associated with significant reduction of late lumen loss and target lesion revascularization. No significant benefits were observed with the addition of paclitaxel to contrast medium.²⁹

In the FemPac trial, Werk et al²² randomized 87 patients with occlusion or hemodynamically relevant stenosis, restenosis, or ISR of femoropopliteal arteries to a standard balloon or a paclitaxel-coated balloon. Angiographic follow-up showed less late lumen loss in the coated balloon group than in the standard balloon group ($0.5 \pm 1.1 \text{ mm}$ vs $1 \pm 1.1 \text{ mm}$; $P = .031$), and target lesion revascularization and binary restenosis were lower in the coated balloon group versus the uncoated balloon group (7% vs 33% and 19% vs 47%, respectively). Also, clinical endpoints up to 24 months were significantly better in the paclitaxel-coated balloon group.

Unfortunately, both FemPac and THUNDER examined small sample sizes, enrolled heterogeneous patient populations, provided incomplete follow-up, and were designed to evaluate short-term angiographic primary endpoints that were not symptom-based. In terms of enrollment criteria, clinical indications were quite variable (ie, including patients in Rutherford classes 0–5) and included de novo lesions, restenotic lesions after balloon angioplasty, and in-stent restenotic lesions (approximately 35%). Lesions were relatively long (6.5–7.5 cm), and 15% to 27% of patients had total occlusions. In spite of these limitations, both studies showed the “proof of principle” that treatment of

TABLE 3. ONGOING CORONARY AND PERIPHERAL TRIALS WITH PEB TECHNOLOGY

Name	Device	Lesions Treated	Study Design	Status
Advance 18 PTX Balloon Catheter Study	Conventional balloon vs PEB	Superficial femoral artery and/or proximal popliteal artery disease	Randomized, open-label study	Recruiting
BELLO	PEB dilatation and provisional spot BMS vs PEB	Small coronary vessels	Prospective, multicenter, randomized (1:1) study	Recruiting
BIOLUX P-I First-in-Man Study	Conventional POBA vs PEB	Single or sequential de novo or restenotic lesions in the femoropopliteal arteries	Randomized, single-blind, safety study	Recruiting
DEBAMI	PEB + BMS vs BMS vs DES	ST-elevation myocardial infarction	Multicenter, randomized trial	Recruiting
DEFINITIVE AR	Atherectomy + PEB vs PEB alone	Restenosis of the superficial femoral artery	Randomized, double-blind study	Not yet open for participant recruitment
EUROCANAL	Conventional balloon vs PEB	Critical limb ischemia	Randomized, safety/efficacy study	Not yet open for participant recruitment
FAIR	Conventional angioplasty vs angioplasty with a PEB	Femoral artery ISR	Randomized, safety/efficacy study	Recruiting
HOST-ISR	PEB vs everolimus-eluting stent	ISR	Randomized, safety/efficacy study	Recruiting
INDICOR	PEB in combination with a CoCr stent	De novo and restenotic coronary artery disease	Controlled, prospective, multicenter, randomized, two-arm, phase 2, real-world study	Enrollment completed
INPACT-DEEP	Conventional balloon vs PEB	Critical limb ischemia	Randomized, open-label study	Recruiting
INPACTSFAI	Conventional balloon vs PEB	Superficial femoral artery and/or proximal popliteal artery disease	Randomized, open-label study	Recruiting
ISAR-DESIRE 3	PEB + limus-eluting coronary stents	ISR	Randomized, single-blind, safety/efficacy study trial	Recruiting
ISAR-PEBIS	Conventional balloon vs PEB	Restenosis of the superficial femoral artery	Randomized, safety/efficacy study	Recruiting
ISAR-STATH	Nitinol stent + conventional balloon vs nitinol stent + PEB	Peripheral arterial disease	Randomized, parallel assignment, single-blind, efficacy study	Recruiting
LEVANT 1	Moxy drug-coated balloon vs standard angioplasty	Superficial femoral artery/popliteal artery (4–15 cm)	Good clinical practice, multicenter, prospective, randomized, controlled trial	Enrollment completed, follow-up ongoing
LEVANT 2	Moxy drug-coated balloon vs standard angioplasty	Superficial femoral artery/popliteal artery (≤ 15 cm)	FDA-approved investigational device exemption, global, prospective, randomized, controlled trial	Enrolling

(Continues)

TABLE 3. ONGOING CORONARY AND PERIPHERAL TRIALS WITH PEB TECHNOLOGY (CONTINUED)

Name	Device	Lesions Treated	Study Design	Status
PACIFIER	Conventional balloon vs PEB	Superficial femoral artery and/or popliteal artery disease	Randomized, single-blind, efficacy study	Recruiting
PACUBA I	Conventional balloon vs PEB	Restenosis of the superficial femoral artery	Randomized, single-blind, safety/efficacy study	Recruiting
PAPPA-pilot	PEB	ST-elevation myocardial infarction	Observation study	Recruiting
PEPCAD CTO	PEB	CTO native vessel	Open-label, historical control, single-group assignment, efficacy study	Enrollment completed
PEPCAD II	PEB	ISR	Randomized, open-label, active control, parallel assignment, safety/efficacy study	Enrollment completed
PEPCAD IV	PEB	Coronary artery disease in diabetes mellitus	Randomized, open-label, active control, parallel assignment, safety/efficacy study	Enrollment completed
PEPCAD V	Drug-eluting balloon	Bifurcation	Open-label, single-group assignment, efficacy study	Unknown
PHOTOPAC	PEB vs laser + PEB	In-stent lesions in femoropopliteal arteries	Randomized, open-label, safety/efficacy study	Recruiting
Prevention of Restenosis After Genous Stent Implantation Using a Paclitaxel-Eluting Balloon in Coronary Arteries	Genous stent with PEB vs Genous stent only	De novo stenosis	Randomized, open-label, safety/efficacy study	Enrollment completed
RESTENOZA/ISR II	Rapamycin-eluting stent vs PEB catheter	ISR	Randomized, open-label, safety/efficacy study	Recruiting
RIBS IV	PEB vs everolimus-eluting stent	ISR	Prospective, multicenter, randomized clinical trial	Recruiting
RIBS V	PEB vs everolimus-eluting stent	ISR	Prospective, multicenter, randomized clinical trial	Recruiting

Abbreviations: CoCr, cobalt chromium; CTO, chronic total occlusion.

femoropopliteal artery disease with PEB is feasible and reduces long-term rates of restenosis.

NONPACLITAXEL DEB APPLICATIONS

Nonpaclitaxel DEB are less studied. In a porcine coronary model, Sheiban et al³⁰ tested the safety and efficacy of a novel genistein-eluting balloon (anti-inflammatory falconoid, 0.7 µg/mm²) preceding coronary stenting. At 4 weeks, they reported a significant reduction of the persistent inflammatory cell count (mononucleocytes, 39 ± 32 per mm² vs 96 ± 29 per mm²; *P* = .019) in the genistein-eluting balloon group, but this effect did not trans-

late to a reduction of neointimal hyperplasia at 6 to 8 weeks (0.13 ± 0.11 mm vs 0.14 ± 0.09 mm; *P* = .835).

In another animal model, Tharp et al³¹ tested a Ca²⁺-activated K⁺ channel inhibitor TRAM-34-coated balloon (20 mg/mL in acetone), showing that the use of a blockade of a Ca²⁺-activated K⁺ channel prevented smooth muscle phenotypic modulation and limited subsequent restenosis compared to control balloon groups.

FUTURE DEVELOPMENTS

Currently, several studies are in progress to evaluate the efficacy of DEB in various vascular diseases (Table 3).

Beyond the coronary vasculature, DEB may potentially be very useful for peripheral, neurovascular, valvular, and pediatric congenital diseases.

The ability to perform therapeutic dilatation followed by local drug delivery to prevent restenosis has generated single experiences with PEB in aortic valvuloplasty and in the treatment of basilar artery, subclavian vein, and arteriovenous hemodialysis fistula stenosis. In the future, the concept of drug-eluting valvuloplasty could also be theorized for mitral and pulmonary vein stenosis.

CONCLUSION

DEB may represent a new revolution in the field of coronary and peripheral arterial intervention. The technology has been hampered at the beginning of its introduction by several biases due to anecdotal case reports, small studies that are often nonrandomized, and a lack of preclinical testing. However, today DEB may represent an excellent therapeutic option for the treatment of coronary and peripheral arterial disease. The efficacy of drug-coated balloons is now proven, especially for ISR, with a good long-term safety profile compared to current DES technology. The treatment of de novo lesions in small coronary vessels, bifurcation lesions, long lesions, pediatric interventions, and valvular diseases are promising indications but still need to be proven in large clinical studies. For DEB technology, we are out of the forest but still in the woods. ■

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