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Novel, vessel anatomy adjusting drug-coated balloon— Preclinical evaluation in peripheral porcine arteries

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Abstract

Background: The diameter of balloons or stents is selected according to the estimated reference vessel diameter and do not adapt to the vessel anatomy. The aim of the present preclinical studies was to investigate a novel, vessel anatomy adjusting hypercompliant drug-coated balloon catheter (HCDCB).

Methods: Hypercompliant balloon membranes were coated in a constricted state with high drug density. Drug adherence was investigated in vitro, transfer to the porcine peripheral arteries and longitudinal distribution in vivo. In young domestic swine, neointimal proliferation was induced by vessel overstretch and continuous irritation by permanent stents. Uncoated hypercompliant balloons (HCB), and standard uncoated balloons and drug-coated balloons (DCB) served as controls. Efficacy was assessed by angiography, optical coherence tomography (OCT), and histomorphometry.

Results: HCDCB lost $18.0 \pm 3.9\%$ of dose during in vitro simulated delivery to the lesion. Drug transfer to the vessel wall was $13.9 \pm 6.4\%$ and drug concentration was $1,044 \pm 529$ ng/mg tissue. Four weeks after treatment, the histomorphometric neointimal area was smaller with HCDCB versus uncoated HCB (2.39 ± 0.55 mm² vs. 3.26 ± 0.72 mm², $p = .038$) and area stenosis (OCT) was less ($11.6 \pm 6.9\%$ vs. $24.7 \pm 9.7\%$, $p = .022$). No premature death occurred and no in-life clinical symptoms or treatment-associated thrombi were observed.

Conclusions: HCDCB were found to inhibit excessive neointimal proliferation. Balloon adaption to different vessel diameters and shapes may provide drug-delivery in irregular lumen and facilitate balloon selection.

KEYWORDS

drug transfer, inhibition of neointimal proliferation, vessel anatomy adjusting drug-coated balloon

Abbreviations: DCB, drug-coated balloon (=standard drug-coated PTA balloon); FU, follow-up; HCB, hypercompliant balloon; HCDCB, hypercompliant drug-coated balloon; MLD, minimal lumen diameter; OCT, optical coherence tomography; PTA, percutaneous transluminal angioplasty; QA, quantitative angiography; RFD, reference diameter; SLD, stent struts-to-lumen distance.

1 | INTRODUCTION

Restenosis after percutaneous transluminal procedures occurs due to the vessel wall trauma induced by balloon dilatation or stent

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deployment in several vascular territories.¹ Drug-eluting stents (DES) and drug-coated balloons (DCB) reduce restenosis by inhibition of neointimal growth by local delivery of antiproliferative drugs. Furthermore, lumen enlargement after angioplasty alone may be induced by paclitaxel-coated balloon catheters.² Currently used noncompliant and semi-compliant balloons are inflated to a predetermined cylindrical shape and as a consequence do not adjust to the natural anatomy of the vessel. To accomplish the required vessel wall contact, the diameter of the cylinder has to be carefully chosen in advance according to the desired or achieved lumen diameter of the treated segment. DCB with too small diameter lack vessel wall contact and thus do not provide sufficient drug transfer, and those with too large diameters cause undesired vessel injury. During dilatation of the main artery of bifurcation lesions with currently available DCB, carina shift into side branches may be adversely affected, and may thus not be reached by the DCB surface. Whereas self-expanding stents adjust within certain limits to the vessel diameter, current DCB do not. Long vessel segments with variable diameters require treatment with more than one DCB with different diameters. The novel concept of a hypercompliant drug-coated balloon (HCDCB) allows for adjustment to a wide range of diameters and irregularities of the vessel shape at low inflation pressure and with no mechanical harm to narrow segments. For treatment of a given vessel territory, the only variable in selecting a suitable HCDCB remains a sufficient balloon length. Therefore, the aim of the present preclinical studies was to investigate a novel, vessel anatomy adjusting paclitaxel-coated balloon catheter.

2 | MATERIAL AND METHODS

2.1 | Balloon catheters and stents

2.1.1 | Hypercompliant drug-coated balloons

Hypercompliant balloons, made of a stretchable biocompatible elastomer, were coated with 60 µg paclitaxel/mm of balloon length (2.7 µg/mm² of 7 mm vessel diameter) in a proven matrix.³ Catheters used for the experiments were equipped with 50 or 200 mm balloons, were 0.035" guidewire compatible, over-the-wire, and sterile. To protect coating during the passage of the hemostatic valve of introducers, a 7F peel-away introducer (Adelante, Oscor, Palm Harbor, FL) was used. Maximum usable diameter of inflated balloons was 12 mm.

2.1.2 | Control balloon catheters

Uncoated hypercompliant and standard percutaneous transluminal angioplasty (PTA) balloon catheters, either uncoated (Admiral Xtreme, Medtronic, Minneapolis, MN) or coated with paclitaxel (In.PACT Admiral, Medtronic), 4.0 × 40 mm length, were used as controls.

2.1.3 | Stents

To promote neointimal proliferation in the efficacy study, Express Vascular SD balloon-expandable stents (4.0 × 19 mm, Boston Scientific, Maple Grove, MN) were implanted in the internal iliac arterial segments to be treated with either balloon.

2.2 | Drug adherence and release

Adherence and loss of the drug coating was tested during in vitro simulated passage of the balloon to the lesion. HCDCB were passed through a blood-filled 7 French guiding sheath (Terumo Destination, 65 cm in length, Terumo Europe, Leuven, Belgium). The balloons were advanced in a vial with stirred heparinized porcine blood at 37°C, kept in blood for 1 min, placed in an empty vial, inflated, and cut off from the catheter shaft.

2.3 | Animal experiments

Animal experiments were conducted in a total of 30 arteries in 15 domestic pigs weighing 21.0–31.0 kg. All applicable institutional and/or national guidelines for the care and use of animals were followed, for example, EU Commission Directive 86/609/EEC and German Animal Protection Act (IMTR 42502-2-1378 and 42502-2-1405, Sachsen-Anhalt, Germany). Before the experimental interventions, animals were treated as described previously.⁴

2.3.1 | Drug transfer and longitudinal drug distribution study

A short marker stent was implanted distal to the end of the segment selected for treatment. HCDCB (200 mm long) were advanced to external iliac and femoral arteries. Under fluoroscopy, the balloons were inflated in their full length with conspicuous formation of protrusions at vessel branches. The duration of each inflation was 120 s. About 20 min after treatment of the last artery, animals were euthanized. Vessel segments were in situ labeled and ligated at defined positions of the treated vessel using surgical thread (Figure 1). Major side branches were closed. The length of each ligated vessel segment was measured or determined on angiograms using the ImageJ program (<https://imagej.nih.gov/ij/>). Following dissection of the whole treated artery including adjacent segments of major side branches the side branches were cutoff from the main vessel, which was then cut at the labeled positions to obtain segments with different diameters. All vessel samples were weighed and kept at –20°C for drug analysis.

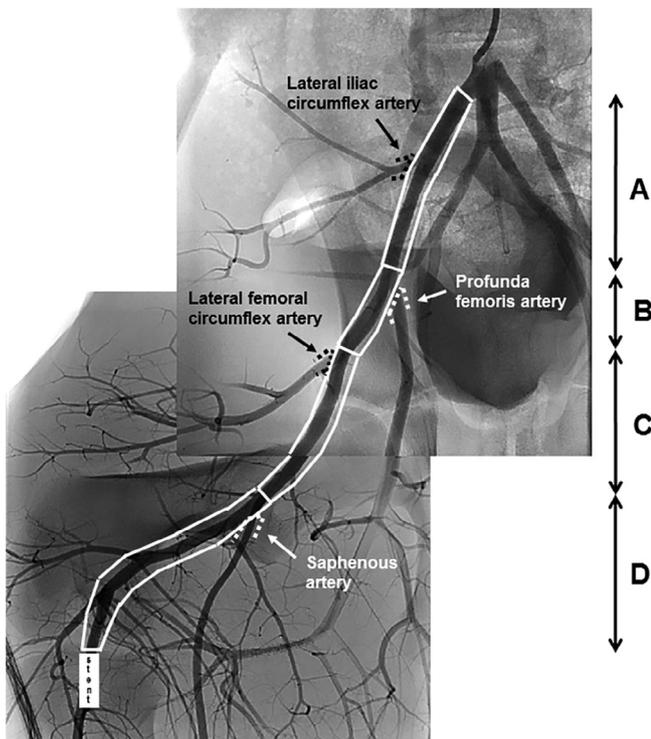


FIGURE 1 Segments of a porcine external iliac/femoral artery for determination of longitudinal drug distribution after inflation of a long hypercompliant drug-coated balloon catheter (HCDCB). Porcine external iliac/femoral artery with segments A–D of the main vessel and side branches as dissected for measurement of drug content after treatment of the artery with a 200 mm HCDCB. Vessel segments A–D (sections marked with white lines) were obtained after cutting at the ligated positions. Side branches were ligated at the orifice and cutoff from the main vessel (sections marked with white or black dotted lines). A stent (white box) was placed distal to segment D to unequivocally label the adjacent but non-balloon-treated distal segment of the vessel

2.3.2 | Efficacy and tolerance study

The study investigating inhibition of neointimal proliferation by HCDCB and tolerance was performed in 12 pigs; the study design is depicted in Figure 2. Starting 2 days before treatment, 75 mg clopidogrel and 100 mg acetylsalicylic acid daily were administered and continued until sacrifice. Solely to enhance neointimal proliferation, balloon expandable bare metal were implanted in right and left internal iliac arteries applying inflation pressures to achieve ~20% overstretch of the vessel diameter. Uncoated HCB or HCDCB (balloon length 50 mm) were introduced into the stented vessel segment as described above. The balloons were placed in the stented vessel segment and were inflated under fluoroscopy by applying minimal pressure allowing full-length expansion. For uncoated and drug-coated PTA balloons, the same procedure as described above was applied except that no peel-away introducer was used. To guarantee sufficient contact with the vessel wall, the balloons were inflated applying 2 atm higher inflation pressure than used for stent implantation. For all balloons, the duration of each inflation was 120 s. After deflation,

the balloons were retracted and kept in tubes for analysis of residual paclitaxel on balloons.

Following completion of all study interventions, the carotid arteriotomy was sutured, and the dermal layers were closed using standard techniques. During treatment and at 4-weeks follow-up, iliac arteries were visualized with fluoroscopy using contrast agent followed by OCT of internal iliac arteries. Thereafter, animals were euthanized as described above. Treated vessel segments were dissected and preserved in 4% formalin solution for histomorphometry.

2.4 | Optical coherence tomography

Optical coherence tomography (OCT) images were recorded using the ILUMIEN™OPTIS™ system (St. Jude Medical GmbH, St. Paul, MN) after stenting followed by balloon treatment (post treatment), and at follow-up. A Dragonfly™ OPTIS™ imaging catheter (St. Jude Medical GmbH) was advanced to the target vessel segment. Images of the internal iliac arterial segment to be investigated were acquired. Qualitative and quantitative analyses were done on the ILUMIEN™OPTIS™ offline review workstation (St. Jude Medical), and cross-sectional parameters were measured after calibration.

2.5 | Quantitative analysis of radiographs (QA)

The CAAS II system (Pie Medical, Maastricht, the Netherlands) was used for quantitative analysis of angiograms by an experienced observer blinded to treatment groups.

2.6 | Histomorphometry

Stented artery segments were prepared for histomorphometry as described in Reference 5, except that the “NIS BR 3.0” image program was used for histomorphometric measurements as described in Reference 6.

2.7 | Analysis of paclitaxel

Paclitaxel contents of unused and used coated balloons and treated vessel segments were determined by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection as described in Reference 5.

2.8 | Statistical analysis

Quantitative angiographic, OCT, and histomorphometric parameters obtained with the different balloon types were compared in a pairwise fashion by unpaired Student's *t* test. A value of $p < .05$ was considered statistically significant. Data are presented as mean \pm SD.

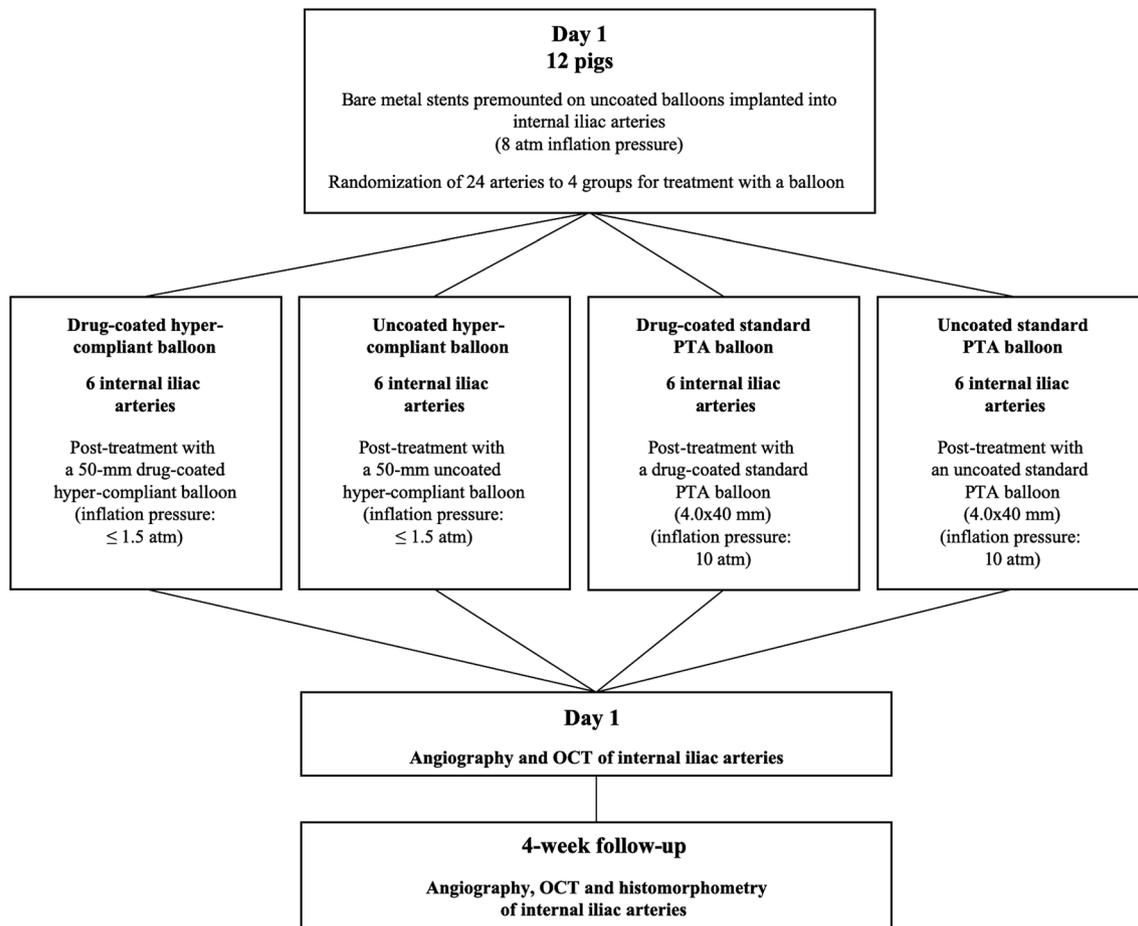


FIGURE 2 Design of the study investigating efficacy and tolerance of hypercompliant drug-coated balloon catheter (HCDCB) in porcine internal iliac arteries. OCT, optical coherence tomography; PTA, percutaneous transluminal angioplasty

3 | RESULTS

3.1 | Properties of the device

HCDCB differ from DCB in the characteristics listed in Table 1. HCB accommodate a wide range of vessel diameters at low inflation pressure and adjust to the endoluminal surface of the artery with circumferential apposition (Figure 3b). By contrast, PTA balloons adjust the vessel lumen and vessel diameter to the predetermined cylindrical shape upon application of high inflation pressure (Figure 3c,d).

3.2 | Drug adherence, release, and transfer to the vessel wall using HCDCB

Advancement of the balloon to the lesion was simulated in vitro by introduction of HCDCB through a membrane valve of a blood-filled Terumo Destination 7F guiding sheath via a 7F introducer and contact of the balloon with stirring blood. Loss of paclitaxel was $18.0 \pm 3.9\%$ of dose, $n = 4$.

In a subsequent study, the transfer of the drug to the vessel wall and its longitudinal distribution were investigated in porcine external

TABLE 1 Differences in physical characteristics of hypercompliant drug-coated balloons (HCDCB) and drug-coated percutaneous transluminal angioplasty (PTA) balloons (DCB)

	HCDCB	DCB
Balloon type	Hypercompliant	Non- or semi-compliant
Balloon before inflation	Contracted	Folded
Balloon after deflation	Contracted to its original state	Irregular shape of folds
Inflation pressure	<1.5 atm	6–16 atm
Surface area upon inflation	Significantly increased	Almost unchanged
Shape and diameter	Conformable, diameter: 3–12 mm	Cylindrical, defined diameter

iliac/femoral arteries. HCDCB, 200 mm long to cover large and narrow diameter segments with the same balloon, were inflated in six external iliac/femoral arteries applying a mean pressure of 0.7 ± 0.4 atm. The mean length of the external iliac/femoral segments treated with HCDCB was 194 ± 4 mm (Table 2). Mean vessel diameter decreased from 5.5 ± 0.1 mm (proximal external iliac artery) to

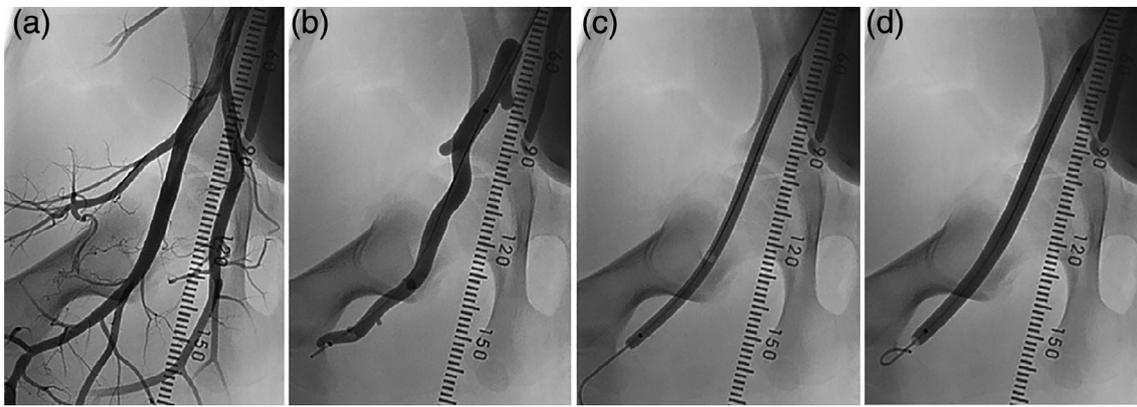


FIGURE 3 Inflation of hypercompliant drug-coated balloon catheter (HCDCB) and percutaneous transluminal angioplasty (PTA) balloons in a porcine external iliac/femoral artery. (a) External iliac/femoral artery before balloon insertion and inflation; (b) hypercompliant balloon (100 mm, full contact to the vessel wall) inflated at 0.7 atm; and (c and d) PTA balloon (4.0 × 100 mm in c: proximal balloon portion without contact to the vessel wall; 5.0 × 100 mm in d: overstretch of the distal artery portion, both inflated at 6 atm, in an external iliac/femoral artery. Images were taken from a separate experiment to illustrate the difference in vessel wall conformity

TABLE 2 Vessel segments and drug transfer from hypercompliant balloons (HCDCB) in each segment and drug in the entire treated vessel (vessel total)

Vessel segment ^a	n vessels	Segment length [mm]	Segment diameter [mm]	Paclitaxel per vessel segment			Paclitaxel per vessel surface area [$\mu\text{g}/\text{mm}^2$ of vessel surface]	Residual paclitaxel on balloon after in vivo inflation in peripheral artery [% of dose on balloon]
				[μg]	[ng/mg tissue]	[% of dose on balloon]		
A	6	59.5 ± 7.6	5.5 ± 0.1	416 ± 280	854 ± 569	3.56 ± 2.39	0.39 ± 0.24	
B	6	26.7 ± 3.9	4.8 ± 0.3	188 ± 77	1,191 ± 555	1.60 ± 0.66	0.46 ± 0.15	
C	6	64.5 ± 5.6	3.6 ± 0.4	517 ± 214	1811 ± 922	4.42 ± 1.83	0.69 ± 0.20	
D	6	43.0 ± 5.9	2.9 ± 0.3	464 ± 476	1,307 ± 1,136	3.97 ± 4.07	1.16 ± 1.12	
Side branches ^b	6			37.8 ± 35.7	133 ± 127	0.32 ± 0.30		
Vessel total	6	194 ± 5		1,622 ± 744	1,044 ± 529	13.9 ± 6.4	3.5 ± 4.8	

^aSegments A–D: see Figure 1.

^bSum of paclitaxel found in all side branches (lateral iliac circumflex, profunda femoris, lateral femoral circumflex, and saphenous arteries, each up to ~5 mm distal of the main artery). Data presented as mean ± SD.

2.9 ± 0.3 mm (distal femoral artery). Drug analysis by vessel segment (A–D, see Figure 1) revealed the highest proportion and amount of paclitaxel in segment C, which extended from the origin of the lateral femoral circumflex artery to that of the saphenous artery (4.4 ± 1.8% of drug on the balloon or 517 ± 214 μg), and the lowest proportion in tissue of the short segment B (1.6 ± 0.7% or 188 ± 77 μg), which extended between the side branches of the profunda femoris and lateral femoral circumflex arteries. The mean sum of paclitaxel proportions in all vessel segments was 1,622 ± 744 μg , corresponding to 13.9 ± 6.4% of dose on the balloons; the mean concentration was 1,044 ± 529 ng/mg tissue. Paclitaxel content in each vessel segment varied with the length of the dissected vessel segment. Paclitaxel content calculated in relation to the surface area of the corresponding vessel segment was depending on vessel diameter (drug in segment A with a vessel diameter of 5.5 ± 0.1 mm: 0.39 ± 0.24 $\mu\text{g}/\text{mm}^2$ of vessel surface area vs. segment D with a vessel diameter of 2.9 ± 0.3 mm: 1.2 ± 1.1 $\mu\text{g}/\text{mm}^2$ of vessel surface area). A small amount of paclitaxel was also found in the short segments of side branches (38 ± 36 μg or 133 ± 127 ng/mg tissue).

3.3 | Efficacy and tolerance study

To stimulate neointimal proliferation stents were implanted in internal iliac arteries of 12 pigs applying significant vessel overstretch. Immediately afterwards, the stented vessel segments were treated with either uncoated or coated hypercompliant or Admiral PTA balloons (i.e., four balloon groups à six arteries; for study design, see Figure 2). No device failures were observed. Hypercompliant or PTA balloons were inflated at pressure less than 1.5 atm or at 10 atm, respectively.

3.4 | Inhibition of neointimal proliferation

3.4.1 | General

Luminal narrowing due to neointimal proliferation was assessed by angiography, OCT, and histomorphometry (Tables 3–5). Baseline vessel measures did not differ between treatment groups.

TABLE 3 Quantitative angiography of in-stent vessel segment of internal iliac arteries at intervention and 4-week follow-up (efficacy and tolerance study)

	Hypercompliant balloon		Standard PTA balloon		p Values HCDCB* versus	
	Coated (HCDCB*)	Uncoated (HCB ^I)	Coated (DCB ^X)	Uncoated (UB ^{II})	Uncoated (HCB ^I)	Coated (DCB ^X)
n (analyzed vessels)	6	6	6	6		
Quantitative angiography at stent implantation followed by balloon treatment						
RFD ^a (mm)	2.12 ± 0.41	2.21 ± 0.26	2.32 ± 0.38	2.48 ± 0.46	0.645	0.403
Stent diameter (mm)	3.00 ± 0.54	2.92 ± 0.22	3.05 ± 0.41	3.40 ± 0.42	0.725	0.875
Overstretch ratio	1.42 ± 0.10	1.32 ± 0.05	1.32 ± 0.08	1.40 ± 0.24	0.054	0.081
At 4-week follow-up						
RFD (mm)	2.47 ± 0.41	2.42 ± 0.20	2.35 ± 0.75	2.83 ± 0.12	0.798	0.767
MLD ^b in-stent (mm)	2.91 ± 0.57	2.52 ± 0.28	2.68 ± 0.68	2.72 ± 0.90	0.164	0.536
Reduction in MLD in-stent at FU ^c (mm)	0.16 ± 0.07	0.48 ± 0.37	0.47 ± 0.43	0.76 ± 0.87	0.071	0.112
SLD ^d (mm)	0.27 ± 0.29	0.75 ± 0.69	1.13 ± 0.71	1.12 ± 1.25	0.145	0.020
In-stent diameter (%)	118 ± 14	101 ± 14	112 ± 18	98 ± 28	0.083	0.608

*Drug-coated hypercompliant balloons; ^I(uncoated) hypercompliant balloons; ^Xdrug-coated PTA balloons; ^{II}uncoated PTA balloons.

^aRFD, reference diameter.

^bMLD, minimal lumen diameter.

^cFU, follow-up; overstretch ratio: stent diameter/reference vessel diameter; reduction in MLD in-stent at FU = MLD stent-MLD lumen FU, SLD.

^dStent struts-to-lumen distance = maximal distance between stent struts and lumen; in-stent diameter (% of RFD) = values larger than 100 indicate persistent oversize of lumen versus RFD. Data presented as mean ± SD.

TABLE 4 OCT analysis of in-stent vessel segment of internal iliac arteries at 4-week follow-up (efficacy and tolerance study)

	Hypercompliant balloon		Standard PTA balloon		p Values HCDCB* versus	
	Coated (HCDCB*)	Uncoated (HCB ^I)	Coated (DCB ^X)	Uncoated (UB ^{II})	Uncoated (HCB ^I)	Coated (DCB ^X)
n (analyzed vessels)	6	6	6	6		
Lumen area (mm ²)	6.29 ± 2.65	4.19 ± 0.83	5.52 ± 1.33	5.20 ± 4.53	0.093	0.540
Stent area (mm ²)	7.07 ± 2.74	5.55 ± 0.71	6.64 ± 1.03	7.29 ± 3.84	0.210	0.734
Neointimal area (mm ²)	0.78 ± 0.42	1.37 ± 0.55	1.12 ± 0.39	2.09 ± 1.44	0.065	0.179
Area stenosis (%)	11.6 ± 6.9	24.7 ± 9.7	17.1 ± 6.0	35.2 ± 28.7	0.022	0.172
Neointimal thickness (mm)	0.09 ± 0.05	0.18 ± 0.08	0.12 ± 0.04	0.23 ± 0.18	0.031	0.203

Note: Neointimal area = difference between inner stent area and luminal area; area stenosis (%) = $[1 - (\text{lumen area}/\text{vessel area})] \times 100$; neointimal thickness = distance from inner surface of stent struts to the luminal border. Data presented as mean ± SD.

*Drug-coated hypercompliant balloons; ^I(uncoated) hypercompliant balloons; ^Xdrug-coated PTA balloons; ^{II}uncoated PTA balloons.

TABLE 5 Histomorphometrical analysis of in-stent vessel segment of internal iliac arteries at 4-week follow-up (efficacy and tolerance study)

	Hypercompliant balloon		Standard PTA balloon		p Values HCDCB* versus	
	Coated (HCDCB*)	Uncoated (HCB ^I)	Coated (DCB ^X)	Uncoated (UB ^{II})	Uncoated (HCB ^I)	Coated (DCB ^X)
n (analyzed vessels)	6	6	6	6		
Vessel diameter (mm)	3.25 ± 0.56	3.10 ± 0.29	3.38 ± 0.37	3.52 ± 0.60	0.591	0.644
Injury score (-)	1.08 ± 0.00	1.02 ± 0.64	1.41 ± 0.55	1.66 ± 0.82	0.878	0.439
Lumen diameter (mm)	2.73 ± 0.57	2.34 ± 0.30	2.69 ± 0.39	2.53 ± 0.94	0.170	0.891
Maximal neointimal thickness (mm)	0.32 ± 0.07	0.47 ± 0.08	0.51 ± 0.08	0.78 ± 0.64	0.0045	0.001
Luminal area (mm ²)	6.13 ± 2.68	4.40 ± 1.06	5.97 ± 1.46	5.61 ± 4.22	0.173	0.898
Neointimal area (mm ²)	2.39 ± 0.55	3.26 ± 0.72	3.21 ± 0.76	4.57 ± 2.32	0.038	0.057
Diameter stenosis (%)	16.4 ± 3.5	24.7 ± 4.7	20.9 ± 5.5	28.9 ± 17.7	0.006	0.121
Area stenosis (%)	29.3 ± 5.8	42.8 ± 7.6	35.8 ± 7.2	47.2 ± 22.3	0.006	0.115
Inflammation score (-)	2.48 ± 0.63	1.57 ± 0.84	2.34 ± 0.38	2.24 ± 0.61	0.058	0.642

Note: Values are mean ± SD (n = 6). *Drug-coated hypercompliant balloons; ^I(uncoated) hypercompliant balloons; ^Xdrug-coated PTA balloons; ^{II}uncoated PTA balloons.

3.4.2 | Effect of HCDCB on neointimal proliferation and comparison to uncoated HCB

At 4-week follow-up, OCT parameters area stenosis and neointimal thickness, were significantly reduced in internal iliac arteries treated with HCDCB compared to uncoated HCB (area stenosis $11.6 \pm 6.9\%$ vs. $24.7 \pm 9.7\%$, $p = .022$; neointimal thickness: 0.09 ± 0.05 mm vs. 0.18 ± 0.08 mm, $p = .031$; Table 4; OCT images in Figure 4a,b). There was also a tendency toward smaller neointimal area with HCDCB versus uncoated HCB (0.78 ± 0.42 mm² vs. 1.37 ± 0.55 mm², $p = .065$). Histomorphometry demonstrated significant inhibition of neointimal proliferation in internal iliac arteries treated with HCDCB versus uncoated HCB (maximal neointimal thickness: 0.32 ± 0.07 mm vs. 0.47 ± 0.08 mm, $p = .0045$; neointimal area: 2.39 ± 0.55 mm² vs. 3.26 ± 0.72 mm², $p = .038$; diameter stenosis: $16.4 \pm 3.5\%$ vs. $24.7 \pm 4.7\%$, $p = .006$; area stenosis $29.3 \pm 5.8\%$ vs. $42.8 \pm 7.6\%$, $p = .006$; Table 5; histomorphometrical images in Figure 4d,e), confirming the OCT findings. QA, however, showed no statistically significant differences between the two balloon types, but a tendency toward less neointima with HCDCB versus uncoated HCB (stent struts-to-lumen distance [SLD]: 0.27 ± 0.29 mm vs. 0.75 ± 0.69 mm, $p = .145$; reduction in in-stent minimal lumen diameter [MLD]: 0.16 ± 0.07 mm vs. 0.48 ± 0.37 mm, $p = .071$; Table 3).

3.4.3 | Comparison of neointimal proliferation after treatment with HCDCB and drug-coated PTA balloons

The QA parameter SLD and histomorphometric parameter maximal neointimal thickness were significantly lower with HCDCB versus drug-

coated PTA balloons (SLD: 0.27 ± 0.29 mm vs. 1.13 ± 0.71 mm, $p = .020$; max. neointimal thickness: 0.32 ± 0.07 mm vs. 0.51 ± 0.08 mm, $p = .001$, Tables 3 and 5). Most other QA and histomorphometric parameters indicated a tendency toward less neointima formation with HCDCB versus drug-coated PTA balloons (reduction in in-stent MLD [QA]: 0.16 ± 0.07 mm vs. 0.47 ± 0.43 mm, $p = .112$; neointimal area [histomorphometry]: 2.39 ± 0.55 mm² vs. 3.21 ± 0.76 mm², $p = .057$; diameter stenosis [histomorphometry]: $16.4 \pm 3.5\%$ vs. $20.9 \pm 5.5\%$, $p = .121$; area stenosis [histomorphometry]: $29.3 \pm 5.8\%$ vs. $35.8 \pm 7.2\%$, $p = .115$). In addition, OCT showed a trend toward smaller neointimal area, stenosis area, and neointimal thickness, and hence less neointima formation, in the HCDCB group versus drug-coated PTA balloon group (neointimal area: 0.78 ± 0.42 mm² vs. 1.12 ± 0.39 mm², $p = .179$; area stenosis: $11.6 \pm 6.9\%$ vs. $17.1 \pm 6.0\%$, $p = .172$, Table 4).

3.4.4 | Injury and inflammation

No significant differences in injury and inflammation scores were observed in overstretched and stented vessel segments, which were subsequently treated with the different balloon types.

3.4.5 | Tolerance

All animals survived the interventional procedure without signs of intolerance. Spasms observed shortly after treatment with either balloon were minor and were without recognizable effect on 4-week results. During the follow-up period, all animals gained weight and showed no signs of pain or abnormal behaviors. No signs of

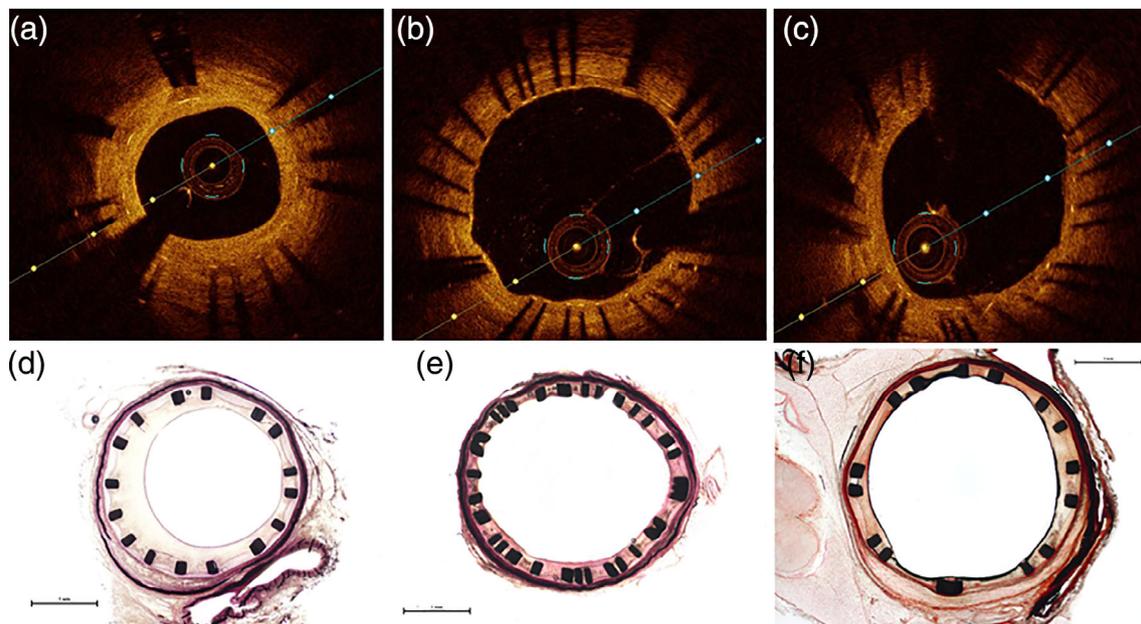


FIGURE 4 Porcine in-stent vessel segments treated with hypercompliant drug-coated balloon catheter (HCDCB) or percutaneous transluminal angioplasty (PTA) balloons at 4-week follow-up. Optical coherence tomography (OCT) and histological images of the in-stent vessel segment in porcine internal iliac arteries at 4-week follow-up. OCT (a–c) and histology (d–f) show neointimal formation in arteries treated with an uncoated HCB (a and d) and suppression of neointimal proliferation in vessels treated with a HCDCB (b and e) or drug-coated PTA balloon (c and f)

TABLE 6 Comparison of paclitaxel proportions in arterial tissue after inflation of HCDCB at low inflation pressure in peripheral arteries with published data on standard DCB inflated at higher pressure in peripheral arteries

Balloon (treatment site)	Dimensions	Drug load (initial dose)	Animals	Inflation pressure [atm]	Inflation time [s]	Paclitaxel concentration in tissue [ng/mg]	Percentage of initial dose found in tissue	Reference
Hypercompliant drug-coated balloon (iliac/femoral)	Length: 200 mm Ø: 7 mm (calculative)	2.66 µg/mm ² (≅ 11.691 µg/balloon)	Domestic pigs	0.68 ± 0.44	120	1.044 ± 529	13.9 ± 6.4	
Lutonix DCB (femoral)	4.0, 6.0 × 80 mm	2 µg/mm ² or 4 µg/mm ²	Domestic pigs	5.7 ± 2.3	60	58.8 ± 54.2 (1 hr after treatment)	N/A	Yazdani et al. ⁷
Freeway balloon (iliac and femoral)	Iliac: 7.0, 8.0 × 40 mm Femoral: 5.0, 6.0 × 20 mm	3 µg/mm ²	Domestic pigs	6–12	60 or 120	140 ± 50 (1 hr after 60 s inflation) 655 ± 187 (1 hr after 120 s inflation)	N/A	Pavo et al. ⁸
SeQuent Please OTW (iliac or femoral)	5.0 or 7.0 × 40 mm	3 µg/mm ²	Domestic pigs	8–14	60	145 ± 50	7.1 ± 6.1%	Speck et al. ⁵

thrombotic or embolic events were noticed during or shortly after the intervention or at reangiography 4 weeks later. Reangiography revealed no vascular abnormalities such as thrombotic occlusion or aneurysms.

4 | DISCUSSION

Coronary angioplasty was introduced clinically by Andreas Grüntzig in 1977.⁷ Later on, stents were developed to cover flow-limiting dissections to prevent early vessel closure.⁸ It was shown that stents lead to a reduction of restenosis compared to conventional angioplasty (POBA).⁹ In the coronary arteries, DES became the therapy of choice for interventional treatment of coronary artery disease¹⁰ due to favorable acute and subacute occlusion rates and low risk of restenosis of new-generation DES. Meanwhile, DCB are accepted alternatives for the treatment of coronary in-stent restenosis¹⁰ and under clinical investigation for coronary de novo disease.^{11,12} In peripheral arterial disease, DCB were about to become the standard therapy for the transfemoral region.¹³

The basic principle of the balloon catheters used has remained the same over the years. The balloons have a defined diameter, which is usually reached at inflation with nominal pressure. Noncompliant balloons almost do not change their diameter even at higher inflation pressures, while semi-compliant balloons can still be stretched by about 10% until the burst pressure is reached.¹⁴ The aim of the current preclinical studies was to explore restenosis inhibition by a single balloon construct that fits all vessel diameters within a certain vessel territory, including treating the origins of side branches in the treated main artery segment. This may be achieved by highly stretchable balloon membranes that inflate at low pressure. In deflated state, these membranes are not folded but contracted forming a tight tube around the catheter shaft with the guidewire lumen. Challenges of this approach are the coating procedure with the aim of a sufficient dose on the small (contracted) surface, advancing the unprotected drug to the lesion, and the drug delivery at a very low inflation pressure.

Encouraged by the findings on feasibility of drug delivery by DCB at low inflation pressure (2 atm)⁶ and high conformability of hypercompliant balloons to vascular anatomy, we performed the preclinical studies presented here to evaluate the HCDCB in terms of in vivo drug deliverability. High-drug loading on contracted small surfaces of stretchable balloon membranes and modest drug loss during passage through hemostatic valves and introductory sheath prompted investigations into inhibition of neointimal proliferation induced by prior overstretch and stent implantation in porcine peripheral arteries. The small surface of hypercompliant balloons in the non-inflated state was coated with high drug density of 14 µg/mm², corresponding to about 60 µg/mm of balloon length. The drug coating density on non-inflated balloons was four times higher than on commercially available DCB with maximum 3.5 µg paclitaxel/mm². However, as the surface area expands during inflation, drug density is reduced.

Loss of drug on the simulated way to the lesion was about 18% of dose for HCDCB, which is close to that found for a drug-coated

PTCA balloon catheter with a preliminary paclitaxel-urea-matrix coating formulation of about 26% of dose⁴ but somewhat higher than for another standard DCB tested in a similar way.⁵ Despite balloon inflation at low pressure (<1.5 atm), HCDCB delivered almost 14% of paclitaxel dose to the external iliac or femoral arteries after a single inflation. This is a high proportion of the drug compared with the yield achieved with drug-coated PTA balloons inflated with significantly higher inflation pressure (Table 6). The porcine overstretch model with simultaneous stent implantation to enhance neointimal proliferation¹⁵ has been extensively used for investigation of numerous coating variations for DCB catheters in coronary and peripheral arteries.^{5,16,17} The study devices were compared with uncoated HCB and Admiral PTA balloons. Furthermore, In.Pact Admiral PTA balloon catheters were used as positive control.¹⁸ Four weeks after stenting with subsequent balloon treatment, the degree of neointimal formation was evaluated by QA, OCT, and histomorphometry. Despite the low inflation pressure applied in peripheral arteries, HCDCB were similarly efficacious in inhibiting neointima formation as drug-coated PTA balloons inflated at much higher pressure. QA showed less SLD and a tendency toward less reduction of MLD after treatment with HCDCB than after treatment with commercially available DCB. This finding was confirmed by histomorphometry. A previous study in porcine coronary arteries⁶ indicates that low-pressure drug delivery by drug-coated PTA balloons is sufficient to reduce neointima proliferation. It may support the use of HCDCB in treating diseased arteries after vessel preparation in order to reach the entire arterial wall independently of lumen diameter.

The results of the 4-week follow-up study presented here demonstrate that treatment of peripheral arteries with HCDCB is tolerated in animal experiments as indicated by survival of all animals without clinical symptoms and without treatment-associated acute or subacute thrombi, vessel obstruction, or other abnormalities in the final 4-week angiograms.

Endovascular treatment of femoropopliteal lesions is complicated by the fact that the superficial femoral artery is one of the longest vessels in the human body, reaching up to 30 cm in length. Vessel preparation using, for example, PTA with uncoated balloons prior to treatment with drug-coated PTA balloons is now an integral part of restenosis prophylaxis. Expansion of the lumen unavoidably results in arterial wall injury.¹⁹ Since common angioplasty balloons tend to adjust the vessel lumen and vessel diameter to the predetermined cylindrical shape at high inflation pressure, they may only be applied to vessel segments with a fairly homogeneous diameter. This requires the prior selection of balloons with an appropriate length and diameter from a stock of a variety of devices with different dimensions, as well as precise placement of balloons. We believe that HCDCB are suitable for vascular treatment after vessel preparation. The clinical field of application is primarily to be seen in the area of long diffusely diseased vessels including the origins of side branches. Since the HCDCB itself has hardly any dilating effect on the blood vessels, lesion preparation is even more important than is the case with DCB anyway. Especially calcified vascular areas require a very intensive pretreatment, for example, by high-pressure PTA or scoring or cutting

balloons and/or debulking strategies such as atherectomy for luminal gain, thrombectomy and plaque modification. This follows from the balloon's long length and its ability to adapt to different vessel diameters in order to guarantee close contact where the vessel diameter is the largest while avoiding unnecessary distal luminal widening and vessel injury.

5 | STUDY LIMITATIONS

The study was limited by its experimental nature. Although anti-restenotic effects of clinically proven drug-coated PTA balloons were shown in the animal model and our data indicate the safety of the tested devices, our current findings cannot predict its clinical performance in patients with peripheral arterial disease, especially in calcified lesions, and sustainability cannot be evaluated in the existing animal model, a known shortage of the model.²⁰

6 | CONCLUSIONS

A novel, vessel anatomy adjusting paclitaxel-coated balloon catheter has been investigated in preclinical models. This concept allows the balloon membrane to be adapted to the natural anatomy of the vessel and thus permits local drug application without additional vascular trauma.

CONFLICT OF INTERESTS

St. Bienek and M. Kusmierczuk are employees of InnoRa. B. Scheller is a shareholder of InnoRa GmbH. All other authors have no conflict of interests to declare.

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