ESC European Society of Cardiology

European Heart Journal (2020) **41**, 2541–2552
doi:10.1093/eurheartj/ehaa049

FASTTRACK CLINICAL RESEARCH
Vascular medicine

COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions

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Received 4 December 2019; revised 20 December 2019; editorial decision 15 January 2020; accepted 23 January 2020; online publish-ahead-of-print 28 January 2020

See page 2553 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa239)

Aims Drug-coated balloons (DCBs) for femoropopliteal interventions have not been tested against each other. We aimed to directly compare efficacy and safety of a high-dose (In.Pact™) vs. low-dose (Ranger™) DCB with nominal paclitaxel densities of 3.5 vs. 2.0 μg/mm^2.

Methods and results Within a prospective, multicentre, non-inferiority, clinical trial 414 patients with symptomatic femoropopliteal lesions (Rutherford classification 2–4) were randomly assigned in a 1:1 ratio to endovascular treatment with either high- or low-dose DCB after stratification for lesion length. Primary efficacy and safety endpoints comprised primary patency and freedom from major adverse events (i.e. device and procedure-related deaths through 1 month, major amputations, and clinically driven target lesion revascularization through 12 months). We set a non-inferiority margin of -10% at 12 months. Total occlusions were observed frequently (>40%) and provisional stenting was performed in every fourth intervention. Non-inferiority was determined for both primary efficacy and safety endpoints at 12 months. Primary patency was 81.5% in the high-dose and 83.0% in low-dose DCB group {difference: 1.5% [lower bound of the 90% two-sided confidence interval (CI) -5.2%]; $P_{\text{non-inferiority}} < 0.01$}. Freedom from major adverse events was determined in 92.6% in high-dose and in 91.0% in low-dose DCB group [difference -1.6% (lower bound of the 90% two-sided CI -6.5%); $P_{\text{non-inferiority}} < 0.01$]. Overall death rate was low (2.0%) and no major amputation occurred.

Conclusion Two DCBs with different coating characteristics exhibited comparable results with excellent effectiveness and safety through 12 months for femoropopliteal interventions including a wide range of lesion lengths.

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Clinical trial registration The trial is registered with ClinicalTrials.gov (NCT02701543).

Keywords Peripheral vascular disease • Drug-coated balloons • Stents • Superficial femoral artery disease • Patency • Restenosis

Introduction

As standard balloon angioplasty for femorpopliteal disease is limited by high restenosis rates up to 70% in complex lesions,[1] novel treatment modalities have been developed to improve patency rates.[2] Next to modern stent-based technologies, the development of drug-coated balloons (DCBs) has been a major step forward by inhibiting neointimal hyperplasia and smooth muscle cell proliferation through brief exposure of the vessel to an antiproliferative agent. Currently, marketed DCBs have been designed based on a similar functional concept using paclitaxel as active drug together with an excipient to facilitate the release and transfer of the drug to the vessel wall. Besides drug dose, the drug and excipient formulations used in their coatings, and the manner in which coatings are applied to the balloons differ between commercially available DCBs. Importantly, several DCBs with different coating formulations were successfully tested for femoropopliteal interventions against plain old balloon angioplasty (POBA) using various excipients and different nominal doses of paclitaxel ranging from 2 to 3.5 μg/mm^2.[3–8] The coating technology and formulation of the active drug may affect the extent of drug delivery and clinical efficacy, and in particular, the dosing of paclitaxel could have a relevant impact on the antiproliferative capacity of these devices. In addition, lesion characteristics and bailout stenting rates differed between various trials further limiting comparability of results. Even in rather short, less complex superficial femoral artery (SFA) lesions as included in randomized trials bailout stenting rates after DCB varied from 2.5% to 15%. In a registry studying DCB for longer lesions with a high proportion of total occlusions and in-stent restenosis, the bailout stenting rate was substantially higher with 23%.[9] In this cohort, patency rates were still favourable after 1 year (79%) but a significant drop to 54% was described at 2 years suggesting only a delay of the restenotic process. Today, it is unclear if the heterogeneity in various DCB formulations of competing manufacturers would ultimately translate into clinically meaningful differences of outcomes, especially in complex lesions with high provisional stenting rates. In a swine model of SFA restenosis, different DCB technologies have been tested before with lower dose DCB achieving comparable degrees of neointimal inhibition as high-dose DCB.[10] While two prior meta-analyses suggested superiority of high-dose DCB compared to low dose,[11,12] these across trial comparisons with differences in patient, lesion and procedural characteristics have not been challenged in a head-to-head study, so far. In addition, as a recent meta-analysis identified a mortality signal for DCB use in femoropopliteal interventions beyond 2 years of follow-up.[13] While this analysis described an association between paclitaxel dose and mortality risk, the underlying assumptions have been widely criticized, in particular, with respect to the dose-time relationship.[14] In addition, subsequent research based on patient-level data and cohort studies also refuted the paclitaxel dose argument.[15–20]

So far, comparative effectiveness of high- vs. low-dose DCB has not been tested within a clinical trial. The COMPARE study was designed to evaluate efficacy and safety of two different coating technologies and paclitaxel dosages in patients with symptomatic femoropoliteal lesions. Importantly, stratification was performed for lesion length ensuring the inclusion of a substantial proportion of long, complex lesion.

Methods

Study design and patient population

The COMPARE study is an investigator-initiated, prospective, randomized, controlled trial aiming to include patients with moderate to severe intermittent claudication or ischaemic rest pain (Rutherford category 2–4) undergoing endovascular intervention in 15 participating vascular centres located in Germany (listed in the Supplementary material online, *Table S1*). Key angiographic inclusion criteria comprised de novo or restenotic femoropopliteal lesions not exceeding the medial femoral epicondyle with a lesion length ≤30 cm and at least one patent tibial runoff vessel. Key exclusion criteria included presence of thrombus or stent in the target lesion or required treatment with alternative therapies, such as stenting, laser, atherectomy, cryoplasty, brachytherapy, and re-entry devices. Detailed inclusion and exclusion criteria are listed in the Supplementary material online, *Table S2*.

Ethics approval was obtained from the University of Leipzig Ethical Committee (Approval No. 321/15-ff) and subsequently at each participating site's ethics board. Patients provided written informed consent before enrolment.

Procedure

Preprocedural data collection included assessment of the patient's medical history as related to peripheral arterial disease (PAD), documentation of Rutherford category and completion of the Walking Impairment Questionnaire (WIQ).

After successful lesion crossing, patients were randomly assigned 1:1 to DCB angioplasty with either high-dose (In.Pact Admiral™ or In.Pact Pacific™, Medtronic Vascular, Santa Clara, CA, USA) or low-dose paclitaxel coating (Ranger™ Paclitaxel-Coated PTA Balloon Catheter, Boston Scientific, Marlborough, MA, USA) using a web-based randomization system (www.randomizer.at, Institute for Medical Informatics, Statistics and Documentation, University of Graz, Austria). Lesions were stratified by length into three categories (lesion length ≤10 cm, >10 cm, and ≤20 cm, >20 cm and ≤30 cm). Pre-dilatation with a conventional undersized (diameter 1 mm smaller than reference vessel) non-DCB balloon catheter was at the operator's discretion in stenotic lesions but mandatory in

case of total occlusions or visually estimated sub-occlusive stenosis. Target lesion was at least 1 cm below the origin of the SFA and above the medial femoral epicondyle with a maximum lesion length of 30 cm. For DCB sizing, the nominal balloon diameter had to match the reference vessel diameter distal to the target lesion. In order to secure full lesion coverage, DCB length was required to be ≥1 cm longer than the pre-dilatation balloon with a DCB inflation time ≥120 s for the first dilatation. In cases with two or more DCB needed overlapping by at least 1 cm had to be accomplished.

Patients with residual stenosis of >50% or major flow-limiting dissection underwent prolonged post-dilatation of at least 180 s. If post-dilatation was unsuccessful bailout stenting with a bare metal stent was performed at the operator's discretion. Calcification was assessed by the core laboratory according to the peripheral arterial calcification scoring system (Grade 0—none; Grade 1—unilateral, <5 cm; Grade 2—unilateral, ≥5 cm; Grade 3—bilateral, <5 cm; and Grade 4—bilateral, ≥5 cm).[21] Clinical assessment and duplex ultrasound of the treated vessel were performed prior to discharge. Technical success was defined as final in-lesion residual diameter stenosis of ≤50% determined by the angiographic core laboratory without device malfunction. Procedural success was defined as technical success without procedural complications [death, major target limb amputation, thrombosis of the target lesion, or target lesion revascularization (TLR)] prior to discharge. The total paclitaxel dose was calculated based on the sum of nominal paclitaxel content for each DCB used for each patient according to the product matrix and paclitaxel content as described in the Instructions for Use.

Medication

Heparin was given intravenously before endovascular treatment according to institutional standards. Antiplatelet therapy in both groups consisted of aspirin and clopidogrel starting at least 24 h before the intervention (or a procedural loading dose of clopidogrel 300 mg orally). Clopidogrel was continued for at least 4 weeks and aspirin indefinitely.

Patient follow-up

Patients were phoned 1 month after the procedure for evaluation of clinical status, medication compliance, and adverse events. In-house follow-up visits were scheduled at 6, 12, and 24 months with assessment of medical conditions, Rutherford category, WIQ, medication, and patency evaluated by duplex ultrasound. Additional follow-up for safety events (death, amputation, and TLR) is performed via an annual telephone call through 5 years. In patients who missed in-house study visits, contact attempts were made at least twice by phone and one by mail as well as contacting the subject's primary physician. In case patients could be reached but declined to return for follow-up visits, information on safety events was obtained by phone. Patients were considered lost to follow-up in case two consecutive study visits were missed and all contact efforts were unsuccessful.

Outcomes

The primary efficacy endpoint was primary patency at 12 months defined as absence of clinically driven target lesion revascularization (CD-TLR) or binary restenosis determined as a peak systolic velocity ratio >2.4 evaluated by duplex ultrasound core laboratory analysis. Clinically driven TLR was defined as a reintervention performed for ≥50% diameter stenosis (confirmed by angiography) within ± 5 mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms of PAD (increase of one Rutherford class or more) and/or drop of ankle–brachial index (≥20% or >0.15 when compared with maximum early post-procedural level).

The primary safety endpoint was a composite of freedom from device and procedure-related death through 30 days and freedom from major target limb amputation and CD-TLR through 12 months post-index procedure.

Protocol pre-specified secondary endpoints included all-cause mortality, CD-TLR, all TLR, target vessel revascularization (TVR), target limb major amputation, and clinical outcomes including haemodynamic and sustained clinical improvements and changes in WIQ scores.

The trial included independent oversight by a data safety monitoring board and clinical events committee (listed in Supplementary material online, *Table S3*) that reviewed and adjudicated all major adverse events.

The study was overseen by independent monitoring services (Vascuscience GmbH, Leipzig, Germany) performing 100% source data verification. Angiographic and duplex ultrasound images were independently analysed by a core laboratory (CoreLab Black Forrest, Bad Krozingen, Germany).

Statistical analysis

The primary aim of the study was to test the hypothesis that a low-dose DCB is non-inferior to high-dose DCB in terms of anti-restenotic efficacy and safety through 12 months. The overall sample size in the randomized trial was selected to preserve adequate statistical power for non-inferiority testing of the primary efficacy and safety endpoint at 12 months. The assumptions for sample size calculation included an 83% primary patency for IN.PACT™ DCB[3] and a one-sided Type I error of 5%. The limit of non-inferiority was set at -10%. A cohort of 414 patients would be needed in order to account for a 15% attrition rate and to retain a minimum of 352 evaluable patients (i.e. at least 80% power) for analysis.

Outcomes were analysed using the intent-to-treat population. Continuous data were given as mean ± standard deviation, categorical data as number (%). Continuous data were compared using independent *t*-test, categorical data using Fisher's exact test. The primary efficacy and safety endpoints were analysed with the use of a Farrington–Manning test for non-inferiority of proportions (one-sided test, with an alpha level of 0.05) with a 10% non-inferiority margin (-0.1). Primary patency and CD-TLR were also assessed using Kaplan–Meier (KM) time-to-event analyses through 410 days (12-month follow-up plus 45-day visit window). Patients without an event at 410 days of follow-up or later were censored at 410 days. The difference in the survival curves between groups was evaluated by log-rank statistics. The difference of 12 months outcome rates as estimated by the KM method were calculated and the Com–Nougue approach was used to estimate 95% confidence intervals (CIs) for the differences.[22]

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NY, USA).

Results

Patient and procedural characteristics

Between December 2015 and September 2018, 414 patients (207 low-dose DCB, 207 high-dose DCB group) were enrolled at 15 sites in Germany (*Figure 1*, patient flowchart). At 12 months, 94% and 87.2% of patients were available for analysis of the primary safety and efficacy endpoint, respectively. An imbalance was seen for follow-up rates between the groups with more missing patients in the high-dose study arm.

The treatment groups were well balanced with respect to baseline demographics and lesion characteristics (*Table 1*). Around one-third

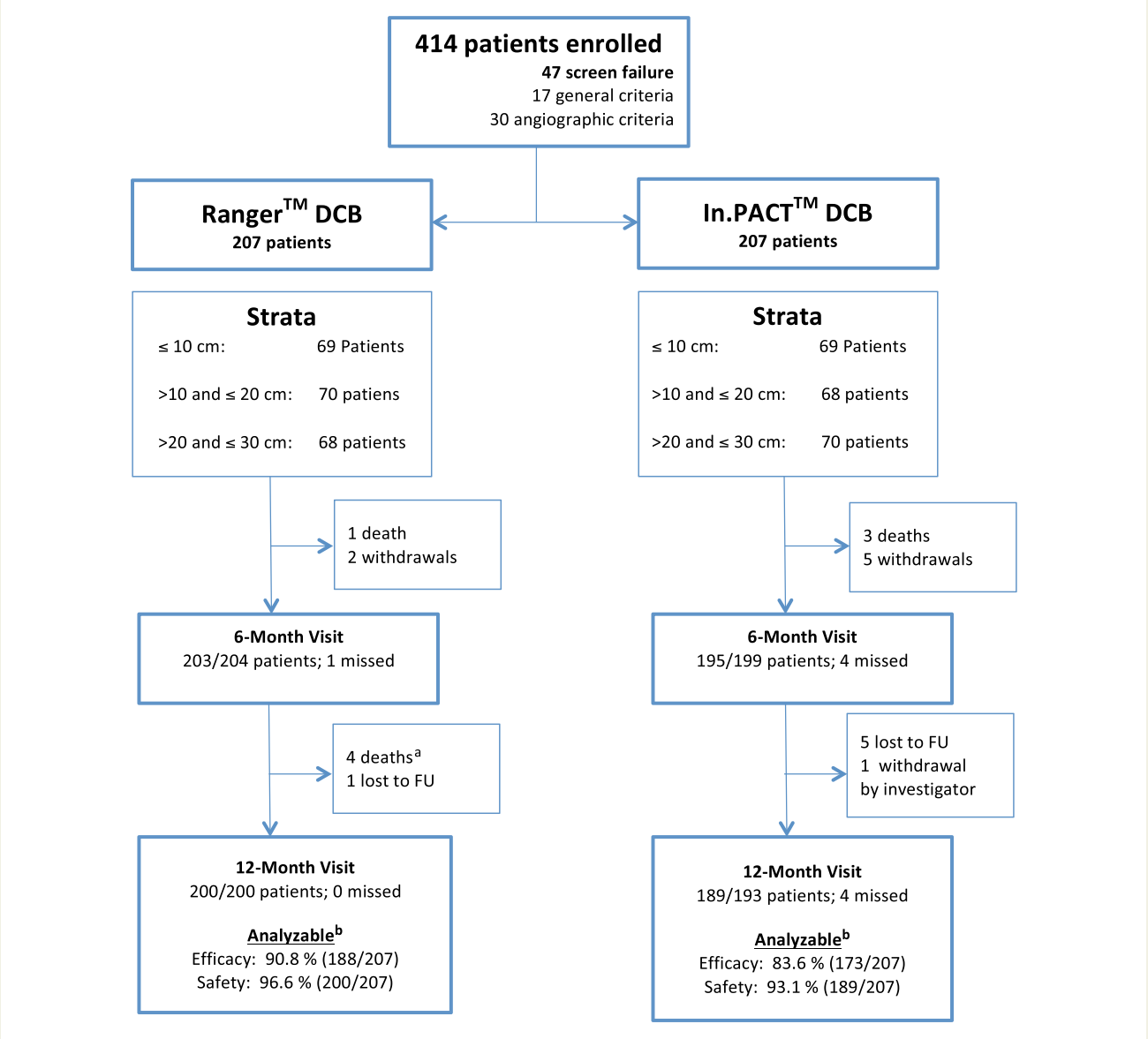


Figure 1 Patient flow diagram. Twelve-month follow-up available in 96.6% treated with low-dose drug-coated balloon and 93.1% treated with high-dose drug-coated balloon. [a]One patient died after 12-month visit but before 410 days and is included in the 12-month analysis set. [b]All endpoint failures occurring prior to study discontinuation are included as analysable. Analysis for primary safety includes evaluable clinical follow-up only, efficacy includes both evaluable Duplex ultrasound and clinical follow-up.

of patients were diabetics with a numerically higher rate in the high-dose group (high-dose group: 36.9% vs. low-dose group: 30.6%; $P = 0.18$). Over 40% of lesions were totally occluded and more than half exhibited moderately severe or severe calcification according to PACCS classification.

Procedural data are given in *Table 2*. Post-dilatation was more common in the high-dose DCB group (high-dose group: 46.9% vs. low-dose group: 38.2%; $P = 0.07$). Bailout stent placement was needed in every fourth intervention with the highest proportion in the long lesion stratum. Relevant intra-procedural complications comprised eight ipsilateral embolic events (five low-dose DCB group and three high-dose DCB group) and one target vessel perforation in each group, which all could be managed adequately by the operators. No device malfunction was reported. Procedural success was observed in 96% of patients.

Effectiveness, safety, and clinical benefit

Non-inferiority was shown for both primary efficacy and safety endpoints at 12 months. Primary patency was observed in 141 (81.5%) from 173 patients in the high-dose and in 156 (83.0%) from 188 patients in the low-dose DCB group [difference: 1.5% (lower bound of the 90% two-sided CI -5.2%); $P_{\text{non-inferiority}} < 0.01$]. Kaplan–Meier curves for primary patency were almost overlapping through

Table 1 Baseline patient characteristics

Variables	Low-dose DCB ($n = 207$)	High-dose DCB ($n = 207$)	*P*-value
Demographic			
Age (years)	68.2 ± 10.0	68.4 ± 9.3	0.79
Female gender	79 (38.2)	75 (36.2)	0.68
BMI (kg/m^2)	26.9 ± 4.6	27.3 ± 4.5	0.38
BMI ≥30 kg/m^2	44 (21.3)	51 (24.6)	0.48
Clinical presentation			
Rutherford class (RC)			0.56
2	23 (11.1)	31 (15)	
3	174 (84.1)	163 (78.7)	
4	7 (3.4)	10 (4.8)	
5	3 (1.5)	3 (1.5)	
Target limb ABI[a]	0.65 ± 0.24	0.63 ± 0.26	0.40
Medical history, *n* (%)			
Hypertension	180 (87)	188 (90.8)	0.21
Hyperlipidaemia	147 (71)	146 (70.5)	0.91
Diabetes mellitus	63 (30.6)	76 (36.9)	0.18
Smoking			0.63
Never	47 (22.7)	51 (24.8)	
Former	65 (31.4)	56 (27.2)	
Current	95 (45.9)	99 (48.1)	
Coronary artery disease	62 (30)	54 (26.1)	0.37
Cerebrovascular disease	29 (14)	24 (11.6)	0.46
Chronic obstructive pulmonary disease	27 (13)	28 (13.5)	0.55
Renal insufficiency[b]	43 (20.8)	45 (21.7)	0.59
Medication, *n* (%)			
Aspirin	168 (81.2)	162 (78.3)	0.46
Clopidogrel	40 (19.3)	35 (16.9)	0.53
Other antiplatelet drug	5 (2.4)	8 (3.9)	0.58
Statins	129 (62.3)	125 (60.4)	0.61
ACE inhibitor/ARB	145 (70.1)	147 (71.0)	0.91
Beta-blocker	111 (53.6)	106 (51.2)	0.62
Other antihypertensive drug	105 (50.7)	107 (51.7)	0.92

Data are shown as mean ± SD or *n* (%).
ABI, ankle–brachial index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index.
[a]Excluding four patients with ABI >1.4 and seven patients with non-compressible arteries.
[b]Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2. There were no statistically significant differences between the groups at baseline.

12 months (*Take home figure*). Analysing patency according to lesion length most restenotic events were observed in the long lesion subgroup >20 cm but comparable results were found for both groups in each stratum (Supplementary material online, *Figure S1A–C*). In a pre-specified Subgroup analysis, primary patency rates were analysed after stratification for bailout stenting. Kaplan–Meier analysis identified relevant differences between the survival curves (log rank $P = 0.02$) with lower patency rates in patients receiving bailout stenting in each treatment arm (*Figure 2*). The composite primary safety endpoint freedom from major adverse events occurred in 175 (92.6%) from 189 patients in the high-dose and in 182 (91.0%) from 200 patients in the low-dose DCB group [difference: -1.6% (lower bound of the 90% two-sided CI -6.5%); $P_{\text{non-inferiority}} < 0.01$] through 12 months. No deaths were determined to be device- or procedure-related, and no major target limb amputation was reported during the first year after the index procedure. Thus, the primary safety endpoint was driven exclusively by CD-TLR. Freedom from CD-TLR per KM estimates through 12 months are presented in *Figure 3*. Additional secondary 12-month outcomes are listed in *Table 3*. All-cause mortality was low with five and three deaths in the low-dose and high-dose DCB group, respectively. Causes of death and time points are shown in Supplementary material online, *Table S5*. Most common causes of death were heart failure (two patients) and cancer (two patients). Other reasons included chronic respiratory disease, post-operative sepsis, polytrauma, and rupture of basilar artery aneurysm.

In parallel with primary sustained clinical and haemodynamic improvements (*Table 3*) most patients in both groups presented with

Table 2 Core lab adjudicated lesion characteristics and procedural data

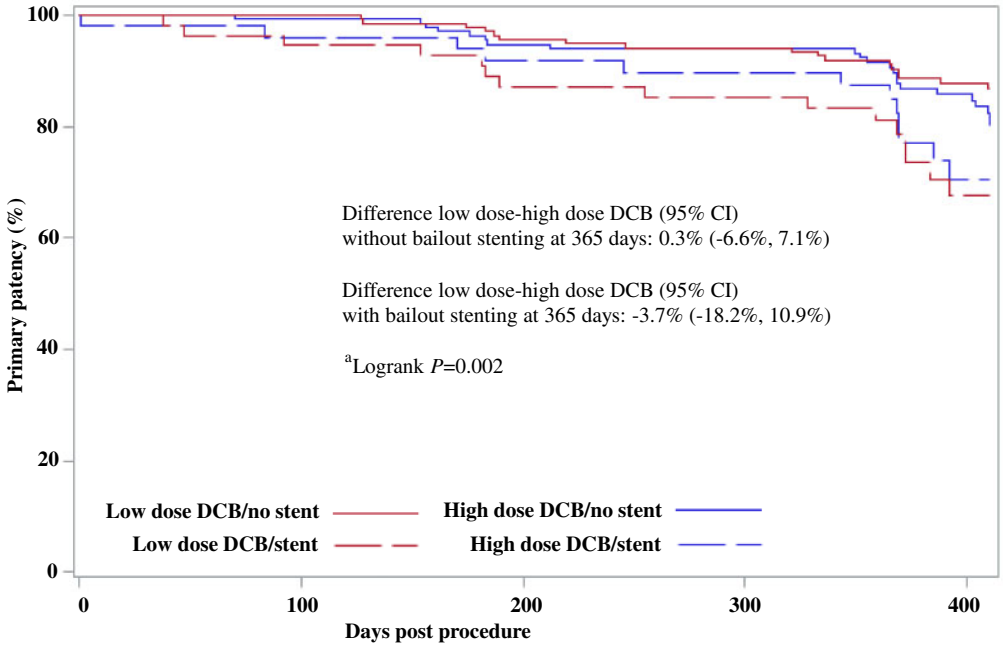
Variables	Low-dose DCB (*n* = 207)	High-dose DCB (*n* = 207)	*P*-value
Lesions			
Arterial segment involved[a]			
Proximal SFA	86 (41.6)	77 (37.2)	0.37
Mid-SFA	142 (68.6)	141 (68.12)	0.92
Distal SFA	147 (71)	154 (74.4)	0.44
Proximal popliteal artery	36 (17.4)	49 (23.7)	0.11
Lesion type			0.86
De novo	190 (91.8)	183 (88.4)	0.53
Restenotic	17 (8.2)	24 (11.6)	
Lesion length (mm)	123.9 ± 97.8	128.3 ± 97.3	0.65
Reference vessel diameter (mm)	4.8 ± 0.6	4.9 ± 0.7	0.66
Diameter stenosis pre-procedure (%)	84.2 ± 16.9	84.2 ± 17.2	0.99
Total occlusions	84 (40.6)	89 (43)	0.62
Length of total occlusions (mm)	130.6 ± 92.4	113.3 ± 95.2	0.23
Calcification[b] (*n* = 409[c])			0.20
Grade 0	19 (9.3)	25 (12.2)	
Grade 1	79 (38.7)	58 (28.3)	
Grade 2	3 (1.5)	5 (2.4)	
Grade 3	67 (32.8)	82 (40)	
Grade 4	38 (17.7)	35 (17.1)	
Patent runoff vessels (*n* = 389[c])			0.89
0	16 (8.2)	12 (6.2)	
1	59 (30.3)	59 (30.4)	
2	71 (36.4)	72 (37.1)	
3	49 (25.1)	51 (26.3)	
Procedure			
Pre-dilatation performed	150 (72.5)	146 (70.5)	0.66
Pre-dilatation balloon diameter (mm)	4.3 ± 0.7	4.3 ± 0.7	0.65
Maximum study device diameter (mm)	5.3 ± 0.6	5.3 ± 0.6	0.52
Total paclitaxel dose (μg), all lesions	6971 ± 4026	13 035 ± 7483	<0.0001
Short lesions (*n* = 138)	2600 ± 1200	5081 ± 2293	<0.0001
Middle lesions (*n* = 138)	6824 ± 1773	12 887 ± 3334	<0.0001
Long lesions (*n* = 138)	11 579 ± 2034	21 101 ± 5112	<0.0001
Post-dilatation performed	79 (38.2)	97 (46.9)	0.07
Bail-out stenting, all lesions	62 (30.0)	53 (25.6)	0.32
Short lesions (*n* = 138)	7 (10.1)	11 (15.9)	0.31
Middle lesions (*n* = 138)	19 (27.1)	14 (20.6)	0.37
Long lesions (*n* = 138)	36 (52.9)	28 (40)	0.13
Dissections post-procedure (*n* = 408[c])			0.61
None	44 (21.5)	46 (22.7)	
Type A	1 (0.5)	0	
Type B	95 (46.3)	83 (40.9)	
Type C	19 (9.3)	20 (9.9)	
Type D	42 (20.5)	52 (25.6)	
Type E	4 (2.0)	2 (1)	
Type F	0 (0)	0 (0)	
Diameter stenosis post-procedure (%)	26.4 ± 12.5	26.1 ± 12.5	0.8
Residual stenosis ≥30%	74 (35.8)	81 (39.1)	0.48
Ipsilateral embolic event	5 (2.4)	3 (1.5)	0.48

Continued

Table 2 *Continued*

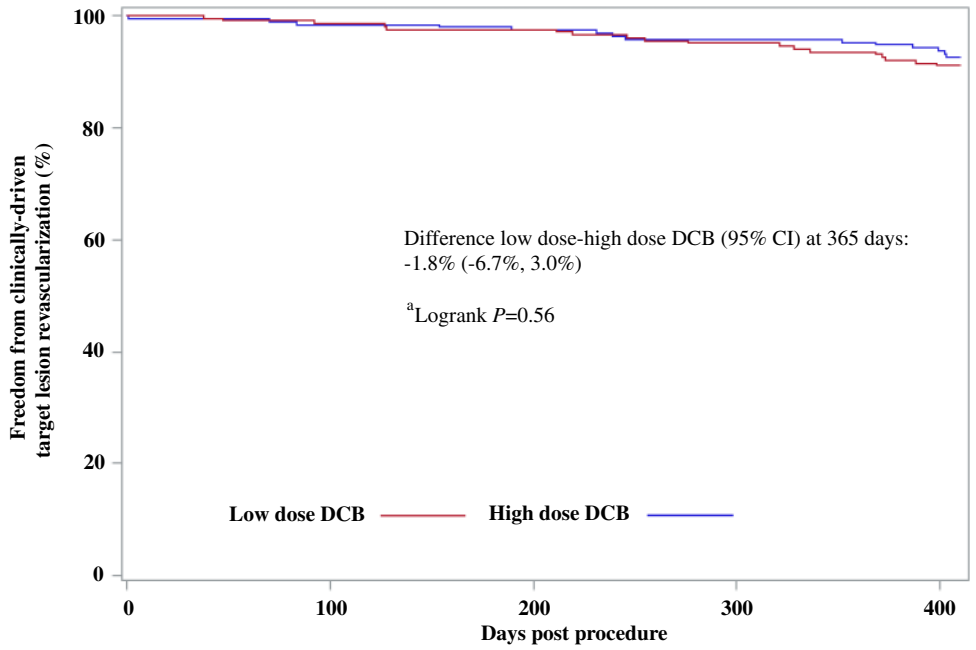
Variables	Low-dose DCB ($n = 207$)	High-dose DCB ($n = 207$)	*P*-value
Technical success[c]	200 (96.6)	200 (96.6)	1.0
Procedural success[d]	199 (96.1)	198 (95.7)	0.8

Data are reported as *N* (%) or mean ± standard deviation when appropriate.
SFA, superficial femoral artery.
[a]More than one segment per patient was allowed.
[b]Calcification assessment according to the peripheral artery calcification scoring system (PACSS).
[c]Number of lesions, which could be adjudicated by the core lab for this variable.
[c]Defined as final in-lesion residual diameter stenosis ≤50% without device malfunction.
[d]Procedural success defined as technical success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or CD-TLR) prior to discharge.



Kaplan Meier Estimates of Event-free Survival (EFS, %)												
Days Post-Procedure	EFS (95% CI)				Cumulative Censored (n)				Remaining at risk (n)			
	Low dose/ No stent	High dose/ No stent	Low dose/ Stent	High dose/ Stent	Low dose/ No stent	High dose/ No stent	Low dose/ Stent	High dose/ Stent	Low dose/ No stent	High dose/ No stent	Low dose/ Stent	High dose/ Stent
0	100 (-)	100 (-)	100 (-)	100 (-)	0	0	0	0	145	154	62	53
180	97.8 (93.4, 99.3)	96.3 (91.3, 98.5)	92.7 (81.8, 97.2)	93.9 (82.2, 98)	7	21	8	5	135	128	50	46
365	91.1 (84.9, 94.9)	90.9 (84.5, 94.7)	81.4 (68.2, 89.5)	85.1 (71.2, 92.6)	20	42	14	12	113	100	38	34
410	86.7 (79.4, 91.5)	82.5 (74.1, 88.4)	67.5 (51.3, 79.4)	70.5 (53.3, 82.4)	38	59	25	22	90	75	22	19

Figure 2 Primary patency for low-dose vs. high-dose drug-coated balloon in patients with and without bailout stenting. Kaplan–Meier estimates of 6 and 12 months primary patency showing event-free survival for low-dose drug-coated balloon without (solid red curve) and with bailout stenting (dashed red curve) as well as high-dose drug-coated balloon without (solid blue curve) and with bailout stenting (dashed blue curve) with corresponding life tables and patients at risk for both groups. CI, confidence interval; DCB, drug-coated balloon. [a]*P*-value for survival analysis based on superiority test.



Kaplan Meier Estimates of Event-free Survival (EFS,%)								
Days Post-Procedure	EFS (95%CI)		Cumulative Failed (n)		Cumulative Censored (n)		Remaining at risk (n)	
	Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose
0	100 (-)	100 (-)	0	0	0	0	207	207
180	97.5 (94.2, 99)	97.9 (94.7, 99.2)	5	4	4	15	198	188
365	93.1 (88.5, 96.0)	94.9 (90.5, 97.4)	13	9	25	36	169	162
410	90.5 (85.3, 93.9)	91.9 (86.7, 95.2)	18	14	50	64	139	129

Figure 3 Freedom from clinically driven target lesion revascularization for low-dose vs. high-dose drug-coated balloon ($n = 414$). Kaplan–Meier estimates showing freedom from clinically driven target lesion revascularization for low-dose drug-coated balloon (red curve) and high-dose drug-coated balloon (blue curve) with corresponding life tables and patients at risk. CI, confidence interval; DCB, drug-coated balloon. [a]*P*-value for survival analysis based on superiority test.

no or mild clinical symptoms (Rutherford category 0 or 1) at 12 months (*Figure 4*). Walking Impairment Questionnaire scores improved significantly at 6 and 12 months when compared with baseline but no differences were observed between the groups after 12 months of follow-up (Supplementary material online, *Table S6*).

Discussion

Prior randomized trials demonstrated superior patency and TLR rates for DCB vs. conventional balloon angioplasty for endovascular treatment of femoropopliteal lesions with moderate complexity, i.e. short and middle length lesions.[3–8] Our study extends the existing evidence by adding a direct comparison of two DCBs with distinct coating formulations in a cohort comprising three different lesion length strata with a high proportion of total occlusions. Despite the inclusion of more complex and longer lesions, both groups exhibited excellent 12-month patency and freedom from TLR rates >80% and 90%, respectively. These rates are comparable to the results observed in the initial proof-of-concepts trials comparing DCB vs. POBA in less complex lesions.[3–8] Importantly, as a consequence of the challenging lesions bailout stenting rates ranged between 25% and 30% for both groups, which are comparable to stenting rates observed in the DCB group of recent trials comparing DCB and drug-eluting stents in patients with more complex femoropopliteal disease.[23,24] In short lesions ≤10 cm, bailout stenting rates around 10–15% fell within the range reported in prior randomized studies comparing DCB and POBA.[3–8] In line with prior DCB data in long lesions,[25] bailout stenting was necessary in almost every second intervention in lesions >20 cm. As a consequence of lesion complexity, 12-month patency curves showed a steeper decline for stented lesions in both groups compared to non-stented. Prior studies with complex lesions indicated a continuous decrease in patency over time after DCB treatment, suggesting only a delay of the restenotic process.[9,24] while in short lesions with a low bailout stenting rate a sustained benefit of DCB compared with POBA has been reported.[26] The ongoing study follow-up up to 2 years for patency and up to 5 years for TLR could give here new insights on the pattern of restenosis in lesions with various complexity.

Table 3 Twelve-month secondary outcomes

Variables	Low-dose DCB ($n = 207$)	High-dose DCB ($n = 207$)	*P*-value[a]	Relative risk[b] (Low vs. high dose)		
				Estimate	95% CI	
All-cause mortality	2.5% (5/202)	1.6% (3/191)	0.73	1.30	0.53	3.20
Clinically driven TLR	9.0% (18/200)	7.4 % (14/189)	0.59	1.12	0.75	1.68
Clinically driven TLR according to bailout stenting status						
No stent	7.6 % (11/144)	5.0% (7/141)	0.47	1.29	0.71	2.33
Bailout stenting	12.5% (7/56)	14.6% (7/48)	0.78	0.91	0.52	1.61
Clinically driven TLR according to lesion length stratum						
Short lesions	7.4% (5/68)	6.3% (4/64)	1.0	1.10	0.51	2.33
Middle lesions	6.0% (4/67)	9.8% (6/61)	0.52	0.78	0.45	1.34
Long lesions	13.9% (9/65)	6.3% (4/64)	0.24	1.68	0.73	3.87
All TLR[c]	9.5% (19/200)	7.4 % (14/189)	0.47	1.16	0.77	1.75
Target vessel revascularization	11.5% (23/200)	7.9% (15/189)	0.31	1.26	0.84	1.89
Primary sustained clinical improvement[d]	79% (147/186)	82.8% (140/169)	0.42	0.87	0.65	1.18
Haemodynamic improvement[e]	78.7% (140/178)	84.1% (137/163)	0.21	0.82	0.60	1.13

Data are reported as percentage (*n*/*N*).
CI, confidence interval; TLR, target lesion revascularization.
[a]*P*-values based on superiority tests (Fisher's exact test).
[b]Cochran–Mantel–Haenszel (CMH) estimates for relative risk and 95% confidence intervals (CIs).
[c]Includes clinically driven TLR and duplex-driven/incidental TLR.
[d]Defined as improvement in Rutherford classification by one or more categories compared with baseline, without TRL.
[e]Defined as an increase in the ankle–brachial index by ≥0.10 compared with baseline or to an ankle–brachial index ≥0.90, without TLR.

The COMPARE study demonstrated non-inferiority of Ranger DCB coated with low-dose paclitaxel (2.0 µg/mm^2) compared to In.Pact DCB coated with high-dose paclitaxel (3.5 µg/mm^2) with respect to both efficacy and safety through 1 year.

While calculation of nominal paclitaxel doses yielded an almost double exposure of paclitaxel in the In.Pact group, this number cannot be translated directly to *in vivo* administration. Besides the actual dose coating technology with differences in the choice of excipients, paclitaxel formulation (crystalline, microcrystalline, or amorphous) and technique of paclitaxel deposition (pulverization or micropipetting), as well as balloon state during deposition (inflated vs. deflated), is considered to profoundly impact paclitaxel drug loss including particulate embolization during delivery and efficacy of tissue transfer. Interestingly, in a swine model of SFA restenosis testing several commercially available DCB, lower drug dose coating was associated with a more mature neointima formation despite lower tissue concentrations.[10] In a rabbit model, the low-dose Ranger™ DCB exhibited the lowest plasma but highest tissue (aortic wall) concentration when compared with four other DCB including high-dose In.Pact™ DCB but clinical implications of such findings remain unclear.[27] For both DCBs tested in the COMPARE study, human pharmacokinetic sub-studies were performed by the manufacturers as part of their investigational device trials showing low systemic exposure with rapid clearance but no direct comparison between the devices is available.[28,29]

Thus, while a number of DCB have demonstrated superiority compared to POBA for femoropopliteal interventions, a class effect of DCB with a comparable clinical efficacy and safety has to be called in question necessitating head-to-head studies. Further, the use of DCBs for femoropopliteal interventions has been challenged by a recent meta-analysis identifying a late mortality signal beyond 2 years in patients who were treated with paclitaxel-coated devices compared to uncoated control devices.[13] While an association between paclitaxel dose and all-cause mortality was postulated in this meta-analysis subsequent publications of individual patient-level data and registries did not corroborate this assumption.[15–17] As a

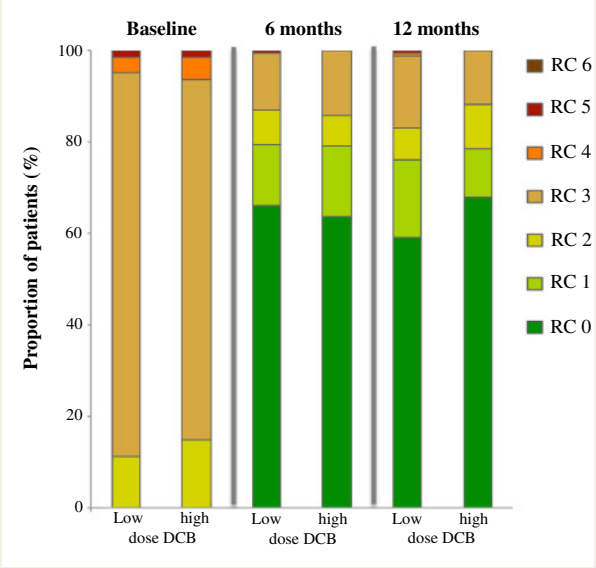
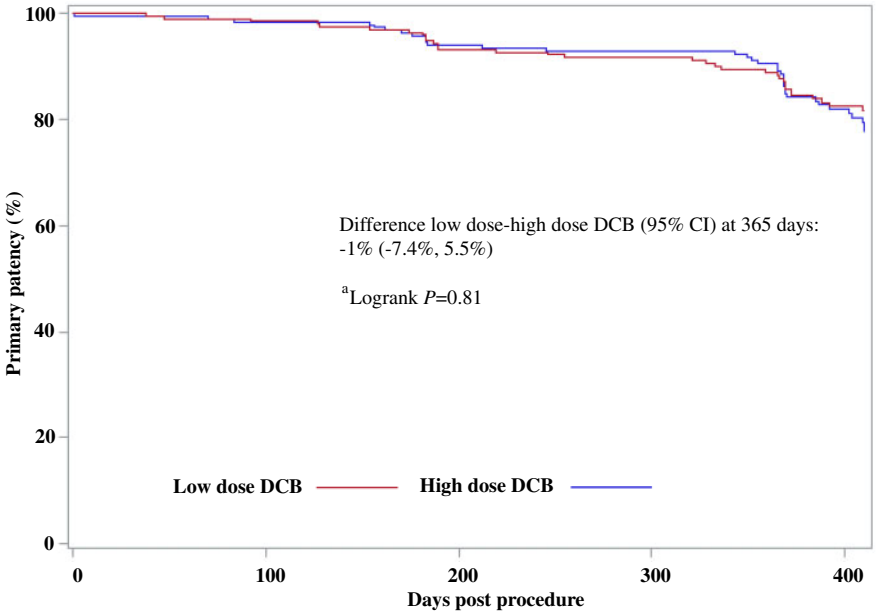


Figure 4 Distribution of Rutherford categories at baseline, 6, and 12 months.



Kaplan Meier Estimates of Event-free Survival (EFS, %)								
Days Post-Procedure	EFS (95% CI)		Cumulative Failed (n)		Cumulative Censored (n)		Remaining at risk (n)	
	Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose
0	100 (-)	100 (-)	0	0	0	0	207	207
180	96.4 (92.6, 98.3)	95.6 (91.5, 97.8)	7	8	15	25	185	174
365	88.4 (82.9, 92.2)	89.4 (83.8, 93.1)	22	19	34	54	151	134
410	81.7 (75.1, 86.8)	79.4 (72, 85.1)	32	32	63	81	112	94

Take home figure Primary patency for low-dose vs. high-dose drug-coated balloon ($n = 414$). Kaplan–Meier estimates of 6 and 12 months primary patency showing event-free survival for low-dose drug-coated balloon (red curve) and high-dose drug-coated balloon (blue curve) with corresponding life tables and patients at risk for both groups. CI, confidence interval; DCB, drug-coated balloon. [a]*P*-value for survival analysis based on superiority test.

consequence regulatoray agencies currently advise cautionary use of DCBs, preferentially in patients at high risk of restenosis. In the COMPARE study, we observed a low 12-month mortality rate without group difference. As a consequence of the ongoing discussion, we modified the study protocol to ensure a 5-year follow-up for safety endpoints.

As a limitation our study was solely designed to assess non-inferiority for primary patency and a combined safety endpoint but not for functional outcomes. While the observed attrition rate was similar to prior studies comparing DCB and POBA.[4,5,7,8] and has been accounted for in the sample size calculation, the imbalance between the groups with a lower follow-up rate in the high-dose DCB arm was unexpected and reasons remain unclear. While the use of dedicated lesion modifying devices was discouraged by the study protocol, these therapeutic options are commonly used in clinical routine limiting generalizability of our study results. A general shortcoming of DCB and other peripheral device trials is the lack of blinding of the operator who is responsible for all procedure-relevant decisions.

Conclusions

In conclusion, we demonstrated that a low-dose paclitaxel-coated DCB was non-inferior to a high-dose paclitaxel-coated DCB with respect to primary patency and TLR through 12 months for femoropopliteal interventions including a wide range of lesion complexity. Both devices showed excellent efficacy with a similar re-assuring safety profile. Longer follow-up will reveal if these positive results can be maintained.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The authors are indebted to Janine Brunotte and Dr Ursula Banning-Eichenseer for study support and data acquisition assistance. They thank Dr Daniela Adolf and Martin Huckauf, MSc (StatConsult GmbH, Magdeburg, Germany) for statistical support.

Funding

COMPARE is an investigator-initiated study, which was designed by the principal investigator (D.S.). Study sponsor is the University of Leipzig with funding through a research grant from Boston Scientific. The funding source was not involved in collecting, monitoring, and analysing study data. Investigators (S.S. and D.S.) prepared all data presentation and manuscript drafts, which were then critically reviewed and edited by the other authors. The funding source had no access to data or manuscript review.

Conflict of interest: The author(s) declared the following relationships in connection with the article: S.S.: Speakers honorarium: Bayer. Research funding: C. R. Bard. A.S.: Consulting/speakers honorarium: C. R. Bard, Cook, and Cordis. T.Z.: Honoraria received from: Abbott Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, TriReme, and Shockwave. Consulted for: Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Spectranetics, Veryan, Intact Vascular, B. Braun, Shockwave, Bayer, and Vesper Medical. Research, clinical trial, or drug study funds received from: 480 biomedical, Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Gore & Associates, Medtronic, Philips, Terumo, TriReme, Veryan, Shockwave, Med Alliance, Intact Vascular, and B. Braun. Common stock: QT Medical. G.T.: ADVB: Medtronic and Philips. Study support: BARD, Bayer, and B. Braun, Biotronik, BSC, CSI, Gore, Veryan, and Shockwave. M.U.: Consulting/speakers honorarium: C. R. Bard, Pfizer, Amgen, and Abbott. R.L.: Consulting and speakers honorarium: Boston Scientific, Biotronik AG, Abbott, Contego Medical, Terumo, Cardinal Health, Alvimedica, B. Braun, and Kardionet. Speakers honorarium: C. R. BARD, Bayer. N.W.: Speakers honorarium or research funding from C. R. Bard, Terumo, Optimed, Amgen, Bayer, Esperion, Pfizer, Pluristem, and Ticeba. D.S. is a consultant or advisory board member for Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, C. R. Bard, Gardia Medical, Medtronic/Covidien, TriReme Medical, Trivascular, and Upstream Peripheral Technologies. The other authors have no conflict of interest to declare.

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