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Drug-Eluting Balloon Versus Drug-Eluting Stent for Complex Femoropopliteal Arterial Lesions

The DRASTICO Study

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ABSTRACT

BACKGROUND Drug-eluting technologies improve 12-month angiographic results of femoropopliteal (FP) interventions, but few data on the comparison between drug-coated balloons (DCBs) and drug-eluting stents (DES) are available.

OBJECTIVES The aim of this study was to compare, after balloon pre-dilation, a strategy of DCB followed by provisional self-expanding nitinol bare-metal stent implantation with a strategy of systematic DES implantation in patients at high risk for FP restenosis.

METHODS Patients presenting with either intermittent claudication or critical limb ischemia undergoing FP intervention were randomly assigned 1:1 to DCB or DES after successful target lesion pre-dilation. The primary endpoint was 12-month target lesion binary restenosis, assessed using Doppler ultrasound. Secondary endpoints were freedom from target lesion revascularization and from major amputation.

RESULTS A total of 192 patients, 96 in the DCB group and 96 in the DES group, with 240 lesions in 225 limbs, were included. Diabetes and critical limb ischemia were present in >50% in both groups. Mean lesion length was 14 cm, and baseline target lesion occlusion reached about 60% of cases in both groups. The systematic DES strategy yielded larger post-procedural minimal luminal diameter and a lower incidence of residual dissection compared to DCB, in which nitinol stents were used in only 21% of the lesions. Twelve-month target lesion restenosis was observed in 22% of DCB-treated versus 21% of DES-treated patients ($p = 0.90$). Clinically driven target lesion revascularization was necessary in 14% of DCB patients versus 17% of DES patients ($p = 0.50$).

CONCLUSIONS DCB was not superior to DES in the treatment of complex FP lesions in a high-risk population, yielding similar rate of restenosis and clinically driven target lesion revascularization. (Paclitaxel-Eluting Balloon Angioplasty With Provisional Use of Nitinol Stent Versus Systematic Implantation of Paclitaxel-Eluting Stent for the Treatment of Femoropopliteal De Novo Lesions; NCT01969630) (J Am Coll Cardiol 2019;74:205–15)

Lower extremity arterial disease, with its main clinical expressions of intermittent claudication (IC) and critical limb ischemia (CLI), is a growing problem in aging Western populations experiencing a diabetes "epidemic" (1,2). Endovascular revascularization is widely considered the first option for severely symptomatic femoropopliteal (FP) atherosclerosis, given its high success rate and benefits in terms of symptoms relief and limb salvage (3,4). In the FP vascular bed, however, restenosis after percutaneous transluminal angioplasty using uncoated balloons or bare-metal stents (BMS) remains a major challenge, leading to repeat revascularization in a large proportion of patients, according to lesion complexity and clinical factors (5). Drug-coated balloons (DCBs) and drug-eluting stents (DES), generally with paclitaxel as an antiproliferative drug, are known to significantly affect FP neointimal

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

BTK = below-the-knee

CDTLR = clinically driven target lesion revascularization

CLI = critical limb ischemia

DCB = drug-coated balloon

DES = drug-eluting stent(s)

DUS = Doppler ultrasound

FP = femoropopliteal

IC = intermittent claudication

MLD = minimal luminal diameter

proliferation (6), albeit with a variable degree of translation into clinical success (7,8). The only available data on the head-to-head comparison between these 2 drug-elution technologies derive from the recently published Real-PTX study, which showed no significant difference in terms of 12-month binary restenosis between DCBs and DES (9).

The potential advantage of DCBs over DES in FP interventions relies on the direct delivery to the arterial wall of an antiproliferative agent without a metal scaffold, which may translate into the absence of chronic vascular trauma, metal- and polymer-related inflammation, and stent fractures, all well-known independent predictors of restenosis (10–13). These negative aspects of stents may be particularly evident in long FP lesions, in which a "full metal jacket" strategy is often applied (5,12,14). In contrast, the absence of a mechanical scaffold may increase elastic recoil and flow-limiting dissections, both negative influencers of vessel patency.

Thus, the aim of our study was to evaluate the effectiveness, in terms of 12-month patency, of a strategy of paclitaxel-eluting balloon angioplasty (Pacific IN.PACT, Medtronic, Santa Clara, California) with provisional bare-metal stenting versus a strategy of systematic paclitaxel-eluting stent implantation (Zilver PTX, Cook Medical, Bloomington, Indiana) for the treatment of complex patients with long FP disease.

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METHODS

STUDY DESIGN. The DRASTICO (DRug-eluting bAlloon verSus drug-eluTIng stent for COmplex Femoropopliteal Arterial Lesions) trial is a prospective, single-center, randomized, parallel-group, open-label involving the blinded evaluation of endpoints trial (15). It was approved by the local ethics committee and carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent.

PATIENTS. All consecutive patients referred to the catheterization laboratory of our institution for peripheral angiography and percutaneous limb revascularization, with either IC or CLI, were evaluated for study enrollment.

Inclusion criteria were: 1) de novo stenosis ≥50% or occlusion of at least 40 mm in length located in the superficial femoral artery or popliteal artery; 2) presence of a clear healthy segment between the lesion in the superficial femoral artery and the common femoral artery and between the popliteal and tibioperoneal trunk; and 3) presence of at least 1 patent tibial vessel with distal runoff (the below-the-knee [BTK] artery was considered patent if free from obstructive lesions determining angiographic stenosis >70%).

Exclusion criteria were: 1) age <18 years; 2) life expectancy <1 year; 3) contraindication to combined antiplatelet treatment; 4) known allergy to nickel or paclitaxel; 5) massive vessel calcification; 6) need for major amputation at the time of enrollment; and 7) failure to reanalyze intended BTK arteries in patients with CLI at risk for major amputation.

Massive calcification was defined as the presence of heavily marked radiopacities noted on both sides of the arterial wall and extending >50% of the lesion length with clear evidence of intraluminal calcium prior to contrast injection or digital subtraction angiography.

Severe calcification was defined as the presence of radiopacities noted on both sides of the arterial wall and extending >1 cm of length prior to contrast injection or digital subtraction angiography.

After optimal balloon pre-dilatation, defined as a residual stenosis <30% without flow-limiting dissection, every patient was randomly assigned 1:1 to undergo either DCB with bailout nitinol stent implantation or systematic DES implantation according to a computer-generated random series of numbers. Randomization was performed in blocks of 10 patients. In patients requiring bilateral FP revascularization, the second limb was treated within 1 month of the first intervention and followed the previous randomization group assignment. Patients with no BTK patent vessel at baseline but with possible BTK treatment underwent first BTK intervention and then, if it was successful, could be randomized for the study.

PROCEDURES. Angiography, angioplasty, and stent implantation were performed according to institutional standards. Vascular access was obtained through the common femoral artery, in either homolateral antegrade or contralateral retrograde fashion, according to anatomic characteristics and lesion location, using a 6-F sheath to achieve adequate support. All patients were administered an intra-arterial bolus of unfractionated heparin (70-100 U/Kg). All lesions were pre-dilated with an uncoated balloon. Thereafter, in patients randomized to DCBs, a further dilation of at least 120 s with a paclitaxel-coated balloon was performed with a balloon/vessel diameter ratio of 1:1. DCBs were inflated from 10 mm proximal to 10 mm distal to the target lesion; in lesions requiring >1 balloon, a 10-mm balloon overlap was done to obtain uniform drug elution in the

treated segment. After DCB placement, self-expanding nitinol stents were used in case of sub-optimal result (flow-limiting dissection or residual lumen stenosis >30%) judged by visual estimation of the operator. Stent dimensions were chosen such that the nominal diameter exceeded the reference vessel diameter by 1 mm, and the length had to be shorter than the DCB-treated segment.

In the DES group, stent selection was based on the manufacturer's recommendation that the labeled diameter be 1 mm larger than the reference vessel diameter. DES post-dilatation was consistently performed, with a balloon/vessel diameter ratio of 1:1.

Technical success was defined as a residual stenosis <30% without flow impairment. Procedural success was defined as achievement of technical success without complications. Femoral sheaths were removed when activated clotting time was <150 s, achieving access-site hemostasis by manual compression in all patients. All patients received dual-antiplatelet therapy for at least 3 months.

FOLLOW-UP. All patient data related to hospital admission, clinical status, procedures, and discharge were prospectively collected in a dedicated electronic database, which also included follow-up data and any clinical cardiovascular events that required hospital readmission. All patients with CLI with wounds followed a pre-specified clinical program focused on continuous monitoring of the foot healing process and vessel patency with a fast-track strategy for reintervention in case of need.

Post-operative evaluation was deferred to physicians unaware of the assigned intervention. At 12 months, target lesions were evaluated using Doppler ultrasound (DUS). All target lesion revascularizations were clinically driven and confirmed angiographically before treatment.

ENDPOINTS AND DEFINITIONS. The final procedural outcome was documented with angiography: before and immediately after the intervention angiography of the target vessel was performed in identical projections (2 orthogonal planes for each treated lesion). The target lesion was identified by an image of the vascular anatomy and specific landmarks (collateral vessels, bone landmarks) and a second image showing the inflated balloon(s).

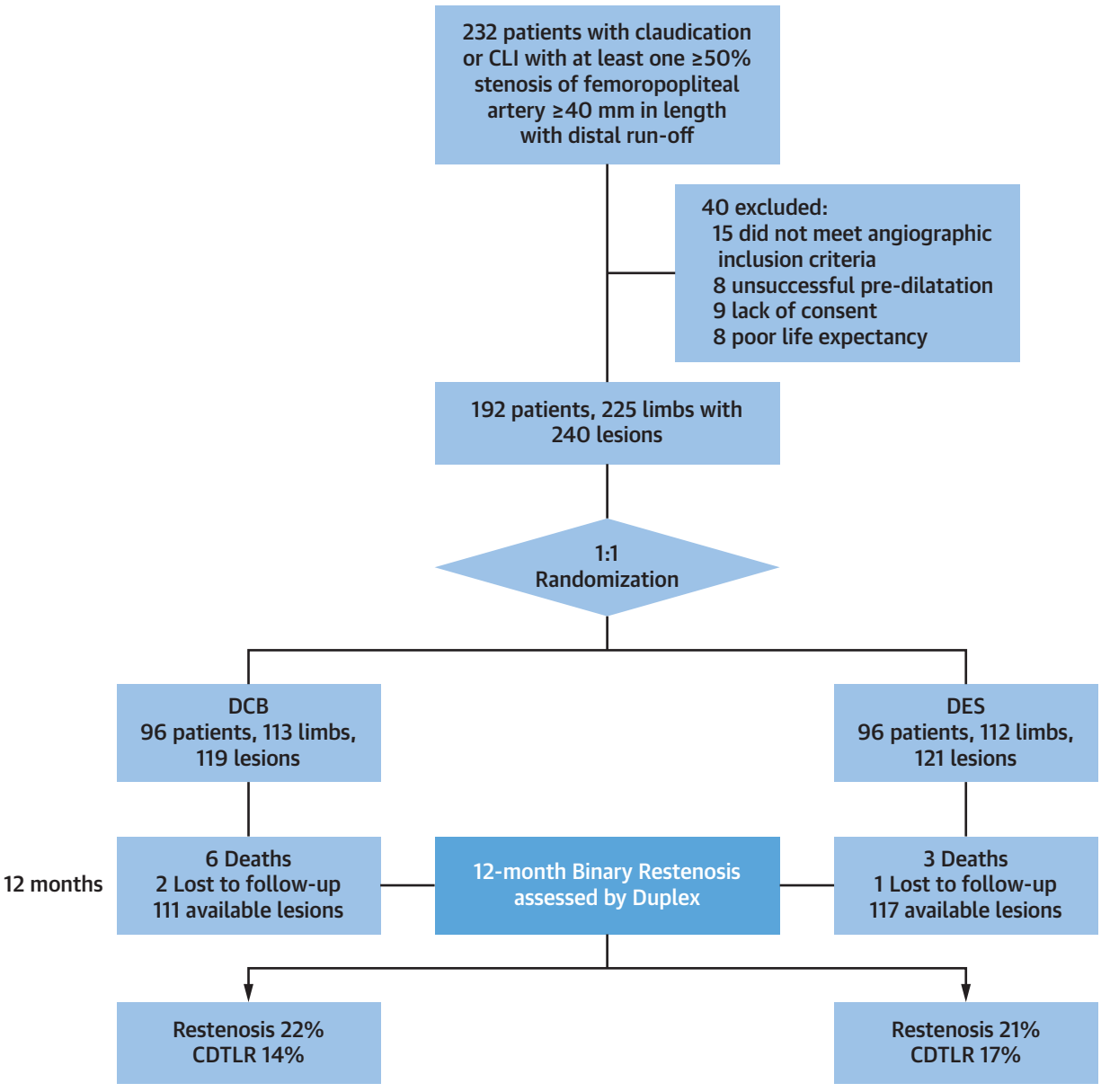
The primary endpoint of the study was the comparison of 12-month binary restenosis rate calculated on DUS as a peak systolic velocity ratio ≥2.4. DUS scans were assessed in a blinded fashion by independent operators and reviewed by 2 readers without knowledge of clinical status and randomization group. The key secondary endpoint was the incidence of clinically driven target lesion revascularization (CDTLR), performed only if clinically indicated (reoccurrence of symptoms, either IC or CLI), and when a target lesion diameter stenosis of ≥50% was present. Major amputation at 12 months, defined as unplanned amputation of the target limb where a prosthesis was required for standing or walking, was also a secondary endpoint.

QUANTITATIVE ANGIOGRAPHIC AND DUS ANALYSIS. Digital subtraction angiography in 2 oblique views of the target lesion and pedal runoff were collected pre- and post-intervention. Quantitative vessel analysis included reference vessel diameter, minimal luminal diameter (MLD), length of the occluded segment, length of the segment treated with DCBs, nitinol stents, and DES, and percentage angiographic residual stenosis post-procedure. DUS evaluation of the target lesion at 12 months included multiple scans of 5 cm with flow velocity samples in each FP segment.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS. Sample size was powered to demonstrate a relative 50% reduction in binary restenosis provided by DCB compared with DES. At the time of study inception, data from the most pertinent related studies were assessed. The ZILVER PTX trial reported a 12-month 17% restenosis rate in low-risk patients (16). However, because our institutional activity is focused on limb salvage, and we planned to include a much larger proportion of patients with diabetes presenting with CLI compared with trials or registries (17) of the Zilver PTX, a 30% restenosis rate was considered appropriate for the DES group. The DEBATE SFA (Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery) trial by our group (18) showed a 1-year restenosis rate of 19% for DCB with systematic BMS; a value of 15% was thus the projected hypothetical restenosis rate for DCB with provisional BMS. Thus, a sample size of 240 lesions was deemed necessary to reach statistical power of 80% ($1 - \beta \geq 0.80$; $\alpha = 0.05$).

Continuous data are expressed as mean ± SD. Categorical variables were compared using the chi-square test or Fisher exact test. Time-to-event outcomes for the primary endpoint of primary patency and the secondary endpoint of CDTLR were evaluated using Kaplan-Meier analysis and the log-rank test on a patient basis. The influence of clinical, angiographic, and procedural variables on 12-month restenosis was evaluated using univariate and multivariate stepwise logistic regression analyses. All variables with a p values ≤0.10 in the univariate analysis were entered into the multivariate model of restenosis to test for independent effects. A p value of <0.05 was considered to indicate statistical

FIGURE 1 Study Flowchart



Inclusion criteria, enrollment by original random assignments, patients excluded, deaths (all-cause), and loss to follow-up through 12 months are shown.
CDTLR = clinically driven target lesion revascularization; CLI = critical limb ischemia; DCB = drug-coated balloon; DES = drug-eluting stent.

significance. Data were analyzed with SPSS version 17 (SPSS, Chicago, Illinois) for Windows.

RESULTS

Between January 2013 and June 2017, we prospectively enrolled 192 patients, 96 patients in the DCB group and 96 patients in the DES group, with 240 lesions in 225 limbs, presenting with either IC or CLI and selected among 232 eligible consecutive patients referred to the catheterization laboratory of our institution for peripheral angiography and percutaneous limb revascularization. The reasons for exclusion in 40 patients were unmet angiographic criteria in 15, suboptimal pre-dilatation in 8 (2 with flow-limiting dissection due to long subintimal aggressive recanalization, 1 with vessel perforation, and 5 with suboptimal results due to

TABLE 1 Baseline Clinical Characteristics

	DCB (n = 96)	DES (n = 96)	p Value
Age, yrs	74.7 ± 9.6	74.2 ± 8.8	0.60
Male	49 (51.0)	73 (76.0)	<0.01
Diabetes	68 (70.0)	58 (60.0)	0.10
Hypertension	73 (76.0)	77 (80.0)	0.30
Smoking	48 (50.0)	53 (55.0)	0.20
Dyslipidemia	57 (59.0)	48 (50.0)	0.10
CAD	33 (34.0)	31 (32.0)	0.40
Previous CAS/CVE	12 (12.0)	10 (10.0)	0.10
Serum creatinine, mg/dl	1.35 ± 1.2	1.32 ± 1.2	0.70
CLI	67 (69.8)	57 (59.4)	0.10
Rutherford class			0.10
3	28 (29.2)	39 (40.6)	
4	7 (7.3)	7 (7.3)	
5	58 (60.4)	50 (52.1)	
6	3 (3.1)	0 (0.0)	
Patients with 2 treated limbs	17 (17.0)	16 (17.0)	0.30
BTK patent vessels 0 or 1	41 (42.7)	35 (36.5)	0.30

Values are mean ± SD or n (%).

BTK = below-the-knee; CAD = coronary artery disease; CAS = carotid artery stenting; CLI = critical limb ischemia; CVE = cerebral vascular event; DCB = drug-coated balloon; DES = drug-eluting stent.

TABLE 2 Procedural and Lesion Characteristics

	DCB	DES	p Value
Number of lesions	119	121	
SFA/POP	94/25	104/17	0.10
Left side	61 (51)	64 (53)	0.50
Severe calcification	37 (31)	46 (38)	0.40
RVD, mm	4.6 ± 0.63	4.91 ± 0.68	0.10
MLD, mm	0.63 ± 0.8	0.53 ± 0.8	0.20
Total occlusions	71 (60)	78 (64)	0.20
Lesion length, mm	146.3 ± 96.4	140.7 ± 86.7	0.20
Treated length, mm	176.8 ± 98.5	165.4 ± 90.6	0.30
Subintimal recanalization	25 (21)	29 (24)	0.30
Largest balloon diameter, mm	4.9 ± 0.6	4.9 ± 0.5	0.70
Inflation time, s	156 ± 42	90 ± 59	<0.001
Maximal inflation pressure, atm	14.4 ± 6.2	15.6 ± 4.1	0.10
Residual dissection	73 (61)	6 (5)	<0.001
Stenting	25 (21)	121 (100)	<0.001
Total stent length, mm	135 ± 60	165 ± 94	0.006
Stent diameter, mm	5.6 ± 0.5	5.8 ± 0.5	0.90
MLD post-procedure, mm	3.51 ± 0.53	4.2 ± 0.60	<0.001
BTK intervention	37 (33)	20 (18)	0.02
Technical success	119 (100)	121 (100)	

Values are n, n (%), or mean ± SD.

MLD = minimal luminal diameter; POP = popliteal artery; RVD = reference vessel diameter; SFA = superficial femoral artery; other abbreviations as in Table 1.

underexpansion of a noncompliant balloon), lack of consent in 9, and poor life expectancy in 8. The study flowchart is depicted in Figure 1. Baseline clinical characteristics of the patient population are reported in Table 1. The whole population enrolled was at high risk for cardiovascular events because of aging, presence of diabetes and CLI in >50%, and coronary artery disease in >30% of the patients, without a significant difference between the 2 study cohorts except for female sex, which was more common in the DCB group. Patients with 2-limb revascularization accounted for 17% of both groups. Baseline procedural and angiographic characteristics are reported in Table 2. There were no significant differences in terms of target vessel treated (superficial femoral or popliteal artery), reference vessel diameter, baseline total occlusion rate, lesion length, calcification, and revascularization technique (centroluminal or subintimal) between the 2 study groups. The systematic DES strategy yielded larger post-procedural MLD and a lower incidence of residual dissection compared with DCBs, for which BMS were used in only 21% of the lesions. The stent length was significantly shorter in the DCB group, in which stents were used only in the dissected segments, compared with the DES group, in which the entire length of the lesion was stented as a procedural strategy. BTK intervention was more common in DCB patients, but all patients had at least 1 tibial vessel runoff prior to target FP lesion treatment. Technical success was obtained in 100% of the target lesions in both groups, and no patient died during hospitalization. Patient medications at hospital discharge are reported in Table 3.

Twelve-month outcomes are reported in Table 4. All patients but 2 in the DCB group and 1 in the DES group completed 12-month follow-up. Ten patients died, 6 (6%) in the DCB group and 4 (4%) in the DES group (p = 0.30). Among these deaths, 2 patients died of acute myocardial infarction, 1 of stroke, 2 of sudden death, 2 of cancer, 1 of sepsis, 1 of head trauma, and 1 of heart failure. No major amputation of the target limb occurred. Binary restenosis was observed in 17 of 87 DCB patients (22%) (25 of 111 = 22% of lesions) and 19 of 92 DES patients (21%) (25 of 117 = 21% of lesions) (p = 0.90). Kaplan-Meyer analysis for freedom from 12-month restenosis on a patient basis is reported in the Central Illustration. A post hoc analysis of freedom from restenosis was also performed for CLI and IC separately (Figure 2), and no significant difference was noted. When DCB lesions treated with nitinol stents were taken out of the analysis, restenosis was 13 of 65 (17%) in DCB-only lesions versus 19 of 77 (20%) with DES (p = 0.50). CDTLR for recurrent symptoms was <20% in both groups, with no statistical difference (Central Illustration). Univariate and multivariate predictors of 12-month restenosis are reported in Table 5.

TABLE 3 Patients Medications at Hospital Discharge

	DCB (n = 96)	DES (n = 96)	p Value
DAPT	95 (99)	94 (98)	0.60
Beta-blockers	39 (41)	42 (44)	0.40
ACE inhibitors/ARBs	67 (70)	61 (64)	0.20
Beta-blockers and/or ACE inhibitors/ARBs	82 (85)	76 (79)	0.30
Statins	80 (83)	75 (78)	0.20
Warfarin or DOAC	6 (6)	4 (4)	0.40

Values are n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DAPT = dual-antiplatelet therapy; DOAC = direct oral anticoagulant; other abbreviations as in Table 1.

DISCUSSION

The aim of the DRASTICO study was to compare, in FP intervention, 2 different drug elution strategies, DCB with bailout nitinol BMS stenting versus systematic DES, in a real-world scenario of an interventional center focused on limb salvage (18). The study thus did not limit the observation to patients presenting with IC but included a large share of patients with CLI, in whom, besides classical tibioperoneal advanced atheroma, significant inflow disease is reported in >50% of cases (18). As a consequence, the study population was characterized by a high incidence (>50%) of diabetes and CLI in both groups, although by play of chance, a higher rate of female sex and the need for BTK intervention occurred in the DCB arm. These differences in baseline conditions seem not to affect the primary endpoint of the study. In contrast, lesion length, the only independent predictor of restenosis, was similar in both study arms.

TABLE 4 12-Month Outcomes

	DCB	DES	p Value
Patients/lesions	96/119	96/121	
Lost at follow-up	2	1	
Death	6/94	3/95	0.30
Available lesions	111 (93)	117 (96)	0.10
Angiographic follow-up	53 (48)	69 (59)	0.10
Doppler follow-up	111 (100)	117 (100)	
Restenosis			
Per patients*	17/87 (22)	19/92 (21)	0.90
Per lesion	25/111 (23)	24/117 (21)	0.90
Major amputation	0	0	–
CDTLR			
Per patients	13 (14)	16 (17)	0.50
Per lesion	17/111 (16)	22/117 (19)	0.60

Values are n, n (%), or n/N (%). *A patient with multiple treated lesions has restenosis if 1 or both the treated lesions have restenosed.

CDTLR = clinically driven target lesion revascularization; other abbreviations as in Table 1.

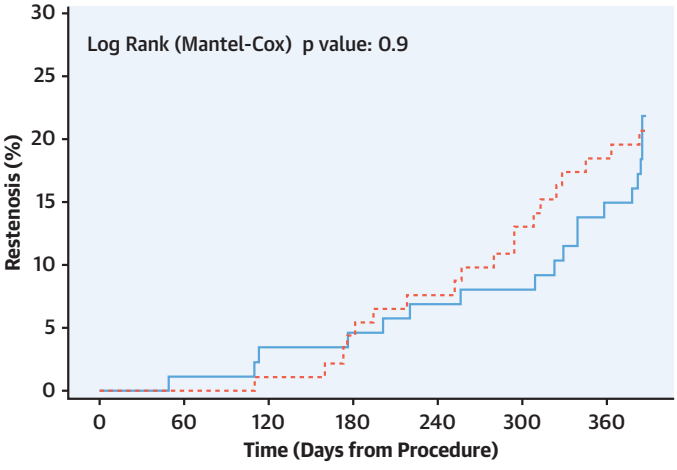
A mean lesion length of about 15 cm and a baseline total occlusion rate of the target lesion in more than one-half of the patients in both arms also clearly highlight a complex lesion setting (5,9,19). As expected, systematic stenting determined a larger MLD post-procedure, with a significant reduction of residual dissection compared with DCB angioplasty, although this difference did not affect procedural and clinical success. The rate of bailout stenting in the DCB group was remarkably low, probably because of the use of long balloon inflation to seal flow-limiting dissection; however, a similar rate of stenting is reported in the setting of TASC C-D lesions (19) and in a recent study comparing the 2 different drug-eluting technologies (9). In other studies, the rate of stenting in DCB angioplasty was significantly higher (up to 40% [20]) and probably linked to an inclination of the operators to use stents instead of prolonged long balloon inflation as a preliminary strategy to seal dissections (21).

The larger MLD provided by DES, however, did not translate into a lower restenosis rate, which was similar in the 2 study groups. This observation supports a higher tendency toward neointimal regrowth for DES compared with DCB, although formal late lumen loss calculation was not performed, because of the low angiographic follow-up rate. A similar rate of restenosis at 1-year follow-up was reported in the recently published REAL PTX study (9) comparing DCB and DES. Although in this study the lesion length and the rate of baseline chronic total occlusion of the target lesion are similar to those observed in DRASTICO, the enrolled population was characterized mainly by patients with claudication with a low prevalence of diabetes compared with the DRASTICO population, composed mainly of patients with diabetes and CLI. Moreover, the DRASTICO results give strength to those reported in the REAL PTX study, extending the observation to CLI.

The efficacy of drug elution technology in preventing intimal hyperplasia and positive vessel remodeling depends on the length of paclitaxel persistence in the vessel wall (22). For DES, the presence of a polymer that controls and prolongs drug release up to several months has been considered a key point for efficacy: the absence of a polymer in the Zilver PTX translates into a short (72 h) drug elution time, although drug persistence in the vessel wall is reported after 50 to 60 days from exposure (16). This elution kinetic is similar to that of DCB, which provide short-term transfer and long-term retention accordingly to the type of coating (6). A hydrophilic coating, such as urea in the IN.PACT technology, provides longer drug vessel retention compared with hydrophobic coatings (6). This type of drug elution may be

CENTRAL ILLUSTRATION **Drug-Coated Balloons Versus Drug-Eluting Stents for Femoropopliteal Interventions: Restenosis and Clinically Driven Target Lesion Revascularization**

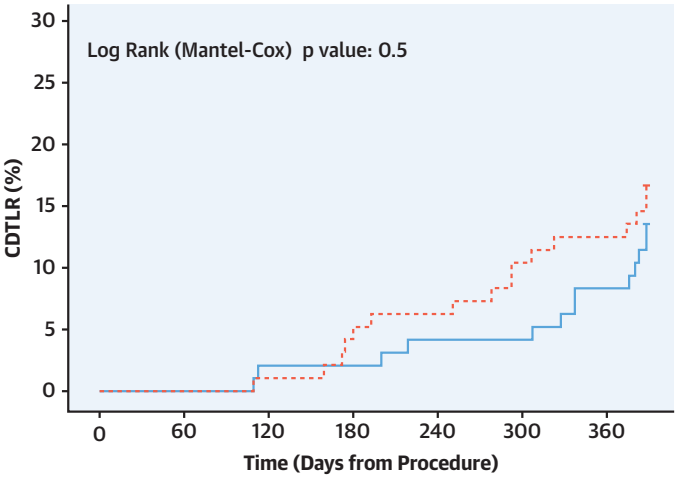
A **Restenosis for Drug-Coated Balloon (DCB) Versus Drug-Eluting Stent (DES) at 12-Month Follow-Up**



Patients at risk

DCB	96	94	92	90	87	84	78	71
DES	96	96	95	92	87	80	77	73

B **Clinically Driven Target Lesion Revascularization (CDTLR) for DCB Versus DES at 12-Month Follow-Up**



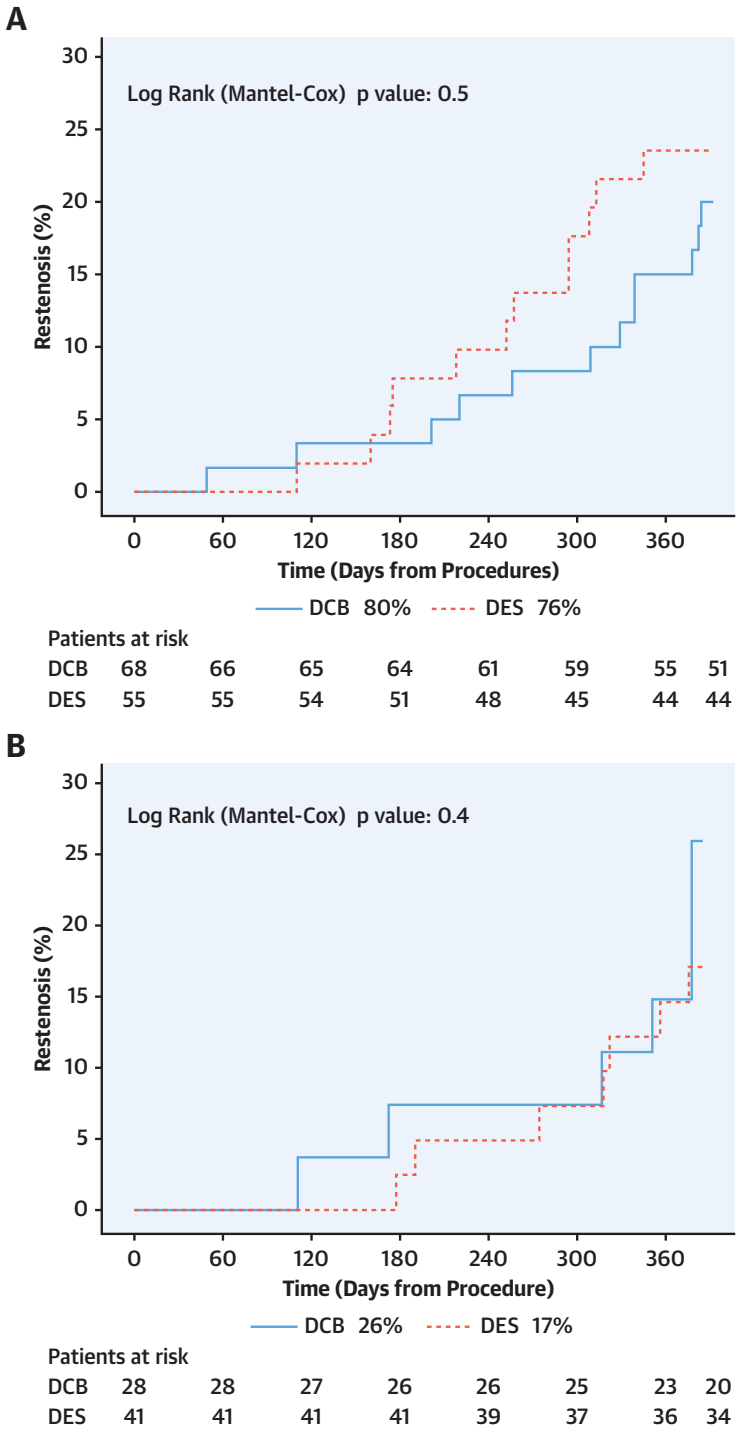
Patients at risk

DCB	96	95	93	92	89	87	83	79
DES	96	96	95	92	88	82	80	78

Liistro, F. et al. J Am Coll Cardiol. 2019;74(2):205–15.

(A) Restenosis for drug-coated balloons (DCBs) versus drug-eluting stents (DES) at 12-month follow-up. Kaplan-Meier estimates of 12-month restenosis for DCBs **(continuous line)** versus DES **(dashed line)** with corresponding patients at risk for both groups. No significant difference is shown. **(B)** Clinically driven target lesion revascularization (CDTLR) for DCBs versus DES at 12-month follow-up. Kaplan-Meier estimates of 12-month CDTLR for DCBs **(continuous line)** and DES **(dashed line)** with corresponding life tables and patients at risk for both groups. No significant difference is shown.

FIGURE 2 Restenosis for Drug-Coated Balloons Versus Drug-Eluting Stents at 12-Month Follow-Up in Patients With Critical Limb Ischemia and Claudication



(A) Restenosis for drug-coated balloons (DCBs) versus drug-eluting stents (DES) in patients with critical limb ischemia (CLI) (n = 123) is shown. Kaplan-Meier estimates of 12-month restenosis for DCBs **(continuous line)** and DES **(dashed line)** with corresponding life tables and patients at risk for both groups. No significant difference is shown. **(B)** Restenosis for DCBs versus DES in patients with claudication (n = 69) is shown. Kaplan-Meier estimates of 12-month restenosis for DCB **(continuous line)** and DES **(dashed line)** with corresponding life tables and patients at risk for both groups. No significant difference is shown.

adequate for the time-limited vascular trauma induced by balloon inflation of DCB angioplasty but may be inadequate for the prolonged, chronic vessel stress induced by permanent stent implantation. Moreover, the benefit of a mechanical scaffold in terms of vessel recoil and flow-limiting dissection may be reduced by inadequate inhibition of intima hyperplasia. A recent comparison of the Zilver PTX DES versus a polymer-based DES with controlled and prolonged paclitaxel elution supports this hypothesis, with better efficacy for the inhibition of intimal hyperplasia with polymer-based DES (23). Permanent polymers have also been considered as a main cause of vessel inflammation and thrombosis, and resorbable polymers are now preferred in coronary intervention (24) and should be evaluated also in peripheral arteries. New technologies for DES and DCB, aimed at optimizing their performance, are already being tested, but final data are still missing (25–28). In the meantime, however, on balance, the DRASTICO results support the concept of provisional stenting after systematic ballooning with DCBs, as similar 12-month results were obtained with the 2 strategies.

A recent meta-analysis suggests an increased risk for late deaths in patients treated with paclitaxel-coated balloons and stents (29). This observation was not confirmed in a large nationwide analysis of Medicare and Medicaid beneficiaries (30). In the DRASTICO trial, overall mortality was 5% in the whole population, comparing well with mortality reported in another study evaluating drug elution technology for FP intervention in patients with CLI (31). Furthermore, none of the deaths observed in the DRASTICO study were related to the procedure or device used. This mortality rate might be slightly higher than that reported in other trials with plain balloon or bare-metal stents (32), but this difference may be due to the higher risk for death in the DRASTICO population, composed mainly of patients with CLI. However, long-term mortality will be analyzed at the patient level to seek any potential relation with paclitaxel drug elution therapy. Five percent mortality, no major amputation, and <20% CDTLR are indeed positive clinical outcomes, considering the baseline clinical and angiographic conditions of this population at high risk for cardiovascular and limb adverse events. This clinical success may be linked to medical therapy with dual-antiplatelet treatment in almost all the patients, statins in about 80%, and either beta-blockers or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in about 80% of patients. Several reports demonstrated a mortality reduction in patients with diabetes and CLI using an aggressive cardiovascular risk management policy (33,34). In addition, all patients with CLI with wounds followed a pre-specified clinical program focused on continuous monitoring of the foot healing process and vessel patency with a fast-track strategy for reintervention in case of need.

TABLE 5 Univariate and Multivariate Analysis for Predictors of 12-Month Restenosis

	Univariate			Multivariate		
	p Value	OR	95% CI	p Value	OR	95% CI
Sex	0.60	1.21	0.63–2.34			
CLI	0.40	0.82	0.45–1.64			
Diabetes	0.80	1.08	0.55–2.10			
Smoker	0.40	0.74	0.39–1.40			
Renal failure	0.20	1.44	0.74–2.81			
Dyslipidemia	0.50	0.98	0.52–1.84			
Hypertension	0.84	1.13	0.51–2.46			
CAD	0.54	0.96	0.48–1.95			
Stent	0.24	1.54	0.78–3.03			
Baseline occlusion	0.10	1.61	0.82–3.17	0.99	0.99	0.45–2.21
Severe calcification	0.39	1.38	0.71–2.65			
Concomitant BTK angioplasty	0.85	0.87	0.42–1.82			
Age	0.10	1.02	0.99–1.06	0.09	1.03	0.99–1.07
RVD	0.87	0.96	0.60–1.53			
Lesion length	0.001	1.006	1.002–1.009	0.006	1.006	1.002–1.010
MLD post-procedure	0.04	0.63	0.40–0.98	0.22	0.75	0.47–1.18
Stent	0.24	1.54	0.78–3.03			

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

STUDY LIMITATIONS. First, this was a single-center study, suffering from potential biases in patient referral pattern and interventional technique; other contemporary device trials in FP interventions, however, share the same limitation (19). Second, no external angiography or DUS core laboratory was available for adjudication of the endpoints. Third, a relatively small sample size accounted for significant imbalances in the baseline characteristics, with a higher prevalence of female sex in the DCB group. Although we cannot exclude an impact of female sex on the final results of the trial, it should be noted that a largely neutral result in a binary endpoint such as lesion restenosis is unlikely to be influenced by statistically significant, but clinically minor, difference in pre-randomization variable. Moreover, this variable did not predict restenosis in a multivariate logistic regression model, which, however, was overfitted because of a small number of events. Finally, clinical results achieved by an integrated multidisciplinary approach to CLI may not be reproduced with DCBs at other centers with different organization.

CONCLUSIONS

DCBs were not superior to DES in the treatment of complex FP lesions in a high-risk population,

yielding a similar rate of restenosis and CDTLR, which, however, appeared to be low. Longer follow-up will give better understanding of whether there is a difference in patency and clinical outcomes between the 2 different drug elution technologies. Larger trials should investigate whether drug-eluting device technologies used after optimal vessel preparation improve long-term clinical outcomes in patients with complex lesions in this arterial segment.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with complex FP artery atherosclerotic lesions and either claudication or CLI, 12-month patency rates of nearly 80% can be achieved with either DES or DCB devices with a similar rate of subsequent CDTLR.

TRANSLATIONAL OUTLOOK: Larger trials should investigate whether, in patients with long FP arterial lesions, optimal vessel preparation with atherectomy or lithoplasty prior to drug-eluting balloon or stent therapy improves long-term clinical outcomes.

REFERENCES

1. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333–41.

2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.

3. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: the European Stroke Organization (ESO) the Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763–816.

4. Bailey SR, Beckman JA, Dao TD, et al. ACC/AHA/SCAI/SIR/SVM 2018 appropriate use criteria for peripheral artery intervention: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. J Am Coll Cardiol 2019;73:214–37.

5. Chalmers N, Walker PT, Belli AM, et al. Randomized trial of the SMART stent versus balloon angioplasty in long superficial femoral artery lesions: the SUPER study. Cardiovasc Intervent Radiol 2013;36:353–61.

6. Granada JF, Stenoien M, Buszman PP, et al. Mechanisms of tissue uptake and retention of paclitaxel-coated balloons: impact on neointimal proliferation and healing. Open Heart 2014;1:e000117.

7. Reekers JA, de Vries CJ. A decade of drug-eluting technology in peripheral arterial disease: blurred by dissembling evidence. Cardiovasc Intervent Radiol 2016;39:1678–80.

8. Feldman DN, Armstrong EJ, Aronow HD, et al. SCAI consensus guidelines for device selection in femoral-popliteal arterial interventions. Catheter Cardiovasc Interv 2018;92:124–40.

9. Bausback Y, Wittig T, Schmidt A, et al. Drug-eluting stent versus drug-coated balloon revascularization in patients with femoropopliteal arterial disease. J Am Coll Cardiol 2019;73:667–79.

10. Iida O, Soga Y, Hirano K, et al. Long-term outcomes and risk stratification of patency following nitinol stenting in the femoropopliteal segment: retrospective multicenter analysis. J Endovasc Ther 2011;18:753–61.

11. Tosaka A, Soga Y, Iida O, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. J Am Coll Cardiol 2012;59:16–23.

12. Schlager O, Dick P, Sabeti S, et al. Long-segment SFA stenting—the dark sides: in-stent restenosis, clinical deterioration, and stent fractures. J Endovasc Ther 2005;12:676–84.

13. Virmani R, Liistro F, Stankovic G, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. Circulation 2002;106:2649–51.

14. Scheinert D, Scheinert S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol 2005;45:312–5.

15. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;1:113–9.

16. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv 2011;4:495–504.

17. Marmagkiolis K, Hakeem A, Choksi N, et al. 12-month primary patency rates of contemporary endovascular device therapy for femoro-popliteal occlusive disease in 6,024 patients: beyond balloon angioplasty. Catheter Cardiovasc Interv 2014;84:555–64.

18. Liistro F, Grotti S, Porto I, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). J Am Coll Cardiol Intv 2013;6:1295–302.

19. Micari A, Vadala G, Castriota F, et al. 1-Year results of paclitaxel-coated balloons for long femoropopliteal artery disease: evidence from the SFA-long study. J Am Coll Cardiol Intv 2016;9:950–6.

20. Scheinert D, Micari A, Brodmann M, et al. Drug-coated balloon treatment for femoropopliteal artery disease. Circ Cardiovasc Interv 2018;11:e005654.

21. Horie K, Tanaka A, Taguri M, Kato S, Inoue N. Impact of prolonged inflation times during plain balloon angioplasty on angiographic dissection in femoropopliteal lesions. J Endovasc Ther 2018;25:683–91.

22. Balakrishnan B, Dooley JF, Kopia G, Edelman ER. Intravascular drug release kinetics dictate arterial drug deposition, retention, and distribution. J Control Release 2007;123:100–8.

23. Gray WA, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. Lancet 2018;392:1541–51.

24. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214–22.

25. Cheng Y, Shibuya M, McGregor J, et al. Biological effect on restenosis and vascular healing of encapsulated paclitaxel nanocrystals delivered via coated balloon technology in the familial hypercholesterolaemic swine model of in-stent restenosis. EuroIntervention 2016;12:1164–73.

26. Clever YP, Peters D, Calisse J, et al. Novel sirolimus-coated balloon catheter: in vivo evaluation in a porcine coronary model. Circ Cardiovasc Interv 2016;9:e003543.

27. Lammer J, Bosiers M, Deloose K, et al. Bioresorbable Everolimus-Eluting Vascular Scaffold for Patients With Peripheral Artery Disease (ESPRIT I): 2-year clinical and imaging results. J Am Coll Cardiol Intv 2016;9:1178–87.

28. Nogic J, McCormick LM, Francis R, et al. Novel bioabsorbable polymer and polymer-free metallic drug-eluting stents. J Cardiol 2018;71:435–43.

29. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2018;7:e011245.

30. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol 2019 Feb 12 [E-pub ahead of print].

31. Bosiers M, Callaert J, Keirse K, et al. One-year outcomes of the paclitaxel-eluting, self-expanding Stentys stent system in the treatment of infrapopliteal lesions in patients with critical limb ischemia. J Endovasc Ther 2017;24:311–6.

32. Vardi M, Lei L, Shangguan S, Doros G. Variability in freedom from loss of primary patency results in trials assessing stent implantation in the superficial femoral artery. J Invasive Cardiol 2014;26:614–7.

33. Schanzer A, Hevelone N, Owens CD, Beckman JA, Belkin M, Conte MS. Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia. J Vasc Surg 2008;47:774–81.

34. McDermott MM, Mehta S, Ahn H, Greenland P. Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease. J Gen Intern Med 1997;12:209–15.

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