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PERIPHERAL

Drug-Coated Balloons for Complex Femoropopliteal Lesions

2-Year Results of a Real-World Registry

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ABSTRACT

OBJECTIVES The authors sought to investigate the efficacy of a drug-coated balloon (DCB) for treatment of complex femoropopliteal lesions.

BACKGROUND Superiority of DCBs compared with uncoated balloon angioplasty for femoropopliteal interventions has been demonstrated in randomized trials for short lesions. Their performance in complex lesions with higher restenosis rates is unclear.

METHODS Patency, target lesion revascularization (TLR) rate, clinical improvement, and safety endpoints of femoropopliteal lesions in 288 limbs (n = 260) treated with the In.Pact Pacific or Admiral DCB (Medtronic, Minneapolis, Minnesota) were retrospectively analyzed for up to 2 years of follow-up. Predictors of restenosis were identified by logistic regression.

RESULTS Lesions were de novo in 51.7%, restenosis in 11.1%, and in-stent restenosis in 37.2%. Mean lesion length was 24.0 ± 10.2 cm, and 65.3% were occluded. Stent implantation was performed in 23.3%. Kaplan Meier estimates of primary patency were 79.2% and 53.7% for all lesions at 1 and 2 years, respectively, whereas freedom from TLR was 85.4% and 68.6%. Primary patency for in-stent restenosis treatment was 76.6% and 48.6%, and freedom from TLR was 83.0% and 58.7% at 1 and 2 years, respectively. Rutherford category improved from a median 3.3 to 1.2 at 1 year, and to 1.1 at 2 years. Major amputation rate was 2.1% at 2 years. No adverse events were thought to be attributable to the coating of the balloon.

CONCLUSIONS These results suggest that DCB are safe and effective in delaying rather than preventing restenosis in long, complex lesions and restenosis of the femoropopliteal tract. Further studies are recommended to confirm these results. (J Am Coll Cardiol Intv 2016;9:715–24) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

CLI = critical limb ischemia

CTO = chronic total occlusion

DCB = drug-coated balloon(s)

ISR = in-stent restenosis

PA = popliteal artery

POBA = plain old balloon angioplasty

SFA = superficial femoral artery

TLR = target lesion revascularization

Interventional treatment of patients with complex atherosclerotic disease of the femoral and popliteal arteries has been limited by the high restenosis rate after angioplasty (1,2). Although nitinol stents have contributed to an overall improvement of treatment options in that vascular segment, patency results obtained in long lesions remain poor at 55% to 65% after 1 year (3,4). In addition, there have been significant concerns regarding the durability of long stented segments and the potential association of stent fractures and reocclusion (5).

Drug-coated balloons (DCB) provide a new therapeutic approach, and several randomized trials have shown superior results for DCBs compared with standard noncoated balloons after femoropopliteal artery treatment in terms of reduced late lumen loss, restenosis, and target lesion revascularization (TLR) rate (6–9). However, the mean lesion length in prior studies was comparatively short, between 4.0 and 8.9 cm (6–11), and there is little in the published literature on the performance of DCB in longer lesions (12). Furthermore, follow-up evaluation after DCB treatment is limited, with most studies appraising performance at 6 or 12 months, and only very few reports in smaller patient cohorts with follow-up longer than 1 year (10,11,13).

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The purpose of this study was to investigate whether DCB would improve patency for more complex femoropopliteal lesions and to assess the durability of results over an extended time, beyond 1 year.

METHODS

PATIENT POPULATION. A retrospective analysis was undertaken of patients undergoing treatment of complex femoropopliteal lesions (defined as de novo atherosclerotic lesions ≥10 cm or restenosis after previous endovascular treatment for de novo disease) using DCBs at a single tertiary vascular center between May 2009 and January 2012. No formal inclusion criteria were applied, but patients had to be treated for symptomatic peripheral arterial disease classified as Rutherford stage ≥1. The only exclusion criteria were nonatherosclerotic disease such as aneurysm, vasculitis, entrapment, and treatment of restenosis/reocclusion of surgical bypass. According to our institution's standard protocol, a medical history was obtained at admission, and all patients underwent physical examination with disease classification according to the Rutherford-Becker classification, measurement of ankle-brachial index (ABI), and color duplex ultrasound if not recently performed.

INTERVENTIONAL TECHNIQUE. All treatment decisions including the use of DCB or additional devices were at the operator's discretion. Patients were treated with either the In.Pact Pacific or In.Pact Admiral DCB (Medtronic, Minneapolis, Minnesota). The balloon is coated with FreePac, a proprietary formulation of 3.5-μg paclitaxel per mm^2 and urea, which serves as a hydrophilic spacer to facilitate separation and release of paclitaxel into the vessel wall.

Before the use of each DCB, pre-treatment with either an uncoated balloon or an atherectomy/thrombectomy device was performed, again at the discretion of the interventionist. The devices used were TurboHawk (Covidien/ev3, Plymouth, Minnesota), Rotarex catheter (Straub Medical AG, Wangs, Switzerland), or excimer laser (Spectranetics Corp., Colorado Springs, Colorado). The DCB diameter was chosen 1.0 mm larger than the uncoated balloon to guarantee contact with the arterial wall after predilation. Vessel diameter and lesion characteristics (such as lesion length, degree of stenosis, calcification, and additional inflow and outflow obstructions) were visually estimated. No quantitative angiographic program was utilized. Extent of calcification was also classified by inspection of the angiogram, with severe calcification defined as compromising both sides of the arterial lumen over a length of at least 5 cm. If more than 1 DCB was used per lesion, overlap of the 2 devices was at least 5 mm. Recommended inflation time was 3 min with 1 min at minimum. In case of flow-limiting dissection or residual stenosis >30%, a prolonged dilation up to 5 min was performed. Self-expanding nitinol stents were used as bailout in case of flow-limiting dissection or recoil. Inflow and outflow lesions were often treated during the same intervention as determined by the operator. Procedural success was defined as <30% residual stenosis in the final angiogram.

PHARMACOLOGICAL THERAPY. All patients were taking aspirin 100 mg daily. After sheath insertion, 5,000 IU of heparin were administered. Dual antiplatelet therapy with daily aspirin 100 mg and clopidogrel 75 mg was given for a minimum of 4 weeks and then converted to a single agent thereafter.

FOLLOW-UP PROTOCOL AND STUDY ENDPOINTS. Before discharge, all patients underwent clinical examination, ABI measurement, and duplex ultrasound to determine interventional success. The same information was captured at each follow-up visit, which was routinely performed at 6, 12, and 24 months after the intervention according to our

institutional standards. In patients who did not return for follow-up, their status was confirmed after 1 and 2 years by telephone contact.

The primary endpoint was vessel patency, defined as freedom from >50% restenosis as determined by either duplex ultrasound (peak systolic velocity ratio <2.4) or digital subtraction angiography, and freedom from TLR.

Secondary endpoints were freedom from TLR, Rutherford class, ABI, and safety endpoints, including amputation rate and death. Any adverse events potentially related to the use of DCBs were captured.

Physicians performing the interventions and the duplex scans were not blinded to the treatment strategy.

This retrospective cohort study was performed without financial support of the industry. The registry was performed in line with the requirements of the local ethics committee, and all patients gave their written informed consent before the procedure.

STATISTICAL ANALYSIS. Descriptive statistics were used to present continuous data as mean ± SD or median (range) as appropriate. Categorical variables were expressed as numbers and percentages. Group comparisons were performed either by the Student *t* test, analysis of variance or chi-square test as appropriate.

Patency rates, freedom from TLR, and patient survival were described using Kaplan-Meier analyses, and the log-rank test was used to compare survival curves between groups.

The influence of clinical, angiographic, and procedural variables on restenosis after 2 years was evaluated by univariate and stepwise logistic regression analyses. All variables with a p value ≤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 statistically significant. Data were analyzed with SPSS version 20 (SPSS, Chicago, Illinois) for Windows.

RESULTS

PATIENT CHARACTERISTICS. Overall, 260 patients were eligible for this analysis, in whom femoropopliteal lesions in 288 limbs were treated. Demographic characteristics are given in Table 1. Mean age was 68 ± 10.8 years, and 63.2% of the study population was male. The majority of patients had hypertension (96.2%) and hyperlipidemia (72.2%), and almost one-half were diabetic (46.2%).

The mean pre-interventional ABI was 0.56 ± 0.22 and mean Rutherford grade was 3.3 ± 1.0. Approximately one-quarter of the patients (26.4%) were treated for critical limb ischemia (CLI) comprising Rutherford stages 4 to 6.

TABLE 1 Demographic Characteristics (N = 260)

Mean age, yrs	68.2 ± 10.8
Male	63.2
Arterial hypertension	96.2
Diabetes mellitus	46.2
Prior/current smoking	60.4
Hypercholesterolemia	72.2
Obesity	34.7
Coronary artery disease	33.3
Renal insufficiency (GFR < 60 ml/min/1.73 m^2)	19.5
Cerebrovascular disease	14.2
Rutherford-Becker classification	
Category 1	1.7
Category 2	3.8
Category 3	68.1
Category 4	11.5
Category 5	9.7
Category 6	5.2

Values are mean ± SD or %. Obesity was defined as a body mass index >30. GFR was calculated by the MDRD (Modification of Diet in Renal Disease) formula.
GFR = glomerular filtration rate.

LESION CHARACTERISTICS AND PROCEDURAL OUTCOMES. Of the 288 lesions treated, approximately two-thirds (63.5%) were found within the superficial femoral artery (SFA) only, 9% were restricted to the popliteal artery (PA), and 26% involved both

TABLE 2 Lesion Characteristics

	Entire Cohort (N = 288)	SFA Only (n = 183)	Popliteal Involvement (n = 105)	p Value*
De novo lesions	149 (51.7)	103 (56.3)	46 (43.8)	0.05
Restenosis	32 (11.1)	19 (10.4)	13 (12.4)	NS
ISR	107 (37.2)	61 (33.3)	46 (43.8)	0.09
Lesion length, cm	24.0 ± 10.1	23.7 ± 8.6	24.6 ± 12.6	NS
Total occlusion	188 (65.3)	110 (60.1)	78 (74.3)	0.02
TASC B	36 (12.5)	20 (10,9)	16 (15,2)	NS
TASC C	62 (21.5)	35 (19.1)	27 (25.7)	NS
TASC D	190 (66.0)	128 (69.9)	62 (59)	0.06
Lesion calcification				
None	91 (32.6)	58 (32.7)	33 (31.4)	NS
Mild	97 (34.3)	71 (38.8)	26 (24.8)	0.014
Moderate	59 (20.5)	33 (18.0)	26 (24.8)	NS
Severe	41 (14.2)	21 (11.5)	20 (19.0)	NS
BTK outflow				
3-Vessel	119 (41.3)	96 (52.5)	23 (21.9)	<0.0005
2-Vessel	78 (27.1)	47 (25.7)	31 (29.5)	NS
1-Vessel	77 (26.7)	37 (20.2)	40 (38.1)	0.001
None	14 (4.9)	3 (1.6)	11 (10.5)	0.001
Outflow PTA	59 (20.5)	14 (7.7)	45 (42.9)	<0.0005

Values are n (%) or mean ± SD. *Comparison between SFA only and popliteal involvement.
BTK = below-the-knee; ISR = in-stent-restenosis; PTA = percutaneous transluminal angioplasty; SFA = superficial femoral artery; TASC = Trans-Atlantic Inter-Society Consensus.

segments. Lesion characteristics stratified according to their location are given in Table 2. More than one-half of interventions were performed in de novo (51.7%) lesions, 37.2% of patients were treated for in-stent restenosis (ISR), and 11.1%, for re-stenosis without prior stent placement. Mean lesion length was 24.0 ± 10.2 cm, and 65.3% were chronic total occlusions (CTO). Two-thirds of the treated lesions were classified as TASC (Trans-Atlantic Inter-Society Consensus) D, and one-third exhibited moderate-to-severe calcification.

All lesions were crossed successfully. In stenotic lesions, crossing was always considered to be intraluminal (100 of 288 limbs; 34.7%). In CTOs, recanalizations were classified as subintimal (n = 78, 27.1%) in case a re-entry device (n = 5) was used or a retrograde wire crossing approach was necessary (n = 38), or when re-entry of the distal true lumen was difficult to achieve (n = 35). All other interventions of CTOs were classified as indeterminate with regard to intraluminal or subintimal passage (n = 110, 38.2%).

Atherectomy/thrombectomy devices were used in 83 of 288 limbs (28.8%), which included the Turbo-Hawk device (5.6%), Rotarex (19.8%), and excimer laser (3.5%). Cutting or scoring balloons were used in 18 of 288 lesions (6.3%) for lesion preparation.

Mean DCB diameter was 5.06 ± 0.66 mm. Diameters were larger for males (5.12 ± 0.62 mm) than for female patients (4.96 ± 0.68 mm; p = 0.04). On average, 3 DCBs were used per lesion (range 1 to 6).

After DCB treatment, most lesions had no dissection (14.2%) or grades A to C (65.3%), whereas grade D to F dissections were observed in 20.5%. Stent implantation was performed in 23.3% to treat either dissection (10.4%) or recoil (12.9%). Focal stenting (74.7%) was preferred over full-lesion coverage (25.3%). The mean length of stented vessel segment was 15.2 ± 10.2 cm. The use of stents increased with the severity of calcification (severe: 36.6%; moderate: 33.9%, mild: 22%, none: 11.1%). Comparing heavily calcified with all other lesions, a statistically higher stenting rate was observed (36.6% vs. 21.2%, p = 0.004).

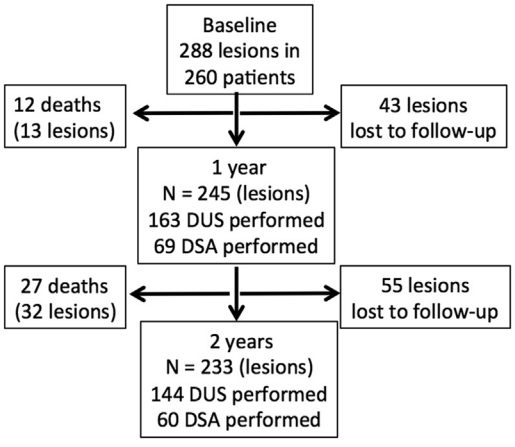
Residual stenosis >30% in the final angiogram was present in 40 cases (13.9%). Inflow lesions were treated in 27 (9.4%) cases, and infrapopliteal outflow lesions in 59 (20.5%).

Periprocedural complications occurred in 14 patients (5.4%) before discharge. They included 7 pseudoaneurysms/local access site bleeding (4 required surgery, 3 were treated by manual compression), 1 arteriovenous fistula with conservative treatment, 2 peripheral embolizations treated successfully with thrombolysis, 2 perforations after the use of a Rotarex catheter, which were successfully controlled with the use of a covered stent, and 1 acute stent thrombosis treated with Rotarex thrombectomy. The mean post-interventional ABI increased to 0.89 ± 0.16.

CLINICAL FOLLOW-UP AND PATENCY RATES. Cumulative mortality rate was 4.6% (12 of 260) at 1 year and 10.4% (27 of 260) at 2 years. Within 30 days of the index intervention, only 1 death occurred, which was due to multiorgan failure in a patient treated for Rutherford class 6 CLI. Another patient died due to septic shock related to wounds of the untreated contralateral limb 82 days after the initial treatment. Other deaths occurred more than 3 months after treatment due to non-intervention-related causes such as cardiac disease, mesenteric ischemia, renal insufficiency, or post-operative complications following orthopedic surgery. Figure 1 exhibits a flow diagram of the number of patients and lesions over the study period.

Clinical improvement of at least 1 Rutherford category was seen in 73.3% of limbs after 1 year and 66.4% after 2 years, no change in 18.6% and 19.6%, and deterioration in 8.1% and 13.1%, respectively. Of the 26.4% of patients treated for CLI, more than two-thirds (69.0%) showed a clinical improvement to Rutherford category 0 to 3 at 1 year and 85.7% at 2 years. Only 11 patients (3.8%) treated for claudication progressed to CLI over the full observation period. Cumulative major amputation rate at 1 and 2 years was very low at 1.4% (4 of 288) and 2.1% (6 of 288), respectively. All major amputations occurred in

FIGURE 1 Trial Flow Diagram



DAS = digital subtraction angiography; DUS = duplex ultrasound.

CLI patients, and 1 amputation was pre-determined before treatment. In the CLI group only, the amputation rate was 5.3% at 1 year and 7.9% at 2 years.

The mean ABI improved from 0.56 ± 0.22 to 0.88 ± 0.16 (1 year) and to 0.80 ± 0.24 (2 years).

Patency rates were indeterminable for 56 of 288 (19.4%) treated limbs at 1 year and 75 of 288 (26.0%) treated limbs at 2 years due to loss from follow-up. Similarly, TLR was indeterminable for 43 of 288 (14.9%) treated limbs at 1 year and 55 of 288 (19.1%) treated limbs at 2 years.

Kaplan-Meier estimates of primary patency were 79.2 ± 2.6% at 1 year and 53.7 ± 3.4% at 2 years for the entire cohort. When stratified according to anatomic location, lesions in the SFA-only had a patency rate of 84.2 ± 2.9% and 57.1 ± 4.1% at 1 and 2 years, in the PA 79.2 ± 8.3% and 58.4 ± 11.0%, and SFA lesions extending into the PA 65.9 ± 6.2% and 42.5 ± 6.8%, respectively (SFA vs. PA: p = NS; SFA vs. SFA + PA: p = 0.002). In those patients with repeated angiography and restenosis (n = 115), the length of restenosis was significantly shorter than the baseline lesion length (14.4 ± 12.3 cm compared with 24.0 ± 10.2 cm; p < 0.0005).

Freedom from TLR was 85.4 ± 2.1% for the entire cohort at 1 year and 68.6 ± 3.0% at 2 years. Kaplan-Meier curves of primary patency and TLR rates are shown in Figures 2 and 3. All patients undergoing reintervention exhibited clinical symptoms, and TLRs were considered clinically driven.

Primary patency and TLR rates at 1 and 2 years according to clinical and lesion characteristics are given in Table 3. Significant differences of survival curves for primary patency were found in several subgroups, including male versus female, diabetic versus nondiabetic, smokers versus nonsmokers, lesions with heavy calcification versus non/mild/moderate calcification, lesion location (SFA only vs. popliteal involvement), and ISR versus in-stent reocclusion. De novo and nonstented restenosis showed a trend toward better patency versus ISR (Figure 4).

Significant differences of survival curves for TLR were found in male versus female and de novo/nonstented restenosis versus ISR lesions.

To identify independent predictors of restenosis after 2 years, stepwise logistic regression was performed including all factors associated with significant differences in patency rates and factors that are thought to be associated with a higher restenosis rate (female sex, lesion length ≥24 cm, ISR, involvement of the PA, severe calcification, TASC C and D lesions, percutaneous transluminal angioplasty without prior atherectomy/thrombectomy, residual stenosis ≥30%, diabetes mellitus, smoking, obesity, and chronic renal insufficiency) (Table 3). Male sex was associated with a >50% risk reduction for restenosis after 2 years (Figure 5). Furthermore, the presence of severe calcification and obesity were independent

FIGURE 2 Patency Rates of the Whole Cohort

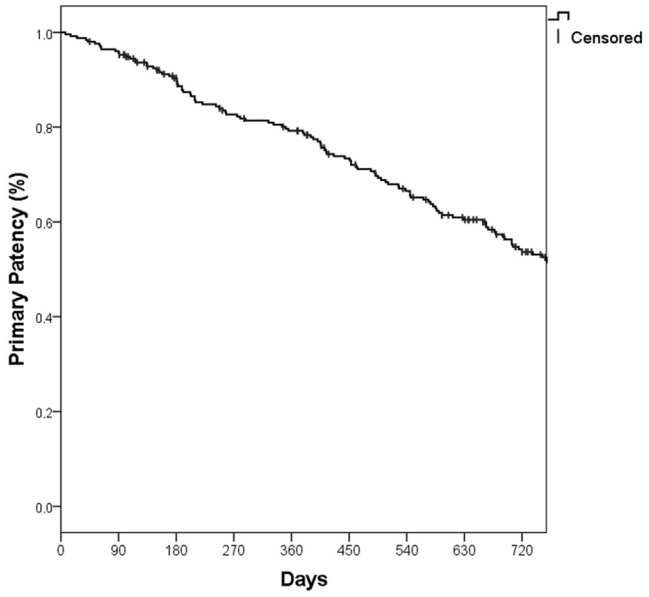
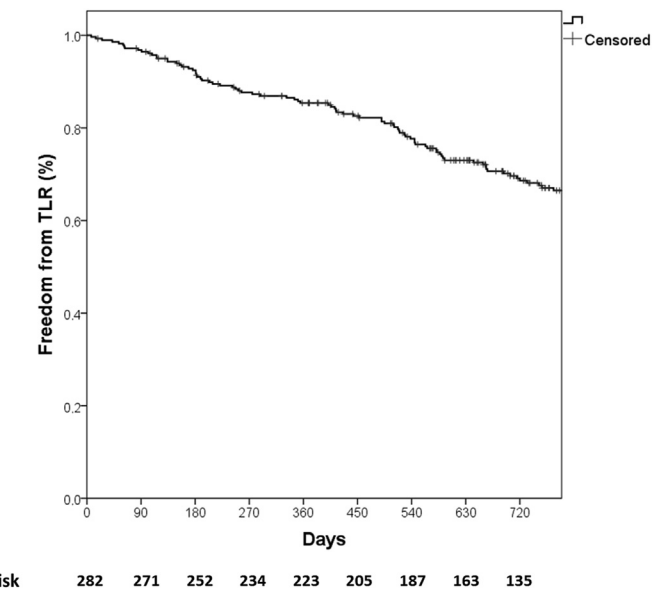


FIGURE 3 TLR Rates of the Whole Cohort



TLR = target lesion revascularization.

TABLE 3 Kaplan-Meier Estimates for Primary Patency and Freedom From TLR According to Subgroups

		Primary Patency			Freedom From TLR		
	N	1 Year	2 Years	p Value*	1 Year	2 Years	p Value*
Female	96	71.6 ± 4.8	39.8 ± 5.6	0.002	79.9 ± 4.0	55.6 ± 5.5	0.001
Male	164	83.6 ± 3.0	61.7 ± 4.1		88.5 ± 2.4	75.6 ± 3.4	
Diabetes	120	71.6 ± 4.4	45.3 ± 5.1	0.027	79.1 ± 3.6	64.3 ± 4.6	NS
No diabetes	140	85.2 ± 3.1	60.1 ± 4.4		90.6 ± 2.4	72.4 ± 3.9	
Nonsmoker	103	72.3 ± 4.6	43.2 ± 5.4	0.027	80.5 ± 3.8	59.4 ± 5.1	NS
Smoker	157	83.6 ± 3.1	60.3 ± 4.3		88.5 ± 2.5	74.6 ± 3.6	
GFR >60 ml/min	209	81.2 ± 2.8	56.8 ± 3.7	0.056	87.0 ± 2.3	70.8 ± 3.2	NS
GFR <60 ml/min	51	70.3 ± 6.9	39.4 ± 7.8		78.3 ± 5.8	59.0 ± 7.4	
Length <240 mm	141	79.7 ± 3.6	54.3 ± 4.8	NS	83.8 ± 3.3	66.3 ± 4.2	NS
Length >240 mm	147	78.6 ± 3.8	52.9 ± 4.8		86.9 ± 2.9	70.9 ± 4.2	
Heavy calcification	41	60.3 ± 8.6	36.3 ± 8.8	0.023	74.6 ± 7.0	60.7 ± 8.5	0.077
Non/mild/moderate calcification	247	82.2 ± 2.7	56.4 ± 3.6		87.1 ± 2.2	69.8 ± 3.2	
Stenosis	100	81.0 ± 4.3	52.6 ± 5.6	NS	86.3 ± 3.5	63.4 ± 5.1	NS
CTO	188	78.3 ± 3.3	54.3 ± 4.2		84.9 ± 2.7	71.8 ± 3.6	
SFA only	183	84.2 ± 2.9	57.1 ± 4.1	0.015	89.2 ± 2.3	71.6 ± 3.6	NS
Popliteal and SFA extending into popliteal	105	69.6 ± 5.1	47.0 ± 5.8		78.4 ± 4.2	63.6 ± 5.2	
De novo and native restenosis	181	80.9 ± 3.3	57.0 ± 4.4	NS	86.7 ± 2.6	74.6 ± 3.5	0.031
In-stent restenosis	107	76.6 ± 4.4	48.6 ± 5.4		83.0 ± 3.8	58.7 ± 5.1	
In-stent restenosis	54	88.1 ± 4.6	54.0 ± 7.3	0.041	92.3 ± 3.7	61.4 ± 7.0	NS
In-stent reocclusion	53	63.3 ± 7.4	42.3 ± 7.8		73.0 ± 6.4	56.1 ± 7.5	
Intraluminal PTA	100	76.8 ± 3.5	54.4 ± 4.2	NS	83.7 ± 2.8	65.6 ± 3.8	NS
Subintimal PTA	78	79.9 ± 5.0	50.4 ± 6.5		86.5 ± 4.0	72.9 ± 5.6	
Atherectomy	83	85.3 ± 4.3	64.0 ± 6.1	NS	89.9 ± 3.4	67.7 ± 5.6	NS
No atherectomy	205	76.8 ± 3.2	49.6 ± 4.0		83.6 ± 2.7	69.0 ± 3.5	
Cutting balloon	18	80.7 ± 10.1	58.8 ± 13.2	NS	82.6 ± 9.1	73.5 ± 11.9	NS
No cutting balloon	270	79.0 ± 2.7	53.2 ± 3.5		85.6 ± 2.2	68.2 ± 3.1	
No dissection and A-C dissections	229	78.4 ± 3.3	53.4 ± 4.2	NS	84.6 ± 2.8	66.3 ± 3.8	NS
D-F dissections	59	80.6 ± 4.2	54.2 ± 5.6		86.6 ± 3.3	71.3 ± 4.8	
No additional stent	67	80.8 ± 3.0	53.0 ± 3.9	NS	84.1 ± 2.5	65.8 ± 3.5	NS
Additional stent	221	76.7 ± 5.7	56.0 ± 7.0		89.4 ± 3.8	78.0 ± 5.5	
Residual stenosis <30%	248	80.8 ± 3.0	53.0 ± 3.9	NS	86.7 ± 2.2	70.3 ± 3.2	0.013
Residual stenosis >30%	40	76.7 ± 5.7	56.0 ± 7.0		75.9 ± 7.0	55.4 ± 8.9	
Outflow PTA	59	73.0 ± 6.4	55.9 ± 7.5	NS	81.8 ± 5.2	71.2 ± 6.3	NS
No outflow PTA	229	80.8 ± 2.8	53.1 ± 3.8		86.3 ± 2.3	68.0 ± 3.4	
Obesity	100	67.1 ± 4.7	41.6 ± 5.7	0.016	83.1 ± 3.9	57.3 ± 5.4	0.017
Non-obesity	188	80.8 ± 3.2	60.3 ± 4.1		86.6 ± 2.5	63.9 ± 3.5	

Values are Kaplan-Meier estimates ± SE. *Log-rank test.
TLR = target lesion revascularization; other abbreviations as in Table 2.

predictors of restenosis 2 years after DCB treatment (Table 4).

DISCUSSION

Recent studies demonstrating the superiority of DCBs compared with standard angioplasty (plain old balloon angioplasty [POBA]) in the femoropopliteal tract were largely performed in relatively short lesions with a low proportion of CTOs (6–11). By contrast, this large registry represents a real-world experience of long lesions with a high proportion of complete occlusions, and our favorable results underline the efficacy of DCB to treat complex femoropopliteal disease. Our 1-year primary patency rate of 78.2% in femoropopliteal lesions with a mean lesion length of 24 cm is promising when compared with similar lesions treated with POBA, which range between 22% and 34% in the contemporary literature (1,2). Furthermore, our data confirm results of a smaller study using the same DCB for treatment of 131 femoropopliteal lesions with a mean length of 19.4 cm and a CTO rate of 52.7% (12).

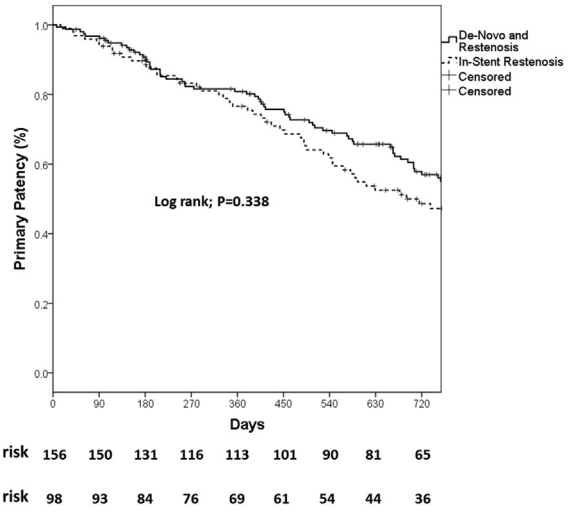
Another challenge is the treatment of in-stent restenosis because disappointing patency rates as low as 27% have been documented 6 months after conventional balloon angioplasty for ISR (14–16). Early results using the In.Pact DCB in 39

femoropopliteal ISR lesions with a mean lesion length of 83 mm were favorable, with a 12-month primary patency rate of 92% (17). Our patency of 76.6% at 1 year is equally promising, considering the longer lesion length, but less favorable patency rates were seen for in-stent occlusions when compared with ISR. Other authors have not observed this difference, which may be related to their smaller sample size (17). Further, we witnessed a late drop off of primary patency to 48.6% at 2 years, which differs from a prior study that evaluated shorter lesions in a smaller cohort (18). Alternative stenting methods using drug-eluting (19) or covered (20) stents showed favorable results for ISR, but the long-term consequences of the altered vessel compliance that inevitably arise with multiple layers of stents in long arterial segments are unclear. Thus, DCBs seem to be a promising alternative for ISR treatment.

Our larger sample size provides an opportunity to study risk factors potentially related to patency after DCB treatment. Patency rates were similar for stenotic and occluded lesions as well as after intraluminal versus subintimal recanalization. Similar findings have been observed by other authors in smaller cohorts (10).

When comparing Kaplan-Meier estimates by log-rank test, several patient and lesion characteristics were associated with reduced patency rates, including diabetes, obesity, heavy calcification, treatment of the popliteal segment, and female sex. Smokers had less restenosis, a phenomenon that has been previously observed after femoropopliteal interventions (21). After adjustment for confounders, female sex, obesity, and severe calcification remained the only independent predictors of restenosis. Similar findings were reported in the PACIFIER (Paclitaxel-Coated Balloons in Femoral Indication to Defeat Restenosis) trial showing less efficacy of DCBs in female patients (8). A potential explanation may be the smaller diameter of female arteries, which is well recognized and supported by the fact that smaller DCB diameters were used in women compared with men (4.96 vs. 5.12 mm; $p = 0.04$). Similarly, after percutaneous coronary interventions, an association between obesity and repeated revascularization has been described (22). This might be mediated by the higher prevalence of cardiovascular risk factors, including insulin resistance, diabetes, and hyperlipidemia, as well as the fact that obesity itself can be considered a chronic low-grade inflammatory state with a higher risk of restenosis. Severe calcification has been postulated before to reduce the anti-restenostic effect of DCB in the femoropopliteal segment (23), which was corroborated in our study.

FIGURE 4 Patency Rates of De Novo and Restenosis Lesions vs. ISR Lesions



ISR = in-stent restenosis.

Calcification may interfere with the transfer and deposition of the active paclitaxel excipient molecular reservoirs, which are necessary to suppress restenosis. As an alternative explanation, the higher risk of recoil and residual stenosis after treatment of such rigid and recalcitrant lesions may be associated with the observed worse outcome. A "leave nothing behind" strategy lacking the mechanical stent scaffold may result in a high percentage of residual

FIGURE 5 Patency Rates of Male vs. Female Patients

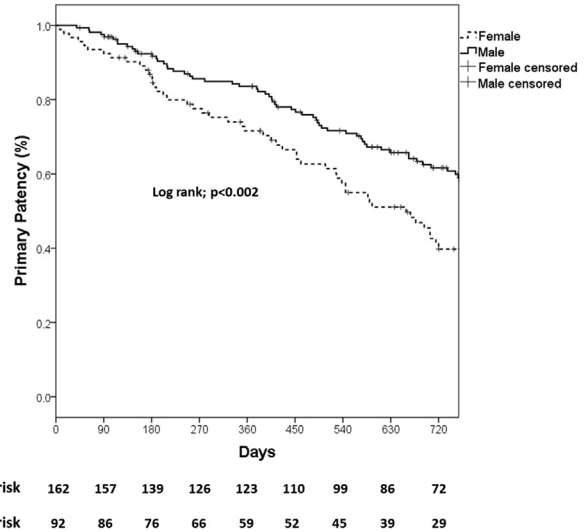


TABLE 4 Binary Logistic Regression Analysis of Predictors for Restenosis

	Coefficient	OR	95% CI	p Value
Male	−0.711	0.491	0.288–0.839	0.009
Severe calcification	0.765	2.150	1.018–4.540	0.045
Obesity	0.602	1.825	1.069–3.116	0.028

CI = confidence interval; OR = odds ratio.

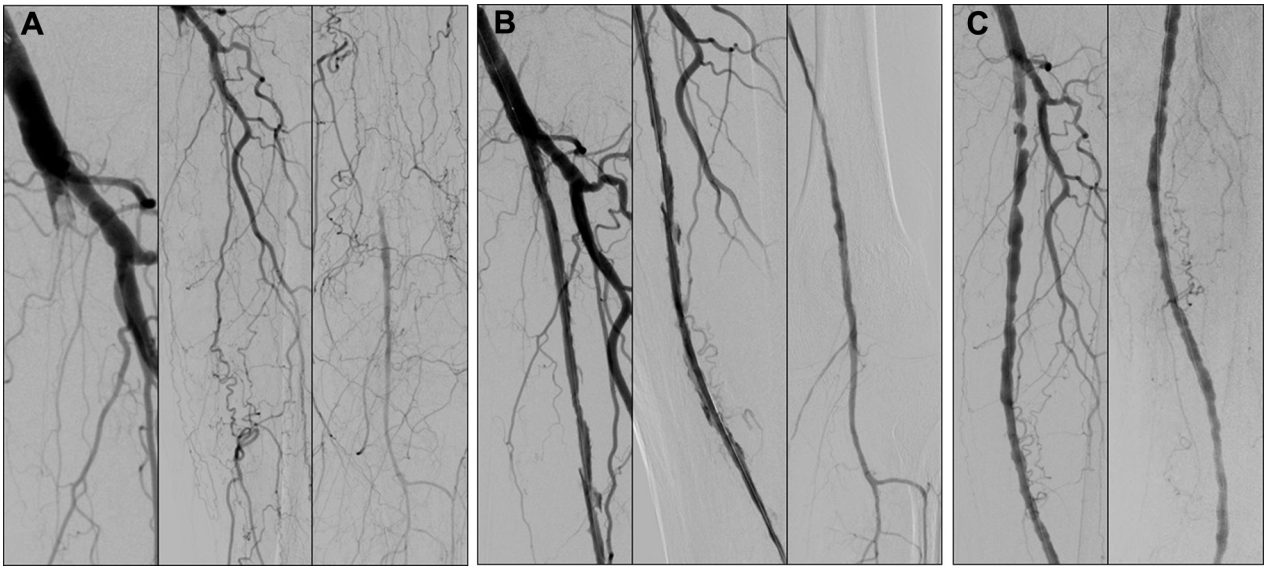
stenosis leading to early clinical failure and subsequent revascularization. Compared with other DCB trials in the field with stent rates between 2.5% and 12% (7-10), our bailout stenting rate of 23.3% is higher but may rather reflect the complexity of the treated lesions. Although the observed stenting rate was highest for severely calcified lesions (36.6%), the smaller patency rate in case of heavy calcification may indicate that an even more liberal use of stents might be necessary in these situations.

Only a few DCB studies have published results beyond 1 year of follow-up. Micari et al. (10) reported a patency-rate of 83.7% and 72.4% at 1 and 2 years, respectively, for native femoropopliteal lesions with a relatively short lesion length of 7.6 cm. Our results for longer, more complex lesions seem to differ, with a drop of patency from 79.2% at 1 year to 53.7% at 2 years. This may reveal a late catch-up phenomenon but may be still superior to POBA for similar lesions.

So far, no randomized, controlled trials have compared DCBs with stents in long, complex femoropopliteal lesions, and valid competitors would be with the latest generation of stents with innovative designs or drug coatings (24,25). These devices appear suitable to treat complex, calcified lesions, but the permanent metallic implant also comes with disadvantages. Reintervention for ISR is associated with both reduced technical success and patency rates, whereas reintervention after DCB treatment is comparatively simple and leaves the door open to a wider range of endovascular options for further treatment. In turn, this may translate into a potentially superior effect on long-term secondary patency. In our patients undergoing repeat angiography, we also observed that restenosis after DCB typically exhibited shorter and more focal lesions (**Figure 6**), simplifying retreatment.

SAFETY. Adverse events attributable to the coating of balloons with paclitaxel have been rarely described (26). We observed 3 cases of uncomplicated local blood vessel wall ectasia following the use of DCB during angiographic follow-up during this study. There have been no adverse events associated

FIGURE 6 Treatment of a Long Femoropopliteal Occlusion of the Leg Limb With In.Pact Drug-Coated Balloons



(A) Long femoropopliteal occlusion of the left leg. **(B)** After treatment with 4 × 5.0/120 mm In.Pact drug-coated balloons. **(C)** Short, focal restenosis 25 months after initial treatment.

with this phenomenon; however, these 3 patients remain under observation.

STUDY LIMITATIONS. This study is a retrospective, single-center analysis that has certain limitations by its very nature. A number of patients did not attend scheduled clinical and duplex follow-up, and were thus temporarily lost until symptoms recurred. This may favorably bias the patency estimate of the Kaplan-Meier curves. Furthermore, several ultrasound studies were not performed at our center, and we were unable to oversee and ensure their quality. Finally, we did not receive TLR information in 14.9% and patency data in 19.4% at 1 year. Dropout is commonly observed in retrospective studies such as ours, and to some extent, seen in prospective studies as well (9). We cannot provide information on patency rates of other femoropopliteal interventions that have been performed during this time interval for comparison with DCB treatment. Because a single DCB technology has been used within this study, it is not possible to extrapolate our results to other DCBs used in clinical practice.

CONCLUSIONS

The treatment of long and complex femoropopliteal lesions with DCB is associated with impressive patency results comparing favorably to historical, uncoated balloon angioplasty at 1 year. However, patency rates drop off significantly after the first year, which may represent a late catch-up phenomenon. Further randomized trials are required to determine a definitive comparison between DCB and modern, stent-based treatment modalities.

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PERSPECTIVES

WHAT IS KNOWN? Superiority of DCB compared with standard angioplasty for femoropopliteal interventions has been demonstrated for short lesions after 1-year follow-up. Long-term data for complex lesions are scarce.

WHAT IS NEW? Our results suggest that DCB are safe and effective in delaying rather than preventing restenosis in long, complex lesions and restenosis of the femoropopliteal tract.

WHAT IS NEXT? Future trials should focus on DCB and modern, stent-based treatment modalities over longer follow-up periods.

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