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NEW RESEARCH PAPER

PERIPHERAL

5-Year Outcomes of Drug-Coated Balloons for Peripheral Artery In-Stent Restenosis, Long Lesions, and CTOs

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ABSTRACT

BACKGROUND Long-term data on drug-coated balloon (DCB) outcomes in complex femoropopliteal atherosclerotic lesions are limited.

OBJECTIVES The authors sought to report 5-year safety and effectiveness outcomes of a paclitaxel DCB for the treatment of de novo in-stent restenosis (ISR), long lesions (LL), or chronic total occlusions (CTOs) in the prespecified imaging cohorts of the IN.PACT Global Study.

METHODS The IN.PACT Global study was a prospective, international single-arm study. Assessments through 5 years included freedom from clinically driven target lesion revascularization (CD-TLR), a safety composite (freedom from device- and procedure-related death to 30 days, and freedom from major target limb amputation and freedom from clinically driven target vessel revascularization within 60 months), and major adverse events.

RESULTS The prespecified imaging cohorts enrolled 132 de novo ISR, 158 LL, and 127 CTO participants. Kaplan-Meier estimates of freedom from CD-TLR through 5 years were 58.0% (ISR), 67.3% (LL), and 69.8% (CTO). The cumulative incidences of the composite safety endpoint were 56.0% (ISR), 65.7% (LL), and 69.8% (CTO). The 5-year freedom from all-cause mortality with vital status update were 81.4% (ISR), 75.2% (LL), and 78.2% (CTO). Within the ISR cohort, 15.9% of participants experienced 2 or more TLRs, compared with 9.5% and 5.5% in the LL and CTO groups, respectively.

CONCLUSIONS Results demonstrate long-term safety and effectiveness of this DCB in all 3 cohorts, with low reintervention rates in the LL and CTO cohorts and no safety issues. These results support the inclusion of this DCB into the treatment algorithm for complex femoropopliteal disease. (J Am Coll Cardiol Intv 2023;16:1065–1078) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CD-TLR = clinically driven target lesion revascularization

CTO = chronic total occlusion

DCB = drug-coated balloon(s)

DES = drug-eluting stent(s)

ISR = in-stent restenosis

LL = long lesion

PTA = percutaneous transluminal angioplasty

TLR = target lesion revascularization

TVR = target vessel revascularization

Adoption of drug-coated balloons (DCB) in the United States has been rapid since their approval nearly a decade ago. Numerous randomized trials[1-5] have demonstrated the superiority of DCB over uncoated percutaneous transluminal angioplasty (PTA) balloons for the treatment of femoropopliteal disease. However, randomized trials often exclude more complex lesions such as in-stent restenosis (ISR), lesions longer than 15 cm, and chronic total occlusions (CTOs). This has resulted in a paucity of data available on the efficacy of DCBs in these patients, especially long-term data. The IN.PACT Global Study had broad selection criteria allowing for inclusion of these complex lesions. Participants with de novo ISR, long lesions (LL) ≥15 cm, and CTO ≥5 cm were prospectively enrolled into an imaging cohort with duplex ultrasound assessment of patency at 1 year[6-9] and follow-up through 5 years.[10]

Previously published 12-month primary patency rates were 88.7% in the ISR cohort,[6] 91.1% in the LL cohort,[7] and 85.3% in the CTO cohort.[8] Although these early outcomes were promising, there is a lack of long-term data on DCB use in these distinct and challenging populations. This is the first publication of prospectively collected 5-year data from prespecified ISR, LL and CTO cohorts of a large global DCB study.

METHODS

The IN.PACT Global Study (NCT01609296) was a prospective, multicenter, international single-arm clinical study.[9,11] All participants received DCB angioplasty (IN.PACT Admiral, Medtronic) during the index procedure. The IN.PACT Global Study design included 3 prespecified cohorts: a clinical cohort, an imaging cohort, and a 150-mm DCB cohort. The imaging cohort comprised 3 cohorts where all treated lesions were: 1) de novo ISR; 2) lesions ≥15 cm; or 3) CTOs (occlusion length ≥5 cm), respectively. This paper describes the results of the prespecified imaging cohort. Long-term results of the full clinical cohort and the 150-mm DCB cohort have been previously published.[11,12]

Key inclusion criteria for the clinical cohort included intermittent claudication and/or rest pain (Rutherford clinical category 2-4), and angiographic evidence of an occlusion or stenosis in the superficial femoral artery and/or popliteal artery (segments P1-P3). Patients who qualified for clinical cohort enrollment were then screened for eligibility in the imaging cohort. Only participants in whom all target lesions met the criteria of the respective cohort during the index procedure were enrolled in the imaging cohort. Each participant could only be enrolled into 1 of the imaging cohorts. In cases where participants had a lesion that met criteria for multiple imaging cohorts, participants were selected into the de novo ISR cohort first, then the LL cohort, and lastly, the CTO cohort. Only eligible sites that were certified by the duplex ultrasound core laboratory were permitted to enroll participants in the imaging cohorts.

Dual antiplatelet therapy was required for 1 month (3 months for stented participants) along with aspirin indefinitely, consistent with standard clinical practice. Participants were followed at discharge, 30 days, 6 months, 12 months, and then annually through 5 years post-index procedure. Follow-up evaluations were conducted via clinical visit through 3 years and by telephone at years 4 and 5. Sites were asked to obtain vital status from participants who withdrew or were lost to follow-up to improve the ascertainment of mortality data.

The primary endpoint of the imaging cohort was primary patency at 12 months. Secondary endpoints included freedom from clinically driven target lesion revascularization (CD-TLR) through 5 years and a composite safety endpoint defined as freedom from device- and procedure-related death through 30 days and freedom from major target limb amputation and clinically driven target vessel revascularization (CD-TVR) through 5 years. Clinically driven target lesion revascularization (TLR)/TVR were defined as any reintervention within the target lesion(s)/vessel(s) due to symptoms or drop of ankle-brachial index of ≥20% or >0.15 when compared with post-index procedure baseline ankle-brachial index.

Independent core laboratories analyzed all images including duplex ultrasound (VasCore, Massachusetts General Hospital) and angiography (SynvaCor Angiographic Core Lab). An independent clinical events committee (Syntactx) assessed the primary and select secondary endpoints to determine whether each met protocol-specified criteria. The study protocol was approved by the institutional review board or ethics committee at each site. Informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws as specified by all relevant governmental bodies.

STATISTICS. Data were summarized using mean ± SD for continuous variables and frequencies and percentages for categorical variables. Time-to-event

outcomes are summarized by the survival estimate or cumulative incidence estimate using the Kaplan-Meier method. The 95% CI were derived for time-to-event outcomes using the log-log transformation. Outcomes are also summarized using the restricted mean survival time with a time horizon of 1,800 days and 95% CI. Baseline demographics, clinical characteristics, and outcomes are reported or analyzed on a participant basis and lesion characteristics are reported on a lesion basis. Data were analyzed per the definition of the cohorts in the protocol, a participant was considered part of the analysis if the study DCB was introduced into the sheath and after the guidewire had successfully passed through the target lesion and all lesions treated met the requirements of the respective imaging cohort. Annual cutoffs for the statistical analysis used 360 days per year (eg, 1,800 days for the 5-year cutoff) and 30 days per month. Univariable Cox proportional hazards models were run to detect variables associated with TLRs. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

The IN.PACT Global Study enrolled 1,535 patients at 64 global centers. This report includes outcomes of the 417 participants enrolled in the imaging cohort: de novo ISR (n = 132), LL (n = 158), and CTO (n = 127). The participant flow chart through 5 years is shown in **Figure 1**. Five-year follow-up visits were completed for 256 participants (ISR: 87 [97.8%]; LL: 93 [93.0%], and CTO: 76 [96.2%]). Median follow-up was 1,800 days (IQR: 1,002-1,835 days).

Baseline demographics are shown in **Table 1**; baseline lesion characteristics and procedural outcomes are reported in **Table 2**. Safety and effectiveness outcomes through 5 years are reported in **Table 3**. Results specific to claudicants are reported in Supplemental Tables 1 to 3. The cumulative incidences of major adverse events were 53.1% in the ISR group, 48.9% in the LL group, and 43.0% in the CTO group. The 5-year rates of thrombosis at the target lesion site were 10.6% in the ISR cohort, 5.0% in the LL cohort, and 7.0% in the CTO cohort. The cumulative incidences of thrombosis over 5 years in all three groups are shown in **Figure 2**.

Freedom from all-cause mortality with vital status data was 81.4% in the ISR group, 75.2% in the LL group, and 78.2% in the CTO group (**Figure 3**). Freedom from CD-TLR per Kaplan-Meier estimates through 5 years were 58.0% in the ISR group, 67.3% in the LL group and 69.8% in the CTO group (**Figure 4**).

The total number of TLRs within each cohort was 91 (ISR), 69 (LL), and 45 (CTO). The number of participants who experienced multiple TLRs across the cohorts is reported in **Figure 5**. Within the ISR cohort, 15.9% of participants experienced ≥2 TLRs, compared with 9.5% in the LL cohort and 5.5% in the CTO cohort. Three ISR participants had ≥5 TLRs. A post hoc analysis was done to examine whether there were any differences in lesion or patient characteristics in those with more than 1 TLR within 5 years (Supplemental Table 4). In all 3 cohorts, participants with multiple TLRs tended to have longer lesions and more progressive peripheral arterial disease, with more participants presenting with higher Rutherford grade at baseline.

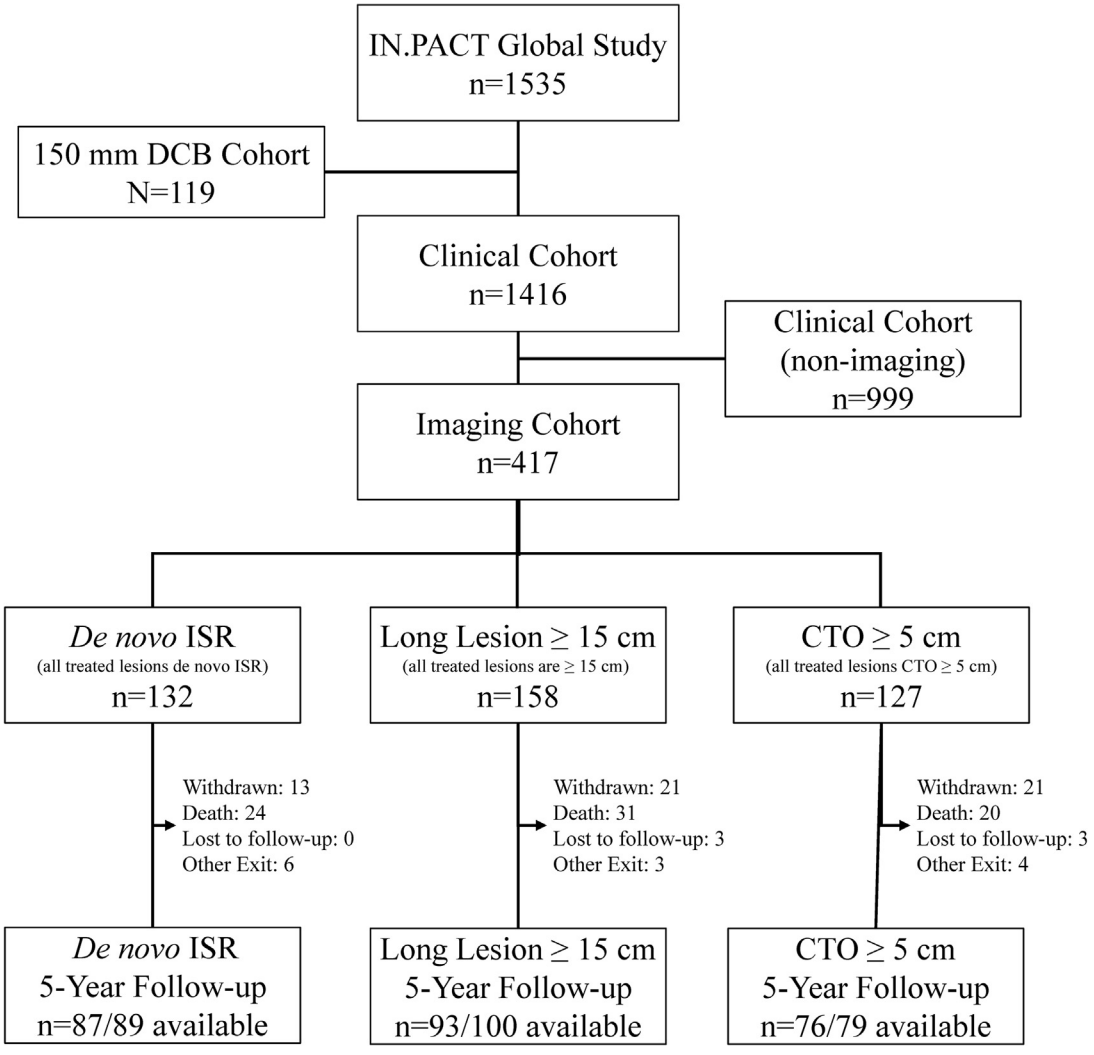
A post hoc analysis examined the incidence of subintimal crossing, calcified lesions and spot stenting (vs partial or whole length stenting) in participants who had a TLR within 5 years vs those who did not have a TLR (**Figure 6**). The use of subintimal crossing was similar in groups of participants with and without a TLR. The per-participant frequency of lesion calcification was 82.4% (28/34) in CTO participants with TLR and 66.7% (62/93) in CTO participants without TLR. Spot stenting was used in 44.4% (4/9) and 30.0% (3/10) of ISR participants with TLR and without TLR, respectively. Supplemental Table 5 contains variables associated with TLR for each subgroup.

DISCUSSION

These analyses were uniquely focused on lesions that are difficult to treat, including longer lesions, CTOs and ISR. Such lesions are often seen in clinical practice and are associated with restenosis,[11,13-16] but are typically excluded from clinical trials, creating a need for long-term data to inform the optimal treatment strategy in these patients.

Baseline participant characteristics in this analysis showed high rates of comorbidities and concomitant below-the-knee disease, typical of more advanced peripheral arterial disease. All cohorts consisted of complex lesions with long lesion lengths, and a preponderance of occlusions and calcification. As previously published, the 12-month primary patency data were promising with rates of 88.7% in the ISR cohort,[6] 91.1% in the LL cohort,[7] and 85.3% in the CTO cohort.[8] Although patency was not assessed through 5 years, participants were rigorously followed through this period to evaluate the incidence of adverse events, including revascularizations. Five-year freedom from CD-TLR in these complex cohorts (58.0% ISR, 67.3% LL, and 69.8% CTO) was similar to the overall clinical cohort of the IN.PACT Global study (69.4%).[11]

FIGURE 1 Participant Enrollment and Follow-Up in the IN.PACT Global Study Imaging Cohorts



The overall 5-year follow-up compliance (the percentage of patients who had a 5-year follow-up, either within or out of the visit window, among those who did not exit the study) was 95.5% (256/268). CTO = chronic total occlusion; DCB = drug-coated balloon; ISR = in-stent restenosis.

LONG-TERM EFFECTIVENESS OF DCBs IN RANDOMIZED TRIALS. Although the populations are not comparable to the present study, 5-year outcomes of several DCB randomized trials all consistently reported a benefit of DCB treatment over PTA.[5,17,18] Within the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) trial, the TLR rate was significantly lower in the DCB cohort (21%) as compared with the PTA cohort (56%; $P = 0.0005$) at 5 years.[19] The THUNDER trial also reported outcomes in patients with long lesions (>10 cm). Although the sample sizes were small (9 in each group), the TLR rate in these patients treated with DCB was markedly lower at 33% than in those treated with PTA (75%). These early promising DCB outcomes were subsequently observed in the larger IN.PACT SFA trial (Randomized Trial of IN.PACT Admiral Drug Eluting Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease) that reported superior freedom from CD-TLR rates in the DCB group when compared with the PTA group (74.5% vs 65.3%; $P = 0.02$).[5] Most recently, 5-year outcomes from the AcoArt 1 trial (Prospective, Multi-center and Randomized Controlled Clinical Study to Verify Effectiveness and Safety of Drug-eluting Balloon in PTA Procedure) reported freedom

TABLE 1 Baseline Participant Characteristics

	De Novo ISR (n = 132)	LL, ≥15 cm (n = 158)	CTO, ≥5 cm (n = 127)
Age, y	67.8 ± 10.1	69.6 ± 10.7	67.4 ± 10.5
Male	68.9 (91/132)	66.5 (105/158)	68.5 (87/127)
Diabetes	35.6 (47/132)	41.4 (35/157)	29.4 (37/126)
Insulin-dependent diabetes	15.9 (21/132)	21.7 (34/157)	10.3 (13/126)
Hypertension	81.7 (107/131)	87.3 (138/158)	81.6 (102/125)
Hyperlipidemia	72.3 (94/130)	76.2 (115/151)	63.9 (78/122)
Current smoker	35.6 (47/132)	34.2 (54/158)	49.6 (63/127)
Obesity[a]	18.2 (24/132)	21.9 (34/155)	20.0 (25/125)
Coronary heart disease	37.0 (47/127)	51.9 (80/154)	23.9 (28/117)
Carotid artery disease	19.7 (23/117)	22.2 (30/135)	19.0 (19/100)
Renal insufficiency[b]	9.8 (11/112)	14.3 (21/147)	9.9 (11/111)
Previous peripheral revascularization	100.0 (132/132)	55.7 (88/158)	33.1 (42/127)
Concomitant BTK disease in target leg	43.0 (55/128)	47.9 (68/142)	41.5 (49/118)
Ankle-brachial index	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2
Rutherford category			
2	32.8 (43/131)	21.7 (34/157)	26.0 (33/127)
3	58.0 (76/131)	61.8 (97/157)	63.0 (80/127)
4	7.6 (10/131)	10.2 (16/157)	8.7 (11/127)
5[c]	1.5 (2/131)	6.4 (10/157)	2.4 (3/127)

Values are mean ± SD or % (n/N). Data have been updated since original publications. Summaries are based on available assessments, therefore the total number of participants for some variables will be less than or equal to the total N. [a]Body mass index ≥30 kg/m^2. [b]Baseline serum creatinine ≥1.5 mg/dL. [c]Because of protocol deviations, participants classified as Rutherford clinical category 5 were enrolled and included in these analyses.

BTK = below-the-knee; CTO = chronic total occlusion; ISR = in-stent restenosis; LL = long lesion.

TABLE 2 Baseline Lesion and Procedure Characteristics

	De Novo ISR (n = 132) (150 Lesions[a]) (145 Lesions[b])	LL, ≥15 cm (n = 158) (162 Lesions[a]) (165 Lesions[b])	CTO, ≥5 cm (n = 127) (129 Lesions[a]) (128 Lesions[b])
Lesion type[a]			
De novo	0.0 (0/150)	83.3 (135/162)	92.2 (119/129)
Restenotic, nonstented	0.0 (0/150)	16.7 (27/162)	7.8 (10/129)
In-stent restenosis	100.0 (150/150)	0.0 (0/162)	0.0 (0/129)
Lesion length[b] cm	17.1 ± 10.5	26.4 ± 8.6	22.8 ± 9.7
Occluded[b]	33.8 (48/142)	60.0 (99/165)	100.0 (124/124)
Length of occlusion,[b] cm	4.9 ± 9.5	9.0 ± 10.9	11.8 ± 8.1
Calcification[b]	59.4 (79/133)	72.0 (118/164)	71.2 (89/125)
Severe[b,c]	8.3 (11/133)	19.5 (32/164)	3.2 (4/125)
Preprocedure RVD,[a] mm	5.2 ± 0.6	5.1 ± 0.6	5.1 ± 0.7
Diameter stenosis preprocedure,[b] %	84.5 ± 15.1	90.7 ± 14.3	100.0 ± 0.0
Participant received predilation[a]	64.4 (85/132)	89.2 (141/158)	94.5 (120/127)
Participant received postdilation[a]	25.8 (34/132)	38.9 (61/157)	49.6 (63/127)
Diameter stenosis postprocedure,[a] %	10.3 ± 11.5	12.3 ± 12.5	9.7 ± 11.2
Provisional stent, per lesion[a]	13.3 (20/150)	39.1 (63/161)	46.5 (60/129)
Clinical success[a,d]	98.5 (130/132)	99.4 (156/157)	98.4 (124/126)

Values are % (n/N) or mean ± SD. [a]Site reported data. [b]Angiographic core laboratory reported. [c]Defined as calcification with circumference ≥180° (both sides of vessel at the same location) and length greater than or equal to one-half of the total lesion length. [d]Defined as procedural success without procedural complications (death, target limb amputation, thrombosis of the target lesion or TVR) prior to discharge. Procedural success was defined as residual stenosis of ≤50% (nonstented subjects) or ≤30% (stented subjects) by visual estimate.

RVD = reference vessel diameter; other abbreviations as in Table 1.

TABLE 3 5-Year Safety and Effectiveness Outcomes

	De Novo ISR (n = 132)	LL, ≥15 cm (n = 158)	CTO, ≥5 cm (n = 127)
Safety composite, freedom from an event[a]	56.0	65.7	69.8
TLR outcomes, cumulative incidence			
CD-TLR	42.0 (50)	32.7 (41)	30.2 (32)
Any TLR	43.1 (51)	33.7 (42)	32.2 (34)
RMST to first CD-TLR, mo	45.2 ± 1.8	47.9 ± 1.7	48.9 ± 1.8
Major adverse events,[b] cumulative incidence			
Major adverse events	53.1 (65)	48.9 (67)	43.0 (48)
All-cause death	16.7 (20)	22.4 (30)	19.1 (20)
CD-TVR	44.0 (52)	32.7 (41)	30.2 (32)
Major target limb amputation	0.8 (1)	1.7 (2)	0.0 (0)
Thrombosis at the target lesion site	10.6 (13)	5.0 (7)	7.0 (8)

Values are %, % (n), or mean ± SE. Percentages are based on Kaplan-Meier estimates. [a]Defined as freedom from device- and procedure-related death to 30 days, freedom from target limb amputation within 60 months, and freedom from clinically driven target vessel revascularization (CD-TVR) within 60 months. [b]Defined as all-cause mortality, major target limb amputation, CD-TVR, or thrombosis at the target lesion site up to 5 years.

CD-TLR = clinically driven target lesion revascularization; CD-TVR = clinically driven target vessel revascularization; RMST = restricted mean survival time; TLR = target lesion revascularization; other abbreviations as in Table 1.

from CD-TLR was 77.5% in the DCB group and 59.1% in the PTA group ($P < 0.001$).[18] Although the lesions treated in these randomized trials were less complex, they demonstrated a long-term treatment effect of DCBs.

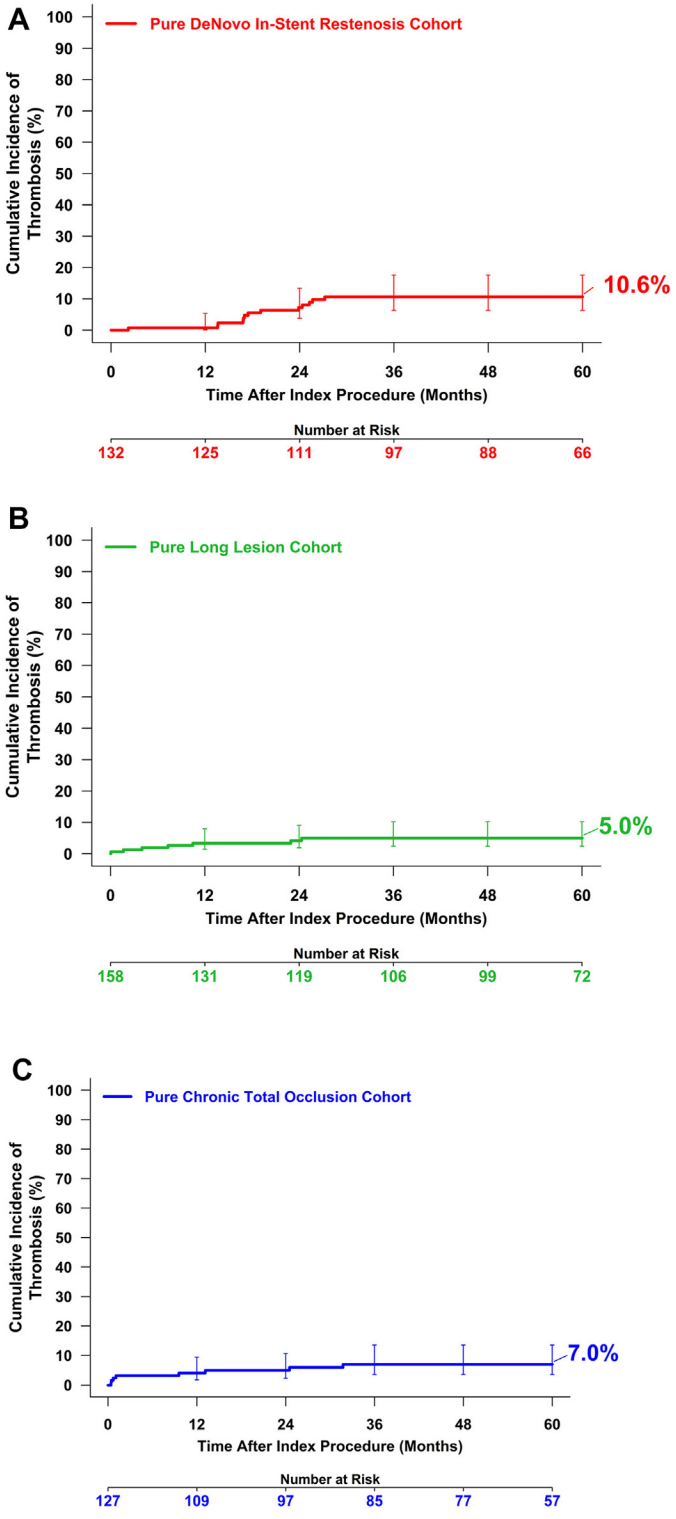
IN-STENT RESTENOSIS. Treatment of ISR is challenging, and outcomes of restenotic lesions are inferior compared with de novo lesions.[20] Occluded ISR (as compared with stenotic ISR) is associated with significantly increased risk of recurrent stenosis,[21] The de novo ISR cohort in the present study had a reasonable CD-TLR rate of 42.0% at 5 years given that the mean lesion length was 17.1 cm and 33.8% were occluded. Tosaka et al[22] evaluated ISR lesions following PTA and reported 2-year recurrence rates ranging from 49.9% in focal lesions ≤50 mm to 84.8% in occluded lesions. Grotti et al[23] reported on DEBATE ISR (Drug Eluting Balloon in Peripheral Intervention for In-Stent Restenosis) 3-year outcomes in diabetic patients with complex ISR lesions and TLR rates at 3 years were 40% for DCB and 43% for historical PTA data. The only other published long-term outcomes on the treatment of ISR that we are aware of is from a subanalysis of the Zilver PTX Japan Post-Market Surveillance Study with 204 ISR lesions treated with the Zilver drug-eluting stent (DES).[24] The mean lesion length was 17.8 cm, and 35.3% were total occlusions, comparable to the ISR cohort enrolled in the present study. The 5-year rate of freedom from CD-TLR was 73.4%.

De novo and restenotic plaque differ in composition; the restenotic tissue consists primarily of collagen-rich extracellular matrix with an inner layer of smooth muscle cells.[25] Yahagi et al[25] explained the mechanisms and pathways that lead to these differences, summarized treatment outcomes, and concluded that the best treatment for ISR may lie in its prevention. This led the endovascular field to a strategy of "leave nothing behind." Indeed, the principal benefit of DCBs over DES is the ability to deliver antiproliferative drug without a permanent scaffold. However, treatment of more complex lesions results in the use of provisional stents because of the physical limitations of angioplasty. Within this study, 39.1% of lesions in the LL group and 46.5% in the CTO group received provisional stenting. Vessel preparation with directional atherectomy use before DCB treatment was shown to reduce the need for provisional stenting in complex and calcified lesions to <10%[26,27] and should be considered when avoiding stents is a priority.

LONG LESIONS. Clinical evidence on the use of DCBs to treat long lesions is limited but promising.[28] The 1-year primary patency rate observed in the present study's LL cohort was 91.1%,[7] and the freedom from CD-TLR through 5 years was 67.3%. Published outcomes of similar populations are limited in duration to 1 year. Micari et al[29,30] reported 1-year primary patency rate of 83.2% and freedom from CD-TLR of 96% in a population with a mean lesion length of 25 cm; efficacy was maintained through 2 years with a primary patency of 70.4%. Yu et al[31] recently reported 1-year results of the Orchid DCB (Acotec Scientific), also with a mean lesion length of 25 cm, and a similar primary patency rate of 82.1%. To date, there has been only 1 study exploring DCBs vs DES for treatment of long lesions. At 1 year, outcomes were similar between DCB and DES for primary patency (76.1% vs 69.6%; $P = 0.319$) and CD-TLR (15.6% vs 19.0%; $P = 0.543$).[32] In the STELLA (Stenting Long de l'Artère Fémorale Superficielle) registry, the primary patency at 30 months following self-expanding bare-metal stent (BMS) implantation in lesions >15 cm was 62.2%.[33] The VIBRANT study (GORE VIABAHN Endoprosthesis Peripheral Vascular Disease Study) randomized participants to treatment with a BMS or endoprosthesis (VIABAHN).[34] The 3-year primary patency rates were similar between the 2 cohorts (25.9% BMS vs 24.2% VIABAHN; $P = 0.39$); of note, 50% of the BMS group experienced stent fractures.[34]

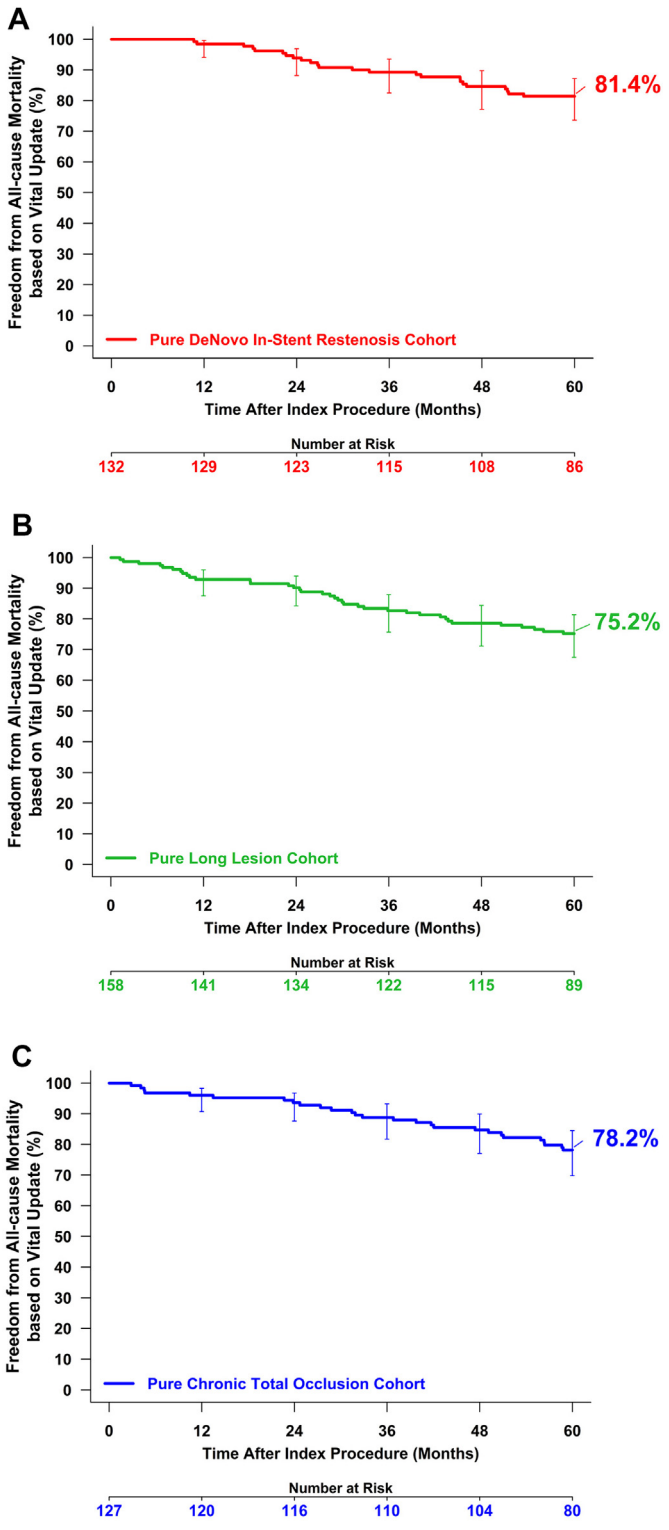
CHRONIC TOTAL OCCLUSIONS. The technique of a subintimal approach was a breakthrough for endovascular treatment of CTOs and has a high technical

FIGURE 2 **Thrombosis**



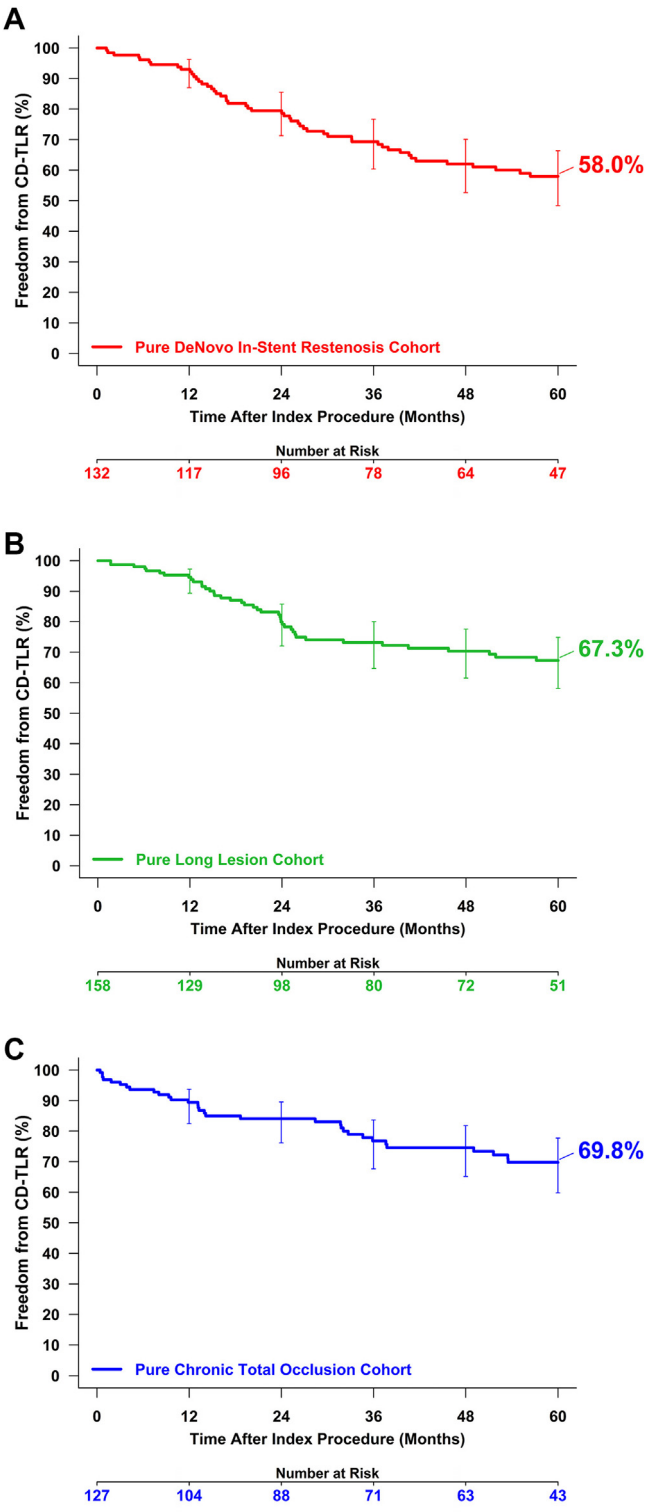
Cumulative incidence of thrombosis through 5 years: **(A)** in-stent restenosis cohort; **(B)** long lesion cohort; **(C)** chronic total occlusion cohort. **Error bars** indicate 95% CIs.

FIGURE 3 Mortality



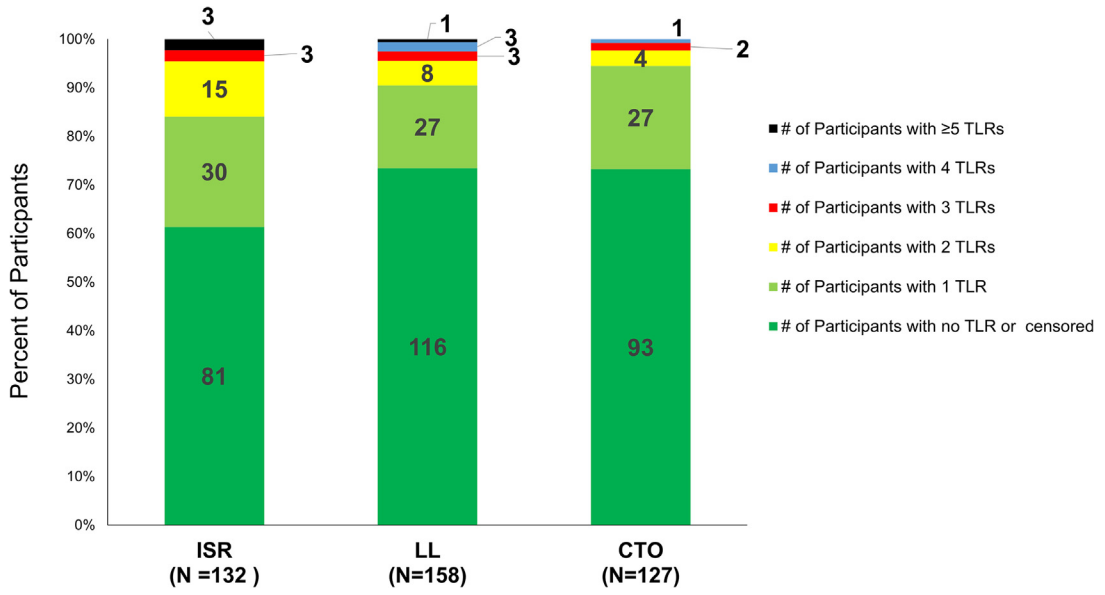
Freedom from all-cause mortality through 5 years with vital status update: **(A)** in-stent restenosis cohort; **(B)** long lesion cohort; **(C)** chronic total occlusion cohort. **Error bars** indicate 95% CIs.

FIGURE 4 **CD-TLR**



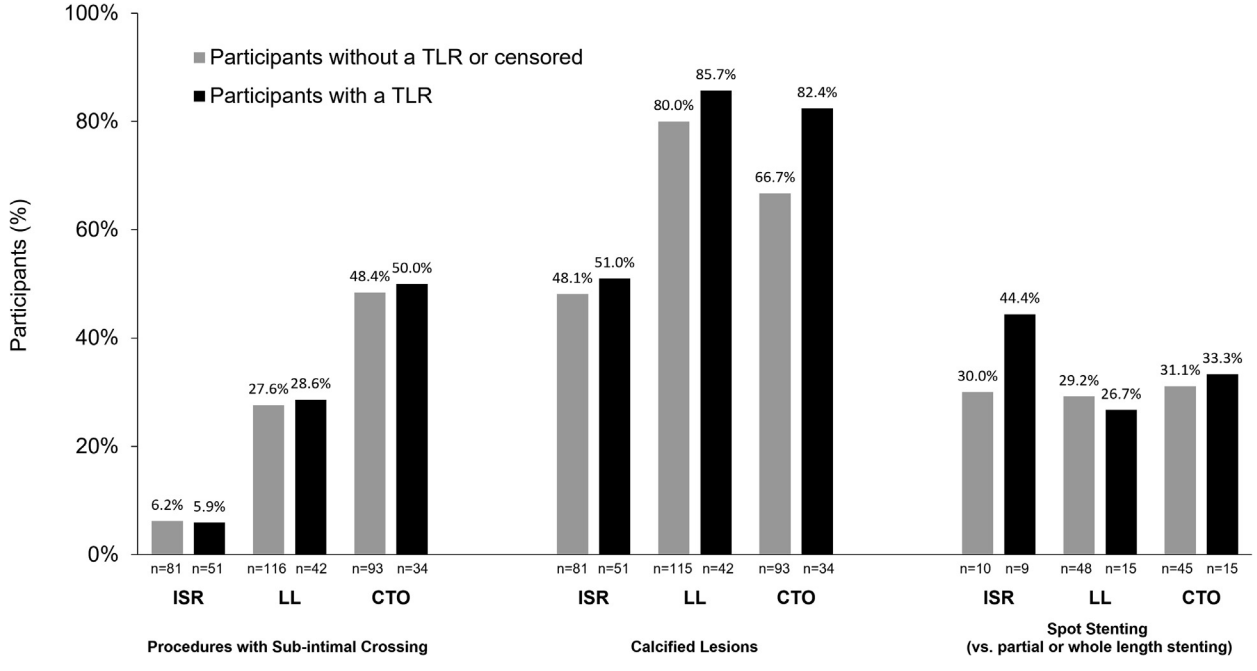
Freedom from clinically driven target lesion revascularization (CD-TLR) through 5 years: **(A)** in-stent restenosis cohort; **(B)** long lesion cohort; **(C)** chronic total occlusion cohort. **Error bars** indicate 95% CIs.

FIGURE 5 Repeat Revascularization



Incidence of repeat TLRs across the ISR, LL, and CTO cohorts. Abbreviations as in Figure 1.

FIGURE 6 Characteristics of Participants With and Without TLR



Occurrence of subintimal crossing (per operator assessment), calcification and spot stenting in participants with and without a TLR. Abbreviations as in Figures 1 and 5.

success rate and comparable mid- and long-term outcomes as compared with an intraluminal approach.[35] Within the present study's CTO cohort, comparing those who had a TLR vs those without a TLR, approximately one-half in each group were crossed within the true lumen and one-half with a subintimal approach. Kim et al[35] found similar patency rates through 2 years in long femoropopliteal CTOs crossed within the true lumen compared with those crossed subintimally.

Within the current study's CTO cohort, the freedom from CD-TLR rate at 5 years was 69.8%. There are little comparable data to put this into context. A post hoc analysis of DCB vs PTA in long femoropopliteal CTOs (mean lesion length of 20 cm) reported that 2-year TLR rates were significantly lower in the DCB group (12.77% vs 45.24% in the PTA group; $P = 0.002$).[36] Another study of long occluded lesions (mean occluded length of 17.8 cm) using cutting balloon angioplasty observed a 2-year patency rate of 60.6%.[37]

REPEAT REVASCULARIZATIONS. Uniquely, this study explored the number of repeat revascularizations that were necessary over the course of follow-up. Of the participants who required revascularization, the majority (66.1%, 84/127) had only a single TLR within 5 years. The ISR cohort had the greatest occurrence of repeat revascularizations with 15 participants having 2 TLRs and 6 having ≥3 TLRs. This is consistent with other reports on the complex nature of ISR pathophysiology. Across all cohorts, there tended to be fewer participants who were categorized as Rutherford clinical category 2 at baseline with ≥2 TLRs compared with those with none or 1, consistent with the belief that early intervention is often best.

The number of TLRs and amputations following the index procedure are the most influential cost drivers of therapies over time.[38] The initial higher cost of the DCB procedure (compared with an uncoated PTA balloon) is offset by the decreased need for reinterventions. DCBs have been shown to be a cost-effective approach across several health care systems.[38-40]

SAFETY OUTCOMES. There were no safety trends observed in any of the cohorts. The 5-year freedom from all-cause mortality rates, with vital status data included, were 81.4% (de novo ISR), 75.2% (LL), and 78.2% (CTO). These rates are comparable to the observed freedom from mortality rates in the full clinical cohort (78.9%)[11] and AcoArt 1 (82.7%),[18] and the all-cause mortality rate in Zilver DES Japan post-market study (25.1%).[24] Schneider et al[41] conducted a survival analysis stratified by paclitaxel dose in patients treated with IN.PACT Admiral DCB(s). That patient-level meta-analysis found no correlation between the level of paclitaxel exposure and mortality.

The occurrence of thrombosis was also examined. Dual antiplatelet medication use was collected through 3 years and reported in Supplemental Table 6. The 5-year rates of thrombosis were 10.6% in the ISR cohort, 5.0% in the LL cohort, and 7.0% in the CTO cohort. The bulk of the thrombotic events occurred earlier within the CTO cohort, whereas they were more delayed and spread out in the other cohorts. It is postulated that provisional stenting during the index procedure could have prevented some of these thrombotic events. There was no occurrence of thrombosis after 3 years in any cohort. The lack of late thrombotic events is consistent with the Zilver DES Japan post-market study, with a 5.0% thrombosis rate at 1 year, an additional 1.3% through 2 years and none reported from years 2 to 5.[24]

STUDY LIMITATIONS. This was a single-arm study without a control group. Long-term follow-up assessments at years 4 and 5 were conducted via telephone, which may result in an underestimation of events and limits the generalizability of outcomes. Additionally, these analyses include patients with critical limb ischemia, a known confounding variable.

CONCLUSIONS

These long-term results from a prospective, real-world cohort of complex lesions, evaluated with angiographic core laboratory and clinical events committee oversight, demonstrated high freedom from CD-TLR rates, low repeat revascularization counts, and no safety concerns (**Central Illustration**). These results bolster the evidence that supports the inclusion of IN.PACT Admiral into the treatment algorithm for complex femoropopliteal disease.

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CENTRAL ILLUSTRATION **IN.PACT Global Prespecified Imaging Cohorts**

Five-Year Outcomes Among Prespecified Complex Cohorts: IN.PACT Global Study

	De novo ISR n = 132	Long Lesion ≥15 cm n = 158	CTO ≥5 cm n = 127
	Baseline Lesion Characteristics		
Lesion Length	17.1 cm	26.4 cm	22.8 cm
Occlusions	33.8%	60.0%	100.0%
Calcification	59.4%	72.0%	71.2%
Five-Year Outcomes	Freedom from All-Cause Mortality		
	81.4%	75.2%	78.2%
	Freedom from CD-TLR		
	58.0%	67.3%	69.8%
	Participants with >1 TLR		
	15.9%	9.5%	5.5%
	Safety Composite (freedom from an event*)		
	56.0%	65.7%	69.8%

*Defined as freedom from device- and procedure-related death to 30 days, freedom from target limb amputation within 60 months, and freedom from clinically driven target vessel revascularization within 60 months.

Tepe G, et al. J Am Coll Cardiol Intv. 2023;16(9):1065–1078.

Five-year outcomes from a prospective, international, single-arm study of patients with femoropopliteal disease treated with drug-coated balloons. Five-year outcomes are Kaplan-Meier estimates. CD-TLR = clinically driven target lesion revascularization; CTO = chronic total occlusion; ISR = in-stent restenosis; TLR = target lesion revascularization.

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PERSPECTIVES

WHAT IS KNOWN? A long-term treatment effect of DCBs has been demonstrated, but in less complex lesions.

WHAT IS NEW? This is the first report of 5-year outcomes of DCB treatment for de novo ISR, long lesions, and CTOs. The reintervention rates for the long lesion and CTO groups were low. There remains room for improvement with treatment of ISR because these patients were more likely to experience multiple revascularizations. There were no safety issues in any group.

WHAT IS NEXT? Future research should focus on the treatment of ISR and the avoidance of stent placement with vessel preparation strategies that overcome the physical limitations of angioplasty balloons potentially leading to provisional stent placement. Future research should also examine how to best treat restenosis after DCB, especially in complex lesions.

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KEY WORDS chronic total occlusions, claudication, femoropopliteal disease, in-stent restenosis, peripheral arterial disease

APPENDIX For supplemental tables and a list of the study investigators and sites, please see the online version of this paper.