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Drug-Coated Balloon Treatment for Femoropopliteal Artery Disease

The Chronic Total Occlusion Cohort in the IN.PACT Global Study

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ABSTRACT

OBJECTIVES This study evaluated the 12-month safety and effectiveness of a paclitaxel drug-coated balloon for treatment of intermittent claudication or rest pain in subjects with femoropopliteal chronic total occlusions (CTO).

BACKGROUND CTOs are difficult to treat, and the optimal intervention remains to be determined.

METHODS The IN.PACT Global Study is an international single-arm study that enrolled 1,535 patients with symptomatic femoropopliteal artery disease. The study contains prospectively defined cohorts with prospectively planned imaging analyses, including a CTO (≥5 cm) cohort in which subjects underwent duplex ultrasonography analyzed by an independent core laboratory. The primary safety endpoint was a composite of freedom from device- and procedure-related mortality through 30 days, and freedom from major target limb amputation and target vessel revascularization through 12 months. An independent Clinical Events Committee adjudicated all adverse events. The primary effectiveness endpoint was primary patency at 12 months, defined as freedom from clinically driven target lesion revascularization and freedom from restenosis.

RESULTS The CTO imaging cohort had 126 subjects with 127 lesions (mean lesion length 22.83 ± 9.76 cm). Primary patency by Kaplan-Meier estimate was 85.3% through 12 months. Provisional stenting was performed in 46.8% of lesions. The primary safety composite endpoint was achieved by 88.7% of subjects. There were no device- or procedure-related deaths through 30 days or major target limb amputations through 12 months.

CONCLUSIONS The paclitaxel drug-coated balloon was safe and highly effective at 12 months after treatment of subjects with CTO ≥5 cm in the femoropopliteal arteries. (IN.PACT Global Clinical Study; NCT01609296)
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There are multiple endovascular treatment options for the management of patients with symptomatic peripheral artery disease (PAD). Advanced technologies including drug-eluting stents and drug-coated balloons (DCBs) have been developed to address some of the concerns, including restenosis, that are associated with traditional interventions, such as angioplasty with a standard uncoated percutaneous transluminal angioplasty (PTA) balloon (1).

DCBs are coated with the antiproliferative agent paclitaxel, which is applied to the artery wall upon inflation. When applied with a urea excipient, paclitaxel has been shown to persist in the vessel wall for up to 6 months (2), and may support prolonged antirestenotic effect without stenting when combined with appropriate angioplasty techniques, such as long inflation time.

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Multiple clinical studies have demonstrated the safety and effectiveness of DCBs up to 3 years for the treatment of patients with femoropopliteal artery disease (3-15), but occluded segments can be especially challenging to treat with traditional interventions. There is limited evidence on the safety and effectiveness of endovascular therapies for the treatment of chronic total occlusions (CTO) in the superficial femoral artery (SFA) or popliteal artery, including 1 retrospective analysis and 2 small prospective studies of a metal stent and stent graft (16-18). There are few clinical reports on the safety and effectiveness of DCBs for the treatment of CTO in the SFA or popliteal artery (19).

The IN.PACT Global Study was designed to evaluate the safety and effectiveness of a paclitaxel DCB (IN.PACT Admiral, Medtronic, Dublin, Ireland) in the treatment of real-world subjects with symptomatic PAD due to complex lesions, including CTO in the SFA and/or popliteal artery. We report the 12-month results from the CTO cohort.

METHODS

IN.PACT GLOBAL STUDY: DESIGN, SUBJECTS, AND TREATMENT. A prospective analysis of DCBs for the treatment of CTO (≥5 cm) was incorporated into the design of the IN.PACT Global Study, a prospective, multicenter, international, single-arm clinical trial assessing the safety and effectiveness of a paclitaxel DCB for the treatment of real-world patients with femoropopliteal artery disease. Additional methods are provided in the Online Appendix.

Patients were enrolled in the CTO imaging subset after anatomic confirmation by the angiographic core lab. Independent core laboratories analyzed all images, including duplex ultrasonography (DUS) (VasCore, Massachusetts General Hospital, Boston, Massachusetts) and angiography (SynvaCor Angiographic Core Lab, Springfield, Illinois). In cases where both angiography and DUS were available at the same assessment, then angiography was preferentially used. An independent Clinical Events Committee (Syntactx Clinical Events Committee, New York, New York) adjudicated all major adverse events, and sites were monitored by a Data and Safety Monitoring Board.

Pre- and post-dilatation were permitted at the discretion of the investigator. Intraluminal or subintimal approach was also at the discretion of the investigator. Atherectomy was not allowed. Provisional stenting with a bare-metal stent was allowed if at least 1 of the following criteria was met despite repeated and prolonged balloon inflations: residual stenosis ≥50% (based on visual estimate), translesional gradient >10 mm Hg, or presence of a flow-limiting dissection. The reason for provisional stenting did not need to be validated by an independent core laboratory. Within this analysis, stenting is split into 3 distinct categories: 1) spot stenting refers to the utilization of the single shortest stent for which the minimal length is sufficient to cover the residual stenosis; 2) whole-lesion coverage is utilization of a stent that is as long as the full lesion; and 3) partial stenting is everything that is not spot stenting or whole lesion coverage.

Subjects were instructed to take daily dose of 75 to 325 mg aspirin indefinitely and daily clopidogrel (75 mg) (or ticlopidine or prasugrel, if required) for at least 1 month following the procedure in case no stent is placed. Clopidogrel should be prescribed to stented subjects for 3 months or longer. Prolonged use of clopidogrel beyond the protocol specified times was left to investigator discretion based on patient's clinical and angiographic profile, pre-existing prescriptions, and concomitant treatment of nontarget lesions during the index procedure.

The Institutional Review Board or ethics committee at each trial site approved the study protocol. Informed consent was obtained from all subjects before enrollment. The trial was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws as specified by all relevant governmental bodies. The trial is registered with the U.S. National Institutes of Health (NCT01609296).

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

CD-TLR = clinically driven target lesion revascularization

CTO = chronic total occlusion

DCB = drug-coated balloon

DUS = duplex ultrasound

PAD = peripheral artery disease

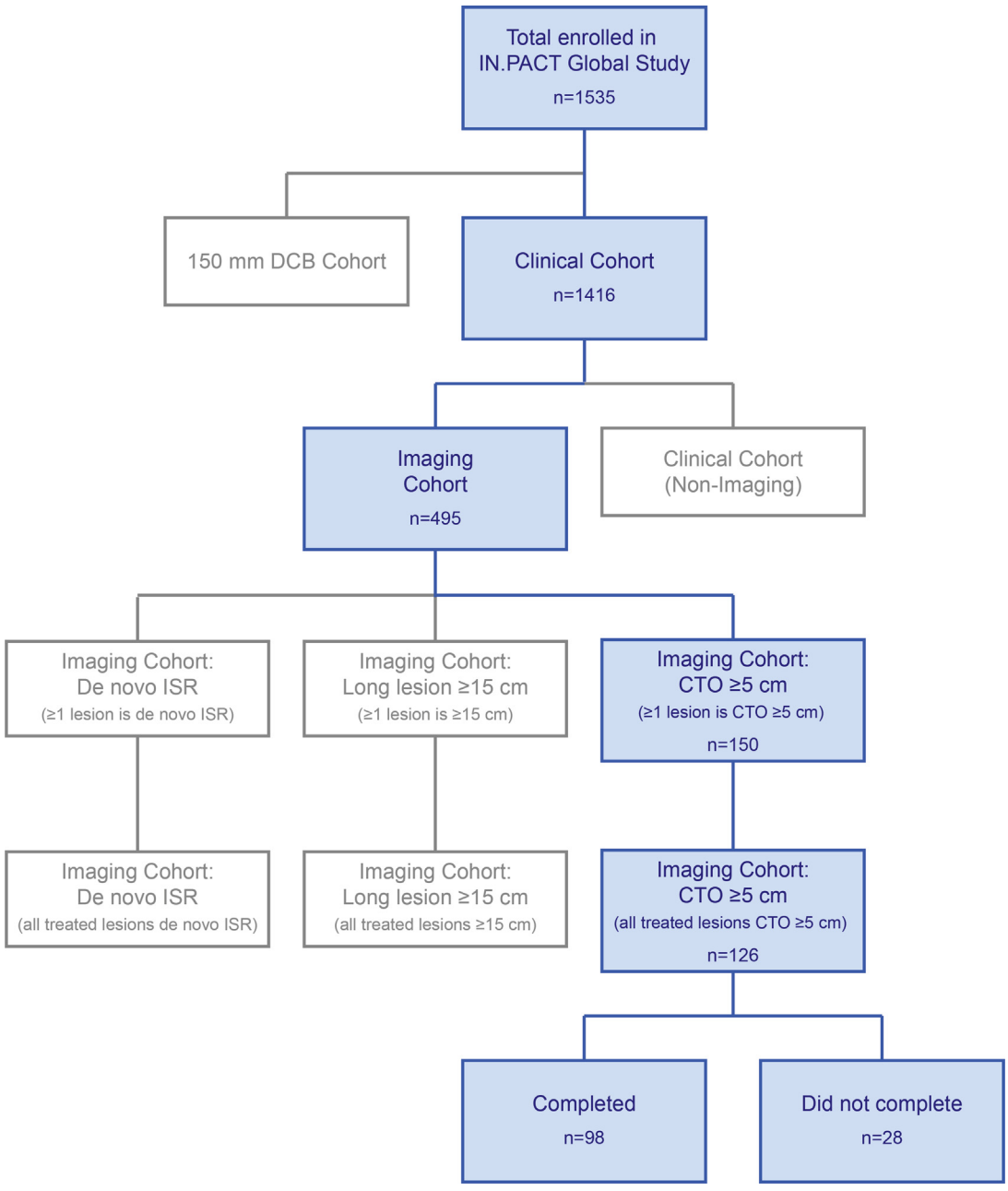
PTA = percutaneous transluminal angioplasty

SFA = superficial femoral artery

TLR = target lesion revascularization

TVR = target vessel revascularization

FIGURE 1 Subject Flow in the IN.PACT Global Study and CTO Imaging Cohort



The clinical cohort contained the imaging cohort, which itself contained 3 prospectively defined cohorts, including chronic total occlusion (CTO) (≥5 cm). Subjects with at least 1 CTO ≥5 cm could be enrolled in the CTO cohort (n = 150), but analysis was restricted to subjects in whom CTOs were the only targets treated during the index procedure (n = 126). Among these 126 subjects, 98 completed the study through the 13-month follow-up window and 28 did not complete the study: 13 withdrew consent, 10 were lost to follow up, and 5 died (see section on Safety Outcomes). DCB = drug-coated balloon; ISR = in-stent restenosis.

ENDPOINTS. The primary effectiveness endpoint was primary patency through 12 months, defined as freedom from clinically driven target lesion revascularization (CD-TLR) and freedom from restenosis (DUS peak systolic velocity ratio ≤2.4). The primary safety composite endpoint was freedom from device- and procedure-related mortality through 30 days, and freedom from major target limb amputation and

TABLE 1 Baseline Demographics and Clinical Characteristics of Subjects in the CTO Imaging Cohort

Characteristic (per Subject)	CTO Imaging Cohort (n = 126)*
Age, yrs	67.5 ± 10.4 (125)
Male	69.0 (87/126)
Body mass index, kg/m^2	27.2 ± 5.0 (124)
Obesity (body mass index ≥30 kg/m^2)	20.2 (25/124)
Diabetes	29.6 (37/125)
Insulin dependent diabetes	10.4 (13/125)
Hypertension	82.3 (102/124)
Hyperlipidemia	64.5 (78/121)
Current smoker	49.2 (62/126)
Coronary heart disease	24.1 (28/116)
Carotid artery disease	19.2 (19/99)
Renal insufficiency†	10.0 (11/110)
Previous peripheral revascularization	33.3 (42/126)
Below-the-knee disease of target leg	41.0 (48/117)
Rutherford clinical category	
2	25.4 (32/126)
3	63.5 (80/126)
4	8.7 (11/126)
5	2.4 (3/126)‡
ABI per target limb, mm Hg§	0.60 ± 0.18 (106)
Bilateral disease	0.8 (1/126)

Values are mean ± SD (N) or % (n/N). *Summaries are based on nonmissing assessments. In some cases, baseline demographic or clinical data were not available, and therefore the total number of subjects for that variable is <126. †Defined as baseline creatinine ≥1.5 mg/dl. ‡Due to protocol violations, 3 subjects classified as Rutherford clinical category 5 were enrolled and included in the analysis. §For subjects with bilateral disease, ankle-brachial index (ABI) is included for each target limb.

CTO = chronic total occlusion.

TABLE 2 Lesion Characteristics From Subjects in the CTO Imaging Cohort

Characteristic (per Lesion)	CTO Imaging Cohort (n = 126, 127 Lesions)*
Pre-procedure	
Lesion type†	
De novo	92.1 (117/127)
Restenotic (nonstented)	7.9 (10/127)
In-stent restenosis	0.0 (0/127)
Vessel‡	
Superficial femoral artery	96.1 (122/127)
Proximal popliteal artery	31.5 (40/127)
Lesion length, cm‡	22.83 ± 9.76 (117)
Occluded lesion length, cm‡	11.86 ± 8.05 (114)
With calcification‡	71.0 (88/124)
With severe calcification‡§	3.2 (4/124)
Reference vessel diameter, mm‡	5.05 ± 0.66 (127)
Diameter stenosis, %‡	100.0 ± 0.0 (123)
TASC lesion type‡	
A	3.4 (4/119)
B	28.6 (34/119)
C	57.1 (68/119)
D	10.9 (13/119)
Procedure	
DCBs used per lesion†	2.2 ± 1.0 (127)
Total DCB length per subject, cm	23.8 ± 10.9 (126)
Pre-dilatation†	94.4 (119/126)
Post-dilatation†	50.0 (63/126)
Provisional stenting†	46.5 (59/127)
Post-procedure	
Device success‖	99.3 (283/285)
Procedural success¶	100.0 (125/125)
Clinical success#	99.2 (124/125)
Dissections‡	
0	32.3 (41/127)
A	4.7 (6/127)
B	19.7 (25/127)
C	19.7 (25/127)
D	10.2 (13/127)
E	11.8 (15/127)
F	1.6 (2/127)

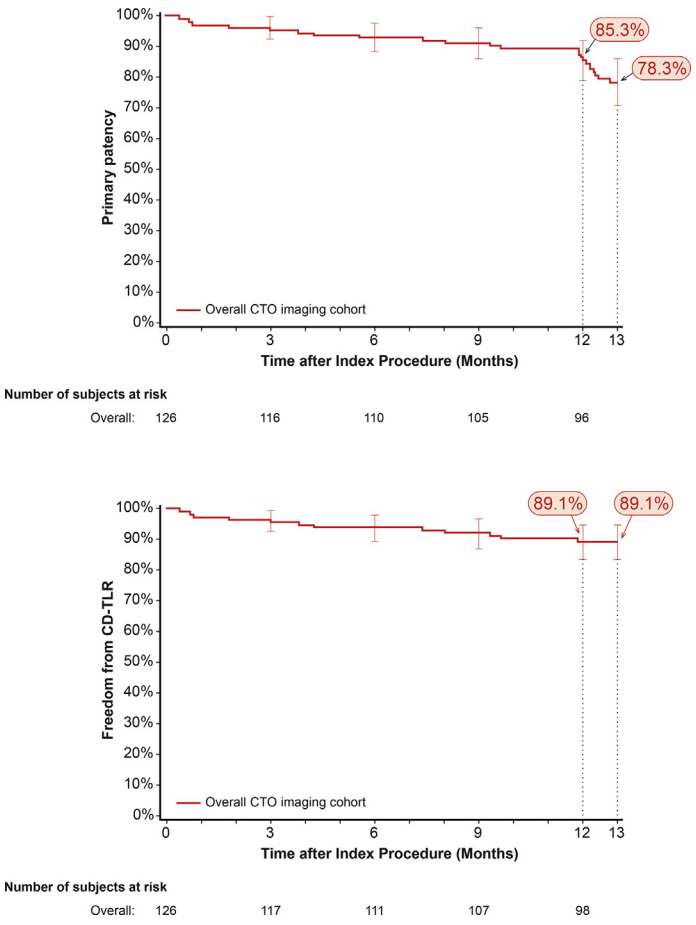
Values are mean ± SD (N) or % (n/N). *Summaries are based on nonmissing assessments. In some cases, baseline or clinical data were not available, and therefore the total number of lesions for that variable is <127. †Data reported by investigational sites. ‡Data reported by independent core imaging labs. §Severe calcification 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. ‖Device success defined as successful delivery, inflation, deflation, and retrieval of the intact study balloon device without burst below the rated burst pressure. This analysis is device (balloon) based. ¶Procedural success defined as residual stenosis of ≤50% for nonstented subjects or ≤30% for stented subjects by core lab assessment (site-reported estimate was used if core lab assessment was not available). This analysis is lesion based. #Clinical success defined as procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or target vessel revascularization) before discharge. This analysis is subject based.

CTO = chronic total occlusion; TASC = TransAtlantic Inter-Society Consensus II.

clinically driven target vessel revascularization (CD-TVR) within 12 months post-index procedure. TVR was assessed at the subject level and defined as the first event that required TVR in the subject. An independent Clinical Events Committee reviewed target lesion revascularization (TLR) and TVR events to determine which were clinically driven, defined as any reintervention within the target lesion(s) due to symptoms or ankle-brachial index (ABI) decrease of ≥20% or >0.15 when compared with post-index procedure baseline ABI. Secondary endpoints included device, procedural, and clinical success, as well as changes in ABI, walking impairment, and Rutherford clinical category through 12 months.

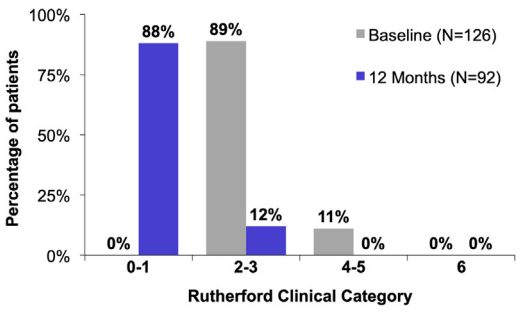
CTO IMAGING COHORT SUBGROUP STATISTICAL ANALYSIS. All summaries were based on nonmissing assessments. Unless otherwise specified, all baseline demographics, clinical characteristics, and procedural characteristics were summarized on a subject basis; lesion characteristics were summarized on a lesion basis. For baseline characteristics, continuous variables were described as mean ± SD; dichotomous and categorical variables were described as counts and proportions. The level of statistical significance was set at $p < 0.05$. The Kaplan-Meier method was

FIGURE 2 Kaplan-Meier Curves of Primary Patency and Freedom From CD-TLR in the Overall CTO Imaging Cohort



(Top) Primary patency (primary effectiveness endpoint, primary patency at 12 months), defined as freedom from clinically driven target lesion revascularization (CD-TLR) and freedom from restenosis (duplex ultrasound peak systolic velocity ratio ≤2.4). **(Bottom)** Freedom from CD-TLR. Number at risk represents the number at the beginning of the 30-day window before each follow-up interval. CTO = chronic total occlusion.

FIGURE 3 Rutherford Clinical Category at Baseline and 12 Months Among Subjects in the CTO Imaging Cohort



Subjects with Rutherford clinical category 2 to 4 were eligible for enrollment in the IN.PACT Global Study. Despite this limitation, 3 subjects with Rutherford clinical category 5 were enrolled in the CTO imaging cohort. This graph shows the distribution of subjects among Rutherford clinical categories at baseline and 12 months after index treatment. Changes between baseline and month 12 were statistically significant ($p < 0.001$). Abbreviations as in Figure 2.

used to evaluate time-to-event data for primary patency and freedom from CD-TLR over the 12-month follow-up period. Censoring was defined as death and exits from the study. In a post hoc analysis of subgroups defined by the presence of baseline clinical or procedural characteristics, the difference in survival curves between subgroups was assessed using the log-rank test. The outcome analysis was performed at a subject level. For event rates that were expressed as a proportion, the number of subjects with an event was the numerator and the total number of subjects either experienced events before 360 days or at least 330 days of clinical follow-up or was the denominator. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE SUBJECT, LESION, AND PROCEDURAL CHARACTERISTICS. The IN.PACT Global Study enrolled 1,535 subjects across 64 sites in more than 25 countries from the European Union, Switzerland, Middle East, Asia, Australia, Canada, and Latin America (Figure 1). Subjects with at least 1 CTO lesion ≥5 cm were prospectively enrolled in the CTO imaging cohort (n = 150). Analysis was limited to subjects in which CTO lesions were the only targets treated during the index procedure (n = 126). For 12-month follow-up, 90 subjects visited within the follow-up window, 8 subjects followed up outside of the visit window, 10 subjects had no follow-up, 13 subjects withdrew, and 5 subjects died, for a compliance rate of 83.3%.

Baseline demographics, lesion, and procedural characteristics of the CTO imaging cohort are reported in Tables 1 and 2. Most lesions were de novo (92.1%, n = 117 of 127) and the remaining 7.9% (n = 10 of 127) were restenotic (nonstented). Mean lesion length was 22.8 ± 9.8 cm and mean occluded length was 11.9 ± 8.0 cm. Seventy-one percent of lesions (n = 88 of 124) were calcified.

Device success was achieved with 99.3% (n = 283 of 285) of devices used (Table 2). Procedural success was achieved in 100.0% (n = 125 of 125) of lesions and clinical success was achieved in 99.2% (n = 124 of 125) of subjects.

Provisional stents were implanted in 46.5% (n = 59 of 127) of lesions in the overall CTO imaging cohort (Table 2). Among lesions that received provisional stents, 32.2% (n = 19 of 59) were spot stented, 32.2% (n = 19 of 59) had partial lesion coverage, and 35.6% (n = 21 of 59) had whole-lesion coverage. The mean total stent length per subject was 14.90 ± 10.23 cm (n = 59). Mean total stent length was 14.90 ± 10.23 cm. The reasons for provisional stenting were persistent residual stenosis ≥50% (29.1%, n = 37 of 127), flow-limiting dissection (23.6%, n = 30 of 127), and other (1.6%, n = 2 of 127). Post-dilatation was used in 50.0% (n = 63 of 126) of lesions.

EFFECTIVENESS OUTCOMES. Primary patency by Kaplan-Meier estimate was 85.3% in the CTO imaging cohort through 12 months (primary effectiveness endpoint) (Figure 2, top) and 78.3% through the 13-month follow-up window. Freedom from CD-TLR by Kaplan-Meier estimate was 89.1% through 12 months and 13 months (Figure 2, bottom). A stratified analysis by occluded lesion length showed no differences in patency or freedom from CD-TLR outcomes.

Changes in Rutherford clinical category between baseline and 12 months were statistically significant ($p < 0.001$) (Figure 3). At baseline, 88.9% of subjects were category 2 to 3 (n = 112 of 126) and 0% were category 0 to 1 (n = 0 of 126). At 12 months, 12.0% (n = 11 of 92) of subjects were category 2 to 3 and 88.0% (n = 81 of 92) were category 0 to 1.

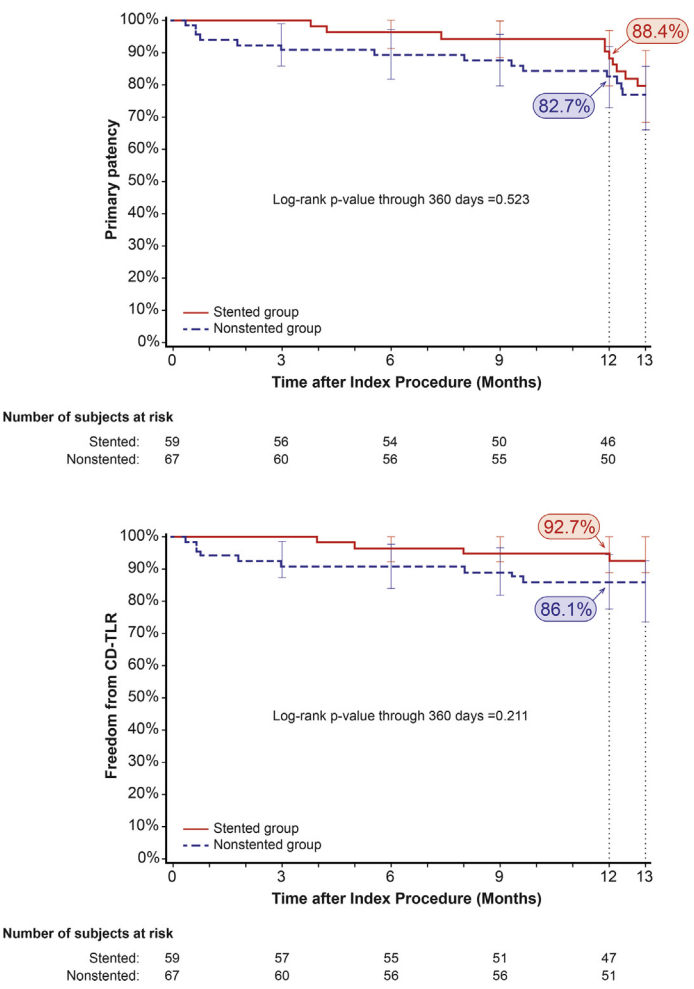
Mean ABI was 0.593 ± 0.180 in the CTO imaging cohort at baseline (n = 106 target limbs) and 0.924 ± 0.244 (85 target limbs) at 12 months. Mean change in ABI from baseline was 0.325 ± 0.282 (73 target limbs).

In a post hoc analysis of subjects categorized by provisional stenting, primary patency by Kaplan-Meier estimate was 82.7% for nonstented subjects (n = 67) and 88.4% for stented subjects (n = 59) through 12 months and 77.1% for nonstented subjects and 79.9% for stented subjects through 13 months (p = 0.523) (Figure 4, top). Freedom from CD-TLR through 12 months by Kaplan-Meier estimate was 86.1% in the nonstented group and 92.7% in the stented group (p = 0.211) (Figure 4, bottom).

In a similar post hoc analysis of subjects categorized by subintimal (n = 61) or intraluminal (n = 65) approach, primary patency by Kaplan-Meier estimate was 79.8% in the subintimal group and 90.3% in the intraluminal group through 12 months and 72.9% in the subintimal group and 83.2% in the intraluminal group through 13 months (p = 0.180) (Figure 5, top). Freedom from CD-TLR by Kaplan-Meier estimate was 86.1% for the subintimal group and 92.0% for the intraluminal group through 12 months and 13 months (p = 0.318) (Figure 5, bottom). Provisional stents were implanted in 49.2% (n = 30 of 61) of lesions in the subintimal group and 43.9% (n = 29 of 66) of the intraluminal group.

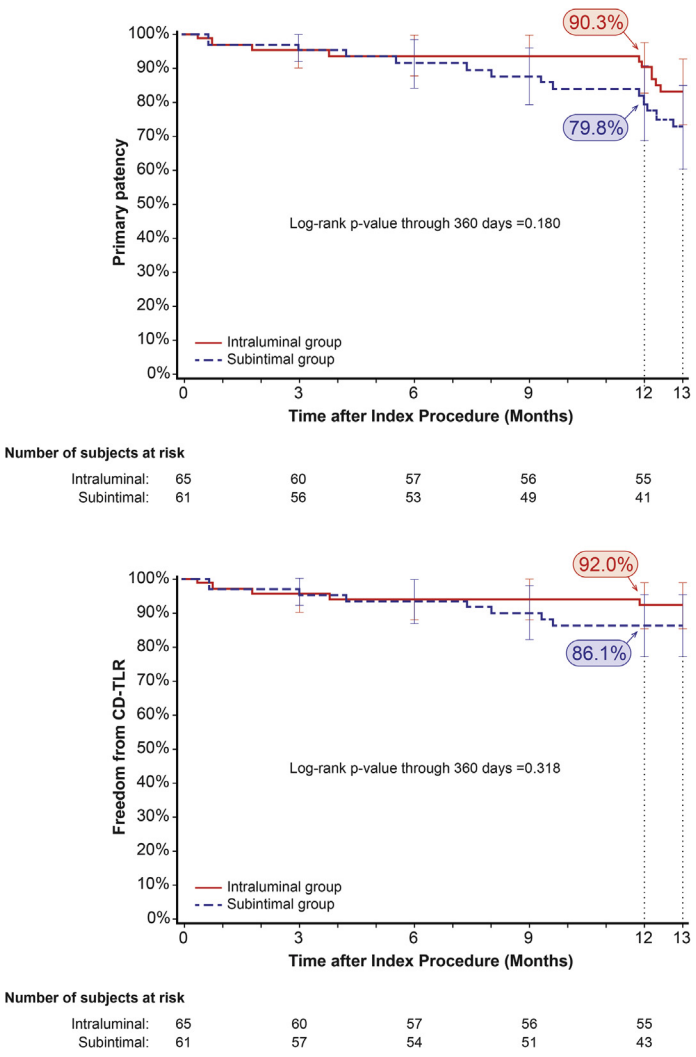
Subjects were also categorized by use (n = 63) or nonuse (n = 63) of post-dilatation during the index procedure. The results of a post hoc analysis show that primary patency by Kaplan-Meier estimate was 88.8% with post-dilatation and 81.6% without post-dilatation through 12 months and 86.6% with post-dilatation and 70.3% without post-dilatation through 13 months (p = 0.028) (Figure 6, top). Freedom from

FIGURE 4 Kaplan-Meier Curves of Primary Patency and Freedom From CD-TLR in the CTO Imaging Cohort, by Stenting



(Top) Primary patency. **(Bottom)** Freedom from CD-TLR. Number at risk represents the number at the beginning of the 30-day window before each follow-up interval. Abbreviations as in Figure 2.

FIGURE 5 Kaplan-Meier Curves of Primary Patency and Freedom From CD-TLR in the CTO Imaging Cohort, by Subintimal or Intraluminal Approach



(Top) Primary patency. **(Bottom)** Freedom from CD-TLR. Number at risk represents the number at the beginning of the 30-day window before each follow-up interval. Abbreviations as in Figure 2.

CD-TLR by Kaplan-Meier estimate was 94.8% with post-dilatation and 83.3% without post-dilatation through 12 months and 13 months ($p = 0.039$) (Figure 6, bottom).

SAFETY OUTCOMES. The 12-month primary safety composite endpoint was achieved in 88.7% ($n = 102$ of 115) of subjects in the CTO imaging cohort (primary safety endpoint) (Table 3). Major adverse events were reported in 15.7% ($n = 18$ of 115) of subjects. There were no device- or procedure-related deaths through 30 days and no major target limb amputations through 12 months. The rate of all-cause death was 4.3% ($n = 5$ of 115). Causes of death were necrotizing fasciitis at 85 days, stroke at 123 days, euthanasia at 136 days, acute pancreatitis at 138 days, and cerebral edema at 313 days.

Thrombosis at the target lesion occurred in 4.3% ($n = 5$ of 115) of all subjects (Table 3). When subjects were categorized by nonstented versus stented, rates of thrombosis were 7.9% ($n = 5$ of 63) and 0.0% (0 of 52 subjects), respectively. When subjects were categorized by subintimal versus intraluminal approach, rates of thrombosis were 3.8% ($n = 2$ of 53) and 4.8% ($n = 3$ of 62), respectively.

DISCUSSION

CTOs are among the most challenging types of lesion to treat with endovascular strategies. Many CTOs are difficult to cross with standard intraluminal guidewire manipulation, and the plaque burden and calcification of CTO lesions can lead to dissections and elastic recoil after PTA. Stenting can resolve some of the mechanical issues associated with PTA treatment of CTO lesions, but not address the risk of restenosis after angioplasty with an uncoated balloon.

The IN.PACT Global Study CTO imaging cohort analysis is the largest prospective multicenter trial of subjects with femoropopliteal CTO, and the first clinical study to evaluate DCBs for the treatment of femoropopliteal CTO. Twelve-month outcomes from this study are better than what has been reported on metal stents or stent grafts for femoropopliteal CTO in the majority of the literature (16-18,20,21). Twelve-month primary patency by Kaplan-Meier estimate was 85.3% in the overall CTO imaging cohort (mean length 22.8 cm), compared with 77% in a prospective study of direct stenting (mean length not reported) (20), 78% in a prospective study of PTA with metal stents (mean length 24.5 cm) (16), 79% in a retrospective study of PTA with metal stents (17), and 80% in a prospective study of PTA with stent grafts (18). In a prospective study of PTA with stent graft for long (>20 cm, mean length 26.5 cm) TASC (TransAtlantic Inter-Society Consensus II) C and D lesions, 92.9% of which were CTO, 12-month primary patency by Kaplan-Meier estimate was even lower, at 67% (22). The exception to this trend is the 34-subject SUPER-SUB (SUPERa stenting after SUBintimal crossing) study, which treated long TASC C/D CTOs and demonstrated a 1-year patency of 94.1% with a mean length of 27.9 cm (21).

Paclitaxel DCBs were safe for the treatment of subjects in the CTO imaging cohort. There was no device- or procedure-related deaths through 30 days and no major target limb amputations through

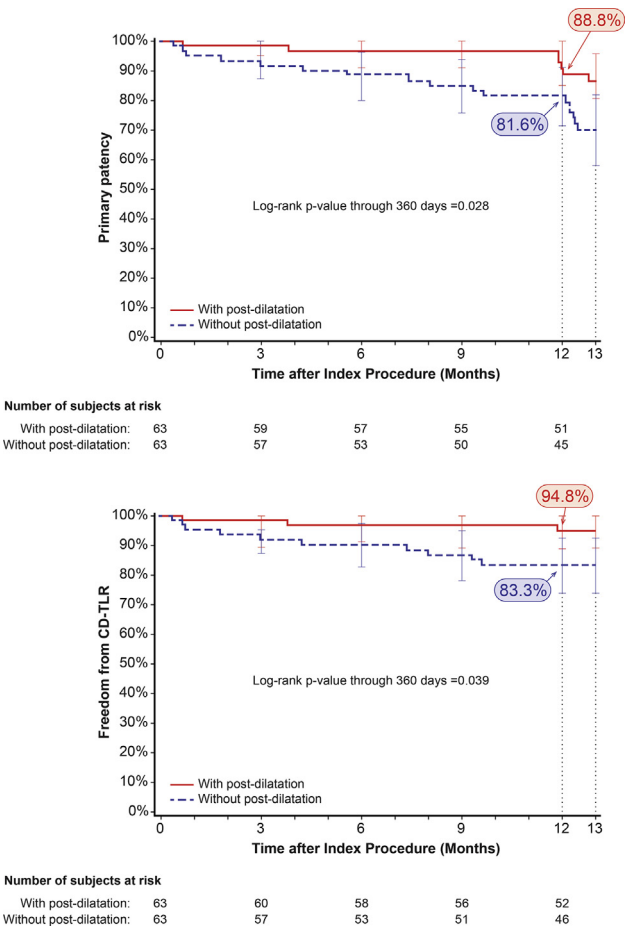
12 months. The 12-month incidence of thrombosis was low (4.3%), and all cases were in the nonstented group. A post hoc subgroup analysis of the CTO imaging cohort evaluated the potential for different outcomes between subjects provisionally stented versus nonstented subjects. Primary patency at 12 months was 82.7% for nonstented subjects and 88.4% for stented subjects. Freedom from CD-TLR at 12 months was 86.1% in the nonstented group and 92.7% in the stented group.

Further subgroup analysis of the CTO imaging cohort evaluated the potential for different outcomes after a subintimal versus intraluminal approach. Twelve-month primary patency and freedom from CD-TLR were higher in the intraluminal group (90.3% and 92.0%) versus the subintimal group (79.8% and 86.1%). While the difference between groups was not statistically significant for either measure in this study, a similar finding was reported from a prospective trial of a paclitaxel drug-eluting stent, which showed that the 12-month rate of restenosis was lower with an intraluminal (35%) versus subintimal (45%) approach in subjects with femoropopliteal CTO (23).

A similar post hoc analysis showed that 12-month primary patency and freedom from CD-TLR were higher among subjects with post-dilatation (88.8% and 94.8%) versus those without post-dilatation (81.6% and 83.3%). To our knowledge, these are the first data to suggest that post-dilatation might have a positive role in supporting patency after DCB use. The reason for the finding is not clear. One theoretical possibility is that post-dilatation could enhance the retention of paclitaxel compared with treatment without post-dilatation. Further research is needed to substantiate our finding. Additional research should also be done to evaluate whether post-dilation has an especially positive effect in a specific subgroup of CTOs with dissections—or if DCB outcomes are generally enhanced by post-dilatation.

Clinical data on the safety and effectiveness of endovascular therapies for the treatment of femoropopliteal CTO are limited, and this CTO imaging cohort analysis is the largest prospective multicenter study to evaluate any endovascular modality in subjects with CTO in the SFA and/or popliteal artery. The CTO imaging cohort analysis is also the first study to evaluate the safety and effectiveness of a DCB for the treatment of CTO in the SFA or popliteal artery. The findings in this analysis are supported by a study design that specifically combined the all-comer approach of an observational registry with the rigor of a clinical trial, such as the independent adjudication of adverse events by a Clinical Events Committee and the independent analysis of all angiography and DUS by core laboratories.

FIGURE 6 **Kaplan-Meier Curves of Primary Patency and Freedom From CD-TLR in the CTO Imaging Cohort, by Use or Nonuse of Post-Dilatation**



(Top) Primary patency. **(Bottom)** Freedom from CD-TLR. Number at risk represents the number at the beginning of the 30-day window before each follow-up interval. Abbreviations as in Figure 2.

STUDY LIMITATIONS. This pre-specified analysis of CTOs from the IN.PACT Global Study was single arm and nonrandomized. In addition, choice of pre- or post-dilatation was left to the discretion of the operator. These data are not generalizable to other DCB platforms. Each DCB must be studied independently and outcomes reported for individual evaluation by the endovascular community. Although all stents used in this study were bare-metal stents, the brand or type was not uniformly collected.

TABLE 3 12-Month Safety Outcomes For Subjects in the CTO Cohort, by Intervention Approach and by Provisional Stenting

Safety Outcome*	CTO Imaging Cohort (n = 115)†	Subintimal (n = 53)	Intraluminal (n = 62)	Nonstented (n = 63)	Stented (n = 52)	With Post-Dilatation (n = 57)	Without Post-Dilatation (n = 58)
Clinically driven TLR‡	13 (11.3)	8 (15.1)	5 (8.1)	9 (14.3)	4 (7.7)	3 (5.3)	10 (17.2)
Clinically driven TVR	13 (11.3)	8 (15.1)	5 (8.1)	9 (14.3)	4 (7.7)	3 (5.3)	10 (17.2)
Primary safety endpoint§	102 (88.7)	45 (84.9)	57 (91.9)	54 (85.7)	48 (92.3)	54 (94.7)	48 (82.8)
Major adverse events‖	18 (15.7)	9 (17.0)	9 (14.5)	12 (19.0)	6 (11.5)	7 (12.3)	11 (19.0)
Death (all-cause)	5 (4.3)	2 (3.8)	3 (4.8)	3 (4.8)	2 (3.8)	4 (7.0)	1 (1.7)
Major target limb amputation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombosis	5 (4.3)	2 (3.8)	3 (4.8)	5 (7.9)	0 (0.0)	2 (3.5)	3 (5.2)
Time to first thrombosis, days	73.0 ± 119.9	17.0 ± 5.7	110.3 ± 153.3	73.0 ± 119.9	–	22.5 ± 13.4	106.7 ± 156.2
Any TLR	14 (12.2)	9 (17.0)	5 (8.1)	9 (14.3)	5 (9.6)	4 (7.0)	10 (17.2)
Any TVR	14 (12.2)	9 (17.0)	5 (8.1)	9 (14.3)	5 (9.6)	4 (7.0)	10 (17.2)

Values are n (%) or mean ± SD. *An independent Clinical Events Committee adjudicated all major adverse events. †Event rates expressed as a proportion: the numerator is the number of subjects with an event and the denominator is the number of subjects with at least 330 days of clinical follow-up. ‡The Clinical Events Committee reviewed all target lesion revascularization (TLR) and target vessel revascularization (TVR) events to determine which were clinically driven (CD), defined as any reintervention within the target lesion(s) due to symptoms or ankle-brachial index (ABI) decrease of ≥20% or >0.15 when compared with post-index procedure baseline ankle-brachial index. §The primary safety composite endpoint was freedom from device- and procedure-related mortality through 30 days, and freedom from major target limb amputation and CD-TVR within 12 months post-index procedure. TVR was assessed at the subject level and defined as the first event that required TVR in the subject. ‖The major adverse event composite was defined as all-cause mortality, CD-TVR, major target limb amputation, and thrombosis at the target lesion site through 12 months.

CONCLUSIONS

The paclitaxel DCB was safe and effective up to 12 months after treatment in a rigorous independently adjudicated study of real-world subjects with CTO (≥5 cm, mean length 22.8 ± 9.8 cm) in the entire femoropopliteal artery.

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PERSPECTIVES

WHAT IS KNOWN? Endovascular intervention is an accepted first-line option for the treatment of patients with symptomatic peripheral artery disease. Complex lesions such as CTOs are especially difficult to manage and there is limited evidence on the safety and effectiveness of endovascular therapies for the treatment of CTO in the SFA or popliteal artery.

WHAT IS NEW? Results from the IN.PACT Global Study CTO imaging cohort analysis show that a paclitaxel DCB was safe and effective up to 12 months after treatment in a prospective independently adjudicated study of subjects with CTO (≥5 cm, mean length 22.83 ± 9.76 cm) in the SFA and/or entire popliteal artery.

WHAT IS NEXT? Future investigations should focus on head-to-head studies of different modalities for treatment of PAD, both endovascular and surgical, and incorporate economic analyses.

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KEY WORDS chronic total occlusions, drug-coated balloon, peripheral artery disease

APPENDIX For an expanded Methods section, please see the online version of this paper.