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Outcomes After Drug-Coated Balloon Treatment of Femoropopliteal Lesions in Patients With Critical Limb Ischemia: A Post Hoc Analysis From the IN.PACT Global Study

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Abstract

Purpose: To report a post hoc analysis performed to evaluate 1-year safety and efficacy of the IN.PACT Admiral drug-coated balloon (DCB) for the treatment of femoropopliteal lesions in subjects with critical limb ischemia (CLI) enrolled in the IN.PACT Global study (*ClinicalTrials.gov* identifier NCT01609296). **Materials and Methods:** Of 1535 subjects enrolled in the study, 156 participants (mean age 71.8±10.4; 87 men) with CLI (Rutherford categories 4,5) were treated with DCB angioplasty in 194 femoropopliteal lesions. This cohort was compared to the 1246 subjects (mean age 68.2±10.0 years; 864 men) with intermittent claudication (IC) treated for 1573 lesions. The CLI cohort had longer lesions (13.9±10.6 vs 11.9±9.4 cm, p=0.009) and a higher calcification rate (76.8% vs 67.7%, p=0.011). Major adverse events [MAE; composite of all-cause mortality, clinically-driven target lesion revascularization (CD-TLR), major (above-ankle) target limb amputation, and thrombosis at the target lesion site], lesion and vessel revascularization rates, and EuroQol-5D were assessed through 1 year. The Kaplan-Meier method was used to estimate survival, CD-TLR, and amputation events; estimates are presented with the 95% confidence intervals (CI). **Results:** Estimates of 12-month freedom from major target limb amputation were 98.6% (95% CI 96.7% to 100.0%) in subjects with CLI and 99.9% (95% CI 99.8% to 100.0%) in subjects with IC (p=0.002). Freedom from CD-TLR through 12 months was 86.3% (95% CI 80.6% to 91.9%) in CLI subjects and 93.4% (95% CI 91.9% to 94.8%) in IC subjects (p<0.001). The MAE rate through 12 months was higher in CLI subjects (22.5% vs 10.7%, p<0.001), and CLI patients had poorer overall survival (93.0%, 95% CI 88.9% to 97.2%) than IC subjects (97.0%, 95% CI 96.0% to 97.9%, p=0.011). Health status significantly improved in all domains at 6 and 12 months in both groups. **Conclusion:** Treatment of femoropopliteal disease with DCB in CLI patients is safe through 12-month follow-up, with a low major amputation rate of 1.4%. The rates of MAE and CD-TLR were higher in CLI subjects and reinterventions were required sooner. Additional research is needed to evaluate long-term outcomes of DCB treatment for femoropopliteal lesions in CLI patients.

Keywords

amputation, claudication, critical limb ischemia, drug-coated balloon, femoropopliteal segment, limb salvage, peripheral artery disease, popliteal artery, stenosis, superficial femoral artery, target lesion revascularization

Introduction

Critical limb ischemia (CLI) is the most advanced stage of peripheral artery disease (PAD) and includes ischemic rest pain and tissue loss, classified as Rutherford category (RC) 4–6. In addition to these symptoms, patients with CLI usually have a high cardiovascular risk profile.[1–3] While all patients with PAD have an increased risk of developing cardiovascular events, this risk is 3 times higher in patients with CLI compared to those with intermittent claudication (IC).[1,3] More than 10% of patients with CLI will eventually require a major limb amputation, resulting in functional impairment that negatively affects quality of life.[4,5] Without revascularization, both all-cause mortality and major

amputation rates are >20% after a median follow-up of 12 months,[6] emphasizing the need for adequate treatment.

Treatment of CLI focuses on revascularization to relieve rest pain and help heal ulcers; the ultimate treatment goal is amputation-free survival while maintaining quality of life and a functional limb. This requires a multidisciplinary and well-coordinated approach that includes wound care, podiatry, optimal medical treatment, and secondary cardiovascular risk management in addition to revascularization procedures.[2] Most guidelines still recommend bypass surgery using a venous conduit as the primary treatment for CLI patients with a life expectancy >2 years.[1]

An endovascular-first strategy is not yet generally recommended given the lack of robust clinical evidence, yet these techniques are increasingly performed in patients with CLI.[3,7] Percutaneous transluminal angioplasty (PTA) has been shown to be effective in patients presenting with CLI referable to femoropopliteal occlusive disease,[8] but higher restenosis rates are seen after PTA than after surgical bypass.[9] However, treatment with PTA demonstrated similar amputation-free survival, a shorter hospital stay, and lower procedure risk compared to bypass surgery, according to a recent Cochrane review.[10] Novel endovascular strategies, including drug-coated balloons (DCBs) and drug-eluting stents, could reduce the incidence of restenosis and improve the efficacy of endovascular treatment long term.[11–13] Randomized controlled trials (RCTs) have demonstrated superior patency and freedom from target lesion revascularization (TLR) using DCBs in femoropopliteal lesions compared to PTA in patients with RC 2–4.[12,14–16] A meta-analysis has confirmed that DCBs reduce the risk for TLR in femoropopliteal lesions within 12 months after treatment.[17]

To date, studies have reported on either patients with IC or mixed groups of patients with IC and CLI, making it difficult to draw conclusions on the primary clinical outcome measures for patients with CLI and disease of the femoropopliteal segment. The IN.PACT Global trial was a prospective study designed to expand the clinical evidence of the IN.PACT Admiral DCB for the treatment femoropopliteal lesions in a real-world patient population consisting of both IC and CLI patients (RC 2–4).[18] This post hoc analysis sought to examine the 12-month results from CLI subjects, including protocol deviations with RC 5, enrolled in the IN.PACT Global study, focusing on outcome parameters particularly relevant for patients with advanced atherosclerotic femoropopliteal disease.

Materials and Methods

IN.PACT Global Study: Design, Subjects, and Treatment

Detailed descriptions of the study design, inclusion and exclusion criteria, and study endpoints have been previously reported.[18] Briefly, the IN.PACT Global study is a prospective, multicenter, international, single-arm clinical study assessing the safety and effectiveness of a paclitaxel-coated DCB (IN.PACT Admiral DCB; Medtronic, Minneapolis, MN, USA) in the treatment of femoropopliteal atherosclerotic disease. Subjects with symptoms of IC and/or ischemic rest pain (RC 2–4) and angiographic evidence of severe stenosis or occlusion [length ≥2 cm; de novo or restenosis in native vessel or in-stent)] in the superficial femoral artery (SFA) and/or popliteal artery (P1-P3 segments) were eligible for enrollment. This post hoc analysis reports on enrollees categorized as RC 4,5 and compares them to RC 2,3. Of note, RC 5 was considered a protocol deviation in the study. Additionally, 1 patient was enrolled as a protocol deviation with RC 1, and 4 patients overall did not have RC noted at baseline.

An independent Clinical Events Committee (CEC) adjudicated all major adverse events (MAE). The institutional review board or ethics committee at each study site approved the study protocol. Informed consent was obtained from all subjects 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.

Baseline Patient Characteristics

A total of 1535 subjects were enrolled in the IN.PACT Global study. Of these, 156 subjects (mean age 71.8±10.4; 87 men) with RC-4 (n=120) or RC-5 (n=36) ischemia were

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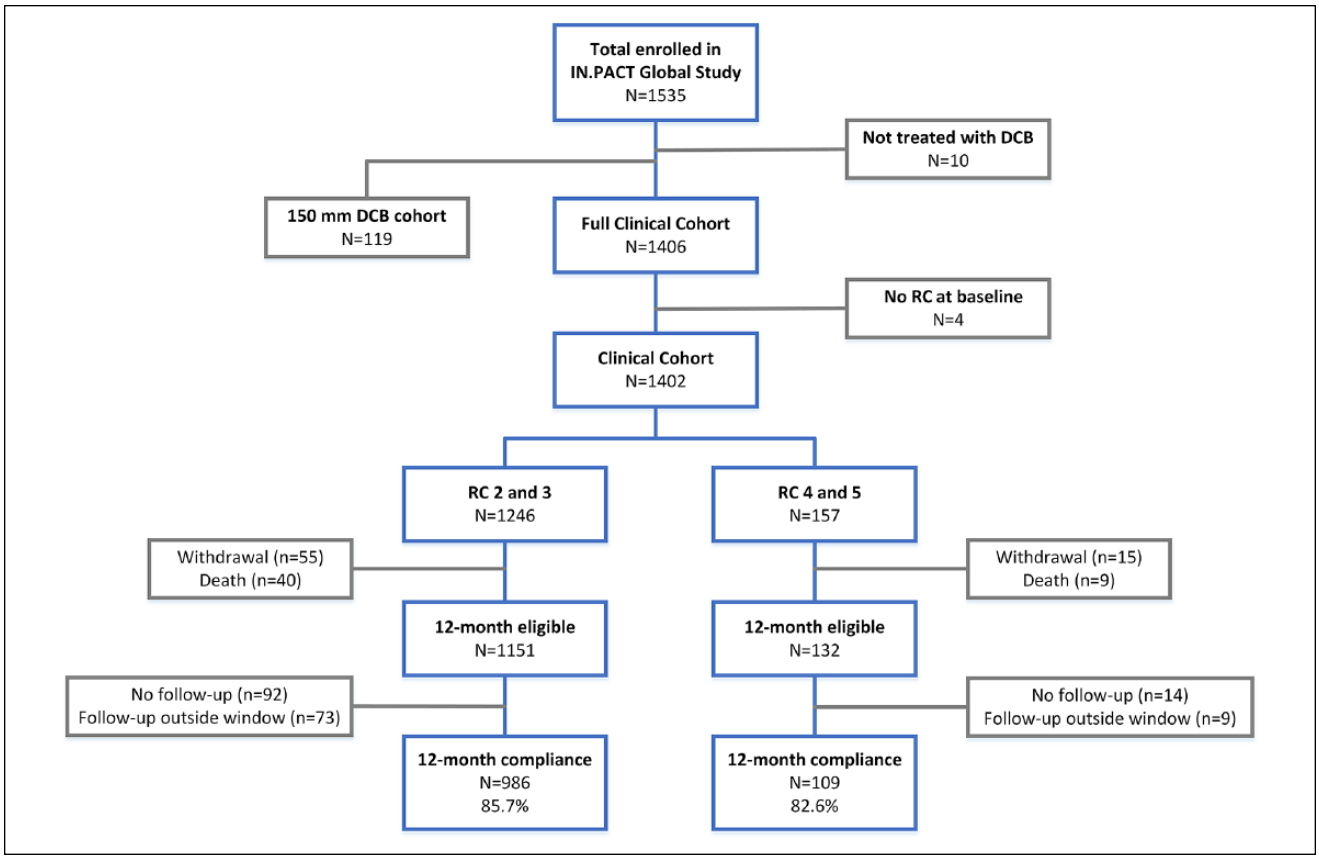

Figure 1. Flowchart of the study population through 1-year follow-up. DCB, drug-coated balloon; RC, Rutherford category.

treated with a DCB for 194 lesions (146 RC 4 and 48 RC 5) and were assigned to the CLI subgroup. The IC subgroup consisted of 1246 subjects (mean age 68.2±10.0 years; 864 men) in which 1573 lesions were treated with a DCB. The flowchart is depicted in Figure 1; baseline patient characteristics are listed in Table 1. Compared with the IC cohort (RC 2,3), subjects with CLI (RC 4,5) were older, more often female, and had more diabetes mellitus and renal insufficiency. In contrast, IC subjects had a higher percentage of current smokers and hyperlipidemia. The ankle-brachial index (ABI) was significantly lower in the CLI group.

At baseline, 87 (55.8%) CLI patients previously underwent peripheral revascularization, compared to 647 subjects with IC (51.9%; p=0.40). Overall, 93 (63.4%) subjects with CLI were previously diagnosed with below-the-knee (BTK) vascular disease of the target limb [75 (65.8%) RC 4 vs 18 (54.5%) RC 5]. Eighteen subjects (12 RC 4 and 6 RC 5) had previously undergone minor amputations on the target limb (RC 4: 11 toe and 1 transmetatarsal; RC 5: 4 toe and 2 transmetatarsal). In addition, 13 subjects had previous amputations on the contralateral limb (4 toe, 2 transmetatarsal, 5 BTK, and 2 above the knee). In comparison, 28 IC subjects had 32 total amputations [21 toe (11 target limb and 10 contralateral limb), 3 above the knee (contralateral limb), 2 BTK amputations (contralateral limb), and 6 transmetatarsal (3 target limb and 3 contralateral limb).

Study Endpoints

The primary safety composite endpoint was freedom from device- and procedure-related mortality through 30 days, as well as freedom from major target limb amputation and clinically-driven target vessel revascularization (CD-TVR) within 12 months after the index procedure. CD-TVR was assessed at the subject level and defined as the first event that required CD-TVR in the subject. The primary effectiveness endpoint was freedom from CD-TLR within 12 months. The CEC reviewed all CD-TLR and CD-TVR events to determine which were clinically driven, defined as any reintervention within the target lesion(s) due to symptoms or ABI decrease ≥20% or >0.15 when compared with the postprocedure ABI. CD-TLRs or CD-TVRs did not include those procedures that were performed on asymptomatic subjects or were based only on diagnostic imaging procedures.

The composite MAE endpoint included all-cause mortality, CD-TVR, major (above-ankle) target limb amputation, and thrombosis at the target lesion site. Sustained

Table 1. Baseline and Lesion Characteristics for Patients With Intermittent Claudication (Rutherford Categories 2,3) vs Critical Limb Ischemia (Rutherford Categories 4,5).[a]

Variables	IC (1246 subjects, 1573 lesions)	CLI (156 subjects, 194 lesions)	p
Clinical characteristics[b]			
Age, y	68.2±10.0	71.8±10.4	<0.001
Men	864 (69.3)	87 (55.8)	0.001
Hypertension	1032 (83.2)	133 (85.3)	0.569
Hyperlipidemia	862 (71.5)	96 (62.3)	0.024
Diabetes mellitus	474 (38.2)	85 (54.5)	<0.001
Carotid artery disease	220 (20.4)	21 (17.8)	0.547
Coronary heart disease	476 (40.1)	62 (44.0)	0.414
Current smoker	411 (33.0)	35 (22.4)	0.008
Renal insufficiency[c]	108 (10.0)	28 (20.1)	<0.001
Obesity (BMI ≥30 kg/m^2)	256 (20.7)	28 (18.4)	0.594
ABI	0.69±0.21 [0.68 (0.00, 1.82)]	0.60±0.26 [0.61 (0.00, 1.76)]	<0.001
Bilateral treated	109 (8.7)	7 (4.5)	0.88
Previous revascularization	647 (51.9)	87 (55.8)	0.395
Angiographic characteristics[d]			
SFA	870 (69.8)	79 (50.6)	<0.001
PA	89 (7.1)	12 (7.7)	0.744
Both SFA and PA	287 (23.0)	65 (41.7)	<0.001
Lesion length, cm	11.56±9.39	13.94±10.55	0.009
Total occlusion	547 (34.8)	80 (41.2)	0.080
Calcification	1064 (67.7)	149 (76.8)	0.011
Severe calcification[e]	159 (10.1)	22 (11.3)	0.615
Lesion type			0.962
De novo	1170 (74.4)	144 (74.2)	
Restenotic	118 (7.5)	17 (8.8)	
In-stent restenosis	285 (18.1)	33 (17.0)	

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CLI, critical limb ischemia; IC, intermittent claudication; PA, popliteal artery; SFA, superficial femoral artery.

[a]Continuous data are shown as mean ± standard deviation [median (min, max)]; categorical data are given as number (percentage).

[b]Clinical characteristics are subject based.

[c]Baseline serum creatinine ≥1.5 mg/dL.

[d]Lesion characteristics are lesion based.

[e]Calcification with circumference ≥180° (both sides of vessel at the same location) and length greater than or equal to half of the total lesion length.

clinical improvement was defined as freedom from major target limb amputation, freedom from TVR, and upward shift of at least 1 RC category.

Health status was assessed at baseline and 12 months using the EuroQol 5 dimensions (EQ-5D) questionnaire and the visual analog scale (VAS) to quantify pain. The participants who could not complete these health-related quality of life scores assessment questions were disregarded in the analysis of this outcome measure.

Statistical Analysis

All analyses were based on the intention-to-treat principle. Unless otherwise specified, all baseline demographics and clinical characteristics were summarized on a subject basis; lesion characteristics were summarized on a lesion basis. All summaries were based on nonmissing assessments. For baseline characteristics, continuous variables were described as mean ± standard deviation (range as minimum-maximum) or median and interquartile range (IQR Q1, Q3) if applicable; dichotomous and categorical variables were described as counts and proportions. 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 with an event or at least 300 days of clinical follow-up was the denominator. For assessment of clinical characteristics at 12 months, subjects were required to have data at baseline and 12 months. The Kaplan-Meier method was used to estimate time-to-event data for survival, freedom from CD-TLR, and freedom from major target limb amputation over the 12-month follow-up. The estimates are presented with the 95% confidence intervals (CI) and were compared with the log-rank test. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Table 2. Procedure Characteristics for Patients With Intermittent Claudication (Rutherford Categories 2,3) vs Critical Limb Ischemia (Rutherford Categories 4,5).[a]

Variables	IC (1246 subjects, 1573 lesions)	CLI (156 subjects, 194 lesions)	p
Characteristics by lesion			
DCBs used per lesion	1.7±1.0	1.8±1.0	0.072
Total DCB length per lesion, mm	157.8±109.5	179.1±119.5	0.012
Maximal inflation pressure of first treatment balloon, atm	8.0 (0, 25)	8.0 (4, 16)	0.262
Postprocedure treated length, mm	144.5±94.7	161.1±106.3	0.039
Postprocedure stenosis, %	11.6 (0, 100)	10.1 (0, 50)	0.080
Provisional stents per lesion	1.3±0.6	1.2±0.5	0.529
Provisional stent length per lesion, mm	117.6±83.5	124.9±98.3	0.612
Provisional stent total (per lesion)	334 (21.4)	39 (20.3)	0.780
Characteristics by subject			
Predilation	978 (78.5)	117 (75.0)	0.355
Length of DCB, mm	199.0±125.9	222.7±123.0	0.026
Postdilation	436 (35.2)	53 (34.4)	0.929
Provisional stents per subject	1.4±0.6	1.3±0.6	0.793
Provisional stent length, mm	123.9±88.8	135.3±103.4	0.473
Provisional stent total	317 (25.6)	36 (23.4)	0.623
Device success[b]	2621/2638 (99.4)	352/353 (99.7)	0.713
Procedure success[c]	1228/1238 (99.2)	154/154 (100)	0.614
Clinical success[d]	1223/1238 (98.8)	152/154 (98.7)	>0.99
Dissections			0.003
0 (no dissection)	875/1572 (55.7)	127/194 (65.5)	
A (luminal haziness)	223/1572 (14.2)	30/194 (15.5)	
B (linear dissection)	230/1572 (14.6)	17/194 (8.8)	
C (extraluminal contrast)	115/1572 (7.3)	10/194 (5.2)	
D (spiral dissection)	73/1572 (4.6)	5/194 (2.6)	
E (reduced flow)	48/1572 (3.1)	2/194 (1.0)	
F (total occlusion)	8/1572 (0.5)	3/194 (1.5)	

Abbreviations: CLI, critical limb ischemia; DCB, drug-coated balloon; IC, intermittent claudication.
[a]Continuous data are shown as mean ± standard deviation or median (min, max); categorical data are given as number (percentage).
[b]Successful delivery, inflation, deflation, and retrieval of the intact study balloon device without burst below the recommended burst pressure.
[c]Residual stenosis ≤50% (nonstented subjects) or ≤30% (stented subjects) by visual estimate.
[d]Procedure success without complications (death, major target limb amputation, thrombosis of the target lesion, or target vessel revascularization) prior to discharge.

Results

Lesion Characteristics

The majority of both IC and CLI subjects had a single (78.2% IC and 83.3% CLI) de novo (74.4% IC and 74.2% CLI) lesion. Compared to subjects with IC, the CLI cohort had longer lesion lengths (13.94±10.55 vs 11.56±9.39 cm, p=0.009), more calcification (76.8% vs 67.7%, p=0.011), and more total occlusions (41.2% vs 34.8%, p=0.080). Moreover, subjects with IC were more often treated in the SFA only (69.8% IC vs 50.6% CLI, p<0.001) than in both the SFA and popliteal artery (23.0% IC vs 41.7% CLI, p<0.001). Detailed lesion characteristics are depicted in Table 1.

Procedure Characteristics

A total of 353 DCBs were used to treat the 194 lesions in the CLI cohort (Table 2). Predilation was used in the majority of subjects [117 (75.0%) CLI vs 978 (78.5%) IC]. Provisional stenting was performed in 36 (23.4%) subjects with CLI and 317 (25.6%) subjects with IC. In 127 (65.5%) of 194 lesions in CLI subjects and 875 (55.7%) of 1572 lesions in IC subjects, no postprocedural dissection was observed. In those subjects with dissections, type A was most common [30 (15.5%) CLI and 223 (14.2%) IC]. Flow-limiting dissections grades D-F were found in 10 (5.2%) lesions in the CLI cohort compared with 129 (8.2%) lesions in the IC cohort. Dissection grades were statistically different between the IC and CLI cohorts (p=0.003).

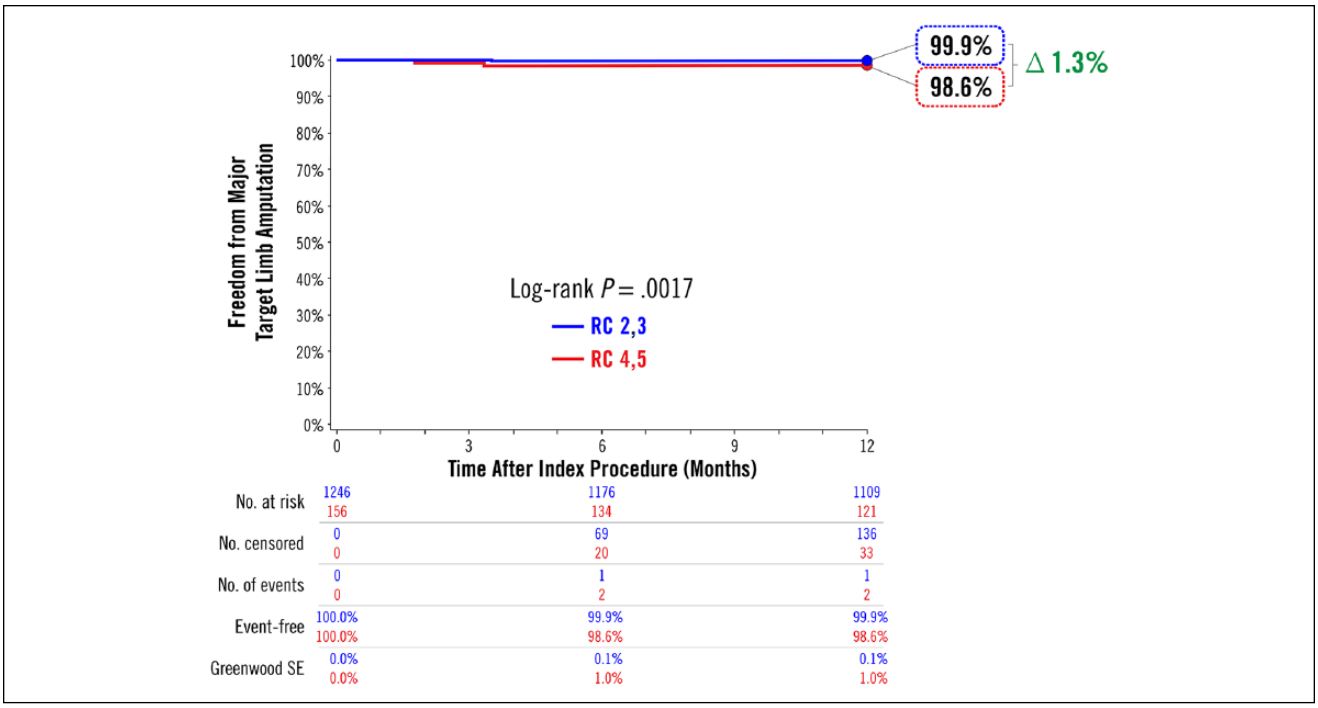

Figure 2. Kaplan-Meier estimate of freedom from major target limb amputation through 12 months in patients with Rutherford category (RC) 2,3 claudication and RC 4,5 critical limb ischemia. SE, standard error.

In the CLI cohort, device success was 99.7% (1 device malfunction) and clinical success was 98.7% (Table 2). Device success in the IC cohort was 99.4% and clinical success was 98.8%. In the CLI cohort, clinical success was limited by 1 site-reported thrombosis and 1 revascularization after 2 toe amputations, considered procedure-related complications as they occurred before discharge. Procedure characteristics were comparable for IC and CLI subjects.

Hospitalization and Complications

The mean hospitalization was 4.9±11.6 days (range 0–90) for subjects with CLI compared with 2.2±6.9 days for IC subjects (p=0.005). There was 1 death adjudicated as procedure- or device-related by the CEC in the RC 5 group 28 days after the procedure. This subject sustained a fatal cardiac arrest while hospitalized for osteomyelitis, which resulted in a toe amputation of the target limb. In the IC group there were 2 procedure- or device-related deaths through 30 days (p=0.297). Two subjects, RC 4 and RC 5, respectively, had a CD-TVR within 30 days of the procedure (1 noted in the previous paragraph). The total incidence of in-hospital complications was low in both CLI and IC subjects and included CD-TVR (1.3% vs 0.2%, respectively; p=0.098), thrombosis (0.6% vs 0.3%, respectively; p=0.446), and CD-TLR (1.3% vs 0.2%, respectively; p=0.098).

Amputation-Free Survival Through 1 Year

The overall estimated freedom from major target limb amputation within 360 days using Kaplan-Meier analysis (Figure 2) was 98.6% (95% CI 96.7% to 100.0%) in subjects with CLI and 99.9% (95% CI 99.8% to 100.0%) in subjects with IC (log-rank p=0.002). In the CLI group, freedom from major target limb amputation estimates were similar in RC 4 (99.1%, 95% CI 97.4% to 100%) vs RC 5 (97.0%, 95% CI 91.1% to 100%, log-rank p=0.369).

Major target limb amputation was performed in 2 CLI subjects between 1 and 12 months. One RC-4 subject underwent an above-the-knee amputation 56 days post–index procedure for wet gangrene. The RC-5 subject had a BTK amputation at 105 days for worsening of preexisting wounds and osteomyelitis. The CEC adjudicated both events as having no relation to the device or procedure.

Major target limb amputation was performed in a single IC subject (RC 3 at baseline) 100 days following the index procedure. The subject developed bilateral trophic lower limb ulcerations following the procedure, and despite rehospitalization, endovascular treatment of a nontarget vessel, ulcer debridement, and patent target vessel, bilateral above-the-knee amputations were performed. The CEC adjudicated the event as having no relation to the device or procedure.

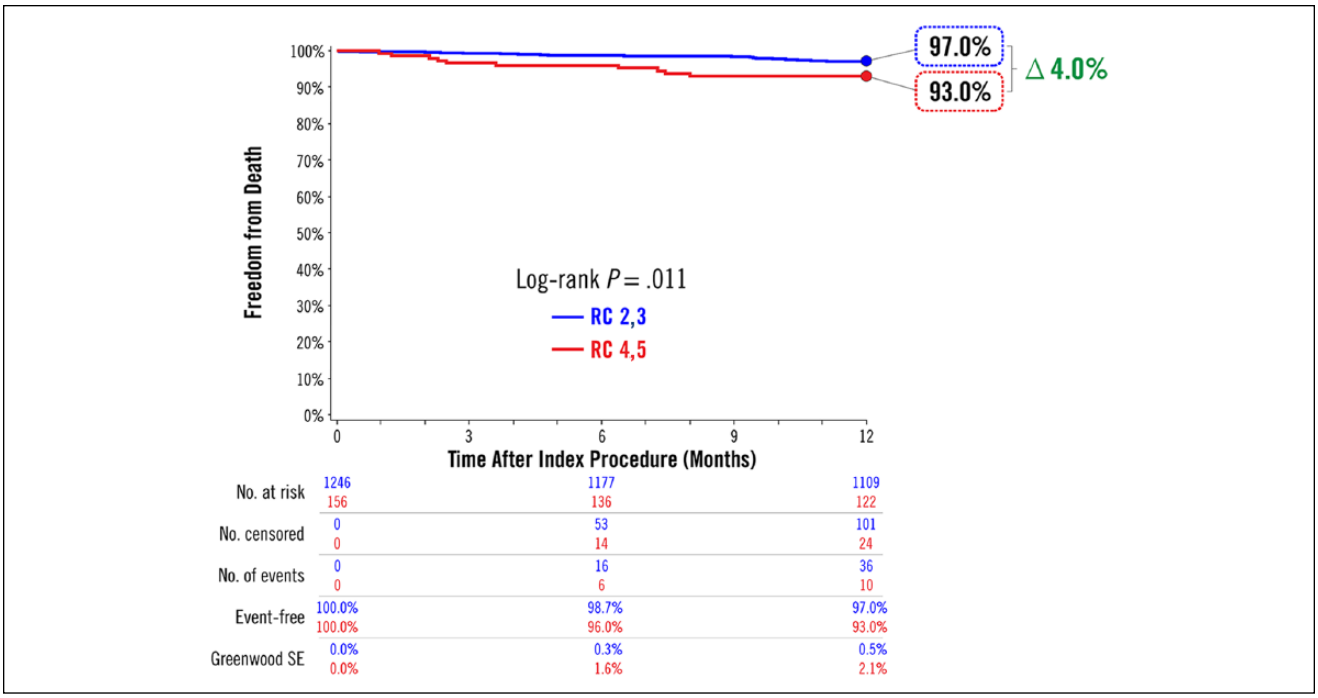

Figure 3. Kaplan-Meier estimate for freedom from death through 12 months in patients with Rutherford category (RC) 2,3 claudication and RC 4,5 critical limb ischemia. SE, standard error.

Overall Survival Through 1 Year

The overall survival estimate (Figure 3) at 1 year was significantly lower in subjects with CLI (93.0%, 95% CI 88.9% to 97.2%) than in subjects with IC (97.0%, 95% CI 96.0% to 97.9%, p=0.011). No significant difference was observed in proportion of freedom from death between RC 4 (93.6%, 95% CI 87.3% to 97.4%) and RC 5 (90.6%, 95% CI 75.0% to 98.0%). Ten CLI (7.0%) subjects died during 360 days of follow-up (7 RC 4 and 3 RC 5).

Major Adverse Events Through 1 Year

The overall MAE rate (Table 3) in CLI patients during the first year following the procedure was 22.5% (vs 10.7% in the IC group, p<0.001); the incidence of thrombosis was 4.9% and was not significantly different from the IC cohort (2.7%).

The primary safety composite endpoint rate was significantly lower in the CLI group (83.1%) compared with IC subjects (92.5%, p<0.001). Although the CLI group had more complications in general, as shown in Table 3, device- or procedure-related deaths within 30 days were similar between groups.

The overall freedom from CD-TLR estimate through 360 days using Kaplan-Meier analysis was 86.3% (95% CI 80.6% to 91.9%) in CLI subjects [86.6% (95% CI 80.3% to 92.9%) in the RC-4 group and 85.5% (95% CI 73.8% to 97.3%) in the RC-5 group (log-rank p=0.688)], which was significantly lower (log-rank p<0.001) compared with the 93.4% (95% CI 91.9% to 94.8%) estimate in the IC cohort (Figure 4). The mean time to CD-TLR was shorter for CLI subjects compared with IC subjects (67.8±76.5 vs 97.8±76.5 days, respectively; p=0.002).

Clinical Outcomes

At 6 and 12 months, 88.1% and 88.8%, respectively, of CLI subjects had an improved RC. In the IC cohort the rates were 91.1% and 88.6% at these time points. The ABI was 0.93±0.21 and 0.89±0.22 in the CLI group at 6 and 12 months, respectively, and 0.94±0.20 and 0.91±0.21 in the IC group (p=0.631 at 6 months and p=0.354 at 12 months). At both 6 and 12 months there were significant increases in ABI in the CLI and IC subjects (p<0.001 and p=0.002, respectively).

Overall, primary sustained clinical improvement was seen in 72.6% and 69.5% of CLI subjects at 6 and 12 months, respectively. However, subjects with RC 5 showed worse results compared to subjects with RC 4 at both 6 months (36.7% vs 82.9%, p<0.001) and 12 months (37.0% vs 78.2%, p<0.001). Within 6 months of follow-up, 88.1% of subjects had improved by at least 1 Rutherford category; the majority (52.4%) was asymptomatic (RC 0). In total, 14 subjects did not show clinical improvement compared with baseline at 6 months (5 RC 4 and 9 RC 5). Only 1 subject worsened from RC 4 to RC 5 over 6 months.

Table 3. Safety Outcomes Through 1 Year.[a,b]

	IC (n=1166)	CLI (n=142)	p
CD-TLR[c]	78 (6.7)	20 (14.1)	0.004
Primary safety composite endpoint[d]	1078 (92.5)	118 (83.1)	<0.001
MAE[e]	125 (10.7)	32 (22.5)	<0.001
All-cause death	36 (3.1)	10 (7.0)	0.026
CD-TVR	85 (7.3)	21 (14.8)	0.005
Major target limb amputation	1 (0.1)	2 (1.4)	0.033
Thrombosis[f]	31 (2.7)	7 (4.9)	0.177
Any TVR	89 (7.6)	21 (14.8)	0.006
Any TLR	82 (7.0)	20 (14.1)	0.007

Abbreviations: CD-TLR, clinically-driven target lesion revascularization; CD-TVR, clinically-driven target vessel revascularization; CLI, critical limb ischemia; IC, intermittent claudication; MAE, major adverse event; TLR, target lesion revascularization; TVR, target vessel revascularization.
[a]Categorical data shown as number (percentage) based on the number of subjects with at least 300 days of clinical follow-up.
[b]An independent Clinical Events Committee adjudicated all major adverse events.
[c]Any reintervention within the target lesion(s) due to symptoms or drop in the ankle-brachial index (ABI) ≥20% or >0.15 when compared with the ABI after the index procedure.
[d]Freedom from device- and procedure-related mortality through 30 days, and freedom from major target limb amputation and CD-TVR within 12 months after the procedure. CD-TVR was assessed at the subject level and defined as the first event that required CD-TVR in the subject.
[e]All-cause mortality, CD-TVR, major target limb amputation, or thrombosis at the target lesion site.
[f]Total occlusion due to thrombus formation that is rapidly evolving as confirmed by sudden onset of symptoms and documented by duplex and/or angiography of the index vessel.

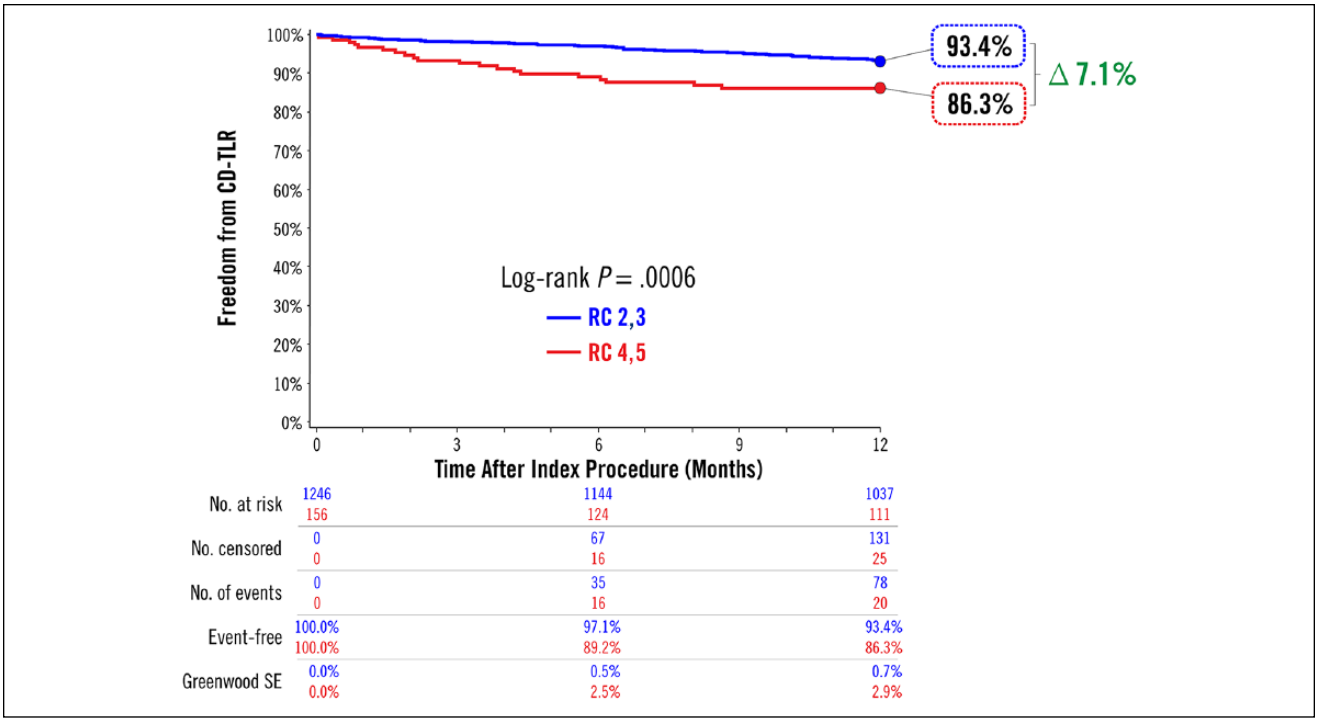

Figure 4. Kaplan-Meier estimate for freedom from clinically-driven target lesion revascularization (CD-TLR) through 12 months in patients with Rutherford category (RC) 2,3 claudication and RC 4,5 critical limb ischemia. All TLR events were adjudicated by the independent and blinded Clinical Events Committee. SE, standard error.

After 12 months of follow-up, 71.6% of the CLI subjects were categorized as RC 3 or better; the majority (51.7%) was asymptomatic. However, 6 subjects in the RC-5 group and 3 in the RC-4 group did not clinically improve compared to baseline. None of the RC-5 subjects worsened in RC status, whereas 1 subject (1.0%, 1/102) in the RC-4

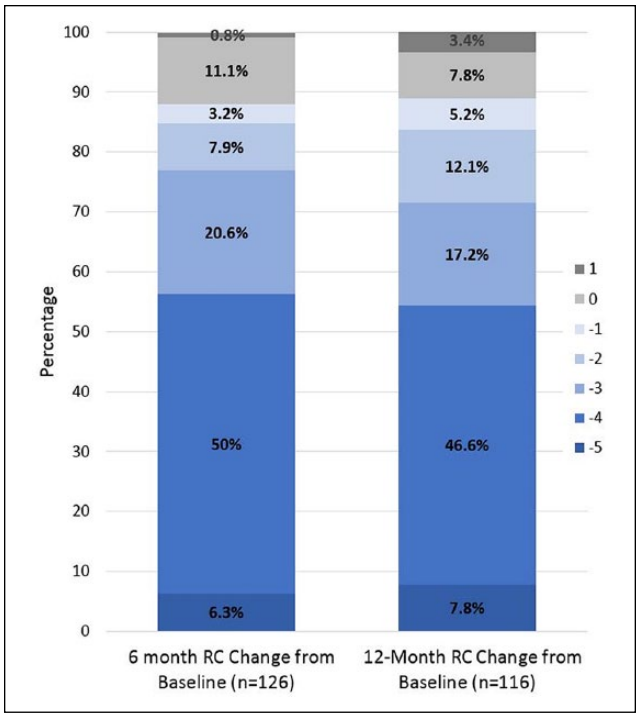

Figure 5. Changes in Rutherford category (RC) through 12 months for patients with critical limb ischemia. The changes from baseline to 6 months and baseline to 12 months were both statistically significant ($p<0.001$).

group worsened to RC 5 during 12 months of follow-up. Details of the RC improvement through 6 and 12 months for CLI subjects are depicted in Figure 5.

Sixty-nine percent of CLI subjects completed the EQ-5D questionnaire and VAS score at 12 months (Figure 6). The overall health status at baseline, measured by the EQ-5D questionnaire, showed higher scores in RC 5 compared to RC 4 ($p=0.007$). Significant improvements were observed from baseline to 6 or 12 months in all domains of the questionnaire, and there was no erosion of questionnaire scores between 6 and 12 months.

Discussion

The current analysis has shown that a high rate of amputation-free survival can be achieved in CLI patients treated with the IN.PACT Admiral DCB for femoropopliteal occlusive disease. However, patients with CLI had a higher CD-TLR rate through 12 months compared to those with IC. In addition, CLI patients required revascularization significantly earlier than IC patients and more MAE were observed, including major limb amputations through 1-year follow-up. The overall rate of survival was high but lower for CLI subjects compared with IC subjects.

These results were anticipated given the more advanced stage of atherosclerotic disease in these subjects: their baseline cardiovascular risk factors were higher and their lesions were more complex. CLI subjects were treated for longer and more calcified lesions compared to IC subjects, and lesions more often involved both the SFA and popliteal artery, while in the majority of IC subjects, only the SFA was treated. Furthermore, data about outflow disease and treatment were not captured as part of the study.

Despite these differences in outcomes, procedure characteristics were similar, showing that DCB treatment can be performed safely in CLI subjects. At 1 year, the majority of CLI subjects had an improved RC. Through 1-year follow-up, over half of the CLI subjects were asymptomatic and more than three-quarters were classified RC 3 or better. In addition, all items of the health status in the CLI cohort were improved compared to baseline.

The main goal in patients with CLI is amputation-free survival and maintenance of quality of life. Only 2 (1.3%) CLI patients had a major target limb amputation (1 in each subgroup) in 1 year, which is remarkable. The 1-year results of several RCTs comparing DCB with PTA in patients with femoropopliteal lesions showed similar overall amputation rates in the DCB groups.[11,12,19,20] Importantly, these RCTs consisted of mixed populations or did not include any patients with CLI.

The ABIs measured in both RC 4 and RC 5 at baseline were higher than would be anticipated in these patients. Although CLI is mainly a clinically-driven diagnosis, an ABI ≤ 0.5 would have been typical.[3] The higher median ABI could have resulted from participants with a falsely high ABI due to calcified arteries, which occurs most often in patients with diabetes, end-stage renal disease, or advanced age.[3,21,22] The clinical value of ABI in CLI patients could therefore be questioned.

There is very little evidence demonstrating the effectiveness of DCBs in CLI patients with femoropopliteal lesions. A real-world registry reported that of the 26.4% of patients who had CLI, 69.0% showed clinical improvement to RC 0–3 at 1 year and 85.7% at 2 years.[23] There are, however, several clinical trials that investigated the effectiveness of DCBs in CLI patients with BTK lesions. Results across these studies varied, and there remains no consensus about appropriate DCB use in CLI patients with BTK lesions, though several additional studies are ongoing. In addition to those studies focused solely on BTK treatment, the CLI-focused BASIL-3 trial started in 2015. It is a multicenter RCT focused on studying the clinical efficacy and cost effectiveness of 3 different treatments for CLI in patients with femoropopliteal or infrapopliteal lesions. Study completion can be expected in 2019.[24] Larger RCTs with head-to-head comparisons are needed to assess whether DCBs are an effective treatment for CLI patients. These trials must also include clinical outcomes, such as limb salvage, wound healing, and cost-effectiveness analyses.

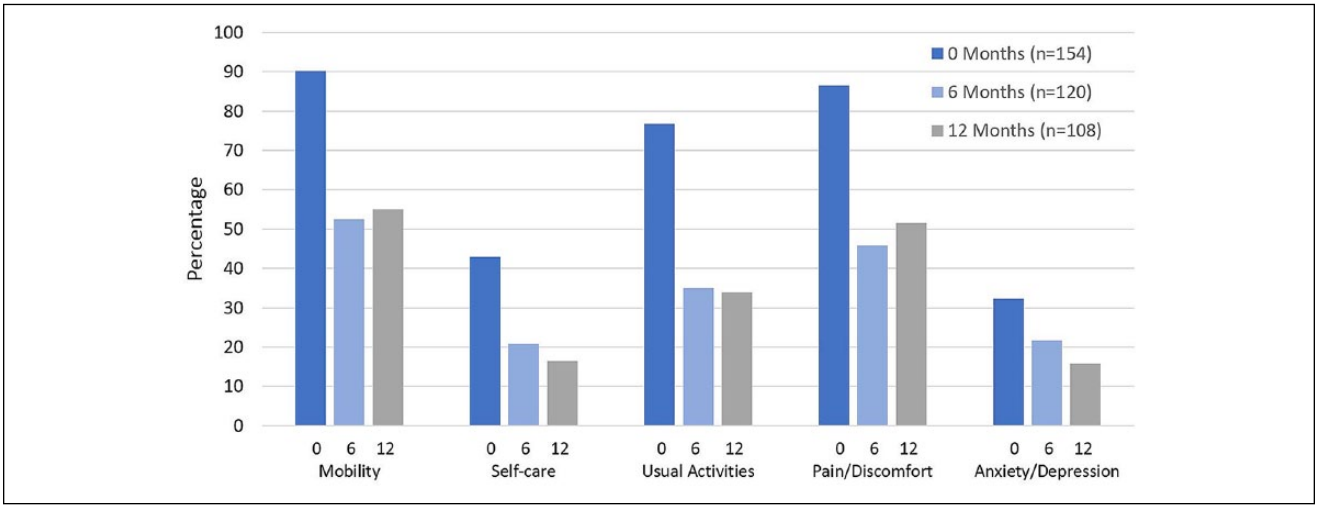

Figure 6. Changes in the EuroQol 5 Dimensions questionnaire results through 12 months for patients with critical limb ischemia.

Limitations

The present study was limited to data from the IN.PACT Global study, in which RC 5,6 were exclusion criteria, meaning only a small number of RC-5 patients were included and may represent a less severe RC-5 group. This has 2 consequences: First, the current cohort is not representative of real-world patients with CLI, which includes patients from RC 4–6, and second, this post hoc analysis was not powered. The results should therefore be interpreted with caution. From a clinical perspective, this analysis disregarded wound healing, which is an important outcome in CLI, as wound healing was not reported.

The concept of vessel preparation was not always applied in the study group, as predilation was performed in only three-quarters of cases overall in the IN.PACT Global study. Finally, data for this particular analysis was limited to follow-up through 12 months, which is relatively short. Longer follow-up in populations of RC 4–6 is necessary to draw conclusions for the efficacy and safety of DCB treatment in femoropopliteal lesions in patients with CLI.

Conclusion

Treatment of femoropopliteal disease in CLI patients using IN.PACT Admiral DCB is safe and effective, with similar performance across IC and CLI groups. Compared with IC patients, CLI patients had higher reintervention and MAE rates, though the amputation rate was low overall. These outcomes are encouraging, and more research is needed to evaluate long-term safety, effectiveness, and cost of endovascular treatment of CLI patients with disease above the knee.

Authors' Note

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Declaration of Conflicting Interests

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