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The IN.PACT DEEP Clinical Drug-Coated Balloon Trial

5-Year Outcomes

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ABSTRACT

OBJECTIVES The goal of this study was to evaluate the 5-year follow-up data of the IN.PACT DEEP (Randomized IN.PACT Amphirion Drug-Coated Balloon [DCB] vs. Standard Percutaneous Transluminal Angioplasty [PTA] for the Treatment of Below-the-Knee Critical Limb Ischemia [CLI]) trial.

BACKGROUND Initial studies from randomized controlled trials have shown comparable short-term outcomes of DCB angioplasty versus PTA in patients with CLI with infrapopliteal disease. However, the long-term safety and effectiveness of DCB angioplasty remain unknown in this patient population.

METHODS IN.PACT DEEP was an independently adjudicated prospective, multicenter, randomized controlled trial that enrolled 358 subjects with CLI. Subjects were randomized 2:1 to DCB angioplasty or PTA. Assessments through 5 years included freedom from clinically driven target lesion revascularization, amputation, and all-cause death. Additional assessments were conducted to identify risk factors for death and major amputation, including paclitaxel dose tercile.

RESULTS Freedom from clinically driven target lesion revascularization through 5 years was 70.9% and 76.0% (log-rank $p = 0.406$), and the incidence of the safety composite endpoint was 59.8% and 57.5% (log-rank $p = 0.309$) in the DCB angioplasty and PTA groups, respectively. The rate of major amputation was 15.4% for DCB angioplasty compared with 10.6% for PTA (log-rank $p = 0.108$). Given the recent concern regarding a late mortality signal in patients treated with paclitaxel-coated devices, additional analyses from this study showed no increase in all-cause mortality with DCB angioplasty (39.4%) compared with PTA (44.9%) (log-rank $p = 0.727$). Predictors of mortality included age, Rutherford category >4, and previous revascularization but not paclitaxel by dose tercile.

CONCLUSIONS Tibial artery revascularization in patients with CLI using DCB angioplasty resulted in comparable long-term safety and effectiveness as PTA. Paclitaxel exposure was not related to increased risk for amputation or all-cause mortality at 5-year follow-up. (Study of IN.PACT Amphirion™ Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia [INPACT-DEEP]; NCT00941733) (J Am Coll Cardiol Intv 2020;13:431–43)

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ABBREVIATIONS AND ACRONYMS

BTK = below-the-knee

CD-TLR = clinically driven target lesion revascularization

CLI = critical limb ischemia

DCB = drug-coated balloon

MAE = major adverse events

PTA = percutaneous transluminal angioplasty

TLR = target lesion revascularization

Critical limb ischemia (CLI) is associated with a high risk for cardiovascular events and mortality and accounts for approximately 90% of major amputations performed worldwide (1,2). Below-the-knee (BTK) bypass surgery with autologous vein grafts was the preferred treatment for CLI in the past (3); however, the presence of various underlying comorbidities and anatomic conditions precludes a significant number of patients with CLI from surgery. In the past decade, endovascular procedures have been on the rise, with decreasing rates of open bypass surgery (4). Standard percutaneous transluminal angioplasty (PTA) has been the primary endovascular therapy used in the infrapopliteal vascular bed, although it is associated with poor long-term patency rates (5). Several randomized clinical trials have demonstrated the superior performance of paclitaxel drug-coated balloon (DCB) angioplasty compared with PTA for femoropopliteal peripheral artery lesions (6–11). However, results remain varied and inconsistent in infrapopliteal trials, ranging from superior outcomes of DCB angioplasty in a single-center trial (12) to no added benefit of DCB angioplasty in multicenter trials (13,14). Furthermore, there are no long-term follow-up data beyond 3 years (15) for any DCB in BTK studies until now.

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The IN.PACT DEEP (Randomized IN.PACT Amphirion Drug-Coated Balloon [DCB] vs. Standard Percutaneous Transluminal Angioplasty [PTA] for the Treatment of Below-the-Knee Critical Limb Ischemia [CLI]) trial was conducted on the basis of the hypothesis that DCBs would significantly reduce angiographically assessed target lesion late lumen loss in patients with infrapopliteal lesions of ≤10 cm and reduce clinically driven target lesion revascularization (CD-TLR) compared with PTA at 12 months. The hypothesis also postulated that DCB angioplasty would be noninferior to PTA with reference to the primary safety endpoint, defined as a composite of all-cause death, major amputation, and CD-TLR through 6 months (16). Outcomes through 12 months were reported previously (13). In the report, DCB angioplasty had comparable primary efficacy with PTA. Although primary safety was met, there was a statistically nonsignificant but numerically higher amputation rate in the DCB arm compared with PTA through 12 months. The observed absence of efficacy superiority compared with PTA and the unfavorable amputation signal resulted in the sponsor's decision to voluntarily discontinue this DCB from the market. Nonetheless, subject follow-up was continued through 5 years as planned. Herein, we report the 5-year outcomes of the IN.PACT DEEP trial. The aim was to evaluate the long-term safety and efficacy of the IN.PACT Amphirion DCB (Medtronic, Santa Rosa, California) in comparison with PTA, focusing on safety parameters, particularly major amputations and mortality.

METHODS

STUDY DESIGN. The IN.PACT DEEP trial was a prospective, multicenter, patient-blinded, randomized controlled trial of the IN.PACT Amphirion DCB versus PTA for the treatment of infrapopliteal arterial disease in patients with CLI in Rutherford class 4 to 6. Details of the trial design and inclusion and exclusion criteria were described previously (13,16). A total of 358 patients were enrolled across 13 European sites from September 2009 to July 2012. Patients were randomized 2:1 to either the IN.PACT Amphirion DCB or PTA. Subjects were followed for a total of 60 months according to the following schedule: 30 days and 3, 6, 12, 24, 36, 48, and 60 months. Subjects had hospital visit evaluations at 30 days and 6, 12, and 24 months. At 3, 36, 48, and 60 months, subjects had phone follow-up and assessments including the occurrence of reintervention, wound status, adverse events, and health status. This trial

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was conducted in accordance with the principles of the Declaration of Helsinki, ISO 14155, and Good Clinical Practices guidelines. The ethics committees of all investigational sites approved the trial protocol, and written informed consent was obtained from all subjects before enrollment.

An independent data safety monitoring and clinical events committee (Genae, Antwerp, Belgium) adjudicated all major adverse events (MAE), including death, target limb major and minor amputations through 5 years, and target lesion revascularization (TLR) through 2 years. Statistical methods were designed by the study sponsor; the raw data were transferred to the Baim Institute for Clinical Research, formerly HCRI (Boston, Massachusetts), and analyzed independently.

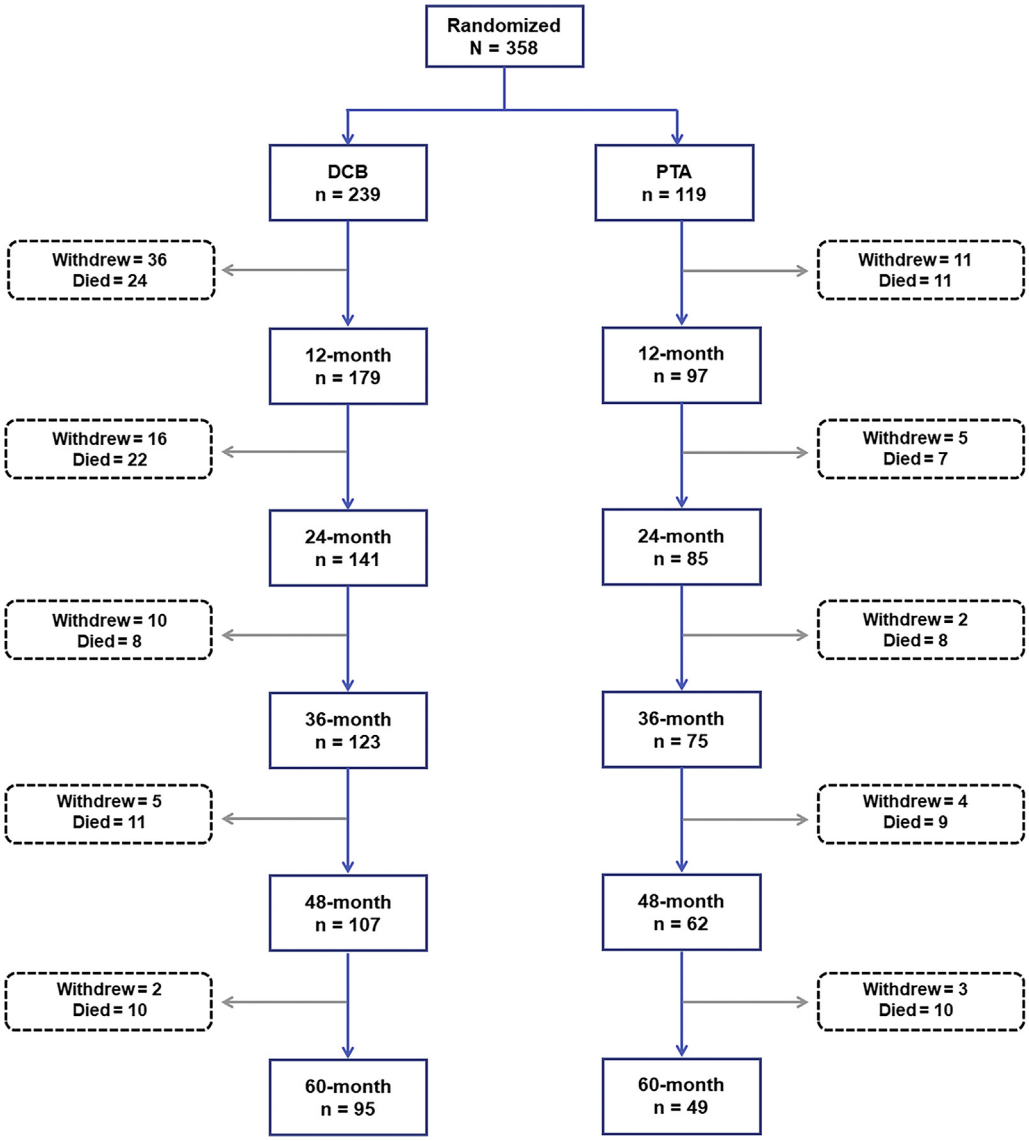
ENDPOINTS AND DEFINITIONS. Assessments through 5 years included freedom from CD-TLR, freedom from major amputation, and all-cause death. CD-TLR was defined as any TLR associated with deterioration of Rutherford category and/or an increase in the size of pre-existing wounds and/or occurrence of new wounds. The safety endpoint was a composite of all-cause death, major amputation, and CD-TLR rate assessed through 60 months. Other secondary endpoints assessed through 5 years included MAE (a composite of death of any cause, major amputation, minor amputation), individual components of MAE and TLR. TLR was defined as any repeat percutaneous intervention or bypass surgery performed on the target limb.

STATISTICAL ANALYSIS. Baseline demographics and clinical characteristics were summarized on a per subject basis; lesion characteristics were summarized on a per lesion basis. Outcome analyses were performed at a subject level. Continuous variables are described as mean ± SD, and the treatment comparison used Student's *t*-tests or Wilcoxon rank sum tests. Dichotomous and categorical variables are described as counts and proportions. The Fisher exact test or chi-square test was used to test the difference between binary variables, and the Cochran-Mantel-Haenszel test was used for comparison of nominal or ordinal variables. The Kaplan-Meier method was used to evaluate time-to-event data. The difference in the survival curves between treatment groups was assessed using the log-rank test. Furthermore, to determine the likelihood of reintervention in the presence of the competing risk for death, the cumulative incidence function from competing-risk methodology was used (17). A nonparametric test using a modified chi-square test statistic was used to compare 2 cumulative incidence functions from each treatment (18). Three hundred sixty-five days was used as the annual cutoff for the analysis of the safety and clinical endpoints. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Paclitaxel dose calculation and tercile survival analysis. This post hoc analysis is not a pre-specified endpoint in the original study protocol but was conducted as a consequence of a recently published meta-analysis suggesting an excess mortality risk following paclitaxel exposure in femoropopliteal artery interventions (19). To assess the potential impact of paclitaxel dose on mortality in this study, nominal paclitaxel dose received by each DCB subject during the index procedure was calculated on the basis of nominal dose matrix provided by the manufacturer (Medtronic). The balloon lengths and diameters received by each patient were captured on the index procedure records, and the nominal paclitaxel dose per balloon was added together to define the total dose of paclitaxel received per patient in the index procedure. The nominal dose determined for each balloon are assumed to have a full effect on each patient in the dose analysis. DCB subjects were stratified by their survival status through 5 years with the nominal paclitaxel doses compared between groups and presented as summary statistics (mean, SD, median, quartiles, and range). To further evaluate a potential correlation of increasing dose of paclitaxel on mortality, DCB subjects were segmented into terciles on the basis of the amount of paclitaxel received during the index procedure (lower, middle, and upper). Paclitaxel dose distribution in each tercile group was calculated and presented as summary statistics. The cumulative incidence of all-cause death was estimated in these 3 groups using the Kaplan-Meier method and compared among dose terciles.

Multivariable analysis. To identify predictive factors for all-cause death and major amputation in all patients, univariate analyses followed by a stepwise multivariable Cox regression model with an entry criterion of 0.2 and a stay criterion of 0.1 were used. If a p value was <0.2 in the univariate analysis, that covariate was included in the multivariable analysis to go through the stepwise selection process (20). Clinically relevant baseline variables were included for variable selection. The terciles of total dose of paclitaxel received per patient in the index procedure were forced into the final multivariable model, ignorant of the statistical significance of the p value. Hazard ratios with 2-sided 95% confidence intervals were calculated.

FIGURE 1 Subject Flowchart in the IN.PACT DEEP Trial Though 60 Months



Three hundred fifty-eight subjects were randomized 2:1 into groups that received angioplasty with the IN.PACT Amphirion drug-coated balloon (DCB) or percutaneous transluminal angioplasty (PTA). Subjects were followed for 5 years. "Withdrew" comprises subjects who could not be included in the analysis at the subsequent time point because of consent withdrawal or withdrawal by the investigator because of major amputation, bedridden, untraceable, or demented or mental health deterioration. Numbers reported here are based on within window visits, defined as 12, 24, 36, 48, and 60 months ± 30 days.

RESULTS

Three hundred fifty-eight subjects were randomized to receive treatment with DCB angioplasty (n = 239) or PTA (n = 119). Subject flow through 60-month follow-up is shown in Figure 1. Subjects were considered withdrawn and excluded from the analysis at the subsequent time point when there was a consent withdrawal or withdrawal by the investigator because of major amputation, bedridden, untraceable, or demented or mental health deterioration. A total of 95 subjects in the DCB group and 49 subjects in the PTA group completed 60-month follow-up. Overall, survival status information,

including data on patients who died during follow-up, was available for a total of 170 patients (71.1%) in the DCB group and 94 patients (79.0%) in the PTA group through 5 years. Full subject baseline data, including clinical, angiographic, and wound characteristics, were described in detail previously (13). **Table 1** summarizes salient baseline characteristics relevant to the present study. Baseline characteristics were similar between the 2 groups with the exception of mean lesion length (10.2 cm with DCB angioplasty vs. 12.9 cm with PTA; p = 0.002) and previous TLR (32.2% with DCB angioplasty vs. 21.8% with PTA; p = 0.047). Subjects in both groups had significant comorbidities, including diabetes, renal insufficiency, and previous coronary revascularization, reflecting the challenging nature of patients with CLI.

EFFICACY OUTCOMES. Kaplan-Meier estimates of freedom from CD-TLR (70.9% vs. 76.0%; log-rank p = 0.406) (**Central Illustration**) and freedom from TLR (68.6% vs. 78.4%; log-rank p = 0.236) (**Figure 2**) were not significantly different between DCB angioplasty and PTA through 60 months. Kaplan-Meier estimates of freedom from CD-TLR in the presence of death as the competing risk were 75.6% for DCB angioplasty and 79.1% for PTA (p = 0.505) (Online Figure 1).

SAFETY OUTCOMES. Safety outcomes through 60 months are reported in **Table 2**. Cumulative incidence rates of the safety endpoint, a composite of all-cause death, major amputation, and CD-TLR, were 59.8% in the DCB group and 57.5% in the PTA group (log-rank p = 0.309) through 60 months. Cumulative incidence rates of major amputation in the DCB and PTA groups were 15.4% and 10.6% (log-rank p = 0.108) through 60 months. Kaplan-Meier survival curves comparing freedom from major amputation in the DCB and PTA arms are shown in **Figure 3A**. For survival analysis, the median follow-up time for DCB angioplasty was 1,158 days (interquartile range: 364 to 1,812 days) and for PTA was 1,543 days (interquartile range: 692 to 1,822 days). There was no safety signal regarding the all-cause mortality rate in the DCB group. The cumulative incidence of all-cause death was numerically lower in the DCB group compared with the PTA group, although it was not statistically significant (39.4% for DCB angioplasty vs. 44.9% for PTA; log-rank p = 0.727) (**Table 2**). **Figure 3B** shows Kaplan-Meier survival curves of freedom from all-cause death in both treatment arms.

Causes of death through 60 months as adjudicated by the clinical events committee are summarized in Online Table 1. There were 20.9% and 17.0% (log-rank p = 0.299) cardiac-related deaths, 6.0% and 3.8% (log-rank p = 0.278) vascular-related deaths, and 16.5% and 29.8% (log-rank p = 0.032) non-cardiovascular-related deaths in the DCB and PTA groups, respectively. Mortality rates in the DCB and PTA arms over the course of the 60-month period (1- to 60-month follow-up) are summarized in Online Figure 2. The MAE composite (death of any cause, major amputation, minor amputation) rates were 60.8% in the DCB group and 58.4% in the PTA group (log-rank p = 0.204) (**Table 2**).

CONTINUOUS AND TERCILE PACLITAXEL DOSE AND SURVIVAL ANALYSIS. The impact of paclitaxel dose on mortality is shown in **Table 3**. DCB subjects who died (n = 76) received a mean paclitaxel dose of

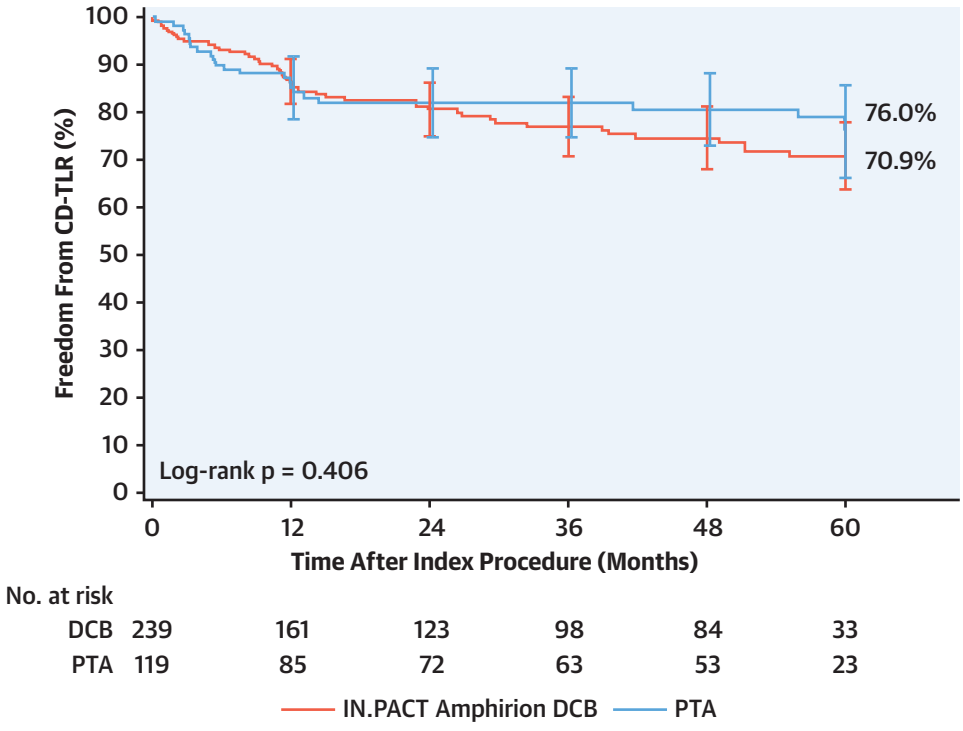
TABLE 1 Baseline Clinical and Lesion Characteristics

	IN.PACT DCB (n = 239)	PTA (n = 119)	p Value
Subject clinical characteristics			
Age, yrs	73.3 ± 8.2	71.7 ± 9.9	0.129
Male	76.2 (182/239)	70.6 (84/119)	0.304
BMI, kg/m^2	27.4 ± 4.9	27.1 ± 4.9	0.620
Hypertension	89.5 (214/239)	89.1 (106/119)	1.000
Hyperlipidemia	73.2 (175/239)	67.2 (80/119)	0.265
Diabetes mellitus	75.7 (181/239)	68.9 (82/119)	0.204
History of smoking	51.9 (124/239)	49.6 (59/119)	0.737
Prior MI	21.9 (50/228)	17.9 (20/112)	0.476
Congestive heart failure (EF <40%)	9.6 (22/229)	6.2 (7/113)	0.409
Renal insufficiency (GFR <30 ml/min)	8.6 (20/233)	12.5 (14/112)	0.254
Cerebrovascular disease	34.3 (82/239)	33.6 (40/119)	1.000
Previous target limb revascularization	32.2 (77/239)	21.8 (26/119)	0.047
Previous amputation	23.4 (56/239)	17.6 (21/119)	0.222
ABI, mm Hg	0.750 ± 0.401	0.806 ± 0.438	0.264
TBI, mm Hg	0.319 ± 0.201	0.464 ± 0.423	0.178
Rutherford category			0.622
0	0.0 (0/239)	0.0 (0/119)	
1	0.0 (0/239)	0.0 (0/119)	
2	0.0 (0/239)	0.0 (0/119)	
3	0.0 (0/239)	0.8 (1/119)	
4	14.2 (34/239)	17.6 (21/119)	
5	84.1 (201/239)	77.3 (92/119)	
6	1.7 (4/239)	4.2 (5/119)	
Baseline lesion and procedural characteristics			
Target lesion length, cm	10.2 ± 9.1	12.9 ± 9.46	0.002
Target lesion RVD, mm	2.5 ± 0.69	2.4 ± 0.56	0.304
Total occlusions	38.6 (135/350)	45.9 (83/181)	0.114
Severe calcification	13.7 (48/350)	10.5 (19/181)	0.336
Provisional stenting	3.9 (14/359)	2.6 (5/189)	0.446

Values are mean ± SD or % (n/N). Numbers are % (counts/sample size), unless otherwise stated.

ABI = ankle-brachial index; BMI = body mass index; DCB = drug-coated balloon; EF = ejection fraction; GFR = glomerular filtration rate; MI = myocardial infarction; PTA = percutaneous transluminal angioplasty; RVD = reference vessel diameter; TBI = toe brachial index.

CENTRAL ILLUSTRATION **Treatment Effect of the IN.PACT Amphirion DCB in Infrapopliteal Lesions Through 60 Months**



Zeller, T. et al. J Am Coll Cardiol Intv. 2020;13(4):431–43.

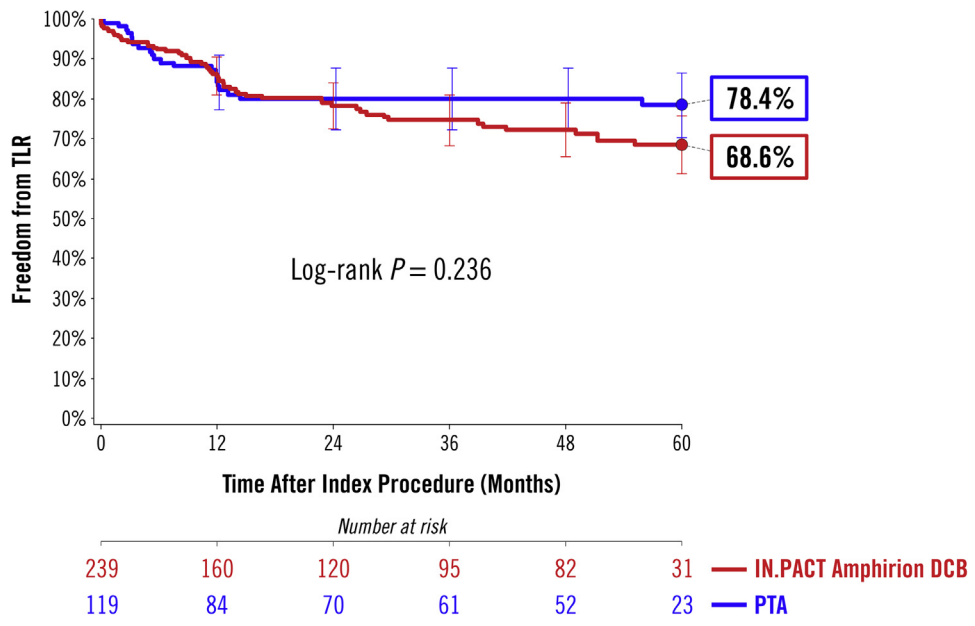
Freedom from clinically-driven target lesion revascularization (CD-TLR) was not significantly different between the drug-coated balloon (DCB) and percutaneous transluminal angioplasty (PTA) groups through 60 months. **Bars** represent 95% confidence intervals.

4,940.5 ± 3,918.9 μg, while DCB subjects who survived (n = 162) received 4,783.7 ± 3,295.4 μg, which was not significantly different between the groups (p = 0.950) (Table 3).

To further assess a potential correlation of increasing paclitaxel dose to mortality, subjects who received paclitaxel during the index procedure (DCB group) were segmented into terciles (lower, middle, and upper) on the basis of the amount of nominal paclitaxel dose given at the index procedure. Cumulative incidence rates of all-cause death at each dose group were evaluated using Kaplan-Meier estimates (Figure 4). The mean dose in each tercile was 1,641.3, 3,999.4, and 8,994.1 μg in increasing order, and the PTA group was referenced as zero paclitaxel dose. All-cause death rates were not significantly different (log-rank p = 0.916) among subjects with different paclitaxel doses, zero (PTA group), lower tercile, middle tercile, and upper tercile (DCB group), demonstrating no correlation with increasing nominal paclitaxel doses during the index procedure and mortality in subjects through 5 years.

PREDICTORS OF MORTALITY AND MAJOR AMPUTATION. A multivariable Cox proportional hazard regression analysis was performed to identify potential baseline predictors of all-cause death through 60 months (Table 4). Age, advanced peripheral artery disease defined as Rutherford category >4, and previous peripheral revascularization were associated with increased risk for death within 60 months in all subjects. Paclitaxel dose terciles were not selected by the multivariate predictors selection process, suggesting that increasing dose of paclitaxel was not a predictor of mortality. Furthermore, it also failed to predict mortality when paclitaxel dose was forced into the final model to show the potential impact. Predictors of increased risk for major amputation through 5 years included renal insufficiency and current smoking (Table 5). Similarly, none of the paclitaxel dose terciles (lower, middle, or upper) were predictors of

FIGURE 2 Treatment Effect of the IN.PACT Amphirion DCB in Infrapopliteal Lesions Through 60 Months



Freedom from target lesion revascularization (TLR) by Kaplan-Meier estimate was not significantly different between the drug-coated balloon (DCB) and percutaneous transluminal angioplasty (PTA) groups through 60 months. Bars represent 95% confidence intervals.

major amputation of target limb in either the regular selection or the forced model.

DISCUSSION

In this final 5-year report from the IN.PACT DEEP randomized trial, safety and efficacy outcomes did not differ significantly between subjects treated with DCB angioplasty and subjects treated with PTA. Previously, we reported a safety signal driven by a statistically nonsignificant but numerically higher (2.4-fold) major amputation rate with DCB angioplasty compared with PTA at 12 months (12). Although the major amputation rate was still slightly higher (1.45-fold) with DCB angioplasty compared with PTA through 5 years, the difference was not significant. In light of the recently published meta-analysis suggesting increased all-cause mortality following drug-eluting technology in femoropopliteal artery disease (19), the findings of this study found no increase in mortality in the DCB group compared with PTA. Furthermore, the results clearly demonstrated that paclitaxel treatment did not correlate with either mortality or major amputation in CLI patients.

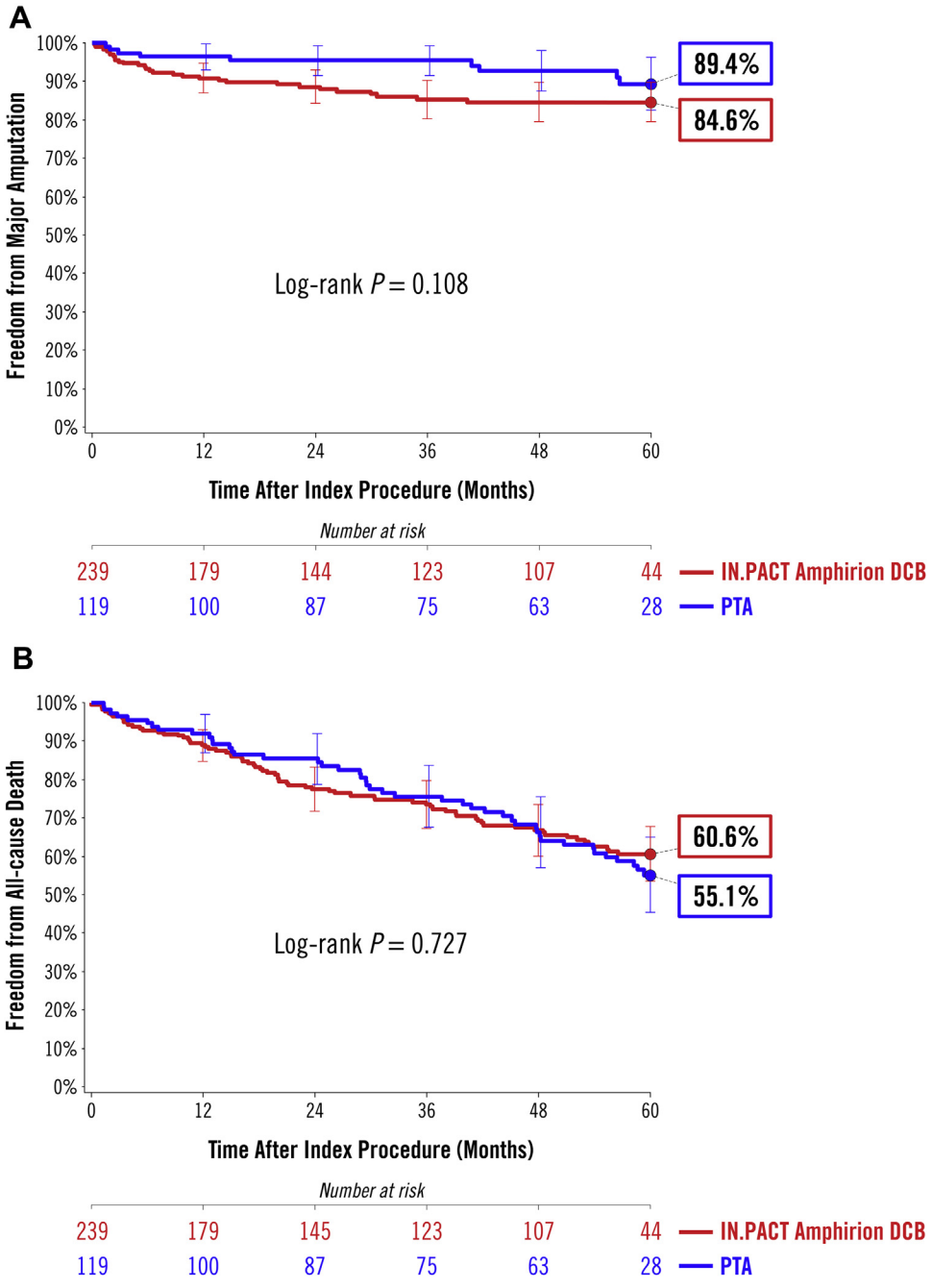
TABLE 2 Safety and Effectiveness Results of All ITT Subjects Through 60 Months by Kaplan-Meier Estimate

	IN.PACT DCB (n = 239)	PTA (n = 119)	Log-Rank p Value
Endpoints through 60 months			
Safety endpoint composite through 60 months*	59.8 (128)	57.5 (61)	0.309
All-cause death	39.4 (74)	44.9 (45)	0.727
Major target limb amputation	15.4 (30)	10.6 (9)	0.108
CD-TLR†	29.1 (50)	24.0 (22)	0.406
Safety events within 60 months			
MAE composite‡	60.8 (134)	58.4 (63)	0.204
All-cause death	39.4 (74)	44.9 (45)	0.727
Major target limb amputation	15.4 (30)	10.6 (9)	0.108
Minor target limb amputation	31.1 (63)	26.0 (28)	0.390
Secondary effectiveness endpoints within 60 months			
TLR§	31.4 (55)	21.6 (22)	0.236
CD-TLR†	29.1 (50)	24.0 (22)	0.406

Values are % (n). Percentages are Kaplan-Meier estimates of cumulative incidence (number of patients with events). An independent clinical events committee adjudicated all MAE, including death, target limb major and minor amputations through 5 yrs, and TLR through 2 yrs. *Defined as a composite of all-cause death, major amputation, and CD-TLR. †Defined as any TLR associated with deterioration of Rutherford category and/or an increase in the size of pre-existing wounds and/or occurrence of new wounds. ‡Defined as a composite of all-cause death, major amputation of target limb, or minor amputation of target limb. §Any repeat percutaneous intervention or bypass surgery performed on the target limb.

CD-TLR = clinically-driven target lesion revascularization; ITT = intention-to-treat; MAE = major adverse events; TLR = target lesion revascularization; other abbreviations as in Table 1.

FIGURE 3 Freedom From Major Amputation and All-Cause Death Through 60 Months



Freedom from major amputation of target limb **(A)** and freedom from all-cause death **(B)** by Kaplan-Meier estimate were not significantly different between the drug-coated balloon (DCB) and percutaneous transluminal angioplasty (PTA) groups through 60 months. Bars represent 95% confidence intervals.

The continuous innovation of endovascular technologies has generated a variety of different modalities and devices, including drug-eluting stents and DCBs for the treatment of lower extremity peripheral artery disease (21,22). Randomized trials have provided both short-term and long-term clinical evidence for the use of DCBs in femoropopliteal lesions (7,10,11,23-25). Indeed, DCBs have become the

treatment of choice for the revascularization of TASC IIA and IIB femoropopliteal lesions and recommended as the intended definitive therapy in this vascular bed (26,27). In contrast, studies reporting the use of DCBs in patients with CLI with infrapopliteal lesions are limited to short-term outcomes (28–31), and only a minority of them are from randomized trials (12–14). Results across these studies varied, and there is no consensus on the use of DCBs for the treatment of patients with CLI with infrapopliteal lesions. To date, the present work is the only trial reporting 5-year follow-up data evaluating the safety and effectiveness of DCB angioplasty in comparison with PTA in patients with CLI with infrapopliteal lesions. Because there are no benchmark 5-year follow data on DCBs, we compared the outcomes of this study with other endovascular modalities and bypass surgery outcomes of BTK studies available. The 5-year repeat revascularization rate was reported in the range of 21% to 50% (32,33) for PTA in published research, compared with TLR rates of 21.6% for PTA and 31.4% for DCB angioplasty in the IN.PACT DEEP trial.

At 5-year follow-up there is no correlation between major amputation rate and paclitaxel exposure. In fact, the rates observed in both the DCB and PTA arms of the IN.PACT DEEP trial are lower than those in other contemporary studies. In the PADI trial, the 5-year major amputation rate was 19.3% in the drug-eluting stent arm and 34% in the PTA bare-metal stent control arm (34) compared with the 5-year major amputation rates of 15.4% for DCB and 10.6% for PTA in the IN.PACT DEEP trial. Conversely, reported 5-year limb salvage or freedom from amputation rates for endovascular and bypass studies range from 75% to 87% (33,35–38) compared with a 5-year rate of freedom from major amputation of 84.6% for DCB angioplasty and 89.4% for PTA in the IN.PACT DEEP trial; both fall in the upper range. Although long-term data are not available, not a single BTK trial comparing DCB angioplasty with PTA has shown a reduction of amputation rates in the DCB arm compared with PTA (12–14). This may potentially be due to a more complex nature of lesions in this patient population, such as the presence of higher calcium burden, which may act as a barrier to drug uptake in the arterial wall and decreases the antiproliferative effect of paclitaxel. Indeed, studies in femoropopliteal lesions have demonstrated unfavorable short- and long-term outcomes of DCB angioplasty in lesions with higher degrees of circumferential calcium (39,40).

In a recent meta-analysis, Katsanos et al. (19) suggested that there was an increased risk for mortality at 2 and 5 years after the use of paclitaxel-coated devices in the femoropopliteal artery. The meta-analysis focused on studies involving femoropopliteal arterial segment with predominantly claudicant patients; nonetheless, it has become a public concern to address the safety of paclitaxel-eluting technologies in all peripheral artery disease treatments, including patients with CLI with infrapopliteal lesions. There is still no clear guideline from regulatory bodies, although a recent update letter from the U.S. Food and Drug Administration provided some recommendations for paclitaxel-coated devices (41). To shed more light on this topic, we used exhaustive methods to evaluate whether there is any mortality signal in the DCB arm in this study. First, 5-year cumulative incidence of all-cause death was compared between the DCB and PTA arms (39.4% vs. 44.9%; log-rank p = 0.727), revealing no statistically significant difference, although it was numerically lower in the DCB group. Causes of death were similar between the 2 arms, and there was no specific pattern. These results are in line with those of Secemsky et al. (42), who also reported a trend toward a lower cumulative incidence rate of all-cause mortality in patients with CLI treated with DCB compared with PTA.

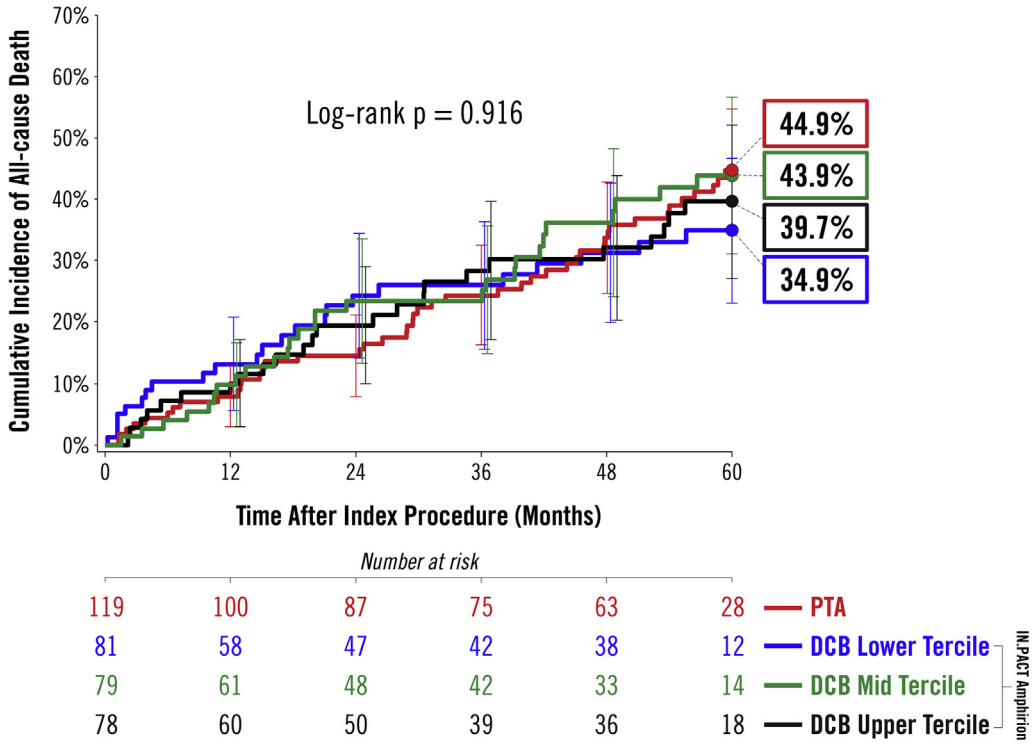
Second, continuous and tercile paclitaxel dose analyses strongly suggested a lack of correlation between paclitaxel dose and mortality. The mean paclitaxel dose of ~5 mg received by DCB subjects in this study is about one-half the amount reported by Schneider at al. (43), although the same dose estimation method was used in both studies. The IN.PACT Amphion DCB, used in the present study, has a drug dose density of 3.0 μg/mm^2, whereas the IN.PACT Admiral DCB (used for femoropopliteal and reported by Schneider et al.) has a drug dose density of 3.5 μg/mm^2. Moreover, BTK lesions and the balloon diameters used are smaller, resulting in a lower mean

TABLE 3 Nominal Paclitaxel Dose in All Drug-Coated Balloon Subjects

	Death (n = 76)	Survival (n = 163)	p Value
n	76*	162†	
Mean ± SD	4,940.53 ± 3,918.86	4,783.67 ± 3,295.44	0.950
Median (IQR)	3,829.12 (1,952.61–6,581.89)	3,851.67 (1,975.16–6,951.84)	
Minimum, maximum	768.09, 22,556.69	768.09, 14,829.57	

Nominal doses of paclitaxel (micrograms) are reported in all subjects in the drug-coated balloon group who died versus survived. The nominal paclitaxel dose per balloon was calculated on the basis of nominal dose matrix provided by the manufacturer (Medtronic). The balloon lengths and diameters received by each patient were captured in procedure records, and the nominal paclitaxel dose per balloon was added together to define the total dose of paclitaxel received per patient in each index procedure. *All subjects who died during the full follow-up period, including 2 deaths after 1,825 days. †One subject in the survival group did not have sufficient information to calculate paclitaxel dose, so paclitaxel dose was calculated on the basis of 162 subjects only.

FIGURE 4 Kaplan-Meier Estimates of Cumulative Incidence of All-Cause Death Through 60 Months by Paclitaxel Dose in All Subjects



Distribution of Paclitaxel Dose in PTA and Each Paclitaxel Dose Group

Paclitaxel Dose	N	Mean (μg)	Std (μg)	Median (μg)	Q1, Q3 (μg)	Range (μg)
0 (PTA)	119	0.0	0.0	0.0	0, 0	0, 0
DCB Lower tercile	81	1641.29	518.32	1536.18	1213.97, 1975.16	768.09, 2344.94
DCB Mid tercile	79	3999.38	1034.45	3860.12	3044.14, 4802.60	2427.94, 5820.86
DCB Upper tercile	78	8994.11	2711.14	8798.15	6951.84, 9951.19	5835.28, 22556.69

Sixty-month all-cause death rates were not significantly different among zero (percutaneous transluminal angioplasty [PTA] group), lower, middle, and upper paclitaxel dose terciles (drug-coated balloon [DCB] group) (log-rank p = 0.905). Bars represent 95% confidence intervals.

paclitaxel dose in the IN.PACT DEEP trial. Despite the drug dose difference, both studies show similar outcomes regarding mortality, which is consistent with a lack of dose-mortality relationship reported by Holden et al. (44).

Finally, the multivariable model to identify predictors of all-cause death did not select any of the paclitaxel terciles as predictors, while traditional risk factors such as older age, Rutherford category >4, and previous peripheral revascularization were identified as predictors. Even when paclitaxel terciles were forced into the final model (skipping the selection criteria), it failed to predict mortality further, demonstrating that there is no correlation between paclitaxel dose and mortality in these subjects. Overall, these findings are in agreement with a series of patient-level meta-analyses (43-47) conducted following the report of Katsanos et al. (19). These recent meta-analysis publications reported either no increase in late mortality or no correlation of paclitaxel with mortality in subjects treated with drug-coated devices (43-47). Furthermore, an extensive search of the published research revealed that 5-year mortality rates of the DCB (39.4%) and PTA (44.9%) arms in this study were well within or lower than the 5-year mortality rates of patients with CLI undergoing endovascular or bypass revascularization, which ranged from 42% to 63% (33-37). Taken together, these results strongly suggest a lack of paclitaxel effect on mortality for patients with CLI. However, the

IN.PACT DEEP trial was not designed to evaluate long-term mortality or drug dose analysis, and these findings are not confirmatory of either way. Further studies in this topic with a real-world, large patient cohort would provide more clarity on this topic.

There are lessons to be learned from the findings of the IN.PACT DEEP trial. The absence of superior effectiveness outcomes of DCB angioplasty in the IN.PACT DEEP trial further emphasizes that although revascularization is the first-line treatment for patients with CLI, several other factors could influence the results of a clinical trial, such as wound care, podiatry surveillance, and secondary cardiovascular risk management. The protocol should include appropriate guidelines to monitor these various factors that may have a role in the outcome. In addition, the inadequacy of the IN.PACT Amphirion DCB itself was postulated. The IN.PACT Amphirion DCB has a paclitaxel-excipient (urea) coating that was applied while the balloon bladder remained in a closed (wrapped) configuration, which leaves approximately two-thirds of the balloon surface uncoated. Additionally, the coating process involved the manual application of the coating, resulting in variations in coating uniformity. The majority of the adherent paclitaxel was thus exposed during delivery and potentially lost during transit to the vessel lesion. There was also a marked difference in the balloon material between the IN.PACT Amphirion DCB and the IN.PACT Admiral DCB (for femoropopliteal indication), possibly resulting in a significant difference in their outcomes. Despite the failure of the trial, the low TLR, major amputation, and mortality rates observed in the IN.PACT DEEP trial compared with previous infrapopliteal studies are highly encouraging for future DCB trials.

There are several ongoing BTK trials for paclitaxel-coated balloons. Six-month outcomes from the Lutonix BTK trial were published (48), and AcoArt II and Ranger BTK single-center study were presented at the Leipzig Interventional Course (49,50). The IN.PACT BTK randomized study, a completely different trial from IN.PACT DEEP, reported enrollment completion; this study compares the IN.PACT 014 DCB (different from the IN.PACT Amphirion DCB) with PTA. The ILLUMENATE BTK study will assess the safety and effectiveness of the Stellarex DCB versus PTA. In addition to paclitaxel-coated balloons, there are limus-eluting devices available worldwide for BTK treatment (51).

STUDY LIMITATIONS. This was a single-blinded (patient-blinded) trial; operators could not be blinded to the assigned treatment. The trial design had other limitations as well. Although IN.PACT DEEP was a large study, the population size was not powered to assess major amputation or mortality as long-term endpoints. Clinical follow-up was not mandatory beyond 24 months according to the study protocol. Despite limiting long-term follow-up to phone contact, a significant rate of loss to follow-up was observed in both treatment groups. An accepted and standardized definition of planned major amputation

TABLE 4 Multivariable Analysis of All-Cause Death in All ITT Subjects Through 60 Months

Predictors of All-Cause Death Through 1,825 Days	Coefficient	SE	Hazard Ratio (95% CI)	p Value
Age	0.04	0.012	1.04 (1.02–1.07)	<0.001
Rutherford category (>4 vs. ≤4)	0.99	0.314	2.70 (1.45–5.00)	0.002
Previous peripheral revascularization (yes vs. no)	0.43	0.192	1.53 (1.05–2.23)	0.027
Renal insufficiency (baseline serum creatinine ≥1.5 ng/dl) (yes vs. no)	0.53	0.276	1.69 (0.99–2.90)	0.057
Previous coronary revascularization (yes vs. no)	0.36	0.199	1.44 (0.98–2.13)	0.067
Hypertension (yes vs. no)	−0.50	0.276	0.61 (0.35–1.04)	0.070
Forced into the multivariable model				
Paclitaxel dose (lower vs. 0)*	−0.32	0.261	0.72 (0.43–1.21)	0.216
Paclitaxel dose (middle vs. 0)*	−0.10	0.247	0.90 (0.56–1.46)	0.673
Paclitaxel dose (upper vs. 0)*	−0.19	0.264	0.82 (0.49–1.38)	0.462

Predictors of death through 5 yrs in all patients are reported. Univariate analyses (Online Table 2) followed by a stepwise multiple Cox regression model with an entry criterion of 0.2 and a stay criterion of 0.1 were used. If a p value was <0.2 in the univariate analysis, that covariate was included in the multivariable analysis to go through the stepwise selection process. Clinically relevant baseline variables were included for variable selection. *The terciles of total dose of paclitaxel received per subject in the index procedure were not selected by the stepwise selection method and were forced into the final multivariable model.

CI = confidence interval; ITT = intention-to-treat.

TABLE 5 Multivariable Analysis of Major Amputation of Target Limb in All ITT Subjects Through 60 Months

Predictors of Major Amputation Through 1,825 Days	Coefficient	SE	Hazard Ratio (95% CI)	p Value
Renal insufficiency (baseline serum creatinine ≥1.5 ng/dl) (yes vs. no)	1.01	0.438	2.75 (1.17–6.50)	0.021
Smoking (current vs. never)	0.98	0.445	2.66 (1.11–6.36)	0.028
Smoking (previous vs. never)	0.27	0.395	1.308 (0.60–2.84)	0.498
Male (male vs. female)	1.02	0.556	2.79 (0.94–8.29)	0.066
Rutherford category (>4 vs. ≤4)	1.33	0.730	3.80 (0.91–15.90)	0.068
Forced into the multivariable model				
Paclitaxel dose (lower vs. 0)*	0.56	0.462	1.74 (0.70–4.31)	0.230
Paclitaxel dose (middle vs. 0)*	0.80	0.435	2.23 (0.95–5.23)	0.065
Paclitaxel dose (upper vs. 0)*	−0.006	0.531	0.99 (0.35–2.82)	0.990

Predictors of major amputation of target limb through 5 yrs in all patients are reported. Univariate analyses (Online Table 3) followed by a stepwise multiple Cox regression model with an entry criterion of 0.2 and a stay criterion of 0.1 were used. If a p value was <0.2 in the univariate analysis, that covariate was included in the multivariable analysis to go through the stepwise selection process. Clinically relevant baseline variables were included for variable selection. Smoking status was self-reported. *The terciles of total dose of paclitaxel received per subject in the index procedure were not selected by the stepwise selection method and were forced into the final multivariable model.

CI = confidence interval; ITT = intention-to-treat.

was not implemented in the trial. The study protocol did not guide or provide standards for wound surveillance and care, and wound management was administered according to the individual sites' standards of care.

CONCLUSIONS

The results of the IN.PACT DEEP randomized controlled trial showed comparable effectiveness and safety outcomes for the DCB and PTA arms. The paclitaxel-coated IN.PACT Amphirion DCB was not efficient in terms of reducing restenosis and TLR rates compared with PTA. However, in the long term, no statistically significantly increased amputation or all-cause mortality rates were found. Further studies using more effective drug coatings in this challenging patient population are warranted.

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PERSPECTIVES

WHAT IS KNOWN? Lower extremity revascularization is the first-line treatment choice in patients with CLI, with the goal of relieving rest pain, improving wound healing, and preventing major limb amputation. So far, short-term outcomes following DCB angioplasty of infrapopliteal arteries are conflicting with regard to technical efficacy and clinical outcomes, and long-term data are not yet available.

WHAT IS NEW? The long-term follow-up data suggest that angioplasty with the IN.PACT Amphirion DCB and PTA are feasible for the treatment of patients with CLI with infrapopliteal lesions. Within the limitations of trial design, no difference in clinical performance was found in patients with CLI treated with the IN.PACT Amphirion DCB or PTA, including major amputation and mortality.

WHAT IS NEXT? In future DCB BTK trials, careful consideration should be given to balloon materials, coatings, drug concentrations, and the inclusion of specific guidelines for wound care, podiatry surveillance, management of comorbidities, and vessel preparation methods to clarify and improve outcomes.

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APPENDIX For a list of trial investigators, as well as supplemental tables and figures, please see the online version of this paper.