PERIPHERAL VASCULAR DISEASE

Original Studies

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EDITORIAL COMMENT: Expert Article Analysis for:
Safety and efficacy of paclitaxel drug-coated balloon treatment of femoropopliteal claudicants: Data and analytic methods matter

Paclitaxel exposure: Long-term safety and effectiveness of a drug-coated balloon for claudication in pooled randomized trials

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Abstract

Background: Paclitaxel drug-coated balloons (DCB) prevent recurrent claudication after angioplasty, yet data from randomized trials with incomplete follow-up have raised uncertainty regarding long-term mortality.

Objectives: To evaluate the effect of paclitaxel exposure on the long-term safety and efficacy of angioplasty of femoropopliteal artery lesions in the combined IN.PACT randomized trials.

Methods: The IN.PACT randomized trials (SFA, $N = 331$ and Japan, $N = 100$) each compared the DCB with standard percutaneous transluminal angioplasty (PTA) for claudication, and consented patients for 5 and 3 years, respectively. To address long-term safety, sites were requested to obtain vital status follow-up. In the pooled, updated data set, we examined the association between randomized treatment and mortality by cumulative incidence and hazard ratio (HR), and freedom from clinically driven target lesion revascularization (CD-TLR). Multivariable Cox regression with adjustment for baseline characteristics was used to evaluate the dose effect. Causes of death were adjudicated by a blinded clinical events committee that included oncologists with paclitaxel expertise.

Results: The rate of long-term vital status ascertainment increased from 81% to 97% for DCB and from 85% to 97% for PTA in the IN.PACT SFA trial. The cumulative incidence of mortality was 14.7% DCB versus 12.0% PTA at 5 years, HR 1.39, log-rank $p = .286$. Paclitaxel dose (mg) was not an independent predictor of mortality (HR 1.02, $p = .381$), but was an independent predictor of reduced risk of CD-TLR (HR 0.79; $p < .001$). Causes of death did not differ by treatment arm.

Abbreviations: CD-TLR, clinically driven target lesion revascularization; CEC, Clinical Events Committee; DCB, drug-coated balloon; FDA, the U.S. Food and Drug Administration; HR, hazard ratio; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.

Conclusions: In pooled randomized trial data with updated vital status ascertainment, paclitaxel was associated with improved efficacy but was not associated with increased mortality.

KEYWORDS

DCB, mortality, paclitaxel, primary patency, target lesion revascularization

1 | INTRODUCTION

Paclitaxel has been effective in preventing neointimal proliferation after percutaneous coronary procedures.[1,2] Large randomized controlled trials (RCTs) of coronary paclitaxel-eluting stents compared to bare-metal stents with 5-year follow-up demonstrated no increase in mortality associated with paclitaxel.[3] As treatment for claudication, several smaller randomized trials of paclitaxel stents and balloons have been conducted among patients treated for femoropopliteal artery disease.[4,5] The IN.PACT SFA and IN.PACT Japan studies were similarly designed randomized trials of the IN.PACT Admiral paclitaxel drug-coated balloon (DCB) that both met their primary efficacy endpoint of patency at 1 year.[6,7] In the IN.PACT SFA study, follow-up at 2 and 3 years showed a higher mortality in the paclitaxel arm that diminished at years 4 and 5 of follow-up.[8]

A summary-level meta-analysis of 28 RCTs including the IN.PACT RCTs reported an increase in mortality risk at 2 and 5 years in patients with femoropopliteal peripheral artery disease (PAD) after treatment with paclitaxel-coated devices compared to uncoated devices.[9] However, patient-level data were unavailable, causes of death were not assessed, vital status ascertainment was incomplete, and data were available only from 12 RCTs at 2 years, and 3 RCTs at 5 years. An advisory panel was convened by the U.S. Food and Drug Administration (FDA) to review available data from pivotal RCTs of paclitaxel-coated devices for femoropopliteal PAD.[10] A higher mortality in the paclitaxel-coated devices compared to uncoated devices was noted, yet the limitations of the available randomized data, small sample sizes, and most importantly incomplete data follow-up of included trials were raised.

To address these limitations, and further evaluate the relationship between paclitaxel and long-term mortality, we conducted a pooled analysis of the IN.PACT randomized trials (IN.PACT SFA and IN.PACT Japan). To improve the ascertainment of mortality beyond 1 year, study sites were requested to obtain vital status data from patients who withdrew or were lost to follow-up in the IN.PACT SFA trial. A Clinical Events Committee (CEC) with paclitaxel expertise was convened to readjudicate all mortality events in a blinded fashion, and the data were examined for dose effect on both mortality and efficacy. The purpose of this analysis was to further evaluate the potential of a causal relationship between paclitaxel and long-term mortality.

2 | METHODS

2.1 | RCT pooled analysis study design

The Baim Institute for Clinical Research (formerly HCRI, Boston, MA) independently performed all analyses. The longest available follow-up patient-level data were pooled from the IN.PACT SFA RCT (IN.PACT SFA I, conducted in Europe and IN.PACT SFA II, conducted in the United States) and MDT-2113 SFA Japan RCT (referred herein as the IN.PACT Japan) to improve the power to evaluate mortality (URL: https://www.clinicaltrials.gov. Unique identifier: NCT01175850 [IN.PACT SFA phase I], NCT01566461 [IN.PACT SFA phase II], and NCT01947478 [MDT-2113 SFA Japan]). The analysis included 430 patients (433 lesions) enrolled at 68 sites across 3 continents and 7 countries.

These trials were originally designed to evaluate the safety and efficacy of the IN.PACT Admiral DCB (Medtronic, Dublin, Ireland) compared with standard percutaneous transluminal angioplasty (PTA) for the treatment of patients with symptomatic claudication from femoropopliteal artery disease on the primary endpoint of primary patency and safety composite at 1 year. Details of the trial design were previously reported.[6,7] In both RCTs, patients were randomized 2:1 to DCB or PTA, and inclusion criteria were identical except for longer lesion length permitted in the Japan trial (Table S1).

Each of these trials included independent oversight by a Data Safety Monitoring Board and CEC (The Baim Institute for Clinical Research, formerly HCRI, Boston, MA), which reviewed and adjudicated all major adverse events including deaths, throughout each study follow-up period. In addition, a newly convened independent CEC (Syntactx, New York, NY), which included oncologists skilled with the use of paclitaxel as a cancer chemotherapeutic, readjudicated cardiovascular and noncardiovascular causes of death based on the definitions in the Hicks classification[11] as well as potential complications related to paclitaxel. The CEC members were blinded to treatment assignment. Both trials were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable laws as specified by all relevant governmental bodies.

2.2 | Vital status collection methods

Study sites were requested to obtain vital status data from patients who withdrew or were lost to follow-up in the IN.PACT SFA trial. After obtaining local ethics committee approval, rigorous efforts were

TABLE 1 Baseline demographic, clinical, and lesion characteristics in all patients of the IN.PACT RCT pooled as treated cohort

Characteristics	IN.PACT DCB[a] (N = 288 patients; N = 289 target lesions)	PTA[a] (N = 142 patients; N = 144 target lesions)	p Value[b]
Demographic and clinical characteristics, per patient[c]			
Age (years)	68.8 ± 9.4 (288)	69.5 ± 8.9 (142)	.452
BMI (kg/m^2)	26.6 ± 5.0 (288)	26.2 ± 4.8 (142)	.421
Obesity (BMI ≥30 kg/m^2)	22.2% (64/288)	19.0% (27/142)	.530
Male	67.0% (193/288)	70.4% (100/142)	.510
Hypertension	89.6% (258/288)	88.7% (126/142)	.868
Hyperlipidemia	81.3% (234/288)	81.7% (116/142)	1.000
Diabetes mellitus	44.8% (129/288)	50.7% (72/142)	.260
Insulin-dependent diabetes mellitus	17.0% (49/288)	17.6% (25/142)	.892
Carotid artery disease	30.7% (84/274)	29.0% (38/131)	.817
Coronary heart disease	55.3% (156/282)	54.3% (76/140)	.917
Smoking			
Active	35.8% (103/288)	34.5% (49/142)	.831
Previous	35.1% (101/288)	35.2% (50/142)	1.000
Never	29.2% (84/288)	30.3% (43/142)	.823
Renal insufficiency (baseline serum creatinine ≥1.5 ng/dl)	8.4% (24/285)	7.9% (11/140)	1.000
On dialysis	0.4% (1/285)	0.0% (0/142)	1.000
Below-the-knee vascular disease of target leg (stenotic/occluded)	39.2% (113/288)	48.6% (69/142)	.078
Previous peripheral revascularization	46.5% (134/288)	52.8% (75/142)	.259
Previous target limb amputation (per target limb)	0.3% (1/288)	0.7% (1/142)	.552
Previous nontarget limb amputation (per limb)	0.7% (2/288)	2.1% (3/142)	.337
Rutherford category			.961
0	0.0% (0/288)	0.0% (0/142)	
1	0.0% (0/288)	0.0% (0/142)	
2	42.0% (121/288)	42.3% (60/142)	
3	53.1% (153/288)	52.1% (74/142)	
4	4.9% (14/288)	4.9% (7/142)	
5	0.0% (0/288)	0.7% (1/142)	
6	0.0% (0/288)	0.0% (0/142)	
Target limb ABI/TBI (mmHg ratio) per patient	0.768 ± 0.211 (277)	0.742 ± 0.183 (137)	.217
Preprocedure Characteristics[d], per lesion			
RVD[e] (mm)	4.69 ± 0.82 (289)	4.68 ± 0.79 (144)	.886
MLD[f] (mm)	0.92 ± 0.77 (289)	0.93 ± 0.73 (144)	.828
Occluded lesion (100% stenosis)	23.5% (68/289)	18.1% (26/144)	.217
Diameter stenosis (%)	80.94 ± 15.19 (289)	80.97 ± 13.31 (144)	.982
Lesion length[g] (cm)	8.93 ± 5.11 (289)	8.87 ± 5.33 (144)	.911
Postprocedure characteristics[d], per lesion			
RVD[e] (mm)	4.92 ± 0.80 (289)	4.82 ± 0.75 (144)	.189
MLD[f] (mm)	3.93 ± 0.75 (289)	3.84 ± 0.71 (144)	.224
Diameter stenosis (%)	20.25 ± 10.14 (289)	20.08 ± 10.22 (144)	.876
Acute gain (mm)	3.02 ± 0.90 (289)	2.91 ± 0.86 (144)	.234

TABLE 1 (Continued)

Characteristics	IN.PACT DCB[a] (N = 288 patients; N = 289 target lesions)	PTA[a] (N = 142 patients; N = 144 target lesions)	p Value[b]
Target lesion length treated with study device (cm)	11.50 ± 5.26 (279)	11.29 ± 5.53 (137)	.711

Note: Values were mean ± *SD* (*n*) or % (*n/N*).

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CI, confidence interval; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial; TBI, toe-brachial index.

[a]One patient randomized to the DCB arm received PTA treatment. One patient randomized to the PTA arm received DCB treatment. One PTA patient did not receive randomized treatment.

[b]For categorical variables, Fisher's exact test is used for binary variables; Cochran–Mantel–Haenszel test is used for multilevel. *t* Test is used for all continuous variables.

[c]Site-reported data.

[d]Angiographic Core Lab reported data.

[e]Reference vessel diameter (RVD) was defined as angiographic measurement of the normal artery proximal and/or distal to the lesion intended for treatment.

[f]Minimum lumen diameter (MLD) was defined as angiographic measurement of the tightest area of obstruction or stenosis located within the segment of interest or the intended area of treatment.

[g]Lesion length was defined as angiographic measurement from the proximal healthy vessel segment to the distal healthy vessel segment (e.g., length of obstruction).

made by the study sites to contact patients and/or family members for current health status. The collected data were limited to survival/ mortality status and did not include reinterventions or other adverse events. In the case of mortality, the date of death and cause of death (if known) were collected. All available vital status data were included in the mortality analyses of this report.

2.3 | Study endpoints and definitions

Study endpoint definitions were consistent across the two RCTs included in this analysis. Endpoints were assessed through the longest-available follow-up: 5 years for IN.PACT SFA and 3 years for IN.PACT Japan. Assessments included Kaplan–Meier estimates of cumulative incidence of all-cause death and freedom from clinically driven target lesion revascularization (CD-TLR) through 5 years, and primary patency through 3 years. Study endpoint definitions are described in Supplementary Methods (Data S1).

2.4 | Paclitaxel dose

Total paclitaxel dose received per patient as part of the index procedure was calculated based on the nominal paclitaxel dose as described previously.[12] Paclitaxel exposure was separately evaluated as a binary variable (treatment assignment), by tercile (lower, middle, upper, compared with no exposure), and as a continuous variable (mg). The cumulative incidence of all-cause death was assessed among the four dose groups (tercile and zero dose [PTA]) using the Kaplan–Meier method. These post hoc analyses were not prespecified endpoints in the original RCTs but were conducted to access the impact of paclitaxel exposure on mortality.

2.5 | Statistical analyses

The safety outcomes were analyzed based on treatment received during the index procedure (as-treated) while efficacy outcomes were analyzed based on the intent-to-treat principle. The analyses were performed based on nonmissing assessments. All baseline demographics and clinical characteristics were presented at a patient level whereas lesion characteristics are reported on a lesion basis. For baseline characteristics, continuous variables are summarized as mean ± standard deviation (SD) and treatment differences were compared by the Student *t* test or Wilcoxon rank-sum test; dichotomous and categorical variables are reported as counts and proportions and treatment differences were compared by Fisher exact test or Cochran–Mantel–Haenszel test with modified ridit scores. Outcome analyses were performed at the patient level. Time-to-event analysis using the Kaplan-Meier method was employed to analyze primary patency through 3 years, the cumulative incidence of mortality, freedom from CD-TLR, and other endpoints through 5 years where applicable. The difference in the survival curves between treatment groups was assessed using the log-rank test. To evaluate all-cause mortality or freedom from CD-TLR consistency across different geographic populations, forest plots of Kaplan–Meier estimates through 60 months were generated. To identify whether dose-related effects of paclitaxel were present, multivariable Cox regression analyses including paclitaxel dose (tercile or continuous) or treatment assignment were performed adjusting for baseline patient and lesion characteristics on the outcomes of mortality and CD-TLR separately (for detailed methodology, refer to Supplementary Methods, Data S1). The level of statistical significance was set at $p < .05$. Tests and 95% confidence intervals (CIs) were not adjusted for multiple comparisons. All statistical analyses were performed using SAS (SAS Institute, Cary, NC) version 9.4.

3 | RESULTS

3.1 | Baseline characteristics of the RCT pooled cohort

This pooled analysis included a total of 430 patients; 288 received the IN.PACT Admiral DCB and 142 received PTA. In the IN.PACT RCT pooled cohort, baseline demographic, clinical, and lesion characteristics of patients treated with DCB versus PTA were well balanced (Table 1). Baseline and lesion characteristics of patients by geography and individual trials (IN.PACT SFA I [Europe], IN.PACT SFA II [the United States], and IN.PACT Japan] are summarized in Table S2. Since the inclusion criteria were closely matched,

participant characteristics were similar. Some differences were observed among these geographically distinct populations. Patients in IN.PACT SFA II (United States) had higher rates of obesity, hyperlipidemia and coronary heart disease compared to those in IN.PACT Japan and IN.PACT SFA I (Europe), whereas more diabetic patients and longer target lesion lengths were treated in IN.PACT Japan compared to IN.PACT SFA I and IN.PACT SFA II.

3.2 | Vital status ascertainment

In the IN.PACT SFA trial, vital status was originally available for 81% of DCB and 85% of PTA patients at 5 years. Additional vital status
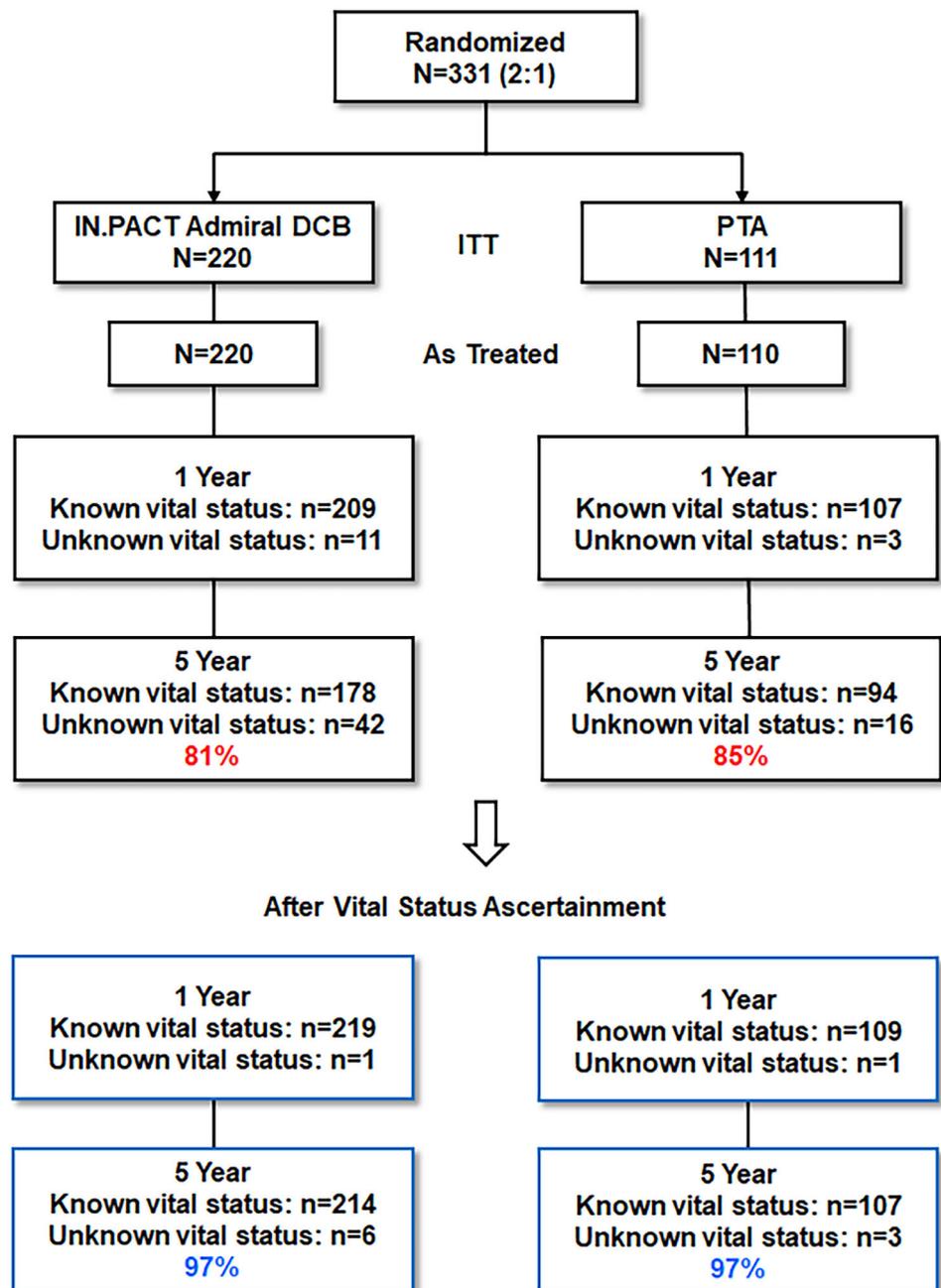

FIGURE 1 Patient flow before and after vital status ascertainment in the IN.PACT SFA trial. DCB, drug-coated balloon; ITT, intention-to-treat; PTA, percutaneous transluminal angioplasty [Color figure can be viewed at wileyonlinelibrary.com]

data collected by study sites from withdrawn and lost to follow-up patients resulted in an increase and balancing of available vital status information (97% of patients in both DCB and PTA) at 5 years (Figure 1). For IN.PACT Japan, 94% of patients had vital status information at 3 years.

3.3 | Cumulative incidence of mortality by treatment

Kaplan–Meier estimates for the cumulative incidence of 5-year all-cause death after vital status ascertainment were similar in the DCB

TABLE 2 Causes of death through 5 years in all patients of the IN.PACT RCT pooled as treated cohort

Cause of death[a,b]	IN.PACT DCB (N = 34/288)	PTA (N = 11/142)	p Value[c]
Cardiovascular deaths	**4.0%** (10)	**3.2%** (3)	.391
Acute myocardial infarction	0.4% (1)	0.0% (0)	.474
Sudden cardiac death	1.1% (3)	1.0% (1)	.694
Heart failure	1.2% (3)	0.0% (0)	.214
Stroke	0.8% (2)	0.0% (0)	.314
Cardiovascular hemorrhage	0.0% (0)	1.1% (1)	.179
Other cardiovascular cause	0.6% (1)	1.1% (1)	.667
Noncardiovascular deaths	**8.9%** (20)	**4.7%** (5)	.126
Pulmonary	0.4% (1)	0.0% (0)	.473
Renal	0.6% (1)	0.0% (0)	.459
Gastrointestinal	0.4% (1)	0.0% (0)	.478
Infection/sepsis (including inflammatory)	2.0% (5)	1.8% (2)	.754
Suicide	0.7% (1)	0.0% (0)	.453
Neurological (non-CV)	1.0% (2)	0.0% (0)	.300
Malignancy	4.3% (9)	2.9% (3)	.483
Undetermined cause	**1.8%** (4)	**2.7%** (3)	.645

Note: Numbers are percentages by Kaplan–Meier estimate (number of patients with events).

Abbreviations: CV, cardiovascular; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.

[a]Causes of death were categorized by system classification[11], adjudicated by a newly convened independent and blinded Clinical Events Committee, which includes oncologists skilled in the use of paclitaxel for cancer chemotherapeutic indications.

[b]Seven additional deaths (4 DCB and 3 PTA) found through vital status data collection were not adjudicated because of the limited source documentation.

[c]Log-rank test p value.

TABLE 3 Potential paclitaxel-related adverse events in all IN.PACT RCT pooled as treated cohort

	1 year			3 years			5 years		
Adverse event[a]	DCB (N = 288)	PTA (N = 142)	p Value[b]	DCB (N = 288)	PTA (N = 142)	p Value[b]	DCB (N = 288)	PTA (N = 142)	p Value[b]
Bradycardia	0.7% (2)	0.7% (1)	.993	1.1% (3)	1.5% (2)	.771	2.4% (5)	1.5% (2)	.750
Neurotoxicity (peripheral neuropathy)	0.0% (0)	2.8% (4)	.004	0.0% (0)	2.8% (4)	.004	0.0% (0)	2.8% (4)	.004
Hematologic	3.5% (10)	3.6% (5)	.994	7.1% (19)	4.3% (6)	.311	9.5% (23)	5.5% (7)	.221
Anemia	3.5% (10)	2.1% (3)	.431	7.1% (19)	2.9% (4)	.096	9.5% (23)	4.0% (5)	.068
Leukopenia	0.0% (0)	0.0% (0)	–	0.0% (0)	0.0% (0)	–	0.0% (0)	0.0% (0)	–
Neutropenia	0.0% (0)	1.4% (2)	.045	0.0% (0)	1.4% (2)	.045	0.0% (0)	1.4% (2)	.045
Thrombocytopenia	0.4% (1)	0.0% (0)	.481	0.4% (1)	0.0% (0)	.481	0.4% (1)	0.0% (0)	.481
Myalgia	0.3% (1)	0.0% (0)	.483	0.3% (1)	0.0% (0)	.483	0.3% (1)	0.0% (0)	.483

Note: Numbers are presented as cumulative incidence by Kaplan–Meier estimate (number of patients with events).

Abbreviations: DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.

[a]Site-reported.
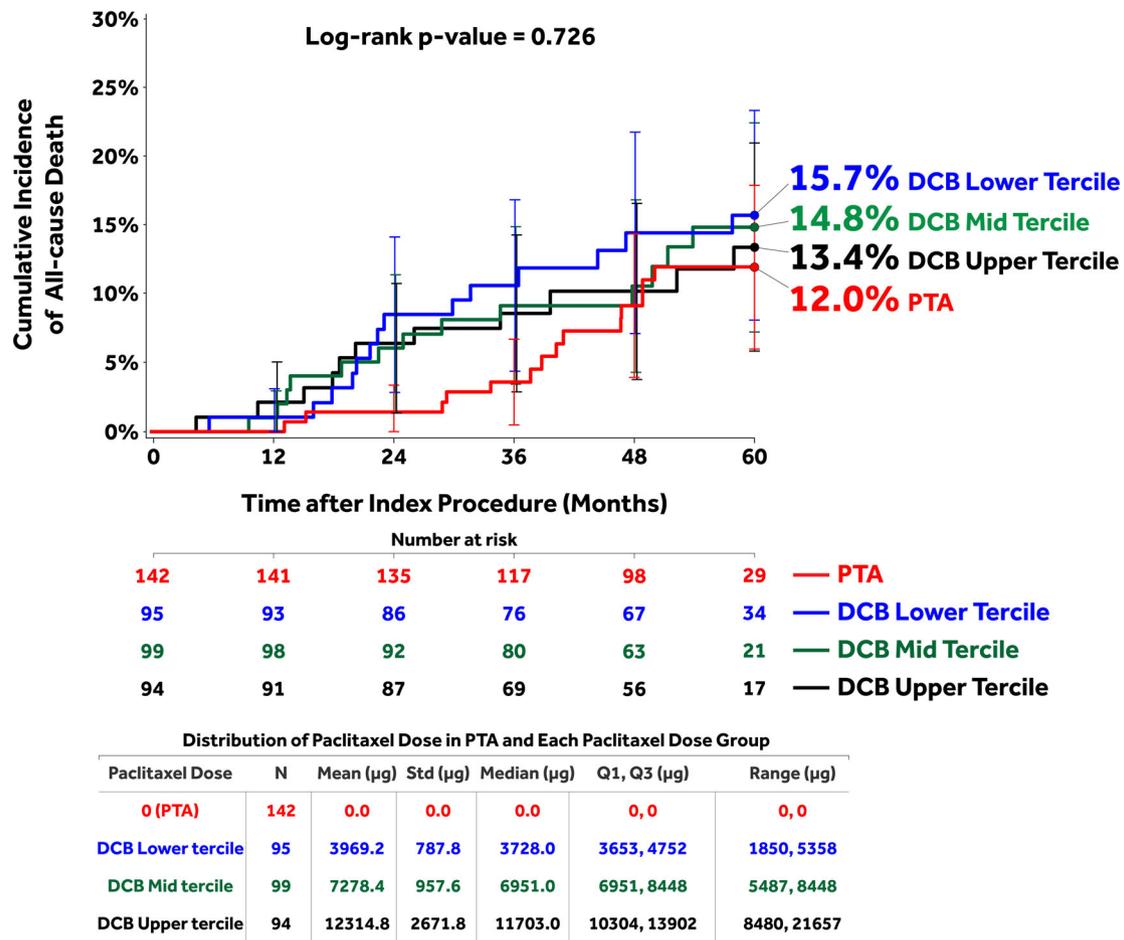
[b]Log-rank test p value.

FIGURE 2 IN.PACT RCT pooled all-cause death by dose. The cumulative incidence of all-cause death by dose tercile through 5 years in the IN.PACT RCT pooled as-treated patients was estimated by Kaplan–Meier analysis. Across the groups, mortality rates were similar, with the highest observed mortality in the lowest dose group (log-rank *p* = .726), indicating that there was no gradient of risk with increasing paclitaxel dose. Error bars represent 95% confidence intervals. DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCT, randomized clinical trial [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Multivariable analysis for predictors of all-cause death in all patients from the IN.PACT RCT pooled as treated cohort through 5 years

Predictors of death through 5 years	Hazard ratio [95% CI]	*p* Value
Age (≥75 vs. <75 years)	2.45 [1.37, 4.38]	.003
Renal insufficiency (baseline serum creatinine ≥1.5 ng/dL) (Y vs. N)	2.63 [1.28, 5.39]	.009
Smoking (current/previous vs. never)	1.65 [0.86, 3.15]	.128
Forced into the model		
Treatment arm (DCB vs. PTA)	1.41 [0.76, 2.60]	.272
Forced into the model		
Paclitaxel dose tercile in DCB (lower vs. PTA)	1.61 [0.76, 3.38]	.212
Paclitaxel dose tercile in DCB (mid vs. PTA)	1.44 [0.68, 3.07]	.344
Paclitaxel dose tercile in DCB (upper vs. PTA)	1.20 [0.54, 2.64]	.660
Forced into the model		
Paclitaxel dose as a continuous variable (mg)	1.02 [0.97, 1.08]	.381

Note: Three separate multivariable Cox regression models with frailty were performed to identify predictors of all-cause death. Paclitaxel exposure was analyzed in all three models: DCB treatment arm, dose tercile, or dose as a continuous variable.
Abbreviations: CI, confidence interval; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.

and PTA arms, with a difference of 2.7% (14.7% for DCB arm and 12.0% for PTA arm; hazard ratio [HR], 1.39; 95% CI, 0.76–2.57; log-rank p = .286] (Figure S1). There was no significant difference in the cumulative incidence of mortality between DCB and PTA within the individual trials as shown in Figure S2 (IN.PACT SFA) and Figure S3 (IN.PACT Japan).

3.4 | Adjudicated causes of death by treatment

Causes of death in the IN.PACT RCT pooled cohort through 5 years are summarized in Table 2. As adjudicated by the new CEC, none of the deaths were identified as procedure-, device-, or paclitaxel- related. The

TABLE 5 Multivariable analysis for predictors of CD-TLR in all patients from the IN.PACT RCT pooled ITT cohort through 1 year

Predictors of CD-TLR through 1 year	Hazard Ratio [95% CI]	P-value
Treatment arm (DCB vs. PTA)	0.13 [0.06, 0.28]	<.001
Rutherford category (>3 vs. ≤3)	2.48 [0.87, 7.06]	.090
Previous peripheral revascularization (Y vs. N)	1.79 [0.91, 3.51]	.092
Coronary heart disease (Y vs. N)	1.67 [0.84, 3.30]	.142
Hyperlipidemia (Y vs. N)	0.60 [0.28, 1.29]	.191
Paclitaxel dose tercile in DCB (lower vs. PTA)	0.10 [0.02, 0.42]	.002
Paclitaxel dose tercile in DCB (mid vs. PTA)	0.20 [0.07, 0.58]	.003
Paclitaxel dose tercile in DCB (upper vs. PTA)	0.09 [0.02, 0.37]	<.001
Paclitaxel dose as a continuous variable (mg)	0.79 [0.70, 0.88]	<.001

Note: Three separate multivariable Cox regression models with frailty were performed to identify predictors of clinically-driven target lesion revascularization (CD-TLR). Paclitaxel exposure was analyzed in all three models: DCB treatment arm, dose tercile, or dose as a continuous variable. Abbreviations: CD-TLR, clinically driven target lesion revascularization; CI, confidence interval; DCB, drug-coated balloon; ITT, intention-to-treat; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.

cumulative incidence of cardiovascular deaths, as estimated by Kaplan–Meier, were 4.0% in the DCB and 3.2% in the PTA arms while non-cardiovascular deaths were 8.9% in the DCB and 4.7% in the PTA arms. Overall rates of death by subcategory did not differ by treatment arm and there was no clustering of deaths to any specific cause.

3.5 | Comparison of paclitaxel-related adverse events by treatment arm

Intravenous paclitaxel have been associated with a specific pattern of adverse events in oncology patients.[13] Reported adverse events were examined for potential patterns of association with paclitaxel, including bradycardia, neurotoxicity, hematologic abnormalities, and myalgia through 5 years (Table 3). Overall, there was no pattern of adverse events after DCB treatment to suggest a known mechanism of paclitaxel-related adverse events.

3.6 | Mortality rates stratified by paclitaxel dose

Mean dosage in each tercile was 4.0, 7.3, and 12.3 mg in increasing order, and the PTA group was referenced as zero paclitaxel dose (Figure 2). Mortality rates were not significantly different among dose terciles (log-rank p = .726, Figure 2). A multivariable Cox proportional-hazards regression with frailty model demonstrated that renal insufficiency and age ≥75 years were associated with increased risk of death within 5 years in the IN.PACT RCT pooled cohort (Table 4). Paclitaxel exposure, as evaluated by DCB versus PTA, dose tercile (upper, middle, lower), or dose as a continuous variable was not selected by the multivariable selection process as a predictor of mortality. When each of these variables (DCB, paclitaxel dose tercile or dose as a continuous variable) was forced into the final model to show the potential impact, these terms remained insignificant (Table 4). The multivariable model demonstrated that DCB treatment, paclitaxel dose as a continuous variable, and paclitaxel dose tercile (lower, middle or upper) versus PTA were all associated with a lower risk of CD-TLR (Table 5).
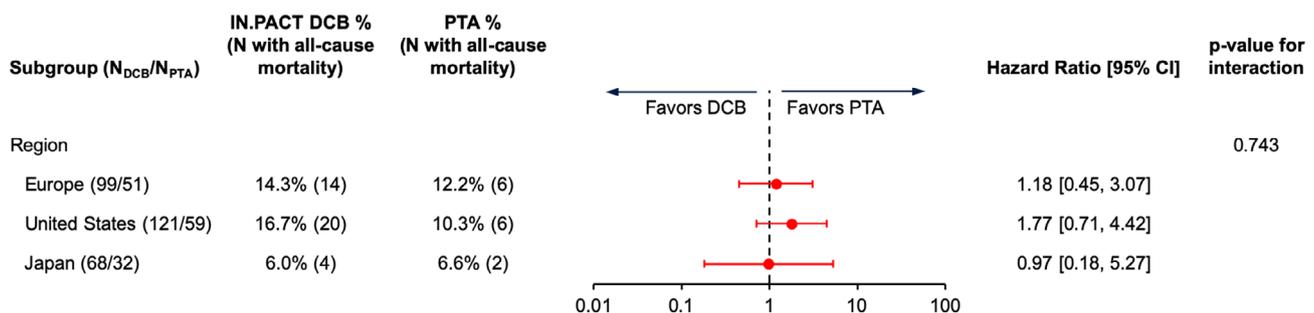

Subgroup (N_DCB/N_PTA)	IN.PACT DCB % (N with all-cause mortality)	PTA % (N with all-cause mortality)		Hazard Ratio [95% CI]	p-value for interaction
Region					0.743
Europe (99/51)	14.3% (14)	12.2% (6)		1.18 [0.45, 3.07]	
United States (121/59)	16.7% (20)	10.3% (6)		1.77 [0.71, 4.42]	
Japan (68/32)	6.0% (4)	6.6% (2)		0.97 [0.18, 5.27]	

FIGURE 3 Forest plot of all-cause mortality through 5 years in the IN.PACT RCTs. The all-cause mortality difference between DCB and PTA was not consistent across different geographic regions. The highest HR was observed for the United States (HR, 1.77; 95% CI, 0.71–4.42) and the lowest for Japan (HR, 0.97; 95% CI, 0.18–5.27). The p-value was derived from the Cox proportional hazard model by testing the treatment-by-region interaction term. CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; PTA, percutaneous transluminal angioplasty; RCT, randomized clinical trial [Color figure can be viewed at wileyonlinelibrary.com]

3.7 | Treatment effects by geography

A forest plot of mortality comparing DCB versus PTA demonstrated that the mortality signal varied numerically across different geographic regions (*p* value for interaction = .743; Figure 3). The IN.PACT SFA II (the United States) had a HR of 1.77 (95% CI, 0.71–4.42), indicating a numerically higher mortality signal in comparison to Europe and Japan where it was diminished or not present

(Europe: HR, 1.18 [95% CI, 0.45–3.07]; Japan: HR, 0.97 [95% CI, 0.18–5.27]).

In contrast to mortality, there was a consistent clinical benefit associated with the DCB treatment across geographic regions. Primary patency rates were higher in the DCB arm compared to PTA (log-rank *p* < .001) at all follow-up time points assessed (1, 2, and 3 years) in both IN.PACT SFA and IN.PACT Japan trials (Figure S4). Similarly, a forest plot of freedom from CD-TLR through 60 months
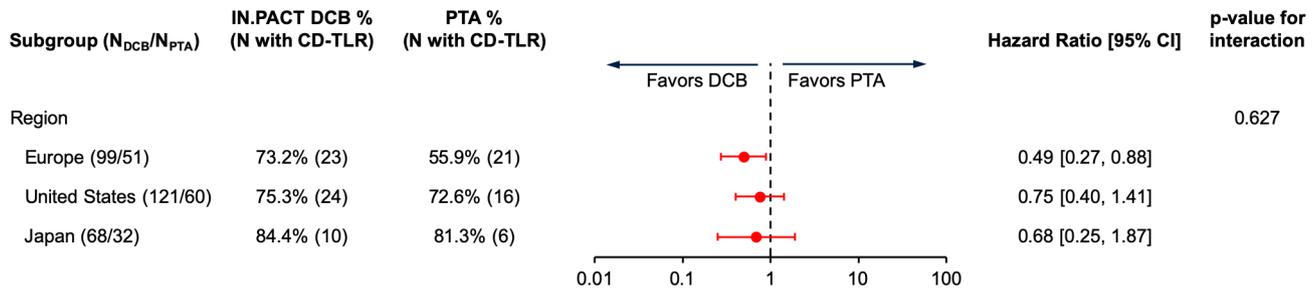
Subgroup (N$_{DCB}$/N$_{PTA}$)	IN.PACT DCB % (N with CD-TLR)	PTA % (N with CD-TLR)		Hazard Ratio [95% CI]	p-value for interaction
Region					0.627
Europe (99/51)	73.2% (23)	55.9% (21)		0.49 [0.27, 0.88]	
United States (121/60)	75.3% (24)	72.6% (16)		0.75 [0.40, 1.41]	
Japan (68/32)	84.4% (10)	81.3% (6)		0.68 [0.25, 1.87]	

Favors DCB ← | → Favors PTA

0.01   0.1   1   10   100

FIGURE 4 Forest plot of freedom from CD-TLR through 5 years in the IN.PACT RCTs. Kaplan–Meier estimates of freedom from CD-TLR are presented. Through 5 years, DCB was favored over PTA across all geographic regions. The *p* value was derived from the Cox proportional hazard model by testing the treatment-by-region interaction term. Note: IN.PACT Japan data were censored at 1095 days. One patient from the IN.PACT SFA II with Rutherford Category 5 was not included in any Rutherford classification group. CD-TLR, clinically driven target lesion revascularization; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCT, randomized clinical trial [Color figure can be viewed at wileyonlinelibrary.com]
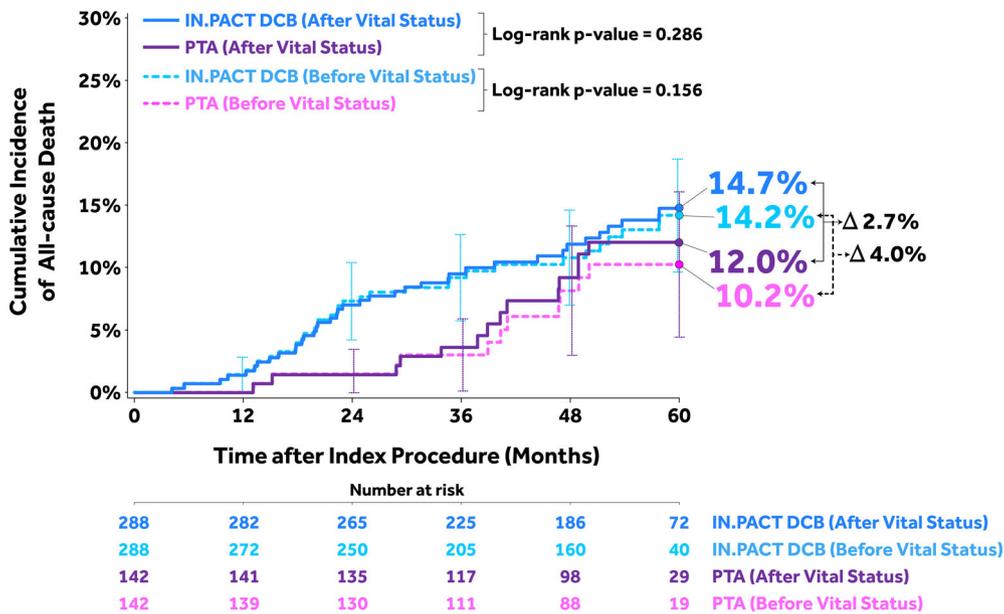

FIGURE 5 Cumulative incidence of all-cause death in the IN.PACT RCT pooled patients as treated before and after vital status ascertainment estimated by Kaplan–Meier analysis. Before vital status ascertainment, the cumulative incidence of mortality through 5 years was 14.2% for DCB arm and 10.2% for PTA arm (difference, 4.0%; HR, 1.63; 95% CI, 0.83–3.21; log-rank *p* = .156). After vital status ascertainment, the difference was further narrowed (difference, 2.7%; 14.7% for DCB arm and 12.0% for PTA arm; HR, 1.39; 95% CI, 0.76–2.57; log-rank *p* = .286). CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial [Color figure can be viewed at wileyonlinelibrary.com]
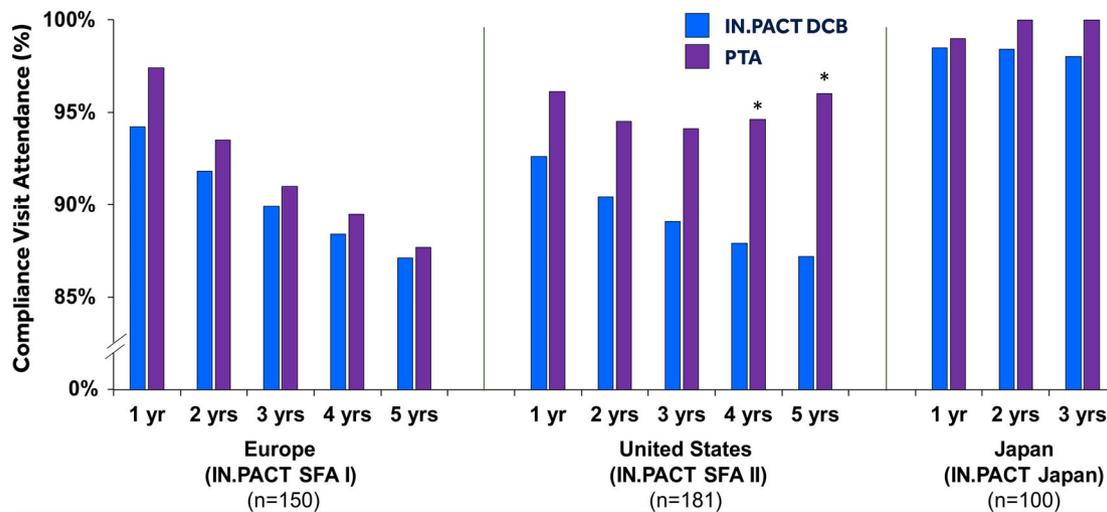
FIGURE 6 Compliance with follow-up visits by region. A trend of lower compliance to follow-up visit attendance was observed in the DCB arm at all time points across all regions, which was statistically significant for the United States (IN.PACT SFA II) at 4 years (88% DCB vs. 95% PTA; *p = .024) and 5 years (87% DCB vs. 96% PTA; *p = .003). DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty [Color figure can be viewed at wileyonlinelibrary.com]

demonstrated that DCB was favored over PTA consistently across geographic regions (Figure 4).

3.8 | Effect of trial design on mortality signal

We considered the impact of trial execution on mortality differences. The impact of vital status ascertainment is shown in Figure 5. The difference in mortality rates between DCB and PTA was 4.0% before vital status ascertainment (14.2% for DCB and 10.2% for PTA; HR, 1.63; 95% CI, 0.83–3.21; log-rank $p = .156$), which was attenuated after vital status ascertainment (difference, 2.7%; 14.7% for DCB and 12.0% for PTA; HR, 1.39; 95% CI, 0.76–2.57; log-rank $p = .286$).

Patients in the PTA arm had more complete follow-up visit attendance compared with DCB at all time points across all regions (Figure 6), which was statistically significant in the U.S. cohort (IN. PACT SFA II) at 4 years (88% DCB vs. 95% PTA; $p = .024$) and 5 years (87% for DCB versus 96% for PTA; $p = .003$). The overall difference in follow-up visit compliance between PTA and DCB patients was greater in the United States (5.8%) than in Europe (0.7%) or Japan (1.6%) through the final follow-up.

4 | DISCUSSION

Concerns were raised regarding a late mortality signal in summary level meta-analysis of paclitaxel-coated devices in the femoropopliteal artery.[9] Reanalysis by the FDA with available data from pivotal RCTs showed a mortality signal associated with these devices.[10] Interpretation of this finding remains inconclusive because of limitations of the available RCT data, including small sample sizes of each trial,

particularly the control arms in the setting of 2:1 randomization, and the high volume of missing data. In the current analysis, multiple steps were undertaken to evaluate the effect of paclitaxel exposure on the long-term safety and efficacy of angioplasty of the superficial femoral artery in the combined IN.PACT randomized trials, including near-complete ascertainment of vital status information, pooling of data from the two RCTs to increase the power to detect mortality difference, and readjudication of causes of death by a blinded CEC with special focus on paclitaxel-related toxicities. Results from this pooled analysis of RCTs using a single device demonstrated no association or dose-dependent relationship of paclitaxel exposure with mortality, and no pattern of imbalance in cause of death or other adverse events by treatment arm, but results did demonstrate a strong association with efficacy.

We acknowledge the presence of a transient mortality signal and this has been previously published within the SFA randomized trial data at years 2 and 3,[14,15] but is no longer evident beyond that period,[8] and is further diminished by obtaining more balanced and complete vital status data in this study. The lack of a correlation between paclitaxel exposure and mortality was further evident by the observation that there was no difference in cause of death in different treatment groups, and no specific patterns of non-fatal events to suggest mechanism. Furthermore, we found no late potential paclitaxel-related adverse events in the IN.PACT RCTs. Neutropenia is the principal toxic effect of paclitaxel reported in the literature.[13] In the current analysis, no case of neutropenia was identified in the DCB arm, while two cases were reported in the PTA arm through 5 years. A potential long-term complication of paclitaxel exposure is peripheral neuropathy characterized by sensory symptoms.[13] None of the patients in the DCB arm developed peripheral neuropathy, suggesting no delayed adverse effects of paclitaxel after the index procedure in the RCT pooled cohort.

In pharmacological studies, it is well established that dose escalation of a drug corresponds to increasing response.[16] A dose response was not evident in this analysis. The present pooled analysis has the advantage of patient-level data, which allowed patient-level dose calculation and dose-effect risk analysis. Paclitaxel dose was not associated with mortality either in tercile analysis or as a continuous measure in multivariable analysis. The same multivariable model identified older age (≥75 years) and renal insufficiency as predictors of all-cause death, which are traditional risk factors associated with increased risk of mortality in this patient population.[17,18] In contrast, a dose-relationship was observed with efficacy; a multivariable analysis identified independent association of paclitaxel treatment and paclitaxel dose with reduced risk of CD-TLR.

Paclitaxel has a well-established role as a safe and effective chemotherapeutic agent since its FDA approval in 1992.[19] It is extensively used in the curative breast cancer setting and is approved and has been administered to pregnant women and no evidence of adverse effect in infants has been demonstrated despite a much higher drug dose than that of PAD devices.[20] These findings showed that the current knowledge of paclitaxel safety is not coherent with the proposed association between paclitaxel and mortality.

In addition to a lack of evidence of causal patterns, data from RCTs may have been affected by follow-up biases that potentially contributed to the observed mortality signal. Within the IN.PACT RCTs, there were more missing vital status data beyond 1 year than are desirable for detecting long-term outcomes such as mortality, and missing data were more prominent in the DCB arm. It is possible that subjects with more efficacious treatment required less frequent follow-up and were therefore less compliant, and that sites did not anticipate the relevance of long-term vital status ascertainment. Though the trials were randomized, patients were blinded for the first year (through the primary endpoint), and it was not feasible to blind the treating physicians, which may have contributed to the imbalance in follow-up between treatment arms. Across regions, an inverse correlation between the mortality difference and compliance visit rate was observed. The highest HR for mortality risk in the DCB arm compared with PTA was found in the United States (IN.PACT SFA II) where compliance with follow-up visit in the DCB arm was lowest. This trend was diminished or not seen in the Europe and Japan cohorts. It may be possible that trials conducted in certain regions adhered to the protocol more closely and patients were more likely to attend the follow-up visits.

Small sample size is a limiting factor in meaningful analysis of an endpoint such as mortality. The 2:1 randomization ratio lead to a small PTA sample size, which resulted in instability in mortality rates at early time points. The PTA arm of the IN.PACT SFA trial has unusually low mortality rates at 1, 2, and 3 years (0.0, 0.9, and 1.9%, respectively) as compared with the PTA arms of other trials.[10] There were only a few events in these early time points in the PTA arm, including no deaths at 1-year follow-up, 1 death and 3 deaths at 2- and 3-year follow-up, respectively. With these small numbers, a difference of one event can result in a twofold underestimation or overestimation of mortality. Over time, mortality rates across studies became more similar as more events accrued. This sample size phenomenon is demonstrated in Figure S5 that summarizes published mortality rates across all FDA-approved paclitaxel-coated device RCTs for femoropopliteal PAD[10].

These pooled RCTs were powered to evaluate the 1-year primary patency and safety composite endpoint (a composite of mortality, amputation and revascularization events). The impact of paclitaxel on long-term mortality risk was not anticipated as a consideration as this drug has been in broad use in coronary stents, and at higher doses for chemotherapy without any concerns related to mortality.[3,19] This is the likely reason that there was less attention to complete follow-up at late time points. It will be important that ongoing and future studies in the patient population have careful attention to late follow-up.

There are several large data sets that have examined the impact of paclitaxel-coated devices on mortality that have not shown evidence for increased mortality.[21-27] The strength of these analyses is the power to detect small differences as well as the completeness of an endpoint such as mortality in these types of datasets that do not rely on in person follow-up. Similarly, patient-level independent analyses have also demonstrated the safety of drug-coated devices.[28-31] Recent efforts from independent investigators, societies and regulatory bodies are crucial for resolving the mortality signal issue.

5 | LIMITATIONS

IN.PACT SFA and IN.PACT Japan were randomized 2:1 and powered to evaluate 1-year efficacy but not long-term mortality or a paclitaxel dose–response. Although the power of analysis has been improved by pooling data from two RCTs, the total sample size is still relatively small. Retrospective vital status ascertainment improved the available data for mortality analysis; however, there were still missing data in this data set, highlighting the need to encourage improved compliance with follow-up. While fewer visits may have resulted in less optimal medical care and introduced bias, information on medication use and compliance with general preventive care recommendations such as smoking cessation or cancer screening was not collected within these trials. Although the trial designs were similar and endpoint definitions were identical, study completion time points were different; subsequently, the number of patients were small through 4 and 5 years. A single type of DCB was studied in this analysis; based on varying dose densities, coating formulations, and excipients, the efficacy and safety cannot be assumed to be completely uniform across different formulations used in other device types.

6 | CONCLUSIONS

In pooled randomized trial data with updated vital status ascertainment for long-term follow-up, paclitaxel DCB was associated with

increased efficacy versus PTA but was not associated with increased mortality. A causal relationship between paclitaxel and mortality could not be identified. Trial design and conduct may have contributed to the demonstration of a safety signal.

CONFLICT OF INTERESTS

Data were transferred for independent analysis to the Baim Institute for Clinical Research. This analysis was supported by Medtronic. Peter A. Schneider has served as a member of the advisory board for Philips, Boston Scientific, and Medtronic; and as a consultant for Cagent, Cardiovascular Systems, Inc., Intact Vascular, Medtronic, Profusa, Silk Road Medical, and Surmodics. Marianne Brodmann has received speaking honoraria from Bard Peripheral Vascular, Biotronik, Medtronic, Philips-Spectranetics, Shockwave, Bayer Healthcare, and VIVA Physicians; and is a consultant for Bard Peripheral Vascular, Bayer, Biotronik, Intact Vascular, Medtronic, Philips-Spectranetics, Sanofi, and Shockwave. Laura Mauri is a full-time employee of Medtronic Inc., Minneapolis, MN. John Laird has served on the advisory board for Abbott Vascular and Boston Scientific; has served as a consultant for Abbott Vascular, Bard/Becton Dickinson, Boston Scientific, Medtronic, and Philips; and has received speaking fees from Medtronic. Yoshimitsu Soga has nothing to disclose. Antonio Micari has served as a member of the advisory board for Boston Scientific and Medtronic and has served as a consultant for Bard, Boston Scientific, and Terumo. Gary Ansel has provided advisory and consultation services for Abbott Vascular, Alucent, Boston Scientific, Cardiovascular Systems, Inc., Contego Medical, Cook Medical, CR Bard, Intact Vascular, Medtronic, Philips Medical, Reflow Medical, Shockwave, Surmodics, Vascular Dynamics, Vatrix, Veryan Medical, VIVA Physicians, and WL Gore. Mehdi Shishehbor has served as a consultant and a member of the advisory board for Abbott Vascular, Boston Scientific, Medtronic, Philips, and Terumo. Prakash Krishnan has served as a consultant to Abbott and Medtronic. Qi Gao is a full-time employee of the Baim Institute for Clinical Research. Kenneth Ouriel is an employee of and holds equity in Syntactx, which reviews research sponsored by Medtronic. Thomas Zeller has received honoraria from Abbott Vascular, Biotronik, Boston Scientific, Cook Medical, Gore and Associates, Medtronic, Philips-Spectranetics, TriReme, Shockwave, and Veryan; has served as a consultant for Bayer, B. Braun, Boston Scientific, Cook Medical, Gore and Associates, Intact Vascular, Medtronic, Shockwave, Spectranetics, Veryan, and Vesper Medical; has received research, clinical trial, or drug study funds from 480 biomedical, Bard Peripheral Vascular, B. Braun, Biotronik, Cook Medical, Gore and Associates, Intact Vascular, Med Alliance, Medtronic, Philips, Terumo, TriReme, Shockwave; and owns common stock in QT Medical and Veryan.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.