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Mortality Not Correlated With Paclitaxel Exposure

An Independent Patient-Level Meta-Analysis of a Drug-Coated Balloon

Peter A. Schneider, MD,[a] John R. Laird, MD,[b] Gheorghe Doros, PHD,[c,d] Qi Gao, MS,[c] Gary Ansel, MD,[e] Marianne Brodmann, MD,[f] Antonio Micari, MD, PHD,[g] Mehdi H. Shishehbor, DO, MPH, PHD,[h] Gunnar Tepe, MD,[i] Thomas Zeller, MD, PHD[j]

ABSTRACT

BACKGROUND Five years of prospective clinical trials confirm that the paclitaxel drug-coated balloon (DCB) (IN.PACT Admiral, Medtronic, Dublin, Ireland) is safe and effective to treat femoropopliteal artery disease. A recent meta-analysis of heterogeneous trials of paclitaxel-based balloons and stents reported that they are associated with increased mortality and that higher doses are linked to higher mortality from 2 to 5 years.

OBJECTIVES The purpose of this study was to determine if there is a correlation between paclitaxel exposure and mortality by conducting an independent patient-level meta-analysis of 1,980 patients with up to 5-year follow-up.

METHODS Data from 2 single-arm and 2 randomized independently adjudicated prospective studies of a paclitaxel DCB (n = 1,837) and uncoated percutaneous transluminal angioplasty (PTA) (n = 143) were included. Analyses of baseline, procedure, and follow-up data of individual patients were performed to explore correlations of paclitaxel dose with long-term mortality. Survival time by paclitaxel dose tercile was analyzed with adjustment of inverse probability weighting to correct baseline imbalances and study as random effect. A standard cohort was defined to compare DCB- and PTA-treated patients with similar characteristics by applying criteria from pivotal studies (n = 712 DCB, n = 143 PTA).

RESULTS A survival analysis stratified nominal paclitaxel dose by low, mid, and upper terciles; mean doses were 5,019.0, 10,007.5, and 19,978.2 μg, respectively. Rates of freedom from all-cause mortality between the 3 groups through 5 years were 85.8%, 84.2%, and 88.2%, respectively (p = 0.731). There was no significant difference in all-cause mortality between DCB and PTA through 5 years comparing all patients (unadjusted p = 0.092) or patients with similar characteristics (adjusted p = 0.188).

CONCLUSIONS This independent patient-level meta-analysis demonstrates that this paclitaxel DCB is safe. Within DCB patients, there was no correlation between level of paclitaxel exposure and mortality. (Randomized Trial of IN.PACT Admiral® Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease [INPACT SFA I], NCT01175850; IN.PACT Admiral Drug-Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery [SFA] and Proximal Popliteal Artery [PPA] [INPACT SFA II], NCT01566461; MDT-2113 Drug-Eluting Balloon vs. Standard PTA for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery [MDT-2113 SFA], NCT01947478; The IN.PACT SFA Clinical Study for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery Using the IN.PACT Admiral™ Drug-Eluting Balloon in a Chinese Patient Population, NCT02118532; and IN.PACT Global Clinical Study, NCT01609296) (J Am Coll Cardiol 2019;73:2550–63) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]Division of Vascular and Endovascular Surgery, University of California at San Francisco, San Francisco, California; [b]Adventist Heart and Vascular Institute, St. Helena, California; [c]Baim Institute for Clinical Research, Boston, Massachusetts; [d]School of Public Health, Boston University, Boston, Massachusetts; [e]Ohio Health, Riverside Methodist Hospital, Columbus, Ohio; [f]Division of Angiology, Medical University Graz, Graz, Austria; [g]Humanitas Gavazzeni Hospital, Bergamo, Italy; [h]Heart & Vascular Institute, University Hospitals Cleveland Medical Center, and Case Western Reserve University School of Medicine, Cleveland, Ohio; [i]RoMed Clinic, Rosenheim, Germany; and the [j]Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany. Data was transferred for independent analysis to the Baim Institute for Clinical Research, formerly HCRI. This analysis was

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A potential longer-term safety concern has been raised about the use of paclitaxel-containing devices in the treatment of femoropopliteal artery occlusive disease in a meta-analysis of summary-level data (1). A higher incidence of late mortality was reported across studies comparing paclitaxel drug-coated balloon (DCB) and drug-eluting stent (DES) therapies with uncoated percutaneous transluminal angioplasty (PTA) or bare-metal stent (BMS) controls. This difference in mortality was ascribed directly to paclitaxel. In addition, the authors reported that "the risk of death beyond one year also seemed to vary among different paclitaxel dosages, being significantly higher in the 3.5 μg/mm^2 devices compared with the lower-dose devices" (1).

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Prior to the publication of this meta-analysis, the body of evidence suggested that DCBs are safe and maintain a positive clinical benefit in the treatment of femoropopliteal disease in patients with peripheral arterial disease (PAD) and Rutherford 2 to 4 symptoms, as reported in the SCAI Consensus Guidelines for Device Selection in Femoral-popliteal Arterial Interventions (2) and the ACC/AHA/SCAI/SIR/SVM 2018 Appropriate Use Criteria (3). Mortality rates across the individual trials of DCBs are well within the ranges reported in other adjudicated nondrug vascular device trials and also reported in epidemiological studies of patients with PAD. However, results of the IN.PACT SFA investigational device exemption trial showed a transitorily higher frequency of mortality between the DCB and PTA arms at 2 and 3 years (4,5). These results were published, noting that this difference was no longer statistically significant at 4 and 5 years (4-7). No higher frequency of mortality was seen with DCBs at any time point in IN.PACT SFA Japan. All major adverse events and deaths were reviewed and adjudicated by an independent clinical events committee (CEC) and none were deemed related to the device.

As the recently published meta-analysis that suggested a safety concern was disadvantaged by its derivation from published or presented results of heterogeneous trials and devices, an independent assessment of adjudicated, individual patient-level data is essential to determine if paclitaxel-coated balloons are associated with an increased risk of mortality.

Reported herein is an independent patient-level analysis of patients treated with a paclitaxel DCB to investigate whether there is a correlation between paclitaxel exposure and mortality, and furthermore, whether increased paclitaxel dose is correlated with increased mortality.

ABBREVIATIONS AND ACRONYMS

CEC = clinical events committee

DCB = drug-coated balloon

MAE = major adverse event

PAD = peripheral artery disease

PTA = percutaneous transluminal angioplasty

METHODS

The Baim Institute for Clinical Research, Boston, Massachusetts, independently performed all analyses.

POOLED ANALYSIS STUDY DESIGN. This independent individual patient-level meta-analysis was designed to establish whether there is a correlation between nominal paclitaxel exposure and mortality

funded by Medtronic. Dr. Schneider has served as a member of the advisory board for Medtronic, Abbott, and Boston Scientific; has served as a consultant for Surmodics, Silk Road Medical, Medtronic, Cardinal, CSI, and Profusa; and is a Chief Medical Officer for Intact Vascular and Cagent. Dr. Laird has served on the advisory board for Abbott Vascular and Boston Scientific; has served as a consultant for Abbott Vascular, Philips, Bard/Becton Dickinson, Boston Scientific, and Medtronic; and has received speaking fees from Medtronic. Dr. Doros is a full-time employee of the Baim Institute for Clinical Research; has served as a consultant for Pfizer and Supernus; and has served on the data safety monitoring board for Takeda, Alnylam, and NeoSync. Dr. Gao is a full-time employee of the Baim Institute for Clinical Research. Dr. Ansel has provided advisory and consultation services for Medtronic, CR Bard, Boston Scientific, Cook Medical, Philips Medical, WL Gore, Veryan Medical, Reflow Medical, Shockwave, Intact Vascular, Abbott Vascular, Alucent, Contego Medical, Cardiovascular Systems. Surmodics, Vascular Dynamics, Vatrix, and VIVA Physicians. Dr. 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, Biotronik, Medtronic, Shockwave, Intact Vascular, Bayer, Sanofi, and Philips-Spectranetics. Dr. Micari has served as a member of the Advisory Board for Medtronic and Boston Scientific; and has served as a consultant for Boston Scientific, Bard, and Terumo. Dr. Shishehbor has served as a consultant and a member of advisory board for Medtronic, Abbott Vascular, Boston Scientific, Philips, and Terumo. Dr. Tepe has received research grants from Medtronic, Bard, Bayer, Gore, Biotronik, and Boston Scientific; and has served as a compensated advisory board member for Medtronic and B Braun. Dr. Zeller has received honoraria from Abbott Vascular, Veryan, Biotronik, Boston Scientific, Cook Medical, Gore and Associates, Medtronic, Philips-Spectranetics, TriReme, and Shockwave; has served as a consultant for Boston Scientific, Cook Medical, Gore and Associates, Medtronic, Spectranetics, Veryan, Intact Vascular, B. Braun, Shockwave, Bayer, and Vesper Medical; has received research, clinical trial, or drug study funds from 480 biomedical, Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Gore and Associates, Medtronic, Philips, Terumo, TriReme, Shockwave, Med Alliance, Intact Vascular, and B. Braun; and owns common stock in Veryan and QT Medical.

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in patients treated with the IN.PACT Admiral paclitaxel drug-coated balloon (Medtronic, Dublin, Ireland) for the treatment of symptomatic femoropopliteal PAD. A total of 1,980 patients among heterogeneous ethnic populations comprised of 2 randomized controlled trials (RCTs) and 2 prospective single-arm studies conducted at 147 sites across 6 continents and 28 countries were included (Online Table 1). The longest available follow-up data from 1,837 patients treated with this paclitaxel DCB and 143 patients treated with uncoated PTA were aggregated. IN.PACT SFA and MDT-2113 SFA Japan (IN.PACT SFA Japan) were prospective, multicenter, randomized, single-blind trials comparing DCB with PTA (8,9). IN.PACT SFA China was a prospective, multicenter, pre-market single-arm study (10). IN.PACT Global was a real-world, prospective, multicenter, single-arm study comprised of pre-specified imaging cohorts and a nonimaging clinical cohort (11). Patients enrolled in IN.PACT Global were more likely to have long lesions, chronic total occlusions, and in-stent restenosis. In addition, greater numbers of patients with Rutherford Clinical Category (RCC) 4 and 5 were part of IN.PACT Global, demonstrating the nonequivalence of the DCB patient population compared with the PTA population from the pre-market RCTs (11). A notable difference among studies is adherence to antiplatelet therapies; recommendations were pre-specified in each group according to the current standard of practice. Aspirin was required indefinitely for IN.PACT SFA and IN.PACT Global. Clopidogrel was required for 3 months in patients who received stents and for 1 month in patients who did not receive a stent in IN.PACT SFA, IN.PACT Global, and IN.PACT SFA Japan.

All major adverse events (MAEs), deaths, target limb amputations, reinterventions, and target lesion thromboses that occurred throughout each study follow-up period were independently adjudicated by a CEC representing varied specialists with no conflicts of interest (Syntactx, New York, New York; Baim/HCRI, Boston, Massachusetts). Per the CEC's manual of operations, device-related death was defined as a complication associated with the device design as it relates to placement, efficacy, or durability that may involve the delivery system.

These 4 studies comprise the largest, most complete, and fully adjudicated database of longitudinally-followed DCB patients to date. This provides added statistical power to evaluate whether paclitaxel played a role in mortality and whether paclitaxel dose had an effect on safety, although there is patient and lesion heterogeneity across studies. Additionally, PTA patients were only included in the 2 randomized trials in a 2:1 ratio. This is appropriate powering for a 1-year patency endpoint, and is appreciable for this analysis, but the low number of PTA patients may limit the power for any comparisons with the PTA group.

ENDPOINT DEFINITIONS. Study endpoint definitions were consistent across all IN.PACT Admiral DCB studies. All were assessed through the longest-available follow-up: 5 years for IN.PACT SFA, 3 years for IN.PACT SFA Japan, 3 years for IN.PACT Global, and 1 year for IN.PACT China. Follow-up of IN.PACT Global subjects to 5 years is in process. Assessment by Kaplan-Meier estimate included MAE and its component events: death from any cause, clinically-driven target vessel revascularization, target limb major amputation, and thrombosis. Clinically-driven reinterventions were defined as reintervention at the target vessel and/or lesion because of symptoms or a decrease in ankle-brachial index (ABI) by $\geq$20% or $>$0.15 when compared with post-procedure baseline ABI. Previously, site-reported causes of mortality were reported and were not categorized by system class. The recent meta-analysis used the site-reported causes of mortality and grouped them (1). For the completeness of this analysis, CEC-adjudicated narratives were reviewed individually, and these results were reported rather than the site-reported causes of death. Using the CEC narratives and the etiology of deaths provided, the causes of death were categorized by organ system classification.

STATISTICAL ANALYSES. All descriptive summaries were based on nonmissing assessments. Unless otherwise specified, all baseline demographics and clinical characteristics were summarized on a patient basis; lesion characteristics were summarized on a lesion basis. For baseline characteristics, continuous variables were described as mean $\pm$ SD and were compared by Student's *t*-test or Wilcoxon rank sum test; dichotomous and categorical variables were described as counts and proportions and were compared by Fisher exact test or Cochran-Mantel-Haenszel test with modified ridit scores. Outcome analyses were performed at the patient level. 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 analyses. Nominal paclitaxel dose per balloon was defined according to the product length and diameter as described in the IN.PACT Admiral Instructions for Use (12). 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.

To assess the association of the paclitaxel nominal dose received by each patient during the index procedure and mortality over time, the group was segmented into 3 terciles based on the amount of paclitaxel received. The unadjusted survival in these 3 groups was estimated using the Kaplan-Meier method. Survival was further compared among dose terciles with the use of propensity scores and inverse-probability-of-treatment-weighting (IPTW) adjustment. IPTW was used rather than adjustment with multiple covariates, as adjustment could potentially lead to lack of model convergence when a small number of events are observed. Details on the propensity score model are included in the Online Appendix. Frailty models, which are extensions of the proportional hazards model, were used to account for clustering of patients by study.

Multivariable analysis. To identify predictive factors for death in all DCB-treated patients, multivariable Cox regression models with frailty were performed. Baseline variables with >15% missing data were excluded from the analysis and included variables with missing data were imputed: simple imputation was applied for missing values, stratified by study, sex, and treatment arm, using the mean for continuous variables or most common values for dichotomous or categorical variables of the non-missing values. Multivariate predictors started from the exact same set of variables used to derive IPTW between paclitaxel dose tercile and were chosen by eliminating 1 of the covariates with the largest p value at a time, until all covariates left in the model except for paclitaxel dose tercile have p value <0.20. Hazard ratios (HRs) with 2-sided 95% confidence intervals (CIs) were calculated.

Additional analyses. To provide additional analyses regarding the effects of paclitaxel, survival in patients treated with DCB versus PTA was evaluated. As patients treated with PTA were only included in the IN.PACT SFA and IN.PACT SFA Japan trials, these baseline imbalances were adjusted by creating a subgroup that included only patients who met the criteria for pivotal studies (IN.PACT SFA, IN.PACT SFA Japan, and IN.PACT China). The group of patients treated with DCB, termed the standard DCB group, included patients with RCC 2 to 4, with a single, de novo lesion ≤20 cm, calcium levels of none to mild, and no in-stent restenosis. This resulted in a group of 712 standard DCB patients, first reported at the Vascular Interventional Advances (VIVA) conference in 2018 (13). Survival was compared in the standard cohort between standard DCB- and PTA-treated patients with the use of propensity scores and IPTW adjustment. Details on the propensity score model are included in the Online Appendix.

Upon inspecting the data, we found evidence that the traditional proportional hazard assumption might not be tenable across the 5-year follow-up period. To further evaluate the difference in survival between the 2 groups, a piecewise exponential model was fit to the data. Technical details on the model are included in the Online Appendix.

Visit compliance was defined as the proportion of scheduled visits attended and was estimated for both treatment groups at each year and overall. Medication use following the index procedure was captured and reported.

RESULTS

BASELINE CHARACTERISTICS. This independent patient-level analysis included 1,980 patients: 1,837 received DCB and 143 received PTA. The mean age of the DCB cohort was 68.5 ± 9.8 years; 68.2% (1,253 of 1,837) of patients were male. Baseline characteristics are summarized in Online Tables 2 to 5. Overall, patients treated with a DCB were more likely to have critical limb ischemia (CLI) compared with PTA. DCB subjects were less likely to have hyperlipidemia, coronary artery disease, and diabetes mellitus than those treated with uncoated PTA.

In the overall cohort of 1,837 DCB patients and 143 PTA patients, 181 patients treated with DCB died, compared with 12 patients treated with PTA through the follow-up period up to 5 years. Baseline characteristics for those who died were similar between treatment groups (Online Table 6). PTA patients who died were more likely to be active smokers than DCB patients who died. DCB patients were more likely to have calcified lesions and diabetes mellitus. There were 32 patients with CLI in the DCB group who died.

Among DCB patients who survived (n = 1,656) or died (n = 181), those in the mortality group were older; had statistically significantly higher rates of comorbidities, including diabetes mellitus (including insulin dependence), carotid artery disease, coronary heart disease, renal insufficiency, and below-the-knee disease; and had a higher incidence of critical limb ischemia (**Table 1**).

SAFETY OUTCOMES. Safety outcomes of DCB and PTA patients through longest follow-up are reported in **Table 2**. After adjusting for the intracluster dependence within study using a frailty model with study as a random effect, the MAE composite (including all-cause mortality, major target limb

TABLE 1 Baseline Characteristics of All Patients Who Survived Versus Died Treated With the Paclitaxel DCB

	Death (n = 181) (192 Target Limbs) (231 Target Lesions)	Survival (n = 1,656) (1,760 Target Limbs) (1,973 Target Lesions)	p Value
Patient characteristics			
Age, yrs	72.7 ± 9.4 (178)	68.0 ± 9.8 (1,649)	<0.001
Male	68.5 (124/181)	68.2 (1,129/1,656)	1.000
Hypertension	89.4 (161/180)	83.0 (1,371/1,652)	0.026
Hyperlipidemia	70.2 (125/178)	69.5 (1,120/1,611)	0.932
Diabetes mellitus	55.0 (99/180)	39.7 (656/1,653)	<0.001
Insulin-dependent diabetes mellitus	31.7 (57/180)	15.4 (254/1,653)	<0.001
Carotid artery disease	31.5 (47/149)	21.3 (309/1,448)	0.007
Coronary heart disease	53.5 (91/170)	41.6 (660/1,585)	0.003
Smoking			
Active	22.7 (41/181)	33.9 (561/1,655)	0.002
Renal insufficiency (baseline serum creatinine ≥1.5 ng/dl)	24.2 (39/161)	8.7 (129/1,483)	<0.001
Below-the-knee vascular disease of target leg (stenotic/occluded)	57.6 (98/170)	45.2 (710/1,571)	0.002
Previous peripheral revascularization	55.2 (100/181)	48.1 (796/1,656)	0.072
Rutherford category			<0.001
0	0.0 (0/181)	0.0 (0/1,653)	
1	0.0 (0/181)	0.1 (1/1,653)	
2	24.9 (45/181)	35.1 (580/1,653)	
3	57.5 (104/181)	55.4 (915/1,653)	
4	13.8 (25/181)	7.7 (128/1,653)	
5	3.9 (7/181)	1.8 (29/1,653)	
6	0.0 (0/181)	0.0 (0/1,653)	
Target limb ABI/TBI (mm Hg ratio) per patient	0.657 ± 0.256 (157)	0.690 ± 0.219 (1,542)	0.118
Pre-procedure per lesion			
Target lesion type per lesion			
De novo	80.5 (186/231)	78.3 (1,544/1,973)	0.498
Restenotic, nonstented	6.5 (15/231)	7.0 (139/1,973)	0.891
In-stent restenosis	15.5 (30/194)	18.4 (290/1,579)	0.373
Calcification	70.1 (155/221)	67.0 (1,290/1,924)	0.365
Thrombus	0.9 (2/221)	0.9 (18/1,920)	1.000
Reference vessel diameter, mm	5.14 ± 0.67 (231)	5.19 ± 0.68 (1,973)	0.254
Occluded lesion, 100% stenosis	32.9 (76/231)	35.6 (702/1,973)	0.467
Diameter stenosis, %	88.29 ± 11.42 (231)	89.28 ± 11.87 (1,973)	0.229
Lesion length, cm	11.83 ± 9.29 (231)	11.49 ± 8.87 (1,973)	0.584

Values are mean ± SD (n) or % (n/N). This data is site-reported. Baseline lesion and demographic characteristics of all patients that survived vs died treated with the paclitaxel drug-coated balloons (DCBs).

ABI = ankle-brachial index; TBI = toe-brachial index.

amputation, CD-TVR, thrombosis) risk was lower in the DCB group (43.6% vs 45.4%; p = 0.051). Safety outcomes of the standard cohort are reported in Table 3.

Causes of death over the length of the follow-up period for all DCB patients included cardiac (3.5%), malignancy (1.8%), respiratory (0.9%), neurological (1.0%), hepatobiliary (0.3%), gastrointestinal (0.6%), renal (0.1%), infection (0.4%), other (0.6%), and unknown (1.8%) (Table 4). These specific causes of death were typical for this patient population and were comparable to what is seen in patients treated with PTA. All patients had their causes of deaths adjudicated by an independent CEC and none were deemed related to the device. A total of 7 deaths were adjudicated as related to the procedure: 1 death on day 1 due to sudden death, a coronary disease on day 7, a myocardial infarction on day 15, a cardiac arrest on day 28, necrotizing fasciitis on day 85, heart failure on day 723, and acutely after a secondary procedure on day 838.

DCB PATIENT MORTALITY AND PACLITAXEL DOSE

Looking specifically at those patients treated with DCB, the overall mean nominal dosage of paclitaxel received was not different between patients who died

TABLE 2 Safety Outcomes Using Kaplan-Meier Estimates Through 5 Years

	DCB (n = 1,837)	95% CI of DCB, %	PTA (n = 143)	95% CI of PTA, %	Hazard Ratio (95% CI)*	p Value*
MAE composite†	43.57 (534)	(34.70–53.61)	45.39 (59)	(31.87–61.46)	0.73 (0.53–1.00)	0.051
Death (all-cause)	15.12 (181)	(9.31–24.02)	11.15 (12)	(4.86–24.47)	1.70 (0.92–3.15)	0.092
CD-TVR‡	32.40 (368)	(23.68–43.30)	37.17 (49)	(23.81–54.82)	0.61 (0.42–0.87)	0.007
Major target limb amputation	1.35 (12)	(0.21–8.47)	0.00 (0)	(0.00–0.00)	–	–
Thrombosis	4.85 (79)	(1.87–12.30)	3.59 (5)	(0.70–17.30)	0.74 (0.25–2.16)	0.584
CD-TLR§	30.99 (350)	(22.53–41.67)	32.56 (43)	(19.59–50.94)	0.63 (0.43–0.92)	0.017
Any TVR	33.00 (378)	(24.18–43.97)	36.78 (49)	(23.44–54.49)	0.63 (0.44–0.89)	0.010
Any TLR‖	31.62 (359)	(23.00–42.46)	34.50 (46)	(21.33–52.58)	0.61 (0.42–0.88)	0.008

Values are Kaplan-Meier estimate % (n) unless otherwise specified. Unadjusted safety outcomes through 5 years of all patients treated with DCB compared with PTA are reported. *Hazard ratios and p values are from frailty model with study as random effect. No other covariate was included. †A composite of death from any cause, CD-TVR, target limb major amputation, and thrombosis. ‡Defined as any reintervention within the target vessel due to symptoms or drop of ankle-brachial index (ABI) ≥20% or >0.15 when compared with post-procedure baseline ABI or toe-brachial index (TBI). §Defined as any reintervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared with post-procedure baseline ABI/TBI. ‖Includes clinically-driven and incidental or duplex-driven TLR.

CD-TLR = clinically-driven target lesion revascularization; CD-TVR = clinically-driven target vessel revascularization; MAE = major adverse events; TLR = target lesion revascularization; TVR = target vessel revascularization.

compared with patients who survived (12,202.1 μg vs. 11,368.7 μg; p = 0.186) (Table 5). A Kaplan-Meier survival analysis stratified nominal paclitaxel dosage into terciles: a low, a mid-, and upper-dose group. Mean dosages for the 3 groups were 5,019.0, 10,007.5, and 19,978.2 μg, respectively. There was no significant difference in mortality between groups, demonstrating no direct effect of levels of nominal paclitaxel dose exposure at the index procedure and survival status in the DCB patients through 5 years (p = 0.731) (Central Illustration). Similar outcomes were observed by terciles in the standard cohort (Online Figure 1).

MULTIVARIABLE ANALYSIS. A multivariable analysis of baseline demographic, lesion, and procedural characteristics was performed in all DCB patients (n = 1,837). Predictors of increased risk for mortality through 5 years included age, insulin-dependent diabetes mellitus, previous target and nontarget limb amputation, renal insufficiency, dialysis status, coronary artery disease, and hyperlipidemia (Table 6). Paclitaxel dose levels were not selected by the model selection process; however, when paclitaxel exposure was forced into the final model to show potential impact, it did not predict mortality. Indeed, the upper tercile dosage showed less risk compared with the lower tercile.

MORTALITY IN DCB VERSUS PTA. In the unadjusted analysis of all patients (DCB n = 1,837 and PTA n = 143), rates of all-cause mortality using Kaplan-Meier estimates through 5 years were 15.1% and 11.2%, respectively (p = 0.092) (Table 2). In the adjusted standard cohort (DCB n = 712 and PTA n = 143), rates of all-cause mortality using

TABLE 3 Safety Outcomes of Standard Cohort Patients Using Kaplan-Meier Estimates Through 5 Years

	Standard Paclitaxel DCB (n = 712)	95% CI of DCB, %	PTA (n = 143)	95% CI of PTA, %	HR (95% CI)*	p Value*
MAE composite†	37.83 (163)	(29.08–48.18)	47.65 (59)	(34.66–62.62)	0.65 (0.48–0.88)	0.005
Death (all-cause)	13.16 (58)	(7.81–21.73)	10.98 (12)	(4.94–23.43)	1.52 (0.82–2.82)	0.188
CD-TVR‡	27.59 (110)	(19.32–38.46)	40.38 (49)	(27.32–56.75)	0.52 (0.37–0.74)	<0.001
Major target limb amputation	0.63 (1)	(0.04–9.08)	0.00 (0)	(0.00–0.00)	–	–
Thrombosis	2.85 (17)	(0.82–9.71)	6.31 (5)	(1.96–19.34)	0.43 (0.19–0.97)	0.043
CD-TLR§	25.25 (98)	(17.35–35.88)	36.33 (43)	(23.44–53.36)	0.51 (0.36–0.72)	<0.001
Any TVR	28.15 (114)	(19.76–39.12)	39.94 (49)	(26.89–56.38)	0.53 (0.38–0.75)	<0.001
Any TLR‖	25.94 (102)	(17.86–36.76)	38.57 (46)	(25.58–55.25)	0.48 (0.34–0.67)	<0.001

Values are Kaplan-Meier estimate % (number of events). Adjusted safety outcomes through 5 years of the standard cohort are reported. *Hazard ratio (HR) and p values are from frailty model with study as random effect. Kaplan-Meier estimates, HR, and p value are adjusted by inverse probability of treatment weighting. †A composite of death from any cause, CD-TVR, target limb major amputation, and thrombosis. ‡Defined as any reintervention within the target vessel due to symptoms or drop of ankle-brachial index (ABI) ≥20% or >0.15 when compared to post-procedure baseline ABI or toe-brachial index (TBI). §Defined as any reintervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared with post-procedure baseline ABI/TBI. ‖Includes clinically-driven and incidental or duplex-driven TLR.

Abbreviations as in Table 2.

TABLE 4 Causes of Mortality

	IN.PACT SFA		IN.PACT SFA Japan					
Causes of Death	DCB (n = 184)	PTA (n = 104)	DCB (n = 67)	PTA (n = 29)	IN.PACT China (n = 139)	IN.PACT Global (n = 1,259)	All DCB Patients (n = 1,649)	All DCB and PTA Patients (n = 1,782)
Cardiac-related	3.3 (6)*	1.0 (1)	0.0 (0)	0.0 (0)	0.7 (1)	4.1 (51)	3.5 (58)	3.3 (59)
Malignancy-related	2.7 (5)	3.9 (4)	4.5 (3)	0.0 (0)	0.0 (0)	1.7 (22)	1.8 (30)	1.9 (34)
Respiratory-related	1.6 (3)	0.0 (0)	1.5 (1)	3.4 (1)	0.0 (0)	0.8 (11)	0.9 (15)	0.9 (16)
Neurological-related	2.2 (4)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.0 (13)	1.0 (17)	1.0 (17)
Hepatobiliary-related	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (4)	0.3 (5)	0.3 (5)
Gastrointestinal-related	1.6 (3)	1.9 (2)	0.0 (0)	0.0 (0)	0.7 (1)	0.4 (5)	0.6 (9)	0.6 (11)
Renal-related	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.1 (1)
Infection-related	1.1 (2)†	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.4 (5)	0.4 (7)	0.4 (7)
Other	0.5 (1)	1.9 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.6 (8)	0.6 (9)	0.6 (11)
Unknown	1.6 (3)	1.0 (1)	0.0 (0)	3.4 (1)	1.4 (2)	2.0 (25)	1.8 (30)	1.8 (32)

Values are reported as % (n). Site-reported causes of death were previously reported (4,5). In this report, they were confirmed by CEC narratives, resulting in updated numbers of cardiac- and infection-related deaths in IN.PACT SFA. Results of IN.PACT SFA are tabulated through 5 years, IN.PACT SFA Japan and IN.PACT Global through 3 years, and IN.PACT China through 1 year. All deaths were adjudicated by an independent CEC. Procedure-related death was defined as a complication associated with the initial placement of the device or any necessary secondary interventions. This includes morbidity associated with either anesthesia or surgical procedure. Device-related death was defined as a complication associated with the device design as it relates to placement, efficacy, or durability that may involve the delivery system. Drug-related death was defined as a complication associated with a patient's physiological response to the paclitaxel drug. *There were 3 site-reported causes of death for DCB subjects reported previously in IN.PACT SFA (infarction of the right cerebral hemisphere in the anterior and medial flow region at day 127, sudden death at day 287, and hemorrhagic stroke at day 788). They were reclassified into neurological-related, unknown, and neurological-related system classes in this report, respectively. †Within the IN.PACT SFA study, there were only 3 cases of sepsis/infection-related causes of death through 5 years; 2 cases of sepsis are classified as infection (sepsis at day 374 and septic shock at day 756) and 1 case of biliary sepsis was reclassified into hepatobiliary sepsis in this report.

CEC = clinical events committee; DCB = drug-coated balloon; PAD = peripheral artery disease; PTA = percutaneous transluminal angioplasty.

Kaplan-Meier estimates through five years were 13.2% and 11.0%, respectively (p = 0.188) (Table 3). Mortality outcomes per study through longest follow-up are reported in Table 7.

For the piecewise exponential model, after inspecting the data in the standard cohort, we chose a knot at 3 years that divided the follow-up times in 2 intervals: 0 to 3 years and 3 to 5 years (i.e., through 0 to 3 years follow-up and 4 to 5 years follow-up). Of the (n = 12) events observed in the PTA group, 4 events were observed in the first interval and 8 events were observed in the second interval (Online Figure 5). After adjusting for data structure using study as random effect and for baseline imbalances using IPTW, we found an increase in hazard of death with DCB in the first time interval hazard ratio comparing DCB to PTA (HR_1: 3.76 [95% CI: 1.22 to 11.55]; p = 0.021), which was significant, and an increase in hazard of death with PTA in the second time interval HR comparing DCB to PTA (HR_2: 0.56 [95% CI: 0.22 to 1.43]; p = 0.227), which was not significant. A test for equality found that the 2 HRs were significantly different in the 2 intervals (p = 0.011) (Online Table 7).

TABLE 5 Nominal Doses of Paclitaxel

	Death (n = 181)	Survival (n = 1,656)	p Value*
n	181	1,655	
Mean ± SD	12,202.06 ± 7,721.66	11,368.72 ± 7,371.19	0.186
Median (Q1, Q3)	10,298.00 (6,340.00, 16,896.00)	8,979.00 (5,809.00, 15,093.00)	
Min, max	(2,553.00, 43,472.00)	(1,850.00, 61,949.00)	

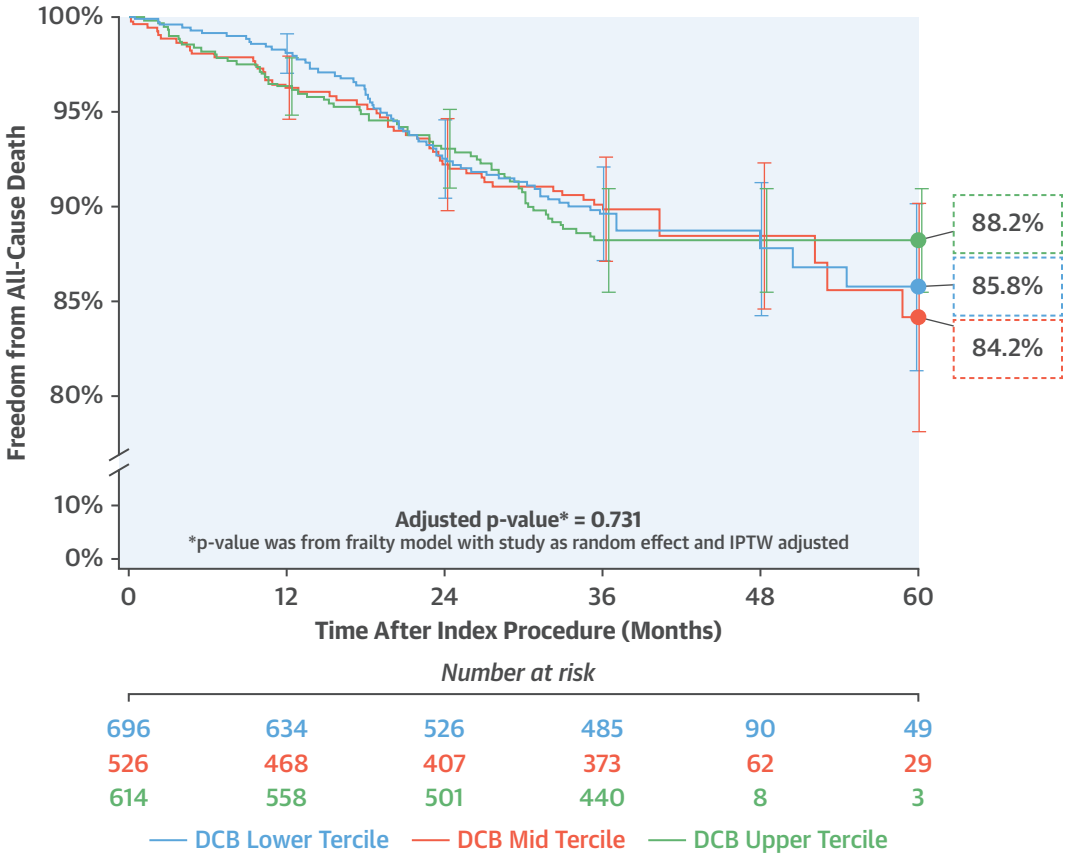
Nominal doses of paclitaxel (μg) are reported in all DCB patients who died and survived. Nominal paclitaxel dose per balloon was defined according to the product length and diameter as described in the IN.PACT Admiral Instructions for Use. The balloon lengths and diameters received by each patient were 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. *p value is from Wilcoxon rank sum test.

Abbreviations as in Table 4.

PRELIMINARY ALTERNATIVE HYPOTHESES. Additional preliminary analyses were conducted to generate hypotheses about how other factors following the index procedure may have contributed to mortality, such as interactions with the health care system and management of comorbidities.

Compliance with scheduled follow-up visits was assessed (Online Table 8). PTA patients exhibited significantly higher rates of scheduled visit compliance compared with DCB patients (95.3% vs. 88.4%; p < 0.001) especially at the 1-, 2-, and 3-year visits (Figure 1A). Visit compliance among DCB patients was higher for patients who survived versus died (88.8% vs. 84.4%; p = 0.009) (Figure 1B). Use of antiplatelet medication beyond the protocol-mandated timepoints was investigated (Table 8). At 6-, 12-, 24-, and 36-month follow-up, PTA patients exhibited significantly higher rates of dual antiplatelet therapy (aspirin + clopidogrel, ticlopidine, cilastazol, or prasugrel) administration compared with DCB patients (p = 0.001 at 12 and 36 months; p < 0.001 at 6 and 24 months).

CENTRAL ILLUSTRATION **Kaplan-Meier Freedom From All-Cause Death by Paclitaxel Dose in All DCB Patients**



Distribution of Paclitaxel Dose in Each Paclitaxel Tercile in DCB

Paclitaxel Dose	N	Mean μg	Std μg	Median μg	Q1, Q3 μg	Range μg
DCB Lower Tercile	696	5,019.0	1,508.6	4,752.0	3,653, 6,924	1,850, 6,951
DCB Mid Tercile	526	10,007.5	1,757.7	9,504.0	8,448, 11,618	6,989, 13,822
DCB Upper Tercile	614	19,978.2	6,122.1	18,654.0	15,399, 22,705	13,902, 61,949

Schneider, P.A. et al. J Am Coll Cardiol. 2019;73(20):2550–63.

Kaplan-Meier estimates of survival are stratified by nominal paclitaxel dosage terciles with all patient-level DCB data available through 5 years. DCB = drug-coated balloon; IPTW = inverse probability of treatment weighting.

DISCUSSION

Paclitaxel is a commonly-used cytotoxic agent originally used in an intravenous application as a chemotherapeutic to treat malignancies. The doses for administration range from a dose per body surface area of 135 to 175 mg/m^2 in 3- or 24-h infusions. This results in total dosage of the drug as a range of 236 to 306 mg for a 65-inch, 150-pound adult, or a range of 302 to 392 mg for a 72-inch, 225-pound adult (14). The number and schedule of these infusions vary depending on the malignancy and the patient response. The mean level of paclitaxel received by patients from the DCB in this study by tercile was approximately 5.0 mg in the lower, 10.0 mg in the middle, and 20.0 mg in the upper tercile.

TABLE 6 Multivariable Analysis for Death in All Patients Treated With DCB Through 5 Years

Predictors of Death Through 5 Years	Coefficient	Standard Error	Hazard Ratio (95% CI)	p Value
Age, yrs	0.055	0.009	1.056 (1.038–1.074)	<0.001
Insulin-dependent diabetes mellitus (Y vs. N)	0.608	0.175	1.836 (1.304–2.585)	<0.001
Previous target limb amputation (Y vs. N)	1.185	0.349	3.270 (1.649–6.485)	<0.001
Renal insufficiency (baseline serum creatinine ≥1.5 ng/dl) (Y vs. N)	0.610	0.212	1.840 (1.216–2.786)	0.004
Previous nontarget limb amputation (per limb) (Y vs. N)	0.958	0.340	2.607 (1.339–5.077)	0.005
On dialysis (Y vs. N)	0.703	0.321	2.019 (1.077–3.787)	0.029
Coronary heart disease (Y vs. N)	0.281	0.158	1.324 (0.971–1.805)	0.076
Hyperlipidemia (Y vs. N)	−0.280	0.169	0.756 (0.542–1.054)	0.099
Paclitaxel dose tercile (upper vs. lower)*	0.043	0.180	1.044 (0.734–1.484)	0.812
Paclitaxel dose tercile (mid vs. lower)*	−0.013	0.191	0.987 (0.678–1.437)	0.947

Predictors of death through 5 years in all patients treated with DCB are reported. Missing univariate/multivariate predictors were imputed this way: simple imputation was applied for missing values, stratified by study, sex, and treatment arm, using the mean for continuous variables or most common values for dichotomous or categorical variables of the nonmissing values. Multivariate predictors started from the exact same set of variables used to derive IPTW between paclitaxel dose tercile, and were chosen by eliminating 1 of the covariates with the largest p value at a time, until all covariates left in the model except for paclitaxel dose tercile had a p value <0.2. Frailty Cox model with study as random effect was conducted to calculate the hazard ratio and p value. *Paclitaxel dose tercile was forced into multivariate model.

Abbreviations as in Table 4.

The dose-limiting form of toxicity experienced in patients treated with paclitaxel intravenously for cancer is a low absolute neutrophil count (14). The other adverse reactions in a pooled analysis of patients with solid tumors receiving paclitaxel were primarily bone marrow-related, although peripheral neuropathy and hypersensitivity reactions were both found (14). Notably, these reactions can also be ascribed to the most common excipient for intravenous paclitaxel, Cremophor EL, a castor oil derivative, and they occurred in the acute and short-term time frames (15).

Paclitaxel is also used on drug-coated devices in the coronary arteries, and first-generation paclitaxel-coated stents are no longer used in coronary arteries due to poor outcomes, including the occurrence of late stent thrombosis (16). It was hypothesized that the paclitaxel-polymer compound was too effective at reducing restenosis and interfered with the critical formation of tissue to cover the stent struts (16). Second-generation coronary stents using paclitaxel analogs are now in use.

The use of paclitaxel as the active component of DCBs for use in the femoropopliteal segment was prompted by the antirestenotic capabilities combined with its hydrophobic, lipophilic qualities. Hydrophobic medication is combined with a hydrophilic excipient, which allows delivery from the balloon surface to the artery surface, and its lipophilic property permits uptake into the artery wall. Theoretical safety concerns in the lower extremity vasculature mainly involve distal washout of paclitaxel crystals into the microvasculature, potentially impeding the healing process, especially in patients with ischemic leg ulcers. In the IN.PACT DEEP trial, a trend toward a higher rate of amputations at 1 year was reported in a CLI population whose below-the-knee lesions were treated by IN.PACT Amphirion, a balloon with different material and coating methodology compared with IN.PACT Admiral (17). In both the PTA and DCB arms, amputation-free survival in this CLI population was >80% at 1 year. The authors highlighted the many other factors that contribute to wound healing and eventual amputation in CLI

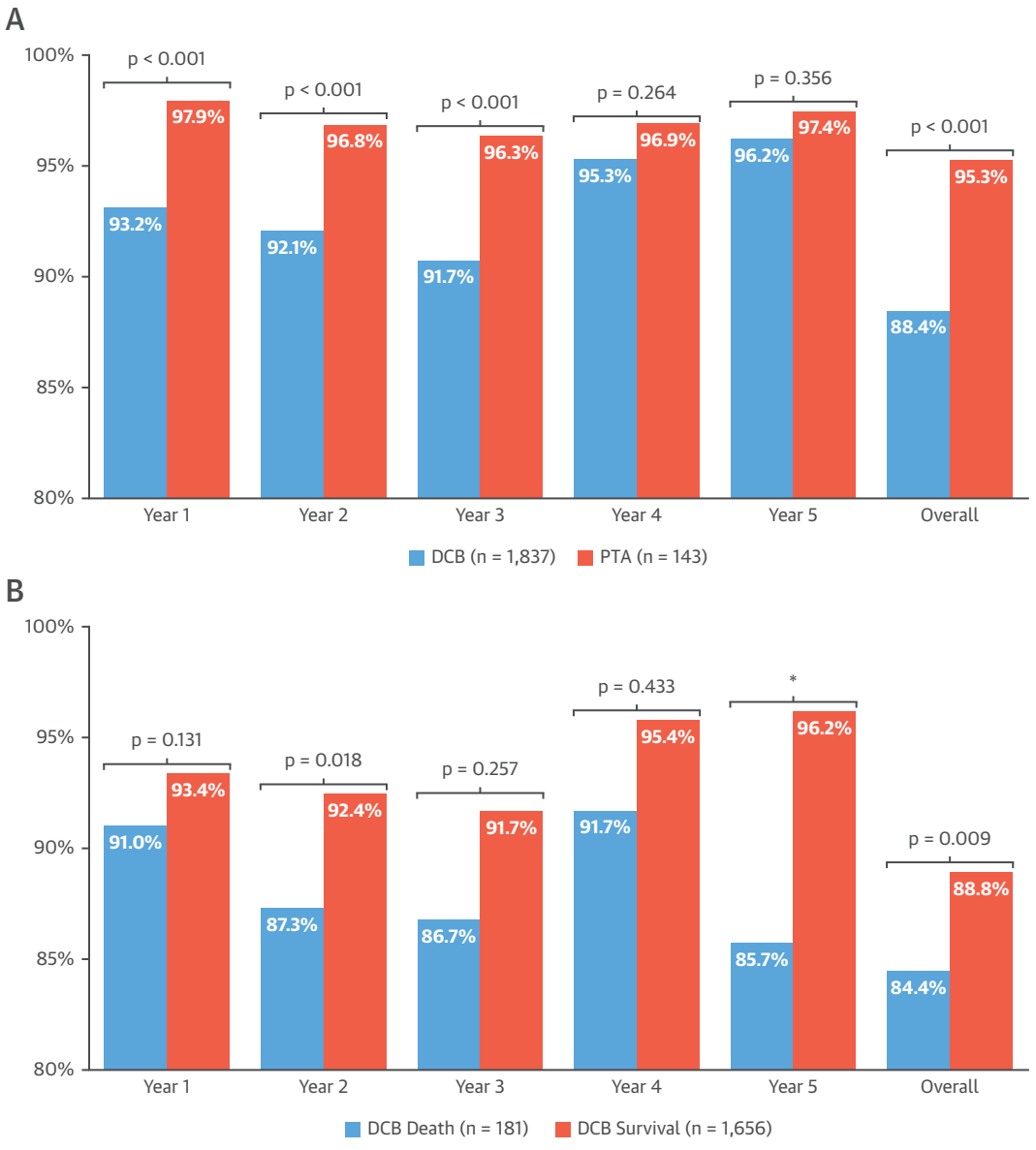
TABLE 7 Mortality Rates Through 5 Years by Study

	IN.PACT SFA			IN.PACT SFA Japan				
	DCB	PTA	p Value	DCB	PTA	p Value	IN.PACT China	IN.PACT Global
1 yr	1.9 (4/207)	0	0.926	0	0	—	2.9 (4/139)	3.5 (46/1,311)
2 yrs	8.1 (16/198)	0.9 (1/106)	0.008	6.1* (4/66)	3.4 (1/29)	1.000	Study went through 1 yr	7.6 (97/1,275)
3 yrs	10.7 (21/197)	1.9 (2/103)	0.006	6.0* (4/67)	6.9 (2/29)	1.000	Study went through 1 yr	11.4 (144/1,259)
4 yrs	13.0 (24/184)	6.8 (7/103)	0.116	Study went through 3 yrs			Study went through 1 yr	Complete data not yet available
5 yrs	15.8 (29/184)	9.6 (10/104)	0.156	Study went through 3 yrs			Study went through 1 yr	Complete data not yet available

Values are % (n/N). Mortality rates through 5 years are reported by individual study for all patients. *At 2-year follow-up in IN.PACT SFA Japan, there were 66 evaluable patients. At 3-year follow-up there were 67 evaluable patients. There were no deaths between years 2 and 3.

Abbreviations as in Table 4.

FIGURE 1 Follow-Up Visit Compliance Through 5 Years Overall and in DCB Patients Who Survived or Died



(A) Follow-up visit compliance rates of drug-coated balloons (DCBs) and percutaneous transluminal angioplasty (PTA) of all patient-level data available up to 5 years. **(B)** Follow-up visit compliance rates of all patients treated with DCBs comparing survival and mortality using all patient-level data available up to 5 years. Results of IN.PACT SFA are tabulated through 5 years, IN.PACT SFA Japan and IN.PACT Global through 3 years, and IN.PACT China through 1 year. *Due to limited data at 5 years, a p value could not be calculated.

patients, including pedal circulation status, the location of the wound or infection, and the quality of the wound care program. This concern is challenging to thoroughly investigate mechanistically in humans, although attempts have been made in animal models to examine particulate embolization (18). Clinical sequelae have not been seen in these experiments; however, healthy swine are not identical to human patients with PAD.

Given the known cytotoxicity of paclitaxel, any safety concern must be aggressively and urgently evaluated. We aimed to investigate a potential correlation between angioplasty of femoropopliteal arteries with a paclitaxel-coated balloon and increased

TABLE 8 Antiplatelet Regimens Through 36 Months

	IN.PACT DCB (n = 1,837)	PTA (n = 143)	Difference (95% CI)	p Value*
Discharge				
ASA	96.4 (1,766/1,832)	98.6 (141/143)	−2.2 (−10.7 to 6.3)	0.231
Clopidogrel	93.6 (1,715/1,832)	95.8 (137/143)	−2.2 (−10.7 to 6.3)	0.370
Cilastazol	4.6 (79/1,711)	3.6 (3/83)	1.0 (−10.0 to 12.0)	1.000
Prasugrel	0.5 (8/1,621)	0.0 (0/111)	0.5 (−9.1 to 10.1)	1.000
Ticlopidine	1.3 (24/1,832)	3.5 (5/143)	−2.2 (−10.7 to 6.3)	0.054
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	92.6 (1,697/1,832)	97.2 (139/143)	−4.6 (−13.1 to 3.9)	0.040
30 days				
ASA	95.2 (1,684/1,768)	97.9 (138/141)	−2.6 (−11.2 to 6.0)	0.205
Clopidogrel	82.5 (1,458/1,768)	88.7 (125/141)	−6.2 (−14.7 to 2.4)	0.063
Cilastazol	4.2 (69/1,652)	3.7 (3/82)	0.5 (−10.6 to 11.6)	1.000
Prasugrel	0.8 (12/1,557)	0.0 (0/109)	0.8 (−8.9 to 10.5)	1.000
Ticlopidine	1.3 (23/1,768)	3.5 (5/141)	−2.2 (−10.8 to 6.3)	0.051
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	81.7 (1,445/1,768)	90.1 (127/141)	−8.3 (−16.9 to 0.2)	0.011
6 months				
ASA	90.5 (1,479/1,634)	99.3 (139/140)	−8.8 (−17.4 to −0.1)	<0.001
Clopidogrel	52.1 (852/1,634)	68.6 (96/140)	−16.4 (−25.0 to −7.8)	<0.001
Cilastazol	5.1 (78/1,529)	3.7 (3/82)	1.4 (−9.7 to 12.6)	0.795
Prasugrel	0.6 (8/1,423)	1.9 (2/108)	−1.3 (−11.1 to 8.5)	0.153
Ticlopidine	1.3 (21/1,634)	3.6 (5/140)	−2.3 (−10.9 to 6.4)	0.049
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	49.4 (807/1,634)	72.9 (102/140)	−23.5 (−32.0 to −14.9)	<0.001
12 months				
ASA	88.9 (1,403/1,578)	94.9 (129/136)	−5.9 (−14.7 to 2.8)	0.029
Clopidogrel	46.9 (740/1,578)	55.9 (76/136)	−9.0 (−17.7 to −0.2)	0.049
Cilastazol	5.4 (79/1,469)	3.7 (3/81)	1.7 (−9.5 to 12.9)	0.797
Prasugrel	0.5 (7/1,367)	1.9 (2/104)	−1.4 (−11.4 to 8.6)	0.129
Ticlopidine	0.8 (13/1,578)	3.7 (5/136)	−2.9 (−11.6 to 5.9)	0.011
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	42.8 (676/1,578)	57.4 (78/136)	−14.5 (−23.2 to −5.8)	0.001
24 months				
ASA	86.6 (1,090/1,258)	93.7 (118/126)	−7.0 (−16.2 to 2.1)	0.024
Clopidogrel	35.6 (448/1,258)	54.8 (69/126)	−19.1 (−28.2 to −10.0)	<0.001
Cilastazol	5.9 (69/1,167)	4.1 (3/73)	1.8 (−10.0 to 13.6)	0.795
Prasugrel	0.7 (8/1,190)	2.1 (2/94)	−1.5 (−11.9 to 9.0)	0.163
Ticlopidine	0.9 (11/1,258)	2.4 (3/126)	−1.5 (−10.6 to 7.6)	0.128
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	30.9 (389/1,258)	54.0 (68/126)	−23.0 (−32.0 to −13.9)	<0.001
36 months				
ASA	85.4 (988/1,157)	87.1 (108/124)	−1.7 (−11.0 to 7.6)	0.688
Clopidogrel	34.8 (403/1,157)	48.4 (60/124)	−13.6 (−22.7 to −4.3)	0.004
Cilastazol	6.9 (74/1,070)	5.6 (4/72)	1.4 (−10.6 to 13.3)	0.812
Prasugrel	0.6 (7/1,089)	2.2 (2/92)	−1.5 (−12.2 to 9.1)	0.151
Ticlopidine	0.6 (7/1,157)	2.4 (3/124)	−1.8 (−11.1 to 7.4)	0.064
ASA + clopidogrel, ticlopidine, cilastazol, or prasugrel	30.4 (352/1,157)	45.2 (56/124)	−14.7 (−23.9 to −5.5)	0.001

Values are % (n/N). Antiplatelet regimens are compared between all DCB and PTA patients through 36 months. Note: Cilastazol was not collected in IN.PACT SFA Phase II. Prasugrel was not collected in IN.PACT China and IN.PACT SFA Japan. Dual antiplatelet therapy (DAPT) was required immediately post-procedure and during follow-up. Nonstented patients required DAPT therapy for a minimum of 1 month and stented patients for a minimum of 3 months. *Fisher exact test is used for binary variables.

ASA = acetyl-salicylic acid (aspirin); DCB = drug-coated balloon; PTA = percutaneous transluminal angioplasty.

all-cause mortality, as was recently reported (1). In this independent patient-level analysis, there was no significant difference in up to 5-year mortality rates between patients treated with DCB and PTA. Among individual DCB patients, the dose of paclitaxel received during the index procedure did not correlate with mortality risk. All deaths in both treatment groups were independently adjudicated and were not clustered to a single cause of death. A multivariable analysis demonstrated several significant predictors of mortality. Paclitaxel exposure or dose were not predictors of mortality. Differences in post-index procedure care may have played a role in mortality and urgently requires further investigation.

Further explanation is warranted as to the differing conclusions from the present analysis and the

recently published meta-analysis that ascribes increased mortality to paclitaxel (1). The summary-level meta-analysis of published and presented data from heterogeneous studies of a variety of devices faced several disadvantages not experienced in the present study. Quality and completeness of the input data and the methods of analyses varied, and data heterogeneity was substantial. Assumptions that must be made in a summary-level meta-analysis include but are not limited to the following; missing data, censored patients, unreported values, study normality (whether studies are similar enough to each other to be compared), and estimations of paclitaxel exposure rather than actual calculations of individual patient doses (Online Appendix). Potential confounders are the inclusion of DCB and DES in the same study (given the different mechanisms of drug delivery and drug dosing), inclusion of studies initiated at disparate timepoints (given steady advances in medical management of PAD patients), and the paucity of published long-term outcomes with paclitaxel-based devices.

Only 3 studies of paclitaxel-containing devices have reported summary-level data extended to 5 years: 2 DCB studies (IN.PACT SFA, THUNDER [Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries]), and 1 DES study (Zilver PTX) (7,19,20). Each of these trials was powered for patency at 1 year and not for mortality alone at 5 years, and a subsequent evaluation of mortality is useful but not conclusive. Patient-level data from the IN.PACT SFA trial is included in the present study.

The mortality in the PTA cohort in the IN.PACT SFA trial was the lowest ever reported in a vascular device trial through 3 years (1.9%; 2 of 103), and this stands in contrast to a more expected level of mortality in the experimental group (10.7%; 21 of 197). The imbalance between the number of events in the PTA arm meant that the traditional proportional hazard assumption through 5 years was potentially untenable. A piecewise exponential model favored PTA through 3 years and DCB in years 4 and 5. This finding was expected given the already reported low rate of mortality in the PTA arm of IN.PACT SFA at 2 and 3 years (4,5). Overall, in the adjusted comparison of DCB- and PTA-treated patients with similar characteristics, there was no significant difference in mortality through 5 years.

The THUNDER trial, initially reported in 2008, was designed to study patients through 2 years. Through 5-year follow up, 48% of the PTA group was lost to follow-up (19). The Zilver PTX study included a double randomization in which those patients with PTA failure were randomized into 2 further groups: BMS and DES (20). Those secondarily randomized into DES were included in the paclitaxel counts in the recent meta-analysis, despite being in a subpopulation where PTA initially failed, arguably a different subpopulation (20). Within this subpopulation of PTA failures there was no significant difference in mortality between the 2 secondary randomization arms at 5 years. Finally, in looking at the Zilver PTX study, DES are coated with paclitaxel differently, and the drug release from a permanent implant is different from the way the drug is deposited on the vessel wall by a DCB.

Although comparative long-term mortality rates in vascular device trials are lacking, there are several adjudicated studies that have reported at 2 and 3 years (Online Figures 2 and 3). Mortality at 2 years in DCB, BMS, DES, and PTA trials ranges from 0.9% (in the PTA arm of IN.PACT SFA) to 15%. At 2 years, the DCB arms of the IN.PACT SFA, Japan, and Global were 8.1%, 6.1%, and 7.6%, respectively, well within the range of mortality seen in other trials for nonpaclitaxel-containing devices (4,11,21). Mortality among multiple trials at 3 years ranges from 1.9% (in the PTA arm of IN.PACT SFA) to 14.0%, whereas the mortality in DCB patients in IN.PACT SFA, Japan, and Global studies was 10.7%, 6.0%, and 11.4%, respectively, also within the range of other vascular device study cohorts (5,22,23). An alternate method of considering mortality rates in endovascular device trials is comparing RCTs of BMS and PTA (Online Figure 4). None of these devices are coated in paclitaxel; yet, an increase in mortality rate is demonstrated for BMS versus PTA across multiple trials at 1 and 2 years. In addition, all of these mortality rates are within the ranges estimated by the recent meta-analysis for paclitaxel-coated devices (1).

Another potential confounder in this meta-analysis is the underlying disease itself. PAD is a particularly challenging disease to characterize given the high burden of comorbidities experienced by patients and the relationship between these comorbidities and disease progression as well as mortality. The list of factors affecting mortality rate is long and includes (but is not limited to) the development of new pharmaceuticals or treatment strategies and the updating of guideline recommendations, compliance of patients to exercise and lifestyle changes, physician and patient behaviors in specific geographies due to varying standards of care, and the aging population. A comprehensive review of mortality rates throughout the published data estimates that the mortality rate through 5 years ranges from 10% to 52% (Online Table 9).

Within this analysis, we generated several hypotheses about the effect of patient care following an index procedure. First, as was pointed out in the recent meta-analysis in Online Figure 2 (1), a key challenge in all of the drug-coated device trials is performance bias, as physicians and participants could not be completely blinded. It is possible that PTA patients were followed-up more rigorously and more effort was spent treating their comorbidities, thus reducing the mortality rate, a hypothesis that has recently been investigated (24). This is supported by the significantly different rates of follow-up compliance between DCB and PTA patients overall and between DCB patients who survived and died. In addition, the significantly higher rate of dual antiplatelet therapy use in the PTA group could affect long-term mortality outcomes. These hypotheses require further research; however, they offer practical and immediately tangible solutions to help our patients: close observation and aggressive management of comorbidities.

We welcome and strongly urge additional studies of already-existing data and interrogation of large databases to provide further information about disease progression and mortality in the PAD patient population.

STUDY LIMITATIONS. All studies included herein were adjudicated by clinical events committees, and endpoint definitions were consistent; yet, pooling data from distinct trials has drawbacks. There are some data that were included in this report that have not yet undergone peer review, sharing the same shortcomings as the recently-published meta-analysis (1). PTA patients were only included in the 2 randomized trials in a 2:1 ratio; these studies were not powered to detect differences in mortality. DCB and PTA patient and lesion populations were heterogeneous, and the small numbers of PTA control patients (<10%) may not be representative of PTA patients in general, limiting the strength of this analysis of mortality. In addition, the small number of mortality events limited the power to compare DCB and PTA. For the dose-response analysis, all available data were used to compare DCB and PTA; however, adjustment methods and definition of a subset with similar lesion characteristics was necessary to ensure comparable baseline characteristics in the 2 groups. Evaluation of DCB and PTA in larger datasets will provide more power. Only patients with RCC 2 to 4 were included in these studies (36 patients with RCC 5 were included as protocol deviations). Data are incomplete regarding the potential for paclitaxel-based treatments to have been administered in subsequent years for those who failed initial treatment and required repeat revascularization.

CONCLUSIONS

Results from this independent patient-level meta-analysis show no difference in mortality between DCB and PTA at 5 years and no correlation between varying levels of paclitaxel exposure and mortality. This paclitaxel DCB is a safe and effective therapy to treat the symptoms of RCC 2 to 4 femoropopliteal PAD. Data transparency and additional analyses are needed to better understand how other factors influence long-term outcomes in this complex patient population.

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ADDRESS FOR CORRESPONDENCE: Dr. Peter A. Schneider, Division of Vascular and Endovascular Surgery, University of California at San Francisco, 400 Parnassus Avenue, Suite A-501, San Francisco, California 94143. E-mail: peterschneidermd@aol.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Paclitaxel DCBs have previously been reported to be safe and effective to treat femoropopliteal PAD. However, a recent summary-level meta-analysis reported that paclitaxel-containing devices are tied to a higher mortality rate.

TRANSLATIONAL OUTLOOK: Additional research investigating post-procedure care for patients with PAD is warranted. More research on the progression and mortality rates is needed. Patient-level follow-up is mandatory for each individual device to exclude potential side effects related to paclitaxel.

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KEY WORDS drug-coated balloon, femoropopliteal artery, paclitaxel

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.