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Original Research

Five-Year Independent Patient-Level Mortality Analysis of the Pooled ILLUMENATE Pivotal and EU Randomized Controlled Trials

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ABSTRACT

Background: There is a need to evaluate the latest information regarding a potential late safety signal in patients treated with paclitaxel-coated devices for peripheral artery disease. We evaluated the 5-year all-cause mortality rate of the Stellarex drug-coated balloon (DCB) compared with percutaneous transluminal angioplasty (PTA).

Methods: An independent third-party performed a patient-level meta-analysis of the pooled ILLUMENATE Pivotal and EU randomized controlled trials. The primary outcome was time to death. Kaplan-Meier estimates of all-cause mortality were compared with the log-rank test. Predictors of mortality were assessed with Cox proportional hazard modeling. A blinded clinical events committee adjudicated all serious adverse events (including death). The follow-up was 60 months.

Results: A total of 589 patients were followed for a median of 4.9 years (IQR, 4.8, 5.1 years); 419 were randomized to Stellarex DCB and 170 to PTA. Vital status was obtained for 93.8%. The 5-year Kaplan-Meier estimates of freedom from all-cause death were 80.4% (95% CI, 76.7%-84.3%) in the Stellarex DCB arm versus 80.4% (95% CI, 74.3%-86.5%) in the PTA arm (log-rank, $P = .7754$). There was no difference in all-cause mortality when stratified by paclitaxel dose terciles. Predictors of mortality included renal insufficiency, reference vessel diameter, age, and lesion length, but not paclitaxel dose nor paclitaxel exposure.

Conclusions: There was no difference in all-cause mortality between the Stellarex DCB and PTA through the final 5-year follow-up window of 2 ILLUMENATE randomized controlled trials. These long-term data build on the previously reported safety of the Stellarex DCB for treating symptomatic femoropopliteal peripheral artery disease.

Introduction

Peripheral artery disease (PAD) affects 230 million people worldwide and is associated with an increased risk of cardiovascular events and a crude mortality rate of 33.2% at 5 years.[1,2] In patients with symptoms that persist despite optimal medical therapy and lifestyle modifications, minimally invasive treatment modalities such as percutaneous transluminal therapy (PTA) are often preferred over open surgical options but remain limited by high rates of restenosis at 1 year.[3] The advancement of drug-coated balloons (DCBs) containing the antiproliferative drug paclitaxel has consistently shown improved patency and reduced

clinically driven-target lesion revascularization (CD-TLR) compared with standard PTA.[4–7] Despite demonstrating superior efficacy, a 2018 systematic review and summary-level meta-analysis performed by Katsanos et al of 28 randomized controlled trials (RCTs) suggested an increased late-term mortality risk in patients treated with paclitaxel-coated devices relative to uncoated devices.[8]

Limitations of the Katsanos meta-analysis[8] included a lack of homogenous, patient-level data and the absence of a mechanism to explain the late mortality signal. Furthermore, because of limited patient follow-up available, the mortality risk was derived from just 12 studies at 2 years and 3 studies at 5 years, totaling 679 patients.

Following a Food and Drug Administration (FDA) advisory meeting in June 2019, it was determined that there was insufficient data to make a final decision regarding paclitaxel-coated device safety, and more complete long-term follow-up data were needed.

A third-party meta-analysis of the 2 ILLUMENATE RCTs performed in 2019 using patient-level data showed there was no difference in all-cause mortality through 3 years between the Stellarex DCB (Philips North America) and PTA.[9] A 4-year meta-analysis following the same methodology also showed no difference in all-cause mortality.[10] The final 5-year follow-up mortality analysis of the Stellarex DCB of the ILLUMENATE RCTs has been eagerly anticipated by the FDA and industry alike.

The current meta-analysis aims to assess all-cause mortality through the 5-year follow-up window of the ILLUMENATE Pivotal and EU RCTs.

Materials and methods

Data sources

The full data sources, study device and procedure, outcomes, and statistical analyses were published previously.[9] Briefly, the study population was pooled from the ILLUMENATE Pivotal (NCT01858428) and ILLUMENATE EU (NCT01858363) RCTs. Both RCTs were prospective, randomized, multicenter, single-blinded studies. Patients with Rutherford 2-4 femoropopliteal disease were randomized 2:1 (Pivotal) or 3:1 (EU) to receive treatment with either the Stellarex DCB or PTA. Because of the differences in device design, operators were not able to be blinded to the actual devices. Follow-up was through 5 years post-procedure and was performed during office visits at 1, 2, and 3 years and via telephone contact at 4 and 5 years.

Inclusion and exclusion criteria were published previously.[9] Of note, patients who had received prior treatment of the target lesion with a paclitaxel-coated device at any time (EU RCT) or within 6 months (Pivotal RCT) were excluded from the study. In addition, in the Pivotal RCT only, patients were also excluded if they had received prior treatment of the contralateral limb with the Stellarex DCB.

Study protocols were approved by either an independent review board or ethics committee at each site and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written consent. Adverse events were monitored at each site for data accuracy and completeness and were adjudicated by an independent clinical events committee (CEC). The study sponsor (Philips North America) oversaw study design and data collection, and an independent third-party, Syntactx, performed all analyses.

To account for differences between the 2 RCTs, variable names and units were harmonized, and the data sets were merged using R software version 3.5.2 (R Foundation for Statistical Computing).

Study device and procedure

Patients were treated with either PTA or the 0.035″ over-the-wire Stellarex DCB. The Stellarex DCB consists of a polyethylene glycol excipient and a hybrid combination of amorphous and crystalline paclitaxel (2 ug/mm^2).

Outcomes

The outcome was time to death over 60 months postindex procedure and was assessed in the vital status cohort, which was comprised of the intent-to-treat population as well as patients who had exited the study but whose vital status was retrospectively obtained. If patients did not reach the end point by the end of the 5-year follow-up period, they were censored at their last day of contact or at 5 years (whichever occurred first). A safety officer classified causes of death according to the Medical Dictionary for Regulatory Activities version 21.0 System of Organ Class. Deaths were recorded as cardiovascular- or noncardiovascular-related, and definitions for each were described previously.[9] Any undetermined cause of death was classified as noncardiovascular.

Paclitaxel dose analyses

In patients treated with the Stellarex DCB, the nominal dose of paclitaxel was stratified into terciles and compared with PTA to assess the relationship between exposure to the drug and all-cause mortality. The mean nominal dosages were classified as no paclitaxel (0 mg) in the PTA arm and low (0.1-3.2 mg), medium (3.3-5.2 mg), or high (≥5.3 mg) paclitaxel doses in the Stellarex DCB arm. The size of the balloon (surface area [diameter and length]) and the number of devices used during treatment were used to determine the maximum potential paclitaxel dose.

Statistical analysis

The full statistical model was published previously.[9] Briefly, the I^2 statistic was calculated to confirm the heterogeneity of the 2 RCTs. The mortality hazard rate was used to evaluate all-cause mortality in the pooled data set. Stata/IC version 15.1 (StatCorp LLC) was used to perform a 2-stage meta-analysis of the patient-level data.

Continuous variables were assessed by the *t* test. Categorical variables were assessed by Fisher exact test and are presented as mean ± standard deviation or median (IQR range). Kaplan-Meier (KM) methodology was used to estimate the hazard rate of all-cause mortality, and the log-rank test was used to compare outcomes. Cox proportional hazards modeling was utilized to identify predictors of mortality from 25 candidate variables. A univariable Cox model was developed for each candidate variable. A *P* value of <.25 was required for entry into the multivariable model, which was performed to adjust for confounding variables. Variables were eliminated stepwise until the *P* value for each was <.05. Two additional multivariable models were developed with paclitaxel forced into the model, either as dose or exposure. Hazard ratios (HRs) and 95% CIs were calculated. A *P* value of <.05 was considered statistically significant. SAS version 9.4 (SAS Institute) was used for all statistical analyses except data mapping and heterogeneity assessments.

Results

Demographic and baseline characteristics

After pooling from the ILLUMENATE Pivotal and EU RCTs, the analysis population consisted of 589 patients (419 in the Stellarex arm and 170 in the PTA arm). The demographic and baseline characteristics have been published previously and are shown in Supplemental Tables S1 and S2.[9] Although characteristics were generally similar between treatment arms, patients treated with the Stellarex DCB were more often smokers (*P* = .05) and were younger (*P* = .02) but were less often treated for recurrent lesions (*P* = .04). The median follow-up was 4.9 years (IQR, 4.8-5.1 years).

Combining data sets

An I^2 statistic was calculated to assess the heterogeneity of the ILLUMENATE Pivotal and EU RCTs. The studies were shown to be congruent and were combined (I^2 = 0; *P* = .893).

Table 1. Kaplan-Meier point estimates of all-cause mortality.

	DCB (n = 419)	PTA (n = 170)
Year 1 (365 d)	97.8% (96.4, 99.2)	98.8% (97.1, 99.9)
Year 2 (730 d)	93.0% (90.5, 95.5)	95.2% (91.9, 98.4)
Year 3 (1095 d)	90.3% (87.4, 93.2)	90.3% (85.8, 94.8)
Year 4 (1460 d)	85.6% (82.2, 89.0)	86.0% (80.7, 91.3)
Year 5 (1825 d)	80.4% (76.7, 84.3)	80.4% (74.3, 86.5)

DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty.

All-cause mortality

The vital status compliance was 93.8% across the ILLUMENATE RCTs. Follow-up was balanced between patients treated with the DCB (93.3% averaging 1660 days) and those treated with PTA (94.6% averaging 1663 days). Table 1 shows the KM point estimates each year. At 1 year, the KM estimate of freedom from all-cause death was 97.8% ± 0.72% (95% CI, 96.4%-99.2%) in the DCB arm compared with 98.8% ± 0.84% (95% CI, 97.1%-99.9%) in the PTA arm. At 2 years, the respective rates were 93.0% ± 1.3% (95% CI, 90.5%-95.5%) versus 95.2% ± 1.7% (95% CI, 91.9%-98.4%). At 3 years, 90.3% ± 1.5% (95% CI, 87.4%-93.2%) versus 90.3% ± 2.3% (95% CI, 85.8%-94.8%). At 4 years, 85.6% ± 1.7% (95% CI, 82.2%-89.0%) versus 86.0% ± 2.7% (95% CI, 80.7%-91.3%). At 5 years, the KM estimates of freedom from all-cause death were 80.4% ± 2.0% (95% CI, 76.7%-84.3%) in the Stellarex DCB arm compared with 80.4% ± 3.1% (95% CI, 74.3%-86.5%) in the PTA arm. There were no differences in all-cause mortality between the 2 arms throughout the full 5-year window (log-rank, P = .7754) (Central Illustration).

Paclitaxel dose and all-cause mortality

KM estimates of all-cause mortality were assessed for association with nominal paclitaxel dose terciles. The mean nominal dosages were classified as no paclitaxel (PTA; 0 mg) and low (0.1-3.2 mg), medium (3.3-5.2 mg), and high (≥5.3 mg) paclitaxel doses. The respective KM estimates of freedom from all-cause death were 80.4% ± 3.1%, 84.4% ± 2.8%, 78.5% ± 3.8%, and 77.0% ± 3.8%. There were no statistically significant differences in KM estimates of freedom from all-cause death assessed as a function of paclitaxel dose (log-rank, P = .5769) (Figure 1).

CEC-adjudicated causes of all-cause mortality

All causes of death were CEC-adjudicated (Table 2). At 5 years, there were 80/419 (19.1%) deaths in the DCB arm and 32/170 (18.8%) deaths in the PTA arm. Of the 80 deaths in the DCB arm, 16/80 (20.0%) deaths were attributed to cardiovascular causes and 64/80 (80.0%) to noncardiovascular causes. Of the 32 deaths in the PTA arm, 6/32 (18.8%) deaths were attributed to cardiovascular causes and 26/32 (81.3%) to noncardiovascular causes. There were no significant differences in any Medical Dictionary for Regulatory Activities System of Organ Class cause-specific deaths between patients treated with DCB compared with PTA. No device- or procedure-related deaths were reported in either arm.

Predictors of all-cause mortality in the DCB arm

The univariable analysis to assess predictors of death included 25 candidate baseline variables. Age, congestive heart failure, lesion length, previous intervention, renal insufficiency, reference vessel diameter, and smoking (protective) were found to be significant predictors of mortality in the univariable model (Table 3). A multivariable model was performed to adjust for confounding variables. Variables were eliminated stepwise until the P value was <.05. In the final multivariable model (Table 4), predictors of mortality included renal insufficiency (HR, 2.363; 95% CI, 1.530-3.650), larger reference vessel diameter (HR, 1.244; 95% CI, 1.019-1.518), older age (HR, 1.052; 95% CI, 1.031-1.074), and longer lesion length (HR, 1.005; 95% CI, 1.001-1.009). When forced into the model, neither paclitaxel exposure (HR, 1.149; 95% CI, 0.761-1.734) nor dose (HR, 1.027; 95% CI, 0.959-1.100) were found to be significant predictors of mortality.

Discussion

This independent meta-analysis of 2 congruent RCTs from the ILLUMENATE clinical program demonstrates that there was no statistical difference in all-cause mortality between patients treated with the Stellarex DCB relative to PTA at any time point through 5 years. Vital status was obtained for 93.8% of the patients for this analysis. Importantly, this patient-level analysis utilized rigorous methodology in the largest, homogenous prospective RCT cohort of a single DCB.

Stellarex was approved by the FDA in 2017 for treating symptomatic PAD. The coating consists of a polyethylene glycol excipient and a hybrid formulation of paclitaxel. Paclitaxel is a cytostatic drug that inhibits smooth muscle cell proliferation and therefore prevents neointimal hyperplasia.[11,12] At much higher concentrations than used to coat DCBs and drug-eluting stents, paclitaxel is considered safe for systemic cancer treatment, even in pregnant women.[13] Paclitaxel was also considered safe to treat coronary disease[14] and was later expanded to treat lesions in the periphery.

The late mortality signal that was flagged by Katsanos et al[8] in relation to paclitaxel exposure was a summary-level study of 28 RCTs that assessed multiple devices with different concentrations and formulations of paclitaxel as well as different excipients. Furthermore, data from the ILLUMENATE RCTs were not included in the 5-year analysis performed by Katsanos et al in 2018. Although a dose-dependent mortality signal was suggested, the authors did not provide a plausible mechanism to explain the causality, which was further hindered by a paucity of data available at 2 and 5 years. Although acknowledging that neither study was sufficiently powered to avoid type I error, it is important to note that this current meta-analysis assessed mortality in patients treated with a single device and included a similar number of patients in magnitude (N = 589) as the original 5-year mortality analysis performed by Katsanos et al[8] (863 enrolled with follow-up in 679 patients).

This final report of all-cause mortality from the pooled ILLUMENATE RCTs builds on the previously established safety of the Stellarex DCB. The primary safety and efficacy end points of both the ILLUMENATE Pivotal and EU were met and published previously.[6,7] In a meta-analysis of the ILLUMENATE clinical program at 3 years[9] and the recent 4-year data,[10] there was no difference in KM estimates of all-cause mortality in patients treated with the Stellarex DCB relative to PTA. Furthermore, the 5-year mortality analysis of the Stellarex DCB reported herein is consistent with other long-term analyses of paclitaxel-coated balloons[15,16] and several large observational studies of paclitaxel-coated balloons in real-world patients.[17–25]

In the present study, neither paclitaxel dose nor exposure was a predictor of all-cause mortality at 5 years. The analysis identified age, renal insufficiency, lesion length, and reference vessel diameter as significant predictors of death. However, because baseline characteristics were collected preprocedurally for each treatment arm, it is unlikely that the association of mortality with lesion length and/or reference vessel diameter was related to paclitaxel exposure or dose. This has been validated as there was no difference in KM estimates of all-cause mortality in patients treated with PTA with low (0.1-3.2 mg), medium (3.3-5.2 mg), or high (≥5.3 mg) doses of paclitaxel. Prior analyses from both the IN.PACT and Lutonix clinical programs[16,26] also did not find an association between all-cause mortality and increasing paclitaxel dose in patients treated with the DCB. In general, the
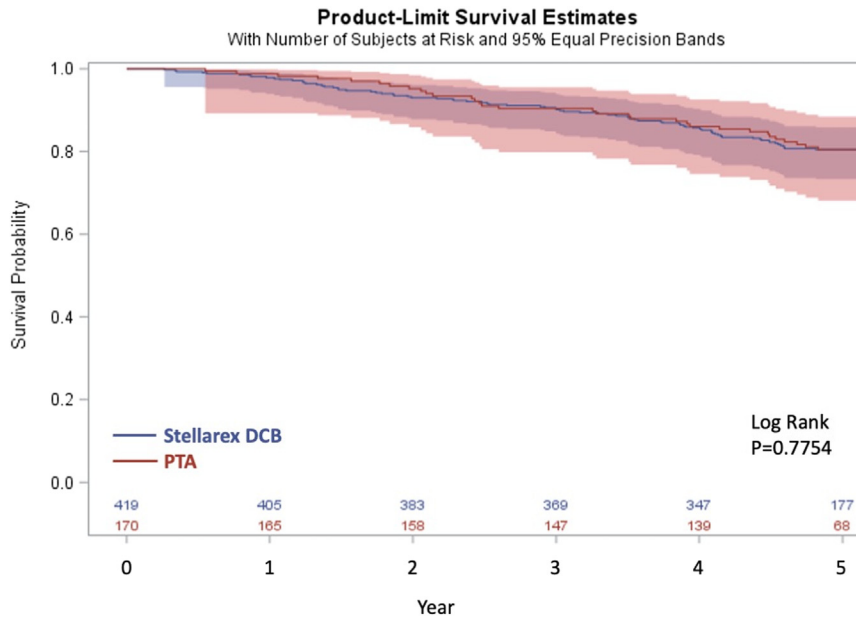
Central Illustration.
Survival in the Pooled RCTs. The pooled RCTs show no significant differences in Kaplan-Meier survival estimates between Stellarex DCB and PTA through 5 years (log-rank, *P* = .7754). DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty; RCTs, randomized controlled trials.

predictors of mortality identified in this analysis are consistent with the common risk factors that are persistent in this patient population.

In a recent study employing a similar methodology as Katsanos et al,[8] Dinh et al[27] reported no difference in rates of all-cause mortality in patients treated with paclitaxel versus uncoated devices at 1 year (34 studies, 7654 patients; relative risk ratio [RR], 0.99; 95% CI, 0.81-1.22; *P* = .94), 2 years (20 studies, 3799 patients; RR, 1.16; 95% CI, 0.87-1.55; *P* = .31), and 5 years (9 studies, 2288 patients; RR, 1.19; 95% CI, 0.98-1.45; *P* = .08).[27] Based on the additional data that was available, the authors concluded that there is no justification to limit the use of paclitaxel-coated devices for the treatment of femoropopliteal PAD.

A cross-industry supported patient-level meta-analysis by the VIVA Physicians group corroborated the findings by Katsanos et al[8] in an analysis of 8 RCTs with a median follow-up duration of 4 years. However, similar to Dinh et al[27] study, the HR diminished from 1.38 to 1.27 when the number of patients lost to follow-up was reduced from 19.6% to 9.5%, respectively.[28] A recent study of the Vascular Quality Initiative showed that patients who received peripheral vascular interventions and were lost to follow-up had an increased risk of mortality (HR, 6.56; 95% CI, 6.16-6.99) at 1 year compared with patients who completed their 1-year follow-up.[29] This suggests that although patients may be randomized in clinical studies, those that miss follow-up may show important differences in demographic characteristics. As such, these findings highlight the importance of ascertaining complete vital status data for any paclitaxel DCB mortality analysis.
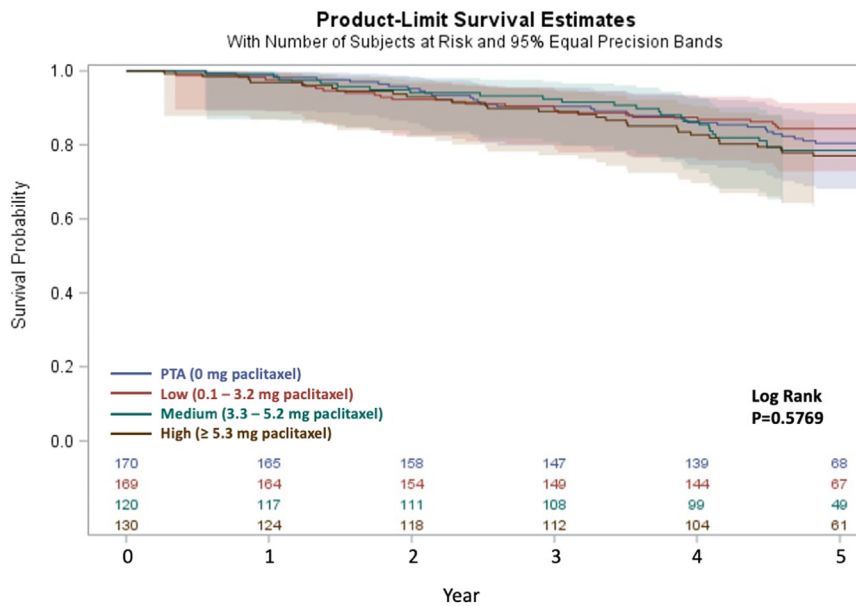
Figure 1.
Survival in the Pooled Randomized Controlled Trials by Paclitaxel Dose Terciles. There were no differences in Kaplan-Meier estimates of all-cause mortality between paclitaxel dose terciles or compared with PTA (log-rank, *P* = .5769). PTA, percutaneous transluminal angioplasty.

Table 2. Clinical events committee-adjudicated causes of mortality for patients treated with Stellarex drug-coated balloon compared with percutaneous transluminal therapy within 5 years (1825 days).

Cause of mortality	DCB	PTA	Total	P value
Cardiovascular	16/80 (20.0)	6/32 (18.8)	22/112 (19.6)	>.9999
Non-cardiovascular	64/80 (80.0)	26/32 (81.2)	90/112 (80.4)	>.9999
Gastrointestinal disorders	2/80 (2.5)	2/32 (6.3)	4/112 (3.6)	.3220
General disorders	0/80 (0.0)	0/32 (0.0)	0/112 (0.0)	>.9999
Hepatobiliary disorders	0/80 (0.0)	1/32 (3.1)	1/112 (0.9)	.2857
Infections and infestations	4/80 (5.0)	1/32 (3.1)	5/112 (4.5)	>.9999
Injury/ poisoning/ procedural	1/80 (1.3)	0/32 (0.0)	1/112 (0.9)	>.9999
Metabolism and nutritional	2/80 (2.5)	2/32 (6.3)	4/112 (3.6)	.3220
Neoplasms benign, malignant	21/80 (26.3)	5/32 (15.6)	26/112 (23.2)	.3227
Nervous system disorders	2/80 (2.5)	1/32 (3.1)	3/112 (2.7)	>.9999
Renal and urinary disorders	2/80 (2.5)	1/32 (3.1)	3/112 (2.7)	>.9999
Respiratory/ thoracic/ mediastinal	5/80 (6.3)	1/32 (3.1)	6/112 (5.4)	.6721
Vascular disorders	4/80 (5.0)	0/32 (0.0)	4/112 (3.6)	.5767
Undetermined	21/80 (26.3)	12/32 (37.5)	33/112 (29.5)	.2579
Total deaths	80/419 (19.1)	32/170 (18.8)	112/589 (19.0)	>.9999

Values are n/N (%).
DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty.

A subgroup analysis of the VOYAGER PAD[30] trial and an interim analysis of the SWEDEPAD[31] trial, which had 99.6% and 100% vital status ascertainment, respectively, each found no significant difference in all-cause mortality in patients treated with paclitaxel-coated devices relative to controls. The final results from the SAFE-PAD study, which was designed with input from the FDA, will further evaluate the long-term risk of all-cause mortality in Medicare beneficiaries with a median follow-up duration exceeding 5 years.[32]

Finally, it is important to consider the clinical benefit offered by paclitaxel-coated devices in the PAD population. In randomized trials, paclitaxel-coated balloons have consistently demonstrated superiority over PTA in terms of improved vessel patency and reduced rates of clinically driven-target lesion revascularization.[5–7] In conjunction with several patient-level analyses and real-world studies demonstrating that an increased risk of mortality is not associated with using paclitaxel-coated balloons, the established efficacy of DCBs must be considered when making clinical decisions about their continued use for the treatment of PAD.

Limitations

This study was limited by randomization ratios leading to fewer patients in the PTA arm of the analysis. Moreover, because of the study design of each ILLUMENATE RCT, specific data on revascularization was not always provided, and therefore it is likely that some patients in the PTA arm were not necessarily paclitaxel naïve. Thus, the percentage of those patients that crossed over is possibly inaccurate, and the true mortality of those with paclitaxel exposure is unknown. However, in a previous crude analysis of crossover patients reclassified

Table 3. Univariable predictors of mortality.

Covariate	Hazard ratio (95% confidence interval)	P value
Age (per y)	1.06 (1.04-1.08)	<.0001
Renal insufficiency[a]	2.77 (1.81-4.23)	<.0001
Smoking (current)	0.44 (0.27-0.71)	.0009
Lesion length (per mm)	1.01 (1.00-1.01)	.0060
Previous intervention	1.63 (1.12-2.38)	.0112
Smoking (previous)	0.55 (0.35-0.89)	.0137
Reference vessel diameter (per mm)	1.26 (1.03-1.55)	.0241
Congestive heart failure	1.82 (1.05-3.13)	.0316
Diabetes mellitus type 2	1.34 (0.92-1.95)	.1292
Myocardial infarction	1.40 (0.89-2.21)	.1425
Chronic obstructive pulmonary disease	1.39 (0.88-2.21)	.1560
Diabetes mellitus	1.29 (0.89-1.88)	.1787
Peripheral vascular disease	1.57 (0.79-3.11)	.1940
Lesion type (de novo)	0.72 (0.41-1.25)	.2420
ABI/TBI (increments of 1)	0.64 (0.29-1.44)	.2796
Angina	1.32 (0.78-2.24)	.3077
Paclitaxel dose (per mg)	1.04 (0.97-1.11)	.3091
Calcium (none vs present)	1.22 (0.83-1.78)	.3171
Hyperlipidemia	0.84 (0.55-1.28)	.4097
Sex (male)	0.86 (0.59-1.27)	.4522
Diabetes mellitus type 1	0.68 (0.16-2.77)	.5863
Rutherford category 4	1.33 (0.46-3.81)	.5956
Paclitaxel exposure	0.92 (0.61-1.37)	.6719
Rutherford category 3	1.09 (0.70-1.69)	.7127
Hypertension	1.07 (0.61-1.88)	.8102

[a] Renal insufficiency was defined as dialysis dependency or serum creatinine >2.5 mg/dL within 30 days of the index procedure.
ABI, ankle brachial index; TBI, tibial brachial index.

accordingly to the paclitaxel treatment arm within the 2 ILLUMENATE RCTs through 3 years, there was no mortality difference between co-horts. Furthermore, the surface area of the balloon and the number of devices used during the procedure were used to calculate the maximum potential of paclitaxel exposure, but this may not represent the true amount of paclitaxel actually delivered to the vessel wall. Drug transfer to the vessel wall depends on many factors, including lesion characteristics, blood flow, and more. An additional limitation of this analysis is that only all-cause mortality was assessed, and the study did not examine additional safety outcomes such as nonfatal severe adverse events or others. Furthermore, neither RCT was prospectively powered to assess mortality. Finally, the results presented in this manuscript cannot be generalized to other paclitaxel-coated balloons because of the differences in design (eg, composition of paclitaxel, excipients).

Conclusion

The primary safety and efficacy end points of the ILLUMENATE Pivotal and EU RCTs were previously met and published, and there were no device- or procedure-related deaths attributed to treatment with

Table 4. Multivariable predictors of mortality.

Parameter	Hazard ratio (95% confidence interval)	P value
Age (per y)	1.052 (1.031-1.074)	<.0001
Renal insufficiency[a]	2.363 (1.530-3.650)	.0001
Lesion length (per mm)	1.005 (1.001-1.009)	.0083
Reference vessel diameter (per mm)	1.244 (1.019-1.518)	.0320

Multivariate predictors were chosen with a stepwise procedure using an entry criterion of 0.25 and a stay criterion of 0.05.
[a] Renal insufficiency was defined as dialysis dependency or serum creatinine >2.5 mg/dL within 30 days of the index procedure.

Stellarex DCB.[6,7] In the independent, pooled, patient-level meta-analysis of the ILLUMENATE US Pivotal and EU RCTs reported herein, there was no difference in all-cause mortality in patients treated with the Stellarex DCB relative to PTA through the full 5-year follow-up. These 5-year data build on the previously reported safety of the Stellarex DCB for treating symptomatic PAD.

Declaration of competing interest

Sean Lyden is a consultant for Endologix, PQ Bypass, Boston Scientific, Medtronic, BD, and Penumbra, a board member for VIVA Physicians, participates in research studies with Endologix, Gore, BD, Bolton, Abbott, Penumbra, Boston Scientific, Merit, Contego Medical, and holds stock options in Centerline Biomedical. Marianne Brodmann is a consultant for Philips, Cagent, Biotronik, Boston Scientific, Medtronic, BD, Shockwave, Reflow Medical, Bolt Medical, and Cook Medical and participates in research studies with Philips, Cagent, Biotronik, Boston Scientific, Medtronic, BD, Shockwave, Reflow Medical, Bolt Medical, and Cook Medical. Andrew Holden is a medical advisory board member for Philips, Medtronic, Boston Scientific, and Gore and participates in clinical research for Philips, Medtronic, Boston Scientific, Gore, Cook, BD-Bard, Shockwave, Abbott, Intact, Reflow, Merit, and Surmodics. Kenneth Ouriel is the chief medical officer for NAMSA. NAMSA is a Medical Research Organization that receives funds from Philips for clinical research services. Trisha Tarra is an employee of Philips. William Gray is a consultant for Philips. Henrik Schroeder reported no financial interests.

Ethics statement and patient consent

This study protocol was approved by either an independent review board or ethics committee at each site, and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written consent.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.100634.

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