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Mortality Assessment of Paclitaxel-Coated Balloons: Patient-Level Meta-Analysis of the ILLUMENATE Clinical Program at 3 Years.

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Circulation

ORIGINAL RESEARCH ARTICLE

Mortality Assessment of Paclitaxel-Coated Balloons

Patient-Level Meta-Analysis of the ILLUMENATE Clinical Program at 3 Years

BACKGROUND: A recent summary-level meta-analysis comprising randomized, controlled trials (RCTs) of femoropopliteal paclitaxel-coated balloon and stent intervention identified excess late mortality in the paclitaxel-treated patients.

METHODS: We evaluated the safety of the Stellarex drug-coated balloon (DCB) for femoropopliteal artery disease with an independently performed meta-analysis of patient-level data from all patients in the Stellarex femoropopliteal clinical program. To compare mortality after DCB or uncoated percutaneous transluminal angioplasty (PTA), we aggregated data from 2 RCTs comprising 419 patients treated with DCB and 170 patients treated with PTA. In an additional analysis, data were aggregated from 6 poolable Stellarex DCB studies (2 RCTs, 3 single-arm studies, and 1 registry). All serious adverse events including deaths were adjudicated by a blinded, third-party, independent Clinical Events Committee. Kaplan–Meier estimates in the RCTs were compared with restricted mean survival time. Predictors of death were assessed with hazard ratios (HRs) and Cox proportional hazards modeling.

RESULTS: Baseline characteristics were similar in the patients treated with DCB and PTA in the pooled RCT analysis, with the exception that the DCB cohort was younger (67.4 ± 9.7 versus 69.4 ± 9.4 years, $P=0.02$), smoked more frequently (86.6% versus 78.8%, $P=0.02$), and were less often treated for recurrent lesions (8.8% versus 14.7%, $P=0.04$). In the RCTs, patients treated with DCB had all-cause mortality rates that were not different from those of patients treated with PTA (Kaplan–Meier estimates 1.8 ± 0.7% versus 1.3 ± 0.9%, 6.5 ± 1.2% versus 5.9 ± 1.9%, and 9.3 ± 1.5% versus 9.9 ± 2.4% at 1, 2, and 3 years, respectively, $P=0.86$). All-cause mortality rates were similar in a 1906-patient pooled nonrandomized DCB data set (Kaplan–Meier estimates of 2.1%, 4.9%, and 7.0% at 1, 2, and 3 years, respectively). Clinical Events Committee–adjudicated causes of death were balanced between the DCB and PTA cohorts. Multivariable Cox modeling identified age (HR, 1.06; 95% CI, 1.04–1.08; $P<0.001$), diabetes mellitus (HR, 1.42; 95% CI, 1.01–2.00; $P=0.04$), congestive heart failure (HR, 1.88; 95% CI, 1.12–3.16; $P=0.02$), and renal insufficiency (HR, 2.00; 95% CI, 1.33–3.01; $P<0.001$) as predictors of mortality. Paclitaxel exposure was unrelated to mortality (HR, 1.04; 95% CI, 0.98–1.10; $P=0.23$).

CONCLUSIONS: The mortality rates for patients treated with the DCB and uncoated PTA were indistinguishable over 3-year follow-up. Additional patient-level, adequately powered meta-analyses with larger RCT data sets will be needed to confirm the generalizability of these findings.

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Clinical Perspective

What Is New?

- A patient-level meta-analysis of 2 randomized, controlled trials has been conducted from the ILLU-MENATE clinical program that demonstrated no difference in mortality when the Stellarex paclitaxel-coated balloon was compared with uncoated percutaneous transluminal angioplasty through 3 years.
- A paclitaxel dose–dependent effect was also not evident.
- The use of Stellarex paclitaxel-coated balloon has not correlated to late all-cause mortality.

What Are the Clinical Implications?

- Paclitaxel-coated balloons have been suggested to be a factor in late all-cause mortality at 2 and 5 years posttreatment.
- The implication derives from a meta-analysis published by Katsanos et al in 2018.
- Although the relationship of paclitaxel use and mortality was found to be statistically significant in that meta-analysis, the causal relationship has not been established.
- Although freedom from target lesion revascularization is improved with the use of a paclitaxel-coated balloon, the relationship to late all-cause mortality must be determined.

Percutaneous transluminal angioplasty (PTA) has long been a mainstay of femoropopliteal peripheral arterial disease (PAD) treatment.[1] As a minimally invasive modality, PTA has advantages over open surgical revascularization and avoids the obligatory, systematic need for implantation of a permanent metallic arterial stent.[2] The durability of femoropopliteal PTA, however, is not ideal. When patients with femoropopliteal disease are treated with uncoated balloons, up to 47.4% experience restenosis in the first year after treatment.[3]

Drug-coated balloons (DCBs) are effective in treating de novo or restenotic lesions of the femoropopliteal arteries.[4] Paclitaxel is a cytostatic and cytotoxic agent widely used to treat various malignancies, and its therapeutic window and pharmacokinetic behavior is well-described.[5] Paclitaxel has significantly decreased the risk of restenosis when delivered to the vessel wall with DCBs and drug-eluting stents in patients with femoropopliteal disease. In previous studies, patients who were treated with DCBs had improved target vessel patency and significant reductions in late lumen loss and target vessel revascularization in comparison with patients treated with PTA.[6–10] Current Society for Cardiovascular Angiography and Interventions guidelines recommend DCB as a standard treatment option for femoropopliteal artery disease.[11]

A recent systematic review and meta-analysis of summary-level data from 28 randomized, controlled trials (RCTs) suggested an increased risk of death after femoropopliteal artery DCB beginning 2 years after the DCB procedure.[12] Furthermore, the risk of death was incrementally associated with exposure to paclitaxel, leading the authors to speculate that late paclitaxel toxicity may be contributing to the observed higher mortality. This analysis has been criticized for its lack of long-term, homogeneous, patient-level data that might have identified confounding factors to better explain the observations.[12]

The present study examines the safety profile of the Stellarex DCB in comparison with uncoated PTA, analyzing patient-level data from the worldwide Stellarex femoropopliteal clinical trials. The study was designed to avoid many of the limitations of the recently published, summary-level meta-analysis. An independent third party, Syntactx, performed the analysis using patient-level data and cause-specific adjudicated deaths, homogeneous populations treated with the same paclitaxel-coated device, and 3-year follow-up after treatment.

METHODS

Data Sources

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Philips, IGT-D Medical Information Services Department at 1-877-878-0012 or medicalinformation.services@philips.com.

The study population comprised 2523 patients: 2353 treated with the DCB and 170 treated with uncoated PTA. The data set included the 7 studies that comprised the Stellarex femoropopliteal clinical program (Table 1). The ILLUMENATE EU RCT trial (CVI Drug-coated Balloon European Randomized Clinical Trial) and the ILLUMENATE Pivotal trial (Pivotal Trial of

Table 1. Patient Cohorts From the Stellarex Femoropopliteal Clinical Program

Study	Study Design	Patients Included	Geography	Follow-Up, mo
ILLUMENATE EU RCT	RCT	289	Europe	60
ILLUMENATE Pivotal[9]	RCT	300	United States, Europe	60
ILLUMENATE Global[13]	Single-arm	372	Europe, New Zealand, Australia	60
ILLUMENATE Global ISR	Single-arm	112	Europe, New Zealand, Australia	60
ILLUMENATE PK[9]	Single-arm	25	New Zealand	24
ILLUMENATE FIH[14]	Single-arm	79	Europe	24
SAVER Registry	Single-arm	1346	Unspecified	36

FIH indicates first in human; ISR, in-stent restenosis; PK, pharmacokinetic; and RCT, randomized, controlled trial.

a Novel Paclitaxel-coated Percutaneous Angioplasty Balloon)[9] are prospective, multicenter, randomized, single-blinded clinical trials that included control arms of patients treated with uncoated PTA. ILLUMENATE Global (Global Study of a Drug-coated Balloon to Treat Obstructive SFA and/or Popliteal Lesions),[13] the in-stent restenosis (ISR) cohort of ILLUMENATE Global, ILLUMENATE PK[9] (Pharmacokinetic Study of Drug-coated Angioplasty Balloons in the Superficial Femoral or Popliteal Arteries, a pharmacokinetic study of 25 patients), and ILLUMENATE FIH[14] (CVI Drug-coated Balloon First in Human Trial) are single-arm studies. The SAVER trial (Stellarex Vascular E-Registry) is an ongoing prospective, multicenter, real-world registry. All trials were approved by independent institutional review boards or ethics committees and all patients provided written informed consent. Adverse events were reported by the investigational sites, and each site was monitored for data accuracy and completeness. On-site monitoring was performed for all trials except SAVER, where remote monitoring was used. Adverse events occurring within the follow-up period of each trial were independently adjudicated by a blinded Clinical Events Committee (CEC) that comprised varied specialists. Variables from the 7 individual studies were harmonized to account for different variable names and units and to create one master variable list for all studies. The data sets were merged using R software (version 3.5.2, R Foundation for Statistical Computing).

Interventions

The 0.035-inch platform DCB was used for intervention in all studies. The device is intended for use in patients with PAD to treat de novo or restenotic lesions. The DCB consists of an over-the-wire dual-lumen catheter with a distally mounted semicompliant inflatable balloon and an atraumatic tapered tip. The balloon's proprietary coating (EnduraCoat) contains a hybrid balance of amorphous and crystalline paclitaxel at a uniform concentration of 2 $\mu g/mm^2$ as the active pharmaceutical agent with a polyethylene glycol excipient. Preclinical evidence demonstrated high coating stability with limited distal embolization and high drug transfer efficiency.[15] A minimum inflation time of 60 seconds is recommended in the instructions for use.

Outcomes

The outcome for the meta-analysis is time to death. Patients who did not reach the end point by 3 years were censored at their last day of contact or 3 years, whichever came first. Deaths were adjudicated by the independent CEC (see the online-only Data Supplement Appendix). Causes of death were classified by a designated Safety Officer, using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 21.0, MedDRA MSSO) System Organ Classes. CEC-adjudicated deaths were grouped into those that were cardiovascular-related or non–cardiovascular-related. Undetermined causes of death were classified as non–cardiovascular-related.

Statistical Methods

A key objective of this investigation was to develop a model of predictors of the mortality in patients treated with DCBs. The hazard rate for mortality (MHR) was used to assess mortality in the 7 Stellarex studies. Unlike the hazard ratio (HR), which compares 2 groups like test versus control, the MHR measures the instantaneous speed at which deaths are accumulating over time for the population being evaluated. To assess the heterogeneity of outcome among the studies, a 2-stage meta-analysis of individual patient data was performed by using Stata/IC (version 15.1, StataCorp LLC). The I^2 statistic was calculated to assess the percentage of variation across studies attributable to heterogeneity rather than chance alone.[16]

The Student t test was used for comparisons of continuous variables and the Fisher exact test was used for categorical variables. Continuous variables were presented as mean±SD or median (range). Kaplan–Meier methodology was used to estimate hazard rates of all-cause mortality, and the restricted mean survival time was used to compare outcome in the randomized treatment arms. Cox proportional hazards modeling was used to assess the relationship between baseline and demographic characteristics and mortality. Candidate variables included baseline and demographic characteristics, treatment (DCB or PTA), and paclitaxel exposure. Exposure, the total amount of drug per patient, was calculated by size (diameter and length) and the number of devices used during treatment. A univariate Cox model was done for each candidate variable. Variables with >15% of values missing were excluded. Imputation of missing data for the remaining variables was performed by using sex-specific mean substitution for continuous variables and mode imputation for categorical variables. A P value of <0.25 was used for entry in the multivariable Cox model. Variables were eliminated stepwise until the P value for each was <0.05. A second multivariable Cox model was done in the same manner, with the exception that paclitaxel exposure was forced into the model. HRs and 95% confidence intervals were calculated. P values of <0.05 were considered statistically significant. With the exceptions of data mapping and heterogeneity assessments, SAS (version 9.4, SAS Institute) was used for the statistical analyses.

RESULTS

Demographic and Baseline Characteristics

Demographic and baseline characteristics were not statistically different in the DCB and PTA arms of the 2 pooled randomized trials (Tables 2 and 3), with 2 exceptions. Patients in the pooled DCB arm were slightly younger (67.4±9.7 versus 69.4±9.4 years, DCB versus PTA, P=0.02) and were more often smokers (86.6% versus 78.8%, DCB versus PTA, P=0.02). The median exposure of paclitaxel in the DCB-treated patients was 3.9 mg (interquartile range, 2.6–6.5 mg). Study design and therefore patient demographics were not collected in the same detail as the RCTs. Therefore, only the RCT trial patient demographics are reported.

Combining Data Sets

An assessment of poolability among the 7 Stellarex studies was done in preparation for the identification of covariates predictive of death after treatment. The estimated MHR for each of the trials declined at a constant rate. The 2 RCTs, ILLUMENATE EU RCT and ILLU-

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Table 2. Baseline and Demographic Characteristics of Patients in the 2 RCTs: Categorical Variables

Characteristic	ILLUMENATE EU RCT		ILLUMENATE Pivotal RCT		Pooled RCTs		P Value
	DCB	PTA	DCB	PTA	DCB	PTA	
Patients in cohort	219	70	200	100	419	170	
Male sex	71.7% (157/219)	67.1% (47/70)	56.0% (112/200)	64.0% (64/100)	64.2% (269/419)	65.3% (111/170)	0.85
Hypertension	77.6% (170/219)	82.9% (58/70)	93.5% (187/200)	94.0% (94/100)	85.2% (357/419)	89.4% (152/170)	0.19
Hyperlipidemia	61.6% (135/219)	68.6% (48/70)	88.0% (176/200)	90.0% (90/100)	74.2% (311/419)	81.2% (138/170)	0.09
Myocardial infarction	13.2% (29/219)	17.1% (12/70)	21.0% (42/200)	22.0% (22/100)	16.9% (71/419)	20.0% (34/170)	0.41
Angina	6.8% (15/219)	7.1% (5/70)	15.0% (30/200)	20.0% (20/100)	10.7% (45/419)	14.7% (25/170)	0.21
Congestive heart failure	6.4% (14/219)	8.6% (6/70)	12.0% (24/200)	8.0% (8/100)	9.1% (38/419)	8.2% (14/170)	0.87
Renal insufficiency	9.1% (20/219)	8.6% (6/70)	18.0% (36/200)	17.0% (17/100)	13.4% (56/419)	13.5% (23/170)	>0.99
Chronic pulmonary disease	16.0% (35/219)	10.0% (7/70)	16.0% (32/200)	21.0% (21/100)	16.0% (67/419)	16.5% (28/170)	0.90
Diabetes mellitus	37.0% (81/219)	35.7% (25/70)	49.5% (99/200)	52.0% (52/100)	43.0% (180/419)	45.3% (77/170)	0.65
Previous peripheral revascularization	20.5% (45/219)	20.0% (14/70)	45.0% (90/200)	48.0% (48/100)	32.2% (135/419)	36.5% (62/170)	0.34
Smoking							
Current	49.8% (109/219)	48.6% (34/70)	35.5% (71/200)	36.0% (36/100)	43.0% (180/419)	41.2% (70/170)	0.05
Previous	39.3% (86/219)	34.3% (24/70)	48.5% (97/200)	40.0% (40/100)	43.7% (183/419)	37.6% (64/170)	
Never	11.0% (24/219)	17.1% (12/70)	16.0% (32/200)	24.0% (24/100)	13.4% (56/419)	21.2% (36/170)	
Rutherford category							
2	15.1% (33/219)	20.3% (14/69)	31.5% (63/200)	35.0% (35/100)	22.9% (96/419)	29.0% (49/169)	0.23
3	83.1% (182/219)	78.3% (54/69)	64.5% (129/200)	60.0% (60/100)	74.2% (311/419)	67.5% (114/169)	
4	1.8% (4/219)	1.4% (1/69)	4.0% (8/200)	5.0% (5/100)	2.9% (12/419)	3.6% (6/169)	
Lesion type							
De novo	91.8% (201/219)	90.0% (63/70)	90.5% (181/200)	82.0% (82/100)	91.2% (382/419)	85.3% (145/170)	0.04
Recurrent	8.2% (18/219)	10.0% (7/70)	9.5% (19/200)	18.0% (18/100)	8.8% (37/419)	14.7% (25/170)	
Calcification	44.3% (97/219)	41.4% (29/70)	65.7% (130/198)	68.0% (68/100)	54.4% (227/417)	57.1% (97/170)	0.58

DCB indicates drug-coated balloon; PTA, uncoated percutaneous transluminal angioplasty; and RCT, randomized, controlled trial.

MENATE Pivotal, had MHRs that were almost identical, 3.95% (95% CI, 2.78%–5.62%) and 3.81% (95% CI, 2.78%–5.63%), respectively (Figure 1). The I^2 statistic was 0.0% (P=0.89), confirming the homogeneity for the 2 Stellarex RCTs. Given that the protocols, clinical operations, and baseline demographics were similar and the effects sizes were almost identical, the 2 RCTs were pooled for the analysis of mortality after treatment with DCB versus PTA.

The annualized MHR in patients treated with DCB shows that the ILLUMENATE PK study was an outlier among the 7 Stellarex studies (Figure 2). The study had 25 patients with 0 deaths. The I^2 statistic was 47.3% (P=0.08) when all 7 studies were included, suggesting a moderate level of heterogeneity.[17] After elimination of the ILLUMENATE PK study from the analysis, the I^2 statistic decreased to 38.6% (P=0.15), indicating moderately low heterogeneity. Eliminating the ILLUMENATE FIH study decreased the I^2 to 27.8% (P=0.24), but the decision was made to combine all studies, only eliminating ILLUMENATE PK for the Cox modeling of covariates predictive of mortality. Among the 2523 subjects in

the 7 studies, 25 subjects in the ILLUMENATE PK study were excluded from combining the studies, as were 3 additional SAVER patients with missing values that precluded sex-specific imputation; accounting for a total of 28 patients that were excluded from the combined data set. There were no deaths in the 28 subjects that were excluded from the combined analysis. In total, 2495 patients remained in the combined analytic data set of the remaining 6 studies; 2325 DCB-treated subjects and 170 subjects treated with PTA.

All-Cause Mortality

In the 589 patients enrolled in the RCT trials, death occurred in 35 of 419 patients treated with DCB (8.4%) and 15 of 170 patients treated with PTA (8.8%) within 3 years of the index procedure. There was no significant difference in all-cause mortality between the 2 cohorts through full follow-up of 3 years (Figure 3, P=0.86, restricted mean survival time analysis). The proportion of patients lost to follow-up was low: 3.7% in the ILLUMINATE EU and 2.3% in ILLUMENATE Pivotal RCTs. Sub-

Table 3. Baseline and Demographic Characteristics of Patients in the 2 RCTs: Continuous Variables

Characteristic	ILLUMENATE EU RCT		ILLUMENATE Pivotal RCT		Pooled RCT		P Value*
	DCB	PTA	DCB	PTA	DCB	PTA	
Patients in cohort	219	70	200	100	419	170	
Age, y							
N	219	70	200	100	419	170	0.02
Mean	66.8±9.2	69.0±8.7	68.2±10.3	69.7±9.8	67.4±9.7	69.4±9.4	
Ankle brachial							
N	214	67	197	100	411	167	0.63
Median	0.7(0.0–1.4)	0.7(0.0–1.5)	0.8(0.0–1.8)	0.8(0.0–1.3)	0.7(0.0–1.8)	0.7(0.0–1.5)	
Lesion length, mm							
N	219	70	200	100	419	170	0.10
Mean	91.3±51.3	94.7±57.3	85.1±41.5	96.1±41.7	88.3±46.9	95.5±48.5	
Reference vessel diameter, mm							
N	218	70	200	100	418	170	0.44
Mean	5.0±0.8	4.8±0.7	4.9±0.9	5.2±1.1	4.9±0.9	5.0±0.9	
Diameter stenosis, % reduction							
N	218	70	200	100	418	170	0.87
Mean	81.7±14.3	83.1±14.2	73.9±16.9	74.8±17.0	77.9±16.0	78.2±16.4	
Paclitaxel dose, mg							
N	219	70	200	100	419	NA	NA
Median	4.3(1.1–15.8)	NA	3.9(1.3–9.4)	NA	3.9(1.1–15.8)	NA	

Data are expressed as mean±SD or median (range). DCB indicates drug-coated balloon; PTA, percutaneous transluminal angioplasty; NA, not applicable; and RCT, randomized, controlled trial.*P value for the comparison of the DCB and PTA cohorts of the pooled RCTs.

jects voluntarily withdrawing before completion in the studies was 12.2% of ILLUMENATE EU and 7.0% of IL-LUMENATE Pivotal trials. The 1-year (360-day) Kaplan–Meier estimate of all-cause mortality was 1.8±0.7% (estimate±SE) in the DCB cohort and 1.3±0.9% in the PTA cohort. At 2 years (720 days), all-cause mortality was 6.5±1.3% in the DCB cohort versus 5.9±1.9% in the PTA cohort. At 3 years (1080 days), all-cause mortality was 9.3±1.5% in the DCB cohort and 9.9±2.4% in the PTA cohort.

In the cohort of 2325 DCB-treated patients from the 6 combined studies, 80 deaths (3.4%) occurred through 3 years. The 1-, 2-, and 3-year Kaplan–Meier estimates

of all-cause mortality were 2.0±0.4%, 5.6±0.7%, and 8.0±0.9%, respectively, in the 6 combined studies (Figure 4). The corresponding estimates for the 1906 DCB-treated patients enrolled in the 4 combined nonrandomized studies were not clinically different from the rates in the RCTs; 2.1±0.4% at 1 year, 4.9±0.8% at 2 years, and 7.0±1.1% at 3 years after treatment (Figure 5).

Adjudicated Causes of Death

The causes of death are summarized in Table 4, categorized by MedDRA System Organ Classes. The CEC-adjudicated cause of death through 3 years was
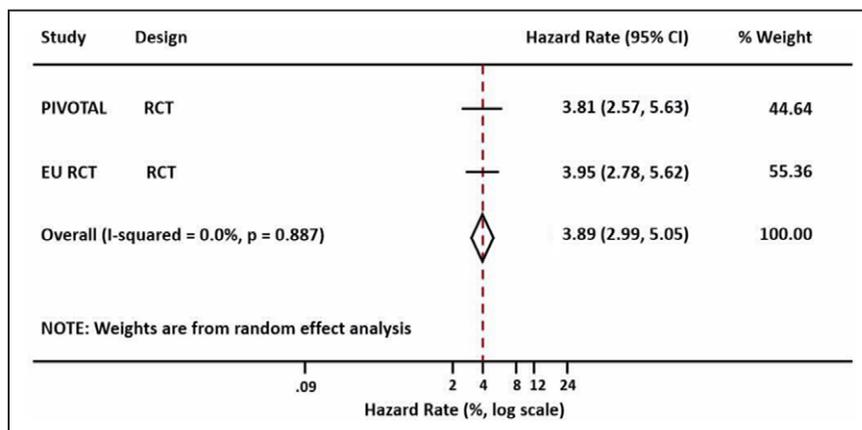

Figure 1. Hazard rates for mortality for drug-coated balloon arms of the 2 randomized, controlled trials (RCTs).
The Pivotal study and EU RCT had nearly identical hazard rates with an overall I² of 0.0%, indicative of homogeneity. EU RCT indicates CVI Drug-coated Balloon European Randomized Clinical Trial; and PIVOTAL, Pivotal Trial of a Novel Paclitaxel-coated Percutaneous Angioplasty Balloon.
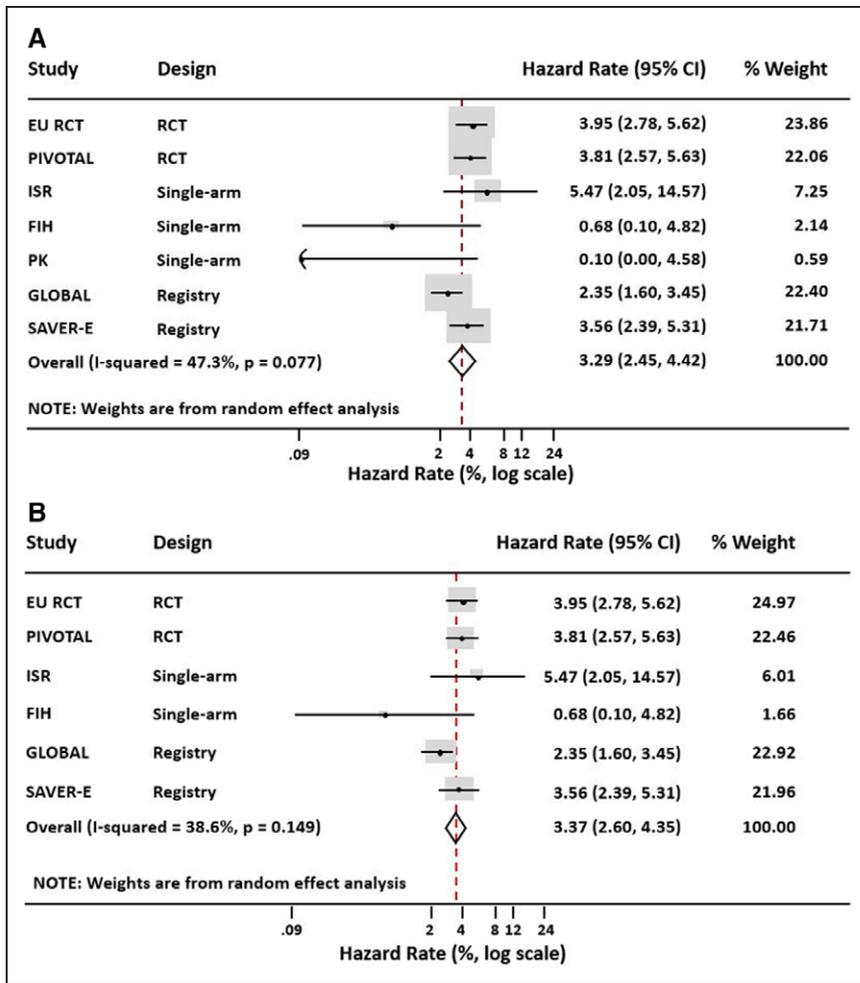
Figure 2. Hazard rates for mortality in patients treated with drug-coated balloons.
A, The hazard rates for mortality in patients treated with drug-coated balloons (DCBs) in the 7 Stellarex studies. Patients treated with DCBs in the 7 Stellarex studies had an overall I^2 of 47.3%, consistent with moderate heterogeneity. ILLUMENATE PK was an outlier, with a hazard rate of 0.10. **B,** Annualized hazard rates for mortality for patients treated with DCBs in the 6 Stellarex studies. After elimination of the PK study, the overall I^2 decreased to 38.6%, reflecting moderately low heterogeneity in the 6 remaining studies. EU RCT indicates CVI Drug-coated Balloon European Randomized Clinical Trial; FIH, first in human; GLOBAL, Global Study of a Drug-coated Balloon to Treat Obstructive SFA and/or Popliteal Lesions; ISR, in-stent restenosis; PIVOTAL, Pivotal Trial of a Novel Paclitaxel-coated Percutaneous Angioplasty Balloon; PK, pharmacokinetic; RCT, randomized, controlled trial; and SAVER-E, Stellarex Vascular E-Registry.

cardiovascular in 20 patients (25%) and noncardiovascular in 60 patients (75%). Among the non–cardiovascular-related deaths in the patients treated with DCB, 17 (21%) were of undetermined cause at the time of this analysis. In the 15 deaths in the PTA cohort, the adjudicated cause was cardiovascular in 4 (27%) and non-cardiovascular in the remaining 11 (73%). The higher proportion of deaths of undetermined cause in the non-
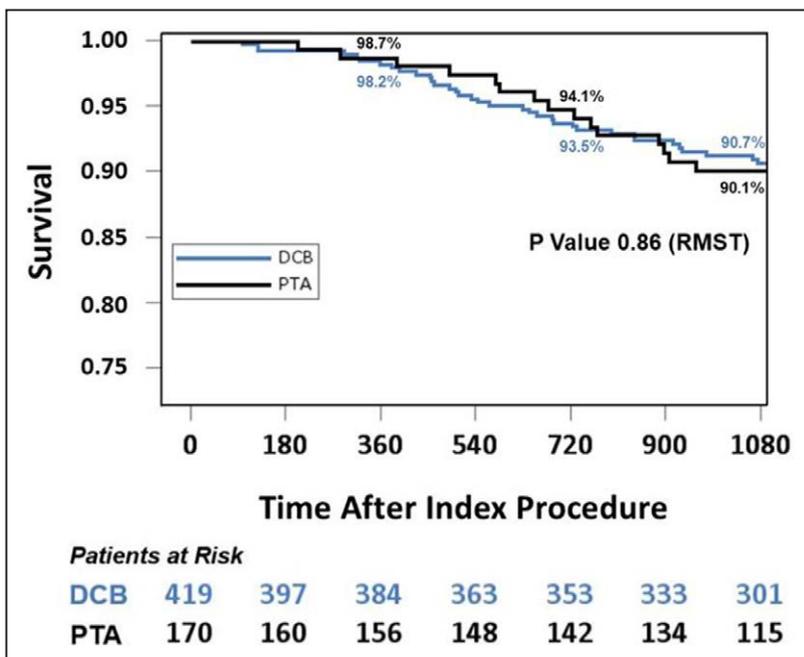

Figure 3. Survival in the pooled randomized, controlled trials (RCTs).
The pooled RCTs show no significant differences in the survival rates in the 2 groups through 3-year (1080-day) follow-up. For further information about pooling, refer to the combining data sets section of the article. The P value tests the null hypothesis that restricted mean survival time (RSMT) for the 2 curves are equal vs the alternative that they are not equal. DCB indicates drug-coated balloon; and PTA, uncoated percutaneous transluminal angioplasty.
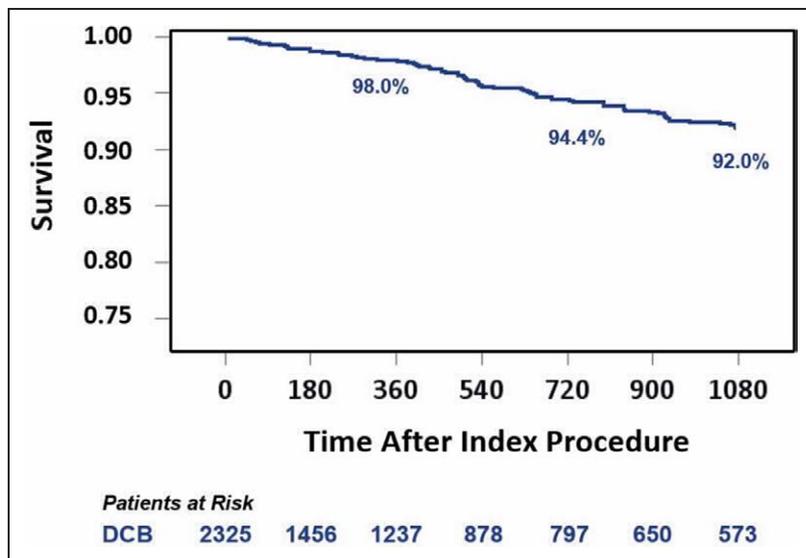
Figure 4. Survival through 3 years (1080 days) in the 6-study pooled data set.
The ILLUMENATE PK study (Pharmacokinetic Study of Drug-coated Angioplasty Balloons in the Superficial Femoral or Popliteal Arteries) was excluded because there were no deaths. The Kaplan–Meier estimates are reported for each year. DCB indicates drug-coated balloon.

randomized DCB cohort was attributable to yet undetermined causes of death in the ongoing SAVER registry.

The most common CEC-adjudicated cause of death after DCB treatment was a cardiac disorder, responsible for 19 of 80 deaths (23.8%), followed by neoplasms (18/80 deaths, 22.5%). In the PTA cohort, general disorders were the most common cause of death (5/15, 33.3%), followed by cardiac disorders (4/15, 26.7%) and neoplasms (2/15, 13.3%). There were no device- or procedure-related deaths adjudicated in the entire series of 2523 patents.

Predictors of Mortality After DCB Treatment

The Cox proportional hazards analysis of mortality in the 6 combined studies included 2495 patients: 589 patients from the 2 RCTs and 1906 patients from the 4 nonrandomized studies. The univariate analysis included 16 candidate baseline variables, 7 of which had HRs with P values of <0.05 (Table 5).

Among the 16 candidate variables, 10 had univariate HRs with P values of <0.25 and were entered into the multivariable Cox proportional hazards model. Variables were eliminated stepwise until the P value for each remaining variable was <0.05. The final model identified 4 significant predictors of mortality (Table 6); age (HR, 1.06; 95% CI, 1.04–1.08; $P<0.001$), diabetes mellitus (HR, 1.43; 95% CI, 1.01–2.01; $P=0.04$), congestive heart failure (HR, 1.86; 95% CI, 1.11–3.12; $P=0.02$), and renal insufficiency (HR, 2.00; 95% CI, 1.33–3.01; $P<0.001$). When treatment (DCB versus PTA) was forced into the model to assess its effect on the risk of death, the use of a DCB was not a predictor of mortality (HR, 1.18; 95% CI, 0.75–1.87; $P=0.47$). Similarly, when paclitaxel exposure (mg) was forced into the model as a continuous variable, exposure did not predict mortality (HR, 1.04; 95% CI, 0.98–1.10; $P=0.23$).
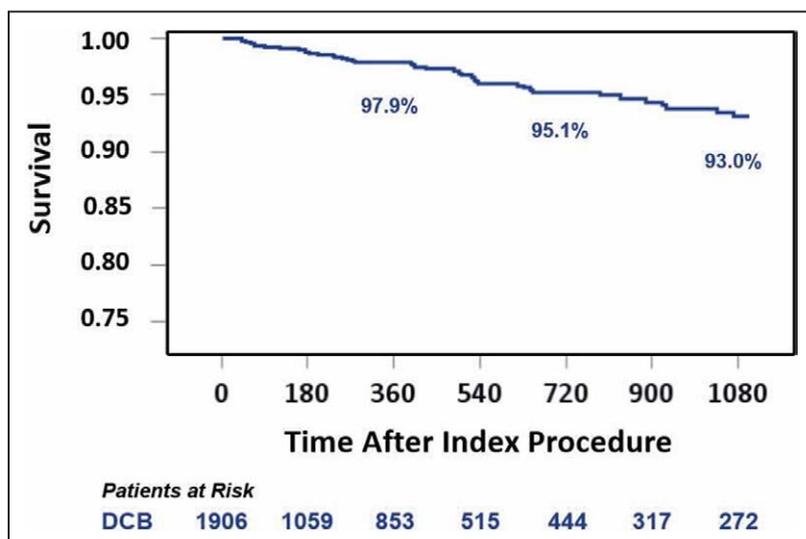

Figure 5. Survival through 3 years in the 4 nonrandomized, pooled studies.
The 3-year mortality estimate for the ILLUMENATE FIH (CVI Drug-coated Balloon First in Human Trial), ILLUMENATE Global (Global Study of a Drug-Coated Balloon to Treat Obstructive SFA and/or Popliteal Lesions), Global-ISR (in-stent restenosis), and SAVER (Stellarex Vascular E-Registry) studies was 7.0% by Kaplan–Meier methodology. DCB indicates drug-coated balloon.

Table 4. Causes of Death in Patients Treated With Paclitaxel-Coated Balloons as Adjudicated by the Clinical Events Committee (MedDRA System-Organ Classes)

Cause of Death	Pooled Studies* DCB n=2325	Non-RCTs* DCB n=1906	Pooled RCTs DCB n=419	PTA n=170
Cardiac disorders	19/80 (24%)	11/45 (24%)	8/35 (23%)	4/15 (27%)
Gastrointestinal disorders	1/80 (1%)	0/45 (0%)	1/35 (3%)	1/15 (7%)
General disorders	8/80 (10%)	5/45 (11%)	3/35 (9%)	5/15 (33%)
Hepatobiliary disorders	1/80 (1%)	0/45 (0%)	1/35 (3%)	1/15 (7%)
Infections and infestations	5/80 (6%)	2/45 (4%)	3/35 (9%)	0/15 (0%)
Injury/poisoning/ procedural	1/80 (1%)	0/45 (0%)	1/35 (3%)	0/15 (0%)
Metabolism and nutritional	1/80 (1%)	0/45 (0%)	1/35 (3%)	0/15 (0%)
Neoplasms benign, malignant	18/80 (23%)	6/45 (13%)	12/35 (34%)	2/15 (13%)
Nervous system disorders	1/80 (1%)	1/45 (2%)	0/35 (0%)	0/15 (0%)
Renal and urinary disorders	0/80 (0%)	0/45 (0%)	0/35 (0%)	1/15 (7%)
Respiratory/ thoracic/ mediastinal	7/80 (9%)	3/45 (7%)	4/35 (11%)	1/15 (7%)
Vascular disorders	1/80 (1%)	0/45 (0%)	1/35 (3%)	0/15 (0%)
Undetermined	17/80 (21%)	17/45 (38%)	0/35 (0%)	0/15 (0%)
Total deaths through 3 y	80/2325 (3.4%)	45/1906 (2.4%)	35/419 (8.4%)	15/170 (8.8%)

DCB indicates drug-coated balloon; MedDRA, Medical Dictionary for Regulatory Activities; PTA, percutaneous transluminal angioplasty; and RCT, randomized, controlled trial.

*Data comprise pooled data sets. There were no deaths in the 28 patients excluded from the pooled analysis.

DISCUSSION

A recent systematic review and summary-level meta-analysis by Katsanos et al[12] raised safety concerns related to the use of paclitaxel balloons and stents for treating femoropopliteal arterial disease. The current analysis was undertaken to further confirm the previously reported safety profile of the Stellarex DCB.[7,9,13,14,18,19] In contrast to the methodology used by Katsanos, the current study used an independent analysis of patient-level data, a single DCB device, and poolable studies. ILLUMENATE PK, a small study with no deaths, was excluded from the analysis because of its heterogeneity. The present findings differ substantially from those of the Katsanos meta-analysis. The current study of the combined Stellarex RCTs showed

Table 5. Univariate Cox Proportional Hazards Analysis of Baseline and Demographic Predictors of Mortality

Covariate	Hazard Ratio (95% CI)	P Value
Male sex	1.08 (0.76–1.55)	0.66
Age, per year	1.07 (1.05–1.09)	<0.01
Lesion length, per mm	1.00 (0.99–1.00)	0.14
Hypertension	0.98 (0.63–1.54)	0.94
Hyperlipidemia	0.97 (0.66–1.44)	0.90
Myocardial infarction	0.98 (0.62–1.55)	0.93
Angina	1.01 (0.58–1.76)	0.97
Renal insufficiency	2.93 (1.98–4.34)	<0.01
Congestive heart failure	2.32 (1.40–3.86)	0.01
Diabetes mellitus	1.45 (1.03–2.03)	0.03
Smoking history*	0.58 (0.39–0.86)	0.01
Previous peripheral vascular procedure	1.26 (0.90–1.79)	0.18
Rutherford 2 vs 3	0.79 (0.52–1.22)	<0.01
Rutherford 4 vs 3	2.15 (1.22–3.79)	
Rutherford 5 vs 3	4.53 (1.66–12.38)	
Lesion type, de novo	0.72 (0.45–1.16)	0.17
Calcification	1.47 (1.02–2.11)	0.04
Paclitaxel dose, per mg	1.02 (0.96–1.08)	0.53

*Hazard ratio for smokers, current and prior.

that patients in the DCB cohort had mortality rates comparable to those in the PTA cohort, an observation that must be considered in the context of the size of the ILLUMENATE studies, none of which were adequately powered to detect differences in long-term mortality. Nonetheless, pooling of patients from the RCT data sets strengthens the validity of the analyses. The current findings confirm and are consistent with the previously reported findings from the ILLUMENATE femoropopliteal clinical program that demonstrated the strong safety and efficacy DCB at 1 and 2 years.[9,14,19]

Paclitaxel is a cytostatic and cytotoxic agent commonly used for cancer chemotherapy. With the advent of local drug delivery technologies, paclitaxel-eluting coronary stents were demonstrated to be effective in the reduction of clinical restenosis in percutaneous coronary interventions.[20] However, first-generation coronary paclitaxel-eluting coronary stents were subject to slightly higher rates of stent thrombosis than bare metal stents.[21] Despite this hazard, paclitaxel-eluting stents have not been shown to have excess mortality in comparison with bare metal stents.[22–24] When used in the femoropopliteal arteries, paclitaxel-coated balloons such as the Stellarex DCB have reduced restenosis, yielding improved long-term patency.[3,14] Paclitaxel exerts its antirestenotic properties through the prevention of smooth muscle cell proliferation by blocking mitosis.[25–27] Paclitaxel DCBs used in the

Table 6.   Multivariable Cox Proportional Hazards Model for Mortality

Covariate	Hazard Ratio (95% CI)	P Value
Without forcing drug dose into the model		
Age, per year	1.06 (1.04–1.08)	<0.01
Congestive heart failure	1.86 (1.11–3.12)	0.02
Diabetes mellitus	1.43 (1.01–2.01)	0.04
Renal Insufficiency	2.00 (1.33–3.01)	<0.01
With drug dose forced into the model		
Age, per year	1.06 (1.04–1.08)	<0.01
Congestive heart failure	1.89 (1.12–3.19)	0.02
Diabetes mellitus	1.45 (1.03–2.04)	0.04
Renal insufficiency	2.03 (1.35–3.06)	<0.01
Paclitaxel dose, per mg	1.04 (0.98–1.10)	0.23

Multivariate predictors were chosen with a stepwise procedure using an entry criterion 0.25 and a stay criterion of 0.05.

femoropopliteal segment have consistently demonstrated improved target vessel patency, with significant reduction in late lumen loss and target vessel revascularization.[4,6,7,9,10,28–30]

Paclitaxel, when delivered systemically for breast, lung, and other malignancies, is used in significantly higher concentrations than the doses used in peripheral vascular applications.[5] In larger doses, the common side effects of paclitaxel include anemia, gastrointestinal symptoms, and renal impairment. Other less common side effects include allergic/hypersensitivity reactions, liver toxicity, neurotoxicity, and cardiac rhythm changes. Outside the toxic reactions leading to death in chemotherapy drug trials for patients with cancer, there are no substantive preclinical or patient-level clinical studies correlating the mechanism of action of paclitaxel with long-term side effects leading to death, including those associated with treatment of PAD.

The meta-analysis by Katsanos et al[12] concluded that there is an increased late mortality risk after the application of paclitaxel-coated balloons and stents in the femoropopliteal arteries of the lower limbs. However, the study has several limitations. The study combined RCTs and examined multiple devices of different applications and doses, including both DCBs and drug-eluting stents.[12] Patient-level data were unavailable to the authors, precluding a granular level of detail for causes of death. In addition, the reporting of death rates used by the study was inconsistent; some studies reported event frequency within time intervals, whereas others reported the rates cumulatively.[12] Last, despite the inclusion of 28 RCTs in the analysis, the mortality conclusions were based on considerably fewer presentations and publications where extended follow-up was available.

The findings of 2 recently published comparisons of DCB to PTA failed to support the conclusions of Katsanos. Schneider et al[31] published outcomes of

a patient-level meta-analysis comprising 2 RCTs and 2 single-arm trials of 1980 patients: 1837 patients treated with a higher-dose paclitaxel-coated balloon from a single manufacturer and 143 patients treated with uncoated PTA. Overall, there was no statistically significant difference in all-cause mortality between patients treated with DCB versus PTA through 5-year follow-up (15.1% versus 11.2%, P=0.09).[31] In the second recent publication, Secemsky and colleagues[32] evaluated all-cause mortality in a retrospective analysis of 16 560 Medicare and Medicaid beneficiaries treated for femoropopliteal disease during calendar year 2016. The authors were unable to detect an association between all-cause mortality and the use of DCBs or drug-eluting stents, with a HR of 0.97 (95% CI, 0.91–1.04; P=0.20). The failure to find a difference, however, is confounded by median follow-up of ≈1 year in this study. This duration may have been too short to observe differences in mortality, differences that became evident at 2 years in the analysis of Katsanos et al.[33]

Currently, there are many RCTs with superior efficacy results for DCB therapy over uncoated PTA for femoropopliteal lesions.[4,6,7,9,10,13,14,19,28] These DCB trials have often met their primary safety outcomes and shown durable safety outcomes. Although DCBs introduce risks as with any endovascular procedure, study results confirm long-term patency, thereby reducing the rate of reinterventions. Current opinion suggests that the benefits continue to outweigh the risks associated with DCB.[1,34,35]

We recommend further adequately powered meta-analyses of RCTs studying paclitaxel-coated DCBs to test the generalizability of the results presented here. Further analyses with cross-industry collaboration, including any associations between device-specific characteristics (eg, paclitaxel dosage, coating morphology) may be warranted. In light of questions raised by the Katsanos meta-analysis, continued enrollment and long-term follow-up of patients treated with DCBs is needed to further reinforce the safety profile of paclitaxel-coated DCBs for the treatment of femoropopliteal PAD.

Limitations

The analysis was limited by the size of the 2 combined RCTs with many fewer patients in the PTA arms, 170 versus 419, and the ongoing follow-up in some of the trials without complete follow-up in all patients, as well. Even together, the trials lacked enough power to ensure the absence of mortality differences. An adequately powered study to identify a clinically relevant reduction of 50% from the annual rates from our DCB studies would require a sample size of from 1600 to 6000 randomly assigned patients with at least 3 years

of follow-up. Although samples size calculations depend on the eligibility criteria and mortality rates that may differ from the current study, an adequately powered study would still be much larger than the current DCB trials. Also, in our comparison of the 2 RCTs, we assumed that patients in the PTA arms were paclitaxel-naïve. However, some patients who received PTA may have been exposed to paclitaxel with other DCBs or drug-eluting stents before enrollment, for instance in the contralateral limb, or during the follow-up period. Our analysis may then underestimate the number of patients treated with any paclitaxel, a limitation inherent with many analyses in the field. In addition, in some studies, as many as 3% of patients were lost to follow-up. Because the mortality rates are low, this may represent a limitation to statistical analysis. Separately, when combining the studies from the Stellarex femoropopliteal clinical program, discrepancies exist between the manner with which data were collected as part of RCTs and data were collected for single-arm trials and registries. Heterogeneity among trials could not be completely eliminated, while adding more events to the analysis resulted in a loss of some degree of homogeneity in the aggregate analytic data set. Finally, commercially available DCBs differ in paclitaxel dosage, excipient, and other properties specific to each device. Therefore, the current observations with the Stellarex DCBs may not be applicable to other DCBs.

Conclusions

Results from this systematic combined analysis of 3-year data from the Stellarex femoropopliteal clinical program demonstrate no significant difference in mortality rates in patients treated with a paclitaxel DCB and PTA. No device- or procedure-related deaths were reported. Although further research with larger RCT data sets is encouraged to test the generalizability of these results, the data presented in this article do not confirm the findings of Katsanos et al. Within the context of studies that were not powered to detect mortality differences, Stellarex DCB remains a viable alternative in the treatment of PAD.

ARTICLE INFORMATION

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