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PERIPHERAL

Safety of Paclitaxel-Coated Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease

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ABSTRACT

OBJECTIVES The aim of this study was to assess safety outcomes of femoropopliteal drug-coated balloon (DCB) angioplasty using patient-level data from the Lutonix clinical program.

BACKGROUND A recent systematic review and meta-analysis of heterogenous trials and summary-level data identified increased long-term mortality in patients treated with paclitaxel-coated balloons and stents.

METHODS We evaluated DCB angioplasty (n = 1,093) and uncoated balloon angioplasty (percutaneous transluminal angioplasty [PTA]) (n = 250) outcomes in LEVANT 1 (The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis), LEVANT 2 (Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries), and the LEVANT Japan Clinical Trial. Hazard ratios (HRs) were calculated with Cox proportional hazards modeling.

RESULTS There were no significant differences in mortality rates between DCB angioplasty and PTA. The 5-year HR was 1.01 (95% confidence interval [CI]: 0.68 to 1.52) in the aggregated LEVANT trials. The 2-year HR after DCB angioplasty was 0.99 (95% CI: 0.25 to 3.95) in LEVANT 1, 1.40 (95% CI: 0.62 to 3.14) in LEVANT 2, and 0.32 (95% CI: 0.05 to 1.92) in the LEVANT Japan Clinical Trial. The 5-year HR was 1.60 (95% CI: 0.94 to 2.72) in LEVANT 2. Adverse events and causes of death were balanced, without clustering between DCB angioplasty and PTA. Patients who underwent paclitaxel or nonpaclitaxel reinterventions had higher survival rates than those who did not undergo reinterventions. Baseline covariates predicting mortality included, among others, age (HR: 1.03 per year; $p < 0.0001$), prior treatment of target lesion (HR: 1.67; $p = 0.022$), arrhythmia (HR: 1.65; $p = 0.031$), and diabetes (HR: 1.18; $p = 0.047$), without differences between the 2 arms. No dose-response relationship was identified when adjusted for key predictors of mortality.

CONCLUSIONS Analyses of patient-level data identified no mortality differences between DCB angioplasty and PTA. Furthermore, the lack of dose-response relationships or clustering of causes of death argues against a causal relationship between paclitaxel and mortality. (LEVANT 1, The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis [LEVANT 1], NCT00930813; Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries [LEVANT 2], NCT01412541; LEVANT 2 Continued Access Registry, NCT01628159; LEVANT Japan Clinical Trial, NCT01816412) (J Am Coll Cardiol Intv 2019;12:2515–24) © 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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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DCB = drug-coated balloon

DES = drug-eluting stent(s)

HR = hazard ratio

PAD = peripheral artery disease

PTA = percutaneous transluminal angioplasty

SAE = serious adverse event

Lower extremity peripheral artery disease (PAD) is an increasingly prevalent global health concern, associated with a 3- to 5-fold increase in mortality risk over that of the general population (1,2). Although endovascular or open surgical revascularization is recommended for patients with symptomatic femoropopliteal PAD, there remains no consensus on the optimal strategy for this patient population (3).

Traditional therapies for femoral popliteal PAD include uncoated balloon angioplasty (percutaneous transluminal angioplasty [PTA]), stent placement, and atherectomy (4). In this landscape, drug-eluting stents (DES) and drug-coated balloons (DCBs) were developed, using antiproliferative agents such as paclitaxel, a commonly used cancer chemotherapeutic agent. Although evidence documented markedly improved patency rates after treatment of femoropopliteal lesions with DES and DCBs compared with PTA (5-8), a recent systematic review and meta-analysis by Katsanos et al. (9) identified an increased mortality signal associated with the use of paclitaxel devices for femoropopliteal PAD.

SEE PAGE 2525

The present review was undertaken to assess mortality after DCB treatment of femoropopliteal disease, using independent patient-level data from the Lutonix clinical program. The availability of independent patient-level data from the Lutonix clinical program allowed a granularity of analysis not possible with research-derived data from meta-analyses.

METHODS

DATA SOURCES. The analyses comprised the 3 randomized controlled trials in the Lutonix femoropopliteal clinical program, LEVANT 1 (The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis), LEVANT 2 (Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries), and the LEVANT Japan Clinical Trial, and the single-arm continued-access arm of the LEVANT 2 trial (**Table 1**). These studies are a subset of the 3,095 patients treated in the Lutonix global femoropopliteal clinical program that enrolled 2,845 patients (91.9%) treated with the Lutonix DCB and 250 (8.1%) with uncoated PTA. The primary analysis focused on the LEVANT 2 randomized trial, the largest of the randomized trials with the longest follow-up duration, spanning 5 years. The LEVANT 1, LEVANT Japan Clinical Trial, and LEVANT 2 Continued Access Registry cohorts were used to identify predictors of mortality and to assess the effect of additional study data on mortality outcomes. All analyses were done on an intention-to-treat basis.

INTERVENTIONAL TECHNIQUE. The Lutonix DCB is intended to treat de novo or restenotic lesions within the superficial femoral or popliteal arteries. The DCB is mounted on a 0.035-inch over-the-wire catheter with a proximal manifold. The surface concentration of paclitaxel is 2 $\mu g/mm^2$, and the dose of paclitaxel delivered was calculated by multiplying the surface concentration by the surface area of the balloon that comes in contact with the vessel. The instructions for use recommend vessel preparation of the target lesion using pre-dilation with an uncoated angioplasty balloon. A minimum inflation time of 120 s is recommended for the Lutonix DCB.

STUDY ENDPOINTS. All deaths were originally adjudicated by a blinded, independent, clinical events committee composed of varied specialists. As part of the current meta-analysis, causes of death in the

Interventions. Drs. Ouriel and Adelman are employees of and hold equity in Syntactx, which receives fees from Bard. Dr. Rosenfield is a consultant to or on the scientific advisory board for Abbott Vascular, Access Closure, BTG, Cordis-Cardinal Health, Eximo Medical, Volcano-Philips, Surmodics, Shockwave, Cruzar, Capture Vascular, Endospan, Janssen, Magneto, MD Insider, Micell, Silk Road, Valcare, Thrombolex, and the University of Maryland; has grants and contracts from the National Institutes of Health and Inari; has equity in Access Closure, AngioDynamics, Contego, Endospan, Embolitech, Eximo Medical, JanaCare, PQ Bypass, Primacea, MD Insider, Silk Road, Cruzar Systems, Capture Vascular, Micell, and Valcare; and is a board member for VIVA Physicians and National PERT Consortium. Dr. Brodmann is the European principal investigator of the Lutonix BTK study and consults for BD. Dr. Peña is a consultant for BD, Abbott Vascular, Boston Scientific, Philips, and Cook Medical. Dr. Geraghty is a consultant or advisory board member for BD, Boston Scientific, and Intact Vascular; and is an equity holder in Euphrates Vascular. Dr. Lee is a consultant for BD and Cardiovascular Systems, Inc.; and is a member of the Speakers Bureaus of Cardiovascular Systems, Inc., Cook Medical, Amgen, Boehringer Ingelheim, and Janssen. Ms. White is a consultant for Syntactx. Dr. Clair does not receive any direct compensation from any company, but is a consultant for Medtronic and Boston Scientific, for which the PHUSC Medical Group receives compensation for his services; and has also served on the data and safety monitoring boards for studies for BD, for which the compensation is paid to the medical group for which he works. Dr. Scheinert has reported that he has no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Global Lutonix Femoropopliteal Clinical Program

	Drug per μm^2	ClinicalTrials.gov Identifier	Enrollment Start	Study Design	Subjects Included (DCB Angioplasty/PTA)	Geography	Follow-Up (Months)
LEVANT 1	2	NCT00930813	June 2009	RCT	101 (49/52)	Europe	24
LEVANT 2 pivotal with roll-in DCB	2	NCT01412541	July 2011	RCT	532 (316/160)*	United States	60
LEVANT 2 (Continued Access Registry)	2	NCT01628159	February 2013	Single arm	657	United States, Europe	60
LEVANT Japan Clinical Trial	2	NCT01816412	March 2013	RCT	109 (71/38)	Japan	24
SAFE-DCB U.S. registry	2	NCT02424383	April 2015	Single arm	1,005	United States	36
Lutonix Global SFA Registry	2	NCT01864278	December 2012	Single arm	691	Europe	24
Total					3,095 (2,845/250)	Europe, United States, Japan	24–60

*There were 56 roll-in subjects treated with DCBs.

DCB = drug-coated balloon; LEVANT 1 = The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis; LEVANT 2 = Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries; PTA = percutaneous transluminal angioplasty; RCT = randomized controlled trial; SAFE-DCB = Real-World Registry Assessing the Clinical Use of the Lutonix 035 Drug Coated Balloon Catheter; SFA = superficial femoral artery.

LEVANT 1 and LEVANT 2 trials were readjudicated by an independent ad hoc adjudication committee comprising vascular surgeons, interventional radiologists, and oncologists with systemic paclitaxel chemotherapy knowledge. Deaths in the LEVANT Japan Clinical Trial were not readjudicated, because of unavailability of original source documents and translations. A 2 + 1 adjudication model and an electronic adjudication system (Syncrony, Syntactx, New York, New York) was used. In a 2 + 1 adjudication model, an interventionalist and an oncologist blinded to treatment, DCB angioplasty or PTA, separately adjudicated the elements of each events. If any element of an adjudication was discordant between the 2 adjudicators, the discordant elements were submitted to a tiebreaking adjudicator, who was always an oncologist.

Deaths in the LEVANT 1 and LEVANT 2 trials were classified by their relationship to the device, procedure, and paclitaxel. They were also categorized as cardiovascular or noncardiovascular. Cardiovascular deaths were further subcategorized according to etiology, namely, acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or other cardiovascular causes, using the guidelines established by Hicks et al. (10). Noncardiovascular deaths were subcategorized and included pulmonary, renal, gastrointestinal, hepatobiliary, pancreatic, infectious or inflammatory, hemorrhagic, procedural, trauma, suicide, drug reaction (prescription and nonprescription), neurological (excluding cardiovascular neurological deaths), malignancy, and other noncardiovascular deaths. If the adjudicator could not determine if a death was cardiovascular or noncardiovascular, the death was classified as undetermined. Paclitaxel relatedness was adjudicated on the basis of known complications associated with the drug and a full review of all reported adverse events between enrollment and death, allowing flexibility for adjudicators to assign paclitaxel relatedness for mechanisms yet undescribed for paclitaxel. The deaths were also classified by the Medical Dictionary for Regulatory Activities version 2.10 (MedDRA MSSO, McLean, Virginia) using system organ classifications.

STATISTICAL ANALYSIS. To create commonality of variables, the datasets from individual trials were combined into analytic databases after mapping the variables using R version 3.5.2 (R Project for Statistical Computing, Vienna Austria). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and Stata/IC version 15.1 (StataCorp, College Station, Texas). All analyses were performed by an independent clinical research organization (Syntactx).

Comparisons of categorical data were done using the Fisher exact test. Comparisons of continuous variables were performed using Student's *t*-test. Freedom from all-cause mortality was estimated for each trial using Kaplan-Meier methodology. Differences were tested using the log-rank test.

The Cox proportional hazards model was used to predict survival up to 5 years. Patients were censored at the time of death, at the date of last contact, or at 5 years, whichever came first. A time-dependent covariate was created when a post-index procedure reintervention was performed on the femoropopliteal vessels of either leg, subcategorized by whether the reintervention was with a paclitaxel-containing device. Models exploring the time-dependent relationship of reinterventions included treatment arm (DCB angioplasty vs. PTA) as a baseline covariate. Cox

TABLE 2 Baseline and Demographic Characteristics of Patients in the Randomized Trials

	LEVANT 1 RCT		LEVANT 2 RCT		LEVANT 2 CAR	LEVANT Japan Clinical Trial	
	DCB Angioplasty (n = 49)	PTA (n = 52)	DCB Angioplasty (n = 316)	PTA (n = 160)	DCB Angioplasty (n = 657)	DCB Angioplasty (n = 71)	PTA (n = 38)
Age, yrs	66.7 ± 8.4	69.9 ± 9.6	67.6 ± 10.0	68.8 ± 9.0	68.5 ± 9.6	72.5 ± 9.8	78.2 ± 8.1
	p = 0.073		p = 0.197			p = 0.002	
Male	69.4 (34/49)	57.7 (30/52)	61.1 (193/316)	66.9 (107/160)	63.8 (419/657)	63.4 (45/71)	68.4 (26/38)
	p = 0.302		p = 0.229			p = 0.676	
Medical history							
Arrhythmia	16.3 (8/49)	17.3 (9/52)	10.4 (33/316)	14.4 (23/160)	11.7 (77/657)	8.5 (6/71)	10.5 (4/38)
	p > 0.999		p = 0.229			p = 0.737	
Hypertension	35.9 (47/49)	86.5 (45/52)	89.2 (282/316)	87.5 (140/160)	88.0 (578/657)	84.5 (60/71)	92.1 (35/38)
	p = 0.162		p = 0.647			p = 0.371	
Dyslipidemia	59.2 (29/49)	69.2 (36/52)	89.6 (283/316)	86.3 (138/160)	83.7 (550/657)	66.2 (47/71)	68.4 (26/38)
	p = 0.308		p = 0.291			p > 0.999	
Myocardial infarction	15.8 (3/19)	47.8 (11/23)	40.1 (63/157)	35.9 (28/78)	44.7 (143/320)	32.3 (10/31)	35.7 (5/14)
	p = 0.048		p = 0.571			p > 0.999	
Angina	10.5 (2/19)	13.0 (3/23)	21.0 (33/157)	19.2 (15/78)	28.4 (91/320)	61.3 (19/31)	85.7 (12/14)
	p > 0.999		p = 0.864			p = 0.165	
Congestive heart failure	8.2 (4/49)	7.7 (4/52)	5.7 (18/316)	3.1 (5/160)	7.0 (46/657)	4.2 (3/71)	15.8 (6/38)
	p > 0.999		p = 0.263			p = 0.063	
Renal failure	20.4 (10/49)	32.7 (17/52)	3.5 (11/316)	4.4 (7/160)	8.8 (58/657)	7.0 (5/71)	5.3 (2/38)
	p = 0.184		p = 0.619			p > 0.999	
CVA	10.2 (5/49)	9.6 (5/52)	11.4 (36/316)	11.3 (18/160)	10.5 (69/657)	18.3 (13/71)	23.7 (9/38)
	p > 0.999		p > 0.999			p = 0.617	
Diabetes	44.9 (22/49)	50.0 (26/52)	43.4 (137/316)	41.9 (67/160)	36.7 (241/657)	46.5 (33/71)	47.4 (18/38)
	p = 0.691		p = 0.770			p > 0.999	
Prior revascularization*	65.3 (32/49)	53.9 (28/52)	66.1 (209/316)	69.1 (101/160)	62.7 (412/657)	47.9 (34/71)	50.0 (19/38)
	p = 0.311		p = 0.542			p = 0.844	
Statins	73.5 (36/49)	67.3 (35/52)	77.2 (244/316)	78.8 (126/160)	73.5 (483/657)	53.5 (38/71)	55.3 (21/38)
	p = 0.522		p = 0.728			p > 0.999	
Smoking							
Current	30.6 (15/49)	38.5 (20/52)	35.1 (111/316)	33.8 (54/160)	35.8 (235/657)	21.1 (15/71)	26.3 (10/38)
	p = 0.531		p = 0.839			p = 0.634	
Previous	36.7 (18/49)	30.8 (16/52)	44.0 (139/316)	48.8 (78/160)	46.3 (304/657)	53.5 (38/71)	42.1 (16/38)
	p = 0.536		p = 0.332			p = 0.316	
Never	32.7 (16/49)	30.8 (16/52)	20.9 (66/316)	17.5 (28/160)	18.0 (118/657)	23.4 (18/71)	31.6 (12/38)
	p > 0.999		p = 0.397			p = 0.507	

Values are mean ± SD or % (n/n). *Refers to peripheral revascularization.
CAR = Continued Access Registry; CVA = cerebrovascular accident; other abbreviations as in Table 1.

proportional hazards modeling was used to identify predictors of time to adverse events, time to serious adverse events (SAEs), and time to death.

RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS. The demographic and baseline characteristics were comparable in patients treated with DCB angioplasty and PTA in the LEVANT trials (Table 2). Patients in the LEVANT 2 study were largely men (DCB angioplasty, 61.1%; PTA, 66.9%), and the most common comorbidities were hypertension, dyslipidemia, and myocardial infarction. Approximately 80% of DCB and PTA patients were current or former smokers. The average target lesion length was 62.1 ± 41.6 mm in the DCB group and 62.3 ± 40.9 mm in the PTA group (Table 3). Most target lesions were de novo (DCB, 87.7%; PTA, 91.9%), and calcification was reported in 59.2% of DCB patients and 58.1% of PTA patients. The most common baseline Rutherford category was 3 (DCB, 62.7%; PTA, 57.5%), and the average ankle brachial index was 0.7 ± 0.2 in both groups. Patients in the DCB arm received a mean paclitaxel dose of 3.6 ± 1.9 mg at the index procedure.

SURVIVAL ANALYSES. A survival analysis of LEVANT 2 revealed a numerically higher 5-year survival in the

TABLE 3 Target Lesion Characteristics and Paclitaxel Dose in the Randomized Trials

	LEVANT 1 RCT		LEVANT 2 RCT		LEVANT 2 CAR	LEVANT Japan Clinical Trial	
	DCB Angioplasty	PTA	DCB Angioplasty	PTA	DCB Angioplasty	DCB Angioplasty	PTA
Rutherford category							
2	0.0 (0/49)	0.0 (0/52)	29.4 (93/316)	34.4 (55/160)	36.5 (240/657)	59.2 (42/71)	55.3 (21/38)
			p = 0.295			p = 0.839	
3	22.5 (11/49)	21.2 (11/52)	62.7 (198/316)	57.5 (92/160)	57.7 (379/657)	40.9 (29/71)	42.1 (16/38)
	p > 0.999		p = 0.276			p > 0.999	
4	71.4 (35/49)	71.2 (37/52)	7.9 (25/316)	8.1 (13/160)	5.8 (38/657)	0.0 (0/71)	2.6 (1/38)
	p > 0.999		p > 0.999			p = 0.349	
5	2.0 (1/49)	3.9 (2/52)	0.0 (0/316)	0.0 (0/160)	0.0 (0/657)	0.0 (0/71)	0.0 (0/38)
	p > 0.999						
6	4.1 (2/49)	3.9 (2/52)	0.0 (0/316)	0.0 (0/160)	0.0 (0/657)	0.0 (0/71)	0.0 (0/38)
	p > 0.999						
Lesion							
De novo	89.4 (42/47)	88.5 (46/52)	87.7 (277/316)	91.9 (147/160)	90.6 (595/657)	95.8 (68/71)	94.7 (36/38)
	p > 0.999		p = 0.213			p > 0.999	
Recurrent	10.6 (5/47)	11.5 (6/52)	12.3 (39/316)	8.1 (13/160)	9.4 (62/657)	4.2 (3/71)	5.3 (2/38)
	p > 0.999		p = 0.213			p > 0.999	
Calcification (% of patients)	NA		59.2 (187/316)	58.1 (93/160)	66.2 (435/657)	46.5 (33/71)	60.5 (23/38)
			p = 0.844			p = 0.228	
Ankle-brachial index	0.8 ± 0.2	0.8 ± 0.3	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.1	0.7 ± 0.1
	p = 0.374		p = 0.825			p = 0.908	
Total lesion length, mm	88.1 ± 36.8	86.2 ± 38.1	62.1 ± 41.6	62.3 ± 40.9	53.9 ± 40.7	67.7 ± 43.5	55.3 ± 51.0
	p = 0.7980		p = 0.949			p = 0.208	
Reference vessel diameter, mm	5.0 ± 0.6	5.2 ± 0.6	4.8 ± 0.8	4.8 ± 0.8	4.8 ± 0.8	4.9 ± 0.7	4.7 ± 0.7
	p = 0.096		p = 0.993			p = 0.397	
Maximum diameter stenosis, %	89.0 ± 9.8	90.1 ± 11.1	80.3 ± 14.8	80.8 ± 14.9	82.2 ± 13.8	80.9 ± 14.8	78.3 ± 13.2
	p = 0.607		p = 0.709			p = 0.357	
Mean paclitaxel dose, mg	2.8 ± 0.7	NA	3.6 ± 1.9	NA	3.5 ± 1.8	2.0 ± 0.9	NA

Values are mean ± SD or % (n/N).
NA = not applicable; other abbreviations as in Tables 1 and 2.

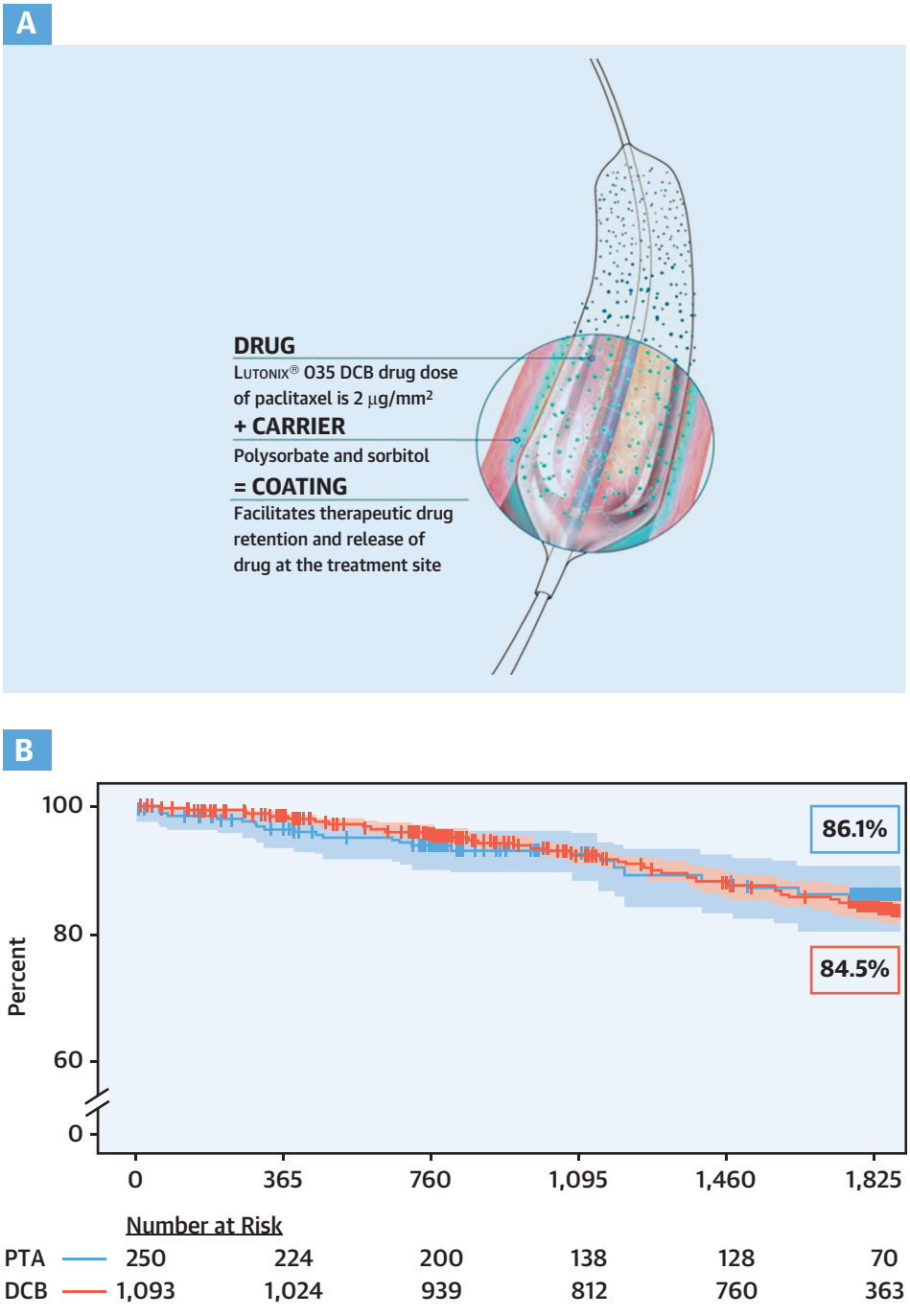
PTA arm (87.7 ± 2.7%) compared with the DCB arm (80.8 ± 2.3%), but the difference did not attain statistical significance (p = 0.084). The 2-year hazard ratio (HR) after DCB angioplasty was 0.99 (95% confidence interval [CI]: 0.25 to 3.95) in LEVANT 1, 1.40 (95% CI: 0.62 to 3.14) in LEVANT 2, and 0.32 (95% CI: 0.05 to 1.92) in the LEVANT Japan Clinical Trial. The LEVANT 2 randomized trial HR for all-cause mortality increased from 1.13 (95% CI: 0.35 to 3.68; p = 0.834) at 1 year to 1.60 (95% CI: 0.94 to 2.72; p = 0.084) at 5 years. The HR was 1.25 (95% CI: 0.765 to 2.045; p = 0.3715) at 5 years in the LEVANT 2 combined randomized and Continued Access Registry DCB cohorts versus PTA. Survival differences between DCB angioplasty and PTA diminished as data from the trials were aggregated. The HR was 1.01 (95% CI: 0.68 to 1.52; p = 0.95) through 5 years (including all visits) in the aggregated analysis dataset of LEVANT 1, LEVANT 2, and the LEVANT Japan Clinical Trial (Central Illustration). The median follow-up duration for the 3 studies was 1,779 days (interquartile range: 892 to 1,847 days).

When the HR was adjusted for post-procedural reinterventions as a time-dependent covariate, the resulting 1-year HR was 0.99 (95% CI: 0.30 to 3.28), and the 5-year HR was 1.64 (95% CI: 0.95 to 2.82). The 5-year HR was unchanged when adjusted for post-procedural reinterventions with paclitaxel-containing devices as a time-dependent covariate (at 5 years, HR: 1.65; 95% CI: 0.95 to 2.84).

CLUSTERING OF DEATH AND ADVERSE EVENTS. The causes of death are summarized in Table 4, as adjudicated by the independent committee. Among the 173 deaths in LEVANT 1 and LEVANT 2 (including the Continued Access Registry patients), 151 occurred in DCB patients (14.0%) and 22 in PTA patients (10.4%). Among these, none were adjudicated as related to paclitaxel.

There was no clustering of deaths in any category; differences in the proportion of deaths of any 1 category within the DCB or the PTA cohorts were not statistically significant. Patients died of cardiovascular causes in 5.1% (55 of 1,078) and 3.8% (8 of 212) of the DCB and PTA groups, respectively (p = 0.489).

CENTRAL ILLUSTRATION Lutonix Drug-Coated Balloon and Study Outcome



Ouriel, K. et al. J Am Coll Cardiol Intv. 2019;12(24):2515–24.

(A) Components of the Lutonix drug-coated balloon (DCB). The Lutonix balloon, indicated for the treatment of peripheral artery disease, is coated with paclitaxel to prevent vessel restenosis. **(B)** Survival in LEVANT 1 (The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis), LEVANT 2 (Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries), and LEVANT Japan Clinical Trial. Aggregated survival outcomes from the 3 trials show comparable 5-year survival rates in the percutaneous transluminal angioplasty (PTA) and DCB angioplasty groups.

Noncardiovascular deaths occurred in 7.3% (79 of 1,078) and 5.2% (11 of 212) of the DCB and PTA groups ($p = 0.304$). There was no difference in the proportion of deaths of undetermined cause in the 2 groups, 1.6% (17 of 1,078) in the DCB group versus 1.4% (3 of 212) in the PTA group ($p > 0.999$).

Cardiovascular deaths were balanced in the DCB and PTA groups. The most common subtypes were heart failure, occurring in 1.9% (21 of 1,078) and 1.4% (3 of 212) of the DCB and PTA groups, respectively ($p = 0.784$), followed by acute myocardial infarction, occurring in 1.3% (14 of 1,078) of the DCB group and 0.9% (2 of 212) of the PTA group ($p > 0.999$). Noncardiovascular deaths were also balanced in the 2 groups. Among subtypes of noncardiovascular deaths, neoplasm predominated; 4.5% (48 of 1,078) in the DCB group versus 3.3% (7 of 212) in the PTA group ($p = 0.577$). Among neoplastic deaths, lung cancer was most common (1.5% [16 of 1,078] in the DCB group and 1.4% [3 of 212] in the PTA group; $p > 0.999$), followed by gastrointestinal malignancies (0.7% [8 of 1,078] in the DCB group and 1.9% [4 of 212] in the PTA group; $p = 0.119$).

We analyzed the frequency of SAEs in the LEVANT 2 randomized cohorts as precursors of death, because new-onset events may not culminate in mortality over the follow-up observation period. Overall, there were 530 SAEs in the 316 DCB patients (1.7 per patient) and 284 in the 160 PTA patients (1.8 per patient). SAEs were balanced in the 2 treatment arms (Table 5). SAEs of any type occurred in 30.4% (96 of 316) of DCB patients versus 27.5% (44 of 160) of PTA patients ($p = 0.525$). Cardiovascular SAEs occurred in 18.0% (57 of 316) versus 18.1% (29 of 160) patients in the DCB and PTA treatment arms, respectively ($p > 0.999$). There were no significant between-group differences in the rates of other types of SAEs, with 2 exceptions: gastrointestinal SAEs occurred in numerically fewer patients in the DCB group (6.6% [21 of 316] vs. 12.5% [20 of 160]; $p = 0.038$), as did peripheral vascular SAEs (32.0% [101 of 316] vs. 40.6% [65 of 160]; $p = 0.067$).

SUBSET ANALYSES. Using the combined randomized and Continued Access Registry cohorts of the LEVANT 2 trial, the results of a stepwise Cox proportional hazards model for mortality rate in LEVANT 2 identified the following covariates predictive of mortality: age, left-sided target limb, Rutherford category, angiotensin II receptor blockers at discharge, prior treatment of the target lesion, anticoagulant agents at discharge, arrhythmia at baseline, and diabetes (Table 6). Dose was not a significant covariate in the model.

The effect of dose was studied further using quartiles corresponding to increasing doses. No significant dose-response relationship was identified using the Cox proportional hazards model when adjusted for the predictors of mortality identified earlier ($p \geq 0.05$).

TABLE 4 Adjudicated Causes of Death

	DCB Angioplasty	PTA	p Value
CV deaths	5.1 (55/1,078)	3.8 (8/212)	0.489
Heart failure	1.9 (21/1,078)	1.4 (3/212)	0.784
Acute MI	1.3 (14/1,078)	0.9 (2/212)	>0.999
CV hemorrhage	0.1 (1/1,078)	0.0 (0/212)	>0.999
Stroke	0.6 (7/1,078)	0.5 (1/212)	>0.999
Sudden cardiac death	0.6 (7/1,078)	0.5 (1/212)	>0.999
Other	0.5 (5/1,078)	0.5 (1/212)	>0.999
Non-CV deaths	7.3 (79/1,078)	5.2 (11/212)	0.304
Neoplasm	4.5 (48/1,078)	3.3 (7/212)	0.577
Blood-based	0.1 (1/1,078)	0.0 (0/212)	>0.999
Brain	0.2 (2/1,078)	0.0 (0/212)	>0.999
Gastrointestinal	0.7 (8/1,078)	1.9 (4/212)	0.119
Lung	1.5 (16/1,078)	1.4 (3/212)	>0.999
Pancreatic	0.1 (1/1,078)	0.0 (0/212)	>0.999
Other	1.2 (13/1,078)	0.0 (0/212)	0.143
Undetermined neoplasm	0.2 (2/1,078)	0.0 (0/212)	>0.999
Non-neoplasm	2.9 (31/1,078)	1.9 (4/212)	0.642
Hepatobiliary	0.1 (1/1,078)	0.0 (0/212)	>0.999
Infection	1.4 (15/1,078)	1.4 (3/212)	>0.999
Pulmonary	0.7 (8/1,078)	0.0 (0/212)	0.367
Renal	0.2 (2/1,078)	0.5 (1/212)	0.417
Suicide	0.2 (2/1,078)	0.0 (0/212)	>0.999
Trauma	0.2 (2/1,078)	0.0 (0/212)	>0.999
Inflammatory	0.1 (1/1,078)	0.0 (0/212)	>0.999
Undetermined deaths	1.6 (17/1,078)	1.4 (3/212)	>0.999
All deaths	14.0 (151/1,078)	10.4 (22/212)	0.186

Values are % (n/N).
CV = cardiovascular; MI = myocardial infarction; other abbreviations as in Table 1.

TABLE 5 Rates of Adverse Events Between Groups

	DCB Angioplasty	PTA	p Value
Serious adverse events			
Cardiovascular	18.0 (57/316)	18.1 (29/160)	>0.999
Bleeding	4.1 (13/316)	3.1 (5/160)	0.800
Infection	8.9 (28/316)	7.5 (12/160)	0.727
Malignancy	6.3 (20/316)	4.4 (7/160)	0.530
Arrythmia	2.8 (9/316)	5.0 (8/160)	0.295
Pulmonary	10.4 (33/316)	7.5 (12/160)	0.325
Orthopedic	8.9 (28/316)	10.6 (17/160)	0.619
Gastrointestinal	6.6 (21/316)	12.5 (20/160)	0.038
Peripheral Vascular	32.0 (101/316)	40.6 (65/160)	0.067
Neurological	7.9 (25/316)	5.6 (9/160)	0.452
Any type	30.4 (96/316)	27.5 (44/160)	0.525
Adverse events*			
Cardiovascular	45.6 (144/316)	50.0 (80/160)	0.383
Bleeding	13.9 (44/316)	12.5 (20/160)	0.776
Infection	32.0 (101/316)	30.6 (49/160)	0.835
Malignancy	12.3 (39/316)	8.8 (14/160)	0.282
Any type	62.7 (198/316)	66.9 (107/160)	0.419

Values are % (n/N). *Includes serious adverse events.
Abbreviations as in Table 1.

TABLE 6 Multivariate Analysis of Mortality

	Hazard Ratio	LCL	UCL	p Value
Age (per yr)	1.03	1.02	1.05	<0.001
Left-sided target limb	1.55	1.12	2.15	0.009
Rutherford category	1.41	1.08	1.84	0.012
ARB at discharge	0.58	0.37	0.89	0.013
Prior treatment to target lesion	1.67	1.08	2.60	0.022
Anticoagulant agents at discharge	2.13	1.10	4.12	0.025
Arrhythmia at baseline	1.65	1.05	2.61	0.031
Diabetes	1.18	1.00	1.40	0.047

Stepwise Cox proportional hazards stepwise regression, propensity adjusted using stratification, LEVANT 2 randomized arms and Continued Access Registry cohort.

ARB = angiotensin II receptor blocker; LCL = 95% lower confidence limit; UCL = 95% upper confidence limit.

The effect of reintervention on survival was evaluated in the LEVANT 2 randomized trial. DCB patients who underwent reintervention, either with or without a paclitaxel device, had a higher 5-year survival rate (87.8 ± 4.3%) than DCB patients without reintervention (79.3 ± 2.7%). Similarly, the 5-year survival rate for PTA patients with reintervention, paclitaxel or not, was higher than the rate for PTA patients who did not undergo reintervention (93.5 ± 4.4% vs. 86.8 ± 3.2%). Reintervention with a paclitaxel-coated or paclitaxel-eluting device versus no reintervention was found to increase survival in the DCB (85.8 ± 5.4% vs. 80.0 ± 2.6%) and PTA (92.0 ± 5.4% vs. 86.8 ± 3.1%) arms.

When stepwise Cox proportional hazards modeling was performed with treatment (DCB angioplasty or PTA) as a covariate, various factors were identified that were predictive of all SAEs and of specific SAE types. Treatment with DCB angioplasty or PTA, however, was not predictive of SAEs in general or for any specific SAE type.

DISCUSSION

Patient-level data from the Lutonix femoropopliteal clinical program refute the observations of increased mortality after DCB angioplasty treatment. Although numerically increased mortality risk was observed in the LEVANT 2 randomized trial, the mortality signal was not statistically significant, paclitaxel did not appear to be a predictor of mortality in multivariate analyses, the relationship between dose and risk was not evident after adjustment for predictors of mortality from the multivariate analysis, and the signal was not present in the other LEVANT randomized trials.

Randomized controlled trials for regulatory approval of DCBs and stents uniformly confirmed the safety and effectiveness of paclitaxel-containing interventional devices for femoropopliteal angioplasty. Published studies met their pre-determined primary safety endpoints and showed a 40% reduction in target lesion reinterventions after DES and DCB treatment compared with uncoated PTA, a finding that persisted through 5-year follow-up (8,11). A study of Medicare beneficiaries also found no differences in mortality in patients with PAD treated with DES or bare-metal stents (4).

The systematic review and meta-analysis of Katsanos et al. (9) found an almost 2-fold increase in the relative risk for all-cause mortality after treatment with paclitaxel-containing devices compared with uncoated PTA for femoropopliteal PAD. It is important to note that none of the studies included in the review by Katsanos et al. (9) were designed to assess or powered to detect a mortality signal, especially in the later years of follow-up (12). As such, the observations should be treated as hypothesis generating only.

The numeric association between paclitaxel and mortality, although demonstrated in several randomized trials, does not confirm causality (6–8,13). In most randomized trials, the treatment groups are balanced at the onset. Demographic characteristics, baseline comorbidities, and the anatomic characteristics of the target lesions are similar in the 2 treatment arms. The composition of the analytic dataset may change over time, however, as patients return for follow-up in a differential fashion between the 2 treatment arms. Originally balanced groups may become unbalanced with respect to comorbidities. Unblinded trials are especially prone to post-treatment population differences, as are trials in which the randomized treatment itself produces differences in patient and physician behavior. For instance, patient follow-up compliance may be different when 1 treatment is associated with marked improvement in effectiveness; patients who have improvement in symptoms may be less likely to continue with a protocol-specified follow-up visit schedule. By contrast, patients who have failed effectiveness, for example, those with target lesion restenosis, may be treated more aggressively for their systemic atherosclerotic disease with more antiplatelet and antihyperlipidemic medications or other medical therapies.

Reintervention itself was protective against mortality. Irrespective of whether patients were in the DCB or the PTA randomized treatment arm, they were less likely to die if they underwent reintervention. The same finding was noted with paclitaxel reinterventions; reintervention with paclitaxel-containing devices was protective against mortality whether a patient was in the DCB or PTA randomized treatment arm.

These observations raise the specter of whether the mortality signal identified by Katsanos et al. (9) and others is from causation, with paclitaxel causing death due to a yet undetermined mechanism, or whether the finding is from a noncausal association with a post-randomization effect. The criteria of Bradford Hill were created more than 50 years ago as a paradigm to identify when an observed association has underlying causation between treatment and outcome (14). Hill proposed 9 aspects of association that have become fundamental tenets of causal inference. The Hill criteria, as applied to the association between paclitaxel femoropopliteal interventions and mortality, begin with the strength of association. The greater the strength, the more likely an association is causal. The Lutonix data demonstrated a weak association between paclitaxel and death; the HRs overlapped 1 in all studies. The second criterion, consistency, was also not upheld. Among the studies, only LEVANT 2 had a mortality signal, and other studies had a numerically lower risk for death with DCB angioplasty. The Hill criterion of specificity (exposure causes the event through 1 specific pathway) was not evident. There was no clustering of adverse event types or causes of SAEs or deaths, as would be expected if paclitaxel observations were causative through 1 pathway, for example, through a cardiovascular, neoplastic, or infectious mechanism. Temporality, epidemiologically the most essential of the criteria, was not evident in the Lutonix analysis. Events occurred years after paclitaxel left the body. The mortality signal becomes evident several years after paclitaxel is cleared from the body, but preclinical studies document absence of paclitaxel in the bloodstream after several hours and clearance from the arterial wall and organs within a few months. If an agent causes an event, there should be a dose-response relationship. Dose was not identified as a predictor of either adverse events or of mortality in the multivariate analyses performed. Biological plausibility and coherence were enigmatic, at least with respect to the current body of knowledge on paclitaxel's known molecular mechanisms and its interaction with other drugs. Despite analyses of the Lutonix studies and those of others, no known mechanism of increased mortality with paclitaxel use has been elucidated. Experimental manipulation, the penultimate Hill criterion, is not relevant to DCB trials, because the duration of exposure cannot be manipulated to ascertain the effect of cessation of treatment on outcome. The last criterion, that of analogy, is also not relevant to paclitaxel studies, because there are few other similar agents that have been studied in this clinical setting. In summary, although the LEVANT 2 randomized trial had a numerically higher 5-year mortality rate in its DCB arm, this association did not satisfy any of the criteria for causation.

STUDY LIMITATIONS. The analyses were limited by the relatively small sizes of the randomized trials and the small numbers of patients in the PTA arms, with a large imbalance in the protocol-defined ratio of DCB to PTA patients. Baseline covariates and concomitant medications were limited to those that were anticipated to be important for trials with clinically driven target lesion revascularization as the primary effectiveness endpoint. Dose-response relationships may be stochastic rather than deterministic and, as such, would not be detected with the present analysis. Loss to follow-up may not have occurred at random and was unbalanced between the 2 treatment arms. The studies were neither powered for mortality nor able to accurately assess potential links between concomitant medications and paclitaxel treatment. The causes of death were not always evident from the original medical records. As well, when aggregating trials or cohorts, no adjustments were made for differences in population or treatment effect. Therefore, there may be measured or unmeasured covariates that differ among the trials or cohorts that could affect the findings. Last, the findings of this meta-analysis may not be generalizable to other commercially available DCBs, as each DCB differs in general properties, paclitaxel dose, and excipient.

CONCLUSIONS

An analysis of individual patient-level data from the full LEVANT dataset (LEVANT 1, LEVANT 2, and the LEVANT Japan Clinical Trial randomized trials as well as the LEVANT 2 Continued Access Registry) demonstrated no increase in mortality with the use of DCBs. The studies were not powered to detect mortality differences, however, and a larger sample size with prospective assignment of mortality as an endpoint would be required to reach a definitive, more robust conclusion. Although a numeric increase in mortality was observed in the LEVANT 2 DCB randomized treatment arm compared with the PTA arm, the difference was not statistically significant. The HR was closer to 1.0 as additional data from the other trials were aggregated. The association between DCB and late mortality does not imply causality, and mortality differences may be better explained by the differences in post-randomization medical treatment in the 2 cohorts, DCB angioplasty and PTA. The identification of factors predictive of mortality after treatment may be due to chance alone; alternatively, the observed

associations may arise from associations between the identified predictor and other, unmeasured covariates. The beneficial effect of reinterventions suggests a survival advantage related to more frequent patient-physician encounters. Further analysis of existing datasets from clinical trials and real-world registries may elucidate these findings.

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PERSPECTIVES

WHAT IS KNOWN? Following publication of a meta-analysis that revealed increased mortality in patients treated with paclitaxel coated balloons, the U.S. Food and Drug Administration held an advisory board meeting to evaluate paclitaxel as an approved medical therapy. After the meeting, the U.S. Food and Drug Administration highlighted a need for studies of better quality with more rigorous data collection before a decision could be formulated regarding the paclitaxel devices from 5 manufacturers.

WHAT IS NEW? This publication reports granular data specific to the Bard Lutonix DCB.

WHAT IS NEXT? While these patient-level data will help a reader evaluate the Lutonix product in clinical practice, they will also form a basis for the design of future studies of paclitaxel devices specifically and lower extremity interventional devices more generally.

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