JACC: CARDIOVASCULAR INTERVENTIONS VOL. 7, NO. 1, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2013.05.022

The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization

CME

First-in-Human Randomized Trial of Low-Dose Drug-Coated Balloon Versus Uncoated Balloon Angioplasty

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CME Objective for This Article:

At the completion of this article, the learner should be able to:

1. Discuss the effect of drug-eluting carrier formulations on the percutaneous treatment of peripheral vascular disease.
2. Define late lumen loss and explain why it was selected as the primary endpoint.
3. Discuss reasons for failed balloon deployment and its impact on sustained prevention of restenosis in target lesions.

CME Editor Disclosure: *JACC: Cardiovascular Interventions* CME Editor Habib Samady, MB, ChB, FACC, has research grants from the Wallace H. Coulter Foundation, Volcano Corp., St. Jude Medical, Forrest Pharmaceuticals Inc., and Pfizer Inc.

Author Disclosure: This clinical trial was sponsored by Lutonix, Inc., a subsidiary of C. R. Bard. Dr. Scheinert serves on the scientific advisory board of Lutonix. Dr. Duda has received study honorarium from Lutonix; and formerly served on the LEVANT-I Steering Committee. Dr. Zeller serves on the advisory boards to Medtronic Invatec, Medtronic Ardian, W. L. Gore & Associates, Angioslide, and Covedian-ev3; has received consulting fees from C. R. Bard, Johnson & Johnson Cordis, Boston Scientific, Straub Medical, Invatec, and Biotronik; and has received research grants from Cook, Krauth Medical, Abbott Vascular, and InnoRa. Dr. Tepe consults for Abbott, Covidien, Medtronic, and Medrad. Dr. Naisbitt is an employee of Lutonix, a subsidiary of C. R. Bard. Dr. Rosenfield consults for Lutonix and Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval:
Issue Date: January 2014
Expiration Date: December 31, 2014

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The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization

First-in-Human Randomized Trial of Low-Dose Drug-Coated Balloon Versus Uncoated Balloon Angioplasty

Objectives This study sought to evaluate the safety and efficacy of the Lutonix drug-coated balloon (DCB) coated with 2 μg/mm^2 paclitaxel and a polysorbate/sorbitol carrier for treatment of femoropopliteal lesions.

Background Percutaneous treatment of peripheral vascular disease is associated with a high recurrence. Paclitaxel-coated balloons at 3 μg/mm^2 formulated differently have shown promising results with reduced restenosis.

Methods Subjects at 9 centers with Rutherford class 2 to 5 femoropopliteal lesions were randomized between June 2009 and December 2009 to treatment with Lutonix DCB (n = 49) versus uncoated balloons (control group [n = 52]), stratified by whether balloon-only treatment (n = 75) or stenting (n = 26) was intended. The primary endpoint was angiographic late lumen loss at 6 months. Secondary outcomes included adjudicated major adverse events (death, amputation, target lesion thrombosis, reintervention), functional outcomes, and pharmacokinetics.

Results Demographic, peripheral vascular disease, and lesion characteristics were matched, with mean lesion length of 8.1 ± 3.8 cm and 42% total occlusions. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 ± 1.13 mm) than for the control group (1.09 ± 1.07 mm; p = 0.016). Composite 24-month major adverse events were 39% for the DCB group, including 15 target lesion revascularizations, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 target lesion revascularizations, 1 thrombosis, and 5 deaths. Pharmacokinetics showed biexponential decay with peak concentration (C_{max}) of 59 ng/ml and total observed exposure (AUC_{all}) of 73 ng h/ml. For successful DCB deployment excluding 8 malfunctions, 6-month late lumen loss was 0.39 mm and the 24-month target lesion revascularization rate was 24%.

Conclusions Treatment of femoropopliteal lesions with the low-dose Lutonix DCB reduced late lumen loss with safety comparable to that of control angioplasty. (LEVANT I, The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis; NCT00930813) (J Am Coll Cardiol Intv 2014;7:10–9) © 2014 by the American College of Cardiology Foundation

Peripheral vascular disease, like coronary artery disease, is a significant source of morbidity and mortality with high clinical and economic costs (1–3). Percutaneous balloon angioplasty of the superficial femoral artery and popliteal lesions is effective at acutely restoring flow, but restenosis occurs in 40% to 60% of patients within 1 year, leading to therapeutic failure and reintervention (4–7). Bare nitinol stents have improved outcomes, with a reduction in 1-year restenosis rates of 20% to 40% (8–11), but durability of patency after existing percutaneous treatment options remains a clinical challenge.

Drug-coated balloons (DCB) offer a mechanism to deliver antiproliferative drugs directly to the diseased artery wall without the need for a stent scaffold. Pre-clinical studies demonstrate even limited exposure of smooth muscle to paclitaxel yields sustained inhibition of proliferation (12,13). The first effective DCB dissolved paclitaxel in organic solvents with the contrast agent iopromide to facilitate application to the balloon (13,14). Early randomized clinical studies in both coronary (15,16) and peripheral (17,18) vascular beds suggest that angioplasty balloons coated with 3 μg/mm^2 paclitaxel formulated with iopromide are effective at inhibiting restenosis.

A wide variety of drug-release profiles and restenosis outcomes have been observed for different drug-eluting stent formulations that deliver similar amounts of paclitaxel

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Manuscript received September 16, 2012; revised manuscript received March 18, 2013, accepted May 9, 2013.

(19–22). Similarly, different outcomes have been reported for DCB formulations containing similar amounts of paclitaxel in animal models (23,24) and human clinical trials (25,26), highlighting the criticality of formulation for local paclitaxel delivery.

The purpose of this randomized study is to evaluate the biologic effect and estimate potential clinical outcomes with use of the Lutonix DCB technology with 2 μg/mm^2 paclitaxel formulated with polysorbate and sorbitol in the superficial femoral or popliteal arteries by direct comparison to uncoated balloon angioplasty. As a measure of antirestenotic effect, angiographic late lumen loss (LLL) was selected as the primary endpoint for consistency with previous DCB studies (15–18).

Methods

Design and study population. LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) was a prospective, single blind (to patient), randomized (1:1) trial comparing LLL in femoropopliteal lesions treated with the Lutonix DCB versus an uncoated balloon. Lesion criteria for enrollment included single de novo or (non–in-stent) restenotic lesions (operator-determined >70% stenosis; length ≥4 cm and ≤15 cm; reference vessel diameter ≥4 mm and ≤6 mm). Eligible participants were ≥18 years old with Rutherford clinical category 2 to 5 claudication or critical limb ischemia. Exclusions included the following: life expectancy ≤2 years; creatinine >2.5 mg/dl or history of hemorrhagic stroke ≤3 months; previous surgery of the target lesion; previous or planned intervention ≤30 days; use of adjunctive therapies (including glycoprotein IIb/IIIa inhibitors); severe lesion calcification; sudden symptom onset; acute or subacute target vessel thrombus or occlusion; absence of ≥1 patent untreated runoff vessel; or significant inflow disease. The study was conducted in full compliance with International Conference on Harmonization Good Clinical Practice, ISO 14155, and the Declaration of Helsinki, and with approval of the local ethics committee.

Abbreviations and Acronyms

DCB = drug-coated balloon(s)
ITT = intention to treat
LLL = late lumen loss
PK = pharmacokinetics
TLR = target lesion revascularization(s)

Study enrollment and randomization. Subjects were stratified after pre-dilation (to less than reference vessel diameter) based on whether the interventionalist intended to use only balloon dilation of the lesion or intended concomitant stenting. After successful pre-dilation or stenting, subjects in each stratum (intended balloon-only or intended stenting) were randomized 1:1 to Lutonix DCB or uncoated balloon (control group) using sequentially numbered sealed envelopes in blocks of 4 via computer-generated random numbers (Integra Group, Brooklyn Park, Minnesota).

Study device. The Lutonix DCB is a low-dose DCB coated with 2 μg/mm^2 paclitaxel. In addition to paclitaxel, the coating on the Lutonix DCB contains a polysorbate/sorbitol carrier. The carrier was selected after screening over 200 formulations for ability to achieve a highly uniform and durable coating, to minimize drug loss during insertion and transit to the target area, and to facilitate drug transfer with redistribution and retention in deep layers of the arterial wall.

Procedure. Angioplasty was performed according to the standard procedure at the investigational site. The Lutonix DCB (Lutonix, Inc., a subsidiary of C. R. Bard, New Hope, Minnesota) was provided in diameters of 5.0 mm and 6.0 mm and lengths of 60 mm and 100 mm. Operators were instructed to ensure DCB placement proximally and distally beyond the margins of the pre-dilated injury segment, to inflate within 3 min of insertion, and to maintain inflation for ≥30 s. If 2 balloons were needed, the marker bands of each sequentially used DCB were overlapped for complete lesion and margin coverage. In the control group, off-the-shelf percutaneous balloon angioplasty balloons were used for dilation. To control bias, bailout nitinol stenting in the intended balloon-only stratum was permitted in either group only for grade C or greater dissections or occlusive complications.

Device success was defined as successful delivery and deployment of the first inserted study device at the intended target lesion and withdrawal of that study device with attainment of <30% final residual stenosis of the target lesion by quantitative angiography. Procedural success was investigator-reported completion of the procedure with <30% residual stenosis of the target lesion after prolonged dilation and stenting, if necessary.

Study medication regimens and schedules were according to local clinical practice with aspirin (100 to 325 mg per day indefinitely) and clopidogrel loading dose (75 or 300 mg) with maintenance for 1 month in balloon-only subjects and 3 months in stented subjects.

Primary endpoint. The primary outcome was angiographic LLL at 6 months in the analysis segment (entire length of the balloon inflation area [the injury segment] plus 5-mm proximal and distal margins) as assessed by independent, blinded angiographic core lab analysis (genae associates, Antwerp, Belgium).

Study outcomes and follow-up. Clinical follow-up was conducted at 1, 6, 12, and 24 months after the procedure. Angiography of the target limb was performed at index procedure and 6 months after the procedure. Duplex ultrasound, Rutherford classification, ankle brachial index, and walking impairment questionnaire were evaluated at baseline, 6, 12, and 24 months. Primary patency rates were based on freedom from target lesion revascularization (TLR) and from angiographic binary restenosis >50% at 6 months or Doppler ultrasound peak systolic velocity ratio ≥2.5 at 12

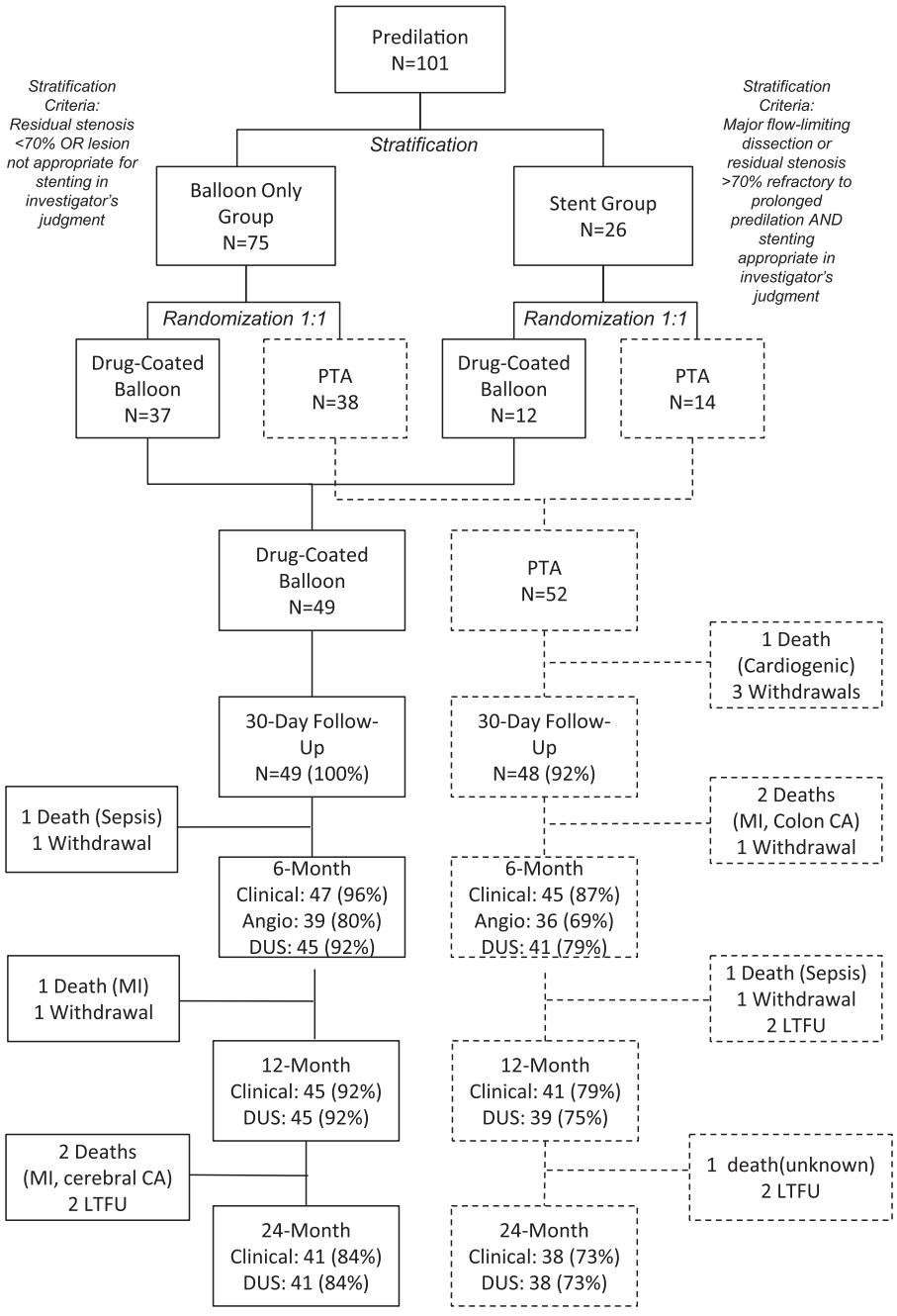

Figure 1. CONSORT Flow Diagram

Participant flow through the trial as shown, including stratification, treatment allocation, follow-up compliance, and analysis. CA = cancer; DUS = Doppler ultrasound; LTFU = lost to follow-up; MI = myocardial infarction; PTA = percutaneous balloon angioplasty.

and 24 months. Major adverse events were independently adjudicated by a Clinical events committee, and a data safety and monitoring board (genae associates) evaluated the progress of the study.

Pharmacokinetic substudy. Pharmacokinetic (PK) analysis was performed in 7 Lutonix DCB subjects on the basis of paclitaxel levels measured pre-procedure, post-procedure, at 1 h, 3 h, and prior to discharge using WinNonlin noncompartmental analysis (Seventh Wave Labs, Chesterfield, Missouri; high-performance lipid chromatography mass spectroscopy by BASi Labs, McMinnville, Oregon). The lower limit of detection was 0.1 ng/ml.

Statistical analysis. Formal a priori hypothesis testing was not performed for this feasibility study. The study required 100 subjects to provide ≥80% power to detect a clinically meaningful difference in LLL of 15% of reference vessel diameter between treatment groups on the basis of a 2-sample Student *t* test with 2-sided alpha ≤0.05. Descriptive statistics were used for analyses on the primary dataset including all randomized participants in both strata on an intention-to-treat (ITT) basis and on post-hoc groups with successful and failed deployment. Continuous variables are presented as mean ± SD, with Student *t* tests. Nonparametric testing was also conducted, and no differences in conclusions compared with those of the parametric tests were observed. Categorical variables are presented as number and percentage of subjects, with chi-square tests.

Results

Enrollment and follow-up. Between June 26, 2009 and December 2, 2009, 101 subjects were enrolled at 9 clinical sites; 49 subjects were randomized to Lutonix DCB and 52 to uncoated balloons (control) as shown in Figure 1. The intended balloon-only stratum had 75 subjects and the intended stenting stratum had 26 subjects.

Demographics and peripheral vascular disease history. Demographic, medical history, peripheral vascular disease status and lesion characteristics (Table 1) were matched between the 2 groups. Mean lesion length was 80.5 mm with 89% de novo lesions. High complexity was evident with 42% total occlusions and 7% popliteal lesions.

Procedural outcomes. Treatment balloon deployment parameters (Table 2) were comparable between the Lutonix DCB and uncoated balloon groups, with mean deployment pressures of 9 atm and inflation durations of approximately 100 s (protocol mandated ≥30 s for drug delivery in the DCB group). Overall stent usage was similar in both randomized groups (p = 0.20), although bailout stenting of subjects in the intended balloon-only stratum was more frequent for the control than the DCB group. The rate of dissections was similar for both randomized groups, but the percentage of dissections that were treated was higher for the control than for the DCB group (80% vs. 33%, p = 0.04).

Device success as assessed by the core lab was lower in the DCB group because of 8 malfunctions resulting in failed deployments. The early failed deployments were

Table 1. Baseline Demographic and Lesion Characteristics

	Lutonix DCB (n = 49)	Uncoated Balloon (n = 52)	p Value
Age, yrs	67 ± 8	70 ± 10	0.08
Male	34 (69)	30 (58)	0.22
Smoking, current	15 (31)	20 (39)	0.69
Type 2 diabetes mellitus	22 (45)	26 (50)	0.61
Hypertension	47 (96)	45 (87)	0.10
Dyslipidemia	29 (59)	36 (69)	0.29
Previous coronary artery disease	19 (39)	23 (44)	0.58
Peripheral vascular parameters			
History of peripheral vascular disease	32 (65)	28 (54)	0.24
Baseline Rutherford category			0.80
2	11 (22)	11 (21)	
3	35 (72)	37 (71)	
4	1 (2)	2 (4)	
5	2 (4)	2 (4)	
Ankle-brachial index (treated side)	0.69 ± 0.23	0.60 ± 0.36	0.18
Baseline lesion characteristics			
Target lesion location			0.62
Superficial femoral artery	45 (92)	49 (94)	
Popliteal artery	4 (8)	3 (6)	
Reference vessel diameter, mm*	4.1 ± 0.6	4.2 ± 0.7	0.44
In-segment diameter stenosis, %*	85.2 ± 16.5	85.3 ± 17.4	0.98
Lesion length, mm*	80.8 ± 37.0	80.2 ± 37.8	0.89
De novo lesions	44 (90)	46 (88)	0.83
Total occlusions	20 (41)	22 (42)	0.88

Values are mean ± SD or n (%). *Quantitative vascular angiography measurements.
DCB = drug-coated balloon.

Table 2. Procedural Outcomes

	Lutonix DCB (n = 49)	Uncoated Balloon (n = 52)	p Value
Pre-dilation			
%DS after pre-dilation (to less than reference vessel diameter)	48 ± 20	46 ± 18	
Study balloon deployment			
Maximal pressure pre-dilation balloon, atm	10 ± 2	9 ± 2	
Balloon deployment pressure, atm	9 ± 2	9 ± 2	
Inflation duration, s	109 ± 61	96 ± 64	
Balloon malfunctions	8 (16)	0 (0)	
Device success, core lab assessed	27 (55)	37 (71)	0.09
Adjunctive procedural steps			
Dissections after randomized treatment	9 (18)	10 (19)	0.90
Treated dissections	3/9 (33)	8/10 (80)	0.04
Bailout stenting, balloon-only stratum	1/37 (3)	6/38 (16)	0.05
Total stent use, intended and provisional	13 (27)	20 (38)	0.20
Procedural outcomes			
Procedural success	49 (100)	51 (99)	0.53
SAE through discharge	2	3	0.74
SAE through 30 days	9	10	0.91

Values are mean ± SD, n (%), or n/N (%).
DCB = drug-coated balloon; DS = diameter stenosis; SAE = serious adverse events.

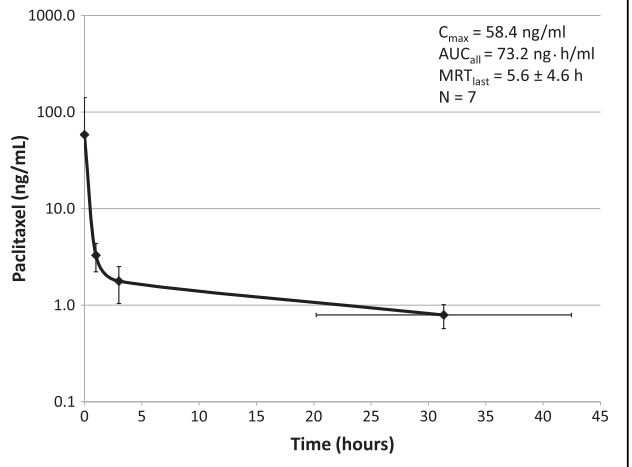

Figure 2. Serum Paclitaxel Concentrations

Mean concentration at each time point (0, 1, and 3 h post-procedure and just prior to discharge) are shown with error bars for standard deviation of concentration **(vertical)** and sample collection time **(horizontal)**. Sample size (n), peak concentration (C_{max}), total observed exposure (AUC_{all}), and mean residence time to last measurable concentration (MRT_{last}) of paclitaxel in serum are shown.

obvious to the operator at the time; the devices were easily removed from the body; and adjunctive measures led to 100% procedural success without safety complications. Investigation showed that 8 of 8 deployment failures were because of a manufacturing defect with twisted balloon folds that prevented proper balloon inflation and expansion. Investigative sites were trained to visually inspect the balloons prior to insertion and to not use abnormally folded balloons.

Pharmacokinetics. Mean paclitaxel concentrations for the 7 subjects treated with 10 DCB in the PK substudy are presented in Figure 2. The paclitaxel PK exhibited the expected biexponential decay with a rapid distribution phase followed by a log-linear elimination phase. Group mean values were as follows: peak concentration (C_{max}) = 58.4 ± 83.2 ng/ml; total observed exposure (AUC_{all}) = 73.2 ± 45.3 ng h/ml; and mean residence time to last measurable concentration (MRT_{last}) = 5.6 ± 4.6 h.

Primary endpoint. Six-month angiographic follow-up for the primary endpoint was available for 39 patients (80%) in the Lutonix DCB group and 36 (69%) in the uncoated balloon group, due in part to 4 deaths and 5 withdrawals. By ITT analysis (Fig. 3), the 6-month primary LLL endpoint was significantly lower in the Lutonix DCB group than in the uncoated balloon group (0.46 ± 1.13 mm vs. 1.09 ± 1.07 mm, p = 0.016). The difference in LLL between the Lutonix DCB and uncoated balloon groups was also significant in the intended balloon-only stratum (0.45 ± 1.18 mm vs. 1.19 ± 1.15 mm, p = 0.024). In the intended stenting stratum, the LLL for the DCB group was 0.49 ± 1.01 mm compared with 0.90 ± 0.91 mm for the uncoated balloon group without statistical significance at this sample size (n = 8 vs. 11).

Safety outcomes. Safety and functional outcomes at 6, 12, and 24 months are shown in Table 3, without obvious differences between the groups on an ITT basis. In the DCB group, there were no thromboses, 1 amputation (with subsequent death), and 4 deaths (adjudicated as due to cancer [1], sepsis [1], and cardiac [2] causes). In the uncoated balloon group, there were 1 thrombosis, no amputations, and 5 deaths (adjudicated as due to cancer [1] and cardiac [4] causes). To 24 months, there were 15 TLR in the Lutonix DCB group compared with 20 TLR in the uncoated balloon group (p = 0.23). Composite major adverse event rate of death, thrombosis, amputation, and reintervention was 39% (19 of 49) for the Lutonix DCB group compared with 46% (24 of 52) for the uncoated balloon group (p = 0.45).

Successful deployment outcomes. As shown in Table 4, subjects with successful Lutonix DCB deployment, defined as full expansion and apposition to the vessel wall, had LLL of 0.39 ± 1.11 mm, whereas subjects with failed deployment had LLL of 0.71 ± 1.27. Primary patency at 24 months was 66% for subjects with successful deployment versus 0% for failed deployment (p = 0.002). Only 24% of subjects with successful DCB deployment had a TLR through 24 months, versus 63% of those with failed deployments (p = 0.031). Figure 4 shows Kaplan-Meier event-free survival for the Lutonix DCB group with successful balloon deployment versus for the uncoated balloon control group.

Geographic miss was identified in 14 subjects with DCB misplacement such that the drug was not delivered to the entire target lesion or pre-dilation injury segment. The post hoc DCB cohort treated with successfully deployed balloons without geographic miss had 6-month LLL of 0.18 ± 0.99 (n = 23), and 24-month primary patency of 73% (19 of 26) and TLR rate of 19% (5 of 26) (data not shown).

Discussion

This randomized study provides the first human proof of the antirestenotic effect of the Lutonix DCB in treating lower extremity occlusive disease, with a 58% reduction in 6-month LLL for the Lutonix DCB-treated group versus the uncoated balloon control group (0.46 vs. 1.09 mm). These findings compare well to first-generation DCB where higher doses of paclitaxel (3 μg/mm^2) resulted in mean LLL of 0.4 mm (17) and 0.5 mm (18), despite the fact that the vessels treated in this study had smaller diameter with longer lesion length and a higher frequency of total occlusion. The antirestenotic benefit of DCB was observed when used alone or in combination with stents. Safety in this patient population persisted out to 24 months.

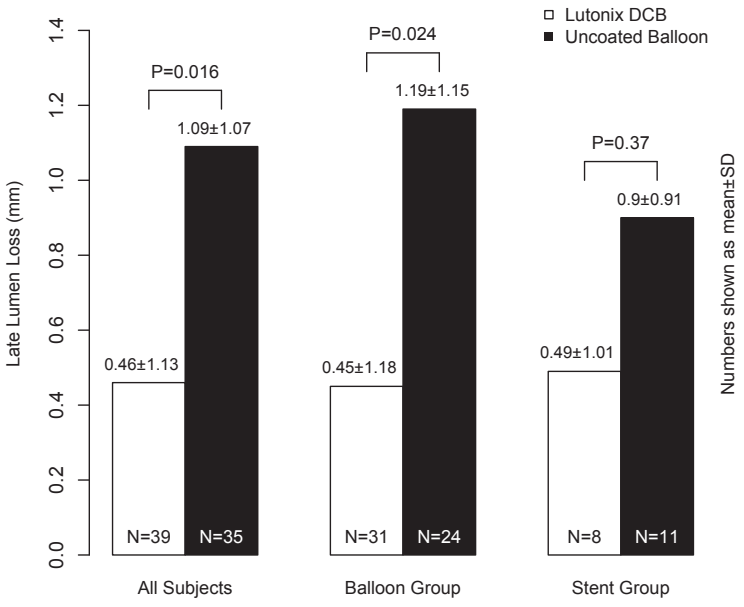

Figure 3. Primary Endpoint

Mean late lumen loss at 6 months is shown for Lutonix drug-coated balloon (DCB) **(open bars)** versus control uncoated balloon percutaneous balloon angioplasty **(solid bars)** in the intention-to-treat population (all subjects in pooled strata) and separately for each stratum (intended balloon or stent groups) with p values. Columns are labeled with evaluable sample size (n) at base and mean late lumen loss ± SD (mm) at top.

The Lutonix DCB uses polysorbate and sorbitol as the drug carrier selected to evenly distribute the paclitaxel in a uniform, durable coating for endovascular drug transfer. PK analysis showed transient serum levels after treatment with the Lutonix DCB that are much lower than those reported for pharmaceutical infusions, with comparable elimination (27).

Deployment success predicts effective drug transfer. In the DCB group, 8 subjects had failed balloon deployment due to a balloon malfunction that prevented full vessel wall apposition. Future lots used a different manufacturing process to resolve this issue, and investigative sites were trained to identify and not use defectively folded balloons. In this group with suboptimal drug delivery and possible

Table 3. Cumulative Clinical Outcomes Through 6, 12, and 24 Months of Follow-Up

	6 Months		12 Months		24 Months	
	DCB (n = 47)	Uncoated Balloon (n = 45)	DCB (n = 45)	Uncoated Balloon (n = 42)	DCB (n = 42)	Uncoated Balloon (n = 41)
Cumulative clinical events						
Target vessel revascularization	6 (13)	11 (24)	13 (29)	15 (37)	15 (36)	21 (51)
Target lesion revascularization	6 (13)	10 (22)	13 (29)	14 (33)	15 (36)	20 (49)
Thrombosis in target vessel	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	1 (2)
Amputation	1 (2)*	0 (0)	1 (2)*	0 (0)	1 (2)*	0 (0)
Death	1 (2)*	3 (6)	2 (4)*	4 (9)	4 (9)*	5 (11)
Primary patency†	28/39 (72)	17/41 (49)	30/45 (67)	23/42 (55)	24/42 (57)	17/43 (40)
Clinical assessments						
Improvement in ABI from baseline	0.20 ± 0.34 (44)	0.22 ± 0.33 (38)	0.18 ± 0.30 (42)	0.20 ± 0.46 (38)	0.20 ± 0.34 (37)	0.18 ± 0.33 (32)
Rutherford class improvement from baseline	1.7 ± 1.3 (45)	1.6 ± 1.5 (42)	1.6 ± 1.3 (45)	2.1 ± 1.3 (38)	2.1 ± 1.1 (39)	1.8 ± 1.1 (33)
WIQ improvement from baseline	35.3 ± 32.5 (26)	36.0 ± 35.1 (25)	29.7 ± 26.1 (28)	34.6 ± 35.3 (23)	40.8 ± 29.5 (19)	40.3 ± 32.0 (21)

Values are n (%), n/N (%), or mean ± SD. *Amputation and death occurred in the same subject. †Primary patency based on freedom from target lesion revascularization and restenosis, restenosis by angiography (>50%DS) at 6 months, and by PSVR ≥2.5 at 12 and 24 months.

ABI = ankle brachial index; PSVR = peak systolic velocity ratio; WIP = walking impairment questionnaire; other abbreviations as in Tables 1 and 4.

Table 4. Outcomes for Successful and Failed DCB Deployment

	Successful DCB Deployment (n = 41)	Failed DCB Deployment (n = 8)
Acute procedure		
Post pre-dilation dissection	39	38
Balloon deployment pressure, atm	8.35 ± 1.65	9.00 ± 2.39
Inflation duration, s	106 ± 59	96 ± 56
Planned stenting	27	13
Bail out stenting	0	0
Procedural complications	0	0
Efficacy		
6-month late lumen loss, mm	0.39 ± 1.11 (31)	0.71 ± 1.27 (8)
6-month primary patency, angiography	25/31 (81)	3/8 (38)
12-month primary patency, PSVR 2.5	28/37 (76)	2/8 (25)
24-month primary patency, PSVR 2.5	23/35 (66)	0/7 (0)
12-month safety, cumulative		
Target lesion revascularization	8 (20)	5 (63)
Target vessel thrombosis	0 (0)	0 (0)
Amputation	1 (2)*	0 (0)
Death	2 (5)*	0 (0)
24-month safety, cumulative		
Target lesion revascularization	10 (24)	5 (63)
Target vessel thrombosis	0 (0)	0 (0)
Amputation	1 (2)*	0 (0)
Death	4 (10)*	0 (0)

Values are %, mean ± SD, mean ± SD (n), n/N (%), or n (%). *Amputation and death occurred in the same subject.

Abbreviations as in Tables 1 and 3.

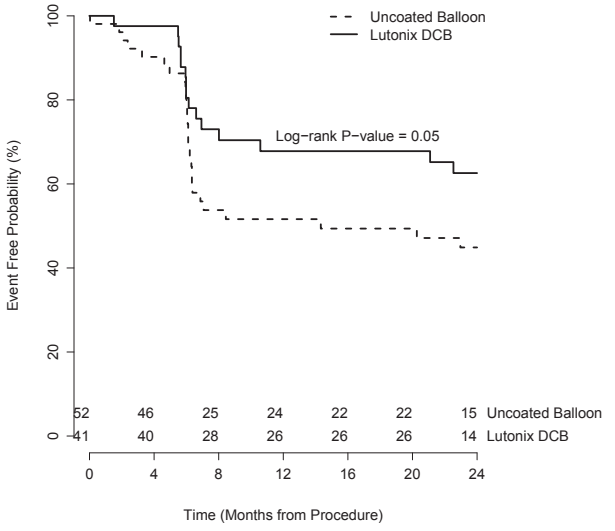

Figure 4. Kaplan-Meier Curves

Freedom from loss of patency, thrombosis, amputation, and death for Lutonix drug-coated balloon (DCB) treatment **(solid line)** and uncoated balloon percutaneous balloon angioplasty control **(dashed line)** for subjects with successful device deployment. Number of subjects at risk over time is provided below curves.

vascular trauma, 6-month LLL was higher, patency was 0, and 24-month TLR was higher than that seen in subjects with successful DCB deployment. The observation that DCB subjects treated with successfully deployed balloons without geographic miss had a high degree of primary patency (73%) and a low TLR rate (19%) through 24 months provides evidence that optimum drug delivery to the target area of the vessel wall is critical for sustained prevention of restenosis.

Lutonix DCB antirestenotic benefit in intended balloon-only or intended stenting strategies. A simple but novel design element of LEVANT I was stratification into intended stenting versus intended balloon-only groups after pre-dilation but before randomization. The merits of this design are that it balances out differences in stent use, sequence of DCB use (before or after stenting), and risk profiles between the DCB and uncoated balloon groups. The intended balloon-only strata included subjects with post pre-dilation residual stenosis <70%, where it was judged that stenting was unlikely. For this stratum, Lutonix DCB reduced LLL by 62% compared with LLL for uncoated control balloons. The intended stenting stratum included subjects with flow-limiting dissections or stenosis ≥70% after pre-dilation. This stratum had a smaller sample size, and although mean LLL trended 48% lower for DCB, a difference between arms was not observed.

Safety and clinical outcomes to 24 months. This study was designed to measure angiographic LLL and was not powered to assess clinical outcomes. However, use of the DCB did not increase major adverse events (composite or individually) when compared with those seen with the use of uncoated balloons. No target vessel thromboses were observed in the Lutonix DCB group, a historic concern for local vascular delivery. On an ITT basis, the TLR rate appears higher for the DCB group than was observed in other randomized DCB studies reporting TLR rates of 15% (17) and 13% (18). However, differences between trials in lesion length, stent use, event definitions, censoring, clinical trial rigor, and variability in angiographic follow-up make direct comparisons difficult. The present study was also complicated by the 8 deployment malfunctions. All 3 studies met their primary endpoint of decreased angiographic LLL for DCB.

Study limitations. LEVANT I was a single blind design. Although angiographic entry and stratification criteria were operator-determined prior to randomization, potential post-randomization procedural and follow-up bias cannot be precluded for unblinded operators. Only limited balloon sizes were available, and the protocol-mandated angiograms at 6 months may have confounded clinical follow-up. The study was limited by small sample size for evaluating binary

outcomes such as clinical events or patency. Runoff was not compared between the 2 study groups. An unexpected limitation to the study was the balloon deployment malfunctions, with poorer late outcomes in the subgroup with failed deployment that diluted the ITT analysis. Despite the clear failure of drug delivery in this subset of subjects, safety and primary endpoint treatment effect were still evident on an ITT basis.

Conclusions

These data demonstrate the safe use of the low-dose Lutonix DCB to attenuate restenotic responses across various procedural approaches (DCB used alone, with provisional stenting, or after stenting) out to 24 months. Treatment of femoropopliteal lesions with the novel Lutonix DCB is feasible, with similar safety and less LLL than has been reported for uncoated balloon angioplasty.

Acknowledgments

The authors thank the investigators, study coordinators, and trial and data management staff. The LEVANT I investigators included Marc Bosiers, MD, Flanders Medical Research Program, Dendermonde, Belgium; Stephan Duda, MD, Center for Minimally Invasive Therapy, Jewish Hospital, Berlin, Germany; Hans Krankenberg, MD, Hamburg University Cardiovascular Center, Hamburg, Germany; Goetz Richter, MD, Katharinenhospital Clinic for Diagnostic/Interventional Radiology, Stuttgart Germany; Jens Ricke, MD, University Magdeburg, Clinic for Radiology and Nuclear Medicine, Magdeburg Germany; Dierk Scheinert, MD, Heart Center Leipzig/Park Hospital, Leipzig, Germany; Horst Sievert, MD, CardioVascular Center, Frankfurt, Germany; Gunnar Tepe, MD, Department of Diagnostic and Interventional Radiology, Klinikum Rosenheim, Rosenheim, Germany; Giovanni Torsello, MD, St. Franziskus-Hospital, Münster, Germany; and Thomas Zeller, MD, Herz-Zentrum, Bad Krozingen, Germany.

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Key Words: angioplasty ■ drug-coated balloon ■ drug-eluting balloon ■ paclitaxel ■ peripheral vascular disease ■ restenosis.

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