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12-Month Results From the First-in-Human Randomized Study of the Ranger Paclitaxel-Coated Balloon for Femoropopliteal Treatment

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ABSTRACT

OBJECTIVES The authors sought to evaluate the performance of the Ranger paclitaxel-coated balloon versus uncoated balloon angioplasty for femoropopliteal lesions at 12 months.

BACKGROUND Drug-coated balloons (DCBs) are a promising endovascular treatment option for peripheral artery disease of the femoropopliteal segment, and each unique device requires dedicated clinical study.

METHODS The prospective, randomized RANGER SFA (Comparison of the Ranger™ Paclitaxel-Coated PTA Balloon Catheter and Uncoated PTA Balloons in Femoropopliteal Arteries) study (NCT02013193) enrolled 105 patients with symptomatic lower limb ischemia (Rutherford category 2 to 4) and stenotic lesions in the nonstented femoropopliteal segment at 10 European centers. Seventy-one patients (mean age 68 ± 8 years, n = 53 men) were enrolled in the Ranger DCB arm, and 34 patients (mean age 67 ± 9 years, n = 23 men) were assigned to the control group. Twelve-month analysis included patency, safety, and clinical outcomes and quality-of-life assessments.

RESULTS The DCB group had a greater primary patency rate at 12 months (Kaplan-Meier estimate 86.4% vs. 56.5%), with a significantly longer time to patency failure (log-rank $p < 0.001$). The estimated freedom from target lesion revascularization rate was 91.2% in the DCB group and 69.9% in the control group at 12 months, with a significantly longer time to reintervention ($p = 0.010$). No target limb amputations or device-related deaths occurred in either group.

CONCLUSIONS Twelve-month results show that patency was maintained longer after Ranger DCB treatment than after conventional balloon angioplasty, and this result was associated with a low revascularization rate and good clinical outcomes. (J Am Coll Cardiol Intv 2018;11:934–41) © 2018 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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Endovascular interventions are increasingly performed to treat femoropopliteal atherosclerotic disease in contemporary practice (1,2). Endovascular options continue to evolve as new technologies are designed to address shortcomings of those previously available. Success of conventional balloon angioplasty, for example, is limited by the occurrence of dissection, recoil, and restenosis. Stents took treatment a step forward but have drawbacks, including the existence of a permanent implant and the possibility of stent fracture (3). Newer nitinol stents, covered stents, and drug-eluting stents have been designed to address some of these issues.

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Drug-coated balloons (DCBs) are alternative treatment options, which have exhibited clear superiority over conventional balloon angioplasty in numerous studies of the femoropopliteal anatomy (4–8). DCB designs vary with respect to the drug dose, the drug and excipient formulations used in their coatings, and in the manner in which coatings are applied to the balloons. These differences could have implications for both efficacy and safety (9,10), and results from studies of 1 device are not generalizable to another. Dedicated clinical trials for the different technologies are required.

The purpose of the RANGER SFA (Comparison of the Ranger™ Paclitaxel-Coated PTA Balloon Catheter and Uncoated PTA Balloons in Femoropopliteal Arteries) randomized clinical study was to evaluate the performance of the Ranger paclitaxel-coated balloon catheter (Boston Scientific, Marlborough, Massachusetts) versus uncoated balloon angioplasty for femoropopliteal lesions, and the primary endpoint of 6-month late lumen loss was shown to be significantly less following treatment with the DCB (11). Here we report results from 12 months of follow-up.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The methodology of the RANGER SFA study and characteristics of enrolled patients have been described previously (11). Briefly, the 105 patients enrolled in the prospective, multicenter, randomized, controlled RANGER SFA study were randomly assigned in a 2:1 ratio to treatment with the Ranger DCB or an uncoated balloon. Key inclusion criteria were symptoms of lower limb ischemia (Rutherford category 2, 3, or 4) and a lesion between 20 and 150 mm in length with ≥70% stenosis located in the native nonstented superficial femoral artery or proximal popliteal segment. Seventy-one patients (mean age 68 ± 8 years, n = 53 men) were randomized to the Ranger DCB arm, and 34 patients (mean age 67 ± 9 years, n = 23 men) were assigned to the control group.

The study protocol was approved by the ethics committees at each trial site, and all patients provided written informed consent prior to enrollment. The trial was registered on the National Institutes of Health Web site (NCT02013193).

FOLLOW-UP. A dual-antiplatelet regimen was prescribed for at least 4 weeks following the index procedure, and at least 1 antiplatelet drug was to be continued indefinitely thereafter. The 12-month (±30 days) follow-up required an in-office visit and included duplex ultrasonography, ankle-brachial index (ABI) and Rutherford category assessments, and administration of the Walking Impairment Questionnaire and EQ-5D-3L and SF-12v2 health-related quality-of-life assessments (12–15).

STUDY DEFINITIONS. Primary patency was defined as freedom from restenosis (binary restenosis defined as a duplex ultrasound peak systolic velocity ratio threshold ≥2.4, as determined by the ultrasound core laboratory), target lesion revascularization (TLR), or bypass of the target lesion. All TLRs were included in the TLR assessment. Clinical success was defined as improvement in Rutherford category by at least 1 level compared with baseline, and hemodynamic success was defined as a positive change in ABI of at least 0.1.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD; categorical data are given as count (percentage). Kaplan-Meier estimates were calculated for rates of primary patency and freedom from TLR. Log-rank p values for Ranger DCB and control groups were determined for the period through 395 days post-procedure. Exploratory post hoc analyses to investigate the influence of various

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index
CI = confidence interval
DCB = drug-coated balloon
TLR = target lesion revascularization

Medical, Veryan, Optimed, and Veniti. Dr. Diaz-Cartelle is an employee of and owns stock in Boston Scientific. Drs. Marx and Ströbel are employees of CERES. Dr. Schult is an employee of Hemoteq. Dr. Scheinert is a consultant or advisory board member for Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, C.R. Bard, Gardia Medical, Medtronic/Covidien, TriReme Medical, Trivascular, and Upstream Peripheral Technologies. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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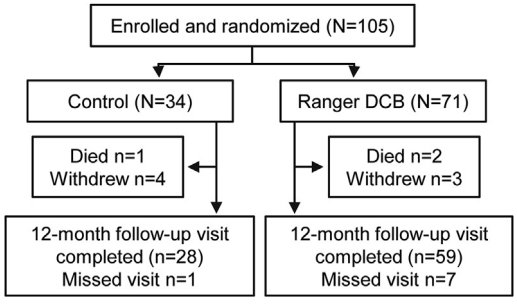
TABLE 1 Baseline Patient and Lesion Characteristics

	Control (n = 34)	Ranger DCB (n = 71)	p Value
Age, yrs	67 ± 9	68 ± 8	0.999
Men	23 (68)	53 (75)	0.605
Diabetes mellitus	12 (35)	28 (39)	0.934
Hyperlipidemia requiring medication	21 (62)	49 (69)	0.606
Hypertension requiring medication	26 (76)	58 (82)	0.610
Smoking			
Current	17 (50)	29 (41)	0.022
Previous	7 (21)	32 (45)	
History of renal insufficiency*	1 (3)	8 (11)	0.292
Coronary artery disease	13 (38)	24 (34)	0.821
Calcification†			
None	5/32 (16)	7/70 (10)	0.236
Mild	9/32 (28)	19/70 (27)	
Moderate	11/32 (34)	17/70 (24)	
Severe	7/32 (22)	25/70 (36)	
NA	0/32 (0)	2/70 (3)	
Occlusions	11/32 (34)	24/70 (34)	>0.999
Target lesion length, mm	60 ± 48	68 ± 46	0.731
Target lesion location			
Proximal SFA	2/32 (6)	12/70 (17)	0.289
Mid SFA	12/32 (37)	31/70 (44)	
Distal SFA	17/32 (53)	25/70 (36)	
Proximal popliteal	1/32 (3)	2/70 (3)	
TASC II			
A	22/32 (69)	46/70 (66)	0.620
B	7/32 (22)	19/70 (27)	
C	2/32 (6)	5/70 (7)	
D	0/32 (0)	0/70 (0)	
NA	1/32 (3)	0/70 (0)	
Reference vessel diameter, mm	4.5 ± 0.83	5.0 ± 0.89	0.039

Values are mean ± SD, n (%), or n/N (%). Modified with permission from Bausback et al. (11). *Renal failure with serum creatinine >2.0 mg/dl. †Calcium grading: none = no calcium on 2 orthogonal views; mild = calcium deposits <180° in circumference and <50% of lesion length; moderate = calcium deposits <180° in circumference and ≥50% of lesion length; severe = deposits ≥180° in circumference and ≥50% of lesion length.

DCB = drug-coated balloon; NA = not available; SFA = superficial femoral artery; TASC = Trans-Atlantic Inter-Society Consensus Document.

FIGURE 1 RANGER SFA Patient Flow Diagram



Random assignments, deaths (all-cause), withdrawals, and 12-month visit completion are shown. DCB = drug-coated balloon; RANGER SFA = Comparison of the Ranger™ Paclitaxel-Coated PTA Balloon Catheter and Uncoated PTA Balloons in Femoropopliteal Arteries.

patient and lesion characteristics on patency and TLR rates included logistic regression modeling of 12-month patency and TLR adjusting for the following variables: study arm (Ranger DCB vs. control), degree of calcium (moderate or severe vs. none or mild), lesion length (continuous), vessel diameter (continuous), diabetes (current diabetes mellitus, yes vs. no), sex (female vs. male), age (continuous), smoking status (current or previous vs. never), occlusion (yes vs. no), and bailout stenting (yes vs. no). Significant covariates identified with the univariate models ($p < 0.10$) were entered into multivariate models to identify independent predictors.

Statistical comparisons were conducted with the following tests, depending on the nature of the variables compared: 2-sample, 2-sided Kolmogorov-Smirnov test (interval scaled variables), Kruskal-Wallis rank sum test (ordinal scaled variables), chi-square independence test (nominal scaled variables), and log-rank test (survival curves). The significance level for all tests was 0.05. Data were analyzed using R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

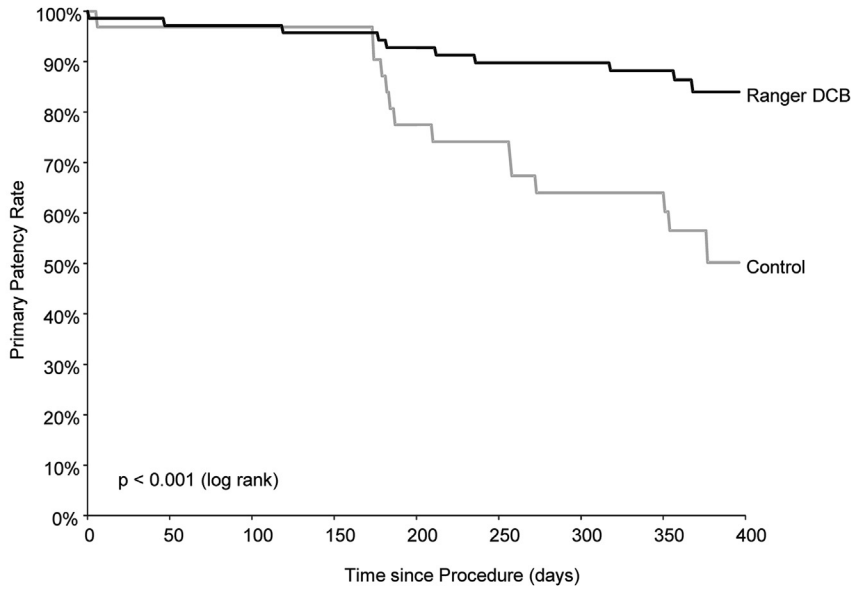
RESULTS

PATIENTS. Baseline patient characteristics were well balanced between the treatment groups (11) and are summarized in Table 1. Most lesions were classified as Trans-Atlantic Inter-Society Consensus Document II A or B, with mean lesion lengths of 68 ± 46 mm in the Ranger DCB group and 60 ± 48 mm in the control group. Approximately one-third of patients had occlusions, and more than one-half had moderate or severe calcification. Bailout stenting was performed in 12% of control group patients (4 of 34) and 21% of patients in the DCB group (11).

The 12-month visit was completed by 59 patients treated with the Ranger DCB and 28 patients treated with a control balloon (Figure 1). In the Ranger DCB group, 7 patients missed the visit, 3 withdrew, and 2 died before the visit. In the control group, 1 patient missed the visit, 4 withdrew, and 1 died. None of the deaths was reported as related to the study device or procedure.

EFFICACY. At 12 months, the Kaplan-Meier estimate of primary patency was significantly greater for the Ranger DCB group than for patients treated with a control balloon (86.4% [95% confidence interval (CI): 78.5% to 95.1%] vs. 56.5% [95% CI: 41.1% to 77.6%], log-rank $p < 0.001$) (Figure 2). The absolute primary patency rate through 12-month follow-up was 86% (44 of 51) for the Ranger DCB group and 52% (14 of 27) for the control group ($p = 0.002$).

FIGURE 2 Kaplan-Meier Estimate of Primary Patency



Days since procedure	0		200		365		395	
	Control	Ranger DCB	Control	Ranger DCB	Control	Ranger DCB	Control	Ranger DCB
Primary Patency±SE	100±0%	100±0%	77.5±9.7%	92.8±3.4%	56.5±16.2%	86.4±4.9%	50.2±20.1%	84.0±5.7%
Cumulative Failed	0	0	7	5	13	9	14	10
Cumulative Censored	2	0	4	4	9	23	15	36
At Risk	34	71	24	63	13	43	6	26

The **black line** shows 86.4% patency rate for the Ranger drug-coated balloon (DCB) group at 365 days, and the **gray line** shows the significantly lower 56.5% rate for the control group. The life table is included. SEs are <10% at all time points for the Ranger DCB group and exceed 10% at 210 days in the control group.

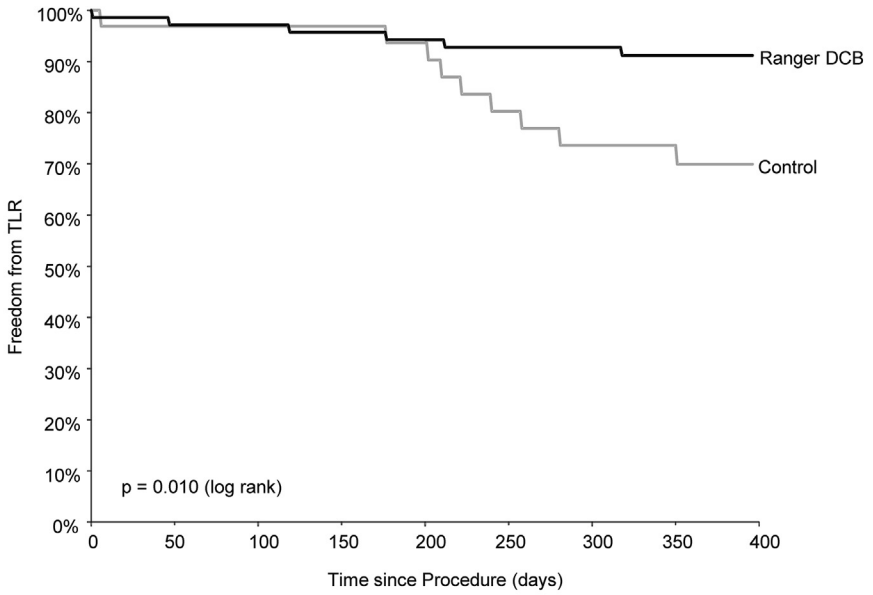
Likewise, the estimated freedom from TLR at 365 days was significantly greater for patients treated with the Ranger DCB than for patients in the control group (91.2% [95% CI: 84.7% to 98.2%] vs. 69.9% [95% CI: 55.2% to 88.5%], log-rank p = 0.010) (Figure 3). The observed incidence of TLR for the Ranger DCB group at 12 months was approximately one-third that of the control group (8.5% vs. 26.5%; p = 0.030), and no major limb amputations had occurred.

Treatment was the only statistically significant predictor of primary patency identified in univariate logistic regression analysis (odds ratio: 5.84; 95% CI: 2.003 to 18.405; p = 0.002), therefore a multivariate model of patency was not constructed. For TLR-free status, treatment and age were the only independent variables with p values <0.10 in univariate logistic regression analyses. In the subsequent multiple logistic regression model, Ranger DCB treatment was associated with greater odds of TLR-free status (odds ratio: 4.37; 95% CI: 1.253 to 16.398; p = 0.023), whereas age was not an independent predictor (odds ratio: 1.05; 95% CI: 0.985 to 1.134; p = 0.132). Consistent with the lack of association between stenting and outcomes observed in the logistic regression analysis, when patients who received bailout stents were excluded in a subgroup analysis, the magnitudes of the differences between Ranger DCB (n = 56) and control (n = 30) groups were similar to the overall sample for primary patency (84% vs. 52%; p = 0.016) and TLR (8.9% vs. 23%; p = 0.131) rates.

PATIENT OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE. At 12 months, a significant improvement in distribution across Rutherford categories was observed in both the Ranger DCB and control groups (Kruskal-Wallis rank sum test p < 0.001 for each group), but the difference between the groups was not statistically significant (p = 0.638). Most patients in the Ranger DCB group presented with no (62.5% Rutherford category 0) or mild (21.4% Rutherford category 1) symptoms at 12 months (Figure 4). Clinical success was achieved in 92.6% of subjects (50 of 54) in the Ranger DCB group and 81.5% of subjects (22 of 27) in the control group (p = 0.261) at 12 months.

ABI measurements were improved significantly over baseline in both groups at 12 months (Kolmogorov-Smirnov test p < 0.001 for each group). ABI (0.96 ± 0.16 vs. 0.93 ± 0.22; p = 0.642) and the rate of

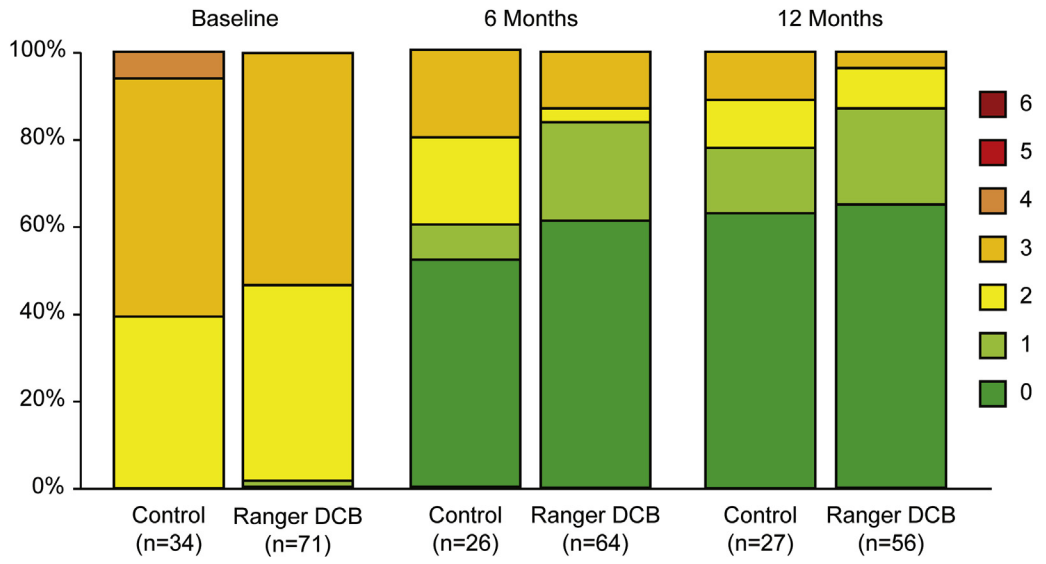
FIGURE 3 Kaplan-Meier Estimate of Freedom From Target Lesion Revascularization



Days since procedure	0		200		365		395	
	Control	Ranger DCB	Control	Ranger DCB	Control	Ranger DCB	Control	Ranger DCB
Freedom from TLR±SE	100±0%	100±0%	93.6±4.6%	94.3±3.0%	69.9±12.1%	91.2±3.8%	69.9±12.1%	91.2±3.8%
Cumulative Failed	0	0	2	4	9	6	9	6
Cumulative Censored	2	0	4	4	10	23	17	37
At Risk	34	71	29	64	17	46	9	28

The **black line** shows the 91.2% freedom from target lesion revascularization (TLR) rate for the Ranger drug-coated balloon (DCB) group at 365 days, and the **gray line** shows the significantly lower 69.9% rate for the control group (log-rank p = 0.010). The life table is included. SEs are <10% at all time points for the Ranger DCB group and exceed 10% at 281 days in the control group.

FIGURE 4 Rutherford Category Distribution



At 12 months, 84% of patients in the Ranger drug-coated balloon (DCB) group and 78% of patients in the control group had symptoms classified as category 0 or 1.

TABLE 2 Walking Impairment Questionnaire

	Control (n = 34)	Ranger DCB (n = 71)	p Value
Distance			
Baseline	24 ± 23	33 ± 30	0.6794
6 months	62 ± 38	75 ± 30	0.3753
12 months	64 ± 37	71 ± 34	0.9303
Speed			
Baseline	28 ± 24	29 ± 20	0.8709
6 months	50 ± 33	54 ± 30	0.9134
12 months	49 ± 31	55 ± 27	0.5425
Stair			
Baseline	48 ± 31	54 ± 30	0.8811
6 months	65 ± 33	69 ± 28	0.9994
12 months	63 ± 35	65 ± 32	0.9135
Distance and speed			
Baseline	26 ± 22	31 ± 23	0.365
6 months	56 ± 34	64 ± 28	0.4733
12 months	56 ± 32	63 ± 28	0.6818
Distance and stair			
Baseline	36 ± 23	43 ± 26	0.5183
6 months	63 ± 33	71 ± 26	0.3506
12 months	64 ± 33	68 ± 31	0.9135
Speed and stair			
Baseline	38 ± 25	42 ± 22	0.4315
6 months	58 ± 31	61 ± 27	0.6347
12 months	56 ± 30	60 ± 27	0.7908
Total			
Baseline	33 ± 22	38 ± 22	0.5384
6 months	59 ± 32	66 ± 26	0.3968
12 months	59 ± 31	64 ± 28	0.7644

Values are mean ± SD; p values from 2-sample, 2-sided Kolmogorov-Smirnov test. Baseline and 6-month data originally appeared as supplementary material in Bausback et al. (11).

hemodynamic success (81.2% vs. 70.4%; p = 0.428) were not statistically different between the Ranger DCB and control groups at 12 months.

Mean total Walking Impairment Questionnaire scores increased from 38 ± 22 at baseline to 66 ± 26 at 6 months and were sustained at 64 ± 28 at 12 months in the Ranger DCB group, with a similar increase observed in the control group (**Table 2**). The Walking Impairment Questionnaire total scores and parameters of distance, speed, and stair climbing did not differ significantly between the Ranger and control groups at any time point (**Table 2**).

Likewise, no significant differences in health-related quality of life scores (EQ-5D-3L, SF12v2) were observed between the Ranger DCB and control groups (Online Tables 1 and 2).

DISCUSSION

The 12-month efficacy results of the RANGER SFA study substantiate the 6-month late lumen loss findings (11), with greater patency rates and fewer reinterventions for patients treated with Ranger DCB compared with patients receiving conventional balloon angioplasty. Similar symptomatic, hemodynamic, walking function, and health-related quality-of-life improvements were observed for both study groups, but this was achieved with about one-third fewer reinterventions for patients treated with the Ranger DCB. Patient characteristics in our study are similar to other publications in the field of femoropopliteal endovascular interventions, with treated lesions mostly classified as Trans-Atlantic Inter-Society Consensus Document A and B. However, one-third of lesions were occluded, and more than one-half exhibited moderate or severe calcification, which has been linked to reduced efficacy of DCB treatment (16).

The recent IN.PACT SFA (Randomized Trial of IN.PACT Admiral® Drug Coated Balloon vs. Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease) (6), LEVANT 2 (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis 2) (5), and ILLUMENATE (ProspectIve, Randomized, SingLe-Blind, U.S. MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon; Prospective, Randomized, Multi-center, Single-blinded Study for the Treatment of Subjects Presenting With De Novo Occluded/Stenotic or Re-occluded/Restenotic Lesions of the Superficial Femoral or Popliteal Arteries Using Paclitaxel or Bare Percutaneous Transluminal Angioplasty Balloon Catheter) (7,8) randomized studies of DCB treatment of femoropopliteal disease provide context for the RANGER SFA results, although direct comparisons are limited because of differences in the devices studied as well as characteristics of included patients and treated lesions. Like the Ranger DCB, the balloons studied in the LEVANT 2 (5) and ILLUMENATE (7,8) studies are coated with paclitaxel at a dose density of 2 μg/mm^2, whereas the IN.PACT balloon coating includes paclitaxel at a dose density of 3.5 μg/mm^2. Twelve-month patency rates reported in these studies range from about 74% to 89%, with the difference compared with control-group angioplasty ranging from approximately 17% to 30%. The RANGER SFA results fall at the high end of this range, with an estimated primary patency of 86.4%, which was approximately 30% greater than for control. In the previous studies, reinterventions were performed between about 1.4 and 7 times less often for patients treated with a DCB versus conventional balloon angioplasty, with the ILLUMENATE European study

reporting a difference similar to that observed in RANGER SFA of about 3 times fewer TLRs. The lack of procedure-related deaths and major amputations associated with paclitaxel-coated balloon use observed in the previous studies was corroborated in the current study.

STUDY LIMITATIONS. Limitations of the RANGER SFA study have been described previously (11) and include the limited complexity of study lesions. Use of bailout stenting could confound interpretation of the effect of the DCB study outcomes, but the differences between Ranger DCB and control observed at 12 months were preserved when patients with bailout stents were excluded from the patency and TLR analyses, and stenting was not significantly associated with patency or reintervention in logistic regression analysis. Likewise, various other patient and lesion characteristics could affect treatment efficacy, possibly differentially between the study groups, but logistic regression analysis did not identify any significant influencers on patency or TLR aside from DCB treatment. Results from these exploratory analyses must be interpreted cautiously, however, because of the small subgroup sizes and 2:1 distribution of patients between study arms. Another study shortcoming is the lack of blinding. The decision to revascularize was made by the treating investigator, who was not blinded to group assignment. Finally, as the primary endpoint was 6 months angiographic late lumen loss, the 12-month results are pre-specified secondary post hoc exploratory analyses.

CONCLUSIONS

Twelve-month results of the RANGER SFA study suggest that the inhibition of restenosis observed angiographically at 6 months translated into improved primary patency compared with standard percutaneous transluminal angioplasty treatment for femoropopliteal lesions.

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PERSPECTIVES

WHAT IS KNOWN? DCBs are a promising endovascular treatment option for peripheral artery disease of the femoropopliteal segment.

WHAT IS NEW? Twelve-month results of the RANGER SFA first-in-human study demonstrate improved primary patency compared with standard treatment for femoropopliteal lesions. The study adds to the available information on peripheral treatment with DCBs, providing clinical evidence unique to the Ranger DCB.

WHAT IS NEXT? On the basis of the promising results of various DCB and novel stent designs compared with conventional balloon angioplasty, comparative effectiveness studies of new treatment modalities for femoropopliteal interventions are needed.

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KEY WORDS drug-coated balloon, drug-eluting balloon, femoropopliteal segment, late lumen loss, paclitaxel, patency, peripheral artery disease, peripheral vascular diseases, popliteal artery, restenosis, stenosis, superficial femoral artery

APPENDIX For supplemental tables, please see the online version of this paper.