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PERIPHERAL

1-Year Results From the RANGER II SFA Randomized Trial of the Ranger Drug-Coated Balloon

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ABSTRACT

OBJECTIVES This study sought to evaluate the safety and effectiveness of the Ranger drug-coated balloon (DCB) (paclitaxel dose density 2 μg/mm^2) for treating superficial femoral artery or proximal popliteal artery lesions.

BACKGROUND Paclitaxel-coated balloon treatment prevents reinterventions, but dose and coating characteristics differ among balloons and necessitate discrete confirmation of safety and effectiveness.

METHODS Patients with symptomatic lower limb ischemia (Rutherford classification 2 to 4) were randomized 3:1 to treatment with the Ranger DCB or standard percutaneous transluminal angioplasty (PTA). Twelve-month primary target lesion patency, freedom from major adverse events (i.e., target lesion revascularization, major amputations, death within 1 month of the index procedure), and patient outcomes were analyzed.

RESULTS Mean lesion length was 82.5 ± 48.9 mm for the Ranger DCB group (n = 278) and 79.9 ± 49.3 mm for the control group (n = 98). Ranger DCB was superior to PTA (82.9% [n = 194 of 234] vs. 66.3% [n = 57 of 86]) with observed 12-month primary patency rates yielding a difference of 16.6% (95% confidence interval: 5.5% to 27.7%; p = 0.0013). Noninferior freedom from major adverse events (94.1% [n = 241 of 256] vs. 83.5% [n = 76 of 91]) was demonstrated with a difference of 10.6% (95% confidence interval: 2.5% to 18.8%; noninferiority p < 0.0001). Primary patency rate curves showed significant separation by Kaplan-Meier analysis (log-rank p = 0.0005), with rates of 89.8% and 74.0% estimated at day 365 for the Ranger DCB and PTA cohorts, respectively.

CONCLUSIONS The low-dose Ranger DCB demonstrated significantly better effectiveness than standard PTA through 1 year and a good safety profile. (Ranger™ Paclitaxel Coated Balloon vs Standard Balloon Angioplasty [RANGER II SFA]; NCT03064126) (J Am Coll Cardiol Intv 2021;14:1123–33) © 2021 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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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

DCB = drug-coated balloon

CD-TLR = clinically driven target lesion revascularization

MAE = major adverse event

PTA = percutaneous transluminal angioplasty

TBI = toe-brachial index

TLR = target lesion revascularization

Paclitaxel-coated balloons have consistently demonstrated improved efficacy (i.e., target lesion patency and reduced clinically driven target lesion revascularization [CD-TLR] rates) compared with uncoated percutaneous transluminal angioplasty (PTA) for femoropopliteal peripheral artery disease (1,2), while offering the same procedural flexibility. Twelve-month results from recent randomized controlled trials have all shown significantly improved target lesion primary patency following treatment with a drug-coated balloon (DCB) compared with PTA (3–6), and most longer-term results likewise suggest a sustained difference in reintervention rates (7,8). DCBs have therefore replaced uncoated balloons for endovascular-first strategies (9,10).

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Performance differences within the DCB class, however, likely stem from differing coating characteristics (11,12). The differing drug doses, excipients, and other characteristics of the coatings on the balloons used in these studies affect release kinetics and thus the efficiency of drug transfer to target tissue, tissue levels, and intraprocedural drug loss (13–15). With a dose density of 2 μg/mm^2, the Ranger Paclitaxel-Coated PTA Balloon Catheter (Boston Scientific, Marlborough, Massachusetts) is among the lowest-dose paclitaxel DCBs. A swine study showed lower tissue drug levels following treatment with the Ranger DCB in an in-stent restenosis model than after treatment with the IN.PACT Admiral (Medtronic, Santa Rosa, California; dose density 3.5 μg/mm^2) but similar local neointimal inhibition than with the higher-dose DCB (13). Preclinical rabbit (14) and swine (15) studies of Ranger DCB suggest efficient drug transfer to target vessel tissue with little downstream loss. The combination of lower dose and efficient drug transfer may translate to a therapeutic effect comparable to that of a high dose paclitaxel-coated balloon, as results from the randomized RANGER SFA (Comparison of the Ranger™ Paclitaxel-Coated PTA Balloon Catheter and Uncoated PTA Balloons in Femoropopliteal Arteries) first-in-human (16,17) and COMPARE (Compare Study for the Treatment of Subjects With Symptomatic Femoropopliteal Artery Disease) (18) randomized clinical studies suggest.

The RANGER II SFA (RANGER™ Paclitaxel Coated Balloon vs Standard Balloon Angioplasty) study expands on the first-in-human and COMPARE studies with a larger sample size and global patient population. The study objective is to evaluate the safety and effectiveness of the Ranger DCB for treating superficial femoral artery or proximal popliteal artery lesions. A concurrent pharmacokinetics substudy was conducted to evaluate systemic paclitaxel levels following DCB exposure.

METHODS

STUDY DESIGN AND PARTICIPANTS. The RANGER II SFA (NCT03064126) randomized controlled trial (RCT) is a prospective, multicenter, single-blind superiority study that enrolled patients at 67 community hospitals, academic hospitals, Veterans Affairs hospitals, endovascular office-based laboratories, and referral centers in Austria, Belgium, Canada, Japan, New Zealand, and the United States. Study sites and investigators are listed in the Supplemental Appendix. The concurrent nonblinded single-group pharmacokinetics substudy was conducted at a subset of American sites which also participated in the randomized trial.

The study protocol was approved (or permission to conduct the trial was granted) by the appropriate Institutional Review Board, Ethics Committee, or Research Ethic Board for each study site, and study conduct was consistent with ISO 14155 and principles originating in the Declaration of Helsinki.

Potential subjects provided informed consent prior to undergoing study-specific tests or procedures. Eligibility criteria for the RCT and the pharmacokinetics substudy were identical. Complete inclusion and exclusion criteria are shown in the Supplemental Appendix. Patients were at least 20 years of age and had chronic symptomatic lower limb ischemia defined as Rutherford classification (19) 2, 3, or 4 and a target lesion in the native superficial femoral artery or proximal popliteal artery to the P1 segment with a reference vessel diameter ≥4 mm and ≤8 mm by visual estimate. Angiographic evidence that the target lesion comprised a single de novo nonstented and nonatherectomy treated or restenotic lesion that was either ≥70% to 99% stenotic with total lesion length up to 180 mm by visual estimate, or occluded with total lesion length ≤100 mm by visual estimate was required.

If the lesion was restenotic, the most recent PTA treatment must have been more than 3 months prior to enrollment. Previous treatment of the target lesion or vessel with atherectomy or a DCB in the past 12 months, or ever with surgery or a stent (e.g., in-stent restenosis) were grounds for exclusion.

Patients had to be free of significant inflow disease that could not be treated prior to the target lesion treatment. Patent popliteal (P2 and P3) and

infrapopliteal arteries (i.e., at least 1 of 3 vessels patent with <50% stenosis to the ankle or foot) were required. Other key exclusion criteria were chronic renal insufficiency with serum creatinine >2.0 mg/dl within 30 days of the index procedure or treatment with dialysis, presence of severe calcification rendering the lesion undilatable, or use of adjunctive primary treatment modalities (e.g., laser, atherectomy, scoring or cutting balloon, other debulking devices) during the index procedure.

The investigator's imaging assessment was used to determine subject eligibility for the trial, but independent analysis from the Angiographic Core Laboratory (Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, Massachusetts) was used for data analyses. The angiographic core laboratory assessed angiograms captured during the index procedure and any subsequent revascularization procedure up to 12 months following the index procedure.

RANDOMIZATION AND MASKING. For the RCT, treatment was randomly assigned after the patient was found to meet the angiographic eligibility criteria and the target lesion was successfully crossed with a guidewire and successfully pre-dilated. A patient was considered enrolled when the Ranger DCB or standard PTA balloon was introduced into their vasculature. A randomization function in the Electronic Data Collection database was used to assign treatment in a 3:1 ratio (Ranger DCB to standard PTA). Randomization was stratified by site with random permuted blocks of varying sizes.

Patients were masked to treatment assigned and treatment received and were to remain blinded through the completion of all 12-month (primary endpoint) follow-up visits. Study center personnel were trained not to disclose the treatment assignment to patients. Core laboratory (vascular ultrasound and angiography) personnel, the Clinical Events Committee, and individuals involved in data analysis for the sponsor were masked to treatment through the primary endpoint analysis.

PROCEDURES. The over-the-wire, semicompliant Ranger Paclitaxel-coated PTA Balloon Catheter has technical characteristics identical to the Sterling Balloon Catheter (Boston Scientific), but is coated with a formulation of paclitaxel and acetyltributyl citrate excipient yielding a paclitaxel dose density of 2 $\mu g/mm^2$ (total weight of drug per unit of balloon surface area). The Ranger DCB is compatible with 0.018-inch (0.46-mm) or 0.014-inch (0.36-mm) guidewires and is equipped with a loading tool to protect the drug coating during insertion into the sheath. Balloon diameters of 4.0 to 8.0 mm and lengths of 30, 40, 60, 80, and 100 mm were available for the study. Nominal pressure is 6 atm for all sizes.

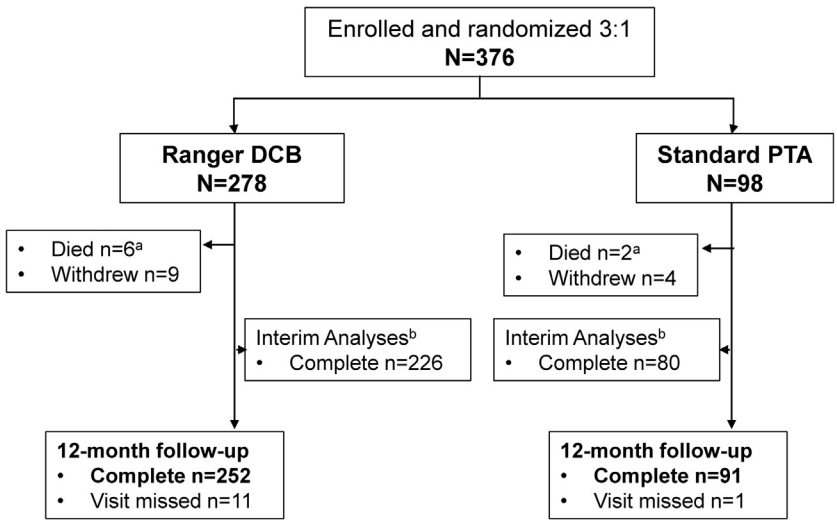
Target lesion preparation was required with successful pre-dilatation of optimally sized non-drug-coated balloon(s) prior to randomization (i.e., the selected balloon dilates the vessel lumen at nominal pressure without flow-limiting dissection [≥ Grade D] or need for intervention such as stenting). Ranger DCB use was in accordance with the device's Instructions for Use, which specified that the Ranger DCB diameter should not exceed the diameter of the targeted artery adjacent to the stenosis. Ranger DCB inflation time was 3 min. Post-dilatation was performed at the investigator's discretion. Control treatment was standard PTA with commercially available nonscoring balloons. Treatment was performed according to the individual device labeling. Bare-metal stents could be utilized to treat peri-procedural situations in which adequate results could not be obtained after prolonged low-pressure balloon inflation (i.e., residual stenosis ≥50% or major [≥ Grade D] flow-limiting dissection).

Anticoagulant and antiplatelet medication prescription was consistent with local clinical practice. Minimum protocol requirements for anticoagulation or antiplatelet therapy applied to all study groups; specific requirements were anticoagulant administration prior to and during the procedure consistent with current clinical practice, and dual antiplatelet therapy for at least 30 days for patients who did not receive a stent and at least 90 days for those who did receive a stent. Single antiplatelet therapy as a minimum was recommended through the duration of trial participation.

CLINICAL FOLLOW-UP. Clinical follow-up visits were scheduled for 1, 6, and 12 months post-procedure. Data collected at these visits included ankle-brachial index (ABI), Rutherford classification, and duplex ultrasonography, medication assessment, and adverse events. Patient outcome measures were the 6-min walk test (6 and 12 months only), Walking Impairment Questionnaire, and the EQ-5D health-related quality of life questionnaire. Follow-up will continue through 5 years.

OUTCOME DEFINITIONS. Primary lesion patency was defined as core laboratory-assessed duplex ultrasound peak systolic velocity ratio ≤2.4 at the 12-month visit in the absence of CD-TLR or bypass of the target lesion. Any reintervention at the target lesion after the index procedure was considered TLR (major adverse event [MAE] component, as described subsequently), whereas CD-TLR (primary patency

FIGURE 1 RANGER II SFA Randomized Controlled Trial Patient Flow



Patient disposition through 12-month follow-up. [a]Death <395 days post-procedure with no 12-month visit performed. [b]The first 306 evaluable subjects were included in the prespecified interim analysis. DCB = drug-coated balloon; PTA = percutaneous transluminal angioplasty.

component) was defined as any reintervention at the target lesion due to recurrent symptoms (i.e., ≥1 level increase in Rutherford classification) or an ABI or TBI (toe-brachial index) decrease of >0.15 or ≥20% as compared with the post-procedure ABI or TBI in the treated segment. TBI was allowed in cases of incompressible vessels. Duplex ultrasound assessment was performed by an independent vascular ultrasound core laboratory (VASCORE, Boston, Massachusetts) and TLR was adjudicated by the Clinical Events Committee.

The independent Clinical Events Committee adjudicated all deaths, TLR, target vessel revascularization, and target limb amputations and determined which events qualified as MAEs (i.e., TLR and major amputations through 12 months, all-cause death within 1 month).

Secondary outcomes for the RCT at 12 months included measures of technical and procedural success and clinical outcomes. At each follow-up visit, changes in Rutherford classification were used to assess clinical improvement, with sustained clinical improvement defined as improvement in Rutherford classification from pre-procedure by at least 1 category without the need for TLR. Hemodynamic improvement was defined as achieving ABI ≥0.90 or improvement of ABI by ≥0.1 as compared with the pre-procedure value without the need for repeat revascularization.

PHARMACOKINETICS SUBSTUDY. All patients in the pharmacokinetics substudy were treated with the Ranger DCB. Baseline venipuncture could occur within 30 days prior to the index procedure. Post-treatment laboratory samples were timed after removal of the last Ranger DCB from the vasculature. Venous blood samples were obtained at 10 ± 5 min, 30 ± 10 min, 1 h ± 10 min, 3 h ± 10 min, 6 h ± 10 min, 24 ± 4 h or 48 ± 4 h, 7 ± 1 days, and 30 ± 7 days. Patients could choose to return for either the 24- or 48-h time point.

Blood samples were shipped to Covance Central Laboratory Services (Indianapolis, Indiana) for independent assessment of paclitaxel levels according to the core laboratory methodology. Paclitaxel levels were analyzed with high-performance liquid chromatography and tandem mass spectrometric detection. Samples were tested with a limit of quantification of <1 ng/ml.

STATISTICAL ANALYSIS. The primary effectiveness hypothesis was that 12-month primary patency for patients treated with the Ranger DCB was superior to that for patients treated with standard PTA. The primary safety hypothesis was that the 12-month MAE-free rate for patients treated with Ranger DCB was noninferior to that for patients treated with standard PTA at a noninferiority margin of -10%. The study was to be considered successful if both the primary effectiveness and primary safety hypotheses showed statistical significance simultaneously, with a prespecified interim analysis planned to be conducted when a minimum of 75% of patients had completed

12-month follow-up. Success criteria were met with the interim analysis and details are provided in the Supplemental Appendix.

Final analysis was performed after all available patients completed 12-month follow-up and included all who signed the informed consent form and were randomized in the RCT, according to the intention-to-treat principle. Because the study reached statistical significance based on the interim analysis, p values for comparisons between treatment groups in the final analysis (e.g., chi-square test for discrete variables, 2-sample Student's *t*-test for continuous variables, log-rank test for time to event variables, unless otherwise noted) were performed for exploratory purposes. Sensitivity analysis for 12-month primary patency was performed by imputing missing patency status at 12 months as patency failure. The Kaplan-Meier product-limit method was used to estimate the event or event-free rates for time-to-event endpoints, namely time to primary patency and time to freedom from TLR. The Kaplan-Meier curve for primary patency is based on the time to event of CD-TLR or 12-month duplex ultrasound patency failure for the full 12-month window up to 395 days. Statistical analyses were performed with SAS (SAS Institute, Cary, North Carolina), version 9.2 or higher.

RESULTS

PATIENTS. For the RCT, a total of 376 patients were enrolled between March 2017 and August 2018 and randomly assigned to treatment with the Ranger DCB (n = 278) or standard PTA (n = 98). The distribution of enrollment across regions was: 60.6% in the United States and Canada, 27.1% in Japan, 9.8% in Europe, and 2.4% in New Zealand. Ten sites enrolled between 10 and 20 patients, 1 enrolled 26 patients (<7% of total enrollment), and 56 sites enrolled fewer than 10 patients each. The patient flow through 12-month follow-up is shown in Figure 1. Patient disposition based on 12-month visit or evaluable death was available for 93.4% (n = 351 of 376) of enrolled patients. A total of 343 patients completed the 12-month follow-up visit. Eight died prior to completing the visit, 6 from the Ranger DCB group and 2 from the control group. The intention-to-treat dataset includes 6 patients who did not meet per protocol criteria due to failure to meet all critical eligibility criteria.

BASELINE CHARACTERISTICS. Baseline demographic and clinical characteristics were similar between the randomized study groups as shown in Table 1. The Ranger DCB group had a greater prevalence of hypertension, and although the distribution across smoking categories differed between the treatment arms, the overall prevalence of any smoking history was similar between groups (85.3% for the Ranger DCB and 84.7% for standard PTA). The ABI was 0.8 ± 0.2 in both groups. Lesion characteristics according to the angiographic core laboratory are shown in Table 2. Baseline between-group differences were noted in the severity of PACSS (Peripheral Arterial Calcium Scoring System) calcification (20) and prevalence of occlusion.

TABLE 1 Baseline Demographic and Clinical Characteristics of the Intention-to-Treat Population

	Ranger DCB (n = 278)	Standard PTA (n = 98)	p Value
Age, yrs	70.6 ± 9.5	69.1 ± 10.3	0.1887
Female	37.8 (105/278)	31.6 (31/98)	0.2769
Race/ethnicity			
Hispanic or Latino	7.6 (21/278)	8.2 (8/98)	0.8459
Caucasian	55.8 (155/278)	60.2 (59/98)	0.4444
Asian (Japanese)	27.7 (77/278)	25.5 (25/98)	0.6753
Black, or African heritage	7.2 (20/278)	4.1 (4/98)	0.2784
American Indian or Alaska Native	0.4 (1/278)	0.0 (0/98)	1.0000*
Other	0.4 (1/278)	0.0 (0/98)	1.0000*
Not disclosed	1.1 (3/278)	2.0 (2/98)	0.6086*
Smoking history			0.0303*
Current	31.3 (87/278)	45.9 (45/98)	
Previous	54.0 (150/278)	38.8 (38/98)	
Never	14.4 (40/278)	15.3 (15/98)	
Unknown	0.4 (1/278)	0.0 (0/98)	
Diabetes mellitus	42.4 (118/278)	43.9 (43/98)	0.8055
Type 1	1.7 (2/118)	0.0 (0/43)	1.0000*
Type 2	96.6 (114/118)	100.0 (43/43)	0.5743*
Unknown	1.7 (2/118)	0.0 (0/43)	1.0000*
Current diabetes mellitus treatment			
Diet only	5.1 (6/118)	11.6 (5/43)	0.1648*
Medically treated	94.1 (111/118)	88.4 (38/43)	0.3063*
Hyperlipidemia	75.9 (211/278)	79.6 (78/98)	0.4561
Hypertension	90.3 (251/278)	81.6 (80/98)	0.0232
Chronic obstructive pulmonary disease	18.9 (52/275)	21.4 (21/98)	0.5893
Coronary artery disease	47.5 (131/276)	44.9 (44/98)	0.6619
Myocardial infarction	16.6 (46/277)	14.4 (14/97)	0.6157
Congestive heart failure	9.4 (26/277)	9.2 (9/98)	0.9527
History of renal insufficiency	10.8 (30/278)	5.2 (5/97)	0.1004
Previous target limb interventions†			
Percutaneous transluminal angioplasty	7.6 (21/278)	5.1 (5/98)	0.4107
Atherectomy	2.5 (7/278)	3.1 (3/98)	0.7246*
Drug-coated balloon	1.1 (3/278)	2.0 (2/98)	0.6086*
Stenting	6.1 (17/278)	2.0 (2/98)	0.1772*

Values are mean ± SD or % (n/N). *Two-sided Fisher exact test. †Prior PTA treatment of the target lesion or vessel must have been more than 3 months prior to enrollment. Three subjects had protocol deviations for the exclusion criterion "target lesion or vessel ever treated with a stent or surgery. Target lesion or vessel treated with atherectomy or a DCB in the past 12 months."

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

TABLE 2 Pre- and Post-Procedure Angiographic Characteristics (Core Laboratory)

	Ranger DCB (n = 278)	Standard PTA (n = 98)	p Value
Pre-procedure			
Lesion location			
Proximal SFA	17.3 (48/278)	18.4 (18/98)	0.8054
Mid-SFA	52.5 (146/278)	44.9 (44/98)	0.1945
Distal SFA	24.8 (69/278)	32.7 (32/98)	0.1325
Proximal popliteal	4.3 (12/278)	4.1 (4/98)	1.0000*
Midpopliteal	1.1 (3/278)	0.0 (0/98)	0.5707*
Lesion length, mm	82.5 ± 48.9	79.9 ± 49.3	0.6551
Reference vessel diameter, mm	5.1 ± 0.9	5.1 ± 0.9	0.7346
Thrombus			
Absent	97.8 (272/278)	99.0 (97/98)	0.6817*
Present	0.7 (2/278)	1.0 (1/98)	1.0000*
Not available	1.4 (4/278)	0.0 (0/98)	0.5764*
PACSS calcification			
Grade 0	35.3 (98/278)	22.4 (22/98)	0.0194
Grade 1	12.6 (35/278)	14.3 (14/98)	0.6681
Grade 2	2.5 (7/278)	1.0 (1/98)	0.6860*
Grade 3	36.3 (101/278)	52.0 (51/98)	0.0064
Grade 4	11.5 (32/278)	10.2 (10/98)	0.7240
Not available	1.8 (5/278)	0.0 (0/98)	0.3325*
TASC II type			
A	59.4 (165/278)	61.2 (60/98)	0.7451
B	30.2 (84/278)	30.6 (30/98)	0.9415
C	9.0 (25/278)	6.1 (6/98)	0.3744
D	1.4 (4/278)	2.0 (2/98)	0.6531*
Diameter stenosis (%)	73.7 ± 16.9	78.2 ± 18.4	0.0294
<50%	3.6 (10/278)	7.1 (7/98)	0.1609*
50% to <100%	78.1 (217/278)	63.3 (62/98)	0.0040
100% (occlusion)	18.3 (51/278)	29.6 (29/98)	0.0193
Post-procedure			
Thrombus			
Absent	98.6 (274/278)	93.9 (92/98)	0.0226*
Present	0.7 (2/278)	1.0 (1/98)	1.0000*
Not available	0.7 (2/278)	5.1 (5/98)	0.0147*
Aneurysm	0.4 (1/278)	1.0 (1/98)	0.4539*
Perforation	2.2 (6/278)	0.0 (0/98)	0.3461*
Distal embolus	0.0 (0/278)	0.0 (0/98)	Undef
Arteriovenous fistula	5.8 (16/278)	7.1 (7/98)	0.6221
Spasm	0.0 (0/278)	1.0 (1/98)	0.2606*
Dissection			
None	24.5 (68/278)	35.7 (35/98)	0.0317
Grade A	0.0 (0/278)	0.0 (0/98)	Undef
Grade B	45.3 (126/278)	37.8 (37/98)	0.1936
Grade C	16.5 (46/278)	16.3 (16/98)	0.9597
Grade D	12.9 (36/278)	5.1 (5/98)	0.0321
Grade E	0.0 (0/278)	0.0 (0/98)	Undef
Grade F	0.0 (0/278)	0.0 (0/98)	Undef
Not available	0.7 (2/278)	5.1 (5/98)	0.0147*

Values are % (n/n) or mean ± SD. *2-sided Fisher's exact test.

PACSS = Peripheral Arterial Calcium Scoring System; SFA = superficial femoral artery; Undef = undefined; other abbreviations as in Table 1.

In both arms, the most frequently used balloon diameters were 6 mm (46.3% [n = 182 of 393 balloons] Ranger DCB and 45.0% [n = 45 of 100 balloons] PTA) and 5 mm (39.2% [n = 154 of 393] Ranger DCB and 42.0% [n = 42 of 100] PTA). The required predilatation was performed in 100% of procedures, and post-dilatation was performed in 13.3% (n = 37 of 278) of Ranger DCB procedures and 21.4% (n = 21 of 98) of standard PTA procedures (p = 0.0557). Bailout stents were implanted in 5.0% (n = 14 of 278) of Ranger DCB procedures and 9.2% (n = 9 of 98) of standard PTA procedures (p = 0.1407).

Procedural success (i.e., residual stenosis of ≤50% [nonstented] or ≤30% [stented] by core laboratory evaluation) did not differ significantly between the study arms (96.8% [n = 269 of 278] Ranger DCB vs. 99.0% [n = 97 of 98] standard PTA; 2-sided Fisher exact test p = 0.4644).

EFFECTIVENESS AND SAFETY. As shown in Table 3, the Ranger DCB group was superior to standard PTA with observed 12-month primary patency rates of 82.9% (n = 194 of 234) and 66.3% (n = 57 of 86), respectively, yielding a difference of 16.6% (95% confidence interval: 5.5% to 27.7%; p = 0.0013). The conclusion was unaltered in sensitivity analysis in which missing 12-month primary patency data from 44 patients in the Ranger DCB arm and 12 patients in the PTA arm were imputed as failures, yielding rates of 69.8% (n = 194 of 278) and 58.2% (n = 57 of 98) for the Ranger DCB and PTA arms, respectively (p = 0.0357). The primary patency rate curves also showed significant separation by Kaplan-Meier analysis (log-rank p = 0.0005) (Central Illustration). Cumulative incidence functions of primary patency failure are shown in Supplemental Figure 1.

For the safety analysis, 12-month freedom from MAE was 94.1% (n = 241 of 256) for the Ranger DCB group and 83.5% (n = 76 of 91) for the standard PTA group, with a difference of 10.6% (95% confidence interval: 2.5% to 18.8%; noninferiority p < 0.0001).

MAEs comprised mainly TLR in both study arms (Table 3). All TLRs were clinically driven. The Kaplan-Meier estimate of freedom from TLR was 94.5% for the Ranger DCB group and 83.6% for standard PTA at 365 days (Figure 2), with significant separation between the study arms (log-rank p = 0.0007).

The all-cause mortality rate was 1.9% (n = 5 of 259) for the Ranger DCB versus 2.2% (n = 2 of 93) for PTA (p > 0.99) through day 365; 1 patient died on day 366 (within the 12-month visit window) and did not complete the 12-month visit, as depicted in Figure 1.

CLINICAL OUTCOME ASSESSMENTS. Hemodynamic improvement, evidenced by improved ABI, occurred significantly more often in the Ranger DCB group (Table 3). Primary sustained clinical improvement was observed in significantly more patients in the

Ranger DCB group at 12 months (Table 3) and 85.7% (n = 215 of 251) of patients in the Ranger DCB group, and 74.7% (n = 68 of 91) of those in the PTA group had Rutherford classification of 0 or 1 (Figure 3).

Six-minute walk test and overall Walking Impairment Questionnaire scores as well as component speed, distance, and stair climbing scores improved significantly from baseline in both groups (Supplemental Tables 1 and 2) but the degree of improvement did not differ significantly between the groups (Table 3).

More than one-half of patients showed improvement by at least 1 category in the EQ-5D mobility and pain dimensions at 12 months (Table 3), with no significant differences between groups. The distributions of problems in each dimension are summarized in Supplemental Tables 3 and 4.

MEDICATION ASSESSMENT. Dual antiplatelet therapy through 30 days was reported for 84.2% (n = 230 of 273) of patients in the Ranger DCB group and 82.5% (n = 80 of 97) in the control PTA group (p = 0.6837); decreasing to 58.1% (n = 143 of 246) and 68.9% (n = 62 of 90), respectively, at 12 months (p = 0.0733). At 12 months, 82.9% (n = 204 of 246) of Ranger DCB-treated patients and 84.4% (n = 76 of 90) of control PTA patients reported acetylsalicylic acid use with or without additional anticoagulation therapy (p = 0.7410).

PHARMACOKINETICS SUBSTUDY. A total of 12 patients were enrolled in the pharmacokinetics substudy. Their mean treated lesion length was 154.2 ± 92.8 mm. Plasma paclitaxel levels were less than the limit of quantification (i.e., <1 ng/ml) for 11 of 12 patients by the 1-h time point following DCB removal and for all patients by 3 h. One patient died 79 days post-procedure and the death was adjudicated as noncardiovascular.

TABLE 3 Full Cohort Clinical Outcomes 12 Months After Balloon Catheter Treatment

	Ranger DCB (n = 278)	Standard PTA (n = 98)	p Value
Primary patency*	82.9 (194/234)	66.3 (57/86)	0.0013
Major adverse events	5.9 (15/256)	16.5 (15/91)	0.0020
All-cause death at 1 month	0.4 (1/256)	0.0 (0/91)	1.0000*
Target limb major amputation	0.0 (0/256)	0.0 (0/91)	Undef
TLR	5.5 (14/256)	16.5 (15/91)	0.0011
Clinically driven	5.5 (14/256)	16.5 (15/91)	0.0011
Hemodynamic improvement†	80.0 (200/250)	67.9 (57/84)	0.0222
Primary sustained clinical improvement‡	87.6 (220/251)	75.8 (69/91)	0.0076
Walking Impairment Questionnaire, change from baseline			
Distance	23.52 ± 36.38	28.22 ± 34.83	0.2886
Speed	15.02 ± 26.69	15.18 ± 28.47	0.9627
Stair climbing	18.62 ± 37.58	14.93 ± 34.62	0.4183
Walking impairment	32.29 ± 39.40	34.72 ± 36.85	0.6101
6-min walk test, change from baseline, m§	36.3 ± 162.2	46.1 ± 115.4	0.6056
EQ-5D dimension improvement‖			
Mobility	56.3 (139/247)	53.3 (48/90)	0.6307
Self-care	10.5 (26/247)	15.6 (14/90)	0.2066
Usual activities	38.1 (94/247)	45.6 (41/90)	0.2139
Pain/discomfort	53.4 (132/247)	56.7 (51/90)	0.5990
Anxiety/depression	23.9 (59/247)	24.4 (22/90)	0.9156

Values are % (n/N) or mean ± SD. *Primary patency defined as duplex ultrasound peak systolic velocity ratio ≤2.4 in the absence of clinically driven TLR. †Improvement of ABI by ≥0.1 compared with the pre-procedure value or to an ABI ≥0.90 without repeat revascularization. ‡Improvement in Rutherford classification by 1 or more categories compared with pre-procedure without repeat TLR. §Total distance walked. ‖ Improving by at least 1 category from baseline.

ABI = ankle-brachial index; TLR = target lesion revascularization; other abbreviations as in Tables 1 and 2.

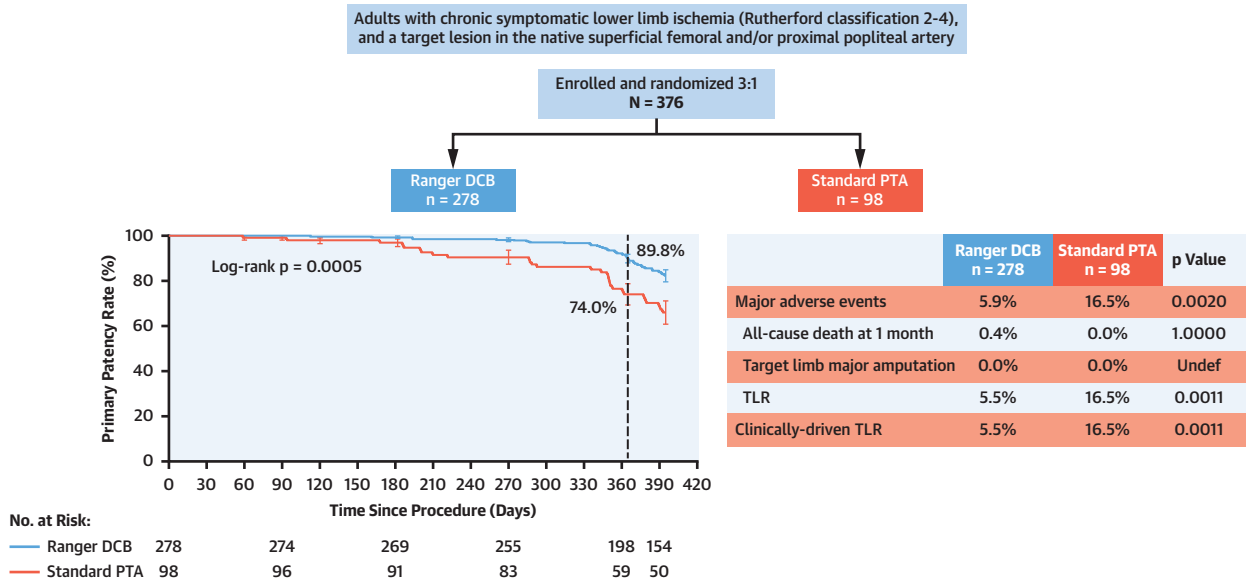
DISCUSSION

The RANGER II SFA study showed significantly better primary patency and MAE rates with the Ranger DCB compared with uncoated PTA. The significant difference in primary sustained clinical improvement suggests that although improvement in Rutherford category was similar between the treatment arms, fewer reinterventions were required to achieve it for the Ranger DCB group.

These results are consistent with those of previously reported clinical studies of Ranger DCB. The randomized first-in-human study conducted in Europe (17) also showed a significantly better primary patency rate for Ranger DCB than for PTA, at a magnitude (86%) similar to the global RCT reported here (82.9%). The primary patency rate is also similar to that observed in the Ranger arm of the head-to-head COMPARE study (83.0%) (18). In the COMPARE study, the lower-dose Ranger DCB demonstrated noninferior efficacy and safety compared with IN.PACT DCB at 12 months.

The study designs and patient populations represented in the randomized trials supporting U.S. Food and Drug Administration approval of other paclitaxel-coated DCBs (3–5) were similar to those represented in the RANGER II SFA study and provide further context for these results, although comparisons between studies are inherently limited. The difference in 12-month primary patency values between DCB and PTA arms across these trials range from 12.6% to 26.2% (3–6), and the RANGER II study results are within this range with a between-arm difference of 16.6%, and a relatively high primary patency rate for the PTA arm. The rate of bailout stent use was consistent with the other noted pivotal trials (range 4.7% to 9%) (3–5) and less than that which occurred in the Ranger DCB first-in-human study and other recent RCTs (14% to 27.8%) (6,17,18). Ranger DCB properties support a therapeutic effect in line with other paclitaxel-coated DCBs, with a good safety

CENTRAL ILLUSTRATION **Primary Patency and Major Adverse Events Through 1 Year in RANGER II SFA**



	Ranger DCB n = 278	Standard PTA n = 98	p Value
Major adverse events	5.9%	16.5%	0.0020
All-cause death at 1 month	0.4%	0.0%	1.0000
Target limb major amputation	0.0%	0.0%	Undef
TLR	5.5%	16.5%	0.0011
Clinically-driven TLR	5.5%	16.5%	0.0011

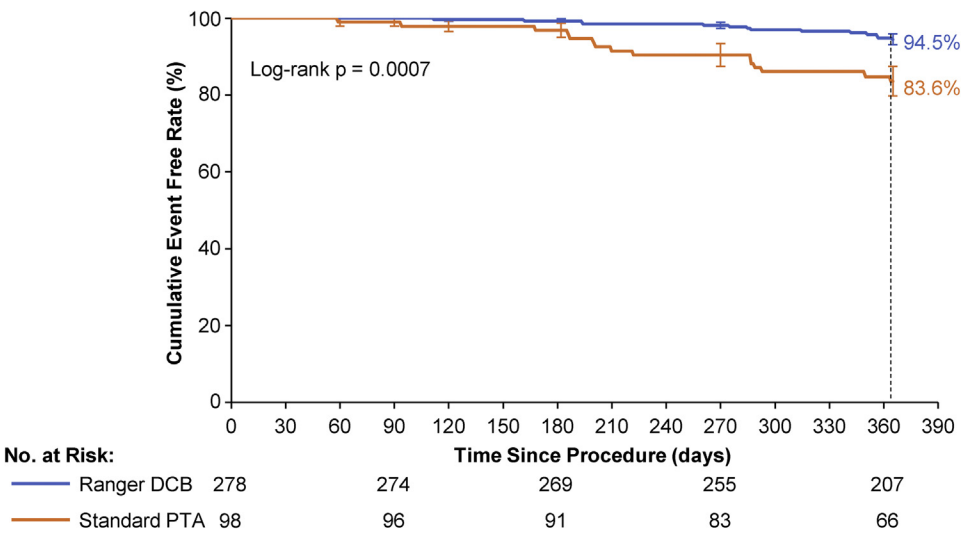
Sachar, R. et al. J Am Coll Cardiol Intv. 2021;14(10):1123-33.

Kaplan-Meier estimate of primary patency with standard errors **(left).** Major adverse event rates **(right).** DCB = drug-coated balloon; PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization.

profile and limited systemic exposure as shown by the pharmacokinetics substudy.

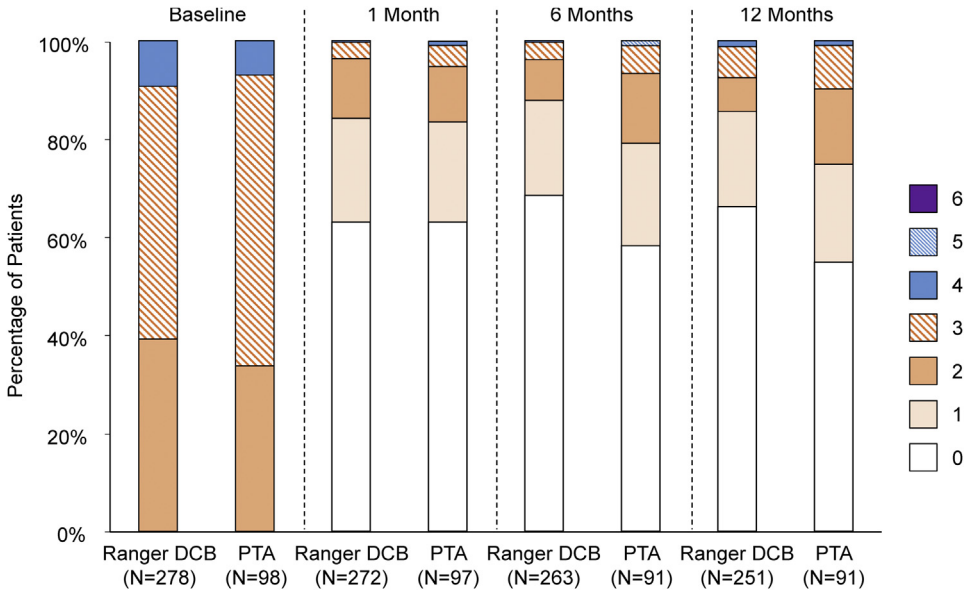
Evidence regarding mortality following treatment with paclitaxel-coated devices continues to accumulate. Longer-term mortality data for the class remains limited by the lack of pre-planned mortality endpoints, but updated mortality analyses from long-running randomized trials show no significant difference between paclitaxel-coated and PTA arms through 3 years (21,22) or 5 years (23,24), and recent real-world

FIGURE 2 **Kaplan-Meier Estimate of Freedom From Target Lesion Revascularization With Standard Errors Through 1 Year**



All target lesion revascularizations met the criteria for clinically driven. Abbreviations as in Figure 1.

FIGURE 3 Rutherford Category Distribution



Abbreviations as in Figure 1.

analyses suggest no excess risk versus uncoated devices (25–27), and a reduced mortality risk in some cases (27). Notably, death incidence did not differ significantly between patients treated with drug-coated versus uncoated devices in recently published analysis from the randomized SWEDEPAD (Swedish Drug-elution Trial in Peripheral Arterial Disease) study of 2,289 patients with complete vital status ascertainment through more than 2 years (28). An increased mortality risk was identified in an independent patient-level analyses of 8 randomized trials (29). The authors acknowledged several major limitations of their analysis, including questionable adequacy of the number of death events to evaluate an unplanned safety endpoint, a lack of comorbidity data, and residual 10% loss to follow-up after efforts to recover vital status data. The reported follow-up period for the RANGER II SFA study is only 1 year, but longer-term follow-up from ongoing studies such as this one that were not included in the aforementioned analyses will provide new independent information.

STUDY LIMITATIONS. Like many other studies of drug-coated balloons for the femoropopliteal segment, generalization of these trial results is limited by the mainly TASC (Trans-Atlantic Inter-Society Consensus) II A/B population represented and exclusion of longer lesions and patients with chronic renal disease. Non-Caucasian patient groups were generally under-represented, although Japanese patients comprised 27% of study enrollees. Excluding adjunctive therapies more cleanly demonstrates the therapeutic effect of DCB treatment, but predictions about the DCB effect in more challenging disease or with complementary treatments are limited. The 3:1 randomization scheme was accounted for in the primary endpoint analyses, but also gives each individual in the PTA arm greater weight in the baseline characteristic calculations and secondary analyses. The baseline distributions of calcification severity and occlusion prevalence are statistically imbalanced despite randomization. However, the primary patency rate for the RANGER II PTA arm was numerically greater than the PTA arms of other studies and the TLR rate was similar, suggesting that the baseline imbalance did not disproportionately disadvantage the PTA arm and thus produce an exaggerated treatment effect. Limitations associated with the short 1-year follow-up period will be mitigated with longer term follow-up planned through 5 years.

CONCLUSIONS

In the RANGER II SFA study, the low-dose Ranger DCB demonstrated significantly better effectiveness

than standard PTA through 1 year, with fewer reinterventions and a good safety profile.

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PERSPECTIVES

WHAT IS KNOWN? Paclitaxel-coated balloons have consistently demonstrated improved efficacy compared with uncoated PTA for femoropopliteal peripheral artery disease, but varied device coating characteristics may contribute to within-class performance.

WHAT IS NEW? Patients with chronic symptomatic lower limb ischemia who receive treatment with a low-dose DCB retained vessel patency and clinical improvement while undergoing fewer reinterventions than patients receiving non-drug-based treatment through 1 year.

WHAT IS NEXT? Additional research is needed to translate findings regarding low-dose paclitaxel-coated balloon treatment from controlled studies to real-world patient populations and typical practice conditions. Longer-term follow-up from ongoing studies will contribute to the risk evaluation of paclitaxel-containing peripheral devices.

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KEY WORDS drug-coated balloon, paclitaxel, peripheral arterial disease, superficial femoral artery, vascular patency

APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this paper.