New insights from Ranger DCB in challenging lesions and demographics

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Disclaimer

- IMPORTANT INFORMATION: These materials are intended to describe common clinical considerations and procedural steps for the on-label use of referenced technologies as well as current standards of care for certain conditions. Of course, patients and their medical circumstances vary, so the clinical considerations and procedural steps described may not be appropriate for every patient or case. As always, decisions surrounding patient care depend on the physician's professional judgment in light of all available information for the case at hand.
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- Results from case studies are not necessarily predictive of results in other cases. Results in other cases may vary.

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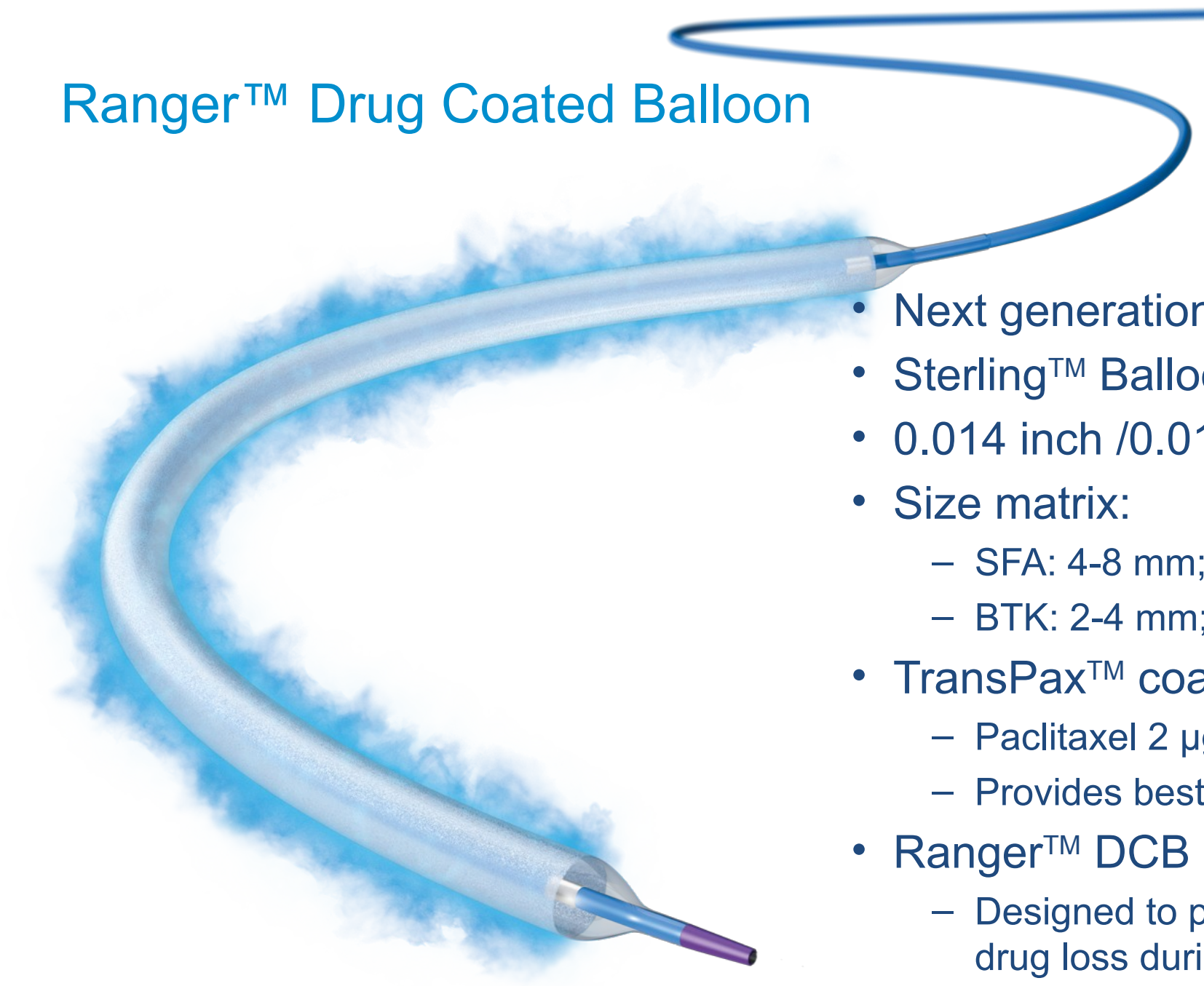
Disclosures

- Consultant: BD BARD, Philips, Medtronic, Bayer Healthcare, Cagent, Surmodics, Biotronik, iVascular, Boston Scientific, Abbot, Shockwave, Intact Vascular
- Speakers' Bureau - BD BARD, Philips, Medtronic, Bayer Healthcare, Cagent, Surmodics, Biotronik, iVascular, Boston Scientific, Abbot, Shockwave, Intact Vascular

RANGER II SFA Global Study Overview

Principal Investigators		Global: Prof. Thomas Zeller, MD United States: Ravish Sachar, MD, FACC		
Study Design		**RCT** (Ranger™ DCB vs Standard PTA) • 3:1 randomized • Single-blind • Superiority design for effectiveness	**Pharmacokinetics Sub-study** (Ranger DCB) • Single-arm	**Long Balloon Sub-study** (Ranger DCB) • Single-arm
Patients		**N=376** (Ranger DCB N=278 vs PTA N=98) • Symptomatic PAD (Rutherford 2-4) • Stenotic lesions of the femoropopliteal segment, **up to 180 mm**	**N=12**	**N=52** • Symptomatic PAD (Rutherford 2-4) • Stenotic lesions of the femoropopliteal segment, **up to 180 mm** • Occlusion up to 150 mm
Balloon Sizes	Diameter	4-8 mm		4-7 mm
	Length	30-100 mm		**120-200 mm**
Investigational Centers		67 study centers: United States, Japan, New Zealand, Europe, Canada	United States	7 study centers: Belgium, Austria, New Zealand

Ranger™ Drug Coated Balloon



- Next generation drug-coated balloon
- Sterling™ Balloon 0.018 inch platform
- 0.014 inch /0.018 inch guidewire compatible
- Size matrix:
  - SFA: 4-8 mm; 30-200 mm
  - BTK: 2-4 mm; up to 150 mm
- TransPax™ coating technology
  - Paclitaxel 2 µg/mm^2
  - Provides best in class coating integrity
- Ranger™ DCB Loading Tool
  - Designed to protect the drug coating and prevent drug loss during insertion

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RANGER II SFA
Pharmacokinetics Sub-Study

- All patients treated with Ranger DCB (N=12)
- Treated lesion length 154.2±92.8 mm
- Plasma paclitaxel less than the limit of quantification (<1 ng/mL):
  - 11 of 12 patients by 1 hour following DCB deployment and removal
  - all patients by 3 hours
- 1 death, non-cardiovascular, 79 days post-procedure

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Protocol required blood draws: baseline, 10 minutes, 30 minutes, 1, 3, 6, 24 or 48 hours, 7 days and 30 days after last Ranger DCB treatment and removal.

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RANGER II SFA RCT
1-Year Safety Data

- Primary safety endpoint met (non-inferiority P<0.0001)
- 12-month MAE-free rate

  94.1% (241/256) Ranger DCB vs **83.5% (76/91) PTA**; P=0.002
- Significantly lower MAE and TLR rates for Ranger DCB vs PTA

	Ranger DCB (N=256)	Standard PTA (N=91)	Difference [95% CI]	P-value
12-Month MAE	5.9% (15/256)	16.5% (15/91)	-10.6% [-18.8%, -2.5%]	0.002
All Causes of Death at 1 Month	0.4% (1/256)	0.0% (0/91)	0.4% [-0.4%, 1.2%]	>0.99
Target Limb Major Amputation	0.0% (0/256)	0.0% (0/91)	0.0% [NA, NA]	Undef
Clinically-Driven TLR	5.5% (14/256)	16.5% (15/91)	-11.0% [-19.1%, -2.9%]	0.001

PTA: Percutaneous transluminal angioplasty; DCB: Drug-coated balloon; MAE: major adverse events; TLR: target lesion revascularization; CI: confidence interval
MAEs were adjudicated by a Clinical Events Committee.

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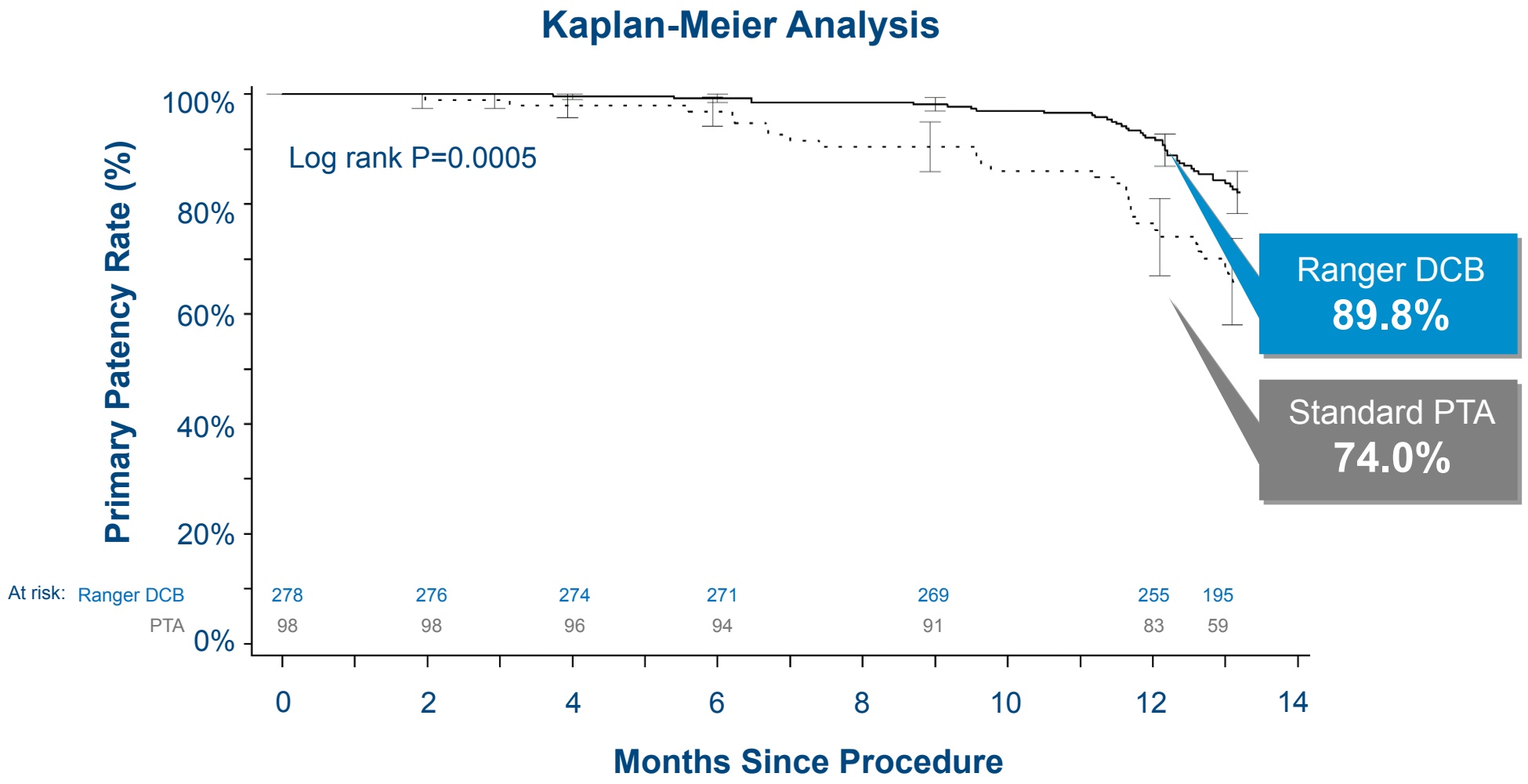
RANGER II SFA RCT
Primary Patency at 12 Months: Full Cohort



Error bars are SE.

PTA: Percutaneous transluminal angioplasty; DCB: Drug-coated balloon

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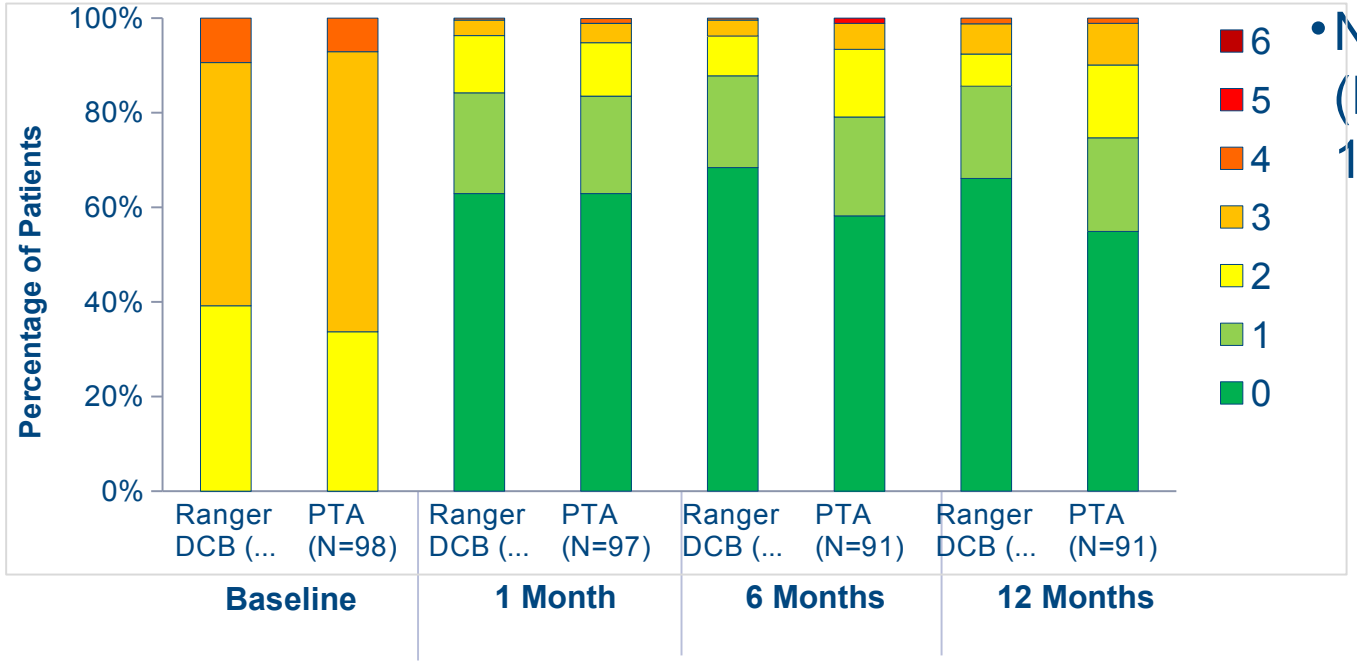
RANGER II SFA RCT
Clinical Outcomes at 12 Months

	Ranger DCB	Standard PTA	Difference	95%CI	P-value
Primary sustained clinical improvement[a]	**87.6%** (220/251)	**75.8%** (69/91)	11.8%	2.1%, 21.5%	0.0076

[a]Improvement in Rutherford classification of one or more categories as compared to baseline without TLR.



- No or minimal symptoms (Rutherford Category 0-1) at 12 months
  - 85.7% Ranger DCB
  - 74.7% PTA

PTA: Percutaneous transluminal angioplasty; DCB: Drug-coated balloon; TLF: total lesion revascularization

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Baseline Characteristics I Ranger DCB
Women & Men

	Women (n=105)	Men (n=173)
Demographics & Clinical History		
Age	70.6±9.7	70.7±9.3
Smoking	71.4%	93.6%
Medically-Treated Diabetes	40.0%	39.9%
Hypertension	89.5%	90.8%
Coronary Artery Disease	41.7%	50.9%
TASC II Type (Site-Reported)		
A	54.3%	45.1%
B	20.0%	39.3%
C	11.4%	9.2%
D	1.0%	1.7%
Core Lab Measurements		
Lesion Length (mm)	75.8±53.2	86.6±45.7
RVD (mm)	4.7±0.8	5.4±0.8
MLD (mm)	1.3±0.8	1.4±1.0
% Diameter Stenosis	73.8±15.7	73.7±17.6

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Safety I Ranger DCB

Women & Men

- 12-month MAE-free rate:

  93.7% (89/95) Women & 94.4% (152/161) Men

- All MAE were clinically-driven TLRs. Similar rates for women and men treated with Ranger DCB

	Women (n=105)	Men (n=173)
12-Month MAE	6.3% (6/95)	5.6% (9/161)
All-Cause Death at 1 Month	0.0% (0/95)	0.6% (1/161)
Target Limb Major Amputation	0.0% (0/95)	0.0% (0/161)
Target Lesion Revascularization	6.3% (6/95)	5.0% (8/161)
Clinically-Driven	6.3% (6/95)	5.0% (8/161)

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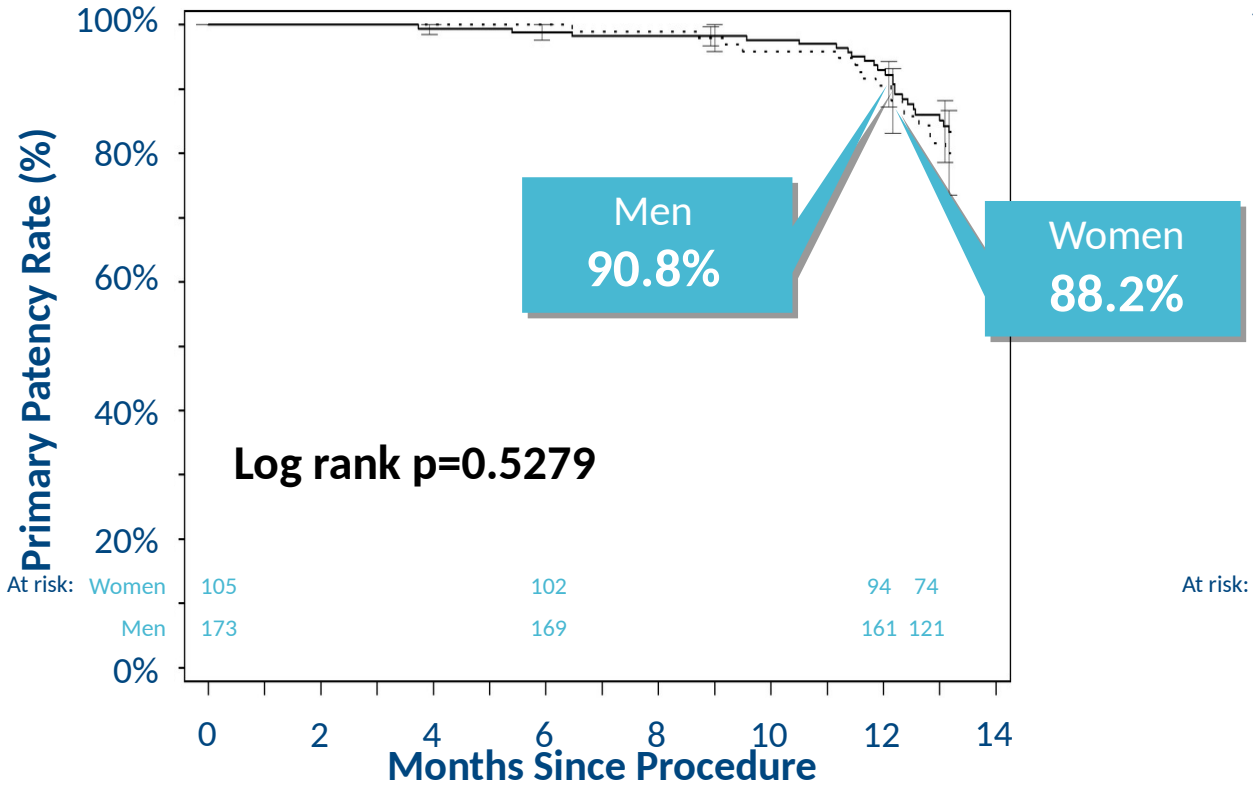
MAEs were adjudicated by a Clinical Events Committee.

Effectiveness I Primary Patency

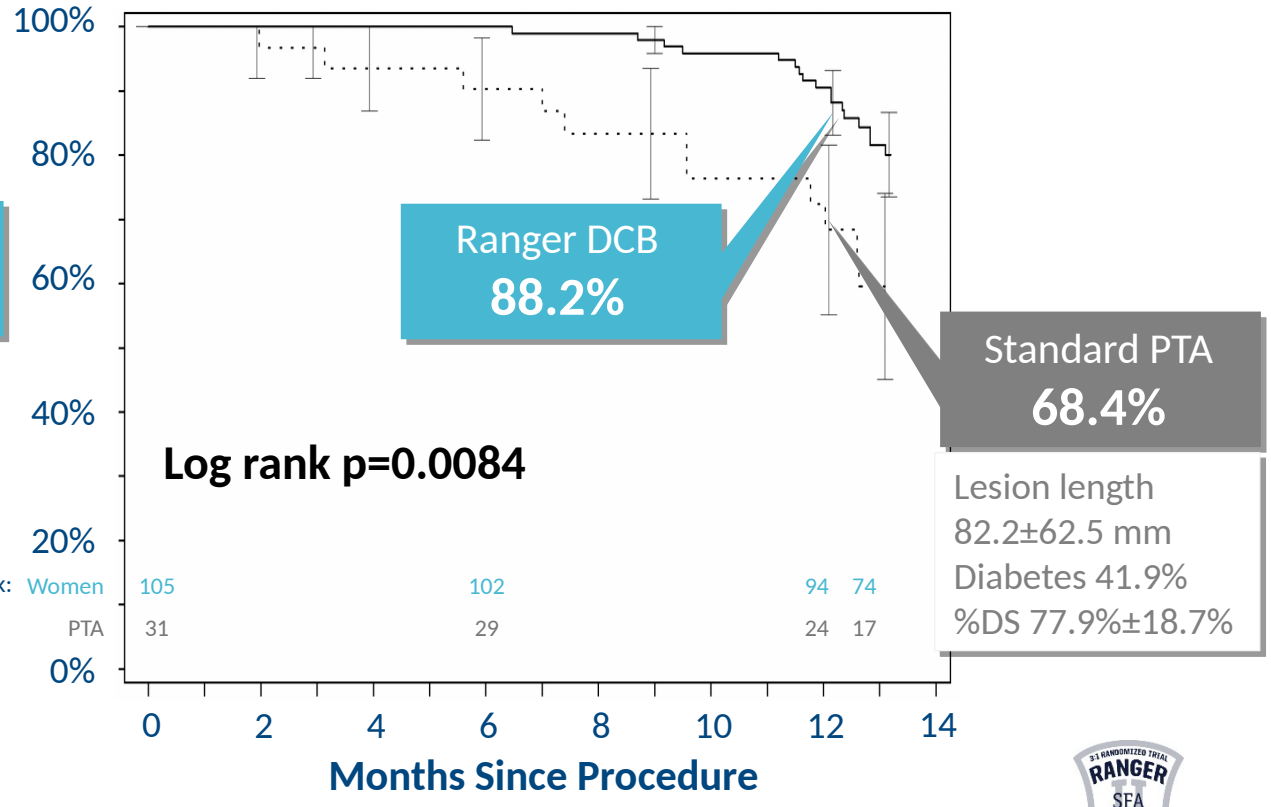
Ranger DCB
Women vs Men

Among patients treated with Ranger DCB, **no difference for women vs men**



Women
Ranger DCB vs PTA

Among women, significantly better primary patency for patients treated with Ranger DCB vs Standard PTA



Kaplan-Meier estimates with standard errors.
Primary patency KM estimate utilizing time-to-event of TLR up to 365 days and duplex ultrasound data at 12 months.

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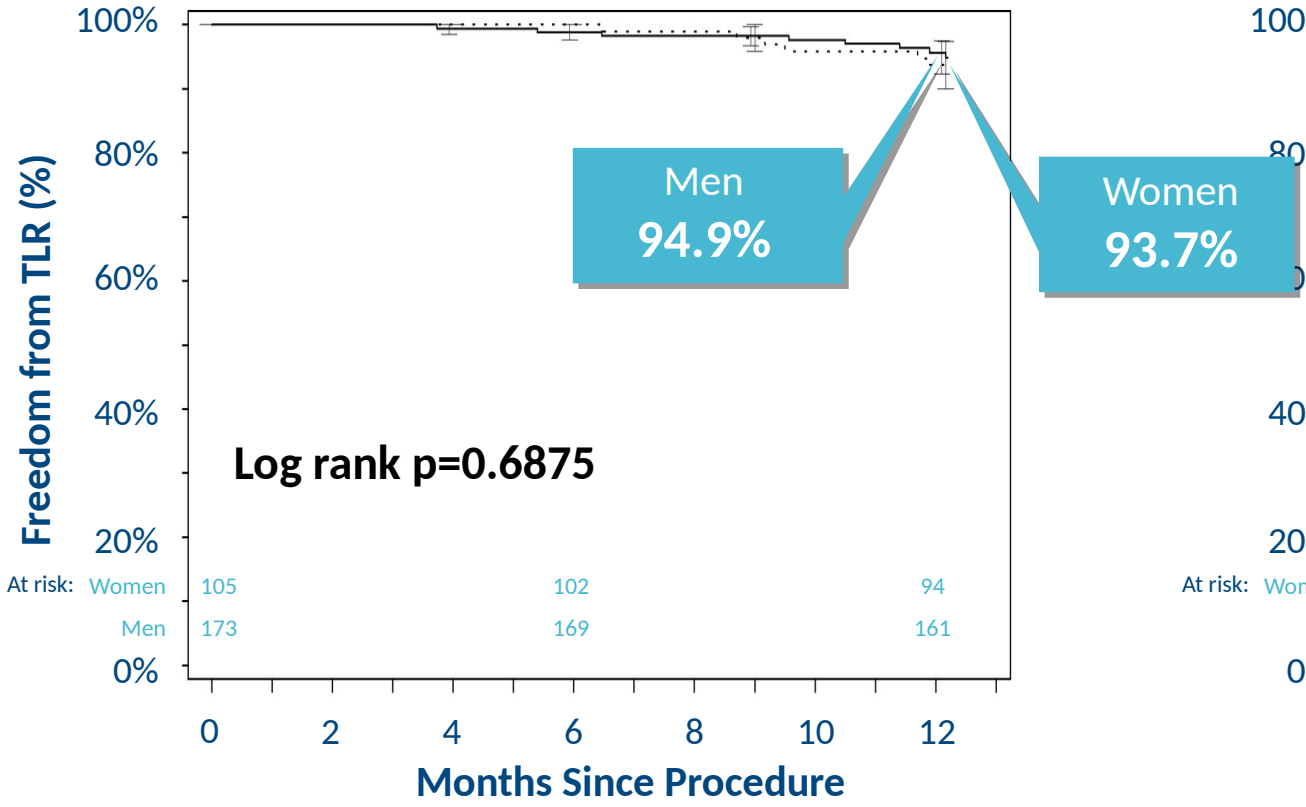
Freedom from TLR

Ranger DCB
Women vs Men

Among patients treated with Ranger DCB, no difference for women vs men



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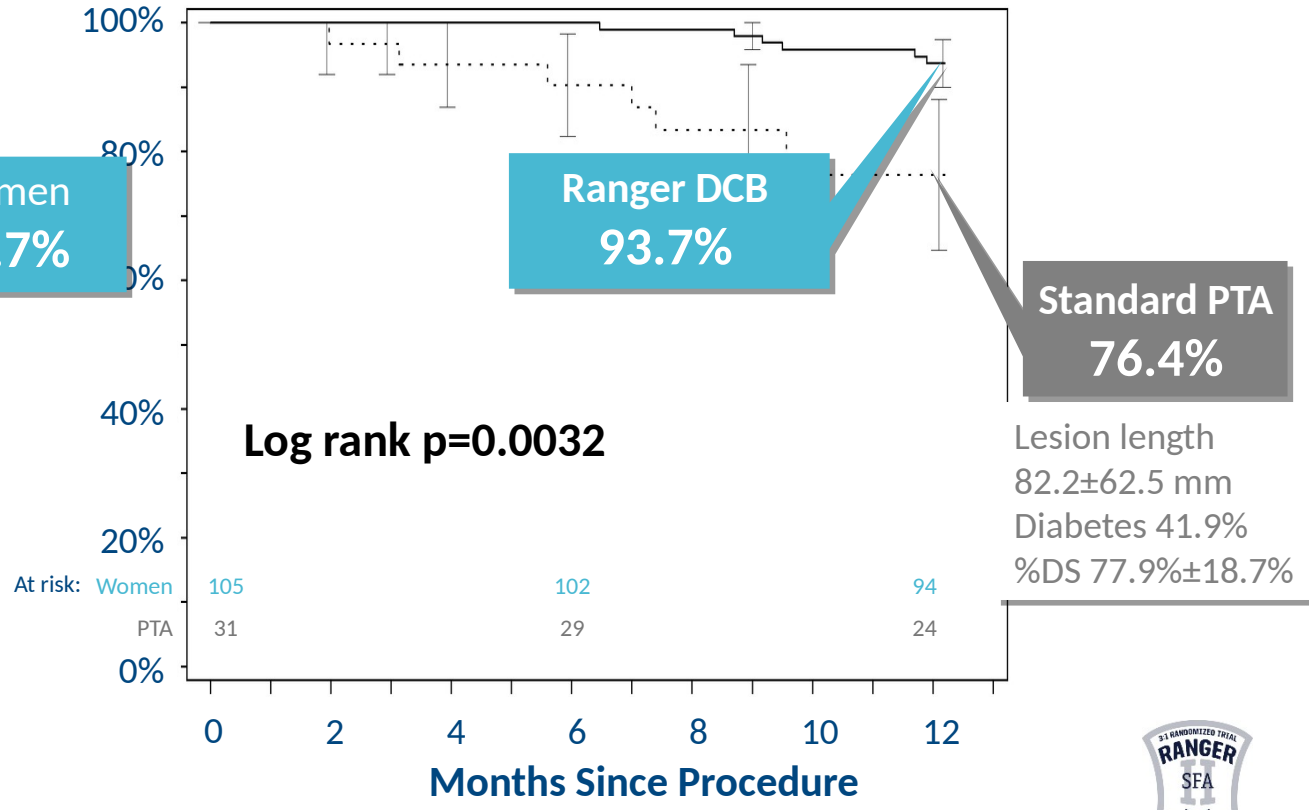

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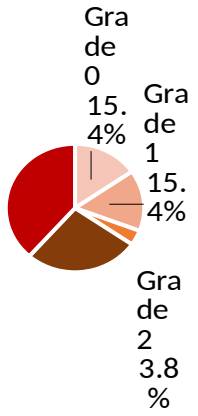
Baseline Characteristics | Long Balloon Sub-study

Demographics and Clinical History	Ranger DCB (N=52)
Age (Year)	70.3±9.9
Female	26.9%
Race/Ethnicity	
Caucasian	98.1%
Black, or African heritage	1.9%
Smoking History	
Current	46.2%
Previous	44.2%
Diabetes Mellitus	32.7%
Hyperlipidemia	82.4%
Hypertension	71.2%
Chronic Obstructive Pulmonary Disease	18.0%
Coronary Artery Disease	26.9%
History of Cerebrovascular Accident	3.8%
History of Renal Insufficiency	11.5%

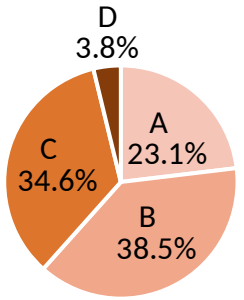
Lesion Characteristics (Core Lab)	Ranger DCB (N=52)
Lesion Length (mm)	130.8±47.2
Lesion Location	
proximal SFA	30.8%
mid SFA	42.3%
distal SFA	26.9%
% Diameter Stenosis	84.2±15.1
Occlusion	38.5%

- Bare metal stent bail out 13.5% (7/52)

Calcification (PACSS)



TASC II Type



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Safety | Long Balloon Sub-study

- 12-Month MAE-free rate: 94.0% (47/50)
- All MAE were CD-TLR
- 12-month mortality 5.8% (3/52)

	Ranger DCB (N=52)
12-Month MAE	6.0% (3/50)
All-Cause Death at 1 Month	0.0% (0/50)
Target Limb Major Amputation	0.0% (0/50)
Target Lesion Revascularization	6.0% (3/50)
Clinically-Driven	6.0% (3/50)

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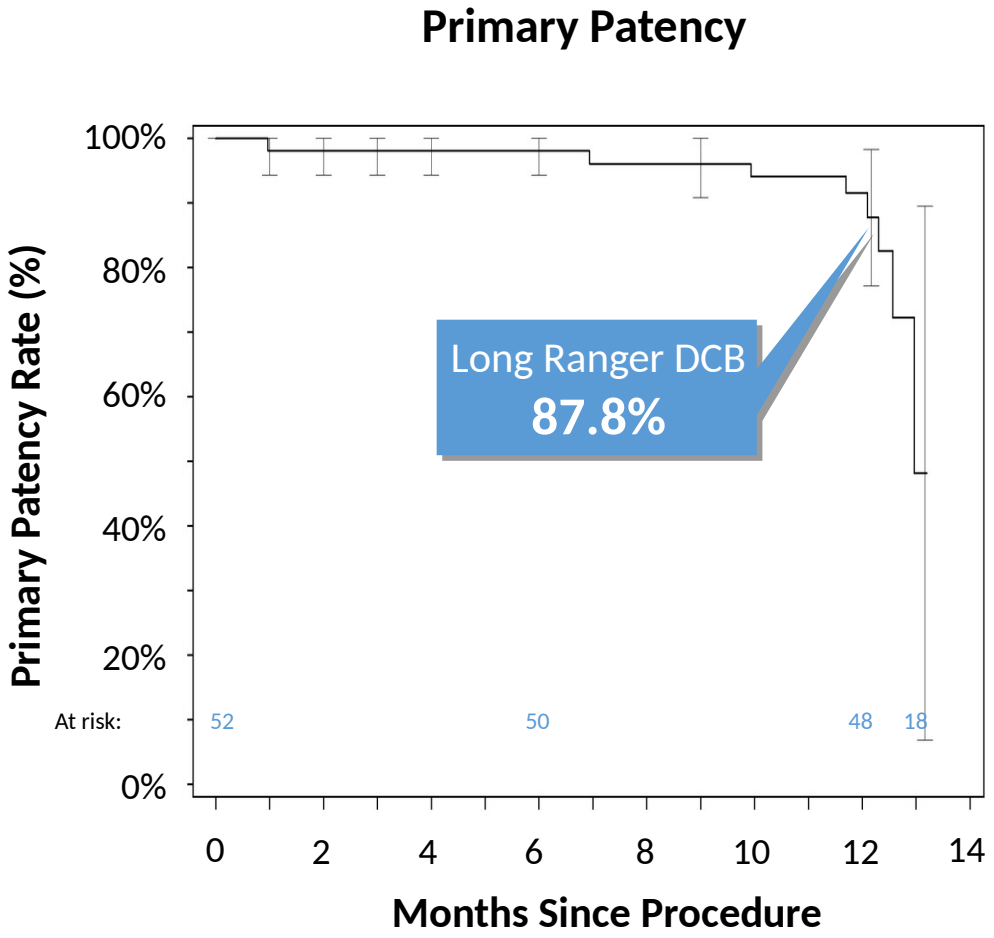
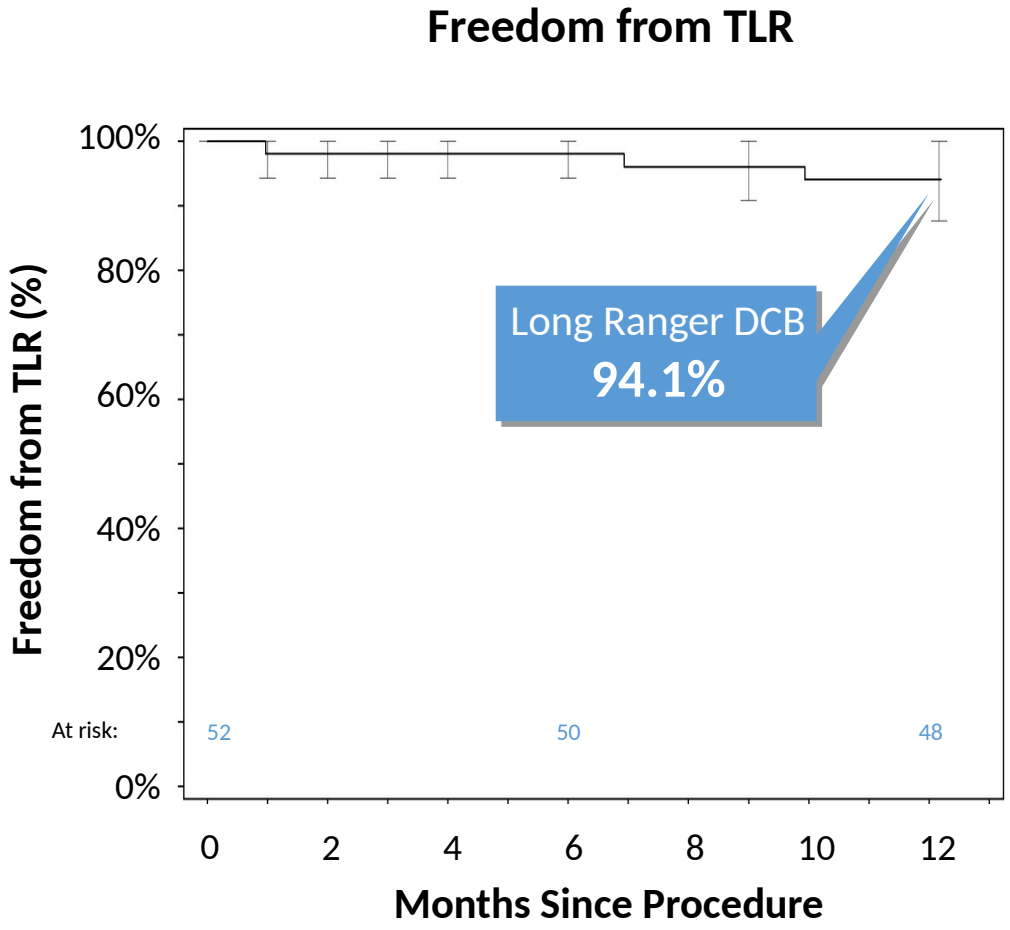
Effectiveness | Long Balloon Sub-study





Kaplan-Meier estimates with standard errors.
Primary patency KM estimate utilizing time-to-event of TLR up to 365 days and duplex ultrasound data at 12 months.

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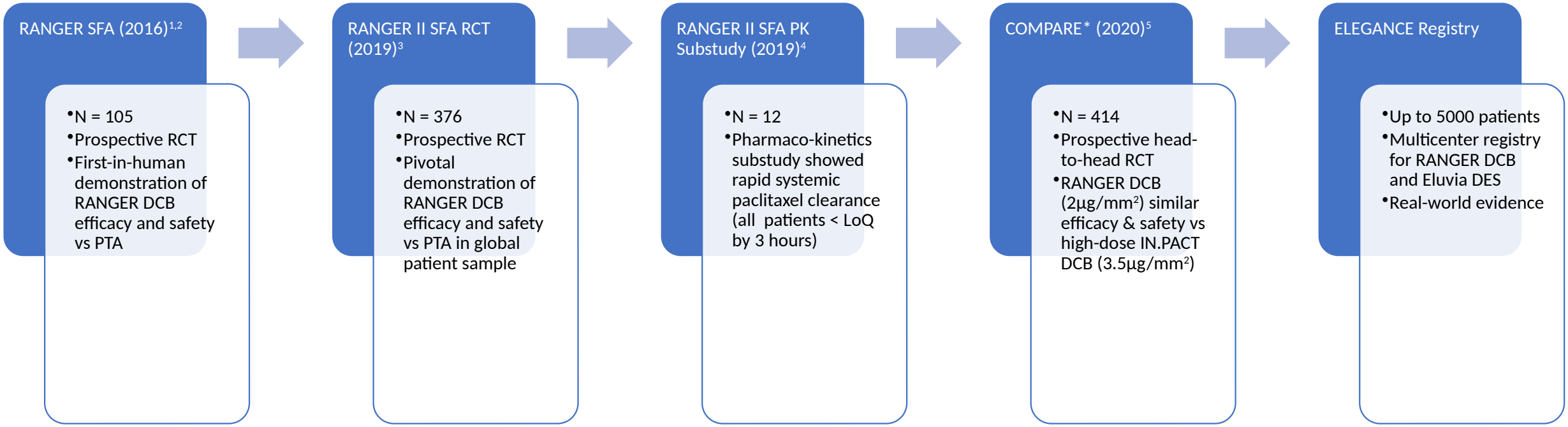
RANGER DCB Evidence Progression

Key Studies



1. Bausback Y, et al. J Endovasc Ther. 2017;24(4):459-467.
2. Steiner S, et al. JACC Cardiovasc Interv. 2018;11(10):934-941.
3. Brodmann M, LINC 2020
4. Sachar R, VIVA 2019
5. Steiner S, et al. Eur Heart J. 2020 Jan 28. pii: ehaa049.

DCB, drug-coated balloon; LoQ, limit of quantification; PK, pharmacokinetics; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial

*This investigator-sponsored study is supported by grant funding from Boston Scientific. Boston Scientific is not responsible for the collection, analysis or reporting of the study which remains the sole responsibility of the investigators. Information for the use in countries with applicable product registrations.

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Conclusions

- RANGER II SFA results demonstrate consistent efficacy and safety results for patients treated with Ranger DCBs in standard or long lengths
- Low-dose Ranger DCB demonstrated superior effectiveness vs standard PTA through 1 year in the RANGER II SFA RCT
- Women and men showed similar primary patency and freedom from TLR benefit through 1 year following treatment with Ranger DCB in the RCT
- Safety and efficacy results from the Long Balloon Sub-study (balloon lengths up to 100 mm) are similar to the previously-reported results for the overall RANGER II SFA RCT

	RCT (N=376)[1]	Women (n=136)[2]	Long Balloons (N=52)[2]
CD-TLR	**5.5%** Ranger DCB vs 16.5% PTA (P=0.001)	**6.3%** Ranger DCB vs 25.0% PTA (P=0.0100)	**6.0%**
Primary Patency (KM)	**89.8%** Ranger DCB vs 79.0% PTA (log-rank P=0.0005)	**88.2%** Ranger DCB vs 68.4% PTA (log-rank P=0.0084)	**87.8%**
Lesion Length (mm)	**82.5**±48.9 (DCB arm)	**75.8**±53.2 (DCB arm)	**130.8**±47.2

1. Brodmann M, LINC 2020
2. Keirse K, LINC 2021

Brief Summary Statement (BSS)
Overview
Product Ranger Drug Coated Balloon – eIFU 50589598

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete “Instructions for Use” for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator’s Instructions.

WARNING
A signal for increased risk of late mortality has been identified following the use of paclitaxelcoated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. See Section 8.1 (in the eIFU) for further information.

INTENDED USE / INDICATIONS FOR USE
The Ranger Drug Coated Balloon (DCB) is indicated for percutaneous transluminal angioplasty (PTA) of de novo or restenotic lesions up to 180 mm in length located in native superficial femoral and proximal popliteal arteries (SFA/PPA) with reference vessel diameters of 4 mm to 7 mm.

CONTRAINDICATIONS
Use of the Ranger DCB is contraindicated in:
• Patients with known hypersensitivity to paclitaxel (or structurally-related compounds).
• Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy.
• Women who are breastfeeding, pregnant, or men intending to father children.
• Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.
• Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries.

WARNINGS
• To reduce the potential for vessel damage, the inflated diameter of the balloon should approximate the diameter of the vessel segment to be treated. The inflated length of the balloon (shoulder to shoulder) may exceed the length of the lesion/stenosis by approximately 10 mm on either side within the targeted artery.
• The safety of using multiple Ranger DCBs with a total drug dosage exceeding 9266 µg of Paclitaxel in a patient has not been studied.
• Using a drug-eluting stent in conjunction with Ranger DCB at the same treatment site has not been studied.

PRECAUTIONS
• The balloon catheter should be used only by physicians trained in the performance of percutaneous transluminal angioplasty.
• The balloon catheter should be used with caution for procedures involving calcified lesions due to the abrasive nature of these lesions.
• The balloon catheter is not intended for injection of contrast medium.
• Full arterial wall apposition of the Ranger DCB is necessary for proper drug transfer to the vessel.
• Do not touch, wipe, bend, or squeeze the balloon. Do not allow it to contact any liquids including organic solvents such as alcohol or detergents prior to insertion. Damage to the balloon coating or premature release of the drug may occur.
• This product should not be used in patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy.
• If treating a long lesion (longer than the maximum balloon length available), each individual segment should be treated only once with a drug-coated balloon. Treat each segment with a new balloon and minimize overlapping of treated segments.

Pregnancy / Lactation
This product has not been tested in pregnant or breastfeeding women or in men intending to father children; effects on the developing fetus have not been studied and the risks and reproductive effects remain unknown.
It is not recommended that the Ranger DCB be used in women attempting to conceive, or who are pregnant.
Prior to use, careful consideration should be given to the continuation of breastfeeding, taking into account the importance of the procedure to the mother. It is not known whether paclitaxel is distributed in human milk. In lactating rats, milk concentrations appeared to be higher than maternal plasma levels and declined in parallel with the maternal levels. Mothers should be advised of the potential for serious adverse reactions to paclitaxel in nursing infants.

Drug Information
The mechanism of action by which paclitaxel reduces or reverses neointima formation and proliferation, leading to restenosis, as demonstrated in clinical studies has not been established. It is known that paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

Drug Interaction
Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated. Drug interactions of systemic chemotherapeutic levels of paclitaxel with possible concomitant medications are outlined in the labeling for finished pharmaceuticals containing paclitaxel, such as TAXOL™.

Carcinogenicity, Genotoxicity, and Reproductive Toxicology
No long-term studies in animals have been published in peer-reviewed literature to evaluate the carcinogenic potential of paclitaxel. Paclitaxel interacts with microtubules; this is the major mechanism by which it inhibits cell growth. One consequence is the loss of whole chromosomes via interactions with spindle microtubules during cell division. As such, paclitaxel is defined as an aneugen (agent causing an alteration in chromosome number). This indirect action is consistent with positive responses in in vitro and in vivo micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT. Paclitaxel administered via IV prior to and during mating produced impairment of fertility in male and female rats at doses > 1 mg/kg. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day caused embryo- and fetotoxicity. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day; teratogenic potential could not be assessed at higher doses due to extensive fetal mortality. For comparison, the worst-case dose of paclitaxel delivered by the Ranger DCB (assuming maximum size and number of balloons used in a lesion) is 9266 µg, which is approximately 6 and 19 times less than the dose that saw effects in rats and rabbits, respectively, when normalizing to body weight.

Pre and Post Procedure Antiplatelet Therapy
It is strongly advised that the treating physician follow the Inter-Society Consensus (TASC II) Guidelines recommendations (or other applicable country guidelines) for antiplatelet therapy pre- and postprocedure.

Brief Summary Cont.
Adverse Events
Potential adverse events include, but are not limited to, the following:
• Allergic reaction (device, contrast medium, medications)
• Arteriovenous fistula
• Death
• Hematoma
• Hemorrhage/Bleeding
• Hypotension/Hypertension
• Infection/Sepsis
• Pseudoaneurysm
• Thromboembolic episodes
• Vascular thrombosis
• Vessel injury (e.g., dissection, perforation, rupture)
• Vessel occlusion
• Vessel spasm
Potential adverse events not captured above that may be unique to the paclitaxel drug coating:
• Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or coating or its individual components
• Alopecia
• Anemia
• Blood product transfusion
• Gastrointestinal symptoms
• Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
• Hepatic enzyme changes
• Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
• Myalgia/Arthralgia
• Peripheral neuropathy
Apart from hypersensitivity reactions (allergic/immunologic reactions), the likelihood of paclitaxel related adverse events is low, due to the low exposure.
There may be other potential adverse events that are unforeseen at this time.