New Insights from COMPARE 2-year Low-Dose vs High-Dose DCB

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Disclosure

I have the following potential conflicts of interest to report:

- Consulting: Bayer
- Research funding: C.R. Bard

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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COMPARE RCT Study Objective

Study aim	To compare **high-dose vs. Low-dose paclitaxel-coated balloons** for the treatment of high grade stenotic or occluded femoropopliteal lesions
Patient population	Patients with Rutherford class 2-4
Principal investigator	Dierk Scheinert, MD University of Leipzig
Sites	German multicenter trial, 15 sites

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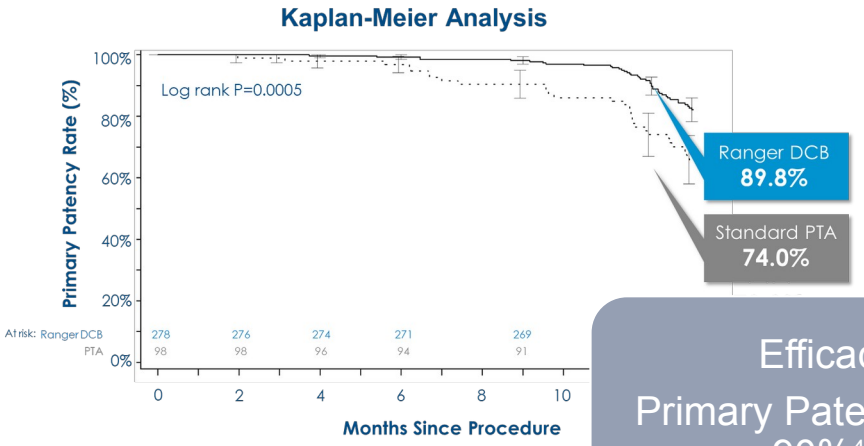
COMPARE RCT Study Devices

	IN.PACT Admiral Medtronic	Ranger™ Boston Scientific
Product Image		
Paclitaxel Dose	3.5 µg/mm^2 (“high dose”)	2 µg/mm^2 (“low dose”)
Coating Technology	FreePac™ hydrophilic coating (excipient: urea)	TransPax coating (excipient: Citrate ester)
Guidewire Compatibility	0.035 OTW	0.14/0.18
Matrix	SFA: 4-7 mm; 40-150 mm	SFA: 4-8 mm; 30-200 mm BTK: 2-4 mm; up to 150 mm
CE Mark	✓	✓
FDA Approval	✓	✓

SFA: superficial femoral artery; BTK: below-the-knee

Endovascular Today Device Guide. https://evtoday.com/device-guide/. BSC Data on file.

Efficient drug transfer with RANGER DCB TransPax Coating



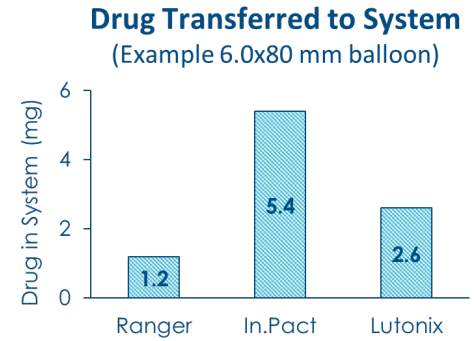
Dose Density (2 µg/mm²)

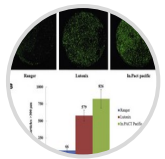
Balloon Length	Ranger (6mm) PTX µg	In.Pact (6mm) PTX µg	Ratio
40	1467	3170	0.46
60	2200	4489	0.49
80	3108	5809	0.54
120	4809	8448	0.57

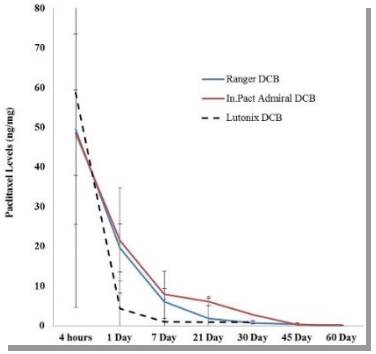
Efficacy

Primary Patency near 90%[4,5]

Drug Loss (Bench model)[1]




Ranger



Systemic Circulation (RANGER II PK Substudy)[3]

Arterial Tissue Levels (swine model)[2]

1. Data on File Boston Scientific. 2. Gongora CA, et al. JACC Cardiovasc Interv. 2015;8(8):1115-1123. 3. Sachar R, VIVA 2019. 4. Brodmann M, LINC 2020. 5. Steiner S, et al. Eur Heart J. 2020;ehaa049. doi:10.1093/eurheartj/ehaa049. Ranger DCB is an investigational device and not available for sale in the US. Preclinical results may not necessarily be indicative of clinical outcomes.

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COMPARE RCT Study Design and Methods

Study Design	➢ Investigator-initiated, prospective, multicenter, **non-inferiority** trial ➢ 414 patients undergoing 1:1 randomization ➢ Stratification according to lesion length ➢ Independent monitoring; 100% source data verification ➢ Independent corelab for angio and duplex ➢ Clinical events committee
Funding	➢ Study sponsor: University of Leipzig ➢ Funding through a research grant from Boston Scientific ➢ Funding source not involved in collecting, monitoring and analysing study data
Follow-up	➢ In-house visits: 6, 12, **24 months (efficacy and safety)** ➢ Telephone calls: 1 month, 36, 48, 60 months (safety)

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Key baseline characteristics

		Low dose DCB (n=207)	High dose DCB (n=207)	P value
Demographics	Age (years)	68.2 ± 10.0	68.4 ± 9.3	0.79
	Female gender	79 (38.2)	75 (36.2)	0.68
	Rutherford class (RC) ≥ 3	184 (88.9)	176 (85)	0.56
	Diabetes mellitus	63 (30.6)	76 (36.9)	0.18
	Previous/current smoking	160 (77.3)	155 (74.9)	0.63
Lesion	Lesion length (mm)	123.9±97.8	128.3±97.3	0.65
	Total occlusions	84 (40.6)	89 (43)	0.62
	Calcification* PACSS 3-4	105 (50.5)	117 (57.1)	0.80
	0-1 run off vessels	75 (38.5)	71 (36.6)	0.89
Procedural	Total paclitaxel dose (µg)	6971±4026	13035±7483	<0.0001
	Bail-out stenting	62 (30.0)	53 (25.6)	0.32
	Type E-F Dissection	4 (2.0)	2 (1)	0.61
	Diameter stenosis pp (%)	26.4±12.5	26.1±12.5	0.8
	Residual stenosis ≥ 30%	74 (35.8)	81 (39.1)	0.48

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Data are given as mean±std or number (%).

Primary endpoint analysis at 12 months

Efficacy: Primary patency

DCB			
Low dose	High dose	Δ (two-sided 90% lower bound)	$P_{non\text{-}inferiority}$
83% (156/188)	81.5% (141/173)	1.5% (-5.2%)	<0.01

Non-inferiority met

Safety: Freedom from MAE

DCB			
Low dose	High dose	Δ (two-sided 90% lower bound)	$P_{non\text{-}inferiority}$
91% (182/200)	92.6% (175/189)	-1.6% (-6.5%)	<0.01

Non-inferiority met

Steiner S et al. Eur Heart J 2020;41(27):2541-2552

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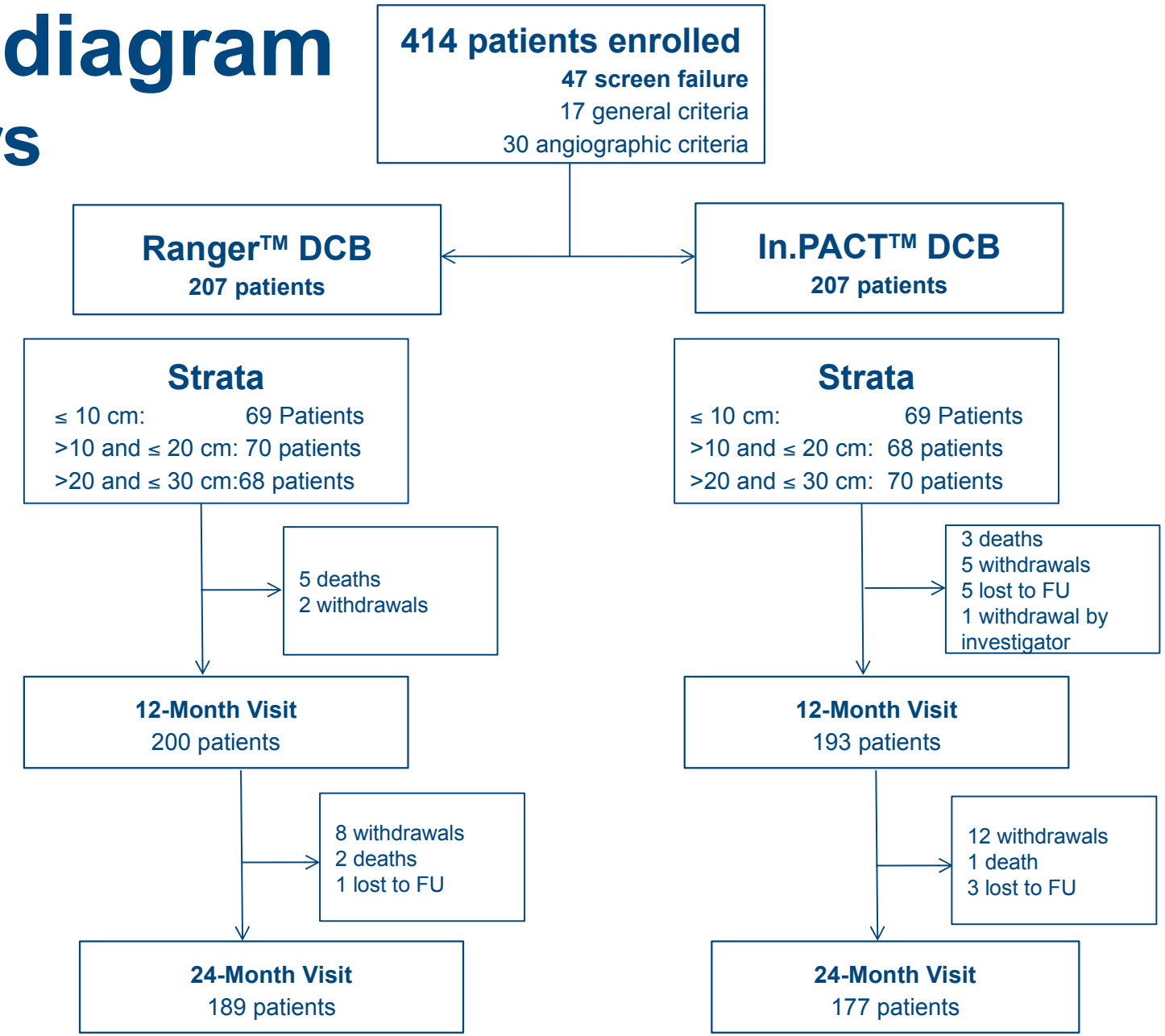
Patient flow diagram through 2 years



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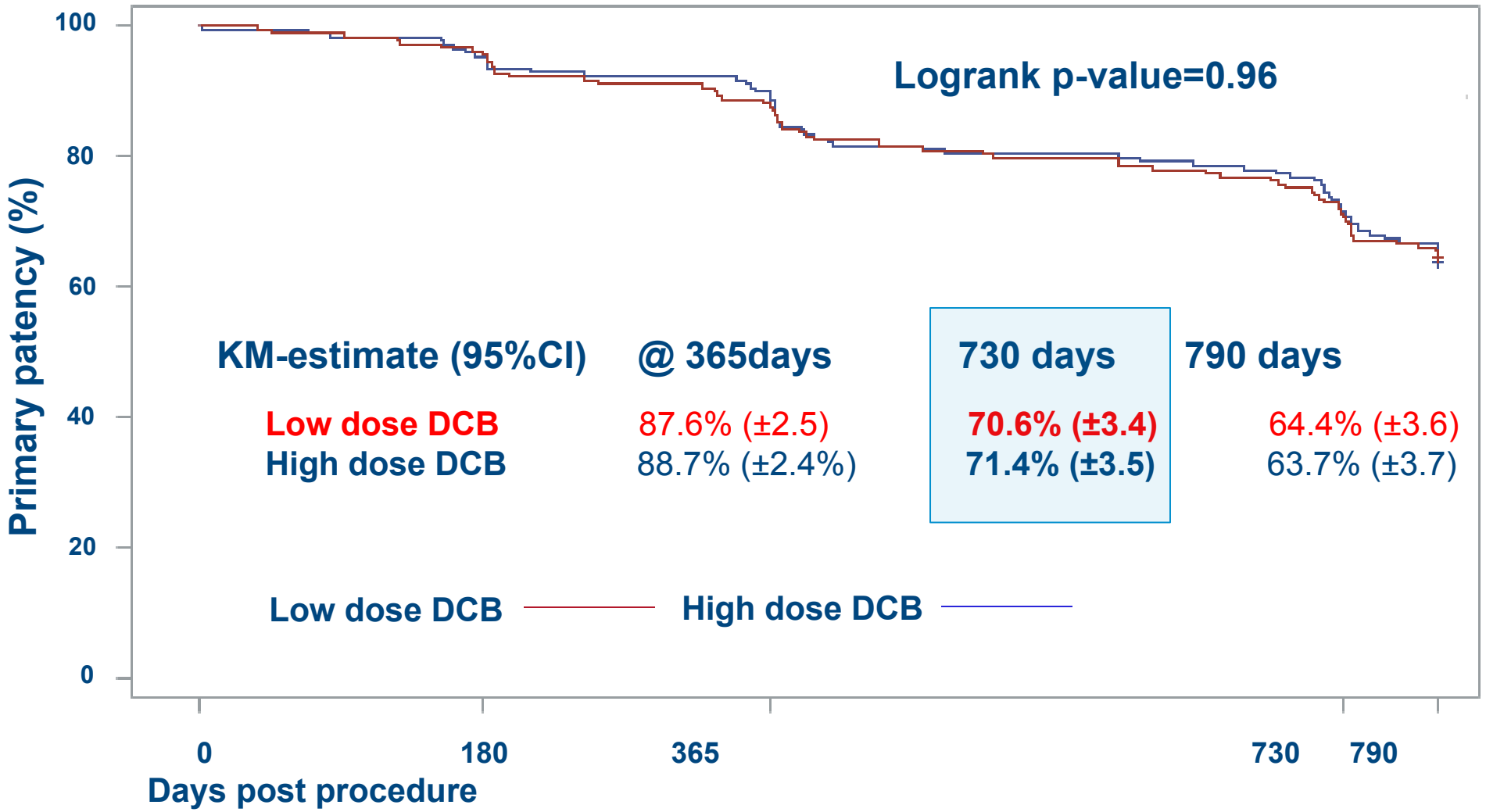
Primary patency through 790 days



Patients without an event at 790 days of follow-up or later were censored at 790 days.

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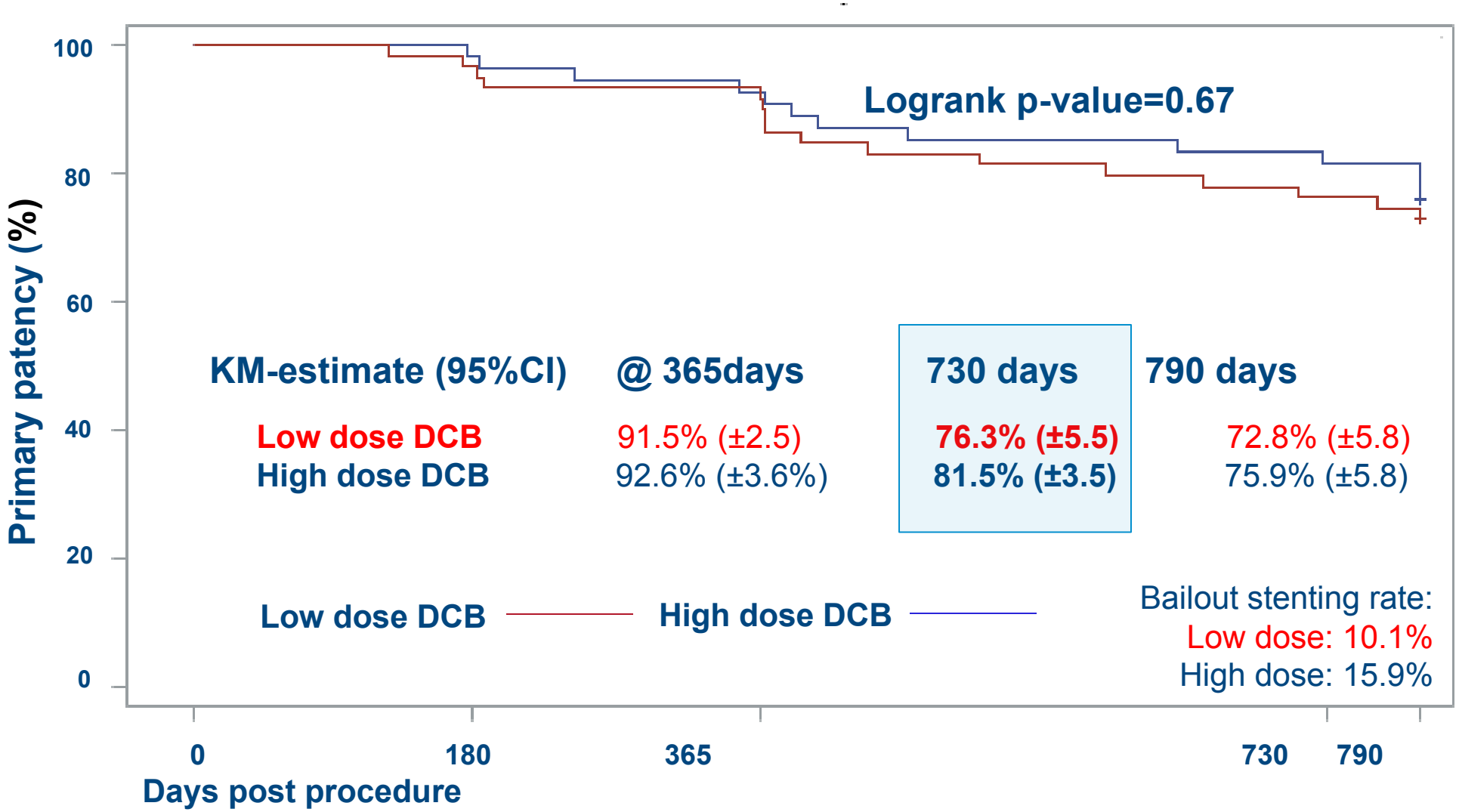
Primary patency – short lesions ≤10cm



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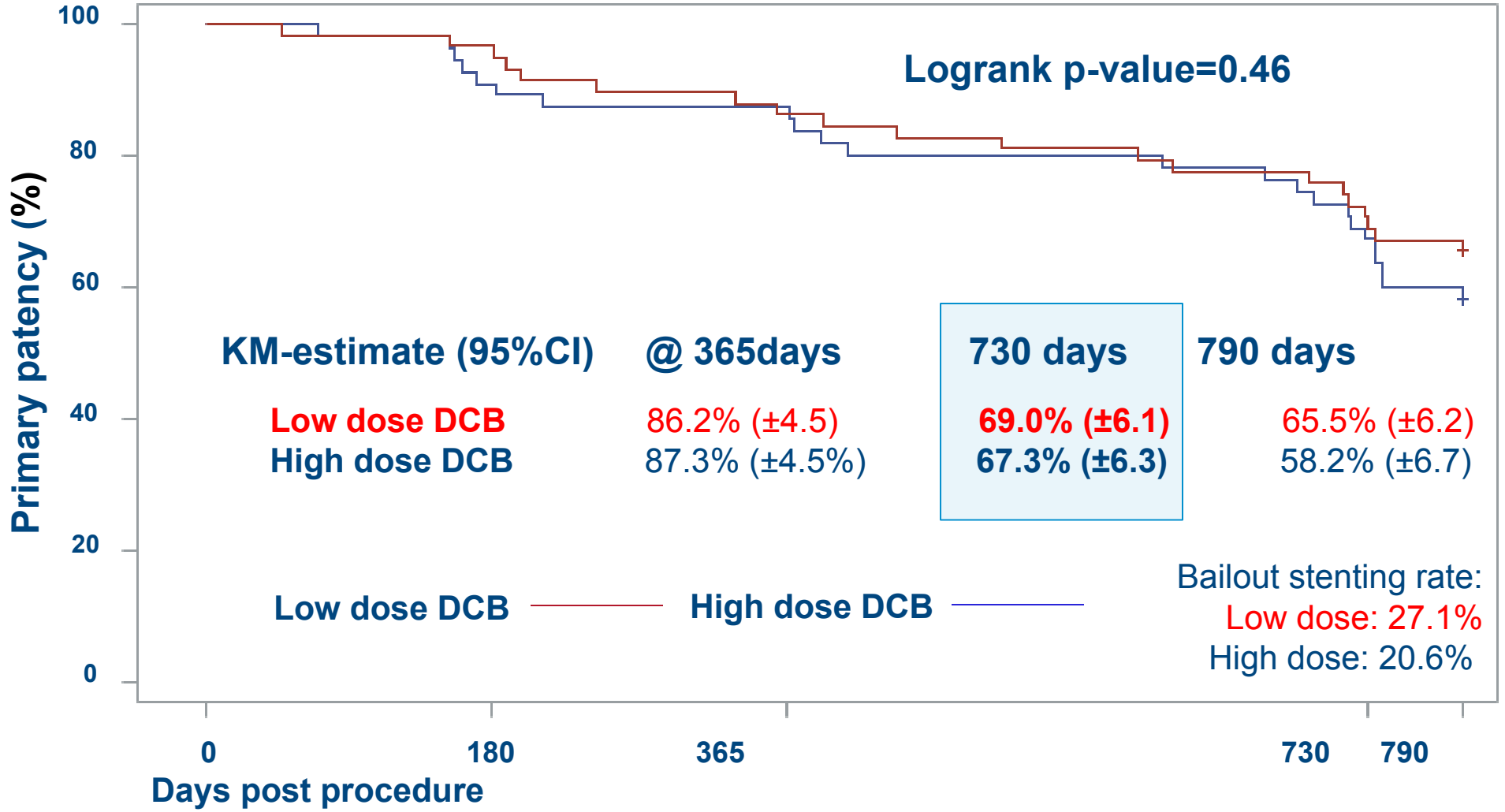
Primary patency – middle lesions >10cm - ≤20cm



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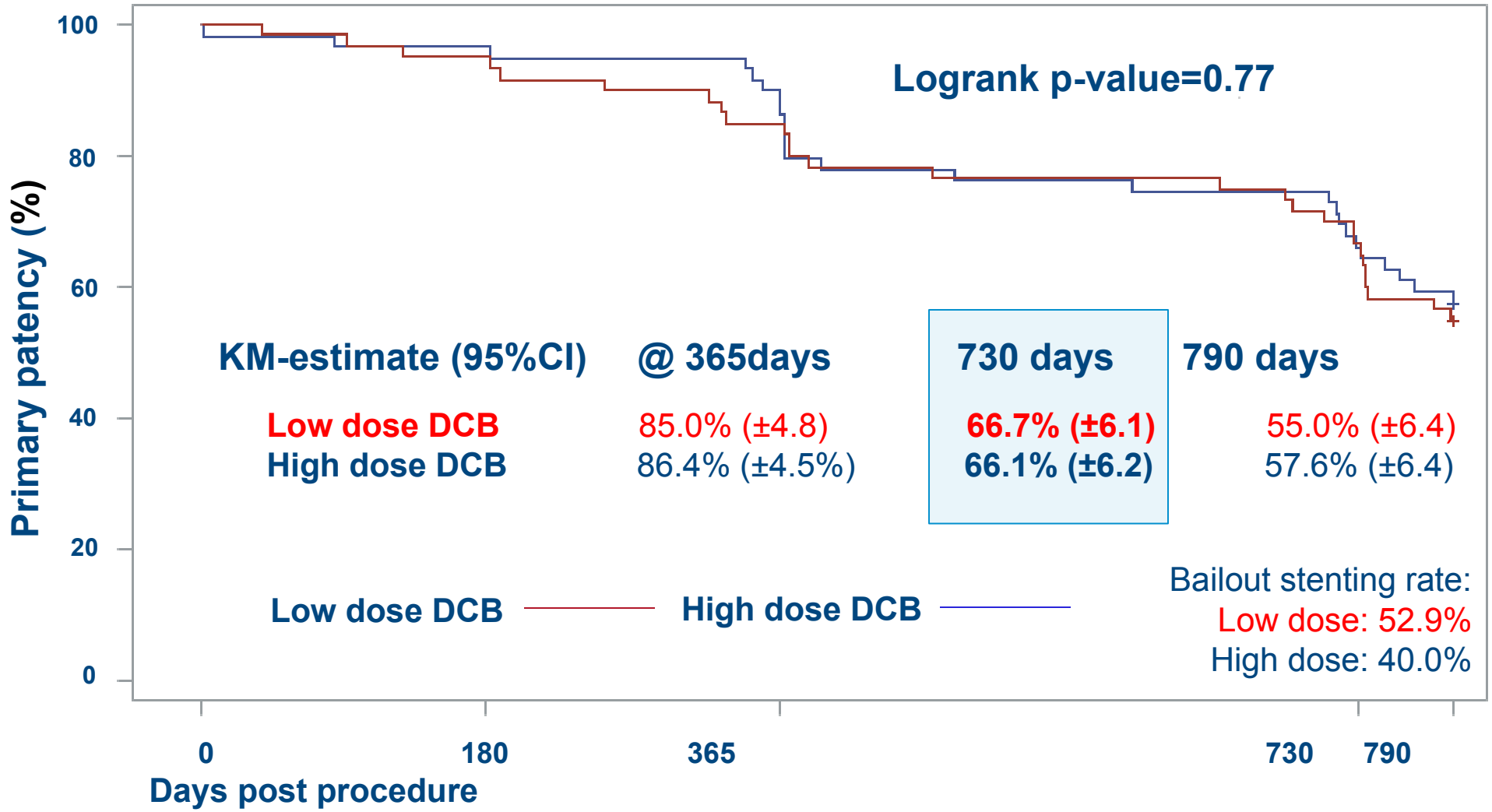
Primary patency – long lesions >20cm - ≤30cm



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Key outcomes through 790 days

	Low dose DCB (n=207)	High dose DCB (n=207)	P value§
All-cause mortality	3.6% (7/196)	2.2% (4/181)	0.6
Device or procedure-related death	0	0	1.0
Major amputation	0% (0/189)	0.6% (1/177)	1.0
Clinically driven TLR	17.3% (33/191)	13.0 % (23/177)	0.3
All TLR*	17.8% (34/191)	13.0 % (23/177)	0.3
Primary sustained clinical improvement†	69.5% (121/174)	74.3% (124/167)	0.4
Haemodynamic improvement‡	69.2% (117/169)	67.3% (107/169)	0.5

Values are percentage (n/N). The numerator is the number of subjects with events prior to the close of the visit window.
The denominator includes subjects with events or those without events having follow-up on or past the opening of the visit window.
*Includes clinically-driven TLR and duplex-driven/incidental TLR.
† Defined as improvement in Rutherford classification by one or more categories compared with baseline, without TRL.
‡ Defined as an increase in the ankle-brachial index by ≥0·10 compared with baseline or to an ankle-brachial index ≥0·90, without TLR.
§ P-values based on Fisher's-exact test.

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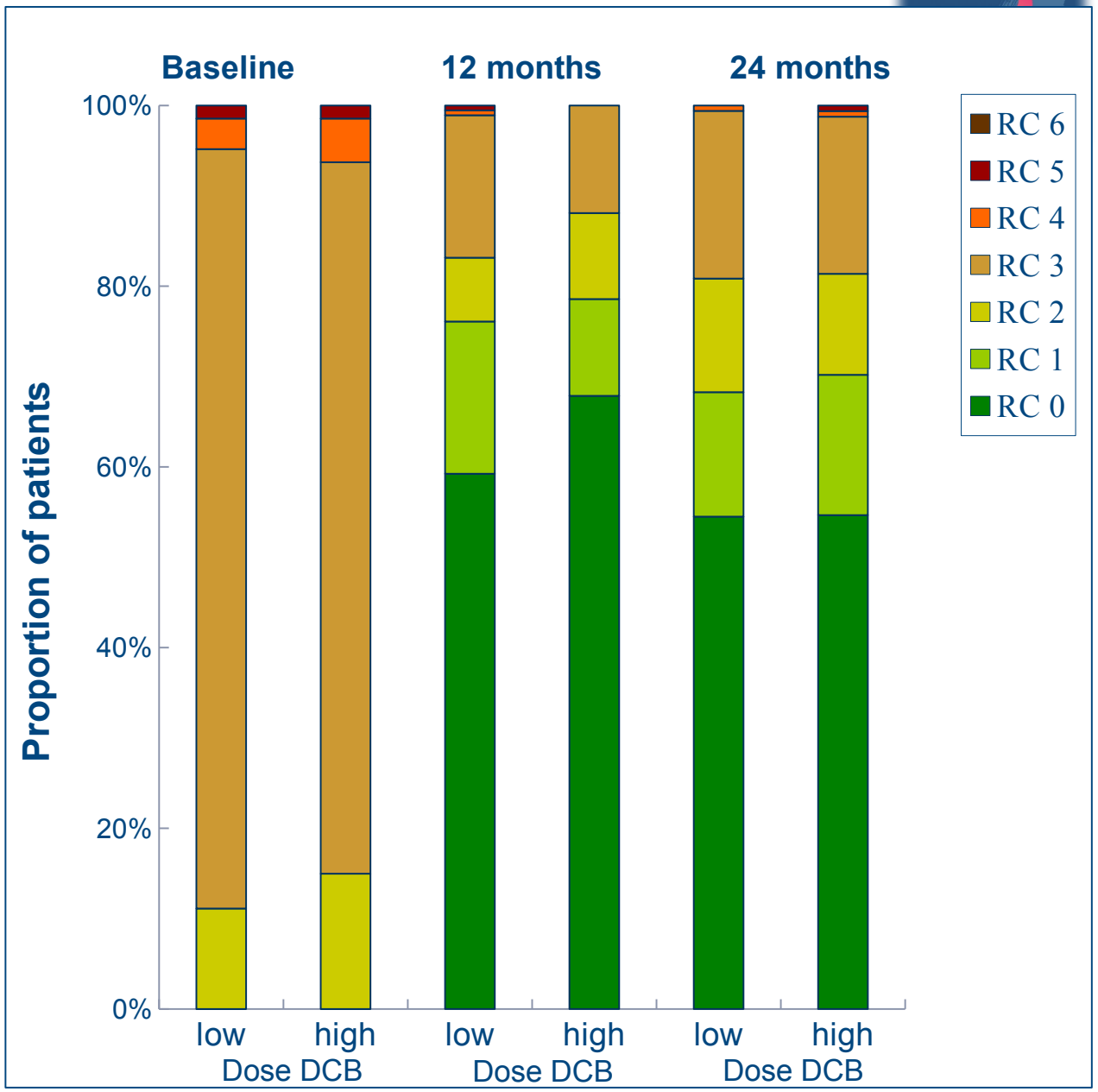
Distribution of Rutherford categories

≈70% of patients with no or minimal symptoms @ 2y



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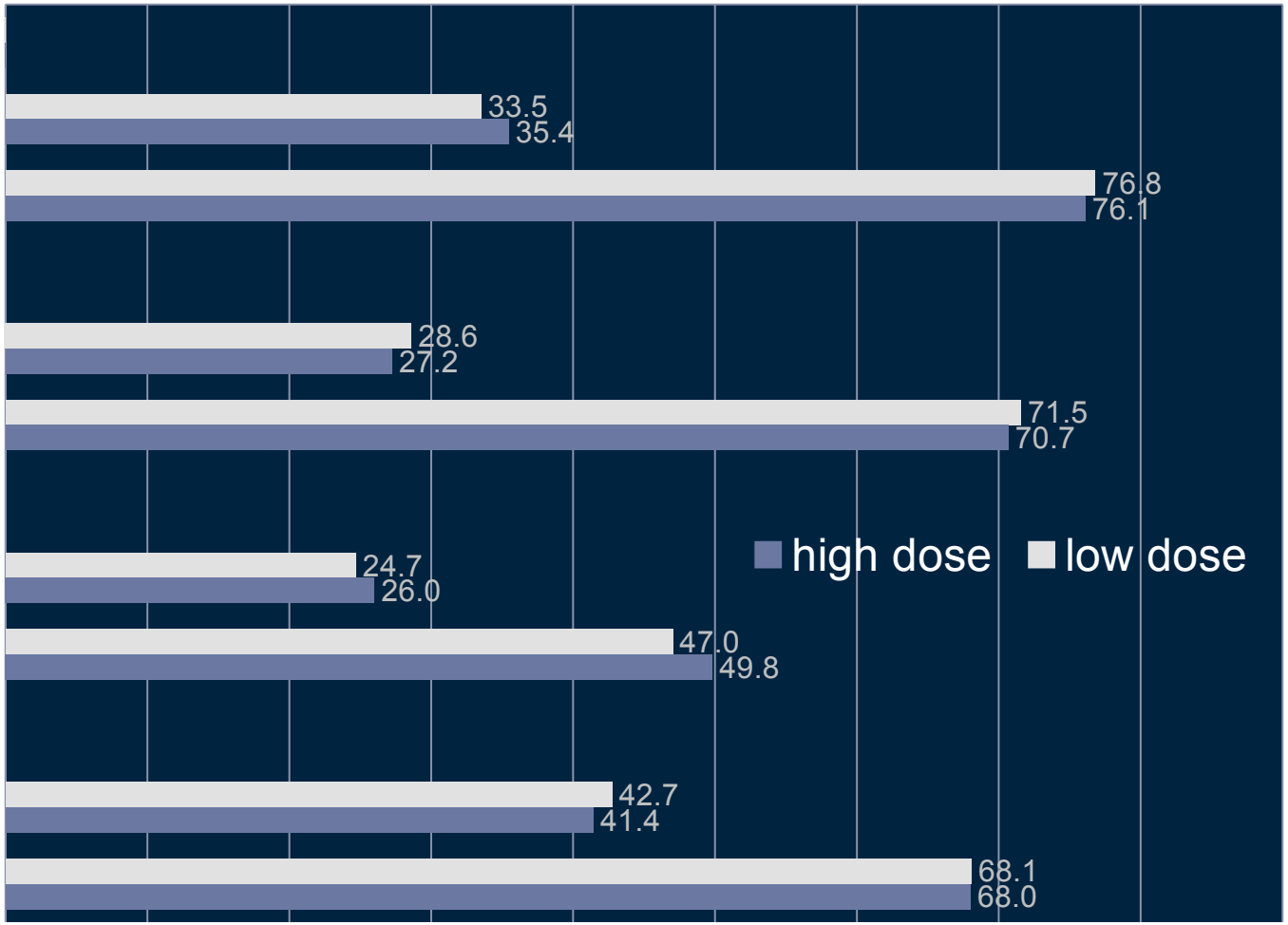
Walking impairment questionnaire



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COMPARE RCT Summary

- First head-to-head comparison of two DCBs with different paclitaxel dosages and coating technologies for femoropopliteal interventions
- Complex real world lesion subset with high proportion of CTO`s >40%
- Low dose DCB (Ranger 2.0µg/mm²) and high dose DCB (IN.PACT 3.5µg/mm²) showing both excellent primary patency and low TLR rates through 2 years
- Low mortality after 2 years; Follow-up ongoing up to 5 years

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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.

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.