CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE
CONTROVERSIES & UPDATES IN VASCULAR SURGERY
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Are Drug-coated balloons Durable ? Level 1 evidence review

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Disclosure

Speaker name: **Koen Keirse, MD**

☐ I have the following potential conflicts of interest to report:

- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ I do not have any potential conflict of interest

DCB Similarities and Differences

12 DCB's

same drug: ptx

≠ Dose (2.0 -3.5 µg/mm²)

≠ Drug Formulation

≠ Excipient

≠ Surface Energy

≠ Coating Method

Manufacturer	DCB
Spectranetics	STELLAREX
Medtronic	IN.PACT
BARD	LUTONIX
BIOTRONIK	PASSEO 18 LUX
COOK	ADVANCE 18 PTX
Aachen Resonance	ELUTAX
Eurocor	FREEWAY
CARDIONOVUM	LEGFLOW
Boston Scientific	RANGER
Vascular	LUMINOR
B BRAUN	SeQuent Please P
BIOSENSORS	Biopath

3 DCB's with robust Pivotal Randomized Trials

DCB Randomized Trials

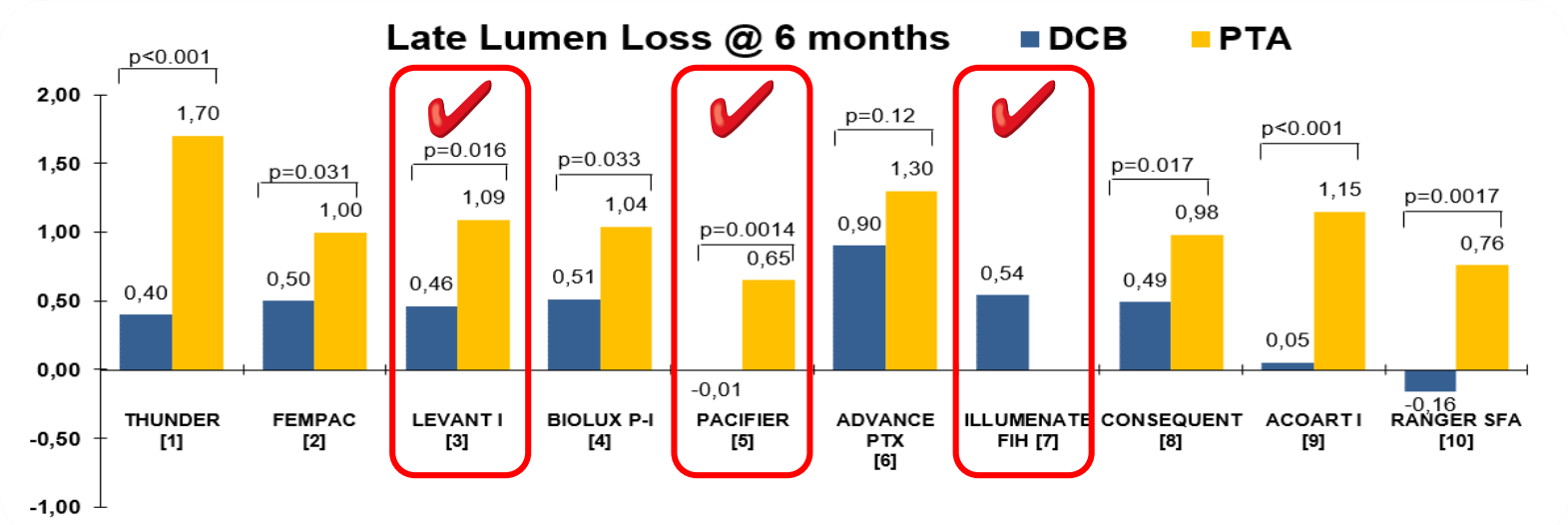
"Pivotal" RCTs: Rigorous and Meaningful

- Prospective, randomized against standard of care
- Sized and powered on a Primary Patency primary endpoint based on a pre-defined statistical plan
- Preceded by proof-of-concept / FIH

DCB FIH / Proof of Concept Evidence

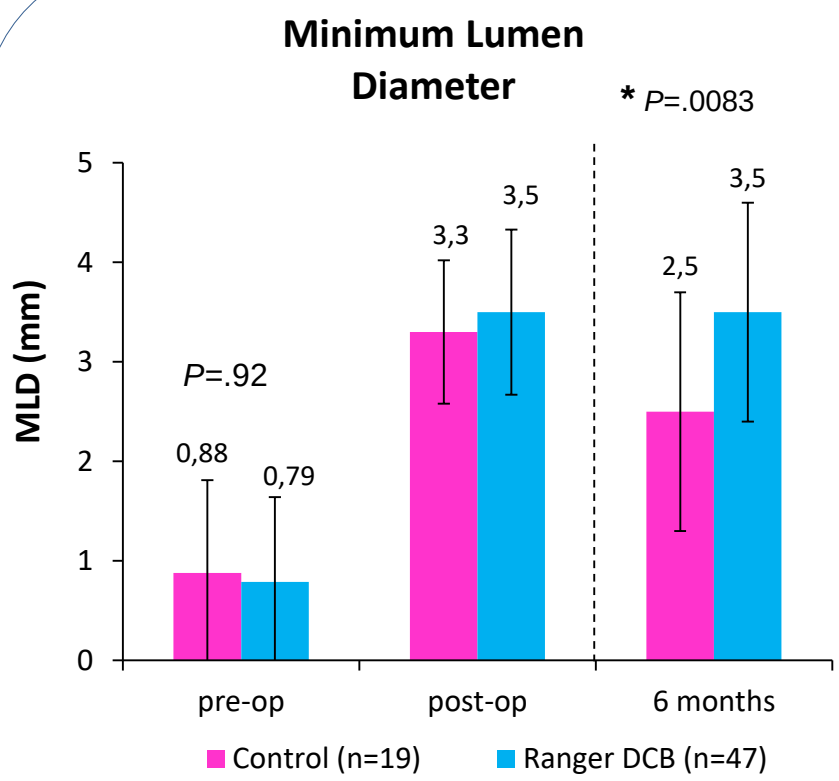
9 DCB Technologies, 10 FIH Trials.

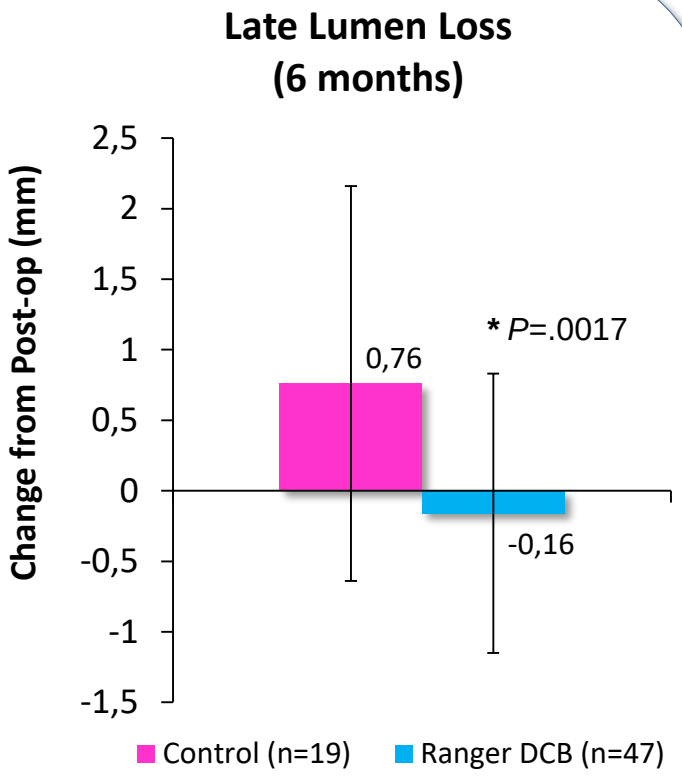
3 DCB's supported by RCT Pivotal Trials with 2yr data



1. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, Claussen CD, Oldenburg A, Scheller B, Speck U. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med. 2008 Feb 14;358(7):689-99
2. Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, Hosten N, Hamm B, Speck U, Ricke J. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation. 2008 Sep 23;118(13):1358-65
3. Scheinert D, Duda S, Zeller T, Krankenberg H, Ricke J, Bosiers M, Tepe G, Naisbitt S, Rosenfield K. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. JACC Cardiovasc Interv. 2014 Jan;7(1):10-9
4. Scheinert D, Schulte KL, Zeller T, Lammer J, Tepe G. Paclitaxel-releasing balloon in femoropopliteal lesions using a BTHC excipient: twelve-month results from the BIOLUX P-I randomized trial. J Endovasc Ther. 2015 Feb;22(1):14-21
5. Werk M, Albrecht T, Meyer DR, Ahmed MN, Behne A, Dietz U, Eschenbach G, Hartmann H, Lange C, Schnorr B, Stiepani H, Zoccai GB, Hänninen EL. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. Circ Cardiovasc Interv. 2012 Dec;5(6):831-40
6. D.Scheinert - Advance 18 PTX Study - LINC 2013 oral presentation
7. Schroeder H, Meyer DR, Lux B, Ruecker F, Martorana M, Duda S. Two-year results of a low-dose drug-coated balloon for revascularization of the femoropopliteal artery: outcomes from the ILLUMENATE first-in-human study. Catheter Cardiovasc Interv. 2015 Aug;86(2):278-86
8. T.Albrecht – Preliminary angiographic and clinical 6-month results of the CONSEQUENT trial - LINC 2016 oral presentation
9. W.Guo - AcoArt I First Prospective, Randomized, Multicenter Clinical Trial for the Use of the Orchid DCB in Femoropopliteal Artery Disease - LINC 2016 oral presentation

Ranger-SFA Study
Primary Efficacy Endpoint – 6 Months

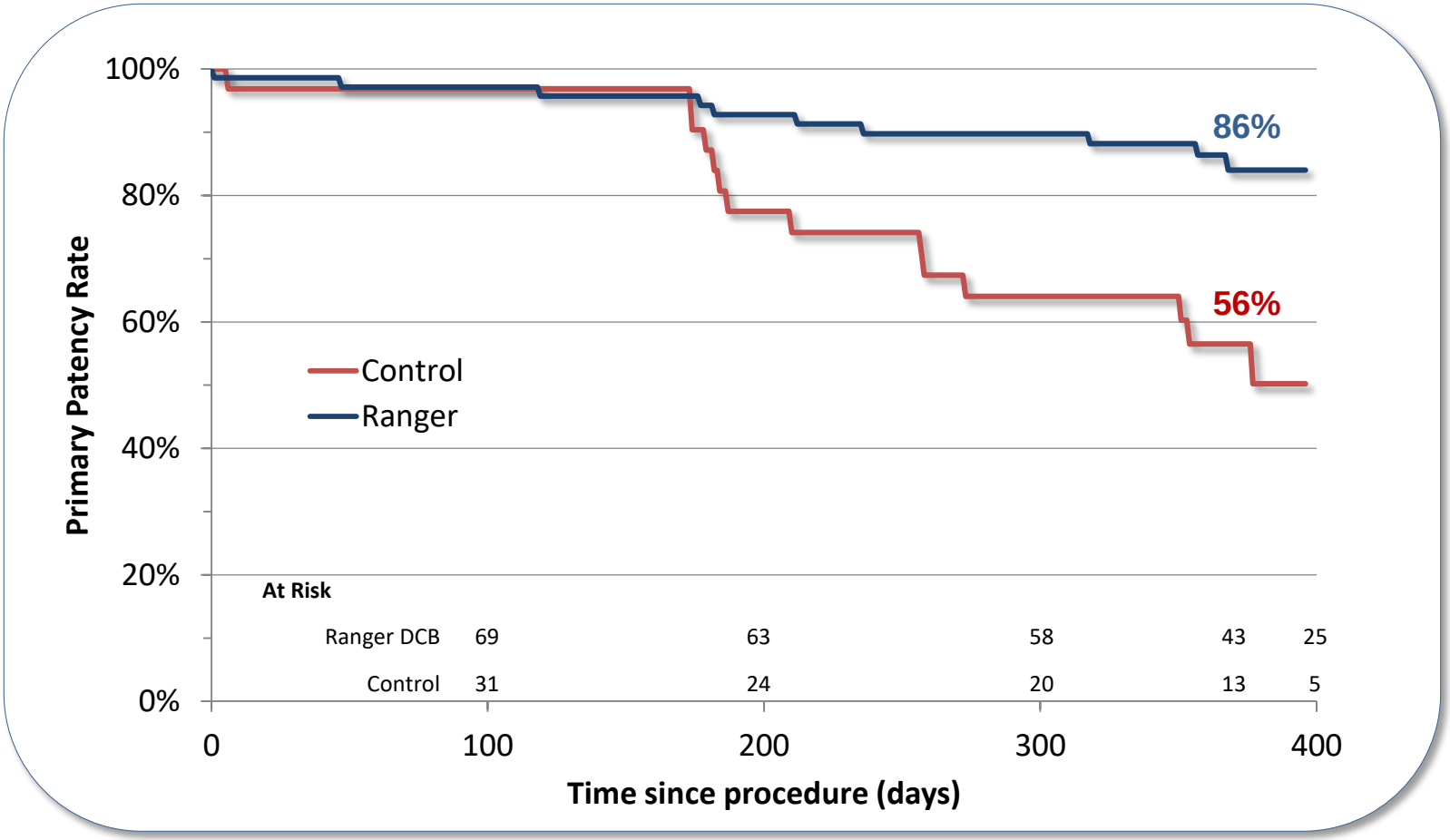




- LLL was significantly less for Ranger DCB than for control (*P*=.0017) Primary endpoint was met

Bausback Y, et al. J Endovasc Ther. 2017;24(4):459-467.

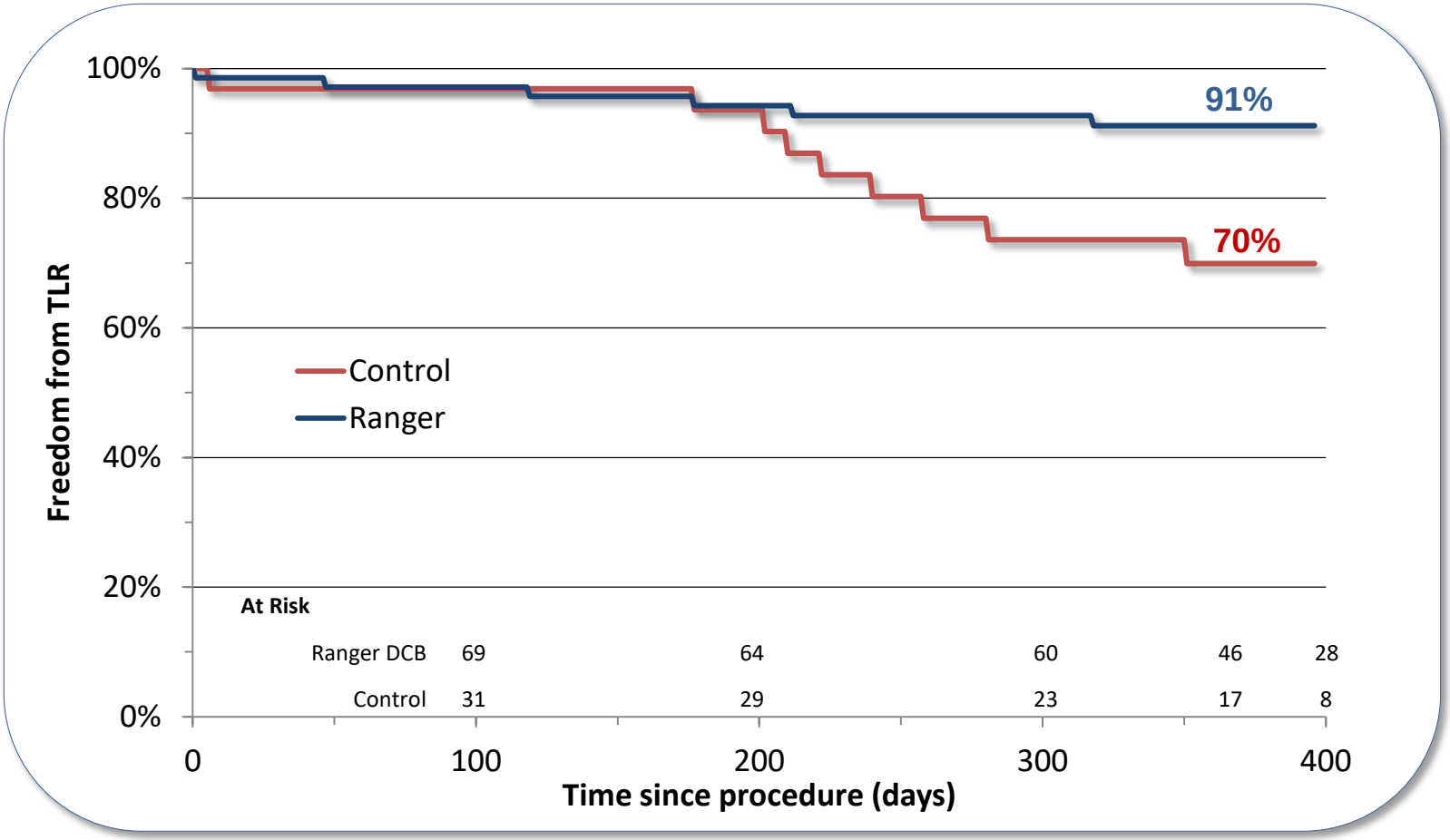
Ranger-SFA Study
Primary Patency – 12 Months



Scheinert, D. Charing Cross 2017.

Primary patency defined as the percentage of lesions without a hemodynamically significant stenosis on duplex ultrasound (PSVR > 2.4) and without TLR or bypass of the target lesion.

Ranger-SFA Study
Freedom from TLR – 12 Months



Scheinert, D. Charing Cross 2017.

3 DCB's with 2 yr data

DCB	In.Pact	Lutonix	Stellarex
Drug	paclitaxel		
Dose	3.5 µg/mm^2	2 µg/mm^2	
Excipient	Urea	Polisorbate and Sorbitol	Polyethylene Glycol

Further differences apply in drug state formulation, surface energy, coating method across the three DCB's

3 DCB's supported by 4 Pivotal RCTs

	IN.PACT SFA [1]	LEVANT 2 [2]	ILLUMENATE EU RCT [3]	ILLUMENATE US Pivotal [4]
Study Device (DCB)	IN.PACT	Lutonix	Stellarex	Stellarex
N Patients	331	476	328	300
Control	PTA with provisional Stenting			
Population / Vessel	RC 2-3-4 / fem-pop			
Objective	Demonstrate safety and efficacy of DCB vs. standard PTA for the treatment of fem-pop arterial disease			
Primary Safety Endpoint	Freedom from 30-day death and from 12-month major adverse events (i.e. death, amputation, clinically-driven TLR or TVR)*			
Primary Efficacy Endpoint	12-month Primary patency*			

*** Differences apply in exact MAE components and definition and in PSVR threshold**

1. Tepe G et al. IN.PACT SFA Trial Investigators.. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015
2. K.Rosenfield et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med 2015
3. Schroeder H et al. Low-dose Paclitaxel-coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease: 1-year Results of the ILLUMENATE European Randomized Clinical Trial. Circulation. 2017 Apr 19. pii: CIRCULATIONAHA.116.026493
4. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results - oral prsentation, TCT 2016

High Scientific Rigor

Independent imaging and clinical event adjudication

IN.PACT SFA [1]	LEVANT 2 [2]	I EU RCT [3]	I US Pivotal [4]
Duplex Ultrasound Core-Laboratory *			
Angiographic Core-Laboratory *			
Clinical Event Committee *			
Independent Data Safety Monitoring Board			
External Monitoring with 100% source data verification			

*** blinded to the assigned treatment**

12 month evaluators also blinded to patient treatment in LEVANT 2 Trial

1. Tepe G et al. IN.PACT SFA Trial Investigators.. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015
2. K.Rosenfield et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med 2015
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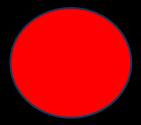
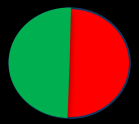
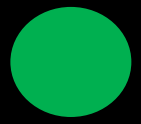
Why Core-lab adj. Primary Patency?

- measurable, objective, free from bias
- most appropriate endpoint to measure the performance of patency-restoring devices

Endpoint	Clinical Relevance	Device-specific correlation	
Primary Patency			1:1 correlation to the primary mandate of revascularization therapies
TLR			Highly clinical relevant but subject bias especially in claudication trials
QoL Walk			Most relevant but highly dependant on concomitant non-lesion related ”confounders”

M.Jaff - Primary Patency reporting in SFA trials – oral presentation - Charing Cross 2014
F.Fanelli - Drug Coated Balloon in the Superficial Femoral Artery: Current Status - oral presentation - Charing Cross 2015
A.Holden - Head-to-Head Comparisons of Drug-coated Balloons - oral presentation - Charing Cross 2017
W. Gray - Debunking the myths of Drug-coated Balloons - oral presentation - Charing Cross 2017

Primary Patency Definition across RCT's

Same definition and reporting method

Freedom from restenosis and TLR @ 12 months

- **Restenosis: Duplex ultrasound, PSVR thresholds: 2.4 or 2.5**
- **TLR: "all TLR" or "clinically driven TLR" ***

✓ **Kaplan Meier reporting method @ 365 or 360-day**

✓ **Independent Duplex core-laboratory adjudication**

✓ **Same Duplex core-laboratory: VasCore, Boston, MA, USA**

*** In.Pact SFA, Illumenate EU RCT and US Pivotal: «clinically driven TLR»; Levant 2: «TLR»**

Similarities across trials

- **Mandatory pre-dilatation***
- **Major common exclusions**
  - ✓RC 5-6
  - ✓ISR
  - ✓Failure to cross target lesion with a guidewire
  - ✓Failed pre-dilatation (based on major flow-limiting dissection or >70% residual DS)
  - ✓Severe calcification that precludes adequate PTA treatment / makes the lesion non-dilatable, etc.

* Except in IN.PACT SFA phase I (European cohort)

Key Baseline Characteristics

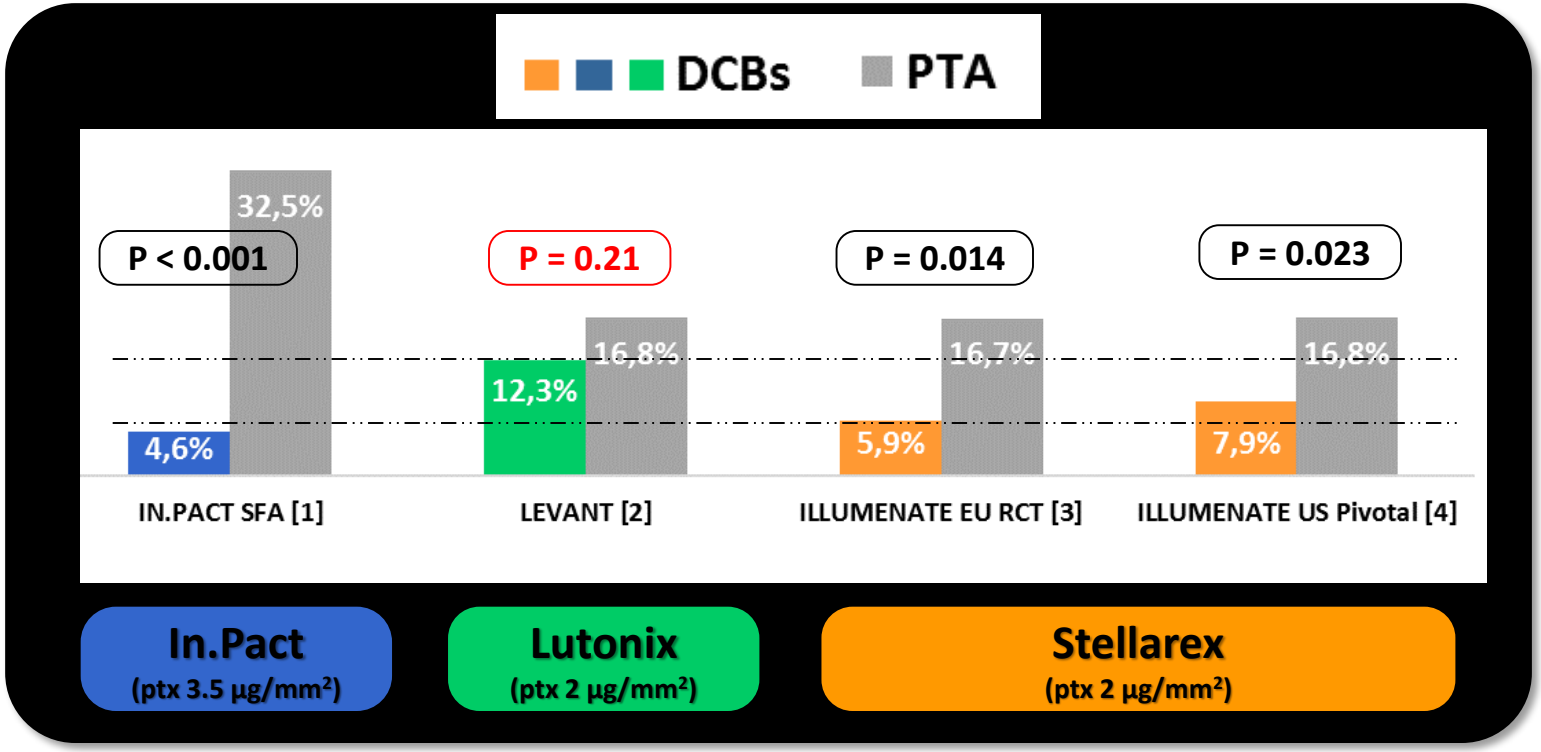
(DCB arm)	IN.PACT SFA [1]	LEVANT 2 [2]	ILLUMENATE EU RCT [3]	ILLUMENATE US Pivotal [4]
Females	35.0%	38.9%	27.9%	**44.0%**
Diabetes	40.5%	43.4%	37.4%	**49.5%**
Renal Insuff.	8.3%	NA	9.0%	**18.0%**
RC≥3	62.3%	70.6%	**84.6%**	68.5%
Lesion length	**8.9 cm**	6.3 cm	7.2 cm	8.0 cm
Severe Calcium*	8.1%	10.4%	12.7%	**43.9%**
CTO's	**25.8%**	20.6%	19.2%	19.0%
Stent rate	7.3%	2.5%	15.4%	6.0%

* different Ca++ definitions may apply across trials

1. Tepe G et al. IN.PACT SFA Trial Investigators.. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015
2. K.Rosenfield et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med 2015
3. Schroeder H et al. Low-dose Paclitaxel-coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease: 1-year Results of the ILLUMENATE European Randomized Clinical Trial. Circulation. 2017 Apr 19. pii: CIRCULATIONAHA.116.026493
4. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results - oral prsentation, TCT 2016

Data in Context: 1-year TLR

CEC adjudicated clinically driven TLR



Calculated through the end of the 1-year follow up window

1. French National Commission of Medical Device Evaluation on IN.PACT SFA (May, 3rd 2016) - http://www.has-sante.fr/portail/jcms/c_2635037/fr/in-pact-admiral
2. K.Rosenfield et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med 2015
3. Schroeder H et al. Low-dose Paclitaxel-coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease: 1-year Results of the ILLUMENATE European Randomized Clinical Trial. Circulation. 2017 Apr 19. pii: CIRCULATIONAHA.116.026493
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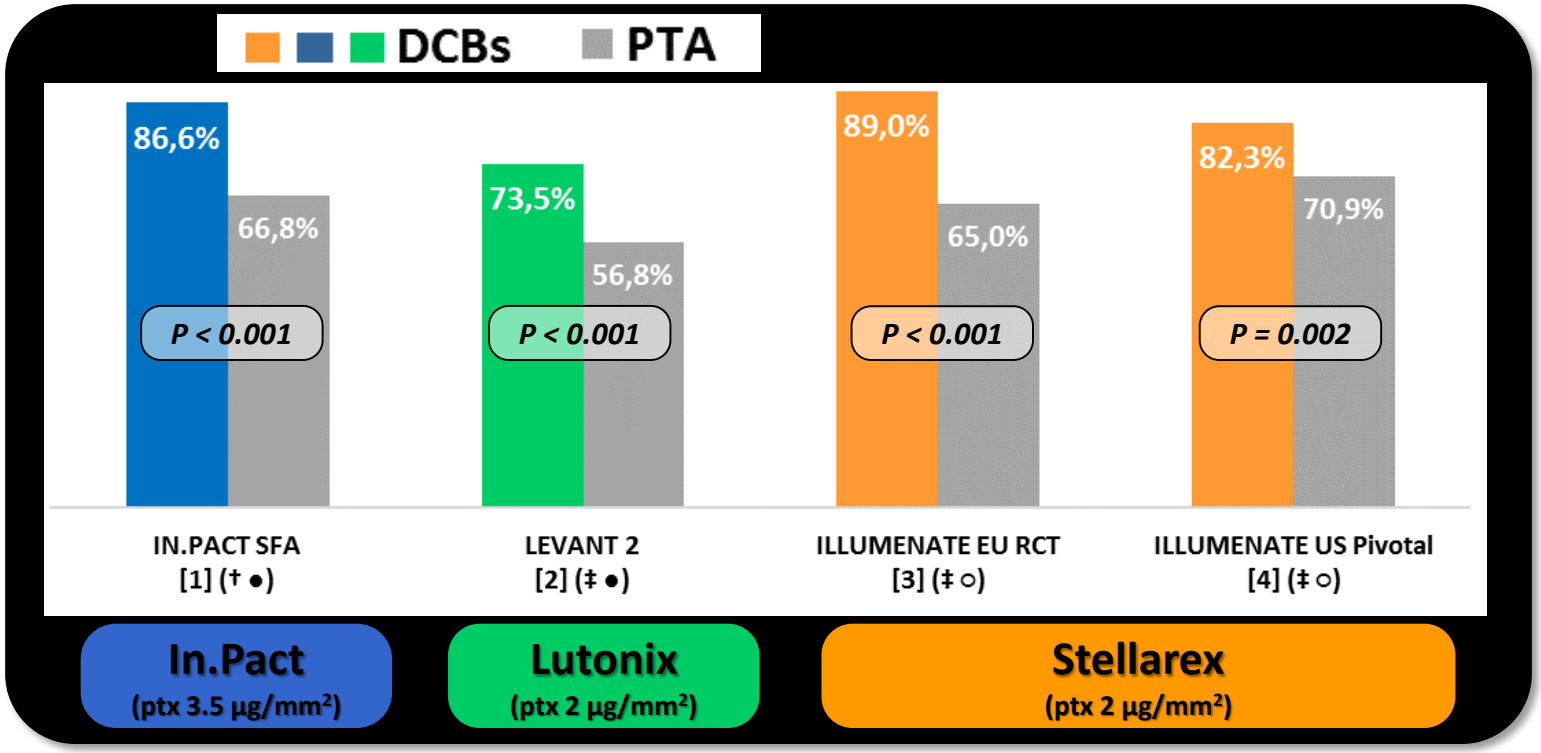
Data in Context: 1-year Primary Patency

Core-lab adjudicated* Duplex derived Primary Patency



Duplex derived Primary Patency based on PSVR ≤2.4 (●) or ≤2.5 (○). KM survival estimates at 360 (†) or 365 (‡) days. * VascCore Core laboratory - Boston, MA, USA)

1. Tepe G et al. IN.PACT SFA Trial Investigators Circulation 2015 + G.Tepe, Charing Cross 2014 oral presentation + Jaff M. Drug-coated Balloon Treatment for Patients with Intermittent Claudication: Insights from the IN.PACT Global Full Clinical Cohort. (Updated data from IN.PACT SFA presented on slide 12) Oral Presentation, VIVA 2016
2. K.Rosenfield et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med 2015
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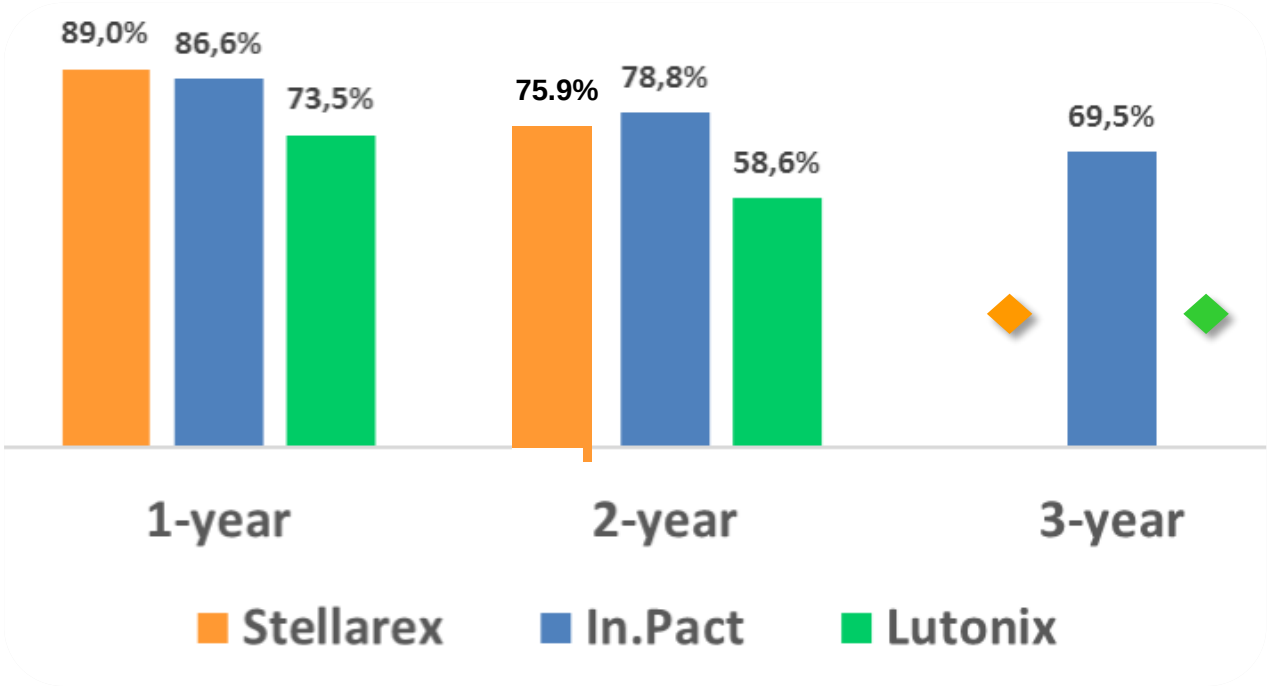
4. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results - Oral Presentation, TCT 2016

Beyond 1 year

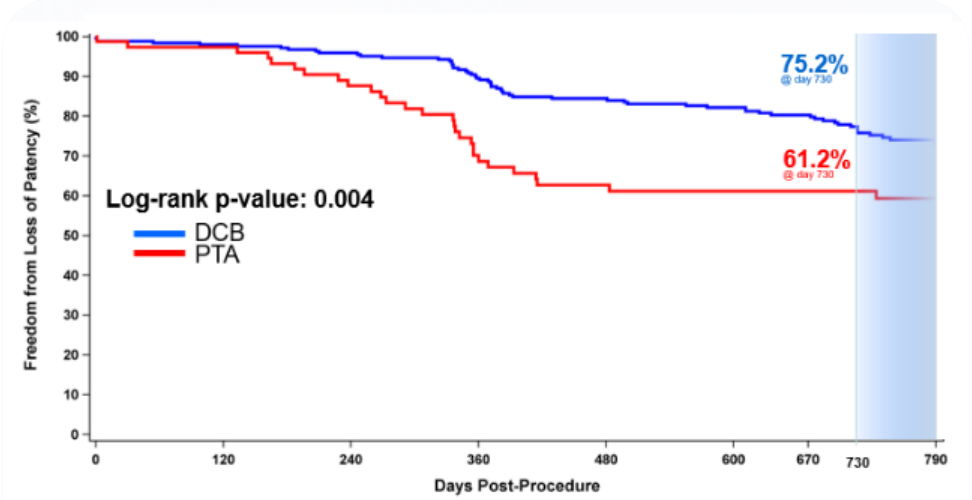
Core lab adjudicated Duplex derived Primary Patency



- Schroeder H et al. Low-dose Paclitaxel-coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease: 1-year Results of the ILLUMENATE European Randomized Clinical Trial. Circulation. 2017 Apr 19. pii: CIRCULATIONAHA.116.026493
- Rosenfield K, et al. The New England journal of medicine. 2015;373:145-53
- Laurich C. Oral Presentation. SVS. 2015
- Krishnan P. Drug-Coated Balloons Show Superior Three-Year Outcomes vs Angioplasty: Results from the IN.PACT SFA Randomized Trial. Oral Presentation at VIVA 2016; September 19-22,2016; Las Vegas, NV
- Jaff M. Drug-coated Balloon Treatment for Patients with Intermittent Claudication: Insights from the IN.PACT Global Full Clinical Cohort. (Updated data from IN.PACT SFA presented on slide 12) Oral Presentation at: VIVA 2016; September 19-22,2016; Las Vegas, NV.

EU RCT: 2-year Primary Patency

Durable treatment effect through 2 years



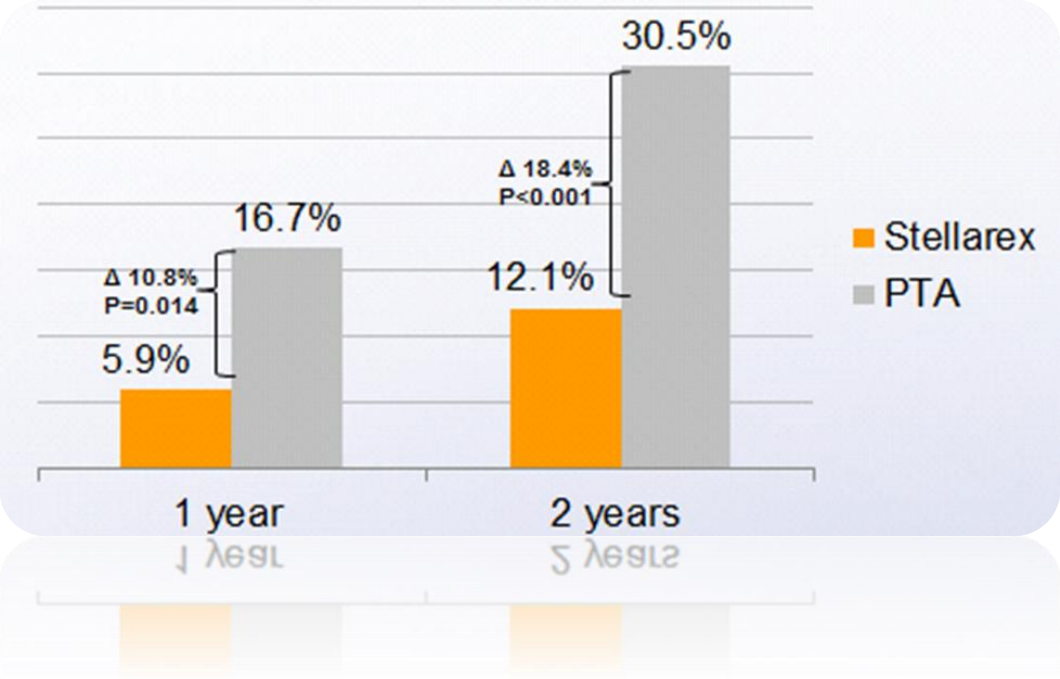
Days	365	730	790
DCB Event Free	89.2%	75.2%	73.3%
PTA Event Free	68.7%	61.2%	59.3%

Primary patency defined as freedom from restenosis (determined by duplex ultrasound with PSVR ≤2.5) and freedom from clinically-driven TLR at 12 months. Assessed per lesion. KM estimates reported at day 395 to capture all patients and events within the full (and legitimate) 335-395 follow-up window. Rates from the middle of the protocol visit window (365 days) reported for consistency and comparative purposes with other trials.

M.Brodmann - ILLUMENATE European Randomized Trial: 2-Year Results – oral presentation, VIVA 2017

EU RCT: 2-year clinically driven TLR

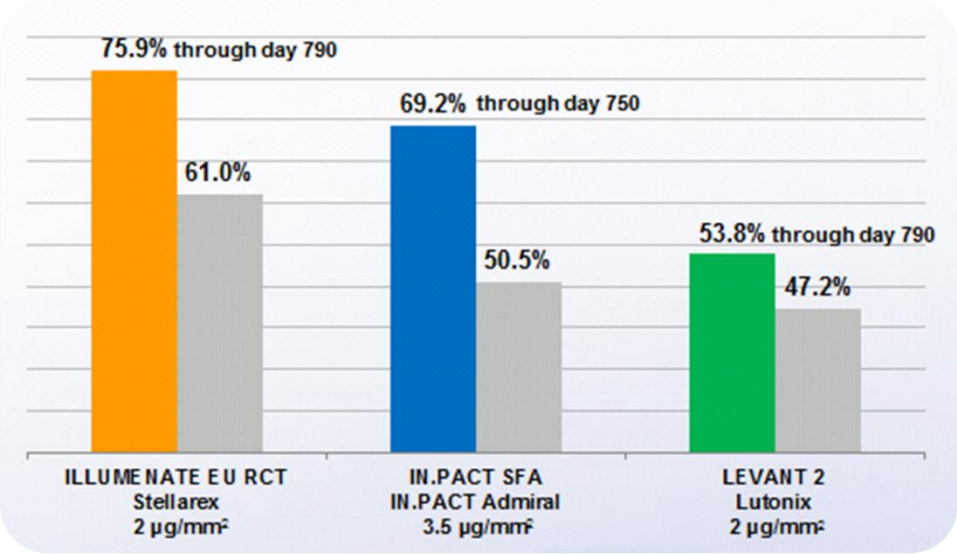
Durable treatment effect through 2 years



M.Brodmann - ILLUMENATE European Randomized Trial: 2-Year Results – oral presentation, VIVA 2017

DCB in context: RCT's @ 2 years

Core lab adjudicated Primary Patency, exact rates



- Medtronic IN.PACT Admiral Instructions for Use, Rev. 1F
- LUTONIX® 035 Drug Coated Balloon PTA Catheter - Instructions for Use - BAW1387400r3
- Brodmann - ILLUMENATE European Randomized Trial: 2-Year Results – oral presentation, VIVA 2017

Studies shown are not head-to-head comparisons, and data presented cannot be directly compared..

Conclusions

- 4 Pivotal RCT's offer level 1 Evidence and highest rigor on the use of 3 DCB's for fem-pop revascularization (R 2-3-4)
- Although some differences apply in baseline characteristics, trial design and methodology are robust and common across the 4 trials
- These 4 trials confirm that DCB class effect does not exist
- Available Level I data suggests that DCB effect is at least durable for two years