Evidence of DCB Treatment for Infrapopliteal Disease: 2021 Update

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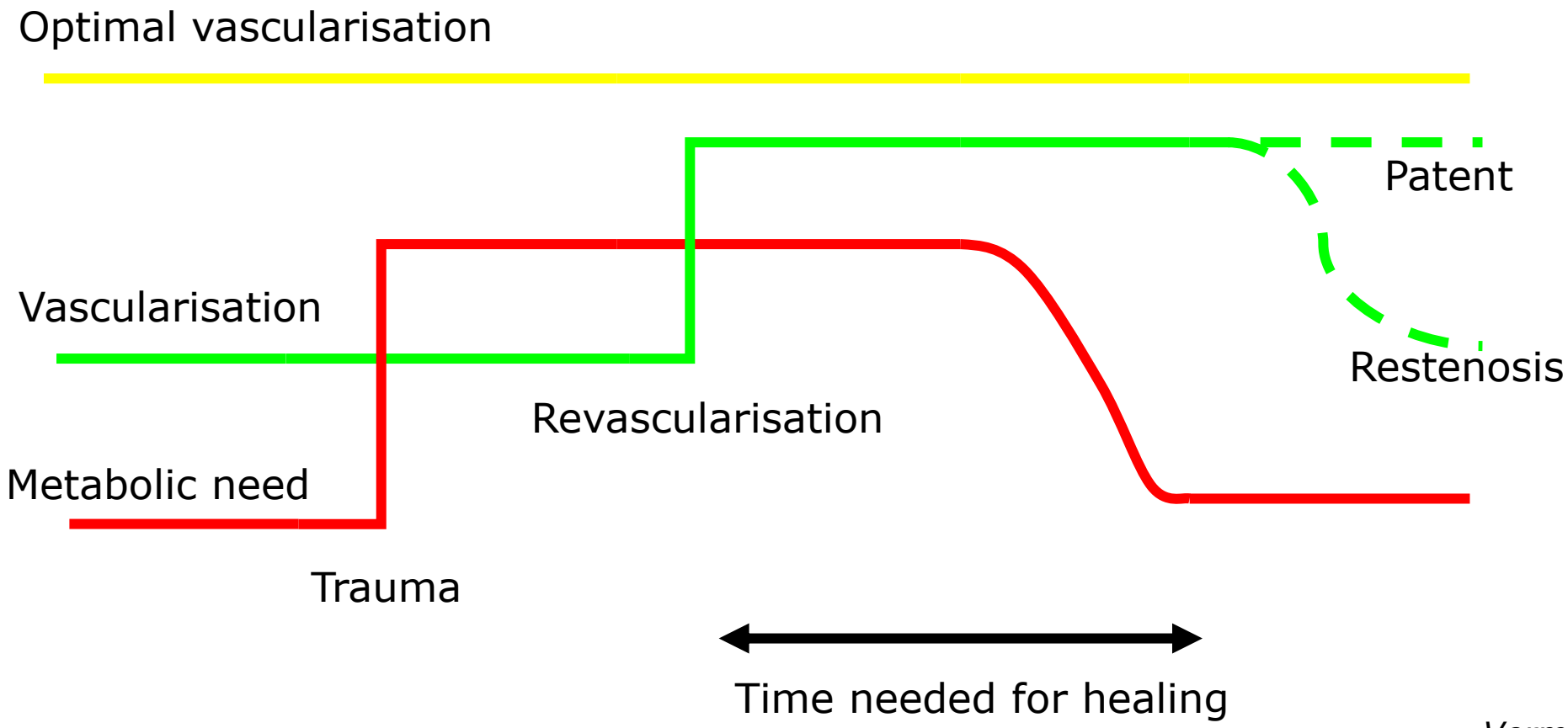
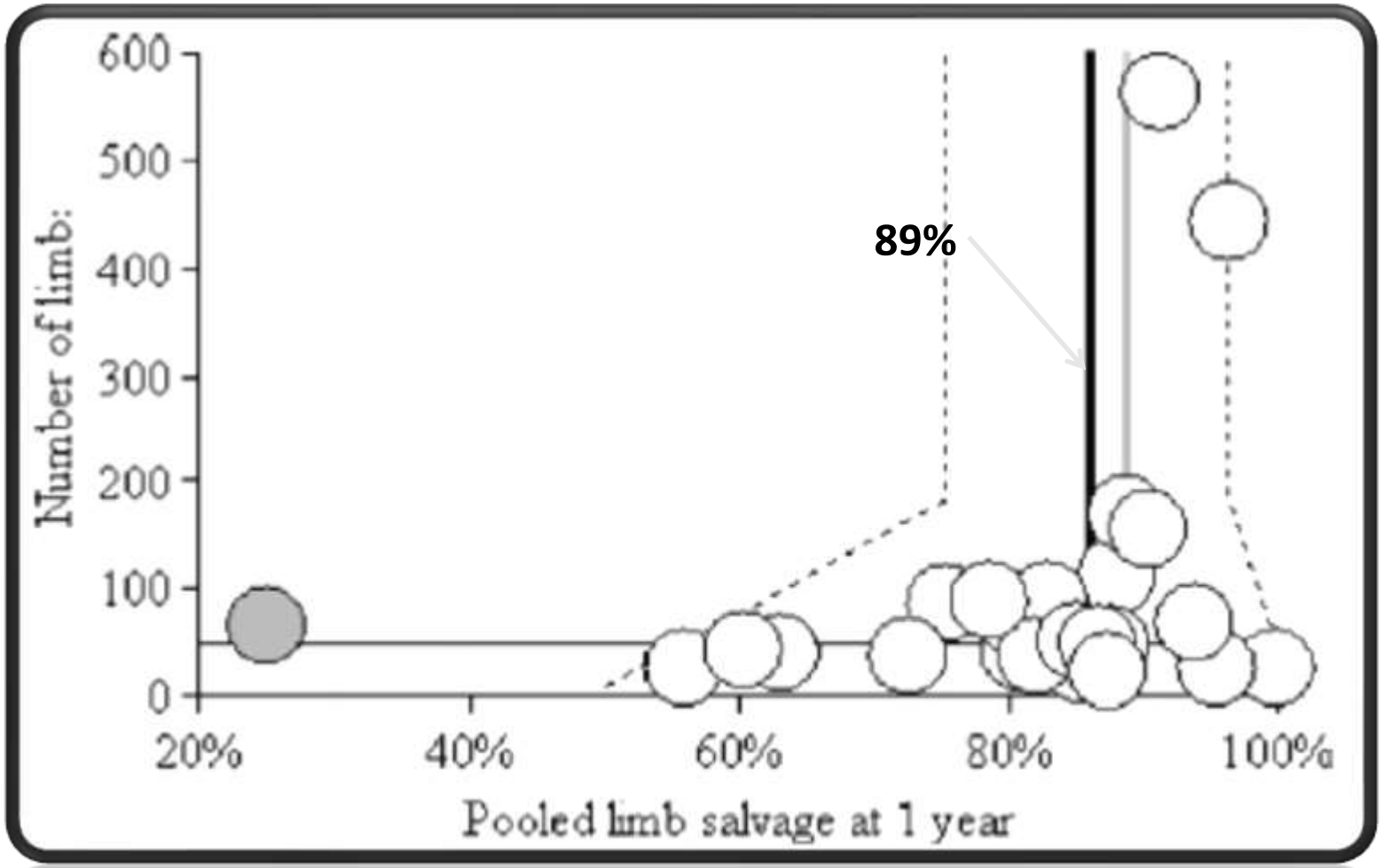
Goal of revascularization in CLI



Vermassen F 2010

Mets-analysis:12 month limb-salvage



J Vasc Surg 2008;47:975-81

Data from meta-analysis of infra-popliteal intervention for CLI

Table II. Meta-analysis results of crural percutaneous transluminal angioplasty and popliteal-to-distal bypass[a]

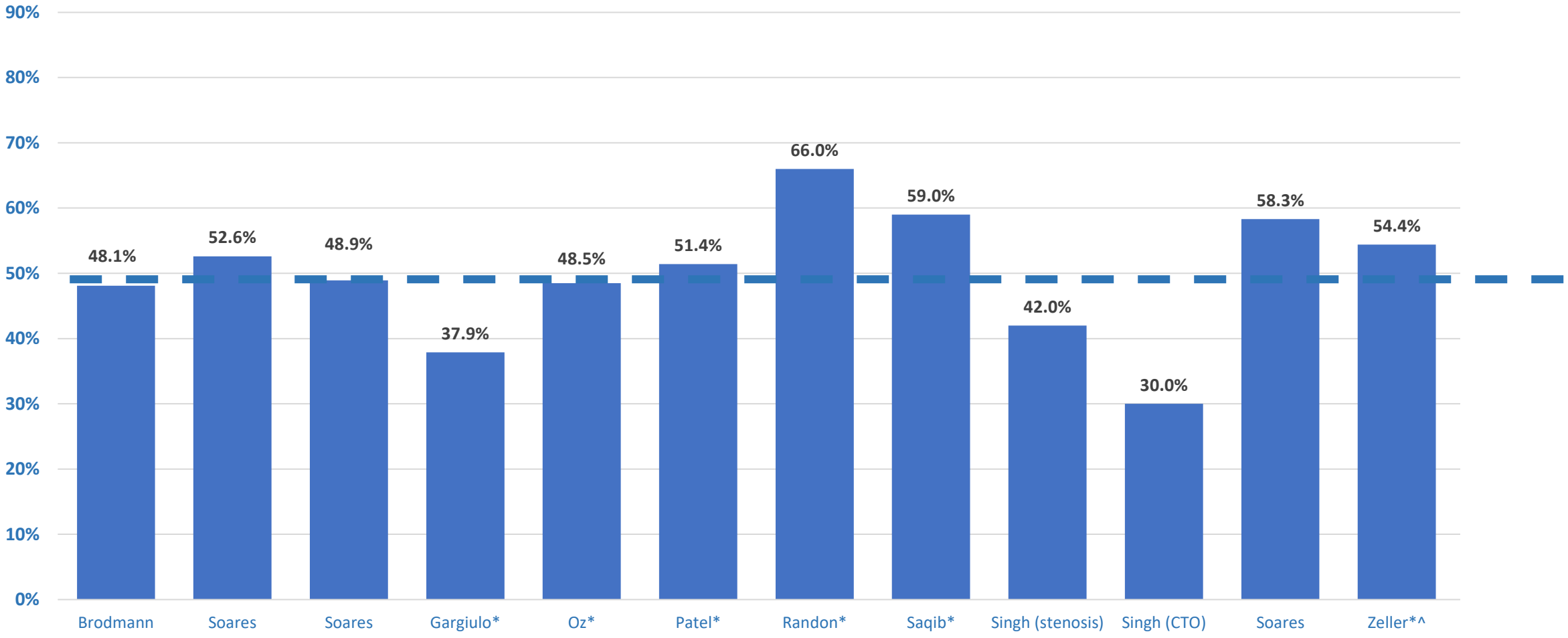
Result	*1 month*	*6 months*	*1 year*	*2 years*	*3 years*
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
P	<.05	<.05	<.05	<.05	<.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
P	<.05	<.05	<.05		
Limb salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Patient survival					
PTA	98.3 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

J Vasc Surg 2008;47:975-81

CLI and Below the Knee (BTK) Disease

- BTK disease is typically involved in the majority of CLI cases and is the sole cause in approximately 20 – 25%
  - High frequency of chronic total occlusion (CTO)
  - Commonly associated with diabetes
  - Calcified disease is common
  - Renal dysfunction common
  - Multivessel disease is common

12M KM Patency in BTK Angioplasty (OPG data sets)



Observational data only • Patient populations and study methodologies differed • Not powered for statistical significance

*Patency includes freedom from CD-TLR
^Core lab adjudicated

What are the randomized clinical data?

Single-center, randomized, non-blinded IN.PACT Amphirion in diabetics: *successful*

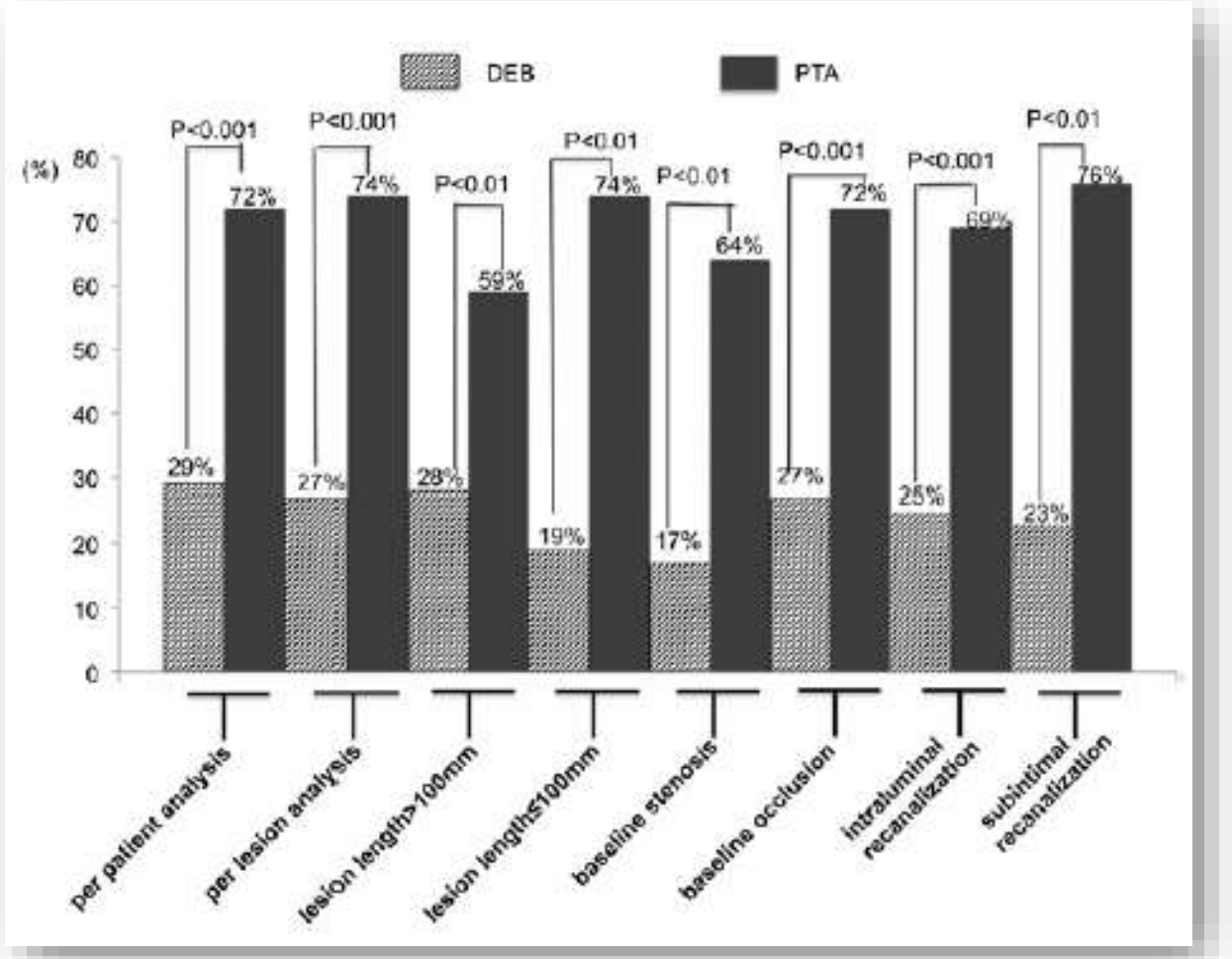
2013

Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK)

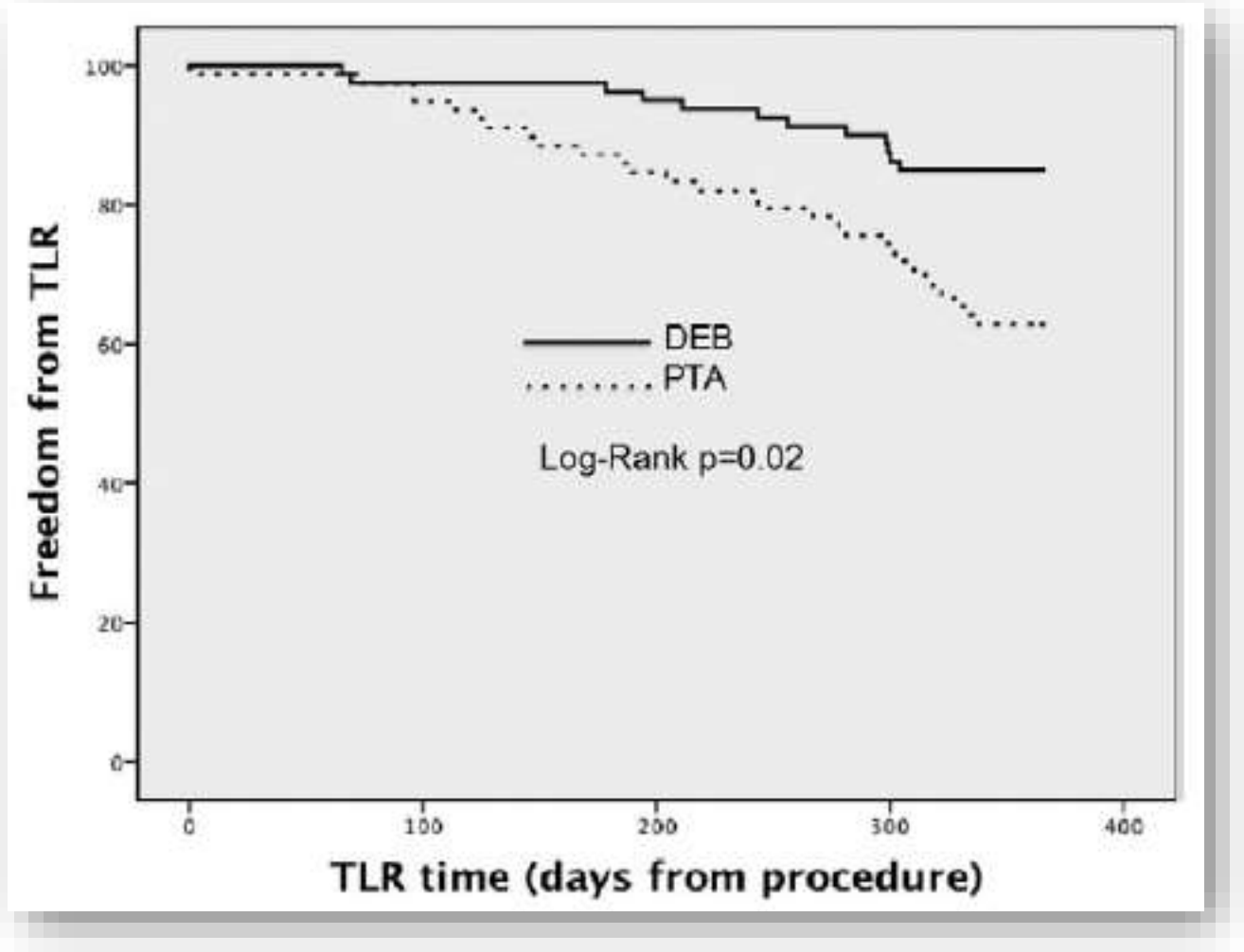
A Randomized Trial in Diabetic Patients With Critical Limb Ischemia

Francesco Liistro, MD; Italo Porto, MD PhD; Paolo Angioli, MD; Simone Grotti, MD; Lucia Ricci, MD; Kenneth Ducci, MD; Giovanni Falsini, MD; Giorgio Ventoruzzo, MD; Filippo Turini, MD; Guido Bellandi, MD; Leonardo Bolognese, MD

DEBATE BTK 12 month angiography: DCB improves patency



DEBATE BTK:
TLR improved with DCB at 12 months



Randomized multicenter trial IN.PACT DEEP:

unsuccessful

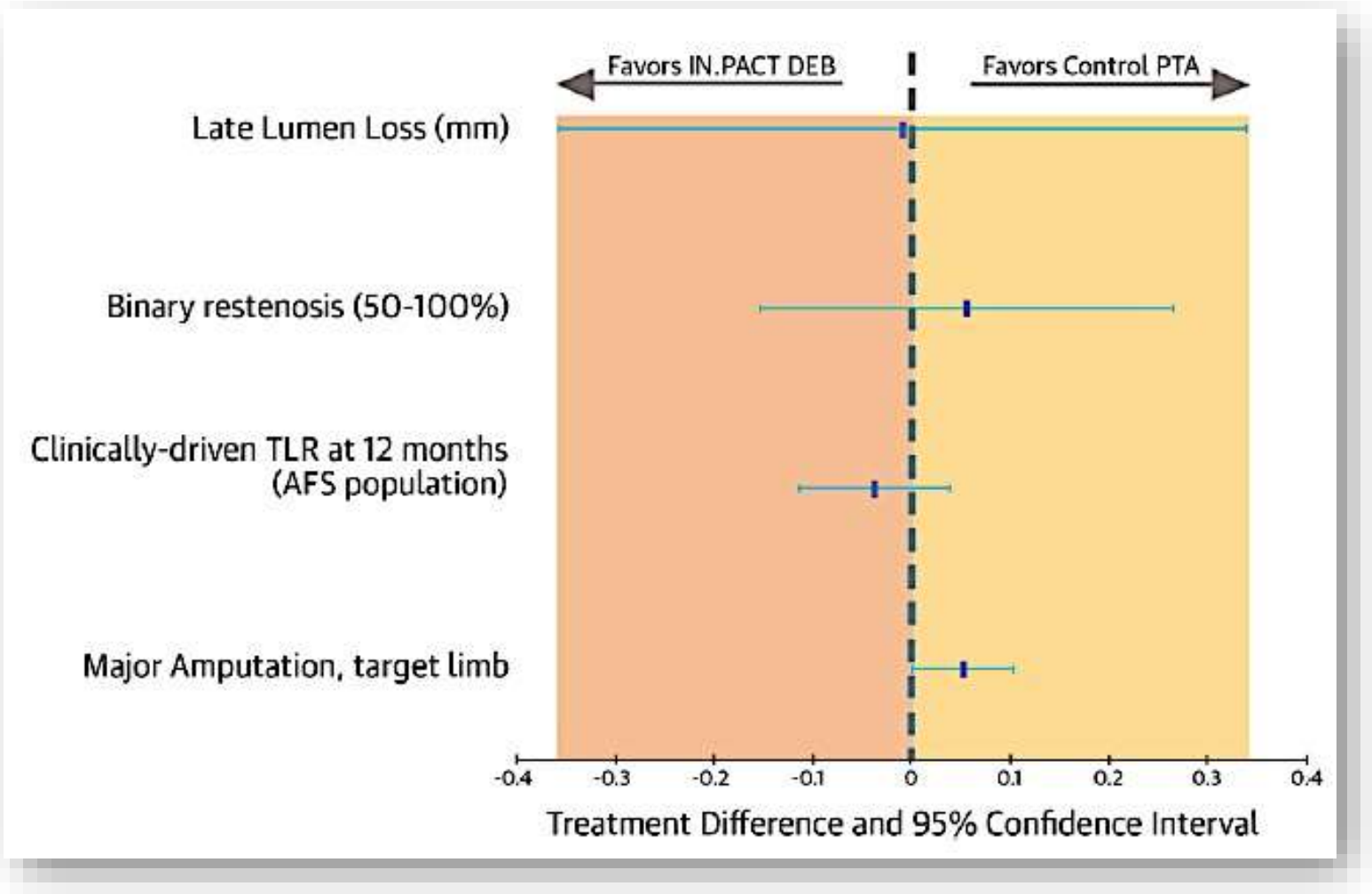
2014

Drug-Eluting Balloon Versus Standard Balloon Angioplasty for Infrapopliteal Arterial Revascularization in Critical Limb Ischemia

12-Month Results From the IN.PACT DEEP Randomized Trial

Thomas Zeller, MD,* Iris Baumgartner, MD,† Dierk Scheinert, MD,‡ Marianne Brodmann, MD,§ Marc Bosiers, MD,‖ Antonio Micari, MD, PhD,¶ Patrick Peeters, MD, PhD,# Frank Vermassen, MD, PhD,** Mario Landini, MS,†† David B. Snead, PhD,†† K. Craig Kent, MD,‡‡ Krishna J. Rocha-Singh, MD,§§ IN.PACT DEEP Trial Investigators

IN.PACT DEEP: Relevant clinical outcomes



Single-center randomized DCB vs. DES: *unsuccessful*

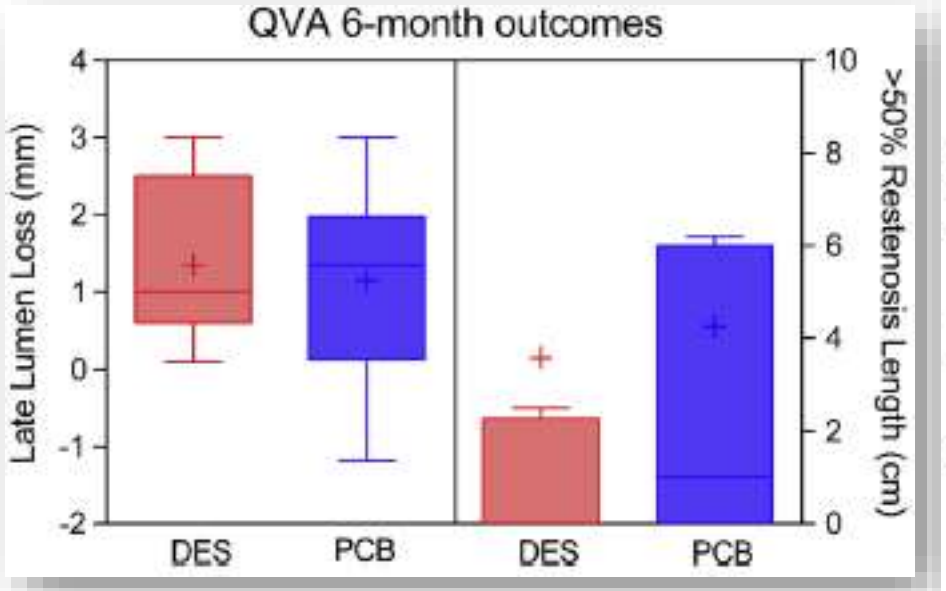
2014

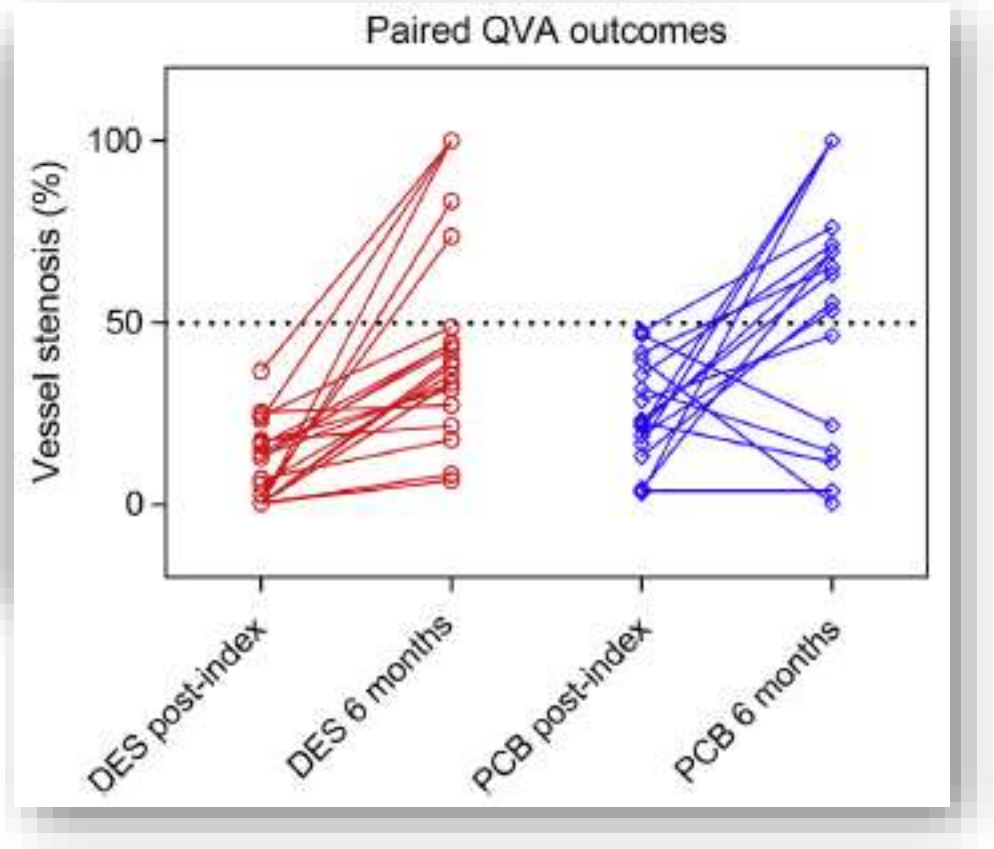
Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting for the Treatment of Infrapopliteal Long-Segment Arterial Occlusive Disease

The IDEAS Randomized Controlled Trial

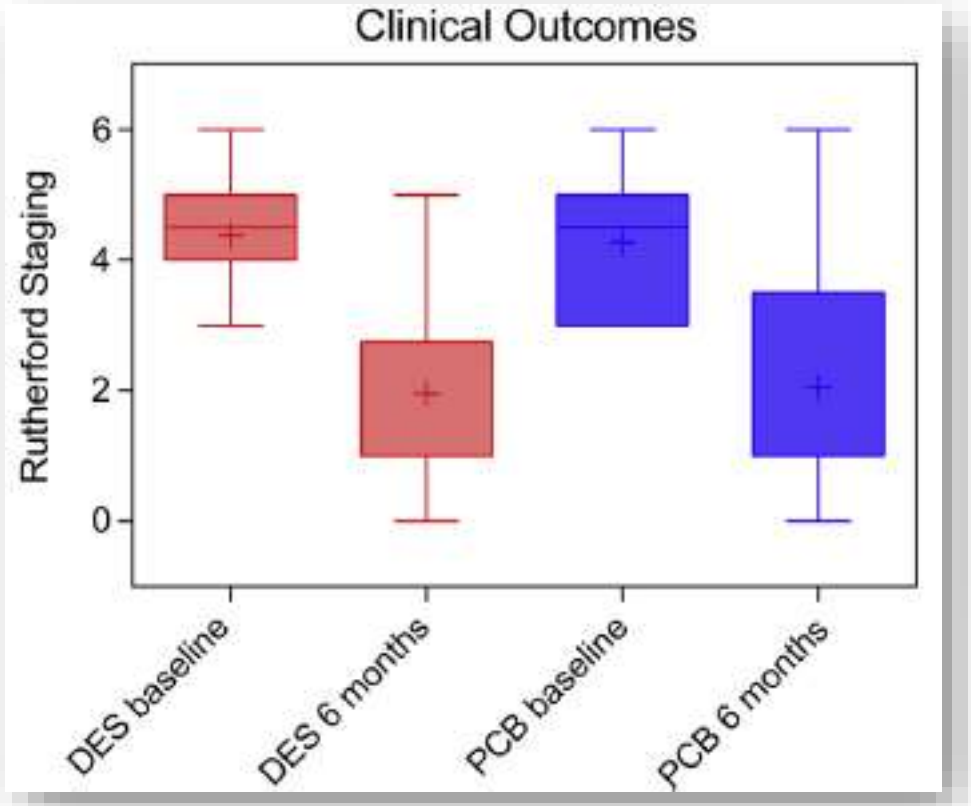
Dimitris Siablis, MD, PhD,* Panagiotis M. Kitrou, MD, PhD,* Stavros Spiliopoulos, MD, PhD,*
Konstantinos Katsanos, MSc, MD, PhD,† Dimitris Karnabatidis, MD, PhD*

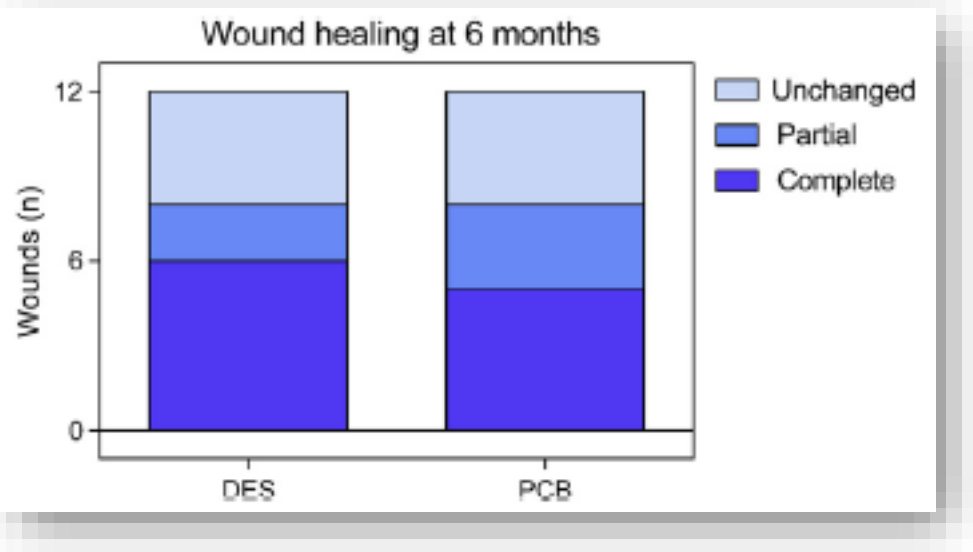
DES better than DCB in angiographic follow-up





Interestingly, clinical outcomes not significantly different





Randomized multicenter trial BIOLUX P-II: *unsuccessful*

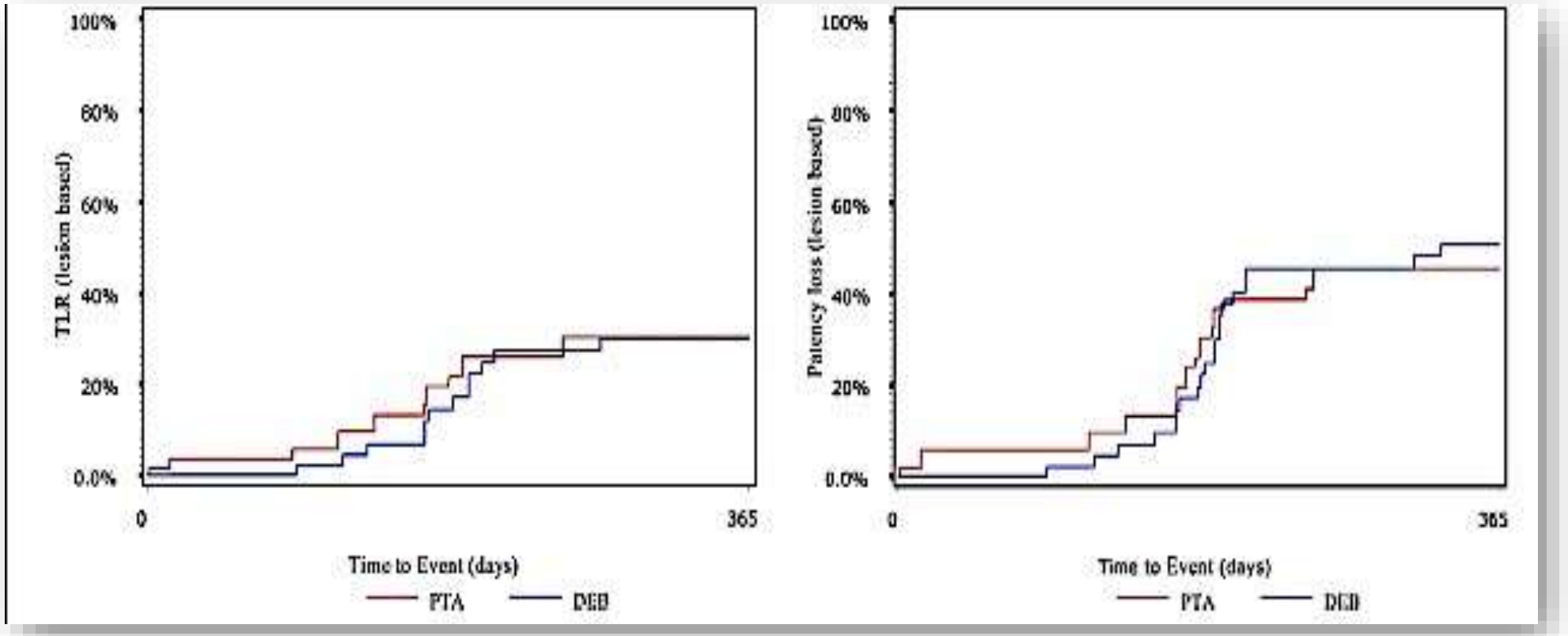
2015

Paclitaxel-Coated Balloon in Infrapopliteal Arteries

12-Month Results From the BIOLUX P-II Randomized Trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries)

Thomas Zeller, MD,* Ulrich Beschorner, MD,† Ernst Pilger, MD,‡ Marc Bosiers, MD,§ Koen Deloose, MD,§ Patrick Peeters, MD,‖ Dierk Scheinert, MD, PHD,¶ Karl-Ludwig Schulte, MD, PHD,# Aljoscha Rastan, MD,* Marianne Brodmann, MD, PHD‡

Biolux P-II: no difference in patency



Lutonix Global BTK Study Enrollment (Randomized)

	DCB (N = 287)	PTA (N = 155)	Total (N = 442)
US 32 Sites	178 Patients 62% of Enrollment	97 Patients 63% of Enrollment	275 Patients 62% of Enrollment
Europe* 14 Sites	84 Patients 29% of Enrollment	43 Patients 28% of Enrollment	127 Patients 29% of Enrollment
Japan 5 Sites	25 Patients 9% of Enrollment	15 Patients 10% of Enrollment	40 Patients 9% of Enrollment

Baseline Angio Data

	Treated Lesions DCB	Treated Lesions PTA
Number of Lesions by Vessel, % (n/N) 1 2 3 6	 85.4% (275/322) 12.1% (39/322) 2.2% (7/322) 0.3% (1/322)	 79.2% (145/183) 18.6% (34/183) 2.2% (4/183) 0.0% (0/183)
Mean Target Lesion Length, mm (n/N)	111.8 ± 92.6 mm (349/352)	94.7 ± 85.4 mm (206/213)
Mean Initial % Stenosis, % (n/N)	86.7 ± 14.5% (352/352)	84.8 ± 14.5% (212/213)

Baseline Angio Data (Cont.)

	Treated Lesions DCB	Treated Lesions PTA
Mean RVD, mm (n/N)	2.5 ± 0.61 mm (350/352)	2.6 ± 0.62 mm (212/213)
Run-off Present through Foot, % (n/N)	94.5% (310/328)	95.0% (192/202)
Any Calcification, % (n/N)	59.9% (211/352)	54.2% (115/212)
Severe Calcification, % (n/N)	15.1% (53/352)	13.2% (28/212)
CTO, % (n/N)	36.1% (137/380)	33.3% (75/225)

Baseline Rutherford Category

DCB (N=287)

PTA (N=155)

~90% of subjects had CLI

Category 3

Category 4

Category 5

P-Value 0.9181

Baseline Angio Data (Cont.)

	DCB	PTA
Lesion Locations, % (n/N)		
Popliteal	8.7% (33 / 380)	7.6% (17 / 225)
Tibioperoneal Trunk	23.9% (91 / 380)	25.3% (57 / 225)
Anterior Tibial	38.4% (146 / 380)	36.0% (81 / 225)
Posterior Tibial	23.7% (90 / 380)	25.8% (58 / 225)
Peroneal	23.4% (89 / 380)	20.9% (47 / 225)

Primary Endpoints

SAFETY

Freedom from Major Adverse Limb Events (MALE) & All-Cause Perioperative Death (POD) at 30 Days

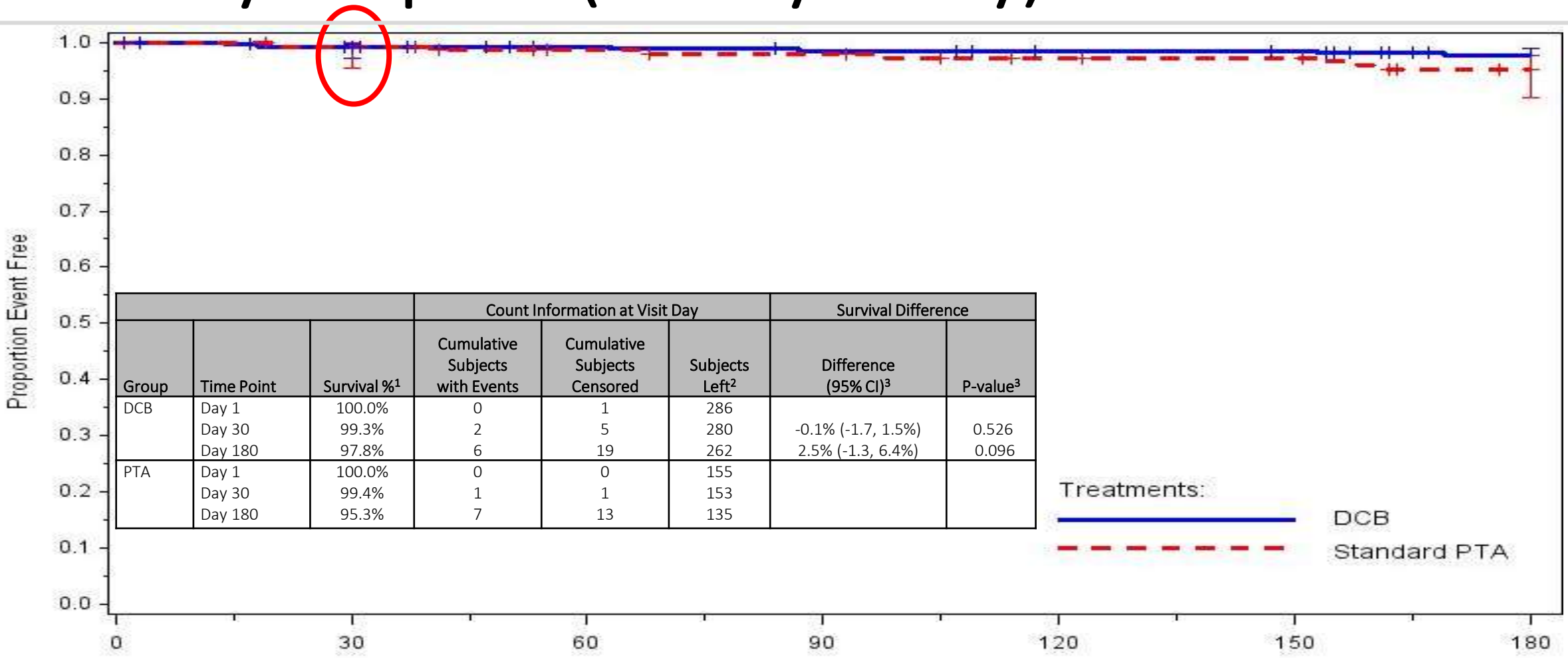
★ ***Amputation (above ankle)***
★ ***Major re-intervention***
- New bypass graft
- Jump/interposition graft revision
- Thrombectomy/thrombolysis

EFFICACY

Composite of Limb Salvage and Primary Patency at 6 Months

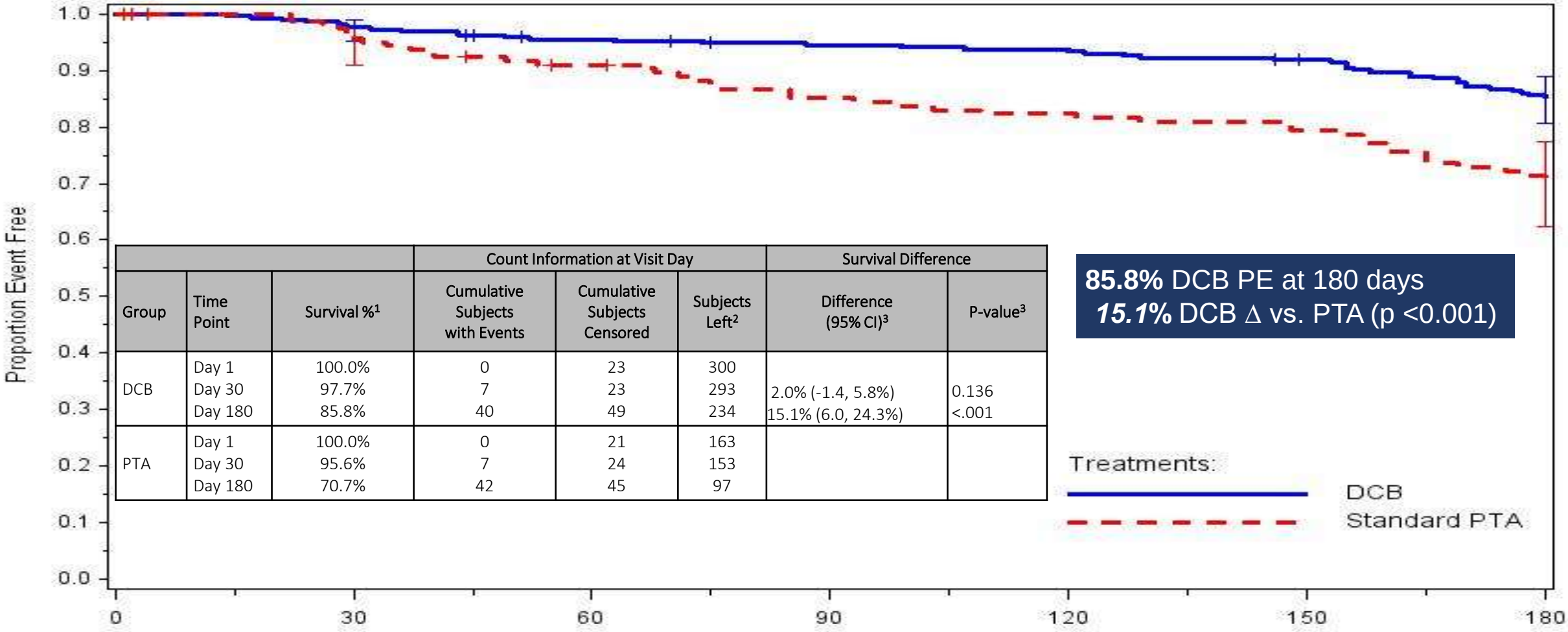
★ ***Defined as freedom from a composite of above ankle amputation, target lesion occlusion, and clinically-driven target lesion revascularization***

Primary Endpoint (30-Day Safety)



			Count Information at Visit Day			Survival Difference	
Group	Time Point	Survival %[1]	Cumulative Subjects with Events	Cumulative Subjects Censored	Subjects Left[2]	Difference (95% CI)[3]	P-value[3]
DCB	Day 1	100.0%	0	1	286		
	Day 30	99.3%	2	5	280	-0.1% (-1.7, 1.5%)	0.526
	Day 180	97.8%	6	19	262	2.5% (-1.3, 6.4%)	0.096
PTA	Day 1	100.0%	0	0	155		
	Day 30	99.4%	1	1	153		
	Day 180	95.3%	7	13	135		

Primary Endpoint* (KM 6 Mo. Efficacy)



			Count Information at Visit Day			Survival Difference	
Group	Time Point	Survival %[1]	Cumulative Subjects with Events	Cumulative Subjects Censored	Subjects Left[2]	Difference (95% CI)[3]	P-value[3]
DCB	Day 1 Day 30 Day 180	100.0% 97.7% 85.8%	0 7 40	23 23 49	300 293 234	 2.0% (-1.4, 5.8%) 15.1% (6.0, 24.3%)	 0.136 <.001
PTA	Day 1 Day 30 Day 180	100.0% 95.6% 70.7%	0 7 42	21 24 45	163 153 97		

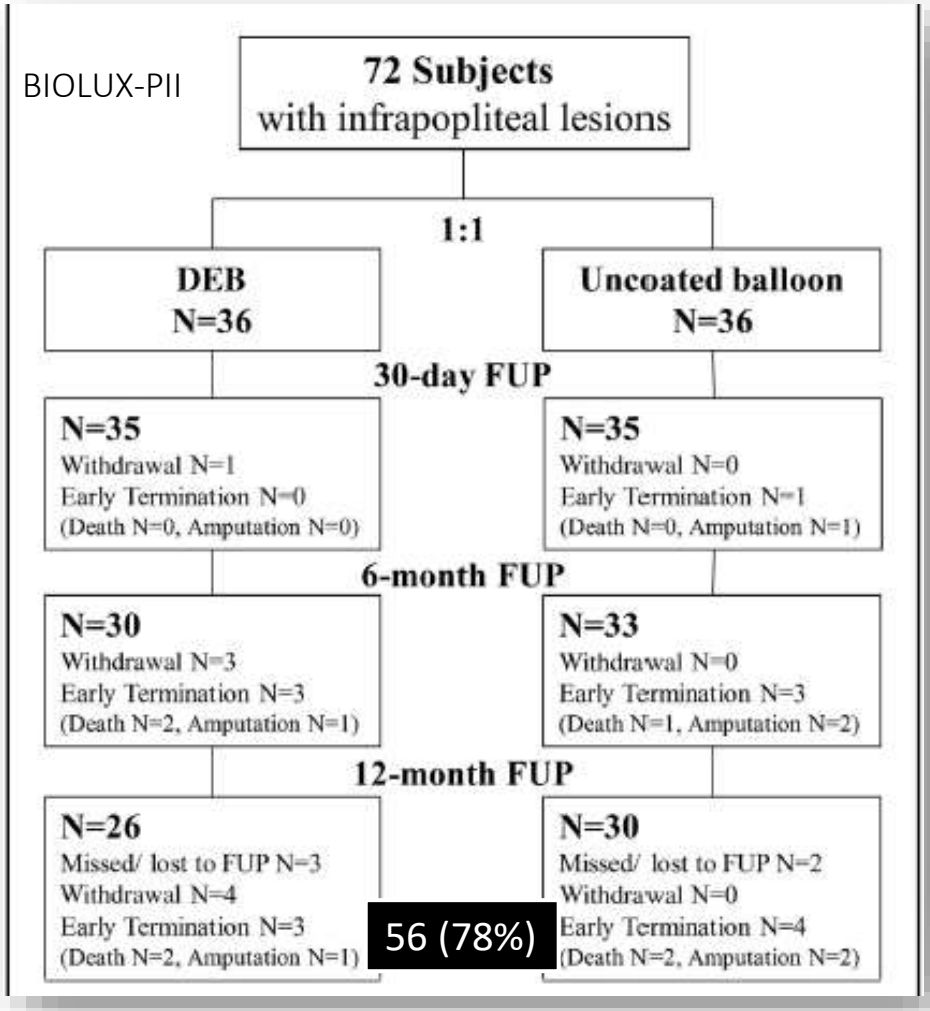
85.8% DCB PE at 180 days
15.1% DCB Δ vs. PTA (p <0.001)

*Composite of Limb Salvage and Primary Patency at 6 Months - Defined as freedom from the composite of above ankle amputation, target lesion occlusion, and clinically-driven target lesion reintervention

What are the causes for DCB failure?

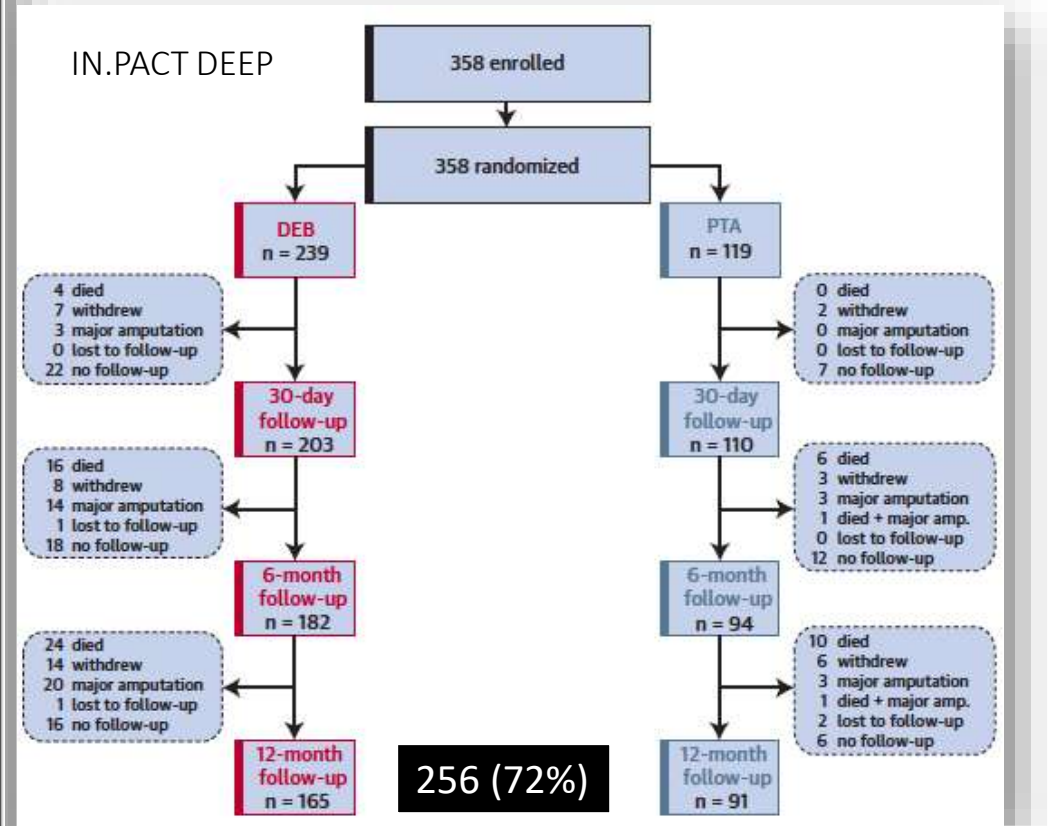
The challenges with BTK trials: subject loss

BIOLUX-PII



56 (78%)

IN.PACT DEEP



256 (72%)

IN.PACT DEEP: Root Cause Analysis

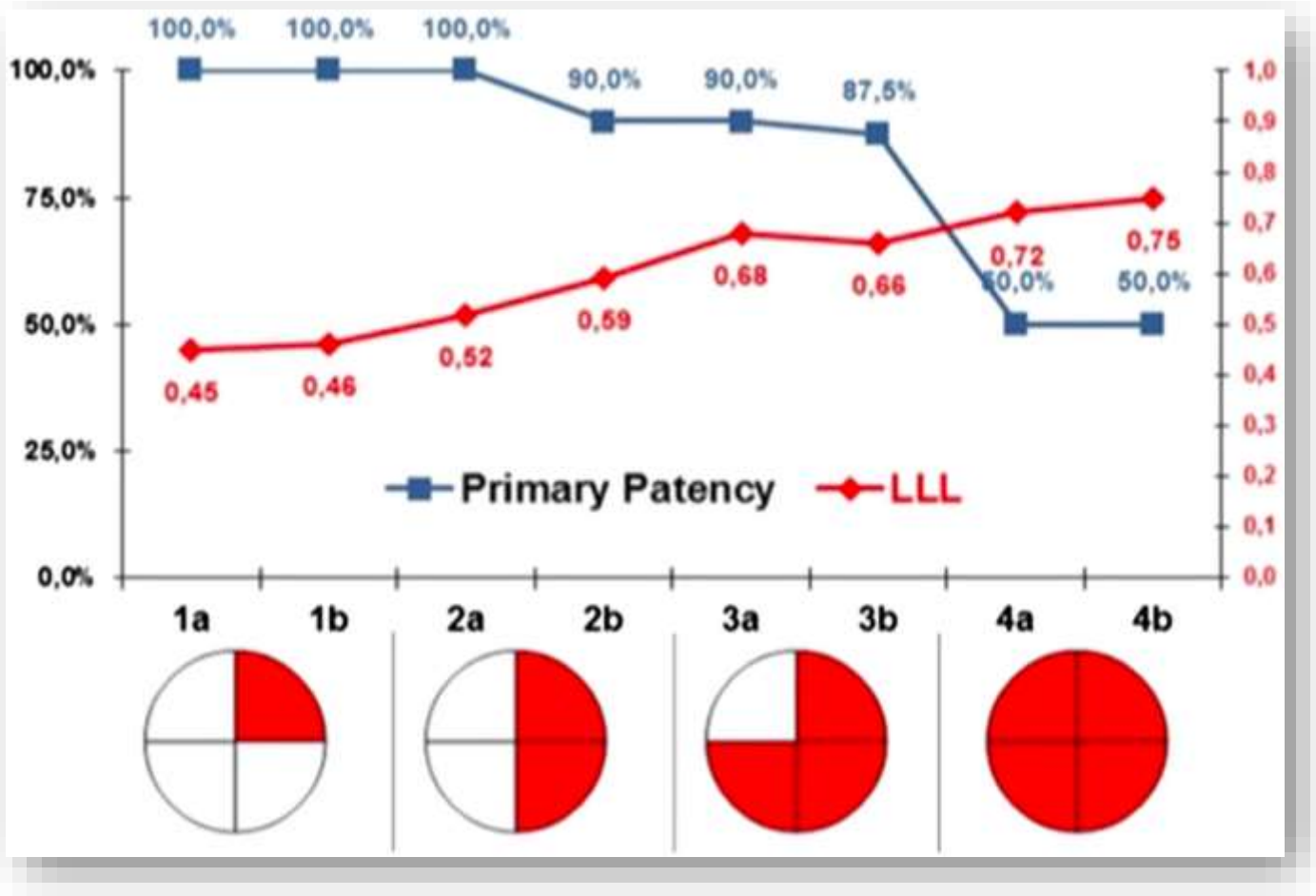
Key Factors:

1. Older technology (balloon material) provided insufficient drug delivery
2. Trial enrolled high risk subjects predisposed to safety event independent of intervention

Contributing Factors / Additional Points of Interest:

1. Procedural differences between study arms led to higher rate of procedural complications in DCB
2. Inadequate sample size and excessive loss of follow-up
3. The DCB major amputation rate was consistent with historical data and there were no unusual events caused by IN.PACT™ Amphirion™
4. Unprecedented, favorable PTA major amputation rate

Is calcium really the problem?



Calcium not prominent in failed trials

TABLE 3 Baseline Angiographic and Procedural Characteristics (ITT Population)

IN.PACT DEEP

	IA-DEB	PTA	p Value
Lesion length, cm	10.15 ± 9.10	12.86 ± 9.46	0.002
Lesion length in angiography cohort, cm	5.91 ± 4.17	7.97 ± 7.46	0.060
Reference vessel diameter, mm	2.46		
Total occlusions	38.6 (		
Restenotic lesions	6.7 (		
Severe calcium	13.7 (		

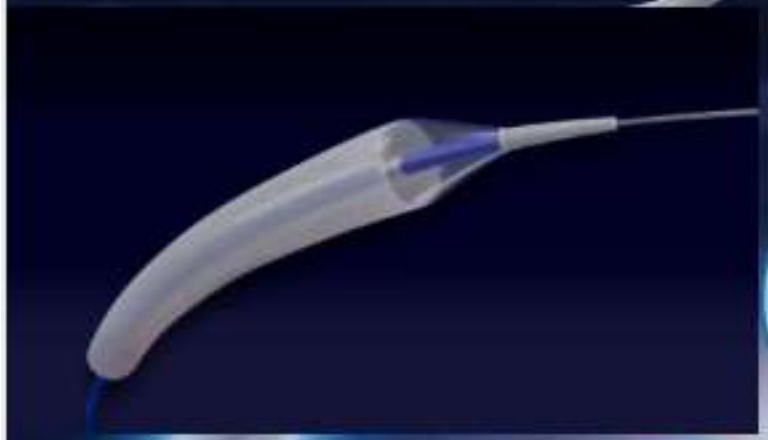
TABLE 2 Lesion Characteristics at Baseline and Follow-Up Per Core Laboratory Assessment

BIOLUX P-II

	Baseline*		
	DEB	PTA	p Value
n	50	54	
Lesion location			
Anterior tibial artery	24 (48.0)	25 (46.3)	
Posterior tibial artery	11 (22.0)	12 (22.2)	0.693
Peroneal artery	7 (14.0)	11 (20.4)	
Tibioperoneal trunk	5 (10.0)	2 (3.7)	
Other	3 (6.0)	4 (7.4)	
Calcification†			–
None	19 (55.9)	31 (81.6)	0.018
Mild	6 (17.6)	4 (10.5)	0.501
Moderate	1 (2.9)	0 (0.0)	0.472
Moderate/severe	3 (8.8)	1 (2.6)	0.338
Severe	5 (4.7)	2 (5.3)	0.243

Sirolimus-Eluting Balloon with Sustained Release

SelutionSLR™
SUSTAINED LIMUS RELEASE



Proprietary MicroReservoir Technology

- Creation of MicroReservoirs combining sirolimus & biodegradable polymer
- Sirolimus - a proven safe & effective cytostatic drug
- Offering a wider therapeutic range

MicroReservoirs: Miniature Drug-Delivery Systems

- Optimal size MicroReservoirs to achieve pharmaco- kinetic release profile comparable to best in class DES
- Consistent and predictable drug release
- Sustained therapeutic effect for up to 90 days [1].

Cell Adherent Technology (CAT™)

Proprietary amphipathic lipid technology which binds MicroReservoirs to the balloon surface

- Contains and protects micro-reservoirs during insertion and inflation
- Enhances drug retention and bioavailability, allowing for a lower drug dose concentration on the balloon surface (1 µg/mm²).
- Optimizes transfer of MicroReservoirs to the tissue and maximizes the cellular uptake of sirolimus.

MedAlliance

1. Drug concentration evident in MicroReservoirs and tissue - Data on file at M.A. Med Alliance SA

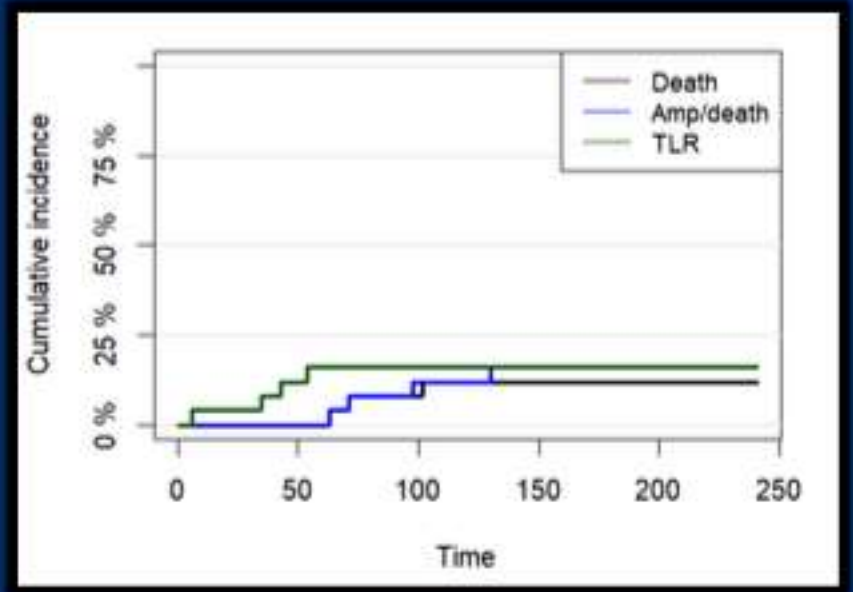
PRESTIGE Trial

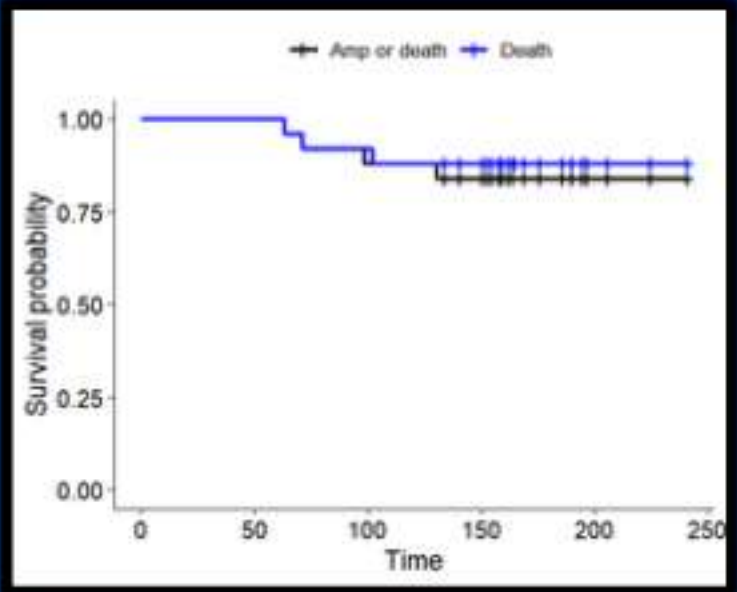
Physician initiated, prospective, non-Randomized single-center trial, investigating the safety and Efficacy of the Treatment with the Selution Sirolimus Coated Balloon in TASC C and D Tibial occlusive disease In patients with critical limb Ischemia from SinGaporE

NCT04071782

At 6 months...

- Technical success : **100.0%**
- Freedom from device- or procedure-related mortality through 30 days : **100.0%**
- Freedom from Target Lesion Revascularization (TLR) : **92.6% (25/27)**
- Amputation Free Survival (AFS): **84.0% (21/25); 3 deaths and 1 BKA**
- Primary Patency rate : **81.5% (22/27)**
- Wound healing : **81.8% (18/22)**





Patient Demographics

Characteristics	Total patients = 25, n (%)
Age, mean ± sd	63.72 ± 9.73
BMI, mean ± sd	24.40 ± 4.88
Male gender	17 (68.0)
Ethnic Group	
Chinese	18 (72.0)
Malay	4 (16.0)
Indian	3 (12.0)
Co-Morbidities	
Diabetes	22 (88.0)
Hypercholesterolemia	19 (76.0)
Hypertension	22 (88.0)
CVA in the past 12 months	1 (4.0)
Myocardial Infarction	3 (12.0)
Angina	2 (8.0)
Congestive Heart Failure	4 (16.0)
End Stage Renal Failure (ESRF)	11 (44.0)
Rutherford Score 5	25 (100.0)
Mean WIFi Score	3.72 ± 1.14
Clinical Stages (Risk of Amputation)	
1 (Very Low Risk)	2 (8.0)
2 (Low Risk)	9 (36.0)
3 (Moderate Risk)	9 (36.0)
4 (High Risk)	5 (20.0)
Toe Pressure (mmHg), median (range)	37.5 (0 – 100)

Search documents and file names for text

88% had DM

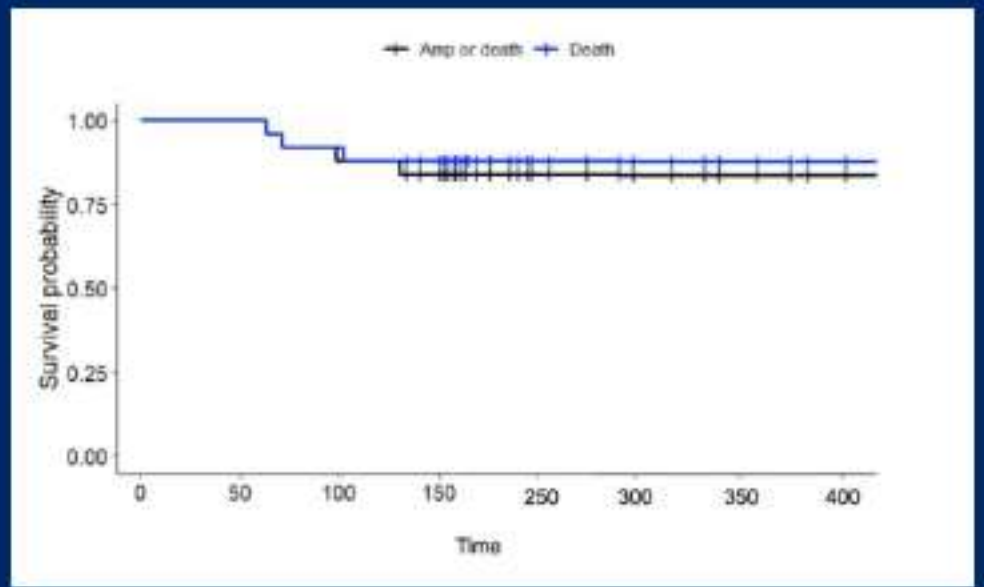
44% w/ ESRF
100% subjects are Rutherford 5

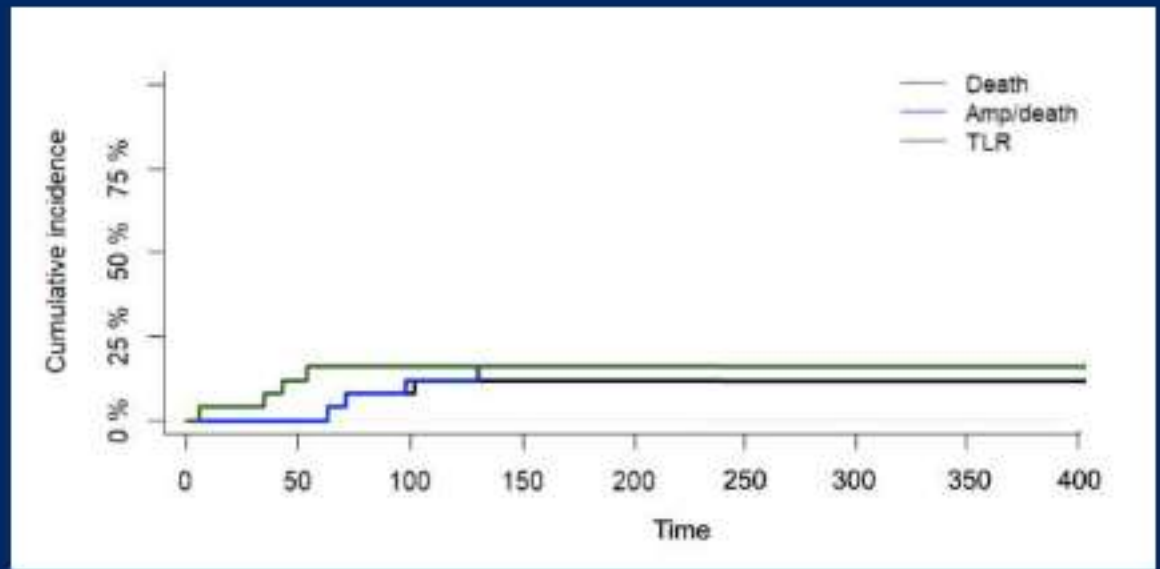
56.0% at moderate to high risk for amputations based on WIFi

At 12 months...

- Freedom from Target Lesion Revascularization (TLR) : 92.6% (25/27)
- Amputation Free Survival (AFS) : 84.0% (21/25): 3 deaths and 1 BKA
- Primary Patency rate : 77.8% (21/27)
- Wound healing : 81.8 (18/22)

Sustained from 6 M





Summary

- There remains very little data supporting the clinical efficacy of DCB BTK
- Specific causes include:
  - Calcification
  - High frequency of death early in follow up
  - Disassociation between patency and clinical outcomes
  - ?ineffectiveness of paclitaxel BTK
- Await novel approaches with non-PTX therapeutics