Drug-coated balloon for SFA and below the knee intervention

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JCR 2014

Speaker's name: Naoto Inoue

■ **I have the following** potential conflicts of interest to report:

- ☐ Research contracts
- ■ Consulting- Terumo, Kaneka, Medicon, Japan Life Line
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ **I do not have any potential conflict of interest**

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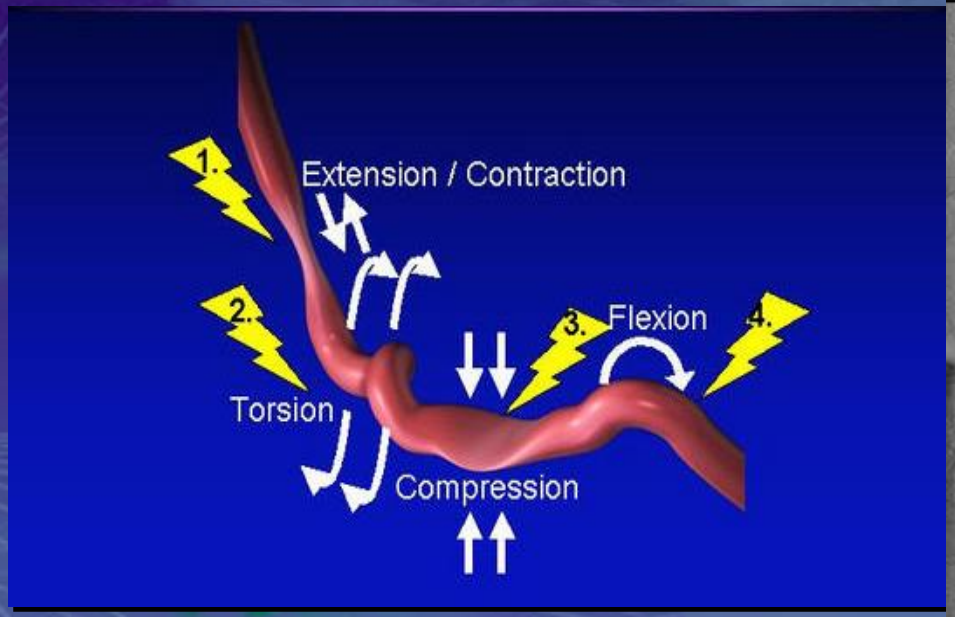
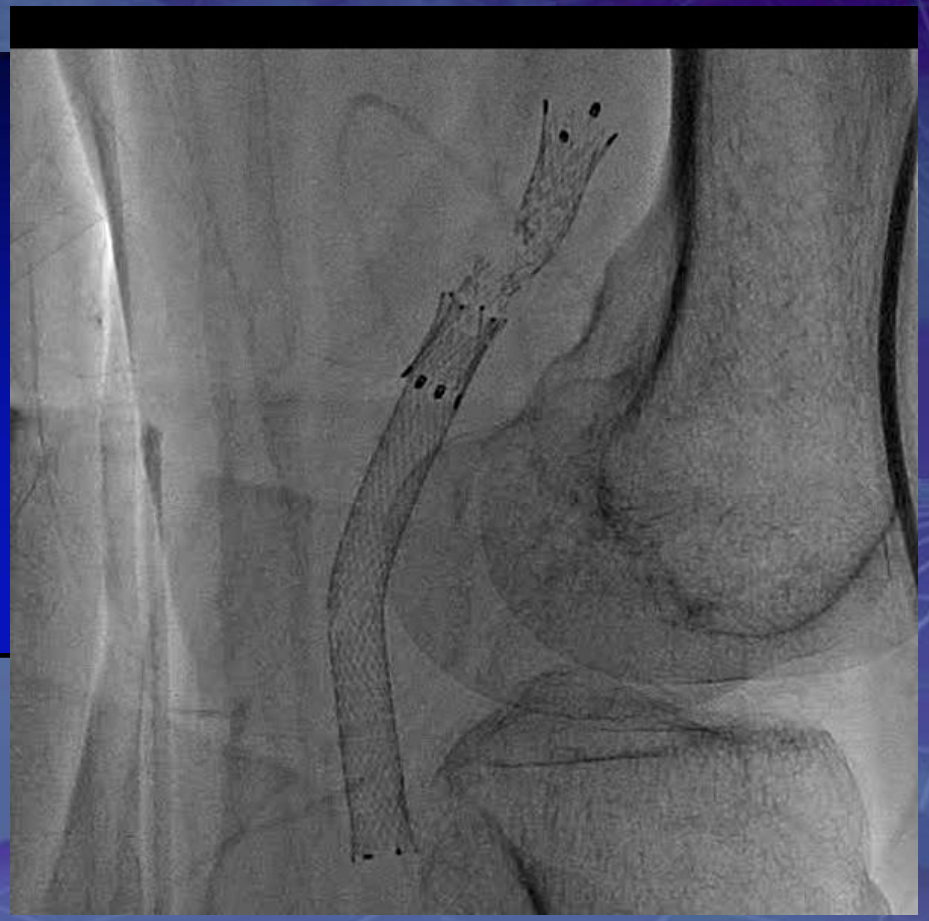
Stent fracture





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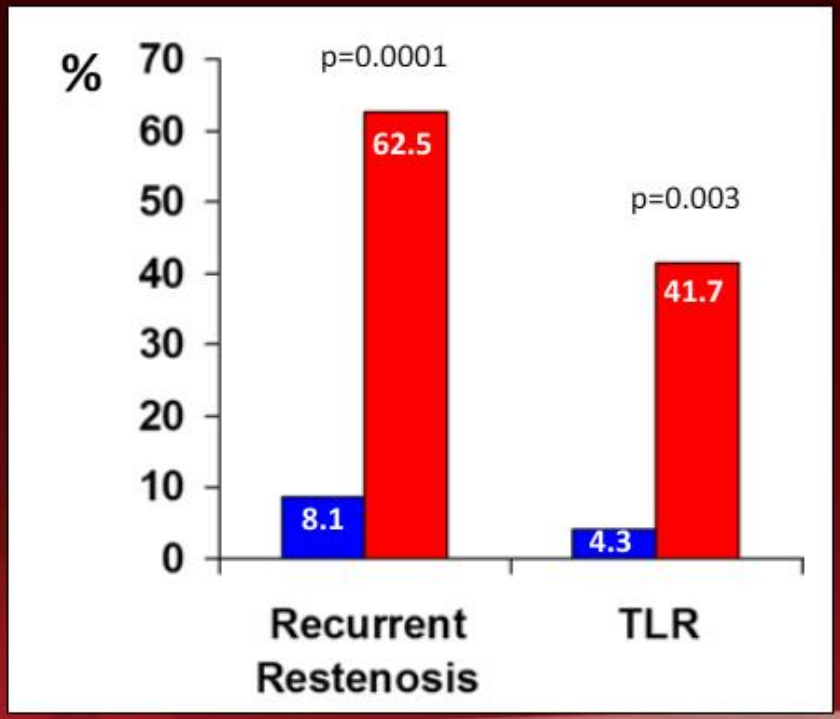
DEB in Coronary Artery Instent Restenosis

R → Paclitaxel-eluting balloon group

Conventional balloon angioplasty group

6 months later: incidence of recurrent restenosis and TLR



Hans Krankenberg, MD

VIVA 11

Harbara S et al. J Am Coll Card 2011;4(2):149-54

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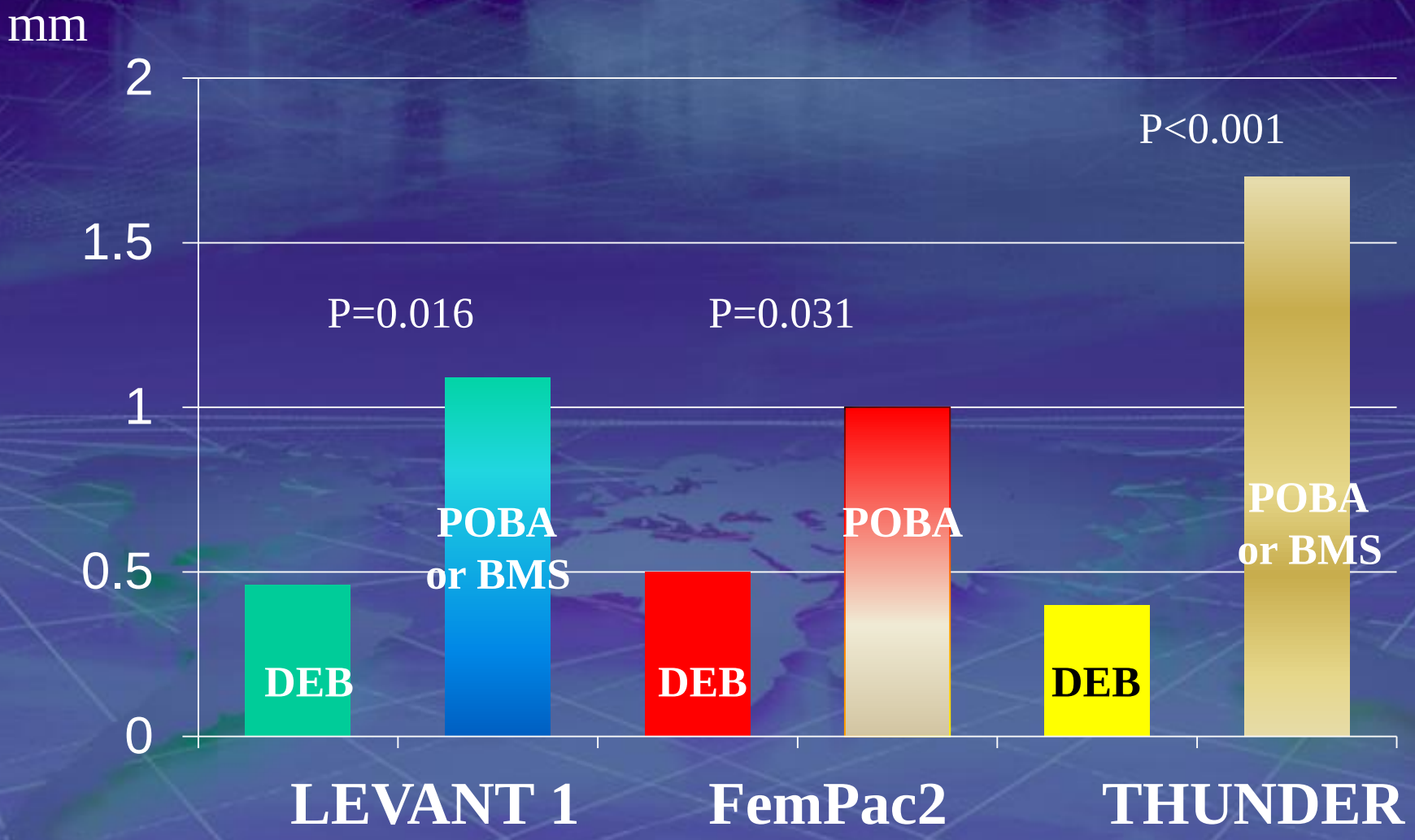
6 month late loss in fomoropopliteal arteries



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IN.PACT AMPHiRiON

Amphirion Deep
Balloon platform

Low entry profile 0.017”
Conform to tortuous vessel
up to 120mm length

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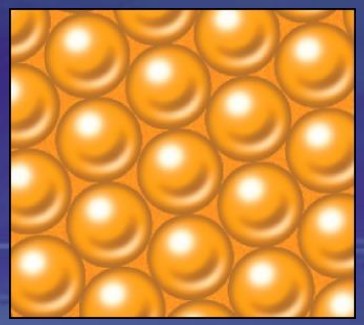
IN.PACT AMPHiRiON

A new therapeutic concept

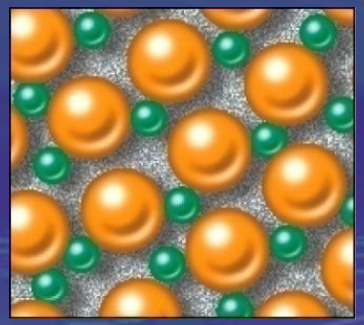
FreePac™

Proprietary hydrophilic coating formulation

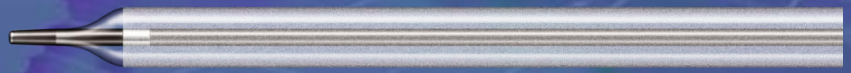
- separates Paclitaxel molecules
- balances hydrophilic and lipophilic properties
- facilitates Paclitaxel elution into the vessel wall



Paclitaxel



Paclitaxel/ separator molecule



Drug dose 3 μg/mm²

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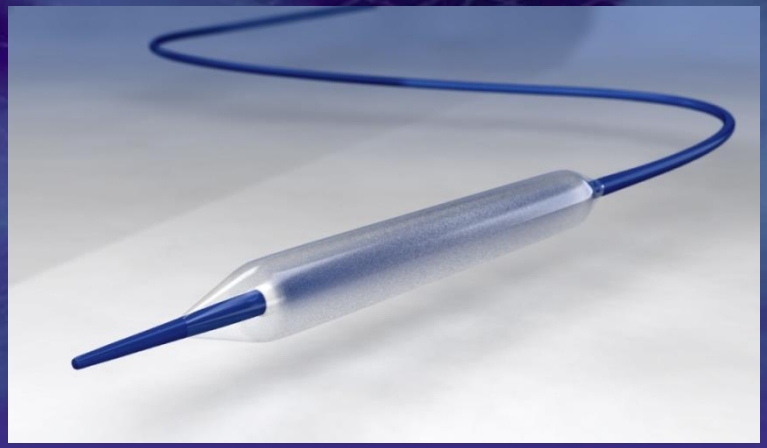
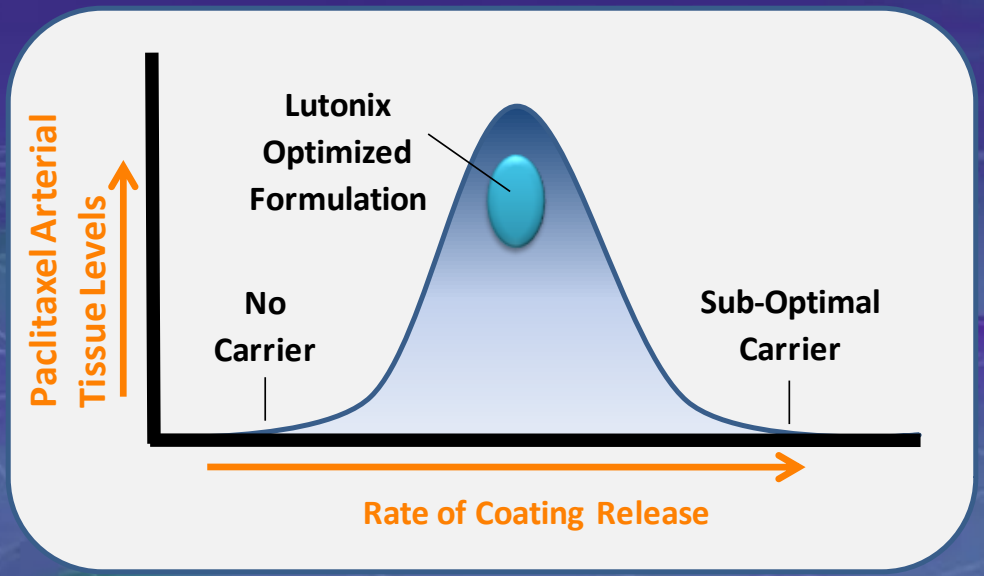
Technology overview





- Proprietary 2 μg/mm² paclitaxel coating with hydrophilic non-polymeric carrier
- Formulation balances drug *retention* during transit and *uptake* upon inflation
- Drug delivered during single 30 second inflation
- Robust, uniform coating

CAUTION: Investigational Device – Limited by Federal (USA) Law to Investigational Use

Park-Krankenhaus Leipzig

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LEVANT 2

A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing DCB vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries

Jihad A. Mustapha, MD, FACC, FSCAI
Director of Cardiovascular Catheterization Labs
Director of Endovascular Interventions
Director of Cardiovascular Research Metro Health Hospital

CAUTION: Investigational Device - Limited by Federal (USA) Law to Investigational Use

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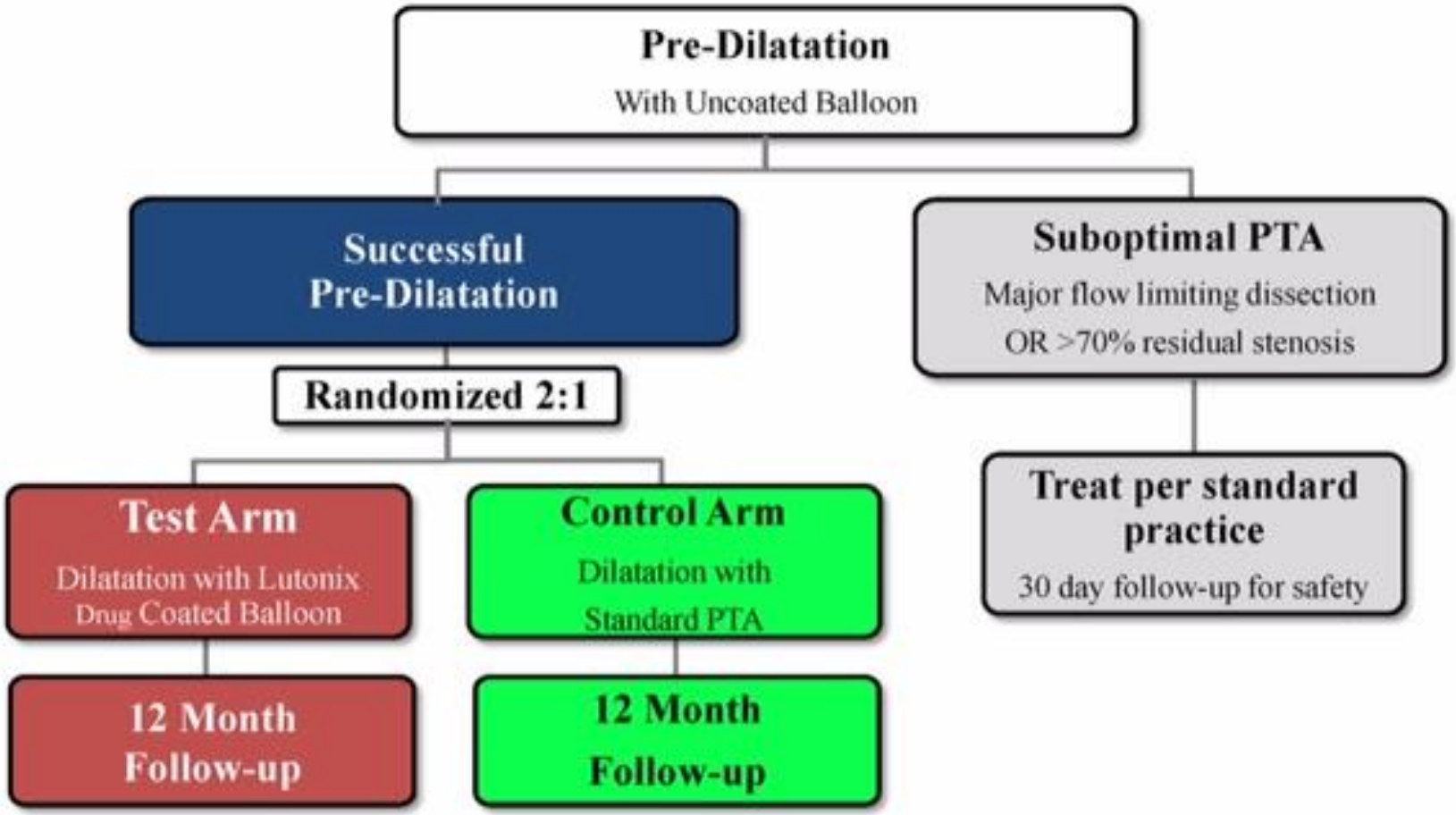
Study Flow



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LEVANT 2 Primary Endpoints

Safety	Efficacy
Composite of freedom from all-cause peri-operative death & freedom at **1 YEAR** in the index limb from: • Amputation (above or below the ankle) • Re-intervention • Index-limb-related death	Primary patency of the target lesion at **1 YEAR**: • Absence of restenosis (defined by DUS PSVR ≥2.5 & freedom from target lesion revascularization (TLR)

CAUTION: Investigational Device - Limited by Federal (USA) Law to Investigational Use

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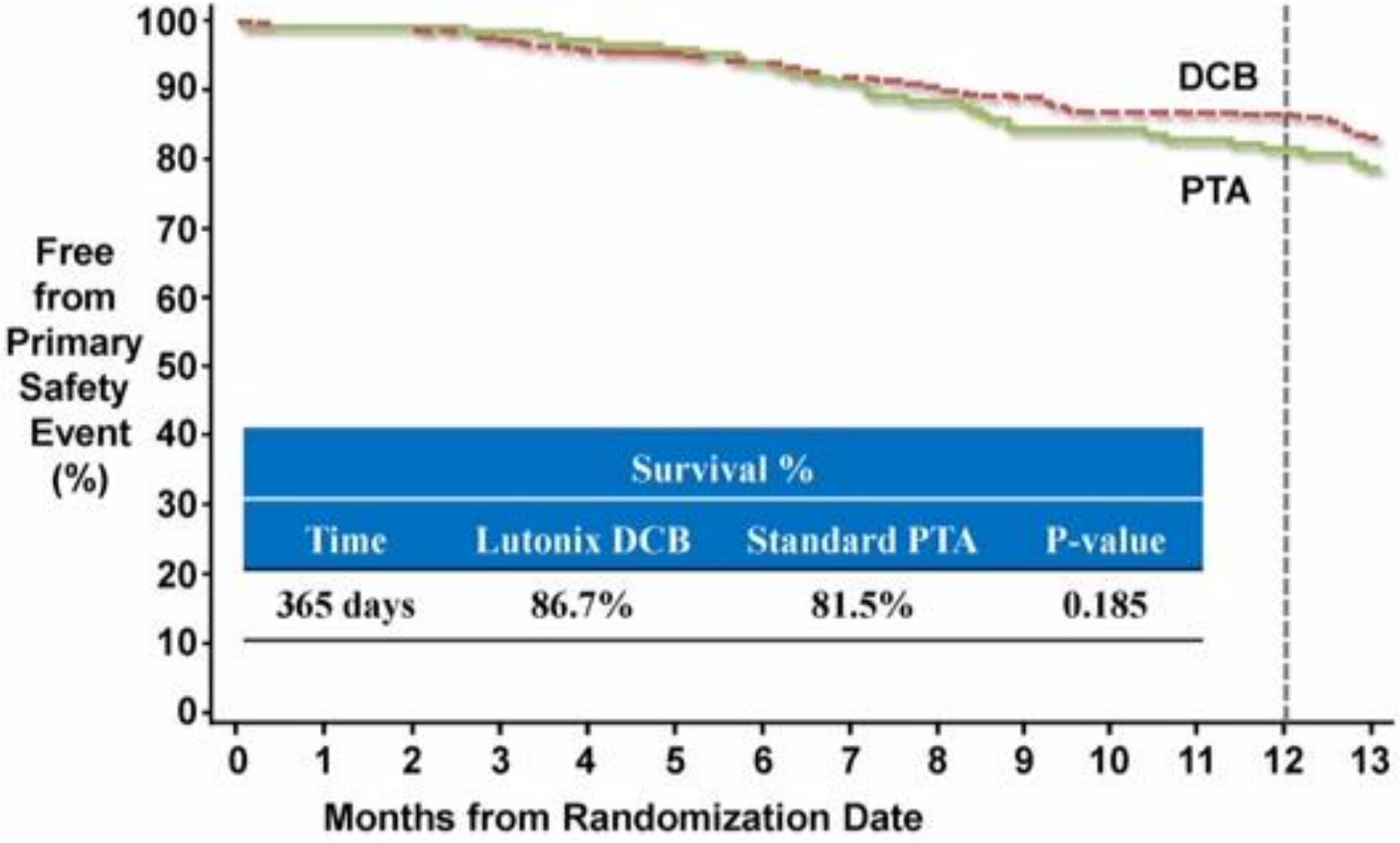
Freedom from Primary Safety Event



Survival %			
Time	Lutonix DCB	Standard PTA	P-value
365 days	86.7%	81.5%	0.185

CAUTION: Investigational Device - Limited by Federal (USA) Law to Investigational Use

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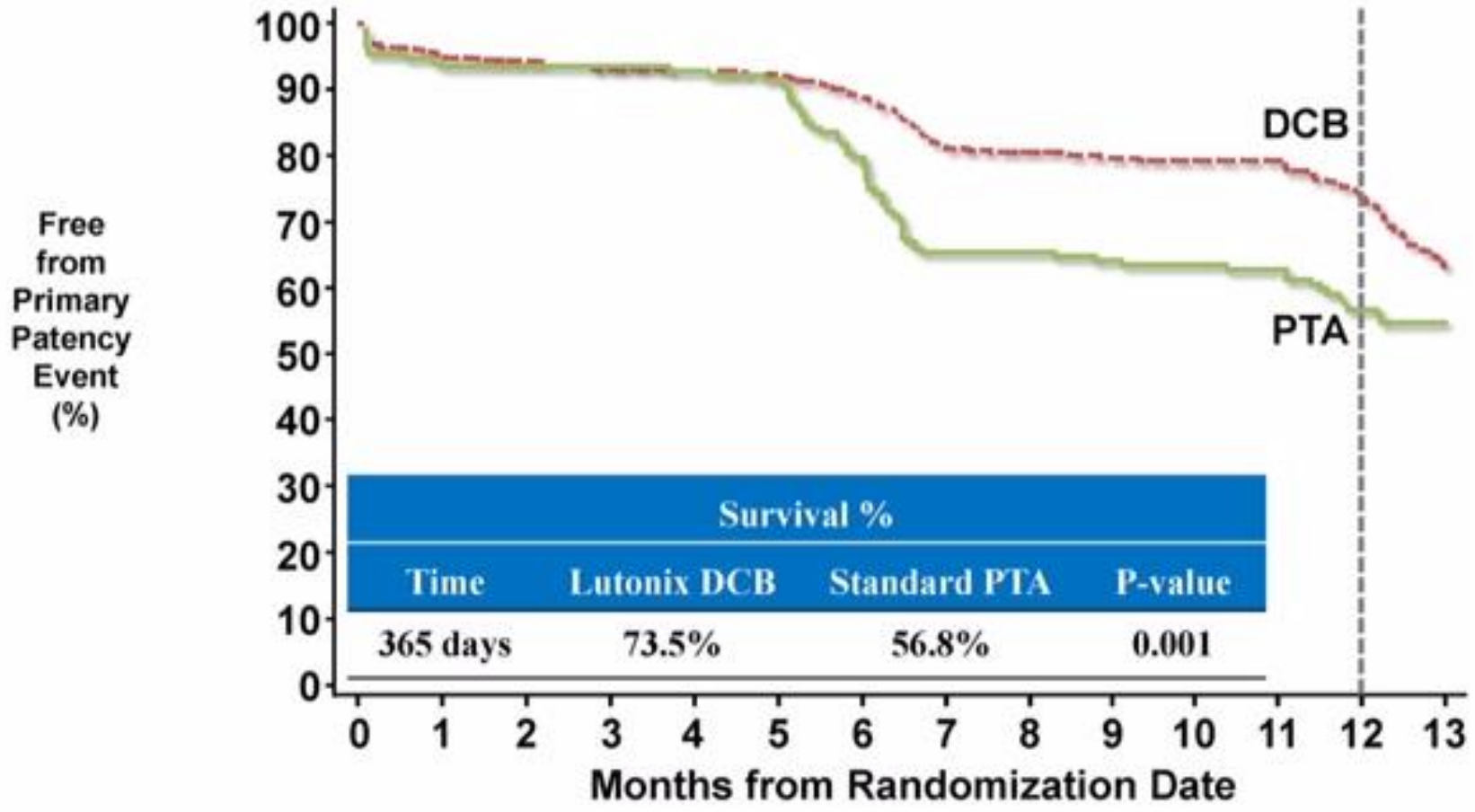
Primary Patency Kaplan-Meier



Survival %			
Time	Lutonix DCB	Standard PTA	P-value
365 days	73.5%	56.8%	0.001

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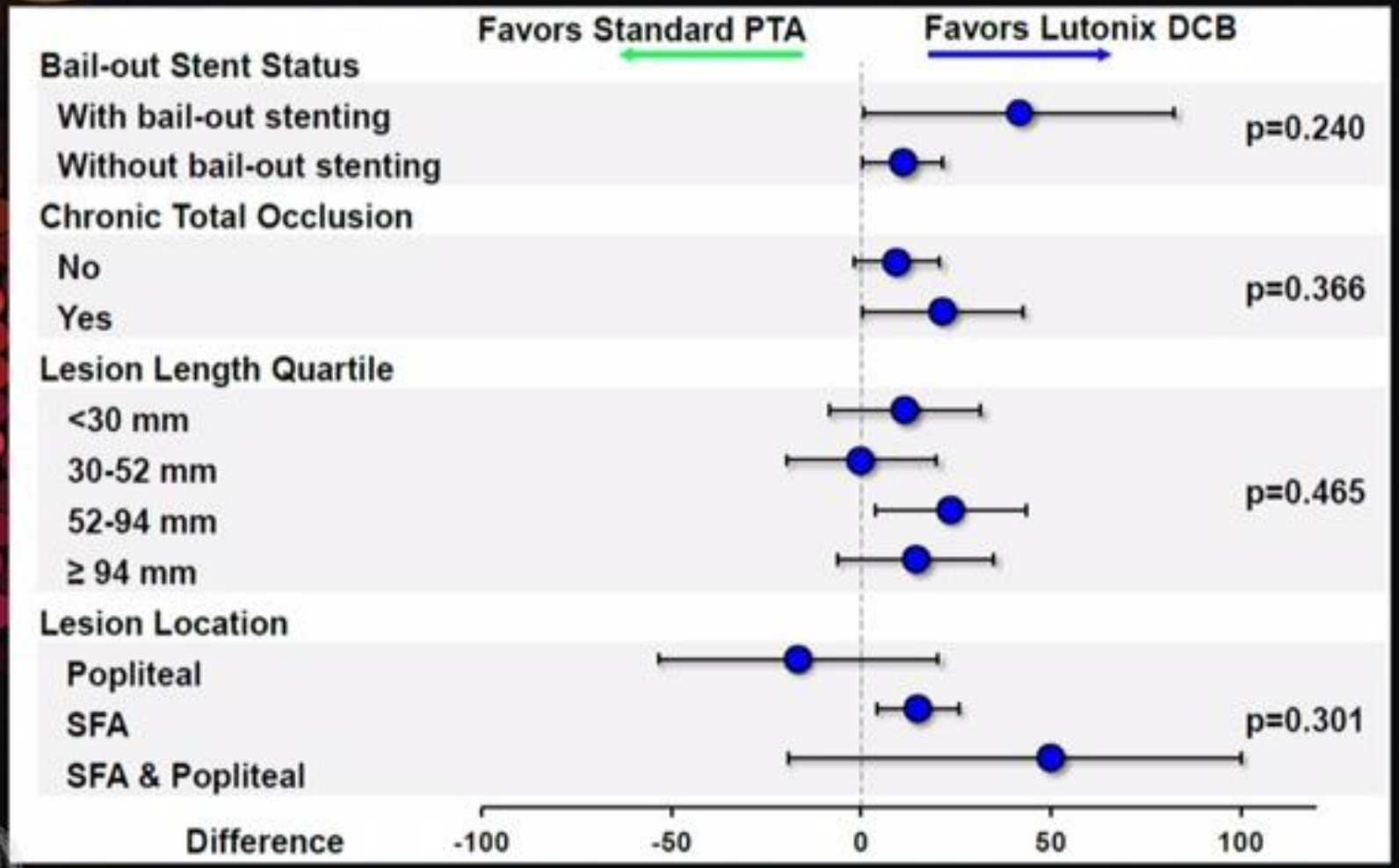
LEVANT II
1-Year Subgroup Analyses



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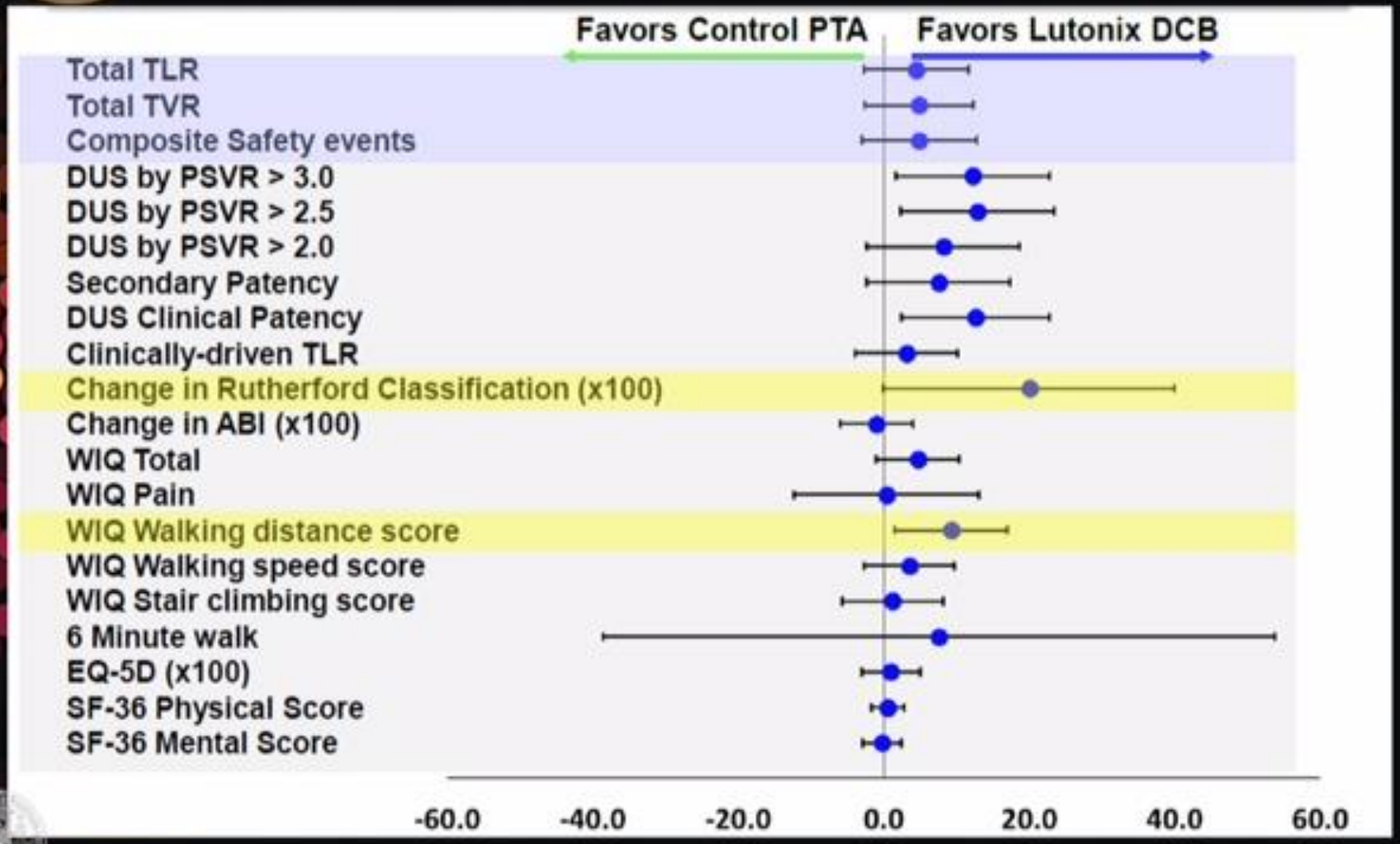
LEVANT II
Summary of 1-Year Secondary Endpoints



Efficacy Summary

- Levant 2 demonstrated superior patency to PTA
  - 30% Improved patency over standard of care PTA
- Clinical Benefits:
  - Freedom from TLR 89.7% and separation continues
  - Significant improvement in Rutherford Class
  - Significant improvement in Walking Distance scores

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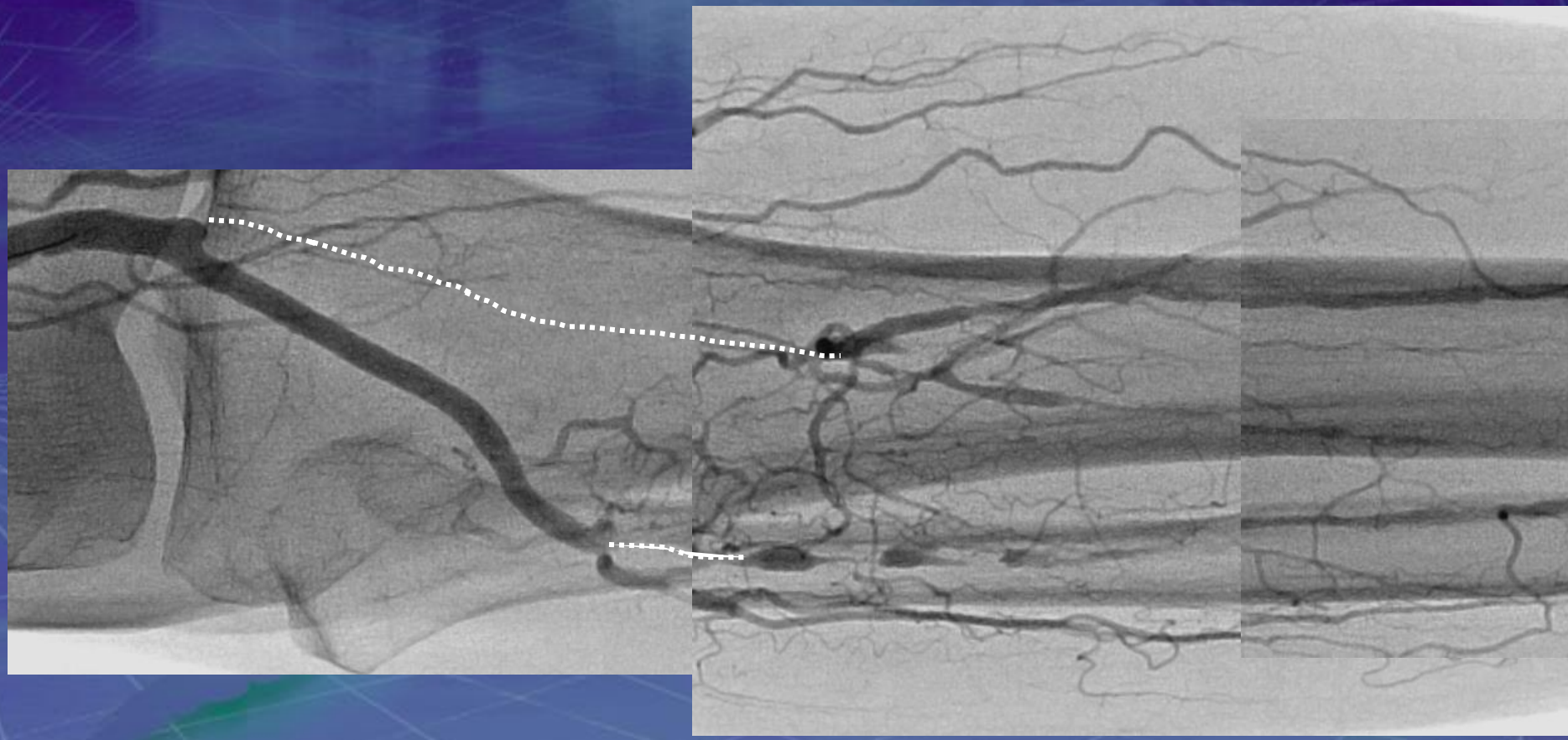
83y.o. male

Rt-foot, Rutherford 4, ABI=0.69

ESRD (4y), DM, HTN,



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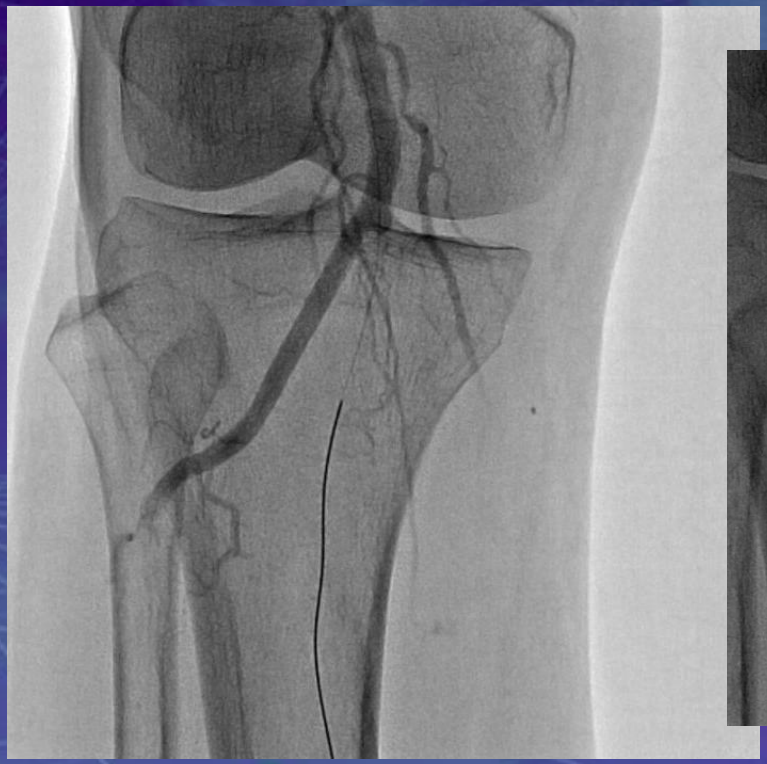
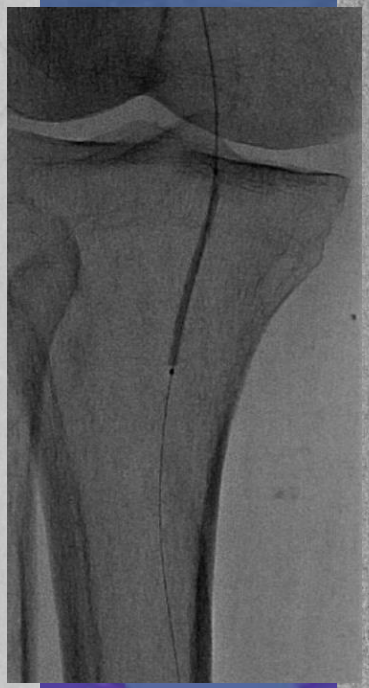
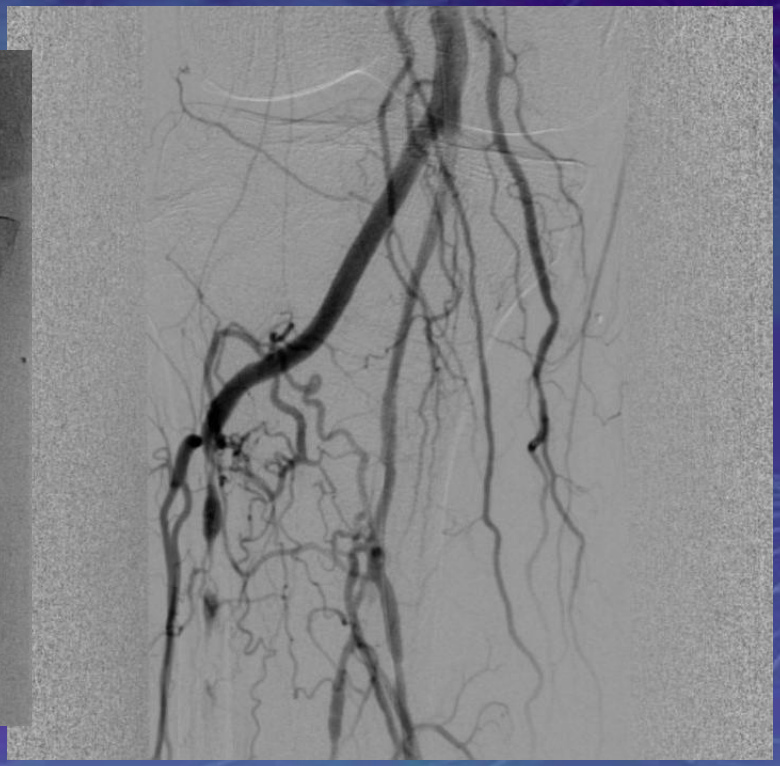
EVT for TPT







Treasure wire 2.0/40mm

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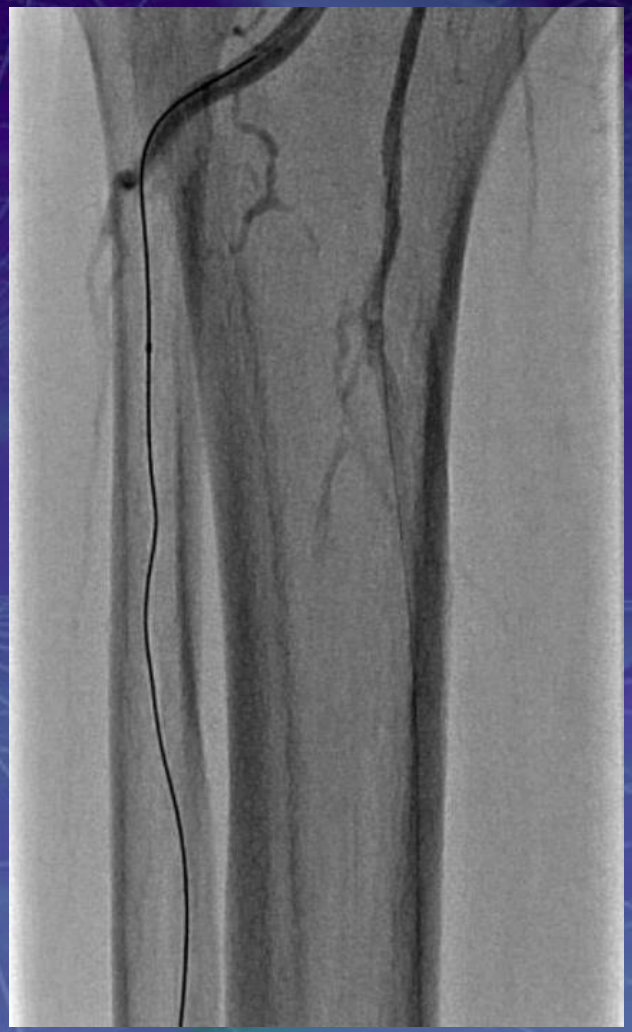
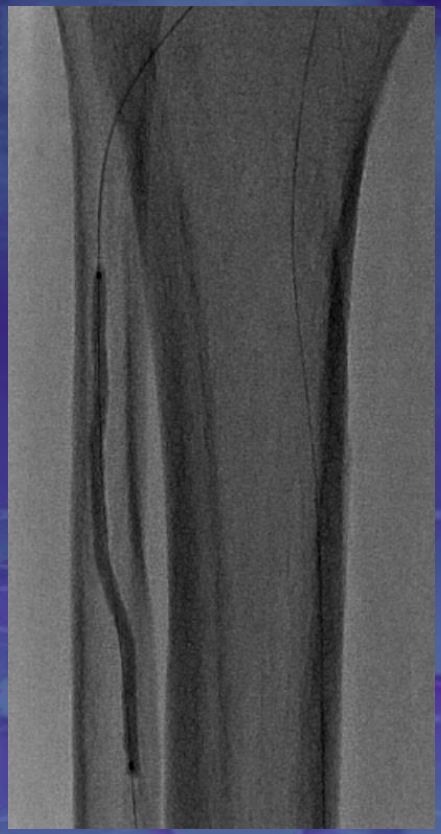
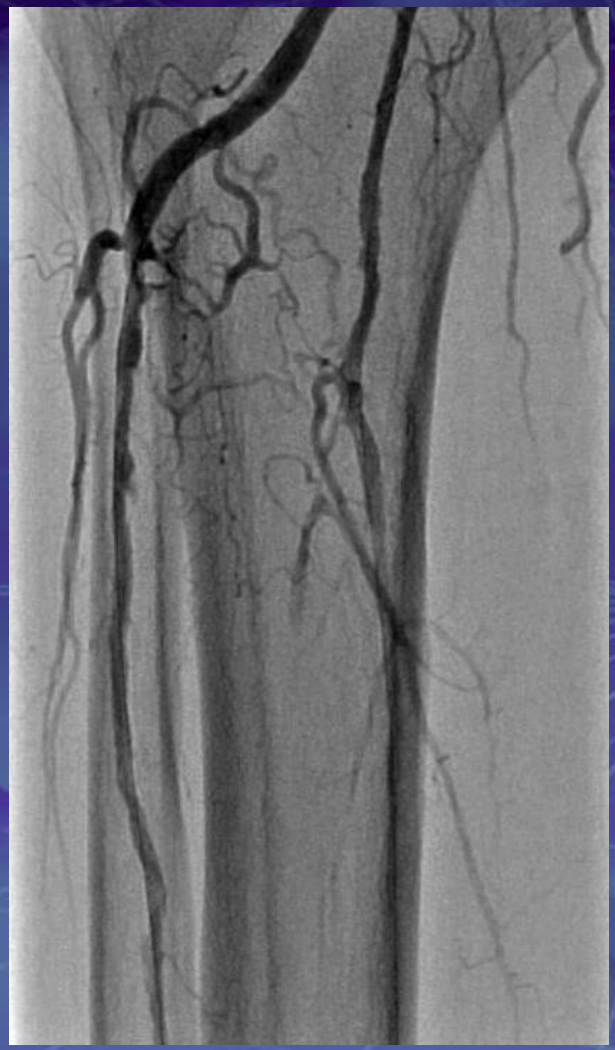
EVT for ATA



Treasure wire



Amphirion deep
2.5/80



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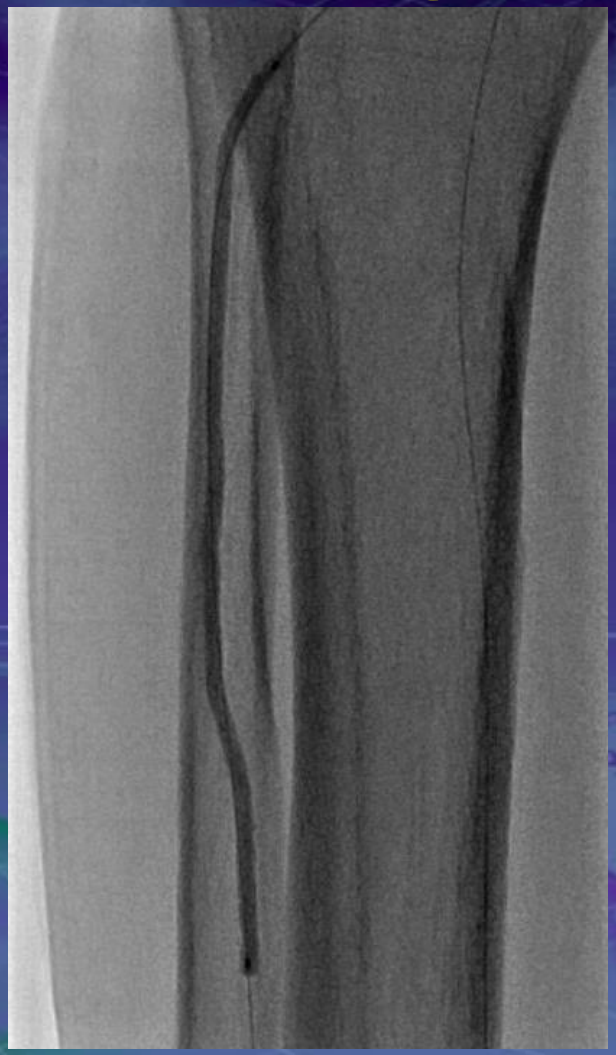
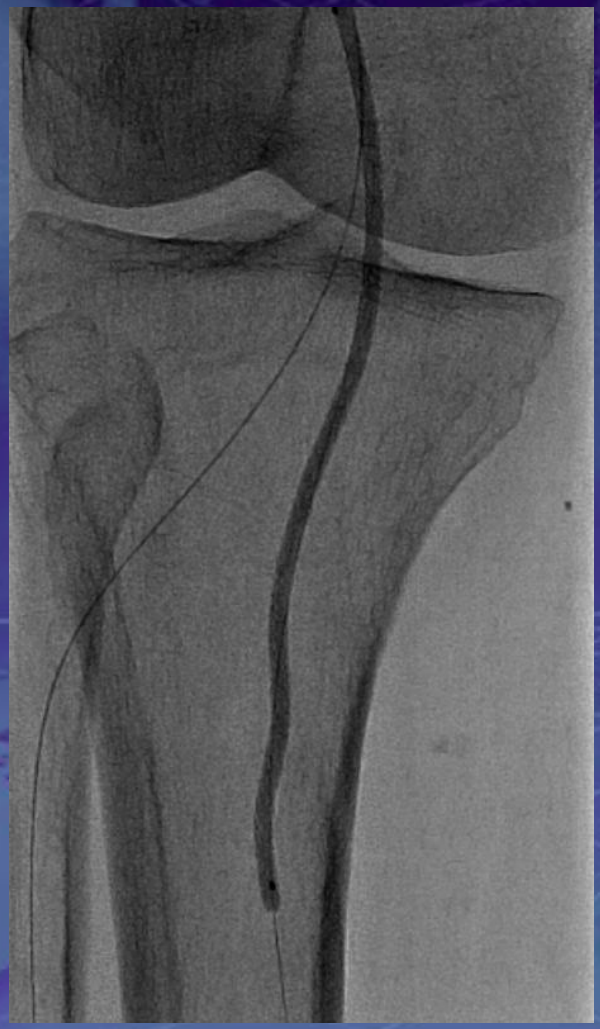
Drug eluting balloon





In.pact Amphirion 2.5/120 Re-use (=POBA)

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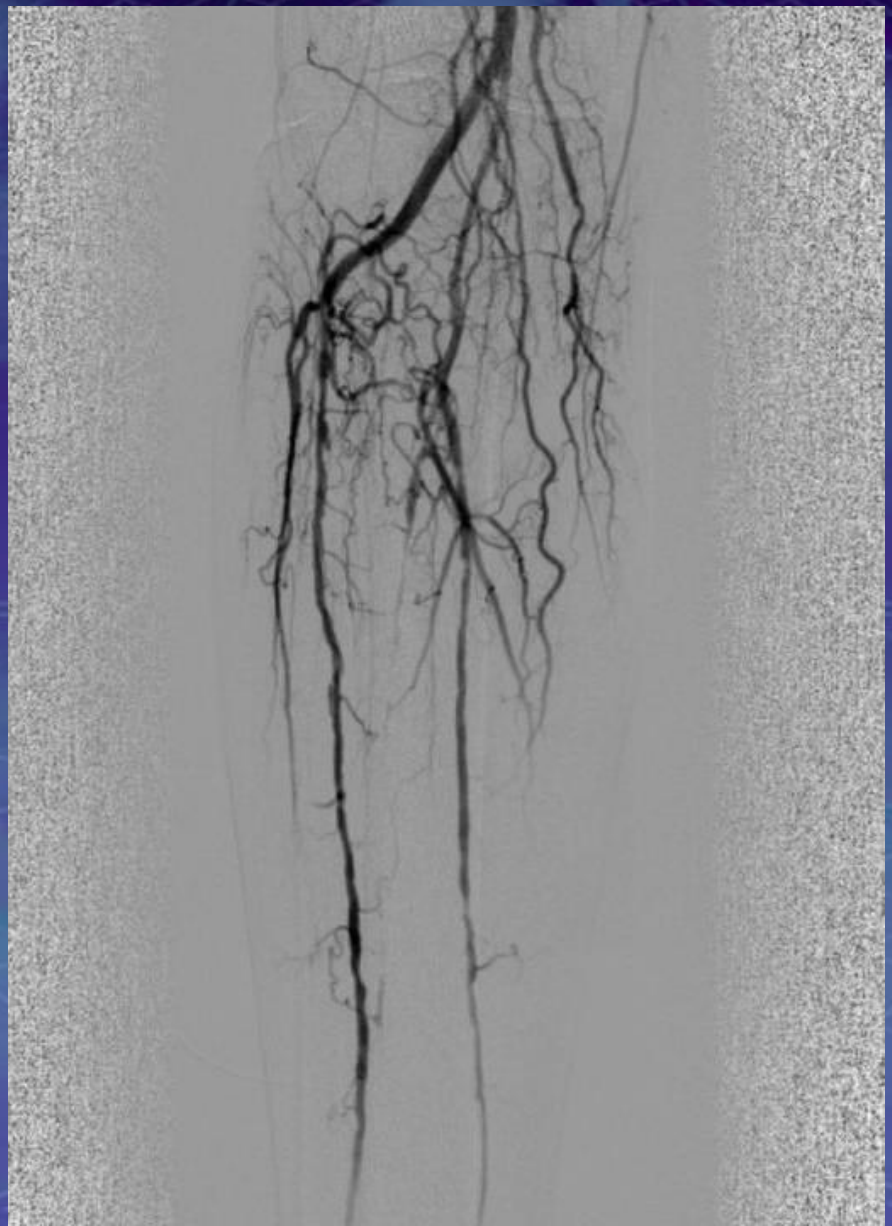
Final result



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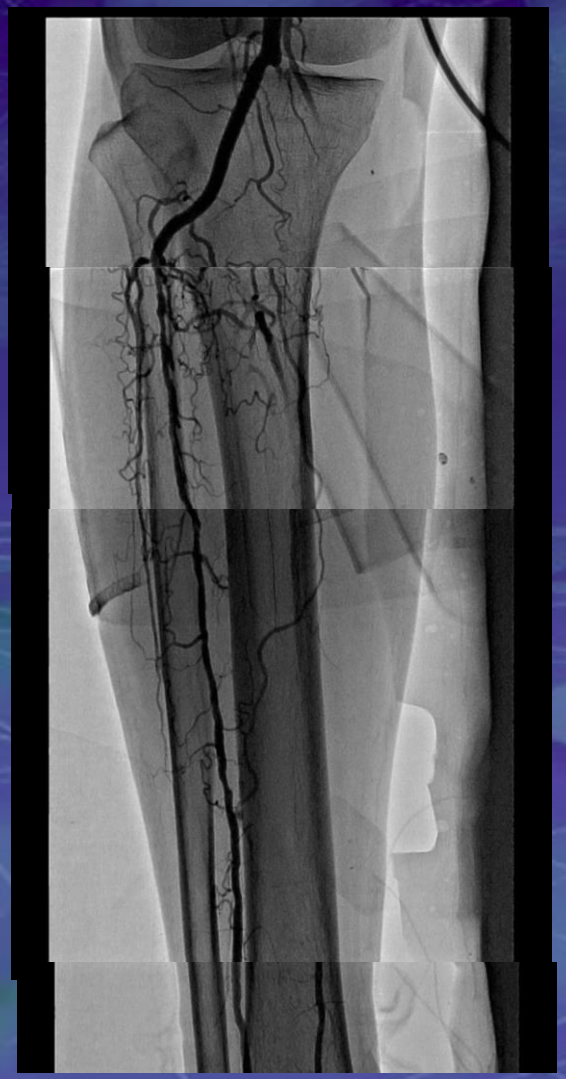
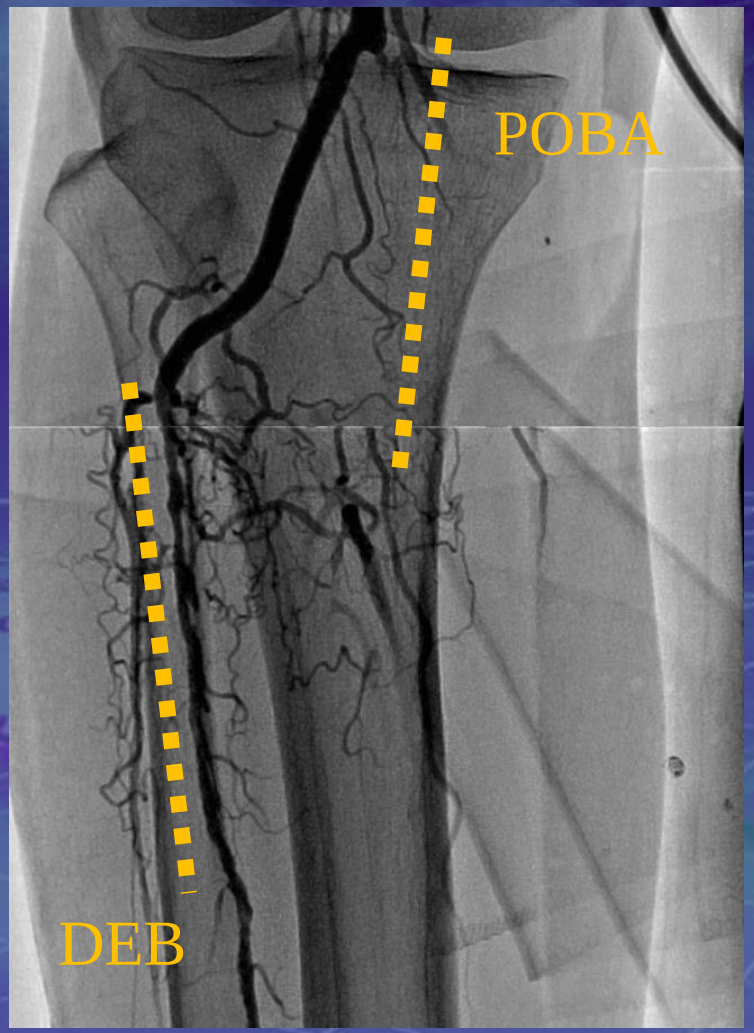
Follow up angiography (3month)





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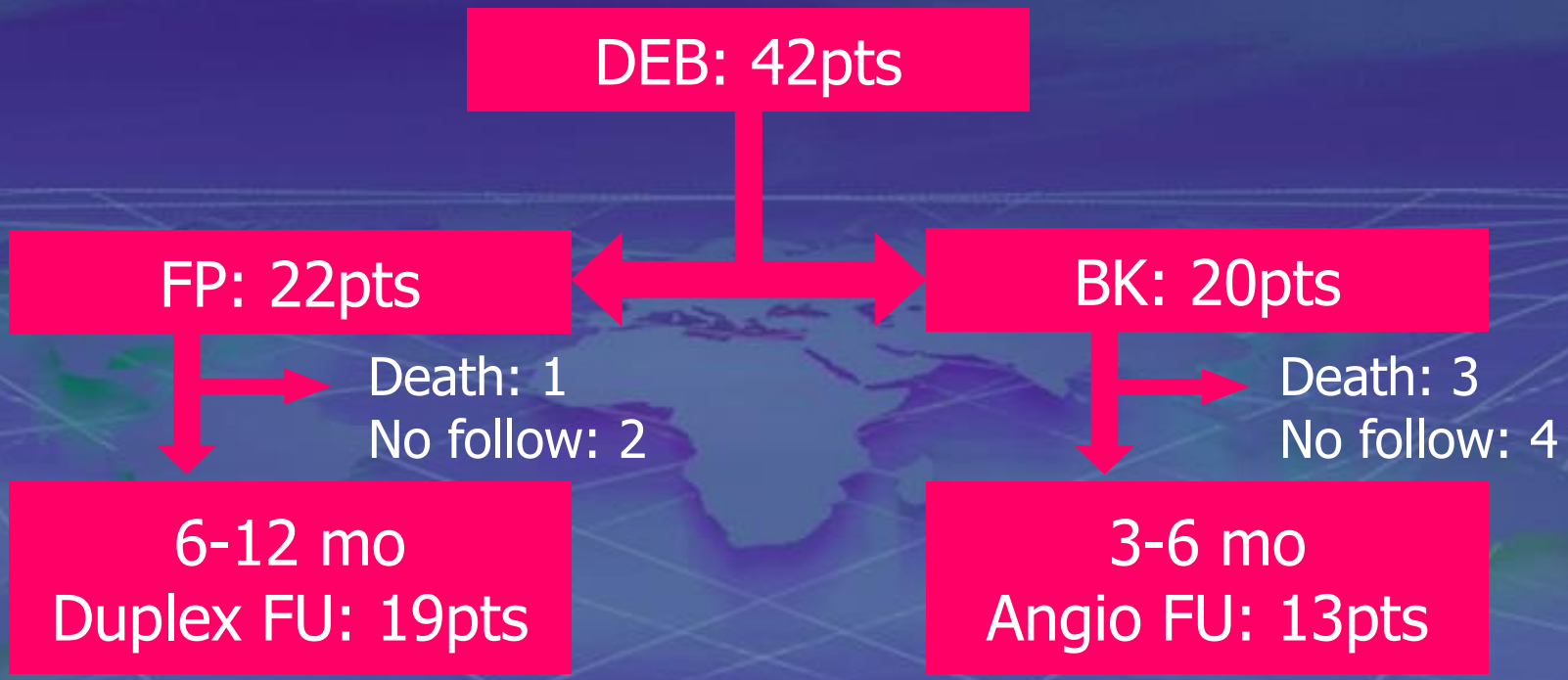
Drug eluting balloon for PAD

Forty-two patients were studied, using DEB for femoro-popliteal (FP) or below knee (BK) lesions.



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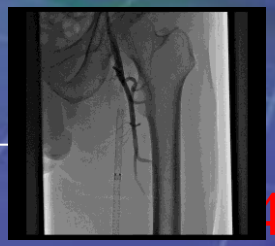
Patient characteristics

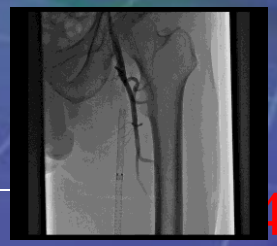
N	22
Age, Year	73.8±6.4
Male/Female	14/8
BMI	23.2±2.4
Diabetes, n (%)	16 (73)
Hypertension	20 (91)
Dyslipidemia	11 (50)
Smoking	13 (59)
Hemodialysis	2 (10)
Family History	3 (16)
CAD	13 (59)
CVD	5 (24)

Rutherford class	
I	0
II	6
III	15
IV	0
V	1
VI	0
ABI	0.64±0.08

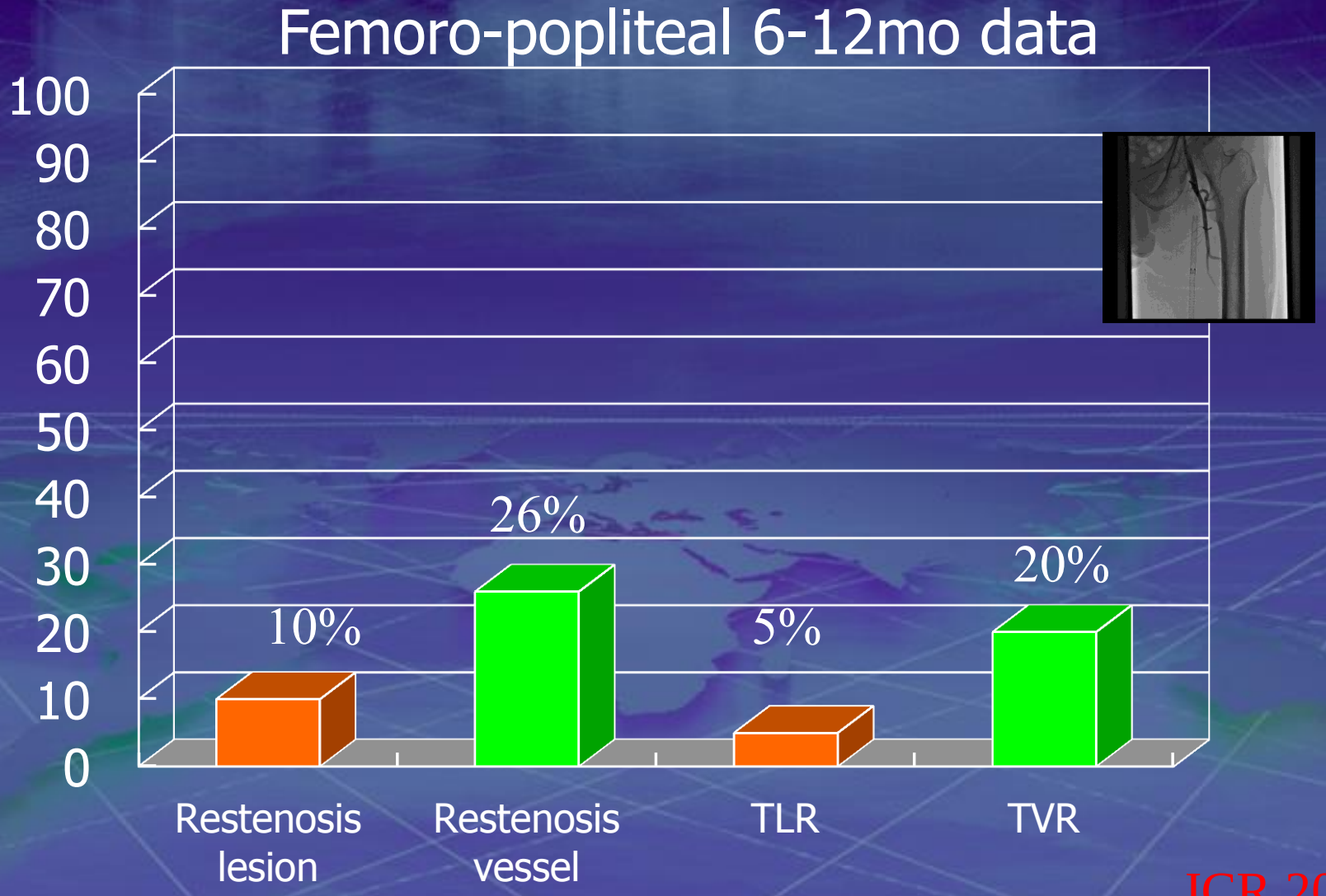


Lesion characteristics

N	22
Lesion site	
Superficial femoral, n (%)	19 (86)
Popliteal	2 (9)
Common femoral	1 (5)
TASC II	
A, B	13 (59)
C, D	9 (41)
Chronic total occlusion	4 (18)
Calcified	3 (14)
Restenosis	20 (91)
Lesion length, mm	153±62
Distal run-off, n	1.9±0.8



Resetenosis, TLR and TVR



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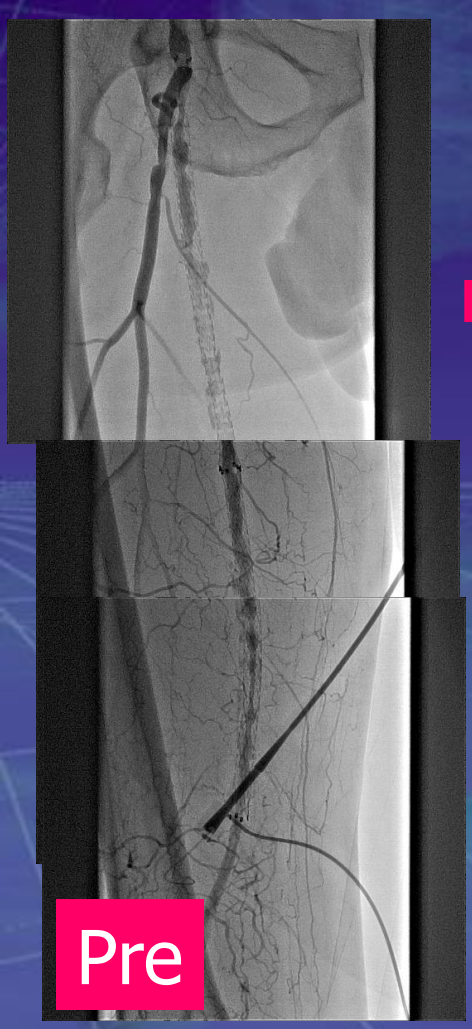
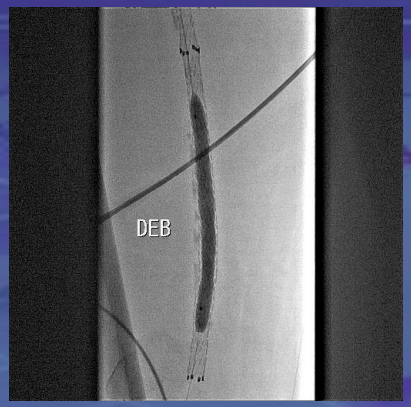
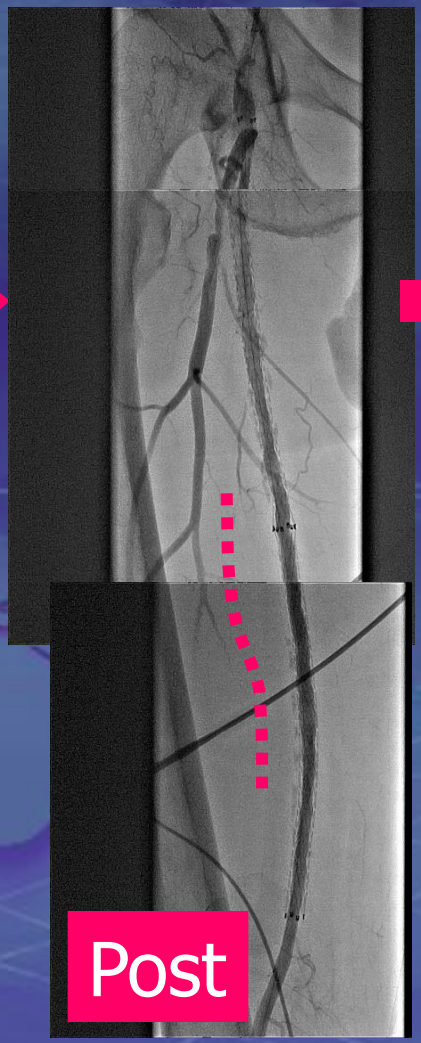
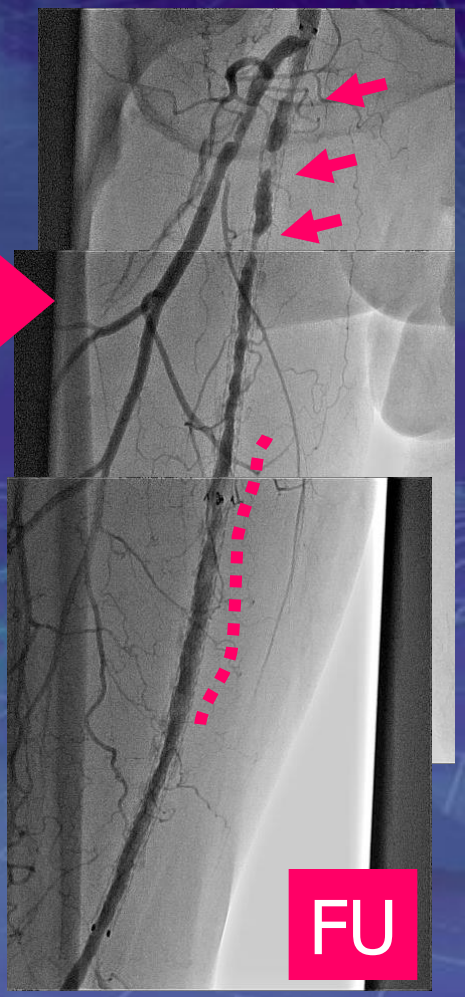
TVF case



DEB
6/80







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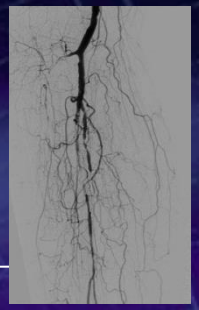
Patient characteristics



N	20
Age, Year	70.2±6.1
Male/Female	14/6
BMI	21.9±1.5
Diabetes, n (%)	16 (80)
Hypertension	17 (85)
Dyslipidemia	8 (40)
Smoking	11 (55)
Hemodialysis	10 (50)
Family History	2 (10)
CAD	9 (45)
CVD	8 (40)

Rutherford class	
I	0
II	0
III	2
IV	6
V	12
VI	0

ABI	0.67±0.23
SPP, mmHg	27±13

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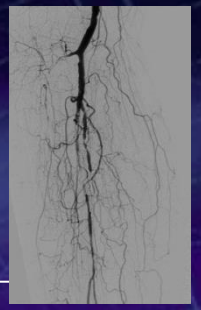
Lesion characteristics



N	20
Lesion site	
ATA	7 (35)
PTA	6 (30)
PA (TPT)	7 (35)
TASC	
A, B	0 (0)
C, D	20 (100)
Chronic total occlusion	11 (55)
Calcified	10 (50)
Restenosis	5 (25)
Lesion length, cm	136±54
Distal run-off, n	0.4±0.5

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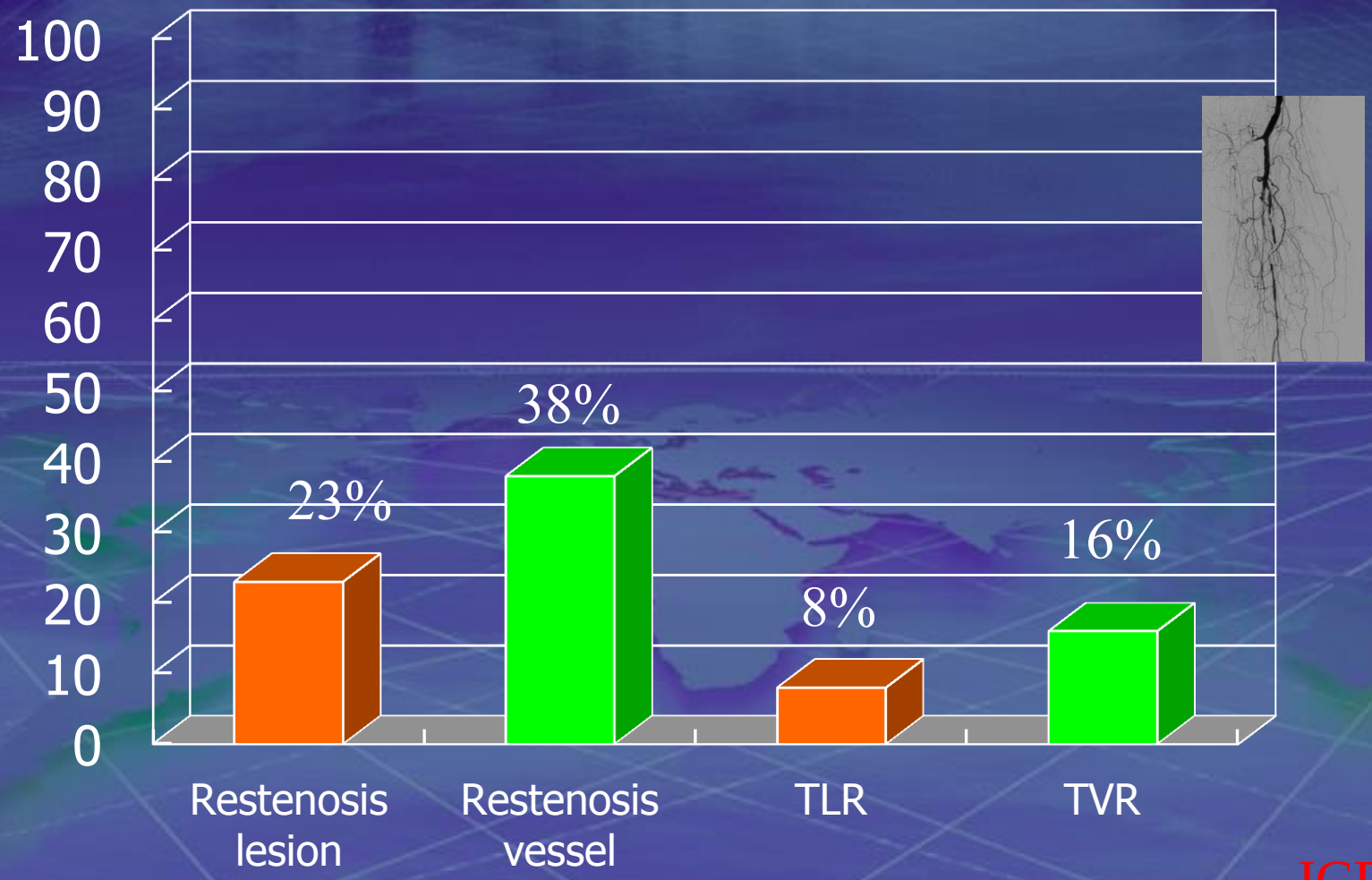
Resetenosis, TLR and TVR



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DEB in BTK

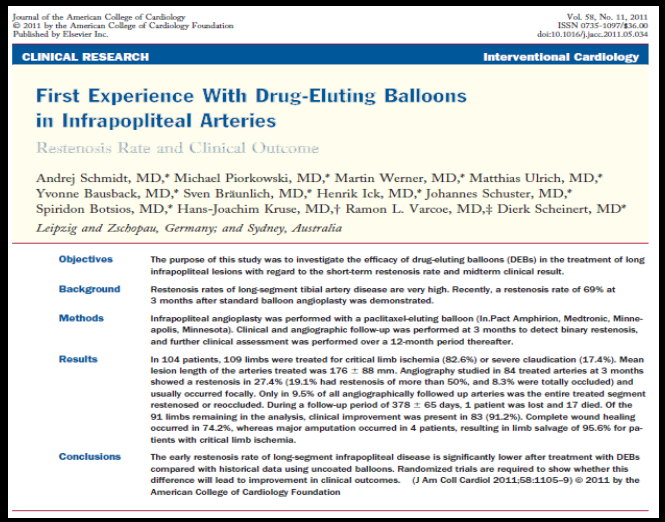
DEB BTK Registry

(A.Schmidt JACC 2011)

104 patients
(angio subgroup 84 arteries)
RC 3-4-5-6

IN.PACT

Primary EP:
3m (angio) Rest. Rate



Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 11, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.05.034

CLINICAL RESEARCH — Interventional Cardiology

First Experience With Drug-Eluting Balloons in Infrapopliteal Arteries

Restenosis Rate and Clinical Outcome

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Leipzig and Zschopau, Germany; and Sydney, Australia

Objectives The purpose of this study was to investigate the efficacy of drug-eluting balloons (DEBs) in the treatment of long infrapopliteal lesions with regard to the short-term restenosis rate and midterm clinical result.

Background Restenosis rates of long-segment tibial artery disease are very high. Recently, a restenosis rate of 69% at 3 months after standard balloon angioplasty was demonstrated.

Methods Infrapopliteal angioplasty was performed with a paclitaxel-eluting balloon (In.Pact Amphirion, Medtronic, Minneapolis, Minnesota). Clinical and angiographic follow-up was performed at 3 months to detect binary restenosis, and further clinical assessment was performed over a 12-month period thereafter.

Results In 104 patients, 109 limbs were treated for critical limb ischemia (82.6%) or severe claudication (17.4%). Mean lesion length of the arteries treated was 176 ± 88 mm. Angiography studied in 84 treated arteries at 3 months showed a restenosis in 27.4% (19.1% had restenosis of more than 50%, and 8.3% were totally occluded) and usually occurred focally. Only in 9.5% of all angiographically followed up arteries was the entire treated segment restenosed or reoccluded. During a follow-up period of 378 ± 65 days, 1 patient was lost and 17 died. Of the 91 limbs remaining in the analysis, clinical improvement was present in 83 (91.2%). Complete wound healing occurred in 74.2%, whereas major amputation occurred in 4 patients, resulting in limb salvage of 95.6% for patients with critical limb ischemia.

Conclusions The early restenosis rate of long-segment infrapopliteal disease is significantly lower after treatment with DEBs compared with historical data using uncoated balloons. Randomized trials are required to show whether this difference will lead to improvement in clinical outcomes. (J Am Coll Cardiol 2011;58:1105–9) © 2011 by the American College of Cardiology Foundation

Low restenosis rates at 3 months in long BTK lesions and occlusions

Key Baseline characteristics

- CLI = 82.6%; Diabetics = 73%
- Avg Lesion length = 173 ± 87 mm
- Tot Occlusions = 61.9%

Angiographic FU	DEB 3-month	PTA* 3-month
Restenosis (>50%)	27.4%	69%
Full-segment Resten.	10%	56%
Restenosis Length	64 mm	155 mm
Clinical FU	**12-month**	**15-month**
Deaths	16.3%	10.5%
Limb Salvage	95.6%	100%
Clinic. Improvem.	91.2%	76.5%
Compl. wound healing	74.2%	78.6%
TLR	17.3%	50%

* PTA historical cohort (A.Schmidt et al. CCI 2010)

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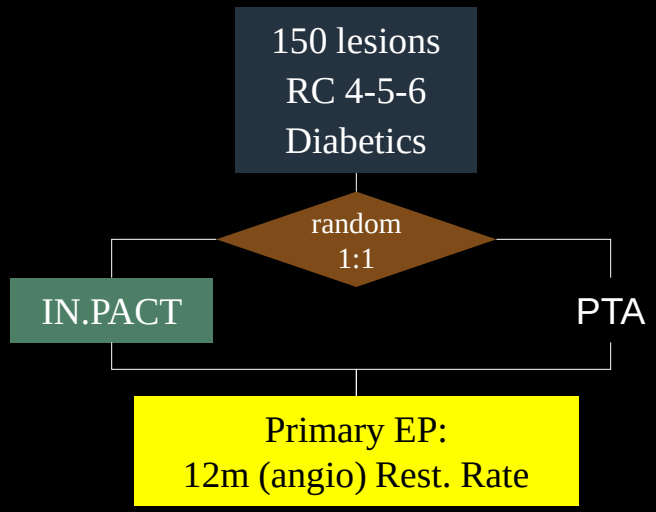
DEB in BTK

DEBATE BTK RCT

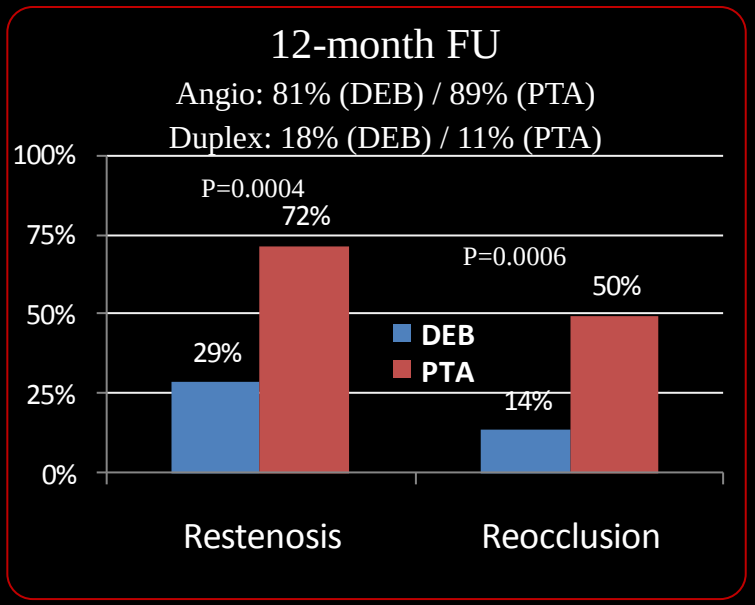
(F.Liistro LINC 2012)



Key Baseline characteristics (DEB vs. PTA):

- CLI = 100%
- Diabetics = 100%
- Mean lesion length = 121 ± 83 vs. 123 ± 68 (p=ns)
- Tot Occlusions = 80% vs. 82% (p=ns)
- Pre-dilat. = 100%

Significant reduction in 12-m Rest. Rate vs. PTA in BTK / CLI / Diabetics



	PTA	DEB	
Death	3(4%)	4(6%)	0.2
Major Amputation	1	0	
CVA	3(4)	2(3)	0.7
AMI	3(4)	3(4)	0.7

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DEB in INFRA-POPLITEAL LESIONS

IN.PACT DEEP

(Randomized Trial of IN.PACT Amphirion DEB vs. PTA for Infrapopliteal Revascularization in Critical Limb Ischemia)

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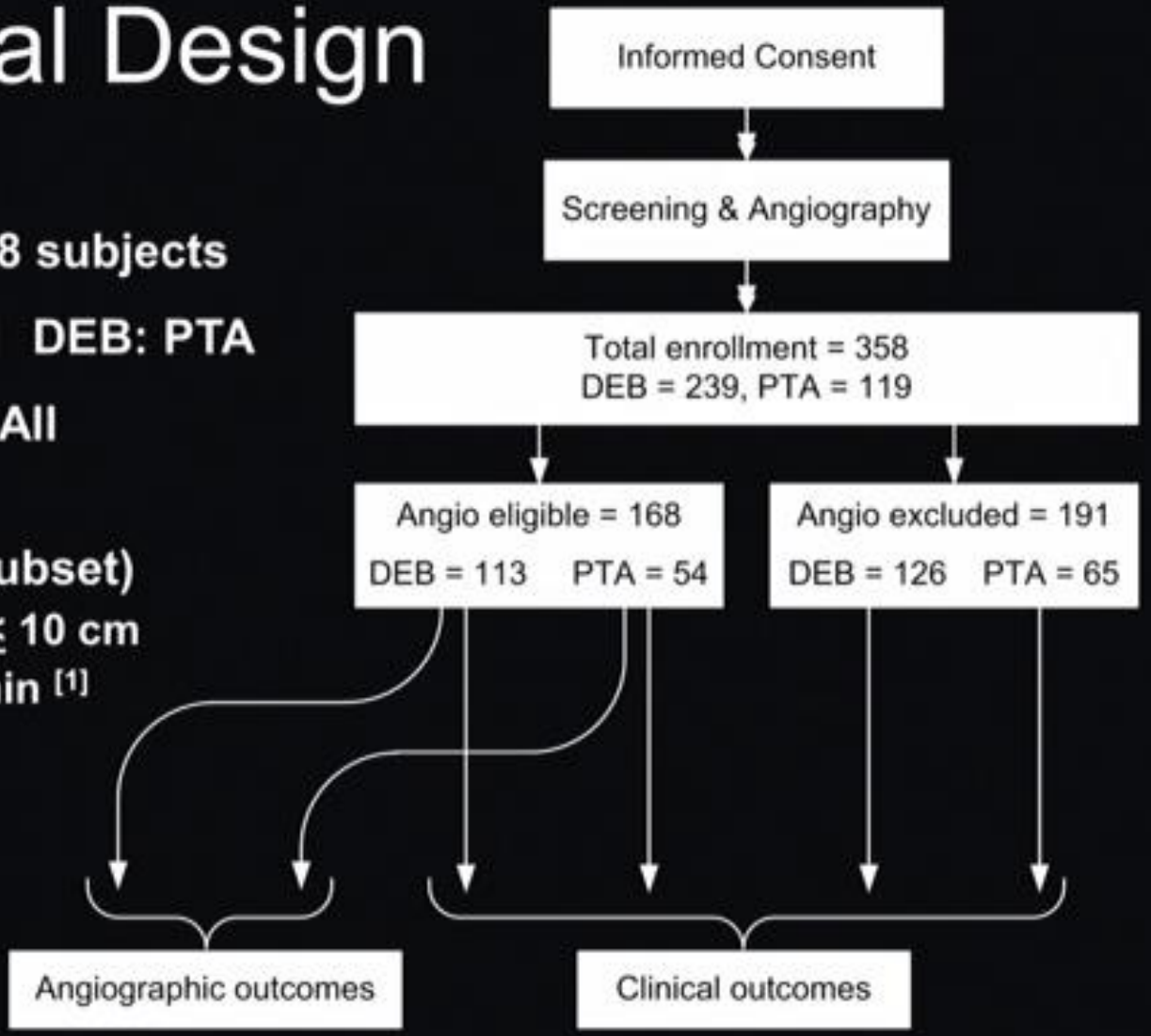
Trial Design

- Enrollment = 358 subjects
- Randomized 2:1 DEB: PTA
- Clinical cohort: All subjects
- Angio cohort (subset)
  - Single lesion ≤ 10 cm
  - GFR ≥ 30 ml/min [1]



1. Except patients with ESRD, on chronic haemodialysis and with life expectancy >1 year

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Primary IN.PACT DEEP Outcomes

Primary Efficacy	DEB	PTA	p
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	*0.950*
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	*0.291*

Primary Safety	DEB	PTA	p
6-month Death, Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*

1. Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab

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Angio Cohort Outcomes

12-month Outcomes [1]	DEB	PTA	p
Mean Lesion Length (mm±SD)	59.1 ± 41.7	79.7 ± 74.6	0.060
Binary (50%) Rest. Rate (%)	41.0% (25/61)	35.5% (11/31)	0.609
Occlusion Rate (%)	11.5% (7/61)	16.1% (5/31)	0.531
Longitudinal Restenosis (%) [2]	62.7 ± 56.2	93.2 ± 60.8	0.167

Revalidated Lumen Loss [3]	DEB	PTA	p
12-month LLL (mm, mean ± SD)	0.51 ± 0.66	0.60 ± 0.97	0.654

1. Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Mean % of stenosis length vs. treated lesion length± SD (Angiographic Cohort, ITT)
3. As evaluated by additional angiographic core laboratory (Beth Israel Deconess Medical Center, Boston, MA) to confirm earlier analysis

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Secondary Safety Outcomes

12-month Safety	DEB	PTA	p
Major Amputation	8.8% (20/227)	3.6% (4/111)	0.080
All-Cause Mortality	10.1% (23/227)	8.1% (9/111)	0.551
Death and Amputations [1]	35.2% (80/227)	25.2% (28/111)	0.064
Death, Major Amp, CD TLR [2]	26.9% (61/227)	23.4% (26/111)	0.496
Amputation Free Survival	81.1% (184/227)	89.2% (99/111)	0.057
Wound Healing (site reported)	73.8% (121/164)	76.9% (70/91)	0.579

1. Death of any Cause, Major or Minor Amputation of target limb (MAE per protocol)
2. Death of any Cause, target limb Major Amputation and clinically driven TLR

Zeller T et al. JACC 2014 submitted

IN.PACT DEEP
Conclusions I

- IN.PACT DEEP was the first large, randomized, Level 1 evidence clinical trial of DEB for BTK CLI
- IN.PACT DEEP did not meet either 1^0 efficacy endpoint
  - PTA outcomes were significantly better than expected
- IN.PACT DEEP Trial met the non-inferiority primary safety endpoint
  - The safety signal towards major amputations, in conjunction with the absence of significant efficacy, led to market withdrawal

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Expectation for DCB

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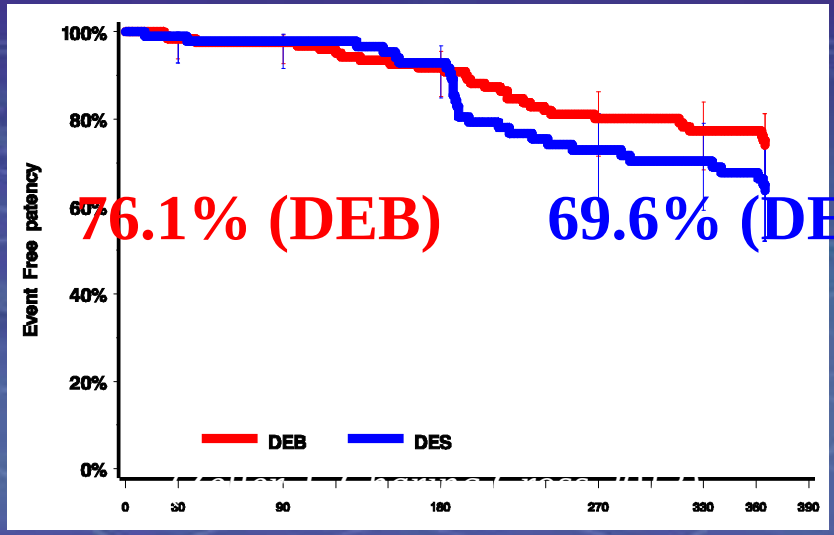
DEB vs. DES in Long SFA lesions

228-Patient retrospective – propensity score based – analysis of DEB vs. DES in long (~19 cm) SFA lesion

- **Non significant difference between IN.PACT DEB and Zilver PTX in long SFA lesions**
- **prov. Stent rate post DEB = 18.3%**

1-year freedom from loss of Primary Patency (PSVR < 2.4)



P=N.S.

(Zeller T. Charing Cross 2013)

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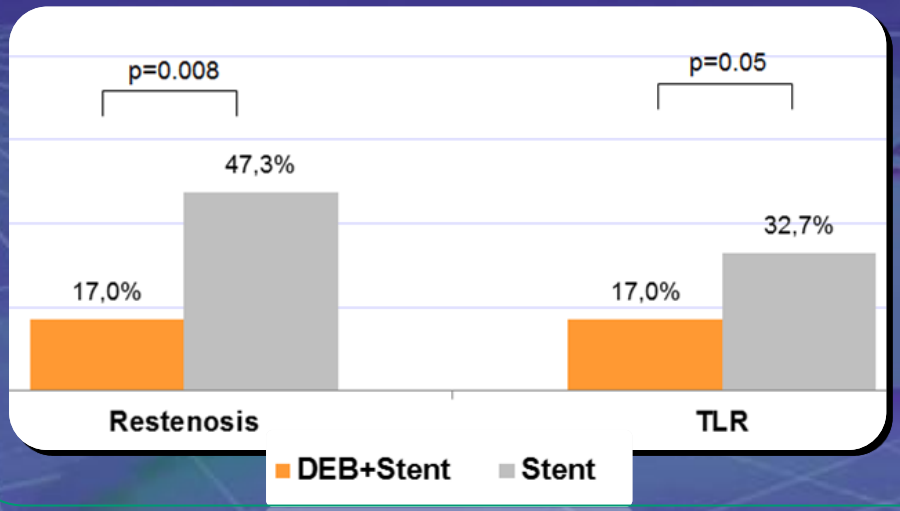
DEB+Stent vs. Stent: DEBATE SFA

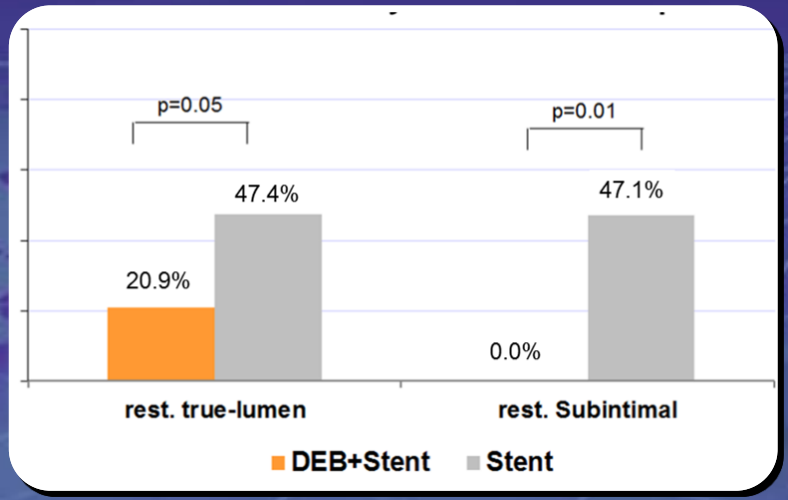
Randomized, 104 Patients (>70% CLI and Diabetics, >60% CTOs), Primary EP: 1y RR

- **DEB significantly improve Stent results**
- **Restenosis ↓↓ maintained irrespective of lesion length and recanalization technique**

1-Year Restenosis and TLR



1-Year Restenosis: subintimal vs. true lumen



(Liistro F et al. J Am Coll Cardiol Intv 2013 – accepted)

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Future direction 1

Avoid full metal jacket in SFA

DEB+ provisional bare metal stenting

Debulking device (Laser, Diamondback, Turbo Hawk etc.) +DEB+ provisional bare metal stenting

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BK stenting

DESTINY study

Drug Eluting Stents
In The Critically Ischemic Lower Leg

*a physician-initiated prospective randomized multicenter trial comparing the implant of a drug eluting stent (**XIENCE V**, Abbott Vascular) vs.*
*a bare metal stent (**MULTILINK VISION**, Abbott Vascular) in the critically ischemic lower leg*

Multilink Vision – BMS

Xience V – DES

TCT2011

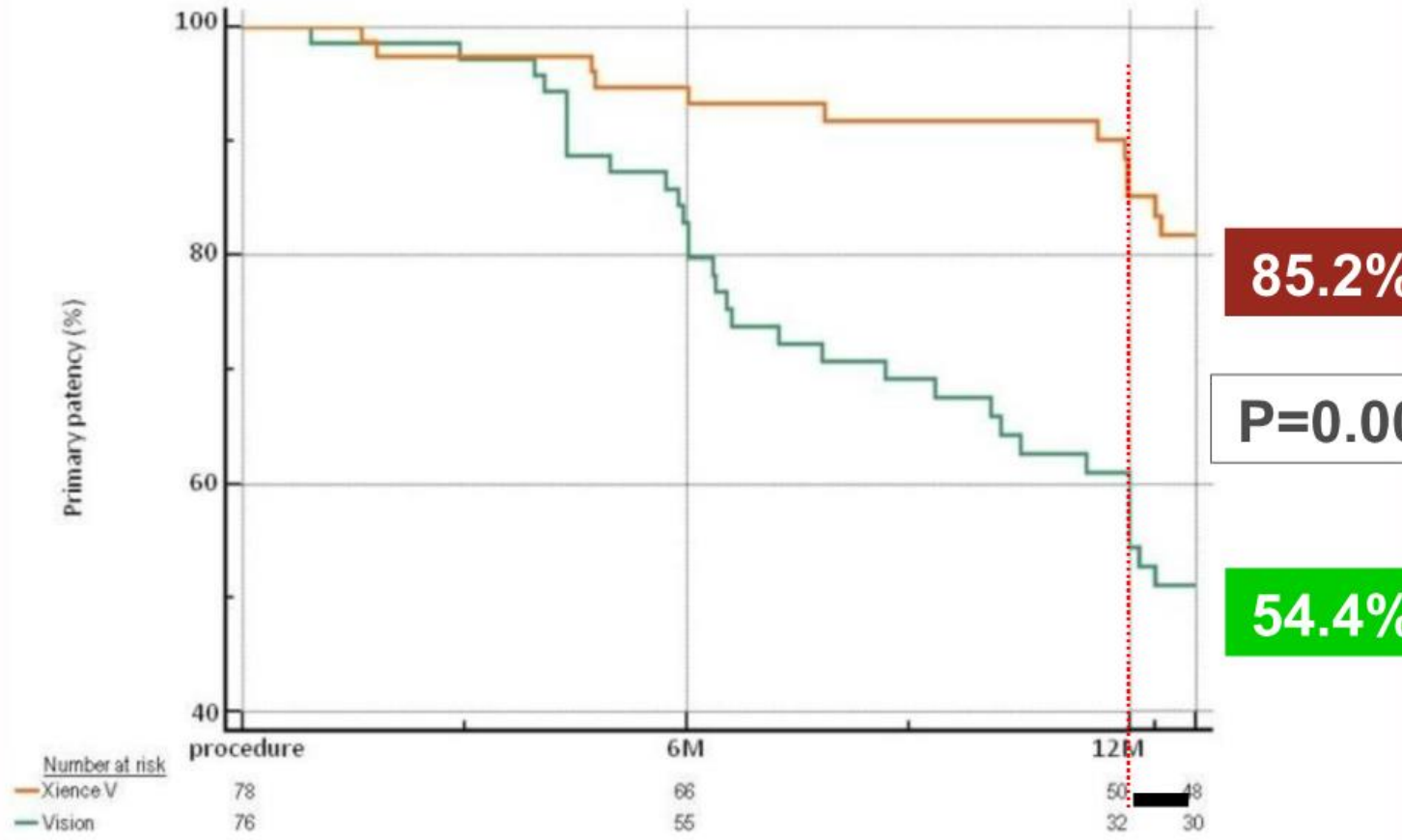
Bosiers M. et al. JVS 2011

CARDIOVASCULAR RESEARCH FOUNDATION

BK stenting

DESTINY - 12-month primary patency

MultiLink Vision vs Xience V



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Future direction 2

BK disease

Short lesion,
Proximal lesion

Long lesion

DES (Balloon expandable)

DCB

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Thank you very much!

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