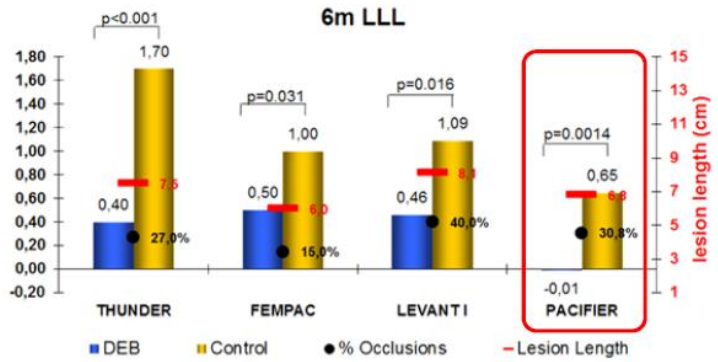
Clinical Data Update for Drug Coated Balloons (DCB)

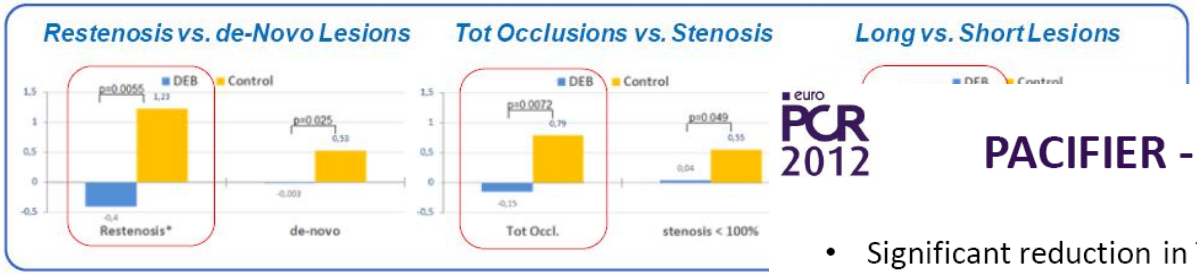
Seung-Whan Lee, MD, PhD

Asan Medical Center, Heart Institute, University of Ulsan College of Medicine,

PACIFIER - 6-Month Angiographic Results

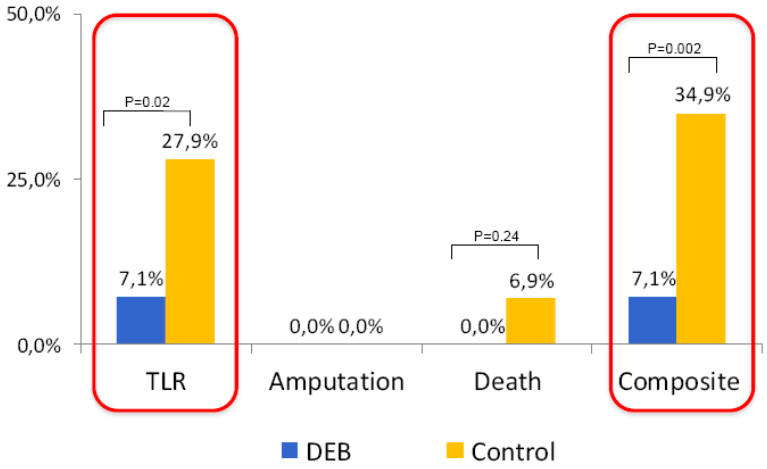


Sub-Group Analysis (6m LLL)



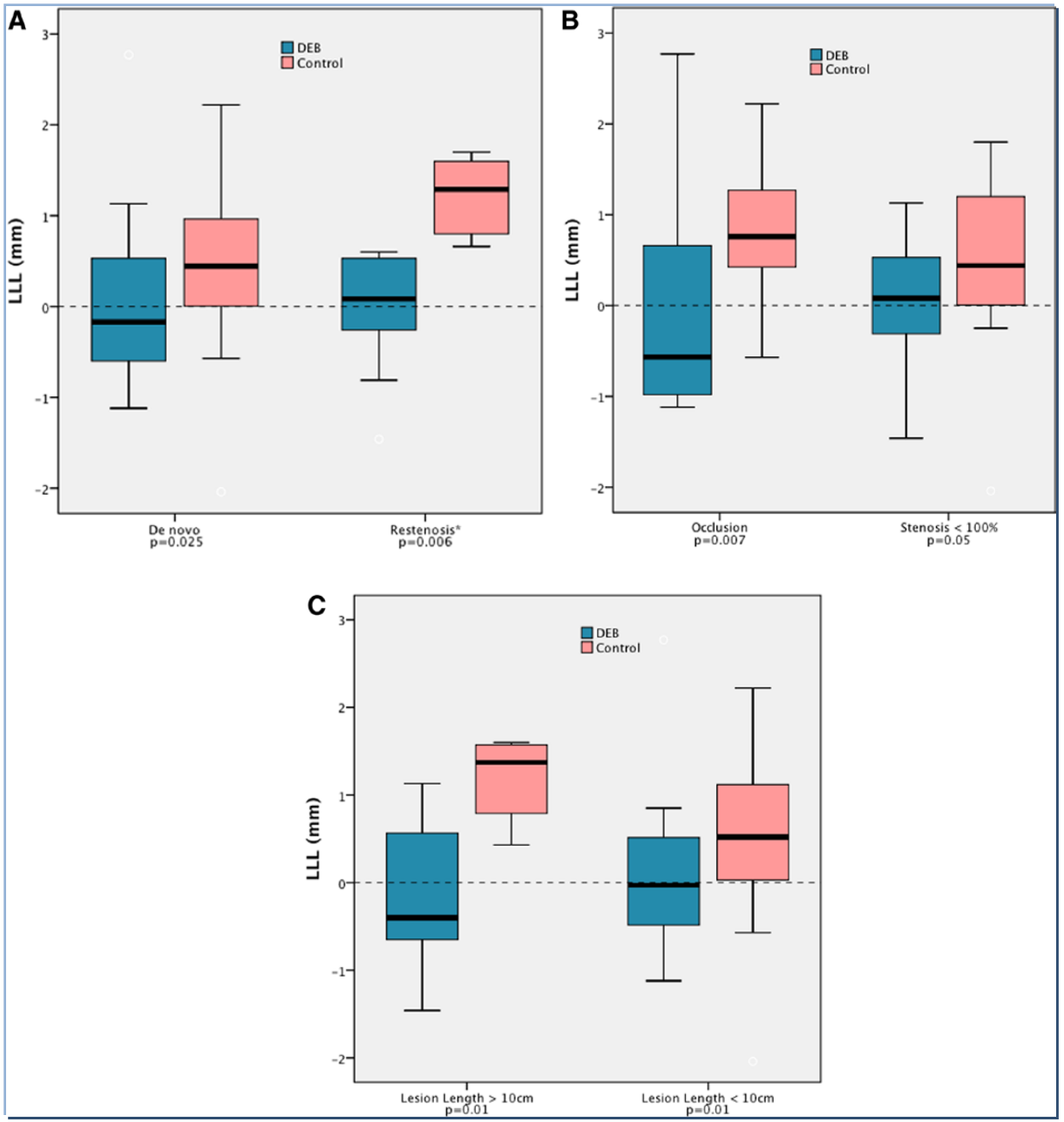
PACIFIER - 12-Month Clinical Results

- Significant reduction in TLR and MAE rates in IN.PACT DEB vs. PTA



Werk et al. Circulation Cardiovasc Intervent 2012

De Novo
vs.
Restenosis

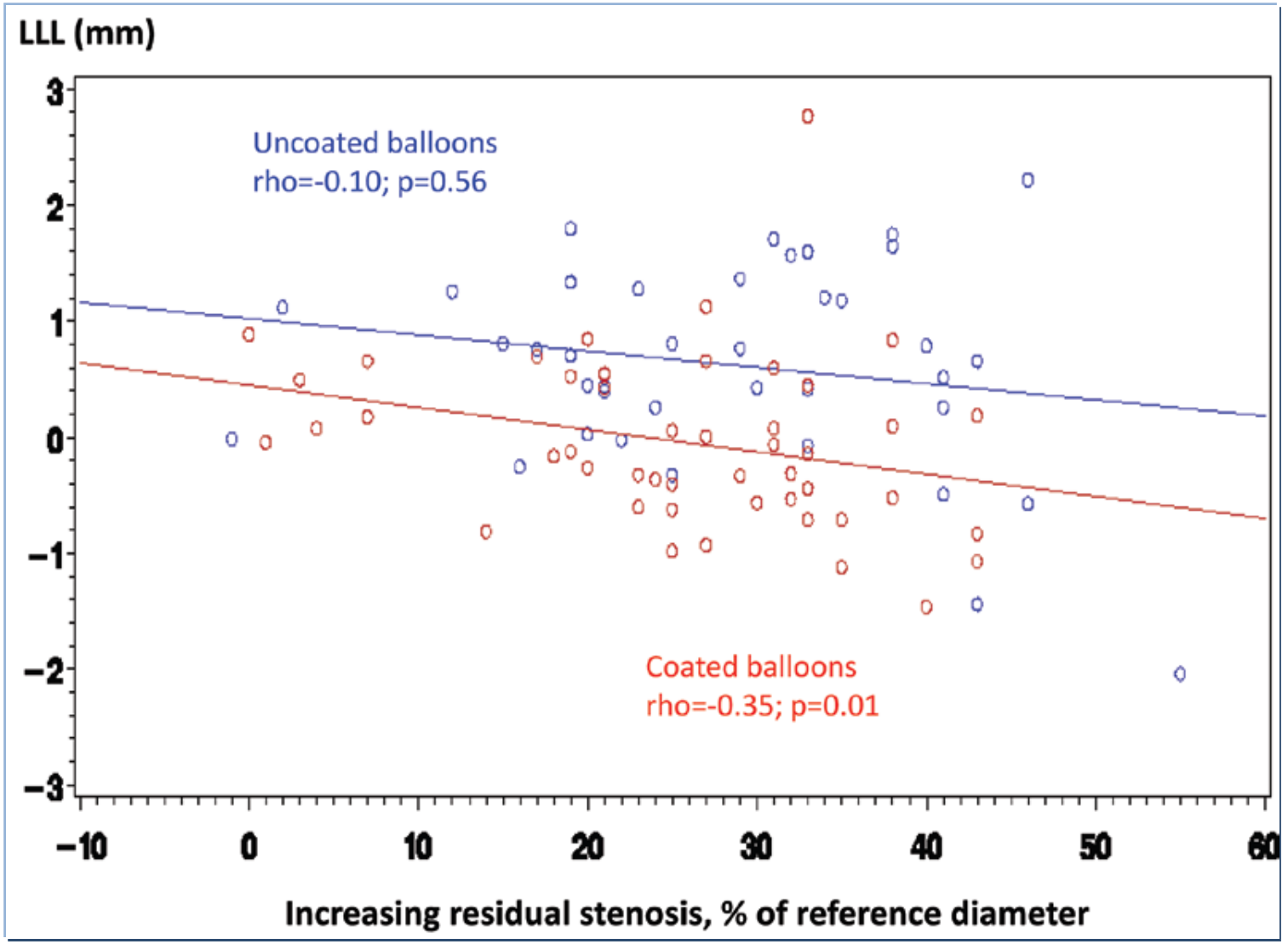


Stenosis
vs.
Occlusion

<10cm
vs.
>10cm

Werk et al. Circulation Cardiovasc Intervent 2012

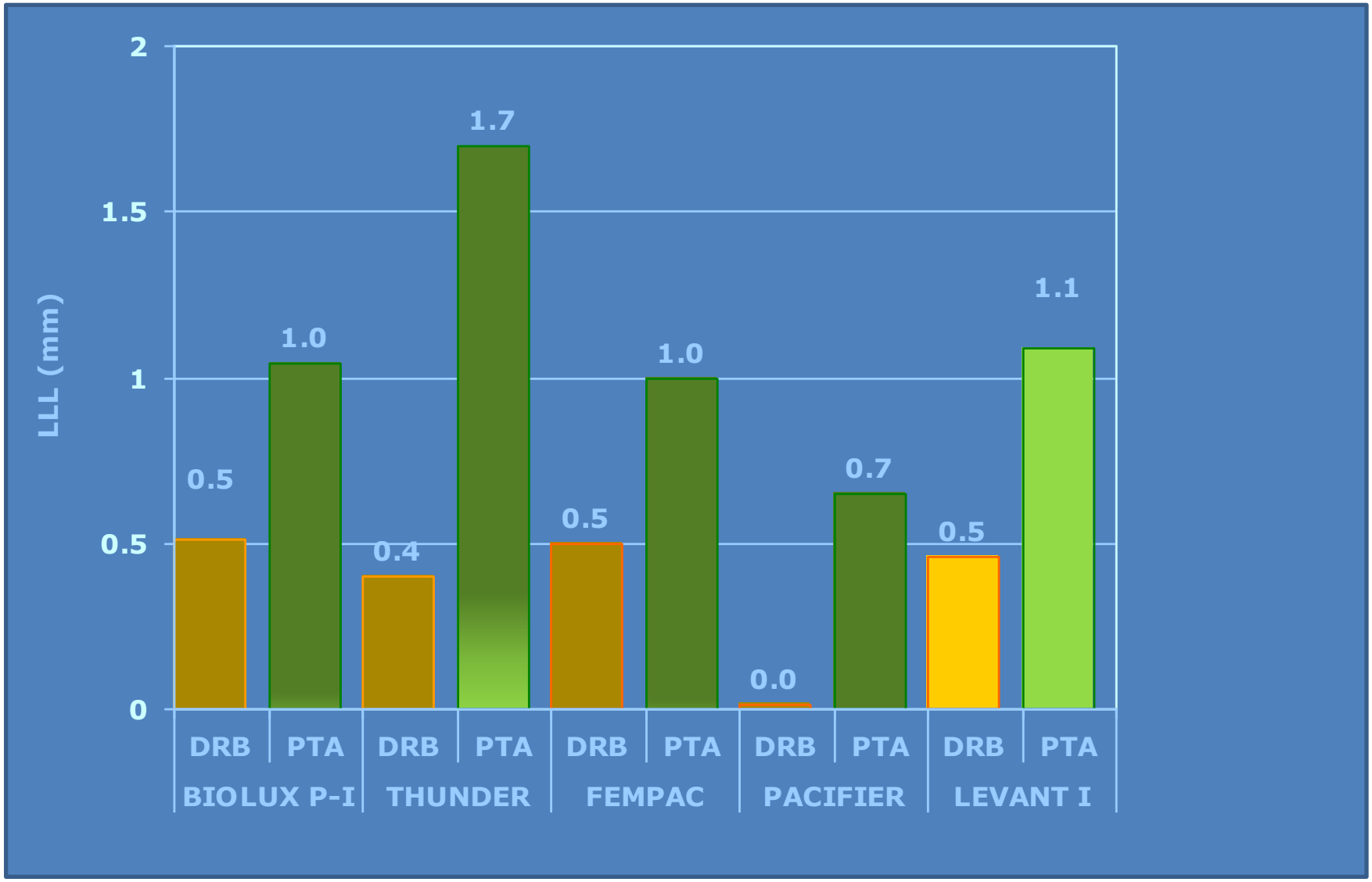
Association between post-procedural residual stenosis severity and 6-month late lumen loss (LLL), with negative late lumen loss values indicating lumen gain



Werk et al. Circulation Cardiovasc Intervent 2012

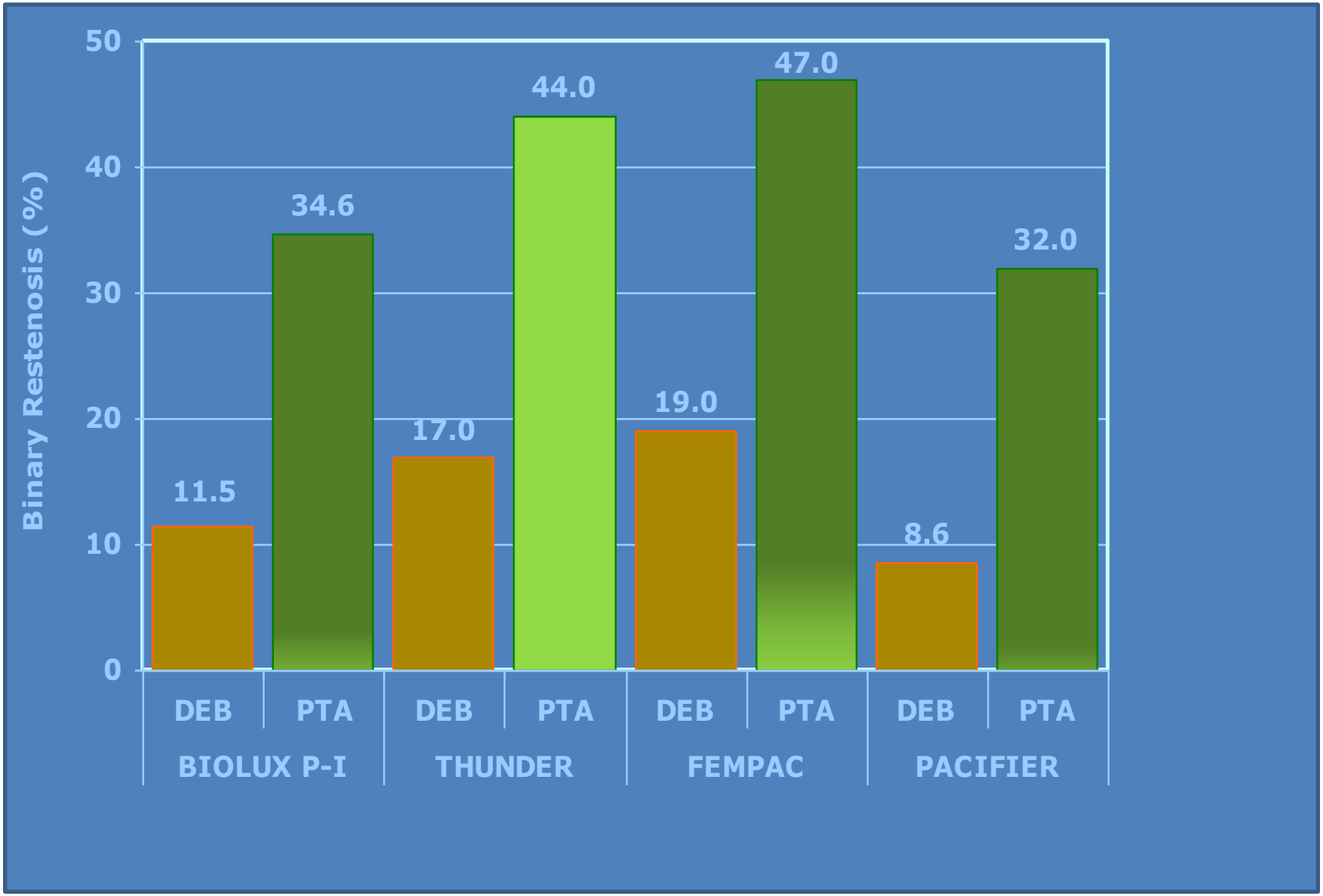
BIOLUX P-I in Context

6 Months Late Lumen Loss



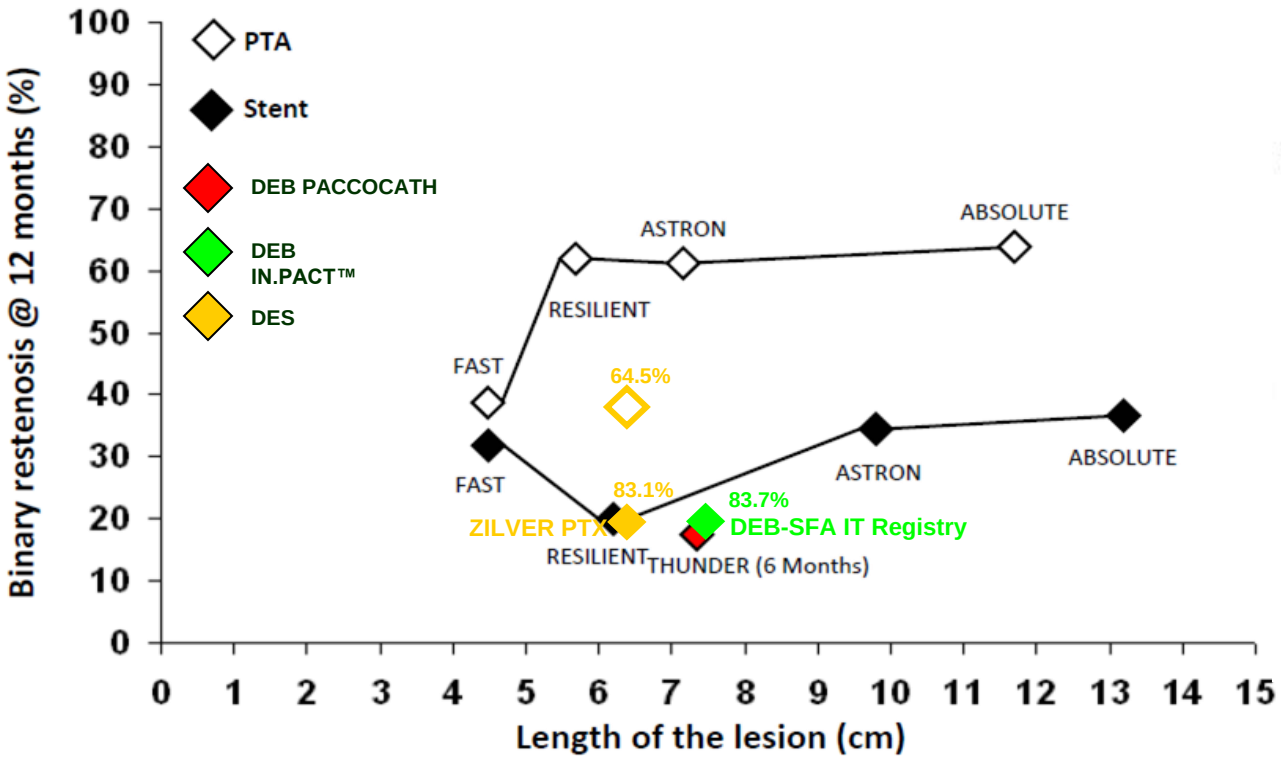
BIOLUX P-I in Context

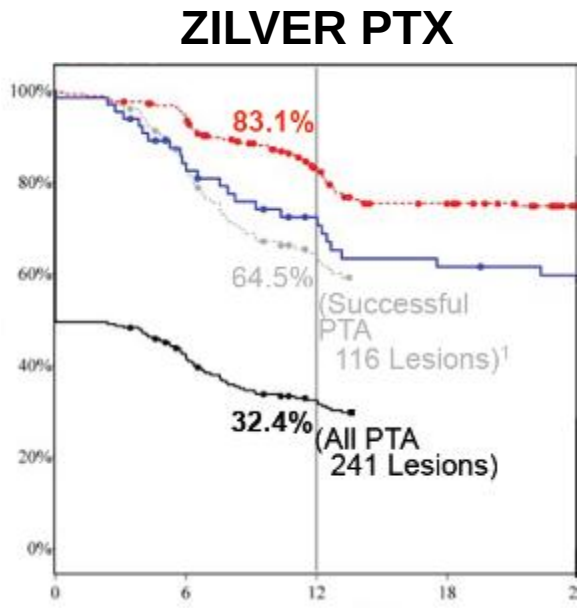
6 Months Binary Restenosis



DCB compared to POBA & Stent

Lesion length as determinant of 12m patency





M.Schillinger, 2008
G. Tepe, N Engl J Med. 2008
M. Dake, TCT 2010

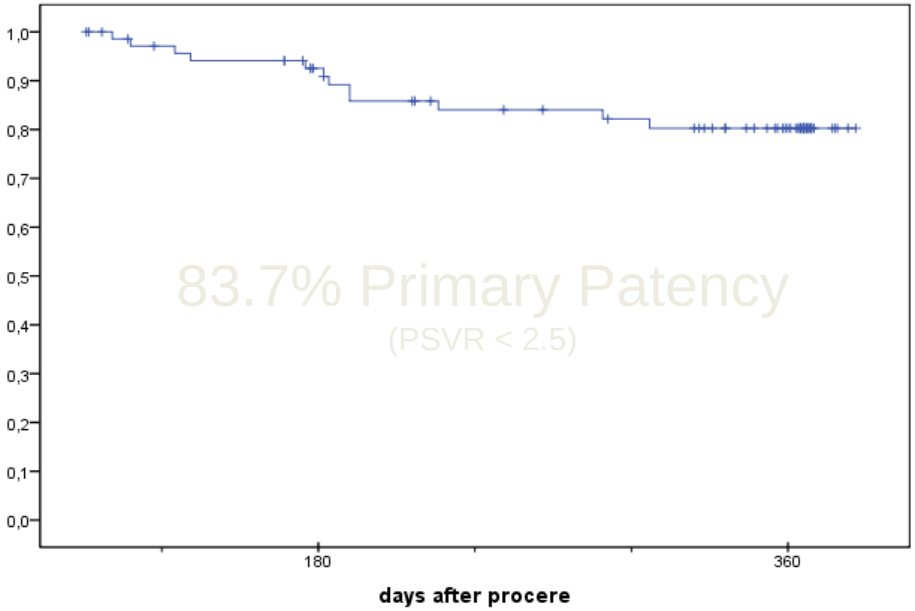
Italian Inpact DEB SFA Registry

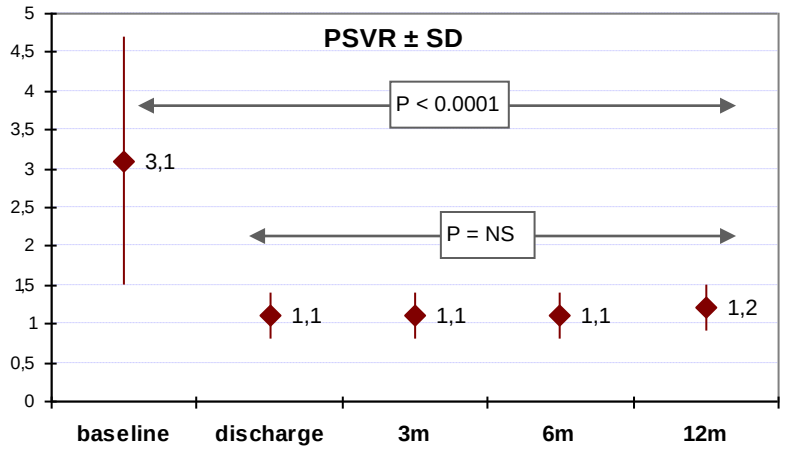
1 year Results

length:76.3 ± 38.3 mm

	0-3 m (89 patients)	0-6 m (90 patients)	0-12 m (92 patients)
Death	1 (1.1%)	1 (1.1%)	2 (2.2%)
Amputation	0%	0%	0%
TLR	1 (1.1%)	4 (4.5%)	8 (8.7%)

12M Survival from TLR, Occlusion, >50% Restenosis





Micari et al. JACC Cardiovasc Intervent 2012

2-Year Results
Kaplan Meier Curve for Primary Patency and MAEs

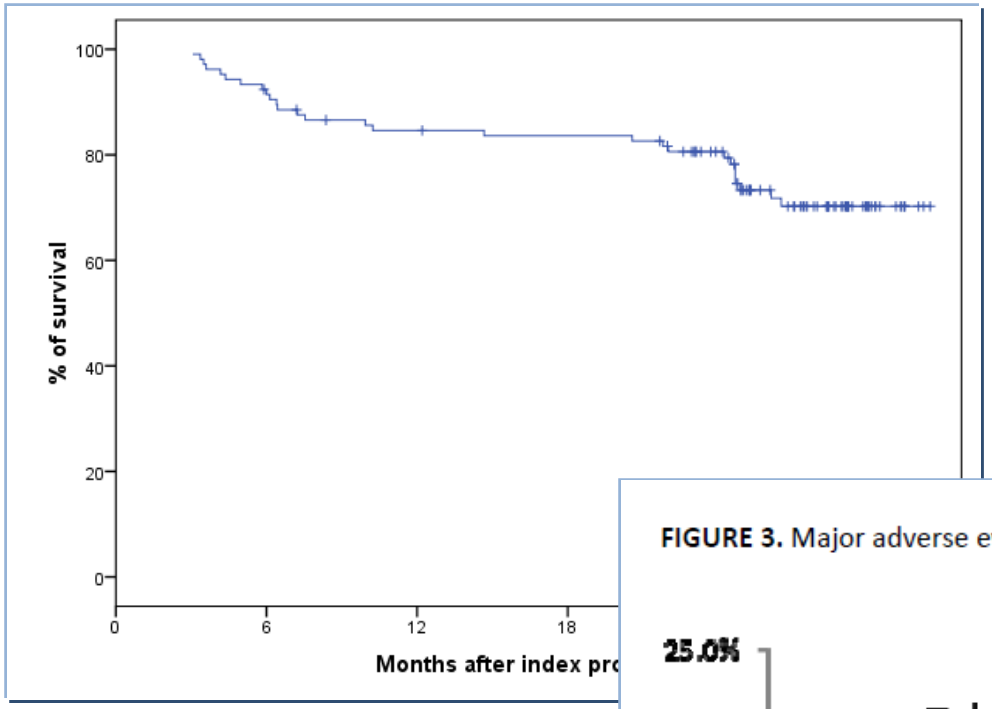
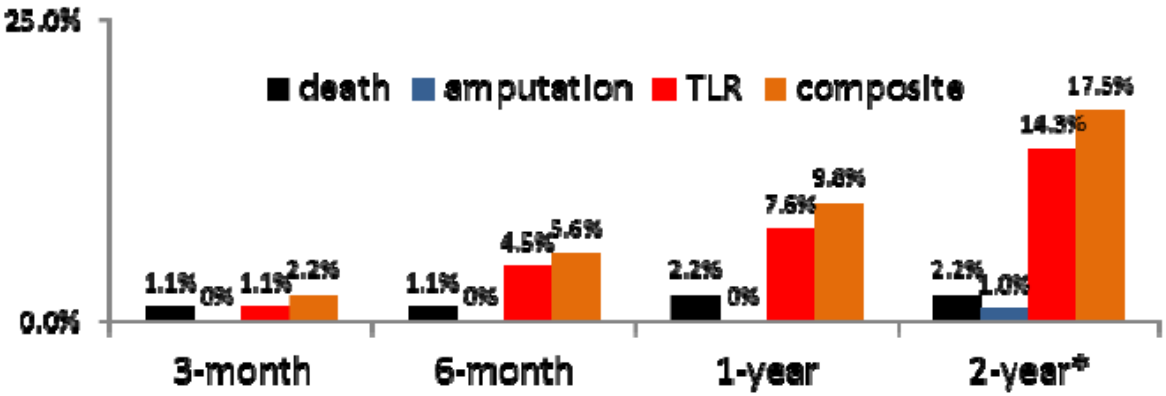
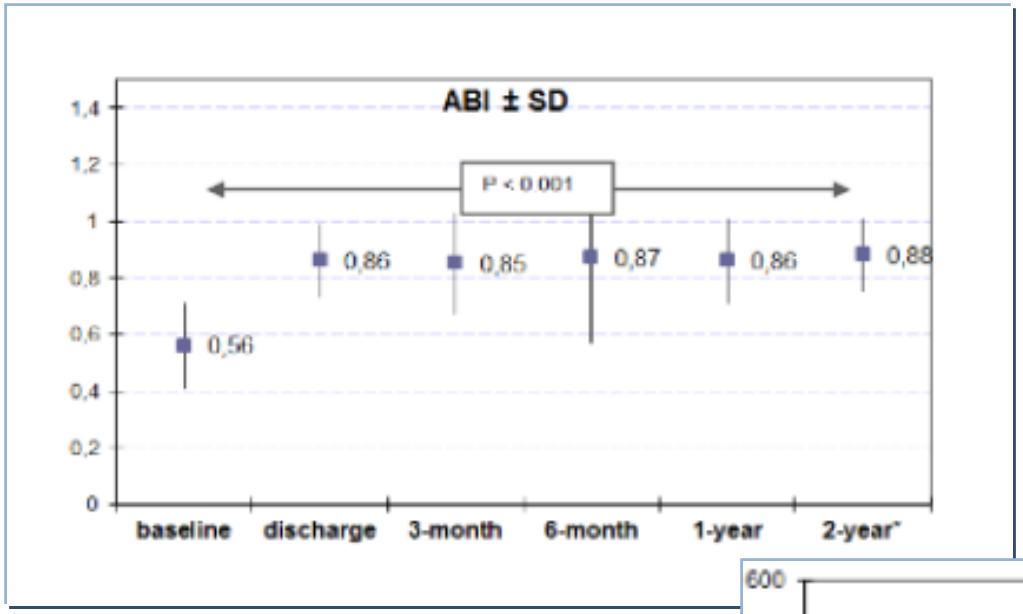


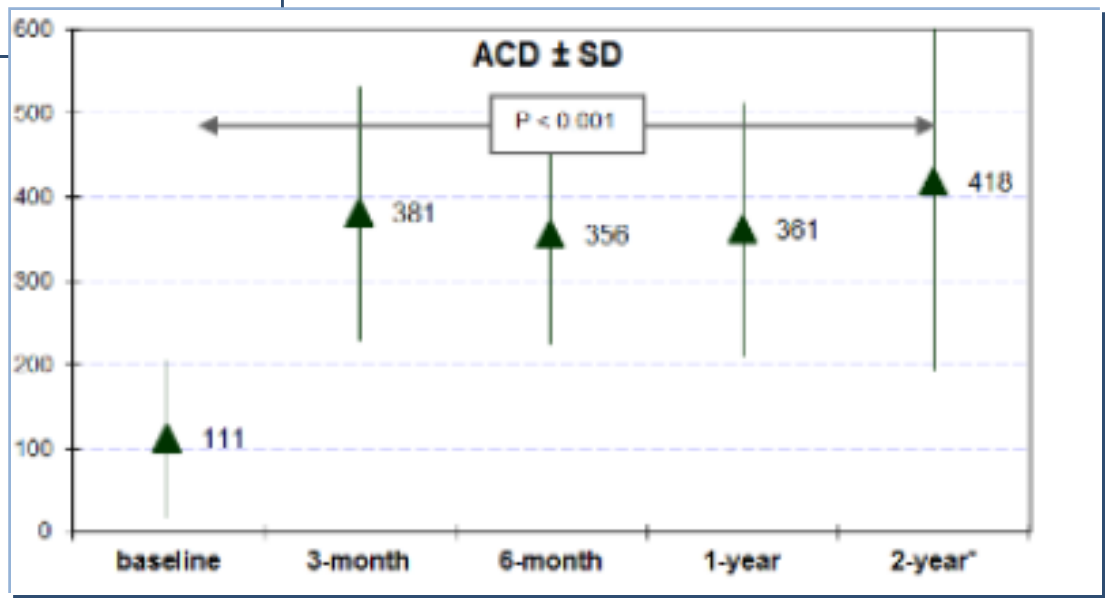
FIGURE 3. Major adverse events during follow-up.



Micari et al. JACC Cardiovasc Intervent

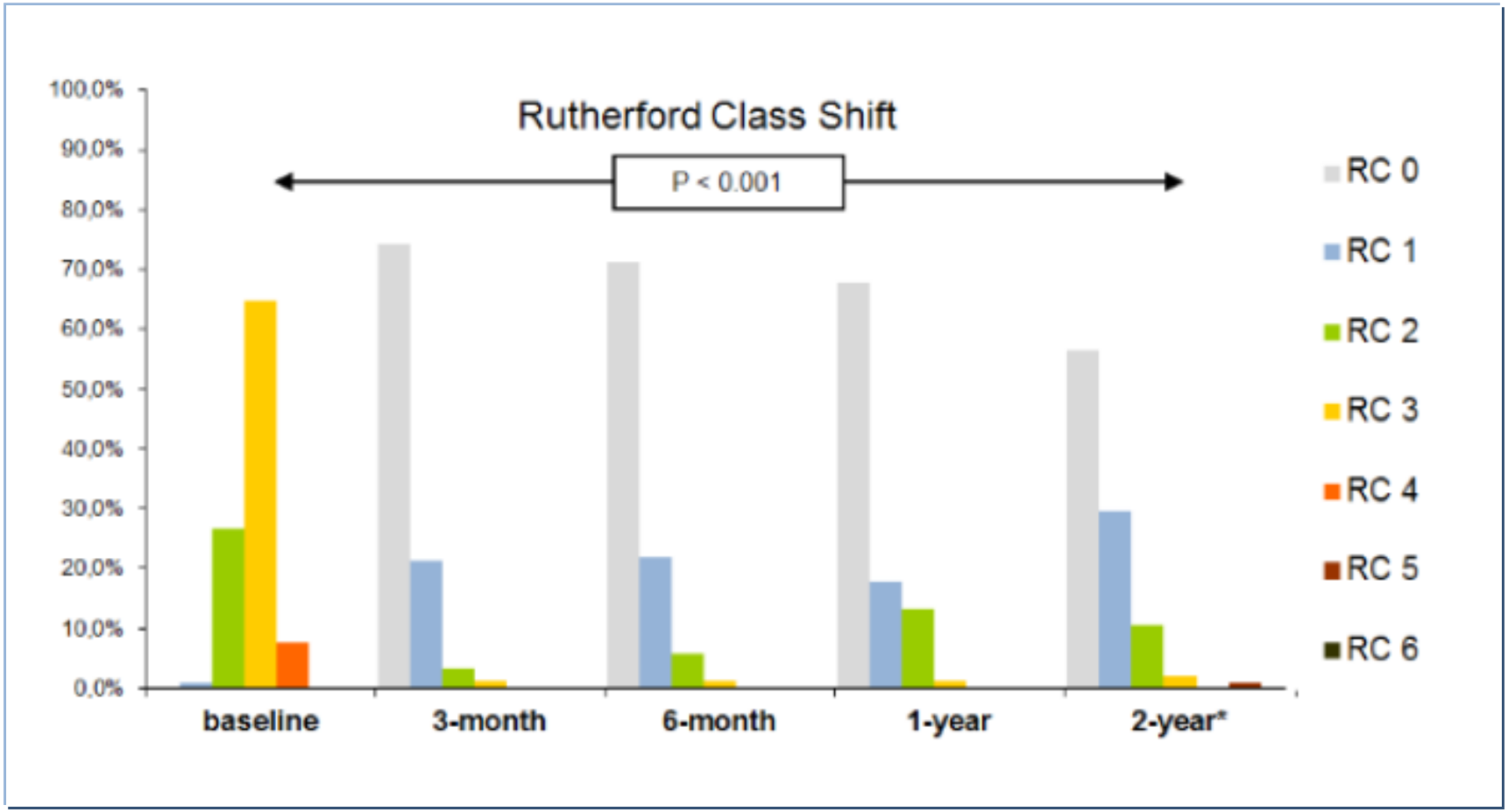
2-Year Results – ABI & AWD





Micari et al. JACC Cardiovasc Intervent 2013

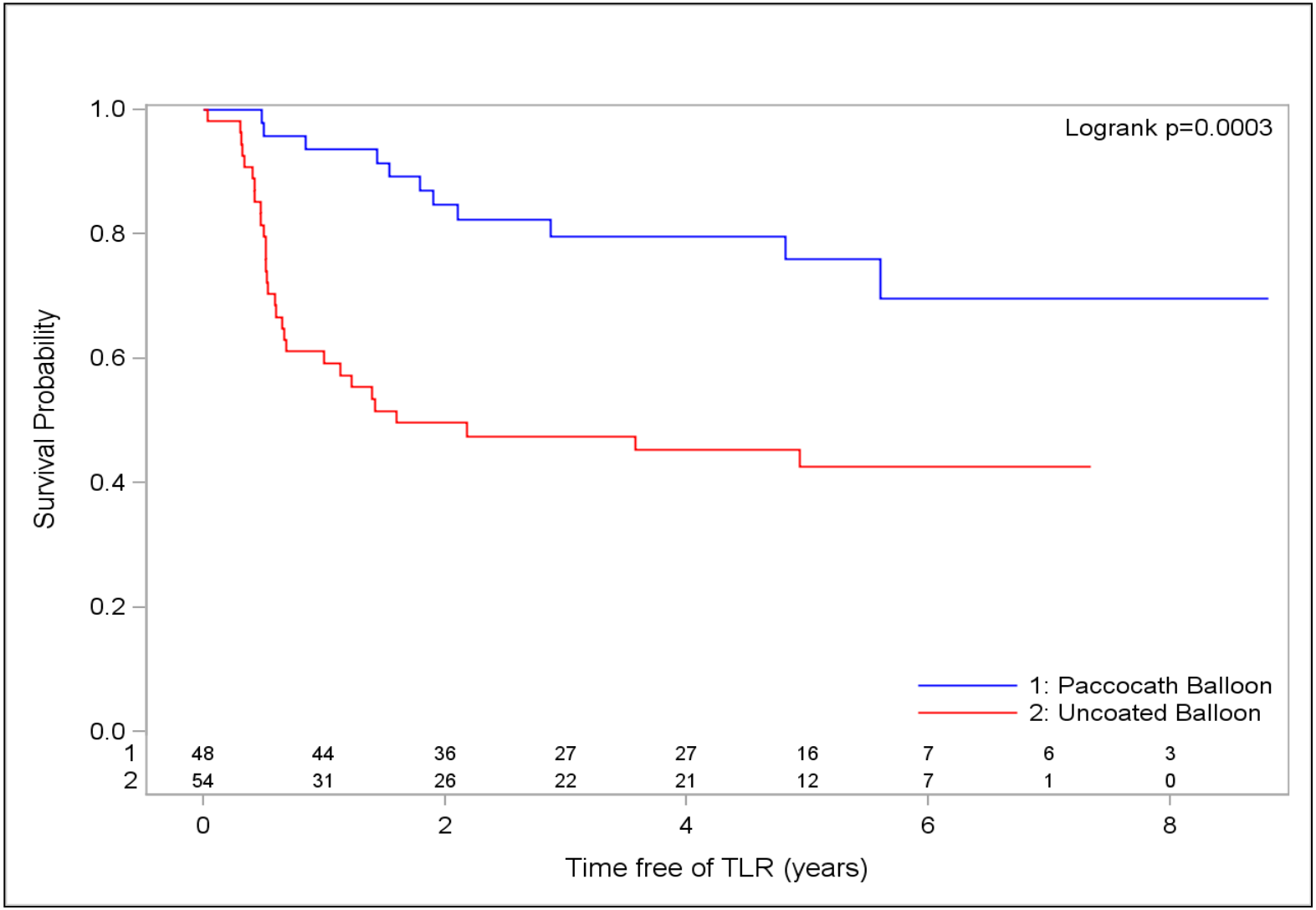
2-Year Results – Shift in RCC



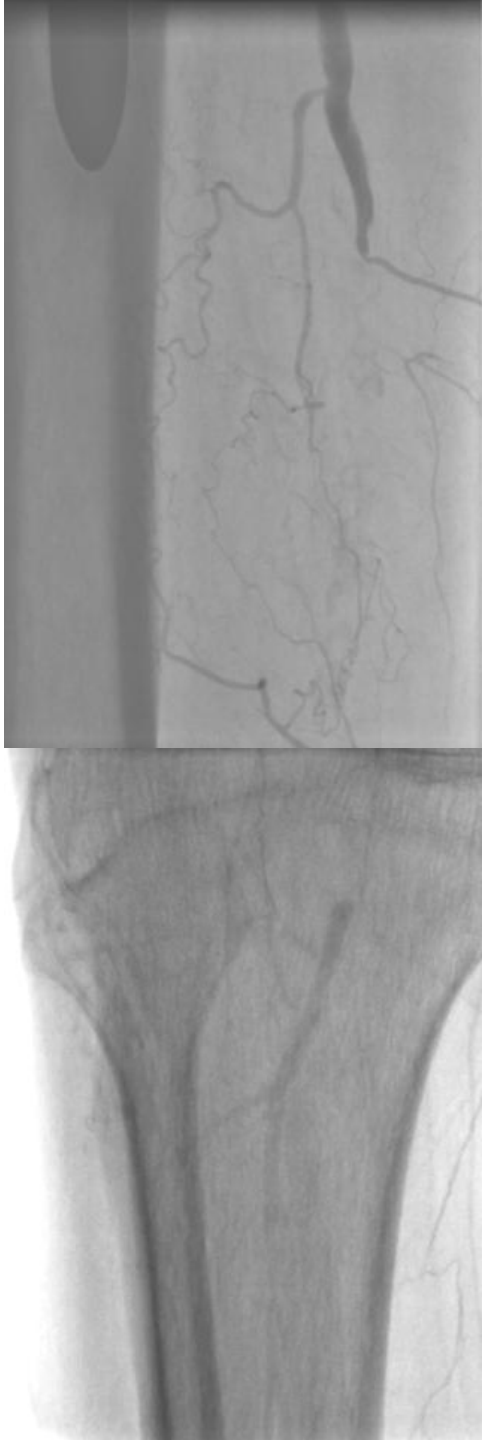
Micari et al. JACC Cardiovasc Intervent 2013 accepted

THUNDER

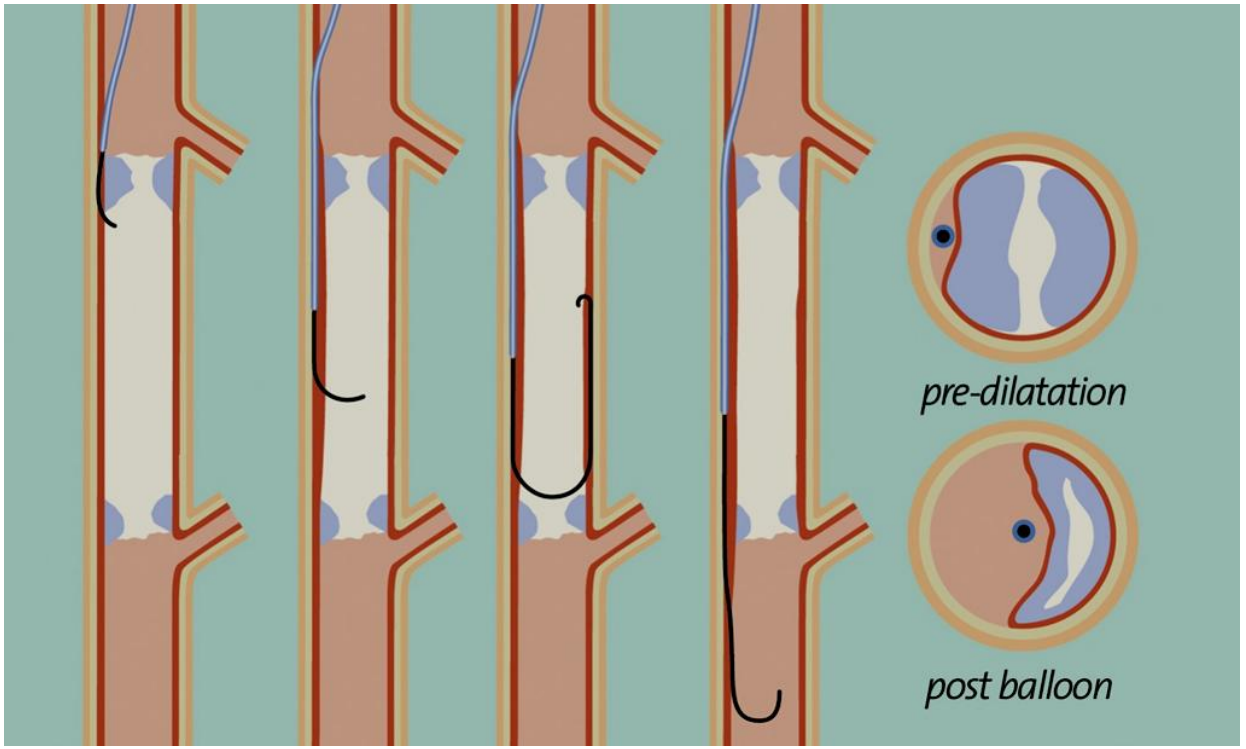
5-Year Outcomes – Freedom from TLR



Tepe, Zeller TCT 2011



Long Lesions / Subintimal Angioplasty



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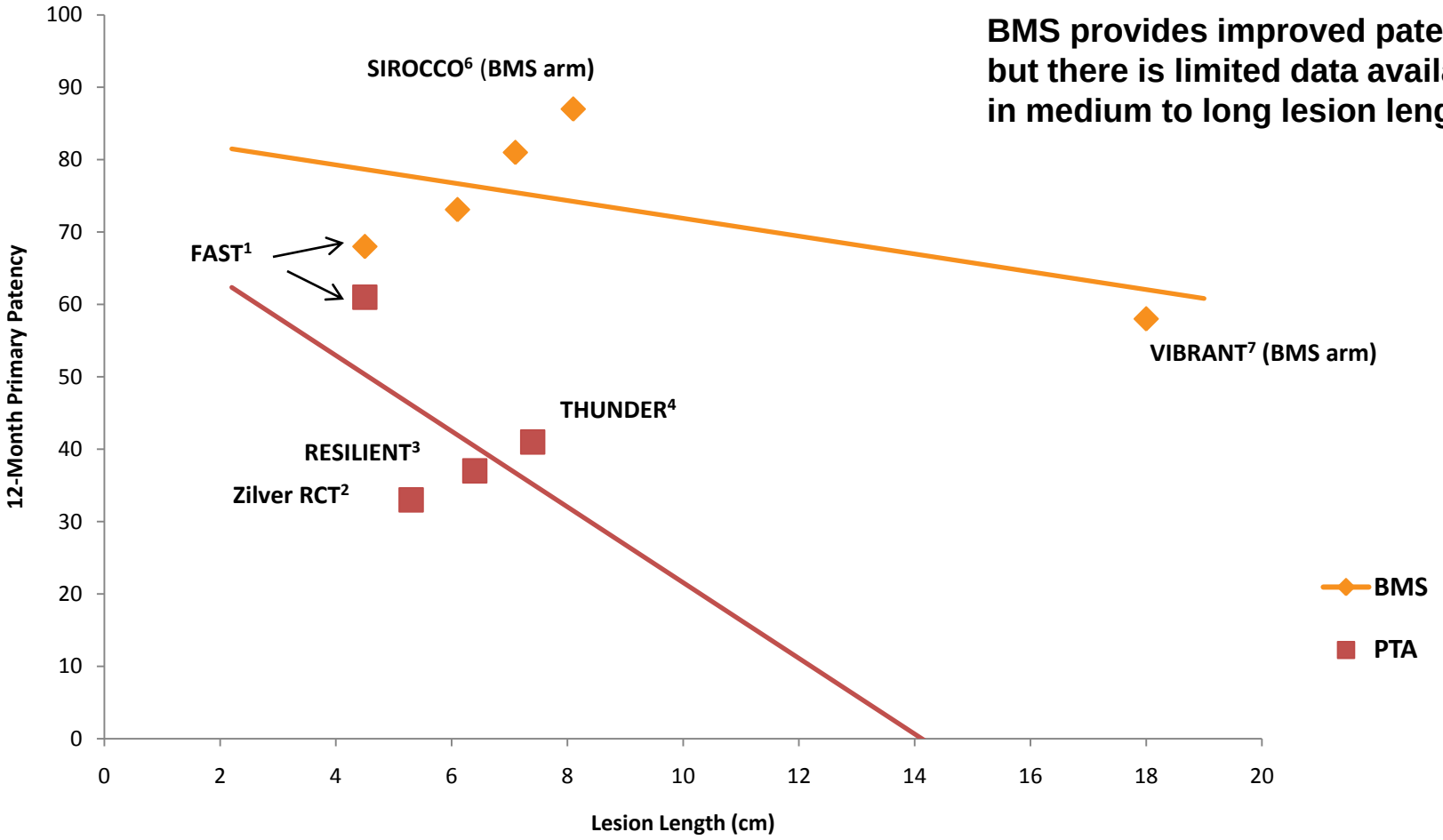
PTA and BMS in SFA

12-Month Primary Patency

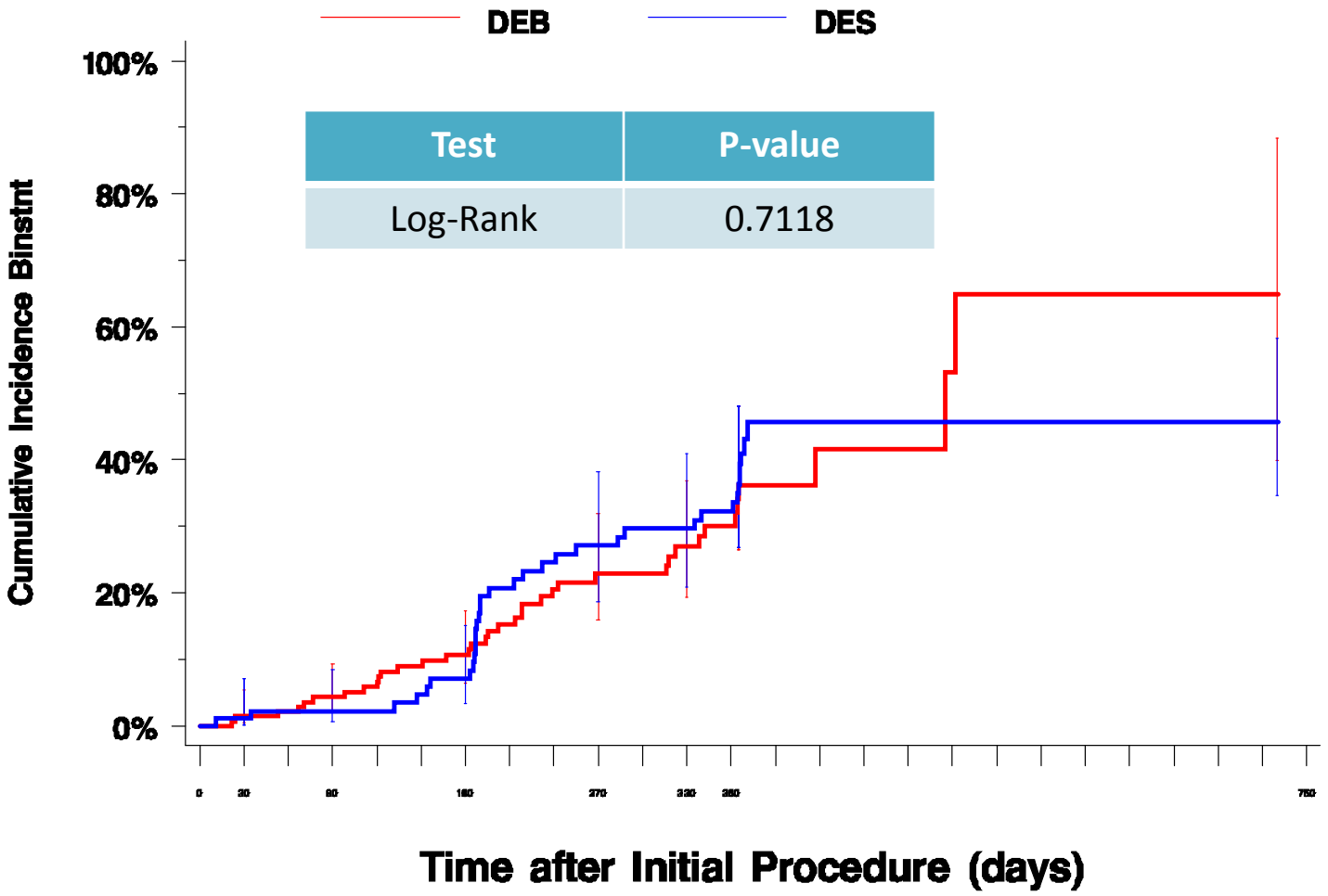


1. Krankenberg et al. Circulation. 2007; 116(3): 285-92
2. Dake et al. Circ Cardiovasc Interv. 2011;4:495-504)
3. Laird et al. Circ Cardiovasc Interv. 2010; 3: 267-276
4. Tepe et al. NEJM 2008;358:689-99
5. Laird, ISET 2012
6. Duda et al. J Endovasc Ther 2006; 13:701-710
7. Ansel, LINC 2010

DCB vs. DES in Long Lesions
Lesion Characteristics

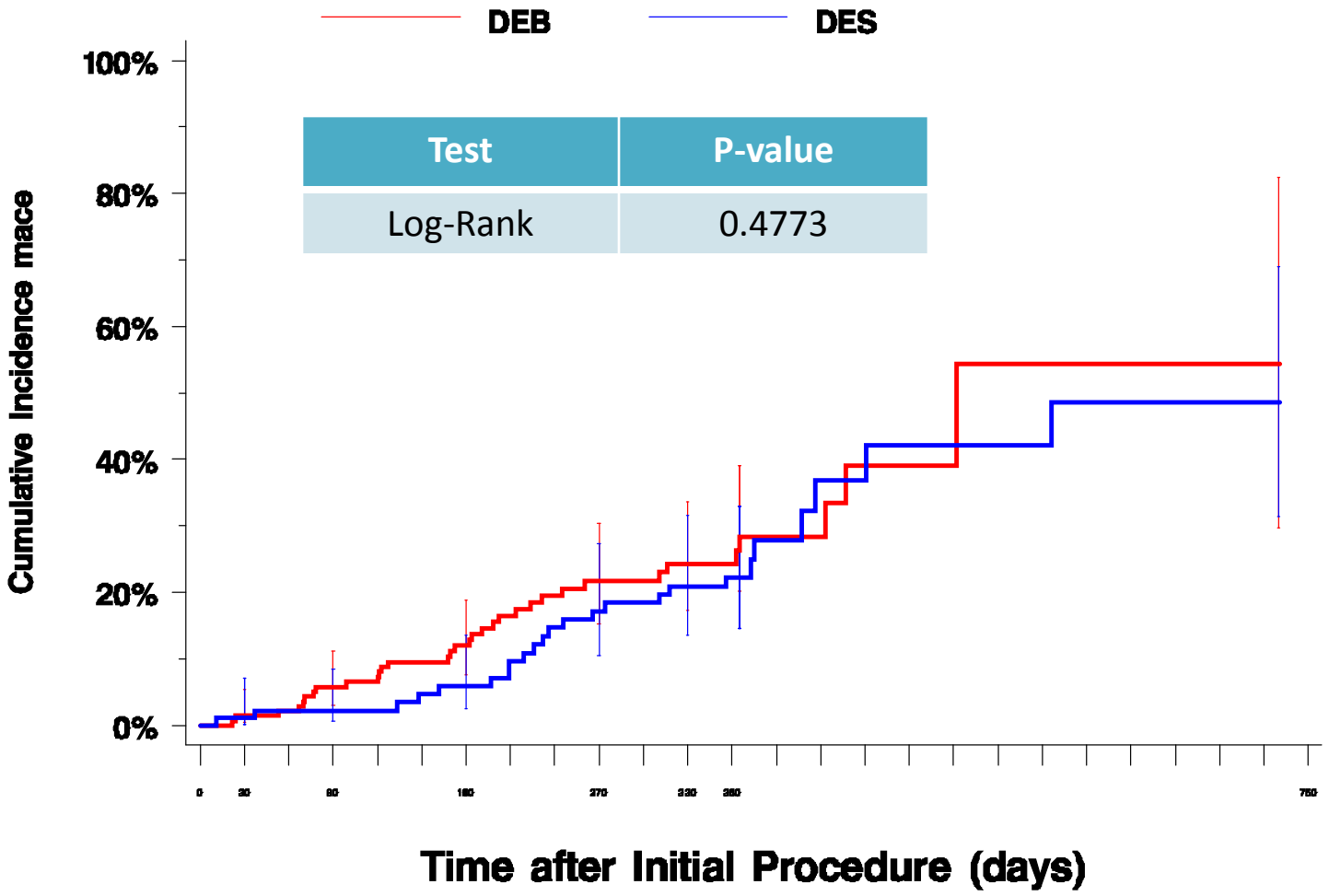
Lesion Characteristics	DEB (N=173)	DES (N=97)	p-value
Proximal SFA	49.1% (85/173)	52.6% (51/97)	*0.587*
Mid SFA	69.4% (120/173)	79.4% (77/97)	*0.075*
Distal SFA	75.7% (131/173)	86.6% (84/97)	***0.033***
P1	23.1% (40/173)	17.5% (17/97)	*0.280*
P2	9.8% (17/173)	0.0% (0/97)	***0.001***
P3	7.5% (13/173)	0.0% (0/97)	***0.006***
TL length (mm)			
N	173	97	
Mean±SD	**189.8 ± 78.9**	**195.0 ± 64.5**	***0.557***
Median	160.0	190.0	
Min,Max	100, 450	100, 350	

DCB vs. DES in Long Lesions
Binary Restenosis: KM Analysis



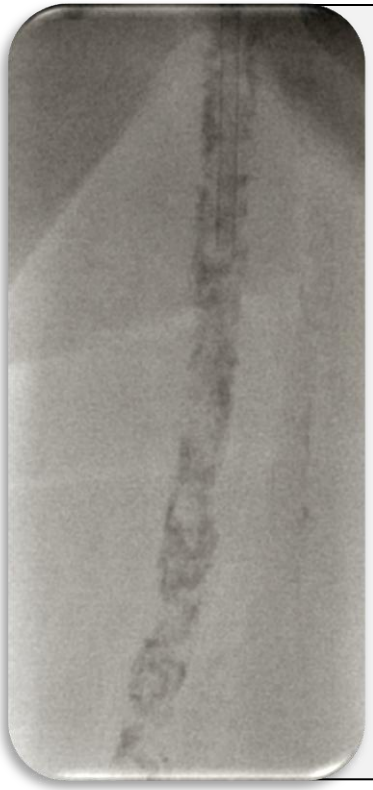
DCB vs. DES in Long Lesions

Composite Death and CD-TLR: KM Analysis



Test	P-value
Log-Rank	0.4773

DCB in Calcified SFA Lesions



- Lack of standardized assessment and quantification methods
- Difficult to detect (needs proper imaging and / or «empiric» assessment via pre-dilatation)
- Frequently observed in long lesions and occlusions as a results of the natural course of disease chronicization
- Diffuse calcification frequently observed in elderly patients, diabetes and chronic renal failure
- Severly calcified lesions constitutes a typical exclusion criterion in most Trials

– Generate false negative ABI
– "Incompressibility", lesion resistance, recoil, dissections, embolism, …
– Cause of stent malapposition and sub-optimal expansion
– Risk factor for Stent fractures

Typical treatment modalities

1. **Endovascular:**
   - Optimal lesion preparation
     - Aggressive pre-dilat. or
     - Scoring balloon or
     - Debulking
   - Elective Stenting
2. **Surgical**

1. ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic) J. Am. Coll. Cardiol. 2006;47;e1-e192
2. O. Schlager et al. Duplex Sonography Versus Angiography for Assessment of Femoropopliteal Arterial Disease in a ''Real-World'' Setting. J Endovasc Ther 2007;14:452–459
3. L. Norgren et al. TASC II Eur J Vasc Endovasc Surg 33, S1 S7 (2007)
4. N.Diehm et al. Clinical Endpoints in Peripheral Endovascular Revascularization Trials: a Case for Standardized Definitions. Eur J Vasc Endovasc Surg (2008) 36, 409e419

SFA Highly Calcified lesions

high promising signal of safety and efficacy in combination with atherectomy to treat severly calcified SFA lesions

Contents lists available at SciVerse ScienceDirect

Cardiovascular Revascularization Medicine

Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: One-year single centre clinical results☆

Angelo Cioppa*, Eugenio Stabile, Grigore Popusoi, Luigi Salemme, Linda Cota, Armando Pucciarelli, Vittorio Ambrosini, Giovanni Sorropago, Tullio Tesorio, Alessia Agresta, Giancarlo Biamino, Paolo Rubino

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ABSTRACT

Background: The use of Directional Atherectomy (DA) for the treatment of calcified femoro-popliteal lesions seems to improve the acute procedural success, however without reducing the long term restenosis rate. Drug coated balloons (DCB) reduced restenosis rate in non heavy calcified lesions. Aim of this study was to demonstrate safety and efficacy of a combined endovascular approach using DA and DCB for the treatment of heavy calcified lesions of the femoro-popliteal tract.

Methods: From January 2010 to November 2010, 240 patients underwent PTA of the femoro-popliteal tract in our institution. Within this cohort a total of 30 patients had Life Limiting Claudication (LLC) (n = 18) and 12 a Critical Limb Ischemia (CLI) with baseline Rutherford class 4.2 ± 1.2 underwent PTA of heavy calcified lesions with intravascular ultrasound guided DA and DCB. All procedures have been performed using a distal protection device. Stent implantation was allowed only in case of flow limiting dissections or suboptimal result (residual stenosis > 50%) by visual estimation. After the intervention patients were followed up to 12 months.

Results: Procedural and clinical success, was achieved in all cases. Bail-out stenting was necessary in only two (6.5%). At twelve month follow up median Rutherford class was 2.2 ± 1.2, ABI was 0.8 ± 0.1 and Limb salvage rate was 100%. Two minor, foot finger or forefoot amputations, were performed to reach complete wound healing and/or preserve deambulation. Duplex control was performed in all the cases (n = 30). In three cases duplex scan showed a significant target lesion restenosis requiring a reintervention (TLR = 10%) leading a total one-year secondary patency rate of 100%. All the three restenosed patients were insulin dependent diabetics and none of them were stented during the procedure.

Conclusion: The data suggest that combined use of DA and DCB may represent a potential alternative strategy for the treatment of femoro-popliteal severely calcified lesions. These very promising data and the considered hypothesis have to be confirmed in a multicentre randomised trial.

30-patient single-center Registry

- **LLC / CLI = 6% / 94%**
- **Diabetics = 60%**
- **Mean lesion length = 115±35 mm**
- **Tot Occlusions = 13%**
- **Calcium Score* 3 = 100%**

dist. Filter + TurboHawk + IN.PACT

- **bail-out Stenting = 7%**

•12-month results:

- Primary Patency = 90%
- TLR = 10%
- Second. Patency = 100%

* 0= absence of calcium; 1= calcium on one side of lumen <1cm length; 2= calcium on both side <1cm length; 3=calcium on both side >1 cm length

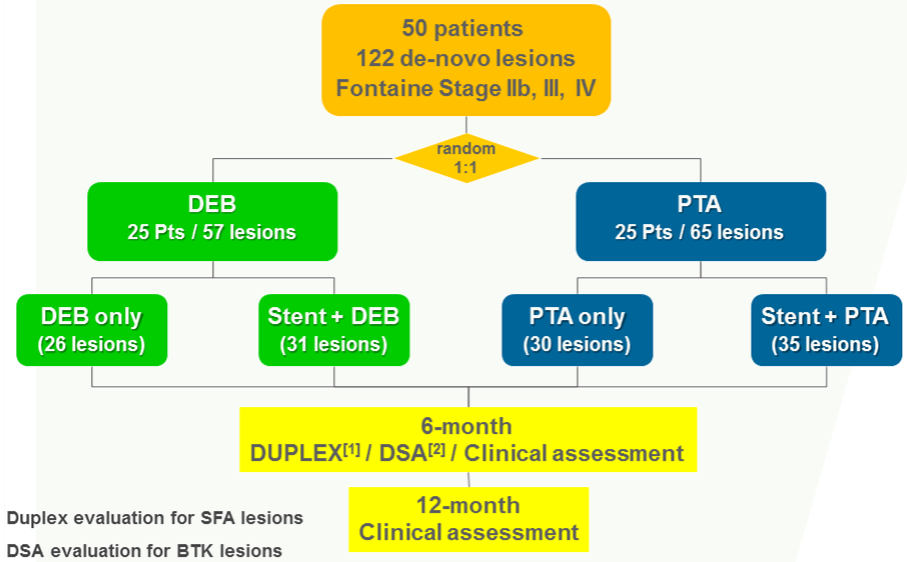
Cioppa A et al. Cardiovasc. Revasc. Medicine 2012

DCB in Multilevel Disease

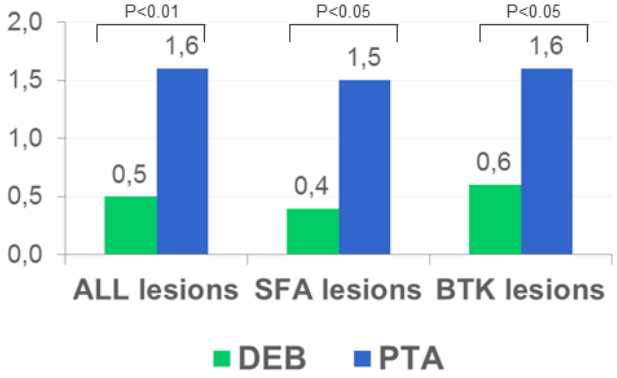
DEBELLUM

Single center RCT of IN.PACT vs. PTA in MULTILEVEL lower limb disease

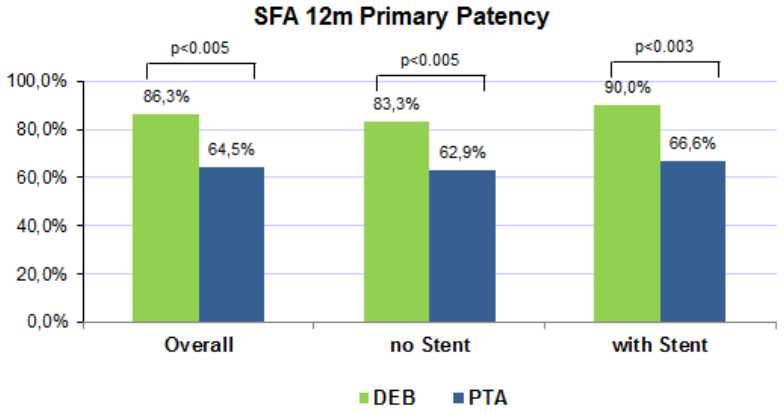
- **Prim. Endpoint: 6m LLL**
- **50 patients**
- **Fempop / BTK / multilevel = 76% / 24% / 40%**
- **LLC / CLI = 62% / 39%**



6-month Angiographic results (LLL)



12-month Primary Patency (SFA)



(F.Fanelli, JEVT 2012)

SFA & DCB

In-Stent-Restenosis

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Drug-Eluting Balloon for Treatment of Superficial Femoral Artery In-Stent Restenosis

Eugenio Stabile, MD, PhD, Vittorio Virga, MD, Luigi Salemme, MD, Angelo Cioppa, MD, Vittorio Ambrosini, MD, Giovanni Sorropago, MD, Tullio Tesorio, MD, Linda Cota, MD, Grigore Popusoi, MD, Armando Pucciarelli, MD, Giancarlo Biamino, MD, Paolo Rubino, MD

Mercogliano, Italy

Objectives The purpose of this prospective registry was to evaluate the safety and efficacy, at 1 year, of the use of drug-eluting balloons (DEB) for the treatment of superficial femoral artery (SFA) in-stent restenosis (ISR).

Background The use of the self-expanding nitinol stent has improved the patency rate of SFA after percutaneous transluminal angioplasty (PTA). As the population with SFA stenting continues to increase, occurrence of ISR has become a serious problem. The use of DEB has showed promising results in reducing restenosis recurrence in coronary stents.

Methods From December 2009 to December 2010, 39 consecutive patients underwent PTA of SFA-ISR in our institution. All patients underwent conventional SFA PTA and final post-dilation with paclitaxel-eluting balloons (IN.PACT, Medtronic, Minneapolis, Minnesota). Patients were evaluated up to 12 months.

Results Technical and procedural success was achieved in every patient. No in-hospital major adverse cardiac and cerebrovascular events occurred. At 1 year, 1 patient died due to heart failure. Primary endpoint, primary patency rate at 12 months, was obtained in 92.1% (35 patients). At 1 year, patients were asymptomatic for claudication, and duplex assessment demonstrated lack of recurrent restenosis (100% rate of Secondary patency). The presence of an occlusive restenosis at the time of treatment was not associated with an increased restenosis rate, when compared with non-occlusive restenosis, at 1 year.

Conclusions The data suggest that adjunctive use of DEB for the treatment of SFA-ISR represents a potentially safe and effective therapeutic strategy. These data should be considered hypothesis-generating to design a randomized trial. (J Am Coll Cardiol 2012;xx:xxx) © 2012 by the American College of Cardiology Foundation

Stabile E et al. J Am Coll Cardiol 2012;60:1739–42

Inpact DEB in SFA ISR

Baseline Characteristics

Table 2 Procedural Characteristics

Contralateral access	39 (100.0)
Pre-dilation	35 (89.8)
Distal protection	6 (15.4)
Excimer laser debulking	4 (10.3)
Stent diameter, mm	6 (6–6.5)
Stent length, mm	150 (95–262.5)
Lesion length, mm	82.9 ± 78.9
Pre-dilation balloon diameter, mm	5 (4.5–5)
Pre-dilation balloon length, mm	120 (80–120)
DEB diameter, mm	6 (5–6)
Number of DEB	2 (1–2)
Cumulative DEB length, mm	160 (120–250)
Fractured stents	4 (10.3)
Bailout stenting (%)	4 (10.3)
Procedural success	39 (100)

N = 39. Values are n (%), mean ± SD, or median (interquartile range).
DEB = drug-eluting balloon(s); IQR = interquartile range.

Stabile E et al. J Am Coll Cardiol 2012;60:1739–42

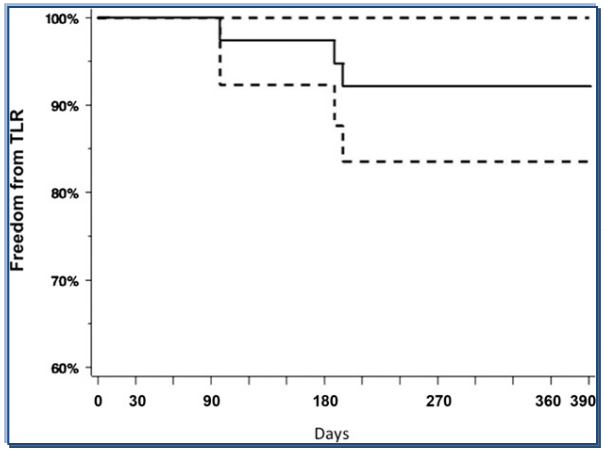
SFA & DCB

In-Stent-Restenosis

high promising signal of safety and efficacy in SFA ISR up to 1 year

39-patient single-center Registry

- **LLC / CLI = 79.5% / 20.5%**
- **Diabetics = 48.7%**
- **mean Stent length = 181.2 mm**
- 12-month results:
  - TLR = 7.8%
  - Rest. Rate = 7.8%



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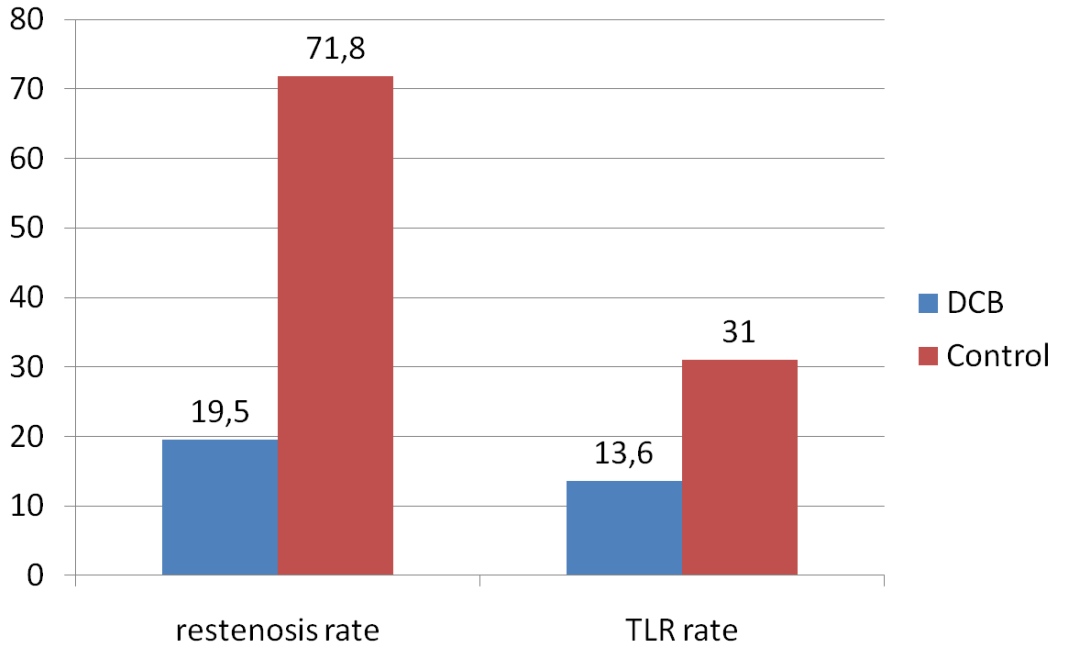
Stabile E et al. J Am Coll Cardiol 2012;60:1739–42

DEBATE ISR

In-Stent-Restenosis

- Single arm study on IN.PACT DEB for the treatment of SFA In-Stent-restenosis compared against an historical patient cohort with matched anatomical and clinical profiles treated with standard PTA ISR of the femoral and proximal popliteal artery
- 44 diabetic patients
  - 36% Claudicants
  - 64% CLI



F. Liistro TCT Poster # TCT-343, 1-year results, TCT 2012 Miami

DCB Below-the-Knee

DCB BTK Leipzig Registry

IN.PACT™ Amphirion in real world BTK complex lesions

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CLINICAL RESEARCH — **Interventional Cardiology**

First Experience With Drug-Eluting Balloons in Infrapopliteal Arteries

Restenosis Rate and Clinical Outcome

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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.

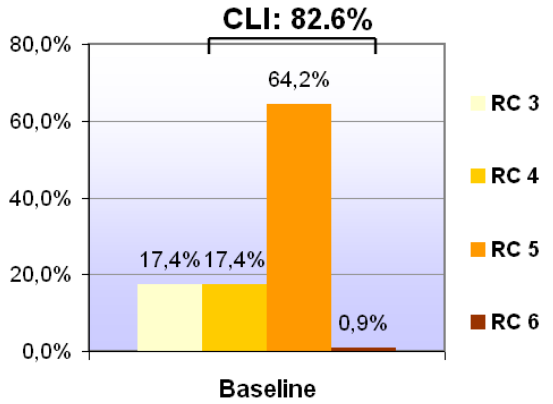
Background Restenosis rates of long-segment tibial artery disease are very high. Recently, a restenosis rate of 69% at 3 months after standard balloon angioplasty was demonstrated.

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

Study type	Prospective single center, single arm, investigator initiated study
Objective	Assess **IN.PACT Amphirion™** efficacy for the treatment of long BTK lesions occlusions
Population	Symptomatic patients with CLI or severe claudication
Eligibility	At least one lesion BTK ≥ 80 mm
Prim. Endpoint	3 month restenosis rate
Nr of patients	104 / 109 limbs



A.Schmidt et. Al JACC 2011

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

	DEB (angio subgroup)	PTA* (historical group)
# patients / limbs	74 / 79	58 / 62
Male gender	51 (68.9%)	38 (65.5%)
mean age (y)	73.5 ± 9.3	70.5 ± 8.08
diabetics	54 (73%)	52 (89.7%)
Renal insuff.	34 (45.9%)	30 (51.7%)
RC 3	16 (20.3%)	0 (0%)
RC 4	14 (17.7%)	16 (25.8%)
RC 5	49 (62%)	46 (74.2%)
RC 6	0 (0%)	0 (0%)
avg lesion length	173 ± 87 mm	183 ± 75 mm
Tot occlusions	61.9%	64.9%

	DEB (angio subgroup)	PTA* (historical group)
	3m Angiographic FU	
Restenosis (>50%)	27.4%	69%
Full-segment Resten.	10%	56%
Restenosis Length	64 mm	155 mm
	12m Clinical FU	**15m Clinical FU**
Deaths	16.3%	10.5%
Limb Salvage	95.6%	100%
Clinical Improvement (1)	91.2%	76.5%
Compl. wound healing	74.2%	78.6%
TLR	17.3%	50%

(1) clinical improvement = reduction in size and/or depth of ulceration or improvement of rest-pain

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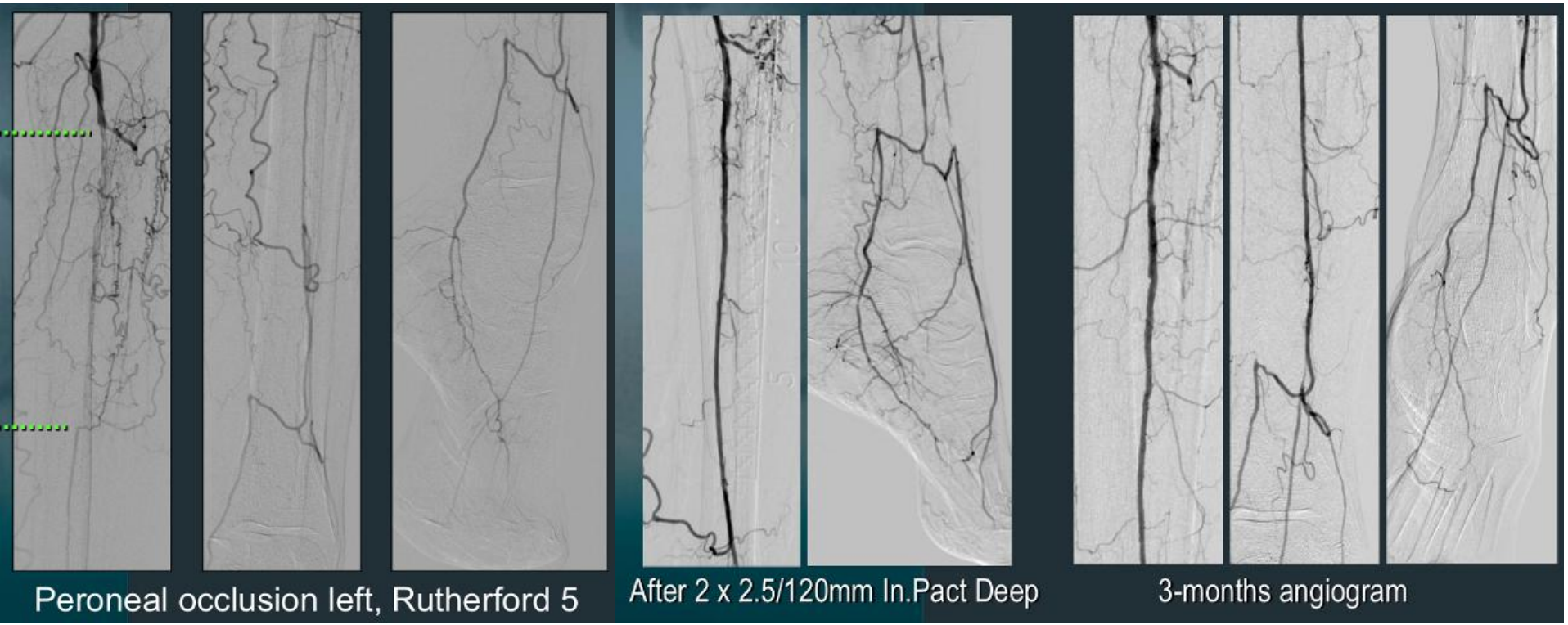
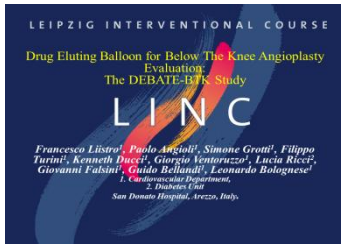




DCB Below-the-Knee
DEBATE Randomized Trial

Single center RCT of IN.PACT Amphirion* vs. PTA in BTK-CLI-DIABETICS de-novo lesions

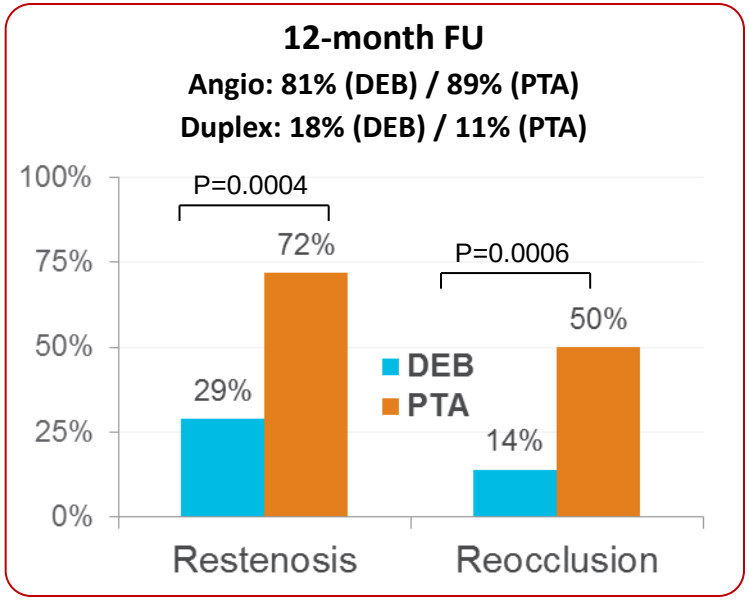
Prim. Endpoint: 12m Restenosirate

120 patients (preliminary results)

Baseline (DCB 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%**

DCB significantly reduces restenosis rate at 12-month 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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Conclusions

- DEB are superior to POBA in femoropopliteal and below-the-knee de novo lesions.
- DEB result in outstanding results in in-stent restenosis.
- Limitations of DEB angioplasty might be resolved by plaque removal or plaque modulation prior to DEB inflation.
- The clinical impact of improved vessel patency after DEB angioplasty in CLI patients must be examined by larger clinical endpoint driven trials.