i-MEET

NEXT GENERATION

Multidisciplinary European Endovascular Therapy

Femoropopliteal disease: This is the "State-of-the-art"

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Disclosure of Interest

Peter A. Schneider

I have the following potential conflicts of interest to report:

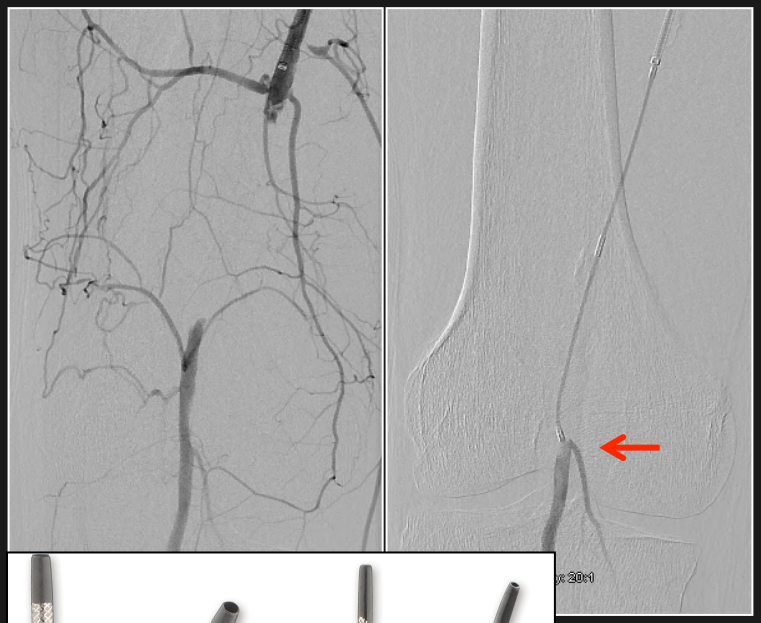
- Noncompensated advisor: Cardinal, Abbott, Medtronic
- Royalty: Cook (modest)
- Co-founder and Chief Medical Officer: Intact, Cagent
- Board member: VIVA (nonprofit)

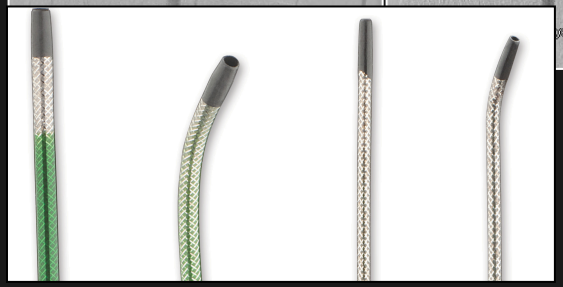
Femoro-popliteal Occlusive Disease In Last 8 Years…

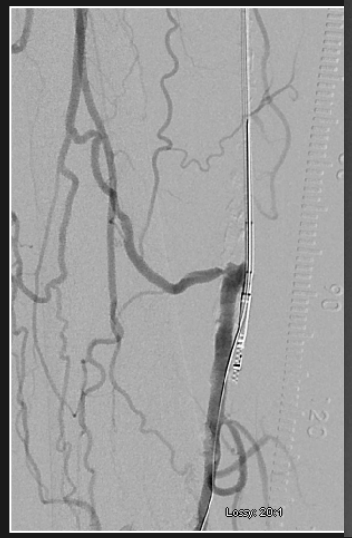
- Can cross most occlusions in the SFA-pop.
- Randomized data with stents, drug coated balloons, drug-eluting stents.
- Era of drugs delivery has arrived.
- Challenges remain

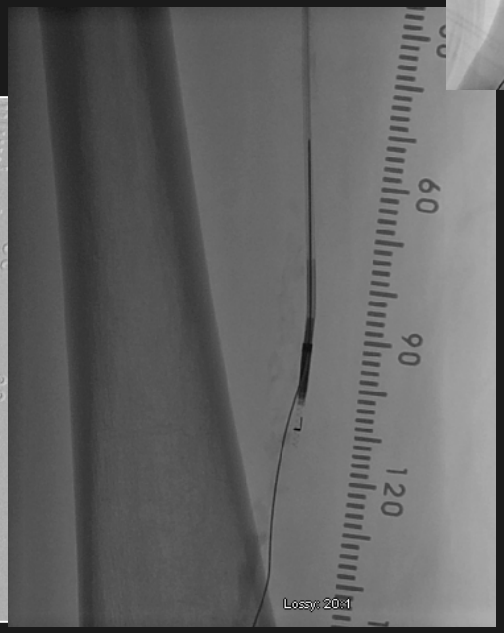
Major Progress in Crossing Lesions

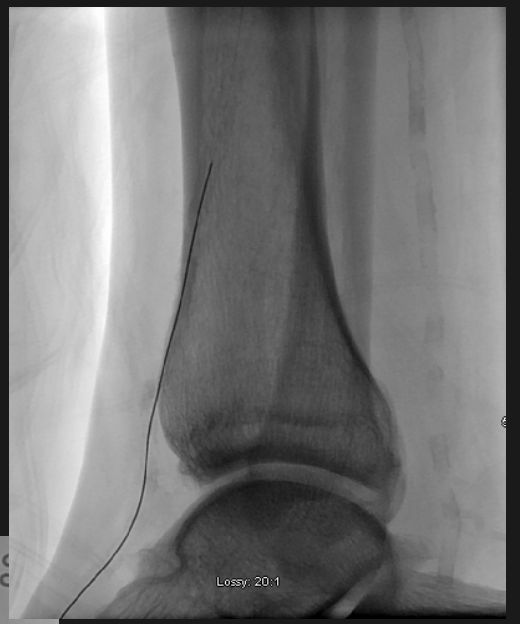
CTO Wires, Support Catheters, Re-entry Devices, Retrograde Access





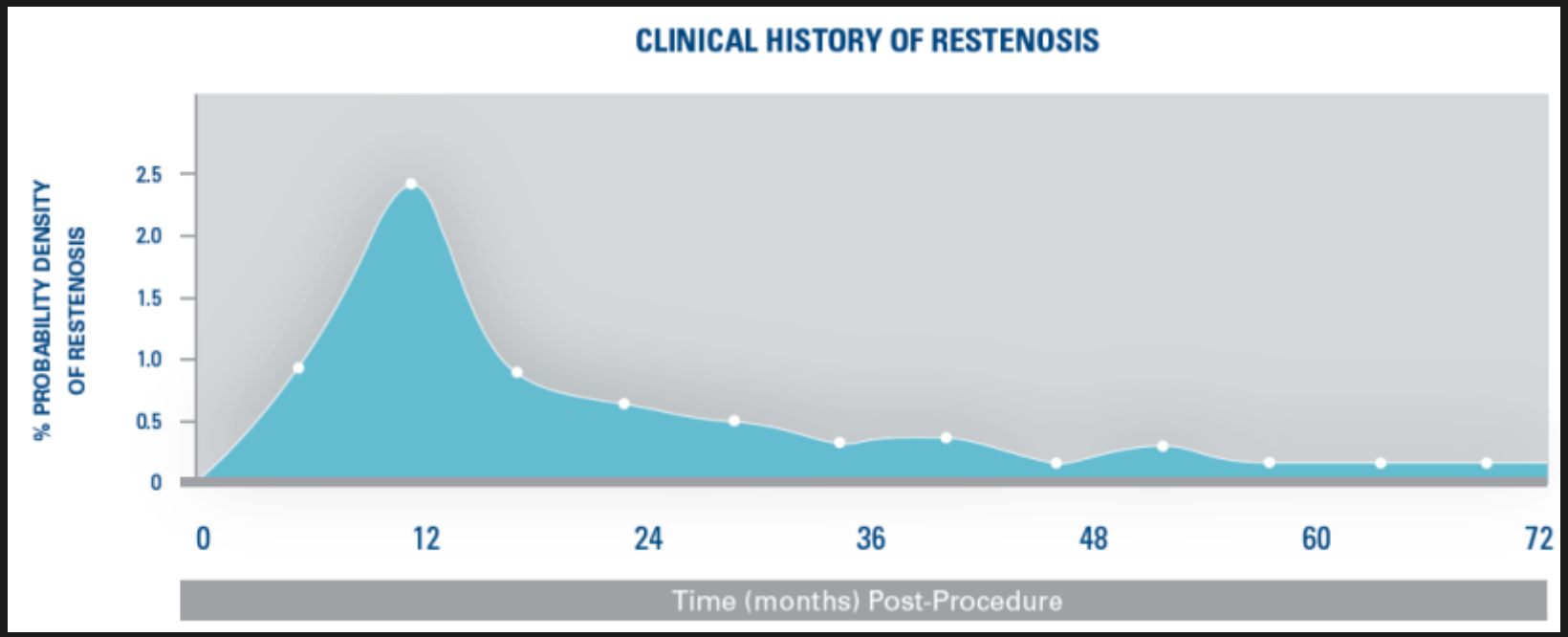






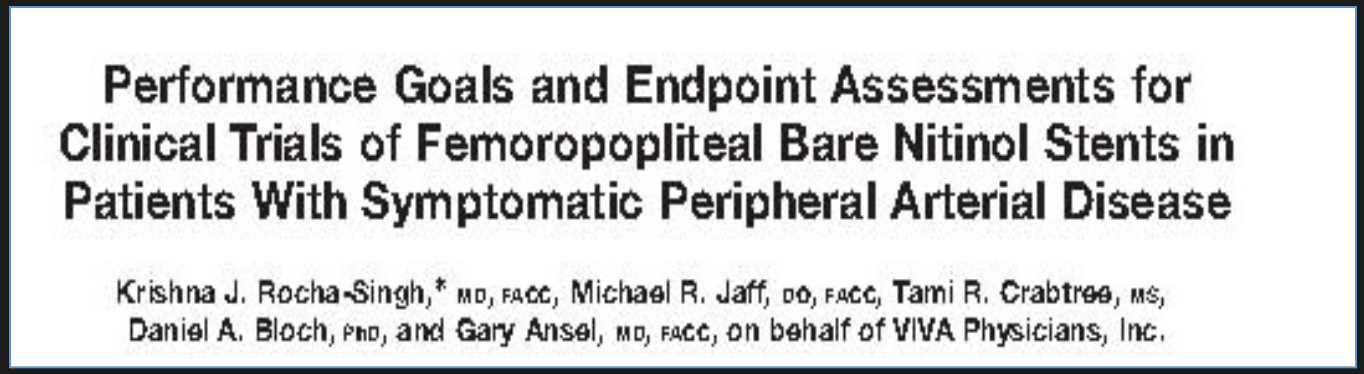
Probability of Restenosis

SFA Restenosis peaks at 12 months



- Timing of SFA restenosis is longer compared to coronary stenting, which predominantly occurs within 6 months after stenting.
- Factors for restenosis in the SFA include the number of runoff vessels, severity of lower limb ischemia, and length of diseased segments.

Iida et al. Cath Cardio Int 2011; 78:611
Kimura et al. N Engl J Med 1996;334:561



Performance Goals and Endpoint Assessments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients With Symptomatic Peripheral Arterial Disease

Krishna J. Rocha-Singh,* MD, FACC, Michael R. Jaff, DO, FACC, Tami R. Crabtree, MS, Daniel A. Bloch, PhD, and Gary Ansel, MD, FACC, on behalf of VIVA Physicians, Inc.

VIVA OPC

- PTA control arm from 3 randomized, industry-sponsored device trials
  - Lesion length = 8.7 cm
  - 12-month duplex patency = 28%
- Results combined with a survey of medical literature from 1990 – 2006
  - Lesion length = 8.9 cm
  - 12-month duplex patency = 38%

Catheter Cardiovasc Interv 2007

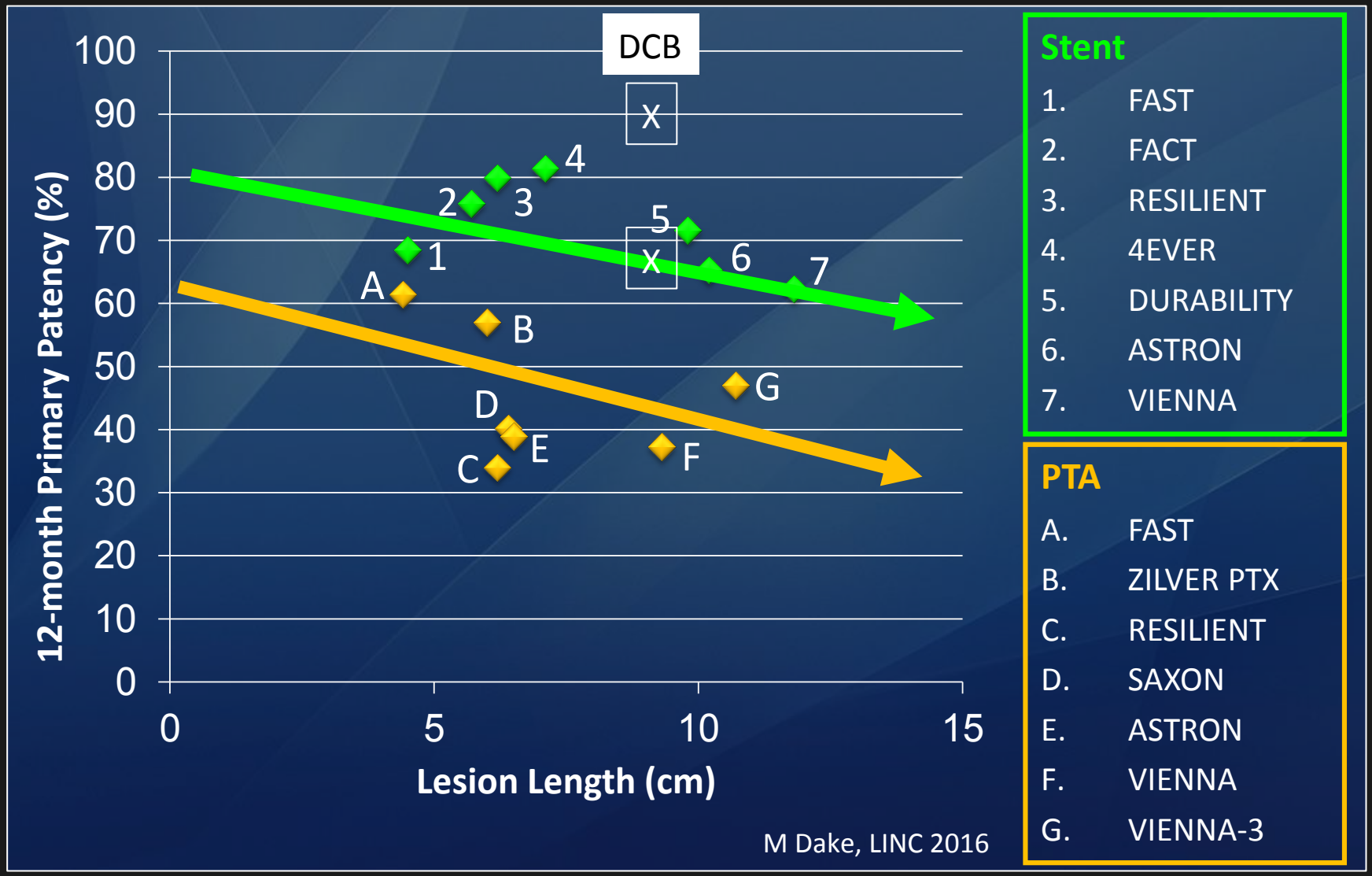
Implant-Based Treatment Paradigm

SFA Stent Studies

Parameter (study start)	LifeStent* Resilient (July 2004)	Everflex* Durability II (August 2007)	Complete SE Vascular	Zilver PTX* (March 2005)	SUPERA Superb
FDA Approval	Feb 13, 2009	Mar 7, 2012	no	Nov 14, 2012	no
Subjects	**206** (72 PTA)	**287**	**196**	**479** (241 ZS / 238 PTA)	**264**
Lesion Length (Min, Max)	**61.85** 57.2 PTA	**109.6** (10.0, 180.0)	**61**	**54.6** / 53.2 PTA	**78**
Primary Patency <2.0 (1 year)	**81.5%** 36.7% PTA	**67.7%**	**72.6**	**82.7%** 32.7% PTA (95.1% ZS / 41.6% PTA – 6 Months)	**86%**
TLR (1 year)	**94.6%** 54.1%- PTA (Freedom From)	**13.9%** -	**8.4%**	**9.6%** 16.3% PTA	**10%**
Design	**2:1 RCT PTA**	**OPC**	**OPC**	**1:1 RCT PTA**	**OPC**

Patency Benefit With Stenting

Primarily in TASC A/B



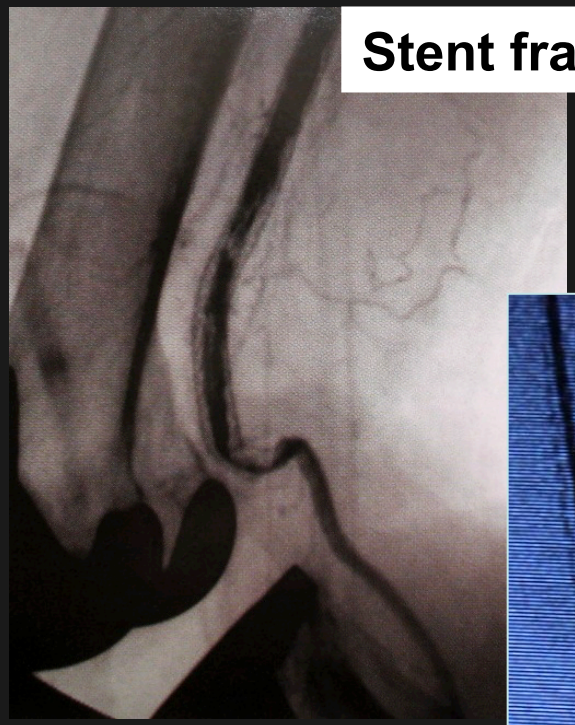
Stent

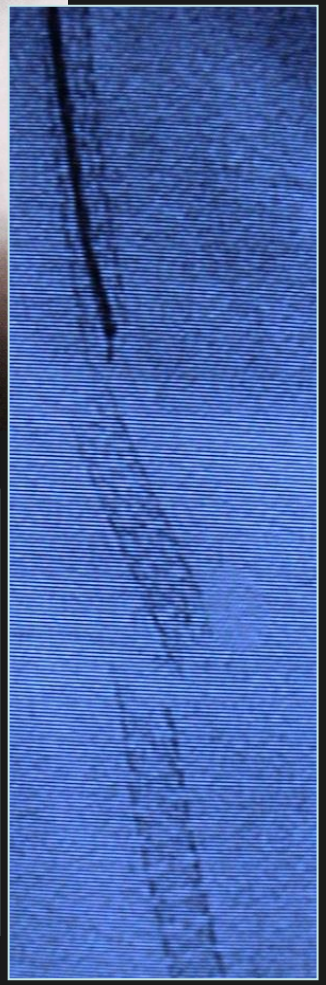
1. FAST
2. FACT
3. RESILIENT
4. 4EVER
5. DURABILITY
6. ASTRON
7. VIENNA

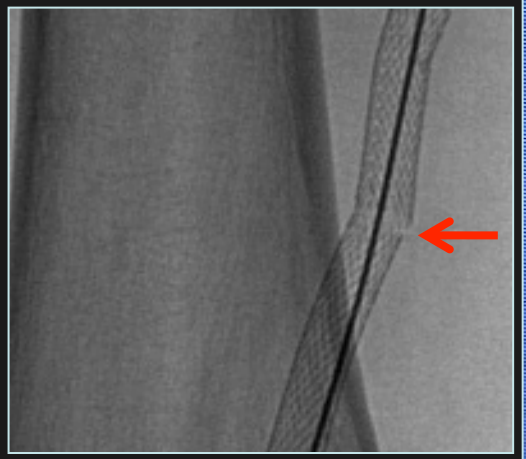
PTA

A. FAST
B. ZILVER PTX
C. RESILIENT
D. SAXON
E. ASTRON
F. VIENNA
G. VIENNA-3

Stent fracture

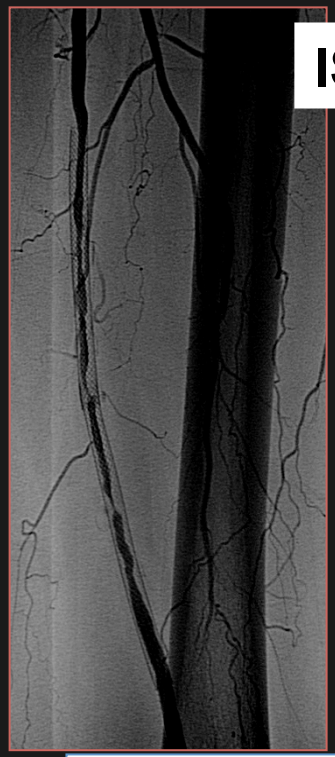


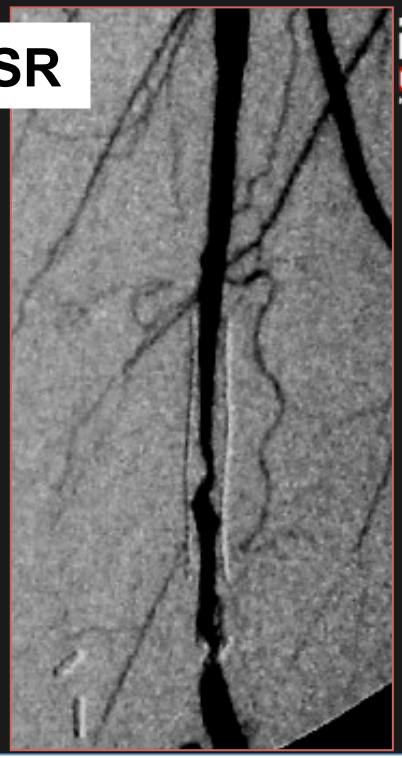


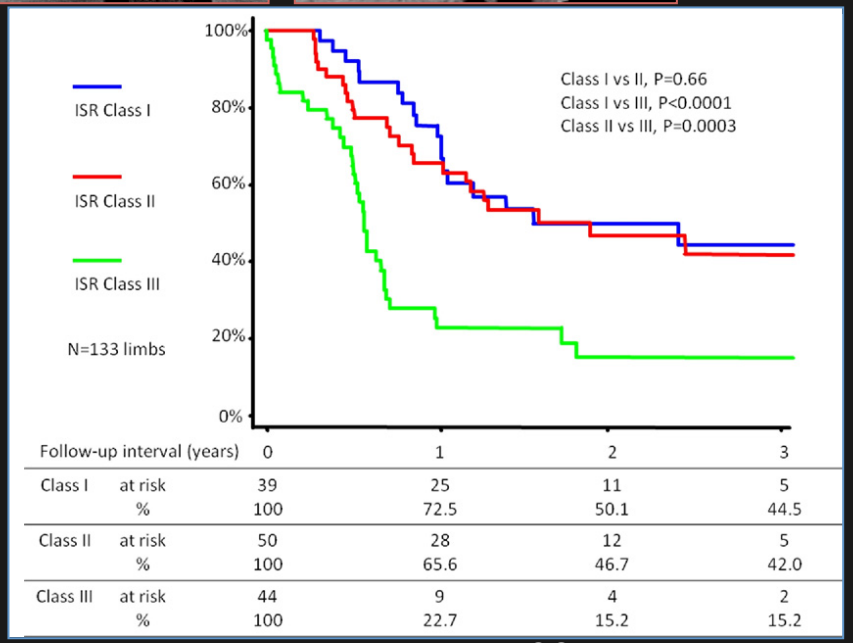


Iida et al. Am J Cardiol 2006;98:272.
Sirocco J Endovasc Ther 2006;13:701.
Scheinert et al. JACC 2005;45.

ISR







Follow-up interval (years)		0	1	2	3
Class I	at risk	39	25	11	5
	%	100	72.5	50.1	44.5
Class II	at risk	50	28	12	5
	%	100	65.6	46.7	42.0
Class III	at risk	44	9	4	2
	%	100	22.7	15.2	15.2

Tosaka et al. JACC 2012;59:16-23

Femoral-popliteal Treatment
Conformational Forces

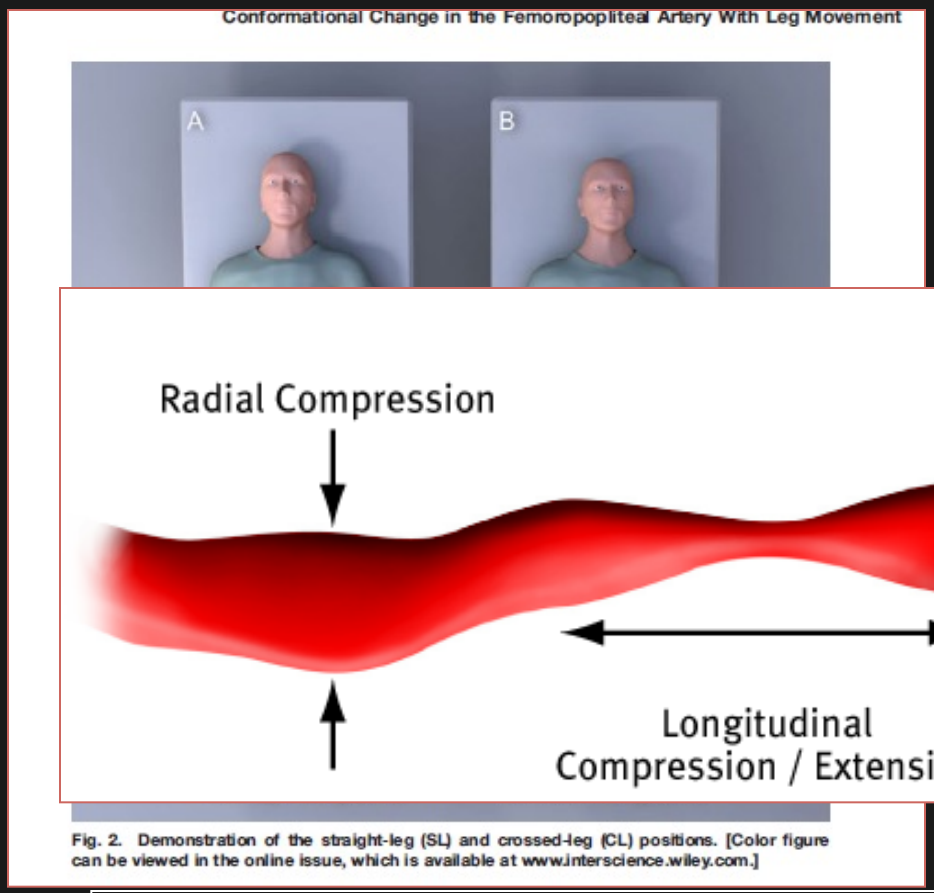
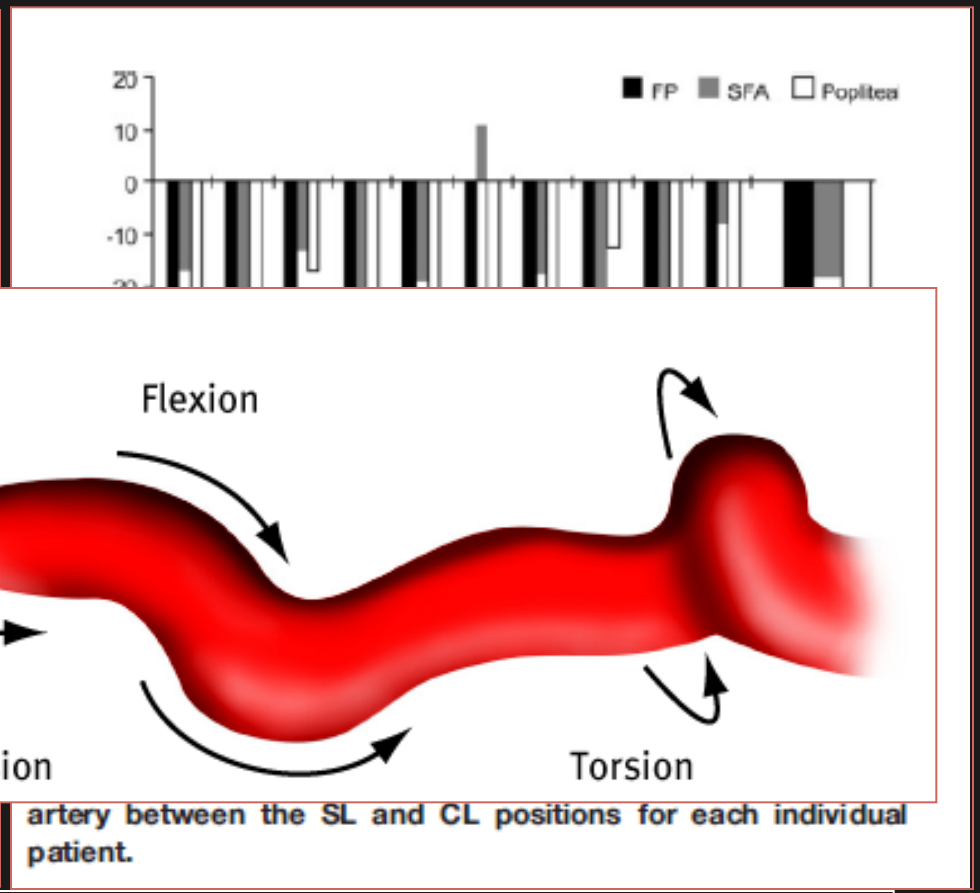


Fig. 2. Demonstration of the straight-leg (SL) and crossed-leg (CL) positions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



artery between the SL and CL positions for each individual patient.

Dramatic changes in configuration with movement.

Klein et al. Catheter Cardiovasc Interv 2009;74:799

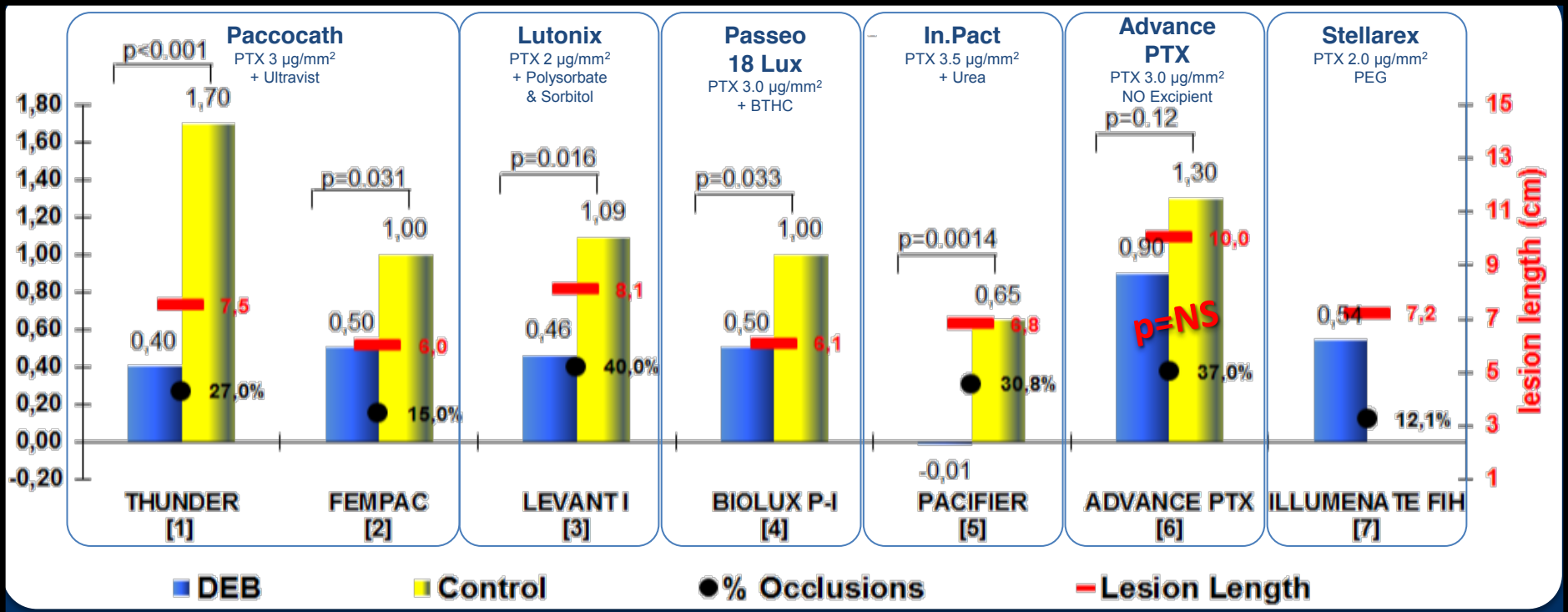
Drug eluting Technologies

Development Issues

- Optimal drug-paclitaxil, limus drugs
- Proper dose and release kinetics
- Excipient-urea, polymers, iopromide, nano-
- Delivery mechanism: balloon or stent
- Vessel preparation
- What to do about dissection?
- Geographic miss?
- Cost

Late Lumen Loss

6 Different Paclitaxel DCB Preparations

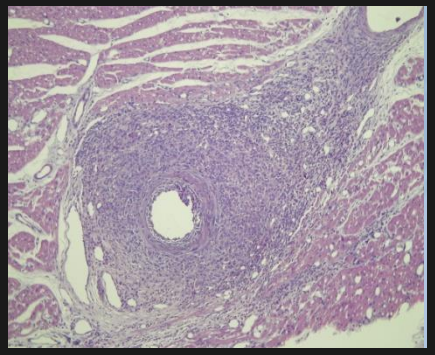


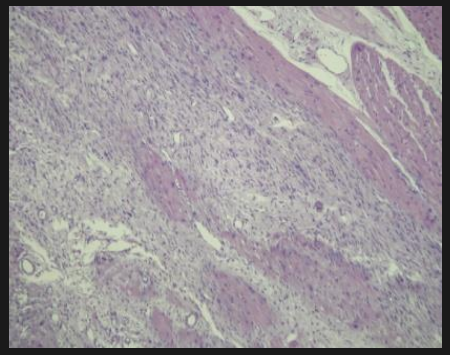
1. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, Claussen CD, Oldenburg A, Scheller B, Speck U. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med. 2008 Feb 14;358(7):689-99
2. Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, 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 – 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 Feb 23

Angiogram at 6 months: substantially less loss of lumen size

Paclitaxel

- Mechanism: slowly dissolving particles in the vessel wall, transferred to wall during balloon inflation
- Cytostatic agent-acts on microtubu
  - No effect on DNA
- Intravascular dose for tumor is 30
- Single dose of 70 mg has no adve
- Maximum dose on a balloon is 10r



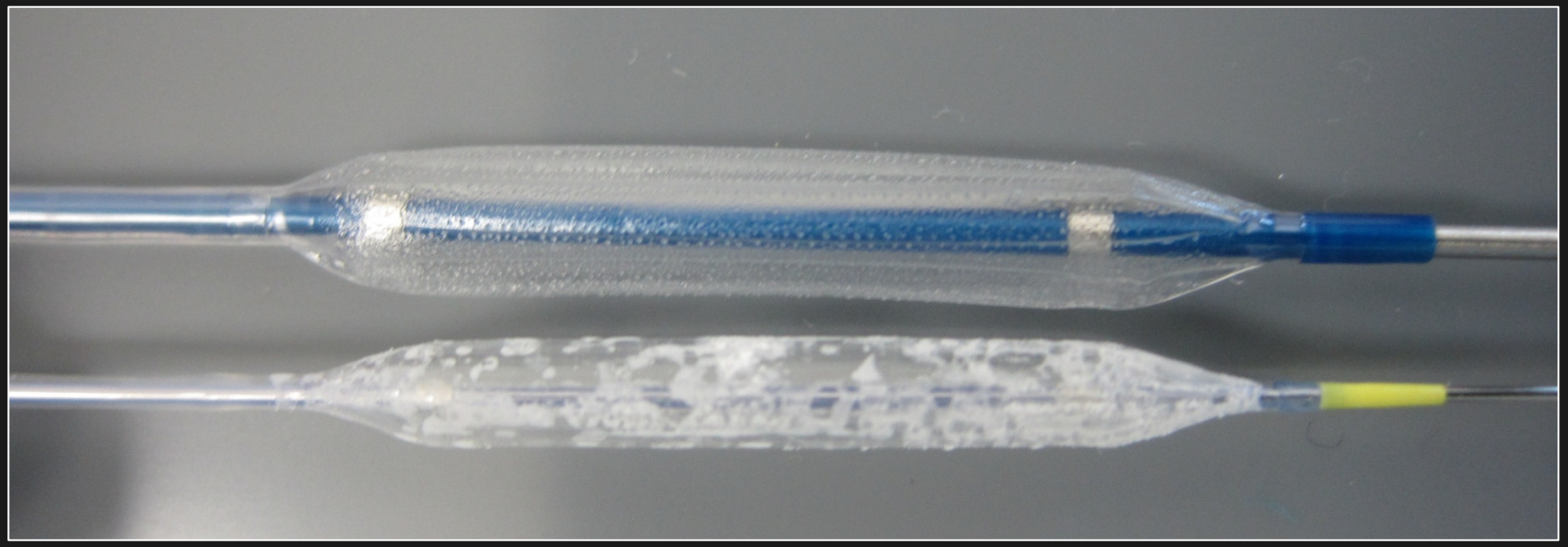


Smooth
Proteo
Distal t

DCB	Dose (µg/mm²)	Excipient
IN.PACT	3.5	Urea
LUTONIX	2.0	Polysorbate and Sorbitol
STELLAREX	2.0	Polyethylene Glycol
PASSEO 18 LUX	3.0	Butyryl-tri-hexyl Citrate
ADVANCE 18 PTX	3.0	none
ELUTAX	2.2	dextrane
FREEWAY	3.0	shelloic acid
LEGFLOW	3.0	shelloic acid
RANGER	2.0	citrate ester
LUMINOR	3.0	unkown
SeQuent Please	3.0	Iopromide
Biopath	3.0	Shellac

Huizing et al. J Clin Oncol 1993;11:2127

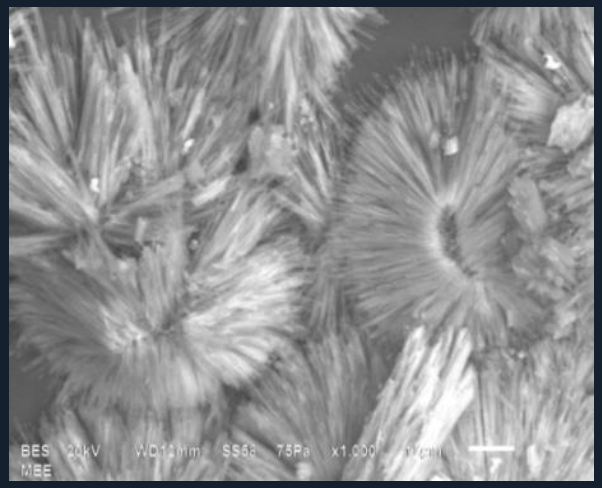
Excipient Determines Coating Characteristics



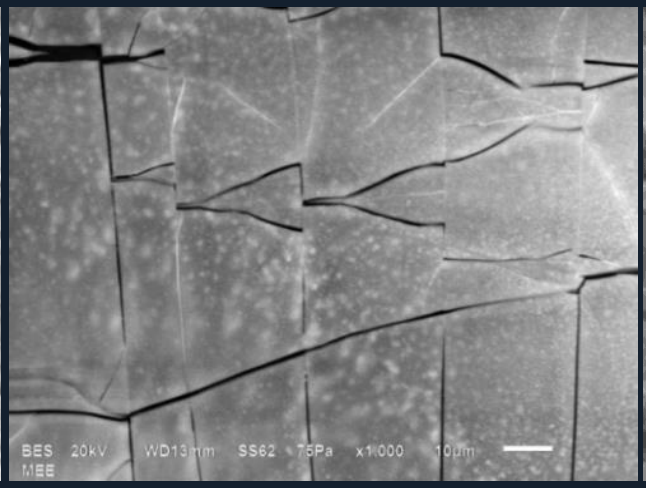
- DCBs differ in the uniformity of their drug coating
- Differences in formulations can result in an uneven coating and a less uniform dose delivery

Courtesy of J Granada

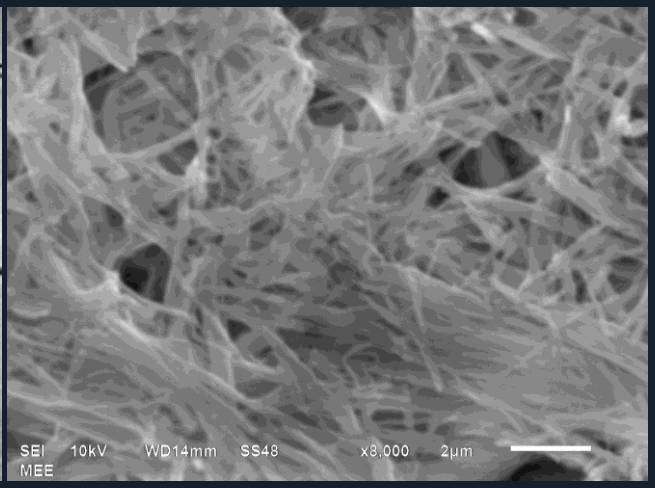
Paclitaxel Coated Balloon Evolution



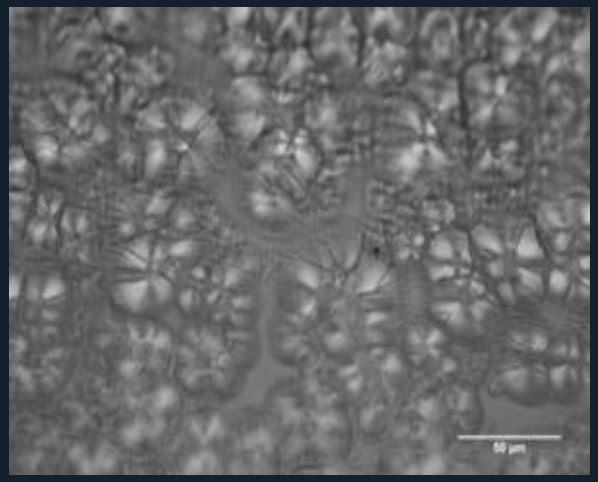
Macro-Crystalline



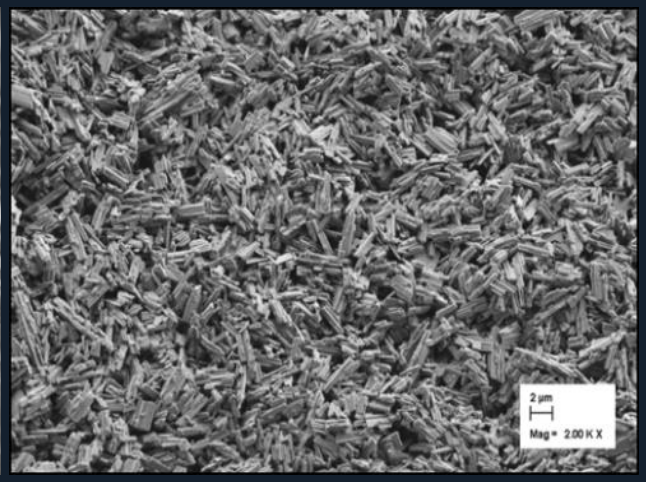
Amorphous Coating



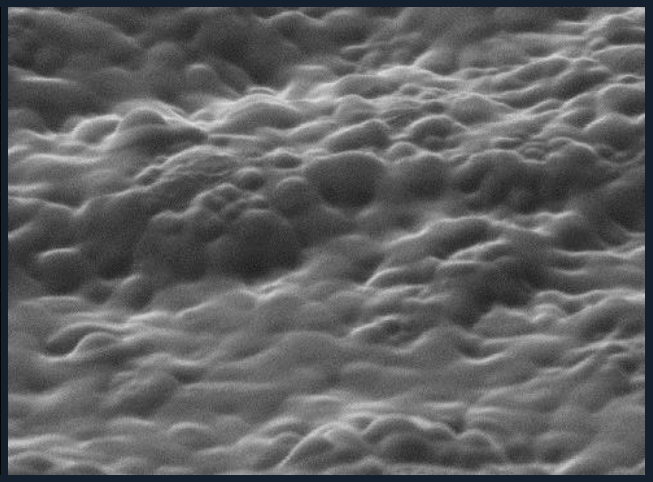
Hybrid Coating



Crystalline Aggregate



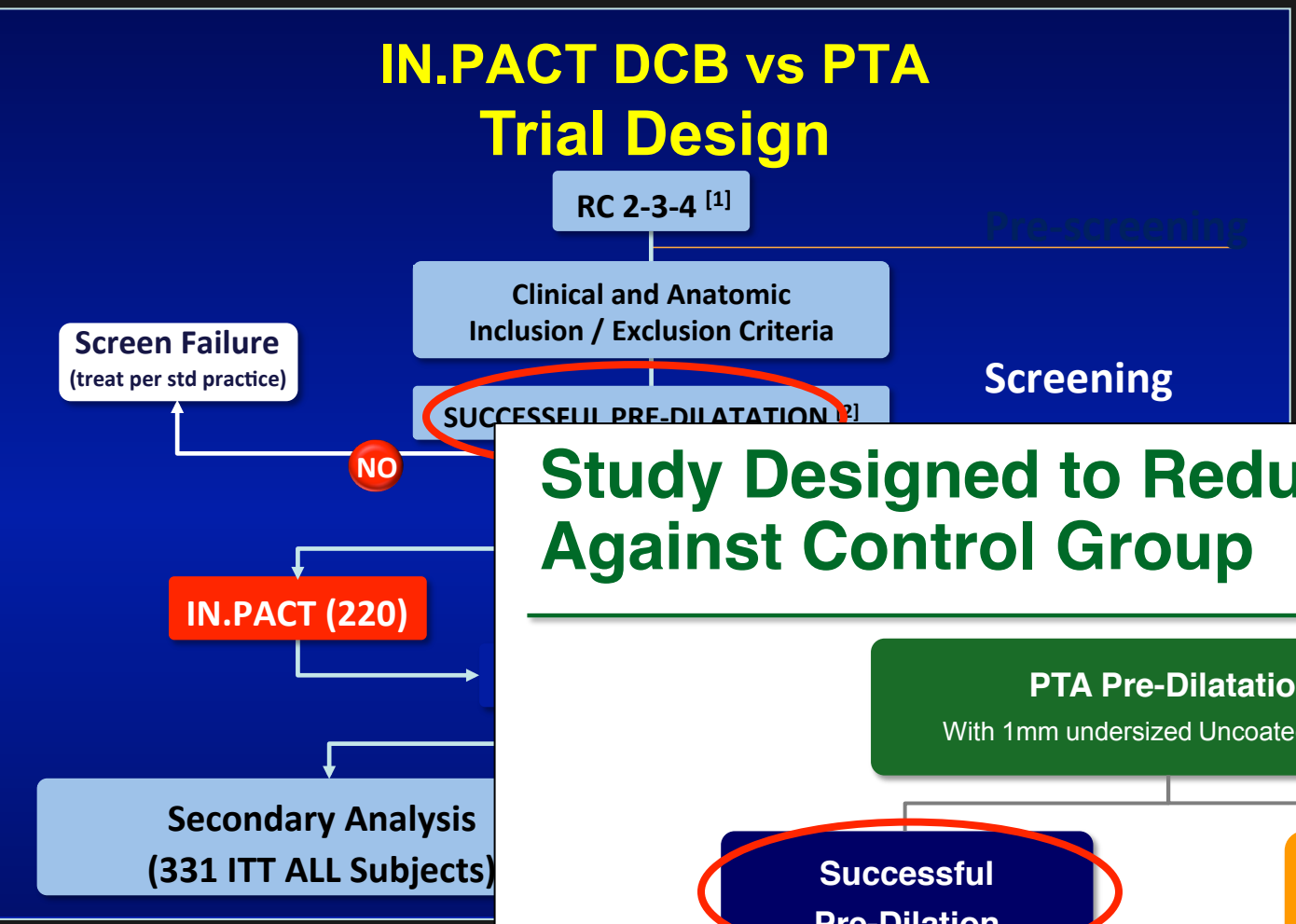
Micro-Crystalline



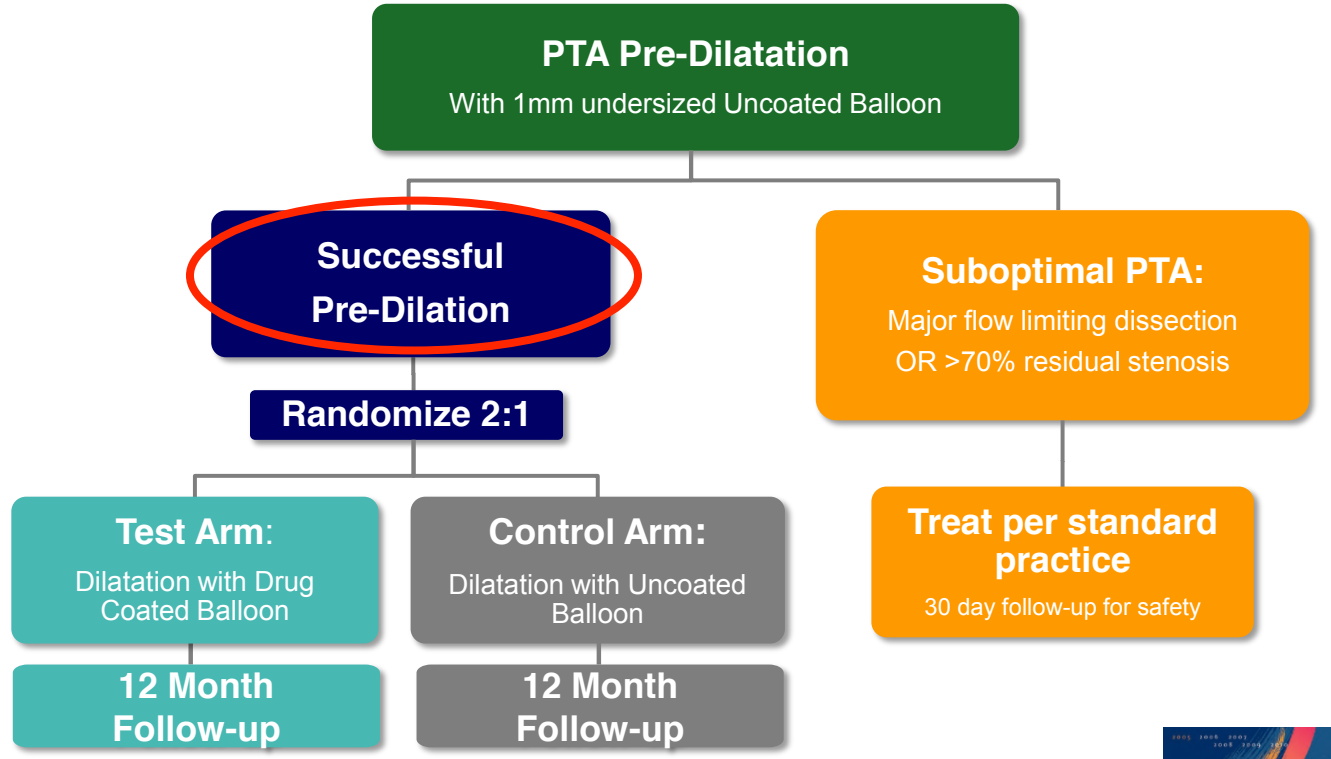
Nano-Encapsulation

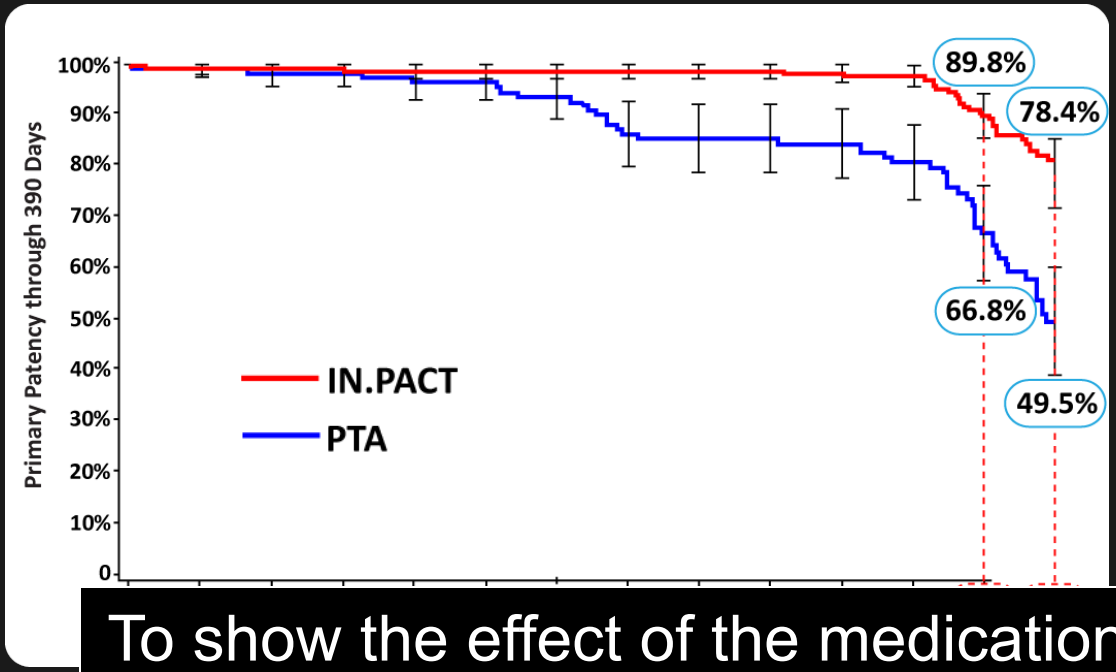
More crystallinity=better transfer to wall=more particulate

IN.PACT DCB vs PTA Trial Design



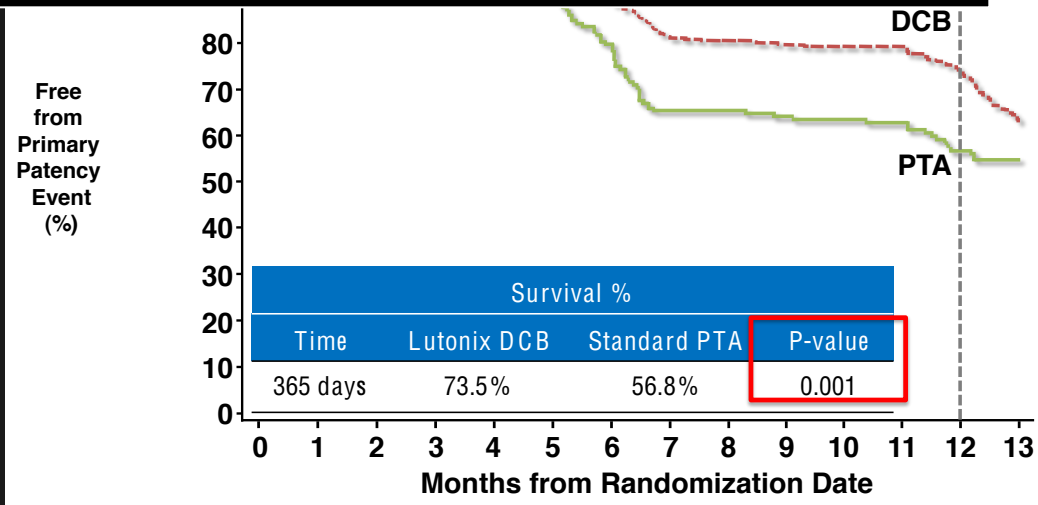
Study Designed to Reduce Bias Against Control Group





To show the effect of the medication, the lesion complexity and the injury of angioplasty had to be minimized.

12-month Primary Patency



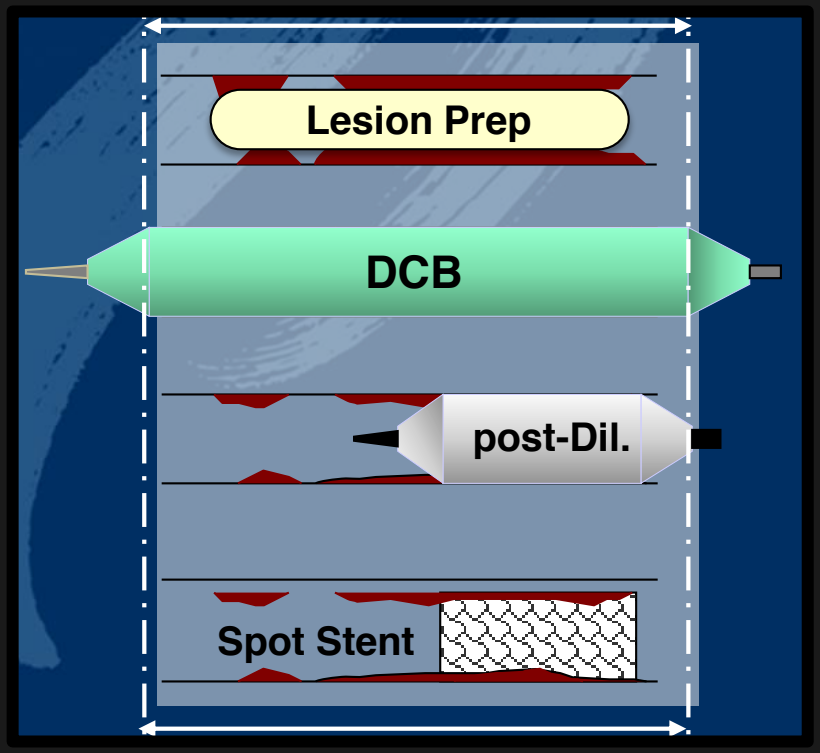
Proportions-based difference was 65.2% for DCB vs. 52.6% for standard PTA → 12.6% difference

IN.PACT SFA
No Late Catch Up

IN.PACT DCB vs. PTA	1 year difference	2 year difference
Primary Patency [1]	31.7%	28.8%
CD-TLR [2]	18.2%	19.2%

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment), analysed by Kaplan-Meier.
2. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI

Technique of DCB Angioplasty



Pre-dilate:1mm smaller diameter)

DCB inflation: balloon to artery ratio of at least 1:1, maintain inflation 3 minutes

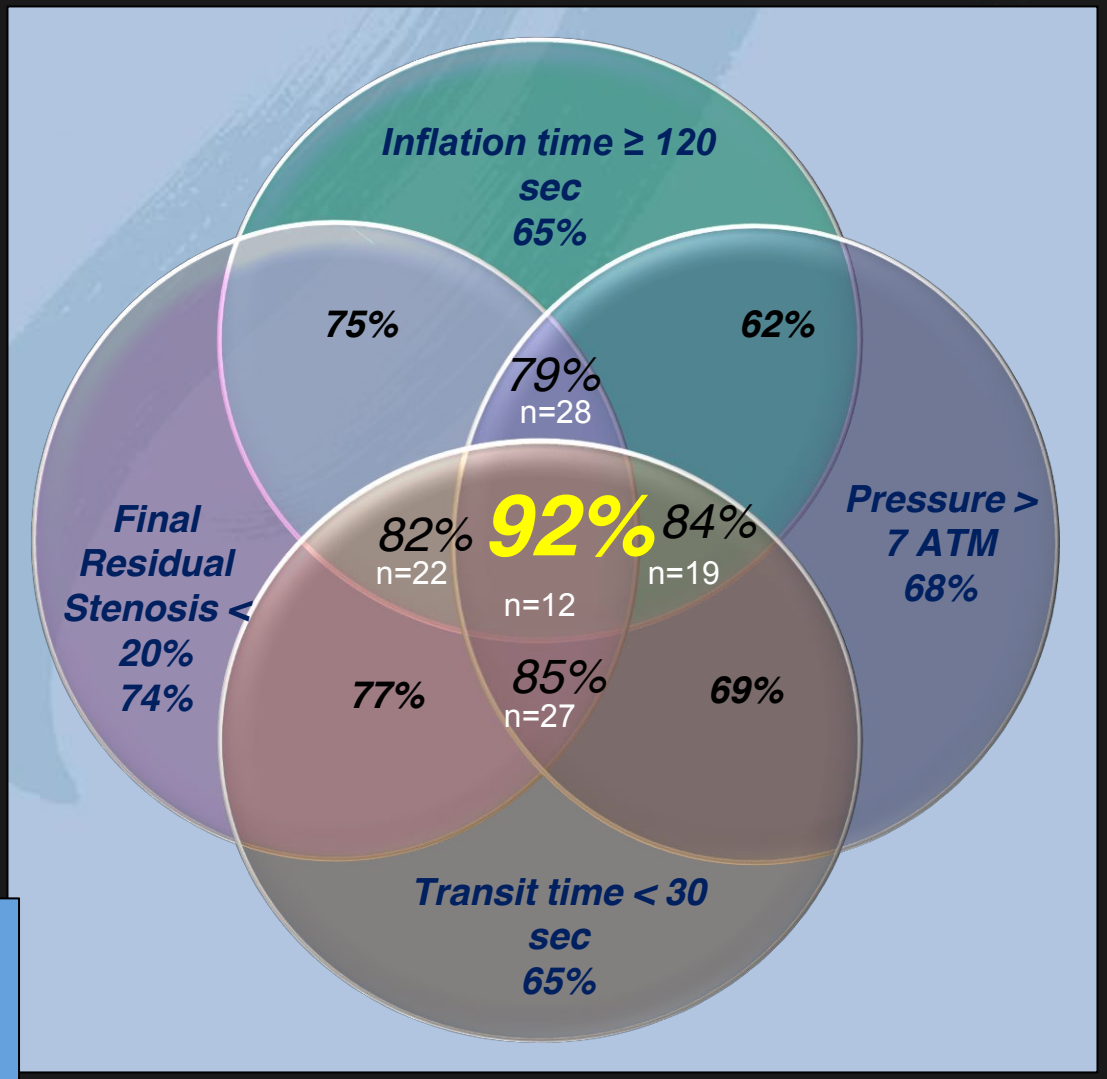
Post-dilate: Focal, as needed for residual stenosis or dissection

Bailout: Spot stent in the case of significant dissection

Where Does the Drug Go?

	Range
Wash off during transit	5-30%
Lost in runoff during balloon inflation	40-70%
Transferred to artery wall	5-20%
Drug on used balloon	0-30%

Key Variables in with Lutonix SFA DCB

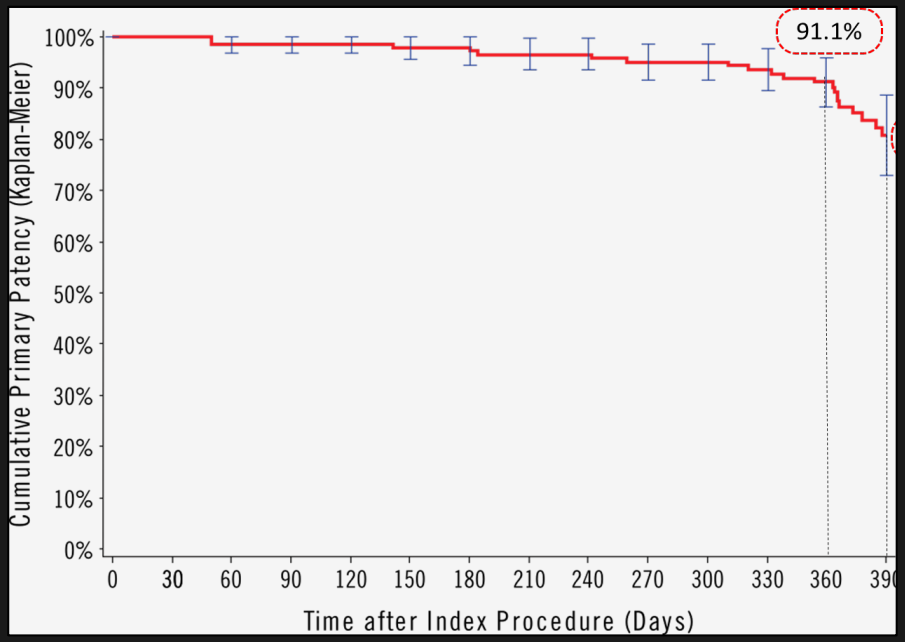


Balloon transit time <30 seconds
Inflation pressure >7atm
Inflation time >2 min
Final diameter stenosis <20%

Scheinert Levant II Subgroup Analysis LINC Jan 2016

IN.PACT Global (>1500 patients)

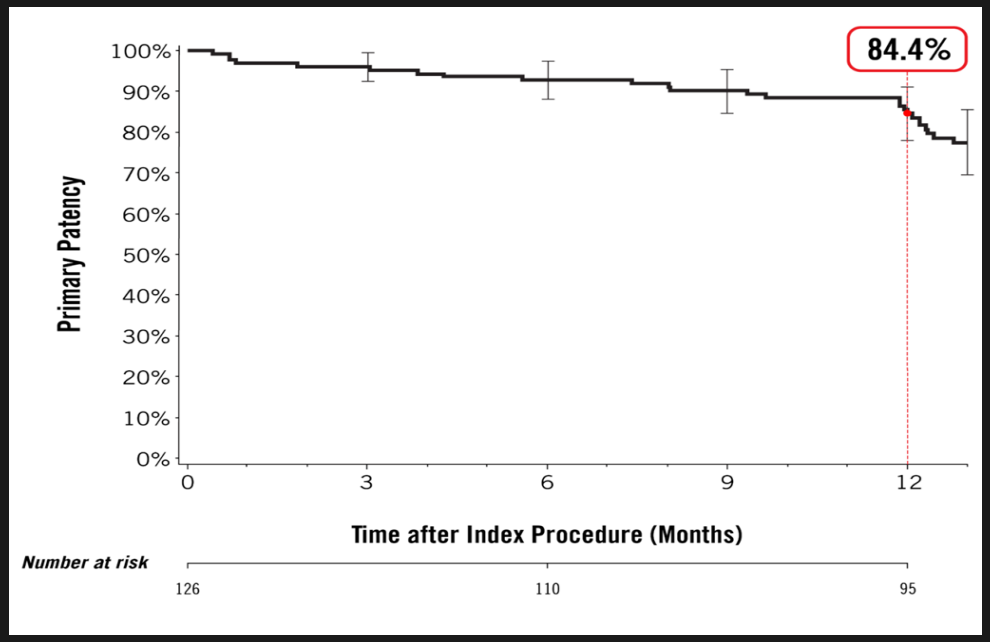
Long Lesions



N=157
Mean length 26.4cm

Provisional Stent	40.4% (63/156)
LL 15-25 cm:	33.3% (33/99)
LL > 25 cm:	52.6% (30/57)

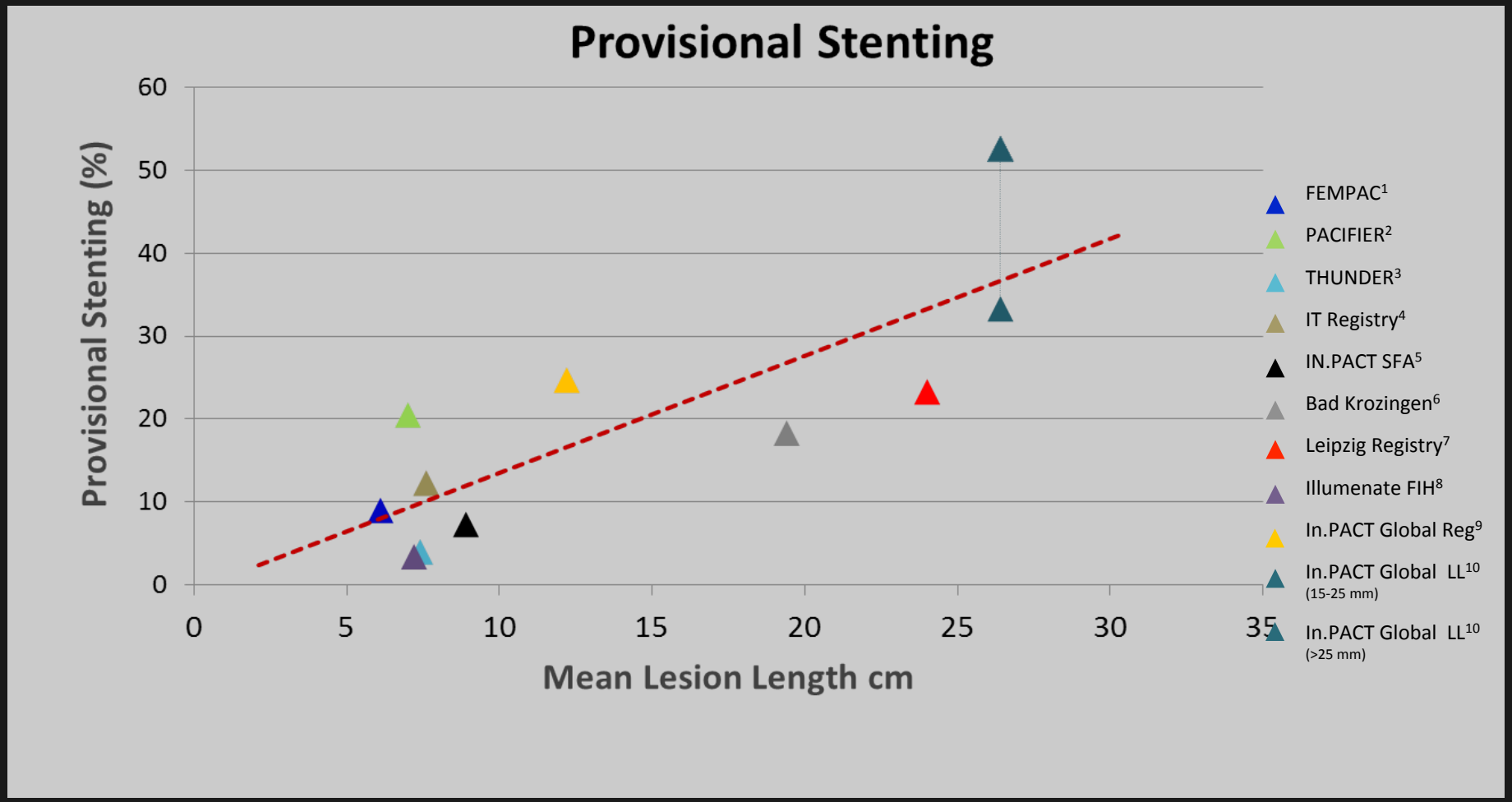
Occlusions



N=126
Mean occlusion length 22.9cm

Provisional Stent	**46.8% (59/126)**

DCB studies: Higher stent usage with increased lesion complexity

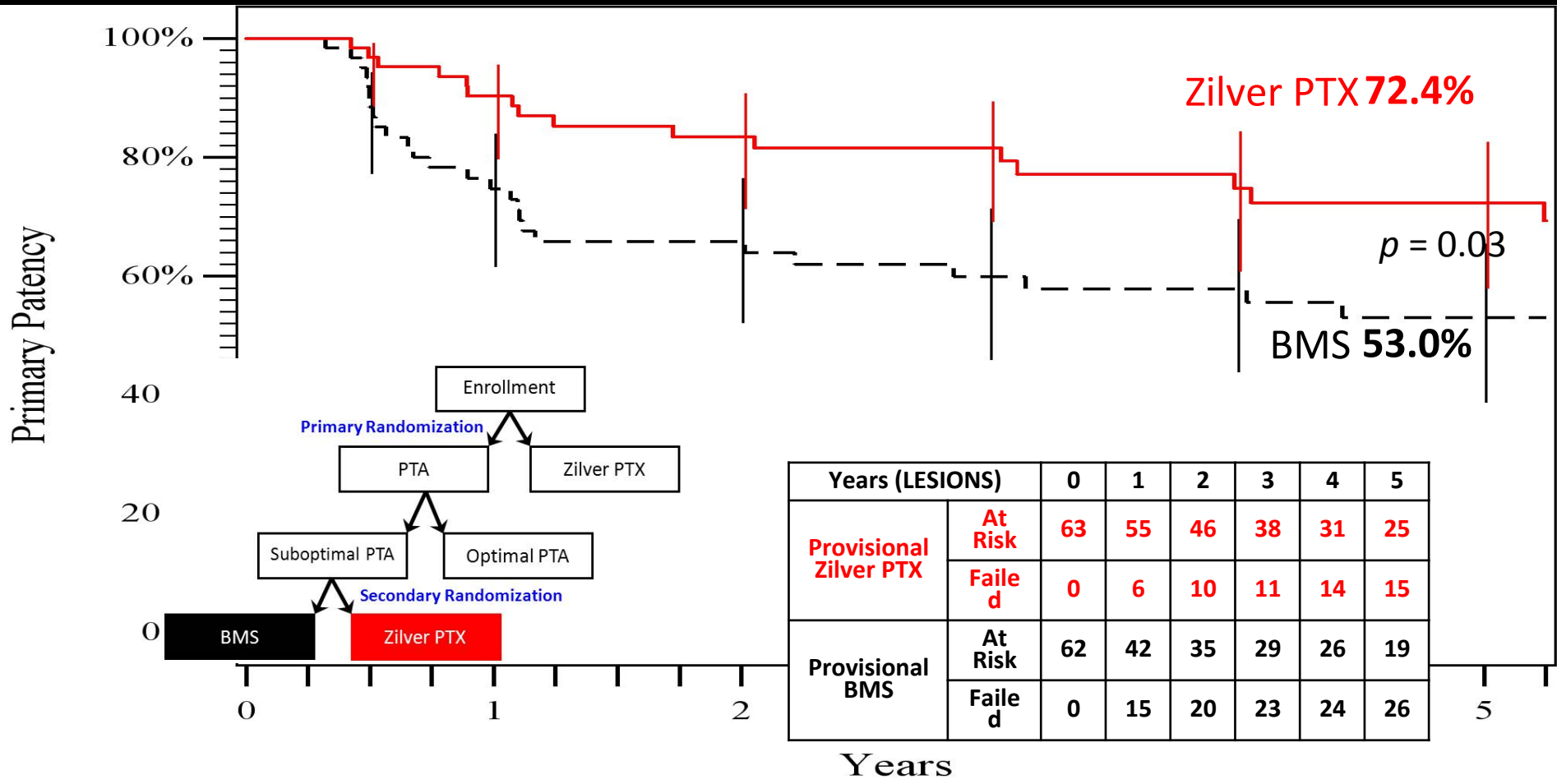


Provisional Stenting in Randomized Controlled Trials may not be representative of actual stenting in studies due to study design

Results from different trials are not directly comparable. Information provided for educational purposes.

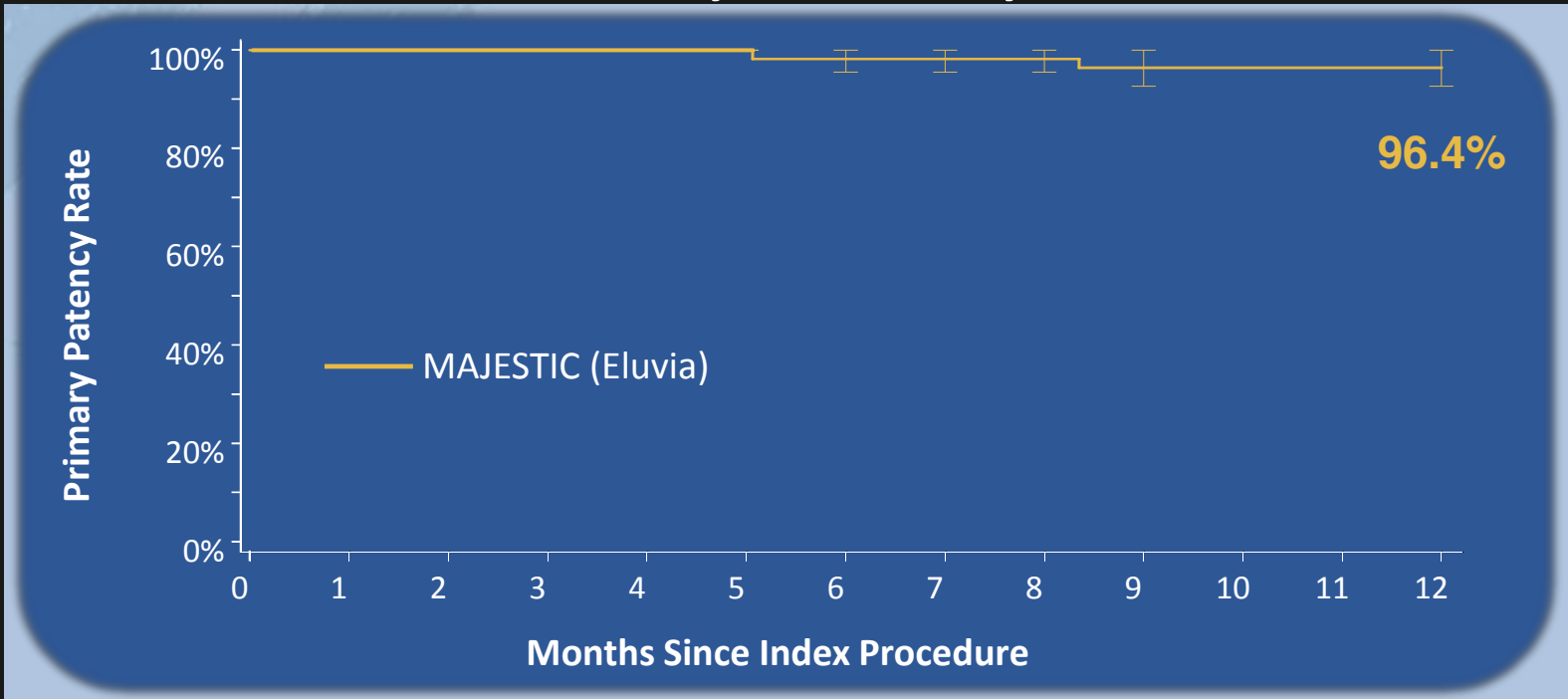
[1]Werk M et al. Circulation 2008; [2]Werk et al. Circ Cardiovasc Interv 2012; [3]Tepe G et al. N Engl J Med 2008; [4]icari A Et al. J Am Coll Cardiol Intv 2012; [5]Tepe et al. Circulation 2015; [6]Zeller T et al. J Endovasc Therapy 2014; [7]Schmidt A. LINC 2013; [8]Schroeder H et al. Catheter Cardiovasc Interv 2015; [9]Laird J. Endovacsular Today Feb 2015. [10]Ansel G. TCT 2015.

Zilver: DES vs BMS
5-year Primary Patency



Years (LESIONS)		0	1	2	3	4	5
Provisional Zilver PTX	At Risk	63	55	46	38	31	25
	Failed	0	6	10	11	14	15
Provisional BMS	At Risk	62	42	35	29	26	19
	Failed	0	15	20	23	24	26

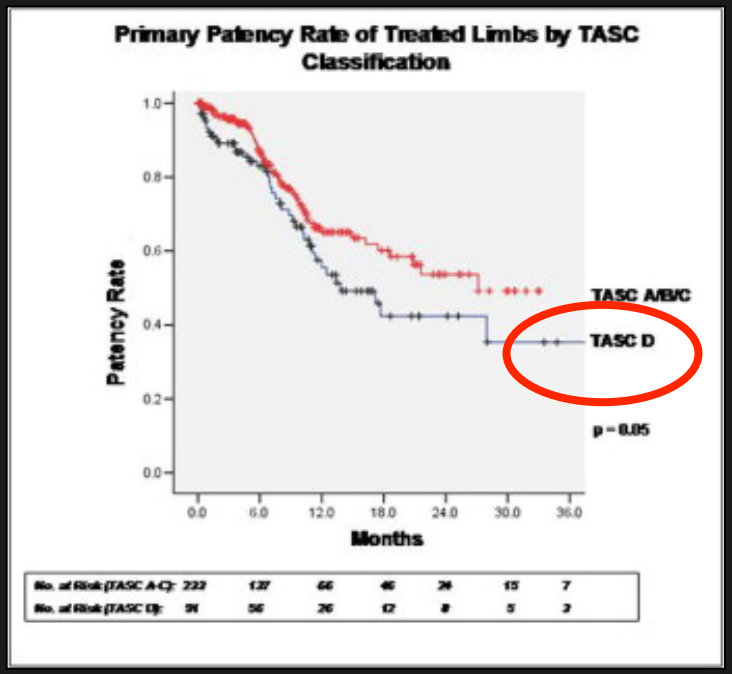
SFA DES: Primary Patency 12 months

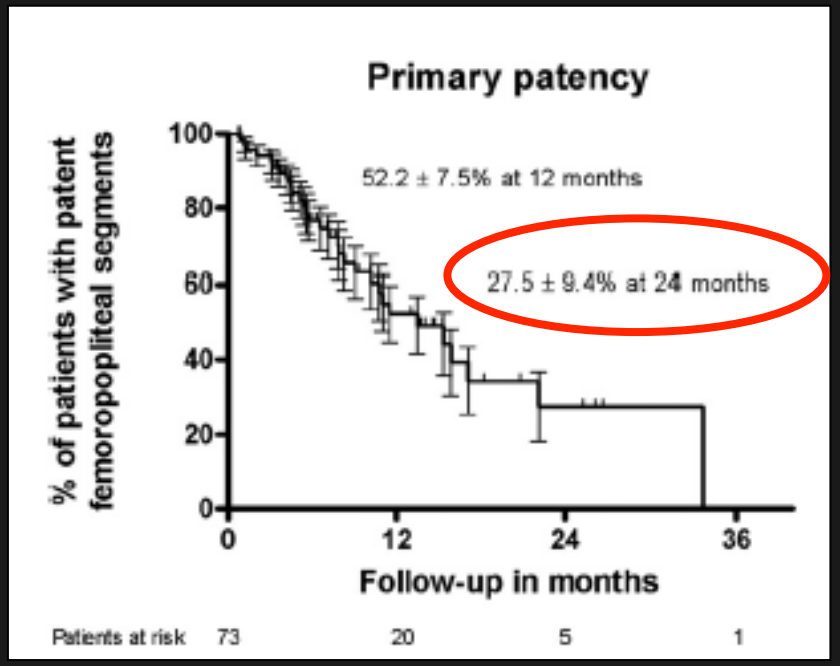


	0	1	2	3	4	6	9	12
Entered	57	57	56	56	56	56	55	53

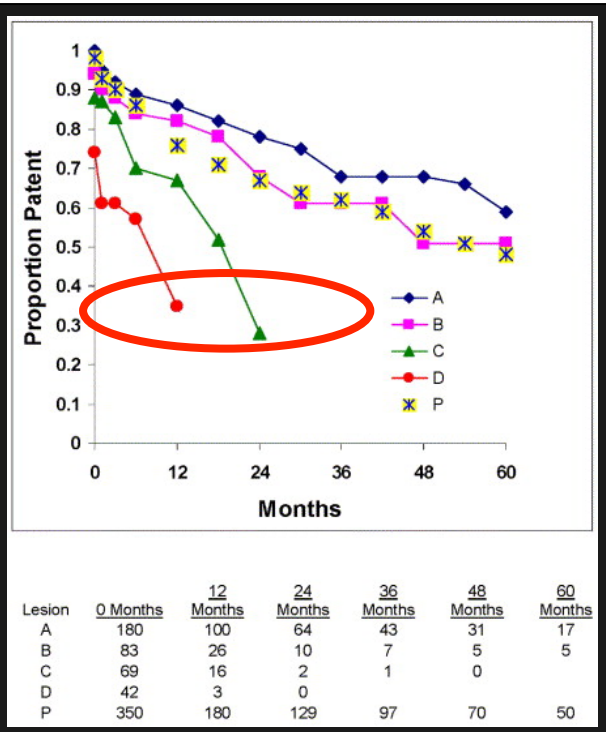
Study Overview: MAJESTIC	
Objective	Evaluate the performance of Eluvia DES System when treating Superficial Femoral (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 110mm in length
Investigational Centers	14 sites (Europe, Australia, New Zealand)
Follow-up	Baseline, Procedure 1 month, 9 months, 1 year, 2 years, 3years
Primary Endpoint	Primary patency

Muller-Hulsbeck VIVA October, 2015





139 limbs	Patency 12 mos	Patency 24 mos
TASC C stent	**83%**	**80%**
TASC D stent	**54%**	**28%**

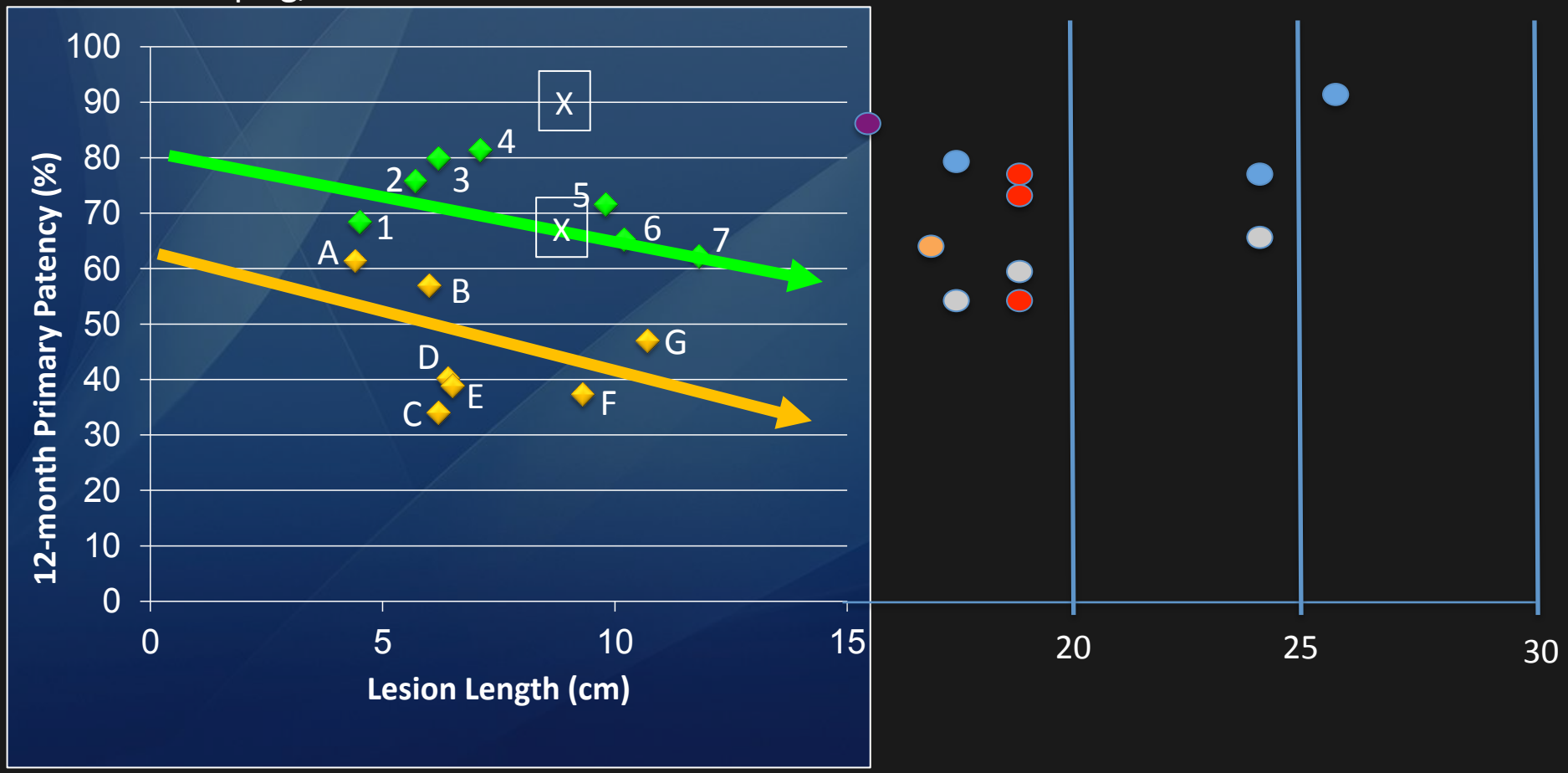


Lesion	0 Months	12 Months	24 Months	36 Months	48 Months	60 Months
A	180	100	64	43	31	17
B	83	26	10	7	5	5
C	69	16	2	1	0	
D	42	3	0			
P	350	180	129	97	70	50

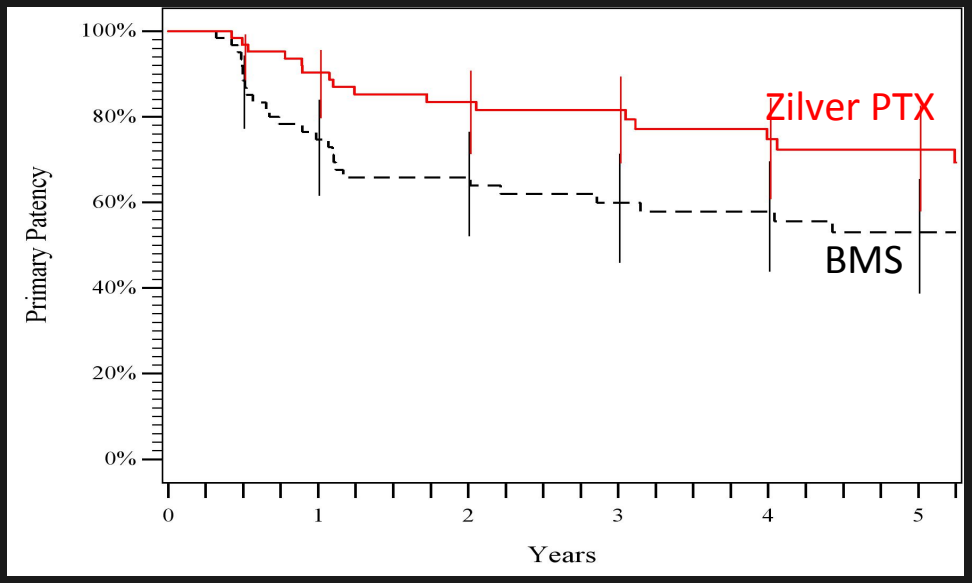
DeRubertis et al. J Vasc Surg 2007
Surowiec et al. J Vasc Surg 2005
Baril et al. J Vasc Surg 2010
Dosluoglu et al. J Vasc Surg 2008;48:1166

Next Step: Longer Lesions

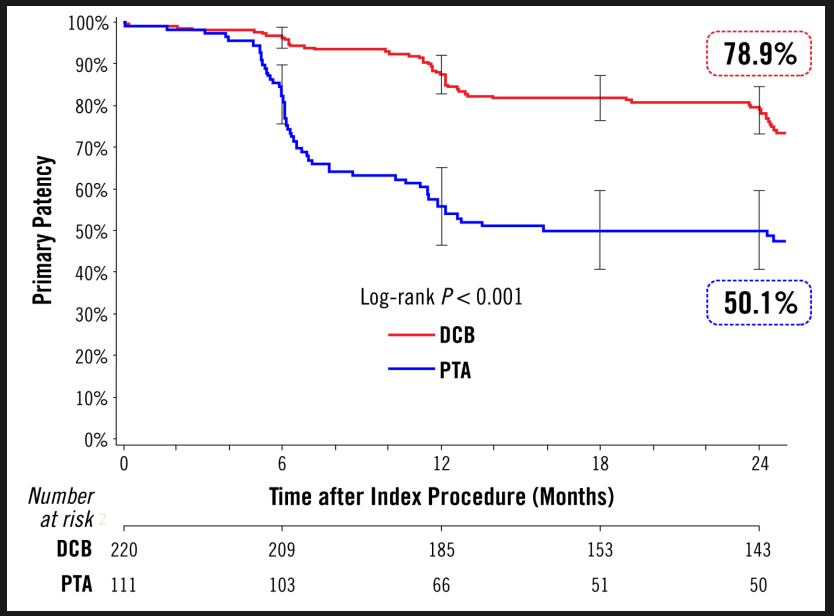
- Self-expanding Nitinol stent: Durability, Viastar, Vibrant
- Supera: Leipzig
- Viabahn: Viastar, Viper, Vibrant
- DES: Zilver Japan
- DCB: Leipzig, IN.PACT Global



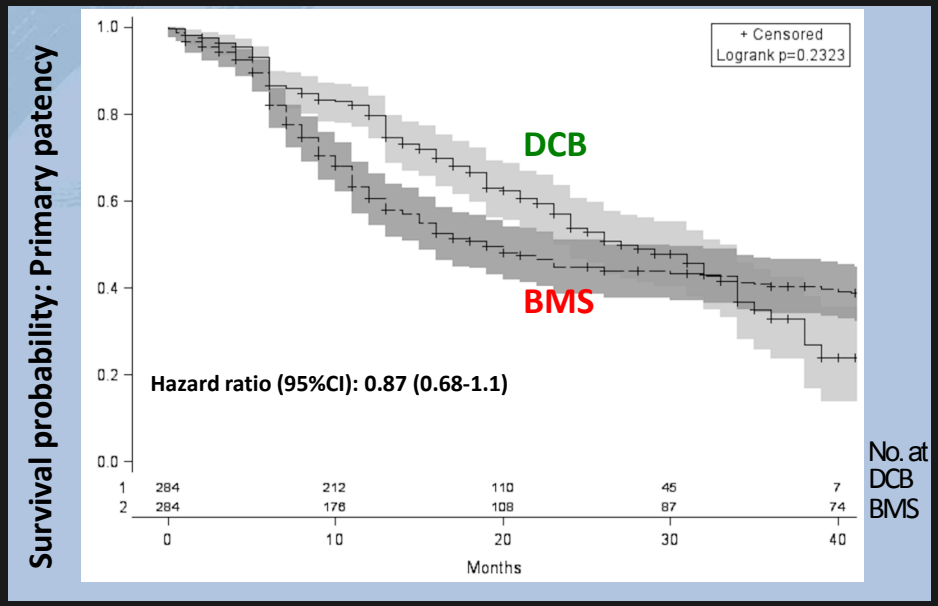
Primary Patency Results Beyond 1 Year



Zilver PTX



IN.PACT SFA



Leipzig Registry

Femoro-popliteal Occlusive Disease Conclusion

- We can cross most lesions but struggle in keeping them open, especially in the worst disease morphologies.
- We are moving away from an “implant-based” approach and toward a drug delivery approach.
- Significant randomized data is accumulating.
- Challenges remain.