Long SFA CTO: Maintaining Patency

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Disclosures

Contego Medical: Shareholder

Medtronic: SMAB

Abbott Vascular: SMAB

Boston Scientific: Consultant

Patients are getting older and continue to have risk factors


I BEAT
ANOREXIA

Unmet Needs in Fem-Pop Disease

- [x] Crossing CTOs
- [x] Calcific Disease
- [ ] Maintaining Patency

Definition of Patency?

BINARY

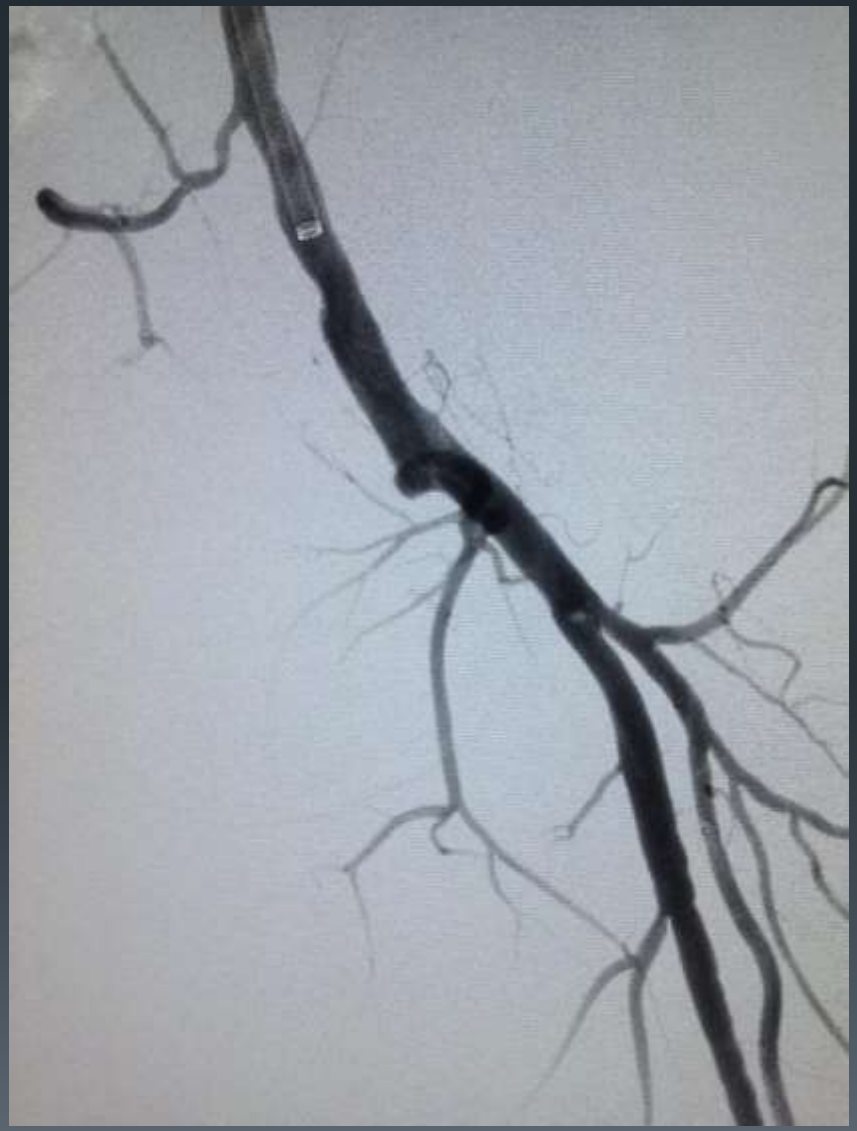
- PSVR (>2.4)
- Angiographic (>50%)
- Allows Comparison Between Trials
- More Objective
- Less patient bias

TLR

- Clinical outcome, more important for patient
- More Subjective
- Risk of bias
  - Follow up
  - Lifestyle
  - Desire for additional procedure

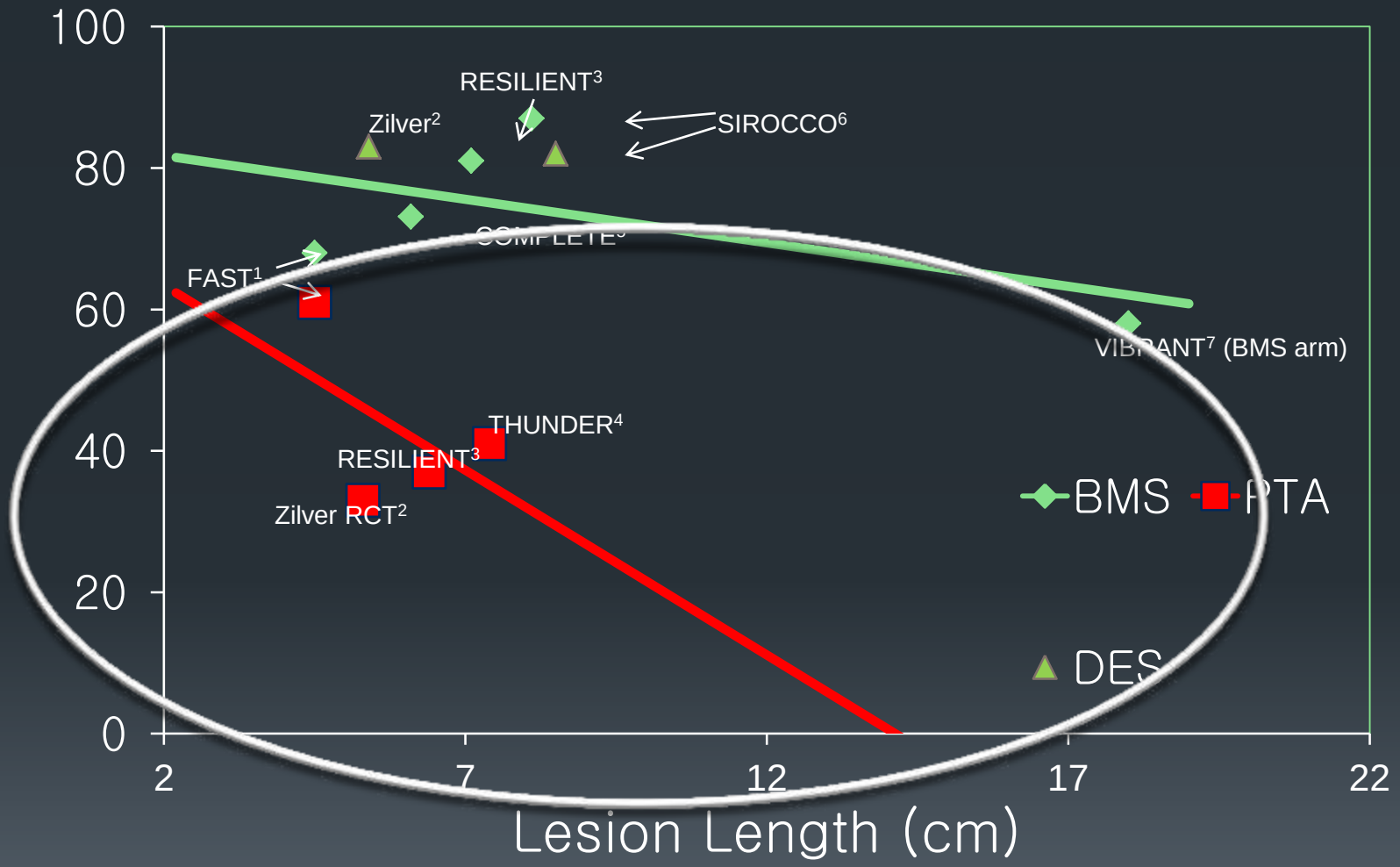
Left SFA CTO -
How should this lesion be treated in 2015?

- PTA alone
- Bare Metal Stents
- Specialty Stents
- Atherectomy
- Drug Eluting Stents
- Drug Eluting Balloons
- Atherectomy + DEB



SFA 12-Month Primary Patency

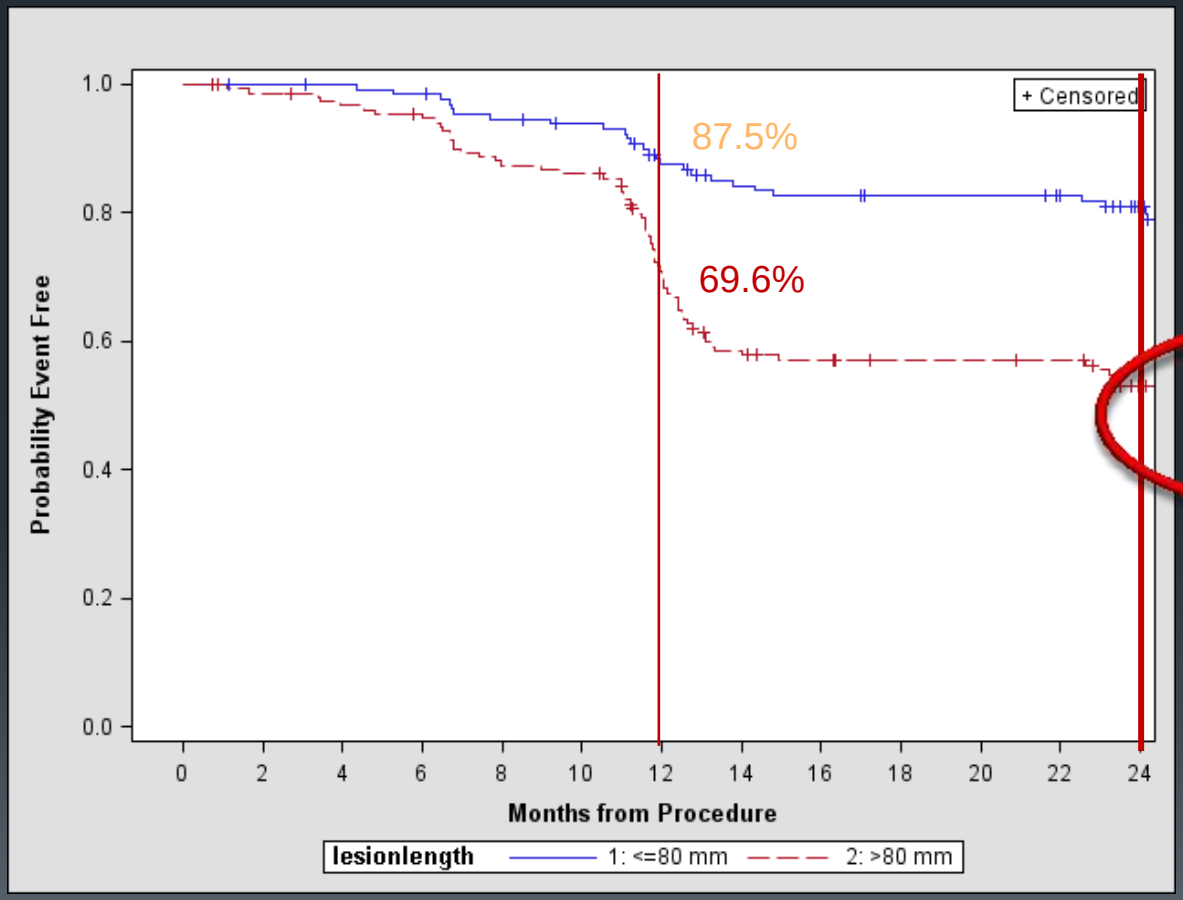
PTA, BMS, DES Sub-Analyses by Lesion Length



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, VIVA 2010

Bare Nitinol Stents

Durability II:
Freedom from Loss of Primary Patency (PSVR < 2.0) at 2 Years



80.8%
Lesions ≤ 80 mm (133)

53.1%
Lesions > 80 mm (154)

Bare Nitinol Stents

Durability II:
Freedom from Loss of Primary Patency (PSVR < 2.0) at 2 Years

Freedom from TLR	1-Year (N= 287)	2-Year (N= 287)	3-Year (N=287)
All Subjects	77.9%	65.9%	60%
≤ 80 mm (n=133)	87.5%	80.8%	71%
> 80 mm (n=154)	69.6%	53.1%	50.5%

CTO: 48.1%
Mean Lesion Length: 8.9 cm
Severely Calcified: 43.2%

Abbott Supera

Primary Patency at 1 Year (PSVR < 2.0)

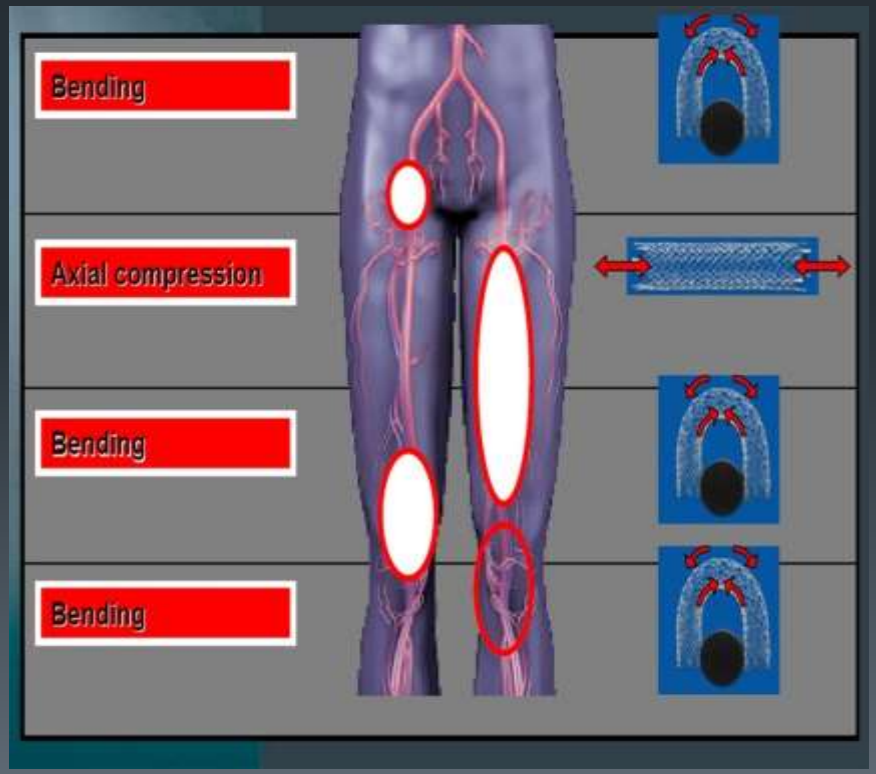
- Superb Study
  - Primary Patency at 1 yr – 86%
  - Mean Lesion Length 7.7 cm

- Supera 500 Registry
  - Primary Patency at 2 years 73%
  - Mean Stent Length 12.2 cm

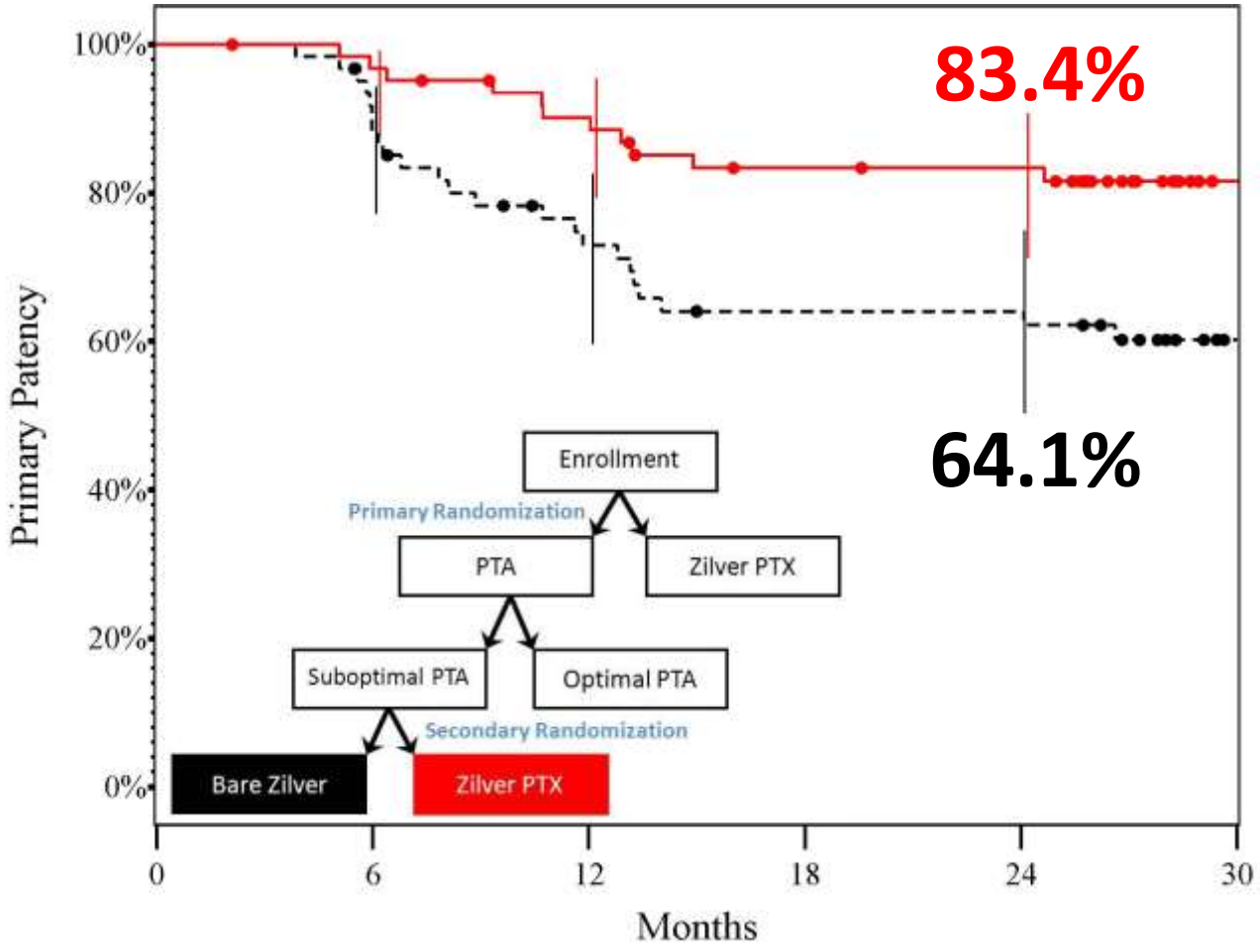
- **Requires Excellent Vessel Prep**
- **Difficulty with severe Ca++**

SFA Restenosis

- Stenting in SFA causes acute and chronic injury
- Ongoing injury due to mechanical stress causes local inflammation
- Inflammatory factors stimulate smooth muscle cells proliferation resulting in restenosis



Cook 24-Month Patency (PSVR < 2.0): Provisional Zilver PTX vs. BMS



Provisional Zilver PTX

Provisional Bare Zilver

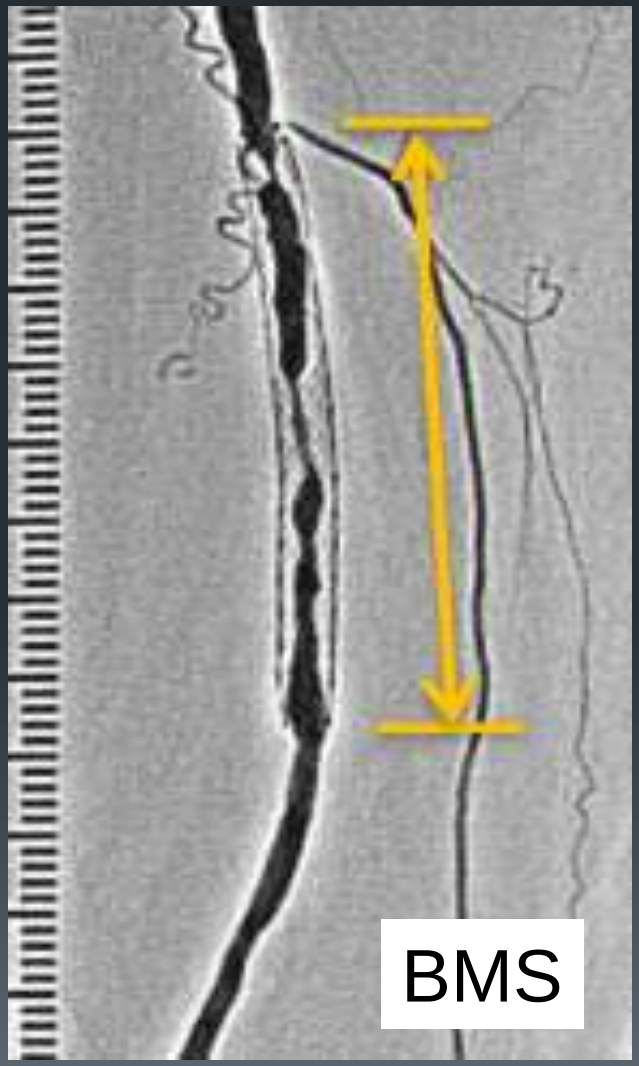
$p < 0.01$

60 Month Patency:
Zilver PTX vs. BMS

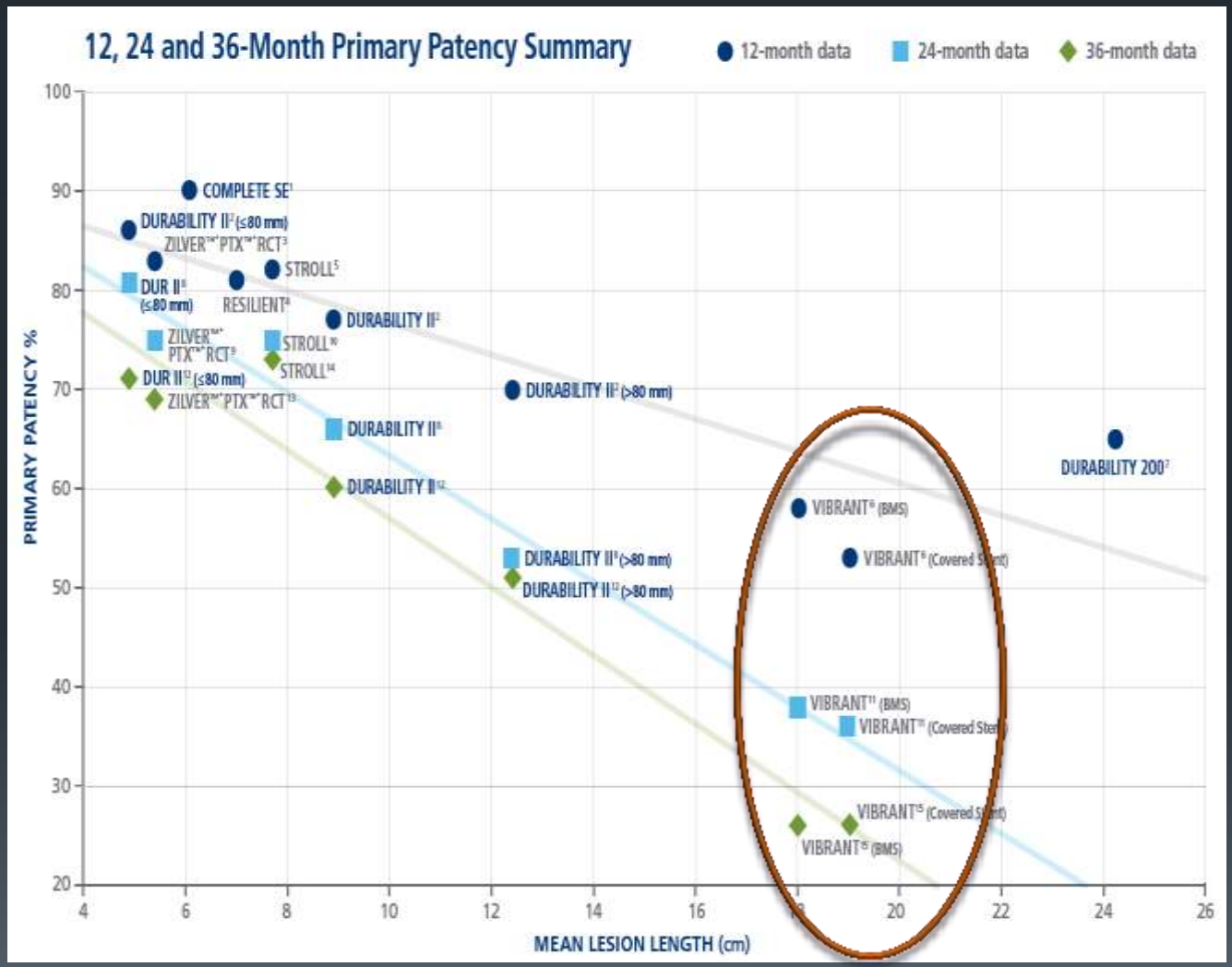
Mean Lesion Length 5.5 cm

Stent	48 Month Patency (PSVR < 2.0)	60 Month Patency (PSVR< 2.0)
Zilver PTX	75%	66.4%
BMS	57.9%	43.4%

Zilver PTX vs BMS: Differing Patterns of Restenosis



Nitinol Stents: Increased lesion length is an independent predictor of decreased patency.



[1]Freed MS, Manual of Interventional Cardiology, [2]Fanelli DEBELLUM, [3]Laird, CCI, June 2010, [4]SMART Control IFU, [5]Matusumura, DURABILITY IIJVS, July 2013, [6]Davaine, European Journal of Vascular and Endovascular Surgery 44 (2012)

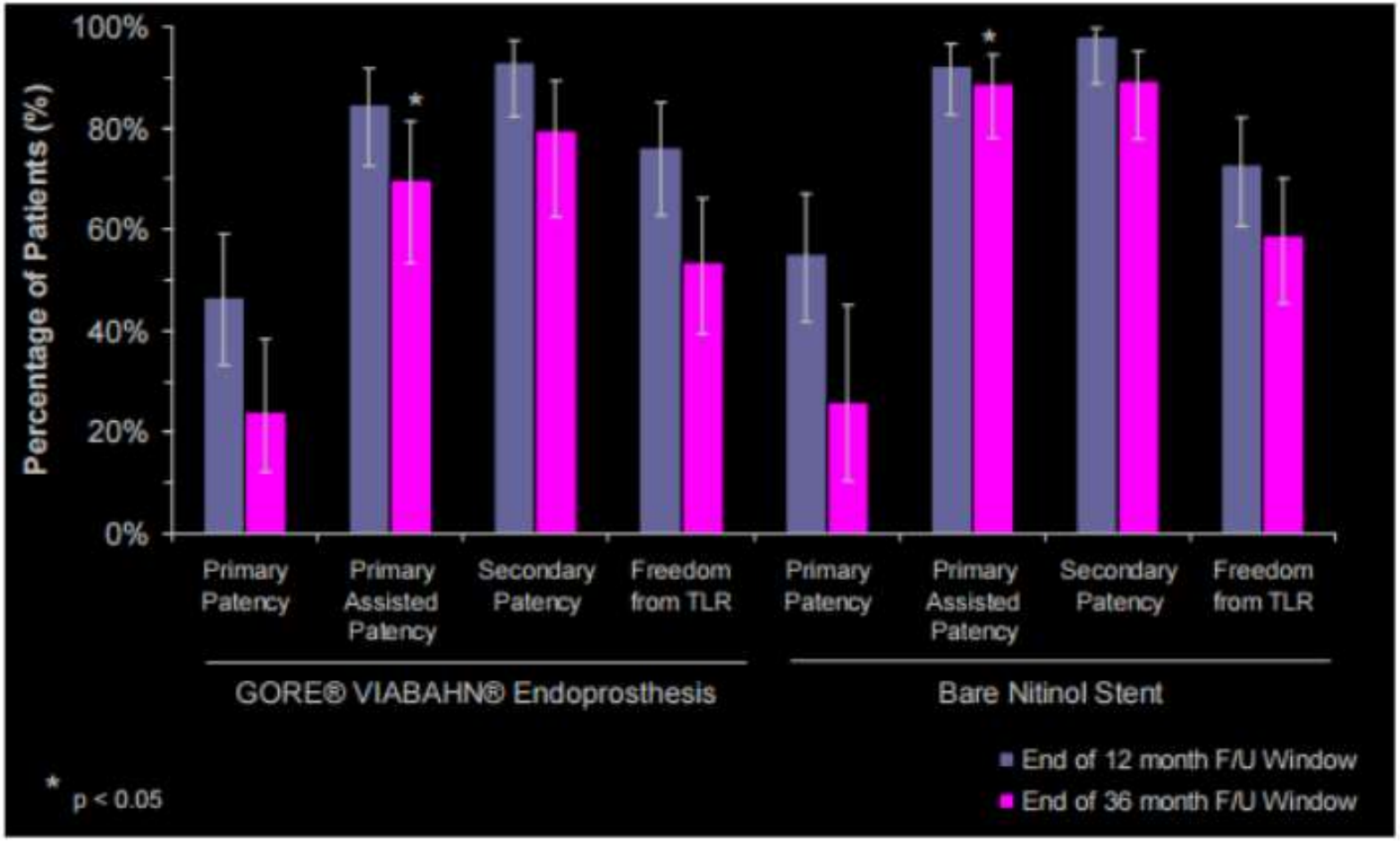
Covered stents: VIBRANT TRIAL

- 148 randomized patients enrolled
- Test Group: GORE® VIABAHN®
  - Endoprosthesis FDA approved for SFA indication
  - Did NOT include Bioactive Heparin Surface
  - Did NOT include Contoured Edge Manufacturing Change n=72
- Control Group: Bare Nitinol Stent
  - Commercially available bare nitinol stent as determined by institutional standard of care when treating SFA occlusive disease and were not devices approved for SFA use
  - n=76

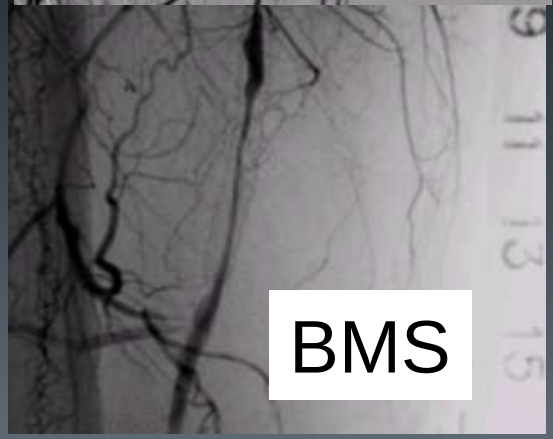
Lesion Characteristics

LESION CHARACTERISTICS			
	VIABAHN Endoprosthesis	**Bare Nitinol Stent**	**p-value**
TREATED OCCLUSIONS	**61.1%**	**56.6%**	**0.62**
TARGET LESION LENGTH (cm)			**0.87**
Mean (Std Dev)	19 (8)	18 (7)	
Median (Range)	20 (8 – 40)	16 (8 – 36)	
LESION CALCIFICATION			**0.01**
None – Mild	37.5%	57.9%	
Moderate – Severe	62.5%	42.1%	
TIBIAL RUNOFF			**0.10**
1 Vessel	15.3%	22.4%	
2 Vessel	50.0%	32.9%	
3 Vessel	34.7%	44.7%	

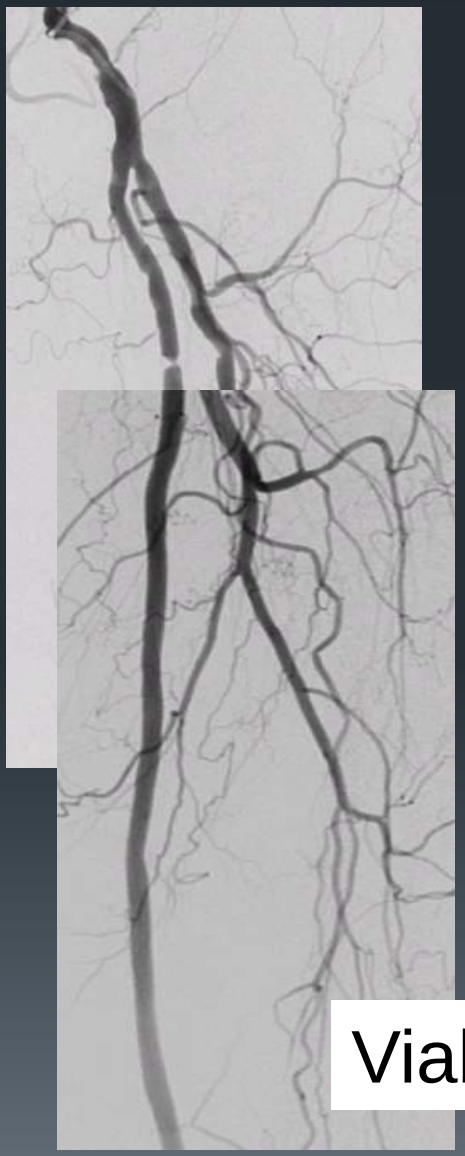
VIBRANT 3 year Data



Different Patterns of Restenosis



BMS



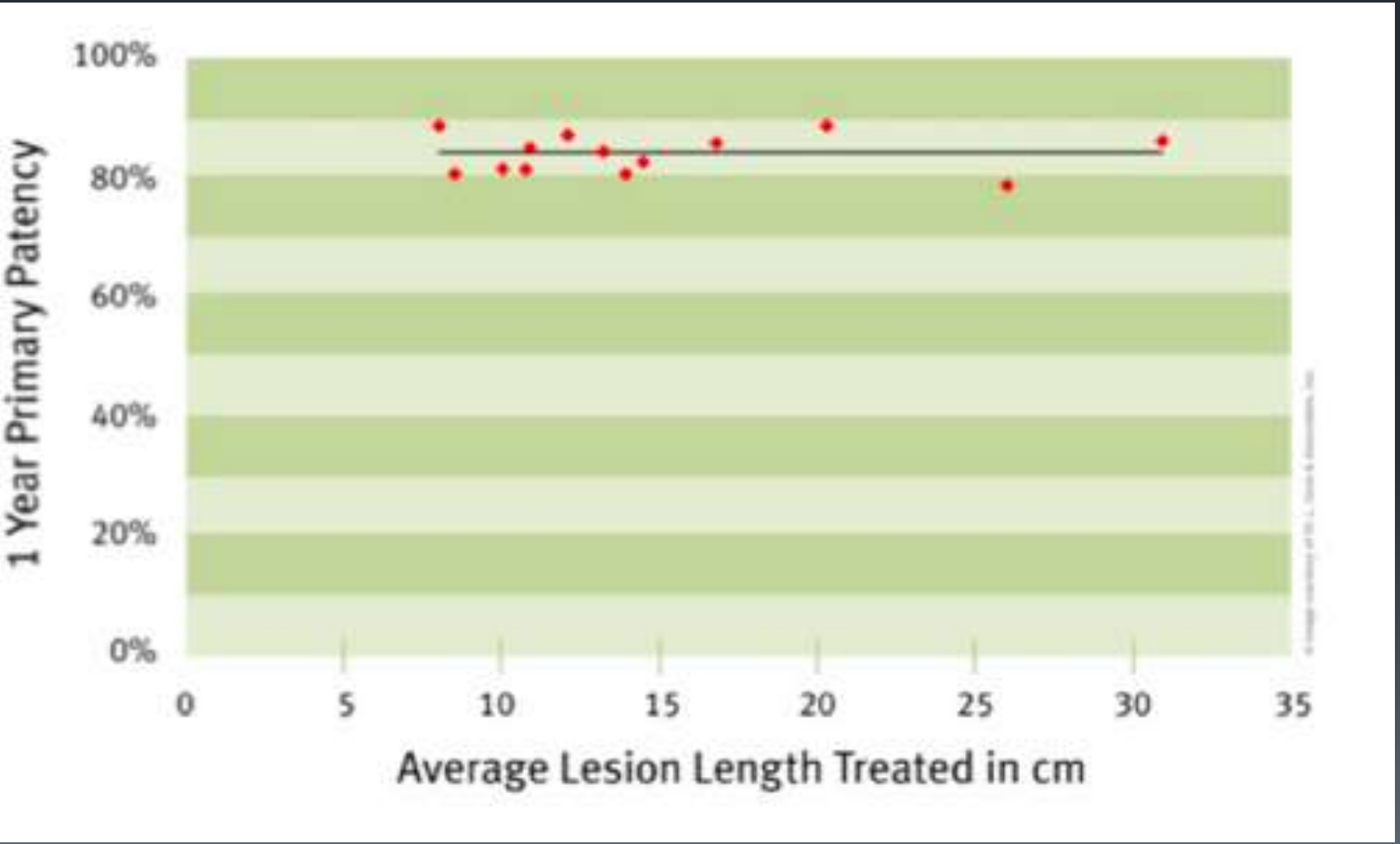
Viabahn

Viastar:

Viabahn Covered Stent with Heparin coating and improvements in edge design

Analysis Type	Covered Stent	BMS	P-value
12 month Patency - ITT	70.9%	55.1%	0.11
12 month Patency - Per Protocol	78.1%	53.5%	0.009
Mean Lesion Length	19.0 +/- 6.3 cm	17.3 +/- 6.6 cm	0.13
Lesions > 20 cm	71.3%	36.8%	0.01
CTO	79%	70%	

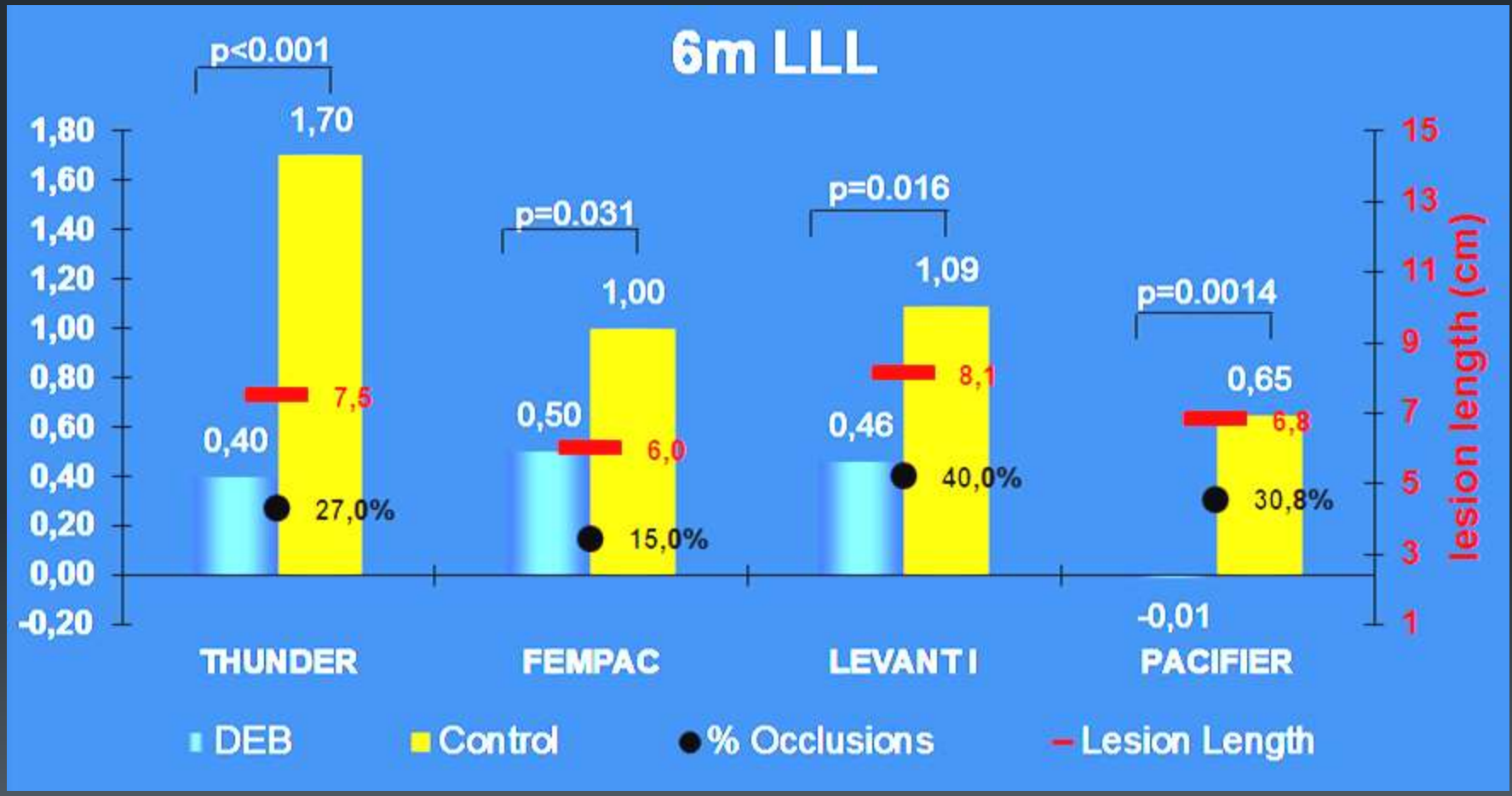
Viabahn restenosis at 12 months: Meta-analysis of 13 trials



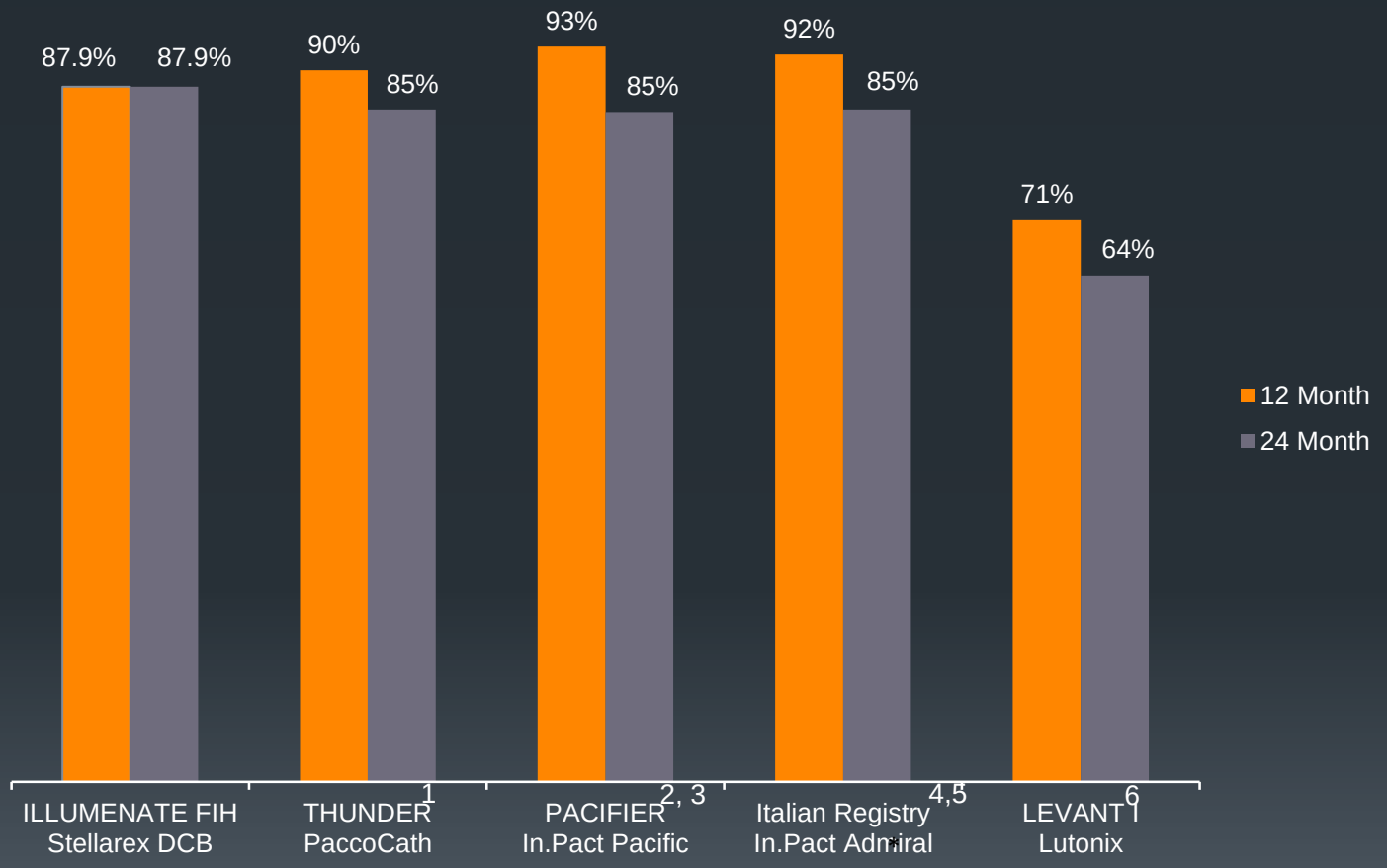
Covered Stents - Questions

- Are heparin-bonded covered stents a reasonable treatment strategy for patients with long SFA disease/CTOs?
- Is patency following implantation of a covered stent graft independent of lesion length?
- Is covering a stent with an ePTFE barrier as effective as anti-restenotic drug?

Drug Eluting Balloons: Early DEB Trials



Freedom from Clinically-driven TLR
Durable Result to 24 Months in ILLUMENATE FIH



1. Tepe, G., et al., N Engl J Med, 2008;358: p. 689-699.
2. Werk M., et al., Circ Cardiovasc Interv. 2012;5(6): p. 831-840.
3. Werk M., Presentation. LINC 2014. Leipzig, Germany; January 28-31, 2014
4. Micari, A., et al., J Am Coll Cardiol Inv, 2013;6: p. 282-289.
5. Micari, A., et al., J Am Coll Cardiol Inv, 2012;5: p. 331-338.
6. Scheinert, D., et al., J Am Coll Cardiol Inv, 2014;7: p. 11-19.

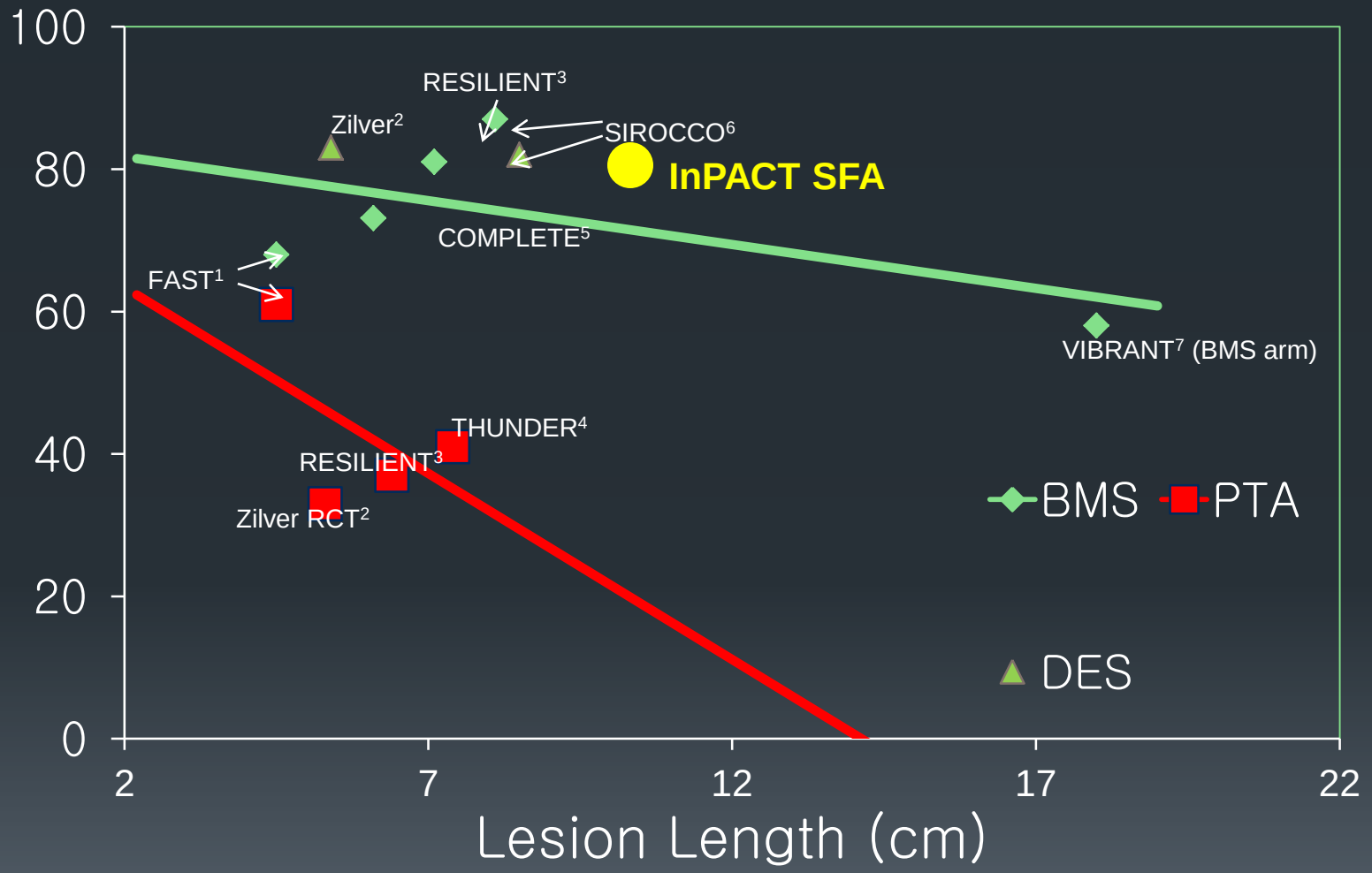
Drug Eluting Ballons
InPACT SFA

One-Year Outcomes: Mean lesion length 8.9 cm

	DEB (n = 220)	**Angioplasty** (n = 111)
Primary Patency	82.2%	52.4%
Clinically Driven TLR	2.4%	20.6%
Primary Sustained Clinical Improvement	85.2%	68.9%
Primary Safety Endpoint	95.7%	76.6%
MACE	6.3%	24.3%

SFA 12-Month Primary Patency

PTA, BMS, DES Sub-Analyses by Lesion Length



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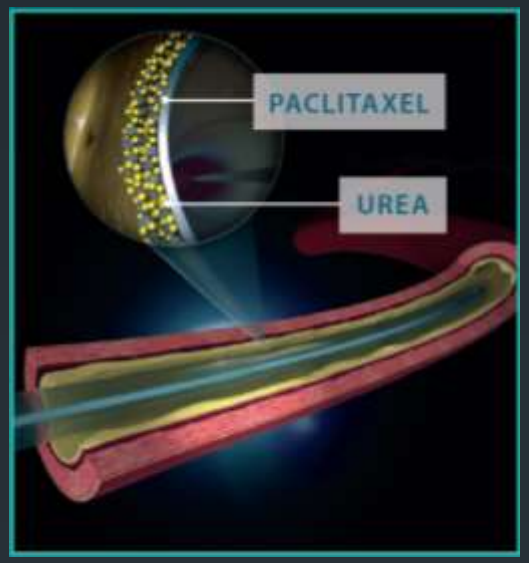
6. Duda et al. J Endovasc Ther 2006; 13:701-710
7. Ansel, VIVA 2010

DCB Technology

Mechanism of action

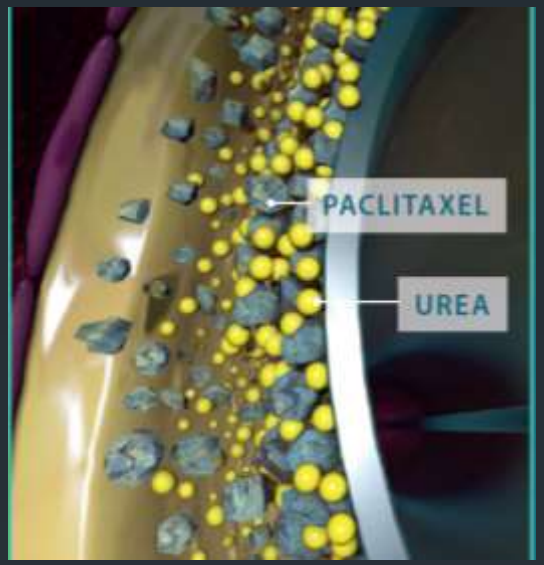


DCB matrix coating:

- Paclitaxel + Urea

During transit to lesion:

- Majority of matrix protected within folds of the balloon



DCB inflation:

- Matrix contacts blood
- Blood hydrates urea
- Urea releases paclitaxel
- Due to its hydrophobic and lipophilic properties, paclitaxel binds to vessel wall

Paclitaxel penetration:

- Through vessel wall deep into the media and adventitia
- Interferes with SMC proliferation
- Can remain in the vessel wall for over 180 days at therapeutic levels[1]

1. Data on file at Medtronic (SFA Study FS209; BTK Study FS516)

Drug Selection

Both Paclitaxel and Rapamycin can limit restenosis, but key differences make Paclitaxel more suitable for DCB

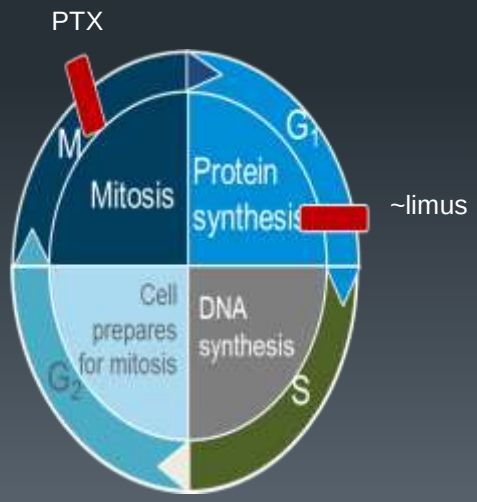
Paclitaxel (Cytotoxic)
Interferes with cell division

Cytotoxic drugs halt cellular replication cycle, inducing apoptosis

Rapamycin (Cytostatic)
Interferes with cell growth

Cytostatic drugs hold a cell in G_0 phase, arresting growth

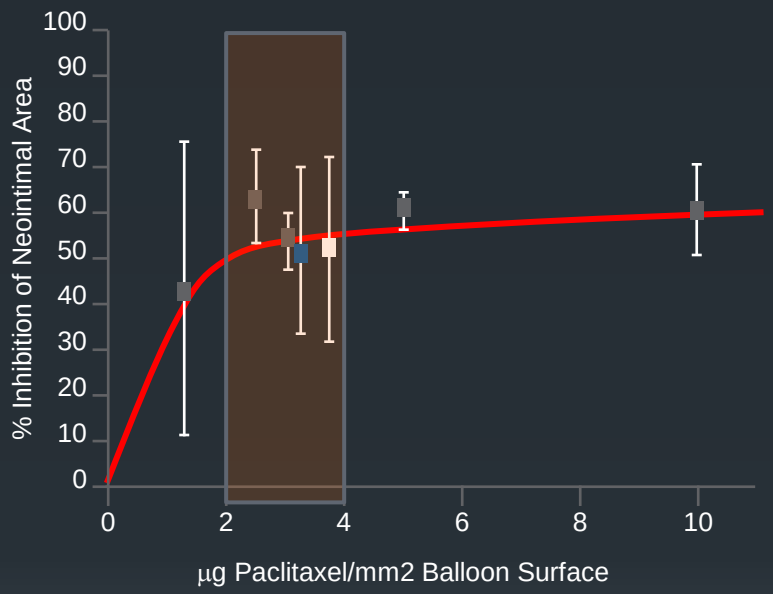
Rapid transfer via excipient allows acute delivery, especially beneficial if no artificial reservoir is present



Prolonged elution via polymeric ‘reservoir’ allows sustained delivery, especially beneficial when foreign body is present

Dose Selection

Paclitaxel offers a wide therapeutic window



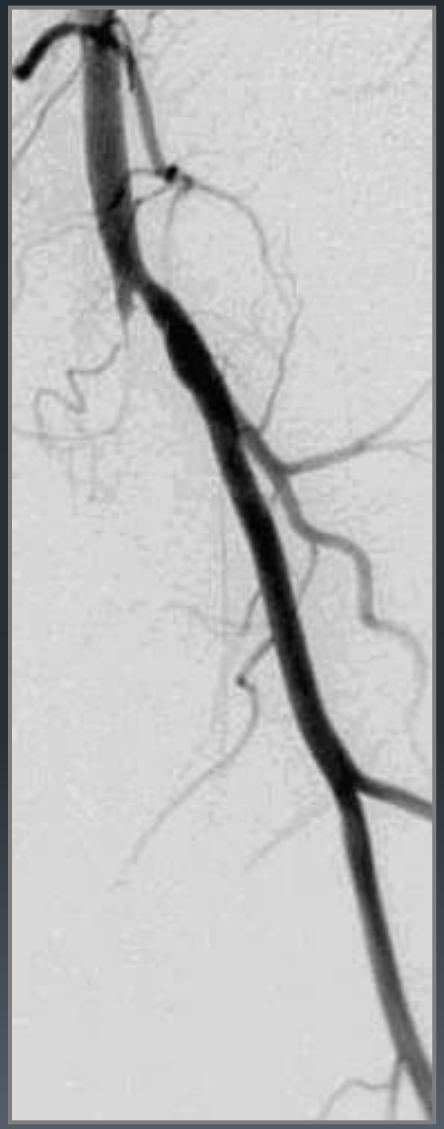
Therapeutic range 2-4 µg/mm^2
IN.PACT Admiral: 3.5 µg/mm^2

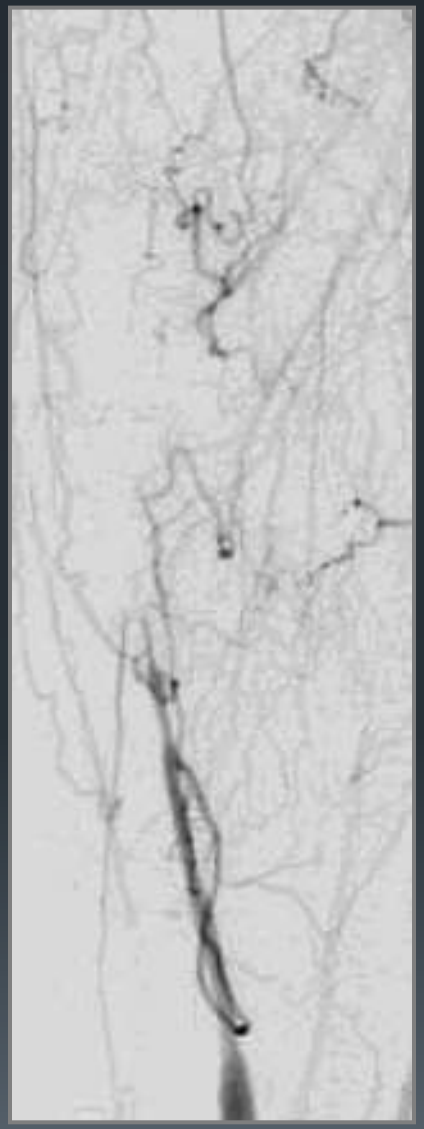
- Dose-dependent response up to 2-4 µg/mm^2
- Wide, stable therapeutic window with no statistically significant differences in neointimal inhibition or local toxic effects from 4 up to 10 µg/mm^2
- Clinically effective drug levels transfer within 60 seconds, with no negative clinical effects from longer inflation time

1. Scheller B, et al. PTX Balloon Coating, a Novel Method for Prevention and Therapy of Restenosis. *Circulation*. 2004;110:810-814. 2. Speck U, Scheller B, Abramjuk C,
et al. Neointima inhibition: comparison of effectiveness of nonstent-based local drug delivery and a DES in porcine coronary arteries. *Radiology*. 2006;240:411– 418.
3. Cremers B, et al. Comparison of two different PTX-coated balloon catheters in the porcine coronary restenosis model. *Clin Res Cardiol*. 2009;98:325–330.
4. Cremers B, et al DEB: Very short-term exposure and overlapping. *Thromb Haemost*. 2009; 101: 201–206. 5. Rowinsky EK, Donehower RC. Paclitaxel (Taxol).
N Engl J Med. 1995;332:1004-1014. 6. Margolis J, McDonald J, Heuser R, et al. Systemic nanoparticle PTX (nab-PTX) for ISR I (SNAPIST-I): A first-in-human safety and dose-finding study. *Clin Cardiol.* 2007;30:165-170

Long CTO

Courtesy of
F. Fannelli MD



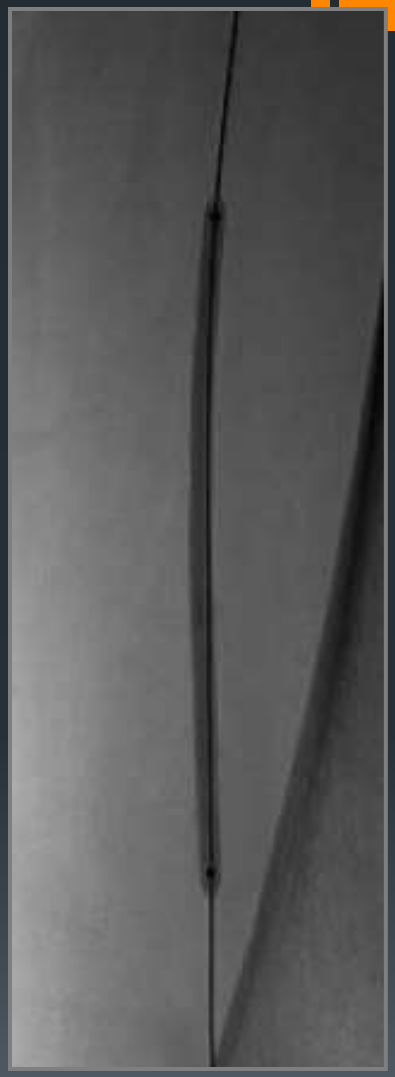


Sub-intimal recan.

Pre-dil:
Admiral
4 x 120 mm

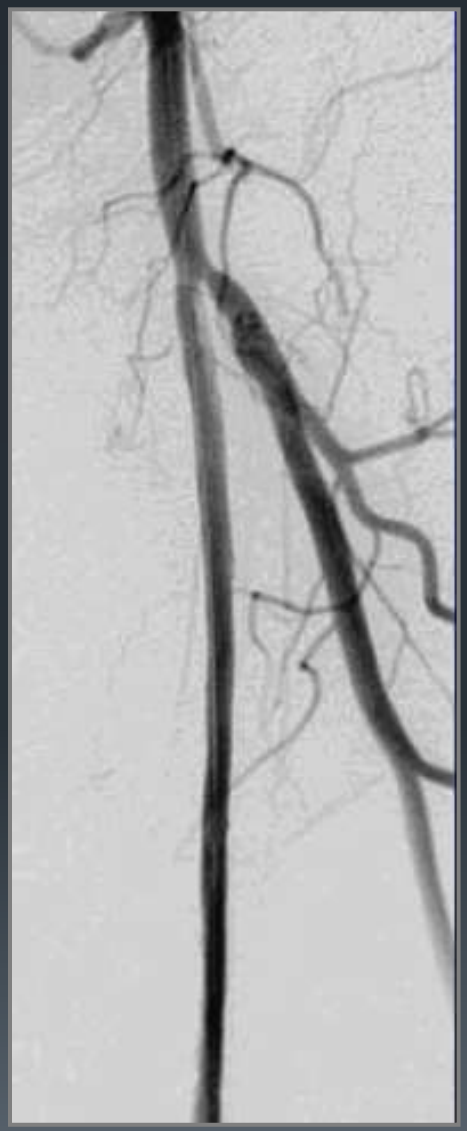
Treatment:
IN.PACT Admiral
5 x 120 mm

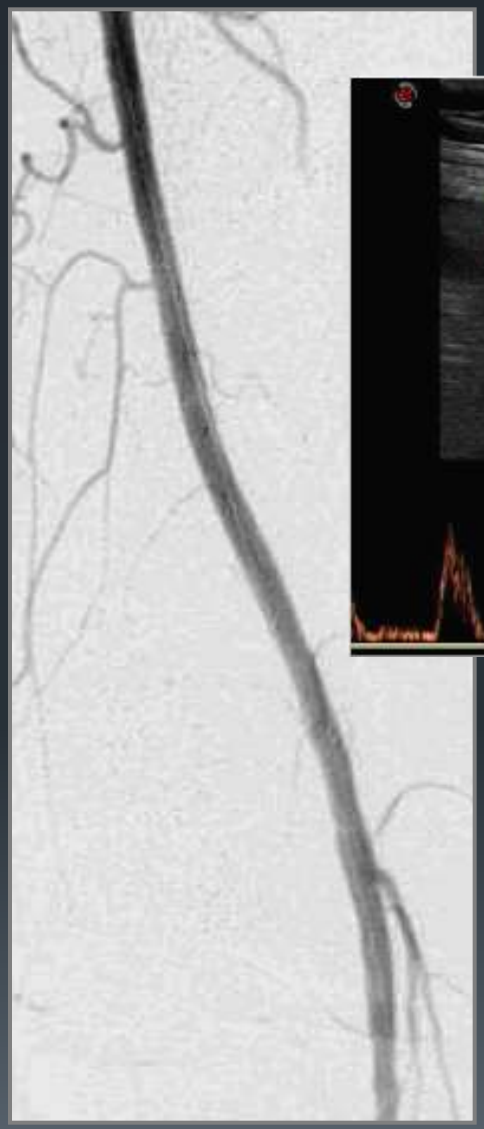
ABI: 0.5

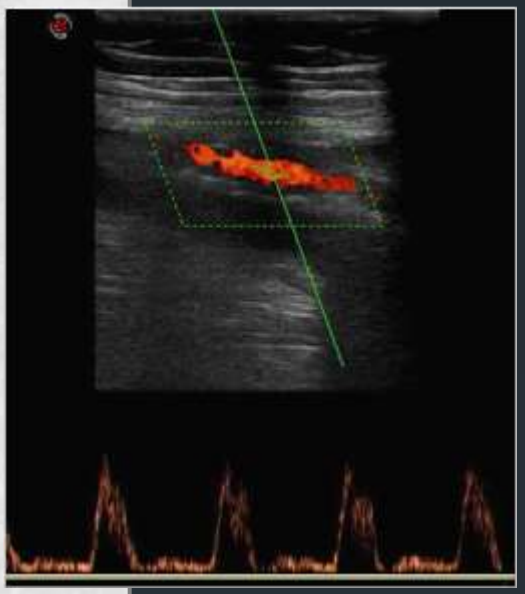


Long CTO, Post DCB 12-month FU Angiogram

Courtesy of
F. Fannelli MD

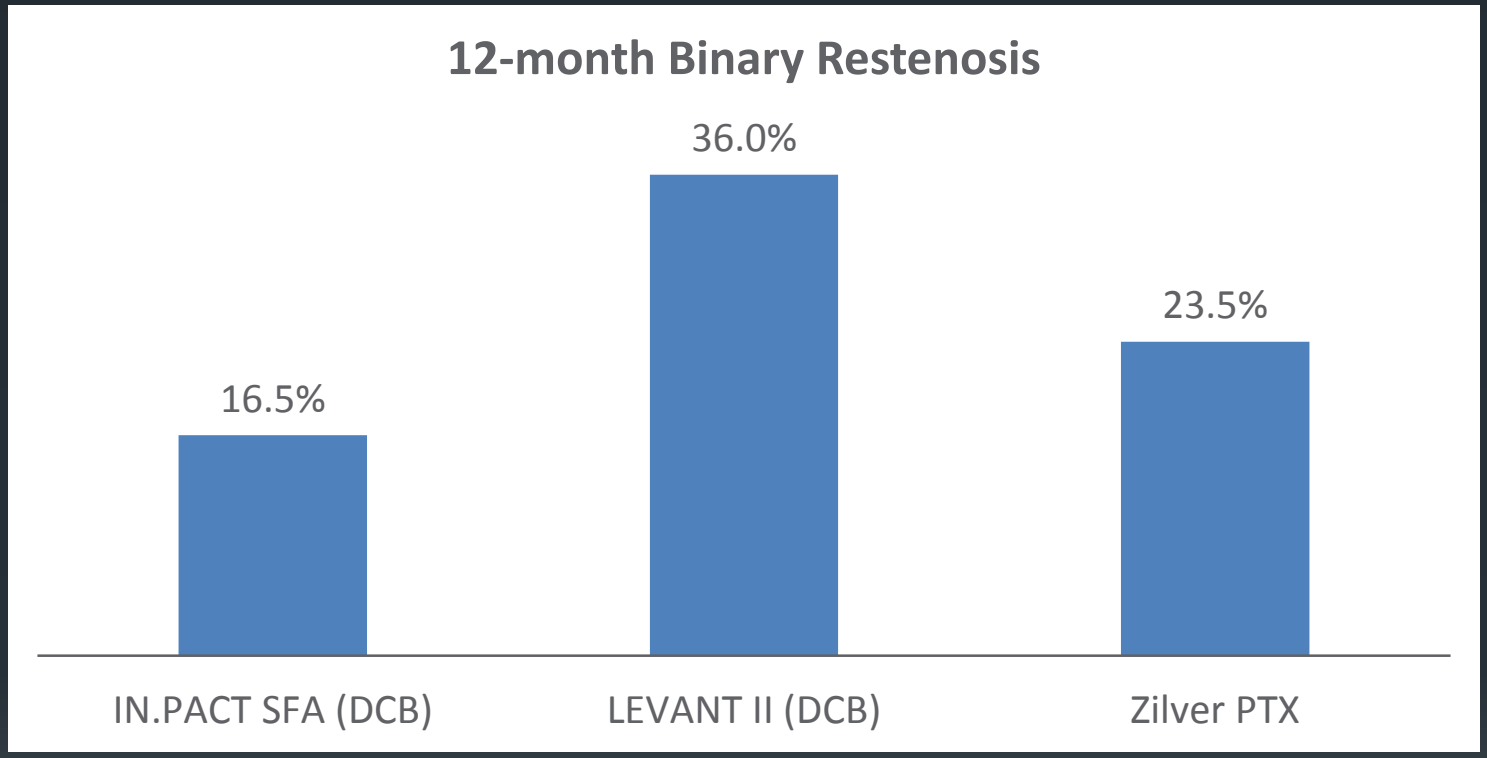






ABI: 0.9

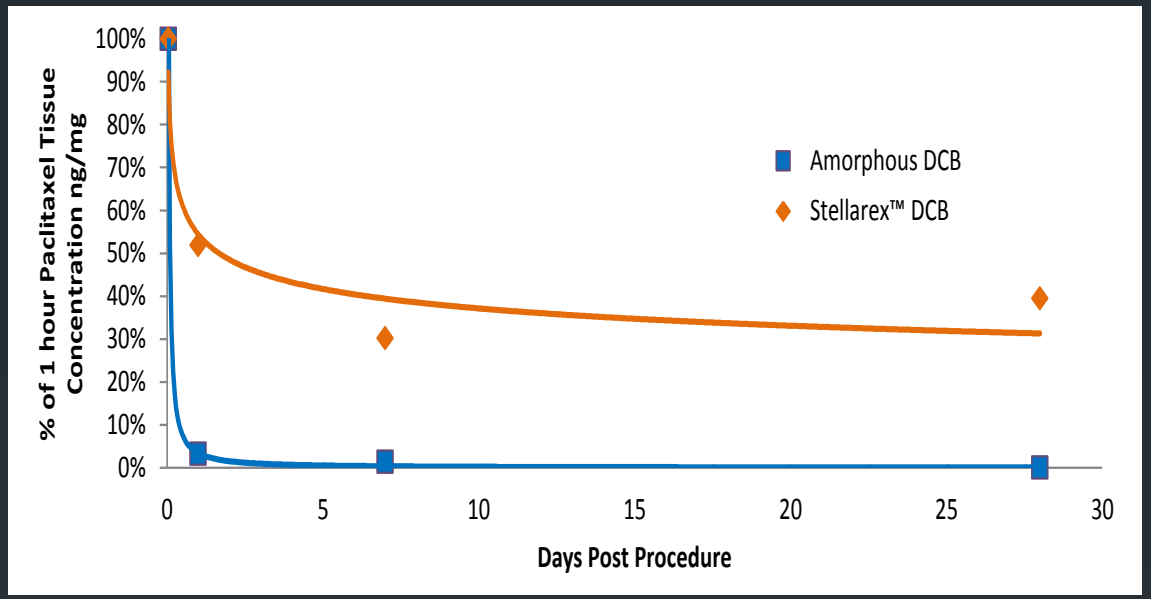
Comparative Data Between DCB and DES Therapies



Mean Lesion Length	8.9 cm	6.3 cm	5.5 cm
	PSVR >2.4	***PSVR ≥2.5***	***PSVR >2.0***
	Source: FDA SSED Table 16	Source: FDA Exec Summary Table 37	Source: FDA SSED Table 25

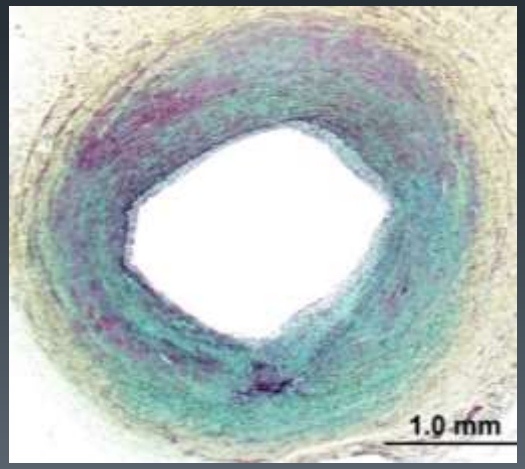
Note: Binary restenosis rates are not directly comparable; chart is for illustration only;
IN.PACT SFA and LEVANT II binary restenosis rates determined by same independent core laboratory.

Pharmacokinetics and Histology



Crystalline Coating

Amorphous Coating

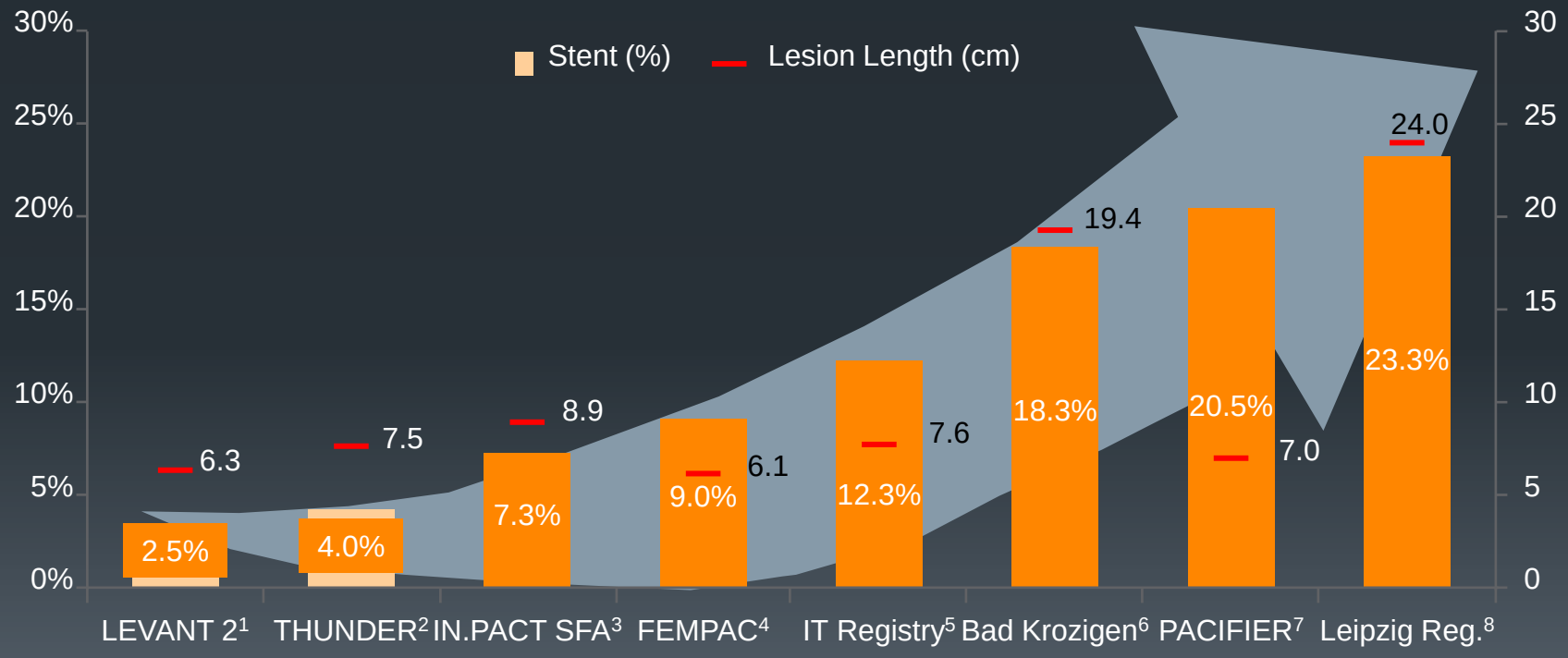


Green staining evidence of PTX in pig model vessel @ 28 days

DCB and Provisional Stenting

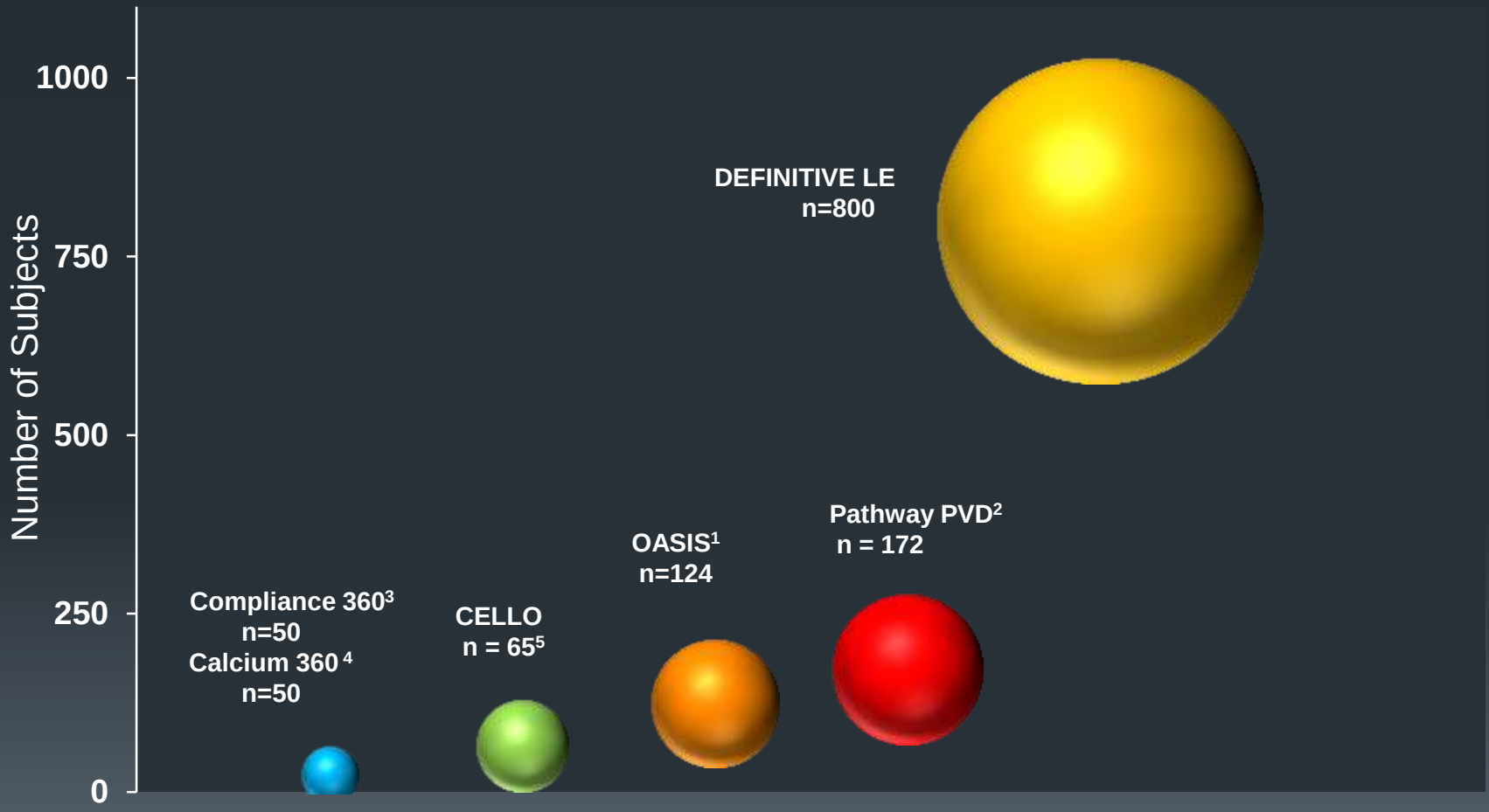
Scaffolds still needed, likely at rates proportional to lesion complexity

Provisional stent rates in DCB trials trend with lesion length



1. Rosenfield K TCT 2013; 2. Tepe G et al. *N Engl J Med*. 2008; 3. Tepe CX 2014; 4. Werk M et al. *Circulation*. 2008; 5. Micari A et al. *J Am Coll Cardiol Intv*. 2012; 6. Zeller T CX 2013 oral presentation; 7. Werk et al. *Circ Cardiovasc Interv*. 2012; 8. Schmidt A LINC 2013 oral presentation

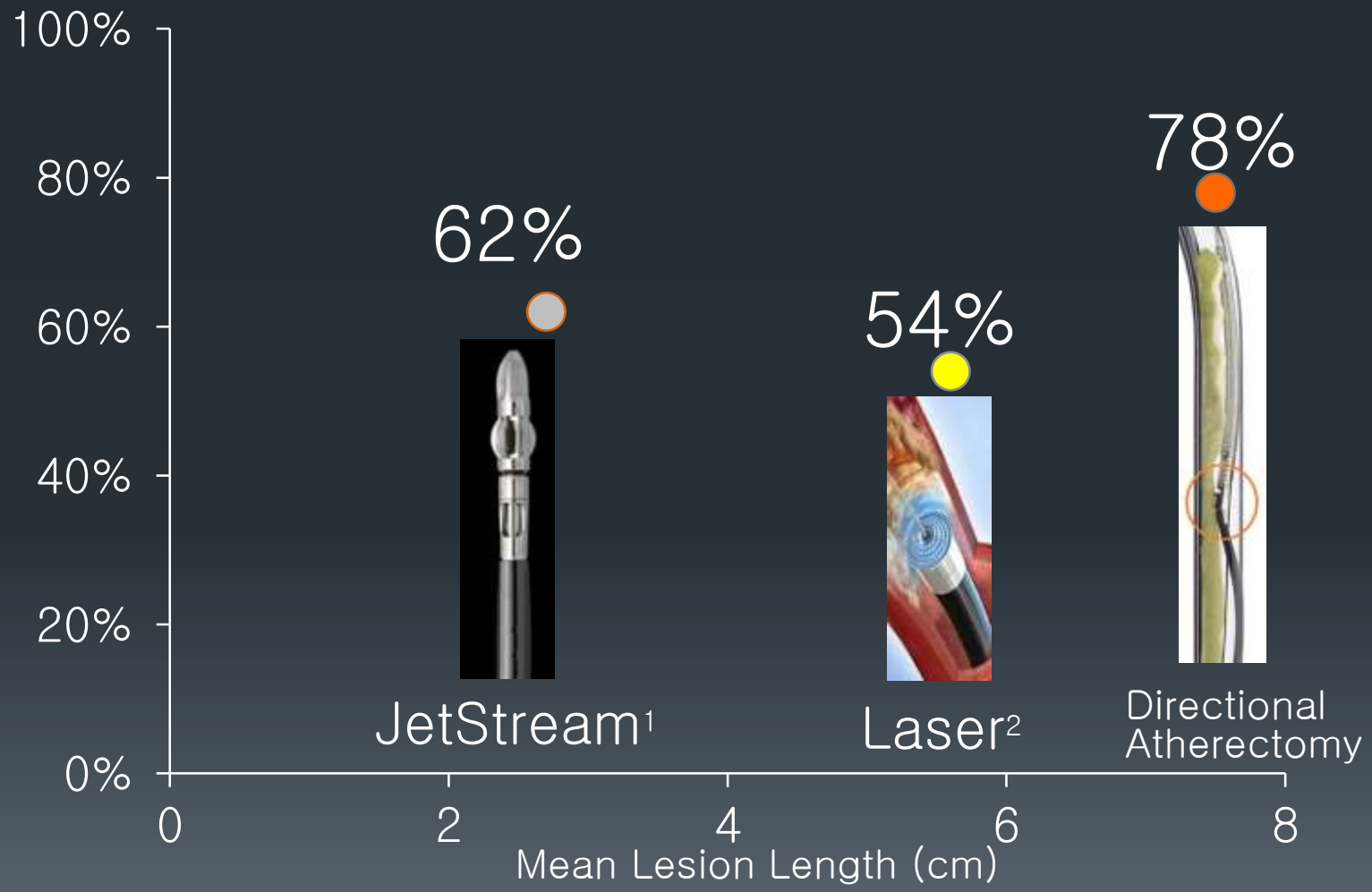
Atherectomy Trials
Wide variation in sample size



1. Safian et al. Cath & Cardiovasc Interv 73:406:412
2. Zeller et al. J Endovasc Ther 2009;16:653-662
3. Dattilo, TCT 2011
4. Shammas et al. J Endovasc Ther 2012;19:480-488
5. Dave et al. J Endovasc Ther 2009;16:665-675

Atherectomy Trials

Core-Lab Adjudicated 12-mo. Patency



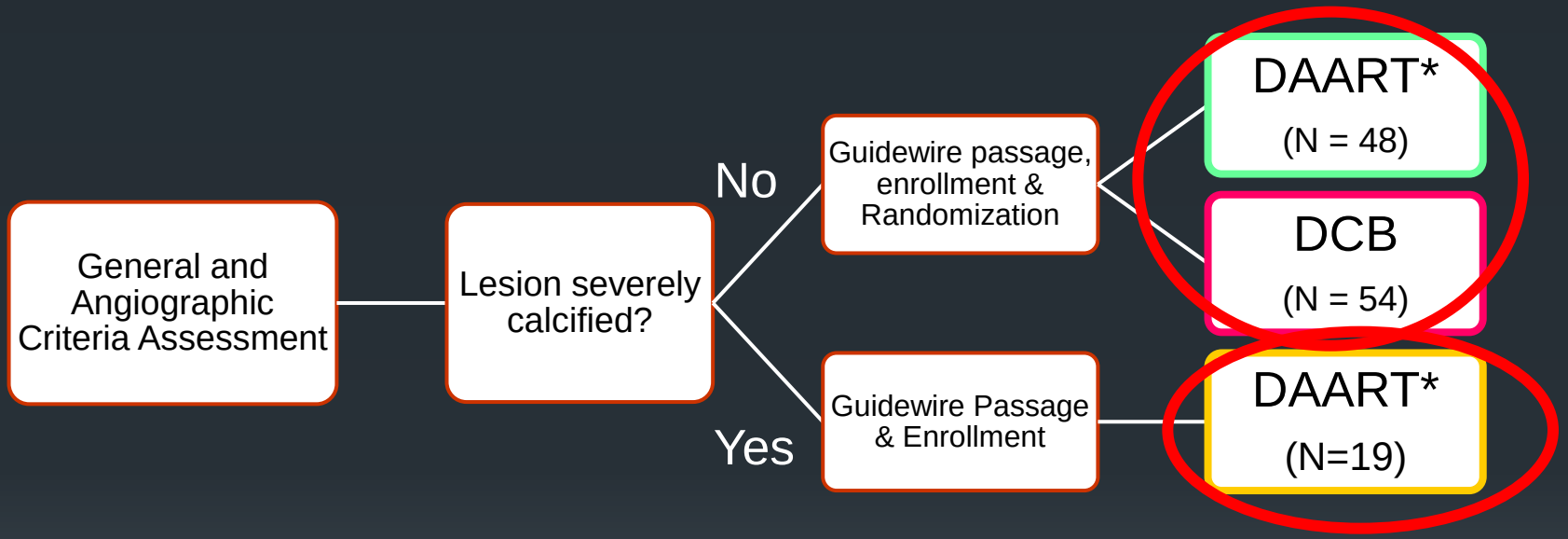
1. Dave J. Endovasc. Ther. 2009;13:665-675
2. Zeller et al. J Endovasc. Ther. 2009;16:653-662

Primary Patency: Stenosis vs. Occlusion

	Patency (PSVR ≤ 2.4)	Lesion Length (cm)
All Claudicants (n= 743)	**78%**	**7.5**
Lesion type		
Stenoses (n=611 lesions)	81%	6.7
Occlusions (n=128 lesions)	64%	11.1

Definitive AR

Purpose: Pilot study designed to assess and estimate the effect of treating a vessel with directional atherectomy + DCB (DAART) compared to treatment with DCB alone



Severe Calcification: Dense circumferential calcification and calcification extending more than **five (5)** continuous centimeters of length prior to contrast injection or digital subtraction angiography

Registry arm for severely calcified lesions created to limit bail-out stenting (and therefore variables) in randomized arm.

* Directional Atherectomy + Anti-Restenotic Therapy

Baseline Lesion Characteristics

Per Core Lab Assessment

	DAART Severe Ca++ Arm (N=19)	DAART (N= 48)	DCB (N = 54)
Lesion Length (cm)	11.9	10.6	9.7
Diameter Stenosis	88%	82%	85%
Reference vessel diameter (mm)	5.1	4.9	4.9
Minimum lumen diameter (mm)	0.7	1.0	0.8

Atherectomy + DEB: Higher Acute Technical Success

Defined as ≤ 30% residual stenosis following the protocol-defined treatment at the target lesion as determined by the Angiographic Core Laboratory.

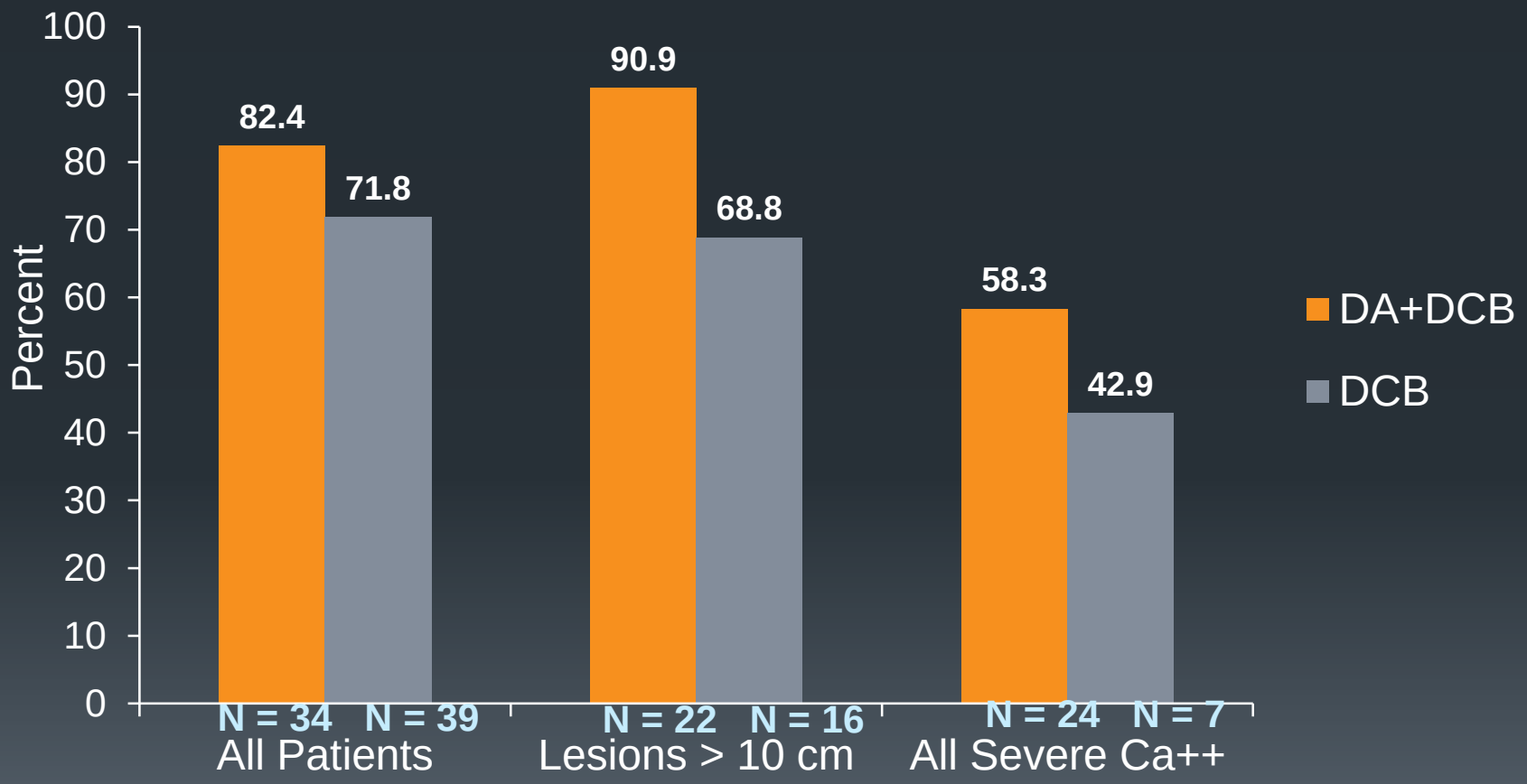
	DAART Severe Ca^{++}	DAART	DCB	P Value (DAART vs. DCB)
Technical Success	84.2%	89.6%	64.2%	0.004

Atherectomy + DEB: Lower need for post PTA and Bail Out Stenting

	DAART Severe Ca^{++}	DAART	DCB	P Value (DAART vs. DCB)
Adjunctive Therapy				
PTA (post-dil)	0	6.3% (3/48)	33.3% (18/54)	0.0011
Bail-out Stent	5.3% (1/19)	0	3.7% (2/54)	0.4968

Angiographic Patency at 12 Months

Angiographic Patency shows similar pattern

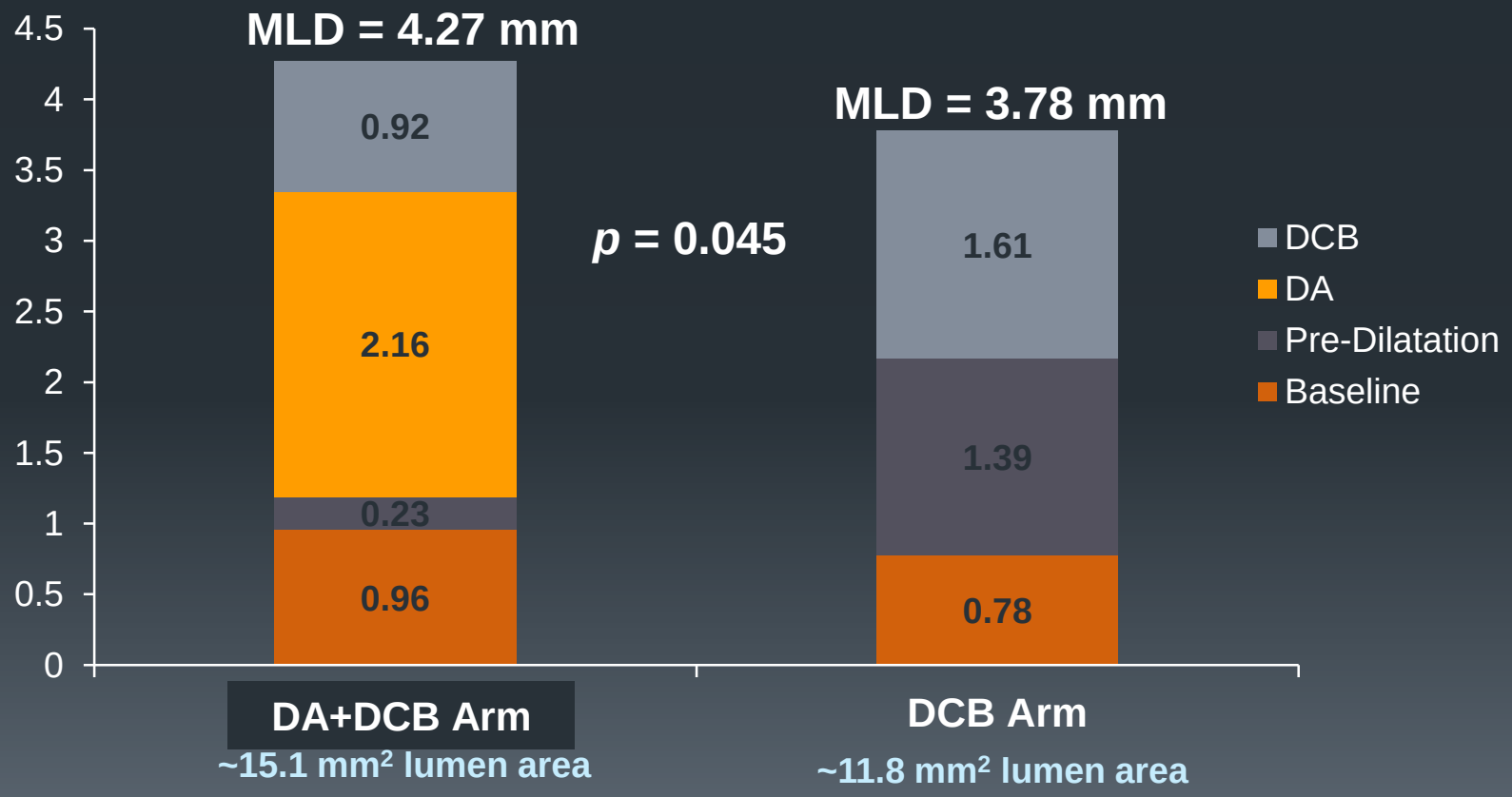


Per Core Lab Assessment. “All Severe Ca++ “ group includes all patients with severe calcium (including randomized and non-randomized. Results for all patients who returned for angiographic follow-up.

What is the Impact of Lumen Gain with DA+DCB?

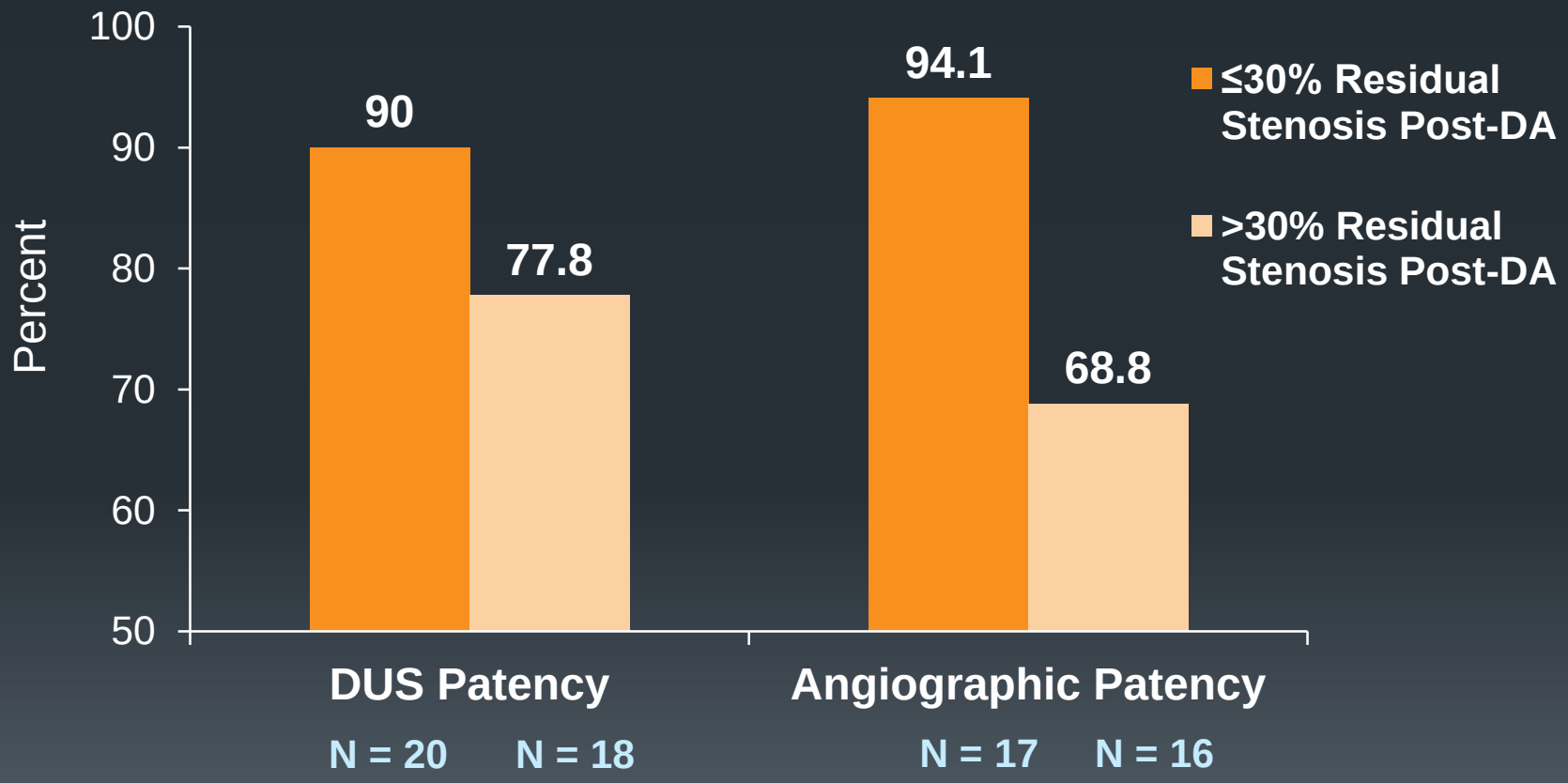
Post Procedure MLD (DA+DCB vs DCB alone)

DA+DCB resulted in a significantly larger minimum lumen diameter (MLD) following the protocol-defined treatment in DEFINITIVE AR



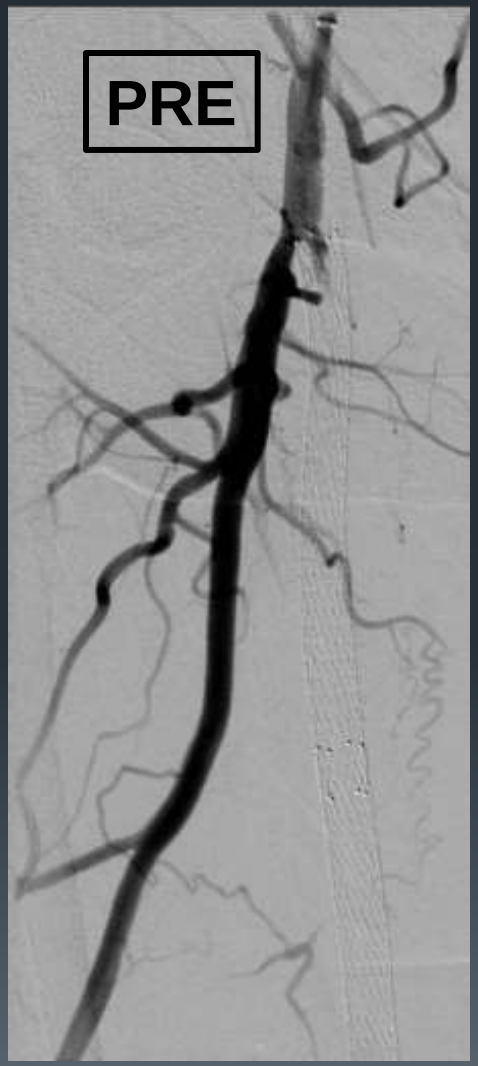
12-Month Patency: DA+DCB RCT Patients

Increased lumen gain with DA before DCB may result in improved 12-month patency



Best Strategy for Long Segment Fem Pop CTOs?

- Cross CTO
- Vessel Prep
  - Pre-Dilation
  - Atherectomy
- Drug Eluting Balloon
  - Optimal PTA – long balloon inflations
  - Does not appear to be a class effect
- Spot stenting if needed for flow limiting dissection
- Role of covered stents?



Long Term Patency: What should we expect in 2015?

- What do we know
  - Fem-pop lesions
  - 7-9 cm mean length, 12 month patency (not TLR) should be 75-85%
  - Below that is probably not acceptable

- Goals
  - Higher Patency, Longer Lesions, More Durability
  - Improved Outcomes in TASC C/D, including CTOs
  - Further trials are needed to understand which combination of DEB, DES, Covered Stent, Atherectomy will get us there
  - Societal consensus is needed to standardize definitions of patency to allow true comparisons