What's the Benchmark: Is there a Gold Standard for SFA Revascularization?

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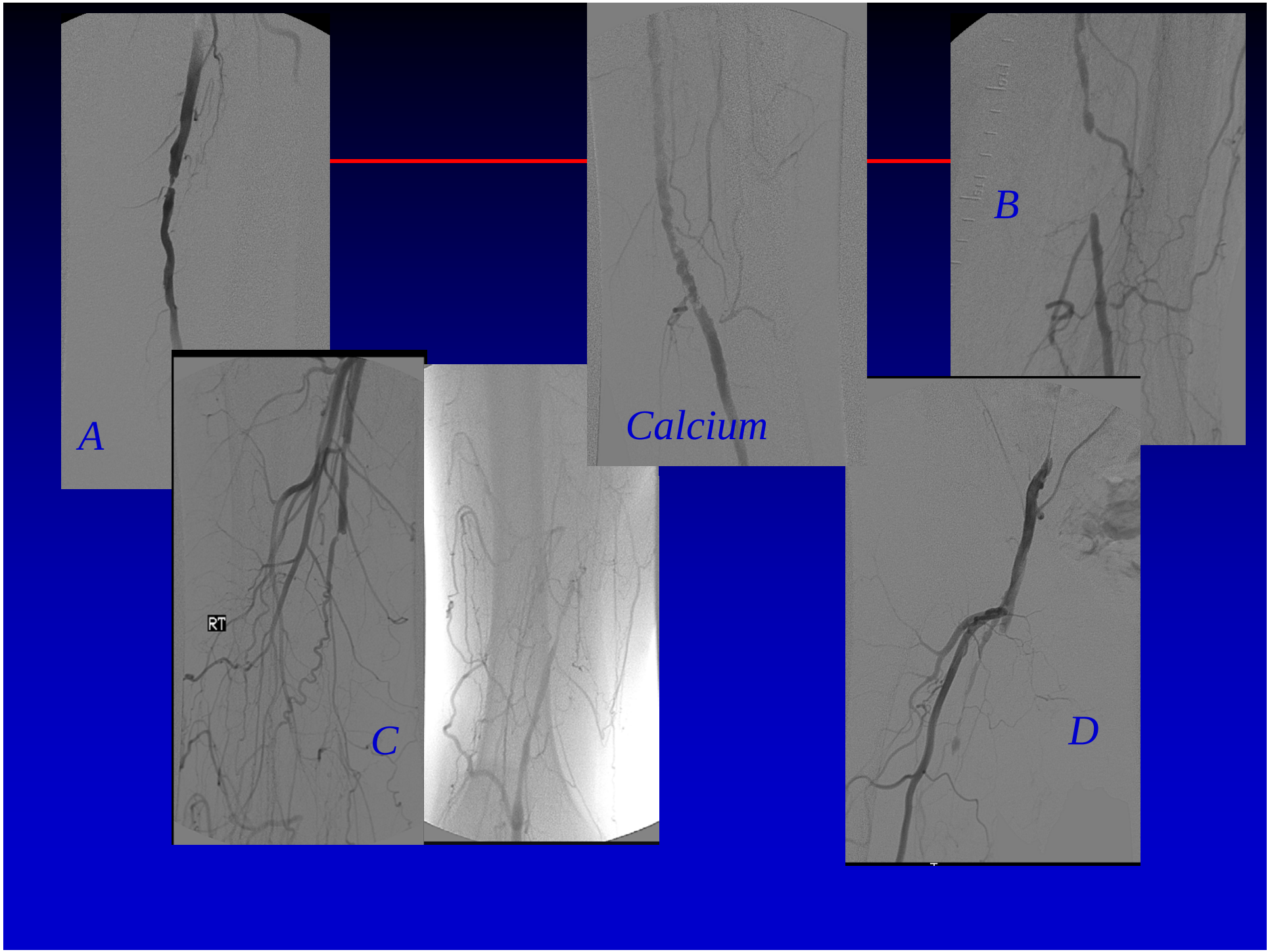
Conflict of Interest Statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Physician Name

L Garcia

Company/Relationship	
BostonScientific	**AdBoard (modest)**
EV3	**Research/AdBoard**
Spectranetics	**AdBoard (unpaid)**
Pathway Medical	**AdBoard (unpaid)**
AngioSculpt	**AdBoard (unpaid)**
iDev Technologies	**Research/AdBoard**
Covidien	**Consultant**
Scion Cardiovascular	**Board of Directors**
Arsenal Medical	**Equity shareholder**
TissueGen Medical	**Equity shareholder**
Primacea	**Equity shareholder**
CVI Technologies	**Equity shareholder**


A
Calcium
B
RT
C
D

Defining the problem

- To date most meaningful studies have evaluated 5-6 cm lesions and only 2 studies have tested long lesions closer to 20 cms
- Determining the “gold” standard is difficult in this data “vacuum”
- Potential options
  - exercise programs
  - simple POBA
  - stenting technologies
    - DES
    - non-medicated
  - DCB and alternative therapies

MIMIC: PTA vs medical therapy

Table 2 Outcomes in the MIMIC femoropopliteal trial.

	Control	PTA		Adjusted result (95% CI) *p*-value[b]
AWD (geometric mean, metres)			Ratio PTA:control	
6 Months ($n = 81$)	167	202	1.21	1.06 (0.80–1.41) $p = 0.69$
12 Months ($n = 75$)	150	224	1.49	1.22 (0.88–1.67) $p = 0.23$
24 Months ($n = 71$)[a]	155	245	1.58	1.38 (1.01–1.90) $p = 0.04$
ICD (% attaining 200 m without claudication pain)			Hazard ratio PTA:control [c]	
6 Months ($n = 81$)	23%	32%	1.56	1.78 (0.99–3.21) $p = 0.05$
12 Months ($n = 75$)	25%	42%	2.18	2.18 (1.15–4.12) $p = 0.02$
24 Months ($n = 71$)	22%	63%	2.83	3.11 (1.42–6.81) $p = 0.004$
Other outcomes at 24 months			Difference: PTA–control	
Mean ABPI ($n = 73$)	0.72	0.83	0.11	0.11 (0.03–0.20) $p = 0.01$
Mean SF36 physical score ($n = 79$)	39.2	40.9	1.7	−0.4 (−4.2 to 3.4) $p = 0.82$
Mean SF36 mental score ($n = 79$)	47.6	51.5	3.9	2.4 (−1.7 to 6.5) $p = 0.25$

AWD absolute walking distance, ICD initial claudication distance, ABPI ankle-brachial pressure index, SF36 short-form 36 summary scores.

[a] Pre-specified primary outcome.

[b] Adjusted for corresponding measure at baseline, age, sex, baseline smoking status and ABPI.

[c] Hazard ratio for comparing probabilities of attaining a particular ICD (see Fig. 4).

Greenhalgh GH et al *EurJVascEndovasSurg 36:2008 680-88*

Balloon Angioplasty versus Implantation of Nitinol Stents in the Superficial Femoral Artery

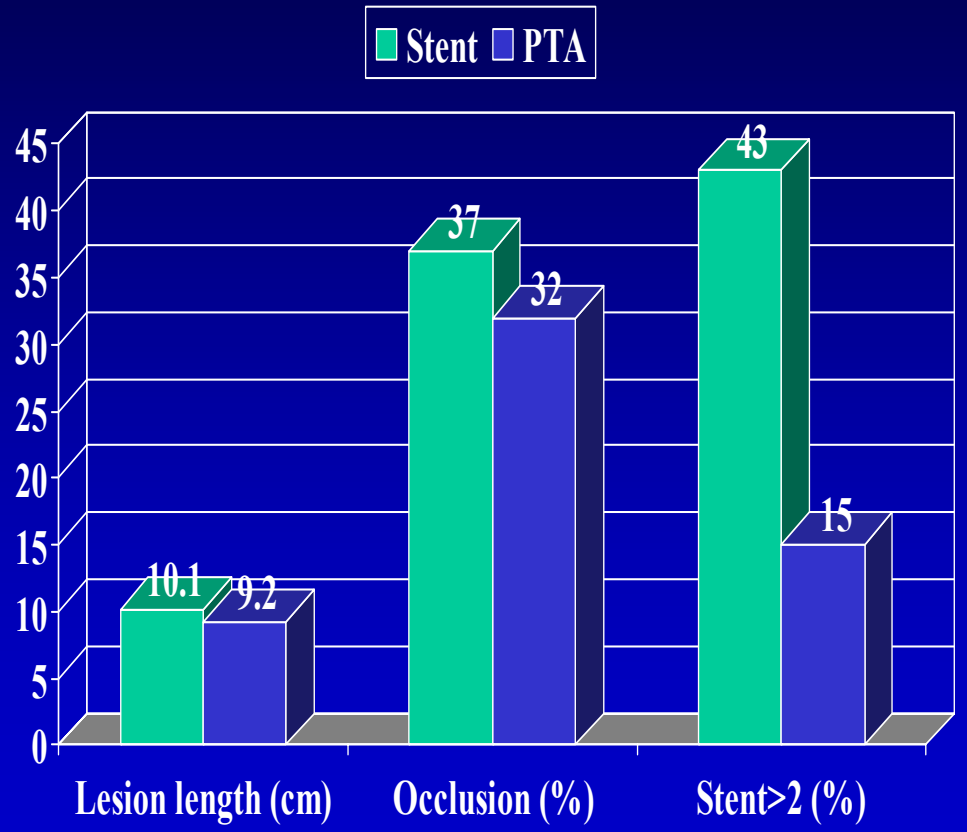
Martin Schillinger, M.D., Schila Sabeti, M.D., Christian Loewe, M.D., Petra Dick, M.D., Jasmin Amighi, M.D., Wolfgang Mlekusch, M.D., Oliver Schlager, M.D., Manfred Cejna, M.D., Johannes Lammer, M.D., and Erich Minar, M.D.

- 104 patients
- Claudicants/CLI

–	Stent	PTA
RB<3	88%	87%
RB>4	12%	13%

- ABI

– Stent	PTA
– 0.57	0.54



Schillinger *NEJM* 2006

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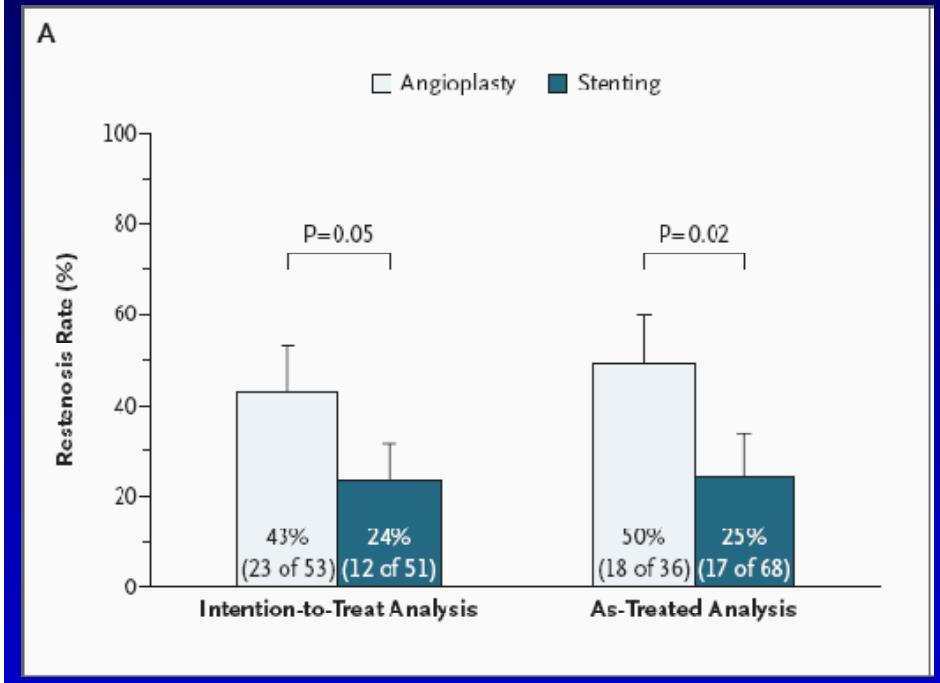
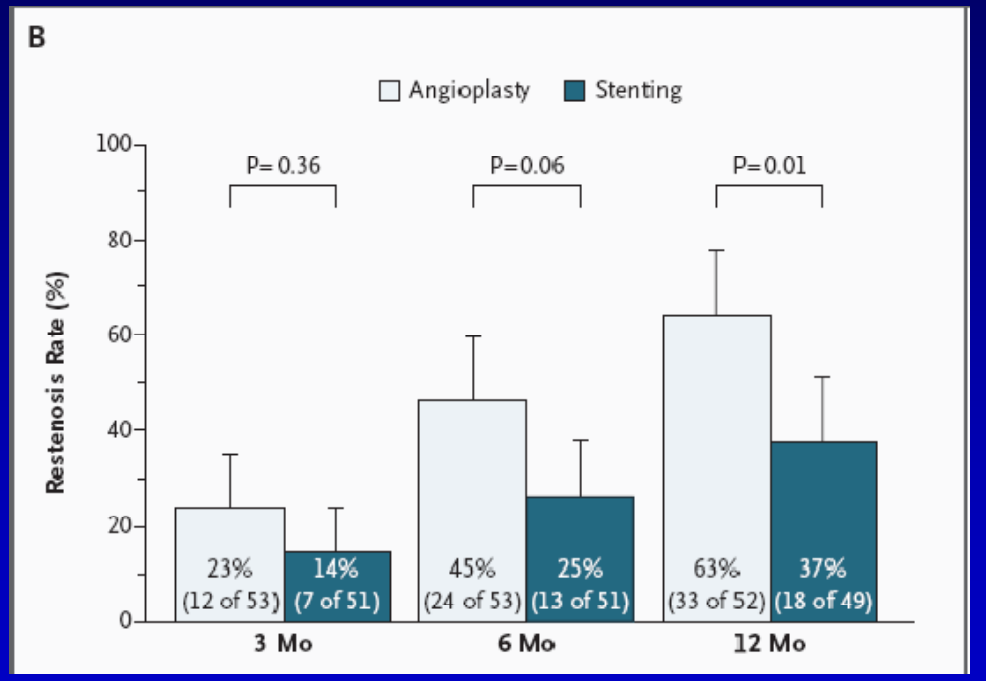
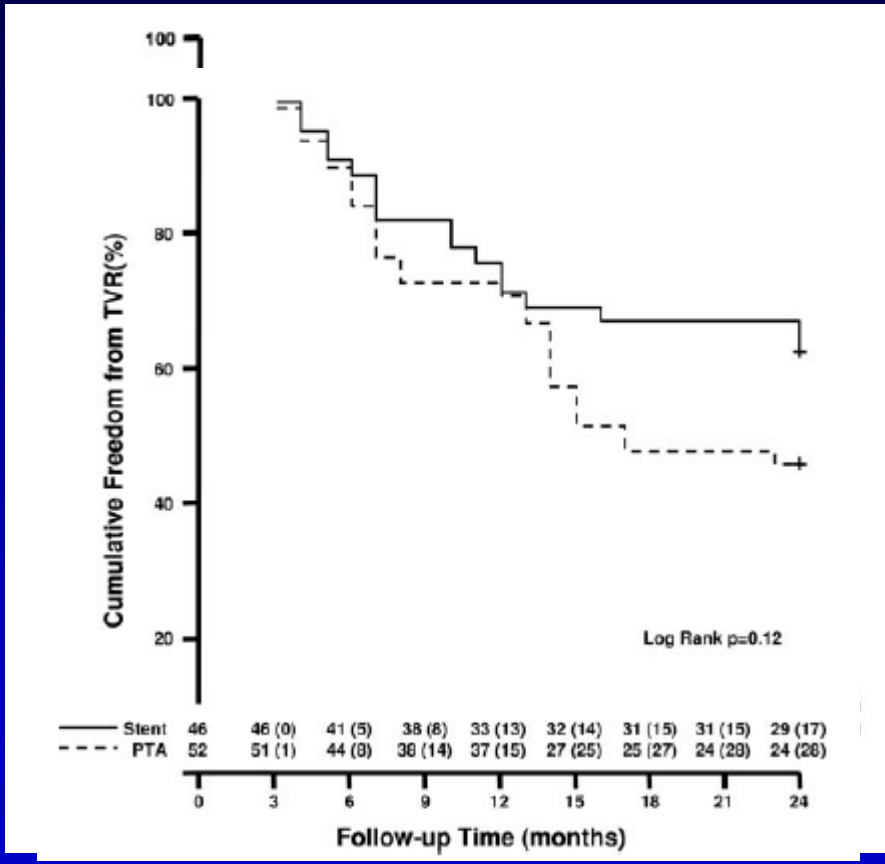




ABSOLUTE 2-year

- At two years PP
  - Stenting 54%
  - PTA 32%
  - *p<0.04*
- Clinical difference
  - 43% vs 33%
  - *P=NS*
- Walking distance
  - No difference

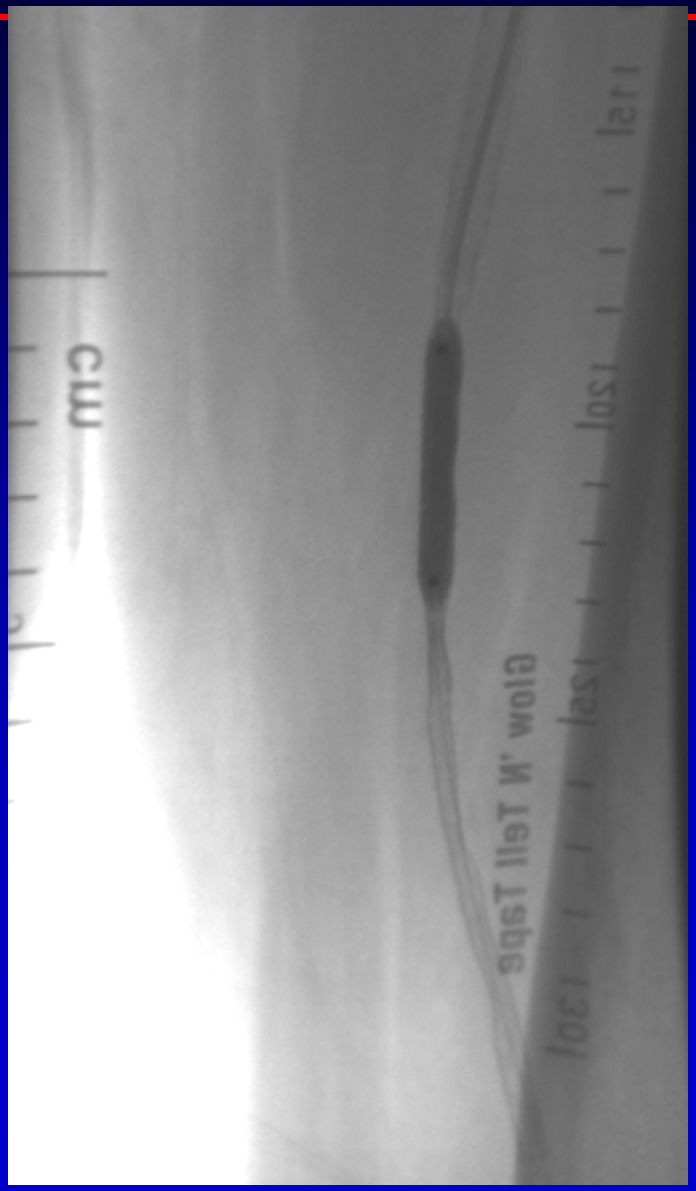


TVR

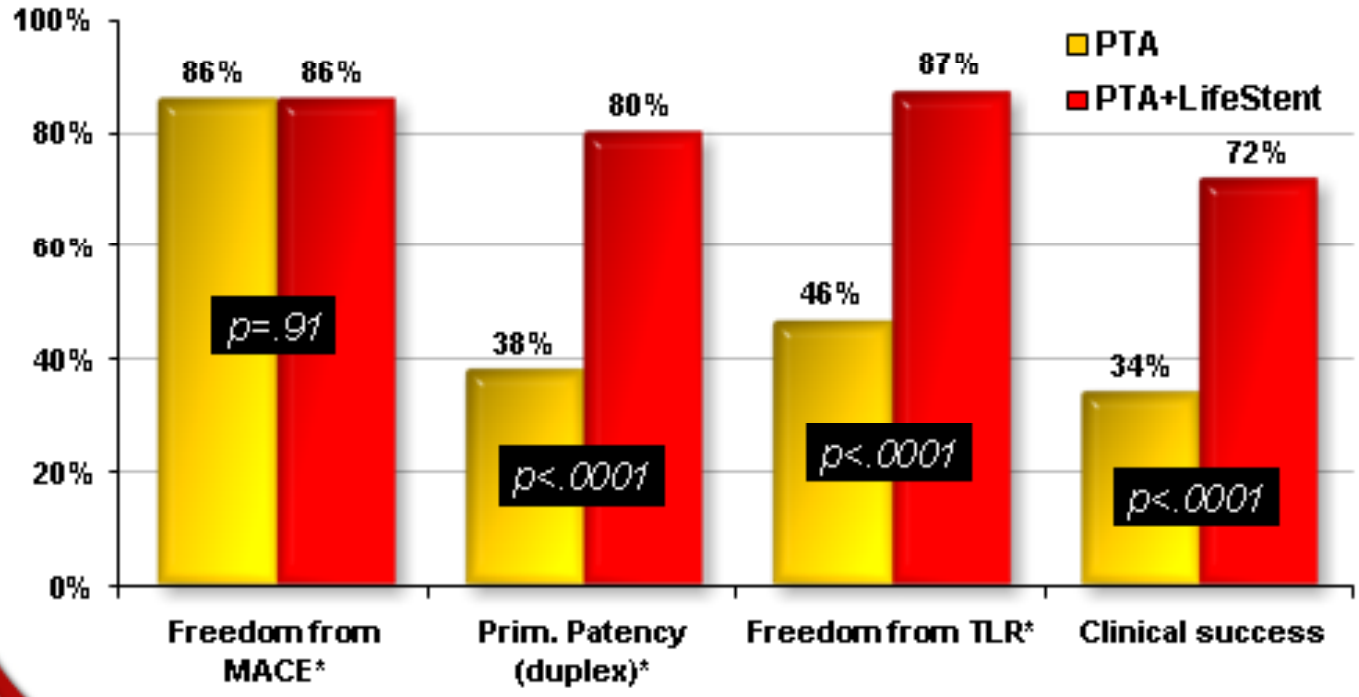
Schillinger *Circ 2007115: 2745-2749*

RESILIENT

- Presented 2007 published 2009
- Lesion lengths up to 14 cm
- Lesions treated
  - PTA 5.7 cm (6.4 cm LL)
  - Stent 6.2 cm (7.0 cm LL)
- 2:1 randomization with PTA
  - PTA failure 40%
- Stent fractures
  - All stents imaged for SF
  - Fracture rate 2%



12-Month Results

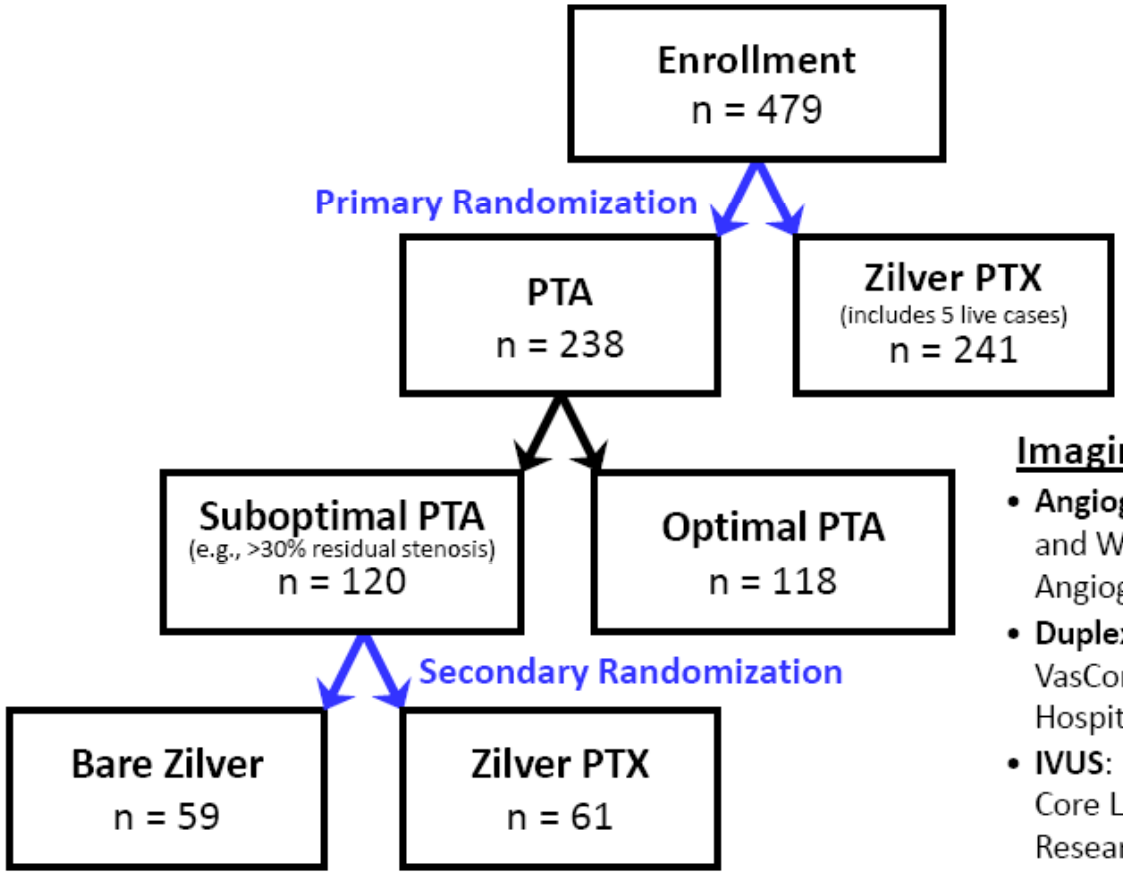


*Data from Kaplan-Meier Survival Analysis

THE RESILIENT TRIAL

Zilver PTX

Clinical Trial Design



Imaging Core Laboratories

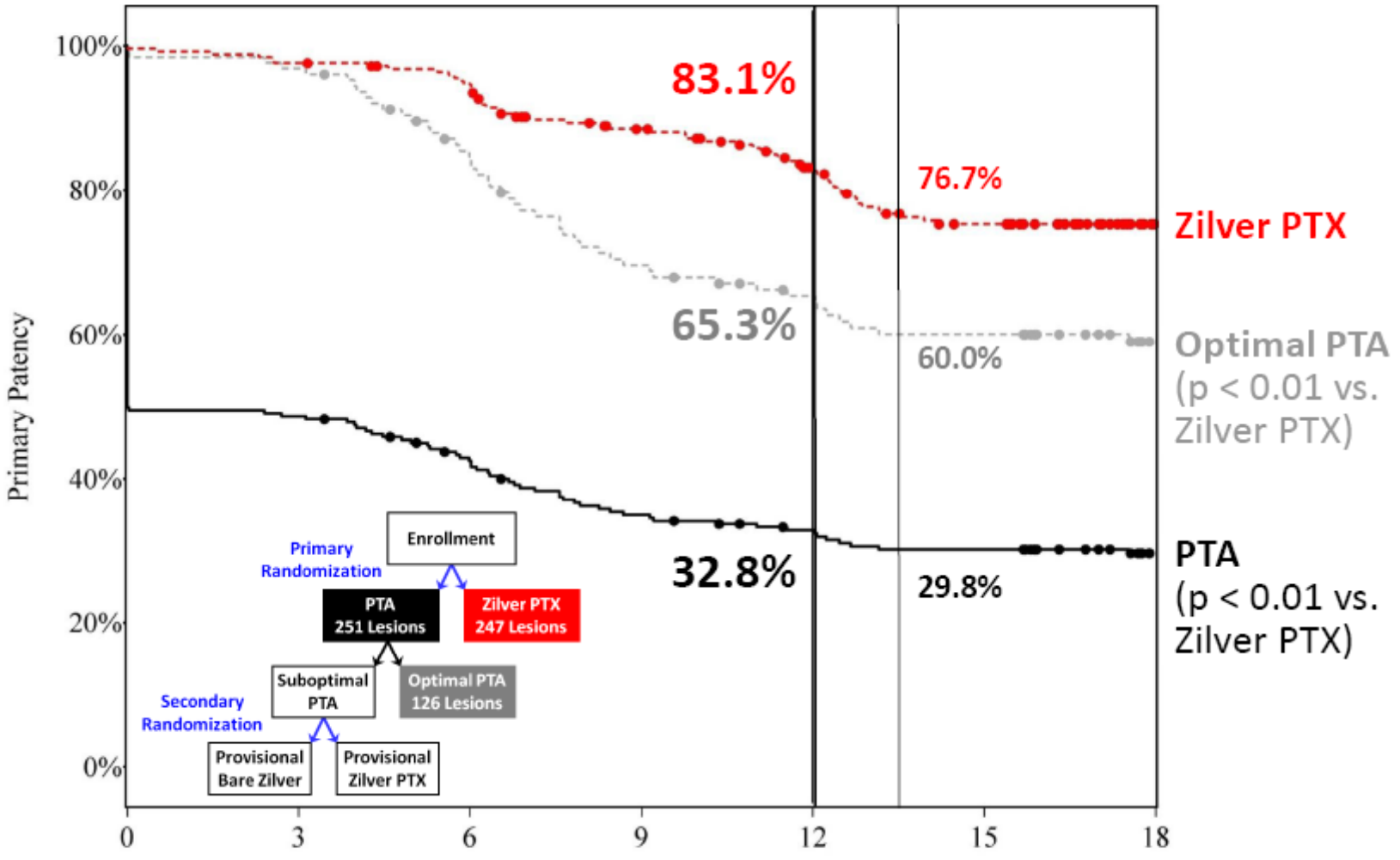
- **Angiography and X-ray**: Brigham and Women's Hospital Angiographic Core Laboratory
- **Duplex Ultrasonography**: VasCore, Massachusetts General Hospital
- **IVUS**: Intravascular Ultrasound Core Lab, MedStar Health Research Institute

		PTA	Zilver PTX	*P*-value
Lesions		251	247	
Normal-to-normal lesion length (mm)		63 ± 41	66 ± 39	0.35
Stenosed lesion length (mm)[1,2]		53 ± 40	54 ± 41	0.76
Diameter stenosis (%)[1]		78 ± 17	80 ± 17	0.44
Total occlusions		25%	30%	0.20
De novo lesions		94%	95%	0.69
Lesion calcification[1]	None	5%	2%	< 0.01*
	Little	38%	26%	
	Moderate	22%	35%	
	Severe	35%	37%	

[1] Angiographic core lab assessment
[2] Region with > 20% diameter stenosis
*Statistically significant

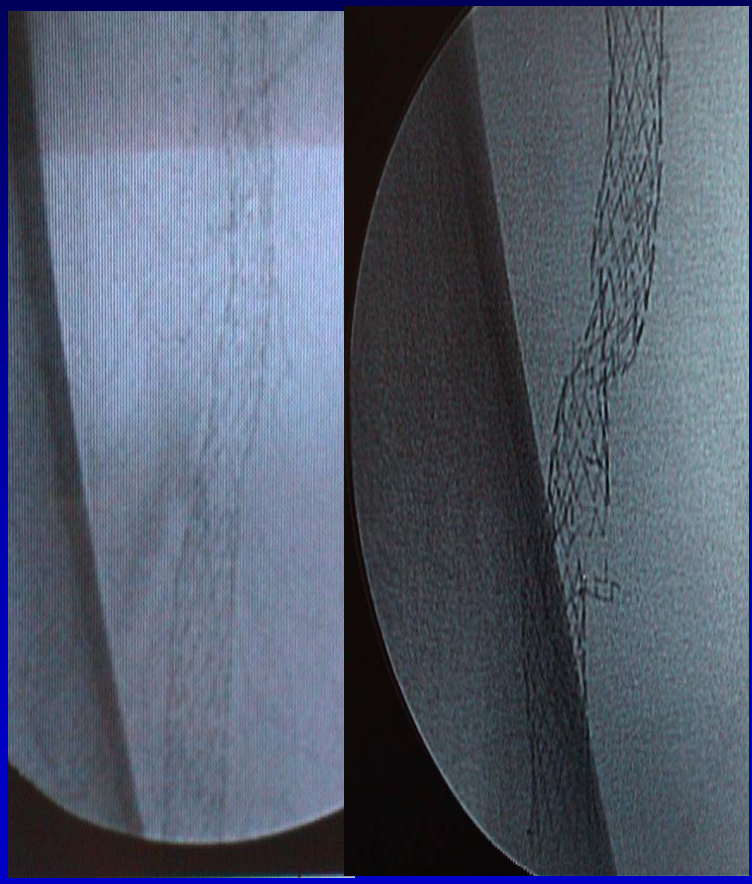
Effectiveness Endpoint

Primary Patency (PSVR < 2.0)



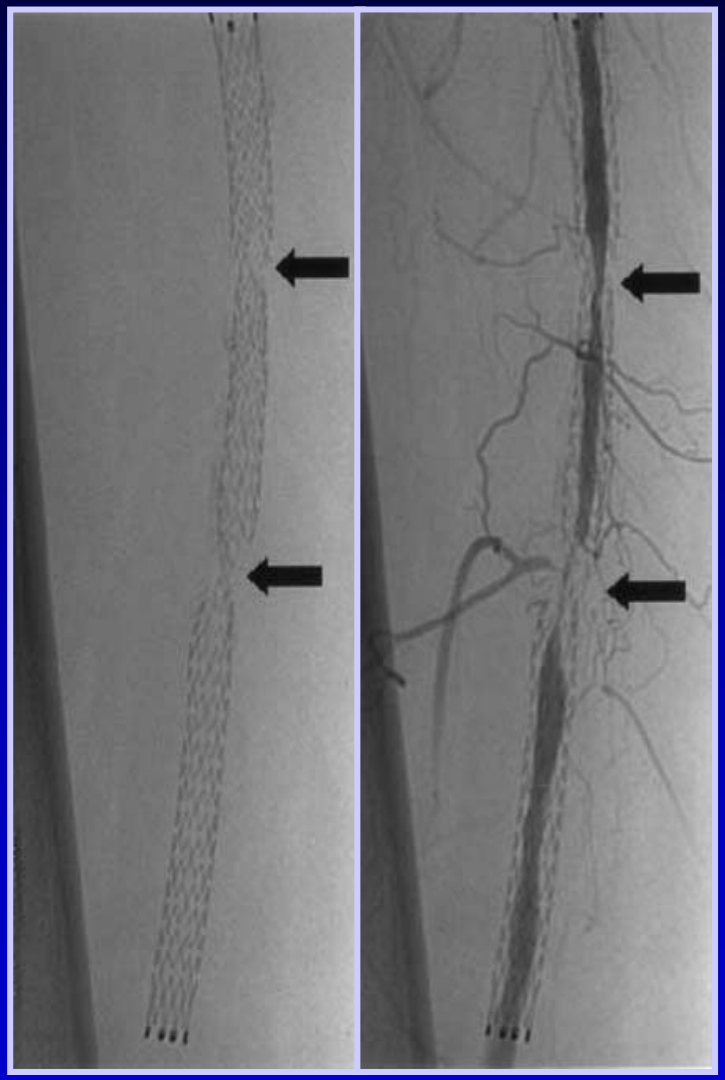
Why do SES stents fail?

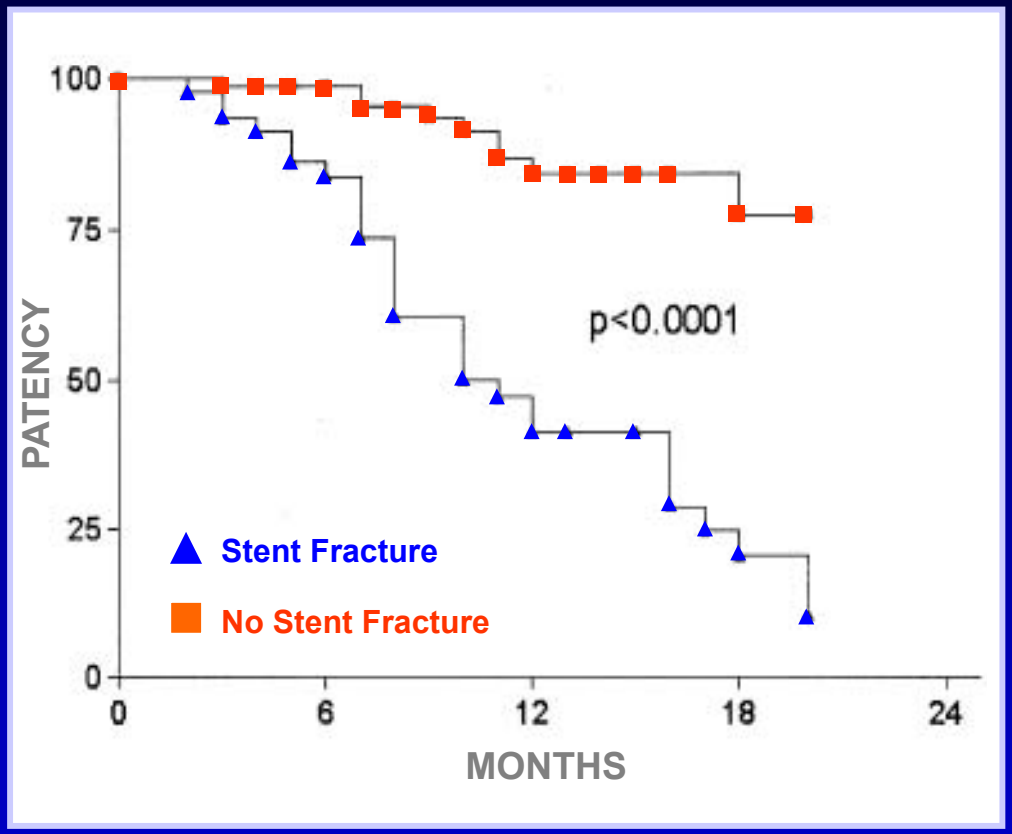
- Dynamic nature of the artery treated
- Metal fatigue
  - Fracture
- Inherent restenosis
- Outflow issues



6 mo *2 yr*

Clinical Implication of Stent Fractures





Prevalence and Clinical Impact of Stent Fractures after Femoropopliteal Stenting. Scheinert *et al*. JACC Vol. 45, 2:312-5, 2005

Covered SES

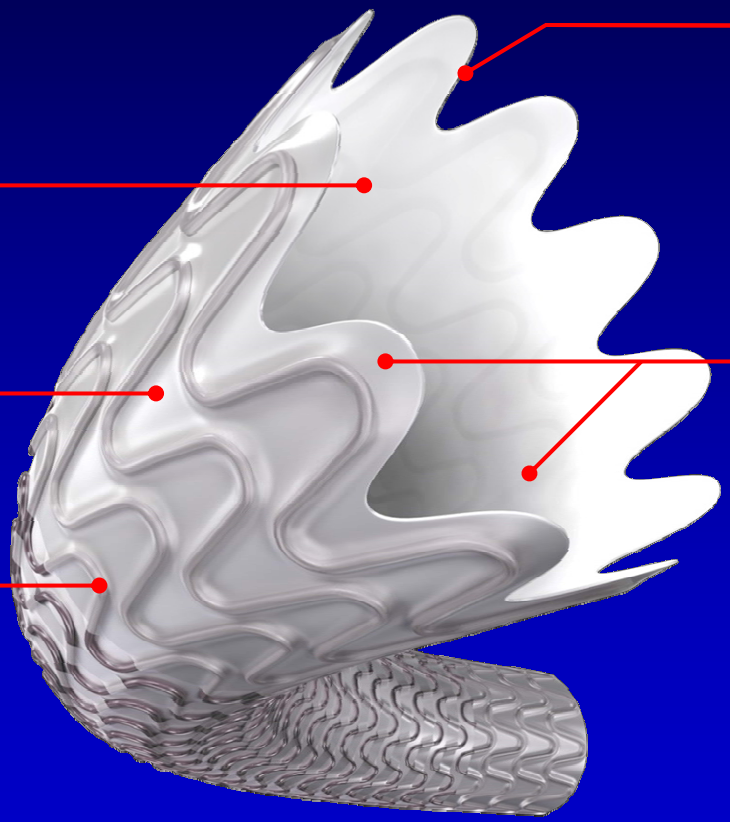
- Single center data
  - Primary patency 85%
    - Wiesinger *JEnvTher* 2005
    - Saxon *JVIR* 2003
    - Farraj *JIC* 2009
- Randomized trial VIBRANT recently completed
  - Results presented VIVA 2009
- “percutaneous bypass”

VIBRANT

- 148 patients (72/76)
- Lesion length 19cm
- Total occlusions 59%
- Primary patency
  - Viabhan 53%
  - SES 58%
- Restenosis
  - Viabhan
    proximal 50%
    distal 6%
  - 9 CTO's at f/u
    - 2 with acute limb (non-covered)
- Fractures
  - Viabhan 1/47 (2%)
  - SES 16/52 (31%)

Ansel presentation *VIVA09 Oct2009*

VIPER



Contoured proximal edge

CARMEDA® Bioactive Surface (CBAS® Surface)

Ultra-thin wall ePTFE tube

Unique, durable bonding film

Polished nitinol support

Lengths: 2.5, 5, 10, 15 cm

Diameters: 5–8 mm

Lesion Characteristics

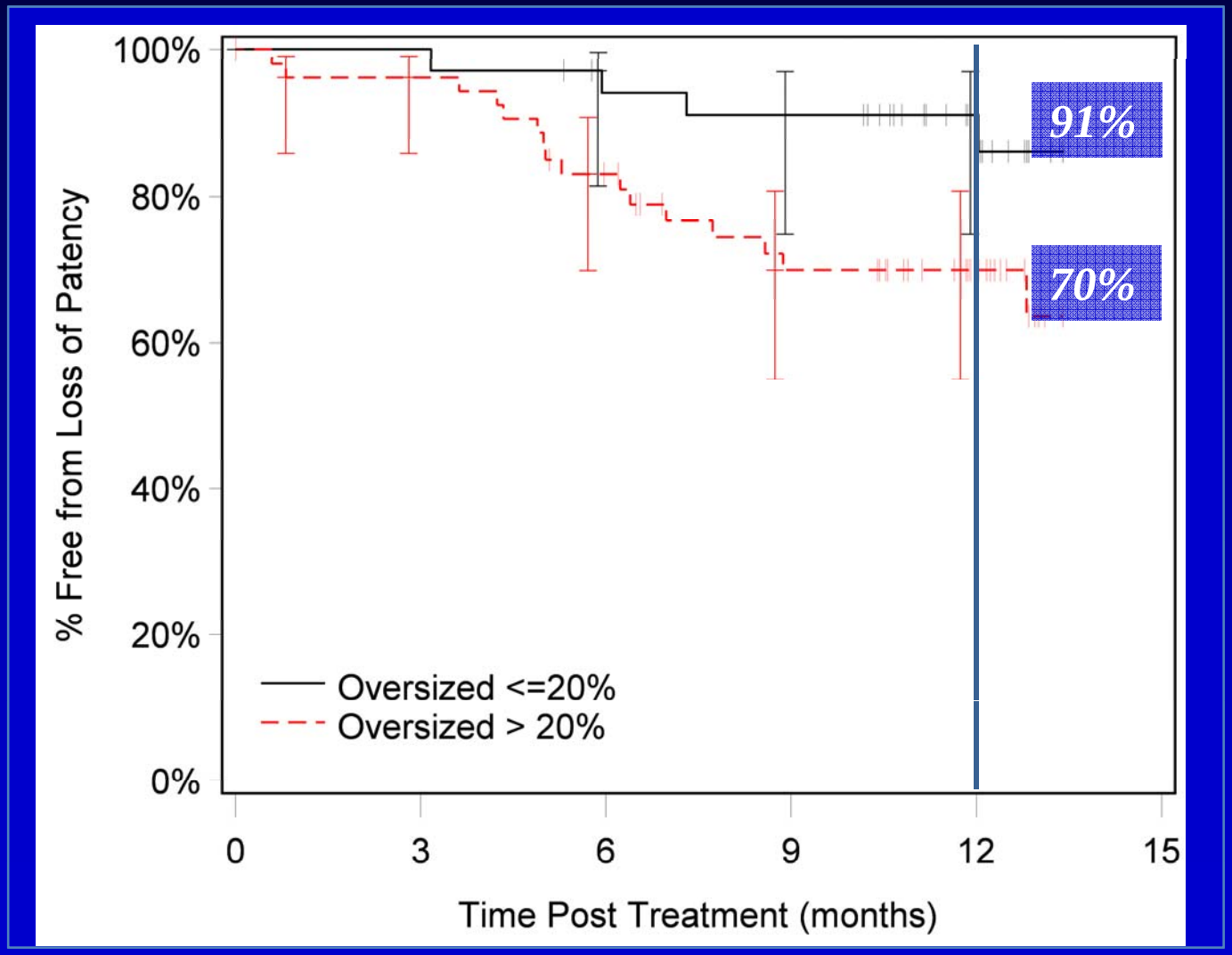
	Gore VIPER Clinical Study
Patients Enrolled	**119**
Treated Occlusions	**56%**
Lesion Length	**19 cm**
Lesion Calcification	
none-mild	**39%**
moderate-severe	**61%**
Tibial Runoff	
1 vessel	**21%**
2 vessel	**33%**
3 vessel	**46%**
Patients Enrolled	**119**

One patient excluded for treatment with device without heparin

One-Year Primary Patency by Subgroup

	Primary Patency
Overall	74%
Device Diameter	
5 mm (n= 23)	79%
6 mm (n= 85)	70%
7 mm (n= 8)	100%
Lesion Length	
≤ 20 cm (n= 68)	75%
> 20 cm (n= 51)	72%
Vessel Diameter at Landing Zone ≥ 4.0 mm by Core Lab (n= 53)	87%

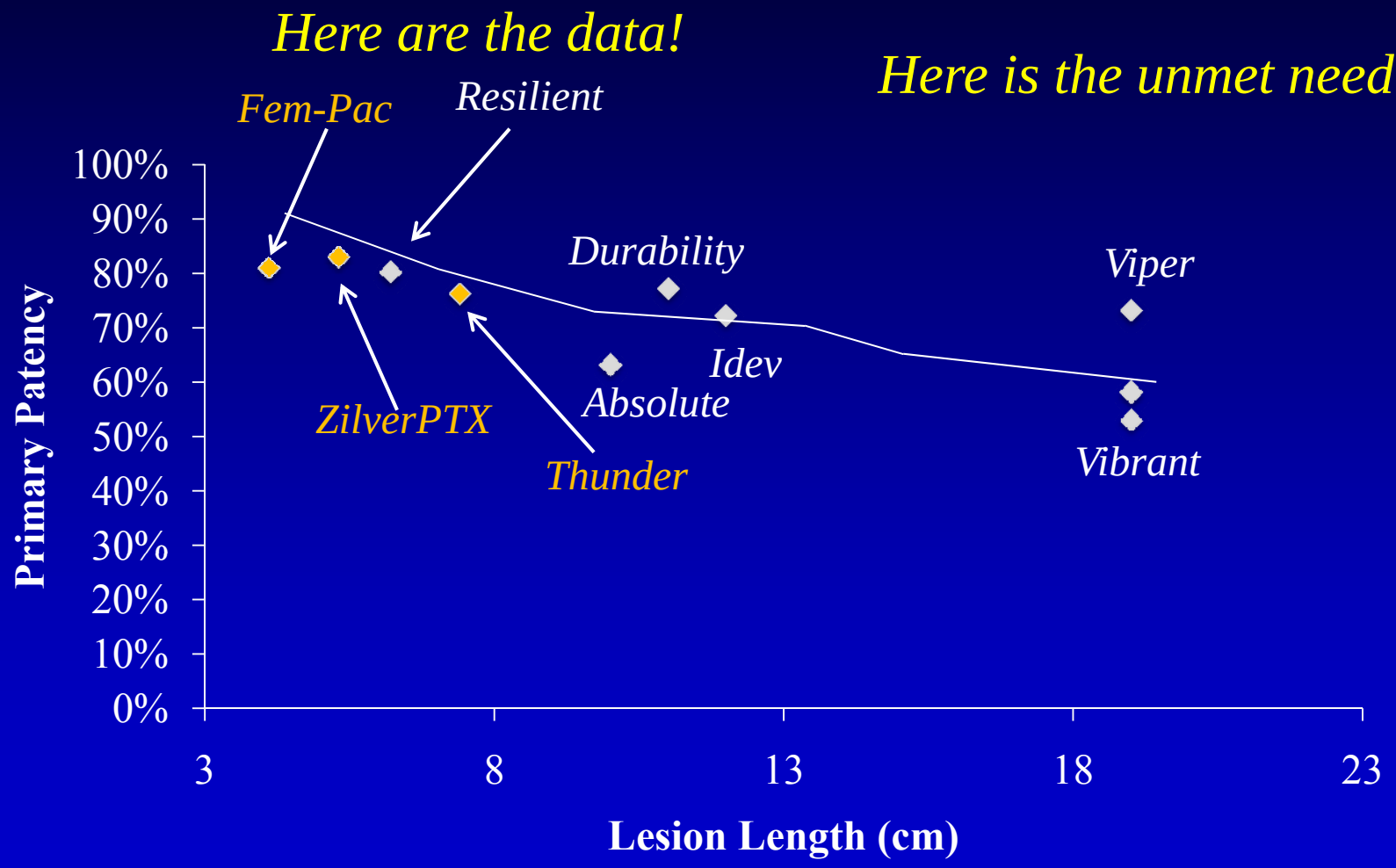
Effects of Device Sizing: Proximal



Current endovascular data

Trial	Patients (n)	Device	Lesion length (cm)	1 year primary patency (%)
MIMIC	81	PTA	NA	NA
ABSOLUTE	104	Stent	10.2	63
RESILIENT	137	Stent	5.7	80
VIBRANT	76	Stent graft	19.6	53
VIPER	119	Stent graft	19.3	70
ZilverPTX	240	DES-SES	5.3	84
THUNDER	75	DEB	7.4	74
LEVANT	50	DEB	8.1	78

Trial Outcomes 2012 at 12 months



Debulking Therapies

- Laser
- Rotational devices
- Directional atherectomy

Primary data

- Many registries with primary outcomes either, patency or safety
- Unfortunately, little primary data exists for primary patency of many atherectomy devices in a core lab driven trial/registry

Rotational devices

Pathway (rotational debulking)

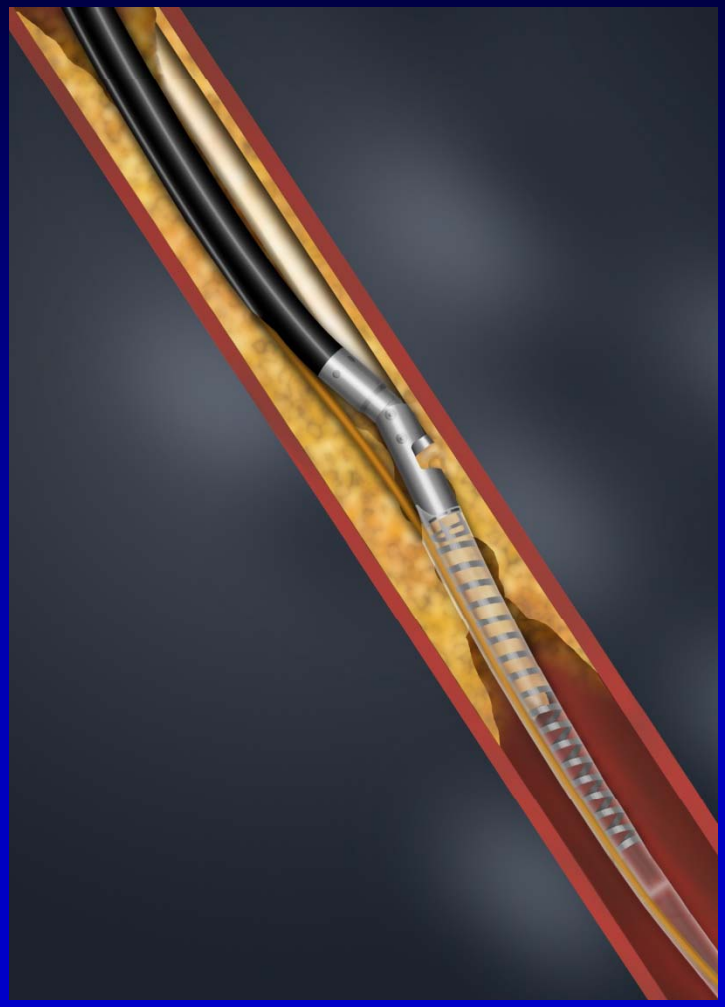
- Rotates, Aspirates, Adjunctive RX
- Early data- 4.9 cm
- JET registry will begin 2012

CSI (sanding debulking)

- Centrifugal force
  - Sands atheroma
  - Debris relatively small
    - <1-7 µm
- Offset burr determines diameter
- Oasis trial used for approval- 3.1 cm
- CONFIRM registry 3000 patients device safety, efficacy study

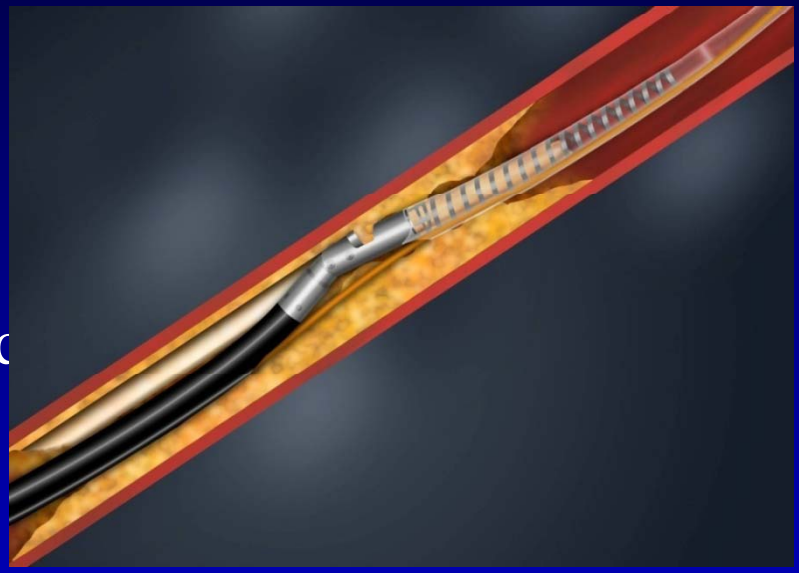
Plaque Excision

- DEFINITIVE LE completed enrollment
  - 800 patients /1200 lesions
  - RCC 1-6
  - Lesion Length ≤ 20 cm
- Definitive LE independent core lab driven data angiographic and ultrasound endpoints
- DEFINITIVE AR start date Q4 2011



Key Eligibility Criteria

- Inclusion Criteria
  - RCC 1-6
  - ≥ 50% stenosis
  - Lesion Length ≤ 20 cm
  - Reference Vessel ≥ 1.5 mm and
- Exclusion Criteria
  - Severe calcification
  - In-stent restenosis
  - Aneurysmal target vessel



Summary of all Lesions (Core Lab)

	Claudication (RCC 1-3)	CLI (RCC 4-6)	All Subjects (RCC 1-6)
Number of Patients	**599**	**201**	**800**
Number of Lesions	**737**	**274**	**1011**
Lesion Length Distribution (mean length-cm)			
10.0 cm and up (mean lesion length: 14.6)	**29.2% (215)**	**24.5% (67)**	**27.9% (282)**
4.0 to 9.9 cm (mean lesion length: 6.5)	**41.3% (304)**	**40.5% (111)**	**41.1% (415)**
Less than 4 cm (mean lesion length: 2.2)	**29.6% (218)**	**35.0% (96)**	**31.1% (314)**
Mean Longest Lesion per Subject - overall (cm)	**8.3 ± 5.4**	**8.3 ± 5.7**	**8.3 ± 5.4**
Mean Lesion Length – overall (cm)	**7.5 ± 5.3**	**7.1 ± 5.4**	**7.4 ± 5.3**

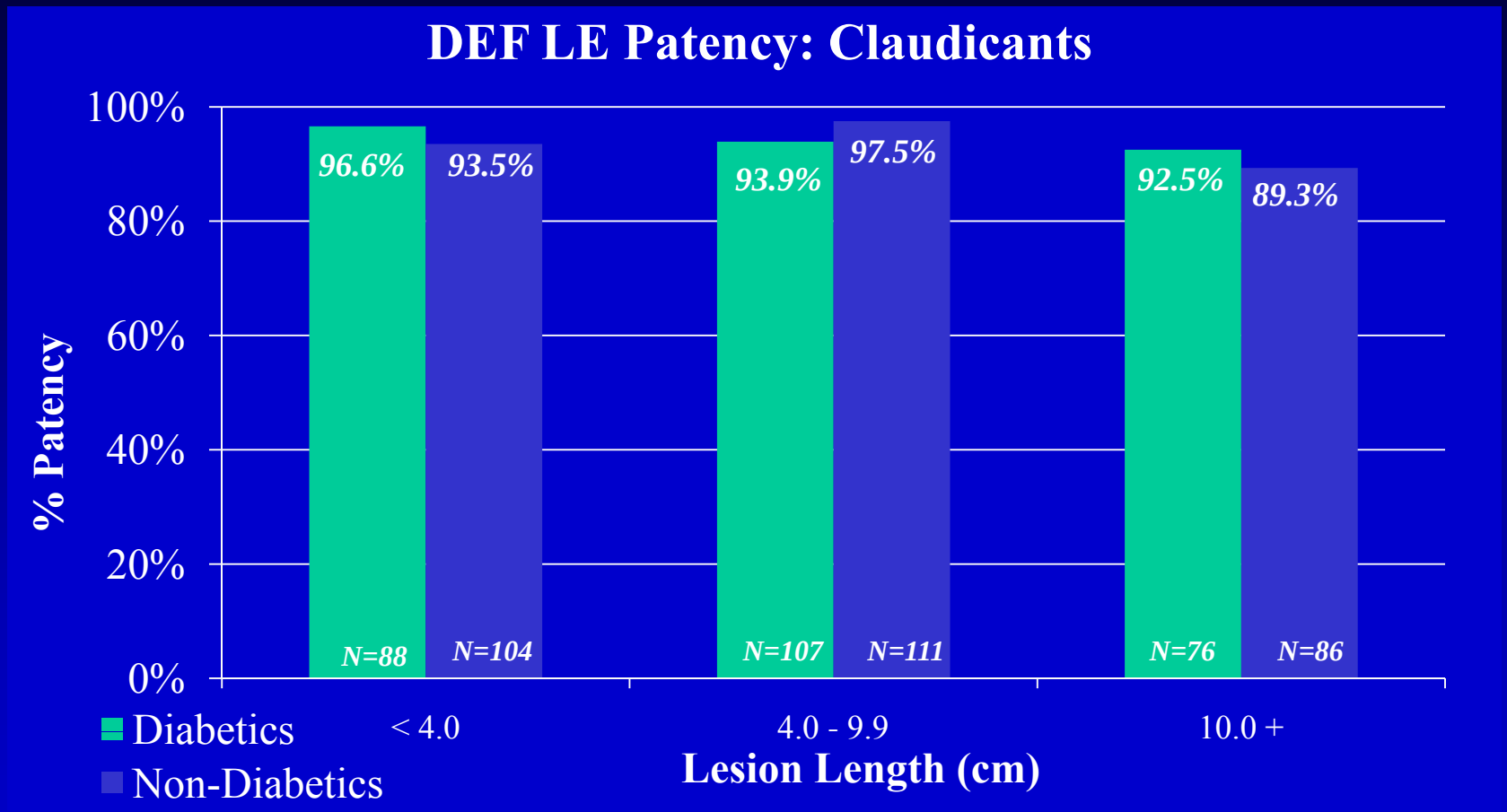
Lesion Length by Vessel (Core Lab)

	Claudication (RCC 1-3)	CLI (RCC 4-6)	All Subjects (RCC 1-6)
Mean Lesion Length by Vessel (cm)			
SFA	**8.2 ± 5.6 (n=532)**	**8.5 ± 6.1 (n=132)**	**8.3 ± 5.7 (n=664)**
Popliteal	**6.0 ± 4.0 (n=113)**	**5.5 ± 3.6 (n=47)**	**5.8 ± 3.9 (n=160)**
Infrapopliteal	**5.5 ± 4.1 (n=92)**	**6.0 ± 4.5 (n=95)**	**5.8 ± 4.3 (n=187)**
% Lesions in SFA	**72.2% (n=532)**	**48.2% (n=132)**	**65.7% (n=664)**
Mean Total SFA Burden (cm)	**9.2 ± 6.1 (n=474)**	**9.9 ± 6.8 (n=114)**	**9.3 ± 6.2 (n=588)**

6-Month Primary Endpoints

Endpoint / Cohort	180 days (6-month visit target)	210 days (End of 6-month window)
Primary Patency (lesions)	Rate (# with endpoint data)	Rate (# with endpoint data)
All Claudicants (n=737)	94.1% (n=571*)	87.6% (n=485)
Diabetics (n=344)*	94.4% (n=274)	87.1% (n=232)
Non-Diabetics (n=393)*	93.7% (n=299)	88.1% (n=253)
Freedom from Amputation (patients)	Rate (# at risk)	Rate (# at risk)
All CLI Subjects (n=201)	97.3% (n=143)	97.3% (n=129)

180-Day Primary Patency, Claudicants by Lesion Length (Core Lab)

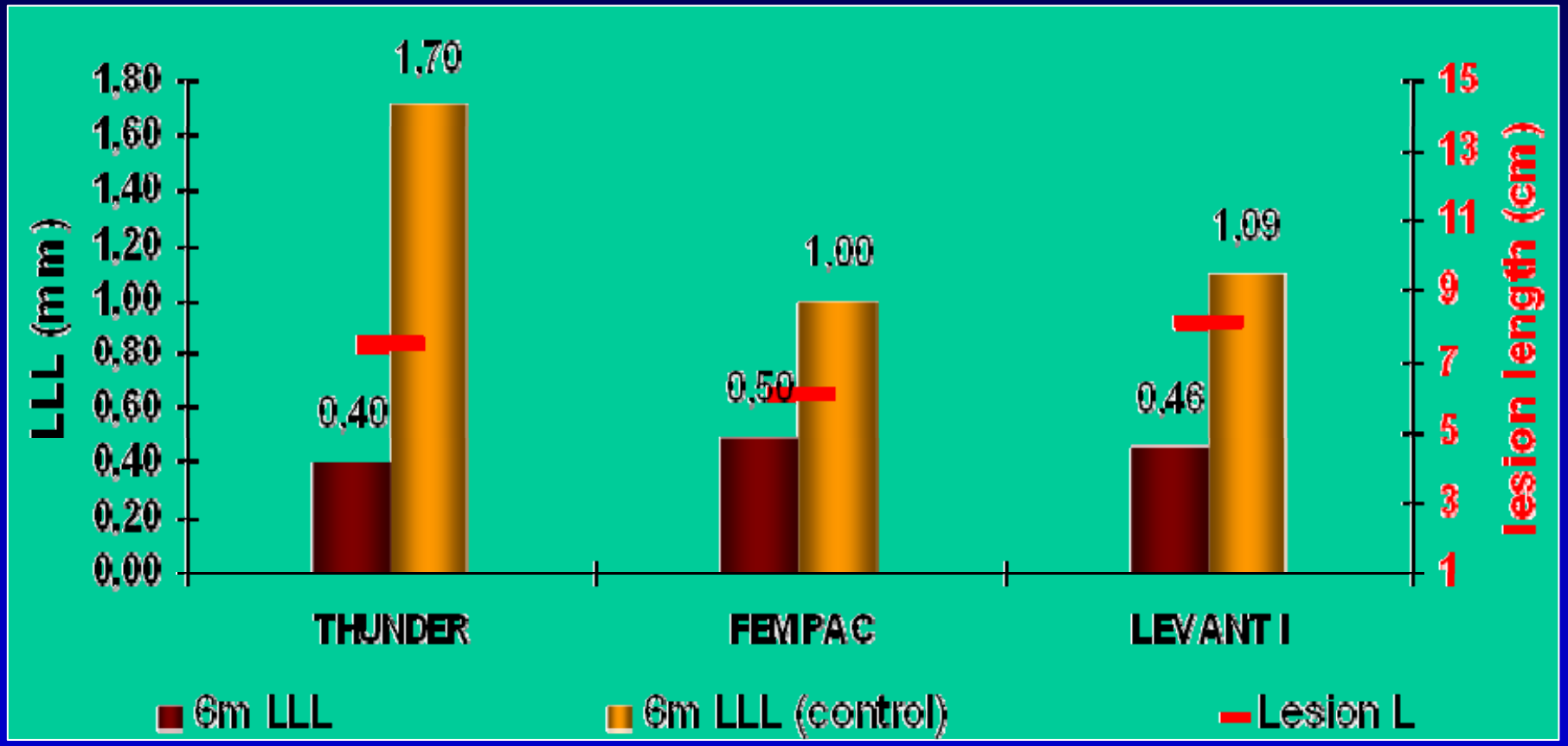


Future Directions

Is this the “Holy Grail”?

DEB in Femoro-popliteal Lesions

Summary 6-Months LLL Outcomes

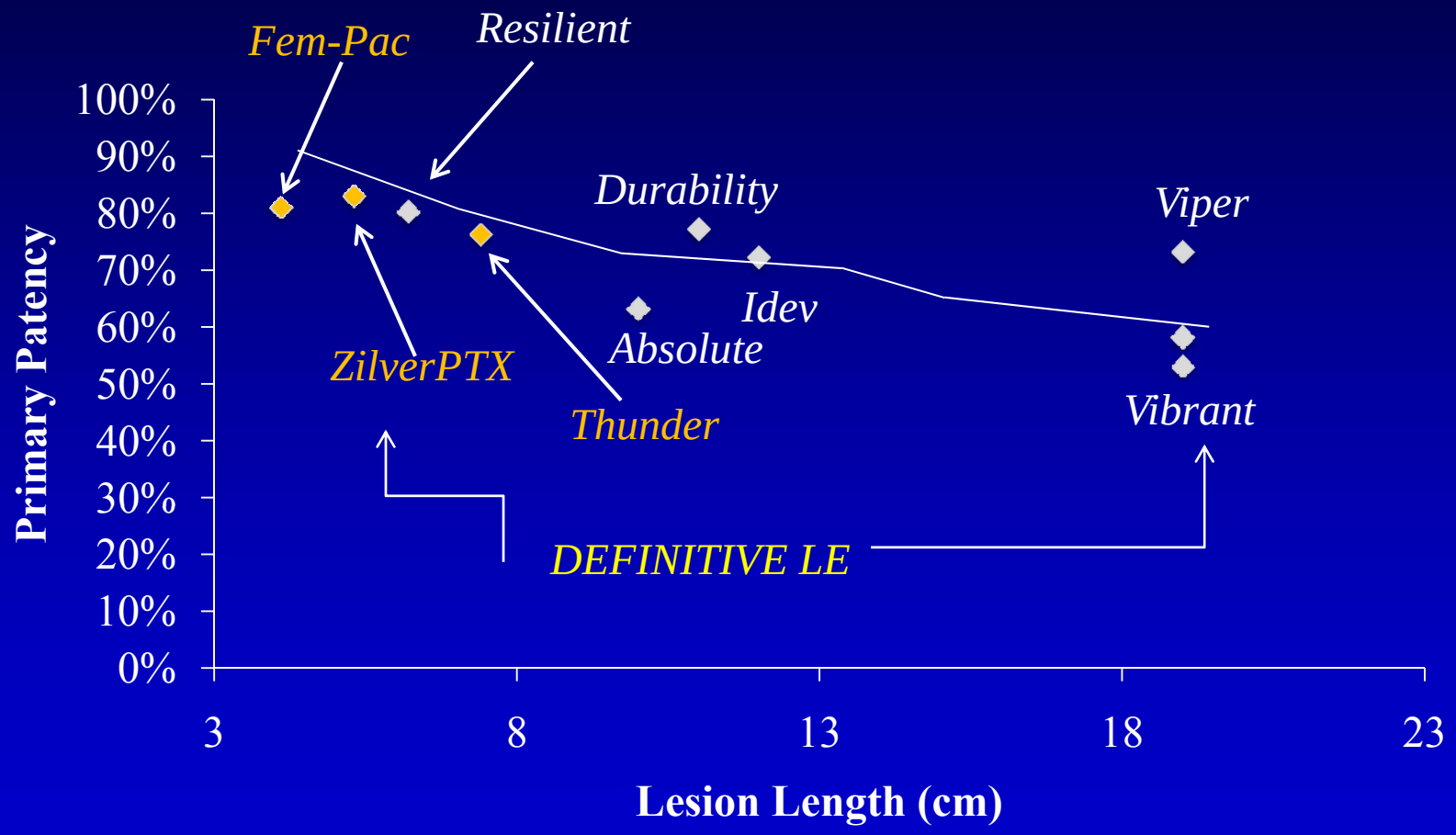


Devices not yet approved in the US

Infra-inguinal revascularization

- Primary patency stenting
  - Long lesions (>10cm)
    - PTA ?<30%
    - Stenting 58-63%
      - Fractures 2-7%
    - Covered stenting 53%
    - DES ??
  - Short lesions (<10cm)
    - PTA 64%
    - Stenting 80%
      - Fractures 2-7%
    - Covered stenting 85%
    - DES 83%
  - Combined therapy No data
- Primary patency alternative Rx
  - Athero-ablative
    - Short lesions ??
    - Long lesions NA
    - Adjunctive Rx ??
  - Rotational atherectomy
    - Short lesions ?50%
    - Long lesions NA
    - Adjunctive Rx ??
  - Directional atherectomy
    - Short lesions >80%
    - Long lesion >?70
    - Adjunctive Rx ??
  - Combined therapy No data

Trial Outcomes 2012 at 12 months



What's the benchmark?

- Unfortunately, current stent data limited to TASC A and B
- DES gain was 4% at 1 year compared with similar 5 cm lesion BMS
- "real world" SFA lengths VIBRANT 53/58% primary patency at 12 months, VIPER 70% with "improved" stent graft technology
- Non-stent technologies, only directional atherectomy has future data coming
  - Preliminary data will include TASC A-C lesions
- Current data would suggest stent technology default therapy with potential repeat revascularization likely
- Alternative therapies, i.e. directional atherectomy, outcomes will be reported shortly. Supplanting stenting will depend on the outcome of the trials
- Combined therapy(s) appears appealing though untested may represent the future benchmark