Treatment Strategies for Peripheral In-Stent Restenosis

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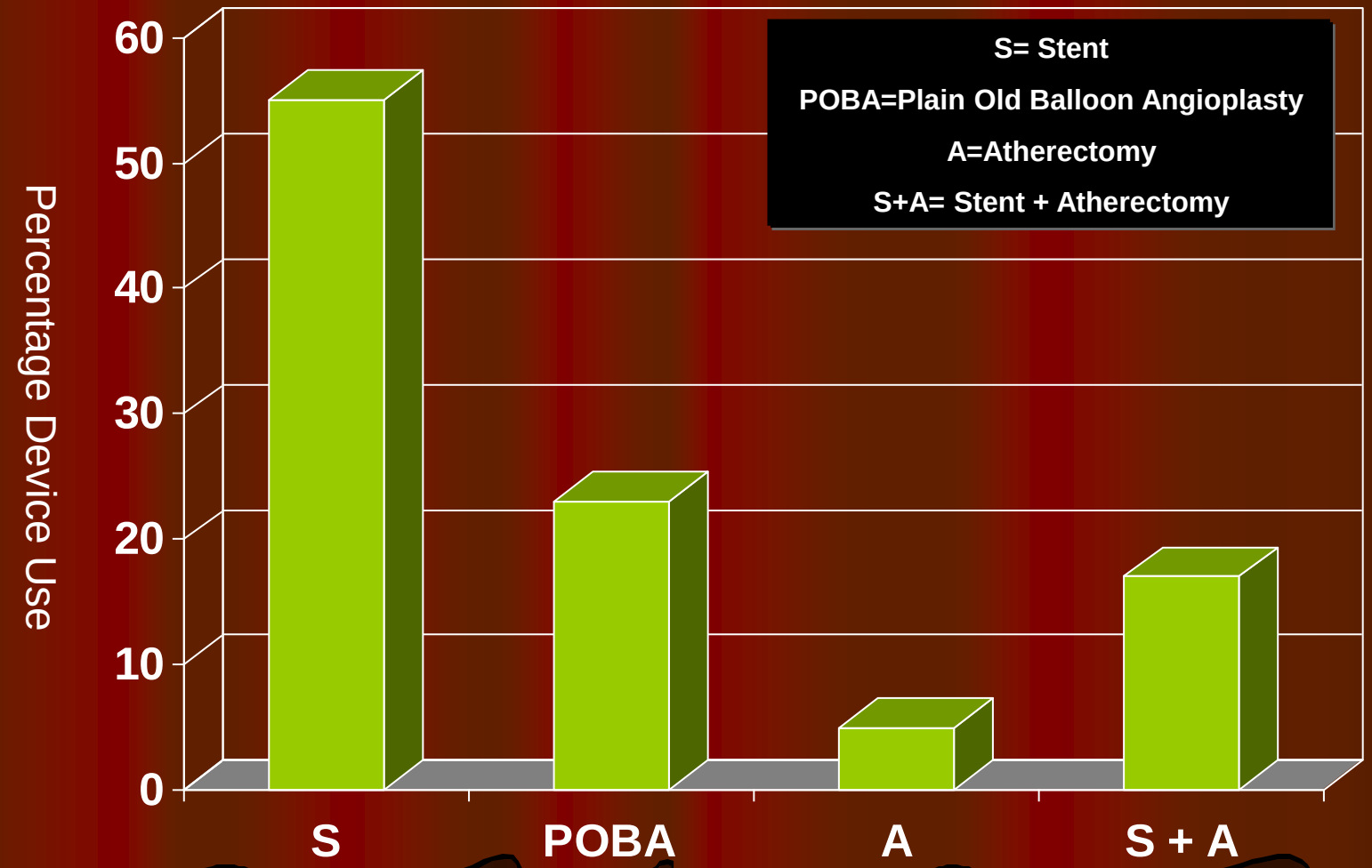
- No equities or bonds in any pharmaceutical or device company

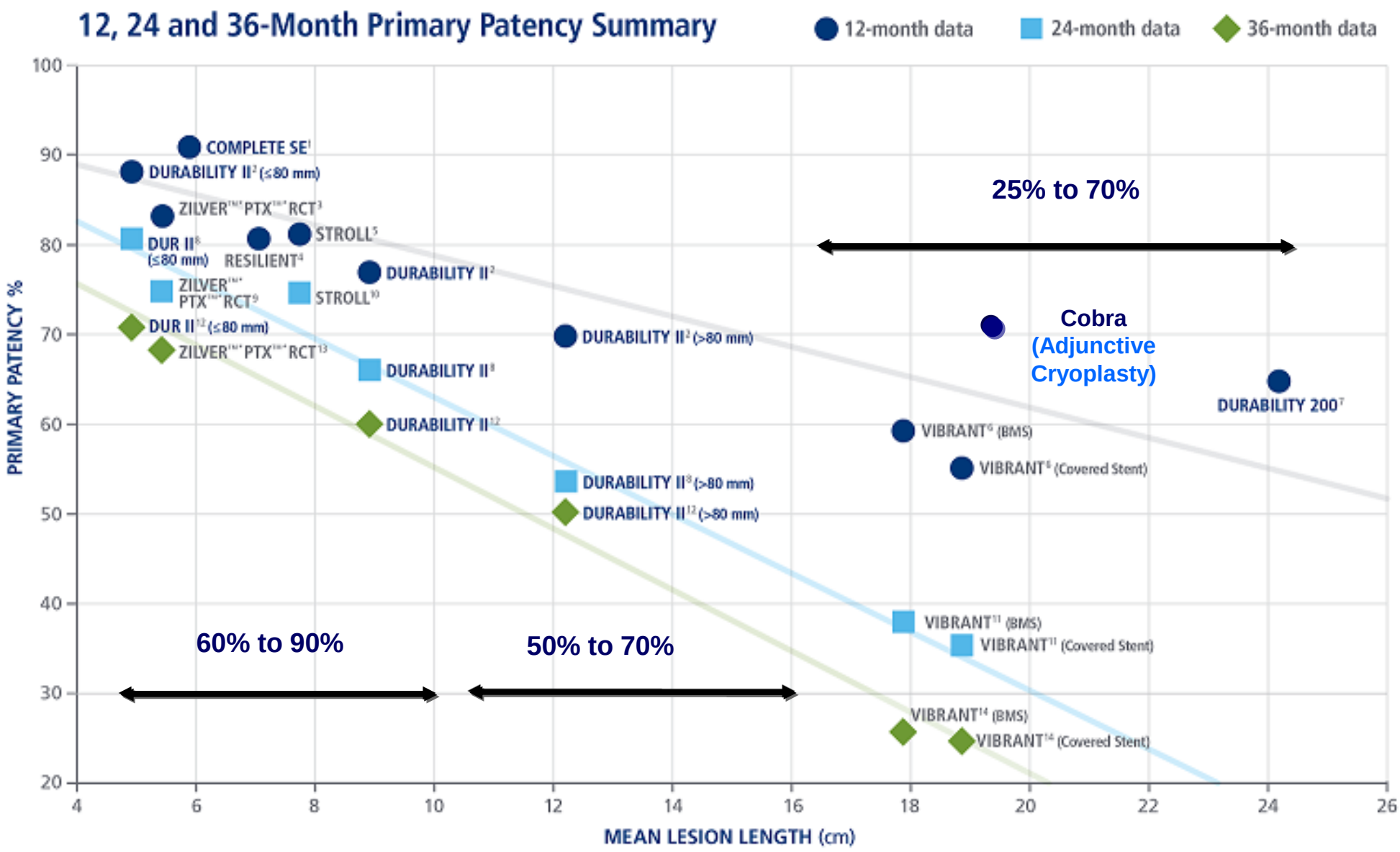
Objectives

- Define the problem of in-stent restenosis (ISR) in FP interventions (The Problem)
- Describe procedural strategies in treating FP ISR and their outcomes (Acute Rx)
- Discuss various options in addressing recurrent restenosis in patients treated for FP ISR (Long term results)

Current Device Application in Treating FP lesions



US Peripheral Device Market, 2012



Modified from Source: COVIDIEN

One-Year TLR in Randomized SFA trials

Mechanisms of ISR

- Vascular injury (Barotrauma)
  - Endothelial loss (early response. Days)
    - Platelet adherence, activation and aggregation…thrombus formation
  - Smooth muscle cell proliferation (intermediate response. Weeks)
  - Extracellular matrix production (delayed response. Months)
- Recoil and negative remodeling has no significant role in ISR (important mechanisms of restenosis in POBA)
- Clinical and angiographic risk factors:
  - DM, CRI, lesion length, TASC D vs ABC, CRP, Poor runoff, Calcification

Mechanisms of ISR

- Other possible mechanisms
  - Stent fracture
  - Stent Design and strut thickness
  - Stent overlap
  - Barotrauma of adjunctive angioplasty post stent
  - Poor stent expansion in calcified vessels
  - Thrombosis (almost all total ISR occlusions are thrombotic-restenotic)
  - Slow flow in the distal vascular beds
  - Smaller vessel size

Restenosis after FP Stenting

- Progressive problem
- Requires repeat revascularization
- Restenosis of long lesions are the "Achilles heel" of FP interventions
- Several strategies to acutely treat FP restenosis but long term outcome is relatively poor with reduced patency and high TLR

Strategies to treat FP ISR

- POBA
- Cutting Balloon
- Atherectomy
- Cryoplasty
- Radiation therapy
- Drug coated balloons
- Restenting
  - Bare metal stent
  - Drug eluting stents
  - Covered stent

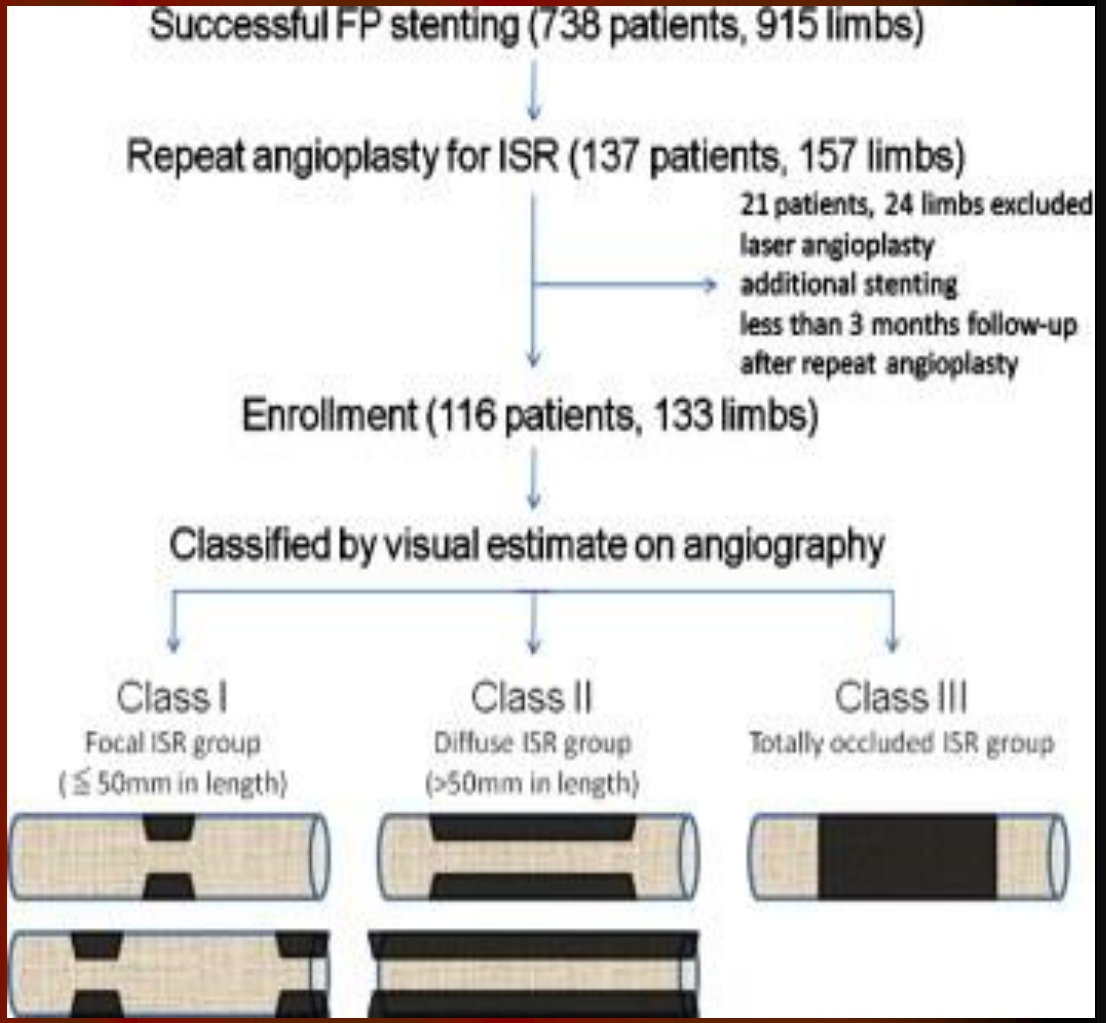
Classification of Restenosis After Femoropopliteal Stenting

multicenter, retrospective observational study
133 restenotic lesions after FP artery stenting

classified by angiographic pattern:
class I included focal lesions (≤50 mm in length),
class II included diffuse lesions (>50 mm in length)
class III included totally occluded ISR.

All patients were treated by POBA for at least 60 s

Restenosis was defined as
>2.4 of the peak systolic velocity ratio
>50% stenosis by angiography.



Tosaka A et al. J Am Coll Cardiol 2012;59:16-23

Classification and Clinical Impact of Restenosis After Femoropopliteal Stenting

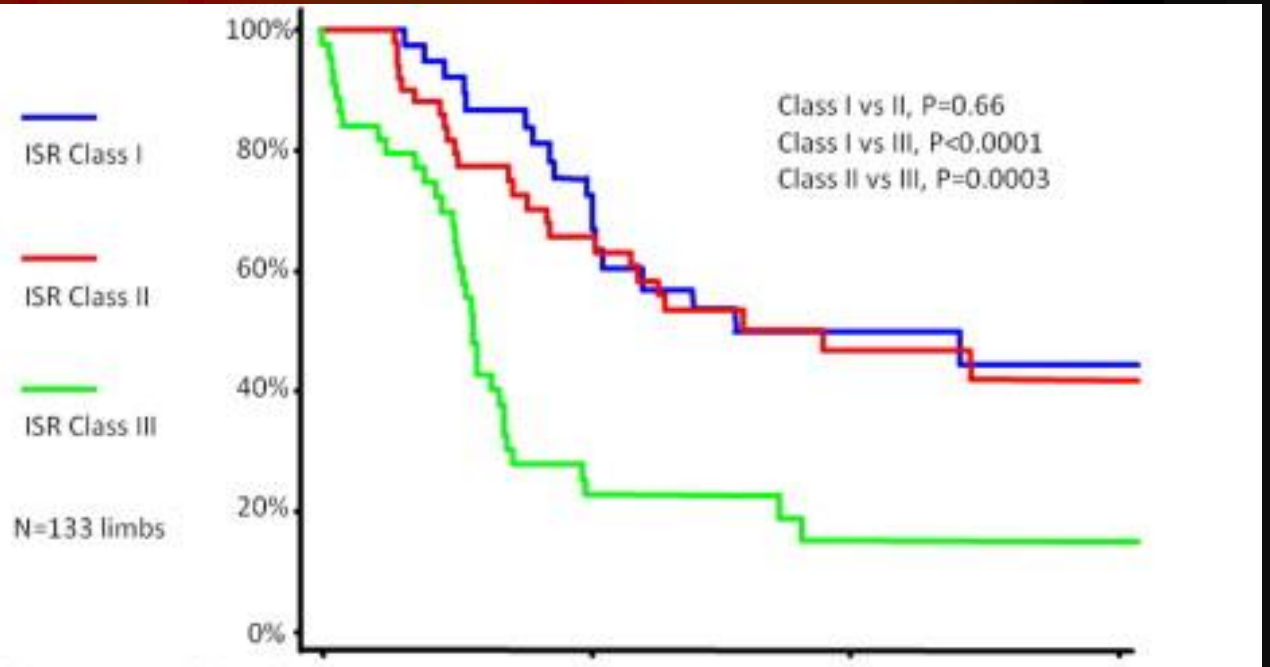
Class I pattern was found in 29% of the limbs,
class II in 38%
class III in 33%

Mean follow-up period was 24 ± 17 months.

All-cause death occurred in 14 patients
bypass surgery was performed in 11 limbs

Rate of recurrent ISR at 2 years was
84.8% in class III
53.3% in class II
49.9% in class I

Recurrent occlusion at 2 years was
64.6% in class III
18.9% in class II
15.9% in class I



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 A et al. J Am Coll Cardiol 2012;59:16-23

POBA vs Cutting Balloons

FP ISR >50% , single center, prospective, randomized, controlled trial, up to 20 cm Lesion length

CBA was performed in 22 patients

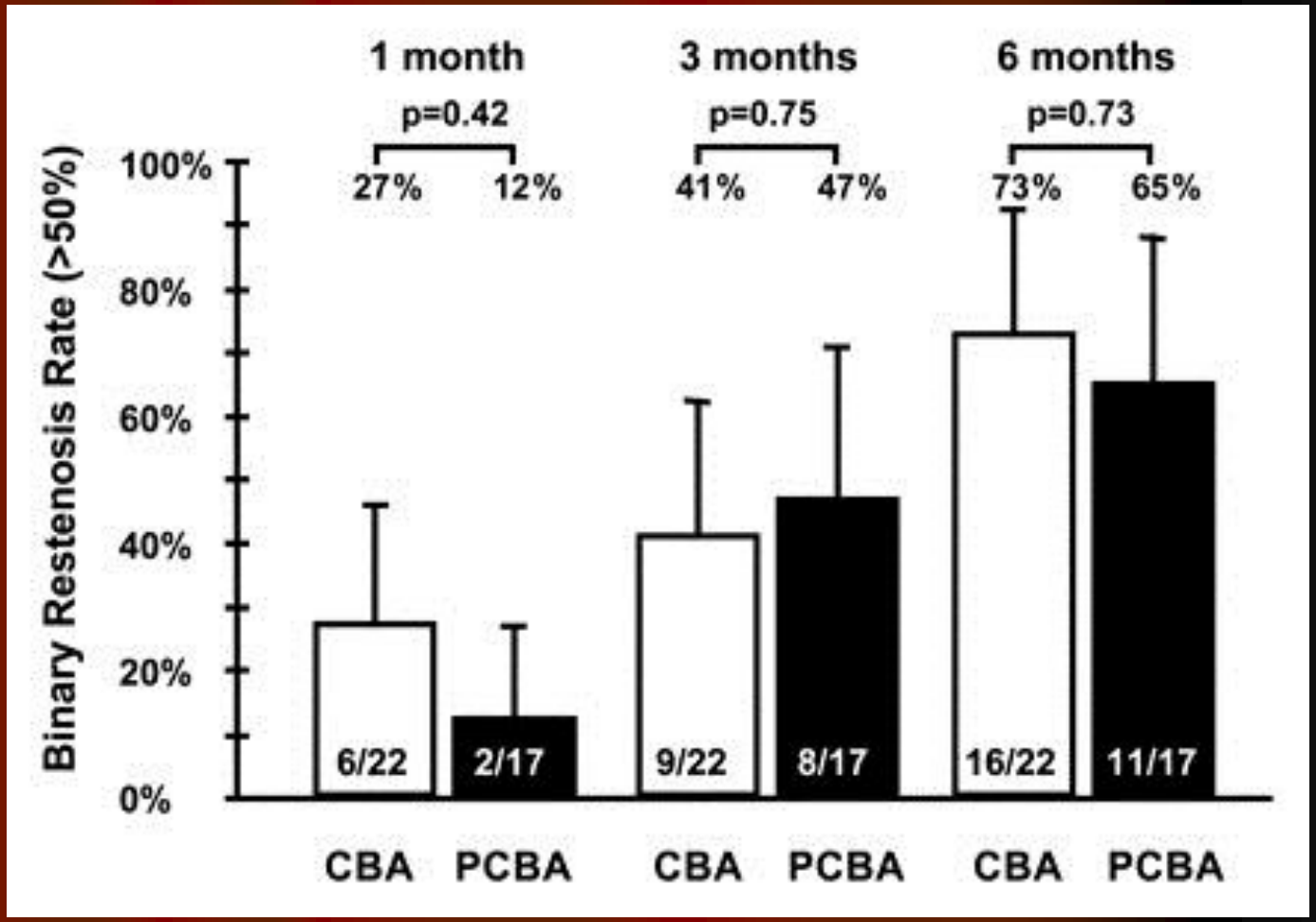
PCBA was used in 17 patients.

Average lesion length was 80 mm +/- 68

Acute stent thrombosis and stent fracture Were not included

Technical success was defined as a residual stenosis of less than 30%

Restenosis defined as PSVR≥ 2.4



Dick et al. Radiology 248;297-302, 2008

Cryoplasty for ISR

10 pts with FP ISR
Twelve cryoplasty procedures
All procedures were successful

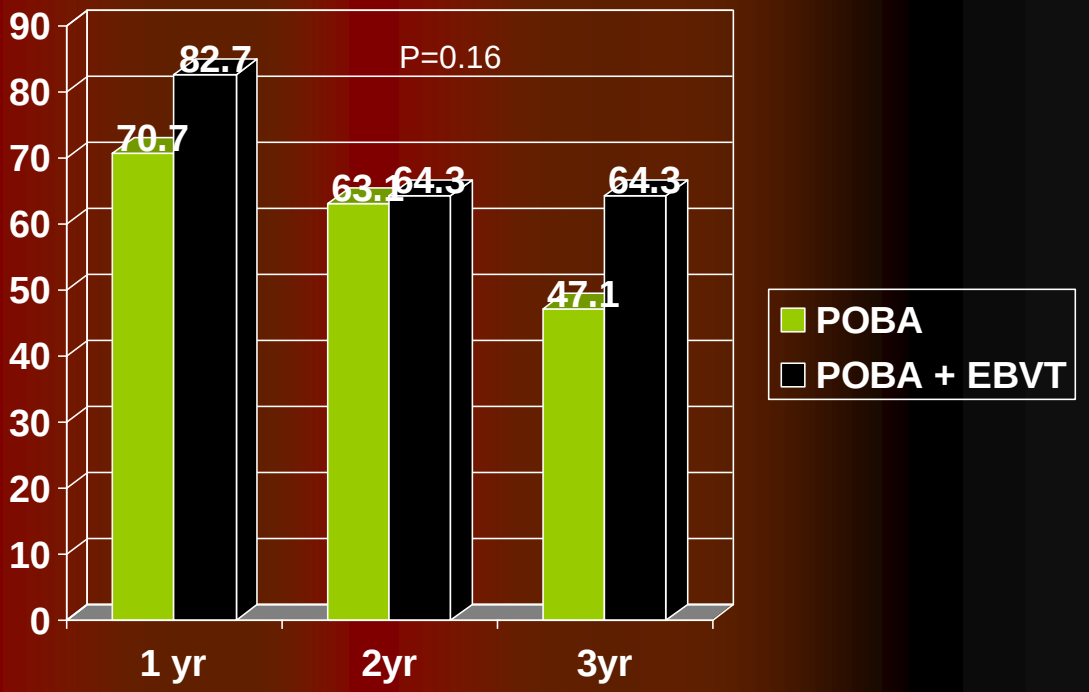
Patency 50% at 6 months
All vessels occluded at 1 year

Cryoplasty is of no value in patients with restenosis in the iliofemoral segment with half the procedures failing within six months and all of them within the first year. Evidence to support the use of cryoplasty in the peripheral arterial restenotic lesions is lacking

Karthik S. Eur J Vasc Endovasc Surg. 2007 Jan;33(1):40-3

Patency after Brachytherapy for FP Restenosis

- 79 patients treated with EVBT for recurrent femoropopliteal lesions
- Clinical follow-up at 1, 3, 6, and 12 months and annually
- clinical follow-up was 32.3+/-21.5 months
- Clinical success rates at 1, 2, and 3 years, respectively, were 84.3%, 82.1%, and 76.4% after BA versus 82.4%, 69.8%, and 67.5% after BA+EVBT (p=0.26 by log-rank)
- Long term patency was not different from POBA alone



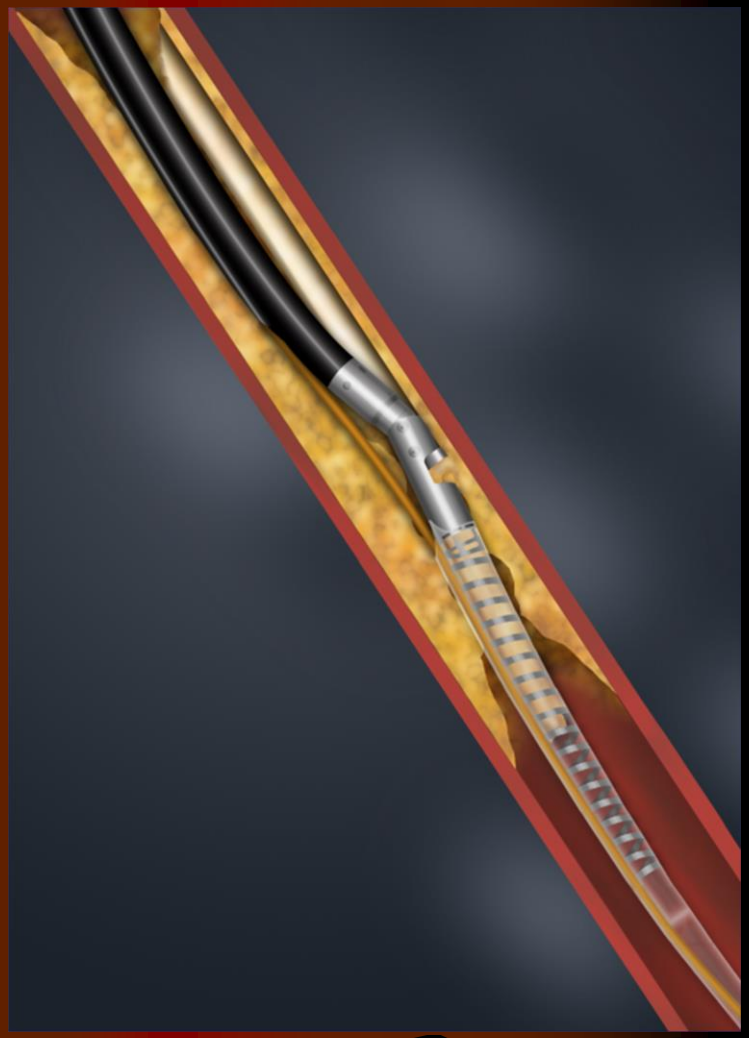
Diehm et al. J Endovasc Ther. 2005 Dec;12(6):723-30.

SilverHawk Atherectomy

Plaque Excision System

Remove plaque by directional atherectomy

Tiny laser-drilled nosecone holes for tissue collection and Removal



Intima-Media Thickness following Silverhawk Atherectomy vs PTA for FP ISR

Randomized, controlled, pilot trial

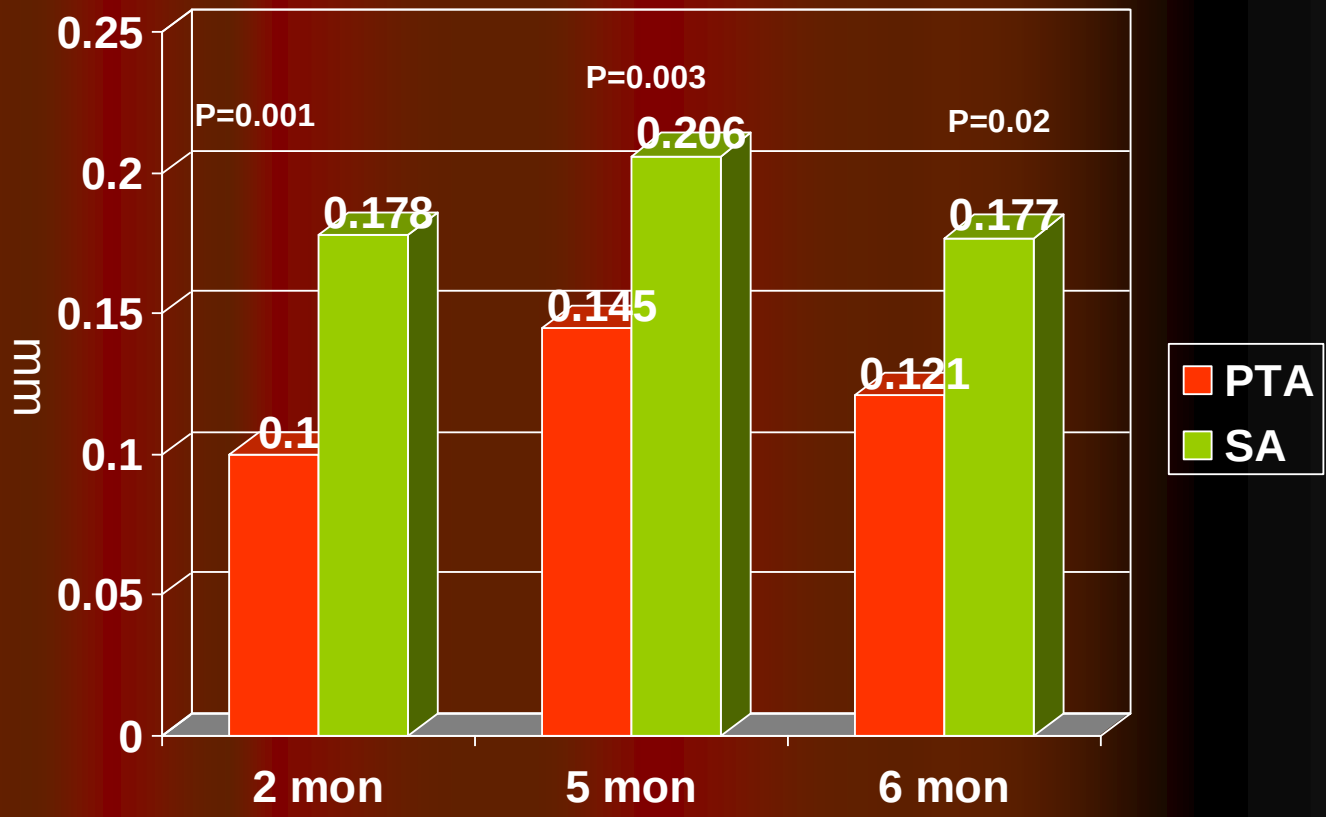
Total 19 patients

9 patients in the atherectomy device

10 patients in the PTA arm

Primary endpoint:
Intima-media thickness
within the treated segment

SA did not perform better than PTA



Brodmann et al. Cardiovasc Intervent Radiol. 2013;36:69-74

Patency of FP segments after Silverhawk atherectomy for ISR

35 lesions in 33 patients

Primary endpoint : treatment success (<50% residual stenosis) and no complications.

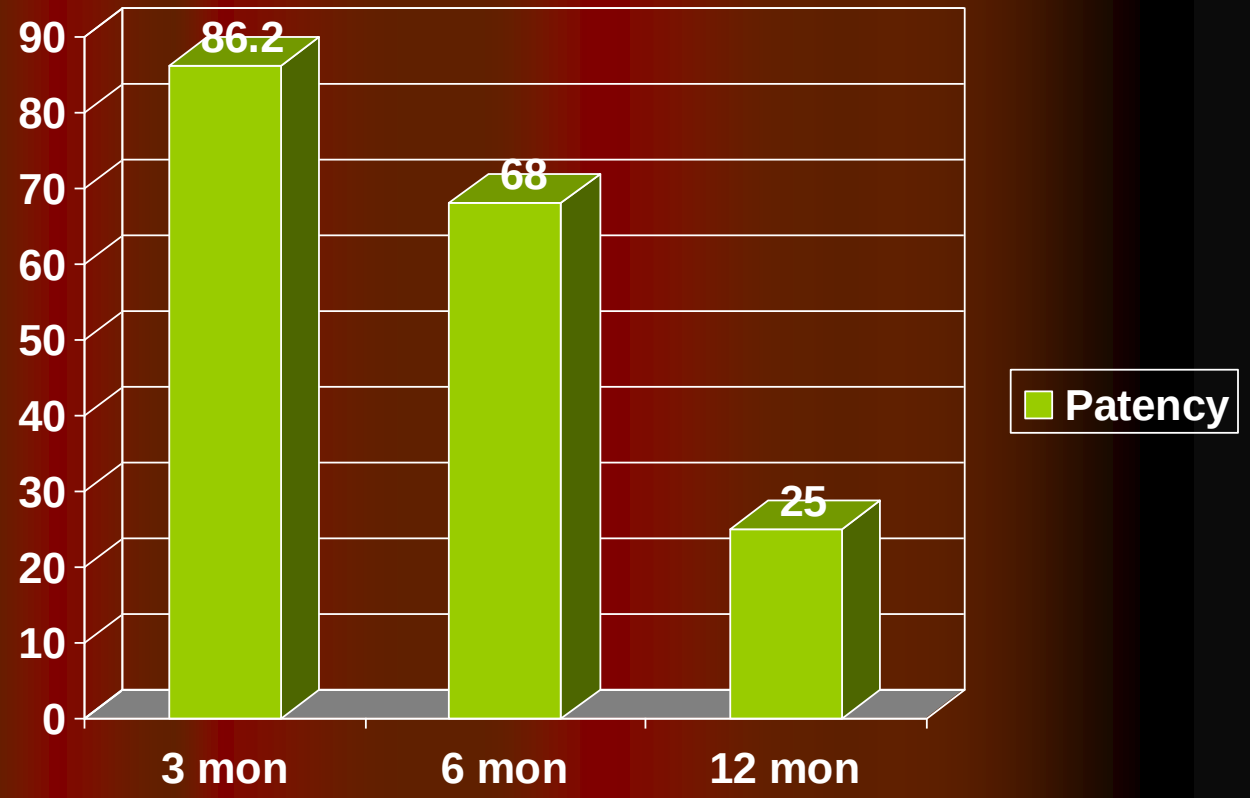
Secondary endpoint : patency as assessed by duplex ultrasound

Mean lesion length 10.8 cm

Atherectomy with adjunctive PTA success 97%

Adjunctive stent implantation 11%

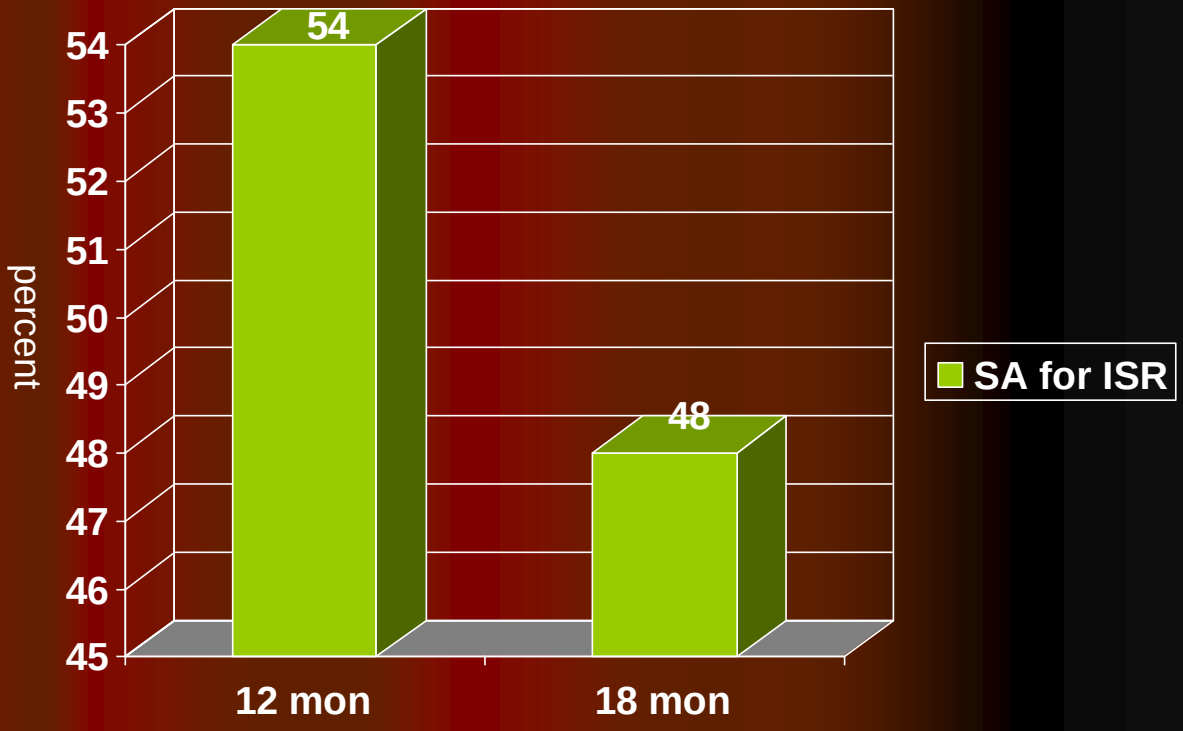
major complication was 18% (6/34), mainly due to distal embolization.



Trentmann J et al. J Cardiovasc Surg (Torino). 2010;51:551-60.

Patency of FP segments after Silverhawk atherectomy for ISR

- 43 limbs with FP ISR
- Mean lesion length **13.1 cm**
- Additional low pressure balloon inflation in 59%
- Primary patency at 12 months: 54%
- Primary patency at 18 months: 49%



Zeller T et al. J Am Coll Cardiol. 2006;48:1573-8

Target Vessel revascularization after SilverHawk atherectomy for ISR

41 consecutive patients in a retrospective registry

Follow-up: mean of 331.63 days

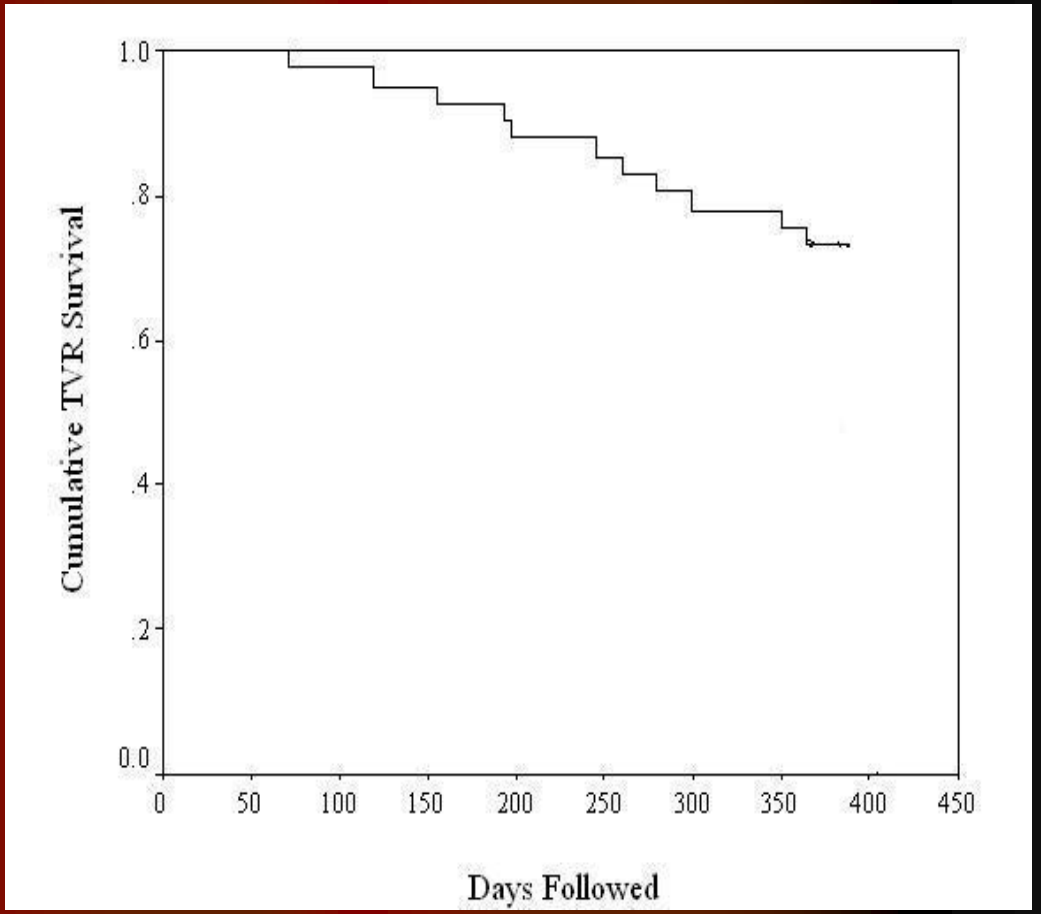
Adjunctive balloon angioplasty 97.6%

Embolic filter protection (EFP) 56.1% of patients.

Distal embolization (DE) requiring treatment 7.3%
Bailout stenting was 24.4%

Acute procedural success occurred in 100%

TLR 31.7%
TVR 34.1%



Shammas NW et al. Cardiovasc Revasc Med. 2012;13(4):224-7

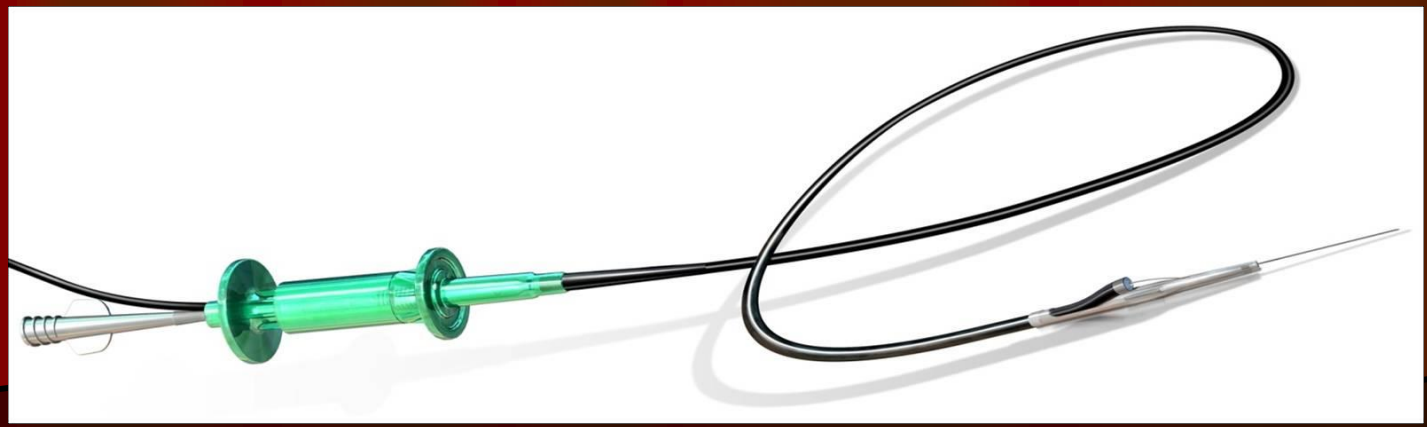
Laser atherectomy for ISR
Mechanisms of Action

Photoablation

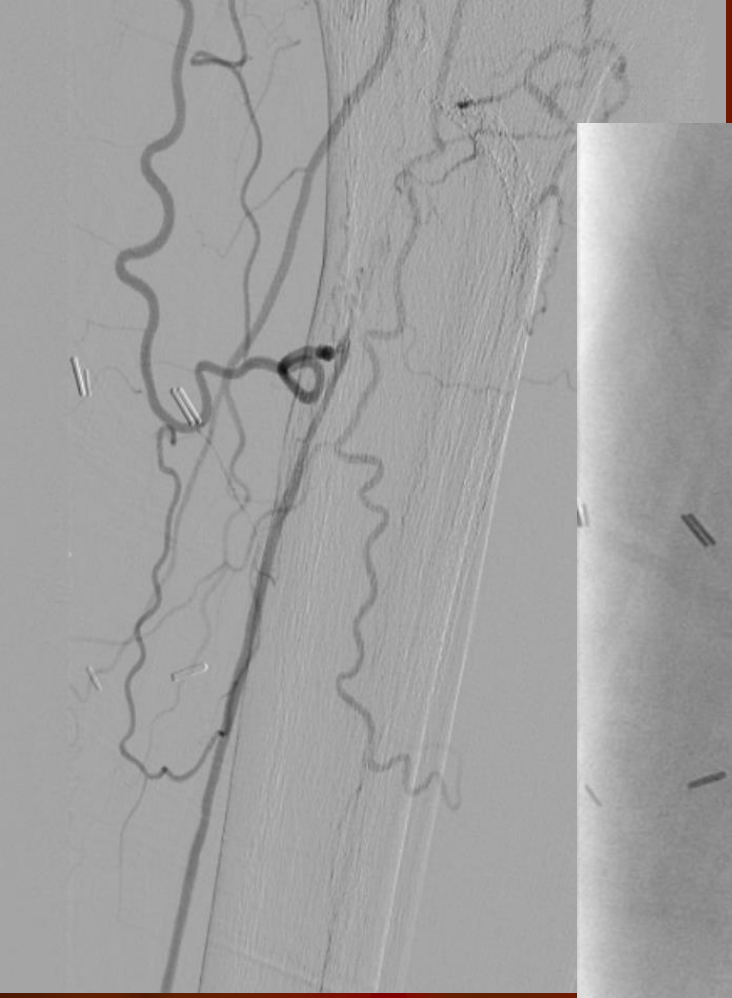
(1) Photochemical : disruption of cellular molecular bonds

(2) Photothermal: heat production with steam vapor disruption of cell membranes

(3) Photomechanical: dissipates cellular debris



Laser atherectomy of ISR of popliteal and AT



Patency Among PATENT FP ISR Study Patients at 1 year

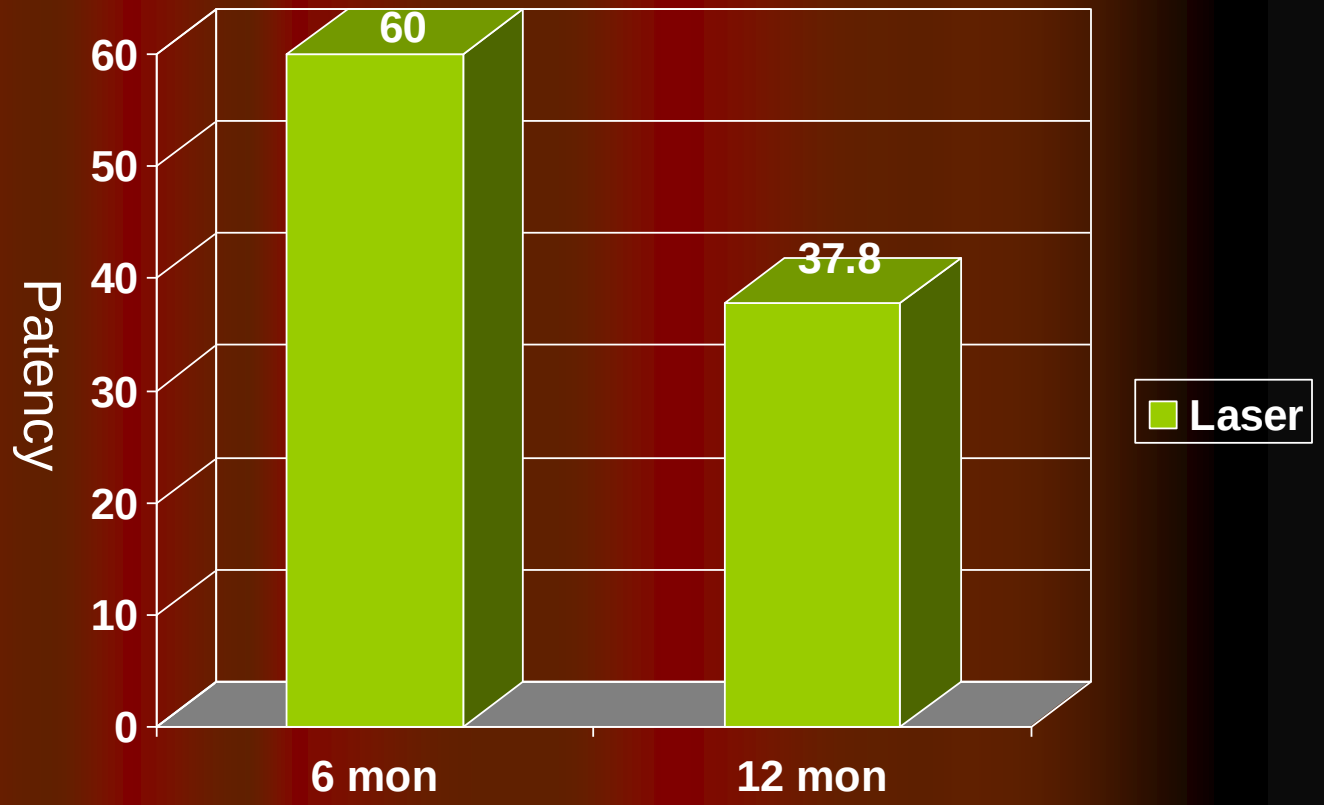
90 patients at five centers in Germany

Laser atherectomy for FP ISR

A nonrandomized prospective registry

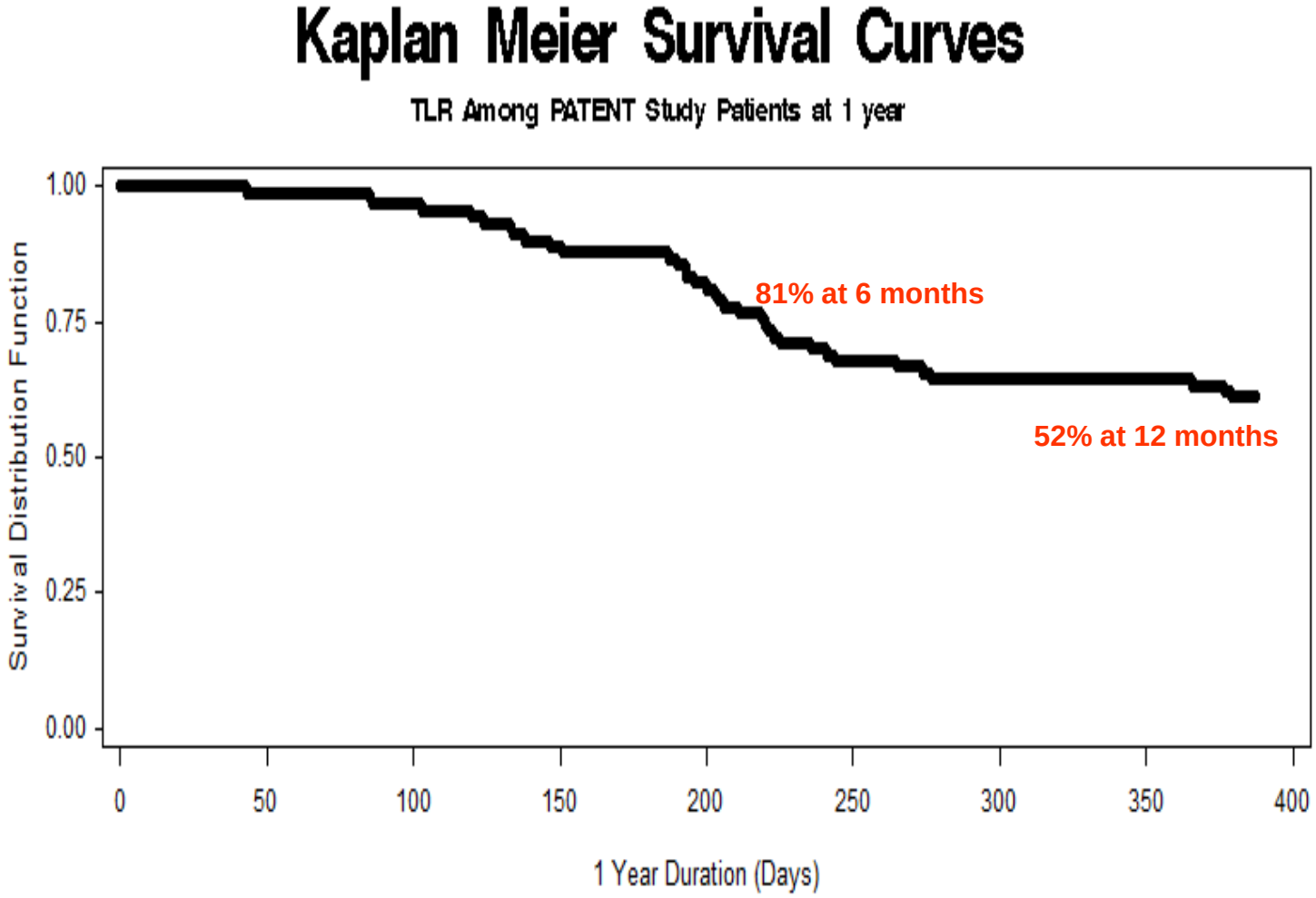
Average lesion length 10.9 cm

Procedural success rate of 98.8%



Zeller T et al. Leipzig Interventional Course (LINC) 2013

TLR Among PATENT FP ISR Study Patients at 1 year



Zeller T et al. Leipzig Interventional Course (LINC) 2013

TLR of FP segments after Laser atherectomy for ISR

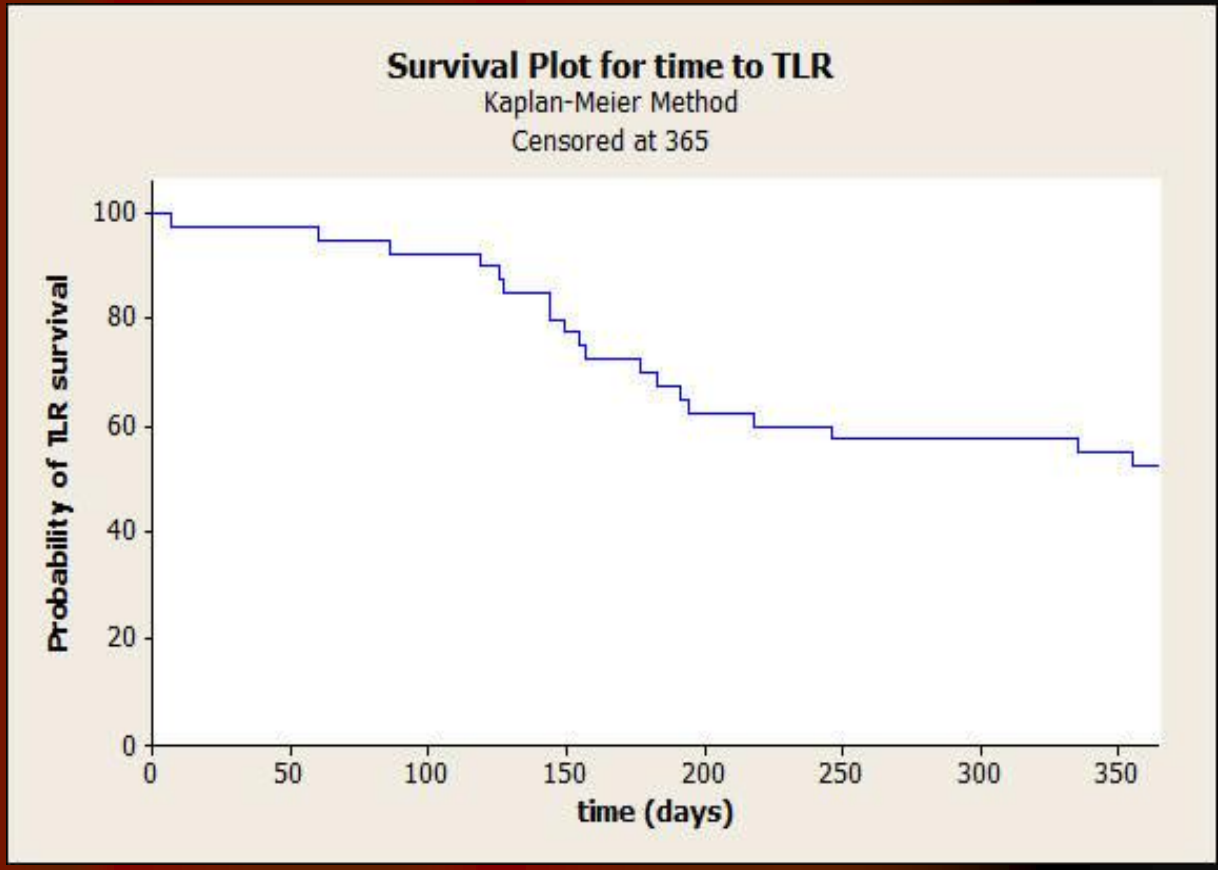
40 consecutive patients

Followed for 1 year

Adjunctive balloon angioplasty 100%

Acute procedural success 92.5%
Embolic filter protection was used in 57.5%
Bailout stenting was 50.0%
Macrodebris was noted in 65.2% of filters
Distal embolization requiring treatment 2.5%

TLR 48.7%
TVR 48.7%



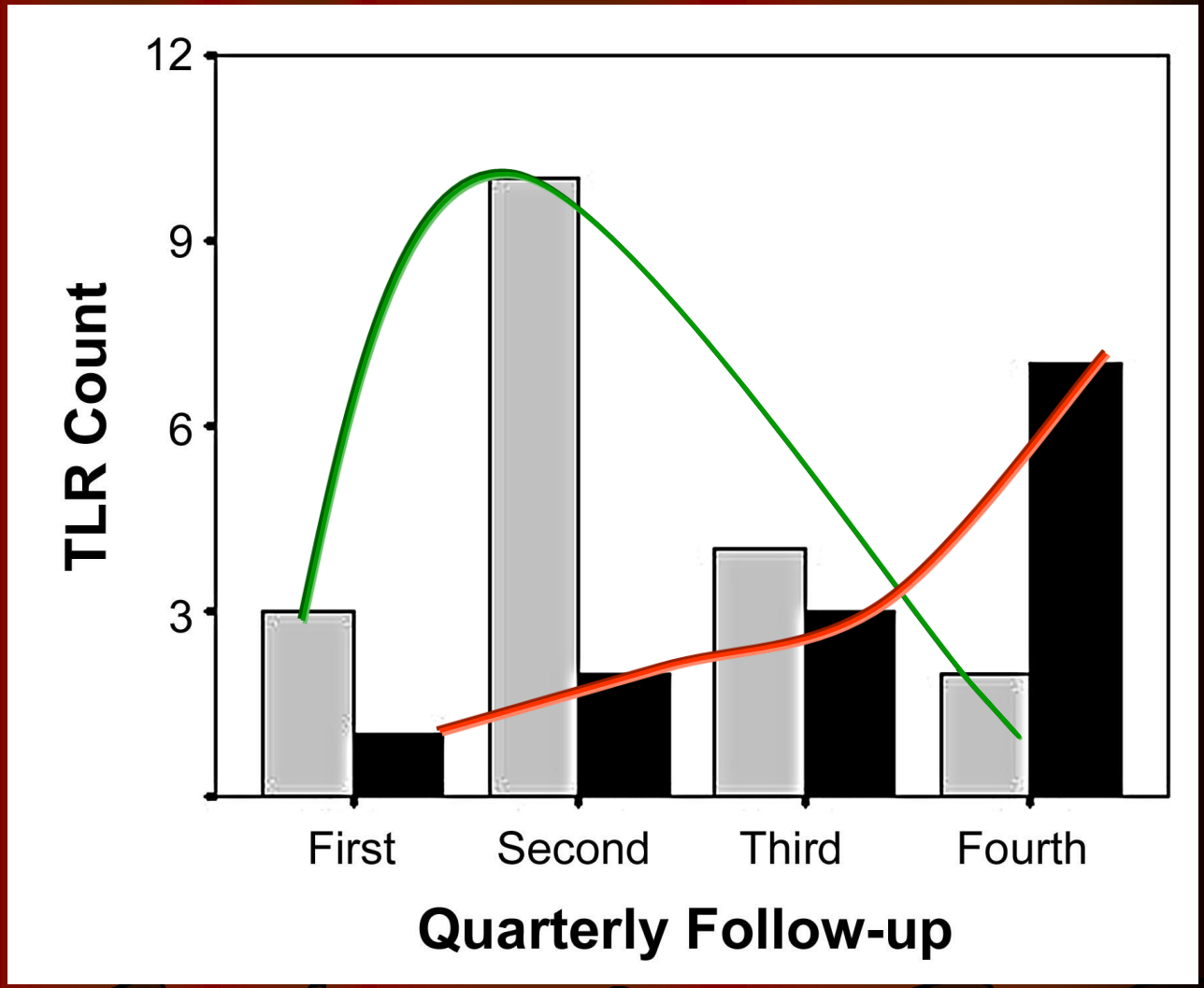
Shammas NW et al. Cardiovasc Revasc Med. 2012;13:341-4

SA vs Laser for FP ISR

ELA was utilized more frequently than SA in

longer lesions 210.4±104 vs. 126.2±79.3
subacute presentation 55% vs. 14.6%
TASC D lesions
angiographic thrombus 42.5% vs. 4.9%

Regression analysis confirmed that SA was a predictor of TLR at 1 year (odds ratio 2.679, 95% CI 1.015 to 7.073, p=0.047).



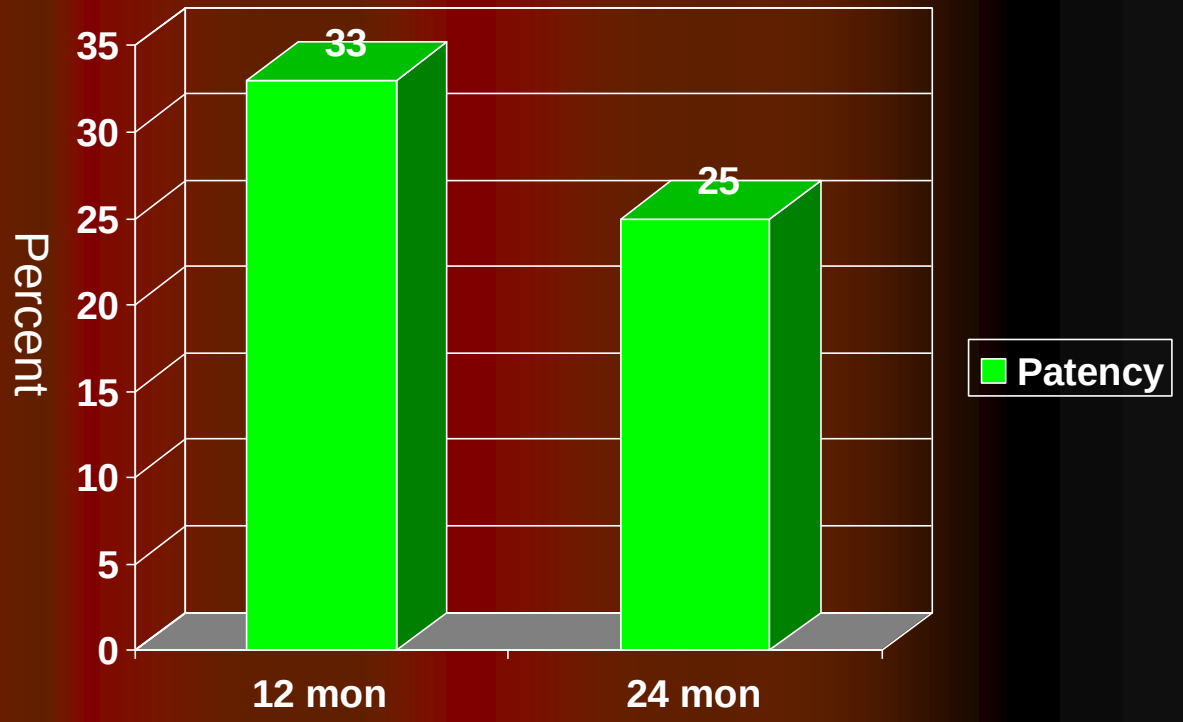
Shammas NW et al. In print in JEVT, Dec 2013

JetStream ISR: baseline, after Jetstream and after adjunctive balloon

Patency of FP segments after Pathway atherectomy for ISR

40 infrainguinal ISR lesions
Treated with Pathway Ather
Primary patency
- 33% at 12 months
- 25% at 24 months

Pathway modified to Jetstream
Ongoing JetStream ISR registry



Beschorner U, et al. Vasa. 2013;42:127-133.

Atherosclerotic Debris Following Atherectomy of FP ISR

SilverHawk registry for FP ISR*
Debris in 81.9% of filters;
36.4% were macrodebris
Distal embolization requiring treatment 7.3%
(3 patients with EFP)

Laser registry for FP ISR **
Macrodebris in 65.2% of filters.
Distal embolization requiring treatment 2.5%
(1 patient with no EFP)

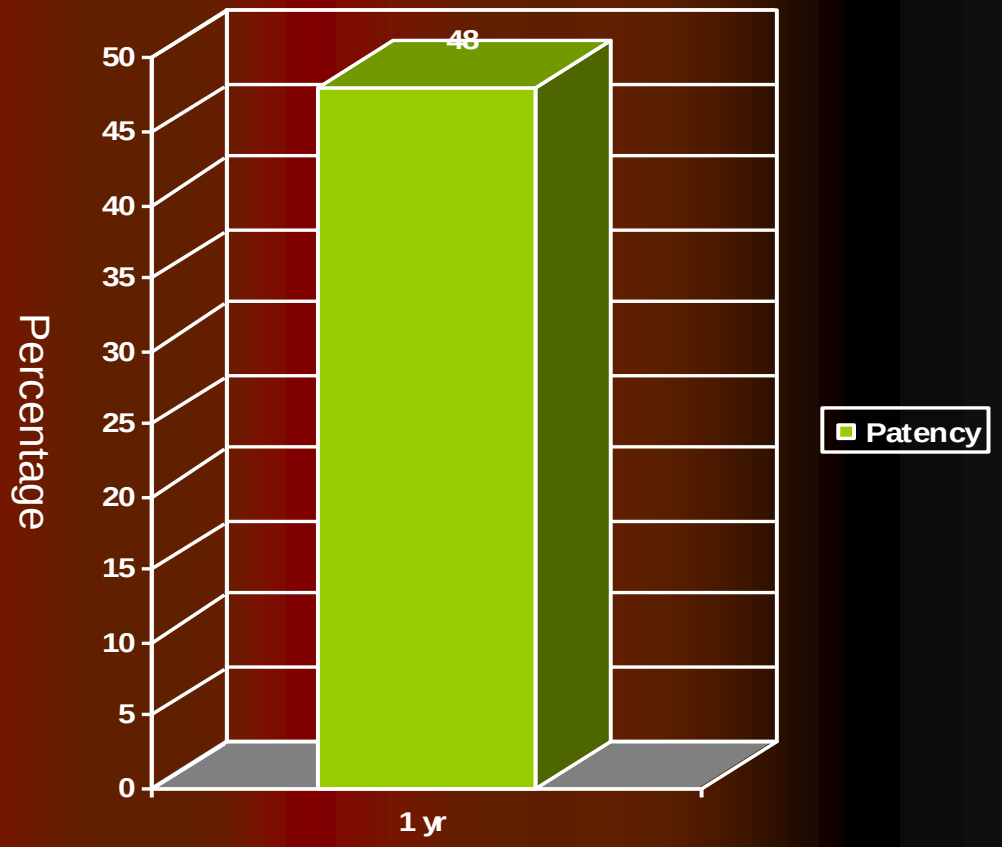
* Cardiovasc Revasc Med. 2012;13(4):224-7
** Cardiovasc Revasc Med. 2012;13:341-4

Atherectomy with Covered Stents for FP ISR: The SALVAGE trial

Multicenter prospective registry involving 9 US centers
Excimer laser and the VIABAHN endoprosthesis
27 patients enrolled
The mean lesion length was 20.7 ± 10.3 cm
TASC (TASC I) C and D (81.4%)

Technical success 100% of cases

Primary patency at 12 months was 48%
The 12-month TLR rate was 17.4%



Laird JR et al. Catheter Cardiovasc Interv. 2012 Nov 1;80(5):852-9

Covered Stent for FP ISR

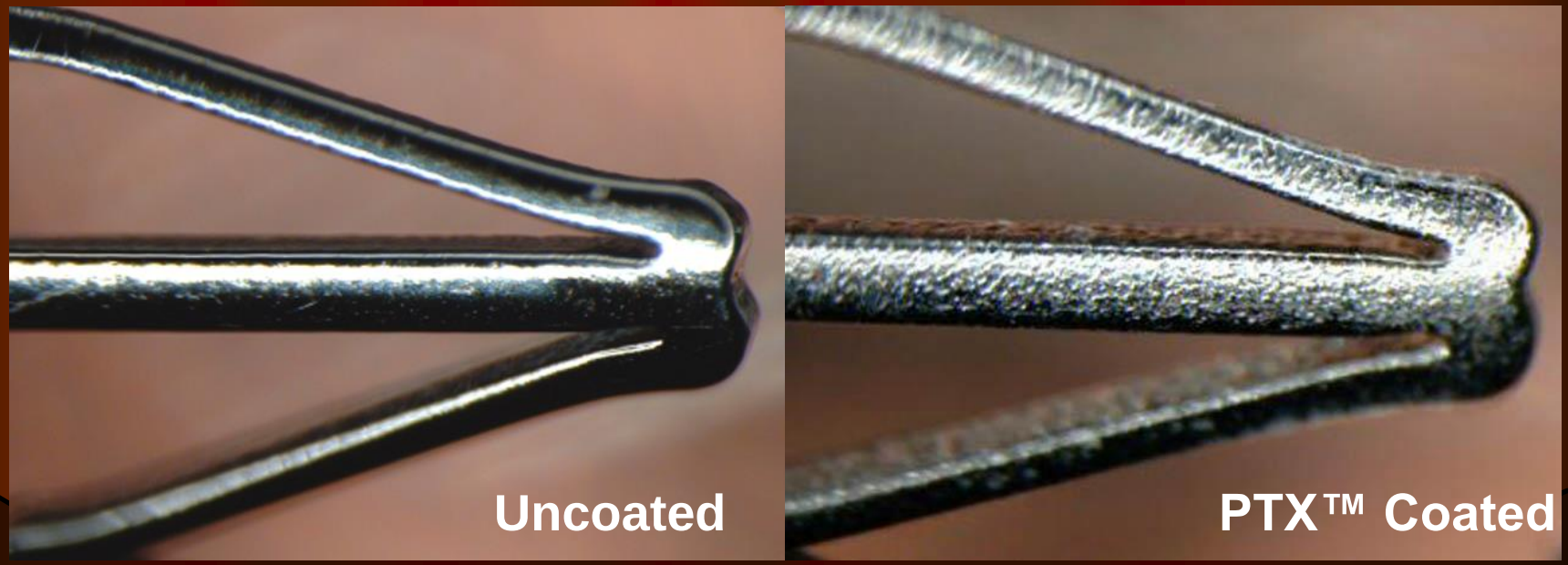
- Retrospective analysis at a single center (n=39)
- Patency: Duplex follow-up (ratio > 2.0)
- No exclusions
- PTA/Laser/Viabahn
- Average follow up 18 mo
- Average lesion length = 27.1 cm (5-44)

- Patency
  - Primary 17/33 (52%)
  - Assisted 23/33 (67%)
  - Secondary 27/33 (82%)

Ansel G et al. TCT 2008

Zilver® PTX™

- Zilver®, self-expanding nitinol stent
- Coated with Paclitaxel
  - No polymer or binder
  - 3 µg/mm² dose density
- No randomized data in FP ISR.
- Observational Data from Zilver PTX registry



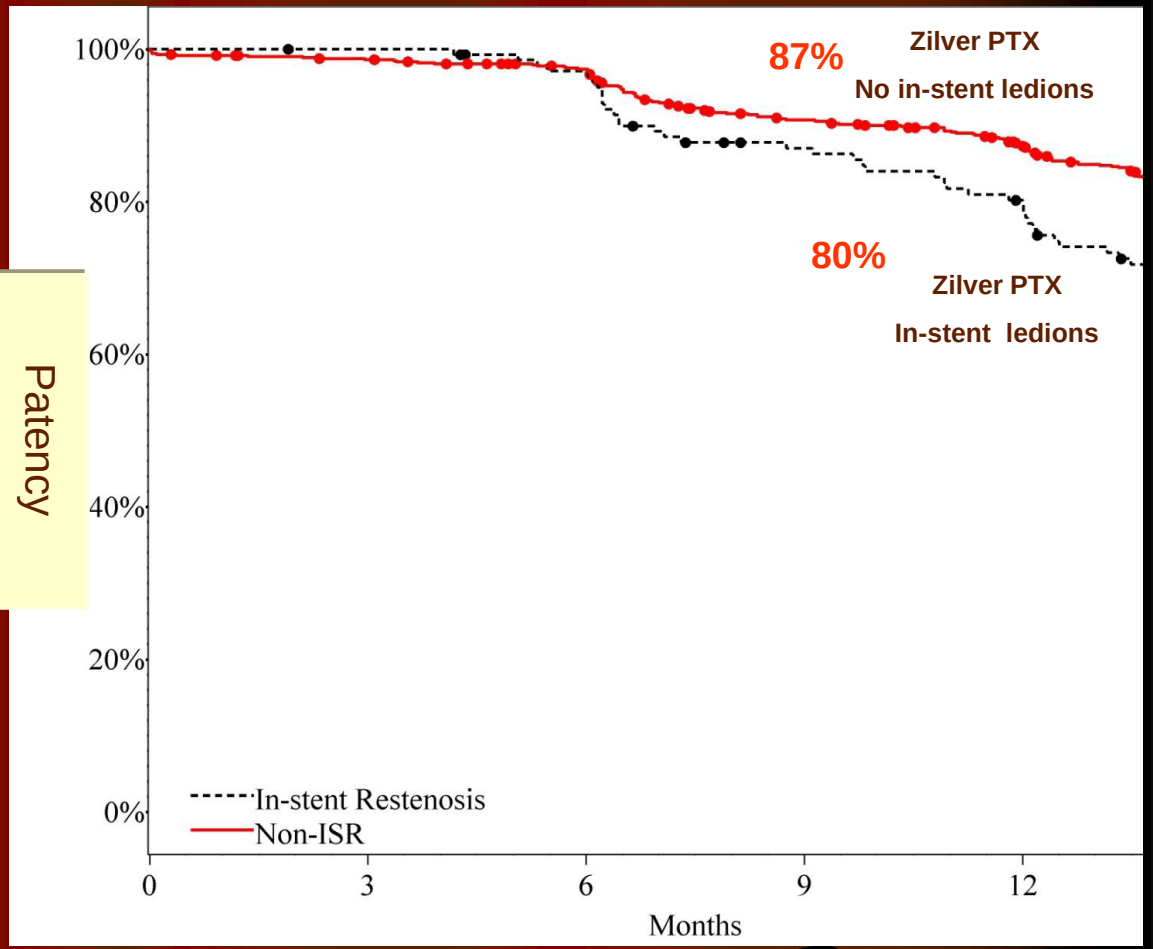
Patency Among Zilver PTX FP ISR Patients

119 ISR lesions in ZILVER-PTX single-arm prospective, multicenter, trial of 787 pts paclitaxel-eluting nitinol stents

Mean lesion length was 133.0 mm
33.6% of lesions >150 mm long
31.1% of lesions totally occluded
Procedural success 98.2%

Primary patency
95.7% 6 months
78.8% at 1 year

Freedom from TLR
96.2% at 6 months
81.0% at 1 year
60.8% at 2 years



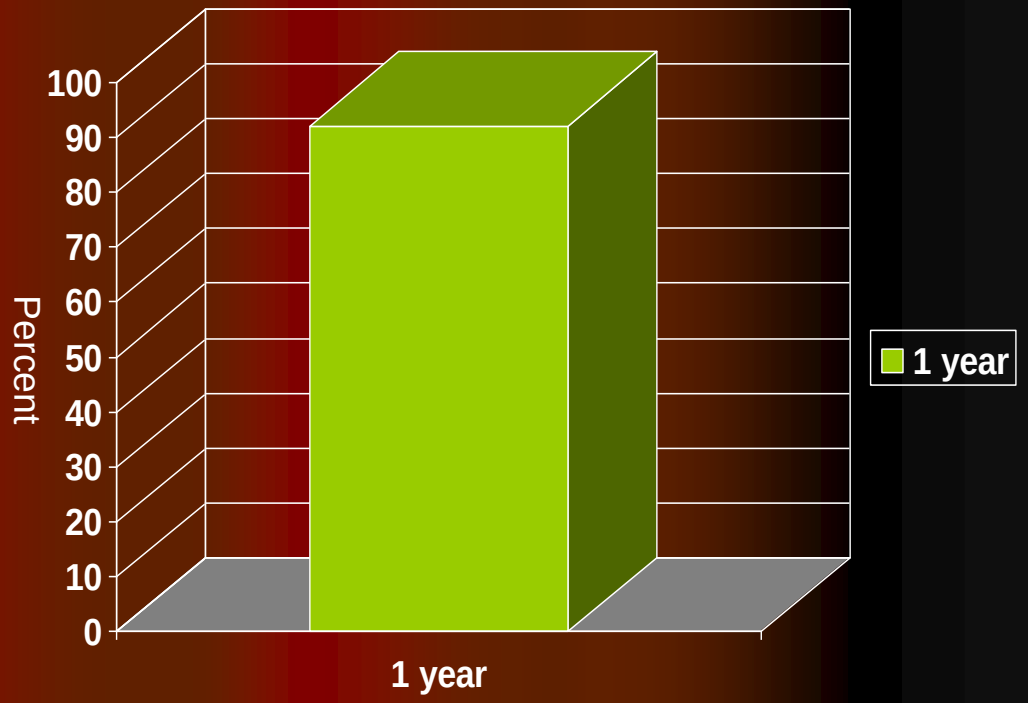
Zeller T et al. J Am Coll Cardiol Intv. 2013;6:274-281

DEB in Treating FP ISR

39 consecutive patients
PTA of SFA-ISR . CLI 20.5%. Diabetics 48.7%
All patients underwent conventional SFA PTA
Post-dilation with paclitaxel-eluting balloons (IN.PACT, Medtronic, Minneapolis, Minnesota)
Bail out stenting 10.3%
Lesion length: 8.3 cm. Stent length 15 cm
DEB length 16 cm (cumulative)
Follow up to 12 months.

Technical success 100%
Procedural success 100%
No in-hospital major adverse cardiac

Primary patency rate at 12 months was 92.1%

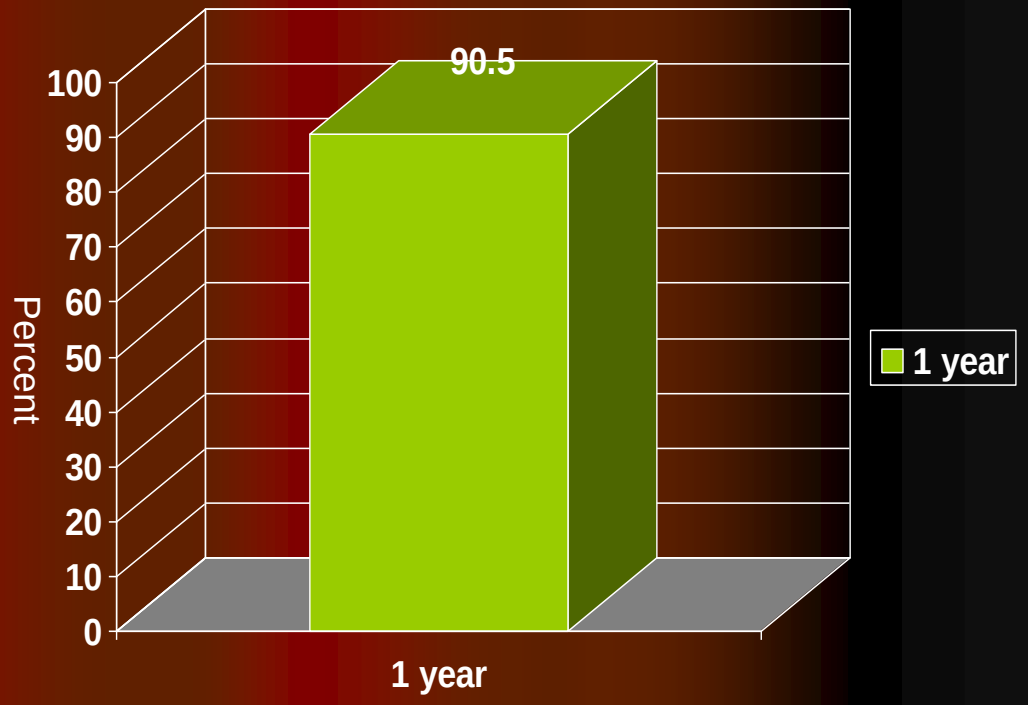


Stabile E et al. J Am Coll Cardiol. 2012 ;60:1739-42

DEB in Treating FP ISR

44 consecutive Diabetic patients
PTA of SFA-ISR . CLI 64%
Paclitaxel-eluting balloon
(IN.PACT, Medtronic, Minneapolis, Minnesota)
Follow up to 12 months.

Primary patency rate at 12 months was 90.5%
TLR at 12 months 13.6%



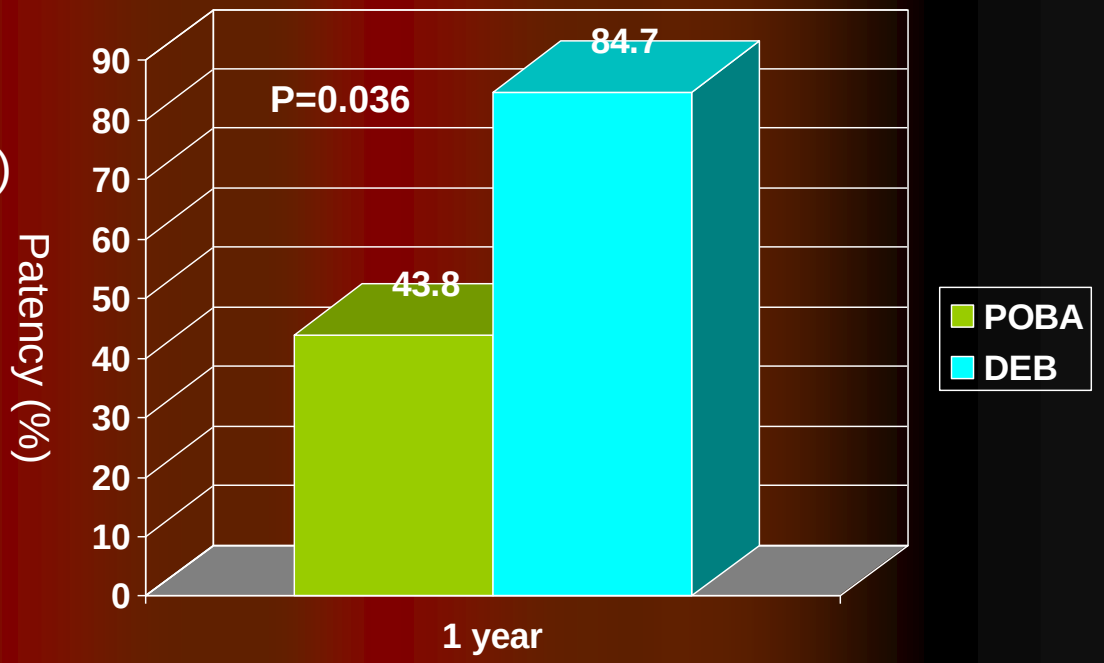
F. Liistro. TCT poster 343, 2012 Miami

DEB after Directional Atherectomy for ISR

Retrospective study
89 lesions of consecutive patients
Adjunctive POBA n = 60 or DEB n = 29
Lesions in- stent (DCB [n = 27] vs PTA [n = 36])

Patency at 1 year:
DEB: 84.7% (70.9%-98.5%)
POBA: 43.8% (30.5%-57.1%)

HR: 0.28 (0.12-0.66; P = .0036) for DEB



Sixt et al. J Vasc Surg. 2013 Sep;58(3):682-6

Pharmacological interventions

No large randomized studies

Possible benefit in smaller studies

Systemic side effects/toxicity

- Cilostazol
- Probucol
- Oral Sirolimus

Unlikley that the answer to FP ISR will be with systemic drug therapy because of high concentration needed to achieve inhibition of restenosis

PhotoDynamic therapy is still highly experimental (Light + Aminolevulinic acid)

Upcoming Studies

- DCB vs. Laser & DCB (PHOTOPAC). Primary endpoint: target lesion percent stenosis at 1 year by angiographic core lab
- RELINE: POBA vs. Viabahn
- EXCITE: POBA vs Laser
- POBA vs. DCB (FAIR, COPA CABANA, etc.)

Summary

- FP ISR remains a challenging problem
- Acute procedural outcomes are generally successful with multiple modalities of treatment but long term outcomes remain overall poor, particularly for long lesions and total occlusions
- Atherectomy can reduce bail out stenting but has high rate of distal embolization. The long term patency compared to POBA is unknown. SA is a predictor of recurrent restenosis compared to Laser at 1 year follow-up
- Promising new technologies include DEB, DES with or without atherectomy are on the horizon

THANK YOU