What is the Optimal Endovascular Treatment for SFA In-Stent Occlusions

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Disclosure Statement of Financial Interest

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- CR Bard
- Lake Regional Medical
- Medtronic
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- **Nitinol stents are being used more commonly in the therapy of SFA, popliteal, and infrapopliteal disease as multiple reports have shown improved patency and better symptomatic relief as compared with balloon angioplasty. (Crucial with flow-limiting dissections)**
- **In-stent restenosis over time is common**
- **Interventional therapy of ISR has historically been associated with high restenosis rates and complications.**

[1]*Schillinger M. Sabeti S. Loewe C. et al. Balloon Angioplasty versus Implantation of Nitinol Stents in the Superficial Femoral Artery. N. Engl J Med. 2006: 354:1879-1888.*

[2]*Edwards' Resilient Trial Demonstrates Statistically Superior Results for Treating Peripheral Arterial Disease in the Leg. Medical News Today, www.medicalnewstoday.com. 24 Oct 2007 American College of Cardiology. 10/23/07.*

[3]*Ms. Sabina A.Murphy. RESILIENT (RESILIENT – Presented at TCT 2007) Cardiosource, American College of Cardiology. 10/23/07.*

- Restenosis is usually secondary to intimal in-growth in a fully expanded stent and reocclusion usually has superimposed thrombus. (Several investigators have noted increased incidence when stent fractures are present.)
- Historically treatment of long diffuse disease and occlusions showed very poor patency (one study < 20%) at 3 months with high embolization rate during intervention.

Rationale of ISR Therapy

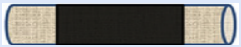
- Suboptimal results with balloon angioplasty are common
  - PTA dilatation of intimal hyperplasia compresses aqueous extra-cellular matrix, however rehydration ensues.
  - Thrombotic material may embolize and is thrombogenic.
  - Elastic recoil (NO POSITIVE REMODELING)
- Suboptimal results with repeat bare metal stenting within ISR
  - Embolization
  - No barrier to intimal ingrowth/won't seal pseudoaneurysms
  - Lumen compromised by at least the stent strut thickness
- Mechanical stabilization of fractured stents with either covered stents or nitinol stents is probably crucial.
- There are three FDA approved therapies for ISR that may be utilized alone or in conjunction (Laser/Gore® Viabahn® Device/DCB).

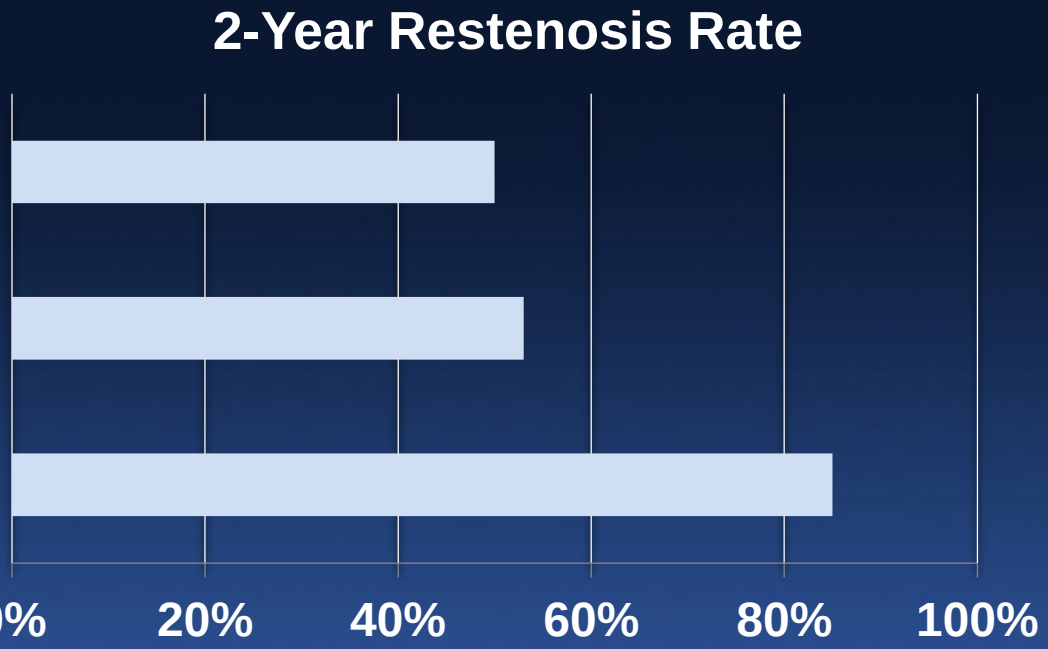
Fem-pop ISR Treatment (PTA)
Tosaka Classification

Class I: Short, focal lesions (≤ 50mm)

Class II: Diffuse lesions (> 50mm)

Class III: Total Occlusions





Treating FemPop In-stent Restenosis

- Factors to consider before attempting FemPop, in-stent restenosis intervention.
  - Length of lesion
  - Location of lesion (in-stent or edge stenosis)
  - Stenosis versus occlusion
  - Acuity of symptoms (old vs. new thrombus)
  - Is the stent fully expanded or compressed
  - Type of stent (covered vs. bare metal)
  - Stent fractures
  - Runoff vessel status
  - Location in the artery
  - Vessel Diameter

EXCITE ISR Trial Overview

Principal investigators: E.Dippel/C. Walker

DESIGN:
Prospective, randomized, multi-center clinical evaluation of excimer laser atherectomy (ELA) for ISR

PRIMARY SAFETY ENDPOINT:
Major Adverse Events (MAE) during hospitalization through 37-day follow-up to include all death, unplanned major amputation, or target lesion revascularization

PRIMARY EFFECTIVENESS ENDPOINT:
Freedom from clinically driven TLR through 6 month follow-up (212 days

252 patients enrolled between June 2011 and March 2014 in 40 clinical sites in United States

252 lesions crossable by guidewire – 7 uncrossable

170 ELA + PTA	82 PTA
Primary Safety endpoint at 37 days (n=158)	Primary Safety endpoint at 37 days (n=77)
Primary Efficacy endpoint at 212 days (n=157)	Primary Efficacy endpoint at 212 days (n=73)

Baseline Lesion Characteristics

Angiographic Core Lab Assessment

	ELA + PTA (N=169)	PTA Alone (N=81)	P- Value
Mean Lesion Length (cm)	19.3	18.9	0.78
Diameter Stenosis	82.0 %	83.5 %	0.49
Popliteal Lesion	21.6 %	22.5 %	0.97
Total Occlusion	31.7 %	35.0 %	0.37
TASC C/D	58.9 %	54.7 %	0.57
Calcium (Mod/Sev)	27.6 %	10.0 %	0.005
≤1 runoff vessel	38.2 %	24.4 %	0.03
Stent Fracture			0.01
None	86.0 %	97.5 %	
Type 1 or 2	11.0 %	2.5 %	
Type 3, 4 or 5	3.0 %	0 %	

- ***Longest lesions in any IDE peripheral study***
- ***20% of lesions > 30 cm***

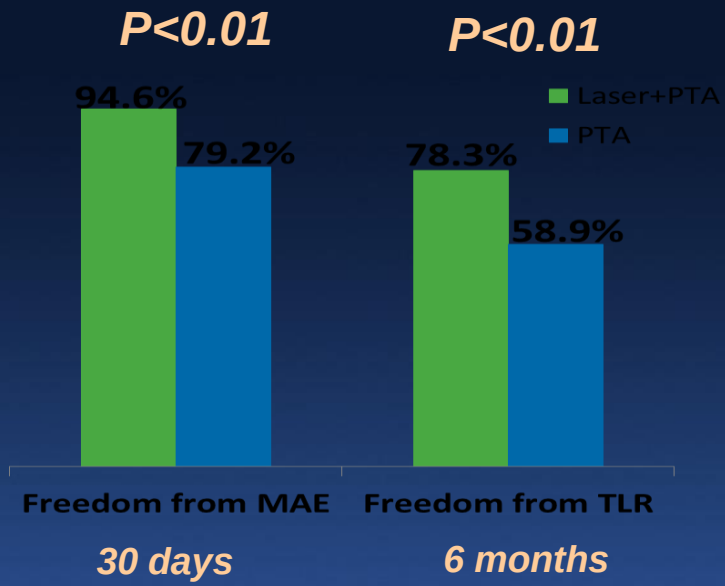
Laser atherectomy is superior to PTA alone for treatment of femoropopliteal ISR

	Laser + PTA n=170	PTA n=82
Mean lesion length	19.6 cm	19.3 cm
Calcium (mod/sev)	27.6 %**	10.0 %
Stent Fracture		
Type 1 or 2	11.0 %**	2.5 %
Type 3, 4 or 5	3.0 %	0 %
Residual Stenosis >30%	4.2%*	13.4%
Procedural Success#	93.5%**	82.7%
Bailout stenting after treatment	4.1%	11.1%
Major dissection	2.4%	7.4%

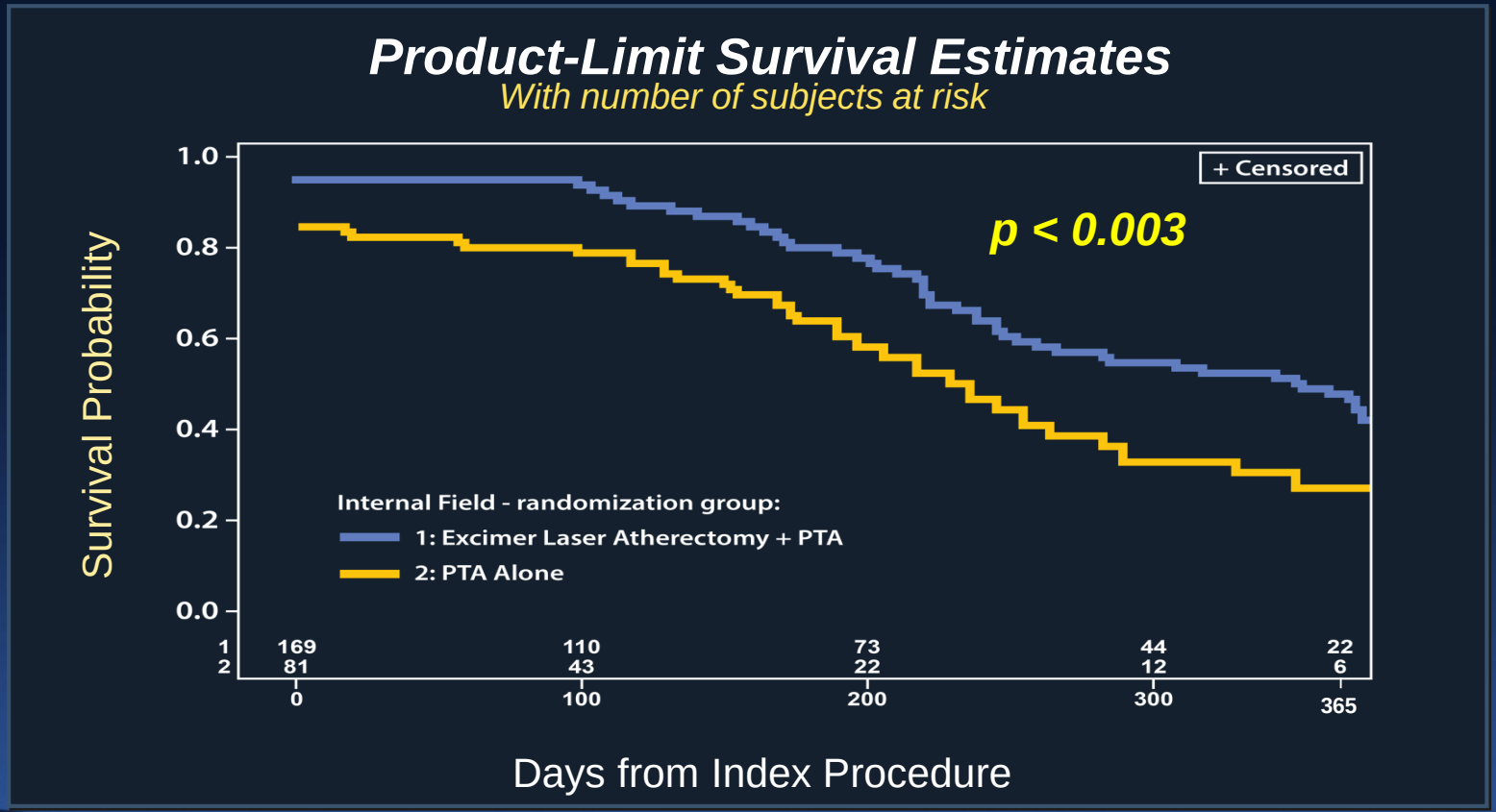
20% of lesions > 30 cm

#<30% residual stenosis by visual assessment without bailout procedure
**P<0.05*
***P<0.01*

Primary Endpoints

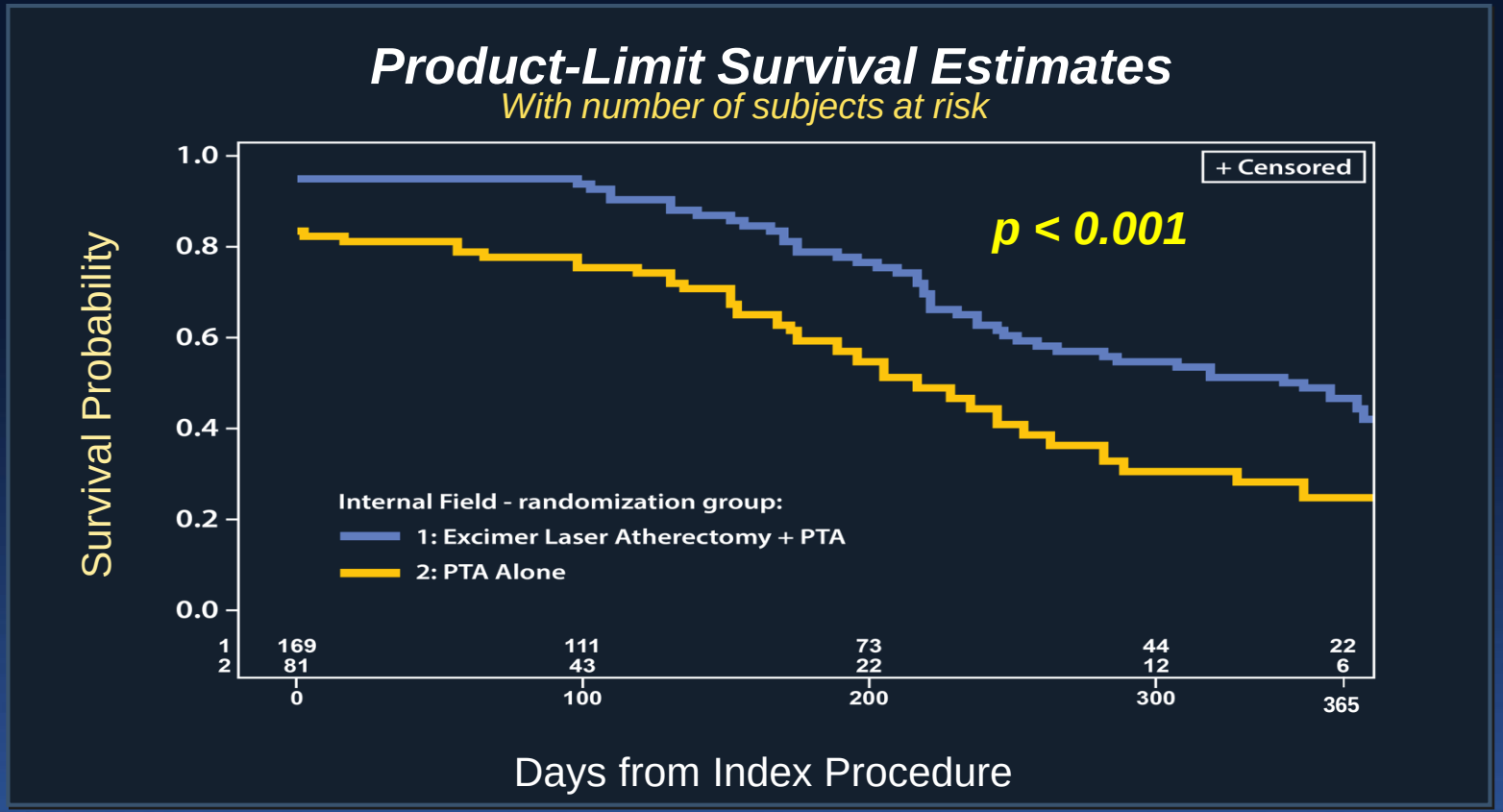


Freedom from TLR



Dippel et al. JACC CI. 2015;8:92-101

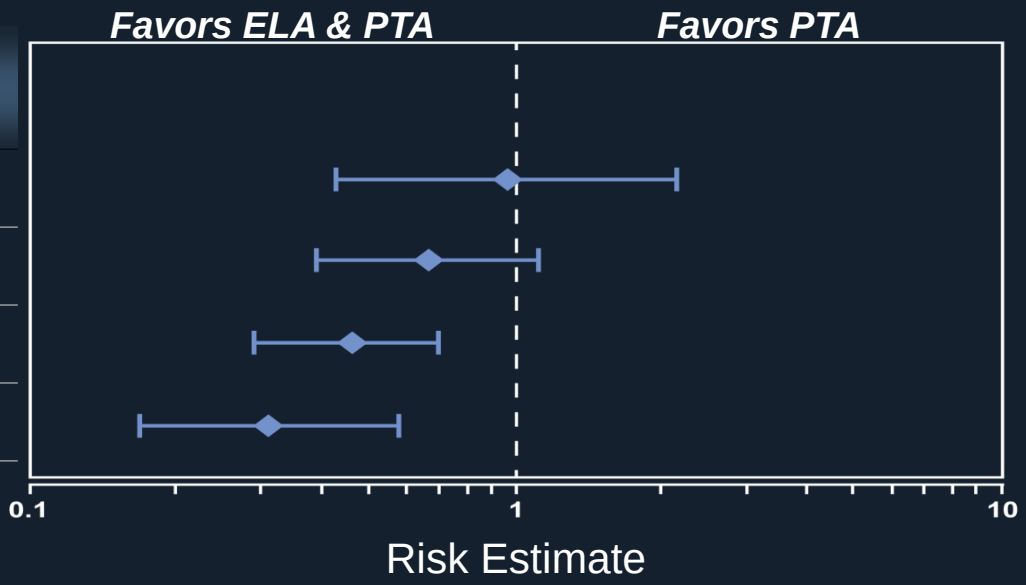
Freedom from MAE



Dippel et al. JACC CI. 2015;8:92-101

Lesion Length and TLR

Variable (Lesion Length)	Estimate	Lower CL	Upper CL
5 cm	0.96	0.43	2.14
15 cm	0.66	0.39	1.12
25 cm	0.46	0.29	0.70
35 cm	0.31	0.17	0.58



Dippel et al. JACC CI. 2015;8:92-101

12 Month Follow Up

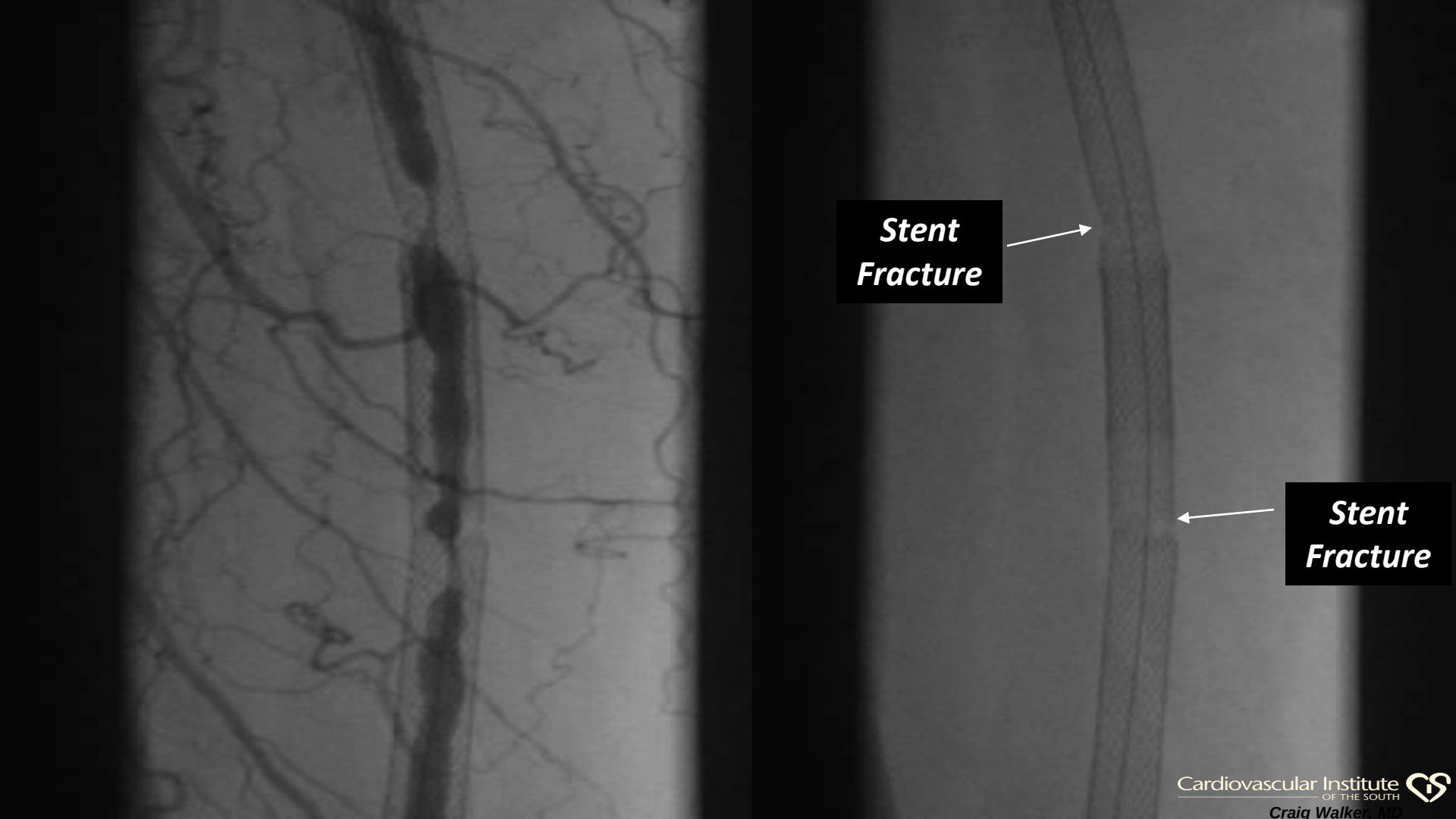
	Laser + PTA	PTA Alone	P- Value
Patients with 12 Month Visit	100 (59%)	42 (51%)	
Average Lesion Length (cm)	19.2	16.3	0.19
TASC C/D Lesion (%)	58.9	20.5	<0.001
Withdrawn/ LTF	24 (14%)	12 (15%)	
Survival (%)	98.3	94.8	0.15*
Freedom from TLR (%)	53.8	41.7	0.02*
Freedom from Amputation (%)	100	98.5	0.14*
WIQ Average	60.5	61.5	0.91
ABI Average	0.8	0.8	0.58
Rutherford Class Average	1.22	0.93	0.20
New Stent Fracture (%)	2.9† (5/170)	3.7 (3/82)	na

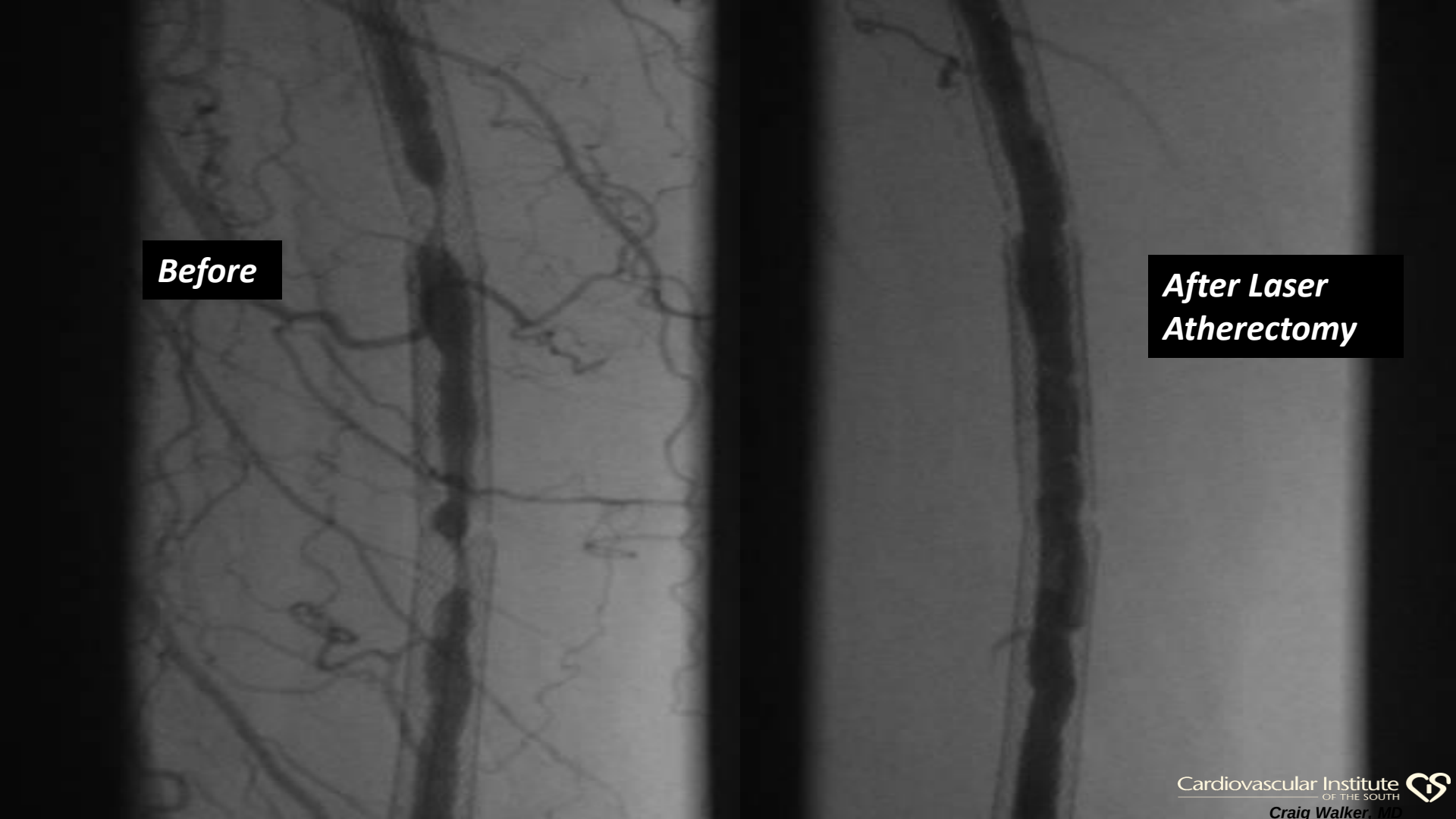
** Kaplan Meier*

† One 12 M stent fracture occurred in non-lased stent deployed post treatment. Four other minor stent fractures occurred at 6 and 12 M in The ELA+PTA arm. Three minor stent fractures occurred at 12 M in the PTA arm.

EXCITE ISR Conclusions

- Laser + PTA is superior to PTA alone for the treatment of femoropopliteal
- 1st FDA approved IDE randomized control study demonstrating the benefits of laser atherectomy in the lower extremities
- Laser+ PTA is the only atherectomy treatment FDA indicated for femoropopliteal ISR





GORE® VIABAHN® Endoprosthesis for In-Stent Restenosis — RELINE Clinical Study[1]

Prospective, randomized trial conducted at seven centers in Europe

GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface*

versus PTA for treatment of in-stent restenosis of the SFA.

Objective	Evaluate the performance of the GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface and PTA in treating in-stent restenosis in the SFA.
Primary Endpoints	Primary Patency at 12 months — Patency loss by PSVR > 2.5 assessed by color duplex ultrasound Proportion of patients experiencing composite adverse events within 30 days of procedure
Secondary Endpoints	Primary patency (hemodynamic and angiographic) Primary assisted and secondary patency Target lesion revascularization Clinical success Serious adverse events Stent fracture at 12 months

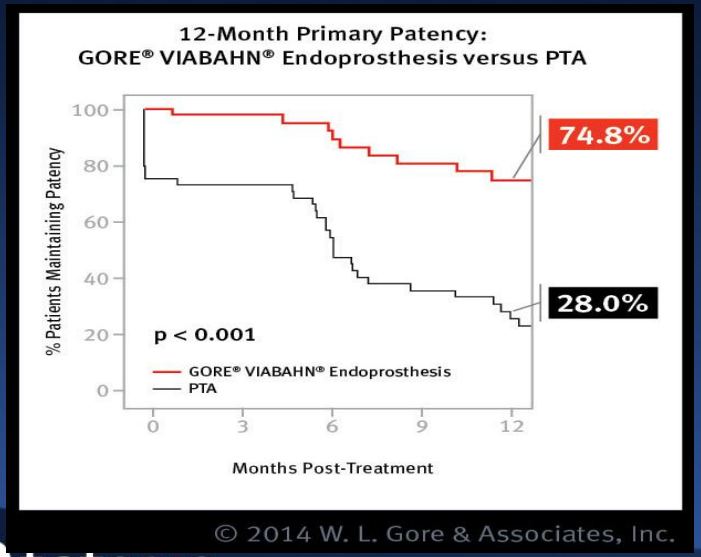
* Note: The GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface is known in some markets as the GORE® VIABAHN® Endoprosthesis with PROPATEN Bioactive Surface.

1. Deloose K. RELINE - randomized clinical trial: Viabahn covered stents vs. PTA. Presented at The Leipzig Interventional Course (LINC) 2014; January 28–31, 2014; Leipzig, Germany.

RELINE Clinical Study Randomization

Primary Patency[1]

Superior primary patency with GORE® VIABAHN® Endoprosthesis in the per-protocol analysis (shown below), intent-to-treat analysis, and in comparison to optimal PTA cohort.



12-Month Primary Patency

	GORE® VIABAHN® Endoprosthesis	PTA	P-value
Intent-to-Treat	72.5%	24.2%	< 0.001
Per-Protocol	74.8%	28.0%	< 0.001
Optimal PTA (As Treated)	74.8%	37.0%	< 0.001

1. *Deloose K. RELINE - randomized clinical trial: Viabahn covered stents vs. PTA. Presented at The Leipzig Interventional Course (LINC) 2014; January 28–31, 2014; Leipzig, Germany.*

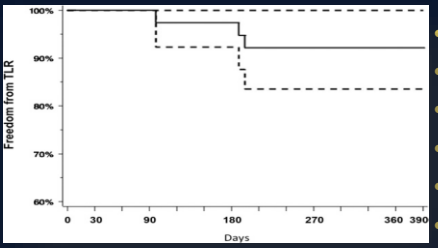
RELINE Clinical Study Conclusions

- Evidence from the RELINE Clinical Study support the safety and effectiveness of the GORE® VIABAHN® Endoprosthesis in relining
  failed bare metal stents.
- Superior primary patency at one year in the GORE® VIABAHN® Endoprosthesis group.
- Patients in the GORE® VIABAHN® Endoprosthesis arm were approximately three times less likely to require a TLR.
- Freedom from serious device-related adverse events similar in both arms of the study.

DEB Experience in SFA ISR

- 3 Prospective Registries
  - IN.PACT SFA ISR
  - DEBATE-ISR
  - PLAISIR
- 4 Prospective Randomized Control Trials
  - PACUBA
  - FAIR
  - COPA CABANNA
  - ISAR-PEBIS—on going

IN.PACT SFA ISR

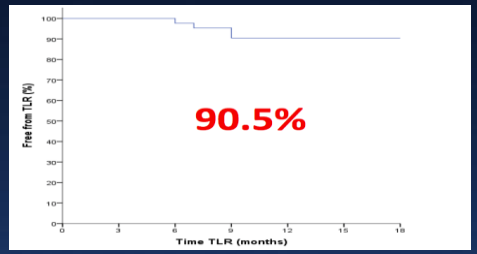


- Prospective
- Single center
- N = 39
- IN.PACT balloon
- 12 mth primary patency 92.1%
- Ave length 82.9mm

Stabile E, et al. JACC, 2012;60:1739-42.

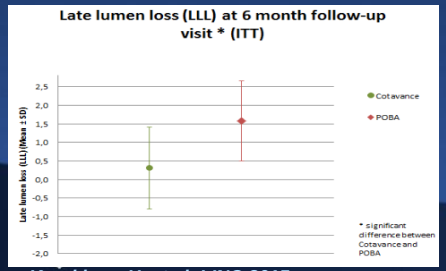
PLAISIR registry

- Prospective
- Multi-center
- N = 45
- IN.PACT balloon
- Freedom TLR 90.5%
- Ave length 91 mm



Goueffic Y, et al. LINC 2015

COPA COBANNA study

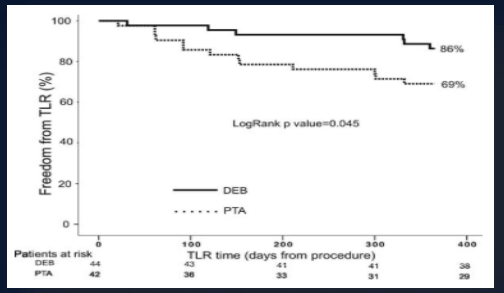


- Prospective
- Multi-center
- Primary end point LLL by DSA
- N = 88
- Cotavance balloon
- Ave length 119 mm
- Core lab

Krankberg H, et al. LINC 2015

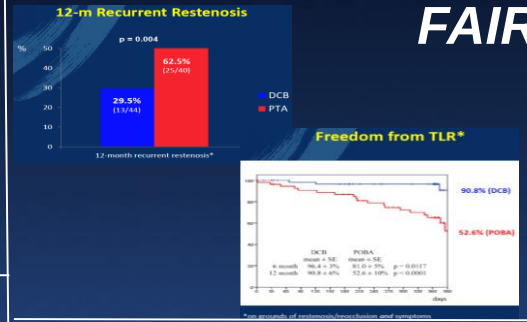
DEBATE-ISR registry

- Prospective
- Single center
- Diabetics only
- PTA historical control
- N = 44
- IN.PACT balloon
- Restenosis
  - 18% DEB
  - 72% PTA
- Ave length 132 mm



Liistro F, et al. J Endovasc Ther, 2014;21:1-8.

FAIR study



- Prospective
- Multi-center
- Primary end pt binary restenosis
- N = 119
- IN.PACT balloon
- Ave length 82 mm
- Core lab

PACUBA study

- Prospective
- Randomized 1:1
- Single center
- N = 60 (planned)
- EuroCor balloon
- No core lab

Preliminary results

	POBA	DEB
Patients	15	21
Age(years)	70	68
Lesion length (cm)	8.1	8.5
Total occlusion	5	5
6 months PP rate	37%	78%

Lammer J, et al. Veith. 2011

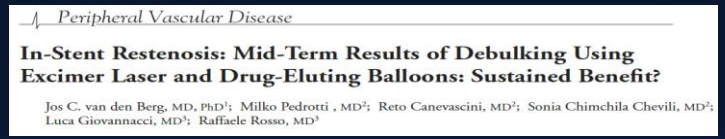
There Are Now Three FDA Approved ISR Therapies

- ISR is a huge clinical problem
- What about combination therapy? (Several studies ongoing in Europe.)
- Will DES play a role?

Laser proven with DCBs in ISR

Van den Berg et al. n=14

- ***Mean lesion length: 13cm***
- ***Technical success: 100%***
  - ***Distal embolization occurred in 2 cases- treated successfully***
- ***Patency at follow up***
  - ***Primary Patency at 12 months: 100%***
  - ***Primary Patency for duration of follow-up:***
    - ***Average 19 months: 91.7%***
      - ***1 restenosis 36 months post-procedure***



Peripheral Vascular Disease

In-Stent Restenosis: Mid-Term Results of Debulking Using Excimer Laser and Drug-Eluting Balloons: Sustained Benefit?

Jos C. van den Berg, MD, PhD[1]; Milko Pedrotti , MD[2]; Reto Canevascini, MD[2]; Sonia Chimchila Chevili, MD[2]; Luca Giovannacci, MD[3]; Raffaele Rosso, MD[3]

Van den Berg J Invasive Cardiol 2014;26(7):333-337

Laser + DCB vs. DCB Along

- RCT laser+DCB (n=24) vs. DCB n=24
- All diabetic CLI and total occlusions
- Treated stent length and lesion length >20cm
- 100% crossing success
- Complications:
  - Distal embolizations
  - Laser+DCB: 1 (4%), DCB: 2 (8%)
  - Zero perforations
  - Zero dissections

Gandini R et al, JET 2013;20:805-813

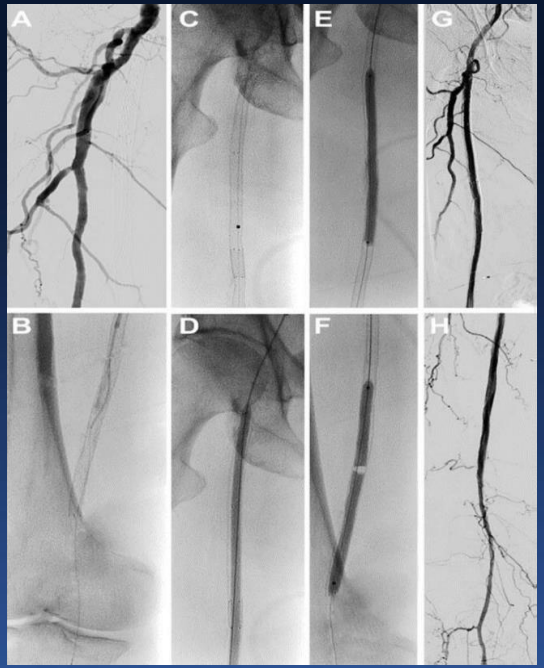
J ENDOVASC THER
2013;20:805–814

CLINICAL INVESTIGATION

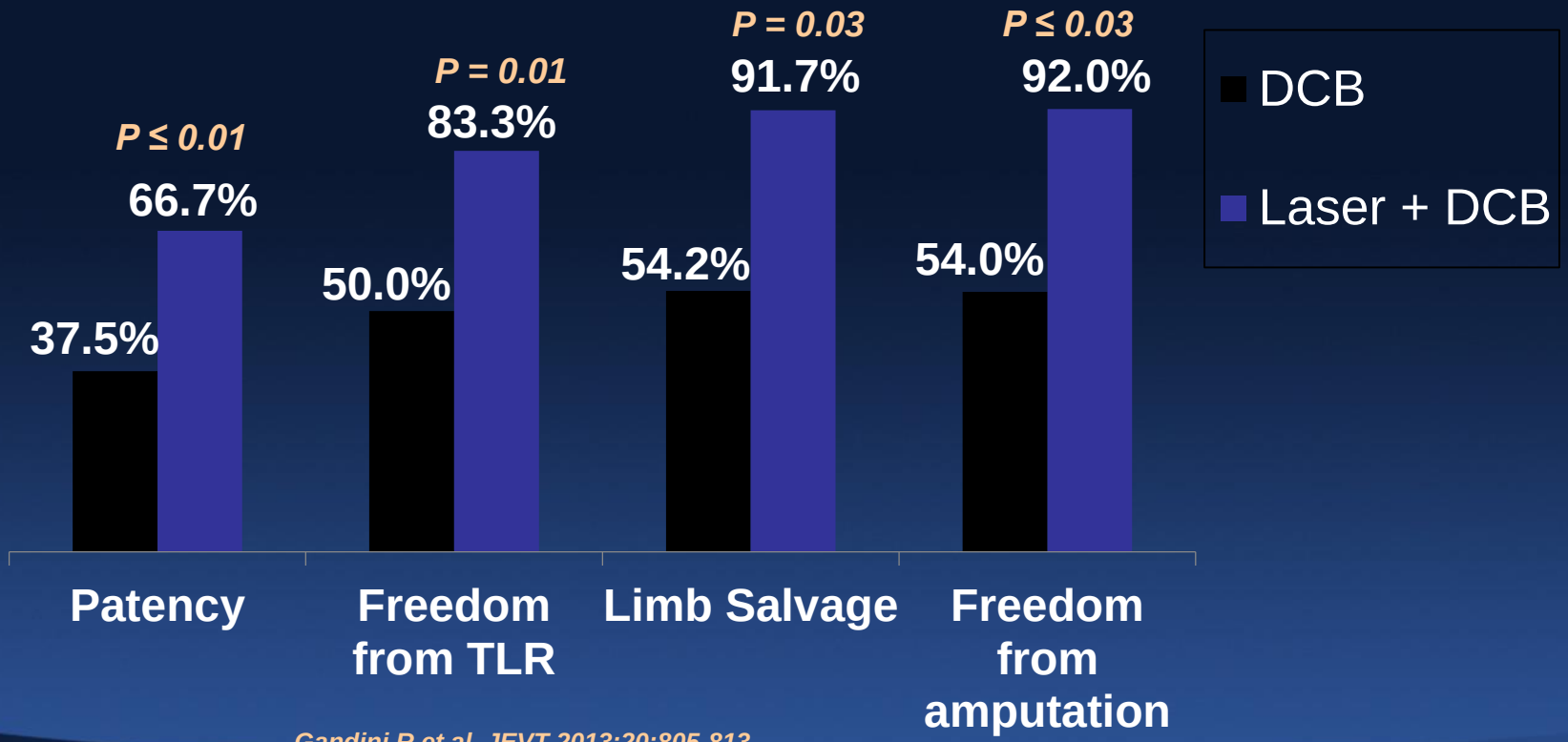
Treatment of Chronic SFA In-Stent Occlusion With Combined Laser Atherectomy and Drug-Eluting Balloon Angioplasty in Patients With Critical Limb Ischemia:
A Single-Center, Prospective, Randomized Study

Roberto Gandini, MD; Costantino Del Giudice, MD; Stefano Merolla, MD; Daniele Morosetti, MD, Enrico Pampana, MD; and Giovanni Simonetti, MD

Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology, Radiotherapy, and Nuclear Medicine, "IRCCS Policlinico di Tor Vergata," Rome, Italy.



12 months result: Laser + DCB had much better outcomes



Gandini R et al, JEVT 2013;20:805-813

Conclusions

- A new paradigm is emerging for the treatment of FemPop ISR
- PTA alone has failed against 3 different treatment strategies
- DCB is effective for lesions less than 10cm
  - More data is needed for Tosaka 3, cost effectiveness
- Both laser atherectomy and Viabahn are effective for long lesions
  - Both are FDA approved for ISR
- Combination therapy needs further investigation

What is the Optimal Endovascular Treatment for SFA In-Stent Occlusions

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