HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Update on PAD Management: What Will Be The Future of SFA Treatment?

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MASSACHUSETTS
GENERAL HOSPITAL
INSTITUTE FOR HEART,
VASCULAR AND STROKE CARE

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Conflicts of Interest

- **Consultant**
  - Abbott Vascular (non-compensated)
  - American Genomics, Inc
  - Astra Zeneca Pharmaceuticals, Inc
  - Biomet Biologics
  - Boston Scientific (non-compensated)
  - Cordis Corporation (non-compensated)
  - Covidien (non-compensated)
  - Ekos Corporation (DSMB)
  - Medtronic (non-compensated)
  - Micell, Inc
  - Primacea

- **Equity**
  - Access Closure, Inc
  - Embolitech, Inc
  - Hotspur, Inc
  - Icon Interventional, Inc
  - I.C.Sciences, Inc
  - Janacare, Inc
  - MC10
  - Northwind Medical, Inc.
  - PQ Bypass, Inc
  - Primacea
  - Sadra Medical
  - Sano V, Inc.
  - Vascular Therapies, Inc

- **Board Member**
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
    - www.vivapvd.com
  - CBSET

April 2014

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Goals of Therapy for PAD

Limb	Life
Improve Functional Capacity **Prevent Limb Loss**	**Identify Co-Existent Athero (Coronary, Cerebrovasc, Renal, Aortic)** **Treat athero. Risk factors**

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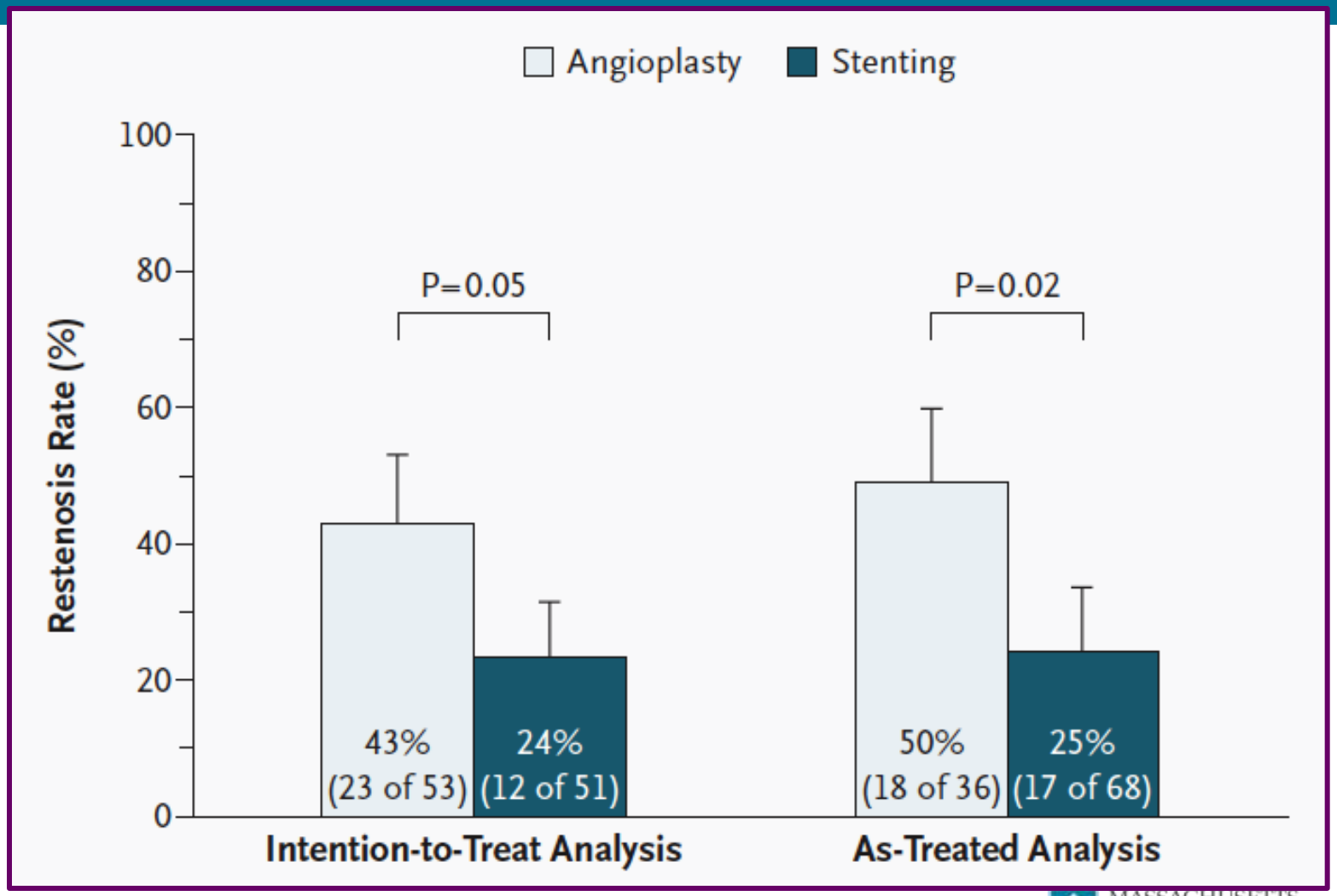
Stent vs PTA in SFA Disease



N Engl J Med 2006;354:1879-88

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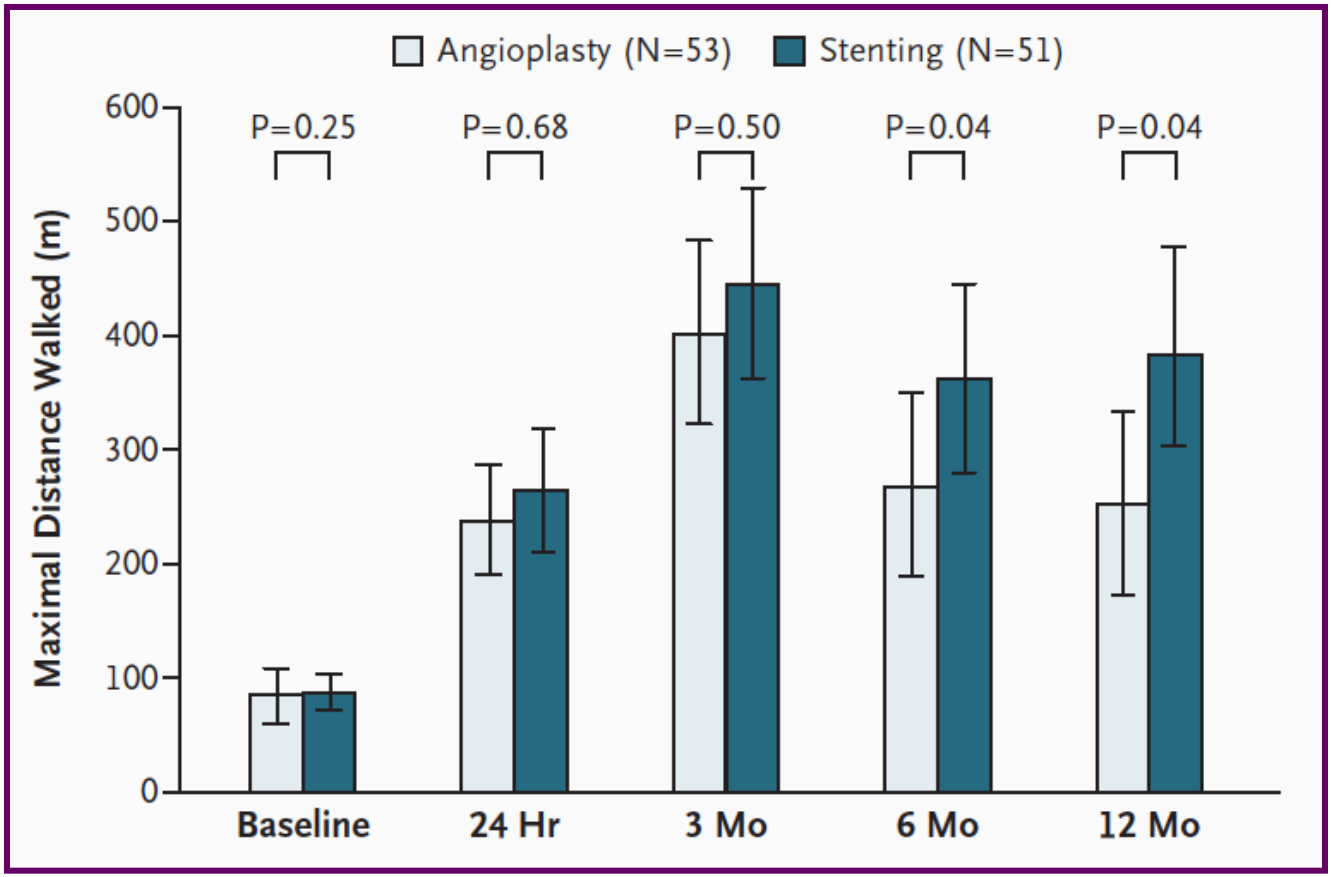
Stent vs PTA in SFA Disease

Treadmill-Measured Absolute Claudication Distance (m)



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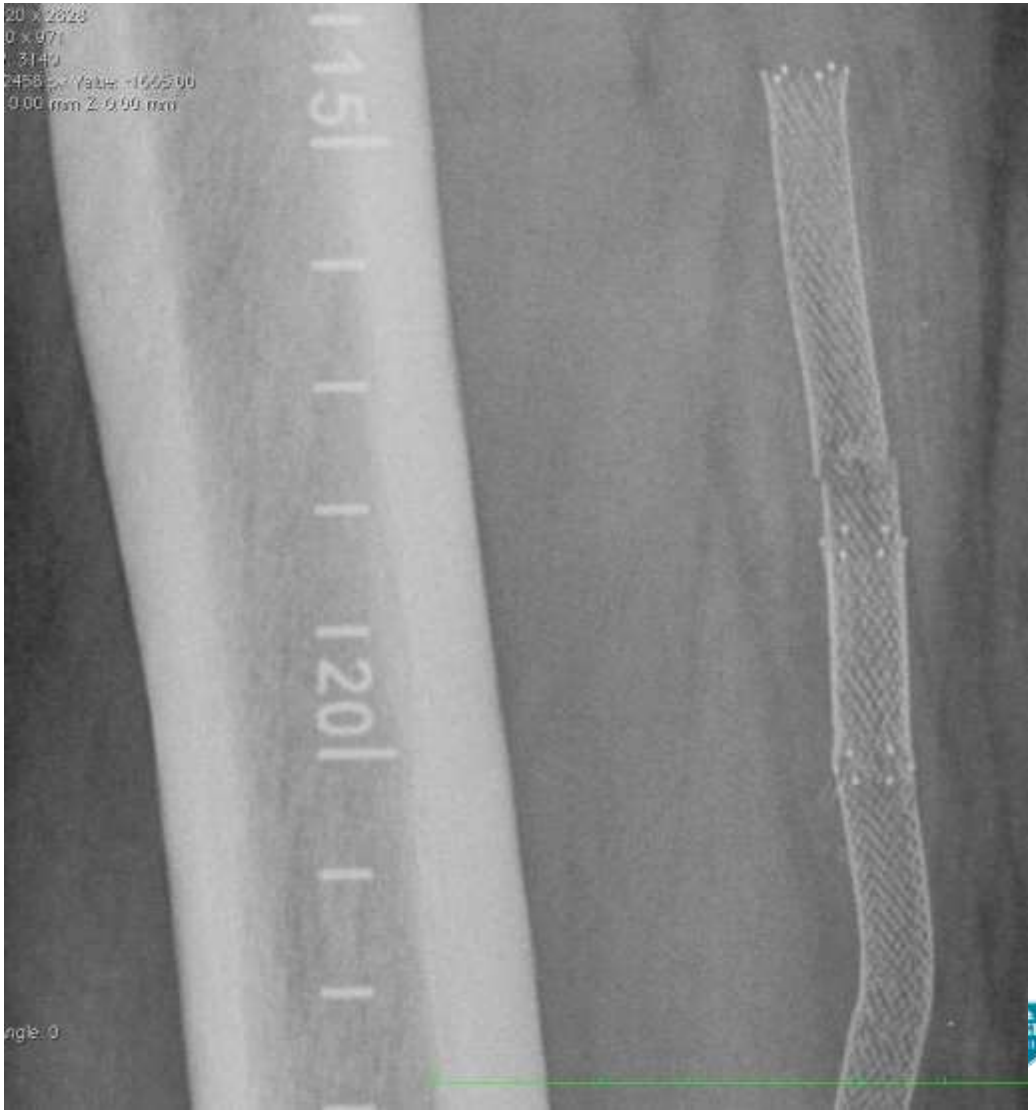
N Engl J Med 2006;354:1879-88

Type IV Stent Fracture



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STROLL: Purpose and Study design

- Prospective, single arm, multicenter trial evaluating the SMART self-expanding nitinol stent in the superficial femoral/popliteal artery.
- Multi-center, single-arm, prospective trial
  - 250 patients, 39 study sites in the United States
  - Follow-up to 3 years
- Primary Endpoints:
  - Safety at 30 days
  - Primary Efficacy (patency) at 12 months
    - DUS 30 day, 6m, 12m, 24m and 36m
- Secondary Endpoint: Incidence of stent fractures.
  - Protocol-mandated X-ray of stents at 30 day, 6m,12m, 24m and 36m

30 d Primary Safety and Major Adverse Events

Primary Safety Endpoint: Freedom from MAEs at 30 days

S.M.A.R.T.® (N=250 Patients N=250 Lesions)	30 Days	12 Months	24 Months	36 Months
Major Adverse Events	0% (0/248)	14.4% (34/236)	24.5% (56/229)	31.5% (70/222)
- Death	0% (0/248)	2.1% (5/236)	4/8% (11/229)	9.9% (22/222)
- Index Limb Amputation	0% (0/248)	0.4% (1/236)	0.9% (2/229)	0.9% (2/222)
- Clinically driven TLR	0% (0/248)	12.3% (29/236)	20.1% (46/229)	22.5% (50/222)

Clinically driven TLR: any intervention in the stented target lesion following documented recurrent symptomatic leg ischemia by Rutherford/Becker Classifcation (2,3,4) with a resting or exercise ABI <0.8 and >50% diameter in-lesion stenosis by angiography. Or >70% in-lesion diameter stenosis by angiography in the absence of ischemic signs and symptoms.

Results: Primary Patency

	12 months	24 months	36 months
Primary Patency (KM estimate) (PSVR < 2.5)	81.7%	74.9%	72.7%
DUS Patency (PSVR < 2.5)	81.1% (154/190)	83.5% (132/158)	83.9% (115/137)
Absence of Clinically Driven TLR	87.4% (202/231)	79.0% (173/219)	75.8% (157/207)

Primary Patency: composite endpoint of absence of clinically driven TLR and DUS assessed binary restenosis defined as diameter stenosis >50% (non-patent).

DUS patency: stent non-patency defined as a diameter stenosis >50% with a specific a peak systolic velocity ratio as measured by Duplex Ultrasonography

Clinically driven TLR: any intervention in the stented target lesion following documented recurrent symptomatic leg ischemia by Rutherford/Becker Classification (2,3,4) with a resting or exercise ABI <0.8 and >50% diameter in-lesion stenosis by angiography. Or >70% in-lesion diameter stenosis by angiography in the absence of ischemic signs and symptoms.

Cumulative stent fracture rate

Stent Fracture	6-month	12-month	24-Month	36-Month
Type I	1.49% (3/202)	2.03% (4/197)	2.3% (4/177)	3.6% (6/169)
Type II	0.0% (0/202)	0.0% (0/197)	0.0% (0/177)	0.0% (0/169)
Type III	0.0% (0/202)	0.0% (0/197)	0.0% (0/177)	0.0% (0/169)
Type IV	0.0% (0/202)	0.0% (0/197)	0.0% (0/177)	0.0% (0/169)
Type V	0.0% (0/202)	0.0% (0/197)	0.0% (0/177)	0.0% (0/169)
Any Stent Fracture	1.49% (3/202)	2.03% (4/197)	2.3% (4/177)	3.6% (6/169)

Only Type I Fractures

Type I Single Strut fracture
Type II Multiple single Strut fracture
Type III Complete transverse linear separation without stent displacement
Type IV Complete transverse linear fracture with stent displacement
Type V Spiral dissection of stent

Health-Related Quality-of-Life: Baseline to 3-Years

	Baseline	1 Month Change vs. Baseline* (95% CI)	3-Year Change vs. Baseline (95% CI)	P-value (3 yr vs. baseline)
PAQ: Summary	66.0 ± 26.6	31.4(28.5, 34.3)	28.0 (24.3, 31.7)	<0.001
PAQ: Physical limitation	54.7 ± 31.3	27.9(23.9, 31.9)	25.0 (20.2, 29.8)	<0.001
PAQ: Quality of Life	69.6 ± 28.3	34.2(31.0, 37.4)	33.6 (29.3, 37.8)	<0.001
PAQ: Symptoms	65.9 ± 29.7	34.0(30.6, 37.4)	29.4 (24.9, 33.9)	<0.001
PAQ: Social Function	72.1 ± 30.9	26.5(22.8, 30.2)	22.6 (17.4, 27.8)	<0.001
WIQ: Distance	41.4 ± 35.5	27.3(23.0, 31.6)	22.4 (17.5, 27.3)	<0.001
WIQ: Speed	37.0 ± 28.7	16.6(12.8, 20.3)	11.4 (7.3, 15.6)	<0.001
SF-12: Physical	38.0 ± 12.1	8.3(7.0, 9.6)	6.7 (4.9, 8.4)	<0.001
EQ-5D: Utility	0.76 ± 0.19	0.13 (0.10, 0.15)	0.08 (0.05, 0.11)	<0.001

* p<0.001 for all

Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease

Twelve-Month Zilver PTX Randomized Study Results

Michael D. Dake, MD; Gary M. Ansel, MD; Michael R. Jaff, DO; Takao Ohki, MD; Richard R. Saxon, MD; H. Bob Smouse, MD; Thomas Zeller, MD; Gary S. Roubin, MD; Mark W. Burket, MD; Yazan Khatib, MD; Scott A. Snyder, PhD; Anthony O. Ragheb, PhD; J. King White, MD; Lindsay S. Machan, MD; on behalf of the Zilver PTX Investigators

Circ Cardiovasc Intervent 2011;4:495-504

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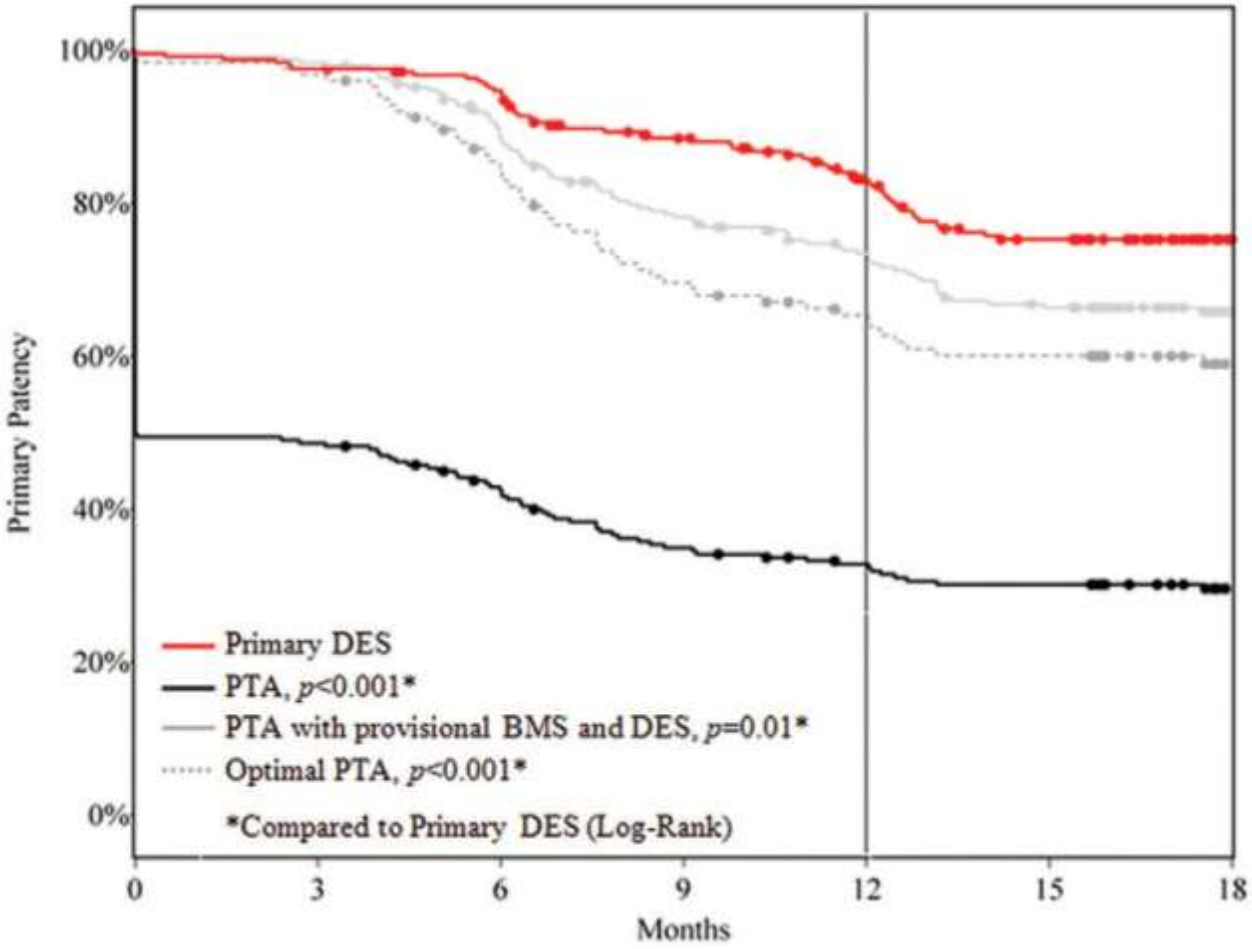
Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease : Twelve-Month Zilver PTX Randomized Study Results

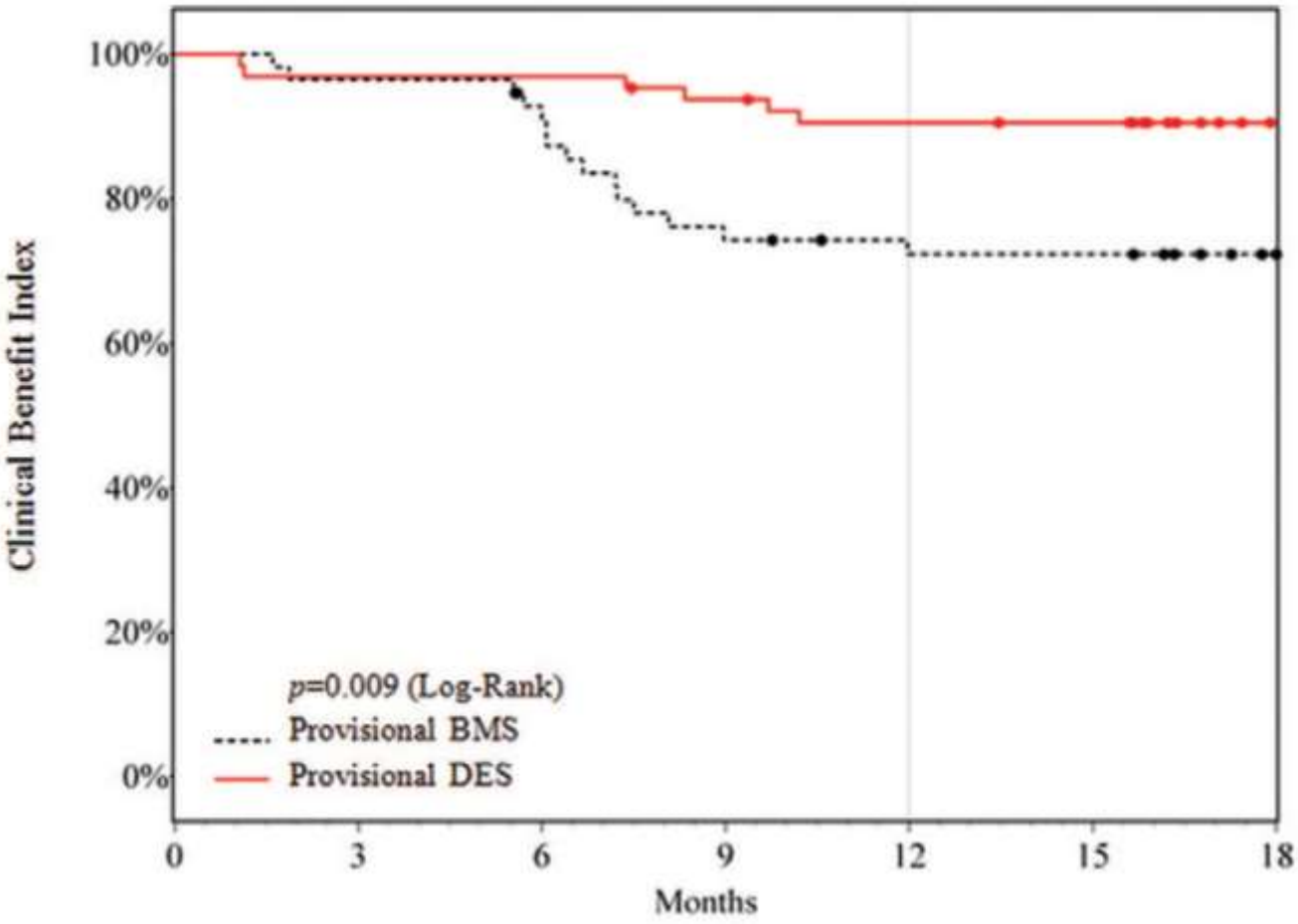
12 Month Primary Effectiveness Endpoint



Circ Cardiovasc Intervent 2011;4:495-504

Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease : Twelve-Month Zilver PTX Randomized Study Results

12 Month Clinical Benefit: BMS vs DES



Circ Cardiovasc Intervent 2011;4:495-504

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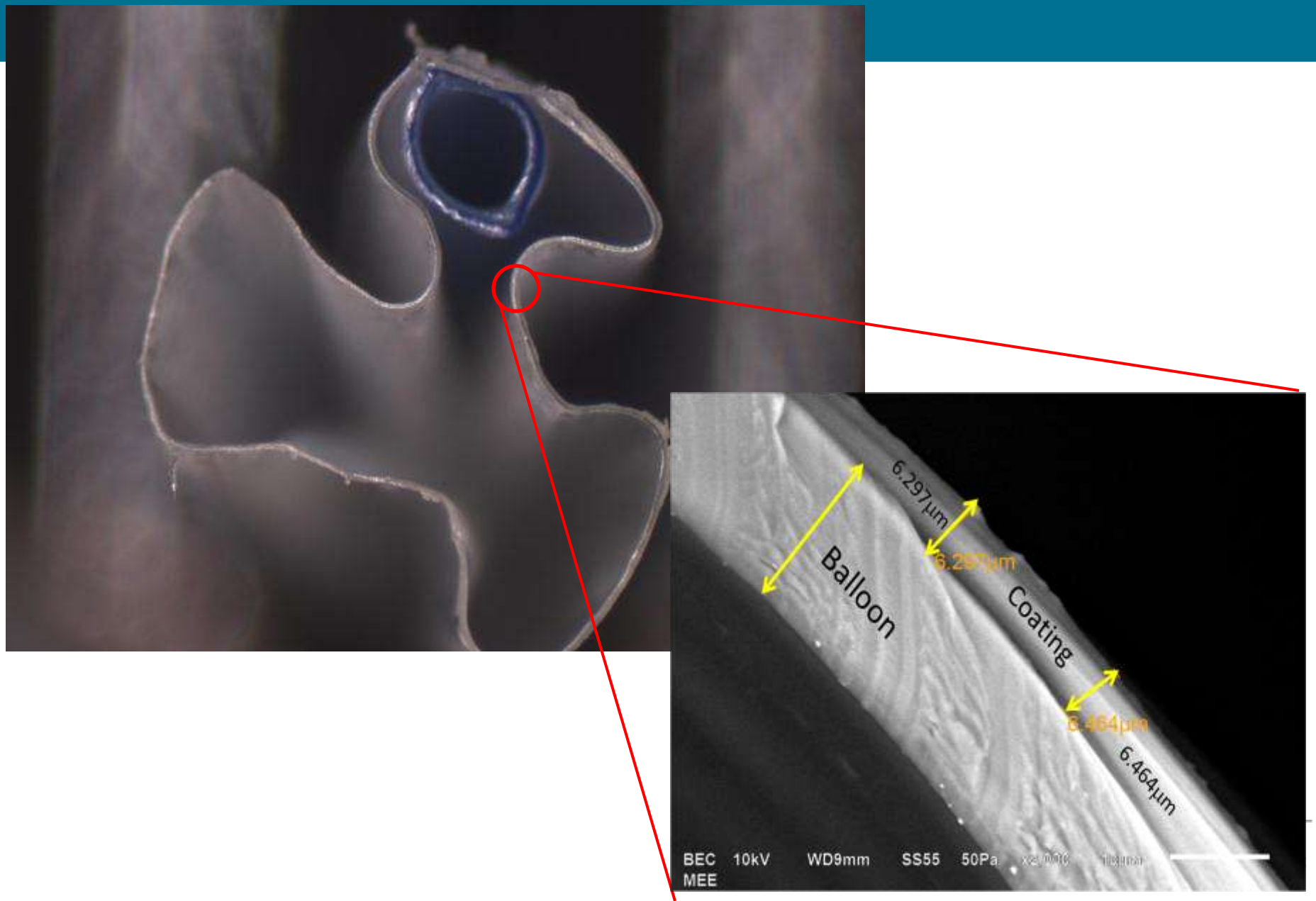
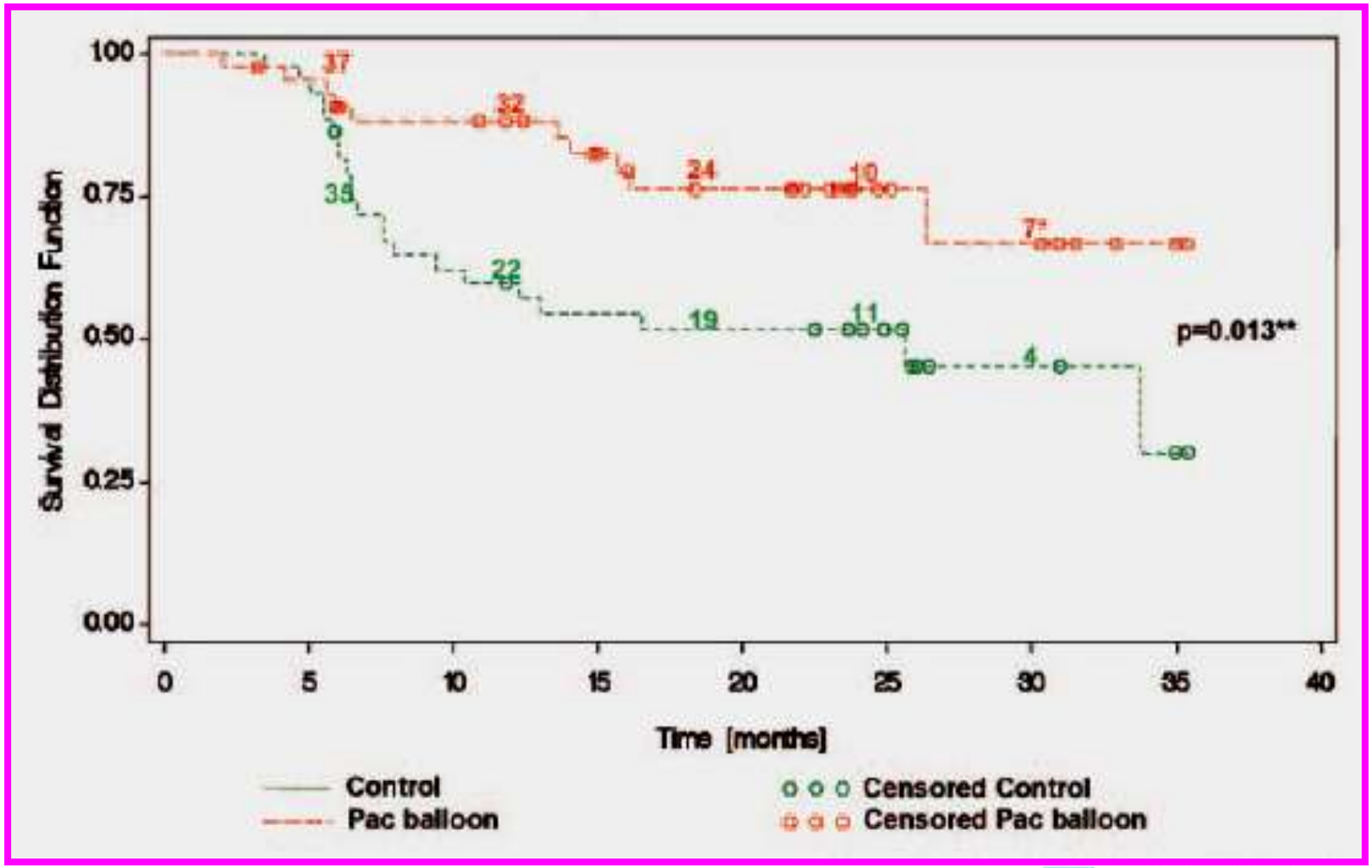
DRUG COATED BALLOONS

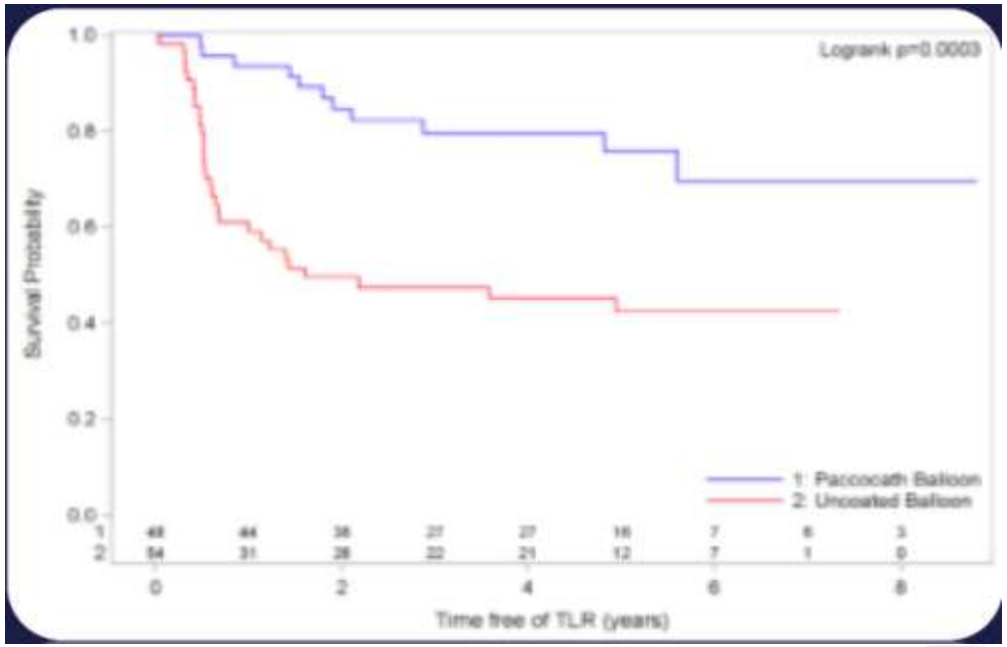


Paclitaxel Coated Balloons for Fem/Pop Disease



Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg

Gunnar Tepe, M.D., Thomas Zeller, M.D., Thomas Albrecht, M.D., Stephan Heller, M.D., Uwe Schwarzwälder, M.D., Jean-Paul Beregi, M.D. Claus D. Claussen, M.D., Anja Oldenburg, M.D., Bruno Scheller, M.D., and Ulrich Speck, Ph.D.



N Engl J Med 2008;358:689

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The Latest in DCB

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 7, NO. 1, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2013.05.022

The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization

CME

First-in-Human Randomized Trial of Low-Dose Drug-Coated Balloon Versus Uncoated Balloon Angioplasty

Dierk Scheinert, MD,* Stephan Duda, MD,† Thomas Zeller, MD,‡
Hans Krankenberg, MD,§ Jens Ricke, MD,‖ Marc Bosiers, MD,¶ Gunnar Tepe, MD,#
Scott Naisbitt, MD, PHD,** Kenneth Rosenfield, MD††

Leipzig, Berlin, Bad Krozingen, Hamburg, Rosenheim, and Magdeburg, Germany; Dendermonde, Belgium; New Hope, Minnesota; and Cambridge, Massachusetts

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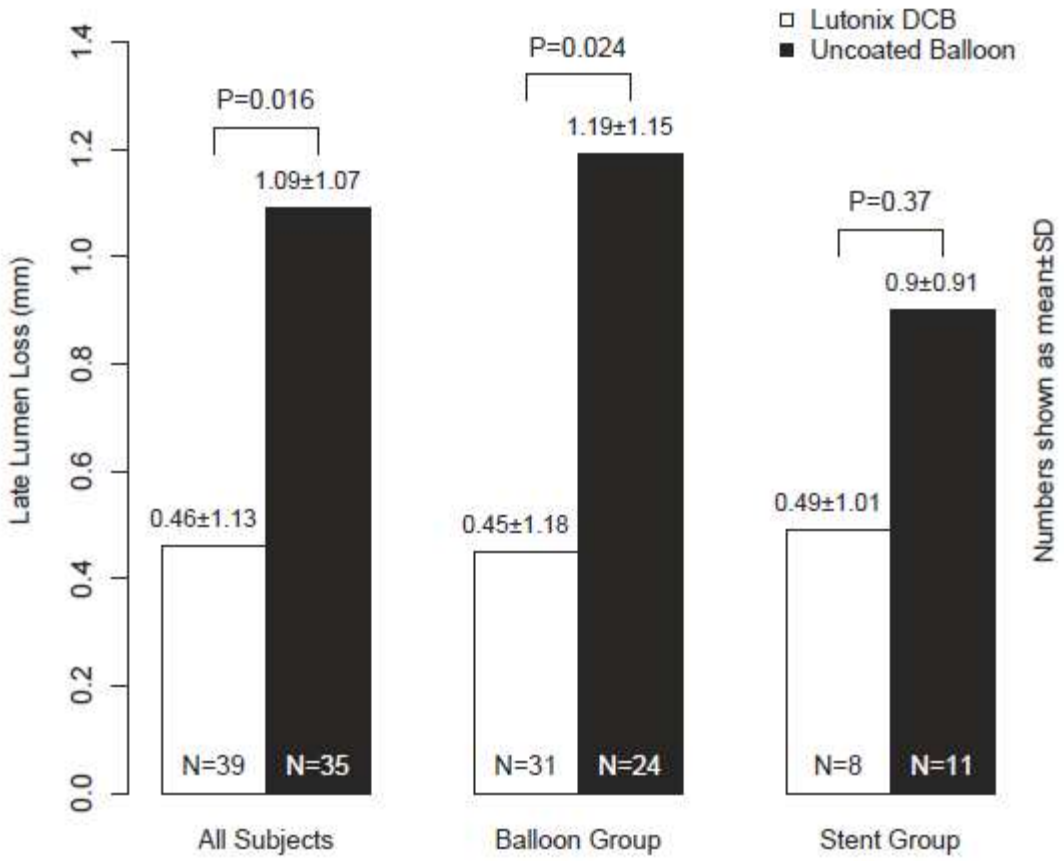
J Am Coll Cardiol Intv 2014;7:10-19.

Levant 1: Primary Efficacy Endpoint



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J Am Coll Cardiol Intv 2014;7:10-19.

The Latest?

IN.PACT SFA

Randomized Trial of IN.PACT Admiral DCB vs. PTA for the Treatment of Atherosclerotic Lesions in the SFA and/or PPA

1-year Primary Outcomes

Gunnar Tepe - RoMed Klinikum Rosenheim, Rosenheim (Germany)

Peter Schneider - Hawaii Permanente, Honolulu, HI (US)

John Laird - UC Davis Medical Center, Sacramento, CA (US)

on behalf of the IN.PACT SFA Investigators

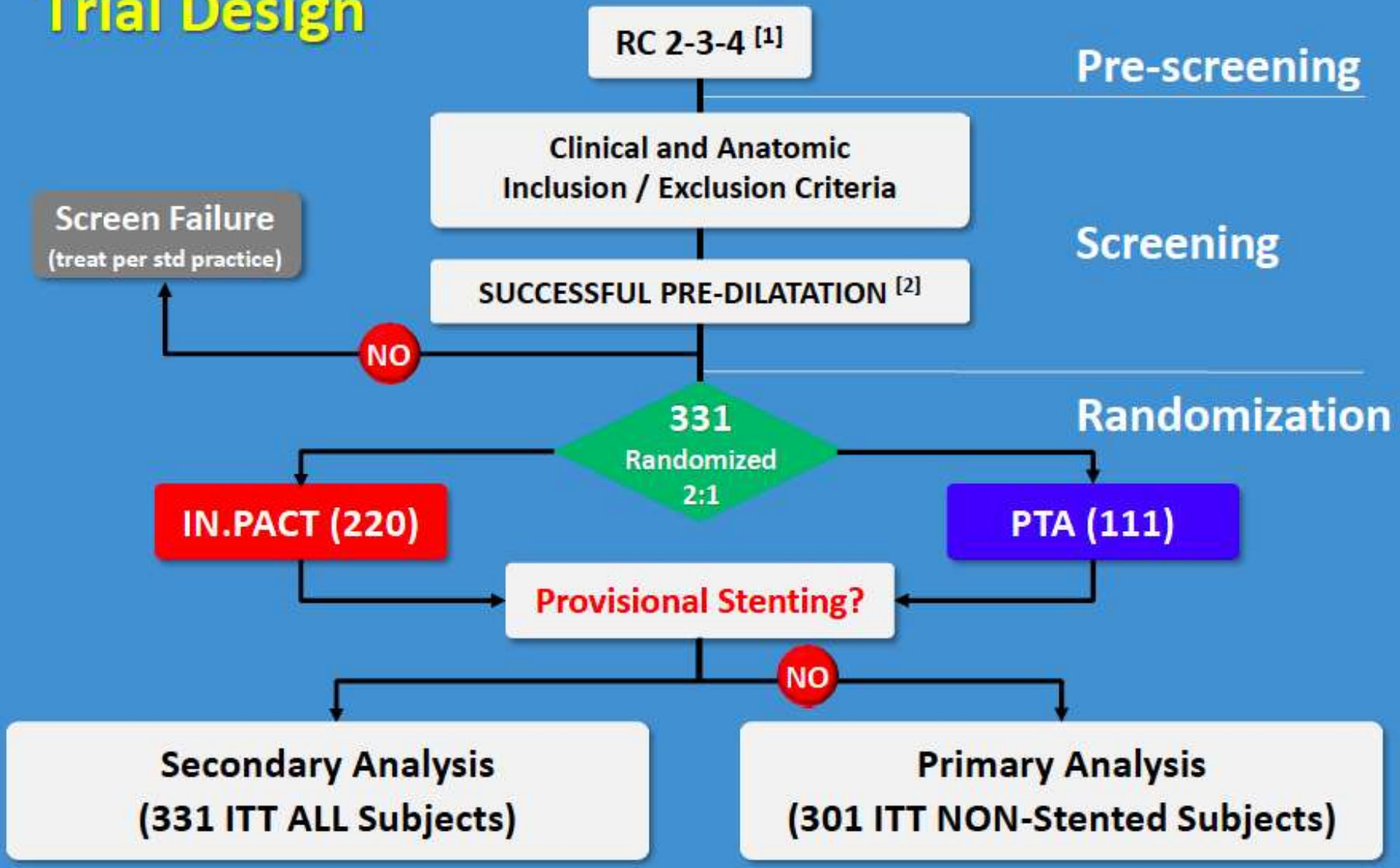
IN.PACT SFA Trial Overview

IN.PACT Admiral DCB vs. standard PTA
for the treatment of superficial femoral and proximal popliteal artery disease due to claudication and rest pain

- Prospective, multicenter EU and US, randomized (2:1), single blinded
- Independent and blinded Duplex Ultrasound Core Lab [1], Angiographic Core Lab [2], and Clinical Events Committee [3]
- Independent Data Safety Monitoring Board [3]
- External monitoring with 100% source data verification
- Subjects followed up to 5 years

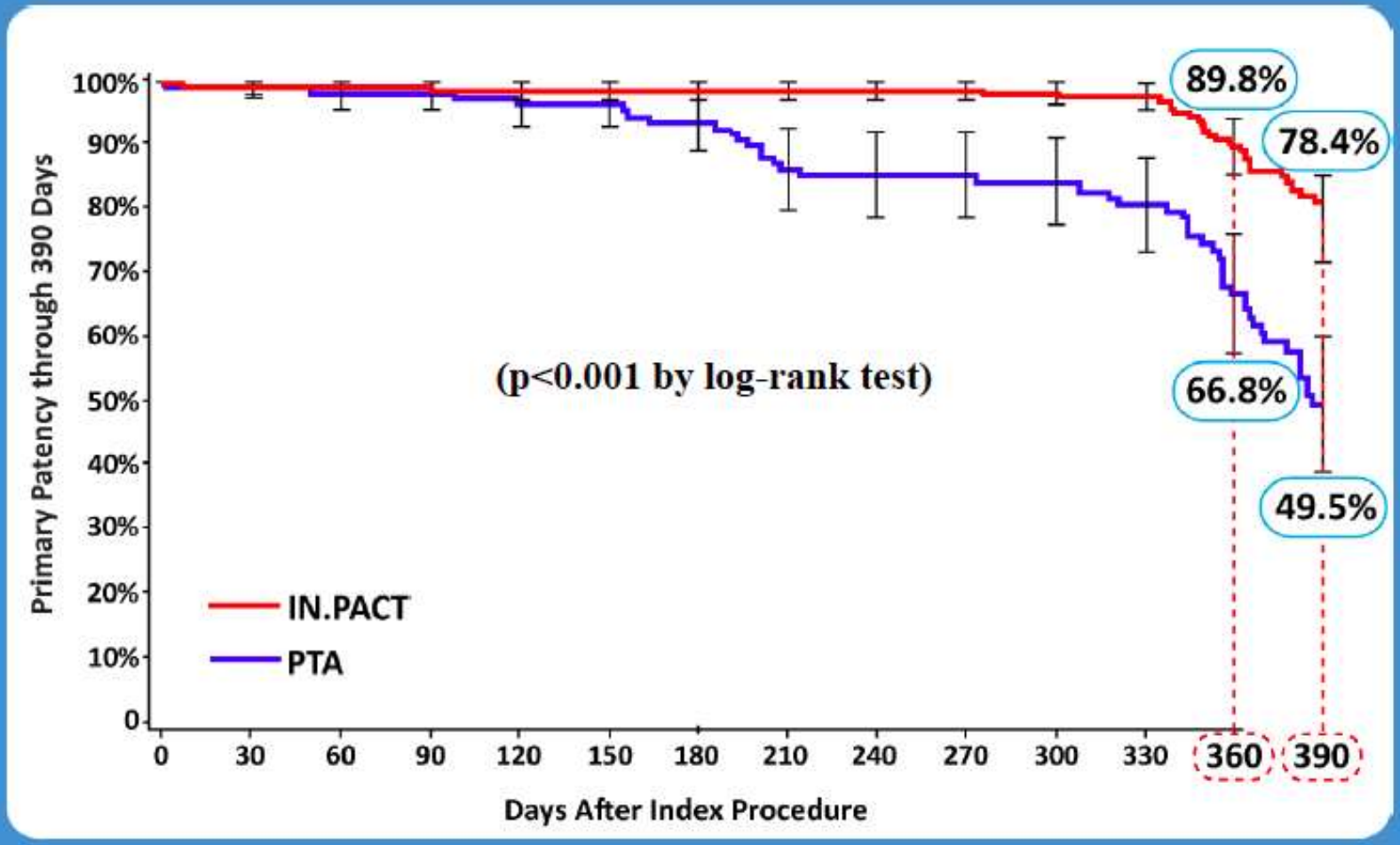
1. VasCore DUS Core Laboratory, Boston, MA, US
2. SynvaCor Angiographic Core Laboratory, Springfield, IL, US
3. Clinical Events Committee and Data Safety Monitoring services provided by HCRI, Boston, MA, US

Trial Design



1. With symptoms of claudication and/or rest pain and angiographic evidence of SFA/PPA stenosis
2. Pre-dilatation mandatory for all subjects in IN.PACT SFA II phase only

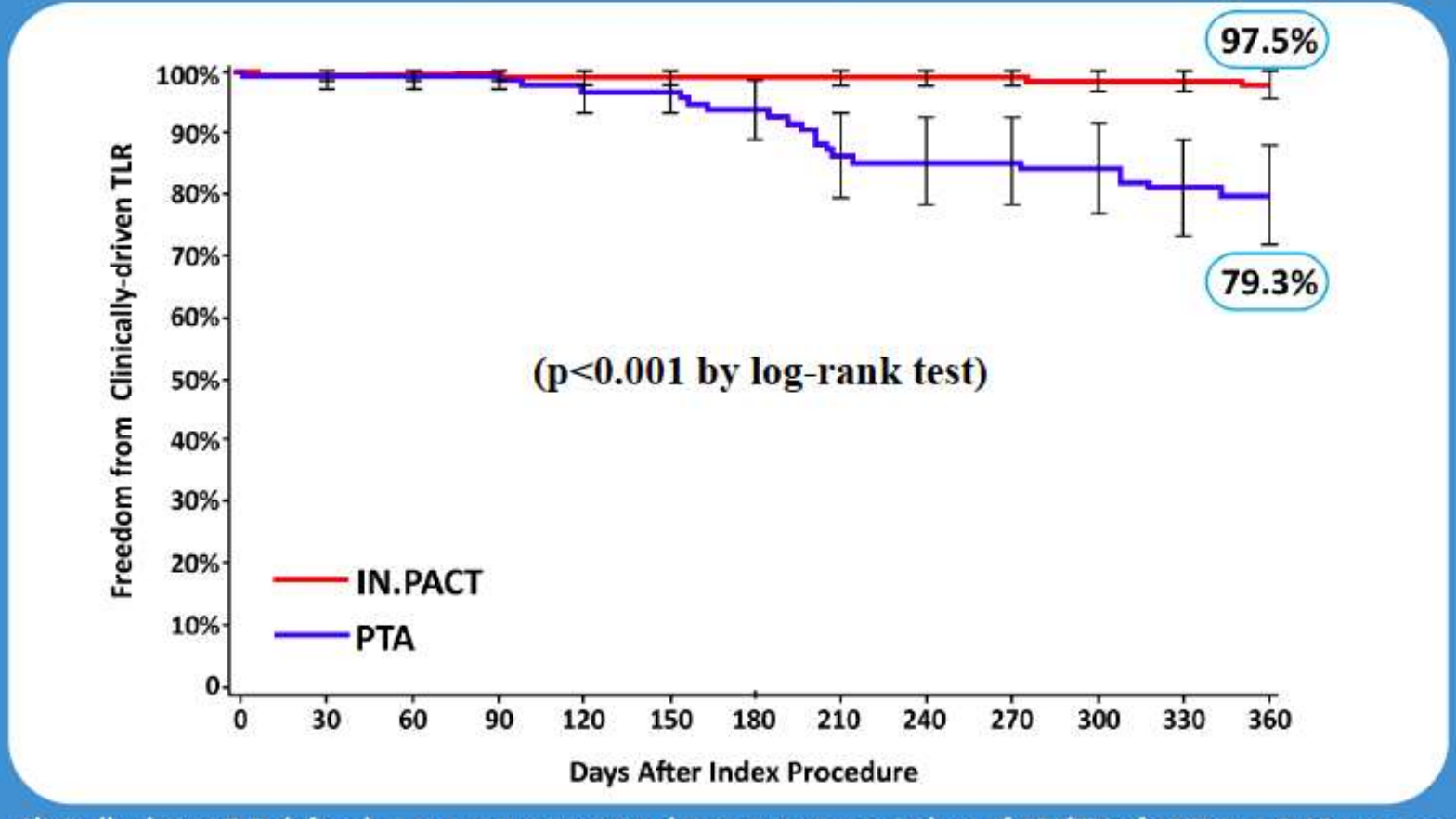
ALL ITT, 12-month Primary Patency [1]



1. Primary patency is defined as freedom from clinically-driven TLR and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4

ALL ITT, 12-month Clinically-driven TLR

	IN.PACT	PTA	*p*
Clinically-driven TLR [1]	2.4%	20.6%	*<0.001* [2]



1. Clinically-driven TLR defined as any re-intervention due to symptoms or drop of ABI/TBI of >20% or >0.15 compared to post-procedure ABI/TBI
2. Actual event rate by frequency ratio algorithm calculation

ALL ITT, Safety Outcomes

	IN.PACT	PTA	p
Primary Safety Composite [1]	**95.7% (198/207)**	**76.6% (82/107)**	***<0.001***
30-day Device- and Proc.-related Death	0.0% (0/218)	0.0% (0/111)	*>0.999*
12-month Clinically-driven TVR	4.3% (9/207)	23.4% (25/107)	*<0.001*
12-month Target Limb Major Amputation	0.0% (0/207)	0.0% (0/107)	*>0.999*
12-month Major Adverse Events [2]	**6.3% (13/207)**	**24.3% (26/107)**	***<0.001***
All-cause Death	1.9% (4/207)	0.0% (0/107)	*0.926*
Clinically-driven TVR	4.3% (9/207)	23.4% (25/107)	*<0.001*
Target Limb Major Amputation	0.0% (0/207)	0.0% (0/107)	*>0.999*
Thrombosis	1.4% (3/207)	3.7% (4/107)	*0.096*

1. Freedom from 30-day device and procedure-related death and target limb major amputation and clinically-driven TVR within 12 months
2. Composite of death, clinically-driven TVR, target limb major amputation, and thrombosis within 12 months

So What's the Future in SFA Therapy?

- Push towards endovascular persists
- Non-stent based approach gaining traction
  - Atherectomy?
  - DCB?
  - Atherectomy PLUS DCB???
- Bioresorbables?