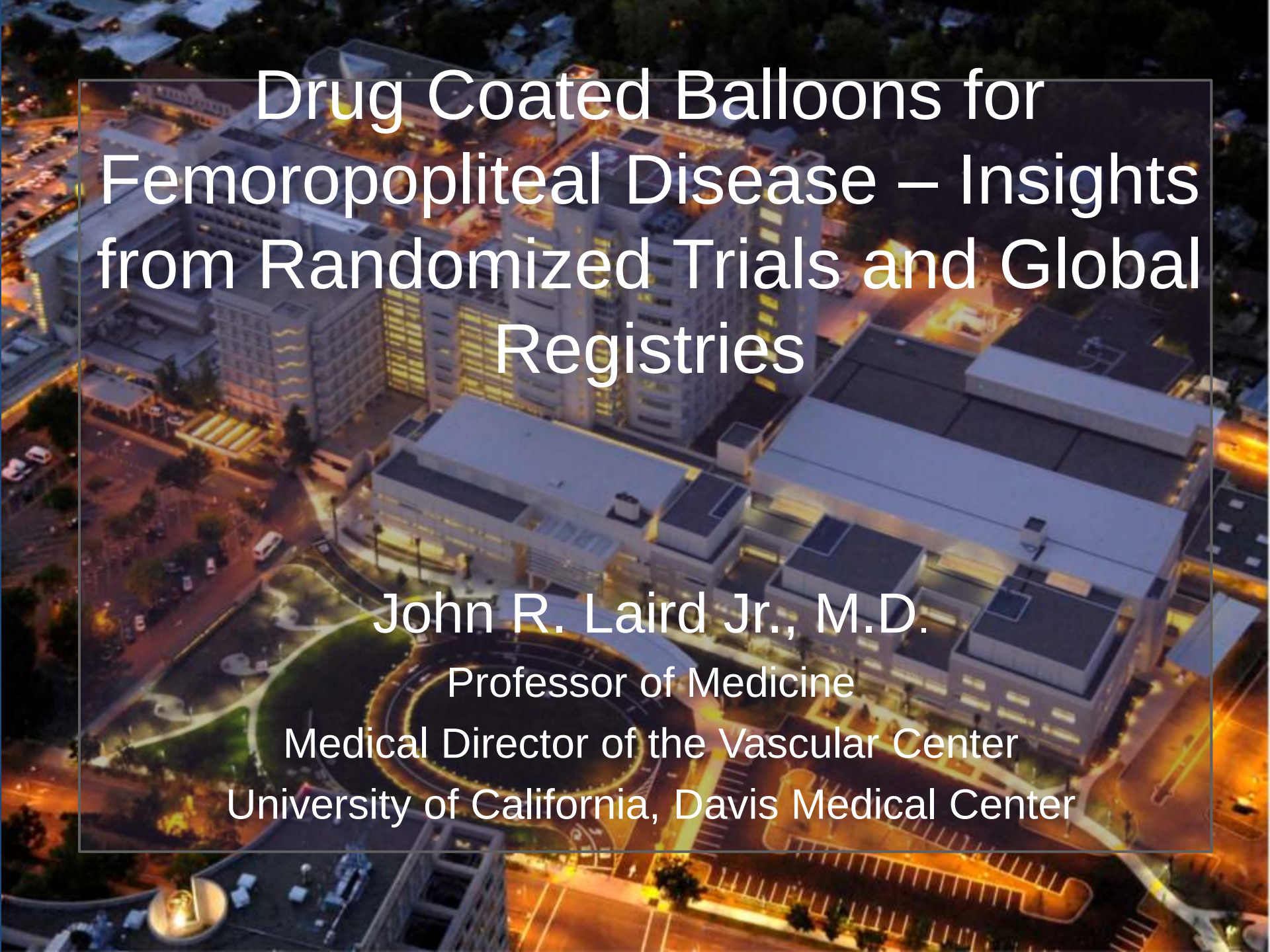


Drug Coated Balloons for Femoropopliteal Disease – Insights from Randomized Trials and Global Registries

John R. Laird Jr., M.D.
Professor of Medicine
Medical Director of the Vascular Center
University of California, Davis Medical Center

Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
• Grant/Research Support	• WL Gore, Medtronic
• Consulting Fees/Honoraria	• Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Cordis, Medtronic

The Evolution of Drug Eluting Balloons

Paclitaxel Balloon Coating, a Novel Method for Prevention and Therapy of Restenosis

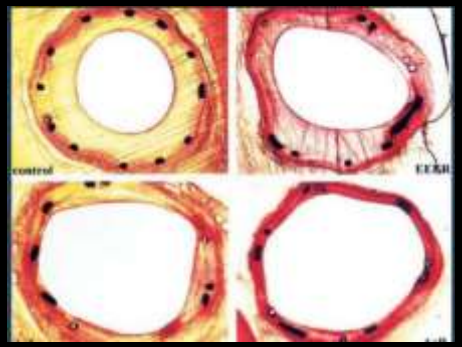
Bruno Scheller, MD; Ulrich Speck, PhD; Claudia Abramjuk, DVM; Ulrich Bernhardt, PhD; Michael Böhm, MD; Georg Nickenig MD

Background—Drug-eluting stents have shown promising antirestenotic effects in clinical trials. Non–stent-based local delivery of antiproliferative drugs may offer additional flexibility and also reach vessel areas beyond the immediate stent coverage. The aim of the present study was to evaluate a novel method of local drug delivery based on angioplasty balloons.

Methods and Results—Stainless steel stents (n=40; diameter, 3.0 to 3.5 mm; length, 18 mm) were implanted in the left anterior descending and circumflex coronary arteries of domestic pigs. Both conventional uncoated and 3 different types of paclitaxel-coated, percutaneous transluminal coronary angioplasty balloons (contact with vessel wall for 1 minute) were used. No difference in short-term tolerance between coated and uncoated balloons and no signs of thrombotic events were observed. Quantitative angiography and histomorphometry of the stented arteries asserted the statistical equality of the baseline parameters between the control and the 3 treatment groups. Paclitaxel balloon coating led to a marked, dose-dependent reduction of parameters characterizing in-stent restenosis (reduction of neointimal area up to 63%). Despite the marked reduction in neointimal proliferation, endothelialization of stent struts was present in all samples. There was no evidence of a significant inflammatory response in the neighborhood of the stent struts.

Conclusions—Paclitaxel balloon coating is safe, and it effectively inhibits restenosis after coronary angioplasty with stent implantation in the porcine model. The degree of reduction in neointimal formation was comparable to that achieved with drug-eluting stents. **(*Circulation*. 2004;110:810-814.)**

Key Words: restenosis ■ angioplasty ■ paclitaxel



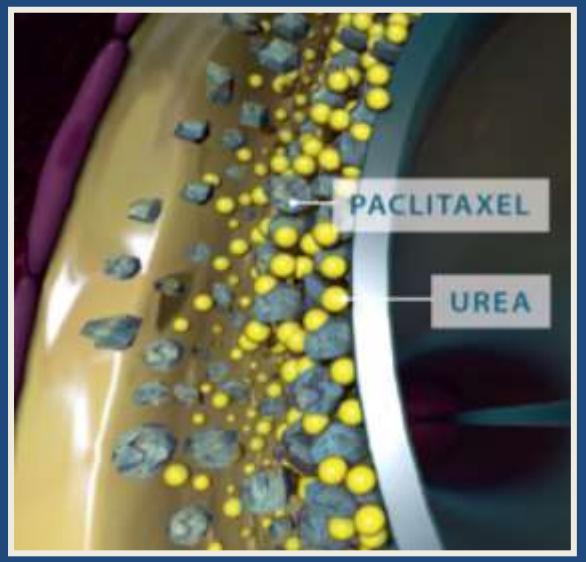
Mechanism of Action

Manufacturing:

- Balloon coated with matrix in semi-inflated state, then wrapped

During Transit to Lesion:

- Majority of matrix protected within folds of the balloon



DCB Matrix Coating:

DCB Inflation:

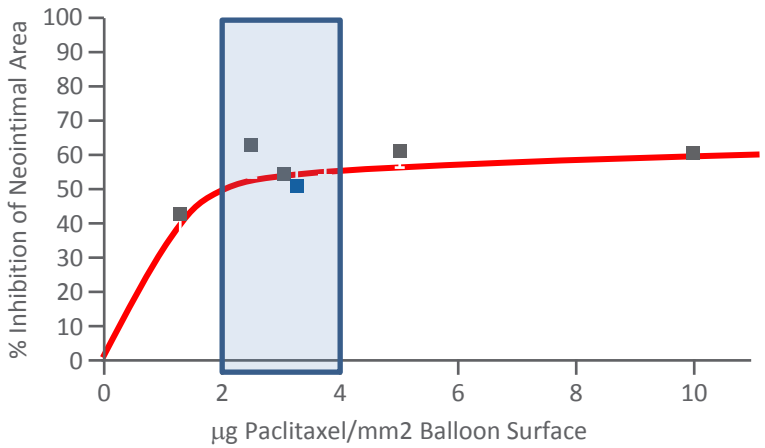
- Matrix contacts blood
- Excipient releases paclitaxel

Paclitaxel Hydrophobic and Lipophilic Properties:

- Facilitates transfer from balloon and stickiness to vessel wall
- Migrates through vessel wall deep into the media and adventitia
- Remains in vessel wall fro over 180 days at therapeutic levels[1]

Paclitaxel Dose Selection

Paclitaxel offers a wide therapeutic window



Therapeutic range 2-4 µg/mm²
IN.PACT Admiral: 3.5 µg/mm²

- Dose-dependent response up to 2-4 µg/mm²
- Wide, stable therapeutic window with no statistically significant differences in neointimal inhibition or local toxic effects from 4 up to 10 µg/mm²
- 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, 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.
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5. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med*. 1995;332:1004-1014.
6. Margolis J, 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.

Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and Popliteal Peripheral Artery Disease

12-Month Results From the IN.PACT SFA Randomized Trial

Gunnar Tepe, MD; John Laird, MD; Peter Schneider, MD; Marianne Brodmann, MD; Prakash Krishnan, MD; Antonio Micari, MD; Christopher Metzger, MD; Dierk Scheinert, MD; Thomas Zeller, MD; David J. Cohen, MD, MSc; David B. Snead, PhD; Beaux Alexander, MBA; Mario Landini, MS; Michael R. Jaff, DO; for the IN.PACT SFA Trial Investigators*

Background—Drug-coated balloons (DCBs) have shown promise in improving the outcomes for patients with peripheral artery disease. We compared a paclitaxel-coated balloon with percutaneous transluminal angioplasty (PTA) for the treatment of symptomatic superficial femoral and popliteal artery disease.

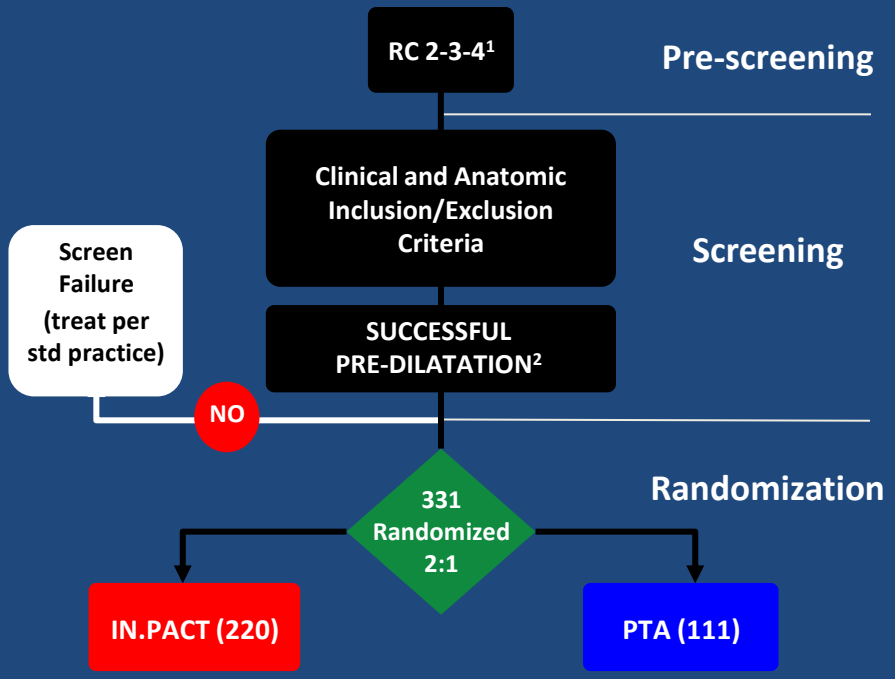
Methods and Results—The IN.PACT SFA Trial is a prospective, multicenter, single-blinded, randomized trial in which 331 patients with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The primary efficacy end point was primary patency, defined as freedom from restenosis or clinically driven target lesion revascularization at 12 months. Baseline characteristics were similar between the 2 groups. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were 8.94±4.89 and 8.81±5.12 cm (P=0.82) and 25.8% and 19.5% (P=0.22), respectively. DCB resulted in higher primary patency versus PTA (82.2% versus 52.4%; P<0.001). The rate of clinically driven target lesion revascularization was 2.4% in the DCB arm in comparison with 20.6% in the PTA arm (P<0.001). There was a low rate of vessel thrombosis in both arms (1.4% after DCB and 3.7% after PTA [P=0.10]). There were no device- or procedure-related deaths and no major amputations.

Conclusions—In this prospective, multicenter, randomized trial, DCB was superior to PTA and had a favorable safety profile for the treatment of patients with symptomatic femoropopliteal peripheral artery disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique Identifiers: NCT01175850 and NCT01566461. (***Circulation***. **2015;131:495-502. DOI: 10.1161/CIRCULATIONAHA.114.011004.**)

Key Words: drug-eluting balloons ■ peripheral arterial disease ■ peripheral vascular diseases

IN.PACT SFA Trial Overview



IN.PACT SFA

Aggregate dataset from Phase I and II

Primary Endpoints:

- **Efficacy**[3]: 12-month Primary Patency
- Freedom from clinically-driven TLR and duplex ultrasound derived restenosis (PSVR ≤2.4)
- **Safety**[4]: 30-day device/procedure death, 12-month amputation, 12-month clinically-driven TVR

Key Inclusion Criteria:

- Rutherford 2-3-4
- SFA and proximal popliteal
- Lesion length 4-18 cm
- Total occlusion ≤10 cm

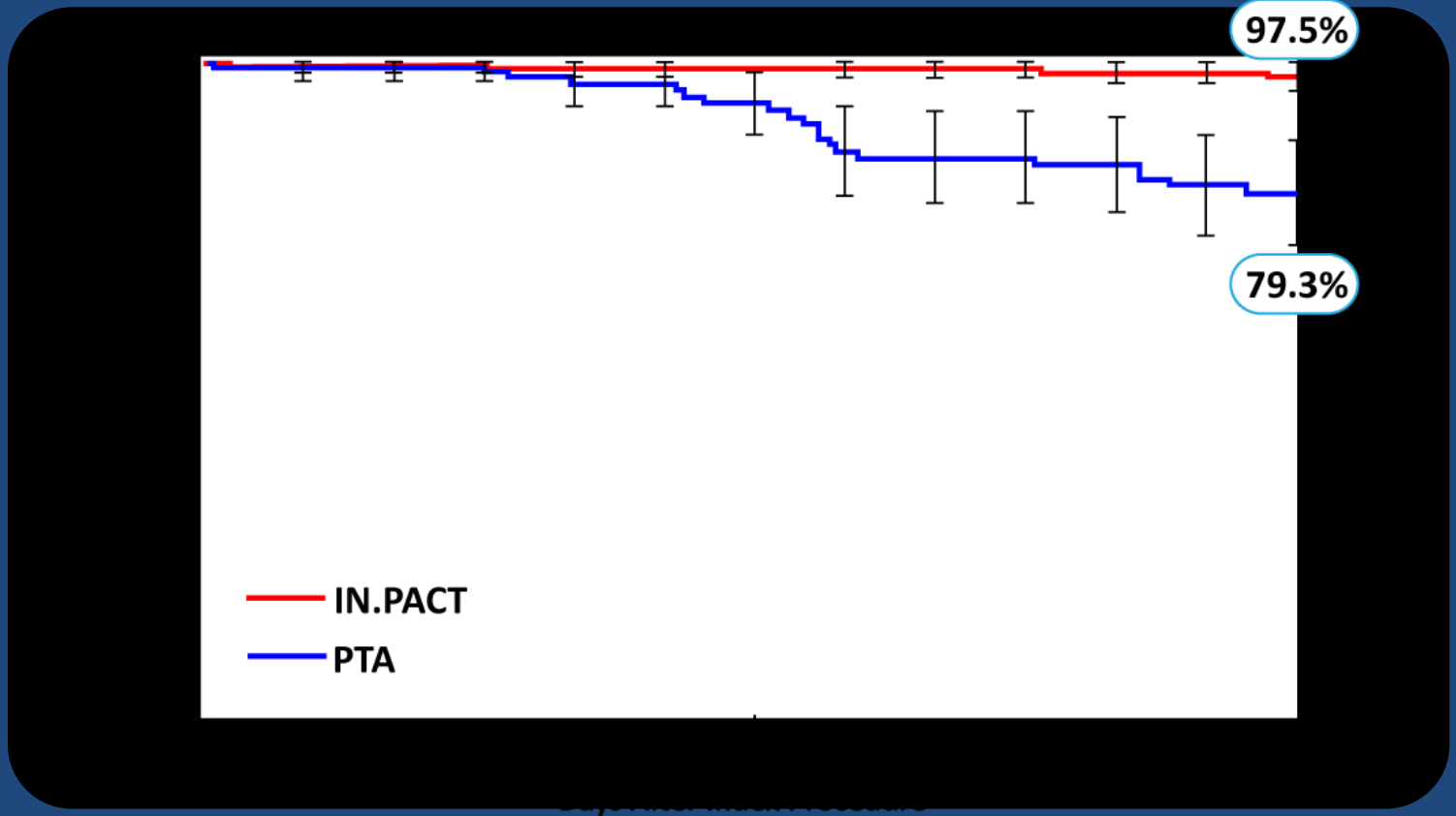
1. With symptoms of claudication and/or rest pain and angiographic evidence of SFA/PPA stenosis
2. Pre-dilatation mandatory for all subjects in IN.PACT SFA II phase only
3. Primary Efficacy Analysis on all ITT non-stented subjects based on superiority assumption of DCB vs. PTA
4. Primary Safety Analysis on all ITT non-stented subjects based on non-inferiority of DCB vs. PTA

Baseline lesion Characteristics

	IN.PACT n = 221 lesions	PTA n = 113 lesions	p
Lesion length (cm ± SD)	8.94 ± 4.89	8.81 ± 5.12	0.815
Total occlusions, % (n)	25.8% (57/221)	19.5% (22/113)	0.222
Calcification, % (n)	59.3% (131/221)	58.4% (66/113)	0.907
Severe calcification, % (n)	8.1% (18/221)	6.2% (7/113)	0.662
Provisional stenting, % (n)	7.3% (16/220)	12.6% (14/111)	0.110

12-month Freedom From Clinically-driven TLR

	IN.PACT DCB	PTA	p
Clinically-driven TLR	2.4%	20.6%	<0.001



Clinically-driven TLR adjudicated by an independent Clinical Events Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI.

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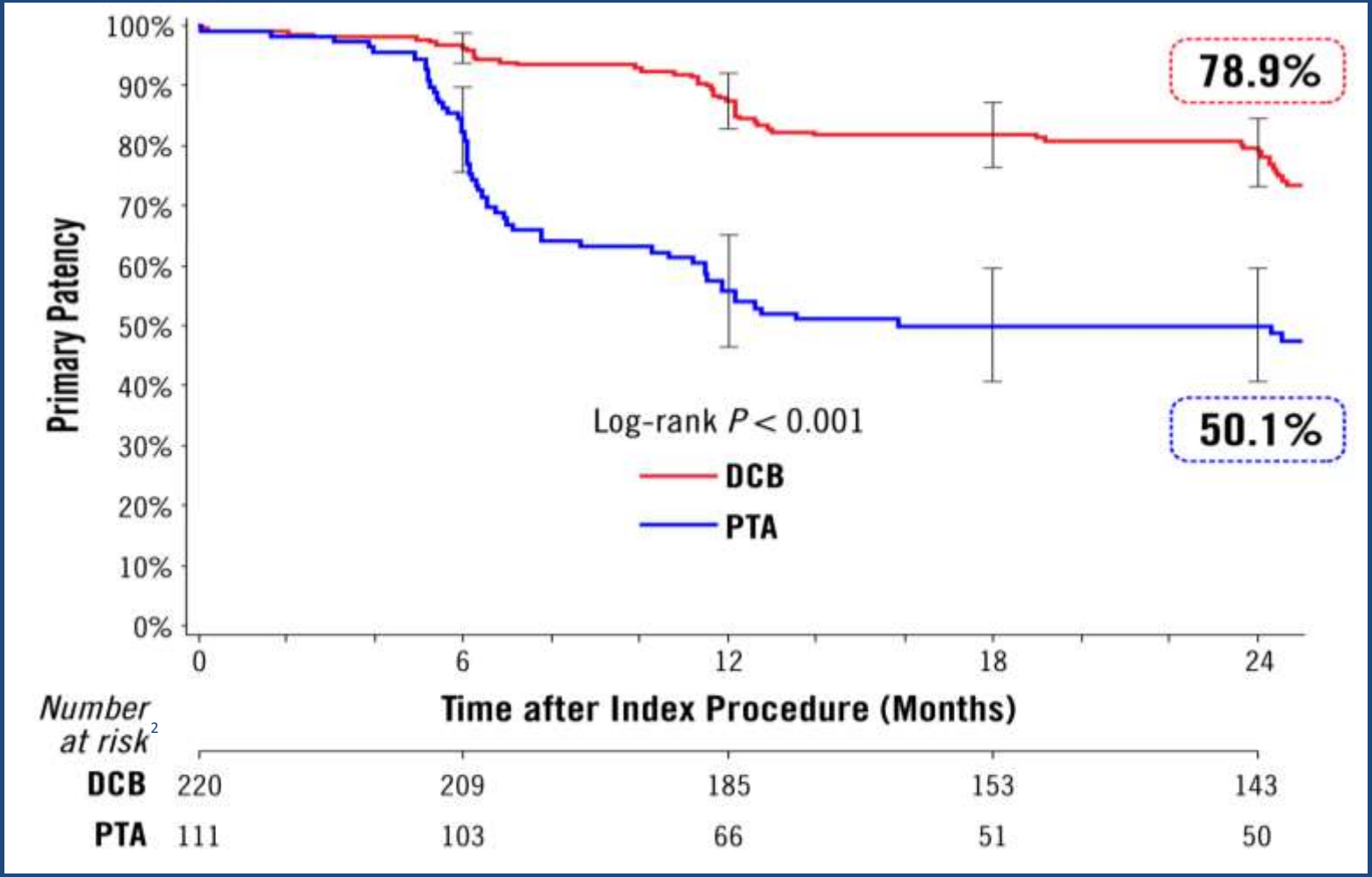
Sustained Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions

24-Month Results of IN.PACT SFA

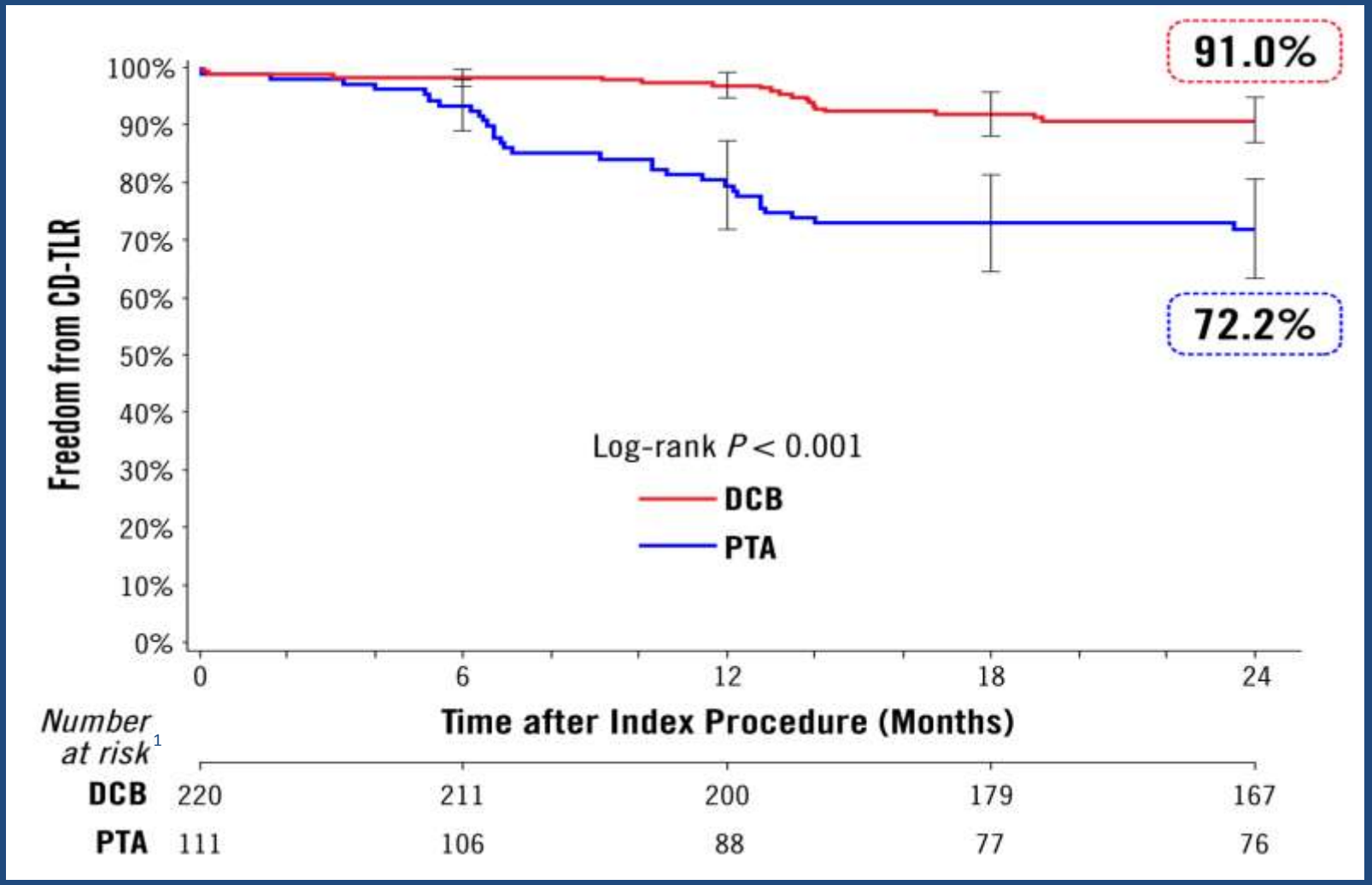
John R. Laird, MD,* Peter A. Schneider, MD,† Gunnar Tepe, MD,‡ Marianne Brodmann, MD,§ Thomas Zeller, MD,‖ Christopher Metzger, MD,¶ Prakash Krishnan, MD,# Dierk Scheinert, MD,** Antonio Micari, MD, PhD,†† David J. Cohen, MD, MSc,‡‡ Hong Wang, MD, MPH,§§ Melissa S. Hasenbank, PhD,§§ Michael R. Jaff, DO,‖‖ for the IN.PACT SFA Trial Investigators

Primary Patency[1] Results through 2 Years



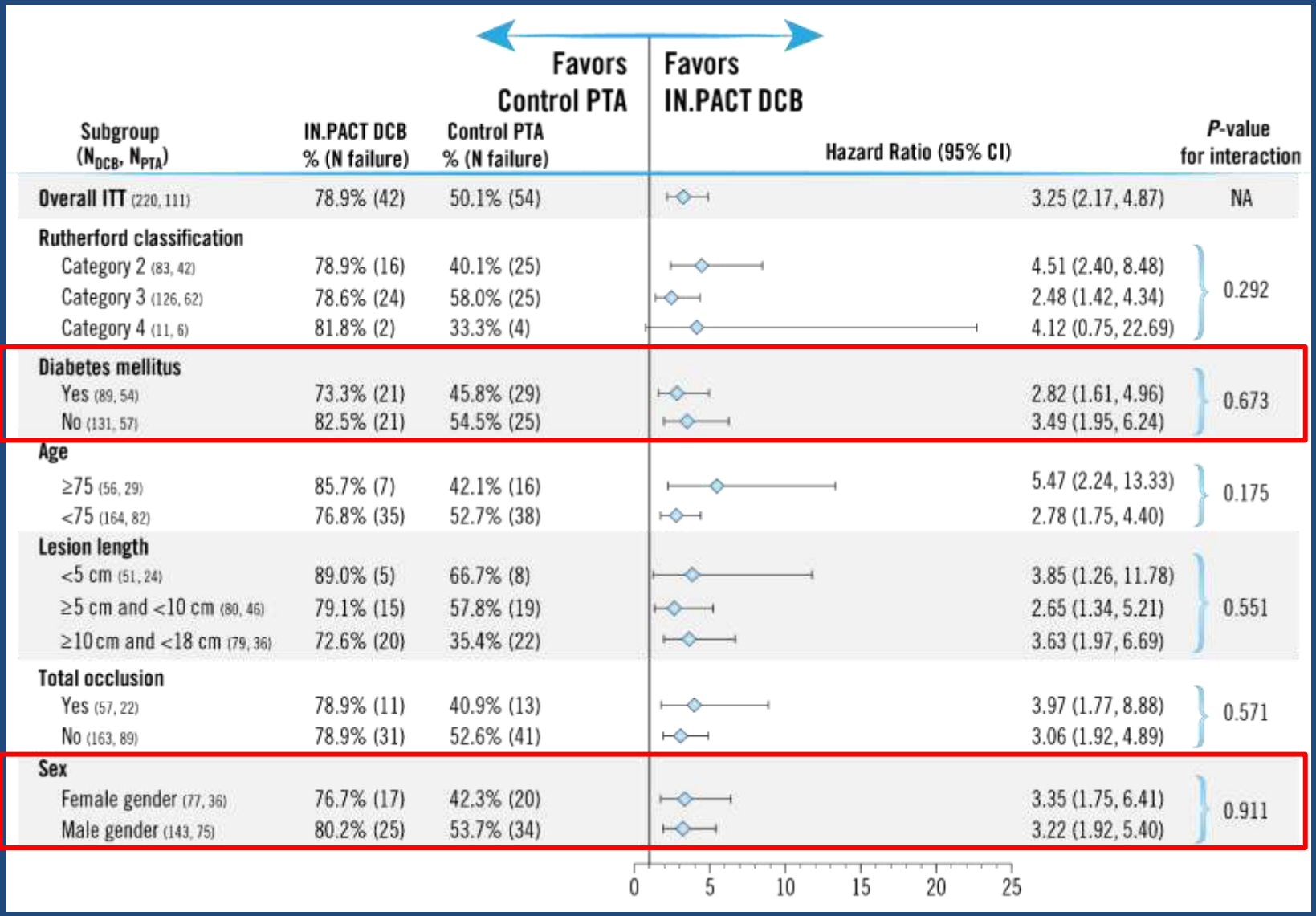
1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)
2. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval

Freedom from CD-TLR through 2 Years



1. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval

IN.PACT SFA Trial Subgroups
Primary Patency Outcomes Through 2 Years



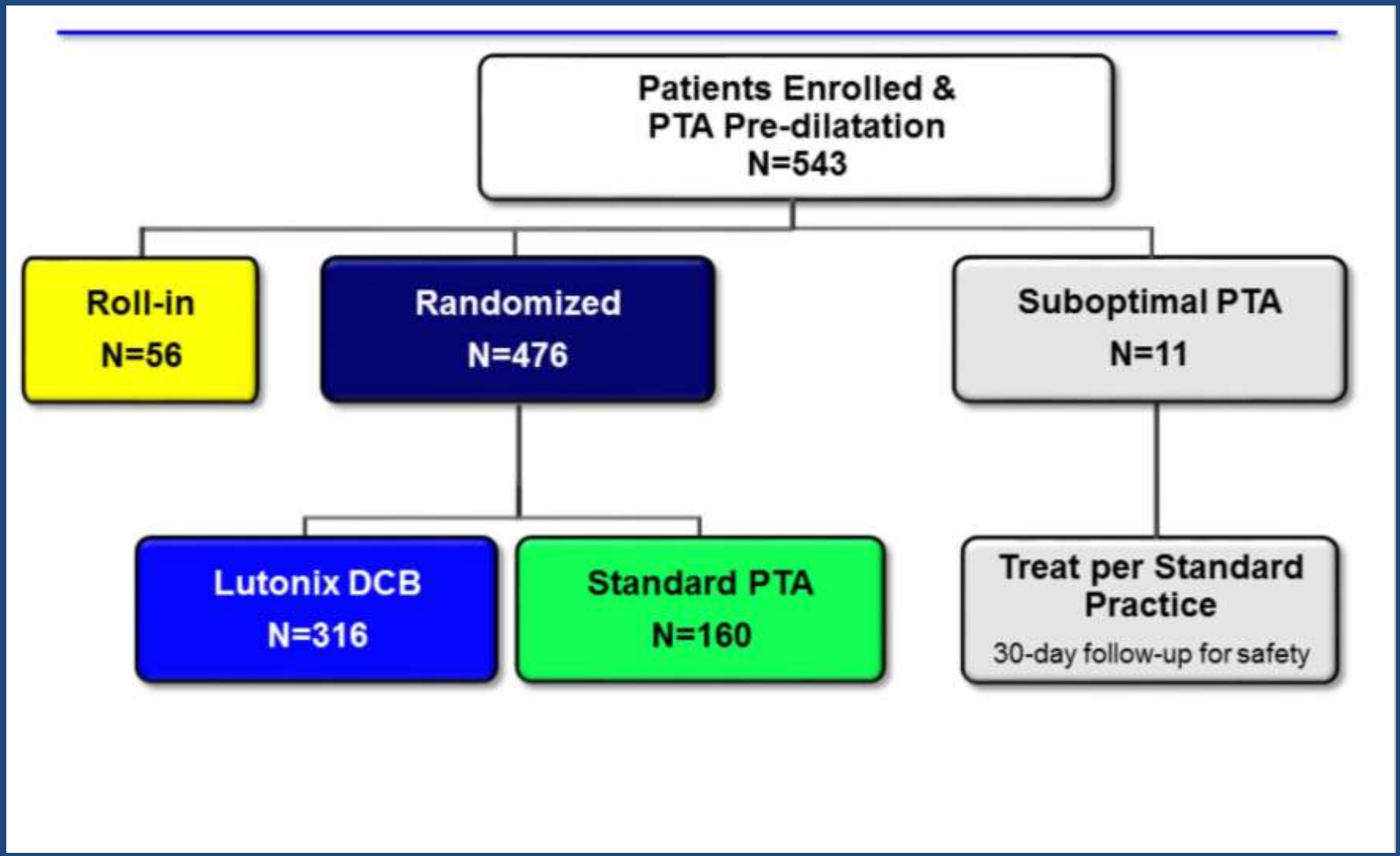
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

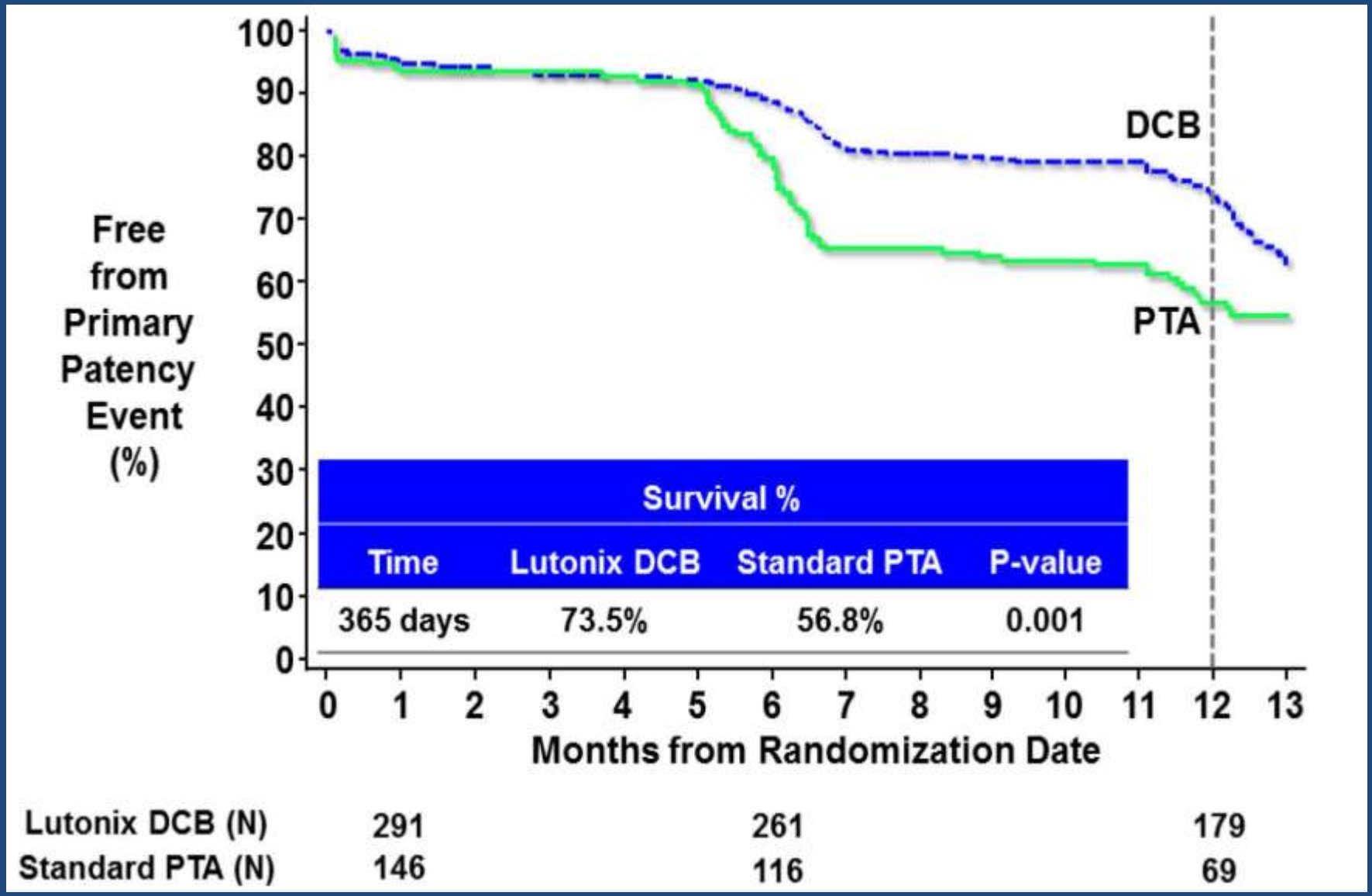
Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease

Kenneth Rosenfield, M.D., Michael R. Jaff, D.O., Christopher J. White, M.D., Krishna Rocha-Singh, M.D., Carlos Mena-Hurtado, M.D., D. Christopher Metzger, M.D., Marianne Brodmann, M.D., Ernst Pilger, M.D., Thomas Zeller, M.D., Prakash Krishnan, M.D., Roger Gammon, M.D., Stefan Müller-Hülsbeck, M.D., Mark R. Nehler, M.D., James F. Benenati, M.D., and Dierk Scheinert, M.D., for the LEVANT 2 Investigators*

Patient Enrollment



Primary Patency Kaplan-Meier

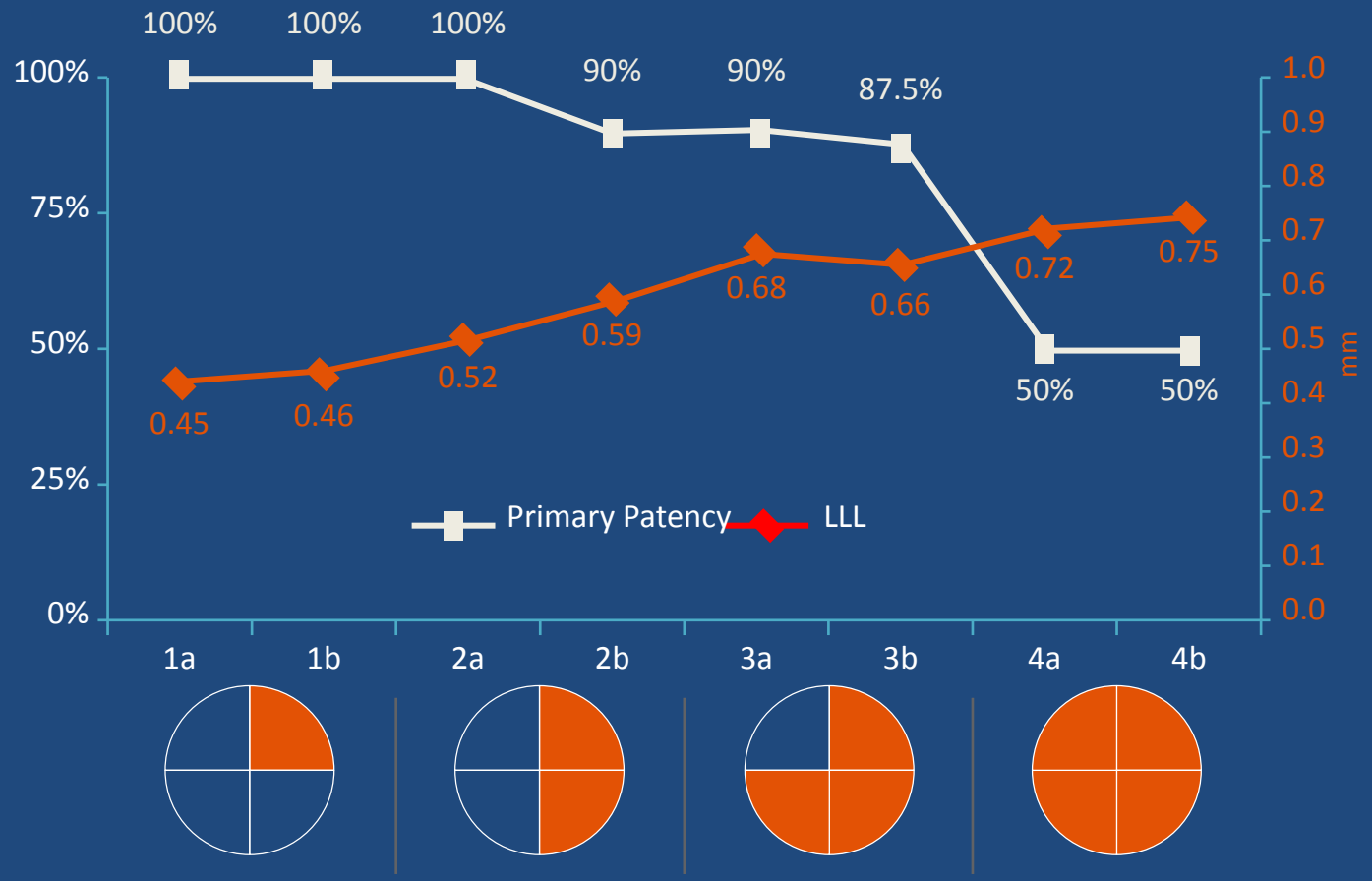


Lesions Not Included in the Randomized Clinical Trials

- Calcified lesions
- Long lesions
- Chronic total occlusions
- Instent restenosis

DCB AND CALCIUM

IN.PACT™ DCB and Calcium Registry Study (n=60) 12-month Results



Calcium distribution evaluation by CTA (circumf.) and DSA (longitud.); "a" <3cm and "b" >3cm

- Calcium distribution and severity affect LLL and primary patency
- Ca^{2+} represents a barrier to optimal drug absorption

(F.Fanelli Cardiovasc Intervent Radiol 2014)

DCB for Longer Lesions, CTOs and Instent Restenosis

Results of the Global Registries

IN.PACT Global Study

Real-world, prospective, multicenter, single arm independently-adjudicated femoropopliteal study

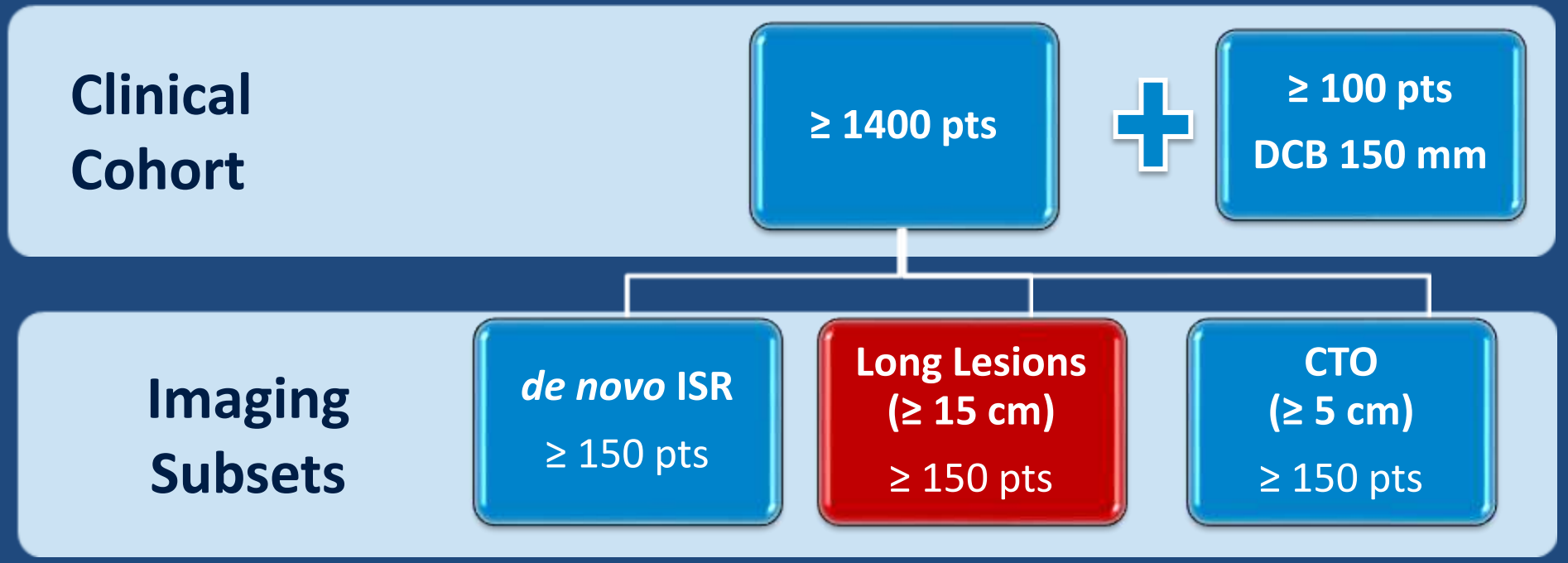
All-comers (RCC 2-4)

- ☑ Bilateral disease
- ☑ Multiple lesions
- ☑ SFA and Popliteal
- ☑ TASC A, B, C, D
- ☑ *de novo* ISR
- ☑ Long Lesions
- ☑ CTOs

- >1500 patients enrolled
- 64 sites in EU, Mid-East, Latin America, Asia
- Independent adjudication by Clinical Events Committee[1]
- Prospective subset analysis with core lab[2,3] reported results
  (*de novo* ISR, long lesions ≥15 cm, CTOs ≥5 cm)
- Safety and effectiveness data on 150 mm DCB

1. Syntactx Clinical Events Committee, New York, NY, US
2. VasCore DUS Core Lab, Boston, MA, US
3. SynvaCor Angiographic Core Lab, Springfield, IL, US

IN.PACT Global Study Patient Cohorts
1538 Patients Enrolled



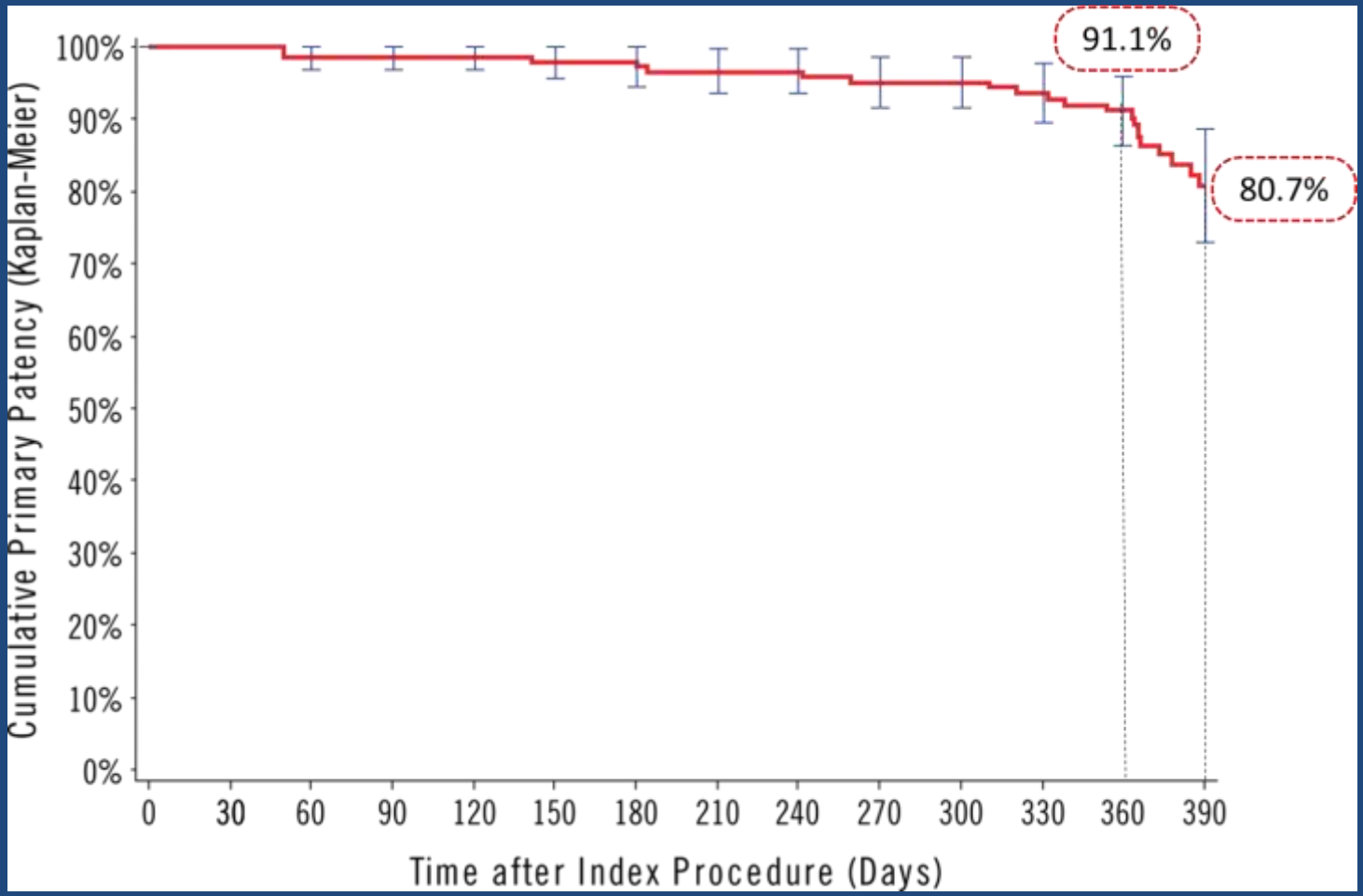
IN.PACT Global Long Lesion Imaging Cohort: Lesion/Procedural Characteristics

Lesions (N)	164
Lesion Type:	
de novo	83.2% (134/161)
restenotic (no ISR)	16.8% (27/161)
ISR	0.0% (0/161)
Lesion Length	**26.40 ± 8.61 cm**
Total Occlusions	60.4% (99/164)
Calcification	71.8% (117/163)
Severe	19.6% (32/163)
RVD (mm)	4.594 ± 0.819
Diameter Stenosis (pre-treatment)	90.9% ± 14.2
Dissections: 0	37.9% (61/161)
A-C	47.2% (76/161)
D-F	14.9% (24/161)

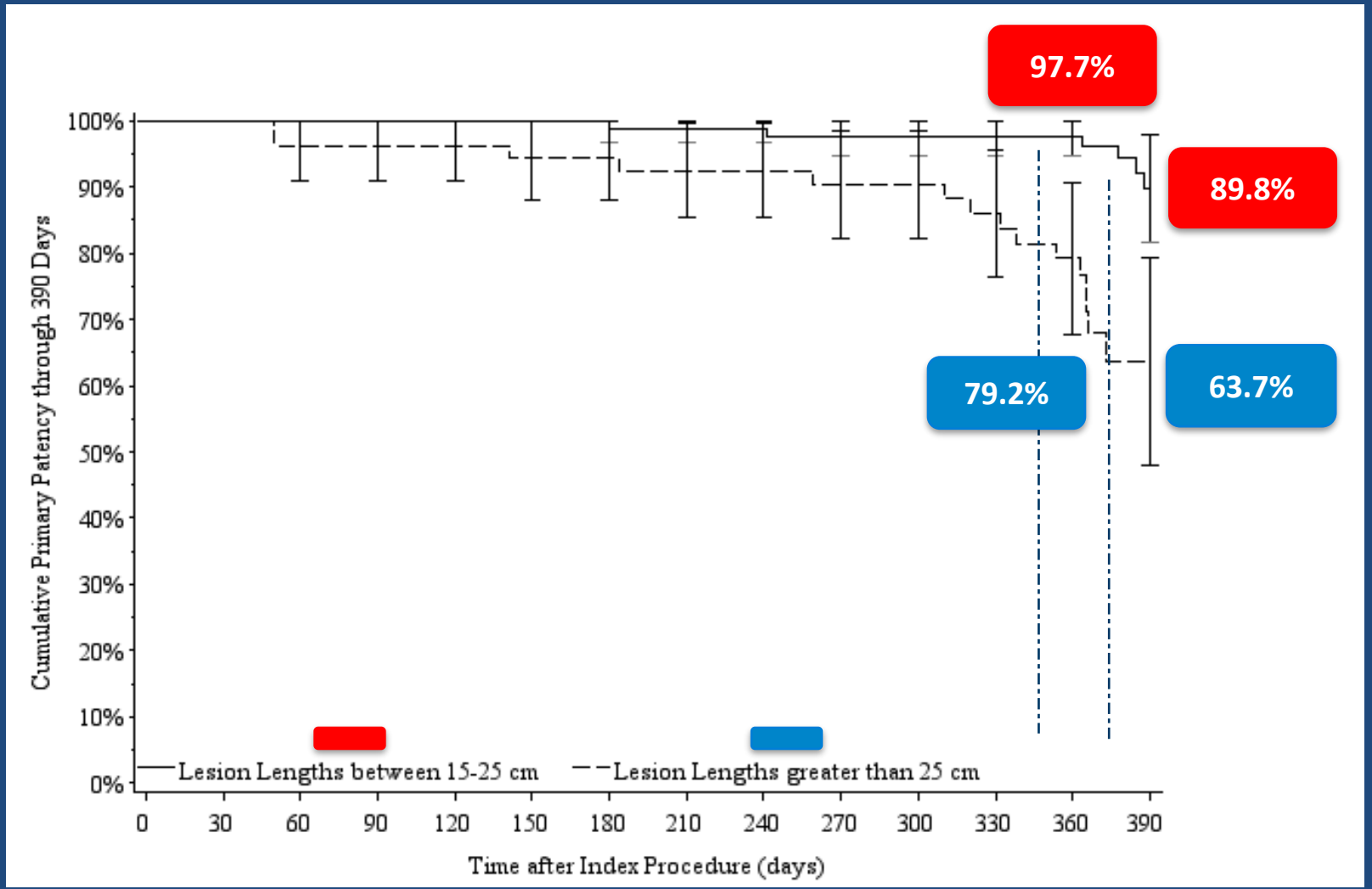
Procedural Characteristics	
Device Success [1]	99.5% (442/444)
Procedure Success [2]	99.4% (155/156)
Clinical Success [3]	99.4% (155/156)
Pre-dilatation	89.8% (141/157)
Post-dilatation	39.1% (61/156)
Provisional Stent	40.4% (63/156)
LL 15-25 cm:	33.3% (33/99)
LL > 25 cm:	52.6% (30/57)

1. **Device success:** successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP
2. **Procedure success**: residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core lab (if core lab was not available then the site reported estimate was used)
3. **Clinical success:** procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge

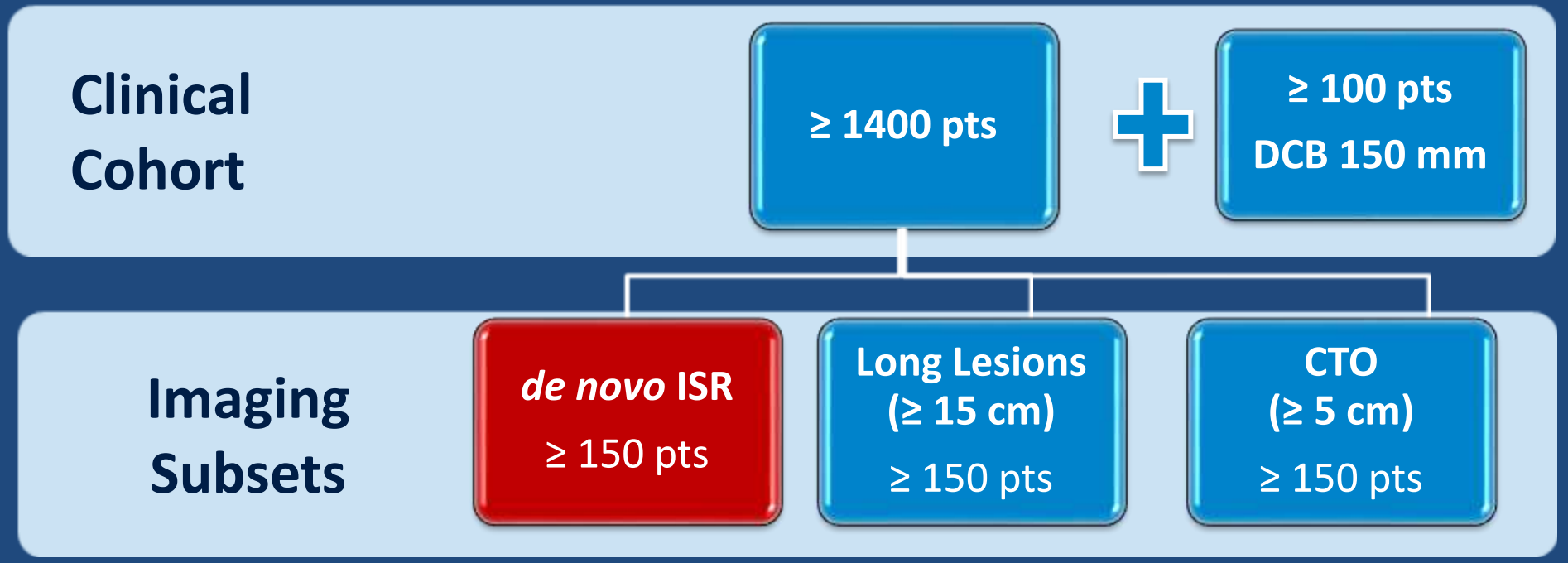
IN.PACT Global Long Lesion Imaging Cohort: Kaplan-Meier Estimate Of Primary Patency



IN.PACT Global Long Lesion Imaging Cohort: Primary Patency By Lesion Length Subgroup



IN.PACT Global Study Patient Cohorts
1538 Patients Enrolled



*ISR is not an approved indication in the US

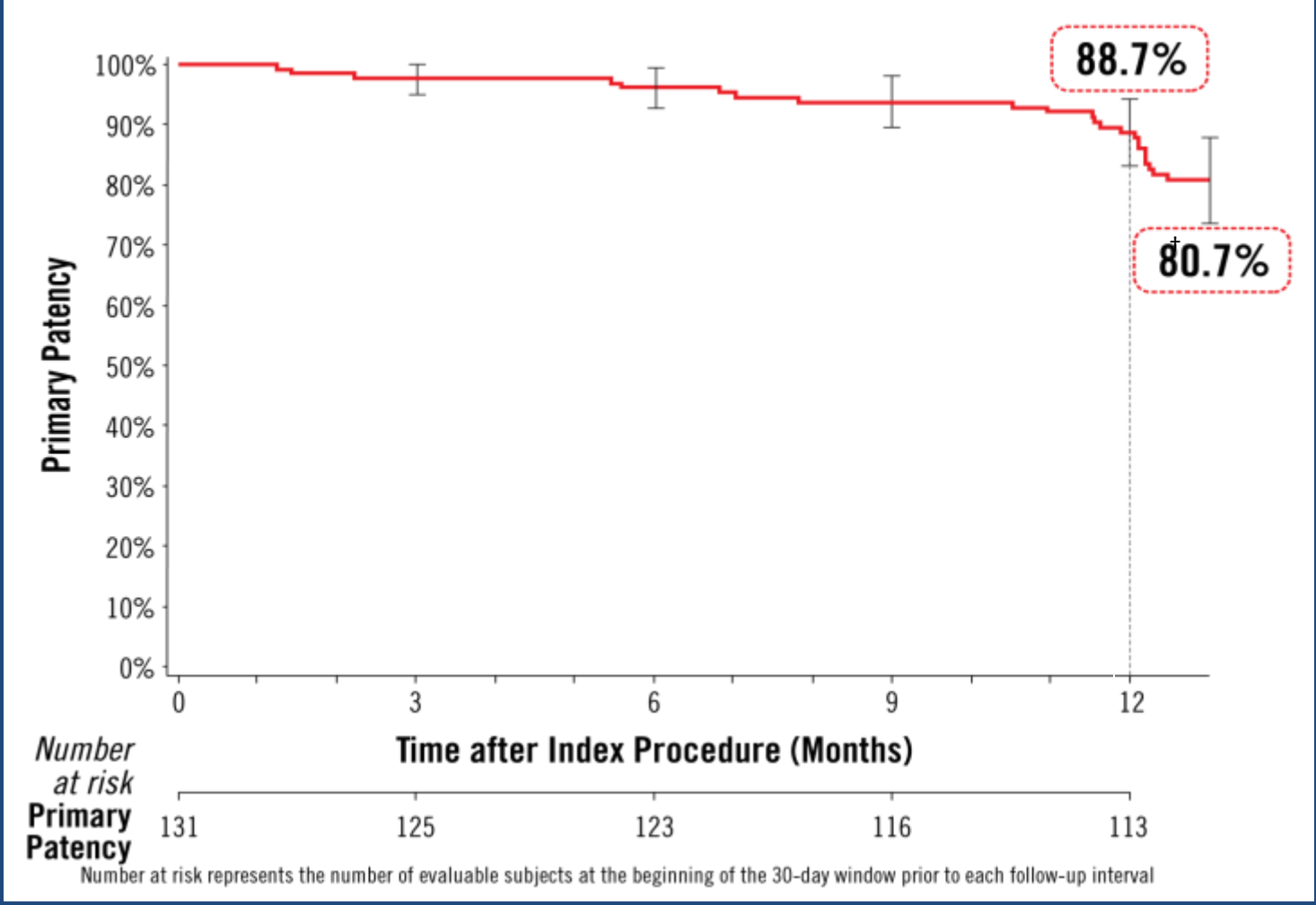
IN.PACT Global ISR Imaging Cohort: Lesion/Procedural Characteristics

Lesion (N)	149
Lesion type:	
De Novo	0.0% (0/149)
Non-stented Restenotic	0.0% (0/149)
In-Stent Restenosis	100.0% (149/149)
Lesion Length (cm)	17.17 ± 10.47
Total Occlusions (%)	34.0% (48/141)
Calcification (%)	59.1% (78/132)
Severe Calcification (%)	8.3% (11/132)
RVD (mm)	5.222 ± 0.601
Diameter Stenosis (pre-treatment) (%)	84.8 ± 14.9
Dissections (%): 0	69.1% (103/149)
A-C	26.2% (39/149)
D-F	4.7% (7/149)

Procedural Characteristics	
Device Success [1]	99.6% (282/283)
Procedure Success [2]	99.2% (130/131)
Clinical Success [3]	98.5% (129/131)
Pre-dilatation	64.1% (84/131)
Post-dilatation	26.0% (34/131)
Provisional Stent	14.5% (19/131)

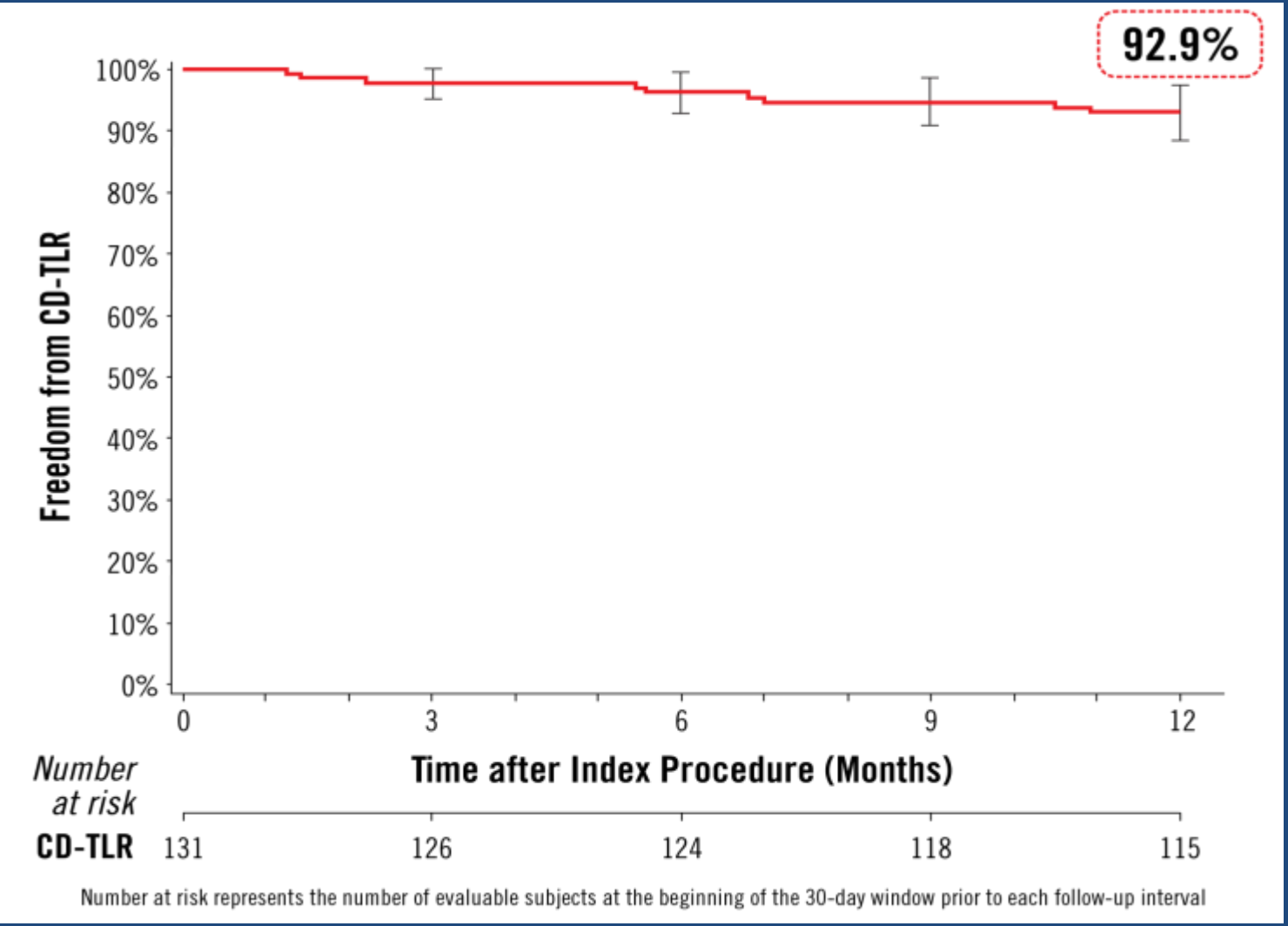
1. **Device success:** successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP
2. **Procedure success**: residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core lab (if core lab was not available then the site reported estimate was used)
3. **Clinical success:** procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge

IN.PACT Global ISR Imaging Cohort: Kaplan-Meier Estimate of Primary Patency



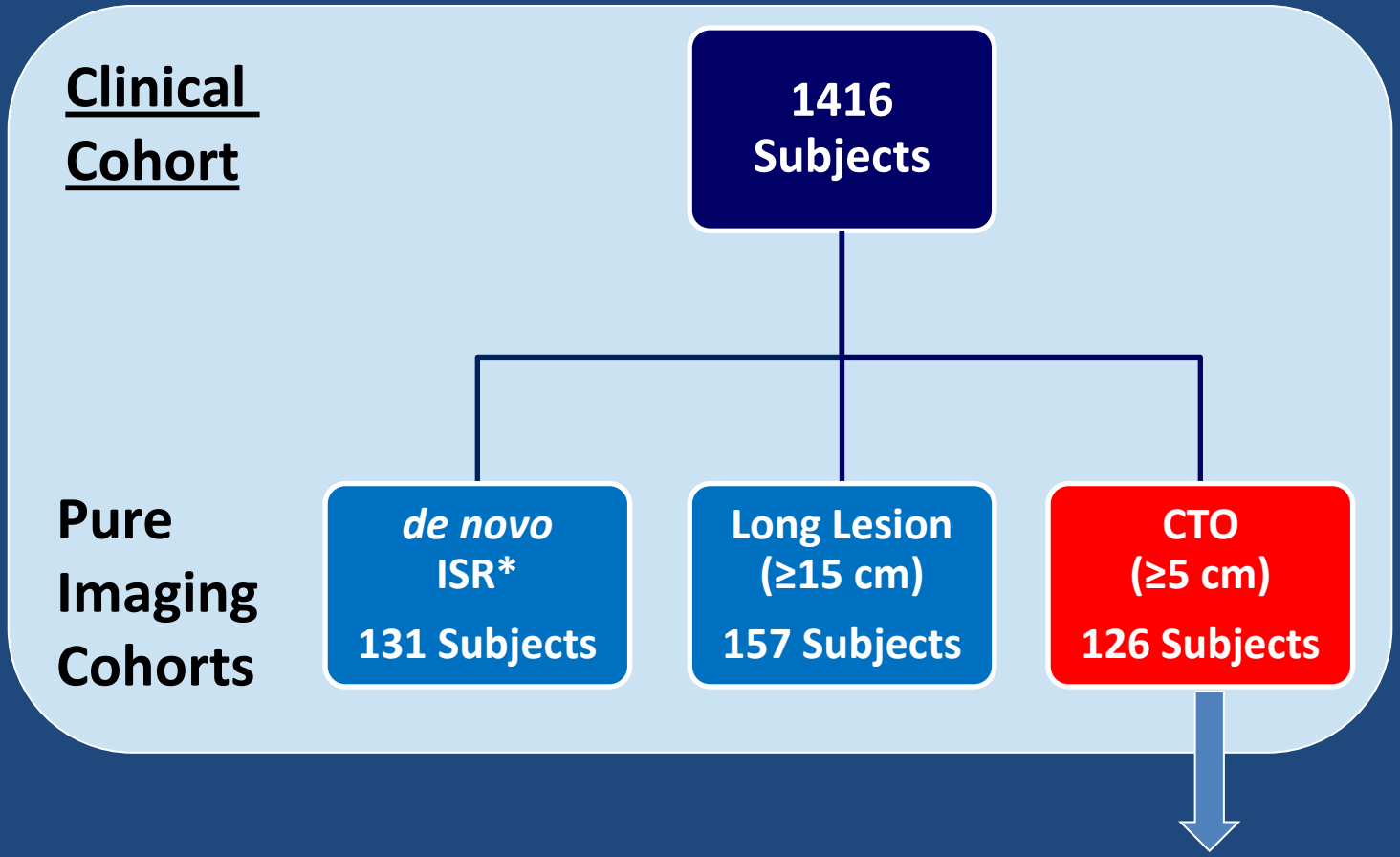
† Kaplan-Meier Estimate of Primary Patency at 13 months

IN.PACT Global ISR Imaging Cohort: Freedom from Clinically-driven TLR



IN.PACT Global Study Architecture

1535 Enrolled



This presentation includes outcome data on the 126 subjects with pure CTO lesions enrolled in the CTO Imaging Cohort.

**ISR is not an approved indication in the US*

Lesion/Procedural Characteristics

Lesion Characteristics	N = 128 Lesions
Lesion Type: **% (n)** De novo Restenotic (non-stented) In-stent Restenosis	 92.2% (118/128) 7.8% (10/128) 0.0% (0/128)
Lesion Length (cm ± SD)	22.90 ± 9.75
Occluded Lesion Length (cm ± SD)	11.97 ± 8.11
Calcification % (n)	71.2% (89/125)
RVD (mm ± SD)	5.056 ± 0.657
Diameter Stenosis (% ± SD)	100.0 ± 0.0
Dissections: 0 A-C D-F	 32.8% (42/128) 43.8% (56/128) 23.4% (30/128)

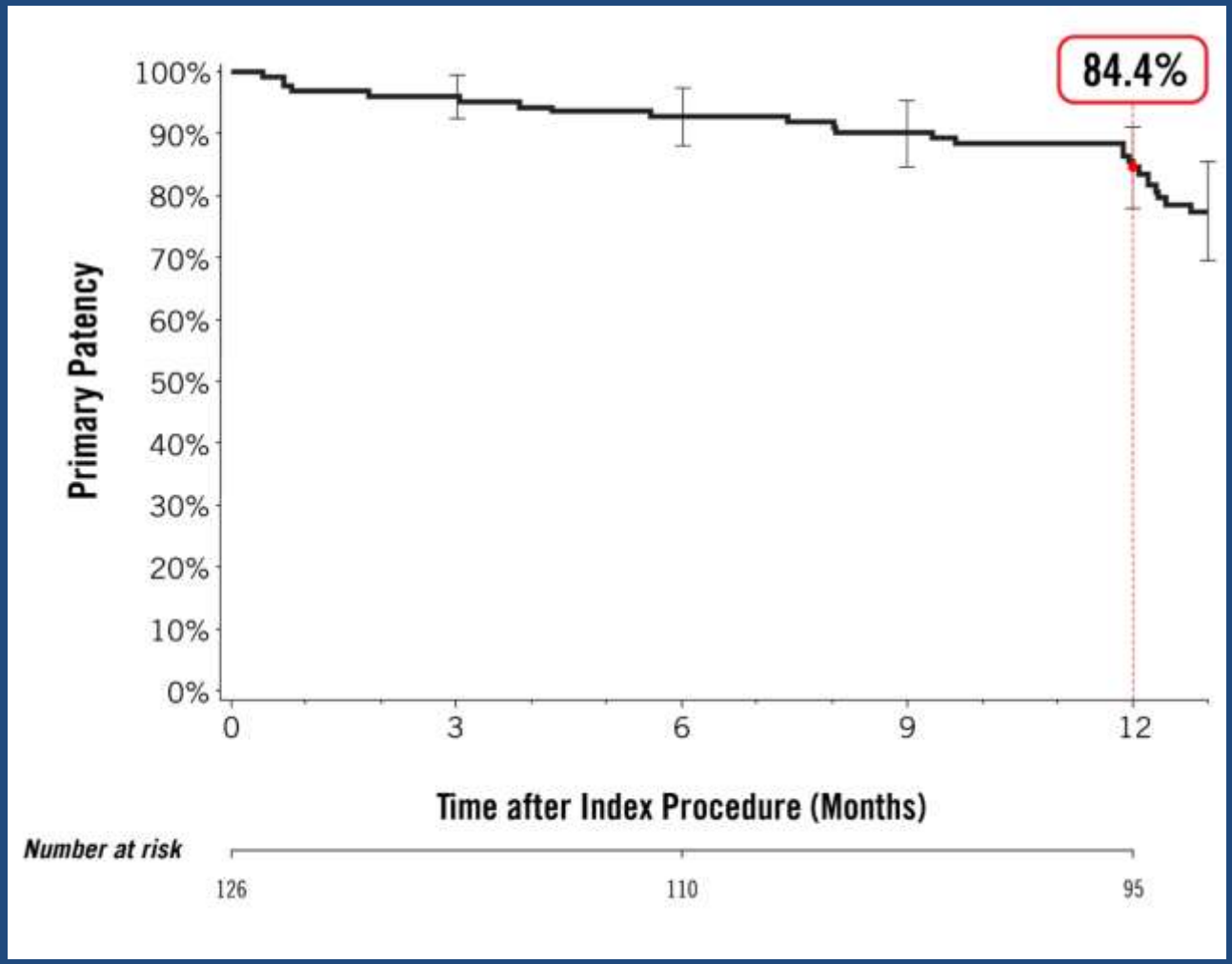
Procedural Characteristics	N = 126 Subjects N = 128 Lesions
Device Success[1] % (n)	99.3% (283/285)
Procedure Success[2] % (n)	100% (125/125)
Clinical Success[3] % (n)	99.2% (124/125)
Pre-dilatation % (n) Post-dilatation % (n)	94.4% (119/126) 50.0% (63/126)
Provisional Stent % (n)	46.8% (59/126)

1. Device success defined as successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP.

2. Procedure success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core lab (if core lab was not available then the site-reported estimate was used).

3. Clinical success defined as procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.

Primary Patency[1] Results through 1 Year



1. *Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 12 months (adjudicated by a Clinical Events Committee)*
2. *Number at risk represents the number of evaluable subjects at the beginning of the 30-day window and prior to each follow-up interval*

Results Across IN.PACT Clinical Studies at 1 Year

Consistent clinical outcomes with the IN.PACT Admiral DCB across studies and complex femoropopliteal lesions.

	IN.PACT SFA (DCB Arm) (N= 220)	IN.PACT GLOBAL Long Lesion Imaging Cohort (N= 157)	IN.PACT GLOBAL ISR Imaging Cohort (N= 131)	IN.PACT GLOBAL CTO Imaging Cohort (N= 126)
Lesion Length (Mean ± SD, cm)	8.94 ± 4.89	26.40 ± 8.61	17.17 ± 10.47	22.90 ± 9.75 (occluded length of 11.97 ± 8.11)
Primary Patency[1]	87.5%	91.1%	88.7%	84.4%
CD-TLR	2.4%	6.0%	7.3%	12.2%
Primary Safety Endpoint[2]	95.7%	94.0%	91.1%	87.8%
Major Target Limb Amputation	0.0%	0.0%	0.0%	0.0%

1. Kaplan-Meier survival estimate at 12 months

2. Composite of 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and clinically-driven TVR.

Summary

- Mounting evidence from randomized trials and global registries that DCBs are safe and effective for SFA angioplasty
  - Short and medium lesions
  - Longer lesions
  - Instent restenosis
- High procedural success even in complex lesions, although provisional stenting more common

Thank You!