IN.PACT DCB and DAART

An Evolution in Clinical Insights and Procedural Technique

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Background

- Femoropopliteal disease remains challenging to manage with no evidence-based standard treatment defined
- PTA exhibits length-dependent efficacy, limiting use in longer, complex lesions…it is no longer the standard of care in such lesions sub-sets
- Reported long-term patency rates with stents range from 60-75%, but concerns persist about in-stent restenosis and stent fractures[1-3]
- Promising early results with drug-coated balloons in randomized trials, but longer term results and effectiveness in complex disease are lacking

1. Dick P, et al. Catheter Cardiovasc Interv 74:1090-5 (2009).
2. Dake MD et al. J Am Coll Cardiol 61:2417-27 (2013).
3. Rocha-Singh KJ, et al. Catheter Cardiovasc Interv 86:164-70 (2015).

IN.PACT SFA Trial Overview

IN.PACT SFA I
150 subjects enrolled at 13 EU sites
Sep 2010 - Apr 2011

IN.PACT SFA II
181 subjects enrolled at 44 US sites
Apr 2012 - Jan 2013

- **Prospective**, two-phase, multicenter (EU and US), **Randomized** (2:1), **single-blinded** (subjects, sponsor trial management)

- **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**

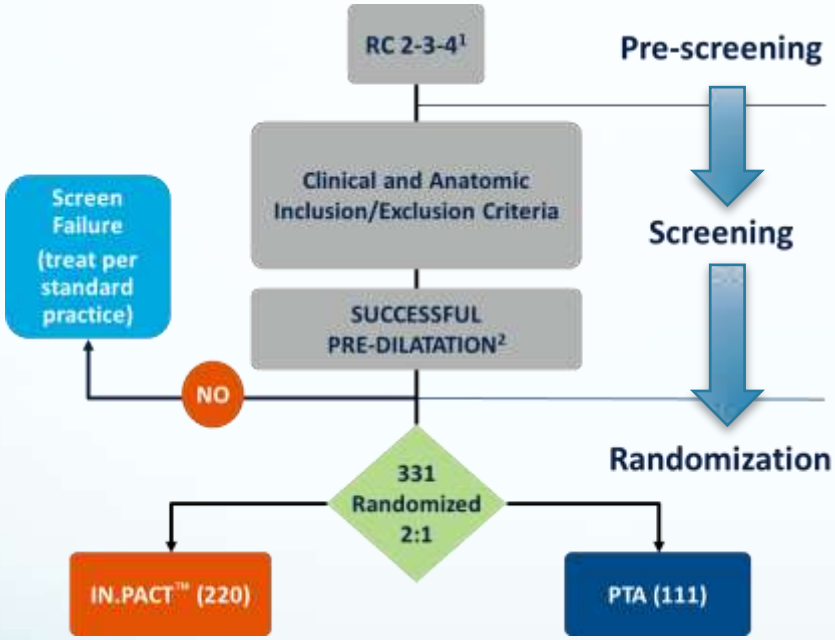
- Subjects followed **up to 5 years**

1-Year Results
Tepe G, et al. Circ 131:495-502 (2015).

2-Year Results
Laird J, et al. J Am Coll Cardiol 66:2329-38 (2015).

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

IN.PACT SFA Trial Endpoints



Primary Endpoints

- **Efficacy[3]**: 12-month Primary Patency
- Freedom from clinically-driven TLR and duplex ultrasound derived restenosis (PSVR ≤2.4)
- **Safety[4]**: Freedom from 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

IN.PACT SFA Trial

BASELINE CLINICAL CHARACTERISTICS

	IN.PACT n = 220 subjects	PTA n = 111 subjects	p
Age, Y ± SD	67.5 ± 9.5	68.0 ± 9.2	0.612
Male, % (n)	65.0% (143/220)	67.6% (75/111)	0.713
Diabetes, % (n)	40.5% (89/220)	48.6% (54/111)	0.161
Hypertension, % (n)	91.4% (201/220)	88.3% (98/111)	0.431
Current smoker, % (n)	38.6% (85/220)	36.0% (40/111)	0.719
Rutherford class, % (n)			
2	37.7% (83/220)	37.8% (42/111)	
3	57.3% (126/220)	55.9% (62/111)	0.898
4	5.0% (11/220)	5.4% (6/111)	
5	0.0% (0/220)	0.9% (1/111)	
ABI / TBI, ± SD[1]	0.769 ± 0.228	0.744 ± 0.189	0.308

1. TBI allowed in cases of incompressible vessels in IN.PACT SFA II phase.

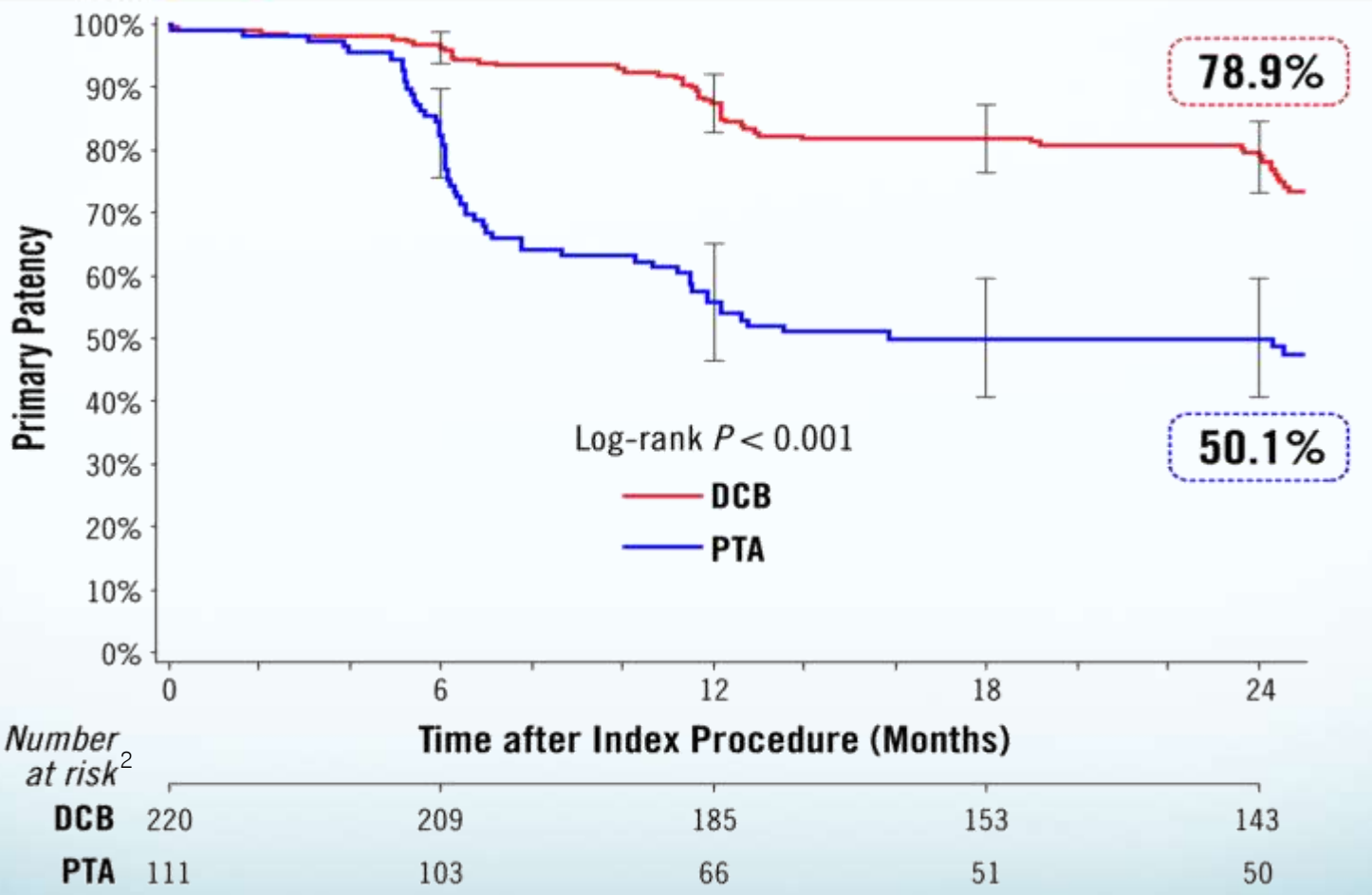
IN.PACT SFA Trial

BASELINE LESION CHARACTERISTICS

	IN.PACT n = 220 Subjects, n = 221 Lesions	PTA n = 111 Subjects, 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

IN.PACT SFA Trial

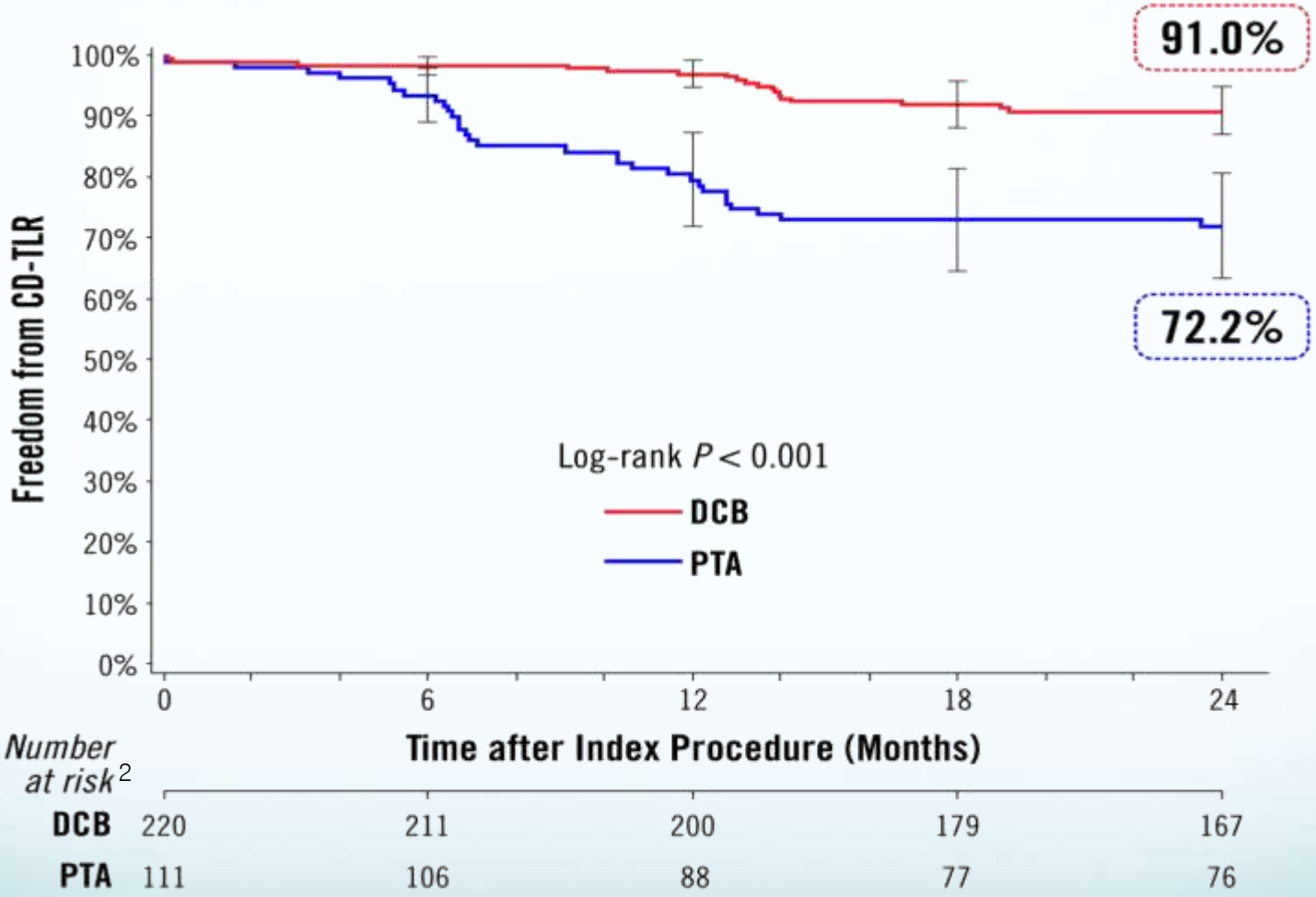
PRIMARY PATENCY THROUGH 2 YEARS[1]



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.

IN.PACT SFA Trial

FREEDOM FROM CD–TLR THROUGH 2 YEARS[1]



1. Clinically-driven TLR adjudicated by an independent Clinical Event 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.
2. 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

EFFECTIVENESS OUTCOMES THROUGH 2 YEARS

	IN.PACT n = 220	PTA n = 111	p[5]
Clinically-driven TLR[1]	9.1% (18/198)	28.3% (30/106)	< 0.001
All TLR[2]	10.1% (20/198)	29.2% (31/106)	< 0.001
Primary Sustained Clinical Improvement[3]	76.9% (133/173)	59.2% (61/103)	0.003
ABI / TBI[4]	0.924 ± 0.261	0.938 ± 0.184	0.611

1. Clinically-driven TLR adjudicated by an independent Clinical Event 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.
2. All TLR includes clinically-driven and incidental or duplex driven TLR.
3. Freedom from target limb amputation, target vessel revascularization (TVR), and increase in Rutherford class.
4. TBI allowed in cases of incompressible vessels in IN.PACT SFA II phase.
5. Unless otherwise indicated, all tests were for superiority using the Fisher's exact test for binary variables and t-test for continuous variables .

IN.PACT SFA Trial

SAFETY OUTCOMES THROUGH 2 YEARS

	IN.PACT n = 220	PTA n = 111	p[4]
Primary Safety Composite[1]	87.4% (173/198)	69.8% (74/106)	< 0.001
Major Adverse Events[2]	19.2% (38/198)	31.1% (33/106)	0.023
All-cause Death[3]	8.1% (16/198)	0.9% (1/106)	0.008
Device- or Procedure-related Death	0.0% (0/198)	0.0% (0/106)	> 0.999
Clinically-driven TVR	12.6% (25/198)	30.2% (32/106)	< 0.001
Target Limb Major Amputation	0.0% (0/198)	0.0% (0/106)	> 0.999
Thrombosis	1.5% (3/198)	3.8% (4/106)	0.243

1. Freedom from 30-day device and procedure-related death and target limb major amputation and clinically-driven TVR within 12 (24) months.
2. Composite of death, clinically-driven TVR, target limb major amputation, and thrombosis.
3. No deaths were adjudicated as device- or procedure-related by the CEC; Median post-index days to death: 564.5 days in DCB vs. 397 days in PTA.
4. p-values are based on Fisher's exact test for superiority with significance level of 0.05.

IN.PACT SFA Trial

PRIMARY PATENCY[1] BY DIABETIC STATUS AT 2 YEARS

Diabetes Subgroup (N_{DCB}, N_{PTA})	IN.PACT % (N failure)	PTA % (N failure)	p
Diabetic (89, 54)	73.3% (21)	45.8% (29)	< 0.001
Non-diabetic (131, 57)	82.5% (21)	54.5% (25)	< 0.001

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).

IN.PACT SFA Trial

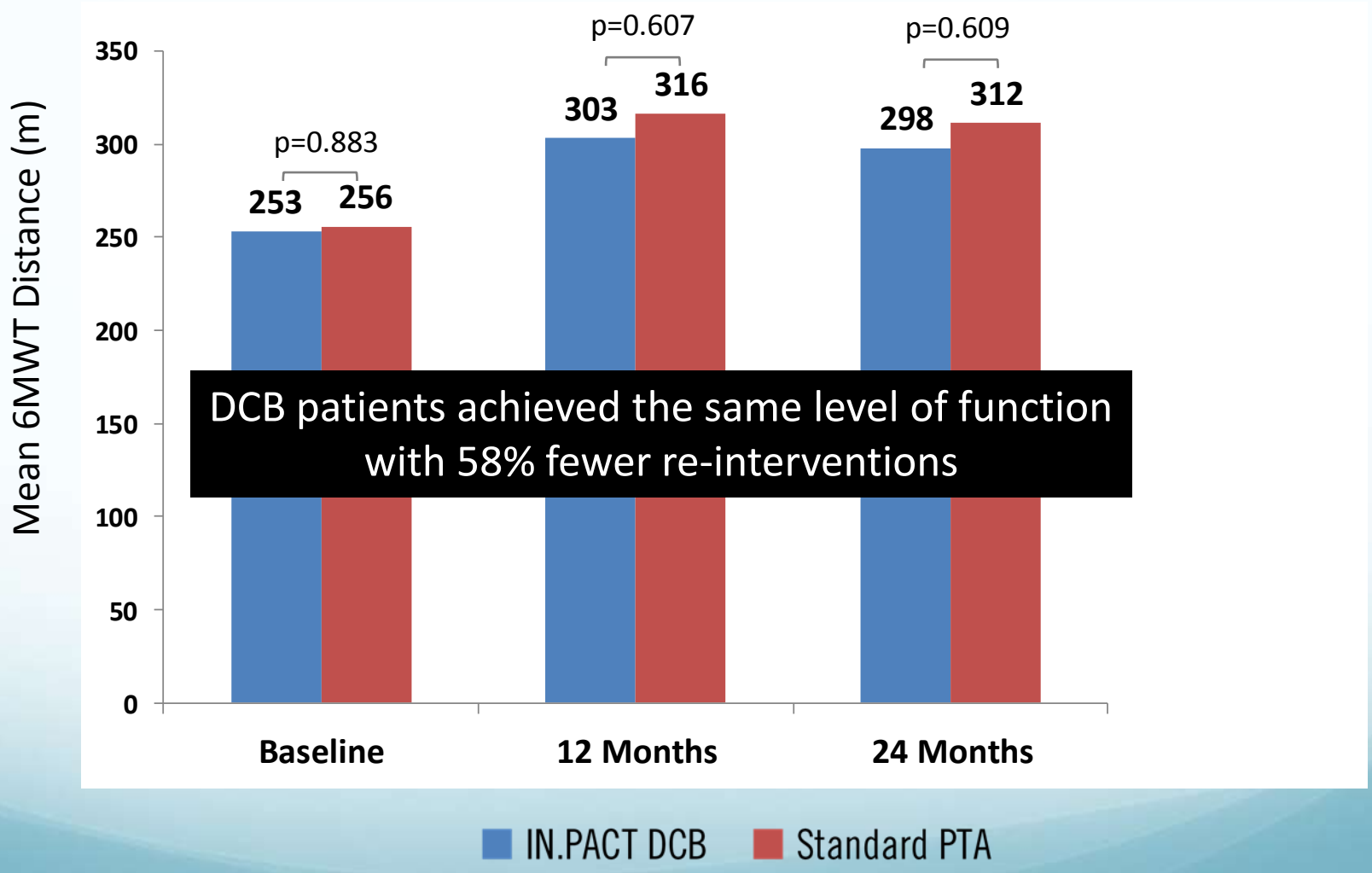
PRIMARY PATENCY[1] BY GENDER AT 2 YEARS

Gender Subgroup (N_{DCB}, N_{PTA})	IN.PACT % (N failure)	PTA % (N failure)	p
Female (77, 36)	76.7% (17)	42.3% (20)	< 0.001
Male (143, 75)	80.2% (25)	53.7% (34)	< 0.001

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).

IN.PACT SFA Trial

2–YEAR FUNCTIONAL OUTCOMES: 6 MINUTE WALK TEST



IN.PACT SFA Trial

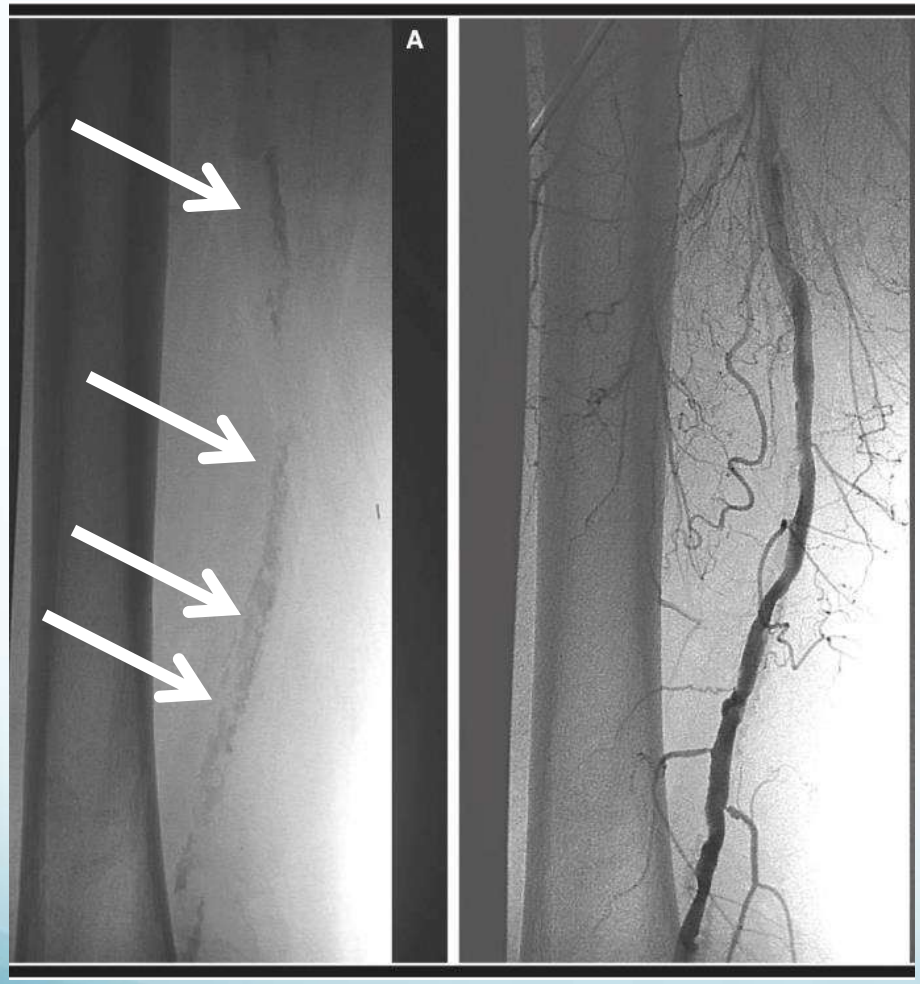
CONCLUSIONS

- Sustained durability of IN.PACT Admiral DCB treatment effect with no late catch-up through 2 years

2-Year Results	IN.PACT	PTA	Δ	p-value
Primary Patency	78.9%	50.1%	28.8%	<0.001
CD-TLR	9.1%	28.3%	19.2%	<0.001

- Consistent, durable results in subgroups including females and diabetics
- IN.PACT Admiral DCB subjects had similar functional outcomes with 58% fewer re-interventions
- *Is there potential for DCB to drive a paradigm shift in SFA interventions?*

Extending DCB Use Beyond Its RCT: The Challenge of the 'Real World'

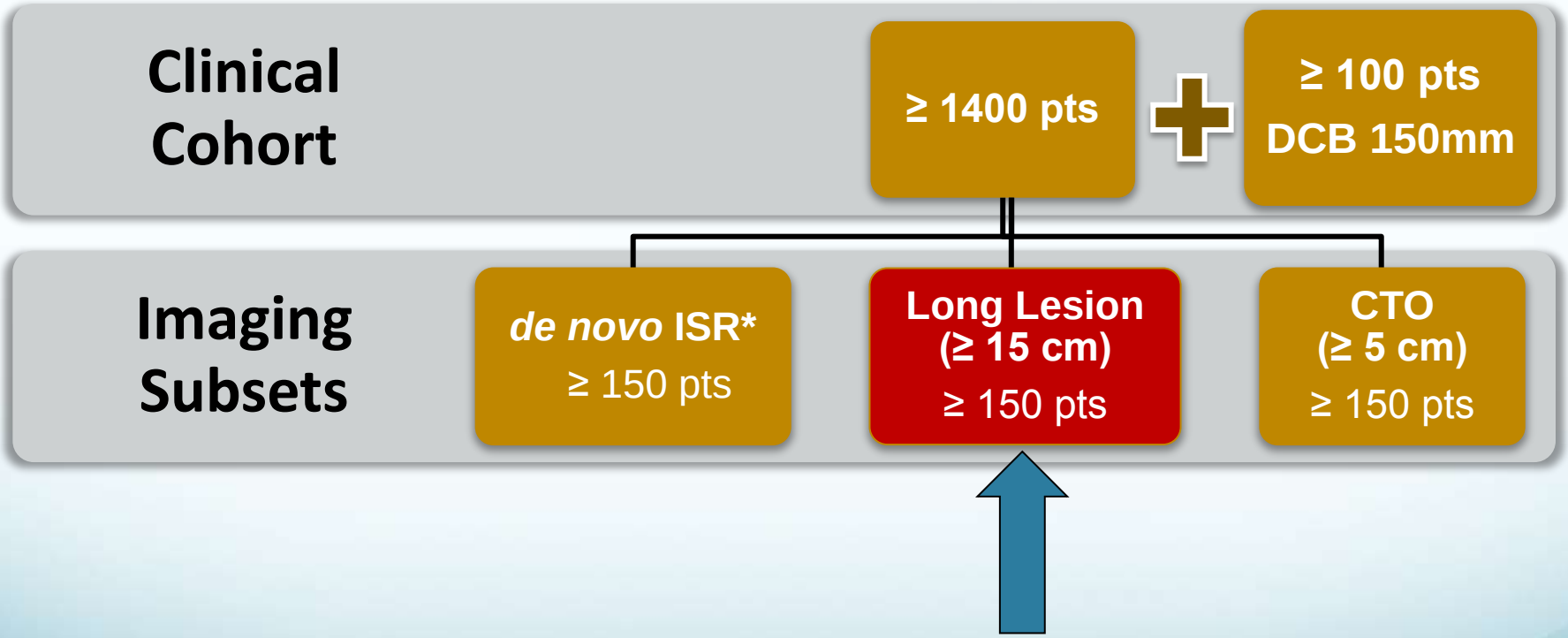


DCB RCT excluded these lesions as 'too complex, high risk'…rightfully so.

We don't have a uniformly accepted/validated methodology for classifying these lesions

But, emerging EU registry data provides some insights

IN.PACT GLOBAL Study Patient Cohorts: 1,538 patients enrolled



*ISR is not an approved indication in the US

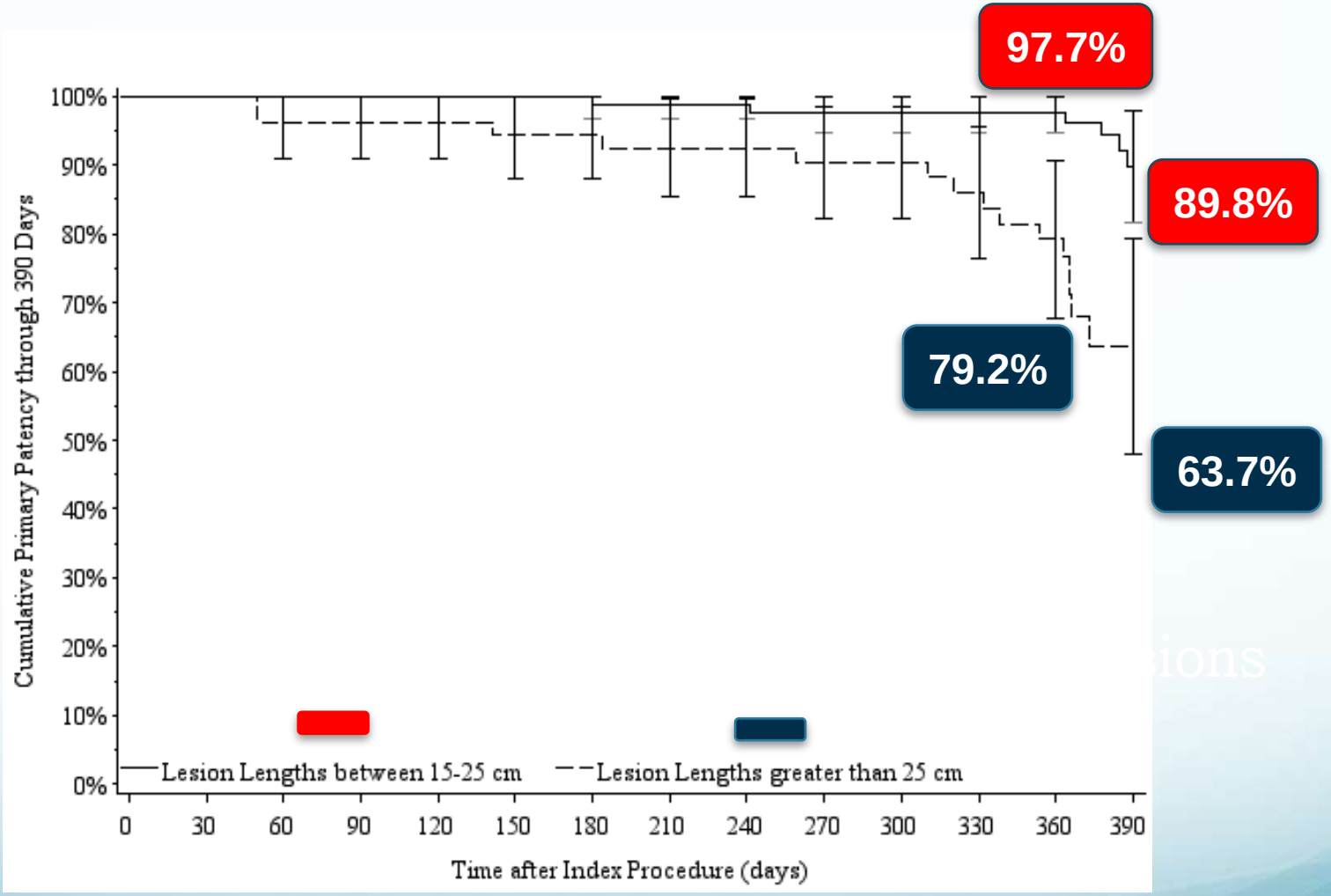
IN.PACT Global Long Lesion Imaging Cohort: Lesion/Procedural Characteristics

Lesions (N)	164
Lesion Type: de novo restenotic (no ISR) ISR	83.2% (134/161) (134/161) 16.8% (27/161) 0.0% (0/161)
Lesion Length	26.40 ± 8.61 cm
Total Occlusions	60.4% (99/164)
Calcification Severe	71.8% (117/163) 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)

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 – LL 15–25 cm: – LL > 25 cm:	40.4% (63/156) 33.3% (33/99) 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: Primary Patency by Lesion Length Subgroup



Scheinert, EuroPCR 2015

Lesion Characteristics

"DEVICE TRIAL" LESIONS ARE NOT ALWAYS WHAT WE SEE

	IN.PACT SFA DCB Arm n = 220 Subjects, n = 221 Lesions	IN.PACT Global Long Lesion Imaging Cohort[3] n = 157 Subjects, n = 164 Lesions	Relative Difficulty
Lesion length (cm ± SD)	8.94 ± 4.89	26.40 ± 8.61	↑
Total occlusions, % (n)	25.8% (57/221)	60.4% (99/164)	↑
Calcification, % (n)	59.3% (131/221)	71.8% (117/163)	↑
Severe calcification, % (n)	8.1% (18/221)	19.6% (32/163)	↑
In-stent Restenosis, % (n)[1]	0.0%	0.0%	↑
Baseline RC >3	5.0% (11/220)	16.7% (26/157)	↑
ABI / TBI, ± SD[2]	0.769 ± 0.228	0.669 ± 0.232 (147)	↑
Dissections: 0	36.2% (80/221)	37.9% (61/161)	↑
A-C	63.8% (141/221)	47.2% (76/161)	
D-F	0.0% (0/221)	14.9% (24/161)	↑
Provisional stenting, % (n)	7.3% (16/220)	40.4% (63/156)	↑

1. In-stent restenosis was excluded in IN.PACT SFA and was enrolled in the In-stent restenosis imaging cohort of IN.PACT Global (not presented here).
2. TBI allowed in cases of incompressible vessels in IN.PACT SFA II phase.
3. "Drug Coated Balloon Treatment for Patients with Intermittent Claudication: New Insights from the IN.PACT Global Study Long Lesion (≥15cm) Imaging Cohort", presented by Scheinert D, EuroPCR Paris 2015.

Drug-Coated Balloons for Complex Femoropopliteal Lesions

2-Year Results of a Real-World Registry

Andrej Schmidt, MD,[a] Michael Piorkowski, MD,[b] Henrik Görner, MD,[a] Sabine Steiner, MD, MSc,[a] Yvonne Bausback, MD,[a] Susanne Scheinert, MD,[a] Ursula Banning-Eichenseer, PhD,[a] Holger Staab, MD,[c] Daniela Branzan, MD,[c] Ramon L. Varcoe, MD,[d] Dierk Scheinert, MD[a]

- A single-center, retrospective, un-adjudicated registry
- Combined de novo, restenotic and ISR lesions; claudicants w/ CLI patients and adjunct devices
- Two-year lost to follow-up:
  → In 26% primary patency could not be assessed
  → In 19.1% freedom from TLR could not the assessed

Schmidt et al; JACC Cardiovasc Interv April 2016

Lesion Characteristics

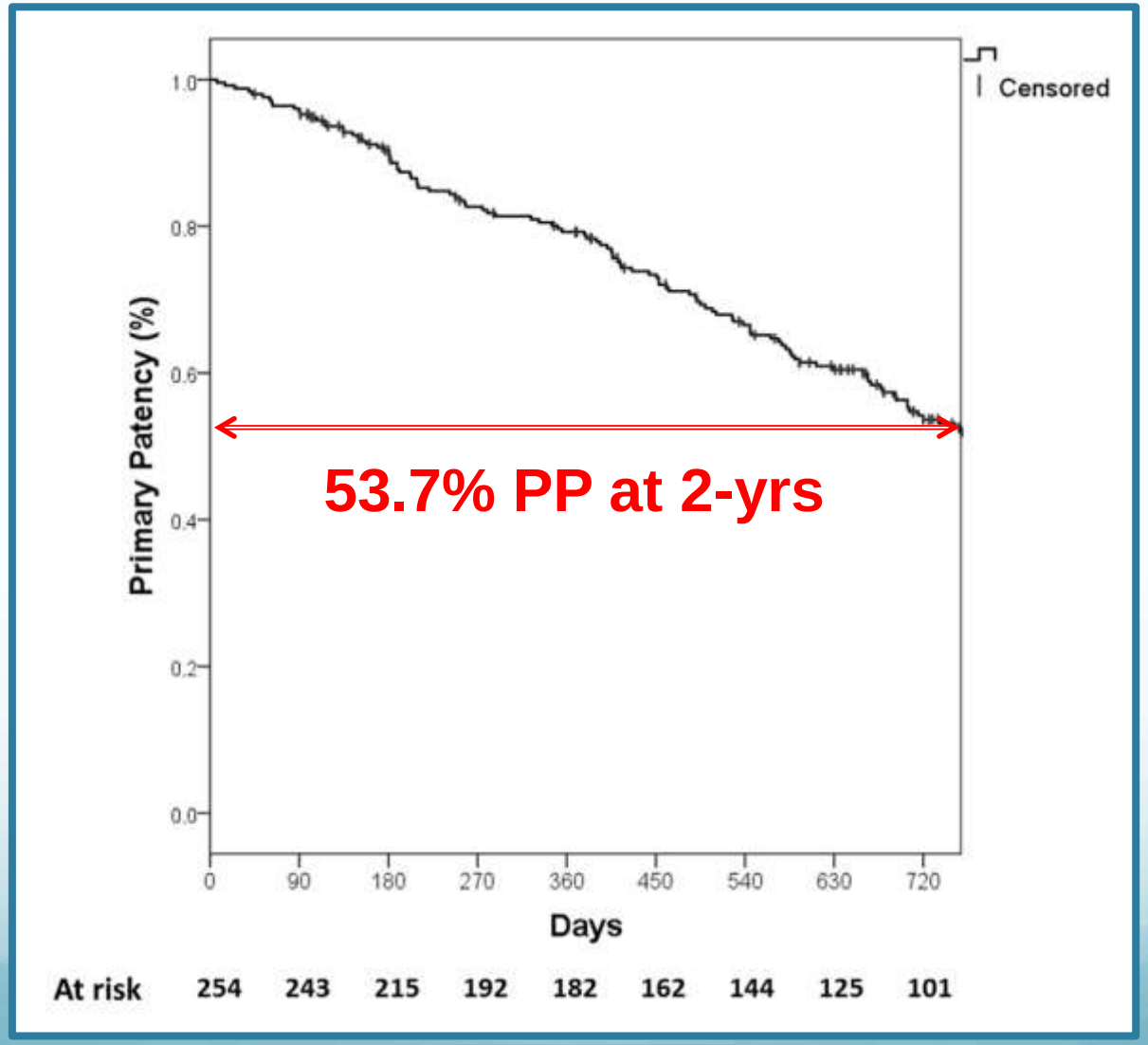
	Entire Cohort (N = 288)	SFA Only (n = 183)	Popliteal Involvement (n = 105)	p Value*
De novo lesions	149 (51.7)	103 (56.3)	46 (43.8)	0.05
Restenosis	32 (11.1)	19 (10.4)	13 (12.4)	NS
ISR	107 (37.2)	61 (33.3)	46 (43.8)	0.09
Lesion length, cm	24.0 ± 10.1	23.7 ± 8.6	24.6 ± 12.6	NS
Total occlusion	188 (65.3)	110 (60.1)	78 (74.3)	0.02
TASC B	36 (12.5)	20 (10,9)	16 (15,2)	NS
TASC C	62 (21.5)	35 (19.1)	27 (25.7)	NS
TASC D	190 (66.0)	128 (69.9)	62 (59)	0.06
Lesion calcification				
None	91 (32.6)	58 (32.7)	33 (31.4)	NS
Mild	97 (34.3)	71 (38.8)	26 (24.8)	0.014
Moderate	59 (20.5)	33 (18.0)	26 (24.8)	NS
Severe	41 (14.2)	21 (11.5)	20 (19.0)	NS
BTK outflow				
3-Vessel	119 (41.3)	96 (52.5)	23 (21.9)	<0.0005
2-Vessel	78 (27.1)	47 (25.7)	31 (29.5)	NS
1-Vessel	77 (26.7)	37 (20.2)	40 (38.1)	0.001
None	14 (4.9)	3 (1.6)	11 (10.5)	0.001
Outflow PTA	59 (20.5)	14 (7.7)	45 (42.9)	<0.0005

Values are n (%) or mean ± SD. *Comparison between SFA only and popliteal involvement.

BTK = below-the-knee; ISR = in-stent-restenosis; PTA = percutaneous transluminal angioplasty; SFA = superficial femoral artery; TASC = Trans-Atlantic Inter-Society Consensus.

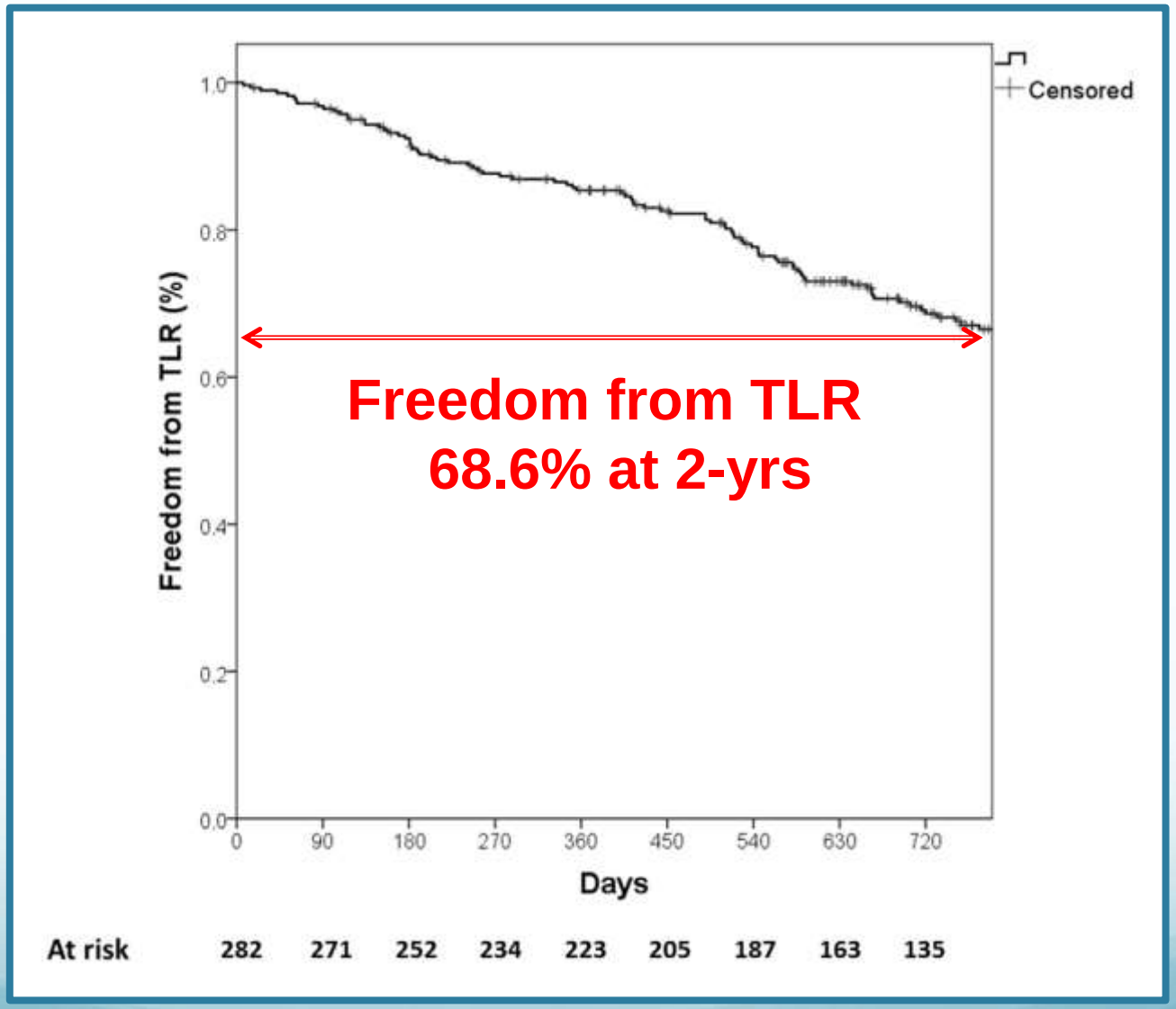
Schmidt et al; JACC Cardiovasc Interv April 2016

Patency Rates of the Entire Cohort



Schmidt et al; JACC Cardiovasc Interv April 2016

TLR Rates of the Entire Cohort



Schmidt et al; JACC Cardiovasc Interv April 2016

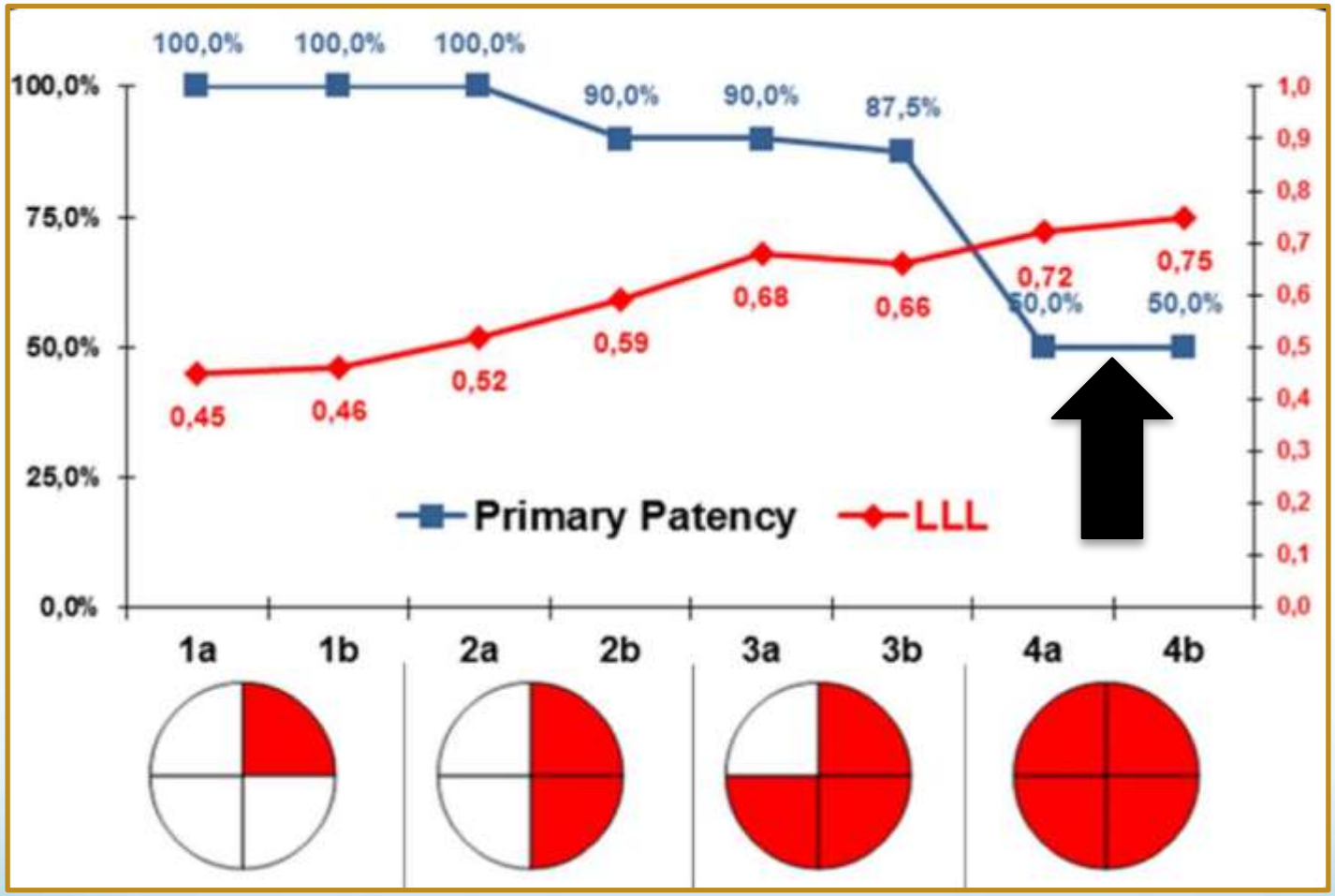
Binary Logistic Regression Analysis of Predictors for Restenosis: Severe Calcification Remains an Issue

	Coefficient	OR	95% CI	p Value
Male	−0.711	0.491	0.288–0.839	0.009
Severe calcification	0.765	2.150	1.018–4.540	0.045
Obesity	0.602	1.825	1.069–3.116	0.028

CI = confidence interval; OR = odds ratio.

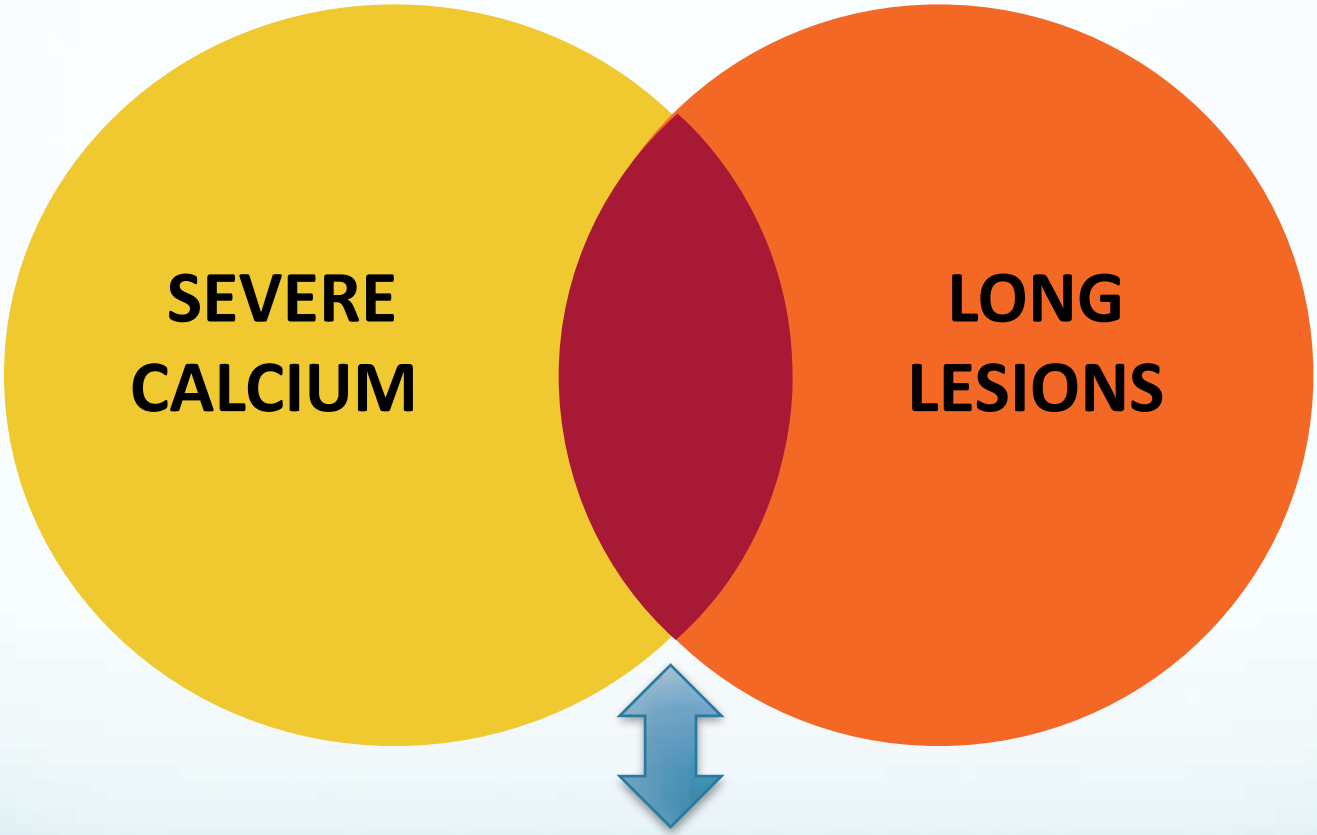
Schmidt et al; JACC Cardiovasc Interv April 2016

Is Circumferential Ca++ the Achilles' Heel of DCB?



Fanelli, et al., Cardiovasc Intervent Radiol 2014.

Defining ‘Challenging’ SFA Lesions



DAART= Directional Atherectomy + Anti-Restenotic Therapy: An Emerging Paradigm

A Telling Tale: DEF Ca++ Directional Ca++ Plaque Excision

Effective Endovascular Treatment of Calcified Femoropopliteal Disease With Directional Atherectomy and Distal Embolic Protection: Final Results of the DEFINITIVE Ca^{++} Trial

David Roberts,[1*] MD, Khusrow Niazi,[2] MD, William Miller,[3] MD, Prakash Krishnan,[4] MD, Roger Gammon,[5] MD, Theodore Schreiber,[6] MD, Nicolas W. Shammas,[7] MD, MS, and Daniel Clair,[8] MD on behalf of the DEFINITIVE Ca^{++} Investigators

clearance in Oct. 2011 for endovascular use when used in conjunction with SpiderFX to treat “mod-severe to severely” calcified lesions

Roberts, et al. CCI. 2014.

DEF Ca++: Baseline Lesion Characteristics

Baseline Target Lesion Characteristics	Site-Reported (N=169)	Core Laboratory-Reported (N=168)
Lesion Length (mm)	43.4 ± 30.5	**39.0 ± 27.0**
Pre-Procedure Diameter Stenosis (%)	88.3 ± 8.5	76.5 ± 15.4
Occlusions	9.5%	17.9%
Restenotic	12.4%	n/a
De Novo	87.6%	n/a
Single Vessel Run-Off	31.6%	32%
Calcification		
None/Mild	0.0%	6.0%
Moderate	47.9%	13.1%
Severe	52.1%	**81.0%**

Roberts, et al. CCI. 2014.

DEF Ca++:
Primary Endpoint Assessments

Primary Safety Endpoint: ***30-day MAE-Free rate: 93.1% (122/131)***

- 1 acute MI
- 1 grade D dissection
- **3 perforations**
- 1 thrombosis
- 3 distal embolizations (all without clinical sequelae)
- 0 deaths, pseudoaneurysms, amputations, or TVRs

Angiographic MAEs were assessed by angiographic core lab, all MAEs were adjudicated by CEC

Primary Effectiveness Endpoint:
Successful Revascularization defined as ≤50% residual diameter stenosis following plague excision

- Per site assessment: 97.0% (162/167)
- Per core lab assessment: 92.0% (150/163)

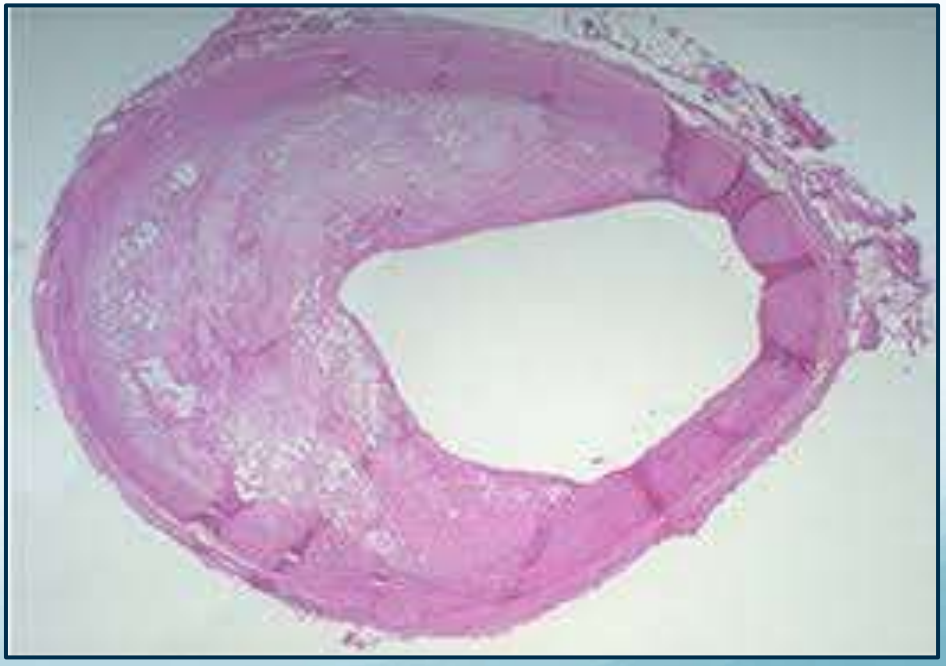
Roberts, et al. CCI. 2014.

Does Severe Ca++ Impact DCB Clinical Effectiveness?

- Although a retrospective review, severe calcium (mean lesion length 5.7cm) was associated with increased LLL at 6 mo. angio assessment—as noted using two different Ca++ grading scales
- ? Procedural details: when and which lesions were pre-dilated and uniformity of DCB use
- ? Could "vessel preparation" improve clinical results in severely calcified vessels

The DA-ART Rationale

- Mechanical recanalization (without over-stretch or deep wall injury)
- Reduce perfusion barrier to PTX diffusion, ? improve clinical effectiveness
- Reduce likelihood of recoil, dissection and need for provisional stenting



DEF AR and DA-ART: A Hypotheses Generating Trial

- ***Pilot study*** designed to assess the effect of treating a lesion with directional atherectomy followed by a paclitaxel-coated balloon (DA-ART) vs. a paclitaxel-coated balloon alone (DCB)

  Small study to detect trends in treatment differences between groups

  Observational investigation of outcomes; non-powered primary outcome

Identify early hypotheses in order to develop further investigational research in this therapy area

DEF AR and DA-ART: A Hypotheses Generating Trial

- Prospective, multicenter, randomized (DAART vs. DCB alone); plus non-randomized DAART registry arm for severely calcified lesions

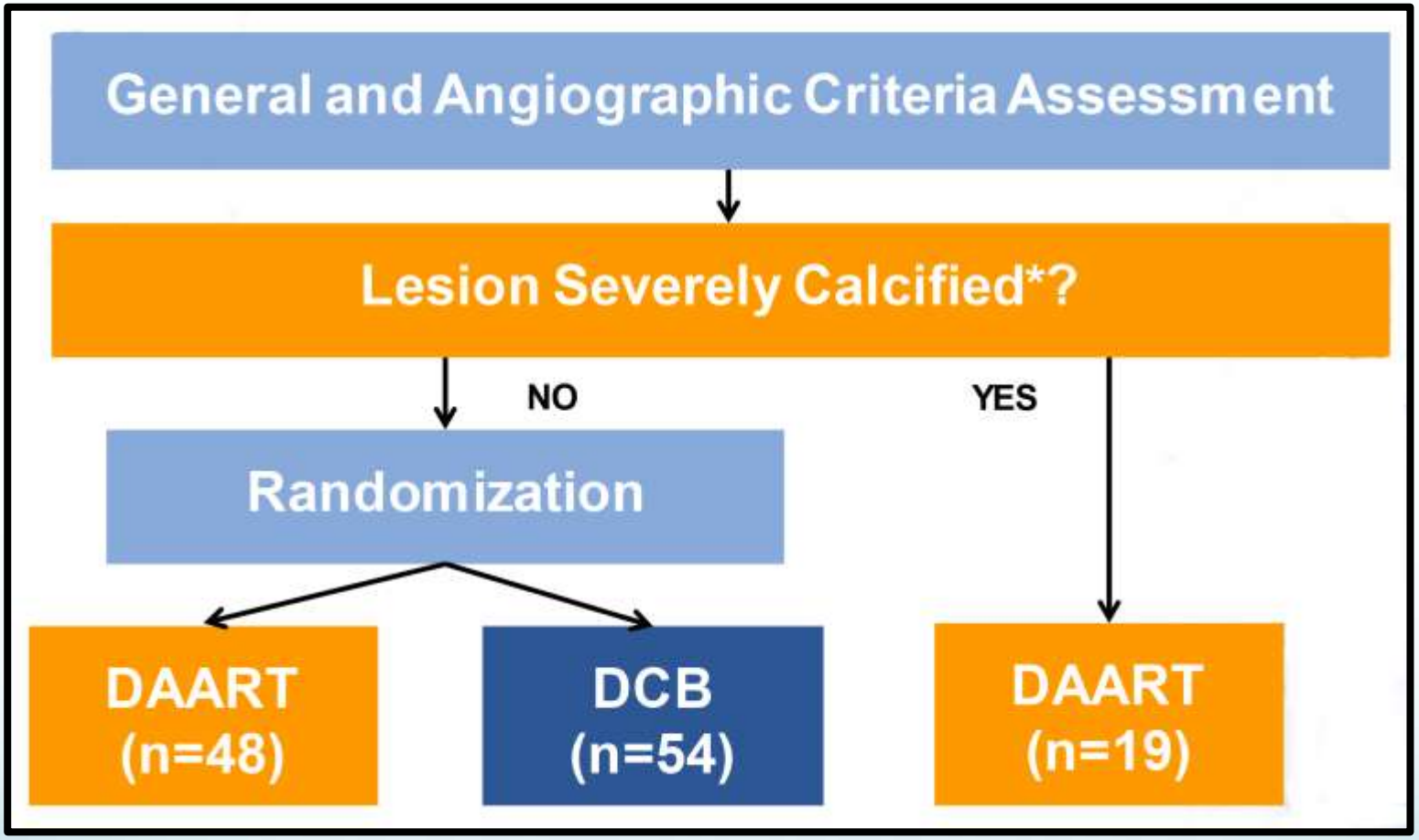
  121 subjects enrolled at **10** investigational sites

- **Primary Outcome: Target Lesion Percent Stenosis at 1 Year:** Defined as the narrowest point of the target lesion divided by the estimated native vessel diameter at that location as determined by the Angiographic Core Laboratory.

  Clinical follow-up: pre-discharge, 30 d, 6 mos., 1 year.

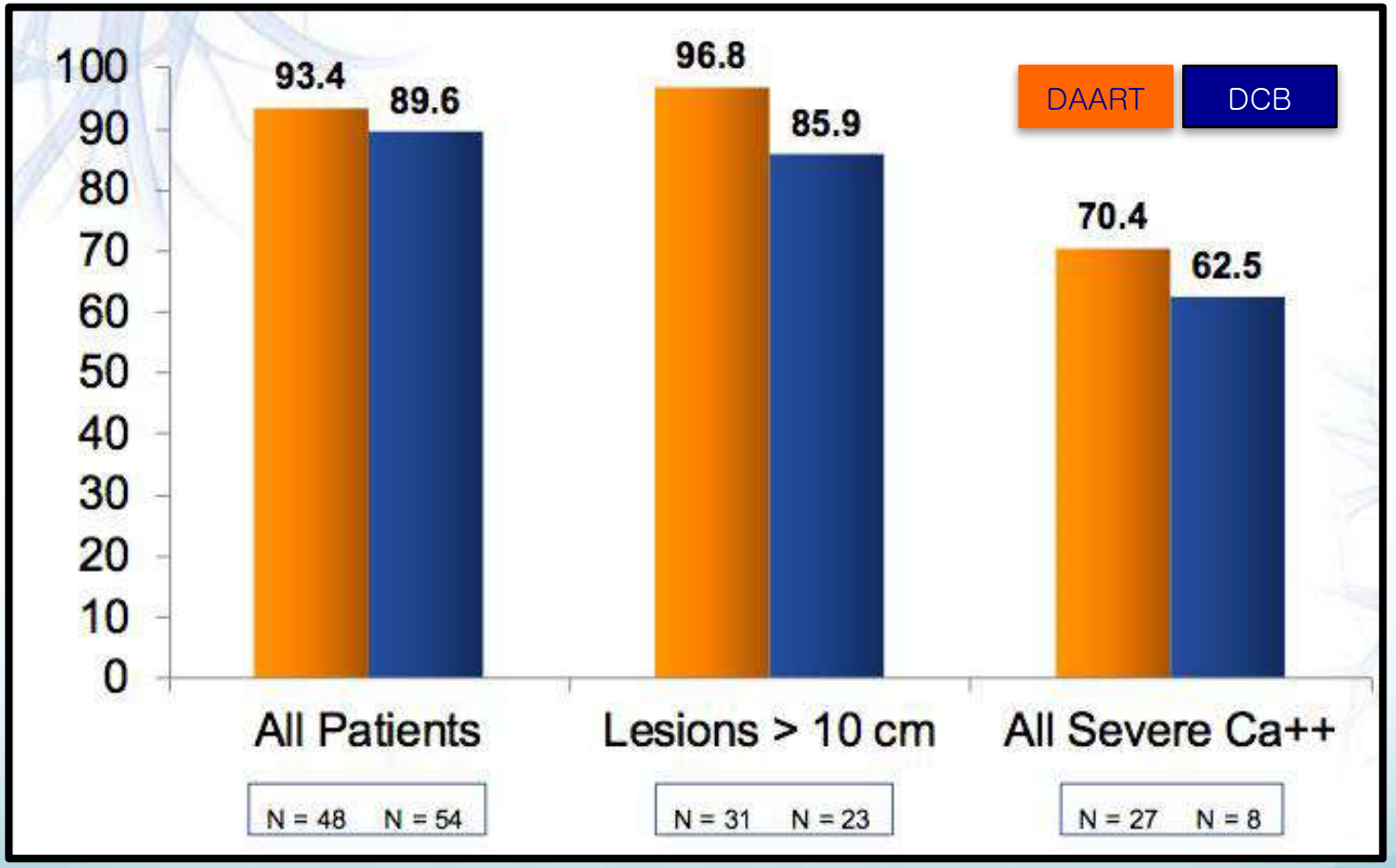
  Independent CEC, Angiographic and DUS Core laboratory analyses

DEF AR Study Design



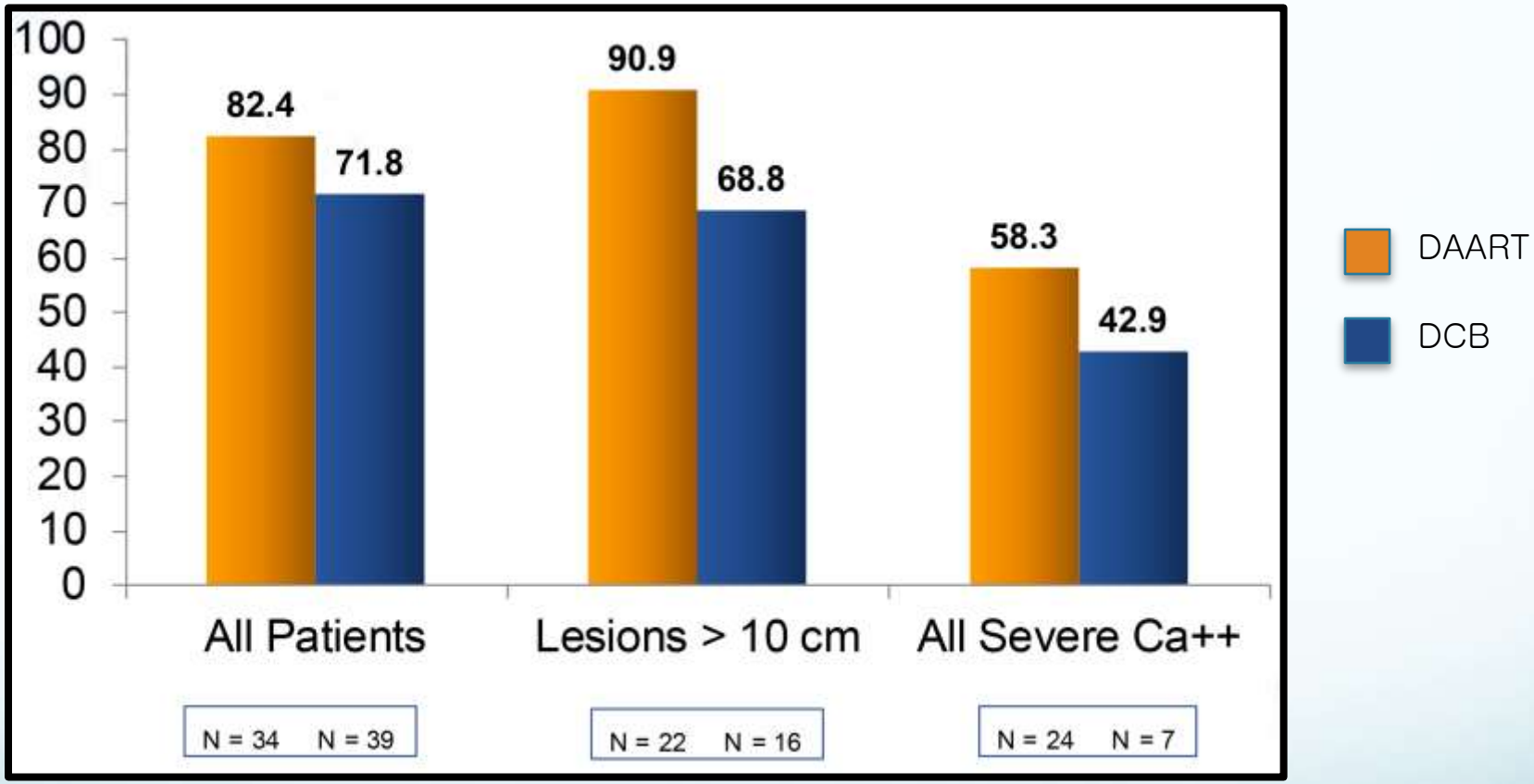
*Defined as: dense circumferential calcification extending > 5 cm

DEF AR and DA-ART: 12 Mo. DUS Patency A Potential Advantage in Long, Severely Calcified Lesions?



Zeller, VIVA 2015

12 Month Angiographic Patency
A similar pattern emerges

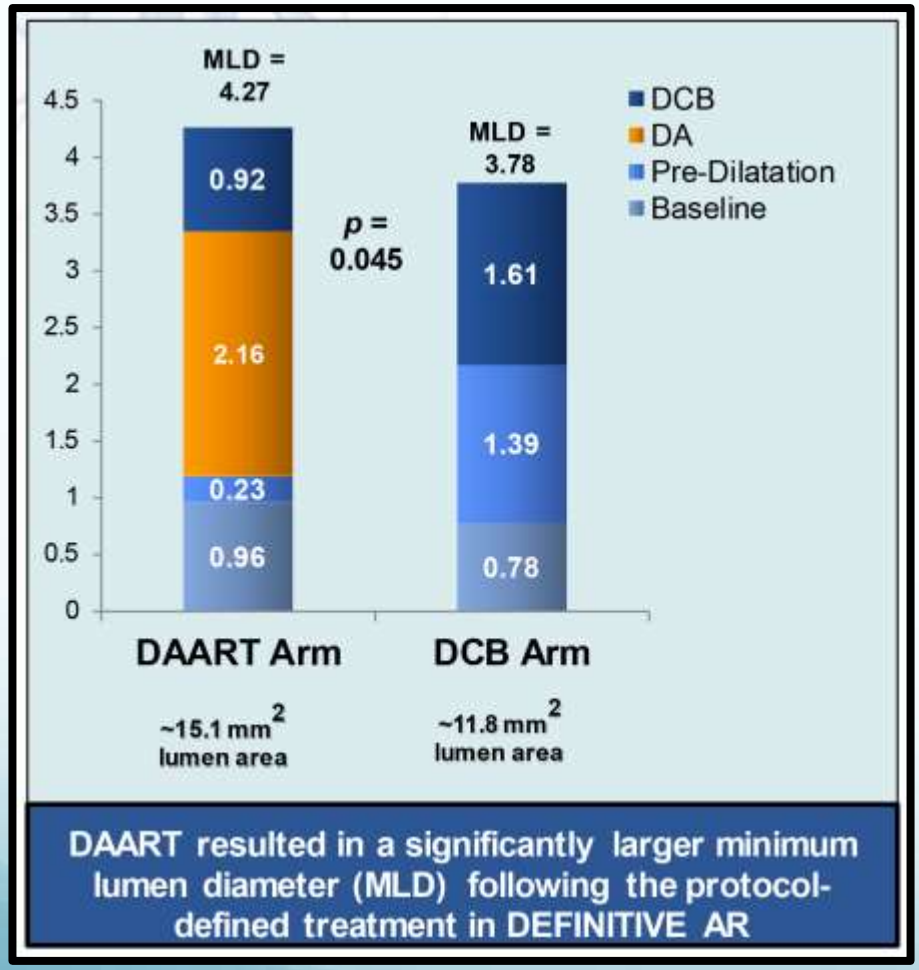


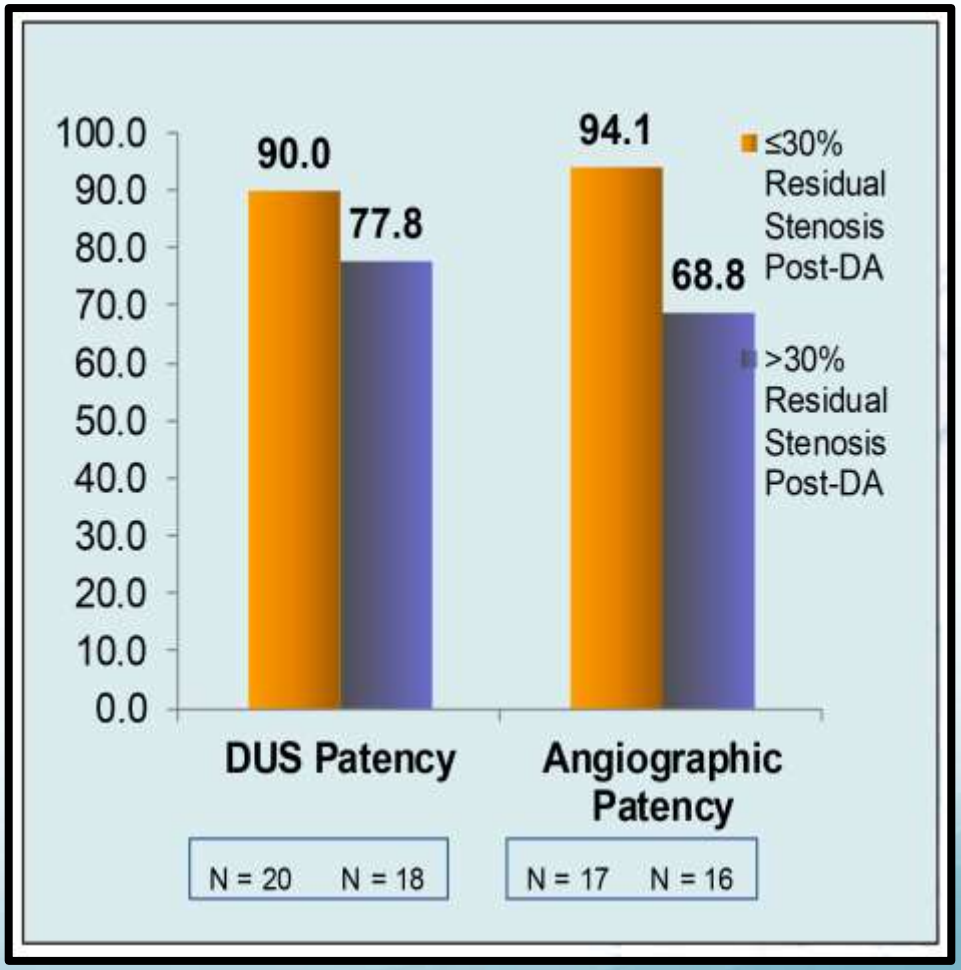
Results for all patients who returned for angiographic follow-up

Zeller, VIVA 2015

12-Month Patency: DA-ART RCT Patients

Minimalizing residual stenosis with directional atherectomy may be important





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Why the *REALITY Study?*

Questions to be Explored:

- Clinical safety/effectiveness of DA *"vessel preparation"* prior to DCB use in *long* (6-25 cm), *severely calcified* SFA lesions in up to 250 RC 2-4 claudicants in the US and Germany.
  --Duplex core lab to assess 12 mo. patency
  --Angiographic core lab to assess technical success after DA and DCB; adjudicate dissection grade and provisional stenting
  --PACSS Calcium grading scale to be validated

Why the REALITY Study?

***Additional** Questions to be Explored:*

- REALITY Sub-studies:

  --IVUS core lab to correlate relationship b/t visual assessment of Ca++ and %DS, effectiveness of DA debulking

  --Histological assessment of extracted atheroma, possible deep wall injury prior to DCB, and clinical events

  --24 mo CD-TLR and clinical event rates

DCB and DAART: An Evolution in Clinical Perspective

- The effectiveness and durability of complex lesion morphologies, *esp. highly calcified lesions*, with stand-alone DCB remains undefined…
- Terminology is evolving: ‘Vessel preparation’ has replaced ‘pre-dilatation’
- The “cost effectiveness” paradigm associated with ‘vessel preparation’ prior to DCB must be evaluated
- Could the next generation of drug delivery therapies (? bioresorbable vascular scaffolds) will be similarly challenged by complex “real world” lesions?

THANK YOU