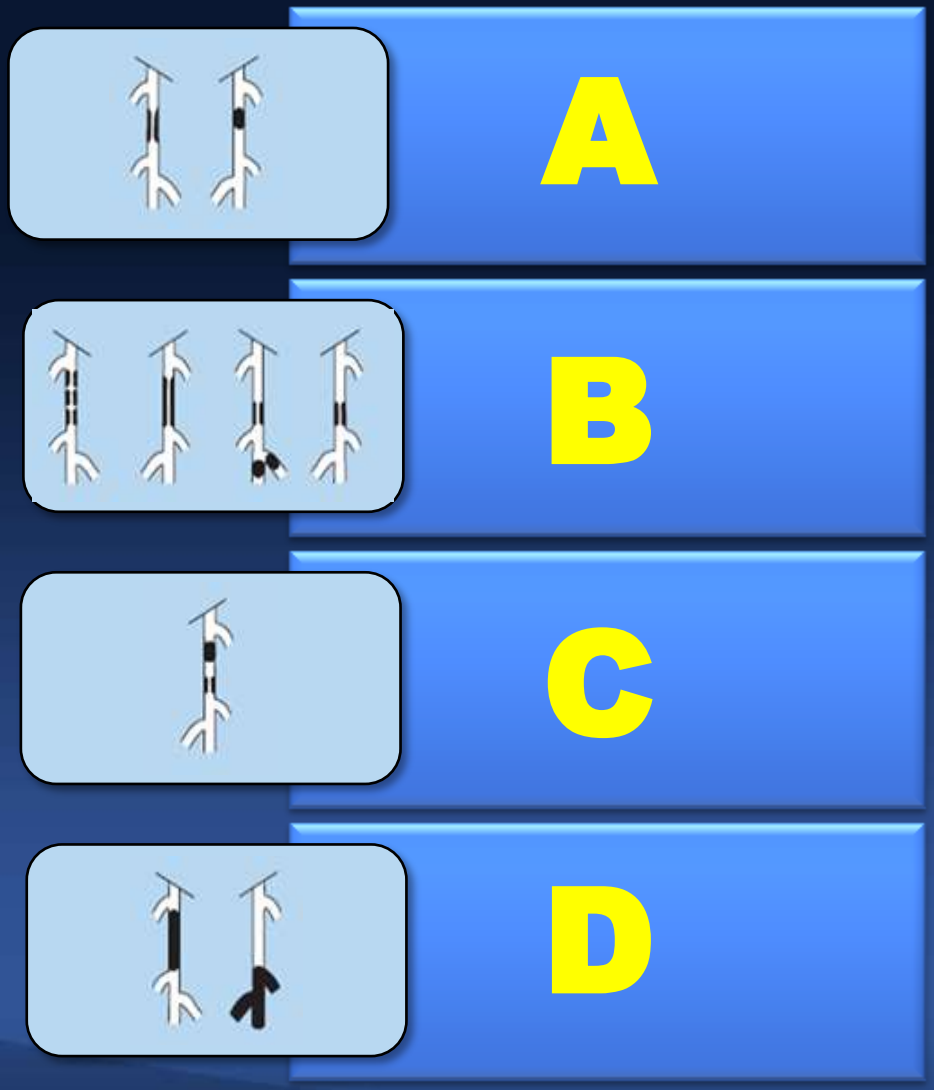
IN PACT SFA Randomized Trial: DCB Becomes First Line Therapy

Seung-Whan Lee, MD, PhD

Heart Institute, University of Ulsan College of Medicine
Asan Medical Center, Seoul, Korea

SFA TASC



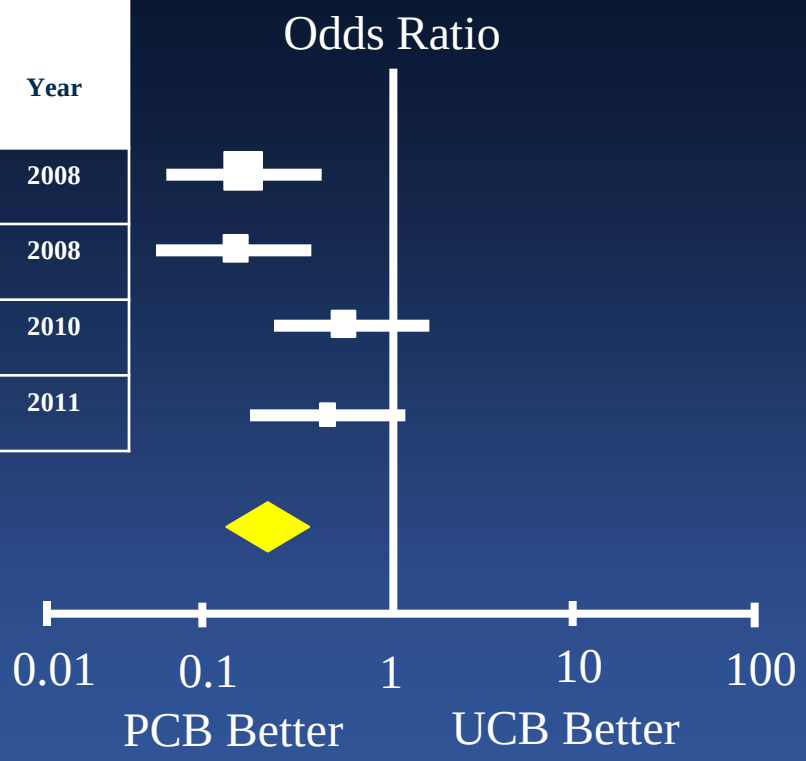
-Thunder trial
-LEVANT 1 trial
-Pacifier trial
-DEBELLIUM trial
-Fempac trial

DEB for de novo lesion

Meta-analysis

Target lesion revascularization

Study or Subgroup	PCB Events	PCB Total	UCB Events	UCB Total	Odds Ratio (95% CI)		Year
THUNDER	7	48	28	54	0.16	0.06-0.42	2008
FemPac	6	45	21	42	0.15	0.05-0.44	2008
LEVANT I	6	47	10	45	0.51	0.17-1.55	2010
PACIFIER	3	40	09	39	0.27	0.07-1.09	2011
Total					**0.23 (0.13-0.40)**		

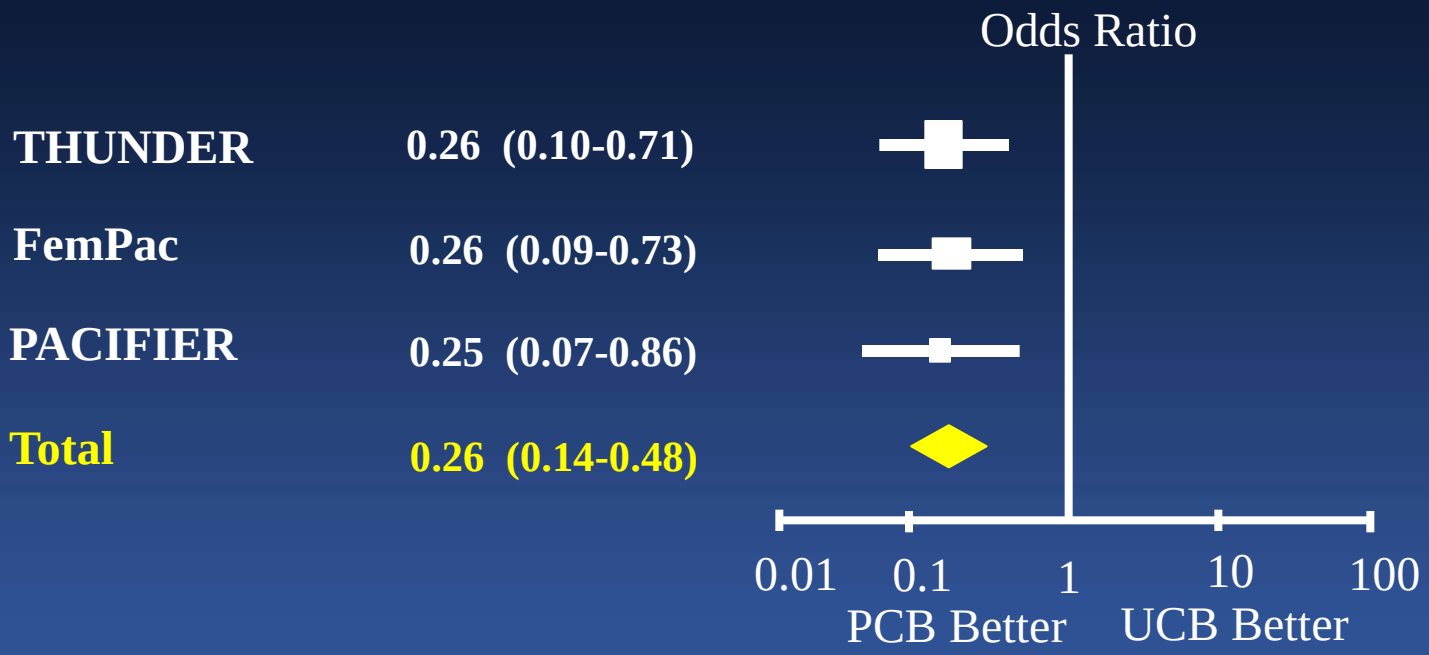


Circ Cardiovasc Interv. 2012;5:582-589

DEB for de novo lesion

Meta-analysis

Binary restenosis

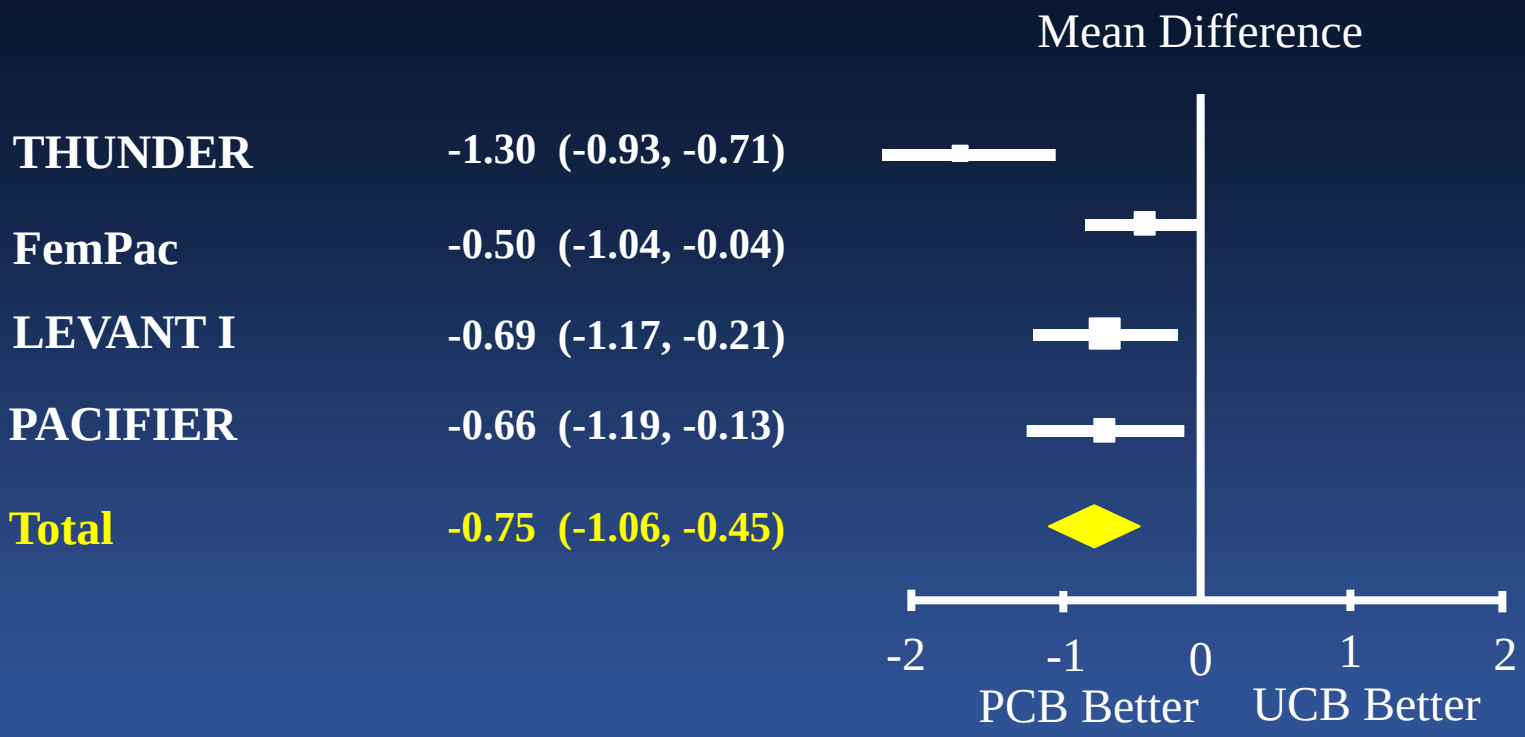


Circ Cardiovasc Interv. 2012;5:582-589

DEB for de novo lesion

Meta-analysis

Late lumen loss

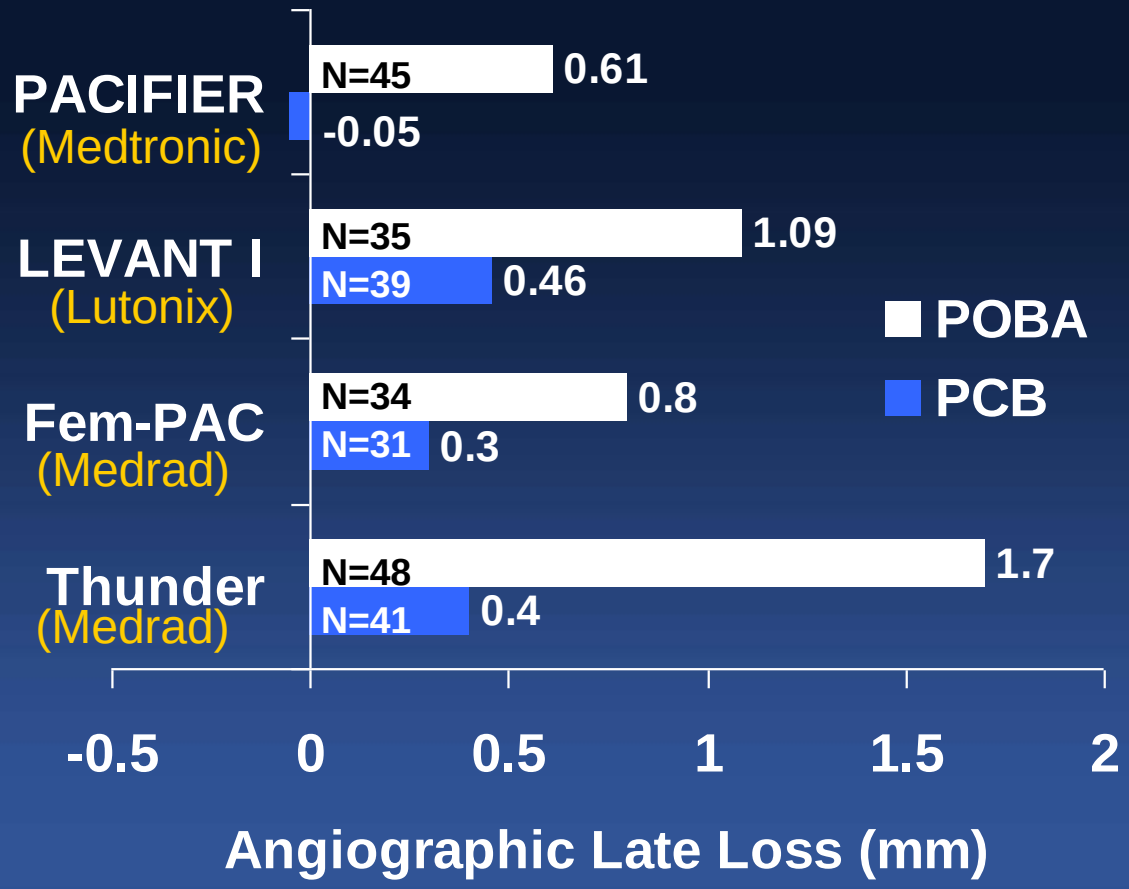


Circ Cardiovasc Interv. 2012;5:582-589

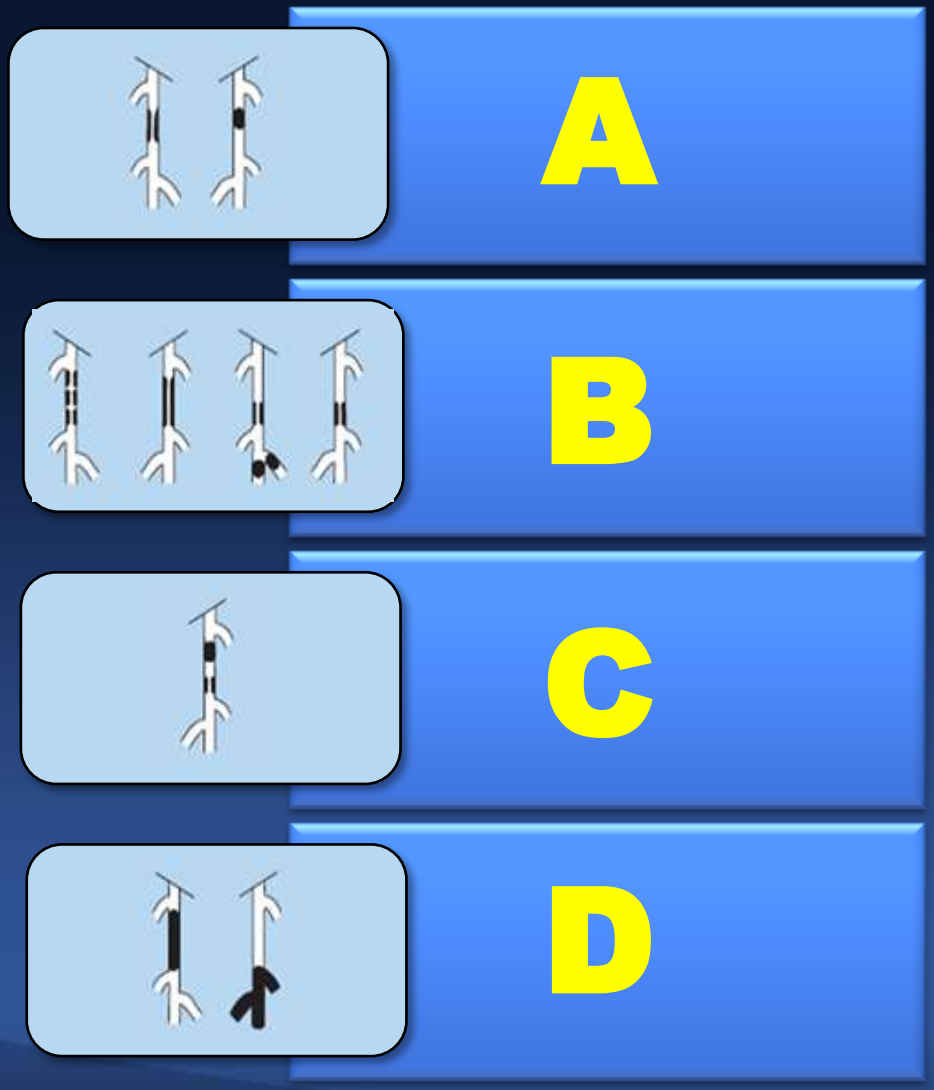
DEB Trials in the SFA

Angiographic Late Loss at 6 Months

RCT of PCB for the Treatment of De Novo SFA Disease



SFA TASC



-IN-PACT SFA randomized trial

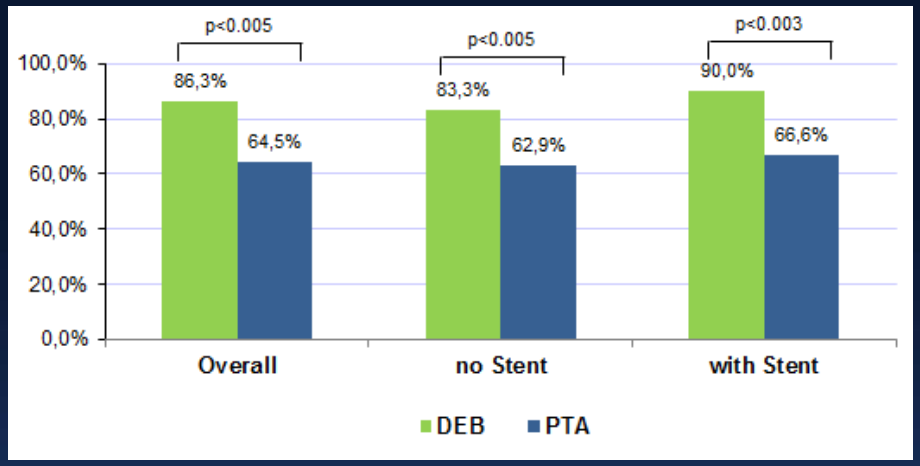
-DEBELLIUM trial

DEBELLUM trial

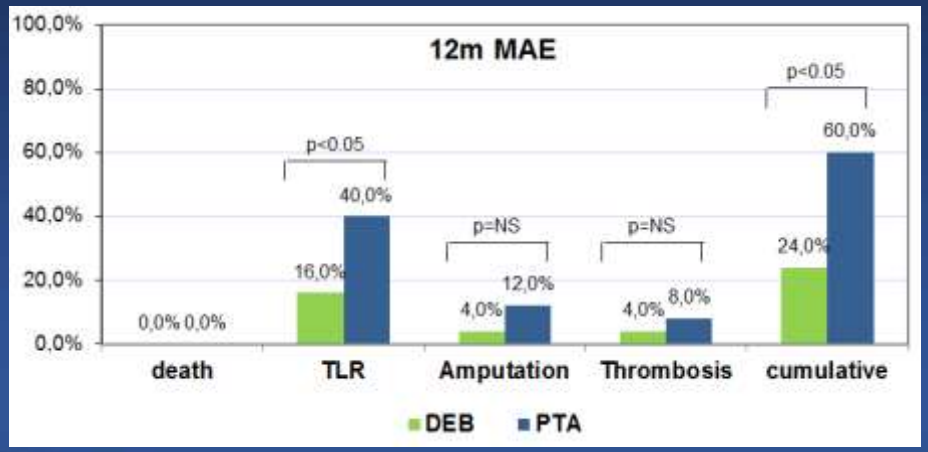
Randomized, 50 Patients 122 lesions (SFA and BTK):

- Significantly ↓LLL and ↑Primary Patency vs. PTA at 6 and 12 months in SFA
- Stents do not compromise DEB outcomes

12-month Primary Patency (SFA only)



12-month Major Adverse Events



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

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

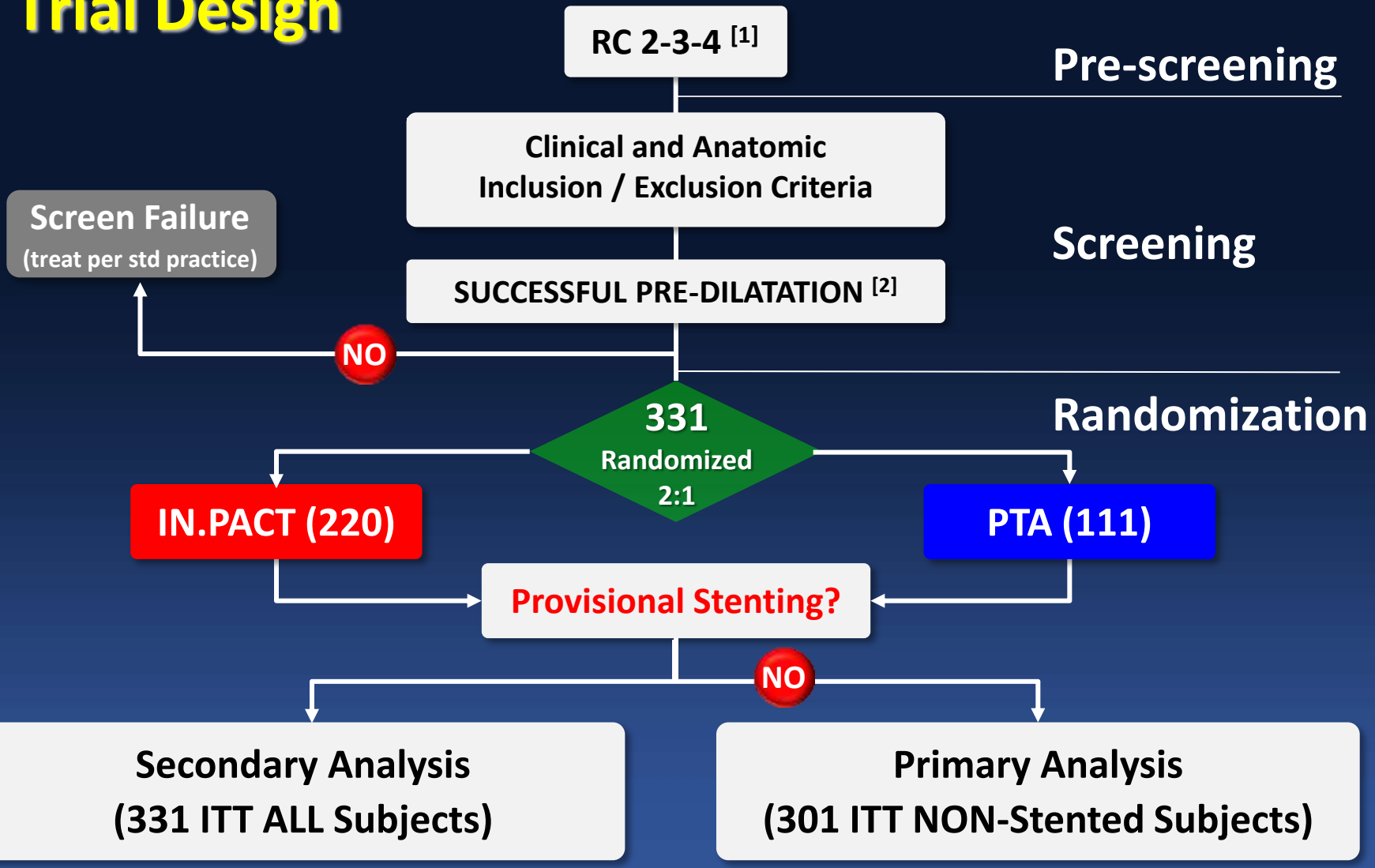
- Prospective, multicenter EU and US, randomized (2:1), single blinded
- Independent and blinded Duplex Ultrasound Core Lab [1], Angiographic Core Lab [2], and Clinical Events Committee [3]
- Independent Data Safety Monitoring Board [3]
- External monitoring with 100% source data verification
- Subjects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

Rigorous Unbiased Assessment

- **Restenosis** assessed either by DUS Core Lab (PSVR >2.4) or Angiographic Core Lab (>50% DS)
- **Clinically-driven TLR** 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
- **Clinically-driven TVR** based on any re-intervention at the target vessel due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI

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

Endpoints

- **Primary Efficacy Endpoint [1]:**

Primary patency: 1-year freedom from clinically-driven TLR and DUS-derived restenosis (PSVR $\leq$ 2.4)

- **Primary Safety Endpoint [2]:**

Freedom from device- and procedure-related death through 30 days, and 1-year freedom from major amputation and clinically-driven TVR

1. Primary Efficacy Analysis on all ITT non-stented subjects based on superiority assumption of DCB vs. PTA
2. Primary Safety Analysis on all ITT non-stented subjects based on non-inferiority of DCB vs. PTA

Key Eligibility Criteria

Key Inclusions

- RC 2-3-4
- Lesion in SFA and/or PPA
- Single *de novo* or non-stented restenotic lesion:

TASC A, B, or C lesions

  - Combination and tandem lesions allowed if criteria above met and lesion gap ≤ 3 cm
- Successful inflow treatment

* IN.PACT SFA I phase did not include pre-dilatation requirement for all subjects and did not exclude major interventions within 30 days prior to index procdure

Baseline Clinical Characteristics

	IN.PACT	PTA	*p*
N	220	111	
Age (Y)	67.5 ± 9.5	68.0 ± 9.2	*0.612*
Male Gender (%)	65.0% (143/220)	67.6% (75/111)	*0.713*
Diabetes (%)	40.5% (89/220)	48.6% (54/111)	*0.161*
Hypertension (%)	91.4% (201/220)	88.3% (98/111)	*0.431*
Hyperlipidemia (%)	84.5% (186/220)	82.0% (91/111)	*0.637*
Current Smoker (%)	38.6% (85/220)	36.0% (40/111)	*0.719*
Coronary Artery Disease (%)	57.0% (122/214)	55.0% (60/109)	*0.813*
Carotid Artery Disease (%)	34.9% (73/209)	31.7% (32/101)	*0.610*
ABI / TBI [1]	0.769 ± 0.228	0.744 ± 0.189	*0.308*
Rutherford Stage (%)			
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)	

All ITT subjects (stented and non-stented)

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

Baseline Angiographic Characteristics

		IN.PACT (N=220 Subjects, N=221 Lesions)	PTA (N=111 Subjects, N=113 Lesions)	*p*
Lesion Type [1]	*De novo*	95.0% (209/220)	94.6% (105/111)	*0.875*
	Restenotic	5.0% (11/220)	5.4% (6/111)	
# Patent Runoff Vessels	0	3.3% (7/212)	4.5% (5/112)	*0.758*
	1	13.7% (29/212)	26.8% (30/112)	*0.006*
	2	41.5% (88/212)	33.0% (37/112)	*0.151*
	3	41.5% (88/212)	35.7% (40/112)	*0.340*
Prox. Popliteal Involvement (%)		6.8% (15/221)	7.1% (8/113)	*1.000*
Lesion Length (cm) [2]		8.94 ± 4.89	8.81 ± 5.12	*0.815*
Total Occlusions (%)		25.8% (57/221)	19.5% (22/113)	*0.222*
Severe Calcification (%)		8.1% (18/221)	6.2% (7/113)	*0.662*
RVD (mm)		4.647 ± 0.841	4.681 ± 0.828	*0.728*
MLD pre (mm)		0.900 ± 0.776	0.933 ± 0.771	*0.711*
Diameter Stenosis pre (%)		81.1 ± 15.5	81.3 ± 13.7	*0.946*

All ITT subjects (stented and non-stented)

1. Site-reported
2. Normal-to-normal by Core Lab QVA evaluation

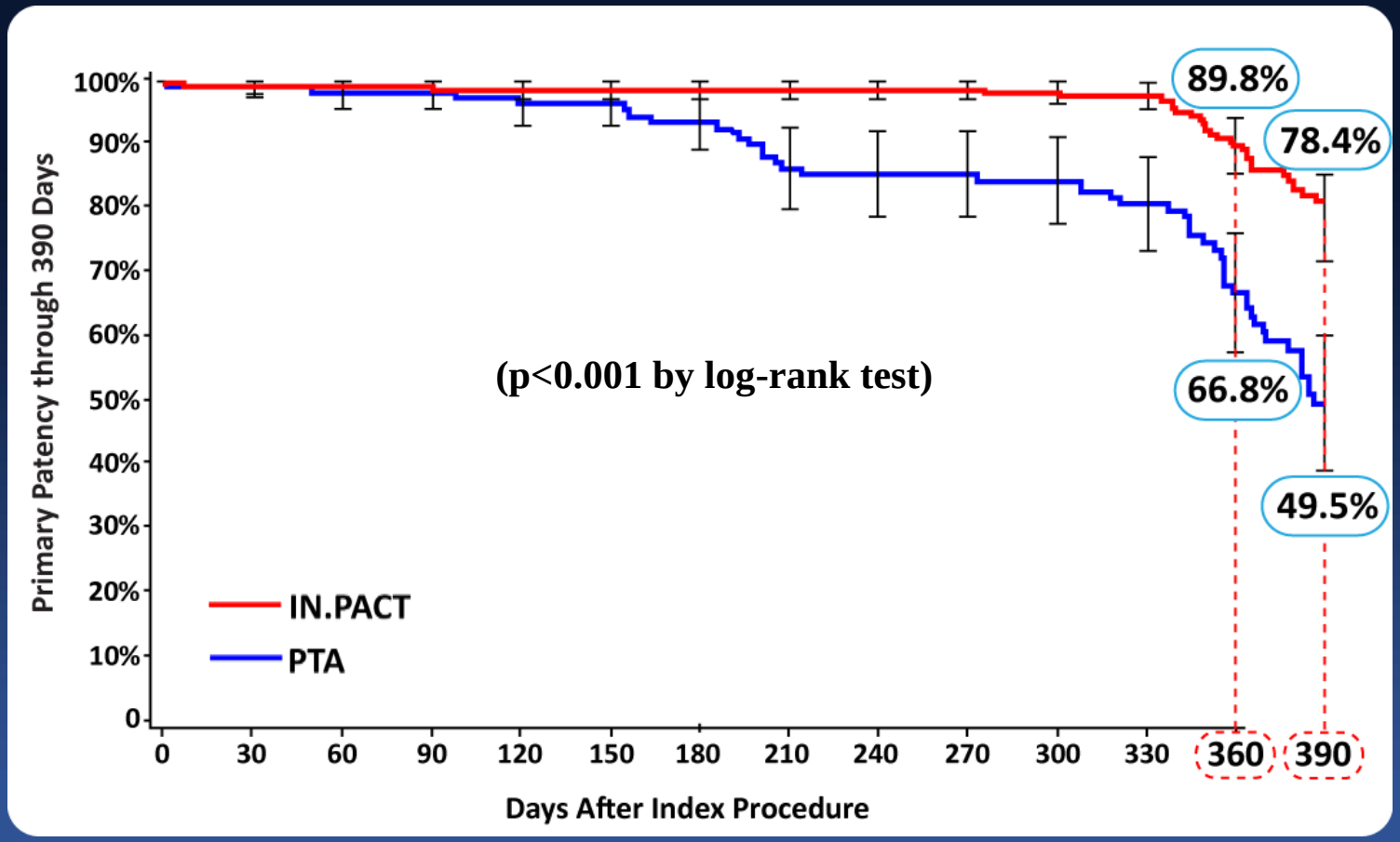
Baseline Procedural Characteristics

	IN.PACT	PTA	*p*
Pre-dilatation (%)	96.4% (212/220)	85.6% (95/111)	*<0.001*
Post-dilatation (%)	26.8% (59/220)	18.9% (21/111)	*0.135*
Dissections (%) 0	36.2% (80/221)	38.9% (44/113)	*0.360*
A-C	63.8% (141/221)	60.2% (68/113)	
D-F	0.0% (0/221)	0.9% (1/113)	
Provisional Stenting (%)	7.3% (16/220)	12.6% (14/111)	*0.110*
MLD post (mm)	3.903 ± 0.750	3.862 ± 0.732	*0.632*
Diameter Stenosis post (%)	19.9 ± 10.4	19.1 ± 10.3	*0.535*
Device Success (%) [1]	99.0% (308/311)	98.5% (128/130)	*0.302*
Procedural Success (%) [2]	99.5% (219/220)	98.2% (109/111)	*0.111*
Clinical Success (%) [3]	99.1% (218/220)	97.3% (108/111)	*0.103*

All ITT subjects (stented and non-stented)

1. Device success: Successful delivery, inflation, deflation, and retrieval of the intact study balloon without burst < RBP
2. Procedural success: Residual DS ≤ 50% for non-stented subjects or ≤ 30% for stented subjects
3. Clinical success: Procedural success without procedural complications (death, major target limb amputation, thrombosis of target lesion, or TVR) prior to discharge

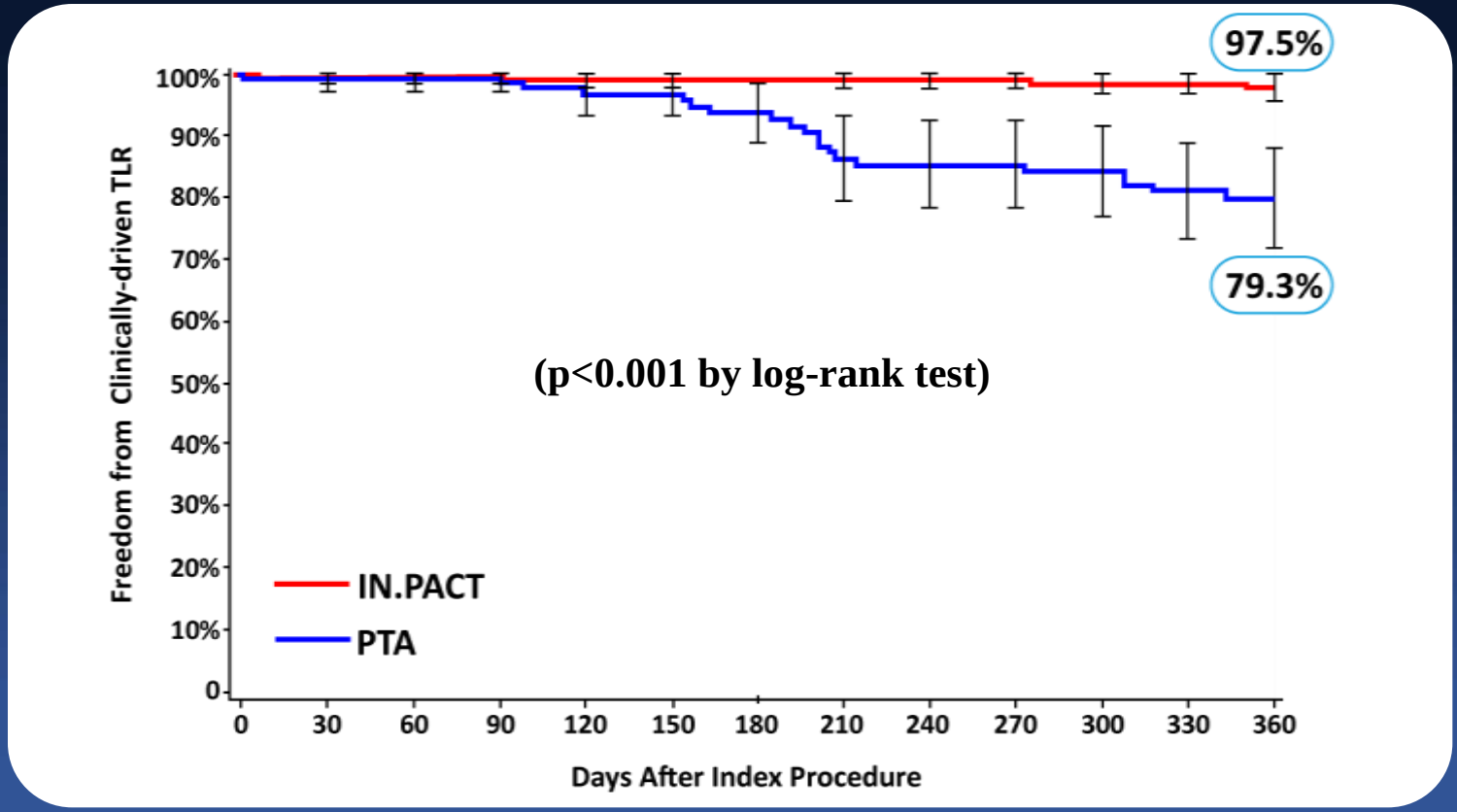
ALL ITT, 12-month Primary Patency [1]



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, 12-month Efficacy Outcomes

	IN.PACT	PTA	*p*
Primary Patency (PSVR ≤ 2.4)	82.2% (157/191)	52.4% (54/103)	*<0.001*
Clinically-driven TLR [1]	2.4% (5/207)	20.6% (22/107)	*<0.001*
All TLR [2]	2.9% (6/207)	20.6% (22/107)	*<0.001*
Primary Sustained Clinical Improv. [3]	85.2% (167/196)	68.9% (73/106)	*<0.001*
ABI / TBI [4]	0.951 ± 0.221	0.886 ± 0.169	*0.002*

1. 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
2. All TLR includes clinically-driven and incidental or duplex-driven TLR
3. An improvement shift in the Rutherford classification of at least one class in amputation- and TVR-free surviving subjects at 12 months post-procedure
4. TBI allowed / used in cases of incompressible vessels in IN.PACT SFA II phase

ALL ITT, Safety Outcomes

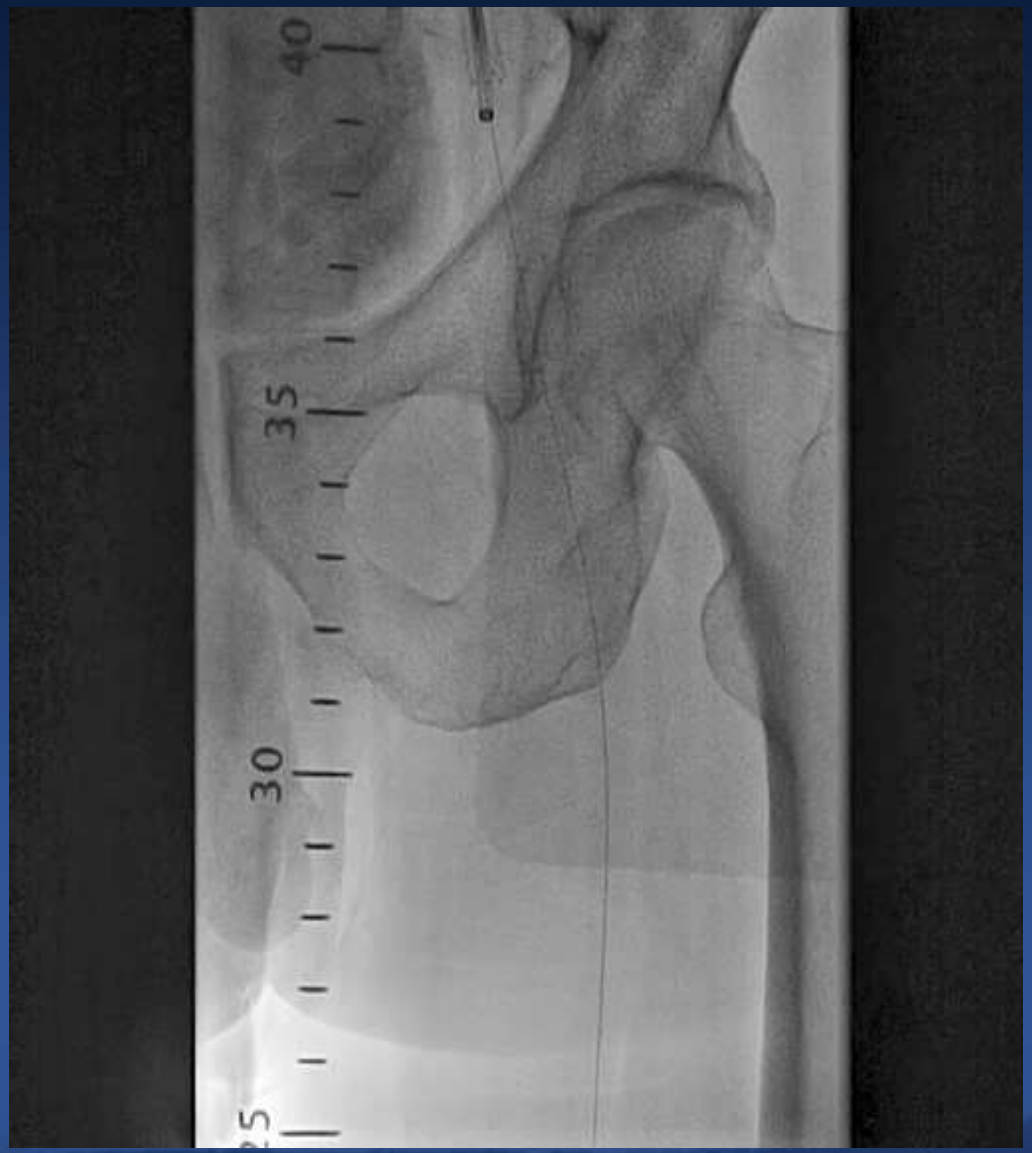
	IN.PACT	PTA	*p*
Primary Safety Composite [1]	95.7% (198/207)	76.6% (82/107)	*<0.001*
30-day Device- and Proc.-related Death	0.0% (0/218)	0.0% (0/111)	*>0.999*
12-month Clinically-driven TVR	4.3% (9/207)	23.4% (25/107)	*<0.001*
12-month Target Limb Major Amputation	0.0% (0/207)	0.0% (0/107)	*>0.999*
12-month 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

Summary

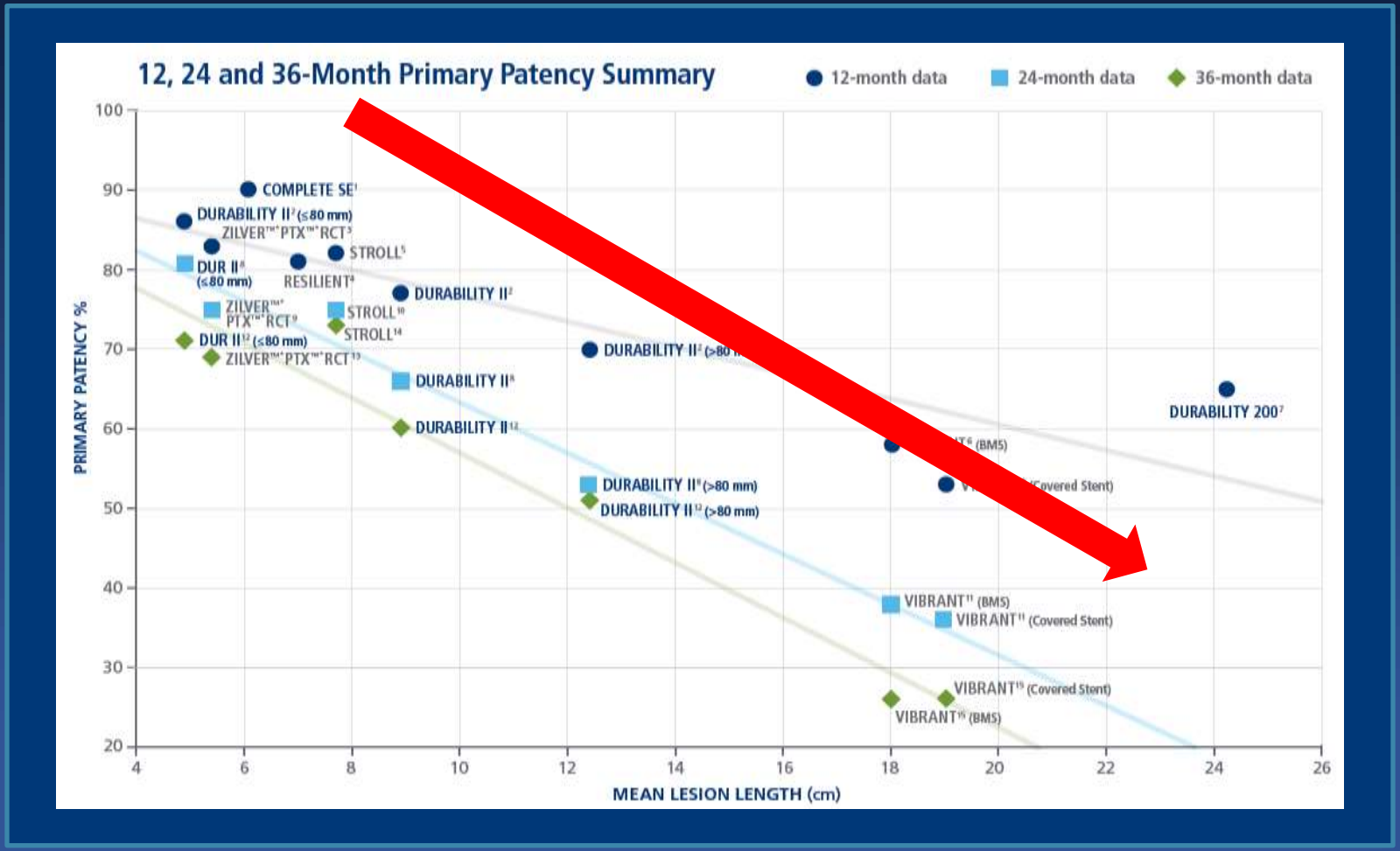
- IN.PACT Admiral: lowest TLR and highest patency rates ever reported
- Potential to become standard of care for SFA treatment

Diffuse long SFA lesions



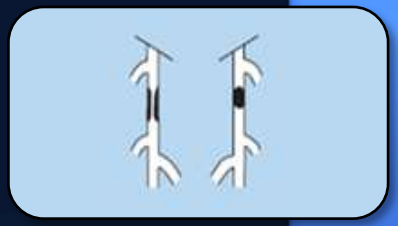
Stent ?

Long lesions are an independent predictor of decreased patency



[1]Freed MS, Manual of Interventional Cardiology, [2]Fanelli DEBELLUM, [3]Laird, CCI, June 2010, [4]SMART Control IFU, [5]Matusumura, DURABILITY IIJVS, July 2013, [6]Davaine, European Journal of Vascular and Endovascular Surgery 44 (2012)

SFA TASC



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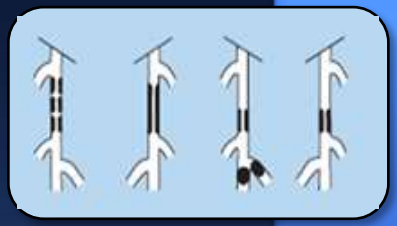

B

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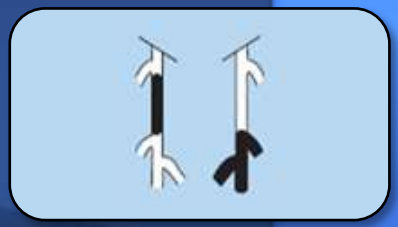


D

-IN-PACT global registry

-Leipzig registry

IN.PACT Global Long Lesions
Lesions & Procedural Characteristics

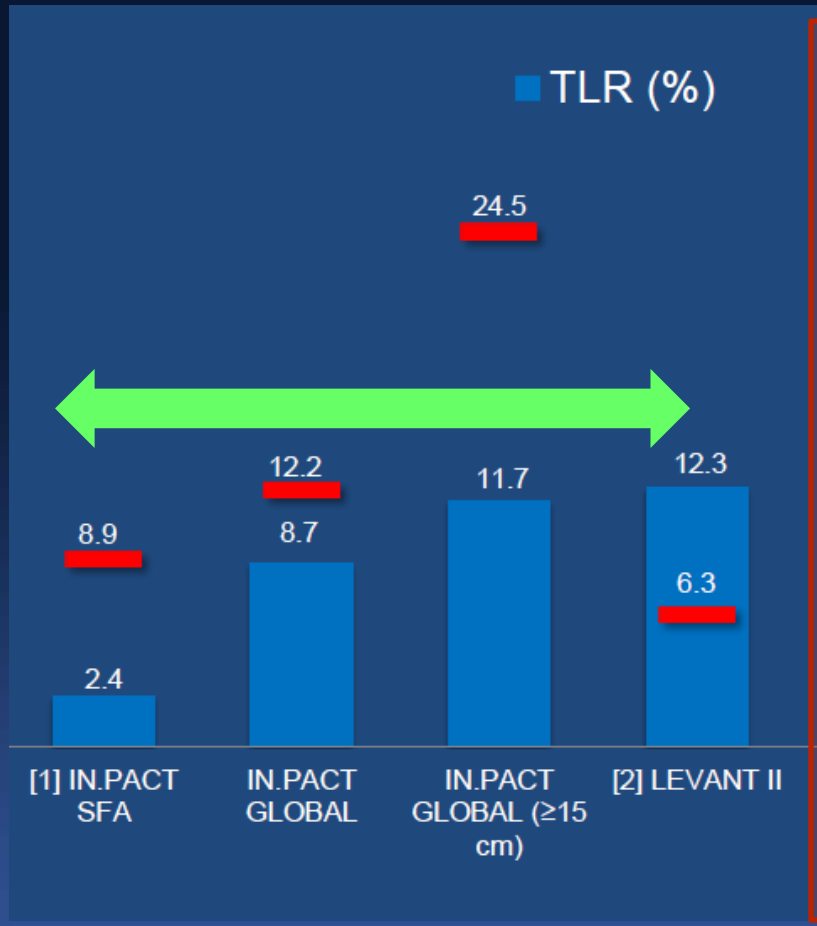
TASC D lesions

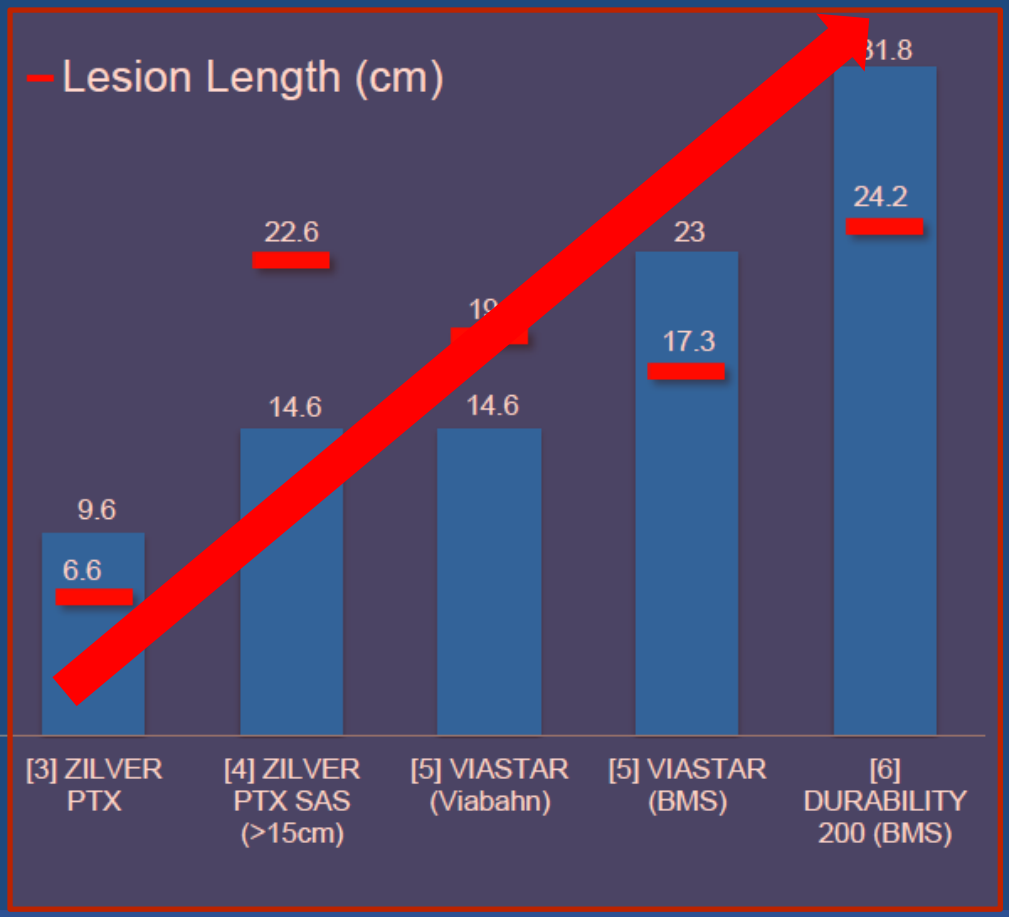
Total occlusion	64.1% (150/234)
Severe calcification	10.3% (24/233)
Provisional stenting	35.4%(80/226)

Long Lesion (≥ 15 cm) Subgroup 12-Month Outcomes

	N = 227 Subjects N = 234 Lesions
CD-TLR within 360 days	**11.7%** (23/197)
Device and Procedure-related Death within 30 days	0.9% (2/225)
Thrombosis at Target Lesion Site within 360 days	5.1% (10/197)
Major Target Limb Amputation within 360 days	0.0% (0/197)
CD-TVR within 360 days	12.2% (24/197)

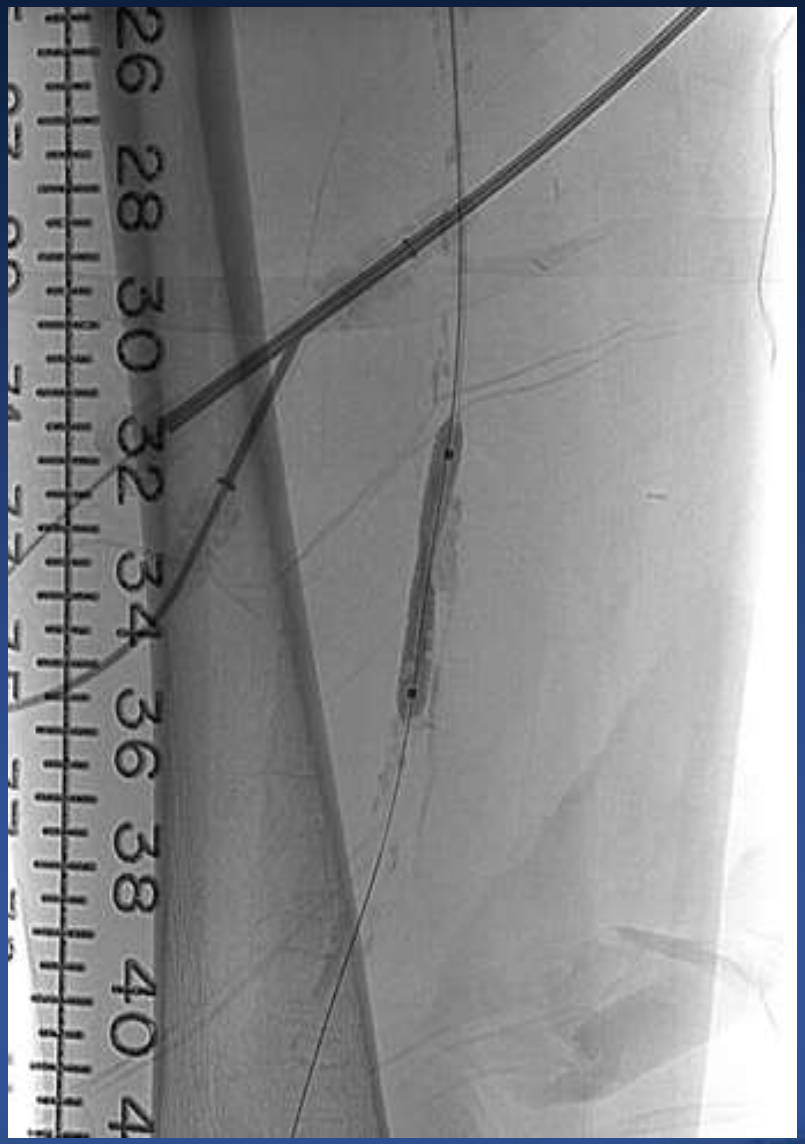
SFA trial comparison





[1] Circulation. 2014 Dec 3 [Epub]; [2] Lutonix FDA Panel Presentation; June 12 2014; [3] Circ Cardiovasc Interv. 2011;4:495-504; [4] J Cardiovasc Surg (Torino). 2013 Feb;54(1):115-22; [5] J Am Coll Cardiol. 2013 Oct 8;62(15):1320-7; [6]J Vasc Surg 2011 Oct;54(4):1042-50

Calcific lesion

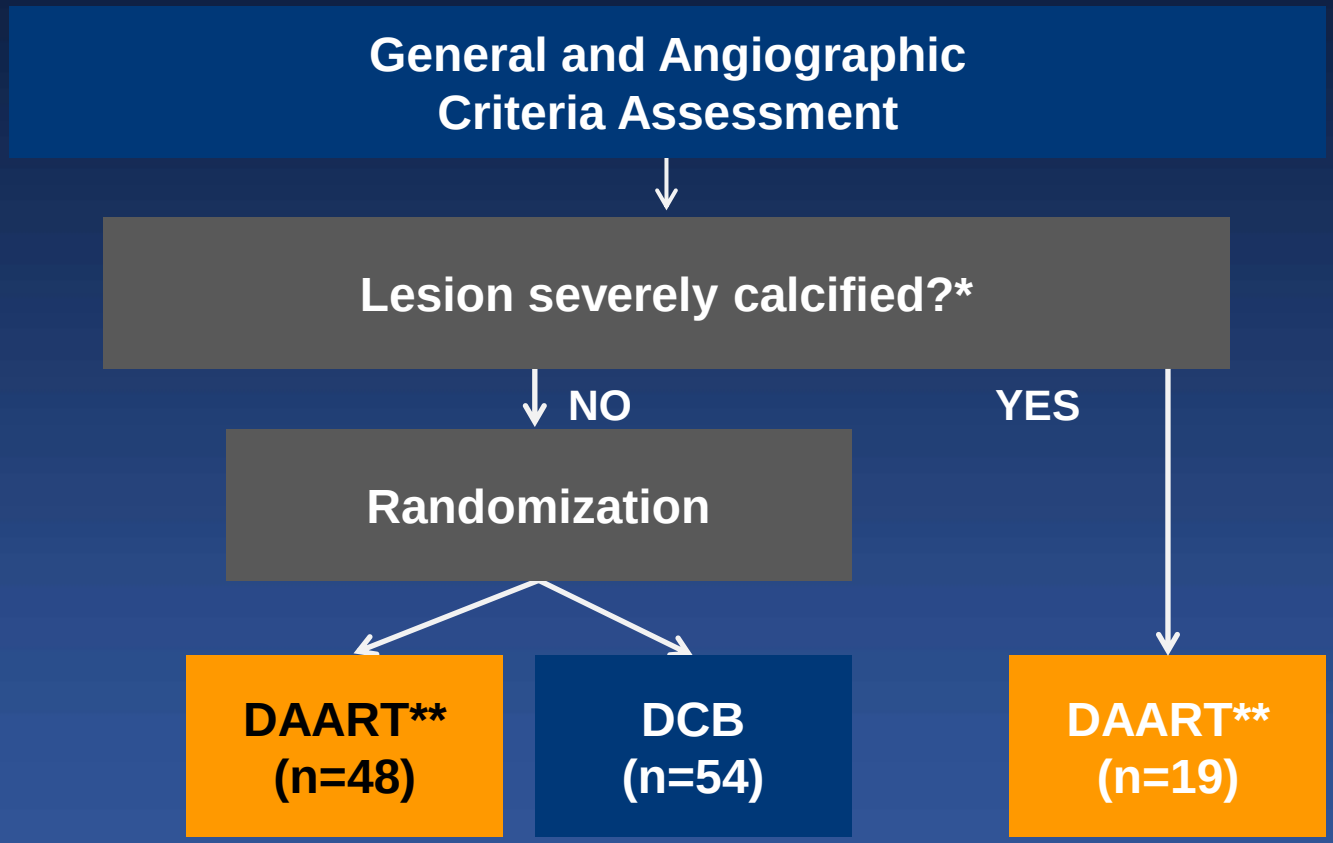


DEFINITIVE AR

A Pilot Study of Anti-Restenosis Treatment

12 Month Results – Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency

Study Design



*Defined as: dense circumferential calcification extending > 5 cm
**Directional Atherectomy and Anti-Restenotic Therapy

Baseline Lesion Characteristics

Per Core Lab

Baseline Characteristics	DAART (N= 48)	DCB (N = 54)	*p*-Value*	DAART Severe Ca++ Arm (N=19)
Lesion Length (cm)	11.2	9.7	0.05	11.9
Diameter Stenosis	82%	85%	0.35	88%
Reference vessel diameter (mm)	4.9	4.9	0.48	5.1
Minimum lumen diameter (mm)	1.0	0.8	0.34	0.7
Calcification	70.8%	74.1%	0.82	94.7%
Severe calcification	25.0%	18.5%	0.48	89.5%

* *p*-value for DAART and DCB groups

Periprocedural Outcomes (per CEC)

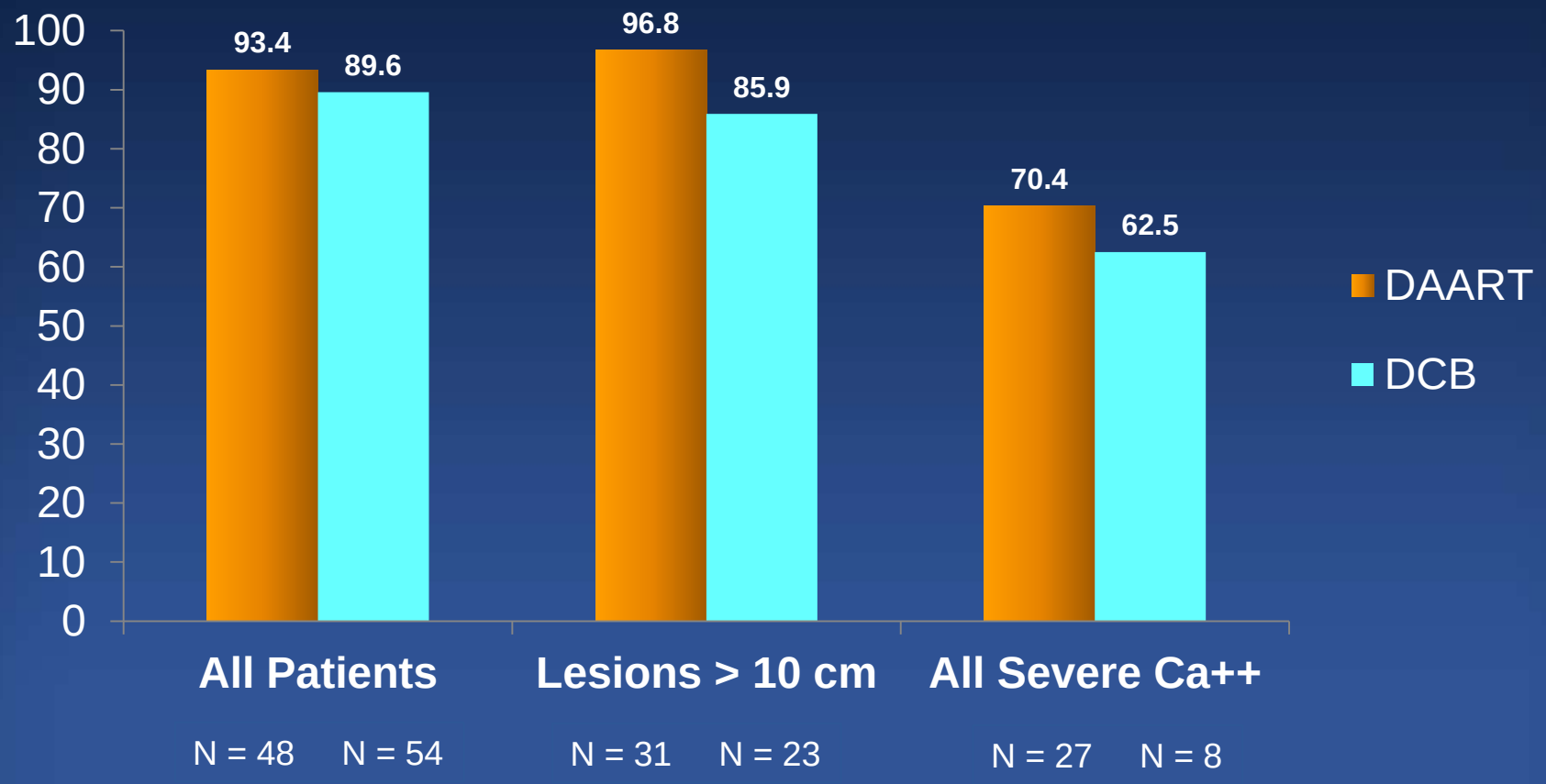
Higher Technical Success and Lower Incidence of Flow-Limiting Dissection in DAART RCT Arm

Outcomes	DAART (N= 48)	DCB (N = 54)	*p*-Value (DAART vs. DCB)	DAART Severe Ca++ Arm
Technical Success	89.6%	64.2%	0.004	84.2%
Distal Embolization	6% (3/48)	0% (0/54)	0.101	5.3% (1/19)
No Intervention	1	0		1
Endovascular Intervention	2	0		0
Bail-Out Stent	0% (0/48)	3.7% (2/54)	0.50	5.3% (1/19)
Dissection (flow-limiting, Grade C/D)	2% (1/48)	19% (10/54)	0.01	0% (0/19)
No Intervention	1	6		0
Endovascular Intervention	0	4		0
Perforation	4% (2/48)	0% (0/54)	0.22	0% (0/19)
No Intervention	0	0		0
Endovascular Intervention	2	0		0

Technical success defined as achieving ≤30% residual stenosis following protocol-defined treatment and before adjunctive therapy (ie post-dilatation). No surgical interventions were required for any patient.

Key Study Outcome at 12 Months

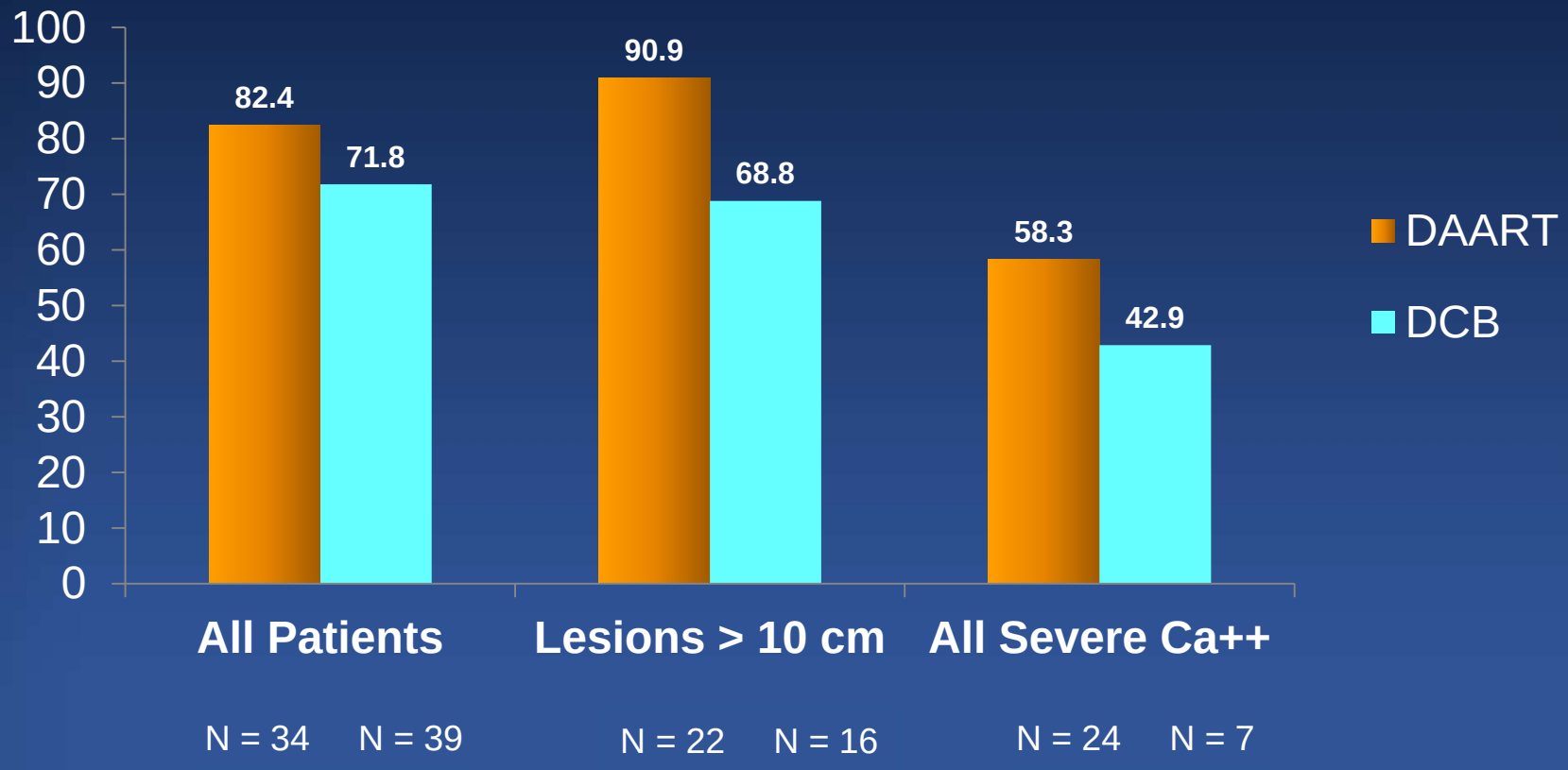
DUS Patency - Potential Advantage Emerging in Long and Severely Calcified Lesions



Per Core Lab Assessment. "All Severe Ca++ " group includes all patients treated with DAART therapy including randomized and non-randomized patients with severe calcium.

Key Study Outcome at 12 Months

Angiographic Patency shows similar pattern



Results for all patients who returned for angiographic follow-up

ISR lesion

DEBATE ISR registry (n=44)

IN-PACT SFA-ISR registry (n=39)

SFA ISR : RCT (n=240, lutonix): enrolling

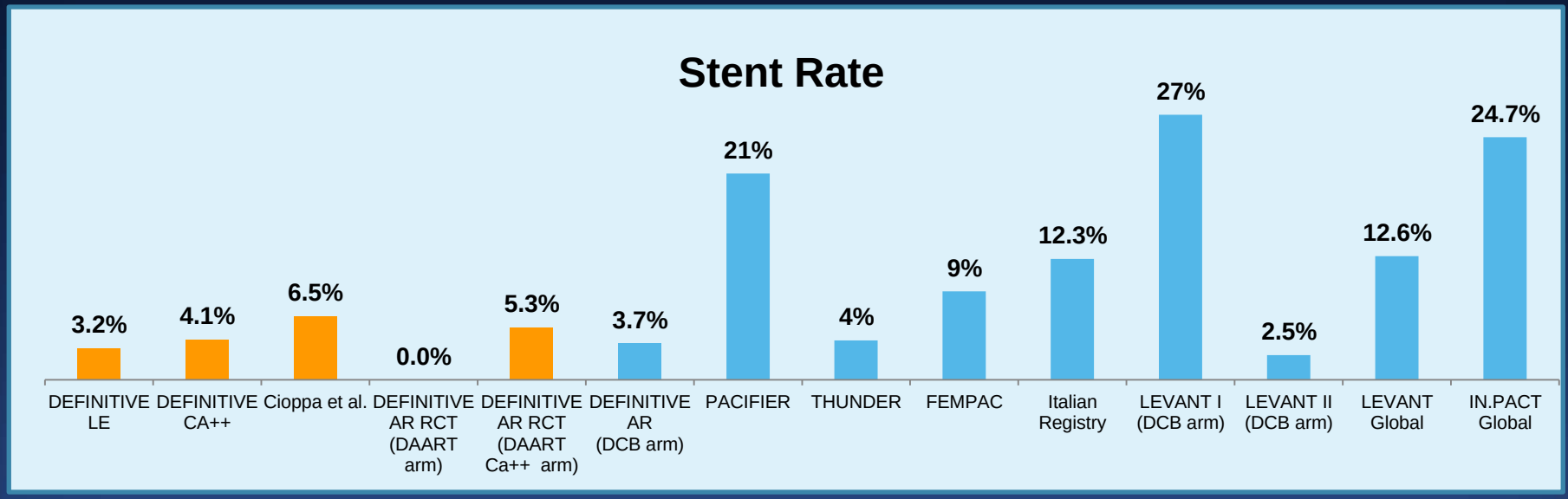
Primary patency

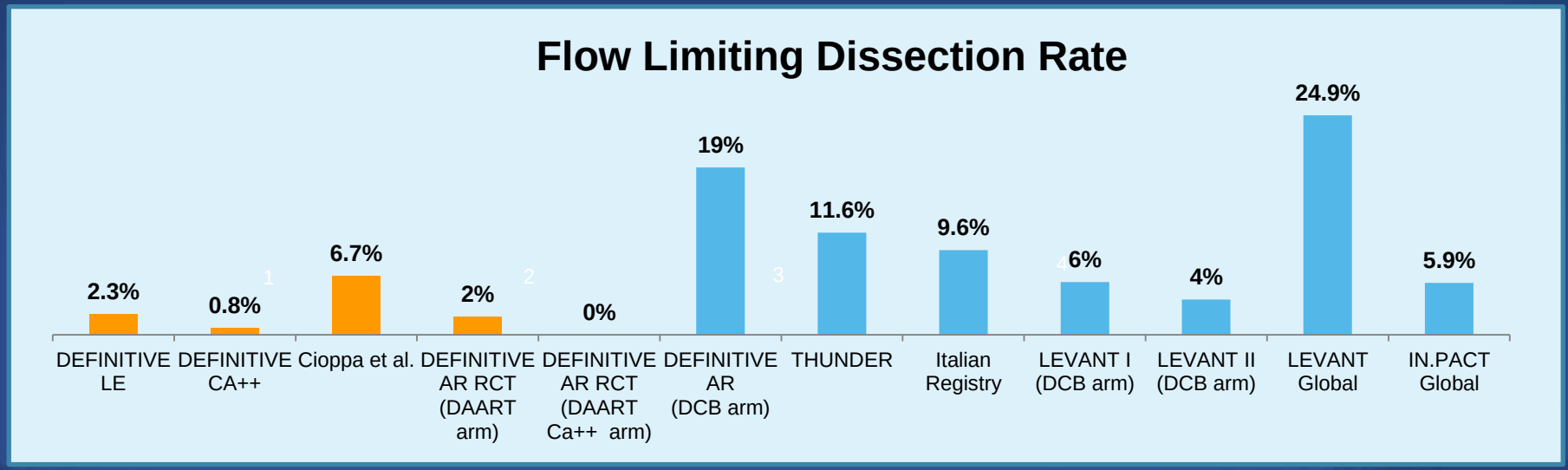
DEBATE ISR registry : 80.5%

IN-PACT SFA-ISR registry : 92.1%

SFA ISR : RCT (n=240, lutonix): enrolling

In DCB, stent and dissection rates are high





Conclusions

- DCB trials and registries already covered all TASC lesions.
- DCB showed promising patency rate in SFA lesions, but dissection and bail-out stent are drawback of DCB (TASC D 35% stent rate)
- Small registry data showed that atherectomy-based DCB strategy showed excellent synergistic patency results even in calcified or long SFA lesions with negligible use of stent.
- Therefore, routine use of DCB with/without plaque modification would be first line therapy in real practice in treating SFA lesions.