IN.PACT drug-coated balloon: Consistent clinical outcomes across patient populations and challenging lesions

John Laird, MD

Professor of Medicine

Medical Director of the Vascular Center

University of California Davis Health System

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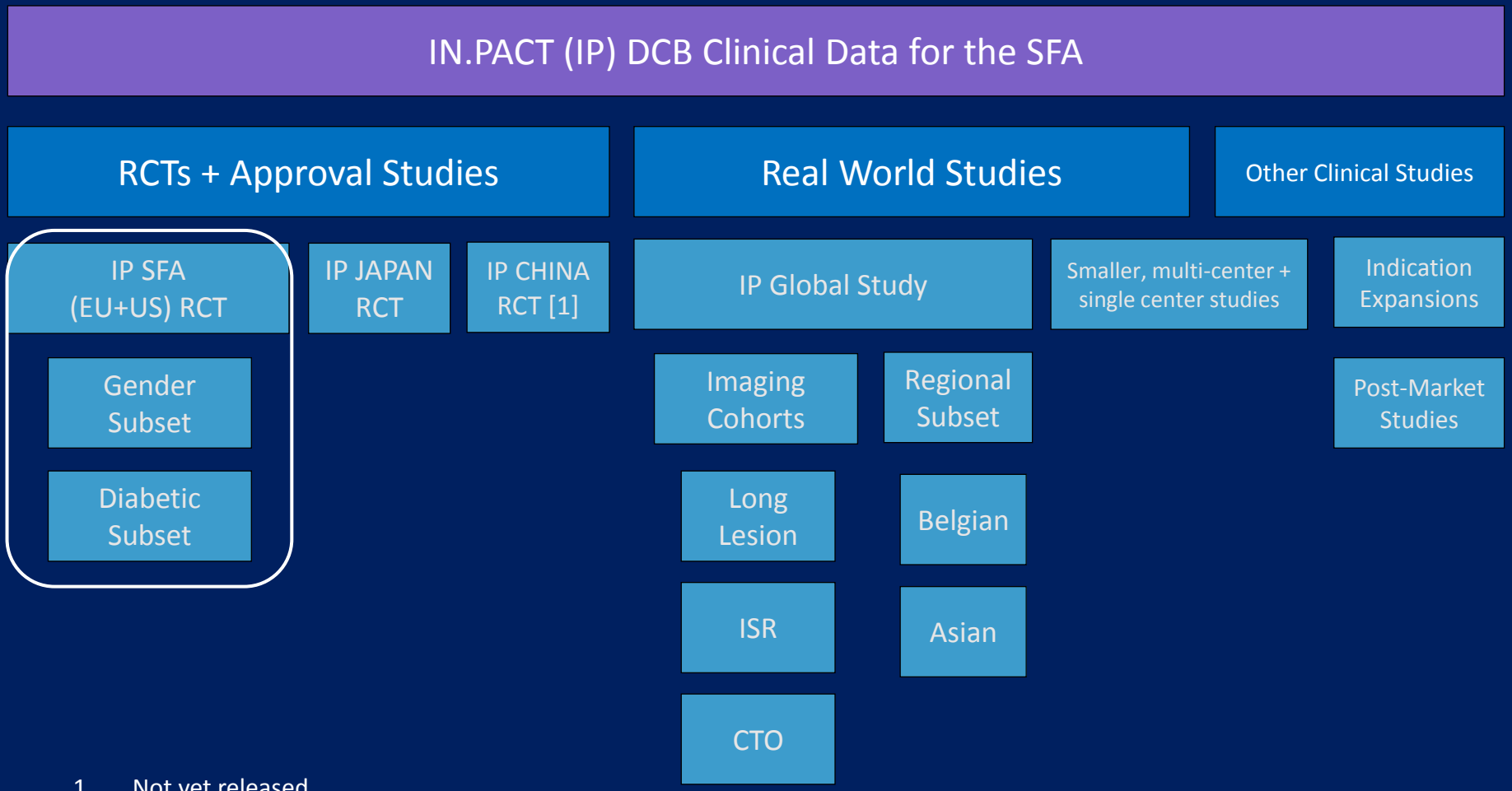
Background

- Drug-coated balloons (DCBs) have emerged as a primary treatment for femoropopliteal (fem-pop) peripheral artery disease.
- However, fem-pop disease remains a challenge to manage in women and diabetic patients due to higher co-morbidities [1-8]
- Lower success rates have been reported in women versus men treated with DCBs [THUNDER[9], LEVANT II[10]]
- Diabetic patients typically present with more advanced, complex PAD affecting small vessels and resulting in increased risk of mortality and limb loss[11]
- A need exists to demonstrate evidence-based effectiveness of DCBs in these challenging populations

1. Roddy SP, et al. J Vasc Surg 37:399-402 (2003).
2. Vouyouka AG, et al. J Vasc Surg 52:1196-203 (2010).
3. Hirsch AT, et al. Circ 125:1449-72 (2012).
4. Ferranti KM, et al. J Vasc Surg 62:990-7 (2015).
5. Stavroulakis K, et al. J Endovasc Ther 22:38-40 (2015).
6. Hernández Mateo MM, et al. Ann Vasc Surg 30:299-304 (2016).
7. Aiello A, et al. Nutr, Metab, Cardiovasc Dis 24:355-69 (2014).
8. Dick F, et al. J Vasc Surg 45:751-71 (2007).
9. Tepe G, et al. JACC Cardiovasc Interv 8:102-8 (2015).
10. Bard Lutonix 035 Instructions for Use DW5159 Rev01 Table 9.
11. DeRubertis BG, et al. J Vasc Surg 47:101–108 (2008).

IN.PACT DCB Clinical Data for the SFA Overview



1. Not yet released

IN.PACT SFA Trial Summary

	IN.PACT SFA Trial
Study Type	Prospective, Multicenter, Randomized, Controlled, Pivotal Trial
Primary Endpoints	Efficacy: Primary Patency[1] Safety: Safety Composite[2]
Rigor + Quality	• Independent adjudication by Clinical Events Committee & Imaging Core Labs • External Monitoring
Patients	331 patients
Sites	57 sites (US, EU)
Key Eligibility Criteria	• Single lesions ≤18 cm, CTO ≤10 cm • TASC A-C • SFA + Proximal Popliteal • No ISR, Ca^{++}

1. Freedom from CD-TLR and DUS-derived restenosis (PSVR ≤2.4) at 12m.
2. Composite 30-day freedom for device-and procedure-related mortality and 12-month freedom from major target limb amputation and CD-TVR.

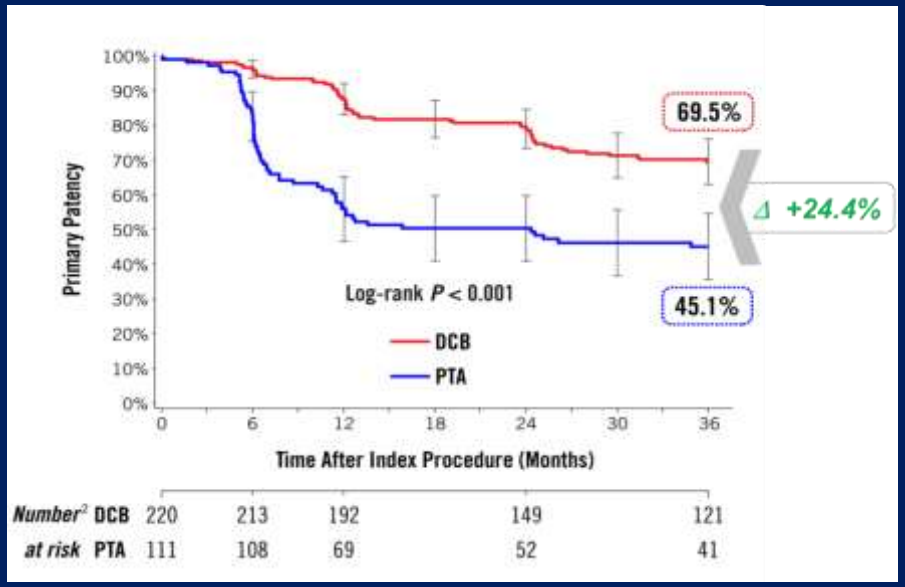
Results for the DCB Arm (n=220)			
	1 Year	2 Year	3 Year
Lesion Length (Mean ± SD, cm)	8.94 ± 4.89		
Primary Patency (KM)	87.5%	78.9%	69.5%
Primary Safety Endpoint[1] / Composite	95.7%	87.4%	81.2%
CD-TLR[2]	2.4%	9.1%	15.2%
Major Amputation Target Limb	0.0%	0.0%	0.0%
Thrombosis	1.4%	1.5%	2.0%

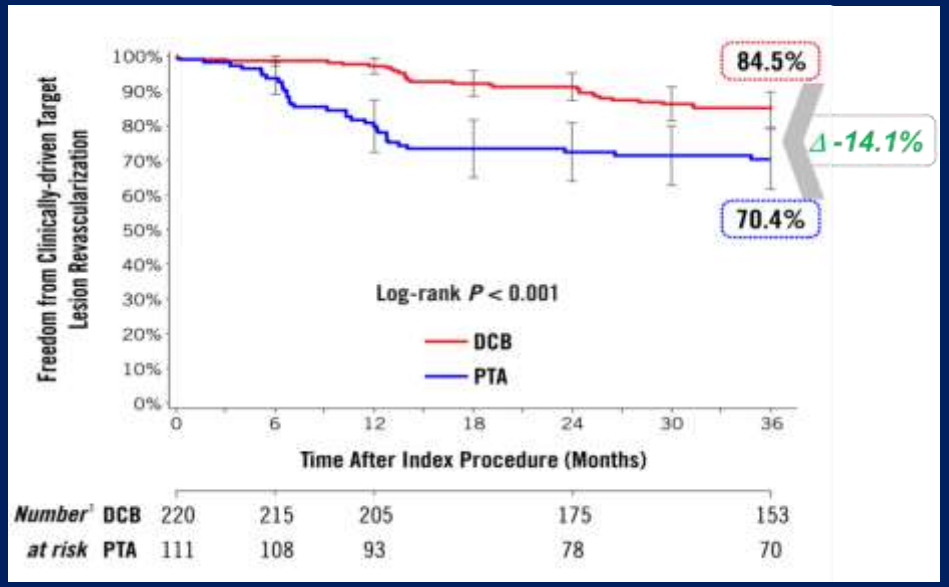
1. Composite of 30-day freedom from device- and procedure-related mortality & 12-month freedom from major target limb amputation/clinically-driven TVR.
2. Any re-intervention within the target lesion(s) due to symptoms or drop of ABI of ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI.

1Y Results: Tepe G, presented at Charing Cross London 2014. Tepe G, et al. Circ :131:495-502 (2015). 2Y Results: Laird JR, presented at TCT San Francisco 2015. Laird JR, et al. J Am Coll Cardiol: 66:2329-38 (2015). Note: 1 year results updated from interval to cumulative KM calculations. 3Y Results: Krishnan P, presented at VIVA Las Vegas 2015.

IN.PACT SFA Trial: 3-year Outcomes Summary[1]

Baseline clinical and lesion characteristics were well matched.

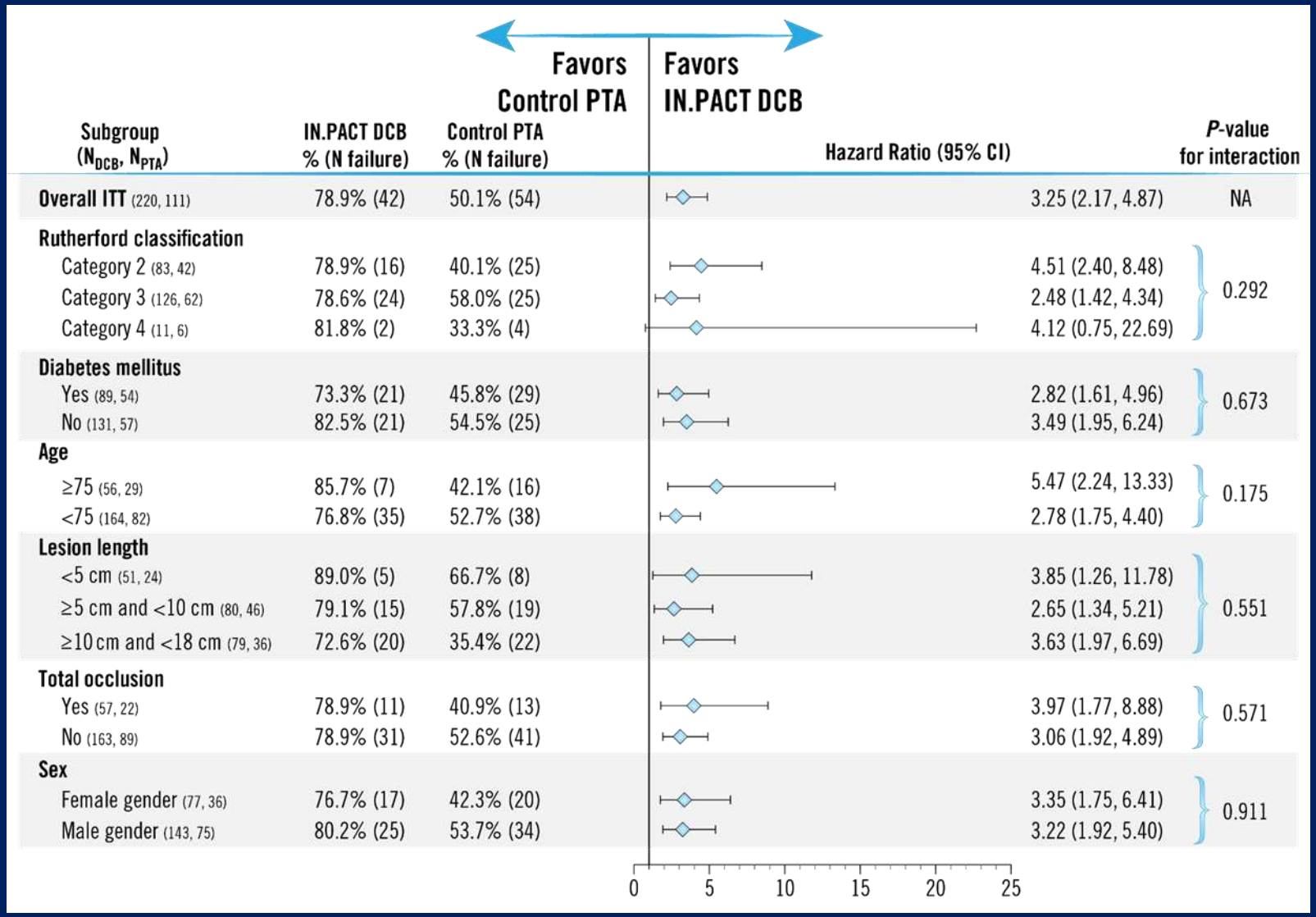




First and only independently adjudicated, randomized pivotal IDE trial to demonstrate durable, superior treatment effect with a DCB over PTA through three years. Primary patency benefit was sustained to 3 years with minimal late catch up. Data support IN.PACT™ Admiral™ as a first-line treatment for symptomatic femoropopliteal disease

1. Krishnan P, presented at VIVA Las Vegas 2015.

IN.PACT SFA Trial: Subgroup Primary Patency through 2 Years



Subgroup (N_{DCB}, N_{PTA})	IN.PACT DCB % (N failure)	Control PTA % (N failure)	Hazard Ratio (95% CI)	*P*-value for interaction
Overall ITT (220, 111)	78.9% (42)	50.1% (54)	3.25 (2.17, 4.87)	NA
Rutherford classification				
Category 2 (83, 42)	78.9% (16)	40.1% (25)	4.51 (2.40, 8.48)	0.292
Category 3 (126, 62)	78.6% (24)	58.0% (25)	2.48 (1.42, 4.34)	
Category 4 (11, 6)	81.8% (2)	33.3% (4)	4.12 (0.75, 22.69)	
Diabetes mellitus				
Yes (89, 54)	73.3% (21)	45.8% (29)	2.82 (1.61, 4.96)	0.673
No (131, 57)	82.5% (21)	54.5% (25)	3.49 (1.95, 6.24)	
Age				
≥75 (56, 29)	85.7% (7)	42.1% (16)	5.47 (2.24, 13.33)	0.175
<75 (164, 82)	76.8% (35)	52.7% (38)	2.78 (1.75, 4.40)	
Lesion length				
<5 cm (51, 24)	89.0% (5)	66.7% (8)	3.85 (1.26, 11.78)	0.551
≥5 cm and <10 cm (80, 46)	79.1% (15)	57.8% (19)	2.65 (1.34, 5.21)	
≥10 cm and <18 cm (79, 36)	72.6% (20)	35.4% (22)	3.63 (1.97, 6.69)	
Total occlusion				
Yes (57, 22)	78.9% (11)	40.9% (13)	3.97 (1.77, 8.88)	0.571
No (163, 89)	78.9% (31)	52.6% (41)	3.06 (1.92, 4.89)	
Sex				
Female gender (77, 36)	76.7% (17)	42.3% (20)	3.35 (1.75, 6.41)	0.911
Male gender (143, 75)	80.2% (25)	53.7% (34)	3.22 (1.92, 5.40)	

IN.PACT SFA Trial
Baseline Clinical Characteristics

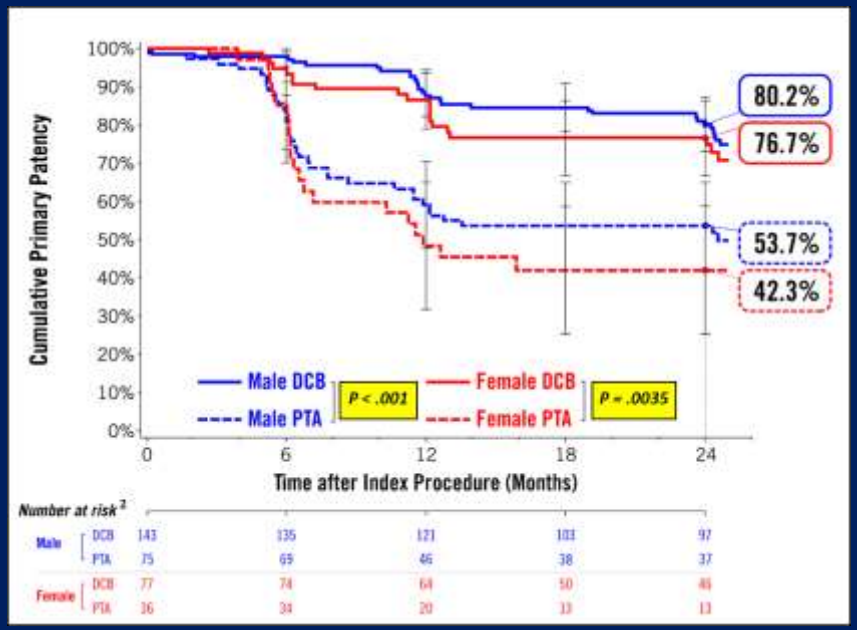
	IN.PACT n = 220 subjects	PTA n = 111 subjects	P-value
Age, Y ± SD	67.5 ± 9.5	68.0 ± 9.2	0.612
Male, % (n)	65.0% (143/220)	67.6% (75/111)	0.713
Diabetes, % (n)	40.5% (89/220)	48.6% (54/111)	0.161
Hypertension, % (n)	91.4% (201/220)	88.3% (98/111)	0.431
Current smoker, % (n)	38.6% (85/220)	36.0% (40/111)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

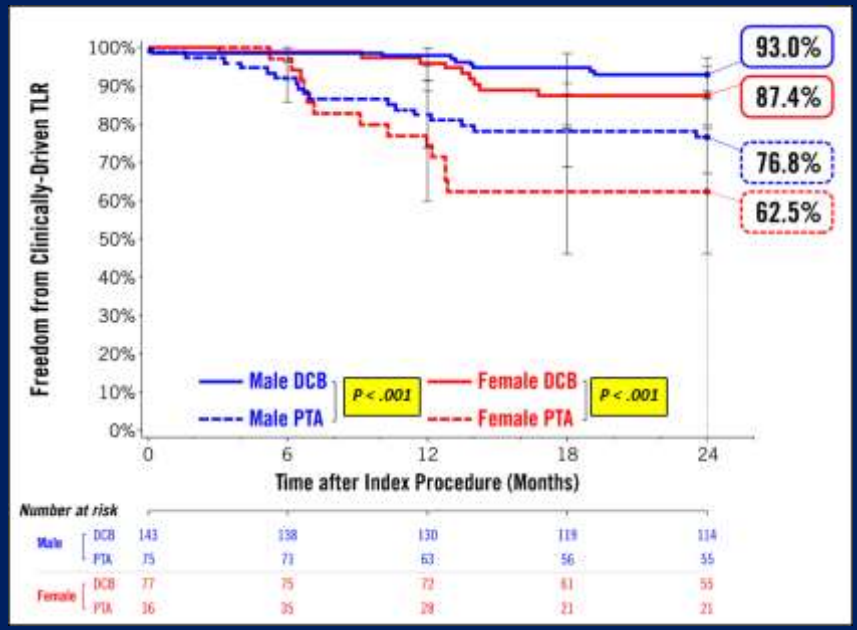
1. TBI allowed / used in cases of incompressible vessels in IN.PACT SFA II phase

1Y Results: Tepe G, presented at Charing Cross London 2014. Tepe G, et al. Circ :131:495-502 (2015). 2Y Results: Laird JR, presented at TCT San Francisco 2015. Laird JR, et al. J Am Coll Cardiol: 66:2329-38 (2015). Note: 1 year results updated from interval to cumulative KM calculations. 3Y Results: Krishnan P, presented at VIVA Las Vegas 2015.

IN.PACT SFA Trial: 2-year Outcomes By Gender Summary[1]

Baseline clinical characteristics were well matched between groups and lesion/procedural characteristics had no difference between groups





A significant patency benefit favoring IN.PACT Admiral DCB over PTA was demonstrated in both women and men. Primary patency benefit was sustained to 2 years with no late catch up for either gender. High primary patency and low CD-TLR rates were achieved in women, despite smaller RVDs.

1. Schneider P, presented at Charing Cross London 2016.

IN.PACT SFA Trial
Baseline Clinical Characteristics

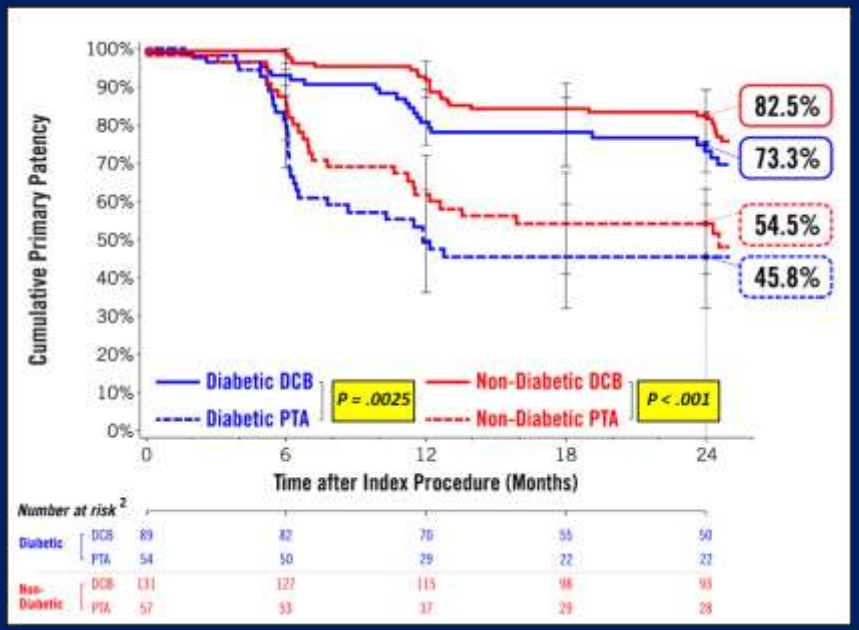
	IN.PACT n = 220 subjects	PTA n = 111 subjects	P-value
Age, Y ± SD	67.5 ± 9.5	68.0 ± 9.2	0.612
Male, % (n)	65.0% (143/220)	67.6% (75/111)	0.713
Diabetes, % (n)	40.5% (89/220)	48.6% (54/111)	0.161
Hypertension, % (n)	91.4% (201/220)	88.3% (98/111)	0.431
Current smoker, % (n)	38.6% (85/220)	36.0% (40/111)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

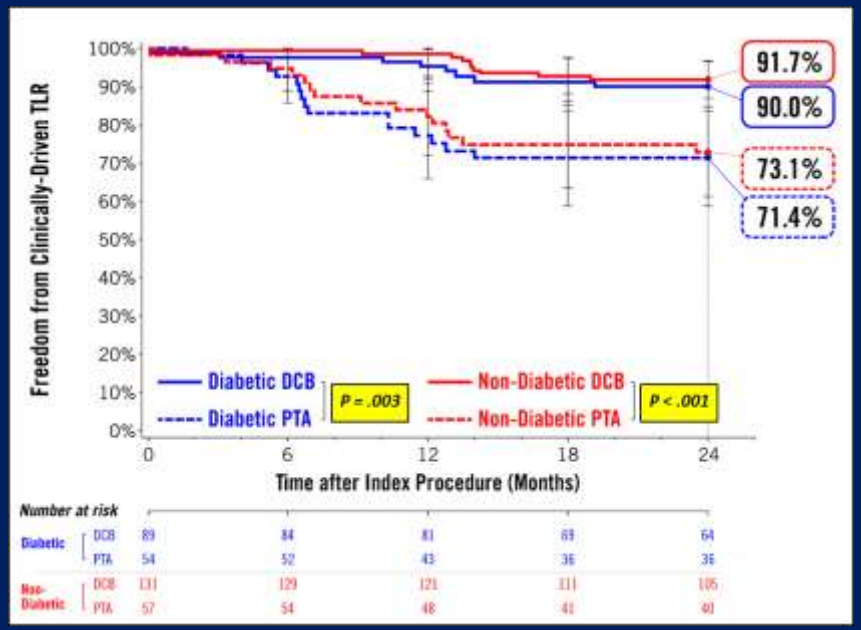
1. TBI allowed / used in cases of incompressible vessels in IN.PACT SFA II phase

1Y Results: Tepe G, presented at Charing Cross London 2014. Tepe G, et al. Circ :131:495-502 (2015). 2Y Results: Laird JR, presented at TCT San Francisco 2015. Laird JR, et al. J Am Coll Cardiol: 66:2329-38 (2015). Note: 1 year results updated from interval to cumulative KM calculations. 3Y Results: Krishnan P, presented at VIVA Las Vegas 2015.

IN.PACT SFA Trial: 2-year Outcomes By Diabetic Status Summary[1]

Baseline clinical characteristics were well matched between groups and lesion/procedural characteristics had no difference between groups.





A significant patency benefit favoring IN.PACT Admiral DCB over PTA was demonstrated in <u>both</u> diabetic and non-diabetic subsets. Primary patency benefit was sustained to 2 years with no late catch up for either subset. IN.PACT Admiral DCB is significantly more effective than PTA in diabetic patients who typically present with advanced, complex PAD.

1. Schneider P, presented at Charing Cross London 2016.

Conclusions

Two-year subset results demonstrate durability and continued superiority of the IN.PACT Admiral DCB over PTA

- Gender & diabetic analyses add to robust body of independently-adjudicated evidence for the IN.PACT Admiral DCB.
- Beneficial DCB treatment effect in historically challenging female patients is unique to the IN.PACT Admiral DCB.
- IN.PACT Admiral DCB is significantly more effective than PTA in diabetic patients who typically present with advanced, complex PAD.
- This new evidence has the potential to continue to drive a paradigm shift in SFA interventions.

IN.PACT drug-coated balloon: Consistent clinical outcomes across challenging lesions

Background

- Complex lesion types including **long lesions, chronic total occlusions (CTOs) and in-stent restenosis (ISR)** remain unmet clinical needs, with no current treatment standard identified.

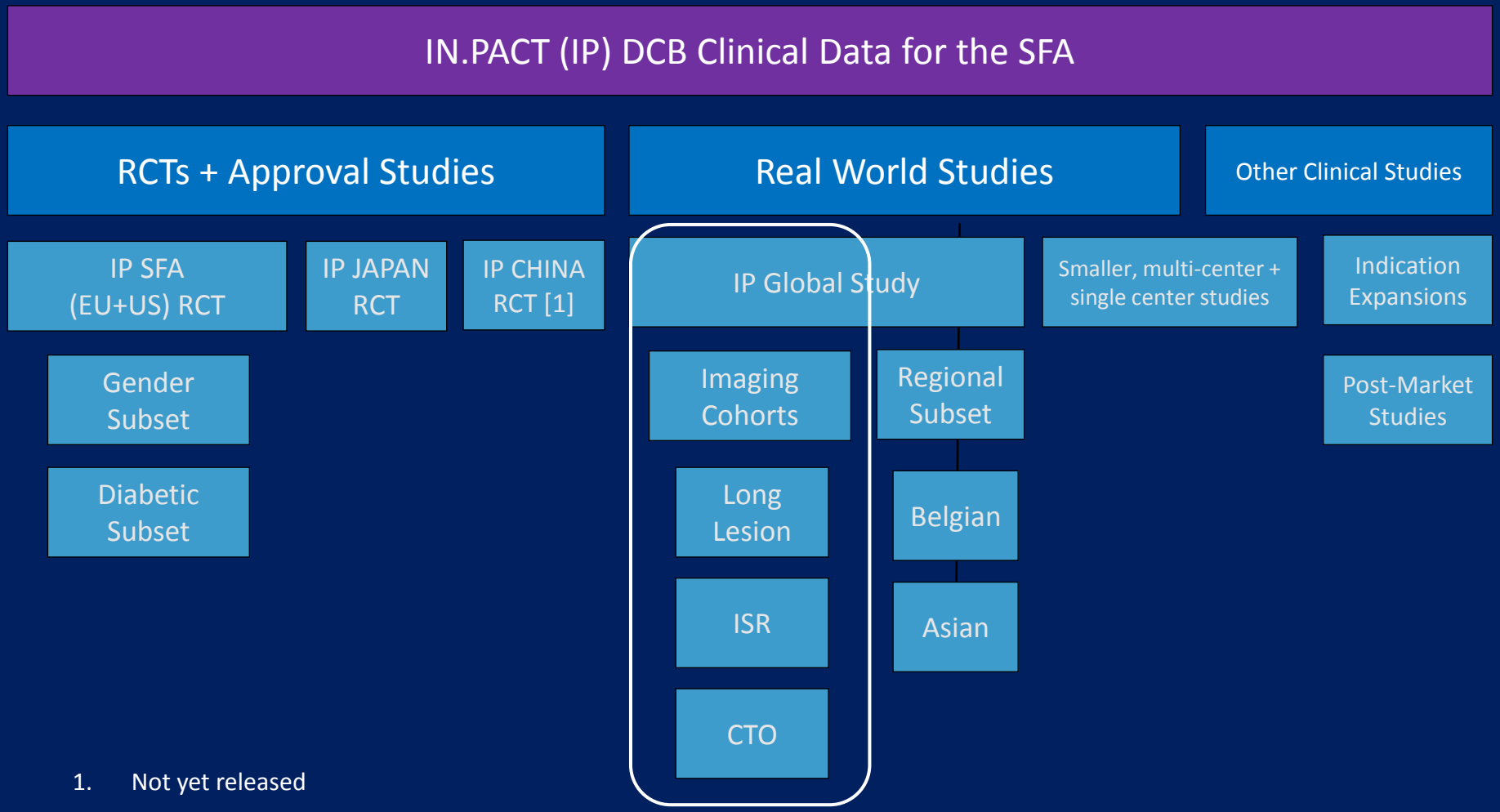
  - **Longer lesion length** is a predictor of lower patency at 12 months post-procedure (35-65%) when associated with "gold standard" therapies of PTA and stenting.[1-2]

  - **In-stent restenosis** or occlusion is estimated to occur in 30-40% of all stents placed in the SFA. Treatment with standard PTA techniques is associated with poor patency outcomes.[3-4]

  - **CTOs** are challenging to treat due to long lesion length, calcification and correlation with future limb loss.[5-8] Evidence is lacking for CTO treatment outcomes: Existing CTO data focuses on access & lesion crossing. There is a need to demonstrate evidence-based effectiveness of DCBs in the treatment of CTOs

1. Lammer J et al. J Am Coll Cardiol 2013;62:1320-7
2. Bosiers M et al. J Vasc Surg 2011;54:1042-50
3. Schlager O, et al. J Endovasc Ther 2005;12:676-84
4. 2. Laird, J et al. J Am Coll Cardiol 2012;59:24-5
5. Staniloae CS, et al. J Invasive Cardiol. 2011 Sep;23(9):359-62
6. Liang, GZ, et al. International Journal of Cardiology. 2013 May;165(3):423–429
7. Bishop PD, et al. Ann Vasc Surg. 2008;22:799-805.
8. Füessl HS, et al. Klinische Wochenschrift. 1985;63:211-216.

IN.PACT DCB Clinical Data for the SFA Overview



1. Not yet released

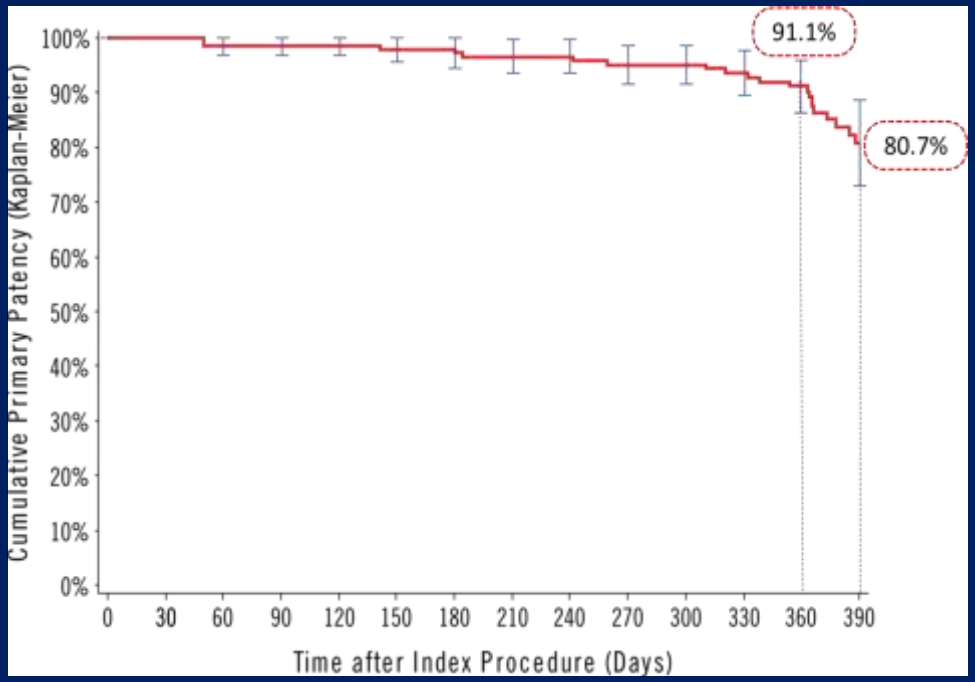
IN.PACT Global Study Summary[1]

	IN.PACT GLOBAL Study
Study Type	Prospective, Multicenter, Single-Arm Study
Primary Endpoints	Efficacy: Freedom from CD-TLR (All Subjects)[4] Efficacy: Primary Patency[2] (Imaging Cohort) Safety: Safety Composite[3]
Rigor + Quality	• Independent adjudication by Clinical Events Committee and Imaging Core Labs (Imaging Cohort)[5] • External Monitoring
Patients	1535 patients
Sites	64 sites (Global OUS)
Key Eligibility Criteria	• Single or multiple lesions ≥2 cm • All TASC • SFA + Full Popliteal • ISR, Ca^{++}, CTO

Results for the IN.PACT Global Study Full Clinical Cohort (n=1406)	
	1 Year
Lesion Length (Mean ± SD, cm)	12.09 ± 9.54
Primary Safety Endpoint[3]	92.1%
Freedom from CD-TLR	92.6%
CD-TLR[2]	7.5%
Major Amputation Target Limb	0.2%
Thrombosis	2.9%

1. Jaff M, presented at VIVA Las Vegas 2016.
2. Freedom from CD-TLR and DUS-derived restenosis (PSVR ≤2.4) at 12m.
3. Composite 30-day freedom for device-and procedure-related mortality and 12-month freedom from major target limb amputation and CD-TVR.
4. Defined as TLR due to symptoms or drop of ABI/TBI of >20% or >0.15 when compared to post-procedure baseline ABI/TBI.
5. IN.PACT Global Study: Only imaging cohort Core Lab Adjudicated (Long lesions, CTO, ISR).

IN.PACT Global Study: Long Lesion Imaging Cohort, 12 M Results[1]

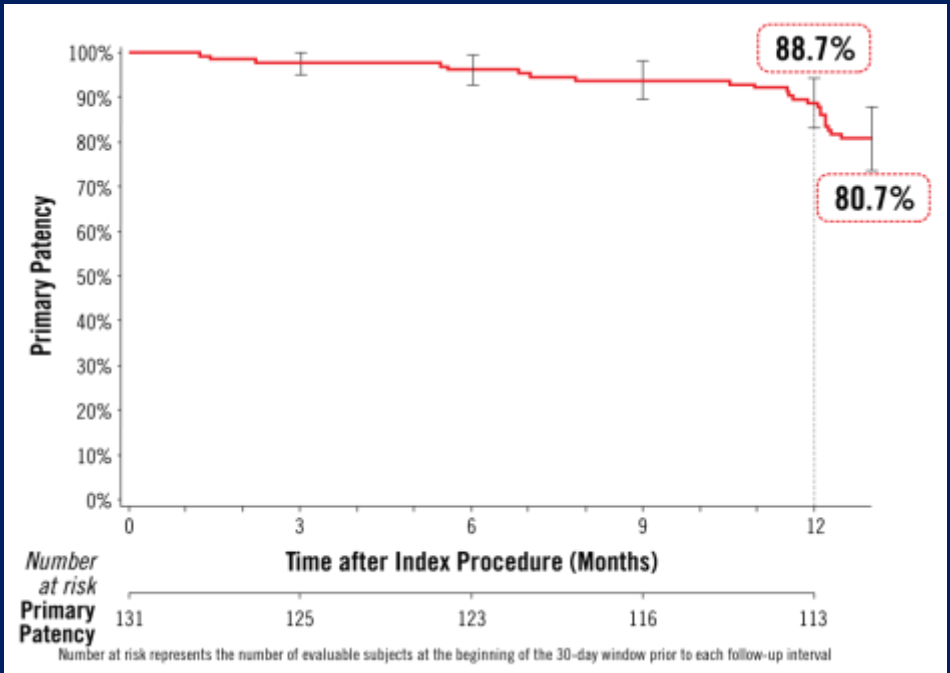


Safety Outcomes	
Clinically-Driven TLR[2]	6.0% (8/134)
Primary Safety Endpoint[3]	94.0% (126/134)
Major Adverse Events[4]	11.9% (16/134)
Death (all-cause)	4.5% (6/134)
Major Target Limb Amputation	0.0% (0/134)
Thrombosis	3.7% (5/134)
Any TLR	6.0% (8/134)
Any TVR	6.0% (8/134)

Results demonstrate remarkable overall effectiveness and safety for patients treated with the IN.PACT Admiral DCB with a mean lesion length of **26.4 cm**. The 360-day primary patency rate of **91.1%** and the CD-TLR rate of **6.0%** are unmatched for this complex patient subgroup.

1. Scheinert D, presented at EuroPCR 2015.
2. Any re-intervention within the target lesion(s) due to symptoms or drop of ABI of ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI
3. Composite of 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and clinically-driven TVR
4. Major Adverse Events: Composite of death, major target limb amputation, clinically-driven TVR, and thrombosis

IN.PACT Global Study: ISR Imaging Cohort, 12 M Results[1]



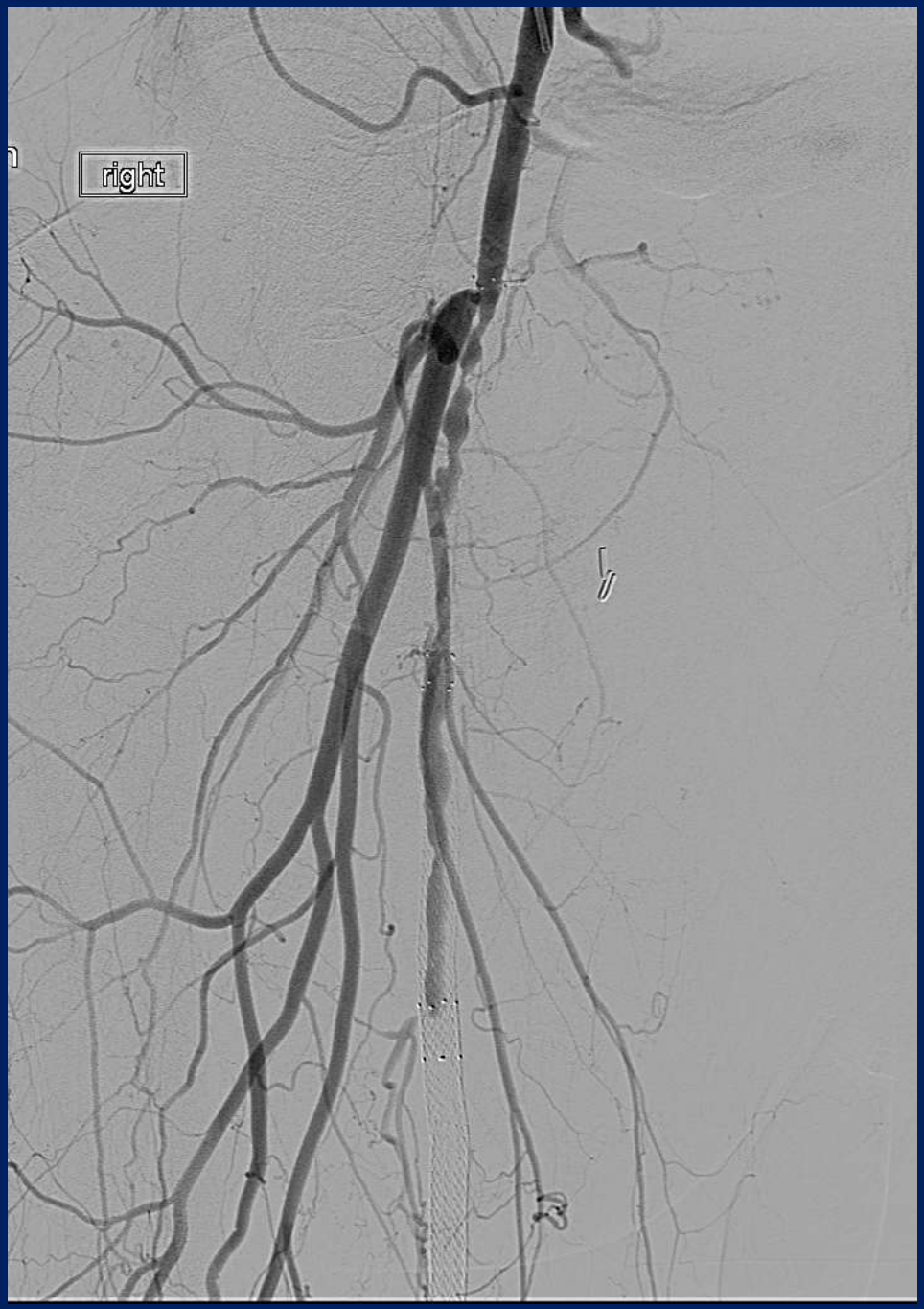
Safety Outcomes	
Clinically-Driven TLR[2]	7.3% (9/124)
Primary Safety Endpoint[3]	91.1% (113/124)
Major Adverse Events[4]	8.9% (11/124)
Death (all-cause)	0.0% (0/124)
Major Target Limb Amputation	0.0% (0/124)
Thrombosis	0.8% (1/124)
Any TLR	8.1% (10/124)
Any TVR	9.7% (12/124)

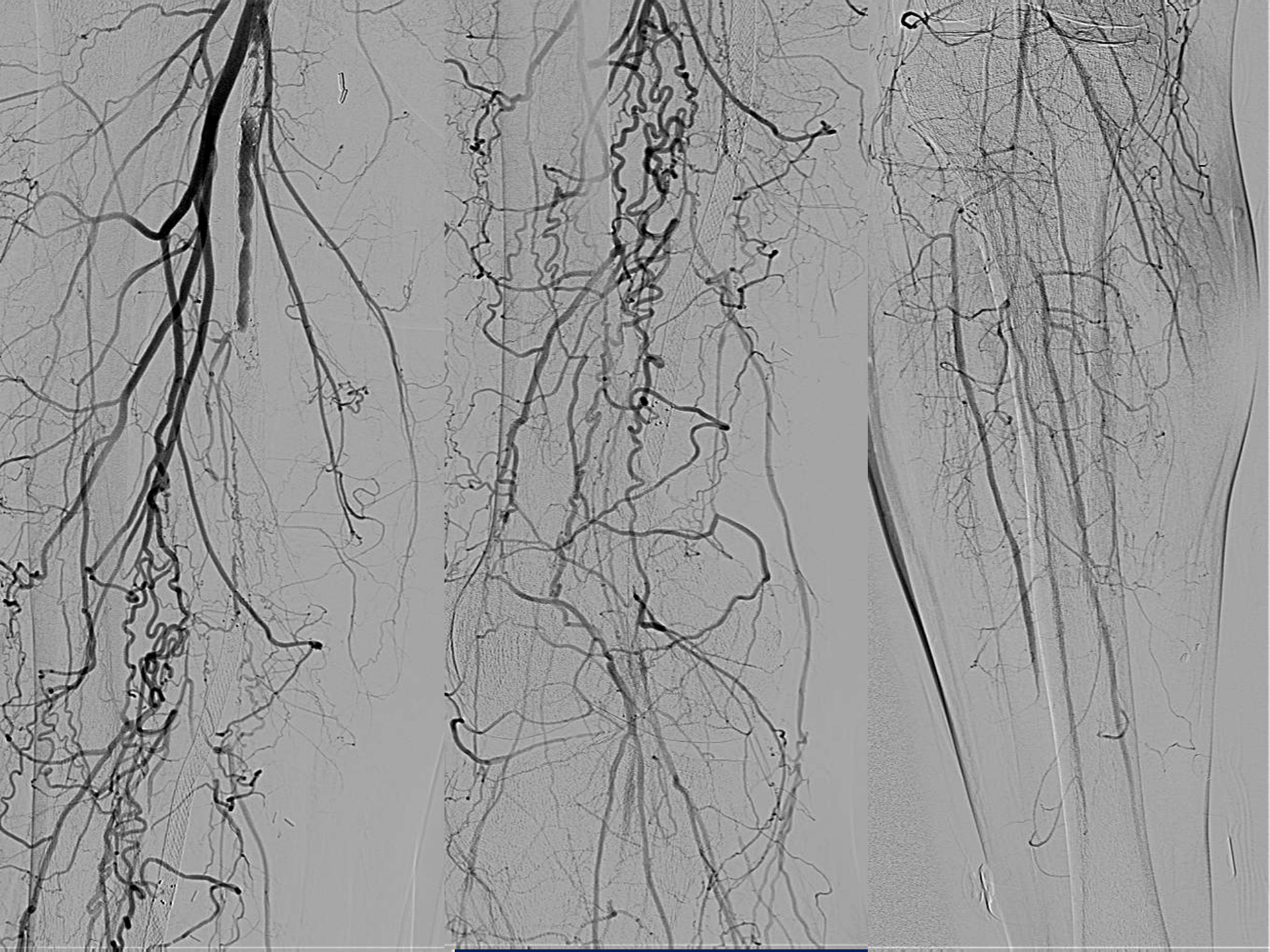
Results demonstrate remarkable effectiveness and safety for ISR patients treated with the IN.PACT Admiral DCB with a mean lesion length of **17.2 cm**. The 12-month primary patency rate of **88.7%** and the 12-month CD-TLR rate of **7.3%** are unmatched for this difficult to treat patient subgroup.

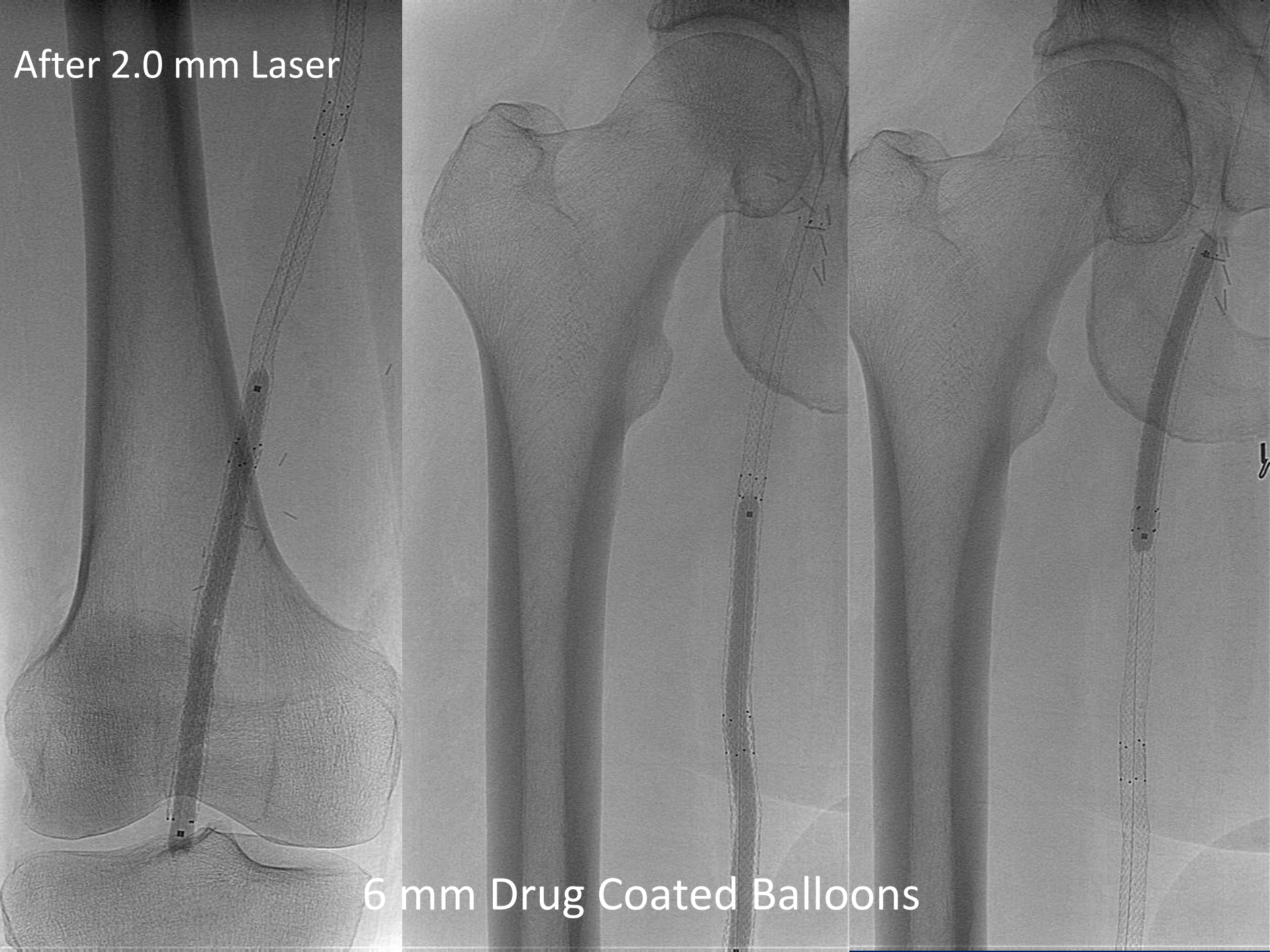
1. Broadmann M, presented at VIVA 2015.
2. Any re-intervention within the target lesion(s) due to symptoms or drop of ABI of ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI
3. Composite of 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and clinically-driven TVR
4. Major Adverse Events: Composite of death, major target limb amputation, clinically-driven TVR, and thrombosis

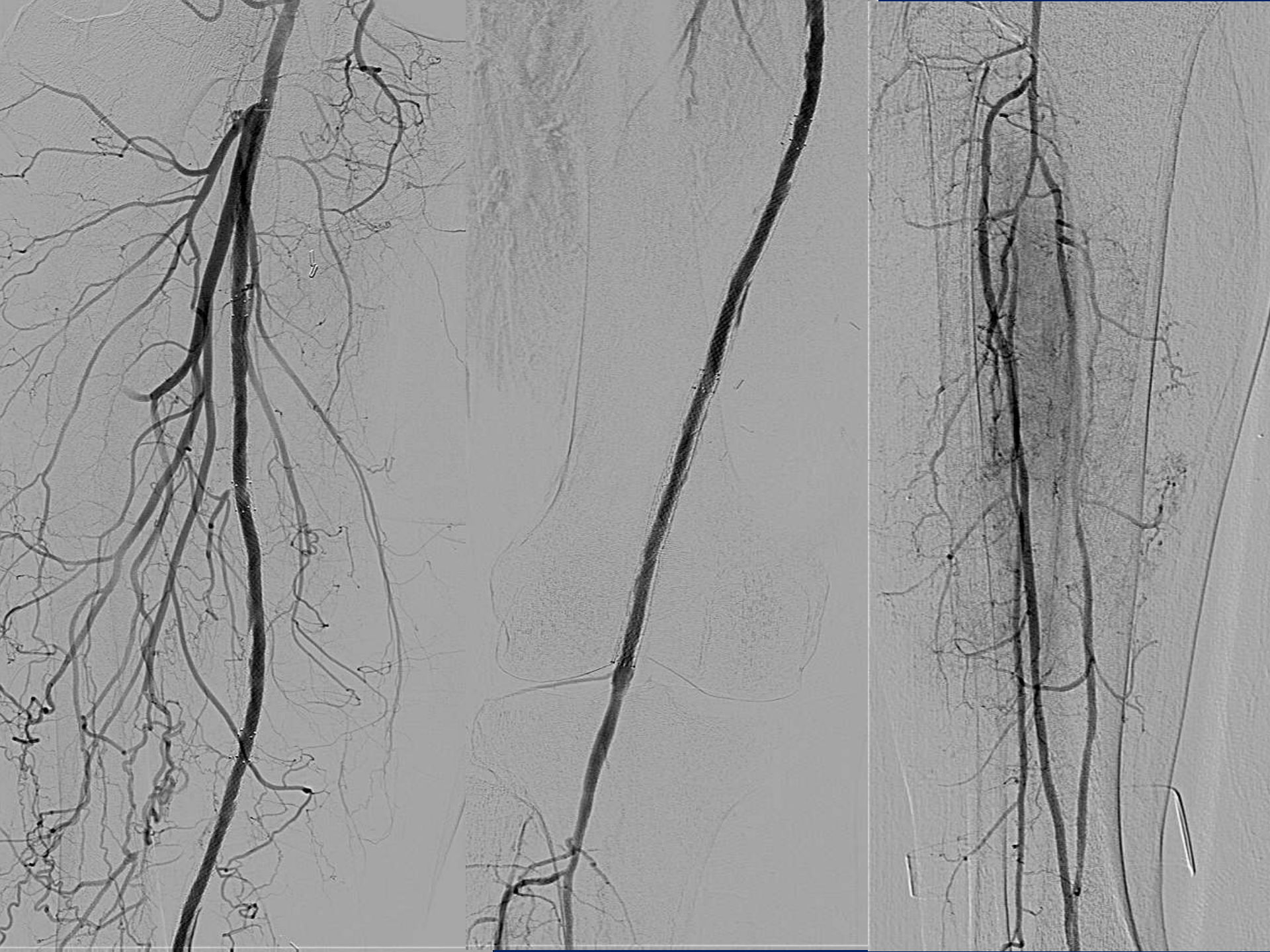
Long Instent Occlusion

- 62 yo male
- Previous right fem-pop bypass at another institution in 2012 that occluded
- Subsequent angioplasty and stenting of long SFA occlusion in 2014
- Recurrent symptoms and reocclusion of SFA in March 2015

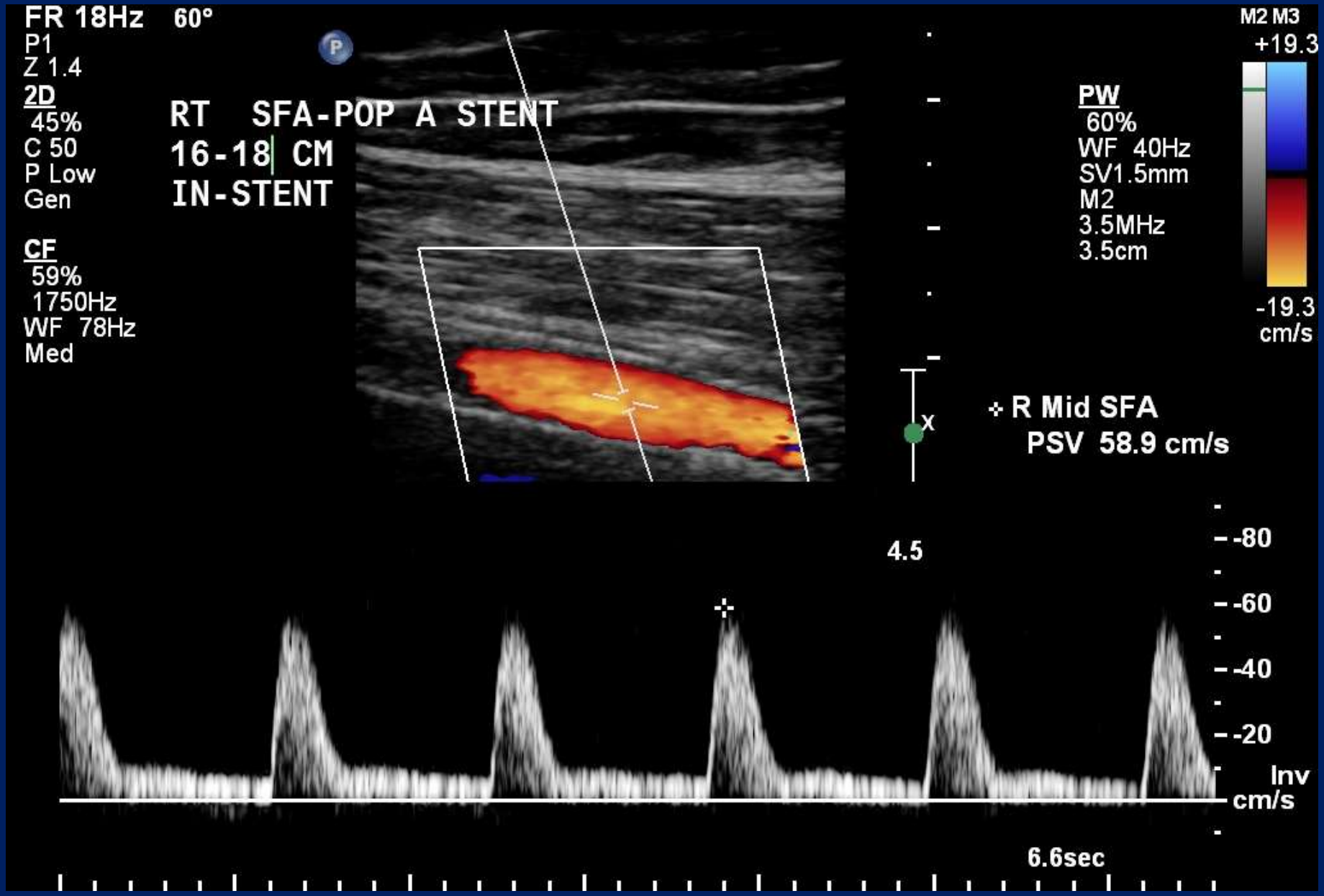




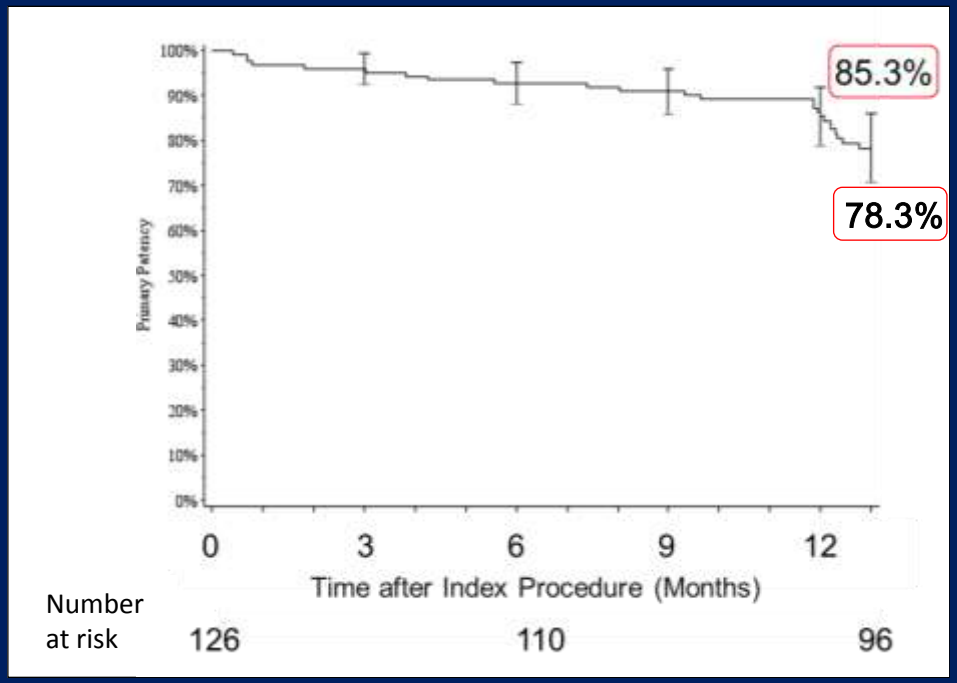

After 2.0 mm Laser
6 mm Drug Coated Balloons



18 Months Later…



IN.PACT Global Study: CTO Imaging Cohort, 12 M Results[1]

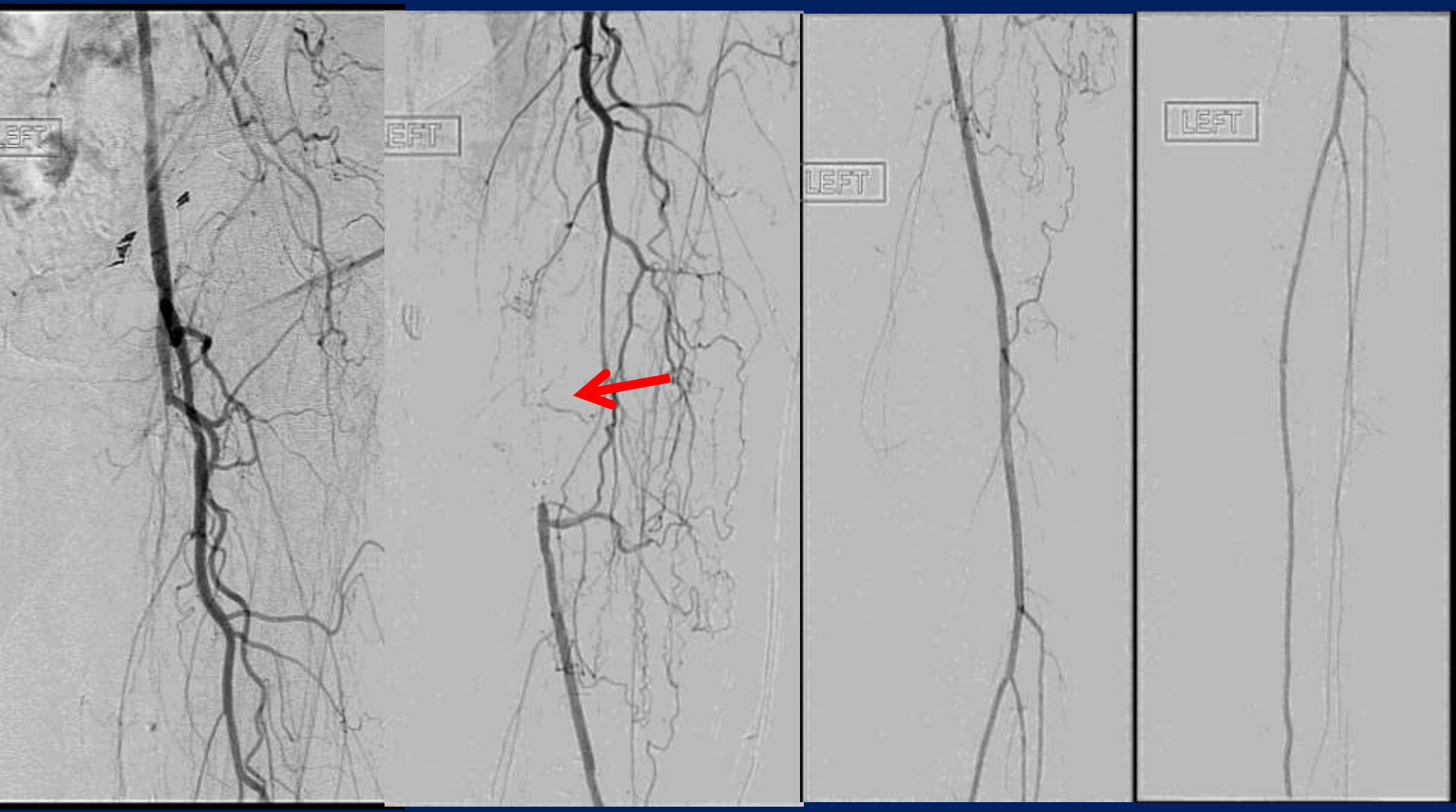


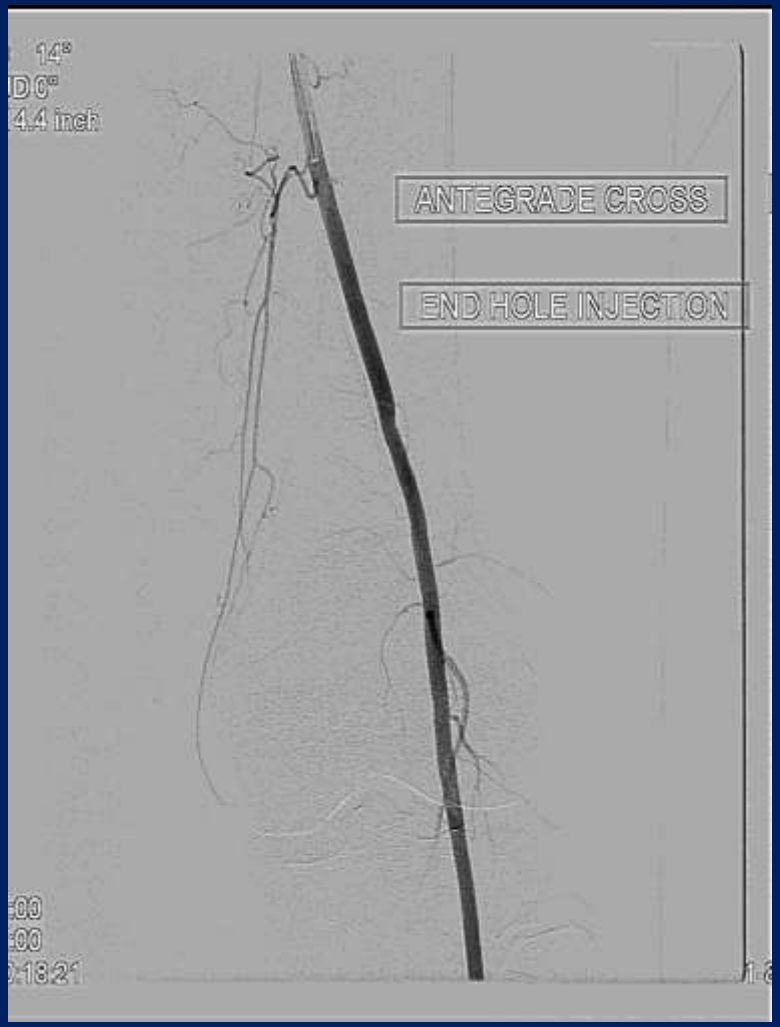
Safety Outcomes	
Clinically-Driven TLR[2]	11.3% (13/115)
Primary Safety Endpoint[3]	88.7% (102/115)
Major Adverse Events[4]	15.7% (18/115)
Death (all-cause)	4.3% (5/115)
Major Target Limb Amputation	0.0% (0/115)
Thrombosis	4.3% (5/115)
Any TLR	12.2% (14/115)
Any TVR	12.2% (14/115)

First-of-its-kind independently-adjudicated CTO data. Remarkable effectiveness and safety confirm IN.PACT™ Admiral™ DCB as a stand-alone device for CTO treatment: Mean lesion length of **22.8 cm** (occluded length of **11.86 cm**). 12-month primary patency of **85.3%** overall. CD-TLR of **11.3%.**

1. Tepe G, presented at Charing Cross 2016 updated per Medtronic Data on file.
2. Any re-intervention within the target lesion(s) due to symptoms or drop of ABI of ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI
3. Composite of 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and clinically-driven TVR
4. Major Adverse Events: Composite of death, major target limb amputation, clinically-driven TVR, and thrombosis

Left SFA Occlusion

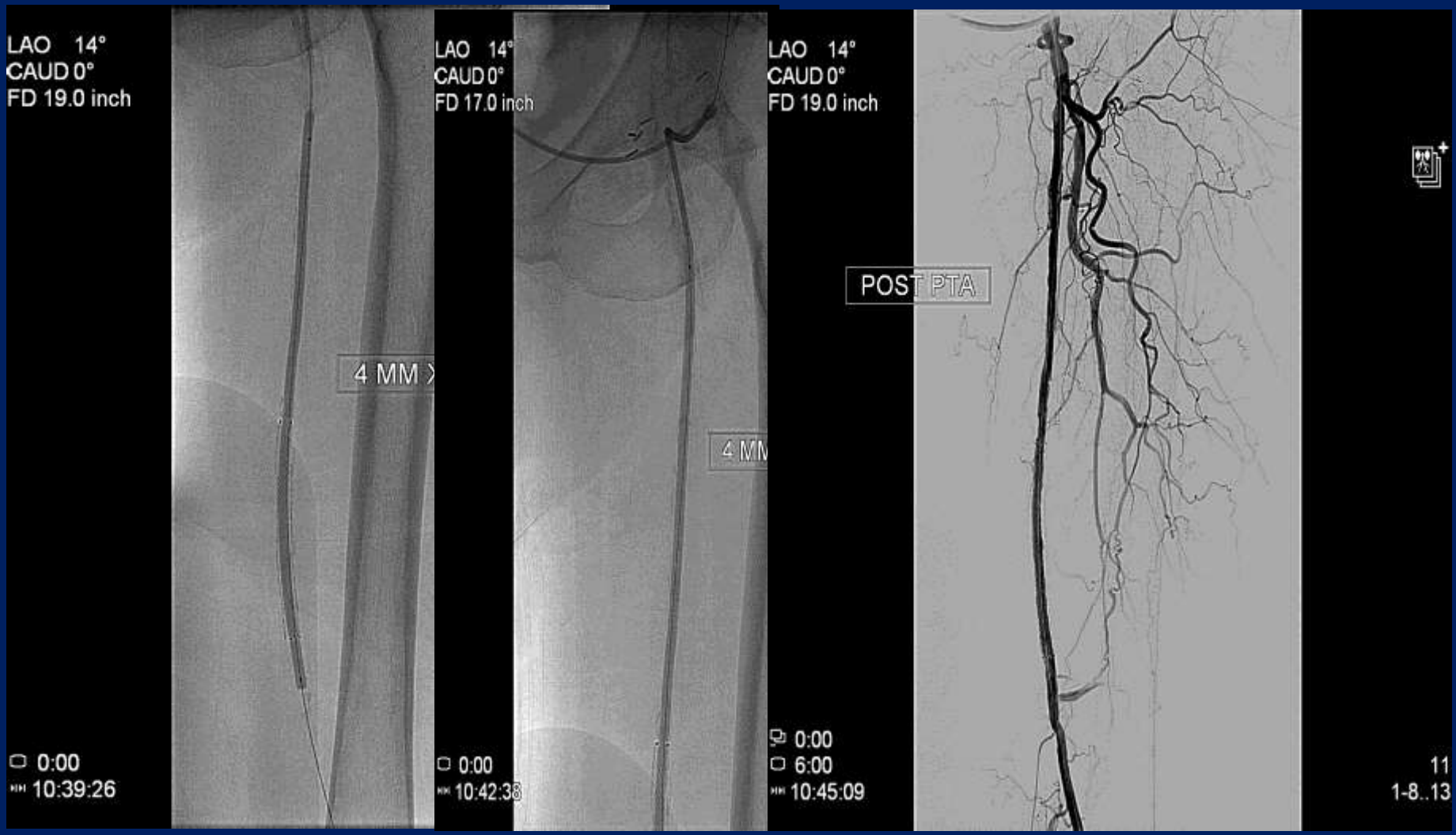



14"
D 0°
4.4 inch
ANTEGRADE CROSS
END HOLE INJECTION

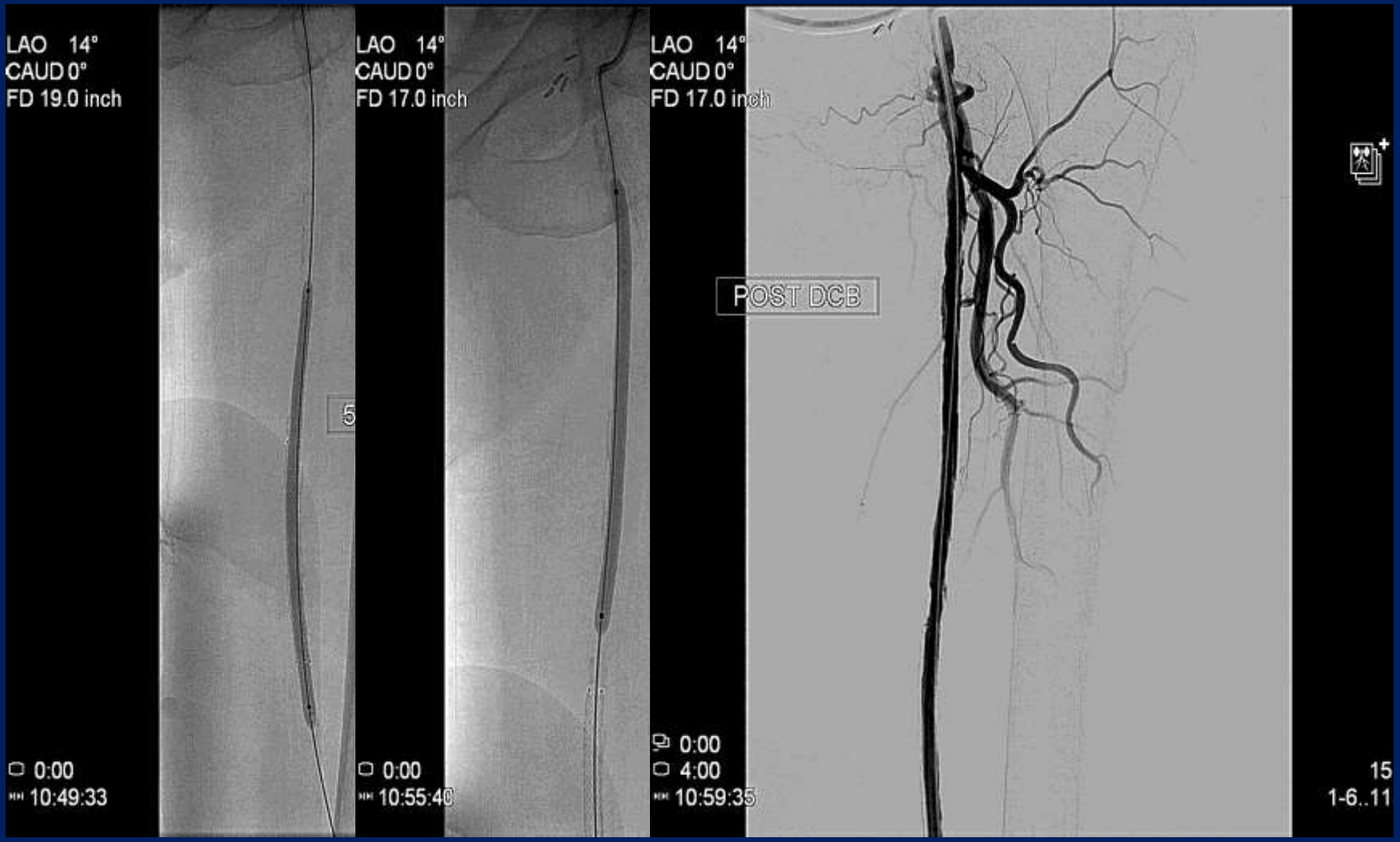

LEFT


LEFT

Predilation



SFA DCB Angioplasty



IN.PACT DCB Clinical Program

12 M Results across IN.PACT Admiral DCB Clinical studies

	IN.PACT SFA (DCB Arm) (N= 220)	IPA SFA Diabetic (DCB Arm) (N=89)	IPA SFA Female (DCB Arm) (N=77)	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)	IN.PACT Global Clinical Cohort (N=1406)	IN.PACT Global Asian Subset (N=114)
Lesion Length (Mean ± SD, cm)	8.94 ± 4.89	9.87 ± 5.21	8.69 ± 4.90	26.40 ± 8.61	17.17 ± 10.47	22.83 ± 9.76	12.09 ± 9.54	17.43 ± 12.43
Primary Patency[1] (KM @ 360 days)	87.5%	80.7%	86.6%	91.1%	88.7%	85.3%	N/A	N/A
Primary Safety Endpoint[2]	95.7%	92.7%	94.6%	94.0%	91.1%	87.7%	92.1%	96.2%
CD-TLR[3]	2.4%	3.7%	4.1%	6.0%	7.3%	11.3%	7.5%	3.8%
Major Amputation Target Limb	0.0%	0.0%	0.0%	0.0%	0.0%	4.3%	2.9%	0.0%
Thrombosis	1.4%	2.4%	1.4%	3.7%	0.8%	0.0%	0.2%	0.9%

1. Freedom from CD-TLR and DUS-derived restenosis (PSVR ≤2.4) at 12m.
2. Composite of 30-day freedom from device- and procedure-related mortality & 12-month freedom from major target limb amputation/clinically-driven TVR.
3. Any re-intervention within the target lesion(s) due to symptoms or drop of ABI of ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI.

Conclusions

IN.PACT Admiral DCB effective across patient populations and varying lesion complexities

- Beneficial DCB treatment effect in historically challenging female patients is unique to the IN.PACT Admiral DCB.
- IN.PACT Admiral DCB is significantly more effective than PTA in diabetic patients who typically present with advanced, complex PAD.
- Robust evidence supporting the benefit of IN.PACT Admiral DCB for complex lesion subsets including very long lesions, CTO, and ISR.