DCB Versus DES for SFA: Which Is Better?

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Method of drug delivery is Important

Parameters	DES	DCB
Drug concentration on the device	Low 3 µg/mm^2	Very High 3.5 µg/mm^2 **6-8x higher total dose!**
Drug protection in transit	Unprotected: Exposed to friction, fluids	Protected: In sheath
Drug transfer at the time of deployment	Slow	Rapid, all at once
Drug transfer time window	Depends of stent design: 7,320 minutes or more	3 minutes
Diffusion	Good	Excellent
Distribution	Uniform, circumferential	Uneven, usually 1 or 2 quadrants

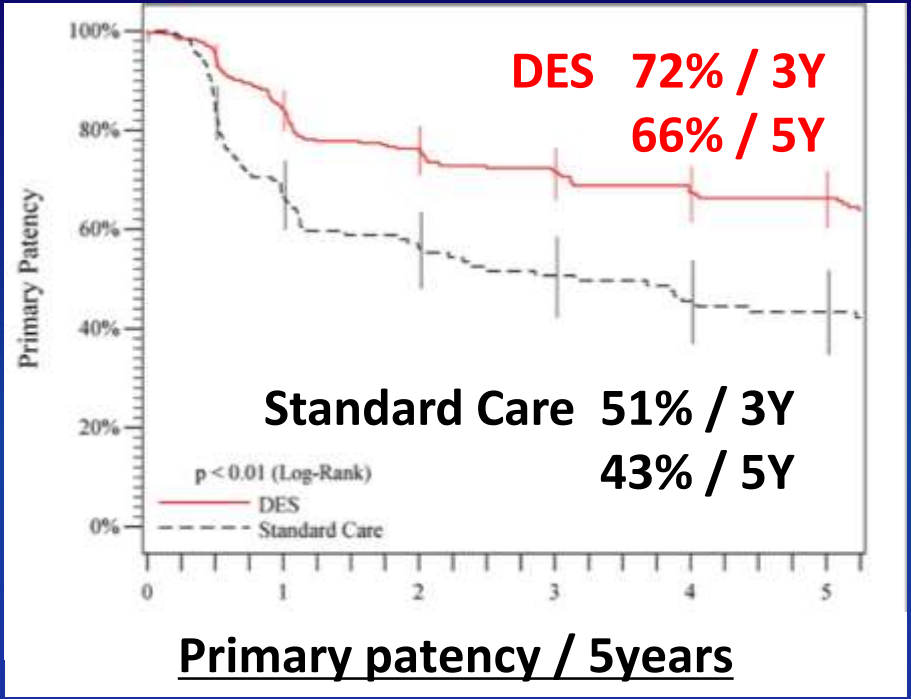
NOTE: Green staining indicates proteoglycans

28 days

14 days (Porcine iliac artery)

Long term efficacy of DES and DCB "looks like" similar, but there are no head to head RCT.

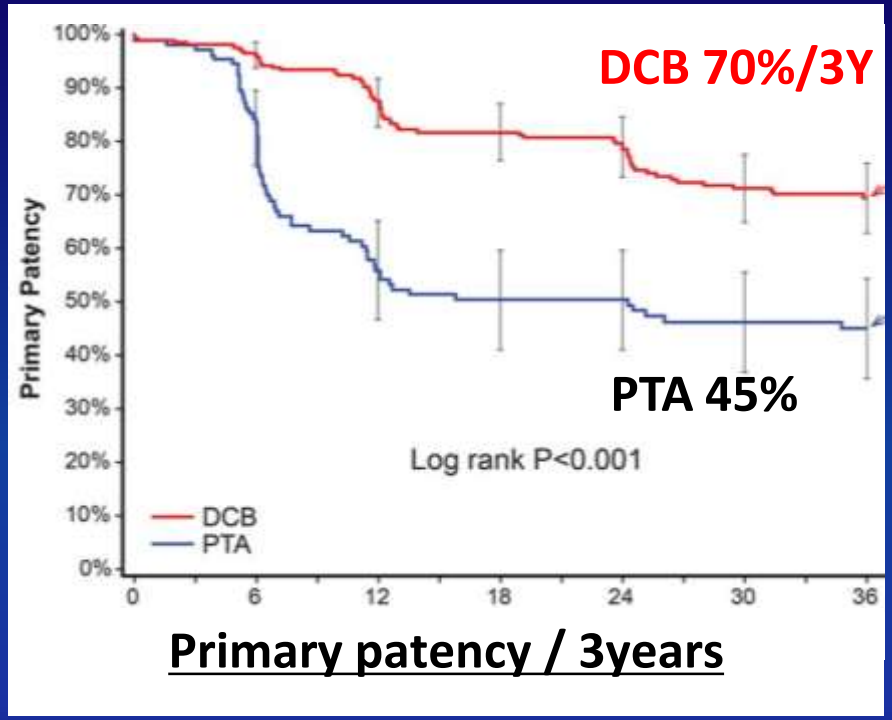
DES (Zilver PTX RCT)



Primary patency / 5years

Dake et al. Circulation. 2016;133:1472-1483

DCB (IN.PACT SFA trial)



Primary patency / 3years

Peter A. Schneider et al. Circ Intev. 2018;11:e005891

Drug Coated Balloon Devices (*Peripheral artery*)

Device	Company	Coating	Drug dose (µg/mm²)	CE mark*
Advance 18 PTX™	Cook Medical, Bloomington, IN, USA	Paclitaxel	3.0	Yes
Cotavance®	Bayer Schering Pharma AG, Berlin, Germany	Paclitaxel–iopromide	3.0	Yes
Freeway™	Eurocor, Bonn, Germany	Paclitaxel–shellac	3.0	Yes
In.Pact™ Admiral,	Medtronic Vascular, Santa Clara, CA, USA	Paclitaxel–urea	3.5	Yes
Lutonix® 035 DCB	BARD, Murray Hill, NJ, USA	Paclitaxel–polysorbate/sorbitol	2.0	Yes
Ranger	Boston Scientific	Paclitaxel–Acetyl Tributyl Citrate 2	2.0	Yes
Passeo-18 Lux®	Biotronik, Bülach, Switzerland	Paclitaxel–butyryl-tri-hexyl citrate	3.0	No → Yes
Stellarex®	Covidien, Mansfield, MA, USA	Paclitaxel	2.0	Yes
SurVeil™DCB	SurModics, MN, USA	Paclitaxel-proprietary photolink®	2.0	No → No

FDA approval

Clinical trial under FDA

Byrne RA, Joner M. et al. Nat Rev Cardiol. 2014;11:13-23

Lutonix

In.Pact

SurModics

ELUTAX

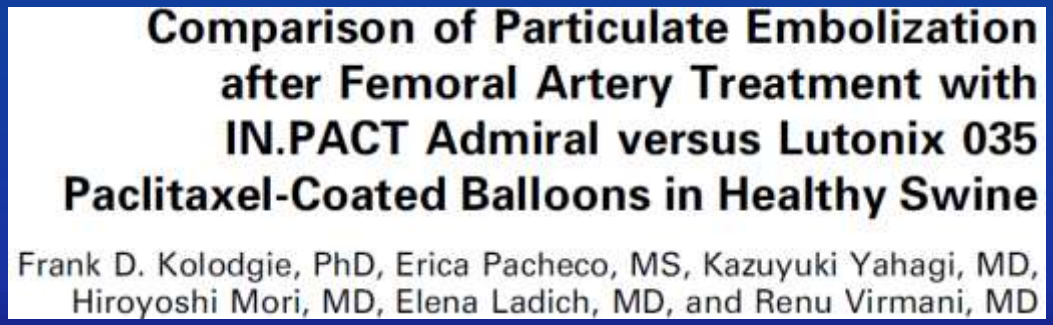
Pantera Lux

Sequent Please

Lutonix® 035 vs. In.Pact™ Admiral

First Comparative Study in Swine

- Blinded study – Side-by-side
- 1x and 3x dose
- Evaluated skeletal muscle and coronary band at 28 and 90 days
  - Distal drug concentration
  - Histology
    - Distal embolization
    - Vascular changes



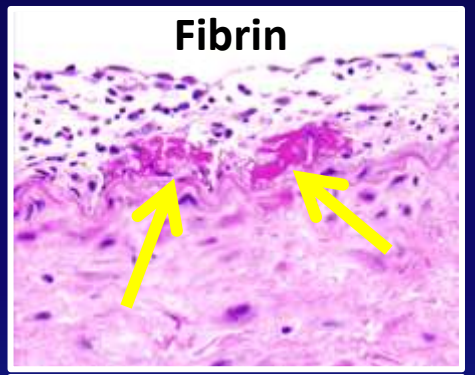
Kolodgie, FD et al. J Vasc Interv Radiol. 2016;15.

Histologic Parameters for Evaluation of DCB Efficacy

Key parameters include:

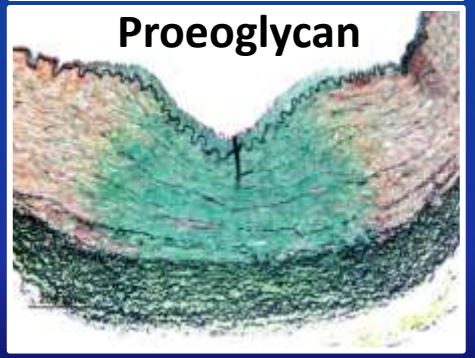
- Endothelial loss
- Fibrin / Platelets
- Inflammation
- Injury
- Medial smooth muscle cell loss
- Matrix replacement
  - Proteoglycan
  - Collagen
- Adventitial fibrosis

H&E



α-SMA

Movat

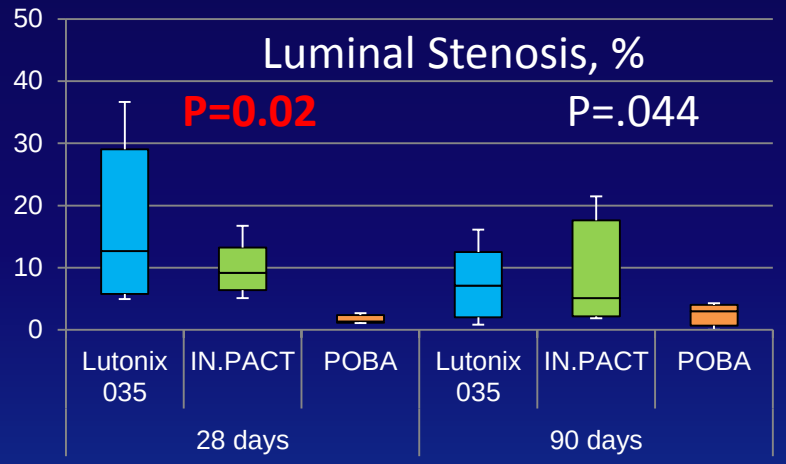


Histologic Vascular Changes following Lutonix vs. In.Pact DCB Treatment (3x)

Lutonix 3x-28d

In.Pact 3X-28d

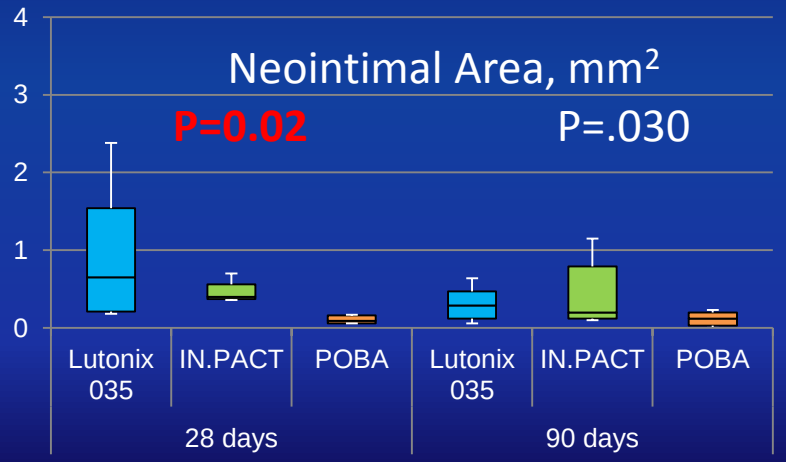
POBA-28d



Lutonix 3x-90d

In.Pact 3x-90d

POBA-90d

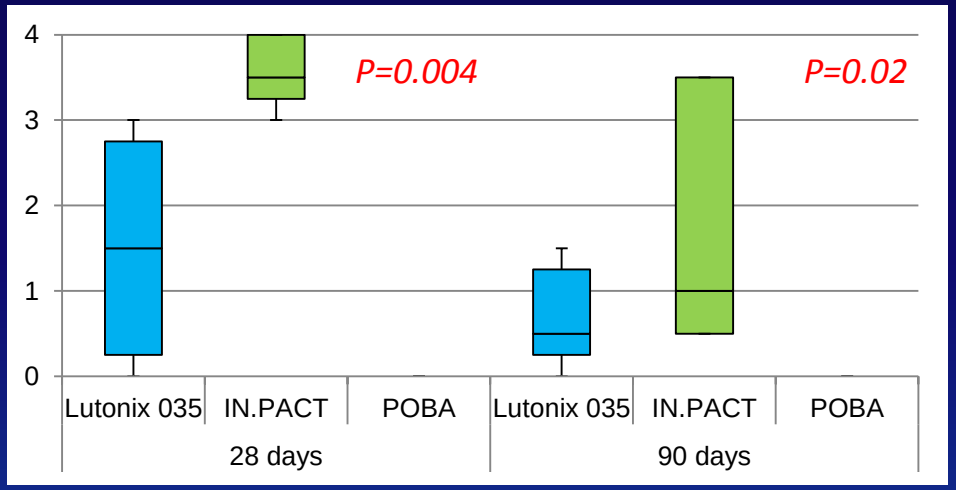


Kolodgie, FD et al. J Vasc Interv Radiol. 2016 Sep 15. pii: S1051-0443(16)30338-4

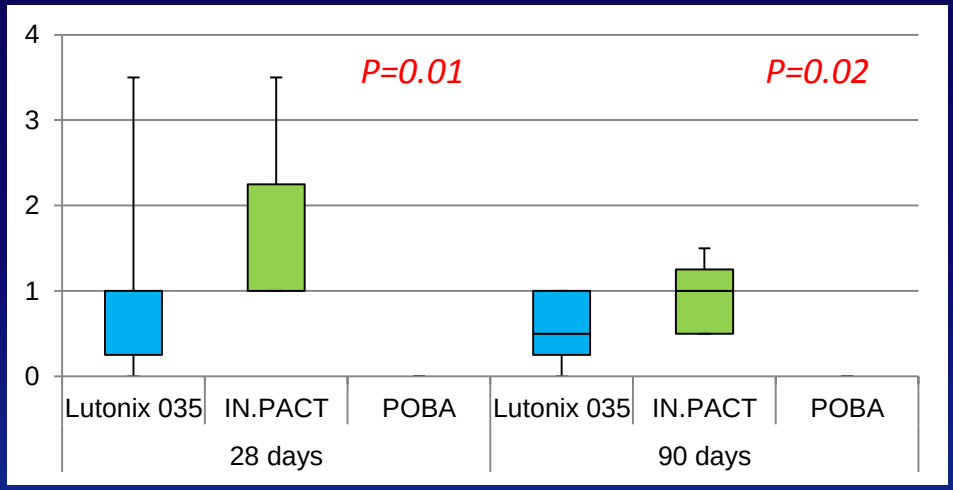
Histologic Vascular Changes following Lutonix 035 vs. IN.PACT DCB Treatment (3x) at 28 and 90 days

Lutonix 035: n=5, In.Pact DCB: n=5, POBA: n=4

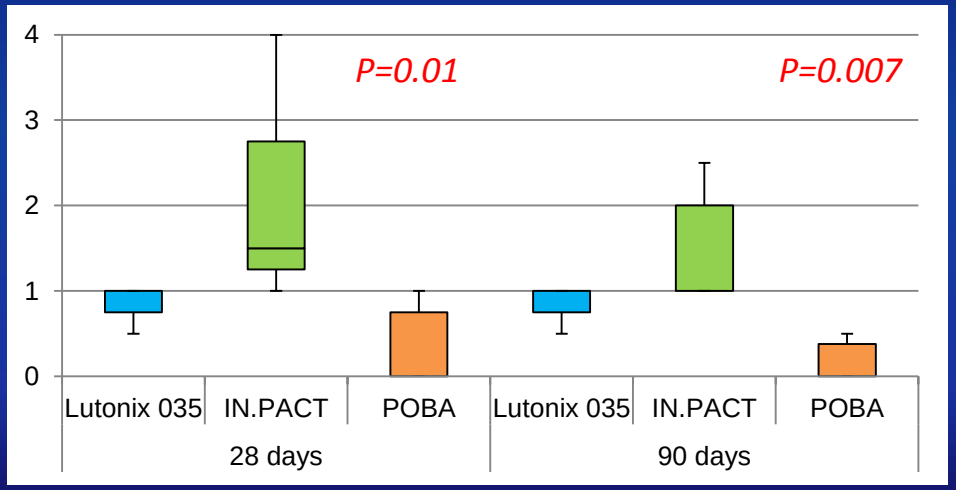
SMC loss score (Depth)



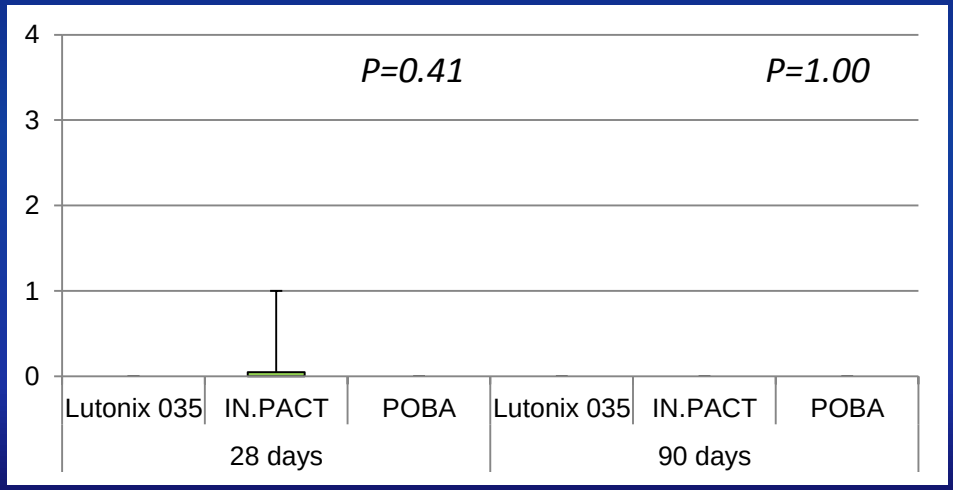
SMC loss score (Circumference)



Medial proteoglycan score



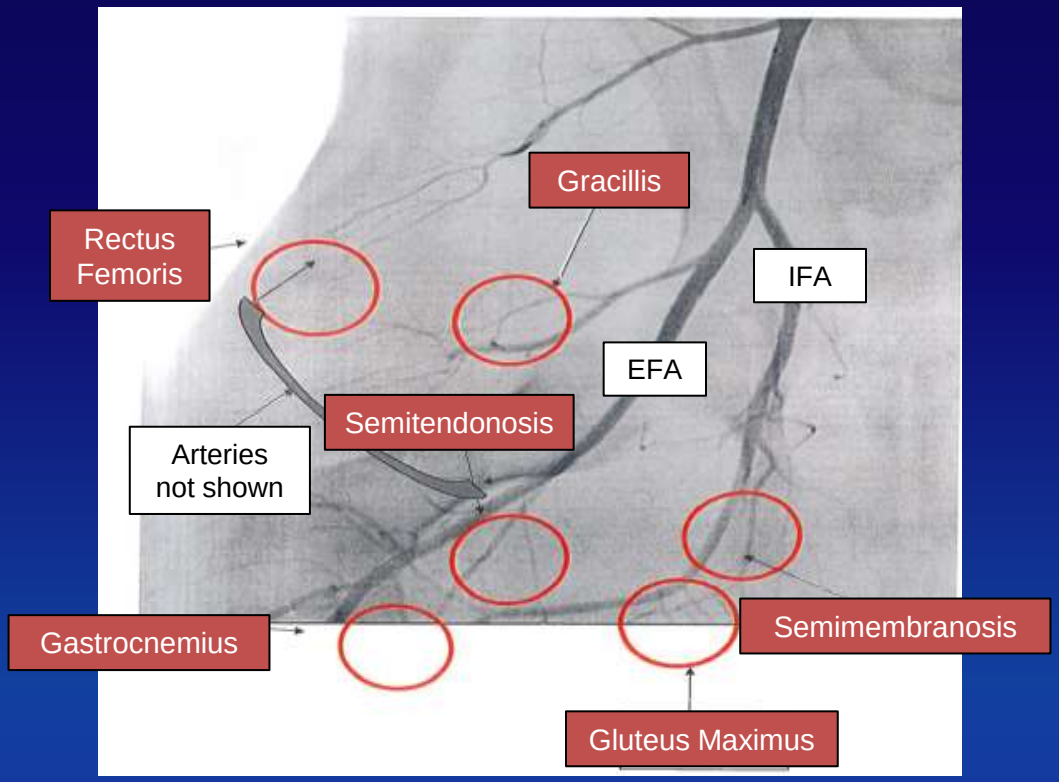
Fibrin/thrombus score

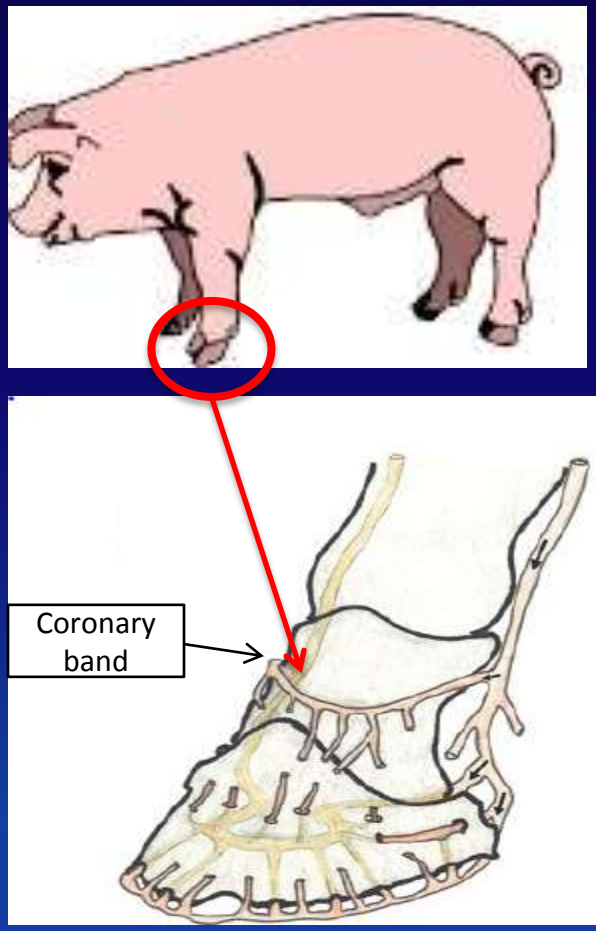


Kolodgie, FD et al. J Vasc Interv Radiol. 2016;15.

Downstream Sampling for Paclitaxel Analysis and Histopathology Assessment

Angiogram of the SFA

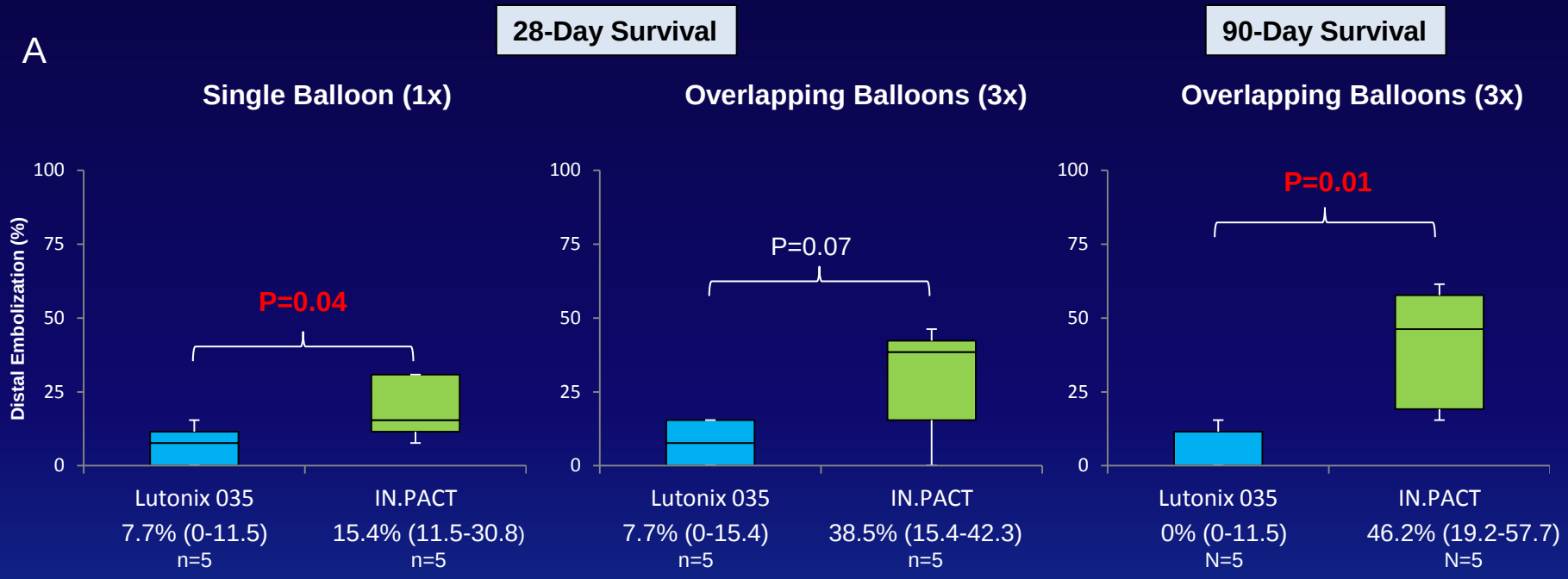




- Evaluated skeletal muscle and coronary band for potential embolic changes
  - Distal paclitaxel concentration
  - Histology
    - Distal embolization
    - Vascular changes

Downstream Incidence of Distal Embolization (%)

A



B

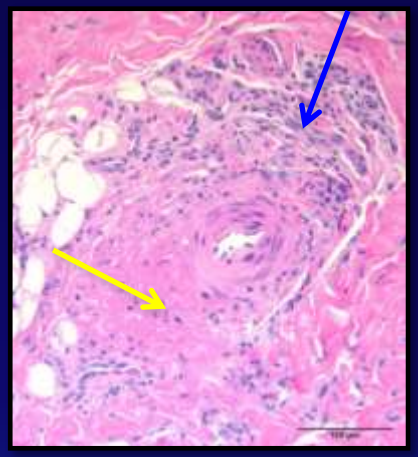
	Survival Treatment & Arteries	Lutonix 035	IN.PACT	*P*-value
Number of micro-vessels with paclitaxel-associated findings	**28-day (1x, n=5)**	1 (0-2)	4 (2-12)	0.03
	28-day (3x, n=5)	1 (0-12)	26 (11-34)	0.07
	90-day (3x, n=4)	0 (0-3)	11 (5-15)	0.02

C

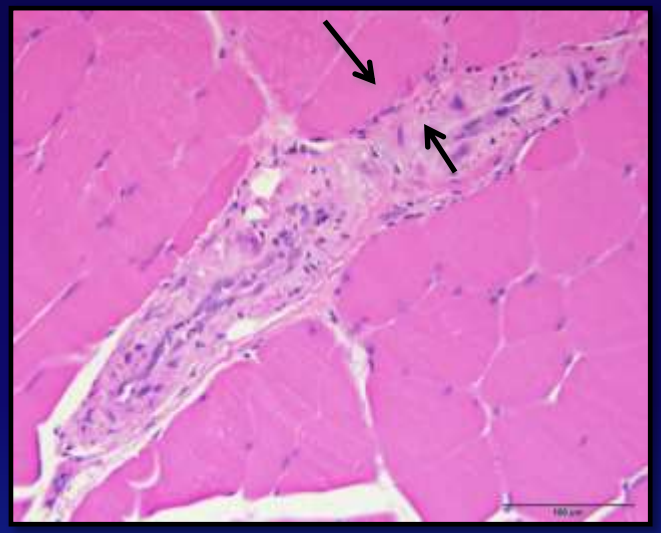
	Survival Treatment & Arteries	Lutonix 035		IN.PACT		*P*-value	
		Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band
Paclitaxel concentration in downstream tissues (ng/g)	**28-day (1x, n=5)**	1.3 (0.6-2.3)	1.5 (1.1-65.8)	60.8 (32.6-118.1)	189.0 (134.0-700.0)	0.009	0.02
	28-day (3x, n=5)	3.7 (1.3-10.9)	31.5 (5.9-54.1)	170.9 (19.7-221.5)	871.0 (567.5-1315.0)	0.08	0.009
	90-day (3x, n=4)	0.6 (0.5-6.4)	2.7 (0.0-25.5)	16.1 (12.8-319.2)	158.0 (6.3-1178.0)	0.009	0.05

Downstream Findings in Porcine Skeletal Muscle (28-Day)

Lutonix (1x) Vascular Change



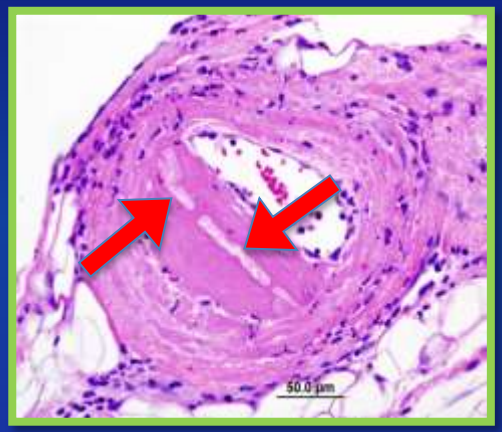
IN.PACT (1x) Vascular Change



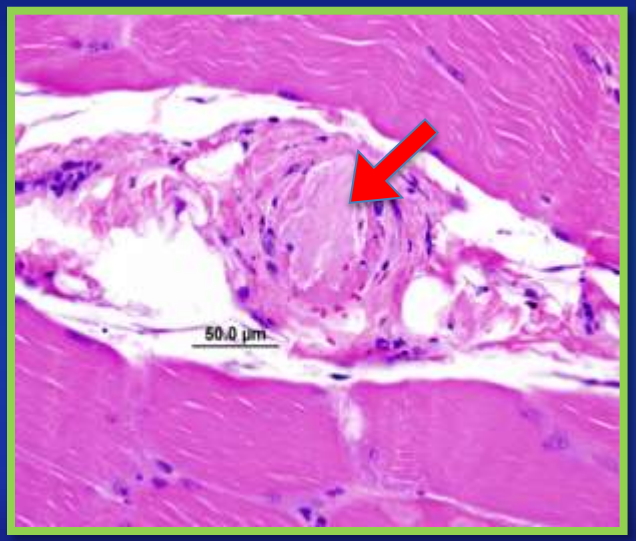
High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

IN.PACT (1x) Crystalline Material



IN.PACT (3x) Crystalline Material



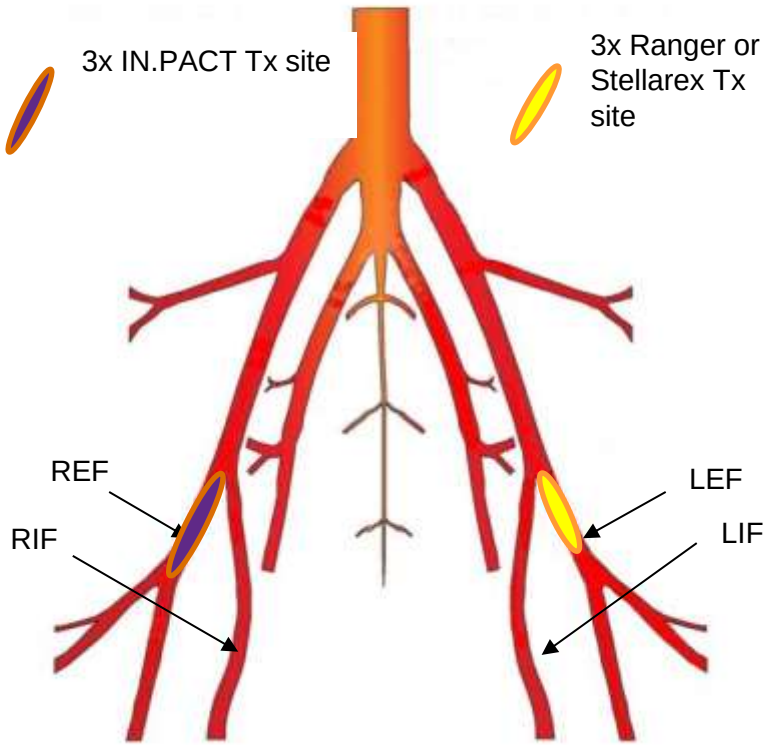
High (40x) power images of crystalline material (red arrows) at 28d

In. Pact DCB vs. Stellarex vs. Ranger

The Second Comparative Study

- Same swine model - 28 day study
- 3x dose, same size DCB
- DCB inflated for 60 secs
- Blinded-device ID
- Same sampling method and evaluation endpoints as the first Lutonix vs. IN.PACT comparative study

Treatment Scheme: A total of 2 treated sites in the external femoral arteries (left or right) in each pig



Results

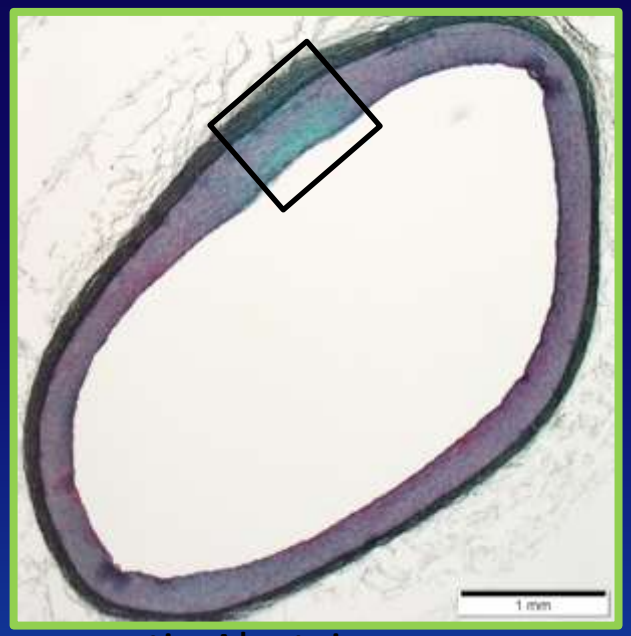
Representative histologic sections of femoral arteries following IN.PACT vs. Ranger vs. Stellarex , dose 3X, 28 days

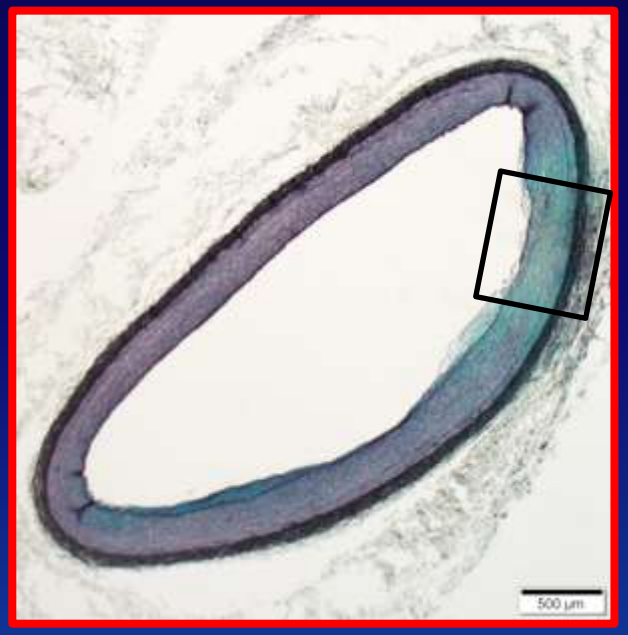
IN.PACT

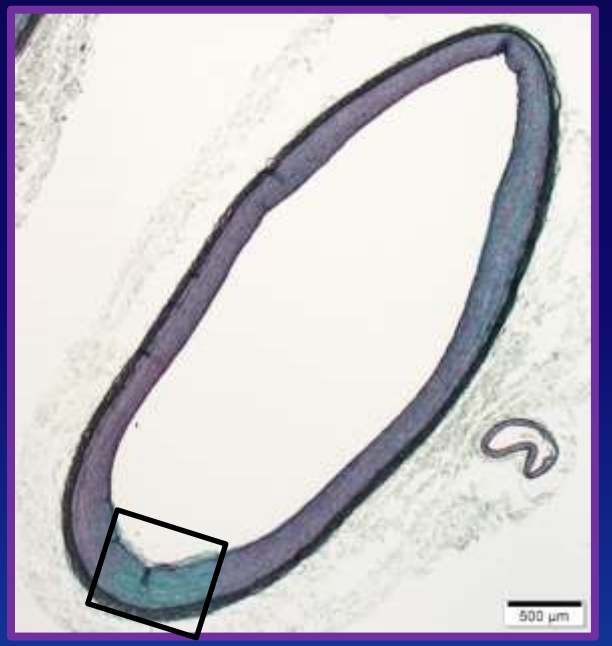
Ranger

Stellarex

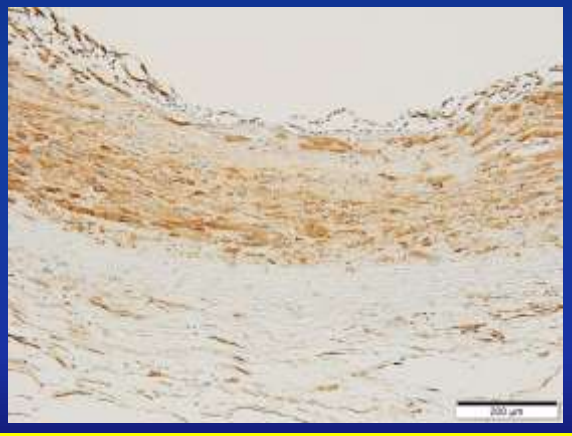
Movat pentachrome

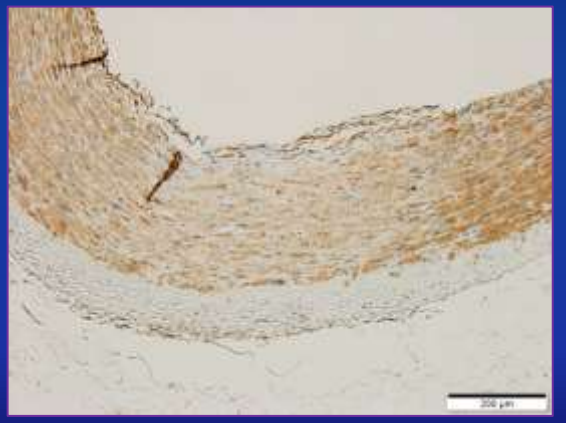






α-actin Ab stain



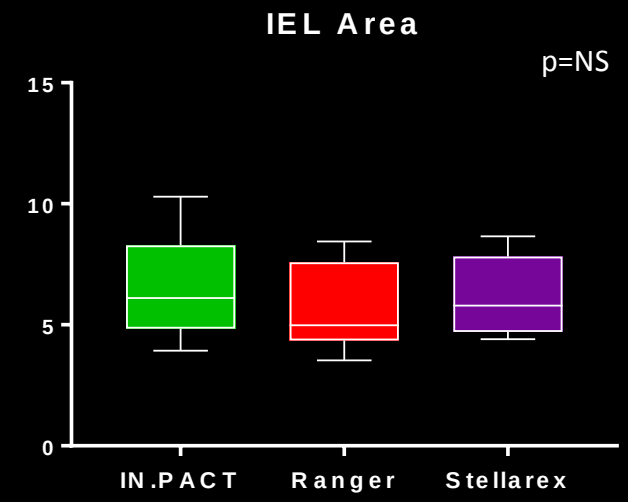


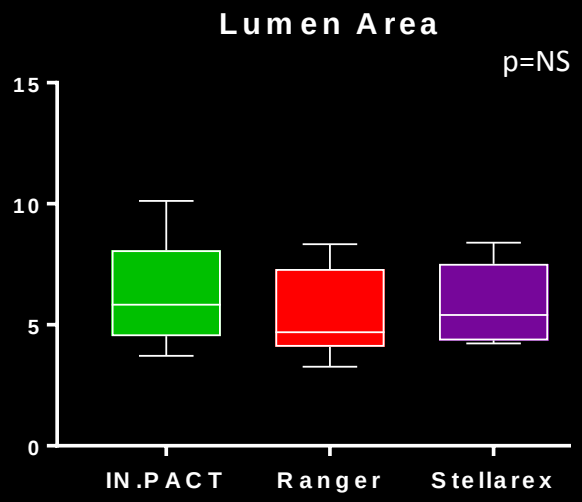
Key Takeaway: Loss of SMC actin in the arterial wall in all 3 DCBs

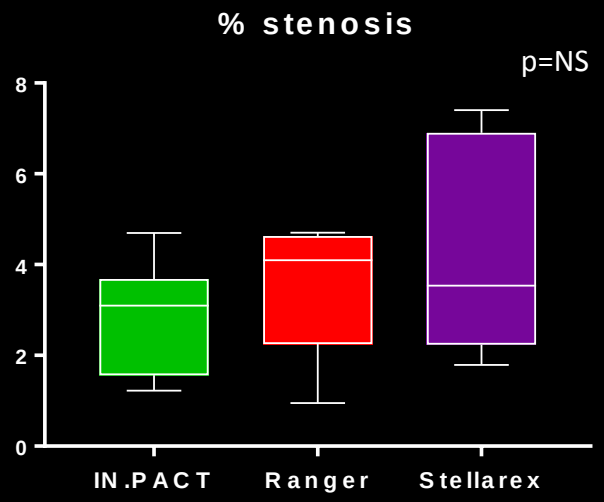
Results

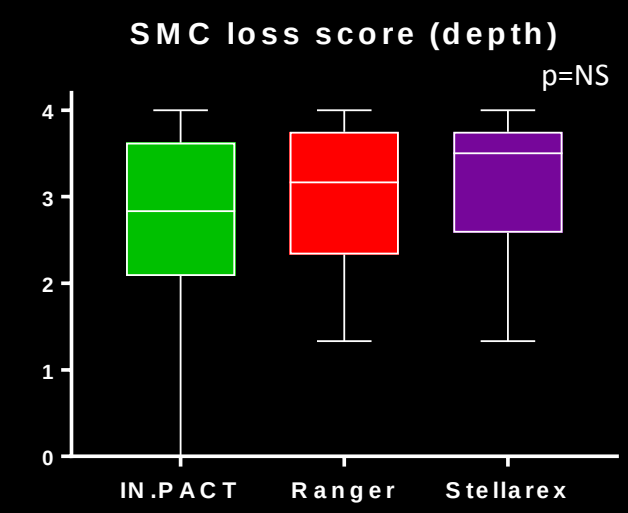
Histologic Vascular Changes following IN.PACT vs. Ranger vs. Stellarex, dose 3X, at 28 days

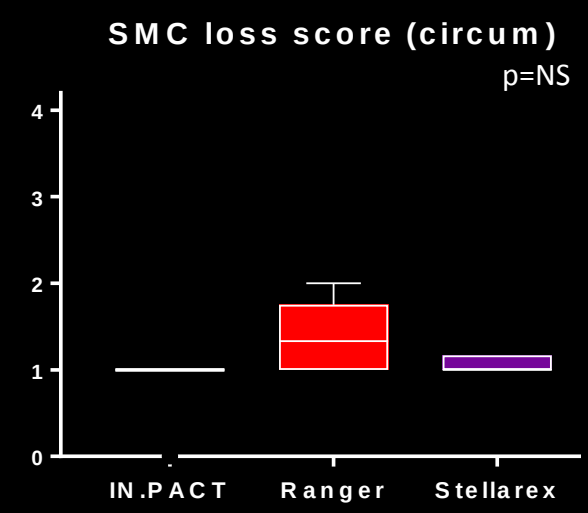
IN.PACT: n=12, Ranger: n=6, Stellarex: n=6

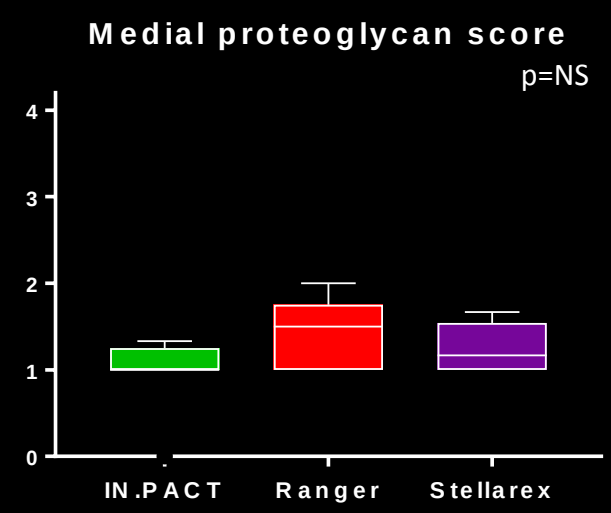






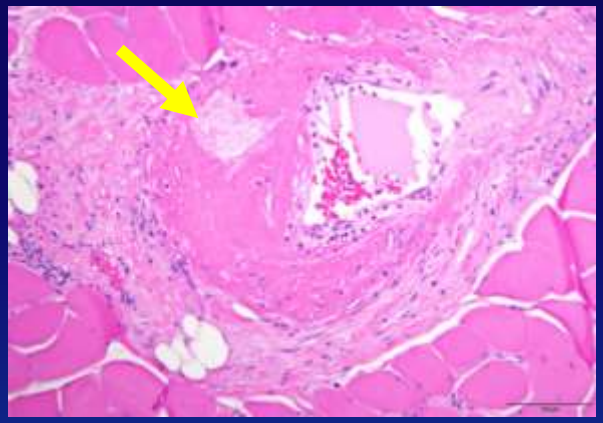






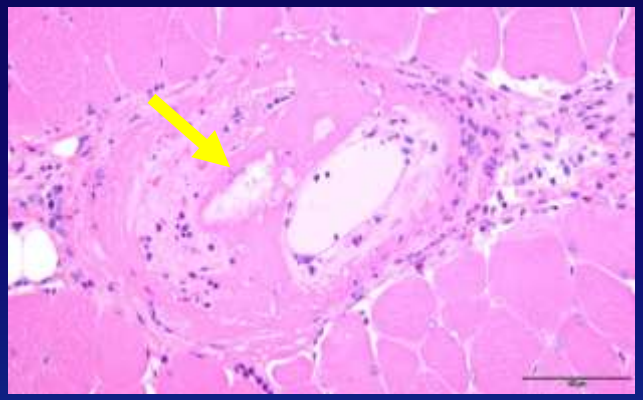
Downstream changes following IN.PACT vs. Ranger vs. Stellarex, dose 3X, at 28 days

IN.PACT



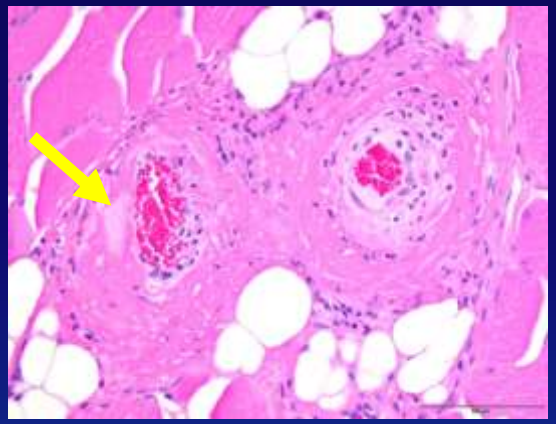
CV38010 R GASTRO1_20x

Ranger

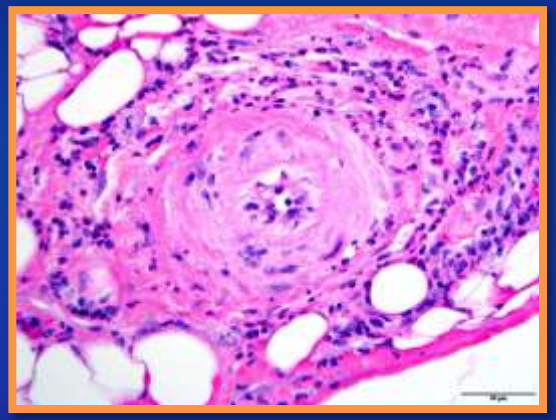


CV38011 L SEMM1_20x

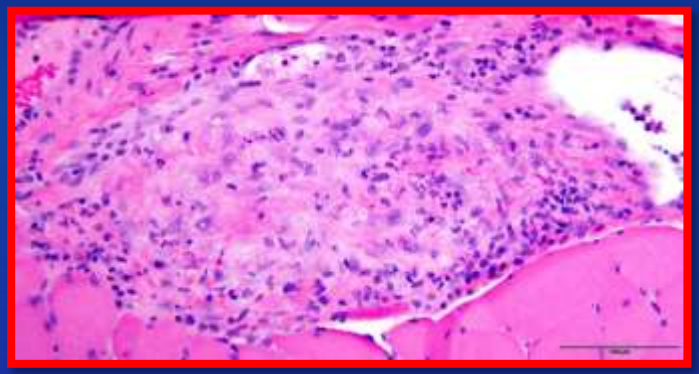
Stellarex



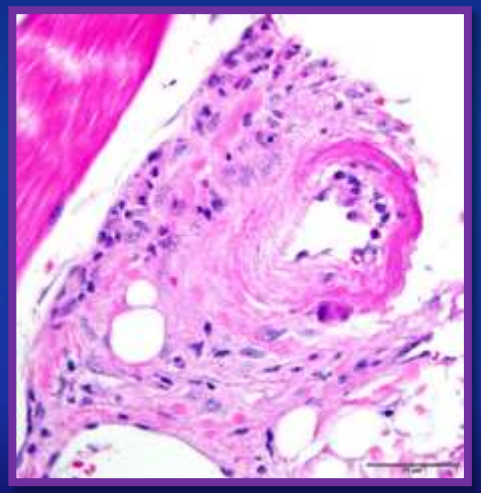
CV38012 L SEMM2_20x



CV38007 Right Gracilis



CV38007 Left Gracilis

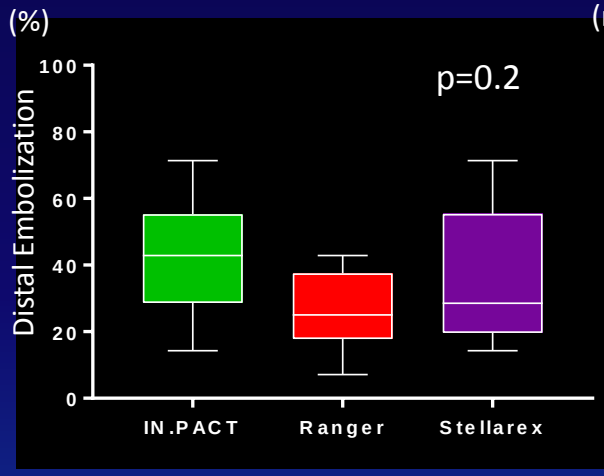


CV38010 Left Gastrocnemius

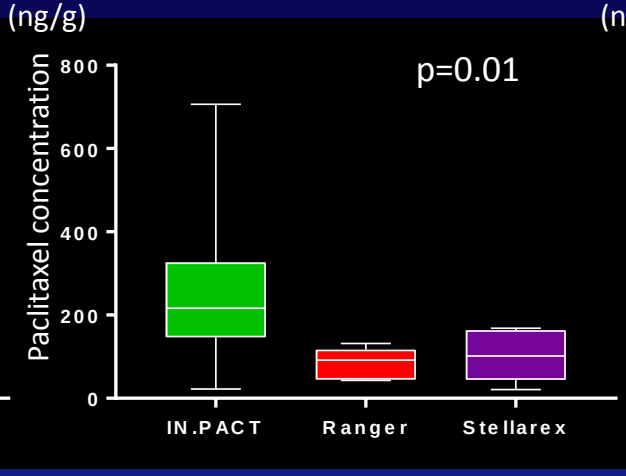
Downstream Incidence of Distal Embolization (%)

Overlapping Balloons (3x), 28-Day Survival

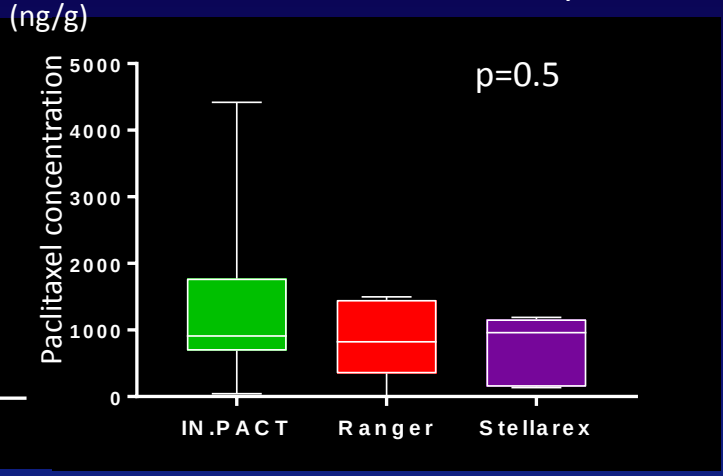
Histologic sections showing Distal Embolization



Paclitaxel concentration in downstream Skeletal muscle



Paclitaxel concentration in downstream Coronary band



	Survival Treatment	Second Comparative Study			First Comparative Study	
		IN.PACT (n=12)	Ranger (n=6)	Stellarex (n=6)	Lutonix (n= 5)	IN.PACT (n=5)
Percentage of sections with vascular changes in downstream nontarget tissues (%)	28-day (3x)	42.9%	25%	30%	7.7%	38.5%

	Survival Treatment	Second Comparative Study						First Comparative Study			
		IN.PACT		Ranger		Stellarex		Lutonix		IN.PACT	
		Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band
Paclitaxel concentration in downstream tissues (ng/g)	28-day (3x)	216.5 (326.1-146.2)	911.3 (691.3-1773.8)	91.5 (44.8-116.9)	822.5 (347.9-1450.6)	101.9 (44.6-163.8)	962.3 (149.9-1160)	3.7 (1.3-10.9)	31.5 (5.9-54.1)	170.9 (19.7-221.5)	871.0 (567.5-1315.0)

Three Case Reports for Downstream Effect of DCB Use: Particulate Embolization Related?

- Downstream Panniculitis Secondary to Drug–Eluting Balloon Angioplasty.
  Ibrahim T et al,
  JACC Cardiovasc Interv. 2016;12;9(17):e177-9.

- Vasculitis resulting from a superficial femoral artery angioplasty with a paclitaxel-eluting balloon.
  Thomas SD et al,
  J Vasc Surg. 2014;59(2):520-3

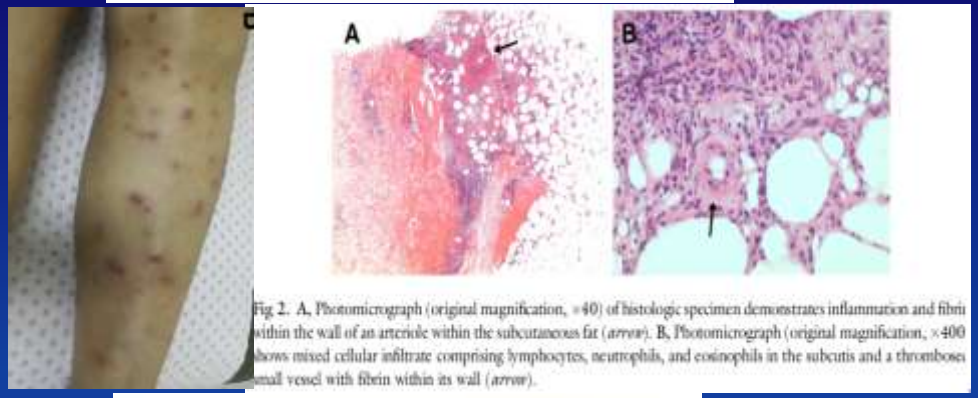
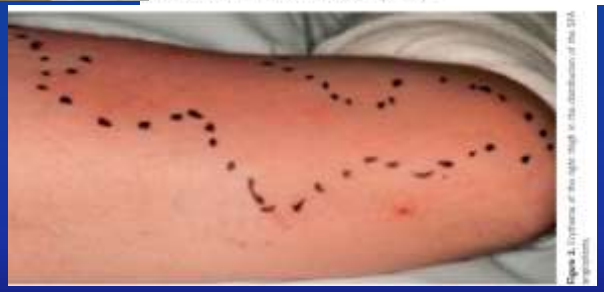
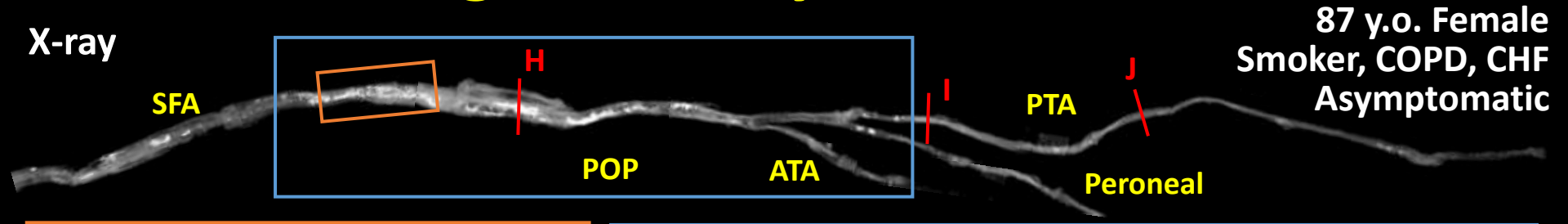


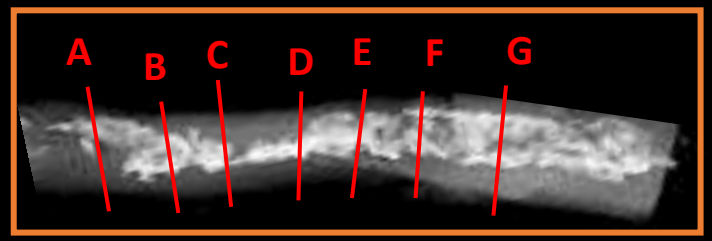
Fig 2. A, Photomicrograph (original magnification, ×40) of histologic specimen demonstrates inflammation and fibrin within the wall of an arteriole within the subcutaneous fat (*arrow*). B, Photomicrograph (original magnification, ×400 shows mixed cellular infiltrate comprising lymphocytes, neutrophils, and eosinophils in the subcutis and a thrombosed small vessel with fibrin within its wall (*arrow*).

- *Acute hypersensitivity reaction to femoral drug-coated balloons*.
  Lake E et al,
  Vasa. 2017 May;46(3):223-225

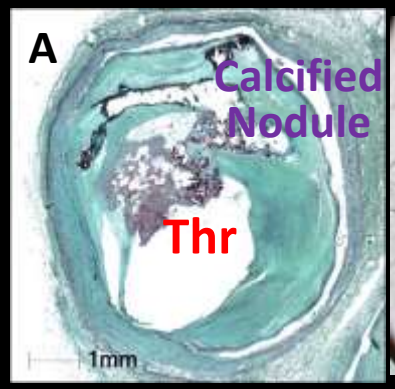


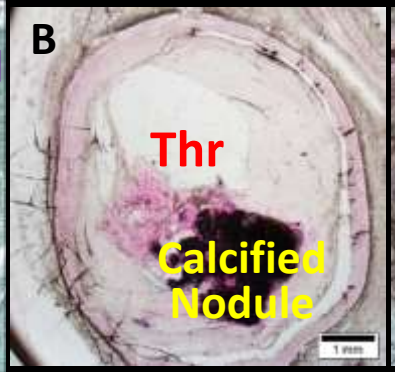
How to manage severely calcified lesion in SFA

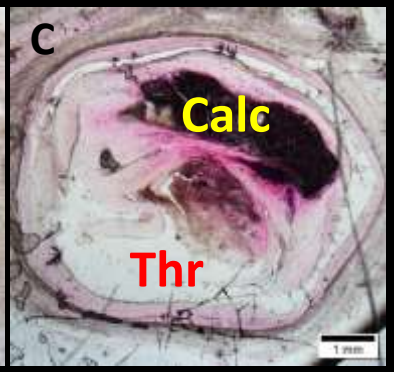


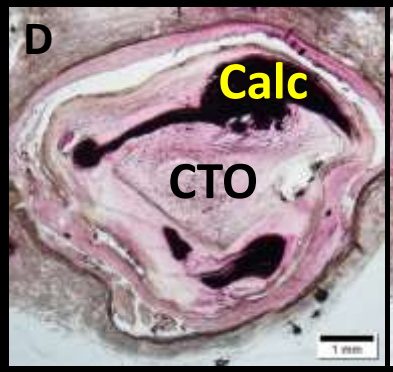


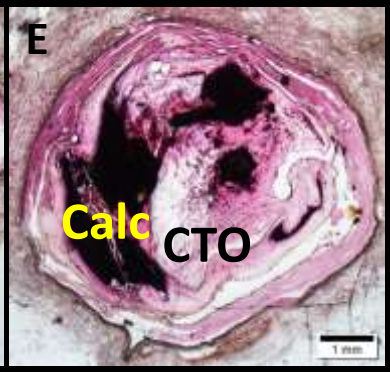
Histology (w/o decalcification)

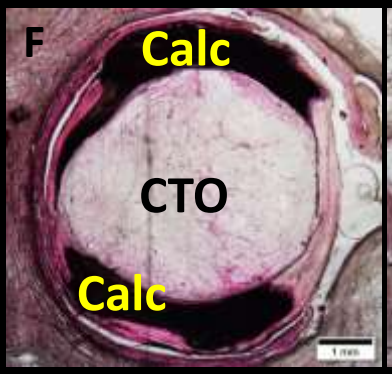


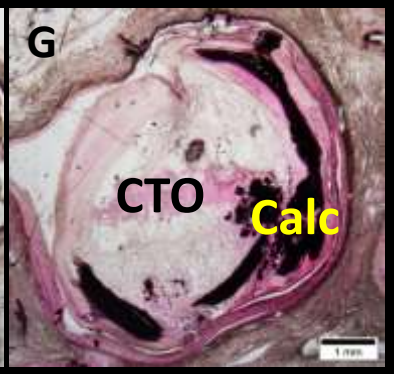


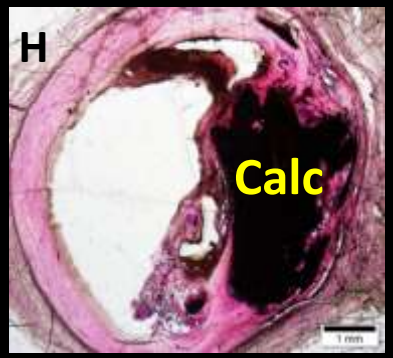


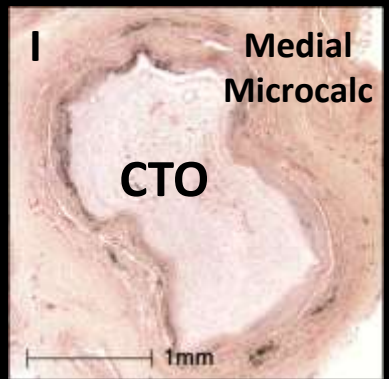


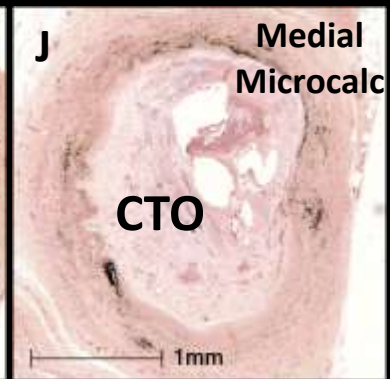




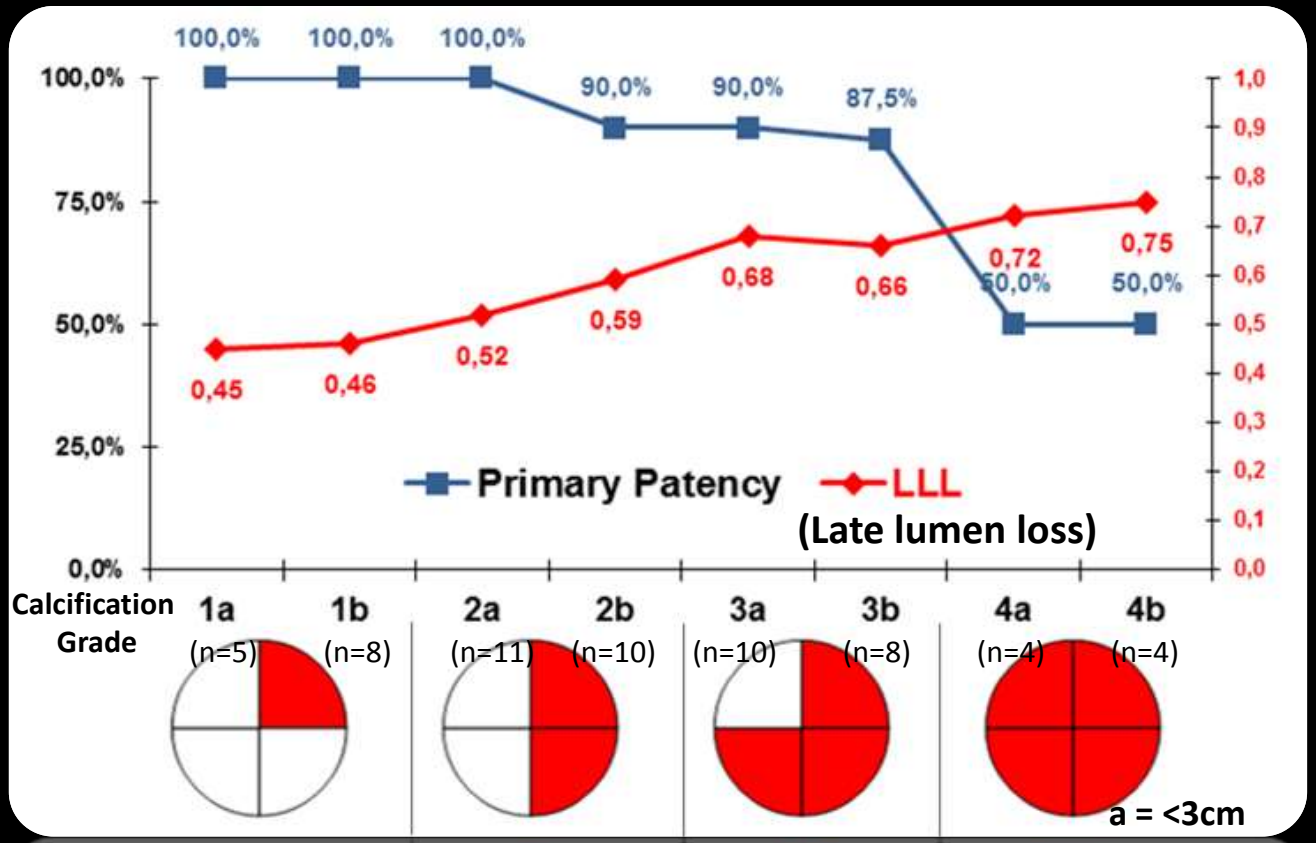


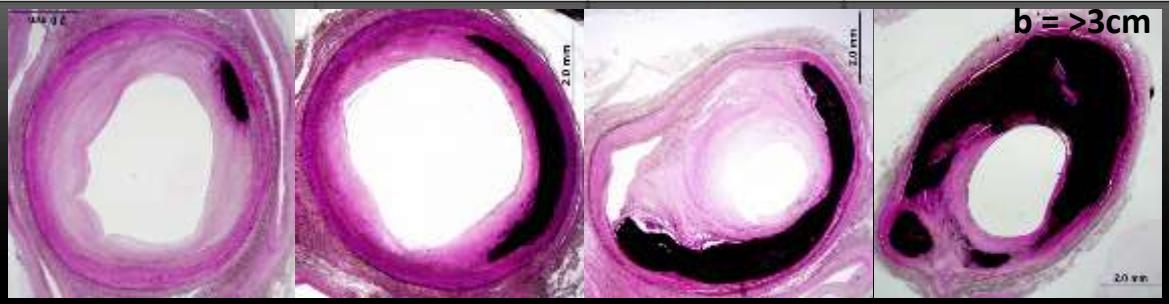






Inverse relationship between the primary patency and late lumen loss (LLL) with calcium groups after 12 months of follow up



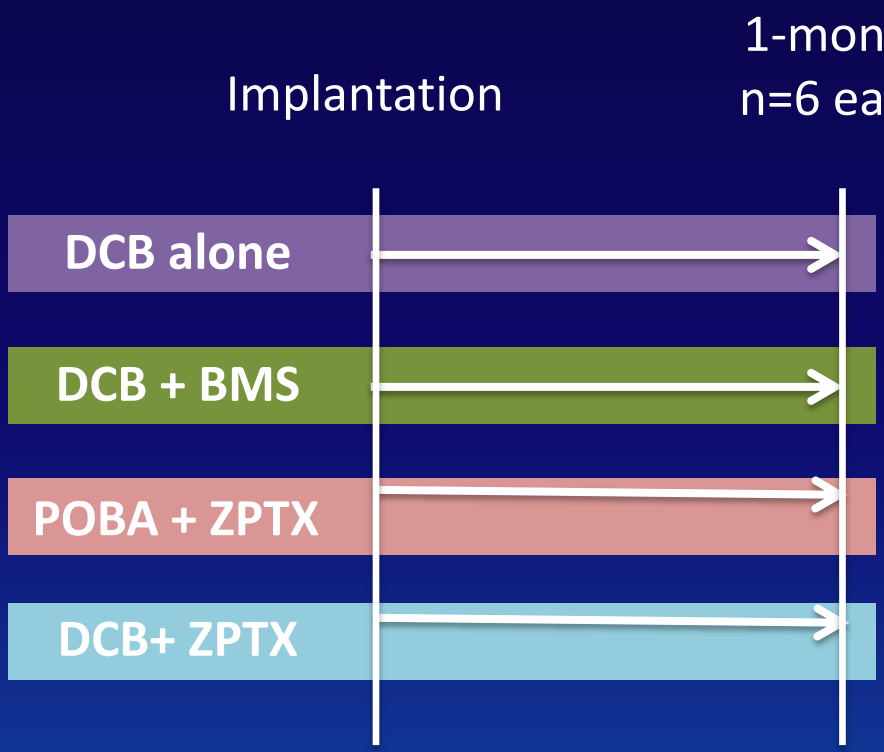


After revascularization
of SFA lesion
by DCB (In.PACT).
Lesion length 3cm-30cm

Symptomatic patients
N=60, mean age 65±21

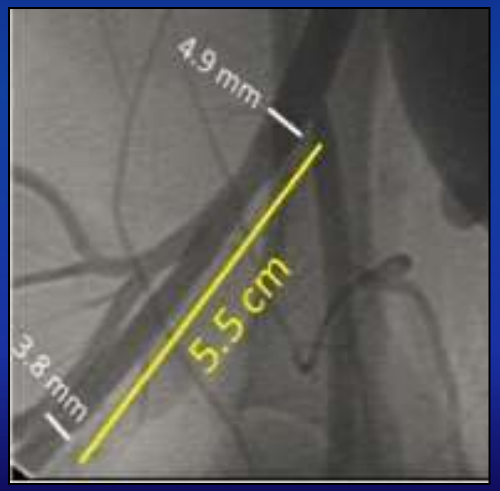
Fanelli et al. Cardiovasc Intervent Radiol (2014) 37:898-907

Study Design:



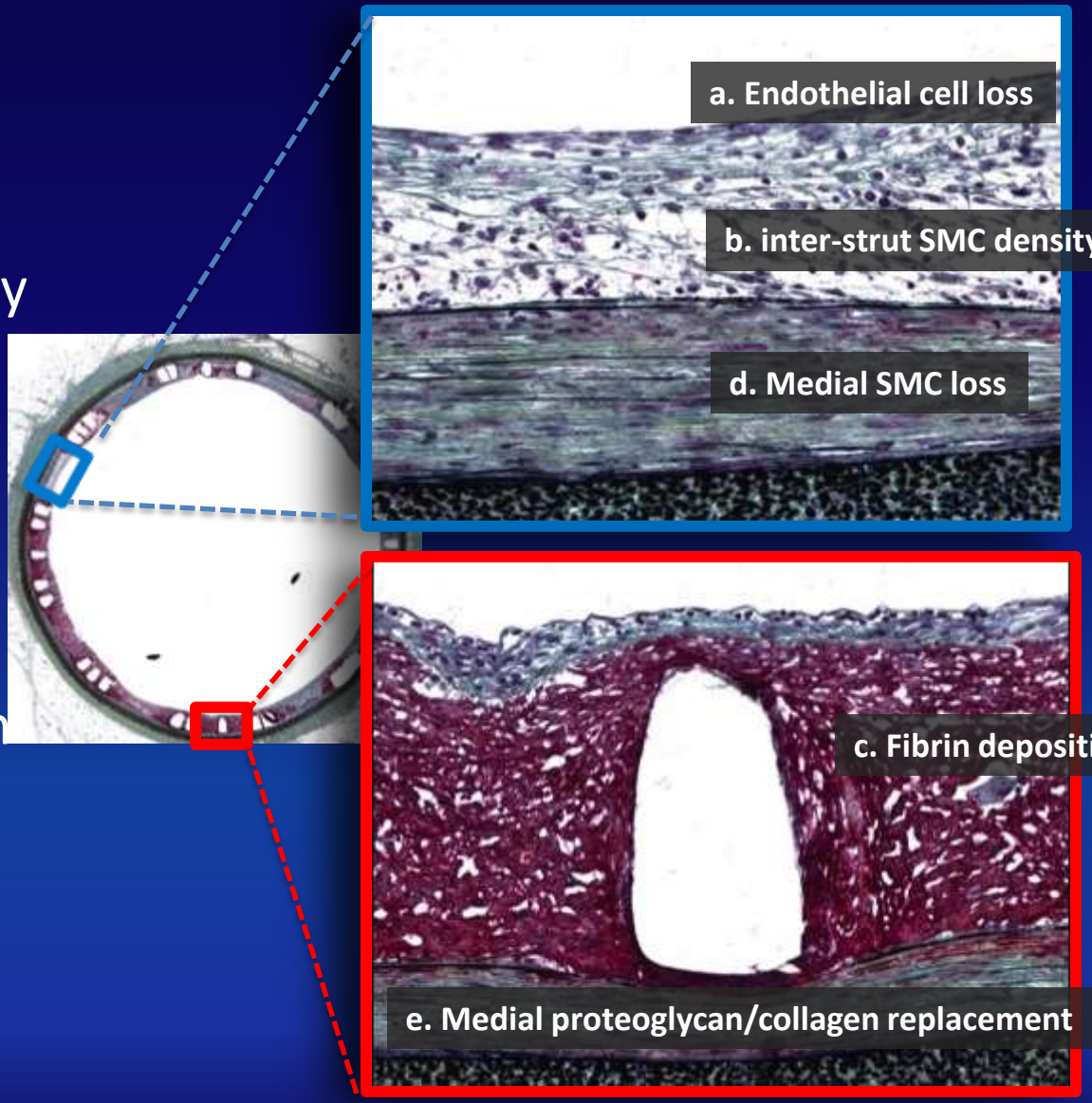
Devices Used in Study:

- DCB = In.Pact Admiral
- DES = Zilver PTX
- BMS = Zilver Bare



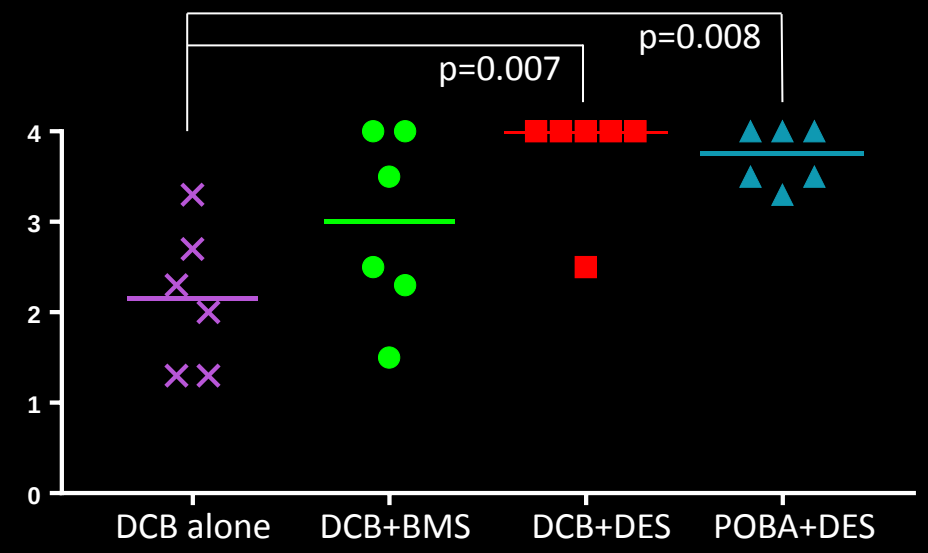
What Histological Markers Indicate Efficacy?

a. Endothelial cell loss
b. Inter-strut SMC density
c. Fibrin deposition
d. Medial SMC Loss (Depth and Circumference)
e. Medial Proteoglycan/Collagen replacement

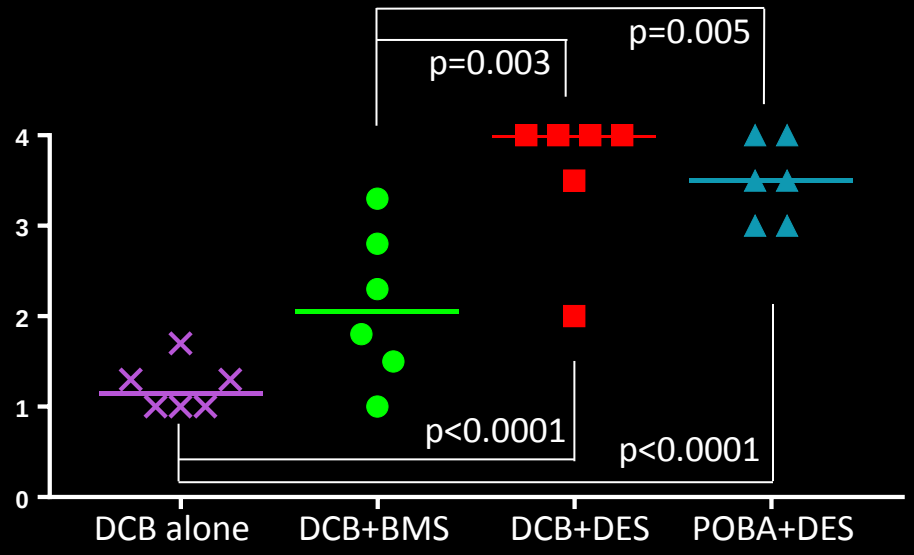


Histological Analysis in Porcine Superficial Femoral Artery

Medial SMC Loss (Depth)

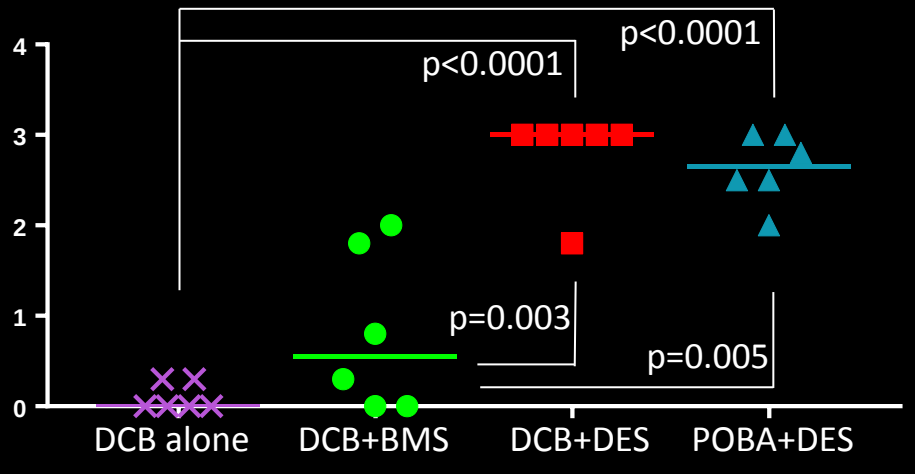


Medial SMC Loss (Circumferential)

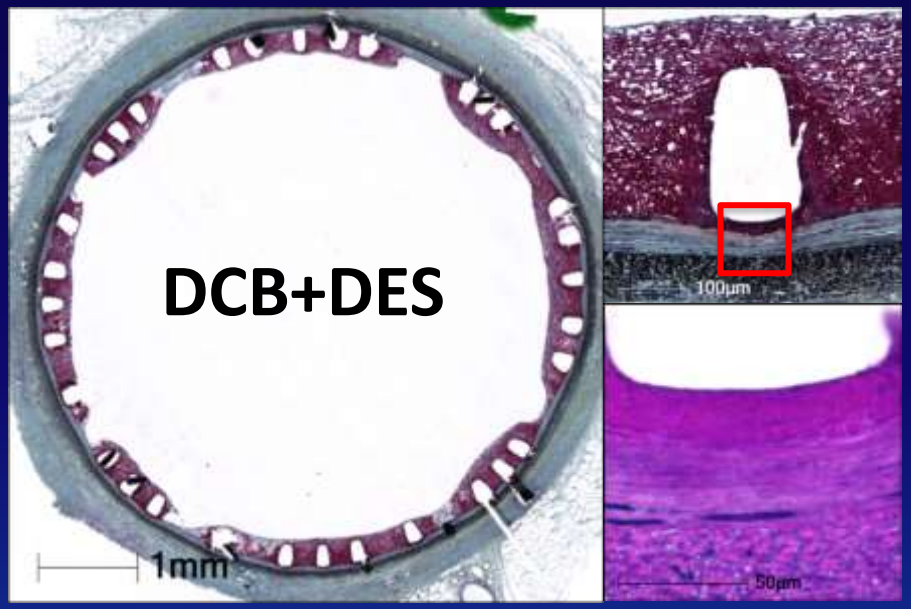


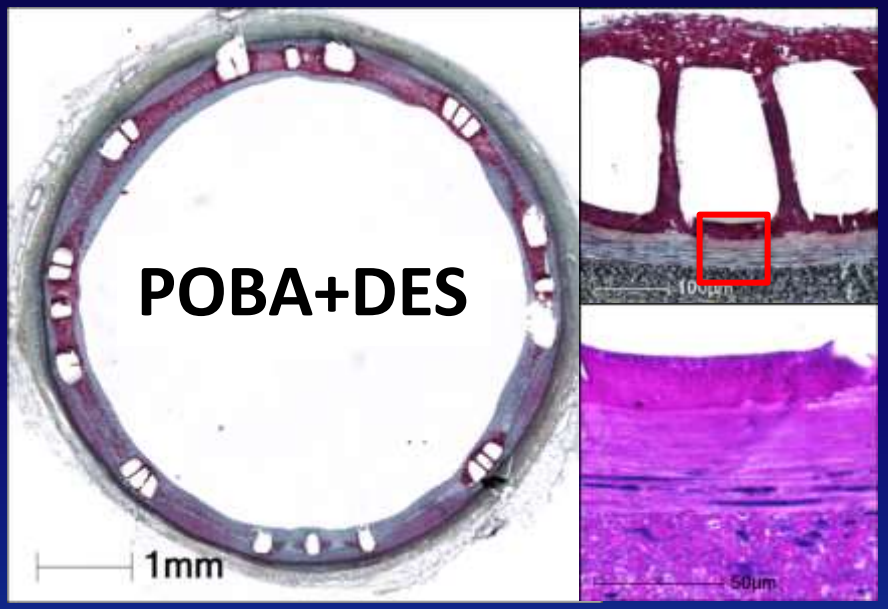
Medial SMC loss (Depth) score	Circumferential
0 none	none
1 SMC loss <25% of medial thickness	<25% of the area
2 25-50%	25-50%
3 51-75%	51-75%
4 >75%	>75%

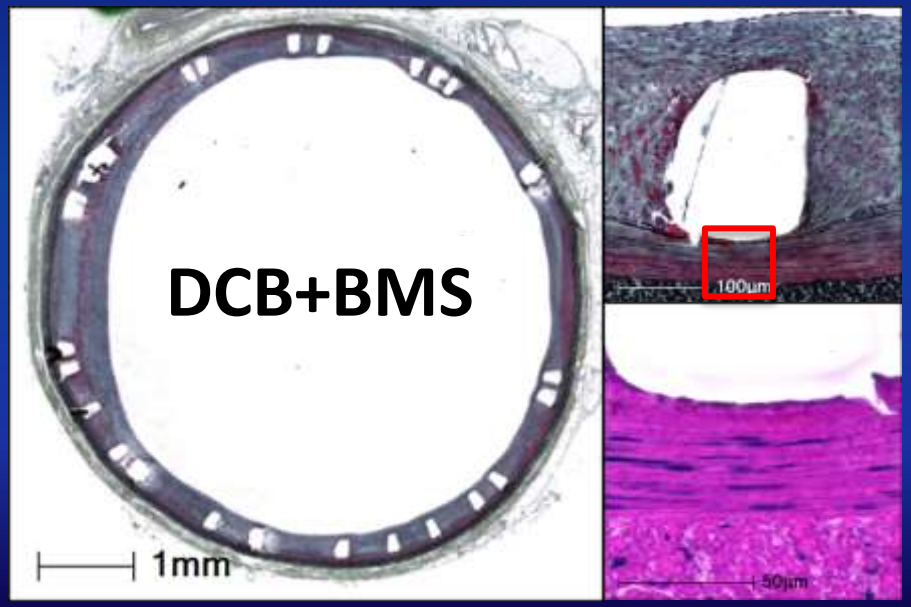
Fibrin Deposition

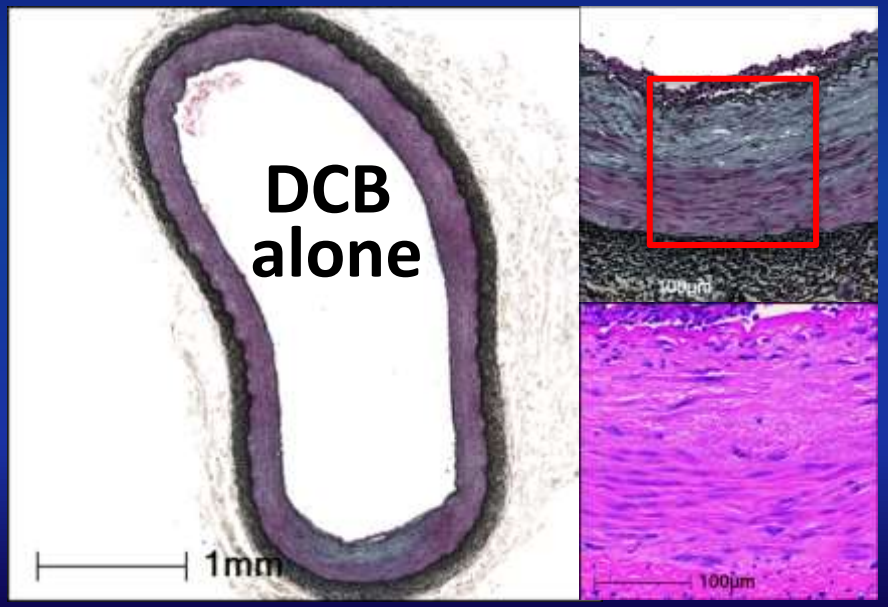


Porcine PTX: 1-month histological images

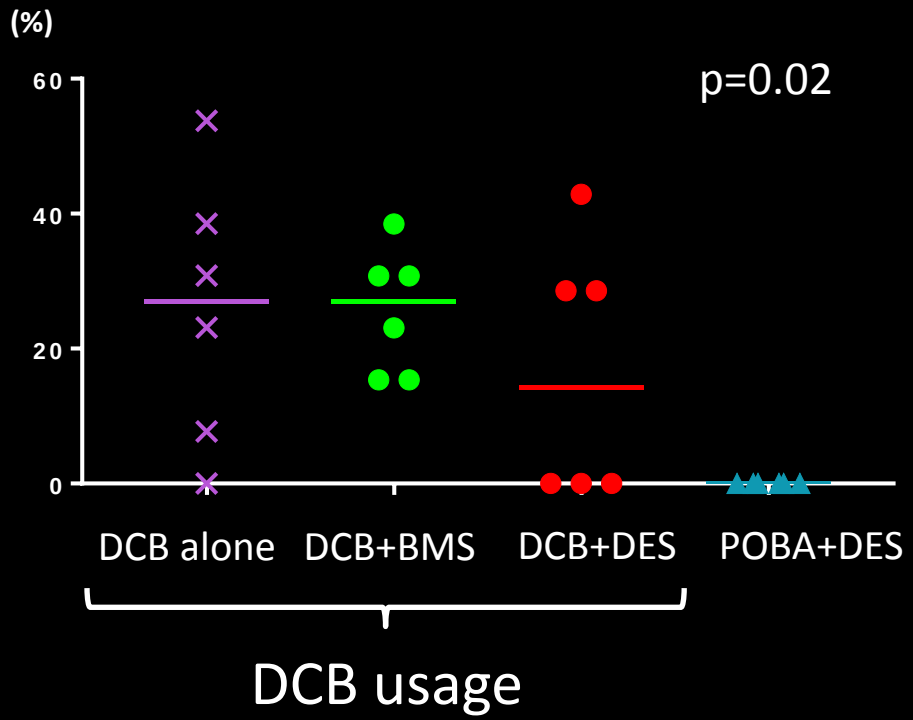




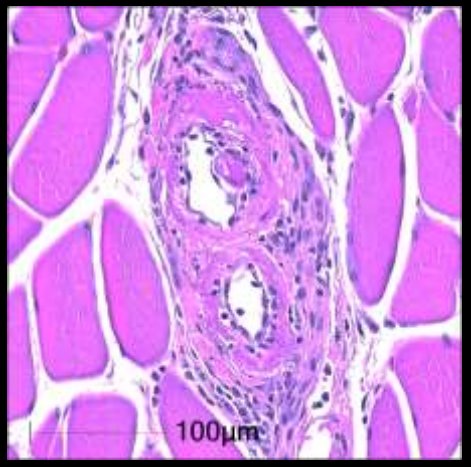




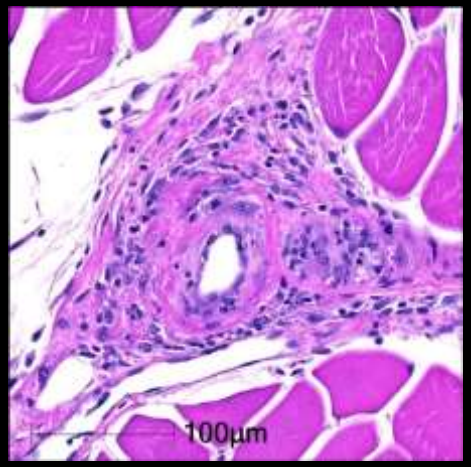
Histologic findings of emboli/vascular changes following stent implantation



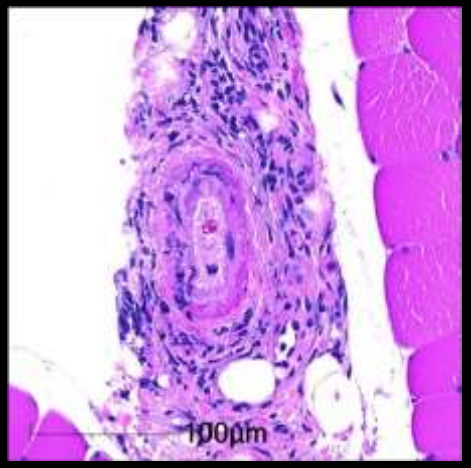
DCB alone



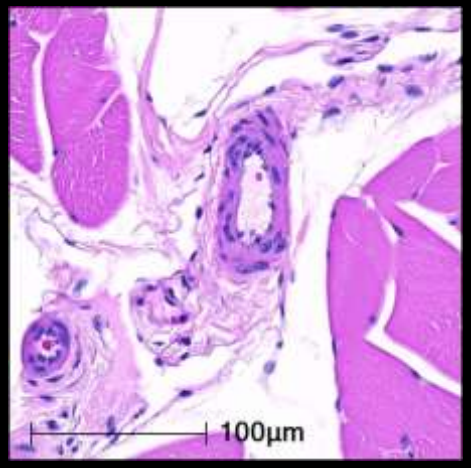
DCB+BMS



DCB+DES



POBA+DES



Summary

- In the absence of randomized clinical data, preclinical studies can provide excellent information about the relative performance of different technologies
- All 4 DCB's tested in our preclinical studies exhibited similar drug effect, however, the prevalence of downstream effects of paclitaxel drug and/or downstream emboli is different between DCBs.
- In the simple, short SFA lesions, DCB should be the primary choice because of the "leaving nothing behind". However, the potential downstream embolic effects with DCB use may present a concern especially in the patients with CLI.
- Intervention in heavily calcified peripheral artery show a poor outcome with DCB because calcification does not allow penetration of the drug.
- DES + DCB or POBA showed greater desired biologic effect as compared to BMS + DCB or DCB alone that indicates DES should be the standard of care after appropriate lesion preparation in the lesions with moderate to severe calcification.
- Following DCB, if angiographic results are poor DES implantation should be the first choice rather than BMS, because animals studies show no safety concerns.

Provisional stenting is mandatory in some cases

In.Pact trials	In.Pact SFA[1]	In.Pact Registry[2]	In.Pact LL Subgroup (15-25cm)[3]	In.Pact LL Subgroup (>25cm)[3]
Provisional stent rates	**7.3%**	**24.7%**	**33.3%**	**52.6%**
Patients	16/220	160/648	33/99	30/57

Modern stent trials	Resilient (PTA arm)[4]	Zilver PTX RCT (PTA arm)[5]
Provisional stent rates	**40%**	**50%**
Patients	29/72	120/238

Medicare Part B claims indicate an SFA stent is used in NEARLY HALF of all SFA cases in U.S. SFA procedures.[6]

1. Laird JR et al. J Am Coll Cardiol. 2015;66(21):2329-38.
2. Ansel, LINC 2015
3. Tepe, LINC 2016
4. LifeStent® Solo™ Vascular Stent System [package insert]. Tempe, AZ: C.R. Bard, Inc.; 2011.
5. Zilver® PTX® Drug-Eluting Peripheral Stent [package insert]. Limerick Ireland: Cook Ireland LTD; 2012
6. Medicare Part B claims indicate an SFA stent is used nearly half of the time. (PSPSF, 2013)