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Are there downstream effects & other adverse effects of DCB?

Koen Deloose, MD

Head Department Vascular Surgery

AZ Sint Blasius Dendermonde, Belgium

Disclosure slide

Speaker name: Koen Deloose, MD

❑ I have the following potential conflicts of interest to report:

- ☒ Consulting: Medtronic, Spectranetics, Biotronik, Abbott, Bard, iVascular, Bentley, Cook, GE Healthcare, Terumo, Contego Medical, Boston Scientific
- ❑ Employment in industry
- ❑ Stockholder of a healthcare company
- ❑ Owner of a healthcare company
- ❑ Other(s)

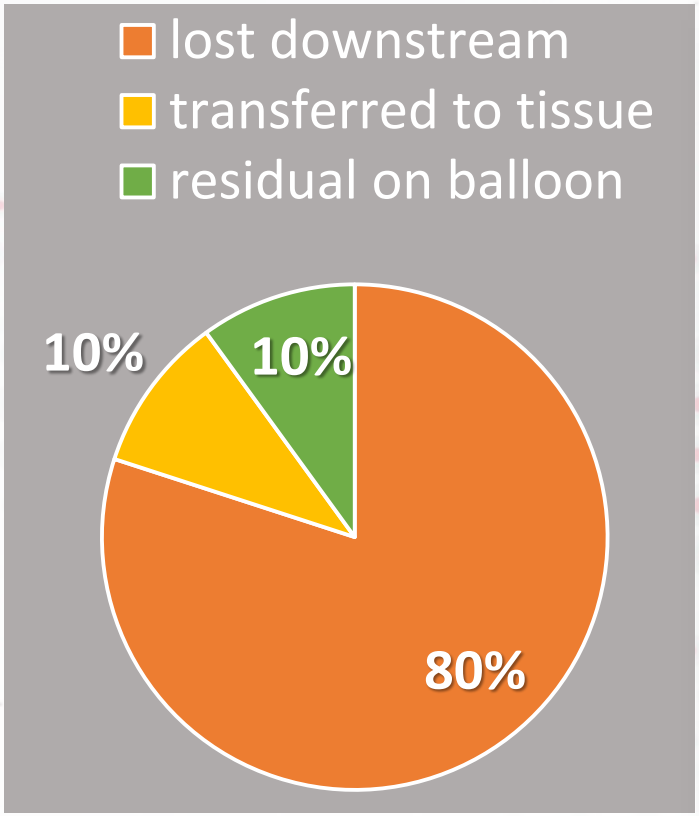
❑ I do not have any potential conflict of interest

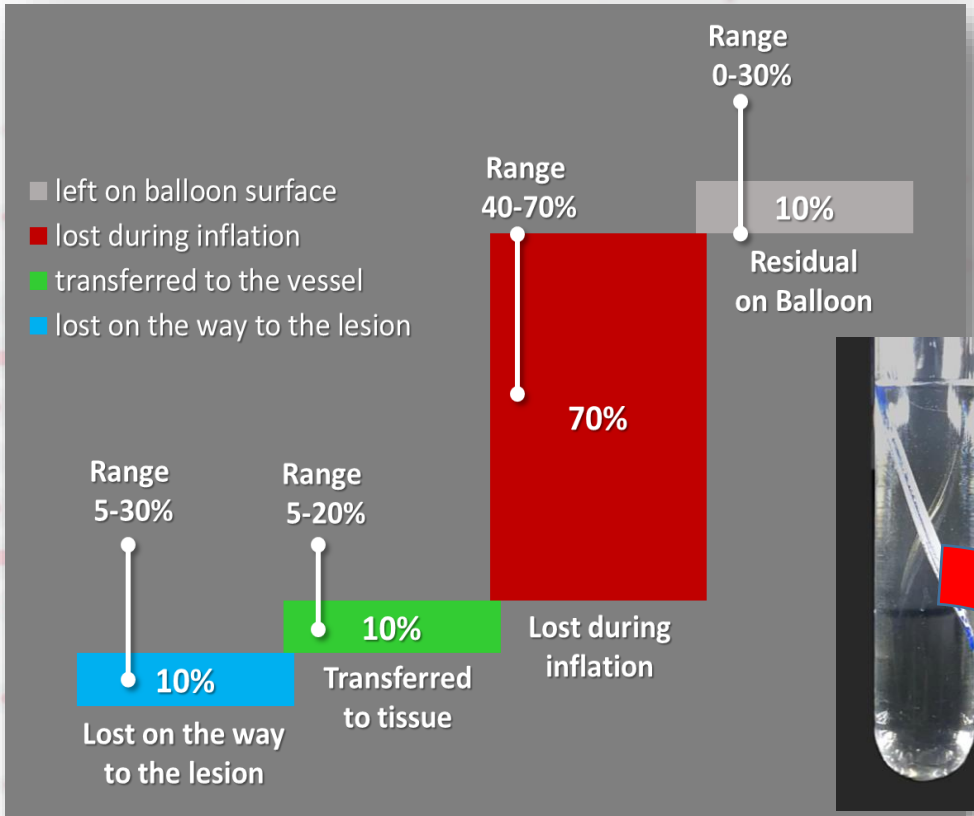
An effective DCB formulation …

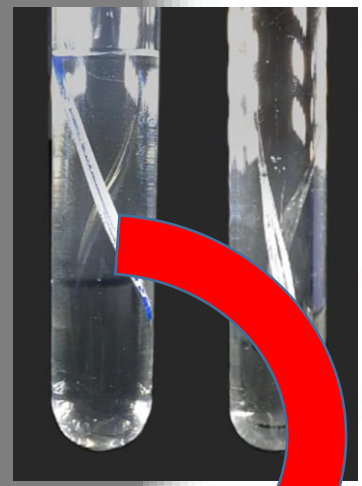
- Must deliver large quantities of the drug within seconds
- Distribute within the media in the first few days
- Therapeutic drug levels must be maintained >4 weeks (histologically proven tissue effect)

- Must allow rapid healing
- Effective drug delivery to target tissue while avoiding non-target effect (i.e. minimize emboli)

Most PTX is lost downstream





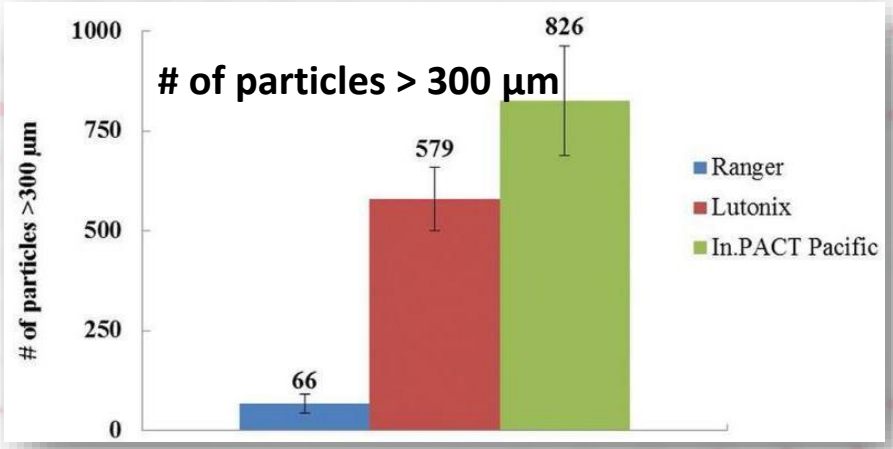


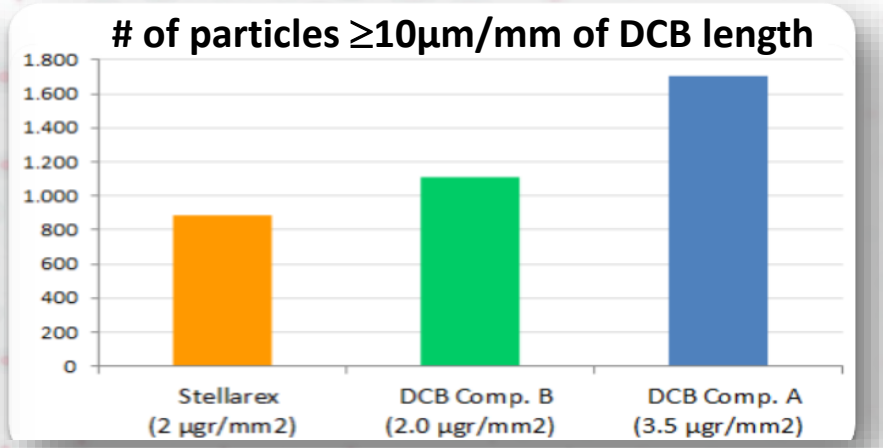
Mass effect : obliteration of microcirculation distally (cfr atherosclerotic debris)

Drug effect : potential local tissue toxicity

Mass effect : obliteration microcirculation

- Particle sizes > capillaries (5~10 µm) should matter





- However ptx mass and size lost from DCB likely smaller compared to atherosclerotic plaque debris released during normal PTA (0.3 – 4.6 mm) [1-2]

1. Gongora CA, Shibuya M, Wessler JD, McGregor J, Tellez A, Cheng Y, Conditt GB, Kaluza GL, Granada JF. Impact of Paclitaxel Dose on Tissue Pharmacokinetics and Vascular Healing: A Comparative Drug-Coated Balloon Study in the Familial Hypercholesterolemic Swine Model of Superficial Femoral In-Stent Restenosis. JACC Cardiovasc Interv. 2015 Jul;8(8):1115-1123
2. Siablis D, Karnabatidis D, Katsanos K, Ravazoula P, Kraniotis P, Kagadis GC. Outflow protection filters during percutaneous recanalization of lower extremities' arterial occlusions: a pilot study. Eur J Radiol. 2005 Aug;55(2):243-9
3. Karnabatidis D, Katsanos K, Kagadis GC, Ravazoula P, Diamantopoulos A, Nikiforidis GC, Siablis D. Distal embolism during percutaneous revascularization of infra-aortic arterial occlusive disease: an underestimated phenomenon. J Endovasc Ther. 2006 Jun;13(3):269-80

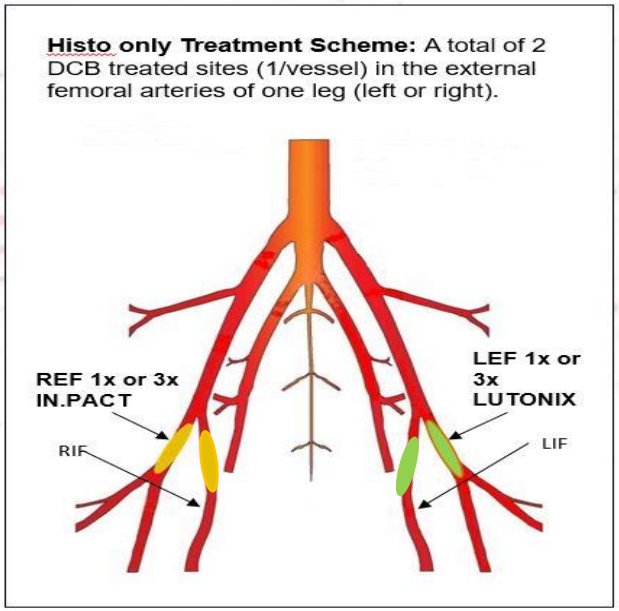
Drug effect : distal PTX effects ?

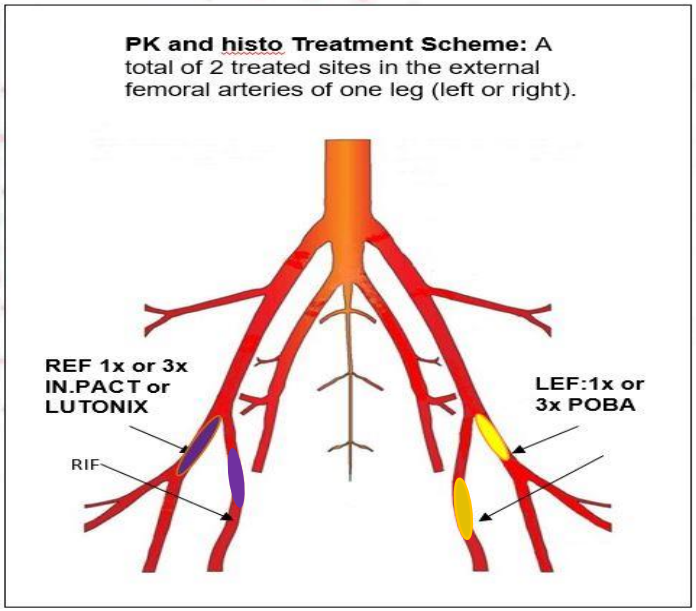
In Vivo Animal Testing :

Comparison of Particulate Embolization after Femoral Artery Treatment with IN.PACT Admiral versus Lutonix 035 Paclitaxel-Coated Balloons in Healthy Swine

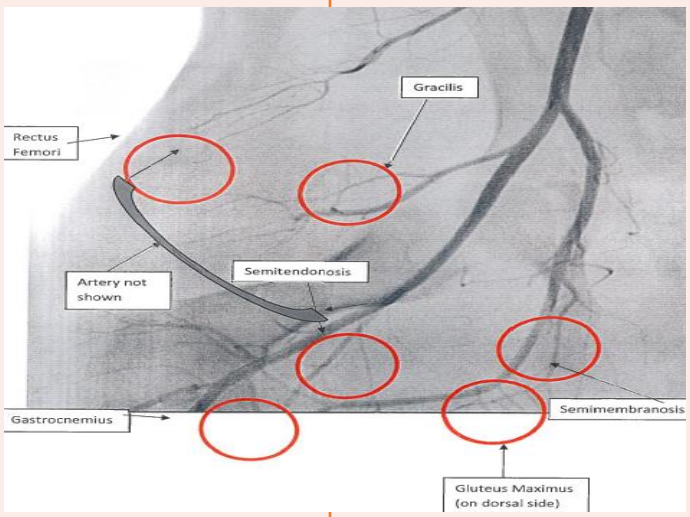
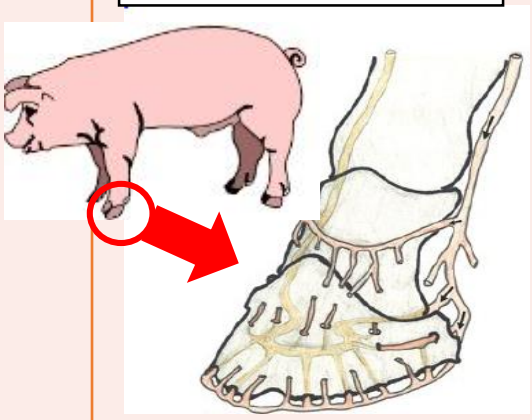
Frank D. Kolodgie, PhD, Erica Pacheco, MS, Kazuyuki Yahagi, MD, Hiroyoshi Mori, MD, Elena Ladich, MD, and Renu Virmani, MD

BLINDED comparison of effect of downstream particulates in distal vascular territories between IN.PACT Admiral vs Lutonix 035 in swine models @28 & 90 days , 1x and 3x dose : **FIRST COMPARATIVE STUDY**





Drug effect : distal PTX effects ?

Study device	LUTONIX DCB	IN.PACT DCB	POBA
Treated sites	SFA, 1x (single); 3x (3 DCB OL)	SFA, 1x (single); 3x (3 DCB OL)	SFA, 0 (single); 3x (POBA)
Tissues assessed for histopathology & distal drug concentration			Coronary band 
28 d treated SFA N	1x = 5 ; 3x = 5,	1 x = 5 ; 3x = 5	1 x = 0 ; 3x = 4
90 d treated SFA N	3x = 5	3x = 5	3x = 4

Drug effect : distal PTX effects ?

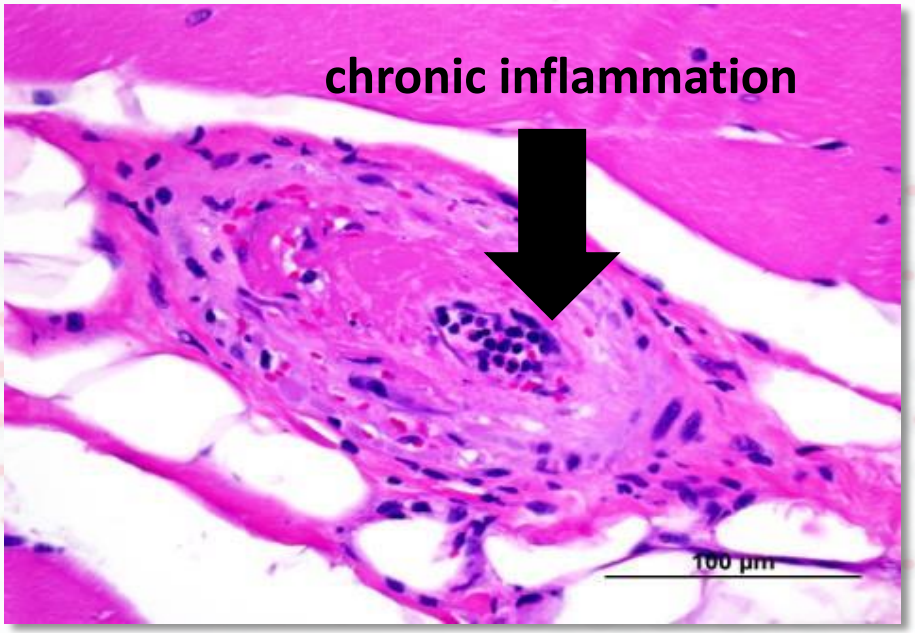
Histological section based analysis of downstream non-target organs (skeletal muscle and coronary band) associated with PTX @ 28 & 90 days post treatment in different concentrations

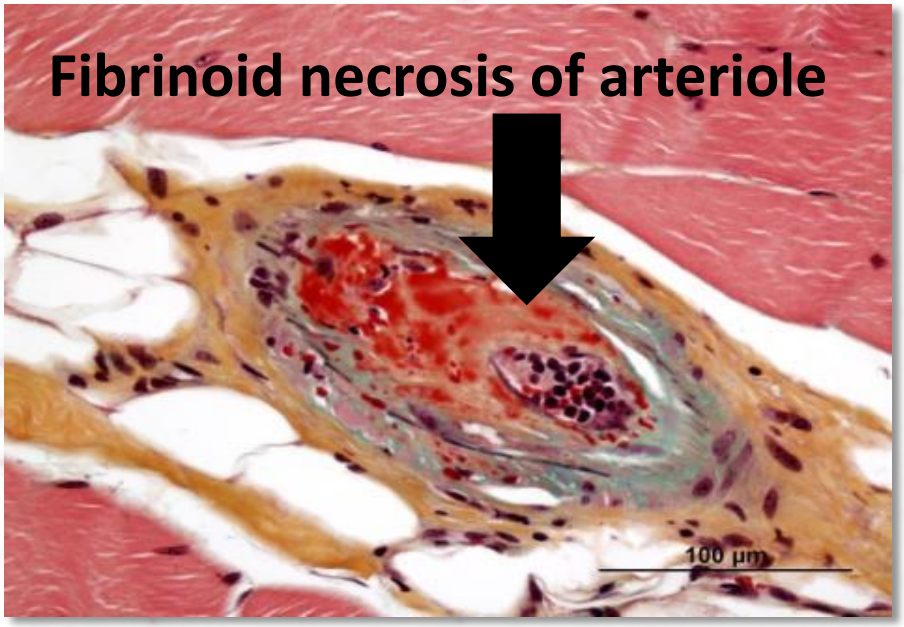
	Survival Treatment & Arteries	Lutonix 035		IN.PACT		P-value	
Paclitaxel concentration in downstream tissues (ng/g)		Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band
	28-day (1x, n=5)	1.3 (0.6-2.3)	1.5 (1.1-65.8)	60.8 (32.6-118.1)	189.0 (134.0-700.0)	0.009	0.02
	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

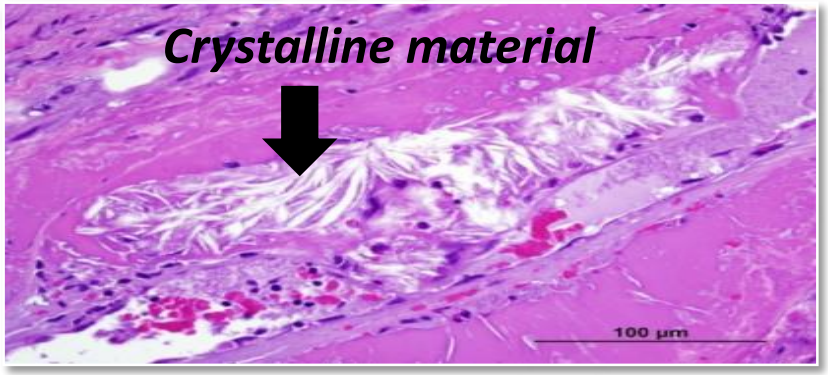
	Survival Treatment & Arteries	Lutonix 035	IN.PACT	P-value
Number of micro-vessels with paclitaxel- associated findings	28-day (1x, n=5)	1 (0-2)	4 (2-12)	0.03
	28-day (3x, n=5)	1 (0-12)	26 (11-34)	0.07
	90-day (3x, n=4)	0 (0-3)	11 (5-15)	0.02

Kolodgie FD et al. J Vasc Interv Radiol 2016 Sep,27(11), 1676-1685 ; with the courtesy of Aloke Finn, CVPath institute Gaithersburg, USA

Drug effect : distal PTX effects ?



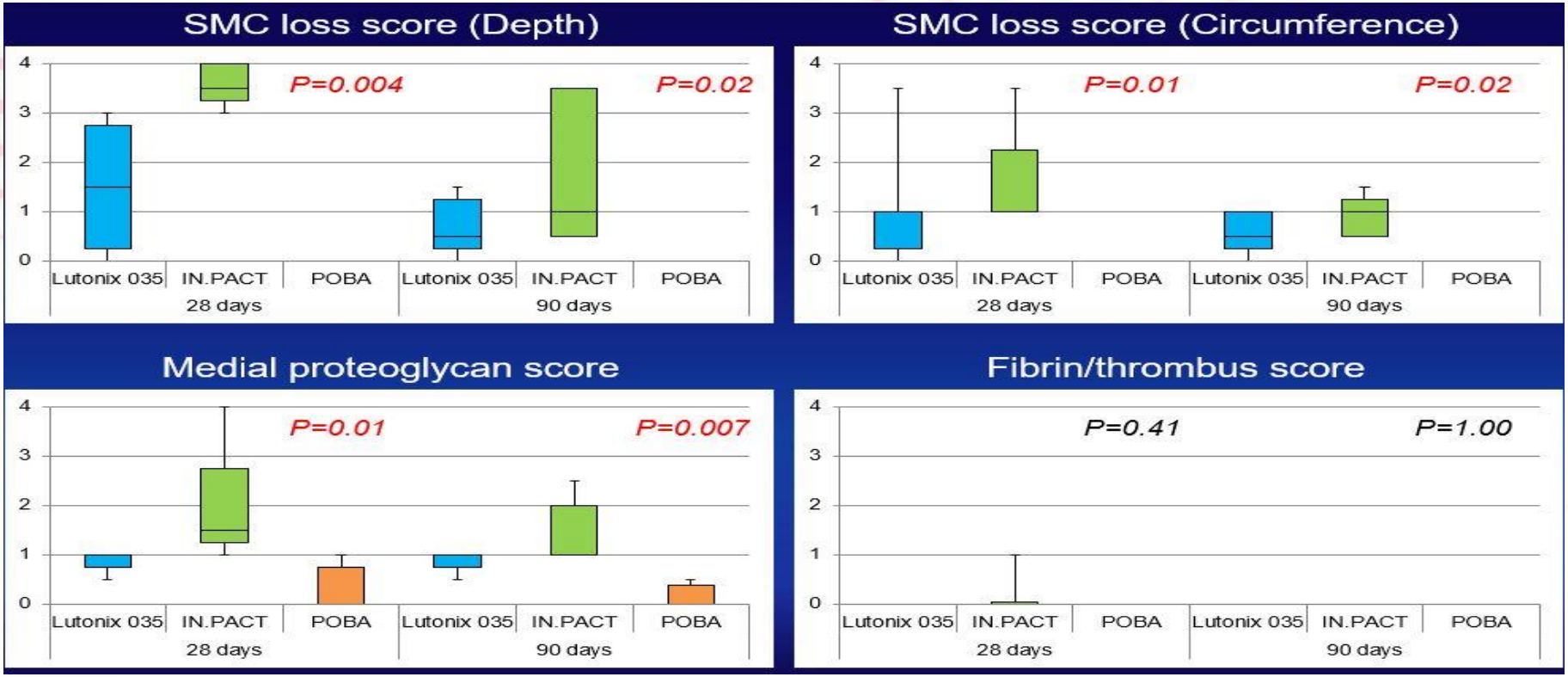




Kolodgie FD et al. J Vasc Interv Radiol 2016 Sep,27(11), 1676-1685 ; with the courtesy of Aloke Finn, CVPath institute Gaithersburg, USA

Drug effect : distal PTX effects ?

Histological vascular changes @28 & 90 days with triple inflations of both DCB's: significant differences in histologic vascular changes between 2 DCB's (triple concentration)



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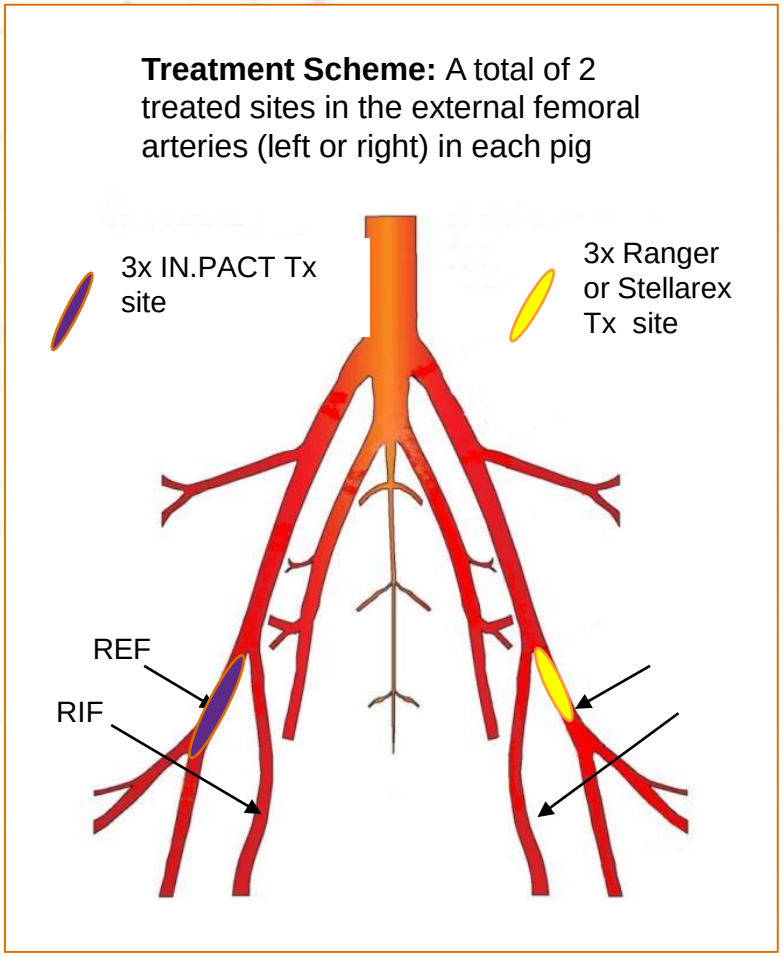
Drug effect : distal PTX effects ?

In Vivo Animal Testing :

SECOND COMPARATIVE STUDY

BLINDED comparison of effect of downstream particulates in distal vascular territories between IN.PACT Admiral vs Stellarex vs Ranger in swine models @28 DAYS, 3x dose



With the courtesy of Aloke Finn, CVPath institute Gaithersburg, USA

Drug effect : distal PTX effects ?

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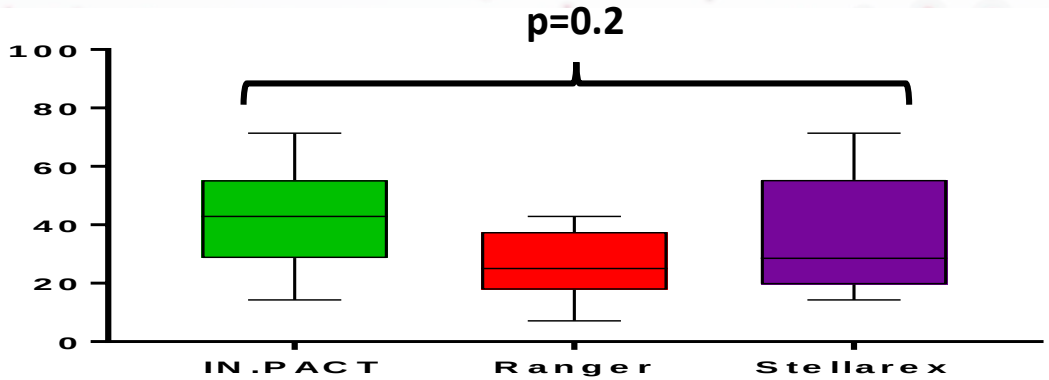


	Survival Treatment	Second Comparative Study		
		IN.PACT (n=12)	Ranger (n=6)	Stellarex (n=6)
Sections with vascular changes in downstream nontarget tissues (%)	28-day (3x)	42.9	25	30

First Comparative Study	
Lutonix (n= 5)	IN.PACT (n=5)
7.7	38.5

	Survival Treatment	Second Comparative Study					
		IN.PACT		Ranger		Stellarex	
		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)

First Comparative Study			
Lutonix		IN.PACT	
Skeletal muscle	Coronary band	Skeletal muscle	Coronary band
3.7 (1.3-10.9)	31.5 (5.3-54.1)	170.9 (19.7-221.5)	871.0 (567.5-1315.0)

With the courtesy of Aloke Finn, CVPath institute Gaithersburg, USA

What is the clinical relevance of these theoretical findings?

12-Month Key Safety Outcomes

	LEVANT II[1]		Global[2]	IN.PACT SFA[3]	IN.PACT Global				ILLUMINATE			
					Long[4]	CTO[5]	ISR[6]	Clinical[7]	FIH	EU RCT	US Pivotal	Global
	PTA	Lutonix 035		PTA	IN.PACT Admiral							
Subjects	160	316	691	111	220	157	126	131	1406	80	328	300	371
All Thrombosis				3.7% (4/107)	1.4% (3/207)	3.7% (5/134)	4.3% (5/115)	0.8% (1/124)	2.9% (38/1311)				
Revasc. due to Thrombosis	0.7% (1/140)	0.4% (1/285)	1.3% (8/634)										
Major Amputation	0.0% (0/140)	0.3% (1/286)	0.5% (3/635)	0.0% (0/107)	0.0% (0/207)	0.0% (0/134)	0.0% (0/115)	0.0% (0/124)	0.2% (3/1311)	0.0%	0.0%	0.0%	0.3%

1. Rosenfield K, et al. NEJM:373:145-53 (2015).
2. Presented by Laurich C, SVS Chicago 2015.
3. Tepe G, et al. Circ 131:495-502 (2015).
4. Presented by Scheinert D, PCR Paris
5. Presented by Tepe G, Charing Cross London 2016.
6. Presented by Brodmann M, VIVA Las Vegas 2015.
7. Presented by Jaff M, VIVA Las Vegas 2016; includes subjects of imaging cohorts

IN CLAUDICANTS, THERE DOESN'T SEEM TO BE ANY IMPACT ON SAFETY

What is the clinical relevance of these theoretical findings?

Primary IN.PACT DEEP Outcomes

Primary Efficacy	DEB	PTA	p
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	*0.950*
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	*0.291*

Primary Safety	DEB	PTA	p
6-month Death, Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*

1. Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab

Secondary Safety Outcomes

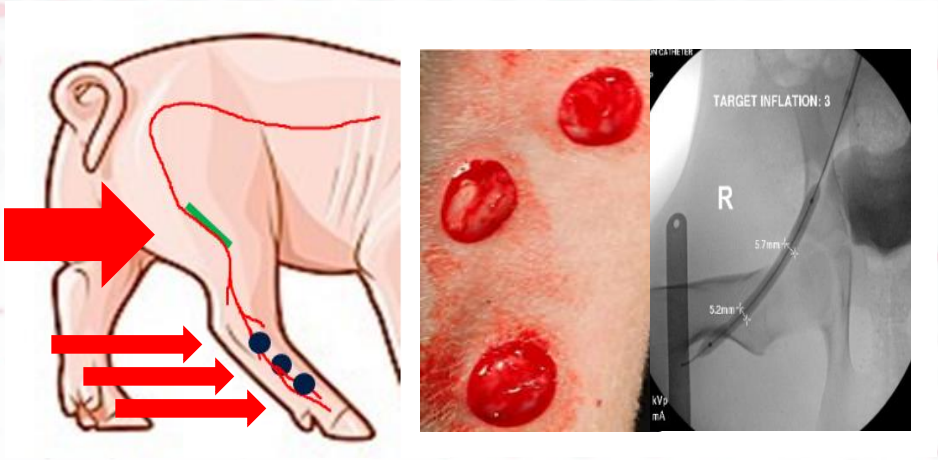
12-month Safety	DEB	PTA	p
Major Amputation	8.8% (20/227)	3.6% (4/111)	*0.080*
All-Cause Mortality	10.1% (23/227)	8.1% (9/111)	*0.551*
Death and Amputations [1]	35.2% (80/227)	25.2% (28/111)	*0.064*
Death, Major Amp, CD TLR [2]	26.9% (61/227)	23.4% (26/111)	*0.496*
Amputation Free Survival	81.1% (184/227)	89.2% (99/111)	*0.057*
Wound Healing (site reported)	73.8% (121/164)	76.9% (70/91)	*0.579*

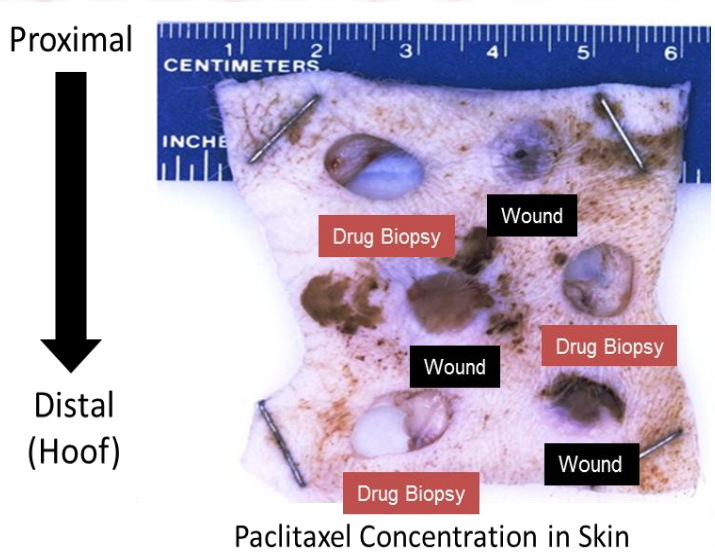
1. Death of any Cause, Major or Minor Amputation of target limb (MAE per protocol)
2. Death of any Cause, target limb Major Amputation and clinically driven TLR

DOES DISTAL DOWNSTREAM PARTICLE EMBOLIZATION IMPACT WOUND HEALING AND COULD IT AFFECT CLINICAL OUTCOMES FOR CLI PATIENTS?

What is the clinical relevance of these theoretical findings?

- Experimental DCB use in presence of distal limb wounds





Paclitaxel Concentration in Skin

Wound Creation; Bilateral Treatment
PTA or DCB x1 vs. DCB x3 (5-6 mm/80 mm)

PK study (PTX concentration)
Histology study (neo-epithelialization/dermal inflammation)

Pictures courtesy of Bob Melder, Medtronic.

What is the clinical relevance of these theoretical findings?

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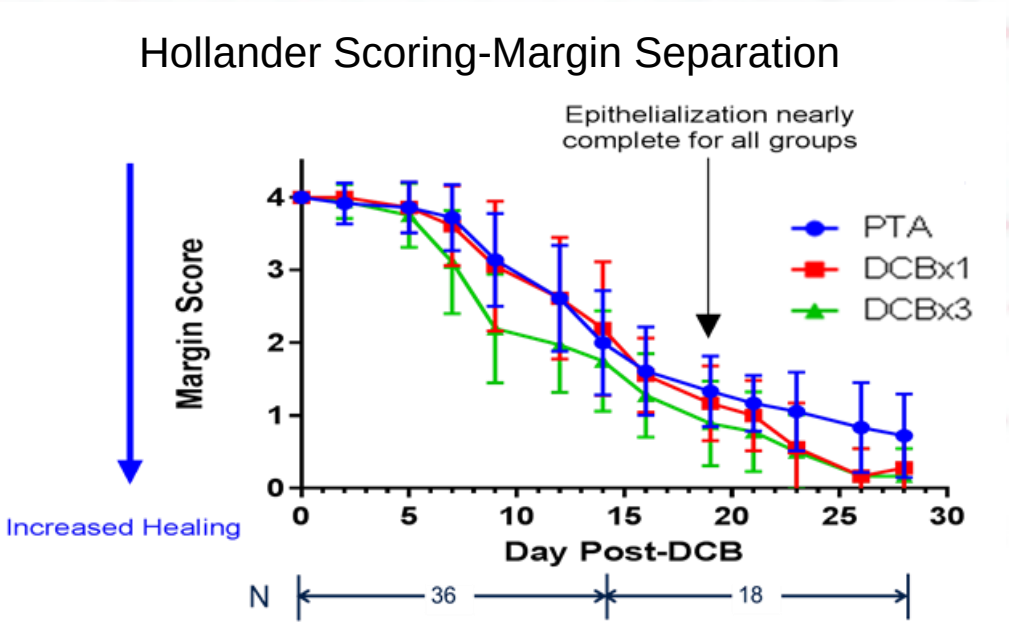
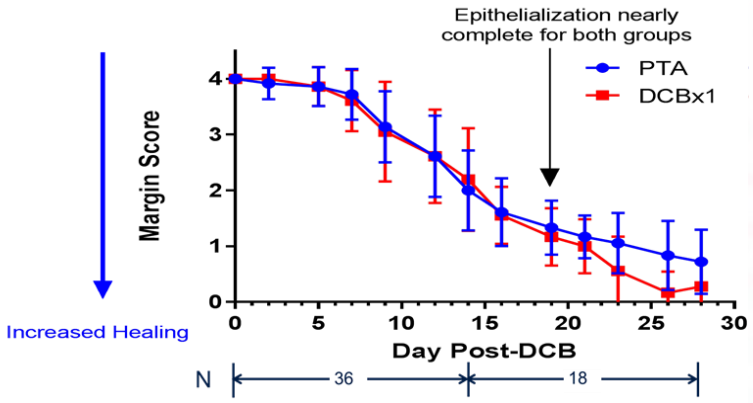
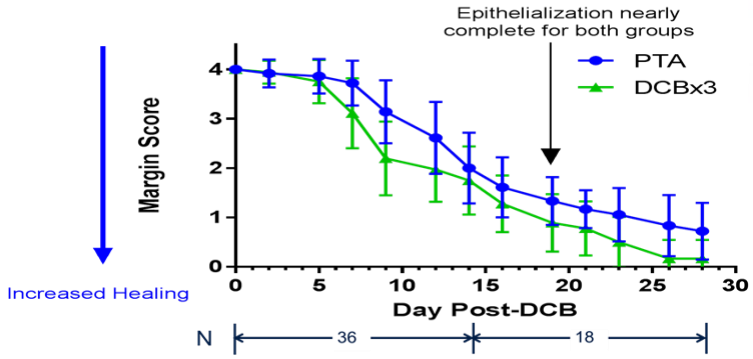


DCB 1x versus PTA



DCB 3x versus PTA



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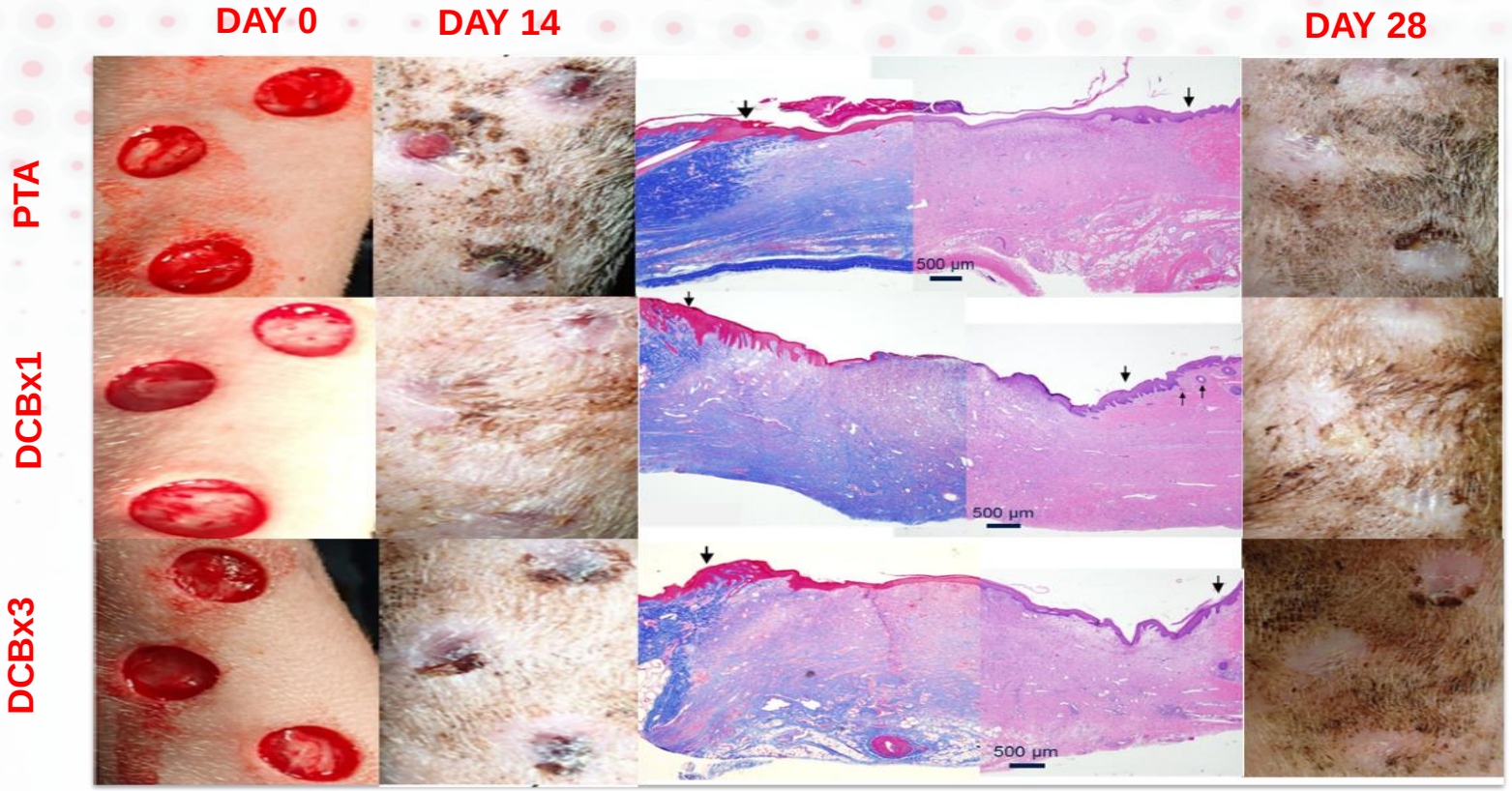

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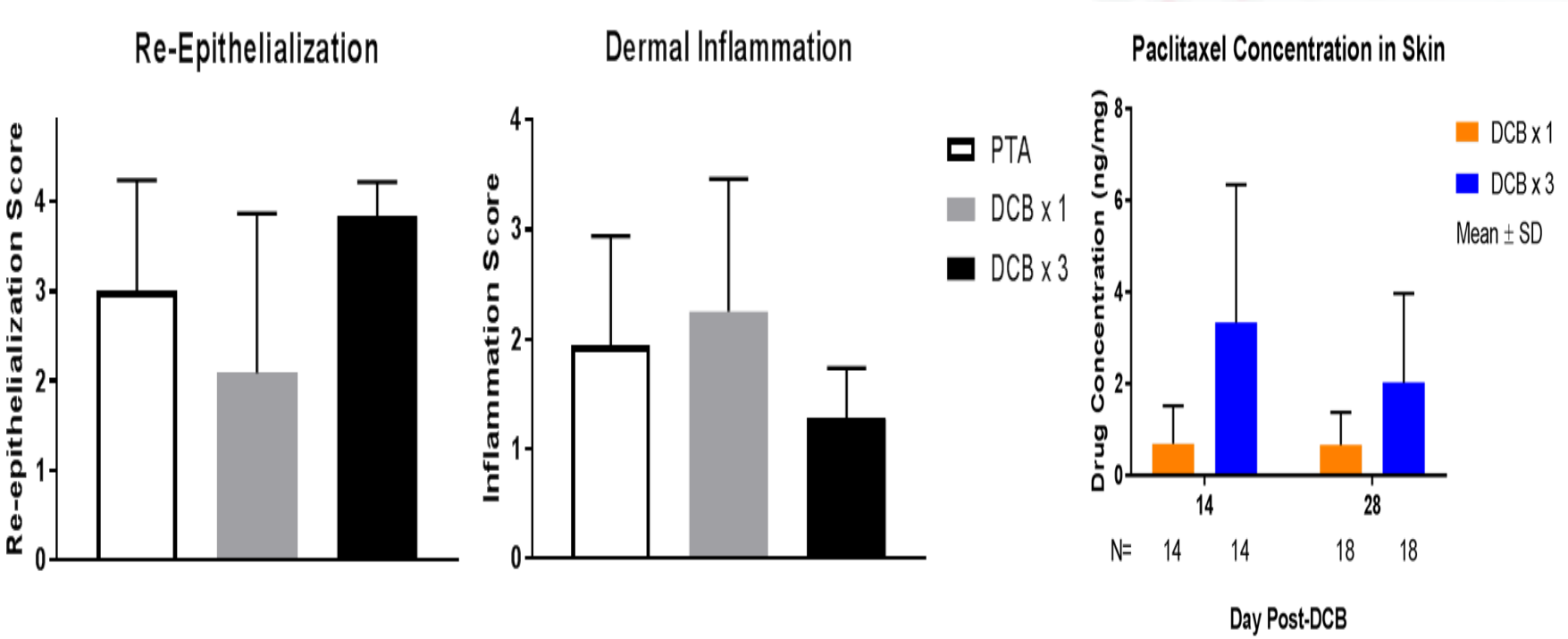

Pictures courtesy of Bob Melder, Medtronic.

Conclusions

- Downstream PTX particulates is a real phenomenon, present post dilatation with all DCB's, but with clear differences between different brands
- Clinical complications following DCB use in the SFA territory of claudicants are non existing
- However, the impact of PTX tissue residence on woundhealing in CLI patients with poor distal vessel run-off is still unknown