



CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE  
CONTROVERSIES & UPDATES  
IN VASCULAR SURGERY

**JANUARY 25-27 2018**  
MARRIOTT RIVE GAUCHE & CONFERENCE CENTER  
PARIS, FRANCE [WWW.CACVS.ORG](http://WWW.CACVS.ORG)



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Are all DCBs the same?  
What does basic science tell us?

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## Disclosure

Speaker name:

Frank Vermassen

I have the following potential conflicts of interest to report:

x Consulting: Medtronic, Abbott Vascular, Bard, W.L. Gore, Terumo, Boston Scientific, Philips

- Employment in industry
- Shareholder in a healthcare company
- Owner of a healthcare company
- Other(s)
- I do not have any potential conflict of interest

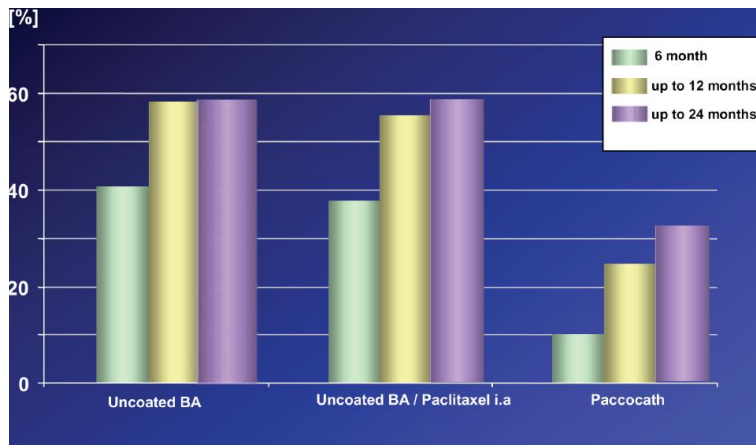


# Drug coated balloons: The start

## *Thunder trial*

Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg

Gunnar Tepe, M.D., Thomas Zeller, M.D., Thomas Albrecht, M.D., Stephan Heller, M.D., Uwe Schwarzwälder, M.D., Jean-Paul Beregi, M.D., Claus D. Claussen, M.D., Anja Oldenburg, M.D., Bruno Scheller, M.D., and Ulrich Speck, Ph.D.



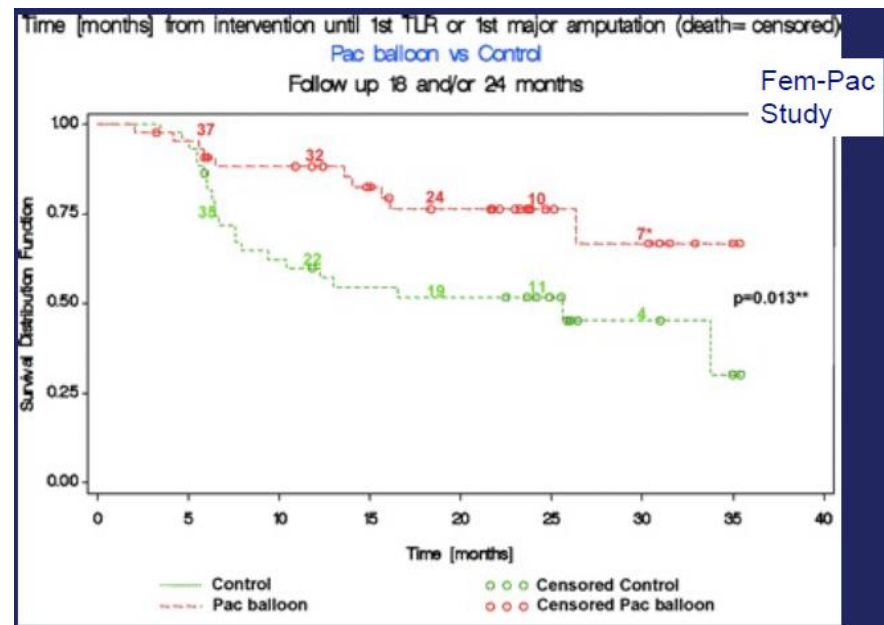
Binary restenosis in SFA lesions

Tepe NEJM 2008

## *Fempac trial*

**Inhibition of Restenosis in Femoropopliteal Arteries: Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial**

Michael Werk, Soenke Langner, Bianka Reinkensmeier, Hans-Frank Boettcher, Gunnar Tepe, Ulrich Dietz, Norbert Hosten, Bernd Hamm, Ulrich Speck and Jens Rieke



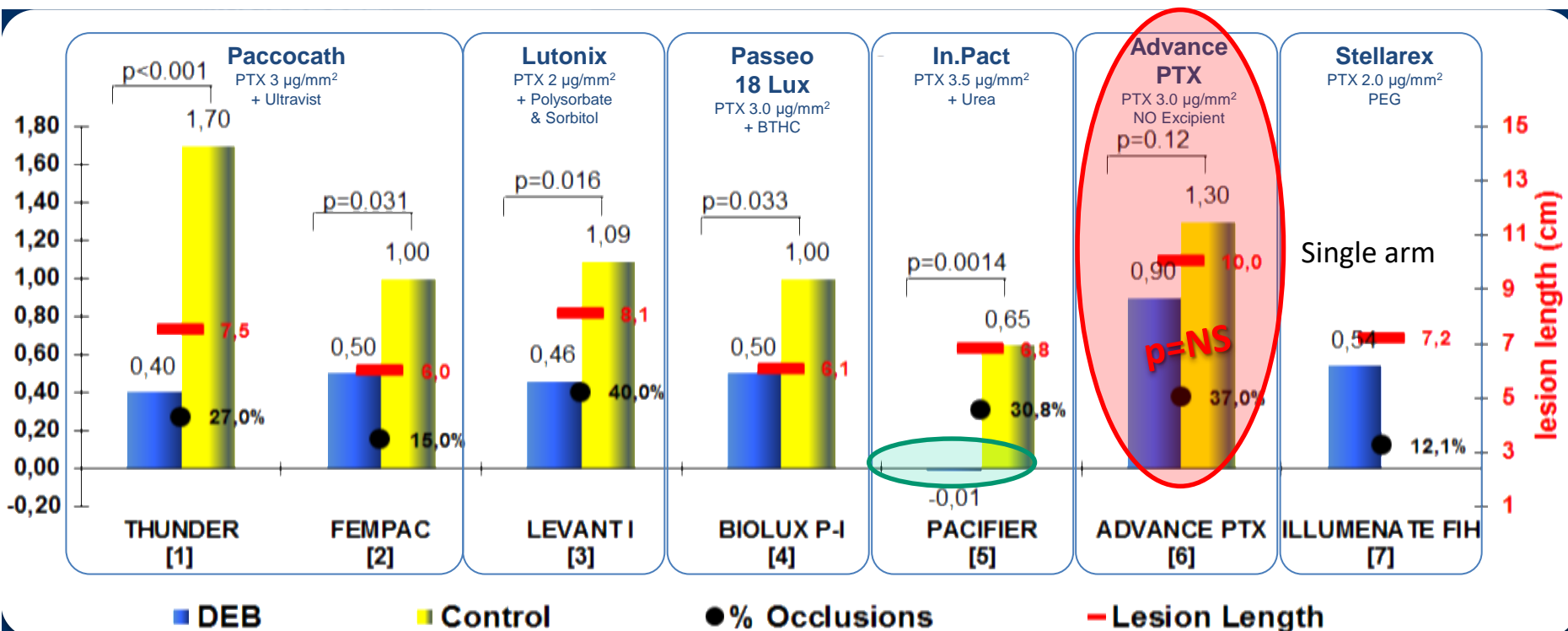
Freedom from TLR in SFA lesions

Werk Circulation 2008



# Early Short term results















## 7 Trials/ 6 DEB technologies – 6 Mo Late Lumen Loss (Primary Endpoint)



1 Tepe G et al. NEJM 2008  
 2 Werk M et al. Circulation 2008  
 3 Scheinert D et al. JACC 2014  
 4 Scheinert D et al JEVT 2015

5 Werk M et al Circ Cardiovasc Interv 2012  
 6 Scheinert D LINC 2013 oral presentation  
 7 Schroeder H Catheter Cardiovasc Interv 2015



Manufacturer	DCB	Drug	Dose ( $\mu\text{g}/\text{mm}^2$ )	Excipient
 Medtronic	IN.PACT	PTX	3.5	Urea
 BARD	LUTONIX	PTX	2.0	Polysorbate and Sorbitol
 Spectranetics®	STELLAREX	PTX	2.0	Polyethylene Glycol
 BIOTRONIK	PASSEO 18 LUX	PTX	3.0	Butyryl-tri-hexyl Citrate
 COOK	ADVANCE 18 PTX	PTX	3.0	none
 Aachen Resonance	ELUTAX	PTX	2.2	dextrane
 Eurocor	FREEWAY	PTX	3.0	shelloic acid
 CARDIONOVUM®	LEGFLOW	PTX	3.0	shelloic acid
 Boston Scientific	RANGER	PTX	2.0	citrate ester
 Vascular	LUMINOR	PTX	3.0	organic ester
 B BRAUN	SeQuent Please	PTX	3.0	Iopromide
 BIOSENSORS INTERNATIONAL	BIOPATH	PTX	3.0	Shellac
 acoXtec Scientific Co., Ltd	ORCHID	PTX	3,0	Magnesium stearate
 SurModics	SURVEIL	PTX	3,0	unknown

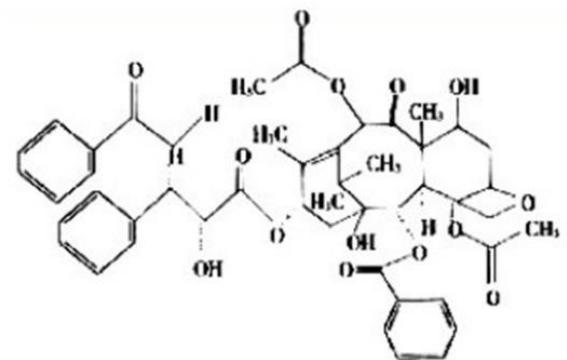
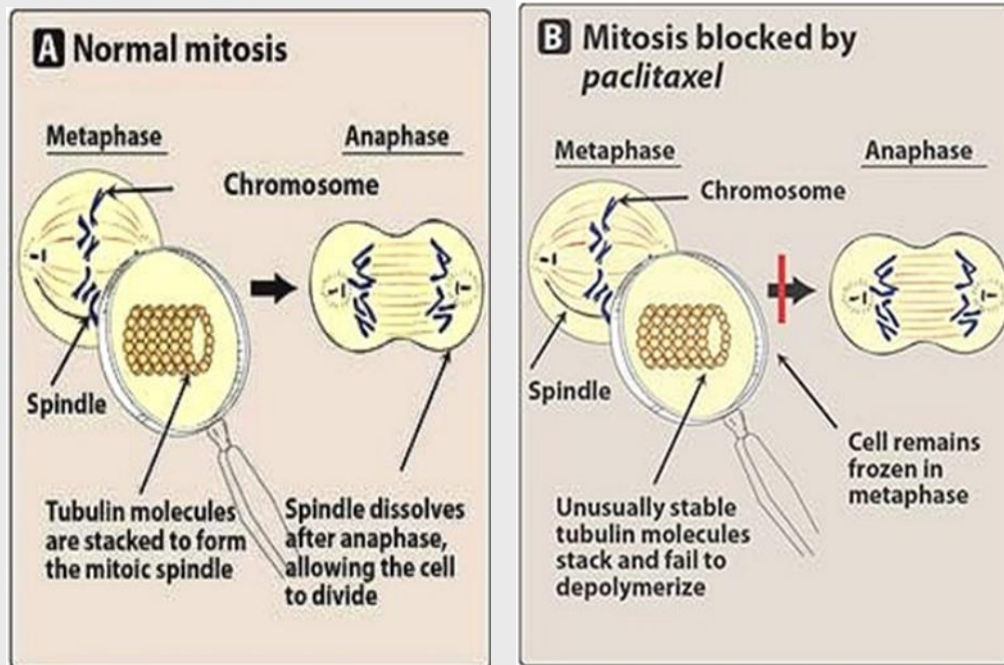




# Paclitaxel working mechanism

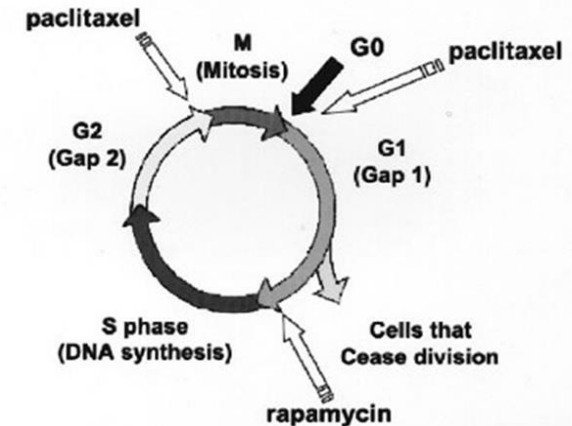
Affects function of microtubules

- Blocks cell division
- Leads to cell death



**Paclitaxel**

$C_{47}H_{51}NO_{14}$  853.92





# Differences in DCB

Manufacturer	DCB	Drug	Dose ( $\mu\text{g}/\text{mm}^2$ )	Excipient
Medtronic	IN.PACT	PTX	3.5	Urea
BARD	LUTONIX	PTX	2.0	Polysorbate and Sorbitol
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Vascular	LUMINOR	PTX	3.0	organic ester
B BRAUN	SEQUENT PLEASE	PTX	3.0	Iopromide
BIOSENSORS	BIOPATH	PTX	3.0	Shellac
aco tec	ORCHID	PTX	3.0	Magnesium stearate
SURMODICS	SURVEIL	PTX	2.0	unknown

Same drug (paclitaxel)

Different:

≠ Dose ( $2.0 - 3.5 \mu\text{g}/\text{mm}^2$ )

≠ Drug Formulation

≠ Excipient

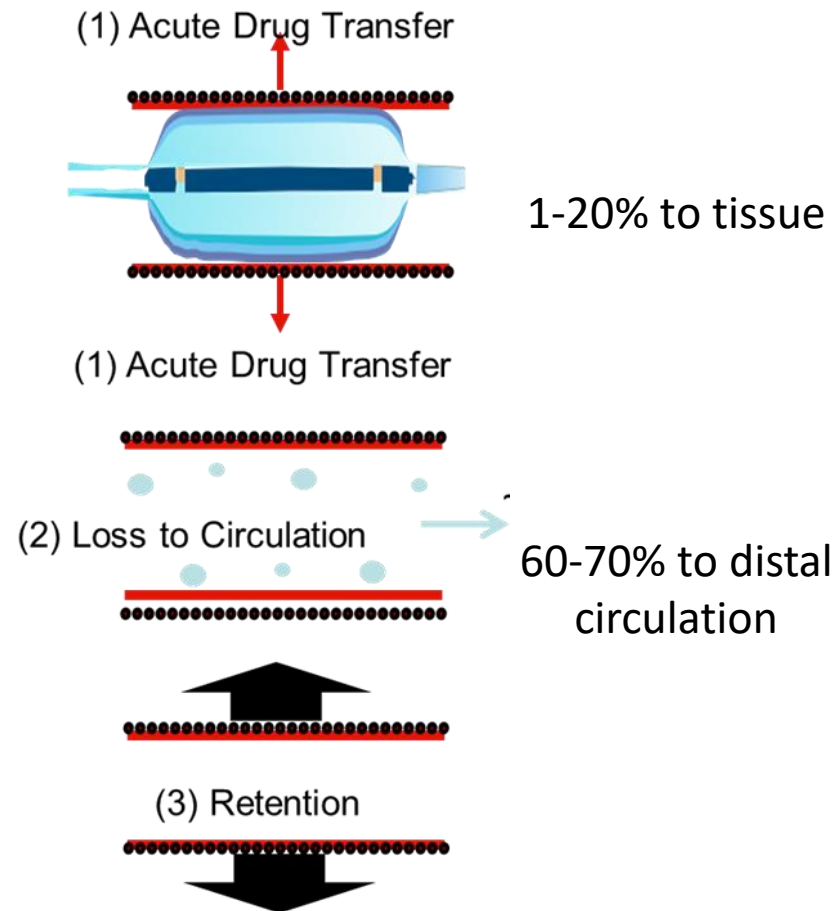
≠ Surface Energy

≠ Coating Method



# Determinants of DCB Biological Effect

- Antiproliferative agent (Paclitaxel)
  - Drug content on balloon surface
- Tissue transfer efficiency
  - Coating characteristics (i.e., hydrophobicity/hydrophilicity)
  - Excipient
  - Coating technique
- Loss to circulation (Insertion-transit-inflation) and risk of:
  - Particulate embolization
  - Systemic effects
- Paclitaxel tissue residency
  - Particle solubility
  - Presence in tissue during restenotic cascade<sup>7</sup> (duration of retention)
  - Homogeneity of distribution





# Architecture of DCB - Coating

## Drug-coated Balloon Coating Characteristics

**Polymer matrix coating:** drug molecules diffuse through a matrix

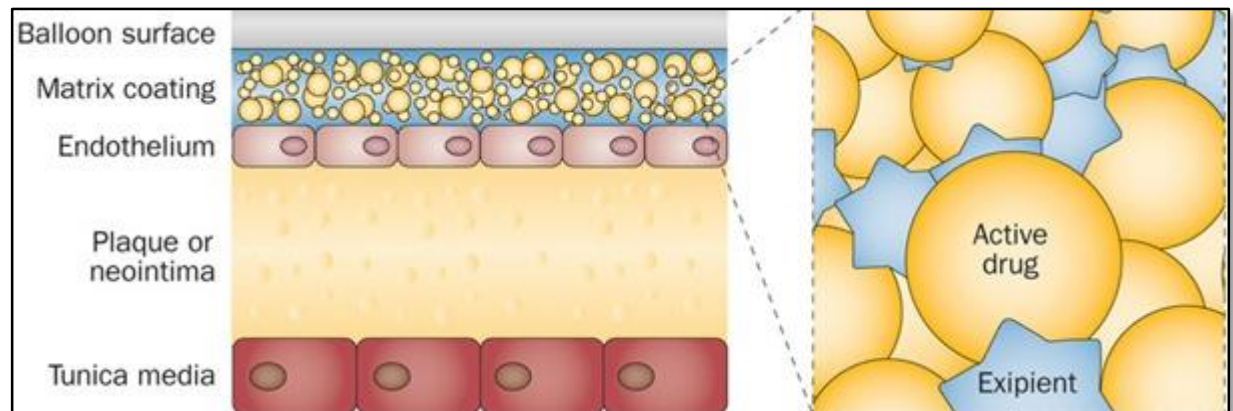
**Porous coating:** drug molecules diffuse through pores

**Resorbable polymer matrix coating:** drug molecules are encapsulated in the polymer and are released with resorption

**Surface deposition:** imprinting of the drug on the balloon surface

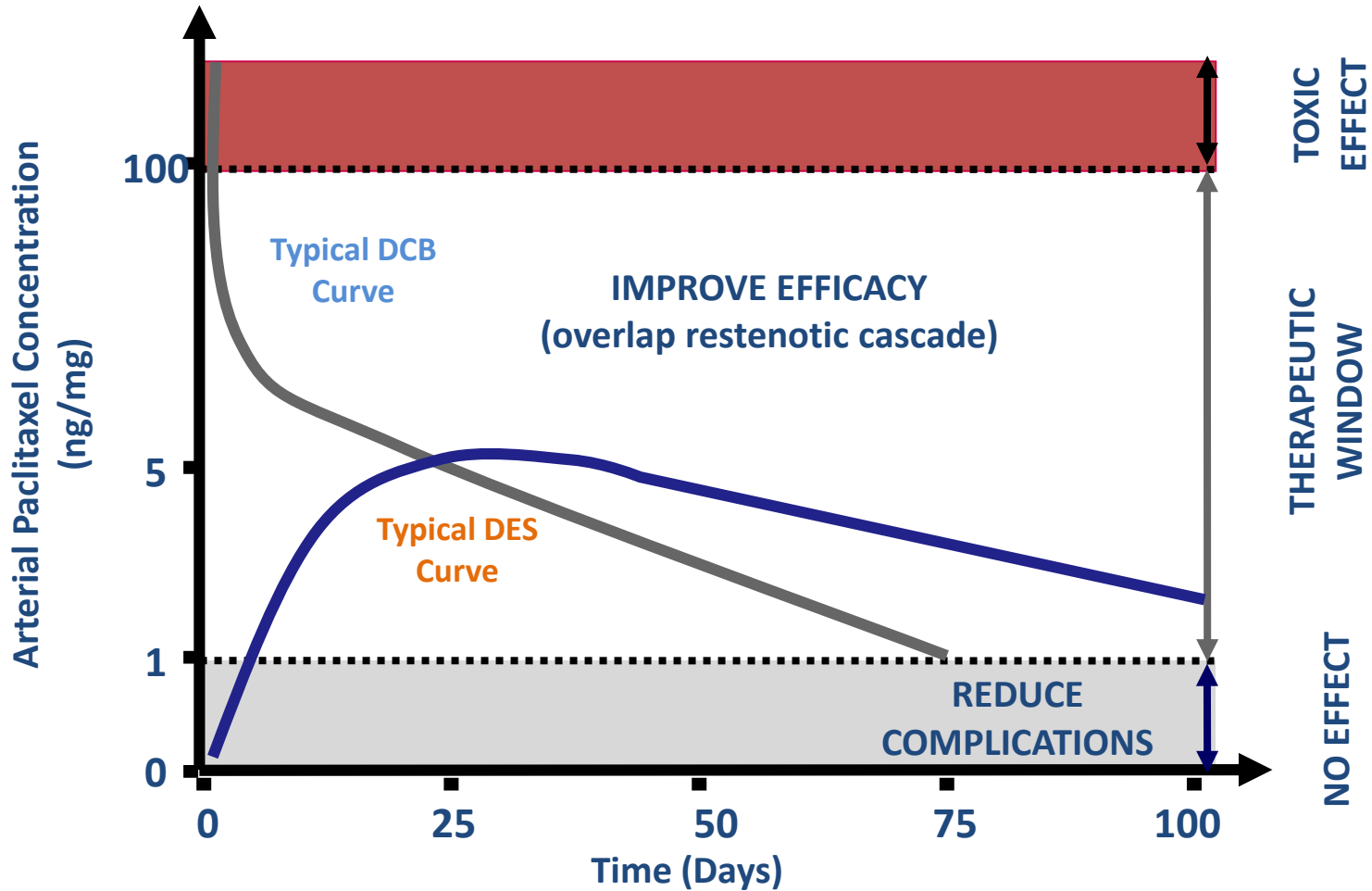
**Drug-balloon surface bonding:** strong enough to maintain drug integrity during transit while allowing efficient drug transfer:

- Minimal drug loss during transit
- Rapid and efficient drug transfer (<60 seconds)



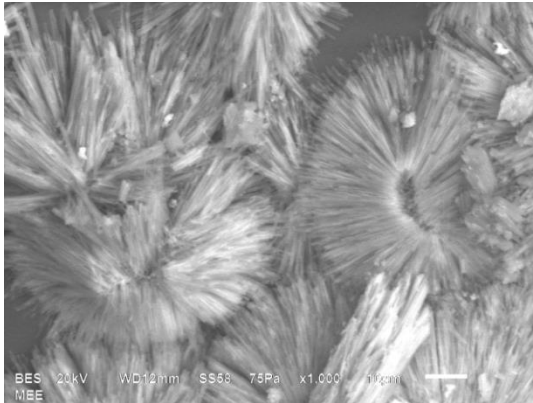


# Difference between DES - DCB

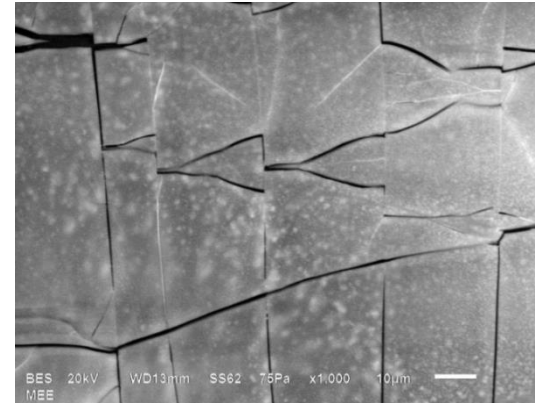


# Paclitaxel Formulation Types

## Impact on Biological Performance



**Crystalline Coating**

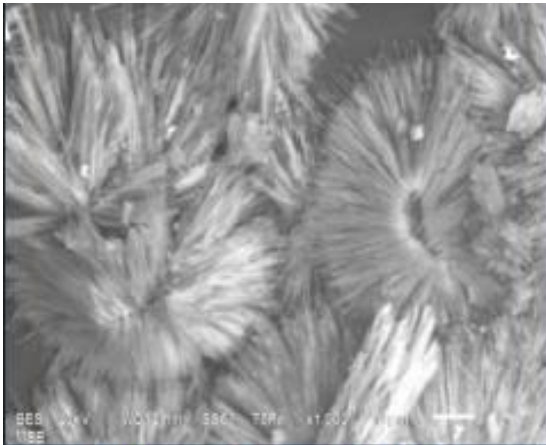


**Amorphous Coating**

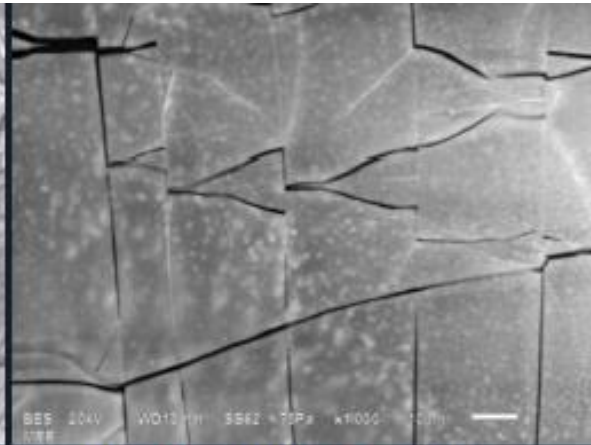
	<b>Crystalline</b>	Amorphous
Particles Released	+++	++
Uniform Coating	++	+++
Drug Transfer to Vessel	+++	+++
Drug Retention vs. Time	+++	+
Biological Effectiveness	+++	++
Vascular Toxicity	+++	++



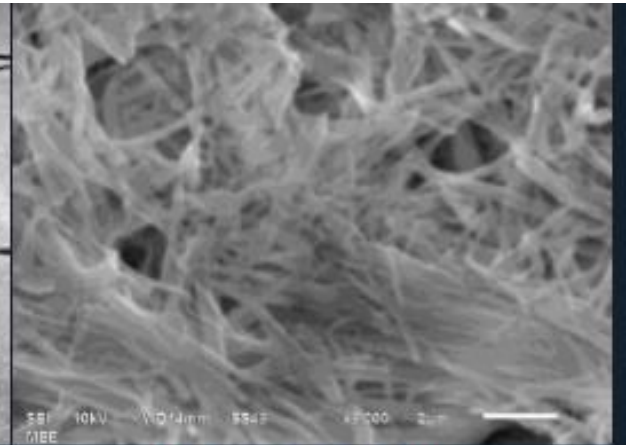
# Coating techniques - evolution



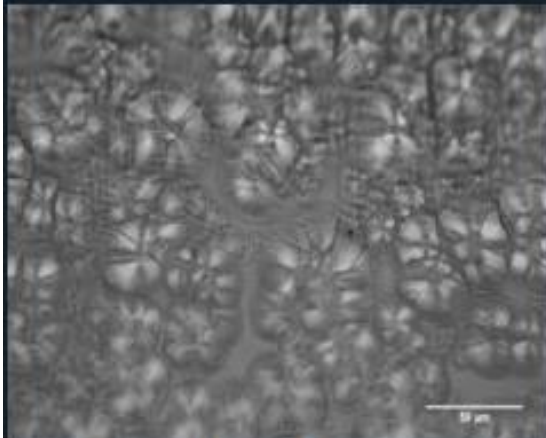
**Macro-Crystalline**



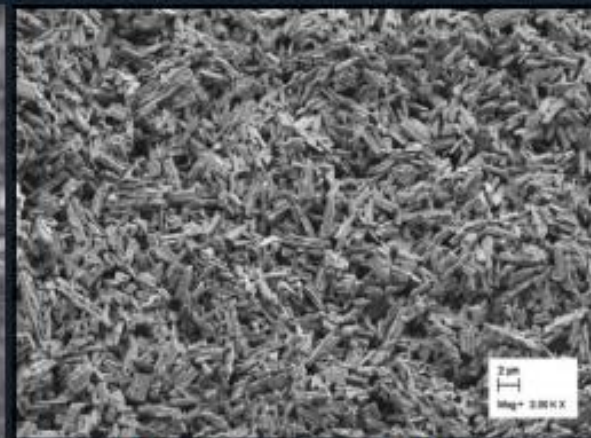
**Amorphous Coating**



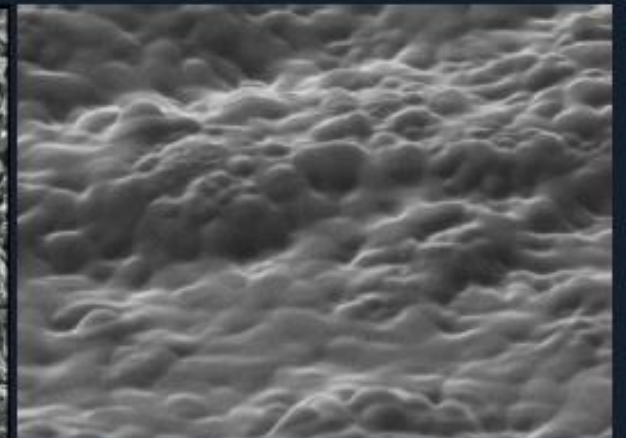
**Hybrid Coating**



**Crystalline Aggregate**



**Micro-Crystalline**



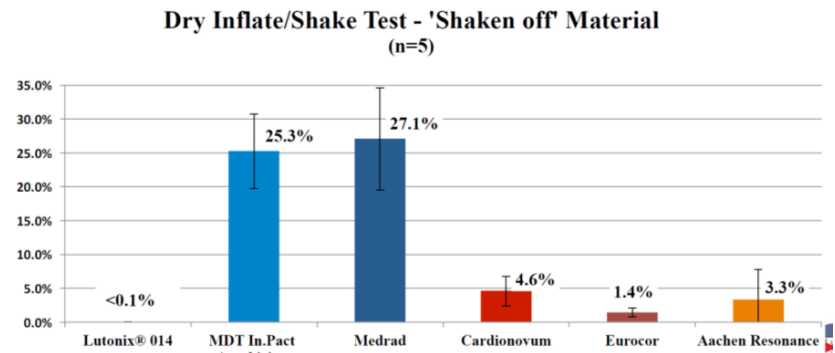
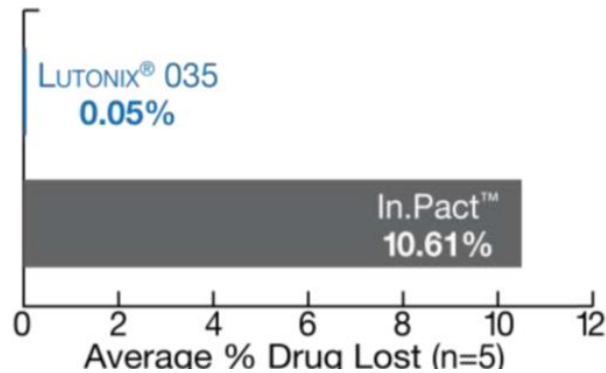
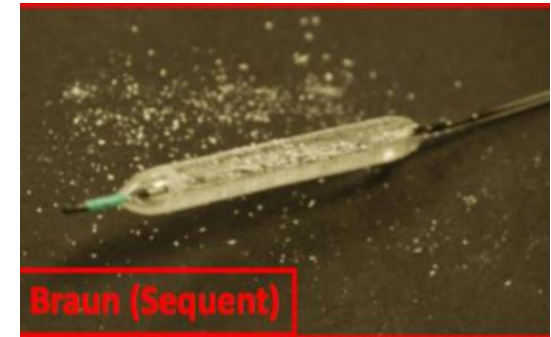
**Nano-Encapsulation**





# Coating integrity

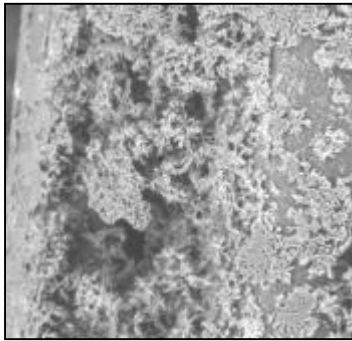
## Simulated shake test



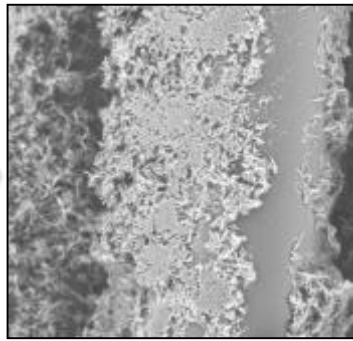


# Coating Integrity: Adherence During Hydration

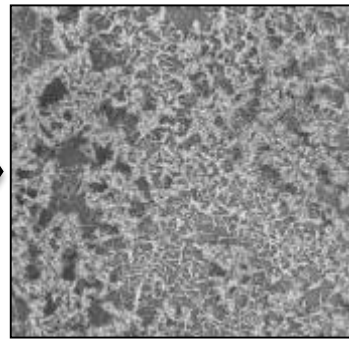
**Balloon A  
Coating  
Hydrophobic  
carrier**



**T = 0 min**



**3 min**

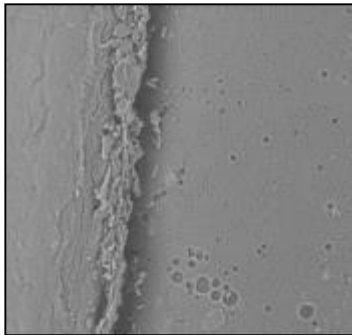


**10 min**

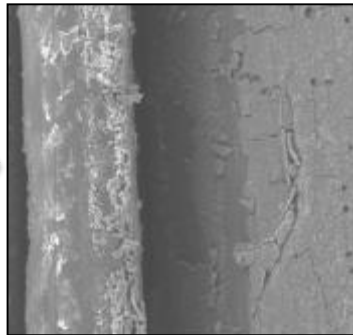


**Coating remained adhered to the balloon during hydration**

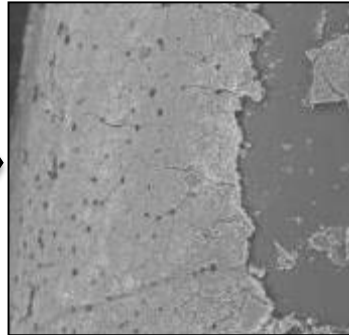
**Balloon B  
Coating  
Hydrophilic  
carrier**



**T = 0 min**



**3 min**



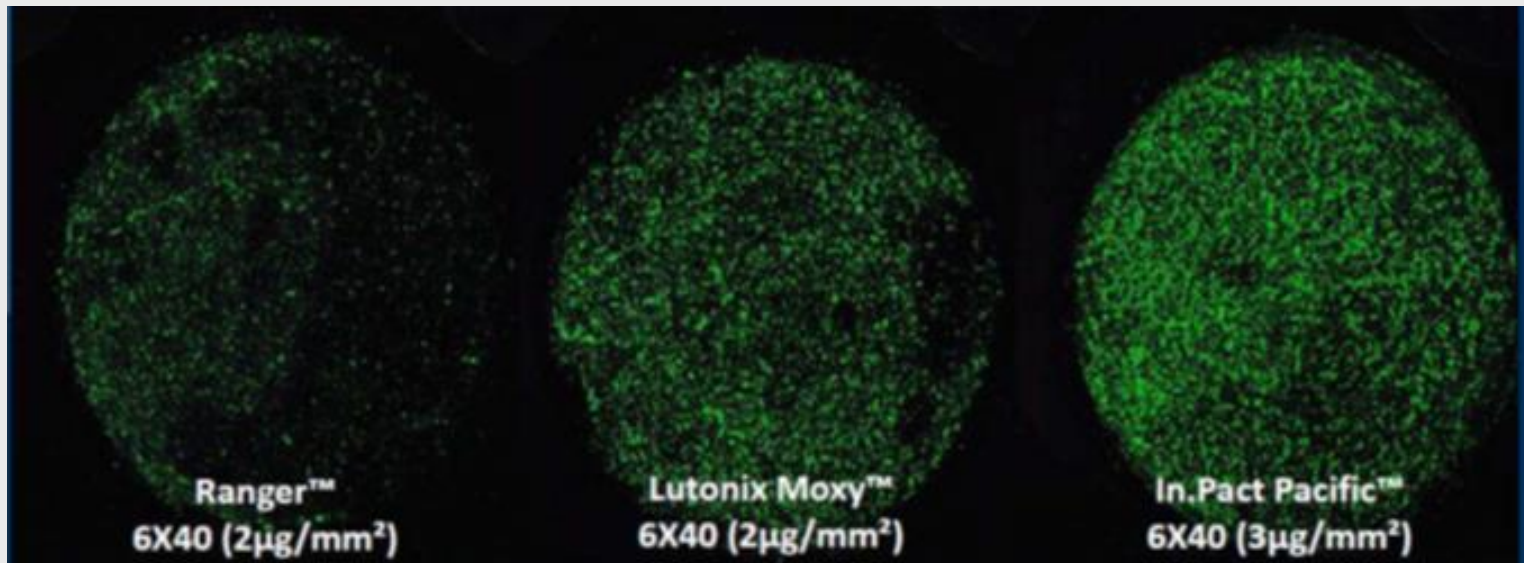
**10 min**



**Coating started to crack and flake off after a few minutes of hydration**



# Loss of particles during transfer



- DCBs were delivered in a peripheral track model with fluid recirculation
- Particulates lost downstream were collected with a 5 µm polycarbonate filter and are shown as green dots





# Vascular changes in downstream skeletal muscle arteries

No difference after 1 inflation; Difference after 3 inflations

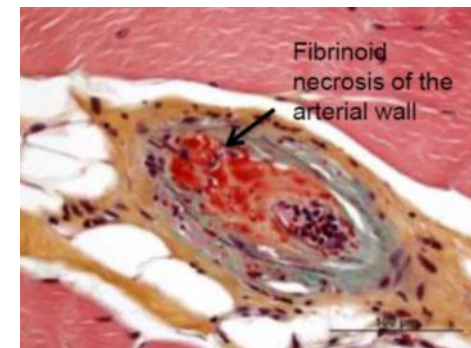
Lutonix 3x at 90 days

No.	No. of sections (Downstream muscle/coronary band)	Vascular Changes	Skeletal Muscle Necrosis/Fibrosis	Crystalline material
1	14 (12/2)	1	0	0
2	14 (12/2)	0	0	0
3	14 (12/2)	4	0	0
4	14 (12/2)	0	0	0
<b>Total</b>	<b>56</b>	<b>5/56</b>	<b>0</b>	<b>0</b>



In.Pact 3x at 90 days

No.	No. of sections (Downstream muscle/coronary band)	Vascular Changes	Skeletal Muscle Necrosis/Fibrosis	Crystalline material
1	13 (12/1)	6	0	0
2	13 (12/1)	5	1	0
3	13 (12/1)	7	2	1
4	13 (12/1)	8	2	1
5	13 (12/1)	8	3	1
6	13 (12/1)	4	1	1
<b>Total</b>	<b>78</b>	<b>38</b>	<b>9</b>	<b>4</b>



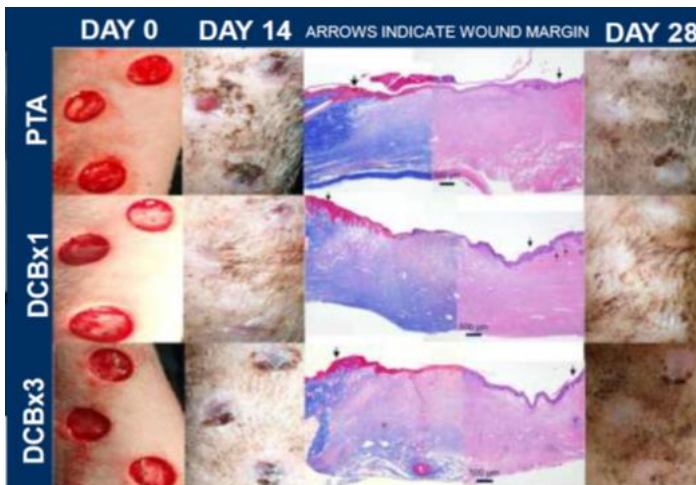
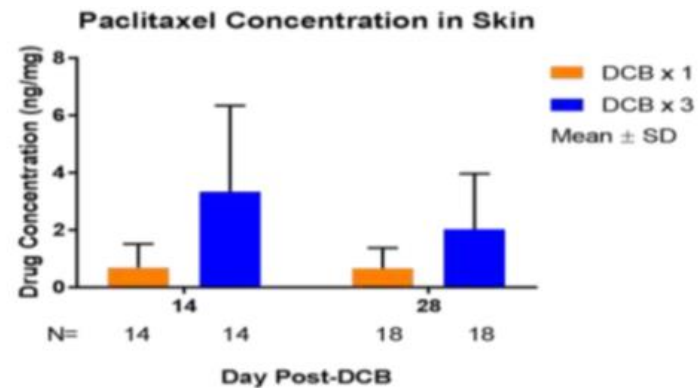




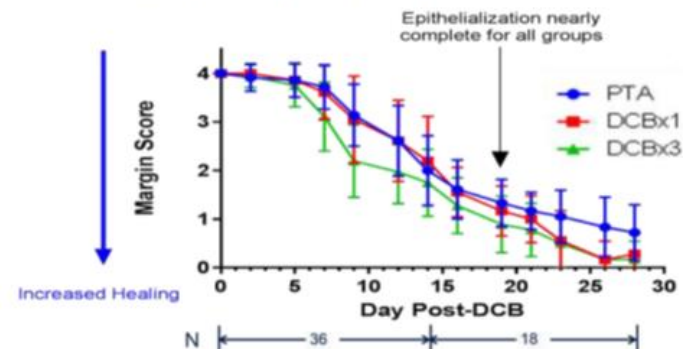
# Effect of embolisation on wound healing



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



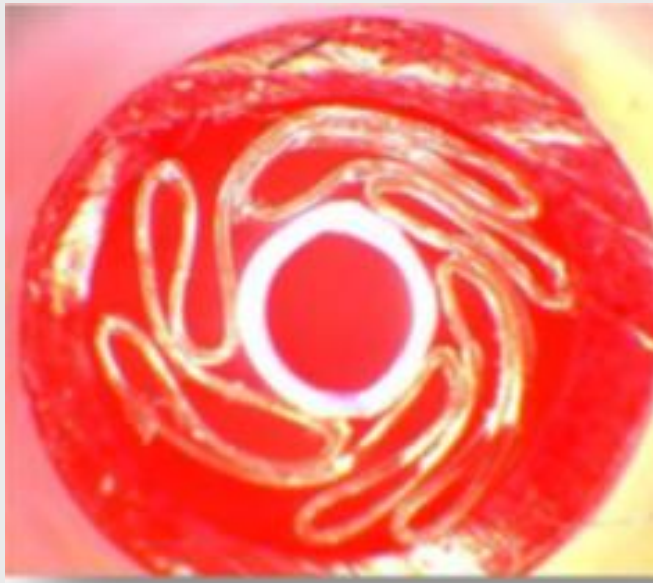
## Hollander Scoring-Margin Separation



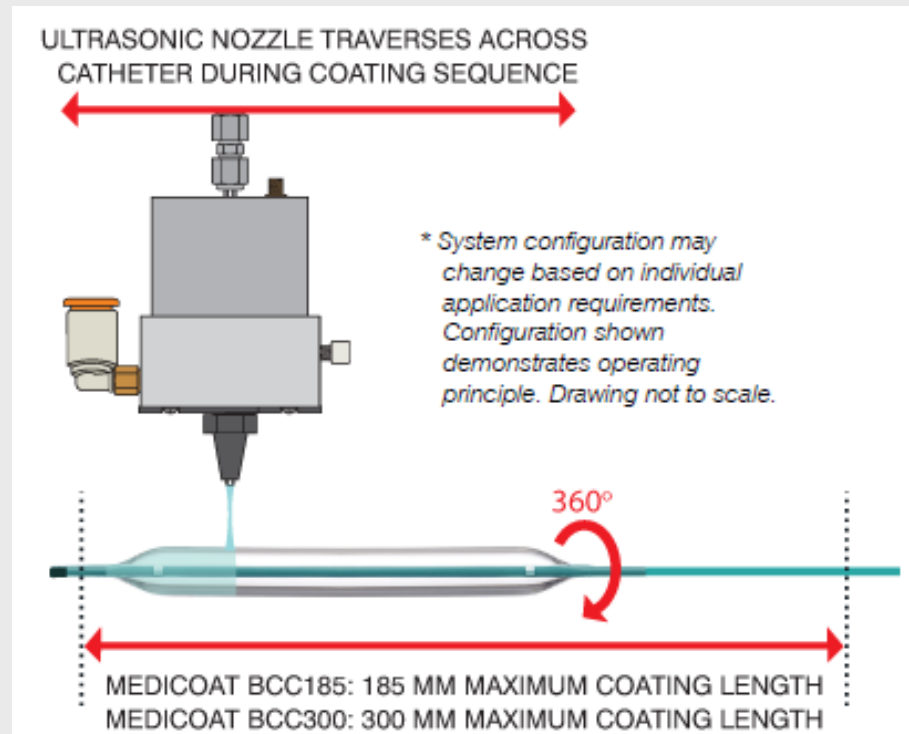


# Coating technique

Goal: homogenous stable distribution of drug



**On (semi-)inflated balloon**



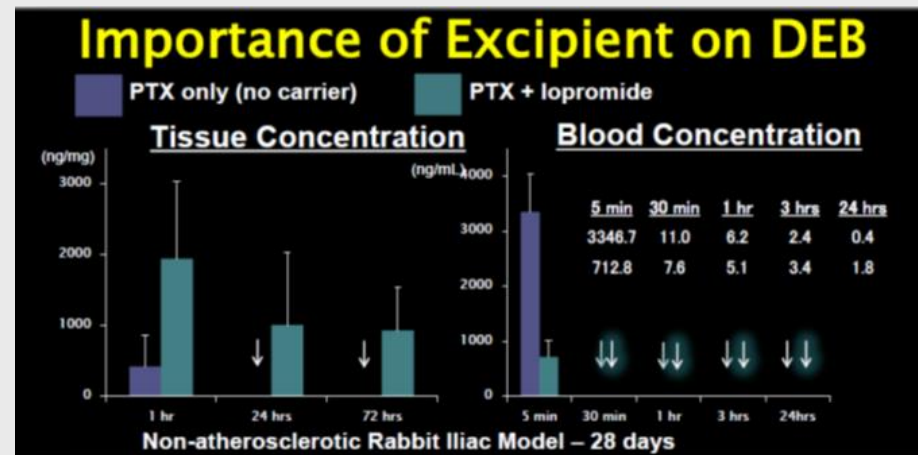
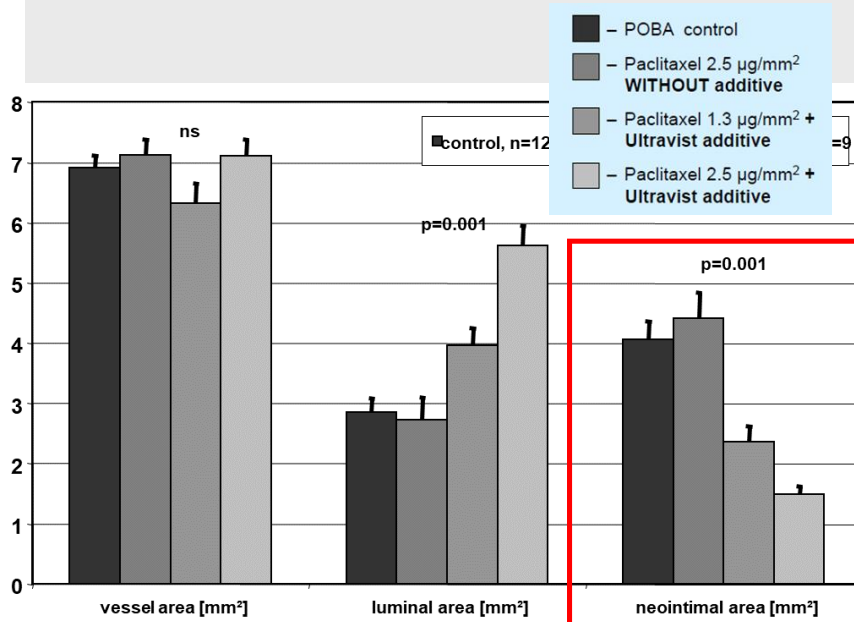
**Uniform longitudinal and circumferential coating**



# Excipient

## Supports the uptake of drug by vessel tissue

- Acts as a molecular spacer to increase paclitaxel surface exposure
- Facilitates paclitaxel transfer through its hydrophylic properties



R. Virmani – CIRSE 2012 Oral Presentation

## DCB- porcine restenosis study

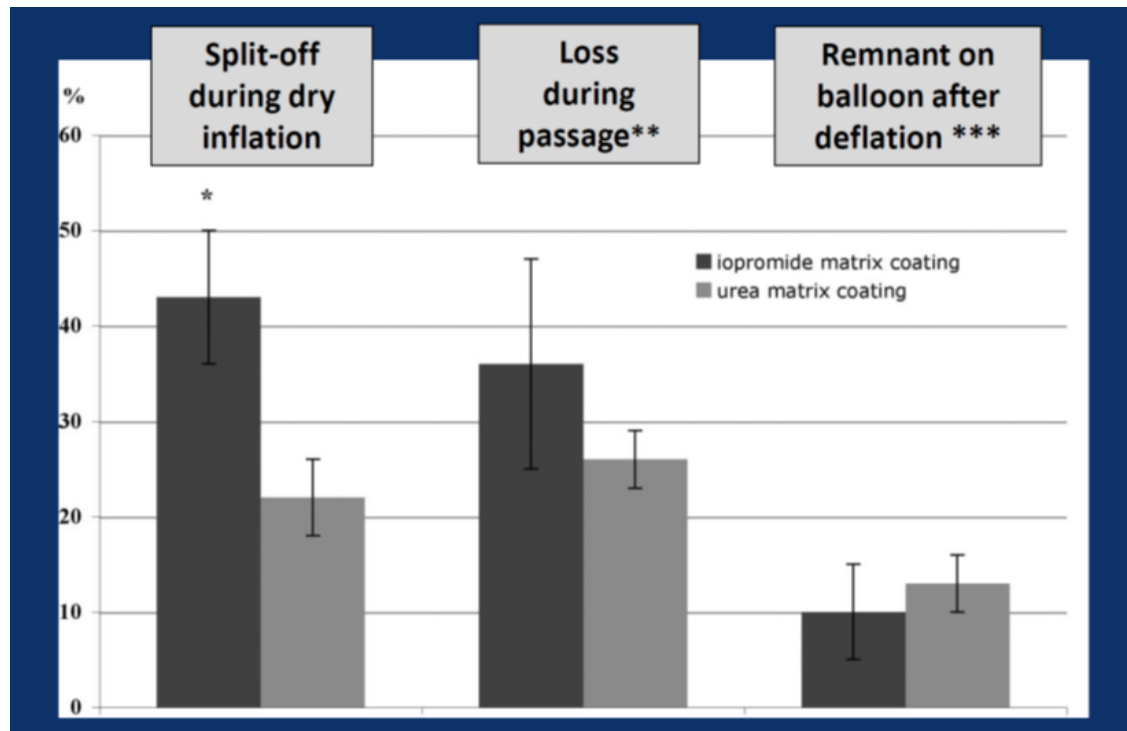
Scheller et al. Circulation 2004;110:810 - 4

## Excipient facilitates tissue transfer



# Different excipients – different properties

## PTX adherence to balloon Iopromide versus urea coating



\*  $p=0.002$

\*\* through a blood-filled hemostatic valve and guiding catheter and 1min in stirred blood

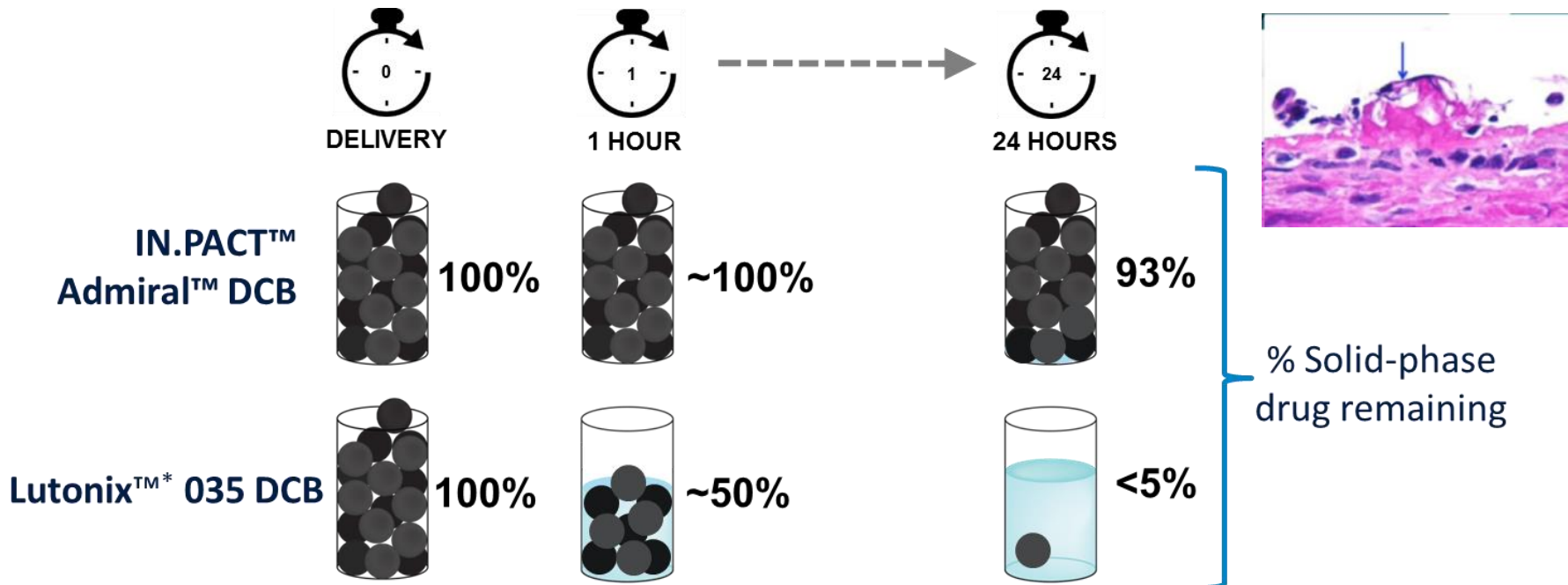
\*\*\* not released during expansion in a coronary artery *Kelsch et al. Invest Radiol. 2011;46:25*





# What happens in vessel wall?

- Transfer of paclitaxel into the tissue and “storage” in the tissue occurs in the “solid phase”.
- Afterwards “solid phase” paclitaxel is slowly dissolved.
- Transition from solid-phase to soluble-phase occurs at different rates
- Crystalline PTX is better retained in the vessels wall than amorphous PTX.





# Sustained Drug Availability

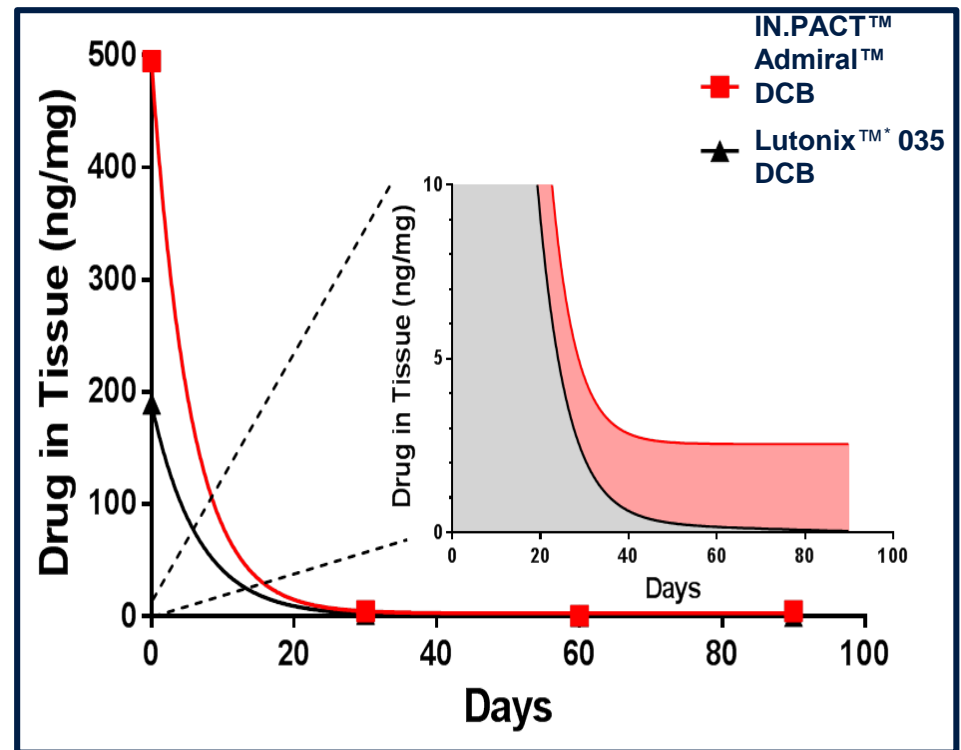
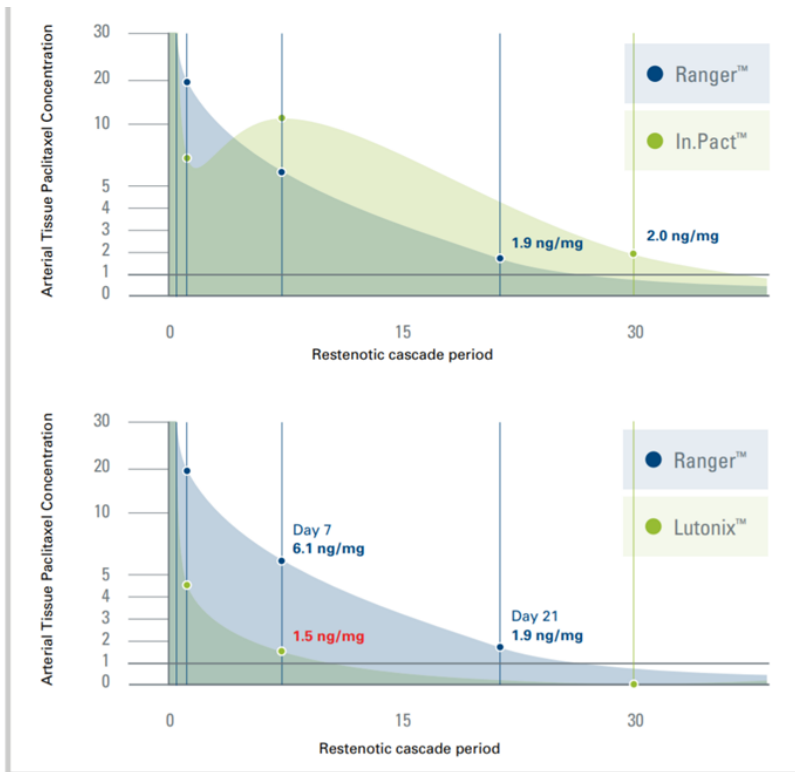






Figure 2. Arterial tissue paclitaxel concentrations over time of Ranger, In.Pact Pacific, and Lutonix.

1. Data on file with Medtronic; Study PS747.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016
3. EVToday Vol 2 no 6



# Peripheral Drug-Coated Balloons

	IN.PACT Admiral Medtronic	Lutonix™ Bard	Stellarex™ Spectranetics	Ranger™ Boston Scientific
Product Image				
Paclitaxel Dose	3 µg/mm <sup>2</sup>	2 µg/mm <sup>2</sup>	2 µg/mm <sup>2</sup>	2 µg/mm <sup>2</sup>
Coating Technology	FreePac™ hydrophilic coating (excipient: urea)	Proprietary hydrophilic nonpolymeric carrier	EnduraCoat™ coating (excipient: Poly-ethylene Glycol)	TransPax coating (excipient: Citrate ester)
Guidewire Compatibility	0.035 OTW	0.035 OTW	0.035 OTW	0.14/0.18
Matrix	SFA: 4-7 mm; 40-120 mm BTK: Recalled	SFA: 4-6 mm; 40-100 mm	SFA: 4-6 mm; 40-120 mm	SFA: 4-8 mm; 30-200 mm BTK: 2-4 mm; up to 150 mm
CE Mark	✓	✓	✓	✓
FDA Approval	✓	✓	✓	



## Conclusion

- DCB is a technology which was rapidly accepted by the medical community thanks to its efficacy in the SFA.
- DCB's are complex devices with different components: drug, drug delivery system, coating, etc. The drug delivery system is available in different forms: drug delivery system on surface, drug delivery system in drug delivery system, etc.
- Although the drug delivery system is the same treatment effect the proper use of the drug delivery system and this will also affect the results.

**DCB's are NOT all the same**