Drug-Coated Balloon Technologies I: Technical Considerations and Controversies

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Disclosure Statement of Financial Interest

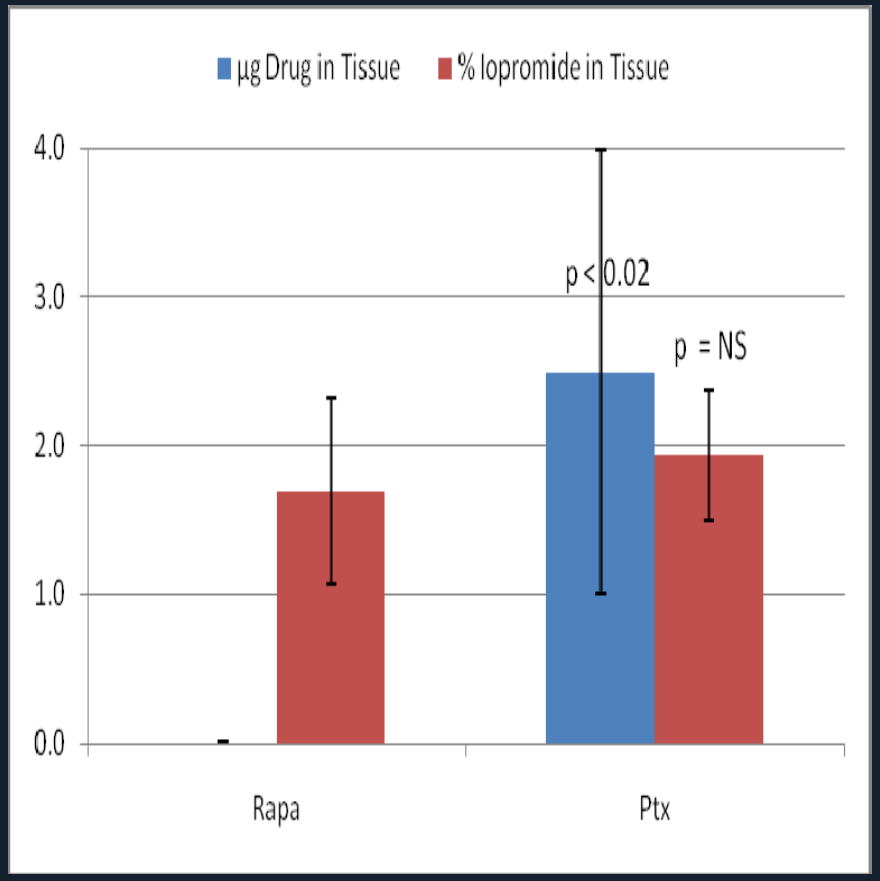
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• BSCI, Abbott, Medrad, Caliber
• Consulting Fees/Honoraria	• Medrad
• Major Stock Shareholder/Equity	• VNT
• Royalty Income	
• Ownership/Founder	
• Intellectual Property Rights	
• Other Financial Benefit	

Mechanism of Drug Delivery and Restenosis Prevention

Can a drug delivered locally, only one time and without a controlled delivery system achieve long-term biological efficacy?

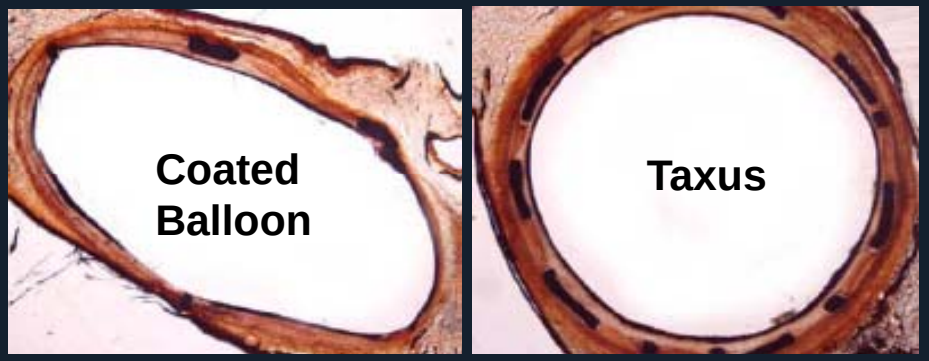
Mechanism of Drug Delivery and Restenosis Prevention



"Hydrophilic Carriers Increase Paclitaxel Transfer"

Effect of Carrier on Paclitaxel Transfer

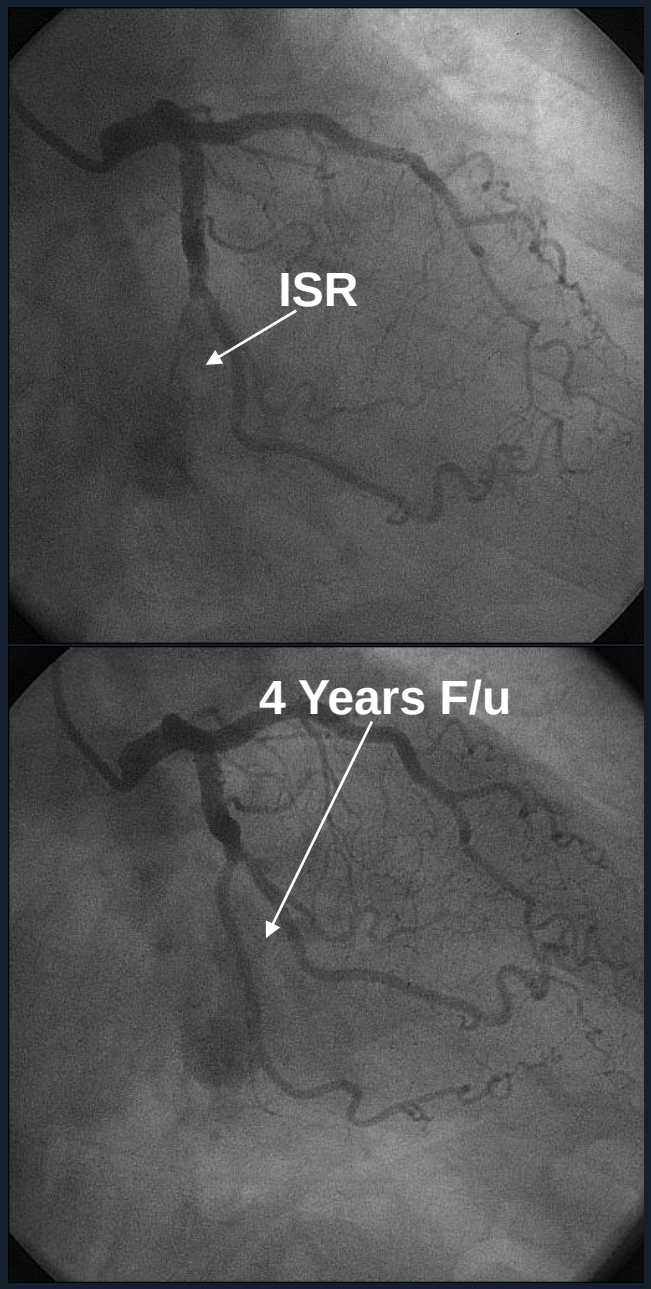
Cremers B. Thromb Haemost. 2009 Jan;101(1):201-6



Long Term Healing

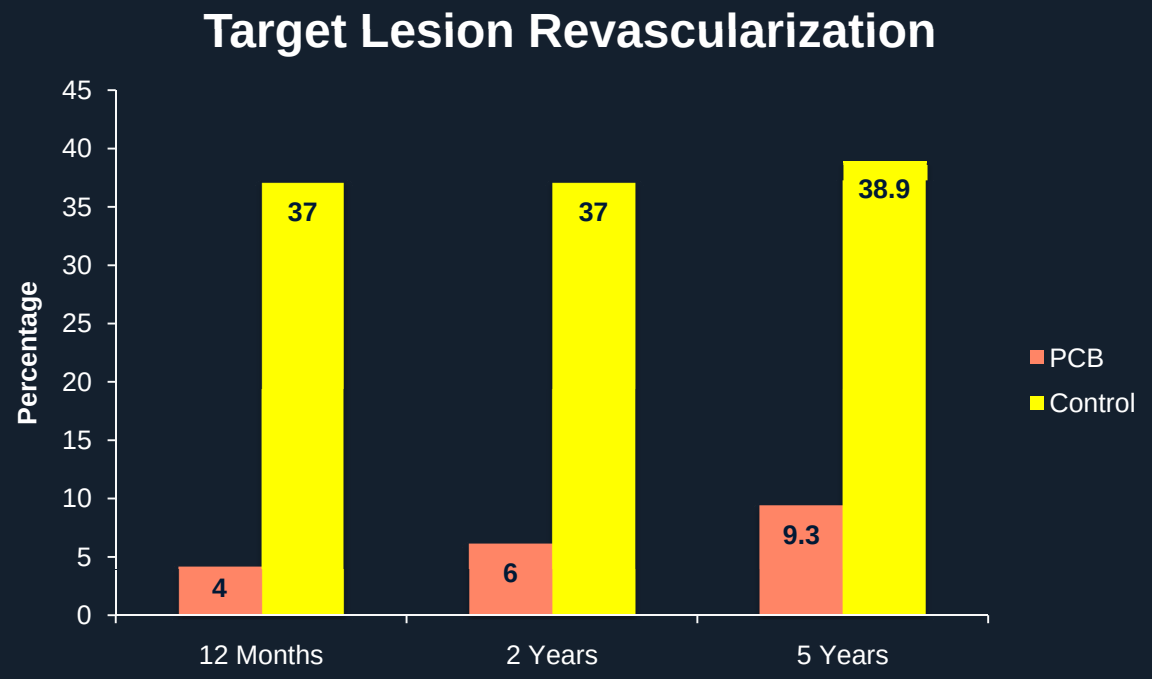
Cremers B. Cath Cardiov Int. April 2012

PACCOCATH ISR– F/U 5 Years Follow Up

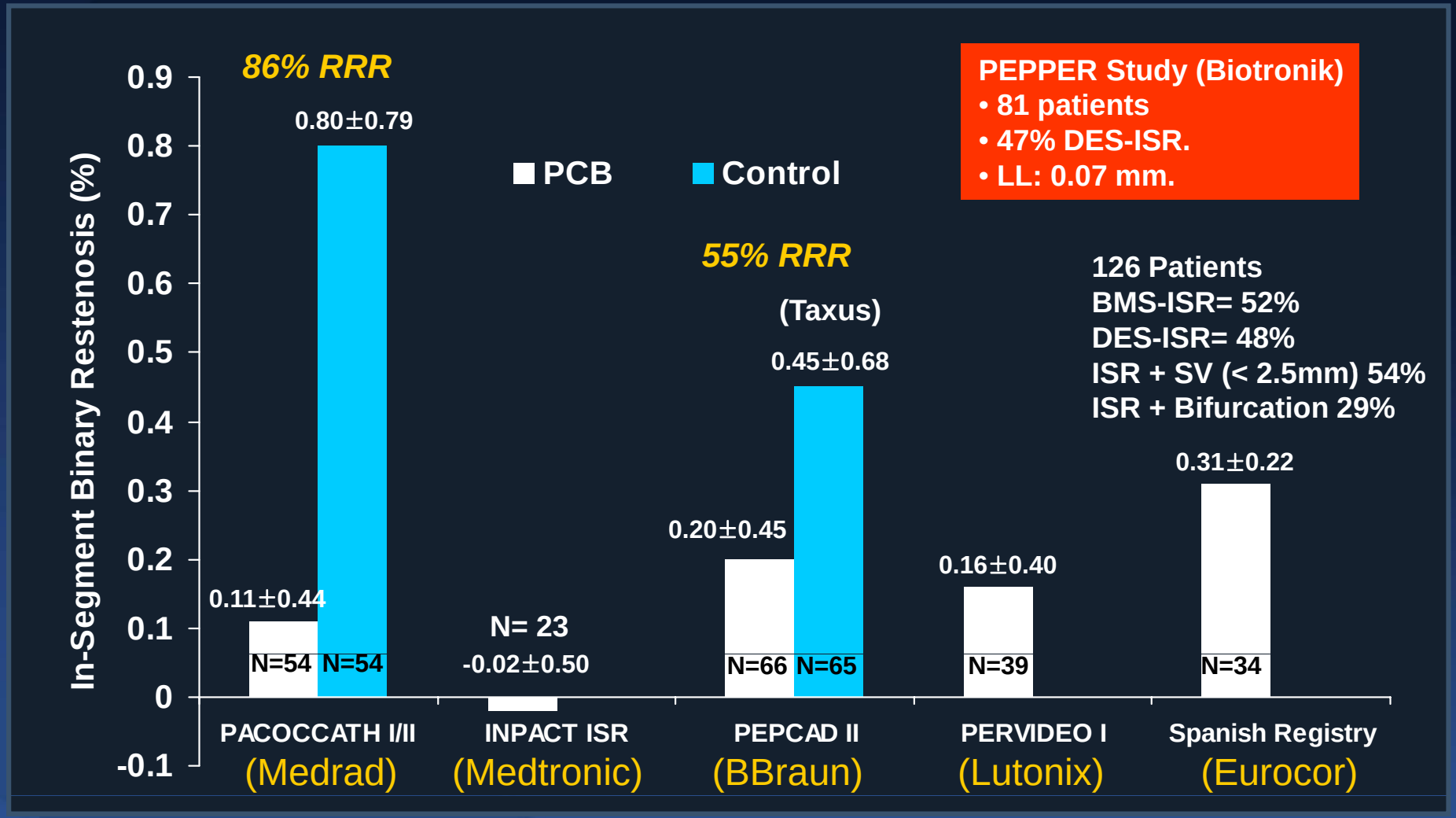


Long-Term Follow-Up After Treatment of Coronary In-Stent Restenosis With a Paclitaxel-Coated Balloon Catheter

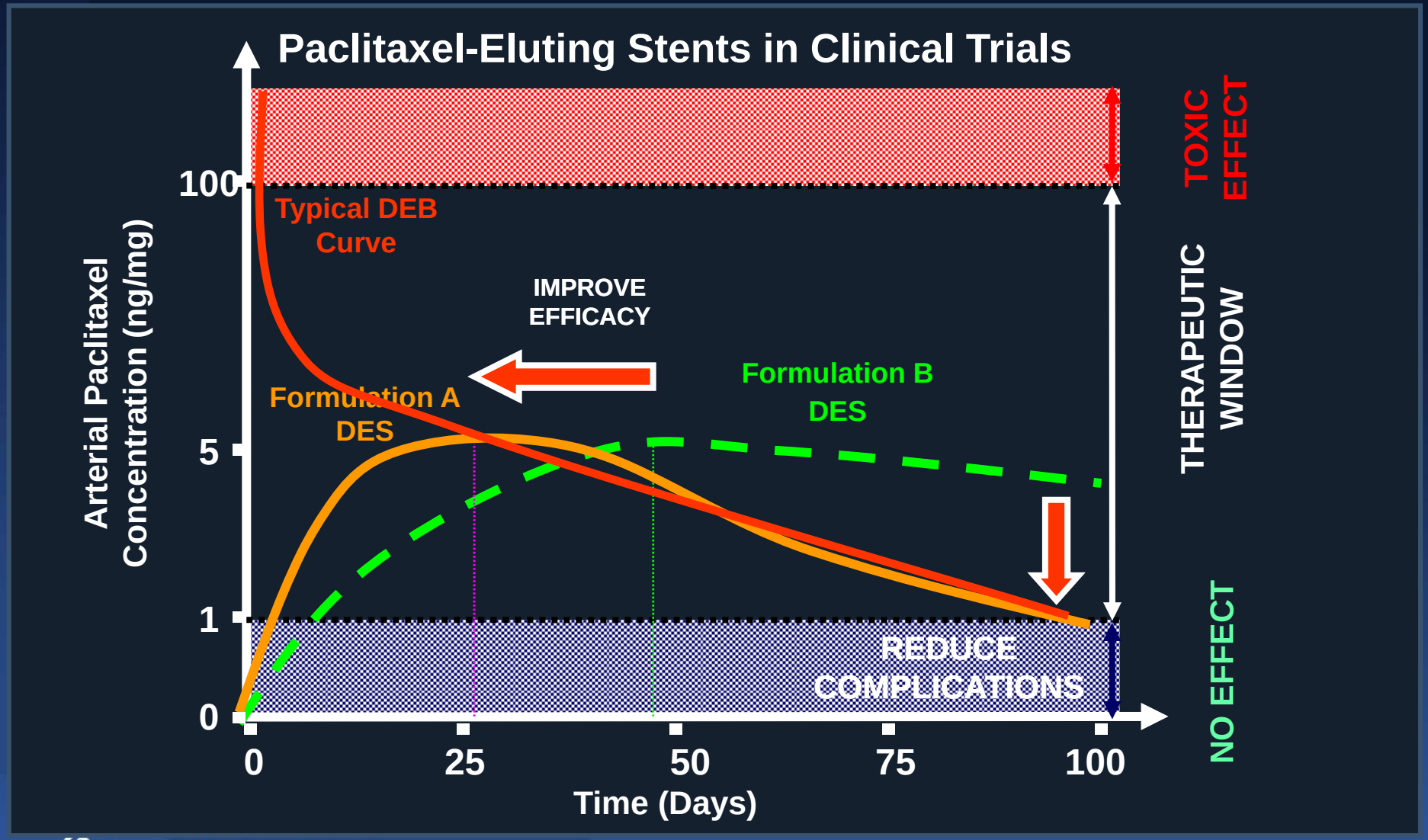
Scheller B, JACC Intv 2012;5:323-30



PCB Efficacy in BMS-ISR is Reproducible in FIH Clinical Trials



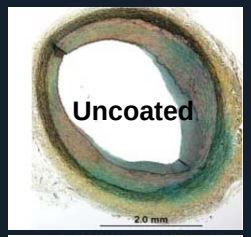
Impact of Drug Retention (PK) on Vascular Toxicity and Efficacy

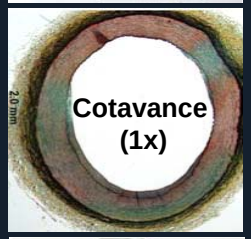


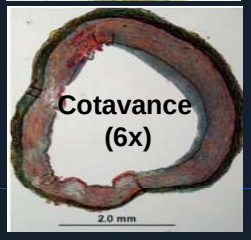
Local Tissue Effects (Safety)

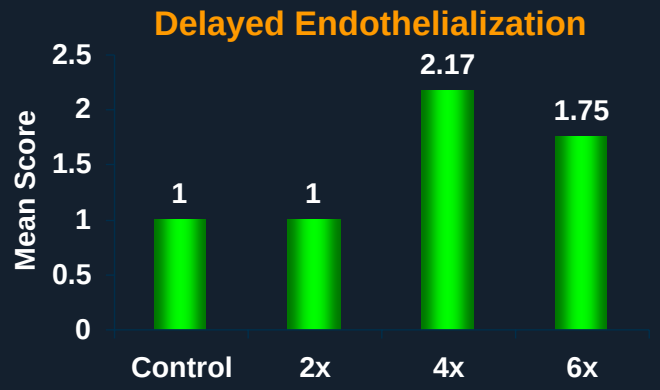
Vascular Healing According to Dose

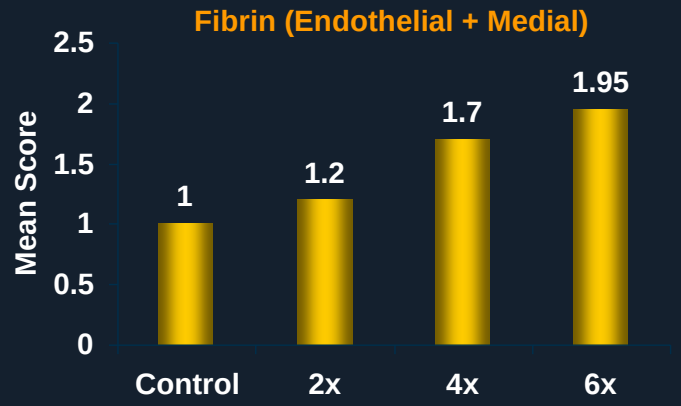
1= Minimal
2= Slight
3= Moderate
4= Marked
5= Massive

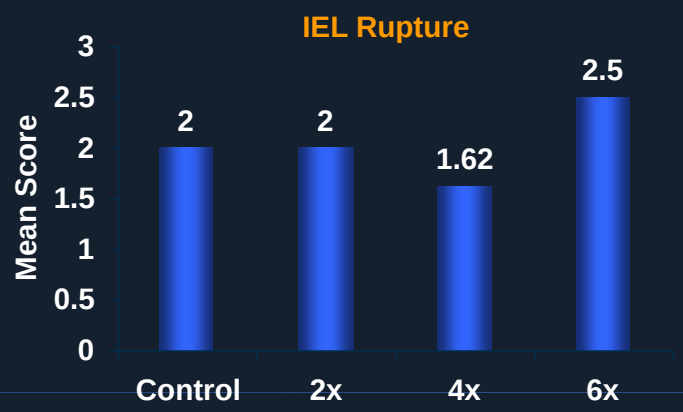


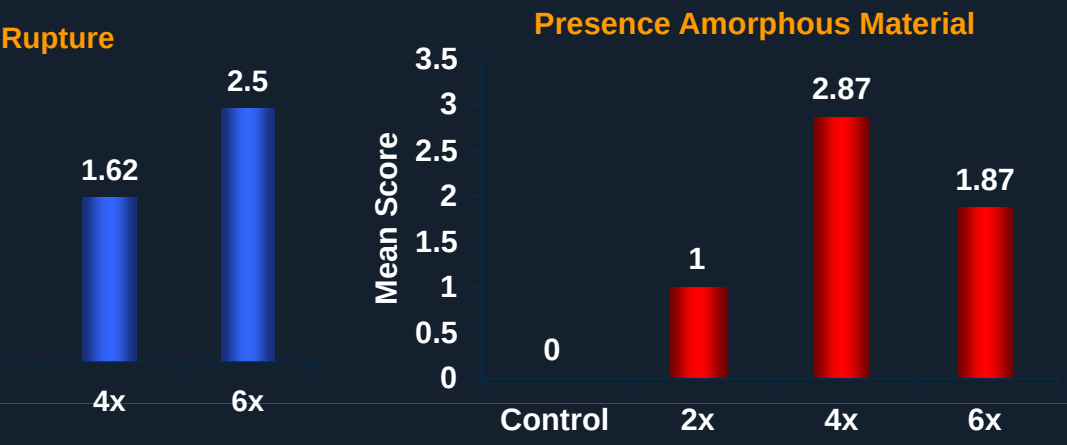












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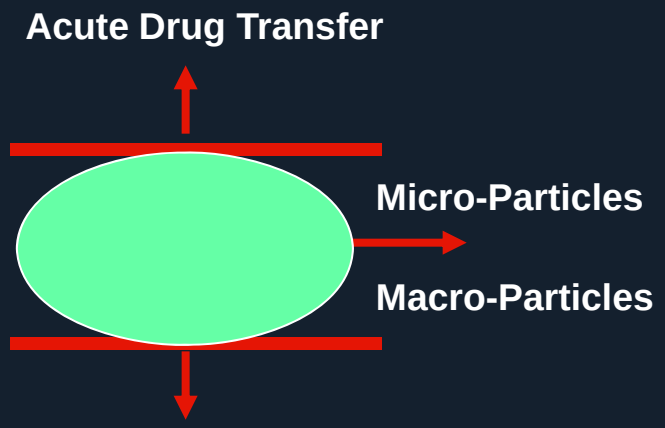
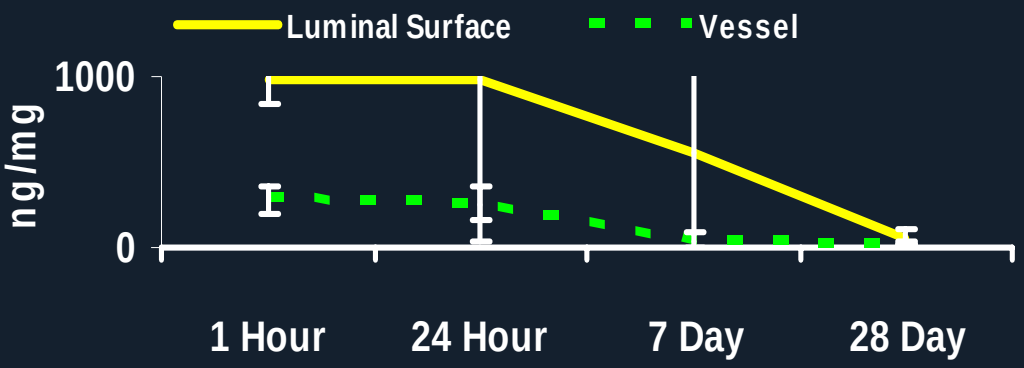
Histology picture obtained from CVPath

Mechanism of Action of DCB: Impact on Drug Retention and Embolization

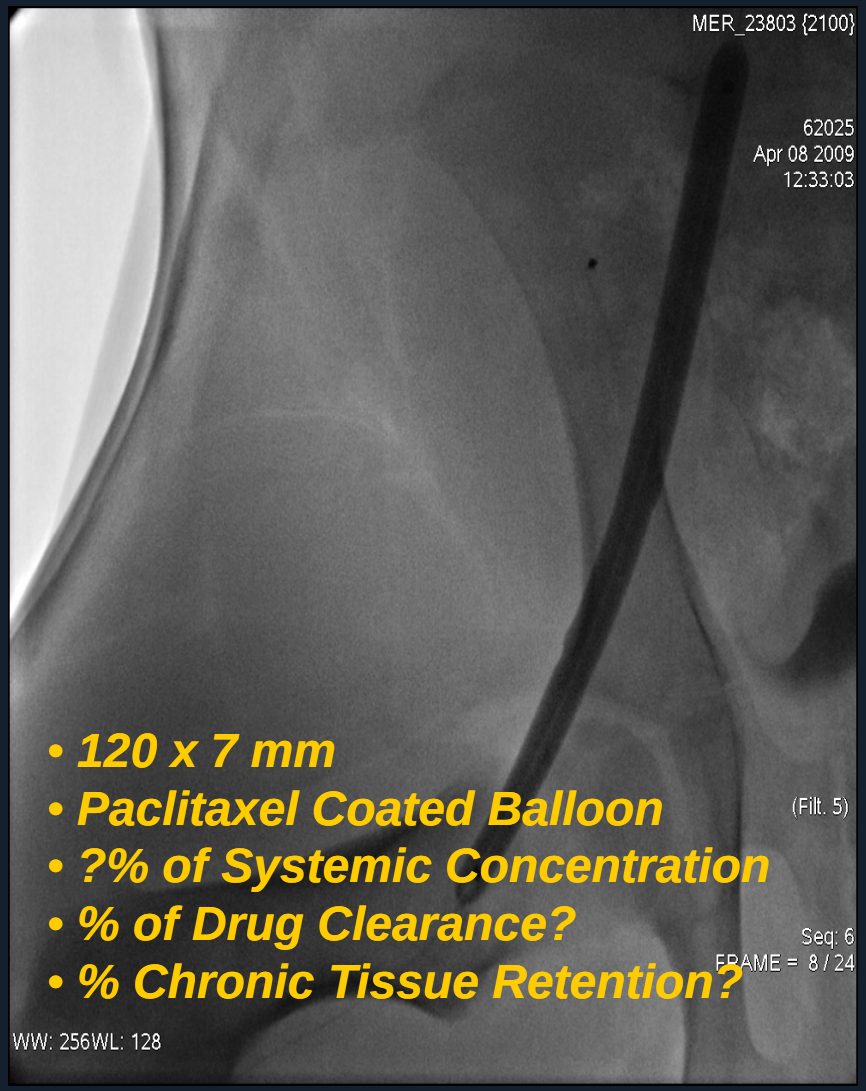


Tissue Transfer*	Distal Circulation*
~1 to 10%	~60 to 70%

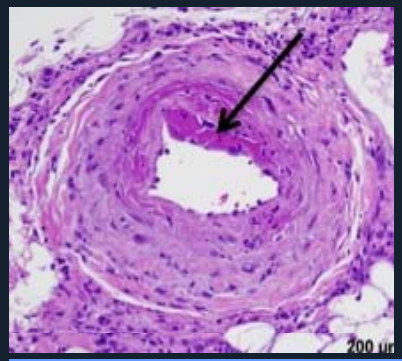


- Most of Paclitaxel remains on the vessel surface
- This "drug-reservoir" creates a gradient and serves as the source for sustained drug delivery
- Once the drug is transferred to the media of the vessel, tissue clearance depends on well described PK curves

Distal Washout of Paclitaxel Coating



- *120 x 7 mm*
- *Paclitaxel Coated Balloon*
- *?% of Systemic Concentration*
- *% of Drug Clearance?*
- *% Chronic Tissue Retention?*

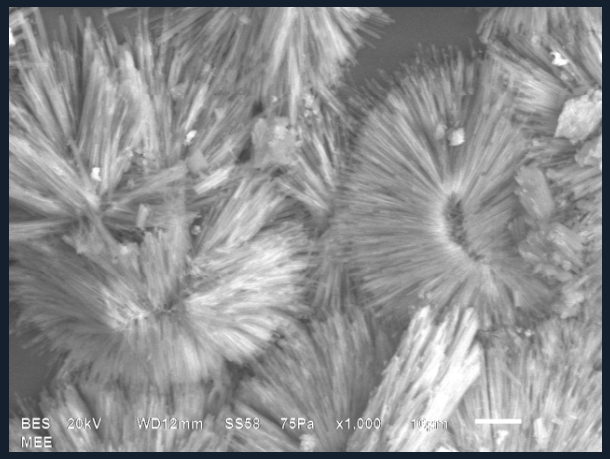


Distal Tissue Effect (Embolization)

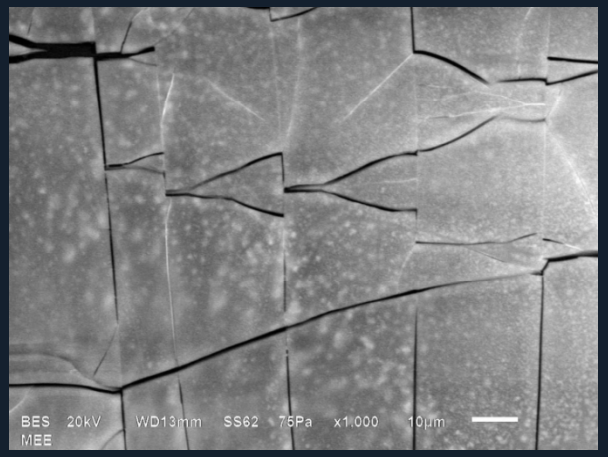
- **Acute Ischemic Events (CLI)**
- **Chronic Tissue Effects**
- **Other Organs Toxicity**

Paclitaxel Formulation Types

Impact on Biological Performance



Coating "A" Crystalline

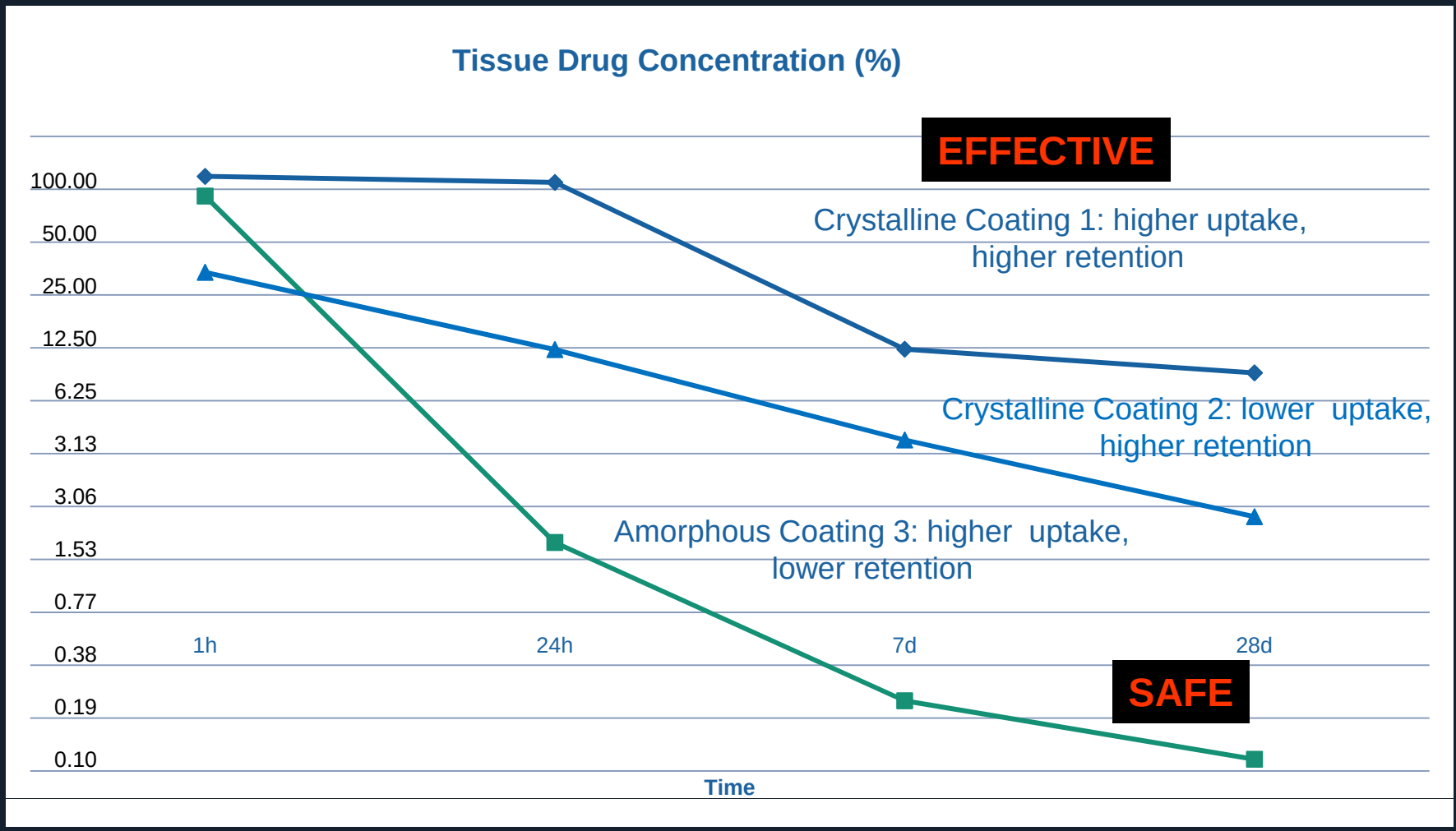


Coating "B" Amorphous

	Crystalline	Amorphous
Particles Released	+++	++
Uniform Coating	++	+++
Drug Transfer to Vessel	+++	++
Drug Retention vs. Time	+++	+
Biological Effectiveness	+++	?

Tissue Transfer and Retention

Crystalline versus Amorphous Coatings



Second Generations Coatings

Paclitaxel Coated Balloon Technologies

- Manual dipping process
- Automated and controlled drug coating

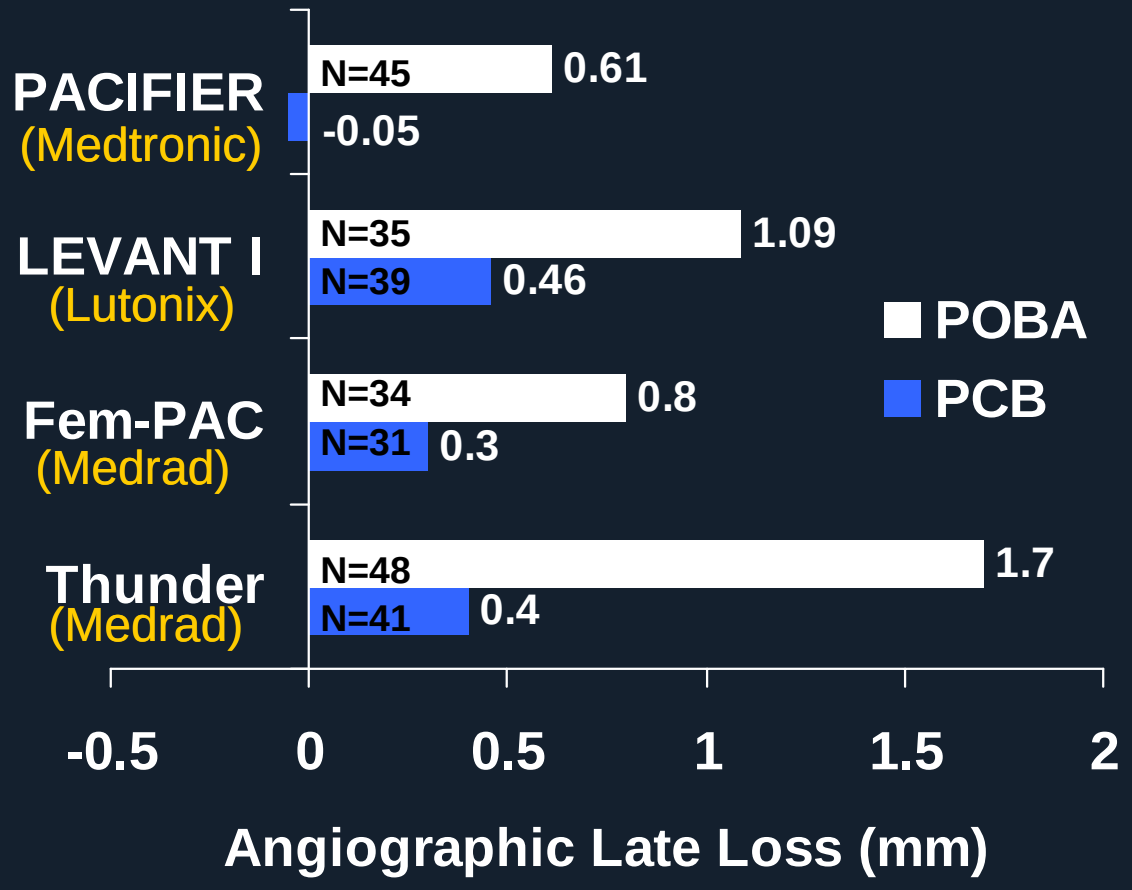
- Inconsistent D:E mixture
- Improved coating mixture and uniformity

- Limited scale production
- Large scale reproducibility

First generation DCB technologies have already migrated into their second generation providing more precise coatings, tissue drug delivery and lower particulate count…

Fact#1: Limited Evidence Based Medicine Leading to Clinical Practice

RCT of PCB for the Treatment of De Novo SFA Disease (ITT= PTA Only)



"Still less than several hundred patients having 6 month angiographic data and long term follow up"

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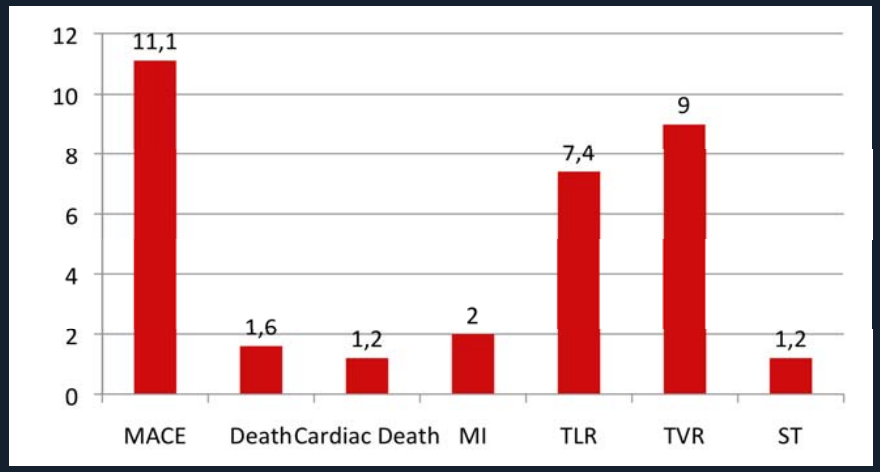
Fact #2: PCB May Have Limited Efficacy in DES-ISR

The Valentines Trial

- DIOR II PCB Technology (3 µg/mm^2)
- 40.6% Diffuse ISR
- Length Covered by PCB 24±9.1 mm
- Follow Up: 228 ± 44 days (97.6% of Patients)

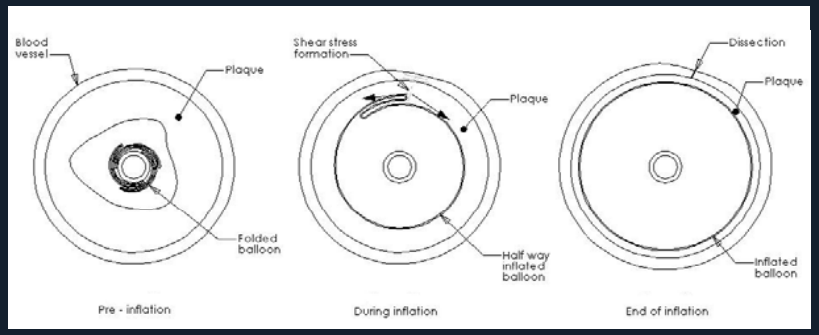


BMS-ISR: 157 Patients.
DES-ISR: 83 Patients.
Frequency of Stent Implantation 4.9%

- In.Pact Falcon (Medtronic)
- 75 patients, 122 lesions
  - ISR 62.7%
  - Diffuse disease 34.7%
- Death/MI/TVR: 13.3%
- Angiographic Follow Up (63.9%):
  - Restenosis 30.8%
    - DES-ISR: 47.5%
    - BMS-ISR: 0%
    - De Novo: 16.1%

J Shannon, TCT-14, TCT2011

Fact #3: A PTA Balloon is Not An Ideal Platform (A Stent May Be Needed!)



Expansion mechanism leads to:

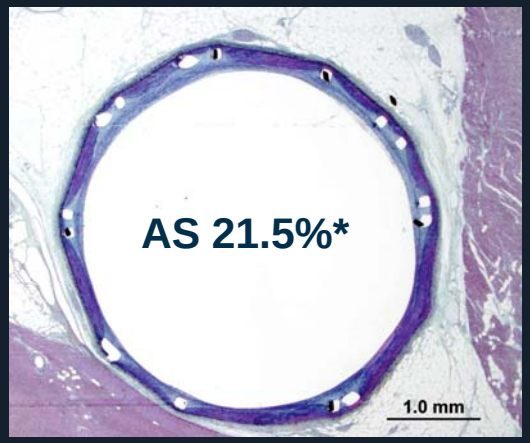
- Expansion in path of least resistance
- Significant shear stress and trauma
- High dissection rate
- Elastic recoil
- Abrupt closure

- **PTA study (2002)**
  - 74 patients
  - 43% major dissections
  - 32% residual stenosis >30%
- **ABSOLUTE: Stent vs. PTA (2006)**
  - 104 patients, 1:1 randomization
  - 32% insufficient PTA result led to cross over to stent
- **RESILIENT: Stent vs. PTA (2008)**
  - 206 patients 2:1 randomization 40% PTA cross over to stent due to flow limiting dissections and residual stenosis
- **Pacifier: DEB vs. PTA (2011)**
  - 91 patients, 1:1 randomization
  - 21% and 35% bail out stenting due to flow limiting dissections and residual stenosis

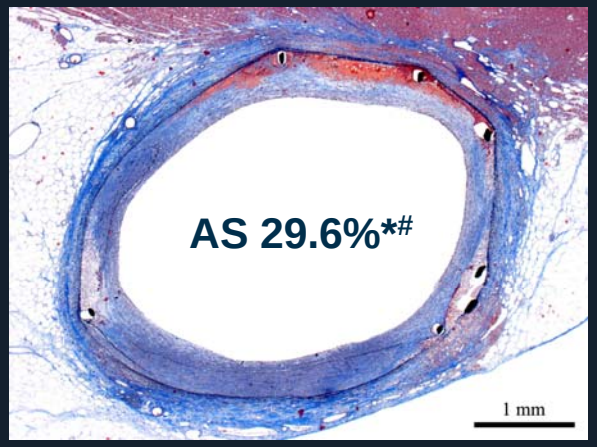
Acute failure reported in ~30 - 40% of PTA case requiring additional treatment

Slide (modified) courtesy of Eitan Konstantino

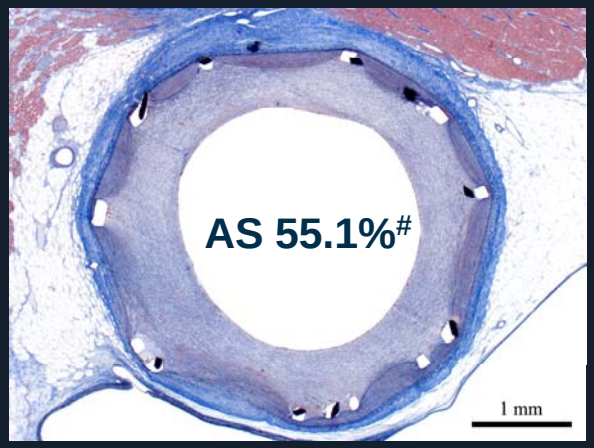
Vascular Healing of BMS-PCB Combination Compared to Taxus Stent in Coronaries of FHS



PES



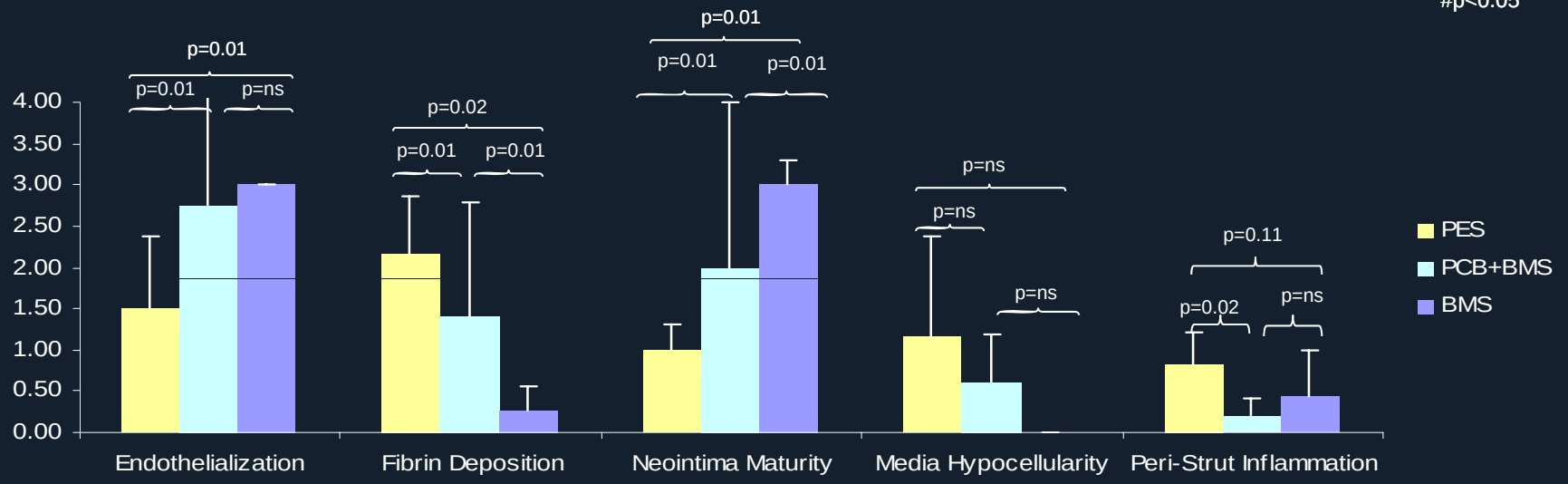
2nd Gen PCB + BMS



BMS

*p=ns

#p<0.05



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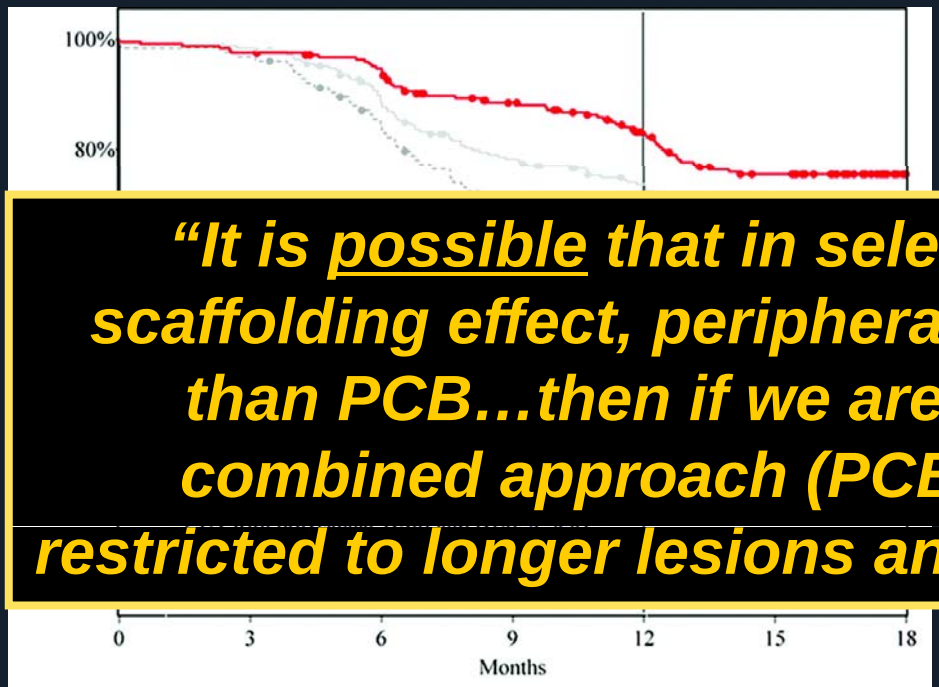
P.P.Buszman et al., TCT2011, SCCR.

Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease

Twelve-Month Zilver PTX Randomized Study Results

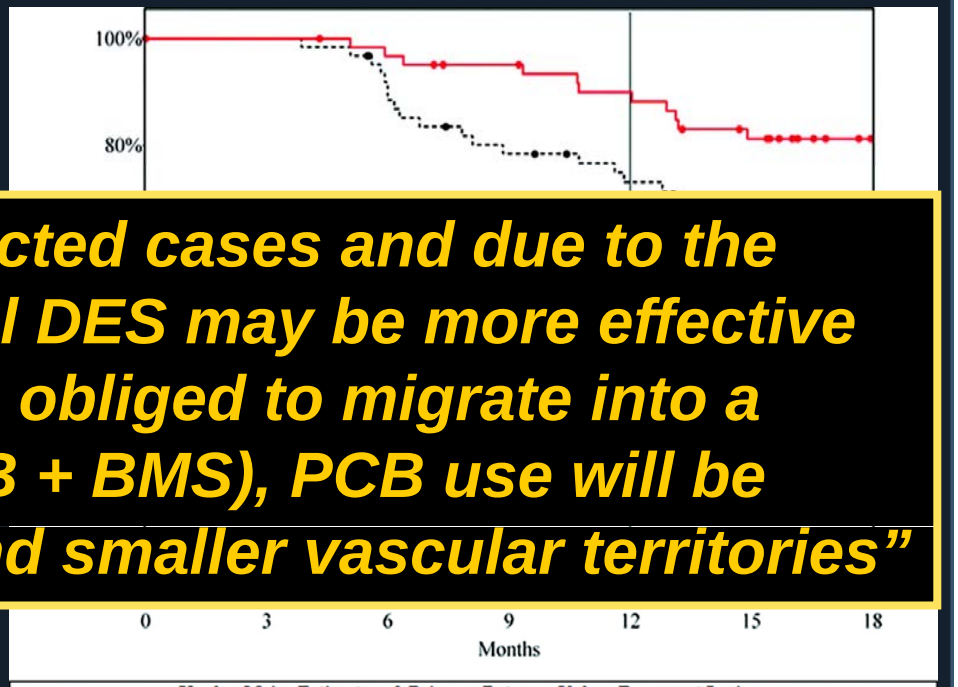
Primary Effectiveness Outcomes



Kaplan Meier Estimates of Primary Patency, Values Represent Lesions

Months Post-procedure	Primary Patency ± Standard Error		Cumulative Failed		Cumulative Censored		Remaining at Risk	
	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES
0	49.8 ± 3.2%	99.6 ± 0.4%	126	1	0	0	125	246
1	49.4 ± 3.2%	99.2 ± 0.6%	127	2	0	0	124	245
6	42.5 ± 3.1%	94.7 ± 1.4%	144	13	5	3	102	231
12	32.8 ± 3.0%	83.1 ± 2.4%	167	40	10	26	74	181

Provisional BMS versus DES



Kaplan Meier Estimates of Primary Patency, Values Represent Lesions

Months Post-procedure	Primary Patency ± Standard Error		Cumulative Failed		Cumulative Censored		Remaining at Risk	
	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	1	62	62
1	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	1	62	62
6	88.4 ± 4.1%	96.7 ± 2.3%	7	2	2	2	53	59
12	73.0 ± 5.8%	89.9 ± 3.9%	16	6	5	5	41	52

"It is <u>possible</u> that in selected cases and due to the scaffolding effect, peripheral DES may be more effective than PCB…then if we are obliged to migrate into a combined approach (PCB + BMS), PCB use will be restricted to longer lesions and smaller vascular territories"

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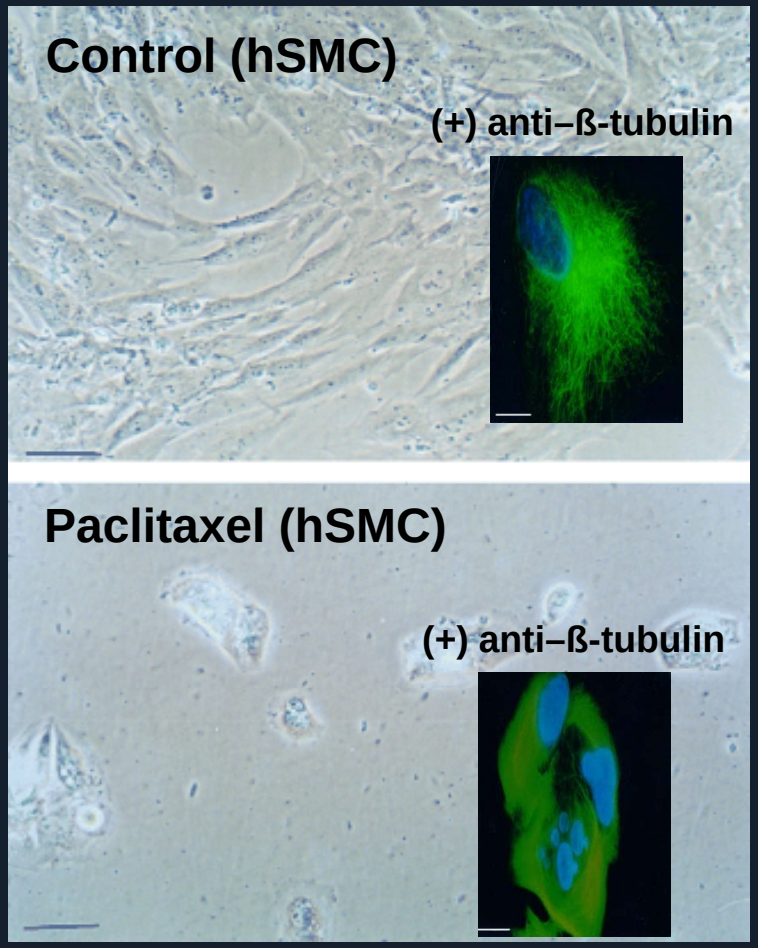
Dake M D et al. Circ Cardiovasc Interv 2011;4:495-504

Fact #4: Sirolimus Analogues

- Rapalogs provide well-established therapeutic benefit
- Rapalogs provide high level of safety – DES "drug of choice"
- PTX chosen for DEB because tissue transfer/absorption is far simpler
- So why we do not use them?

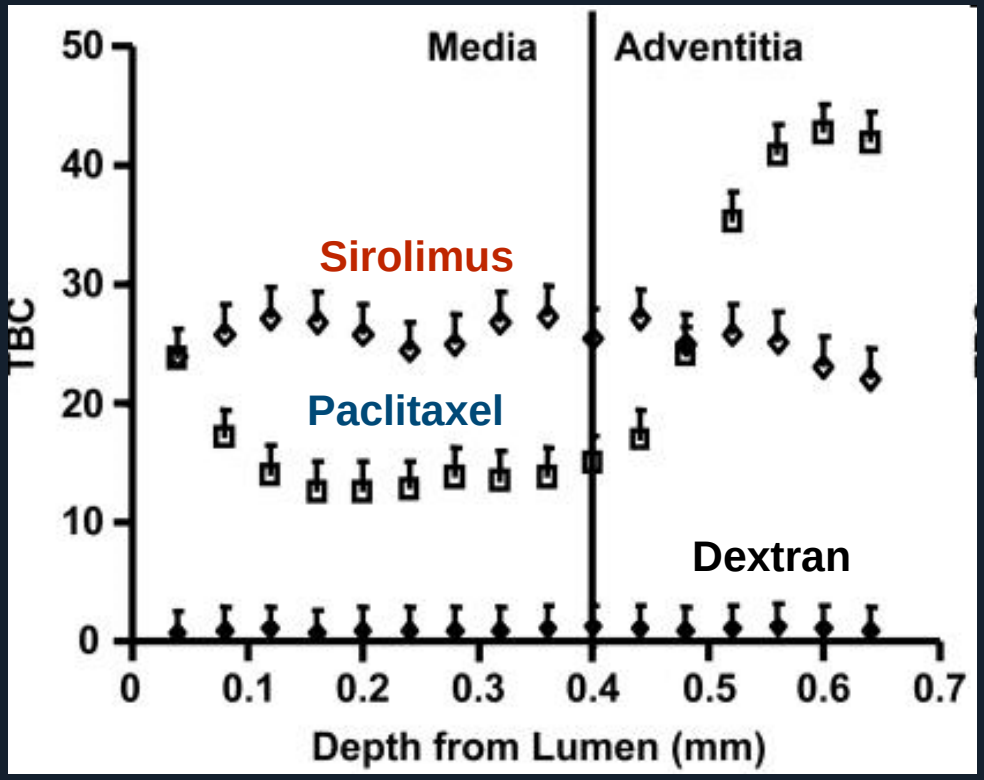
Attribute	Rapamycin (or Analogs)	Paclitaxel	Advantage
Mode of Action	Cytostatic	Cytotoxic	Rapamycin
Margin of Safety	10,000 fold	100 fold	Rapamycin
Anti-restenotic	YES – Lower Late Loss	YES	Rapamycin
Tissue Absorption	Longer	Shorter	Paclitaxel
Level of Competition	Low	Very high	Rapamycin
Physician Perception	Positive	Controversial	Rapamycin

Paclitaxel Irreversibly Inhibits Arterial SMC Proliferation and Migration Using a Single Dose



Axel DI. Circulation. 1997;96:636-645

Tissue Distribution and Retention of Paclitaxel Make it an Ideal Agent for Local Drug Delivery

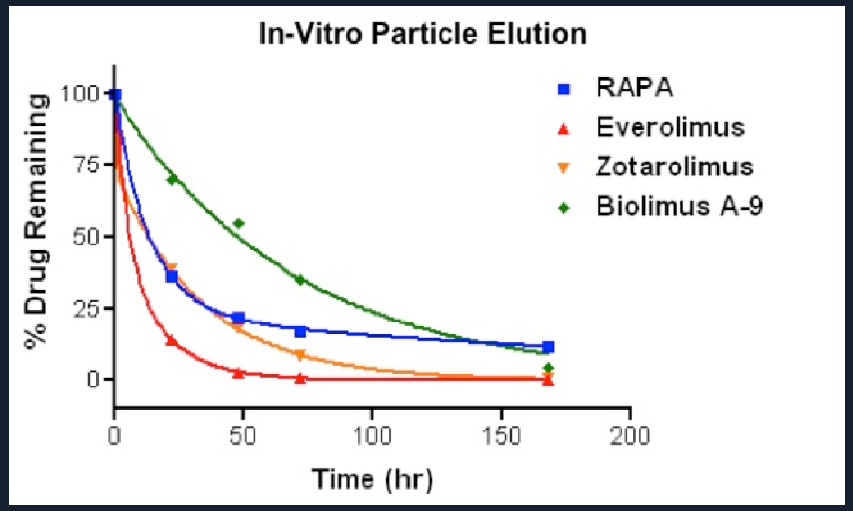


A. Levin et al., Proc Natl Acad Sci USA, 2004, 101, 9463-9467.

Drug Eluting Balloon Nanoparticle Based (Sirolimus) Balloon Dilatation System

Nanoparticle delivery technology

- Enhanced tissue penetration
- Protection from rapid degradation
- Controlled and sustained release
- Complete degradation



Speed of elution of Limus-containing NPs
Each Data point is n = 1

Angioplasty balloon dilation system

- Fully integrated combination device
- Semi-compliant balloon
- Full range of sizes and diameters

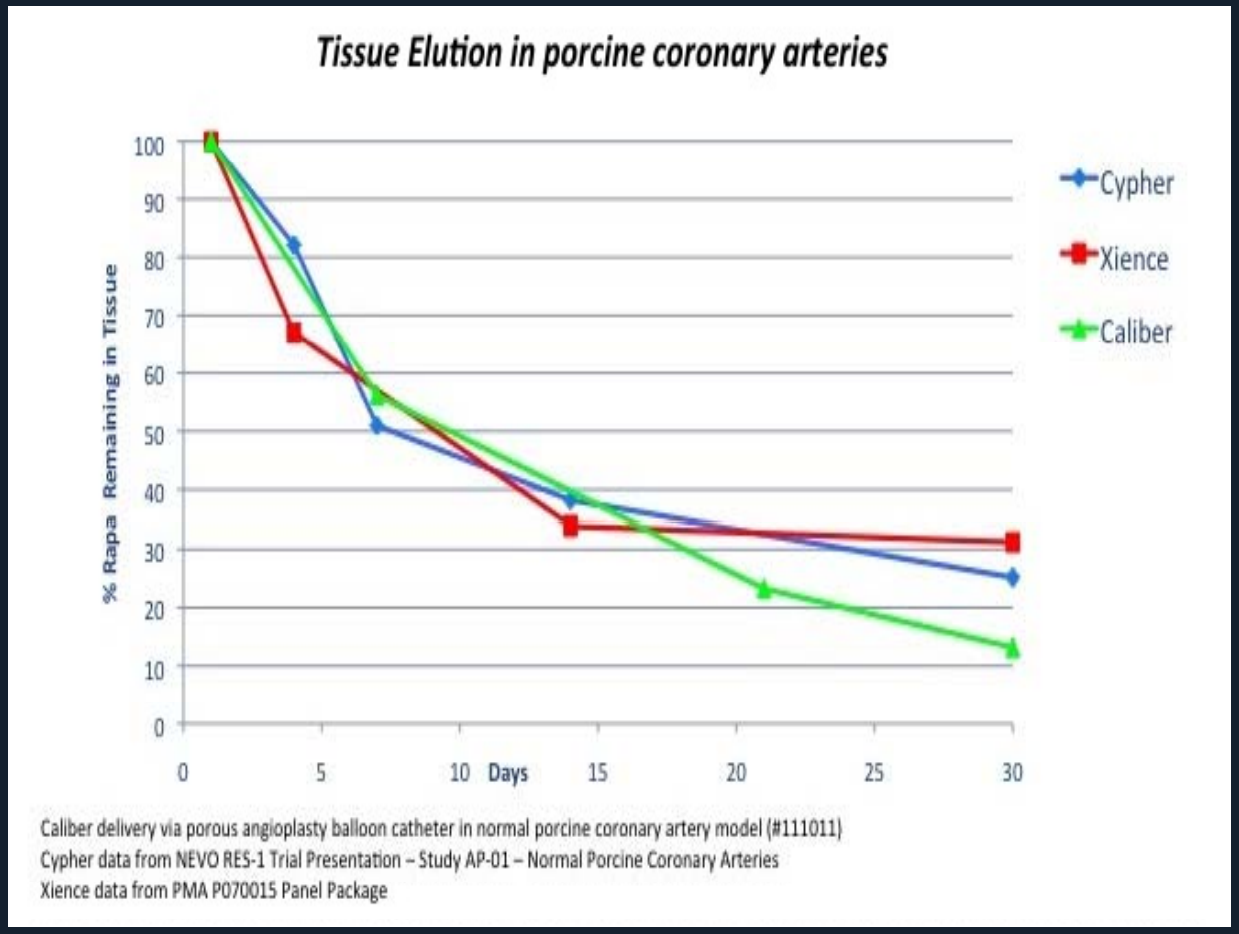
Regular dilatation pressures plus Sirolimus nanoparticle delivery

Slide courtesy (modified) of Caliber Therapeutics

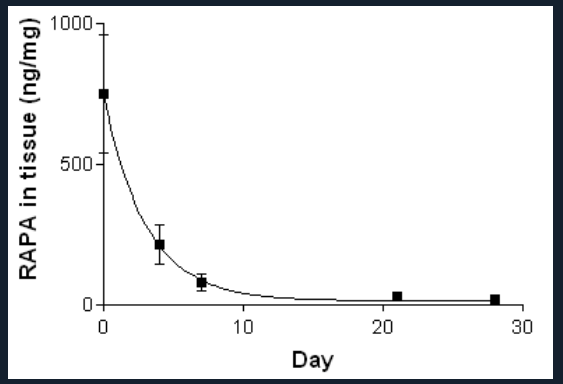
Elution Control and Dose Feasibility

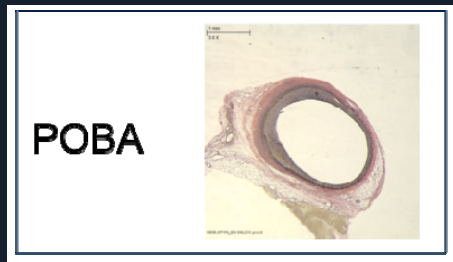
Sirolimus Delivery Using a Porous Balloon

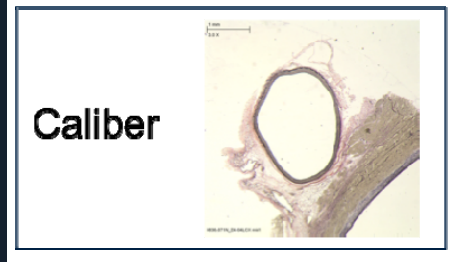
Tissue PK at 28 Days Following Sirolimus Delivery



Caliber delivery via porous angioplasty balloon catheter in normal porcine coronary artery model (#111011)
Cypher data from NEVO RES-1 Trial Presentation – Study AP-01 – Normal Porcine Coronary Arteries
Xience data from PMA P070015 Panel Package







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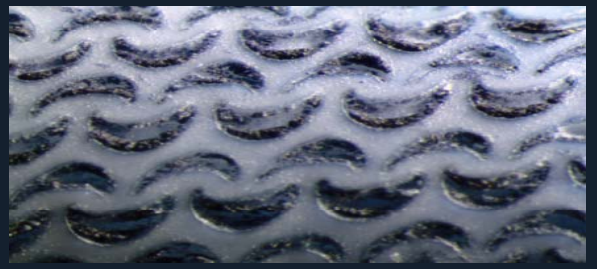
Slide courtesy (modified) of Caliber Therapeutics

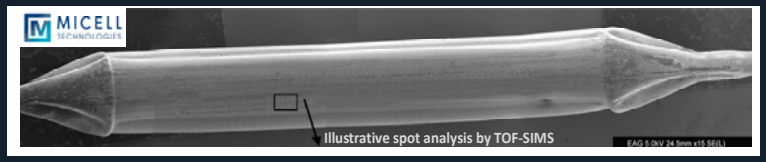
Opportunities for Improvement

SIROLIMUS
DEB Nanoparticle Based Balloon Dilatation System (CALIBER)

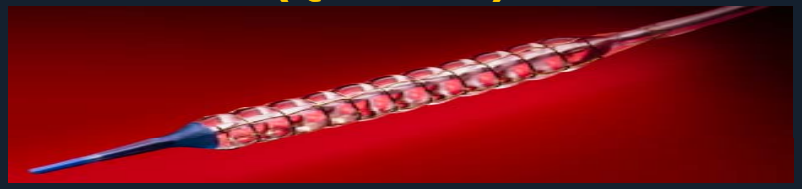
Balloon Surface Modification Technologies (AVIDAL)



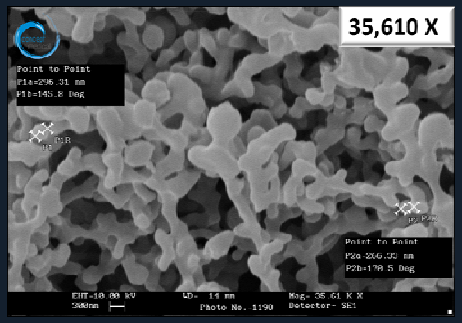
DCB Microcrystalline Coating (MICELL)



Dedicated DCB Platforms (QUATRO)



DCB Nanocrystalline Coating (CMI)



Niche DCB Platforms (CONIC)

DCB Conclusions

- PCB are technological suited to become the ideal interventional tool for the treatment of ISR and SFA disease
- Although efficacious for the treatment of BMS-ISR, its overall efficacy to treat DES-ISR needs to be further studied
- The DCB+BMS combination may lead to similar DES-like clinical outcomes (i.e., stent thrombosis). Then, the synergistic use of these devices deserves further investigation in a prospective manner
- Second generation PCBs appear to offer improved coating platforms providing more precise drug transfer to the tissue
- However, there is still a lot of room for improvement in regards to dosing, method of transfer and PK behavior
- Emerging data involving competitive devices (i.e., DES) will determine the clinical applicability of DCB in the cath-lab
- However, the DCB field has reached a feasibility phase, is rapidly evolving and is here to stay for the long run