Update on the role of drug eluting balloons

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Update

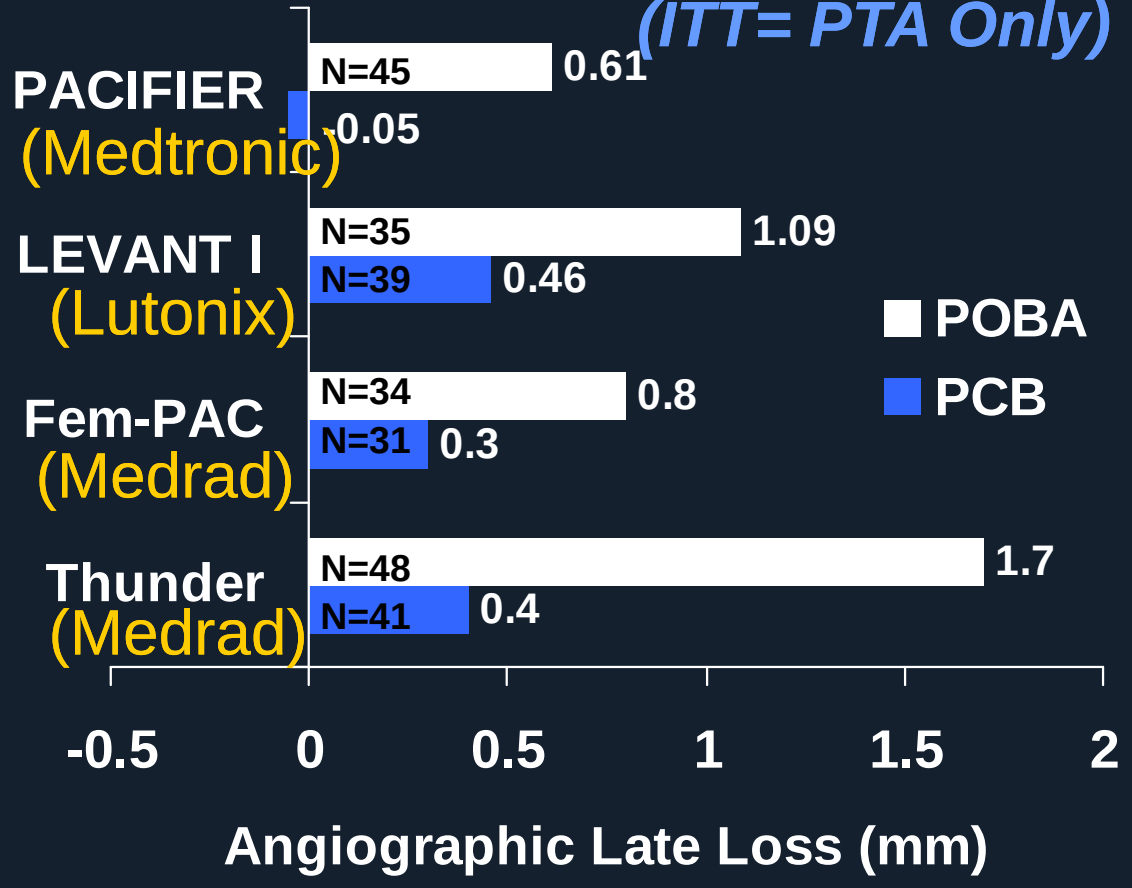
- SFA
  - De novo
  - ISR
- BTK
  - De novo
- Combination lesions
- Opportunities

TRIAL	THUNDER	FEM-PAC	Levant 1	PACIFIER
DCB	Medrad/Cotavance	Medrad/Cotavance	Lutonix/Moxy	Medtronic/InPact
Number of patients	154	87	101	91
Rutherford category	1-5	1-4		2-5
Primary endpoint	6/12 LLL	6/12 LLL	6/12 LLL	6/12 LLL
Primary outcomes	0.4+/- 1.2mm vs. 1.7+/- 1.8mm (p<0.001)	0.5+/- 1.1 vs. 1.0 +/-1.1mm (p= 0.031)	0.46mm vs. 1.09mm (p=0.016)	-0.05mm vs. 0.61mm (p=0.003)
Mean lesion length	7.5cm	6cm	8.1cm	7cm
Diabetics	50%	47%	47%	43%
Ca++ (mod/severe)	46%	52%	n/a	64%
Occlusions	50%	13%	41%	23%
Restenosis	22% vs. 14% ISR*	27% vs. 7% ISR	11%	10% vs.31% (p=0.03)
12 month patency	75%	81% (6 mo)	72% (6 mo)	Pending

PCB Trials in the SFA Territory

Angiographic Late Loss at 6 Months

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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Thunder 5 Year Sub-Study Analysis

	Uncoated Balloon (Mean ± SD)	Pac Balloon (Mean ± SD)	P-value
Intermediate TLR	44%	9%	0.08
Diameter Stenosis [%]	55 ± 34	39 ± 23	0.45
MLD [mm]	2.1 ± 1.7	3.0 ± 1.7	0.25
LLL [mm]	1.5 ± 1.3	0.7 ± 1.9	0.54

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Slide courtesy (modified) of Gunnar Tepe

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Effectiveness of Paclitaxel Coated Balloons for Treating In Stent Restenosis (The PACUBA Trial)* *(EuroCor)*

PTA in-stent restenosis: 70% restenosis at 6/12‡

1: 1 RCT

In-stent restenosis SFA/popliteal (P1)

Rutherford 2 - 5

Freeway 0.035” (EuroCor)

‡ Schillinger M JEVT 2003; 10:288-297

****Lammer J***

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Preliminary Results: PACUBA (Eurocor)

	PTA	DCB
Patients	15	21
Age (years)	70	68
Lesion length (cm)	8.1	8.5
Total occlusions	5	5
6 months PP rate	37%	78%

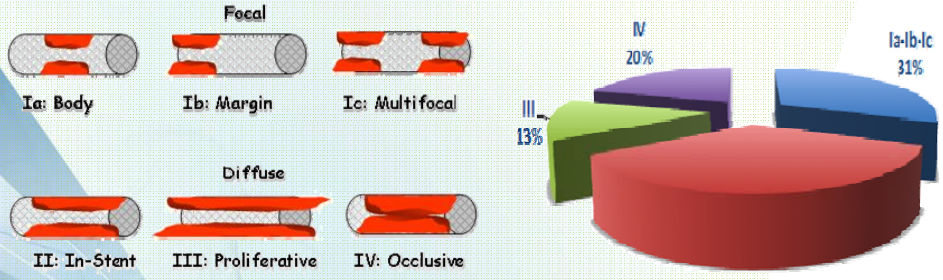
IN.PACT in SFA In Stent Restenosis

E.Stabile LINC 2012

Singe center registry of IN.PACT Admiral for SFA ISR

(Eugenio Stabile MD – Mercogliano, Italy)

- **Primary Endpoint: 1y Prim. Patency**
- **39 patients**
  - **LLC / CLI = 79.5% / 20.5%**
  - **Diabetics = 48.7%**
  - **Mean Stent length = 181.2 mm**



69% diffuse ISR

12-month Results

- **12m TLR = 7.8%**
- **12m Rest Rate = 7.8%**

Medtronic

DEFINITIVE AR study (Zeller, Tepe):
RCT infrapopliteal atherectomy &DCB vs. DCB (Cotavance)

The Rock Trial (Zeller, Tepe): RCT DCB & rotational atherectomy vs. DCB & BMS vs. PTA in calcified & long occlusions

The SPORTS study (Tepe):
RCT Cook Zilver PTX vs. Medtronic InPact DCB

- Mechanically re-canalize artery without overstretch
- Remove diffusion barrier → better & more effective, homogenous drug uptake
- Reduce likelihood of bail-out stenting & preserve

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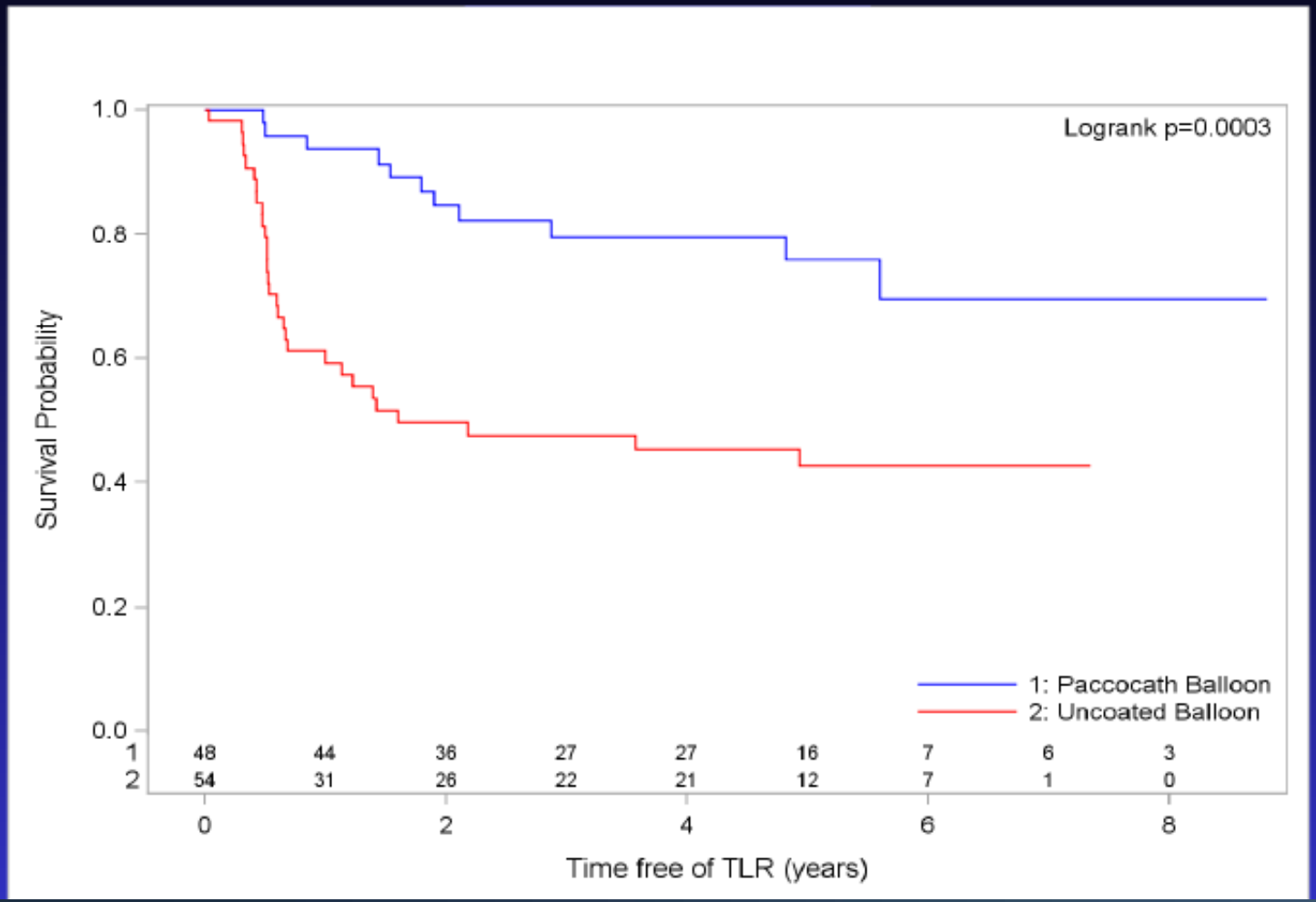
Thunder Five Year Outcomes:

Freedom from TLR: Kaplan-Meier



Presented by G Tepe, TCT 2011

IN.PACT + Atherectomy in High Calcium

A.Cioppa LINC 2012

Singe center registry of IN.PACT Admiral + Atherectomy for highly calcified de-novo SFA lesions

(Angelo Cioppa MD - Mercogliano, Italy)

- **Primary Endpoint: 1y Prim. Patency**
- **30 patients**
  - LLC / CLI = 6% / 94%
  - Diabetics = 60%
  - Mean lesion length = 115 ± 35 mm
  - Tot Occlusions = 13%
  - Calcium Score* 3 = 100%
- **dist. Filter + TurboHawk + IN.PAC**
  - bail-out Stenting = 7%

12-month FU

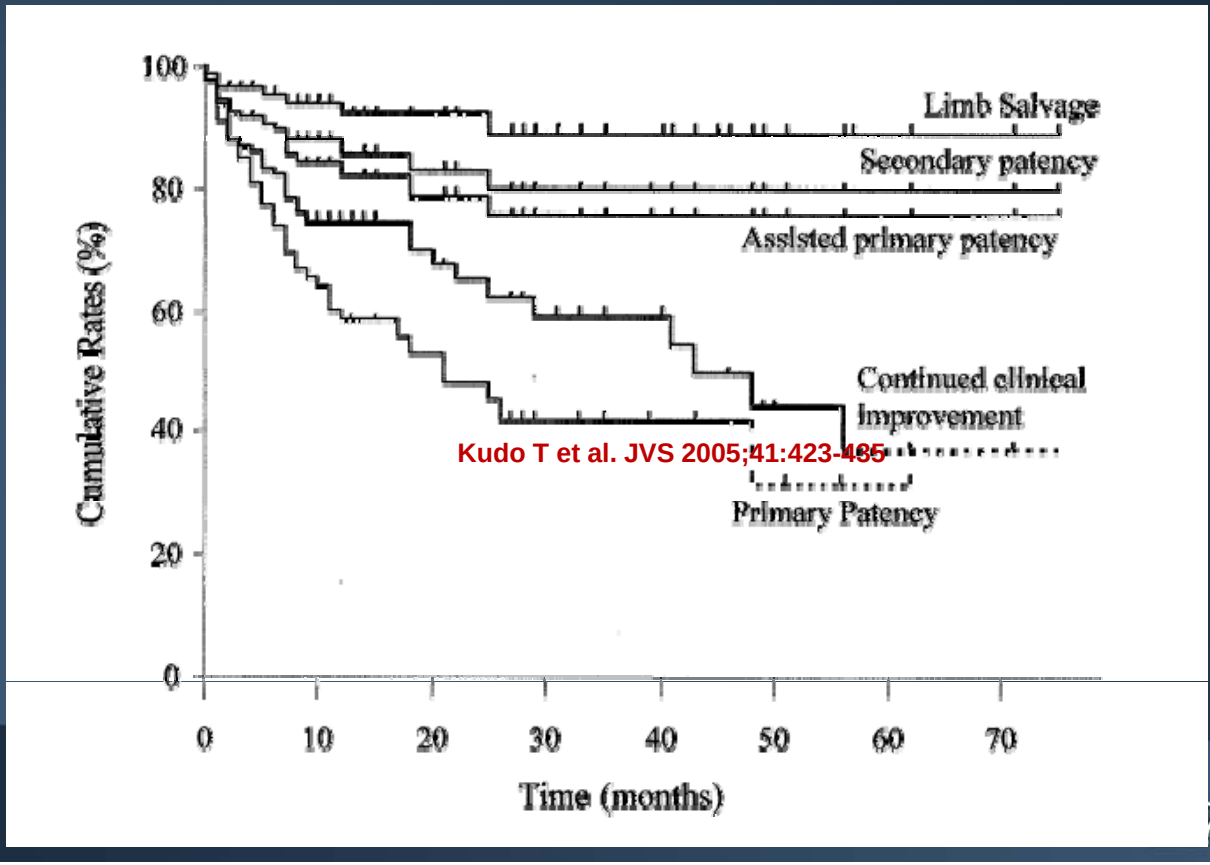
- **Primary Patency = 90%**
- **TLR = 10%**
- **Second. Patency = 100%**

* 0= absence of calcium; 1= calcium on one side of lumen <1cm length; 2= calcium on both side <1cm length; 3=calcium on both side >1 cm length

Medtronic

Patency and Limb Salvage

Poor correlation between patency and limb salvage due to a variety of concomitant / factors concurring to wound healing



Leipzig DEB BTK Registry

Singe center Registry of IN.PACT Amphirion for long BTK lesions / occlusions

(Andrej Schmidt MD – Leipzig, Germany)

- **Prim. Endpoint: 3m Angio Rest. Rate**
- **104 patients**
  - **Angio subgroup:**
  - **–CLI = 82.6%**
  - **–Diabetics = 73%**
  - **–Avg Lesion length = 173 ± 87 mm**
  - **–Tot Occlusions = 61.9%**

27.4% angiographic Restenosis Rate at 3 months with 17.3 TLR rate at 12 months

	DEB (angio subgroup)	PTA* (historical group)
	3m Angiographic FU	
Restenosis (>50%)	27.4%	69%
Full-segment Resten.	10%	56%
Restenosis Length	64 mm	155 mm
	12m Clinical FU	**15m Clinical FU**
Deaths	16.3%	10.5%
Limb Salvage	95.6%	100%
Clinical Improvement (1)	91.2%	76.5%
Compl. wound healing	74.2%	78.6%
TLR	17.3%	50%

**A.Schmidt et al. CCI 2010*

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A.Schmidt et al. JACC 2011

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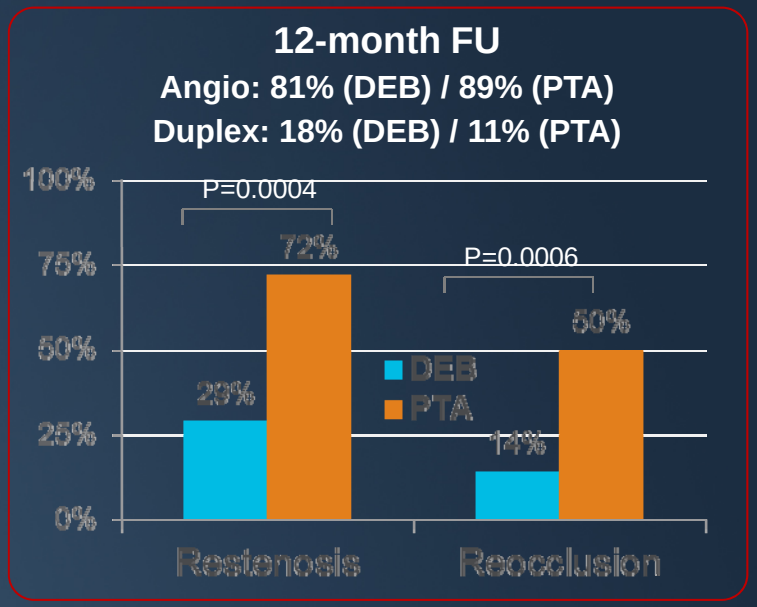
DEBATE Randomized Trial

Single center RCT of IN.PACT Amphirion vs. PTA in BTK-CLI-DIABETICS de-novo lesions

(Francesco Liistro MD – Arezzo, Italy)

- **Prim. Endpoint: 12m Angio Rest. Rate**
- **120 patients (preliminary results)**
- **Baseline (DEB vs. PTA):**
- **CLI = 100%**
- **Diabetics = 100%**
- **Mean lesion length = 121 ± 83 vs. 123 ± 68 (p=ns)**
- **Tot Occlusions = 80% vs. 82% (p=ns)**
- **Pre-dilat. = 100%**

IN.PACT significantly reduces Restenosis Rate at 12-month vs. PTA in BTK-CLI-Diabetics



	PTA	DEB	
Death	3(4%)	4(6%)	0.2
Major Amputation	1	0	
CVA	3(4)	2(3)	0.7
AMI	3(4)	3(4)	0.7

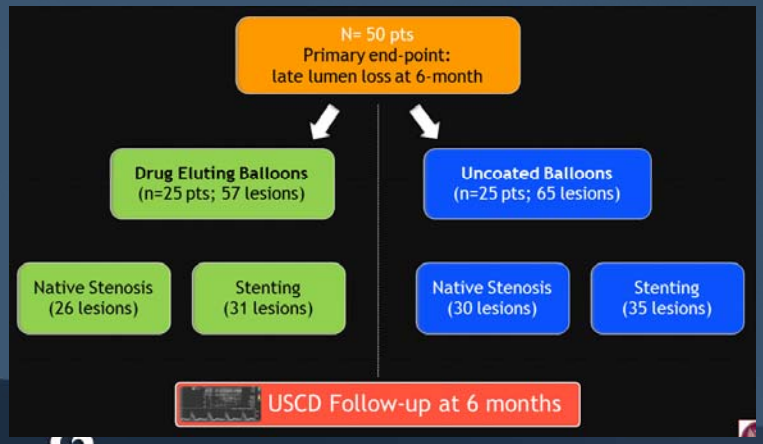
DEBELLUM Randomized Trial

Drug Eluting Balloon Evaluation for Lower Limb mUltilevel treatMent

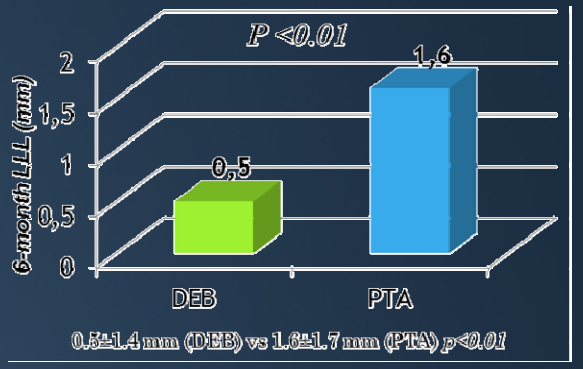
Single center RCT of IN.PACT vs. PTA in MULTILEVEL lower limb disease

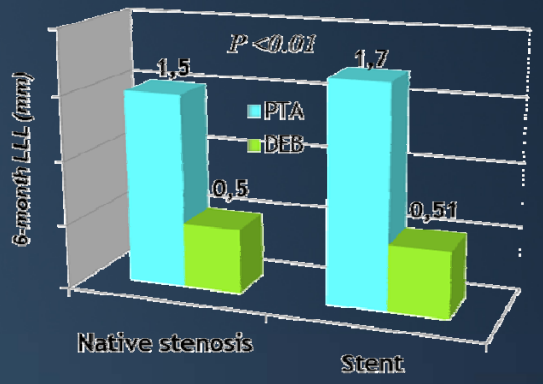
(Fabrizio Fanelli MD - Roma, Italy)

- **Prim. Endpoint: 6m LLL**
- **50 patients**
- **Fempop / BTK = 76% / 24%**
- **LLC / CLI = 62% / 38%**



IN.PACT shows reduction of restenosis vs. PTA in multilevel (SFA + BTK) disease with and without Stent





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F.Fanelli LINC 2012

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Opportunities for Improvement

Drug	• All available DCBs use Paclitaxel • Change in Paclitaxel form, size or chemical features • Drug micro encapsulation or advanced drug systems • Alternative drugs (limus-based or others)

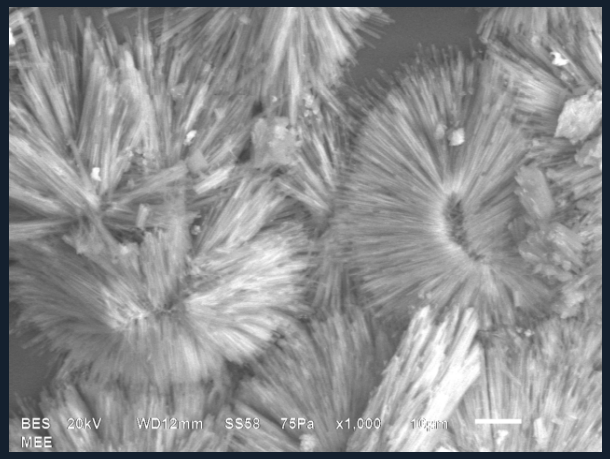
Carrier	• Alternative carriers aiming to improve coatings:
	  • Reduce total drug concentration
	  • Enhance tissue transfer
	  • Increasing tissue drug retention

Balloon Catheter	• Plaque modification delivery systems • Low-injury balloon techniques • Optimized delivery carrier surfaces • Local tissue delivery

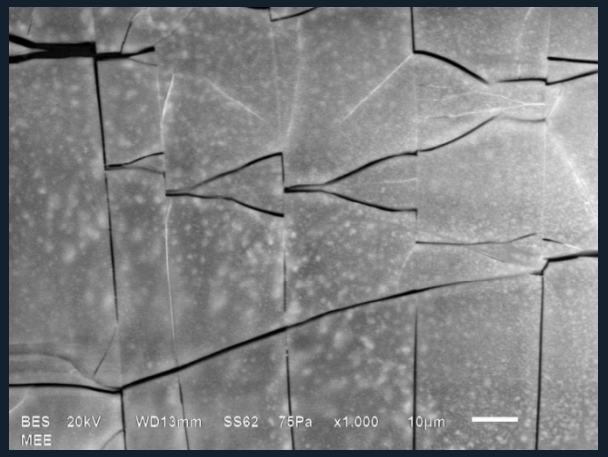
Others	• Adjunctive technologies
	  • Atherectomy & stents
	• Dedicated niche applications
	  • Bifurcations, AMI, calcified lesions, etc…

Paclitaxel DCB Types

Impact on Biological Performance



Coating "A" Crystalline

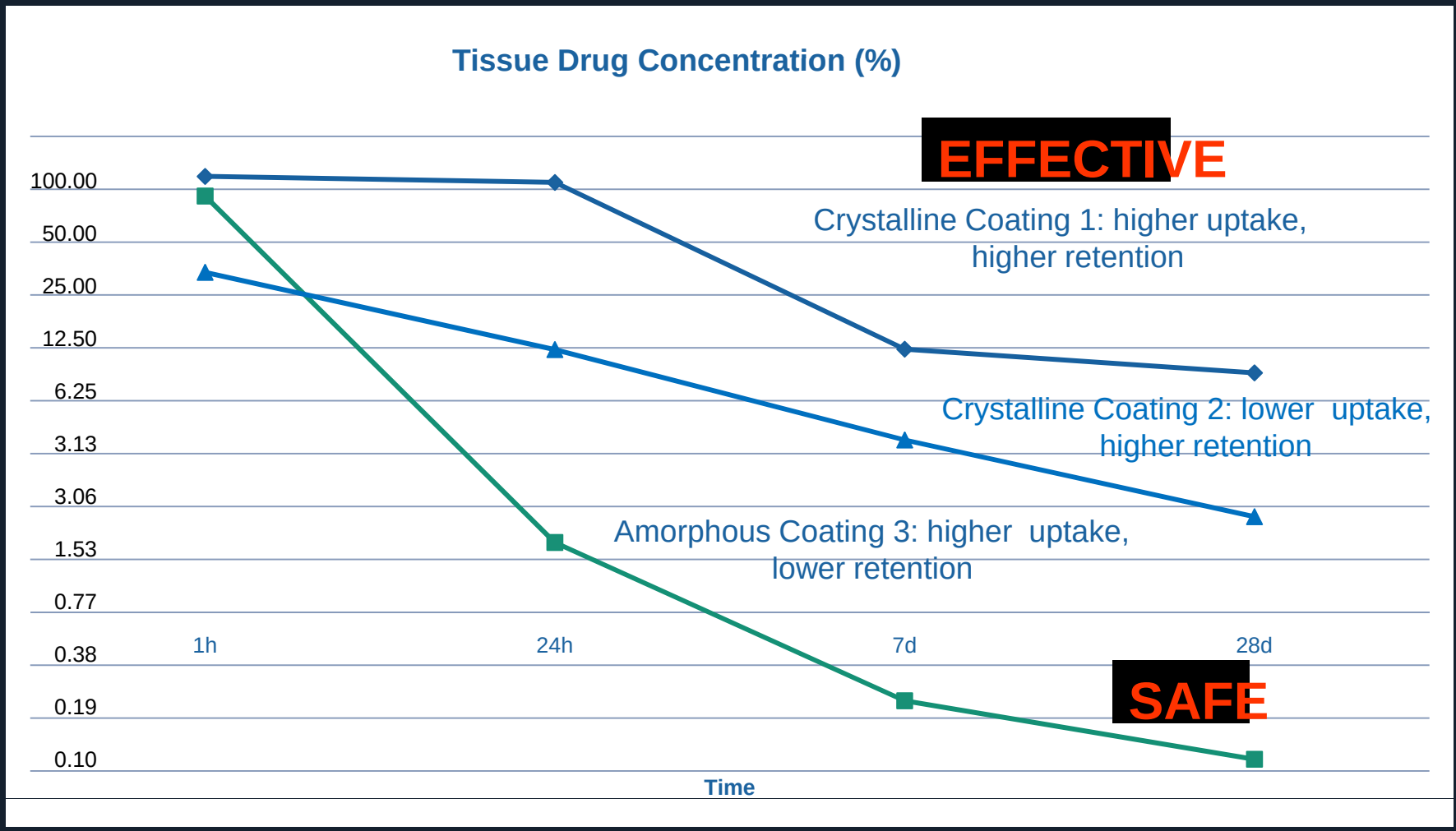


Coating "B" Amorphous

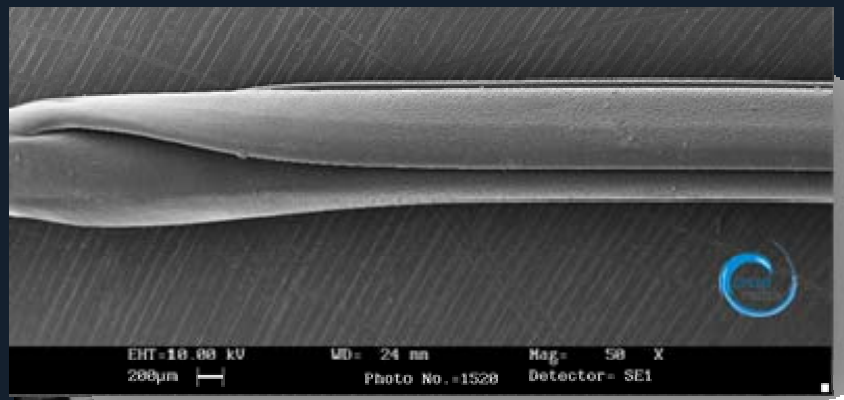
	Crystalline	Amorphous
Particles Released	+++	++
Uniform Coating	++	+++
Drug Transfer to Vessel	+++	++
Drug Retention vs. Time	+++	+
Biological Effectiveness	+++	?

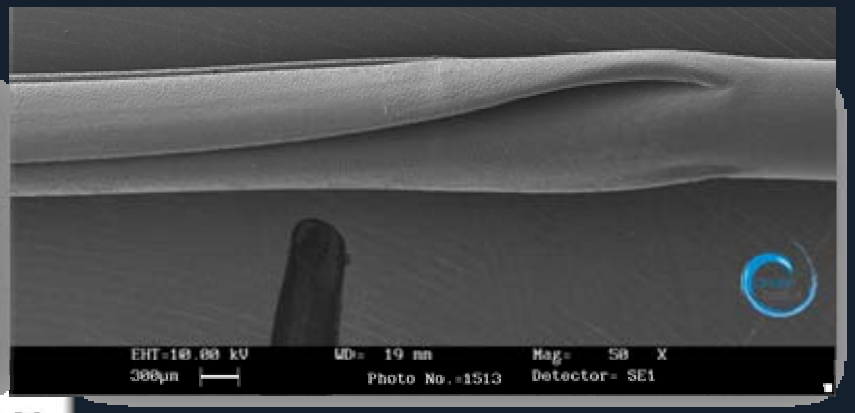
Separate Variables to be Optimized

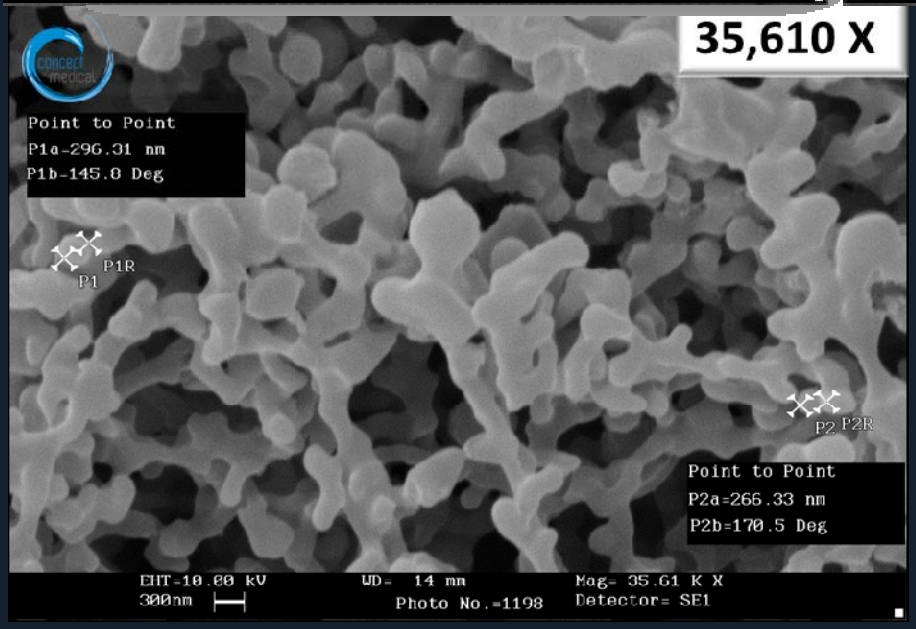
Crystalline vs Amorphous; Tissue Uptake vs. Retention

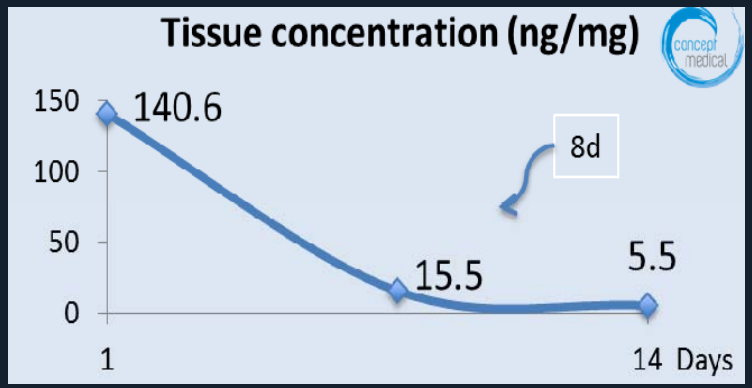


Sirolimus-Based Nanocrystal Balloon Coating Technology









Drug Load:
180µg on 3.0x15 mm balloon

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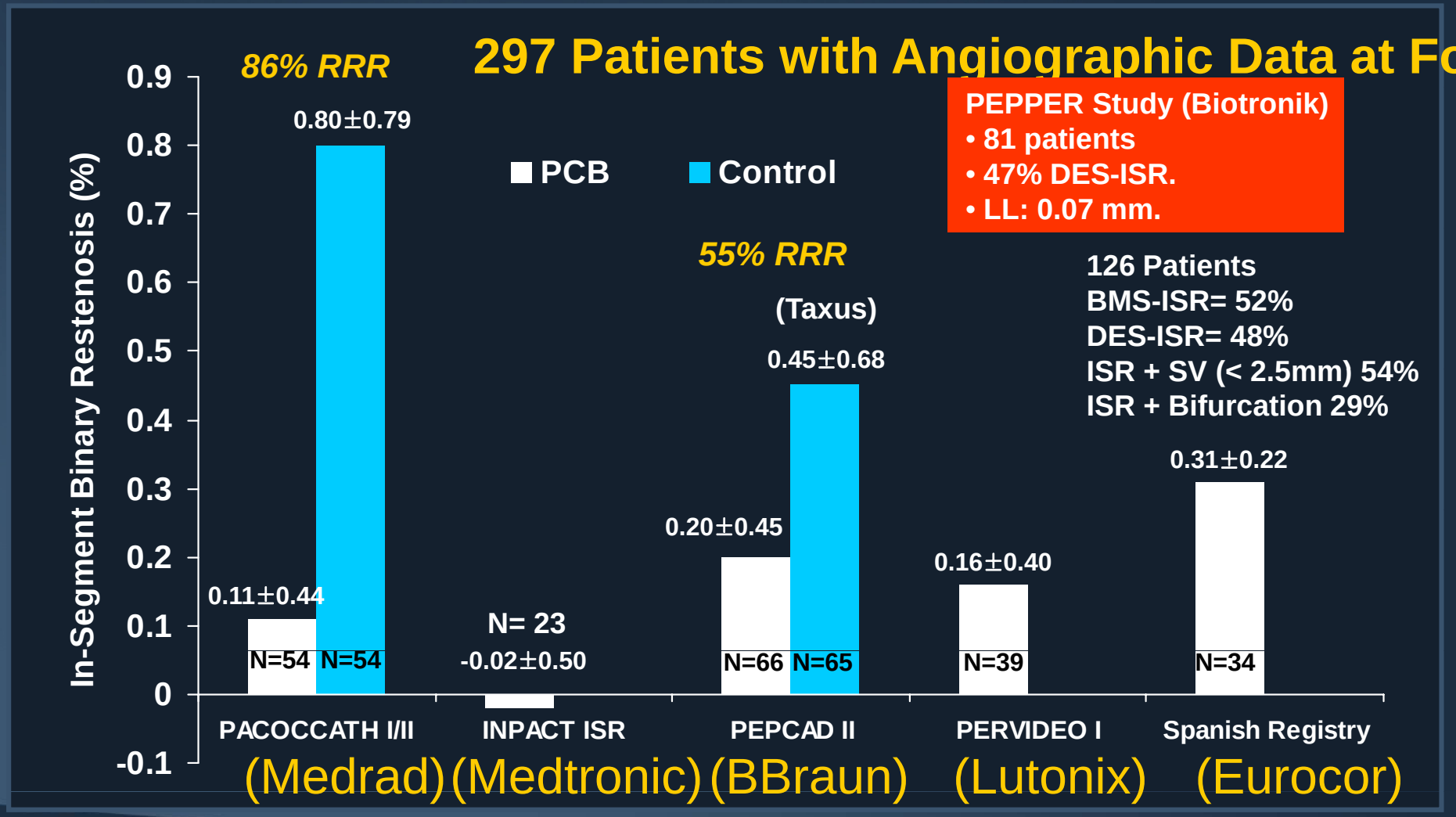
PCB for the Treatment of ISR

Angiographic Outcomes (Absence of Stent)



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Angiographic Outcomes: PCB Trials for "De Novo" Applications

- **PEPCAD III:** BMS Crimped on PCB (3 µg/mm²) versus Cypher Stent
- **Lutonix** De Novo Registry: Pre or Post Dilatation Using PCB (2 µg/mm²)