

# Drug Coated Balloons: Present Status and Future of the Technology

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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.

**Consultant: Abbott Vascular; Boston Scientific; Celonova; Cook Medical; Cordis; CSI; Edwards Lifescience; Lutonix Bard; Medtronic; OrbusNeich Medical; ReCore; Sinomedical Technology; Spectranetics; Surmodics; Terumo Corporation; W. L. Gore; Xeltis.**

**Employment in industry: No**

**Honorarium: Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; Cordis; CSI; Lutonix Bard; Medtronic; OrbusNeich Medical; CeloNova; SINO Medical Technology; ReCore; Terumo Corporation; W. L. Gore; Spectranetics.**

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**Owner of a healthcare company: No**

**Stockholder of a healthcare company: No**

# Elements of 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 for more than 4 weeks

Must allow rapid healing as compared to DES

No need for long-term anti-platelet therapy

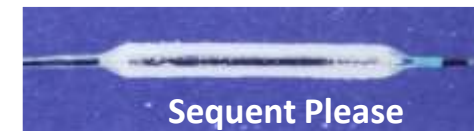
Biologic effects must be observed by histology at 28-days

**Effective drug delivery to target tissue while avoiding non-target effect (i.e. minimize emboli)**

# Ptx Drug Coated Balloon Devices (Peripheral artery)

| Device            | Company                                   | Coating                              | Drug dose ( $\mu\text{g}/\text{mm}^2$ ) | 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   | 2.0                                     | 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  |

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



# Ptx DCBs Better for Above Than Below the Knee

Table 2: Comparison of Pivotal Clinical Trials of Paclitaxel-coated Balloons

| Study                                  | Balloon         | Company           | Number of Patients (Lesions) | Rutherford Class 2/3/4/5 (%) | Lesion Length (mm) | De novo Lesion (%) | Total Occlusions (%) | Severe Calcification (%) | Primary Endpoint                   | Evaluation                         | Follow-up Duration |
|--|-----------------|-------------------|------------------------------|------------------------------|--------------------|--------------------|----------------------|--------------------------|------------------------------------|------------------------------------|--------------------|
| IN.PACT SFA 2015/2018 <sup>19,20</sup> | IN.PACT Admiral | Medtronic         | 220 (221)                    | 37.7/57.3/5.0/0              | 89.4 ± 48.9        | 95.0               | 25.8                 | 8.1                      | Freedom from CD-TLR                | Duplex ultrasonography (PSVR ≤2.4) | 1 and 3 years      |
| LEVANT 2 2015 <sup>21</sup>            | Lutonix         | CR Bard           | 316 (322)                    | 29.4/62.7/7.9/0              | 62.8 ± 41.8        | 76.6               | 20.6                 | 10.4                     | Freedom from CD-TLR and restenosis | Duplex ultrasonography (PSVR <2.5) | 1 year             |
| ILLUMINATE 2017 <sup>23</sup>          | Stellarex       | Philips           | 222 (254)                    | 15.0/83.0/4.0/0              | 72.0 ± 52.0        | 92.0               | 19.0                 | 13.0                     | Freedom from CD-TLR                | Duplex ultrasonography (PSVR ≤2.5) | 1 year             |
| RANGER SFA 2017 <sup>5</sup>           | Ranger          | Boston Scientific | 71 (71)                      | 46.2/53.8/0/0*               | 68.0 ± 46.0        | 74.0               | 34.3                 | 35.7                     | Late lumen loss                    | Angiography                        | 6 months           |
| CONSEQUENT 2017 <sup>25</sup>          | SeQuent Please  | B. Braun          | 78 (87)                      | 5.1/94.9/0/0                 | 137.0 ± 122.0      | NA                 | 23.1                 | NA                       | Late lumen loss                    | Angiography                        | 6 months           |

Continuous variables shown as mean ± SD. \*Exact number is not available. The number was inferred from the figure.

DCB = drug coated balloon; CD-TLR = clinically driven target lesion revascularisation; NA = not available; PSVR = peak systolic velocity ratio.

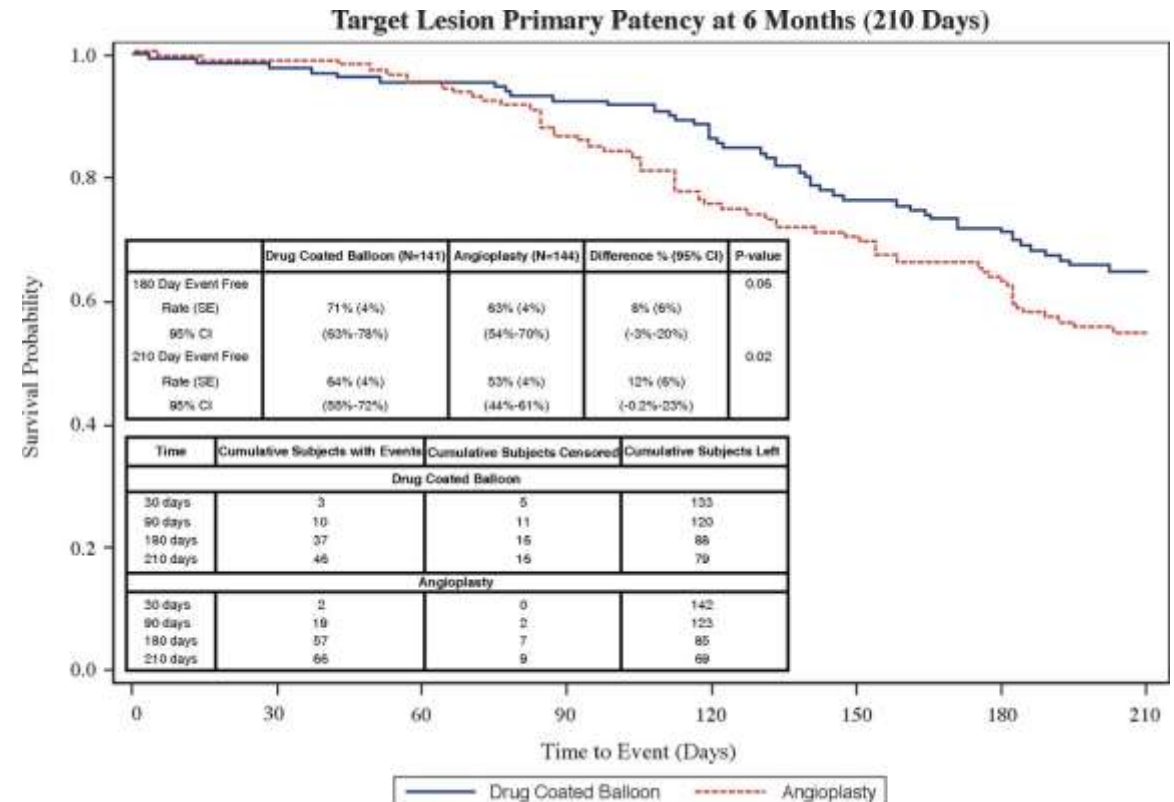
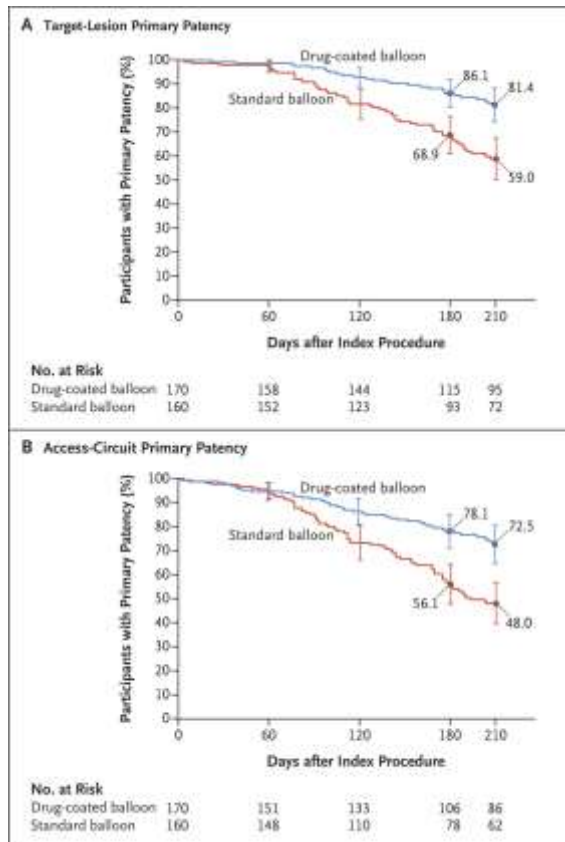
Table 3: Clinical Studies Evaluating Paclitaxel-coated Balloon Treatment for Critical Limb Ischaemia

| Study                                       | Balloon                  | Number of Patients (lesions) | Rutherford class 4/5/6 (%) | Lesion length (mm)                  | De-novo Lesion (%) | Total Occlusions (%) | Severe Calcification (%) | Follow-up Duration | Freedom From TLR (%) | Primary Patency (%) | Freedom From Major Amputation (%) |
|---|--------------------------|------------------------------|----------------------------|-------------------------------------|--------------------|----------------------|--------------------------|--------------------|----------------------|---------------------|-----------------------------------|
| Phair et al. 2020 <sup>32</sup>             | IN.PACT, Lutonix         | 32 (NA*)                     | 0/65.6/34.4                | 86.0 ± 39.4 (SFA), 69.0 ± 5.5 (POP) | 100                | 12.5                 | NA                       | 1 year             | 85.7                 | 58.1                | 71.1                              |
| XLPAD registry 2020 <sup>33</sup>           | IN.PACT Admiral, Lutonix | 105 (NA*)                    | NA                         | 150.0 ± 123.3                       | 86.7               | 59.1                 | 31.2                     | 1 year             | 83.8                 | NA                  | 88.6                              |
| IN.PACT Global Study 2019 <sup>34</sup>     | IN.PACT Admiral          | 156 (194)                    | 76.9/23.1/0                | 139.4 ± 105.5                       | 74.2               | 41.2                 | 11.3                     | 1 year             | 86.3                 | NA                  | 98.6                              |
| Spanish Luminor Registry 2020 <sup>35</sup> | Luminor                  | 148 (180)                    | 16.0/84.0/0                | 77.4 ± 50.3                         | 91.1               | 53.9                 | 56.7                     | 1 year             | 92.1                 | 87.7                | 84.7                              |

Continuous variable shown as mean ± SD. \*No available information regarding number of lesions. †Based on the history of past intervention. DCB = drug-coated balloon; TLR = target lesion revascularisation; NA = not available; SFA = superficial femoral artery; POP = popliteal.

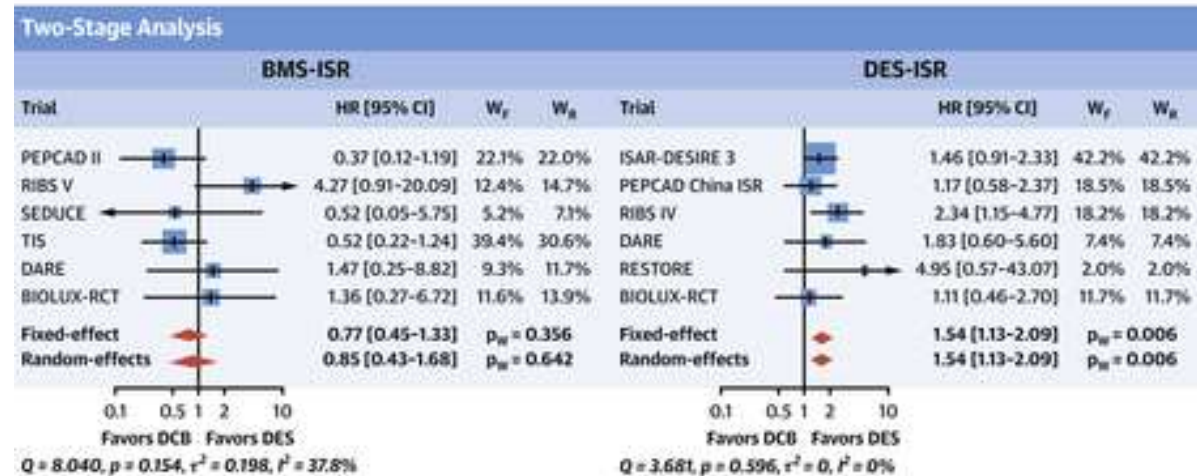
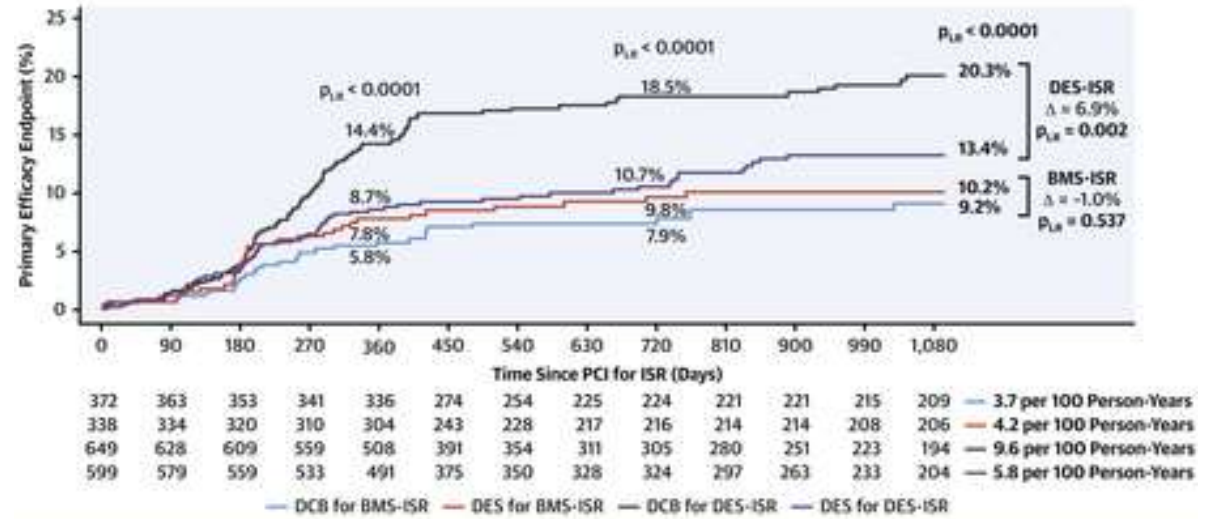
# Drug Coated Balloon Devices for AVF stenosis

| Device            | Company                                  | Coating                         | Drug dose ( $\mu\text{g}/\text{mm}^2$ ) | CE mark* |
|-------------------|--|---------------------------------|---|----------|
| 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      |



RAI Lookstein et al. N Engl J Med 2020;383:733-742.

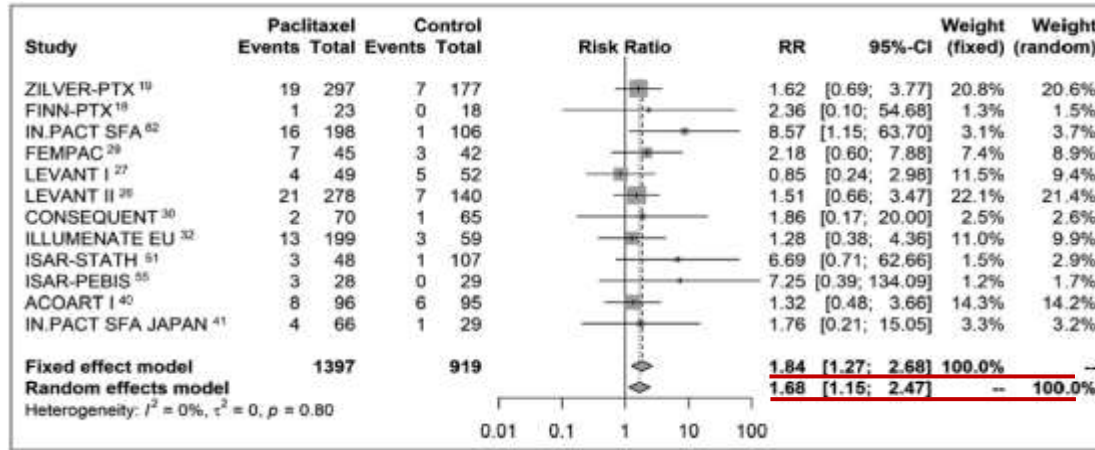
# DCB > DES for BMS ISR But DES > DCB for DES ISR



Daniele Giacoppo et al. *J Am Coll Cardiol* 2020; 75:2664-2678.

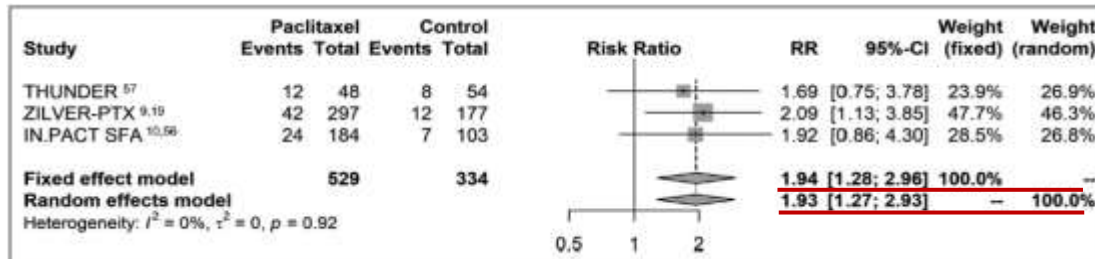
# Risk of Death following Application of PES and PCB in Femoropopliteal artery

Random effects forest plot of all-cause death at 2 years



Causes of Death

|                | Paclitaxel-Coated Balloon (IN.PACT SFA) at 3 Years <sup>10,62</sup> |         | Paclitaxel-Coated Stent (ZILVER PTX) at 2 Years <sup>19,23</sup> |         |
|----------------|---|---------|--|---------|
|                | Paclitaxel  | Control | Paclitaxel   | Control |
| Cardiovascular | 9   | 0       | 18   | 8       |
| Cancer         | 2   | 2       |  |         |
| Infectious     | 5   | 0       |  |         |
| Pulmonary      | 3   | 0       |  |         |
| Other          | 3   | 0       | NA   | NA      |



Katsanos K, et al. J Am Heart Assoc. 2018;7:e011245



# Ptx Safety Concerns Persist

NEWS - INTERVENTIONAL

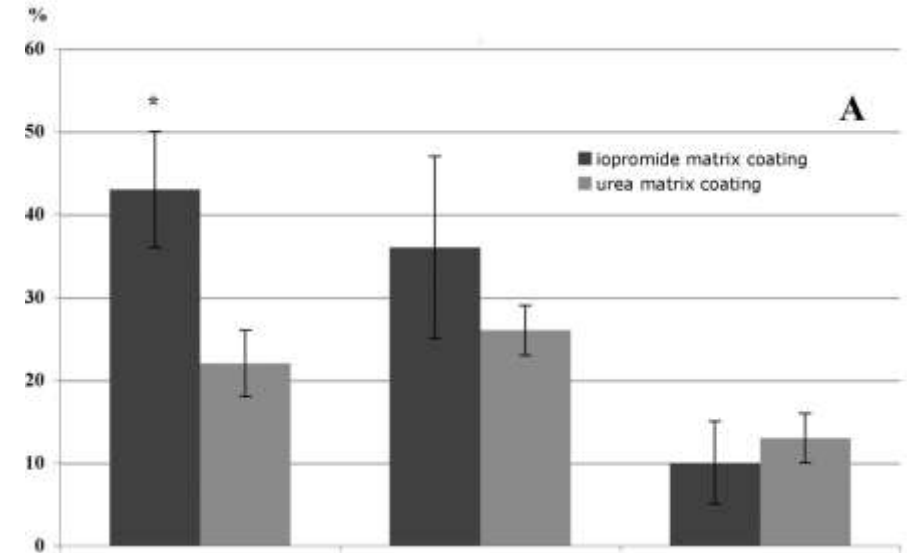
## FDA Says Newer Paclitaxel Data Are 'Comforting' but Limited

Acknowledging the recent, reassuring SWEDEPAD data, the agency says it's not yet ready to update its advice to doctors.

BY L.A. MCKEOWN | JANUARY 12, 2021

### Total Dose of Ptx Delivered on In.Pact Balloon

| Diameter | Length |      |      |      |       |       |       |       |
|----------|--------|------|------|------|-------|-------|-------|-------|
|          | 20mm   | 40mm | 60mm | 80mm | 120mm | 150mm | 200mm | 250mm |
| 4        | 1.1mg  | 2.0  | 2.8  | 3.7  | 5.5   | 6.8   | 9.0   | 11.2  |
| 5        | 1.5    | 2.6  | 3.7  | 4.8  | 7.0   | 8.6   | 11.4  | 14.1  |
| 6        | 1.9    | 3.2  | 4.5  | 8.5  | 4.5   | 10.4  | 13.7  | 17.0  |
| 7        | 2.3    | 3.8  | 5.4  | 6.9  | X     | X     | X     | X     |

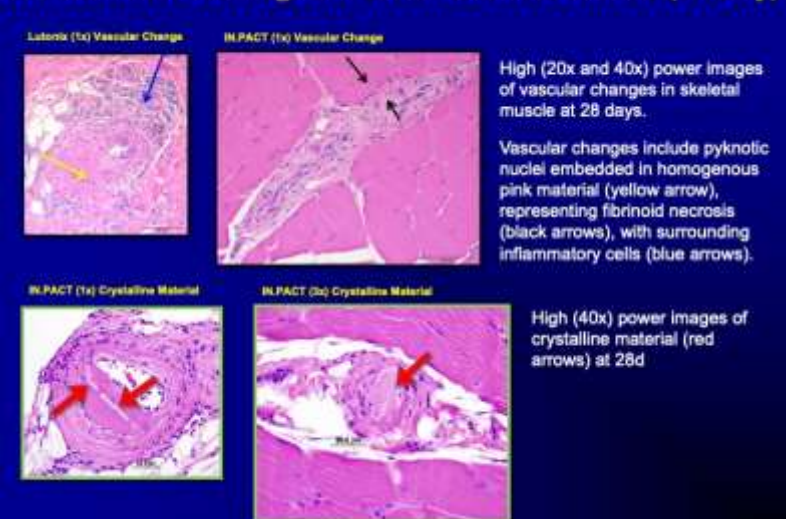


Kelsch et al. Invest Radiol. 2011;46:255-263

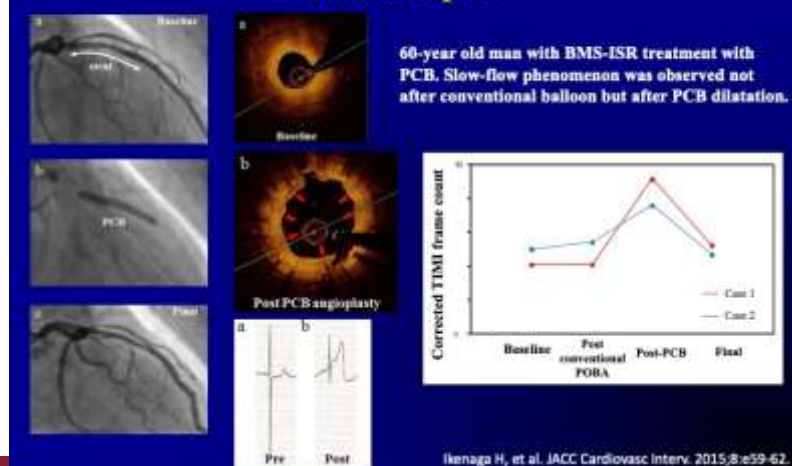
# Do We Need a Sirolimus DCB?

- Sirolimus is the standard for coronary artery disease treatment via DES and proven to be safe and effective
- Ptx modifications (crystalline form) means coating integrity and transfer are variable with substantial portion lost downstream into blood and tissues
- Loss of Ptx into body remains a significant safety concern which was further exacerbated by Katsanos analysis in published in JAHA

## Downstream Findings in Porcine Skeletal Muscle (28-Day)

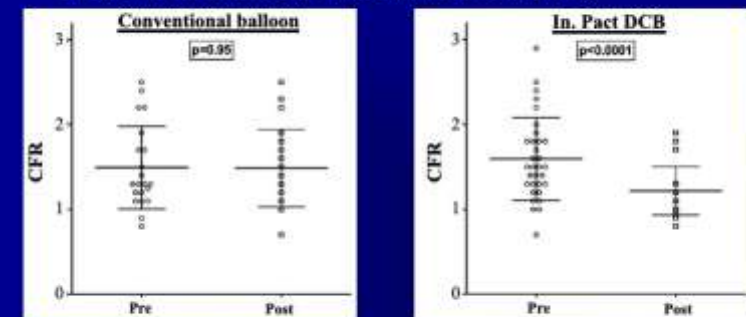


## How about in Coronary Angioplasty? Transient Slow-Flow Phenomenon After PCB Angioplasty : 2 case report



## PTCA With Drug-Coated Balloons Is Associated with Immediate Decrease of Coronary Flow Reserve (CFR)

32 stable CAD or ACS patients who were treated with conventional balloon and In Pact DCB for ISR or de novo lesion in coronary artery



Young M, et al. Catheter Cardiovasc Interv. 2013;81:582-6.

Decreased CFR (dysfunction of microcirculation) suggests the potential adverse effect of DCB in terms of downstream microvascular endothelial function.

# Sirolimus offers potential benefits over Paclitaxel

|                                 | SIROLIMUS (OR ANALOGS) | PACLITAXEL      |
|---------------------------------|------------------------|-----------------|
| Inhibition of SMC proliferation | ++                     | ++              |
| Inhibition of SMC migration     | ++                     | +               |
| Inhibition of EC proliferation  | ++                     | ++              |
| Pro-apoptotic effects           | (+)                    | ++              |
| Therapeutic range               | <b>WIDE</b>            | <b>NARROW</b>   |
| Safety margin                   | <b>10'000 fold</b>     | <b>100 fold</b> |
| Anti-Restenotic impact          | ++                     | +               |
| Anti-inflammatory properties    | ++                     | (+) / -         |
| Tissue Absorption               | <b>SLOW</b>            | <b>FAST</b>     |
| Tissue Retention                | <b>SHORT</b>           | <b>LONG</b>     |

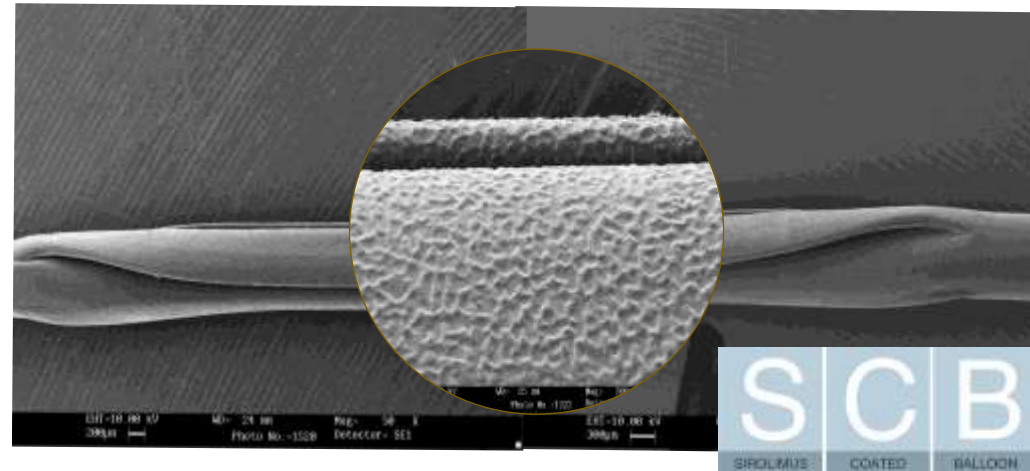
# Sirolimus Coated Balloons – Technical challenges

- **Enhance tissue absorption**
  - Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently
- **Extend tissue retention**
  - Sirolimus must be continuously delivered over time, so some form of “time release mechanism” must be employed to maintain therapeutic levels

# ***MAGIC TOUCH – Sirolimus Coated Balloon***

- MAGICTOUCH® – SCB is Sirolimus Coated Balloon to treat coronary artery disease
- Delivers drug in 60 seconds
- Sub-micron phospholipid particles

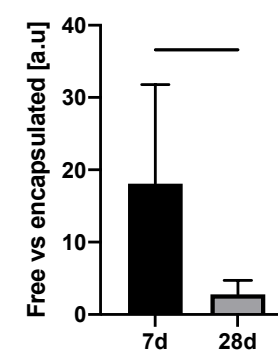
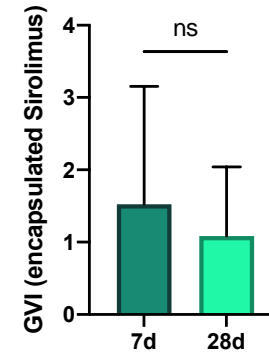
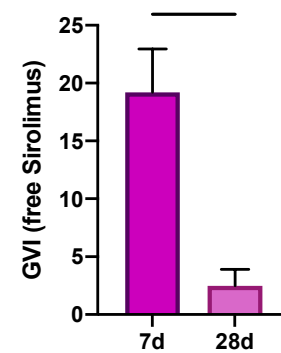
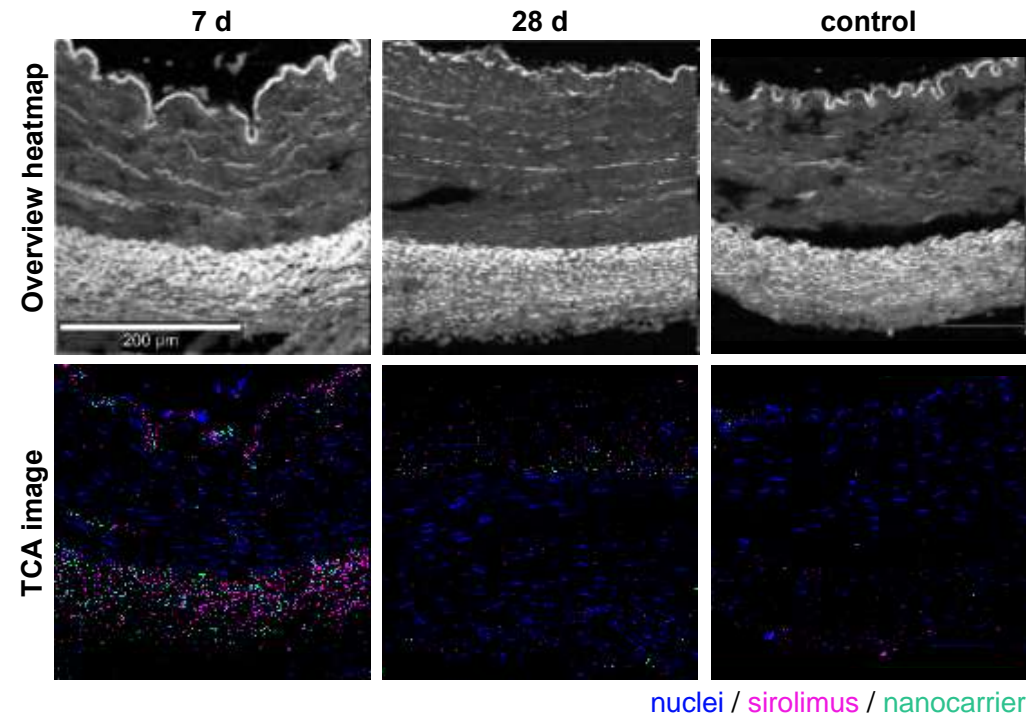
## **Nothing Leaves Behind**



## Raman imaging – free vs encapsulated sirolimus

### Preliminary results

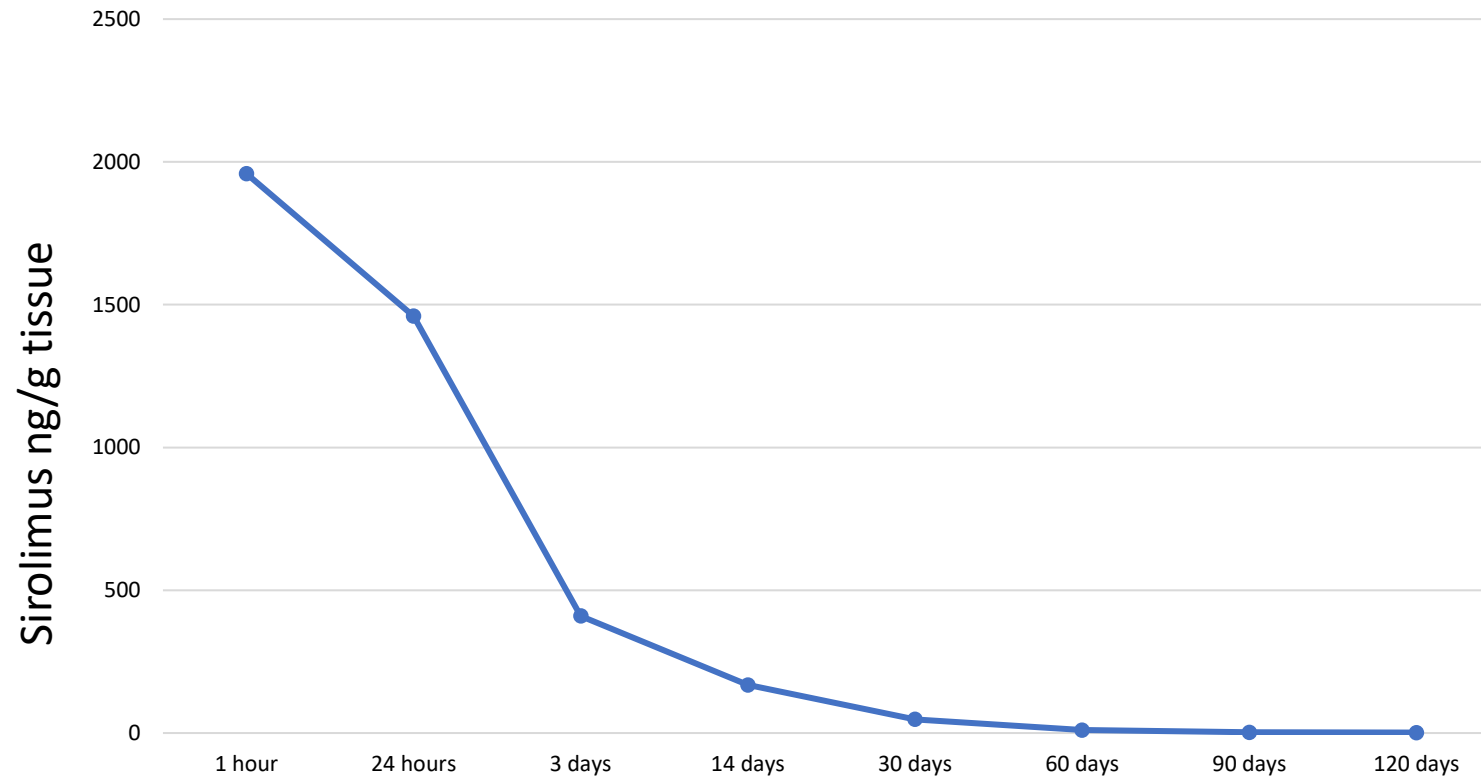
- (1) Raman maps were evaluated by TCA with the reference components for sirolimus and the nanocarrier-encapsulated drug
- (2) Mean GVI were determined for Raman images of free and encapsulated sirolimus



TCA: true component analysis

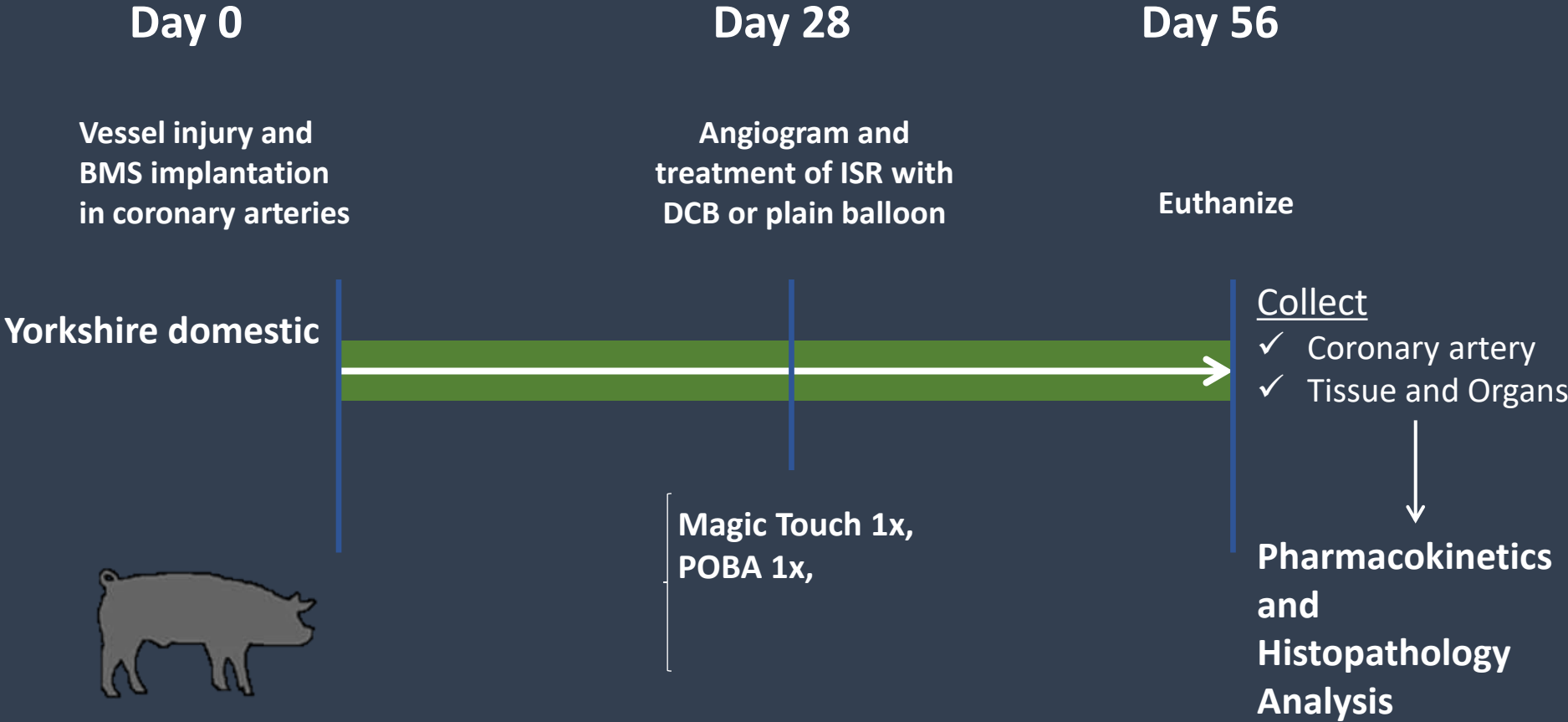
GVI: gray value intensity

### Arterial Wall Sirolimus (ng/g tissue) after MagicTouch



| 1 hour | 24 hours | 3 days | 14 days | 30 days | 60 days | 90 days | 120 days |
|--------|----------|--------|---------|---------|---------|---------|----------|
| 1451.3 | 1301.2   | 309    | 108     | 60.5    | BLQ     | BLQ     | BLQ      |
| 1541.3 | 1586.4   | 432.9  | 194     | 114     | 11.63   | 6.88    | 3.99     |
| 3147.3 | 1013.7   | 632.2  | 193.7   | 26.7    | 12.54   | BLQ     | BLQ      |
| 1791.7 | 1255.4   | 327.3  | 76.4    | 56.6    | 14.33   | BLQ     | BLQ      |
| 2210.7 | 1158.5   | 406.6  | 293.1   | 18.3    | 13.1    | BLQ     | BLQ      |
| 1613.9 | 2444.4   | 351.7  | 143.4   | 10.2    | 10.21   | 6.94    | 4.43     |
|        |          |        |         |         |         |         | BLQ      |

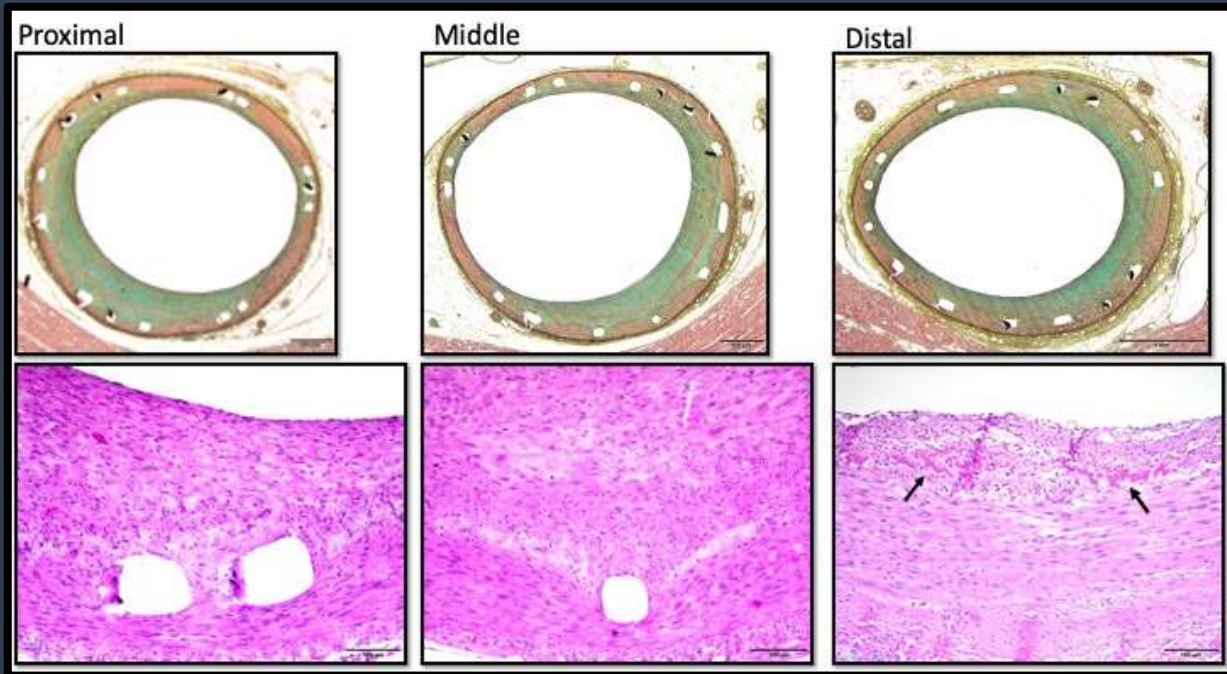
# Pre-clinical study ; swine coronary ISR lesion



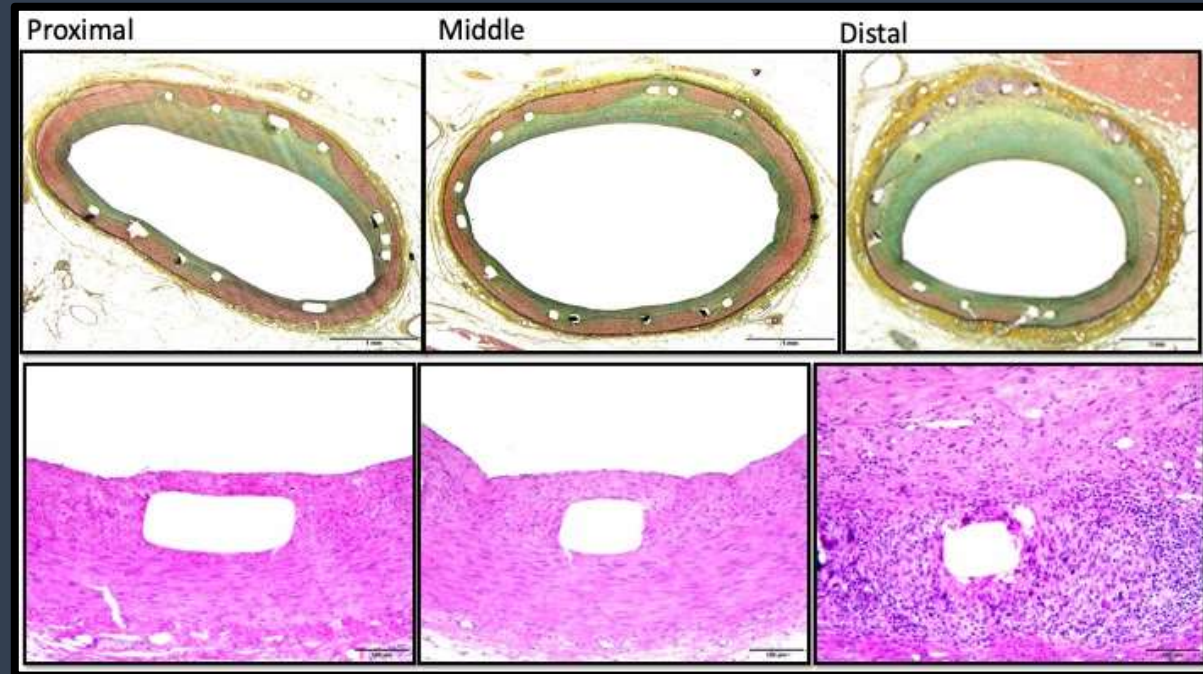


# 28 Day Histology

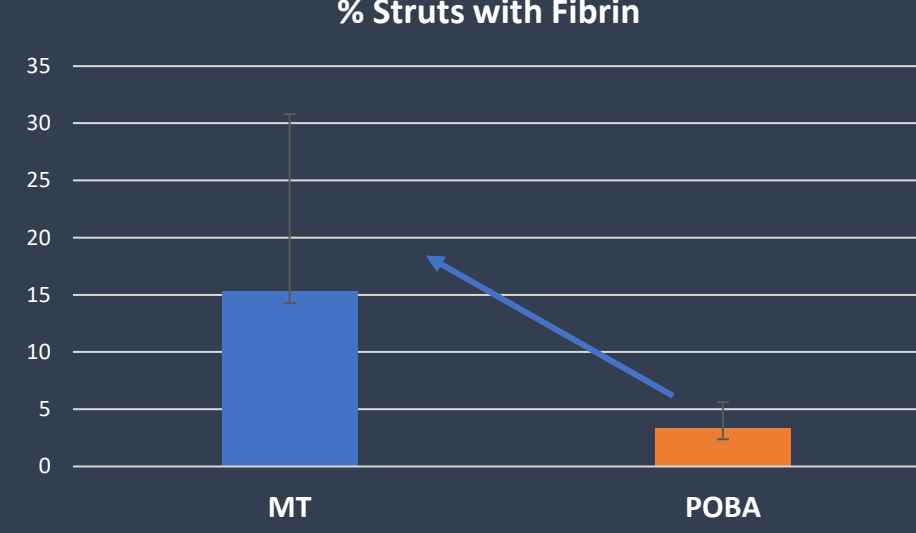
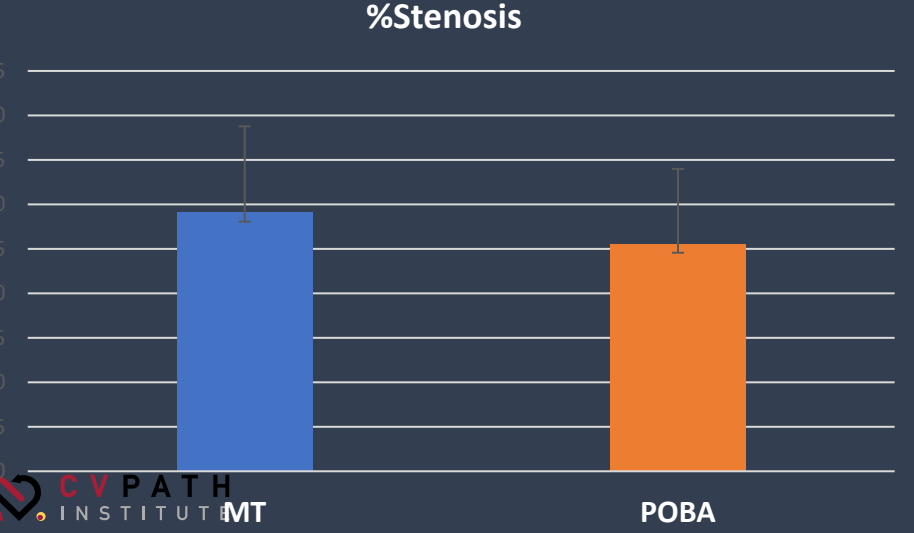
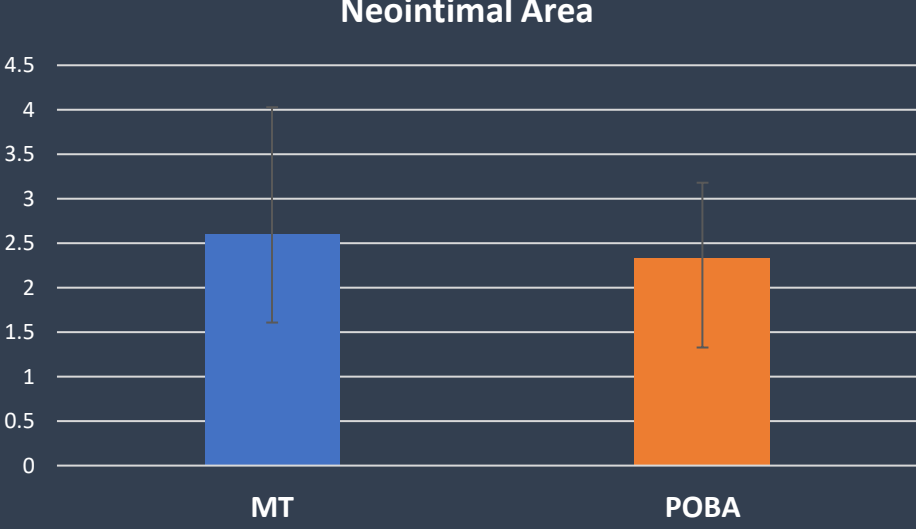
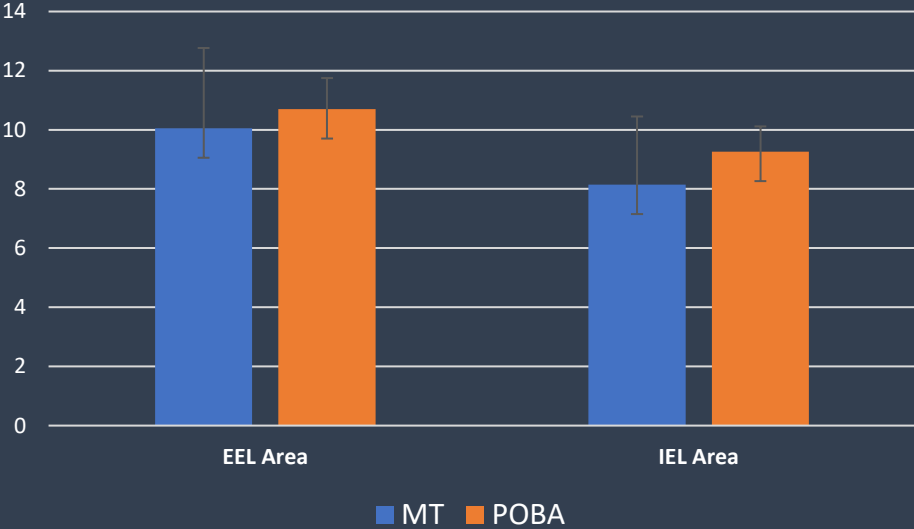
## MagicTouch



## POBA



# 28 Day ISR Histology MagicTouch



# Downstream Findings

- Total of 84 sections of myocardium were examined
- No incidence of myocardial infarction in either group
- Microscopic scarring observed in 2 downstream myocardium sections from MagicTouch and 3 sections from POBA treated areas
  - ALTHOUGH THERE WAS NO DIRECT VISUAL EVIDENCE OF DOWNSTREAM EMBOLI

# Magic Touch-FASICO registry

-all-comer registry of the first consecutive SCB patients (April-September 2016) at the first European centre that had the device available

-at least 6 months of follow up

-we investigated the immediate technical and short-term clinical performance of this device.

n=32, lesions=34

Age, mean [SD] 68.56 [ $\pm$ 9,45]

Male gender, % 11

Diabete mellitus, % 38

ACS, % 32

ISR, % 47

*ISR and failure of PCB* 31

*Moderate/severe calcifications* 32

*Multivessel disease* 50

|   |             |
|---|-------------|
| SCB length, mean, mm (SD)   | 21.02 (4.7) |
| SCB diameter, mean, mm (SD)   | 2.6 (0.52)  |
| Inflation time, mean, sec (SD)  | 50 (16.7)   |
| Inflation pressure, mean, atm. (SD)                                   | 11.6 (4.73) |
| Minimal lumen diameter pre, mean, mm (SD)                             | 0.39 (0.08) |
| Minimal lumen diameter post, mean, mm (SD)                            | 2.20 (0.44) |
| Hybrid approach SCB + DES on the same vessel, n (%)                   | 9 (26.5)    |
| Hybrid approach SCB + stent on another vessel (same procedure), n (%) | 5 (14.7)    |
| TnI peak after PCI, average value, $\mu$ g/l (SD)                     | 40 (21.6)   |
| Angiographic success, %   | 100         |
| Procedural success, %   | 100         |

Clinical follow up (average: 6.9  $\pm$  1.7 months).

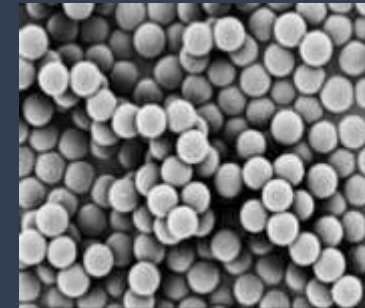
|  |           |
|--|-----------|
| DAPT ongoing, n [%]                    | 10 [31.6] |
| All-cause death, n [%]                 | 0         |
| Cardiac death, n [%]                   | 0         |
| Target lesion revascularization, n [%] | 3 [9.4]   |
| MI, n [%]                              | 0         |
| MACE, n [%]                            | 3 [9.4]   |

# ***Sirolimus DEB with SELUTION: MedAlliance***

- Micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus:

**Controlled** and **sustained** drug release mechanism

**Maintains** therapeutic effect in tissue over long period of time



- Novel Cell Adherent Technology – CAT:

CAT transfer membrane **houses** and **protects** micro-reservoirs during balloon insertion, lesion crossing and expansion.

CAT transfer membrane with embedded micro-reservoirs **releases** from balloon delivery system and **adheres** to vessel lumen with short balloon Inflation.



# Preclinical Study (Porcine Coronary Model)



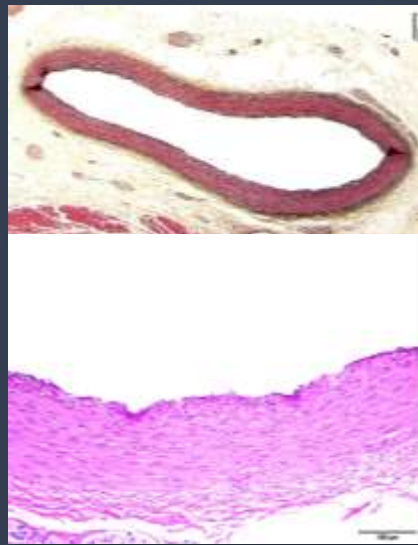
## Balloon (3.0 or 3.5 × 15 mm)

1. Excipient coated balloon : n=6
2. Non coated balloon : n=6
3. SELUTION 1× dose : n=6
4. SELUTION 3× dose : n=6

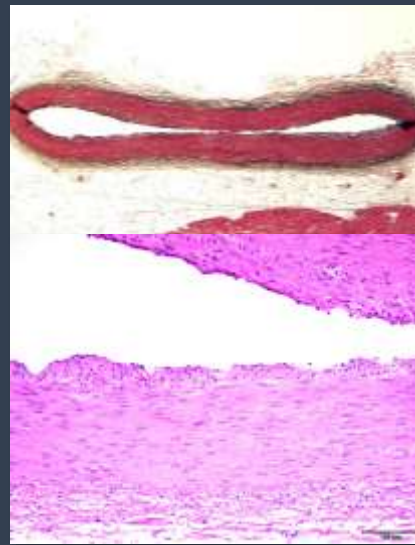
## Assessment of myocardium

1. Anterior, lateral, posterior, septal wall and right ventricle at similar level, and surrounded treated vessels area were sampled.
2. Ischemia area, Inflammation, foreign material and Thromboembolus were examined

# 30 Day Representative Histological Images



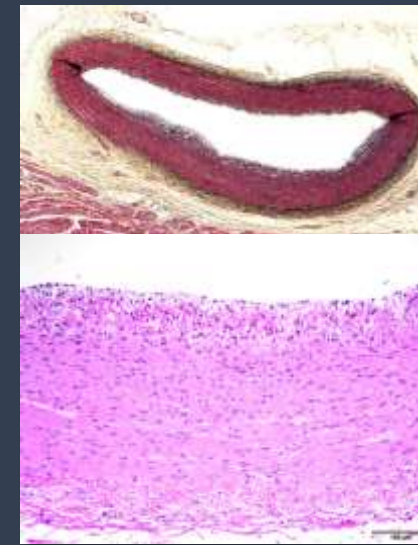
Excipient coated balloon



Non coated balloon

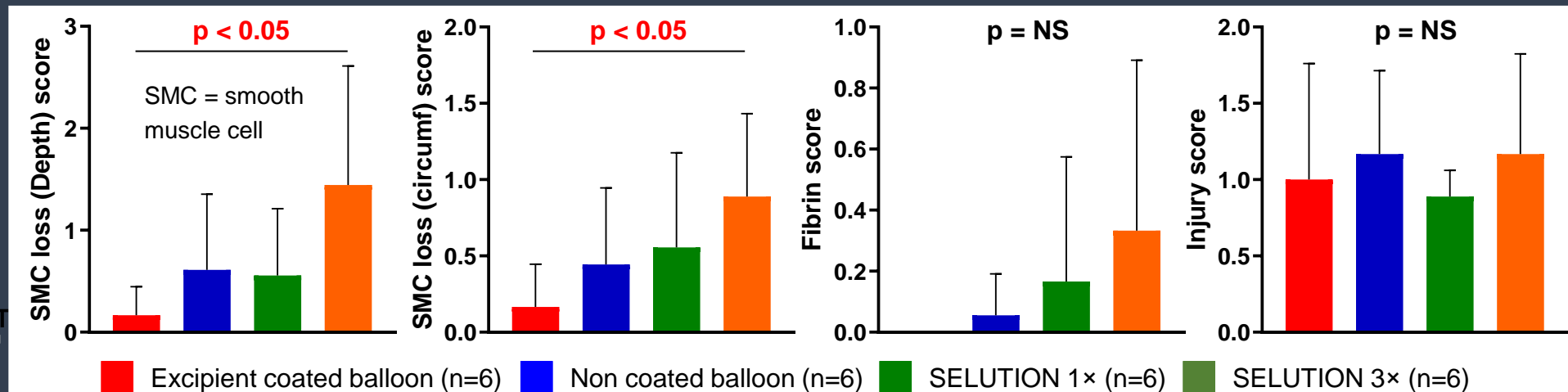


SELUTION 1x

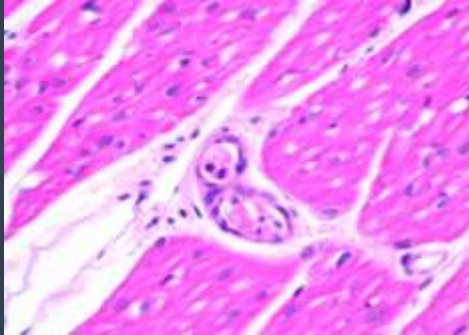


SELUTION 3x

## Morphometry analysis

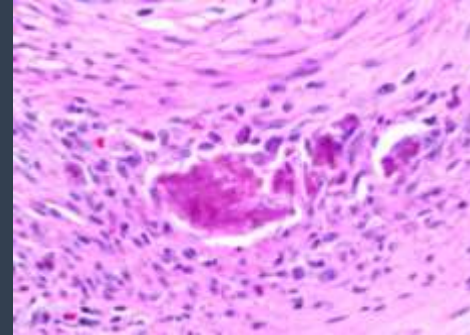


# 30 Day Downstream Findings in Porcine Myocardium



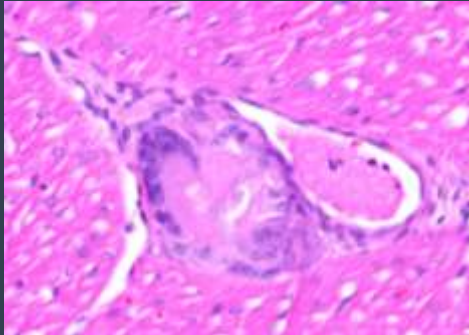
## Excipient balloon

Adjacent small arterioles show embolic amorphous material.



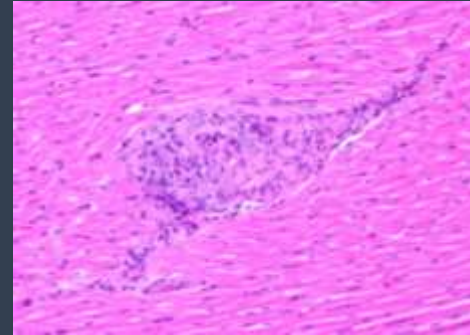
## SELUTION 1x

Epicardial coronary artery shows early calcified fibrin surrounding inflammatory reaction.



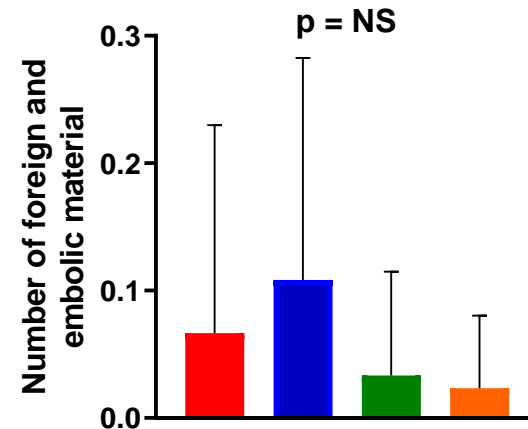
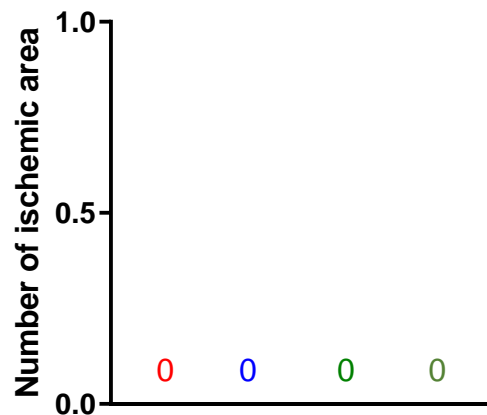
## Non coated balloon

Adjacent arterioles show amorphous foreign material with inflammatory reaction.



## SELUTION 3x

Giant cells surrounding a minute birefringent foreign material.



Excipient coated balloon (n=6) Non coated balloon (n=6) SELUTION 1x (n=6) SELUTION 3x (n=6)



# Peripheral FIH – SELUTION

## SFA

ClinicalTrials.gov ID: NCT02941224



### OBJECTIVES

To assess the safety and efficacy of the SELUTION DCB in treatment of de-novo occluded/stenotic or re-occluded/restenotic lesions of SFA and/or PA, assessed at multiple time points clinical, angiographic and/or ultrasound assessment



### PRINCIPLE INVESTIGATOR

▶ **Thomas Zeller**, Bad Krozingen, Germany



### DESIGN

- ▶ Prospective, controlled, multi-center, open, single-arm clinical investigation
- ▶ 50 patients
- ▶ 4 centers in Germany



### PRIMARY ENDPOINTS

- ▶ **Angiographic Late Lumen Loss (LLL) by QVA – 6 months**

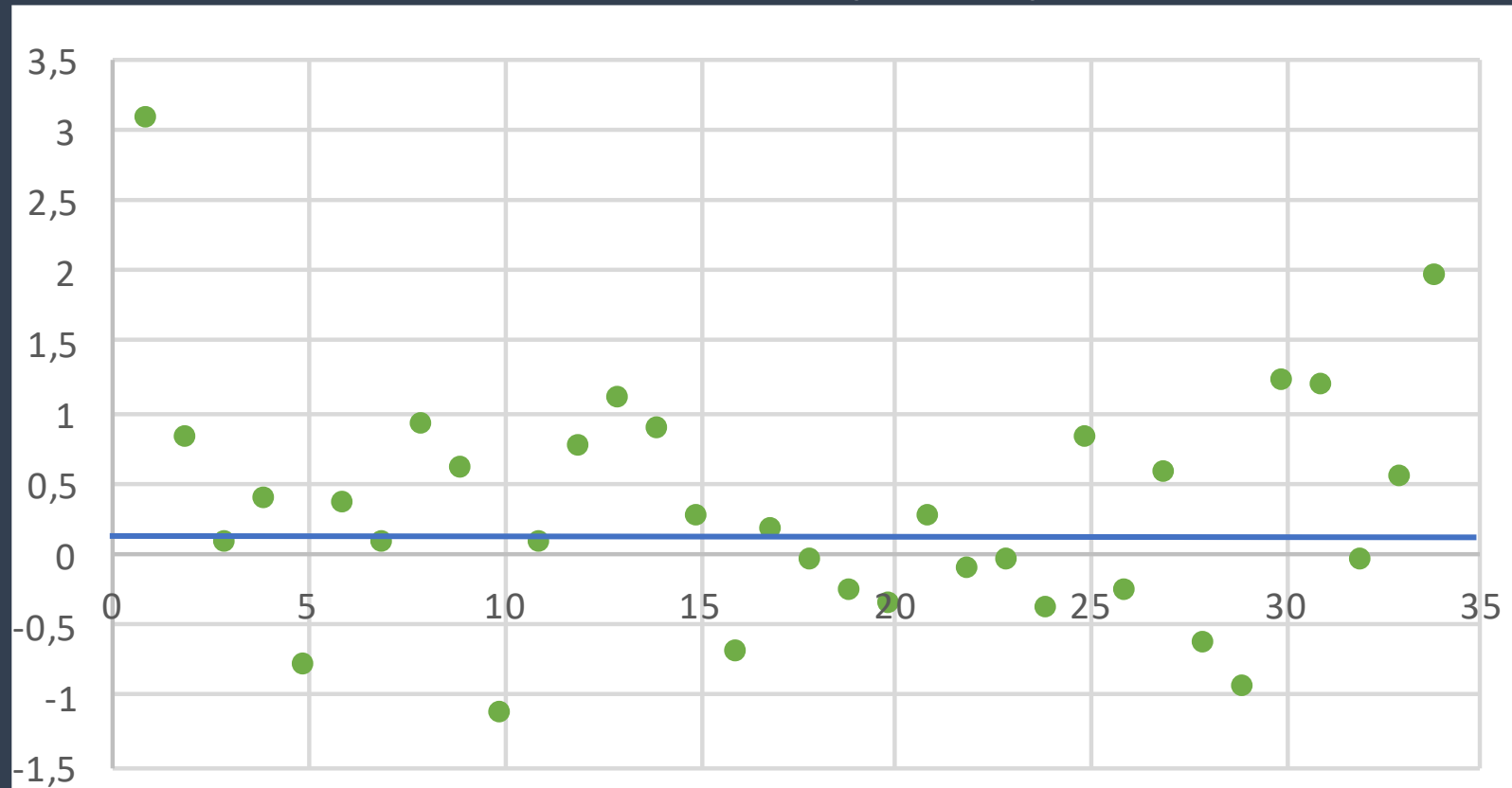


### SECONDARY ENDPOINTS

- ▶ **Major adverse Events** (Death, Thrombosis, Amputation, CD-TLR) **6 months**
- ▶ **Primary Patency** – Freedom from CD-TLR and absence of Restenosis by DUS - **6, 12 and 24 months**
- ▶ **Angiographic Binary Restenosis (ABR) by QVA - 6 months**
- ▶ **Composite of Freedom from Amputation and Freedom from CD-TVR – 12 and 24 months**
- ▶ **Change of ABI, WIQ and Qol - 6, 12 and 24 months**

# SELUTION PRIMARY ENDPOINT

LLL at 6 months (LLL N=34)



**0.19 mm\***  
**(-1.16; 3.07)**

# SELUTION Results in Context



► Results from different trials are not directly comparable. Information provided for educational purposes.

| Trial                   | RANGER SFA | PACIFIER        | Tepe et al        | LEVANT I | FemPac     | BIOLUX-PI     | ILLUMENATE | SELUTION |
|-------------------------|------------|-----------------|-------------------|----------|------------|---------------|------------|----------|
| Therapy                 | Ranger     | IN.PACT Pacific | DCB not specified | Lutonix  | Ptx coated | Passeo-18 Lux | Stellarex  | SELUTION |
| Mean Lesion Length (mm) | 6.8        | 7.0             | 5.7               | 8.1      | 5.7        | 6.1           | 7.2        | 6.4      |
| Bailout Stenting (%)    | 21%        | 21%             | 11%               | 3%       | 9%         | N/A           | 5%         | 8%       |

# Conclusion / Take-home Message

- DCB are a newer technology which are here to stay and paclitaxel coated DCBs have demonstrated efficacy in a number of important clinical indications (ISR, Above the Knee De Novo Disease, AVF/AVG)
- Concerns regarding the safety of paclitaxel DCBs remain although these have been somewhat allayed by the SWEDEPAD data
  - PTX WITH NARROW THERAPEUTIC INDEX
  - SIGNIFICANT LOSS OF PTX INTO BODY AND DOWNSTREAM EMBOLI
- Sirolimus DCBs are emerging as a formidable competitor to both DES (both for De Novo Disease and for ISR) but larger more convincing trials are needed
- Because sirolimus DCBs require carriers (for the most part), it is important to evaluate safety of these devices at later timepoints when sirolimus levels in tissues have declined
- Several new randomized trials of sirolimus DCBs are expected to launch this year