# *The Magic Touch - PTA Sirolimus Coated Balloon - Insights from pre-clinical evaluation*

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# *Disclosure*

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

**Employment in industry: No**

**Honorarium**:

Amgen; Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

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**Owner of a healthcare company: No**

**Stockholder of a healthcare company: No**

# *Elements of an Effective DCB Formulation*

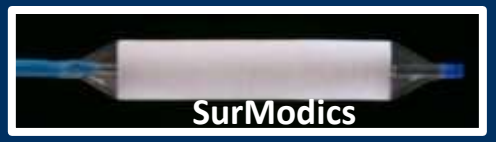
- ✓ Must deliver large quantities of the drug within seconds
- ✓ Distribute within the media in the first few days
- ✓ Therapeutic drug levels must be maintained for more than 4 weeks
- ✓ Must allow rapid healing as compared to DES
- ✓ No need for long-term anti-platelet therapy Biologic effects must be observed by histology at 28-days
- ✓ Effective drug delivery to target tissue while avoiding non-target effect

# *Drug Coated Balloon Devices (Peripheral artery)*

| Device | Company | Coating | Drug dose (µg/mm²) | 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*

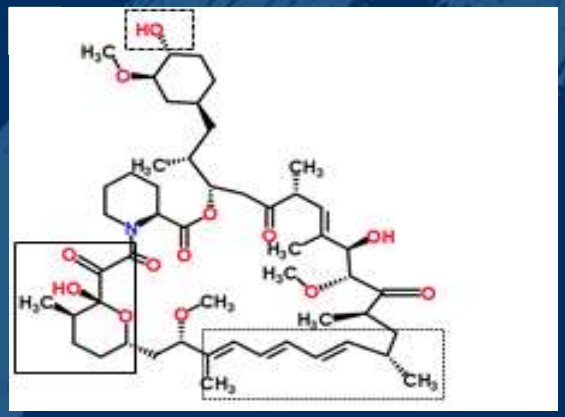






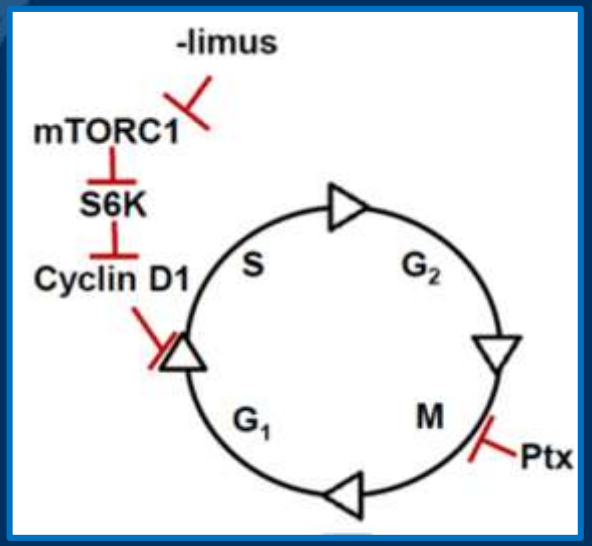

# *Sirolimus and Paclitaxel*

## *Sirolimus*



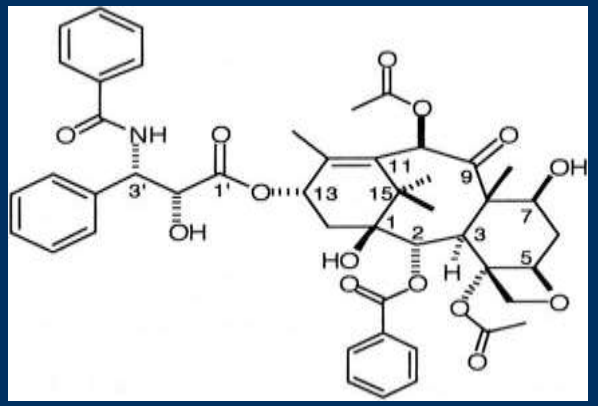
Solid line : FKBP12 binding site
Dotted line : mTOR binding site

**Sirolimus inhibits mTOR and is part of the phosphatidylinositol kinase-related family of serine/threonine kinases.**




Habib et al. Interventional Cardiology Clinics 2016;5:321-329

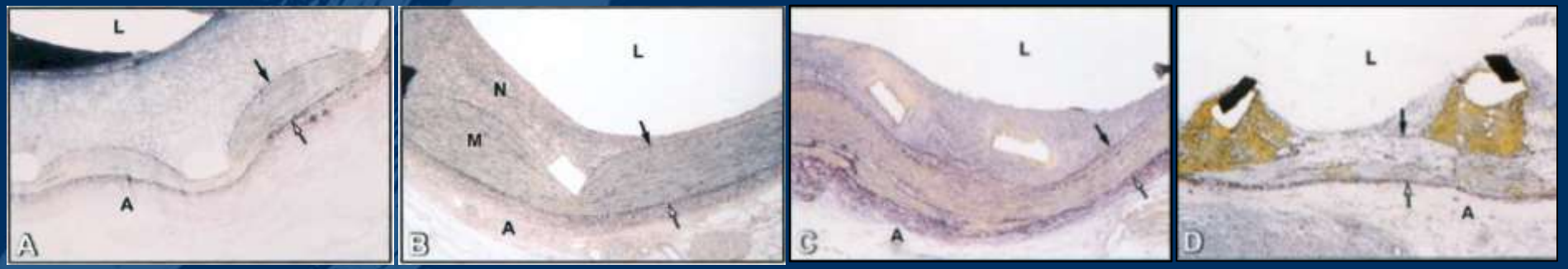
## *Paclitaxel*



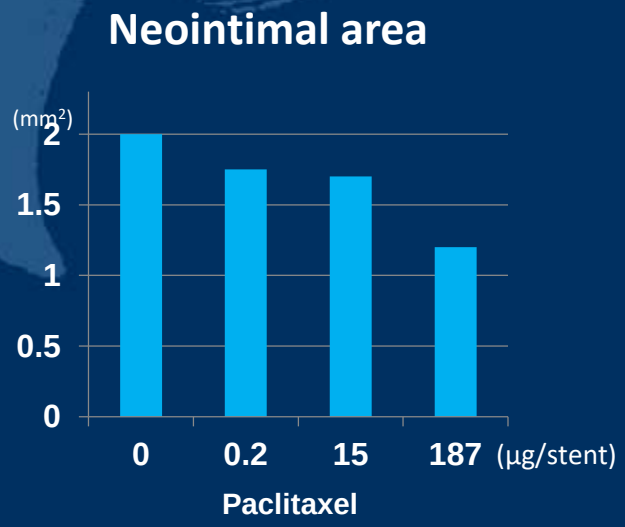
**Paclitaxel binds to beta-tubulin and impairs microtubular disassembly and halts the cell cycle between G2 and M**

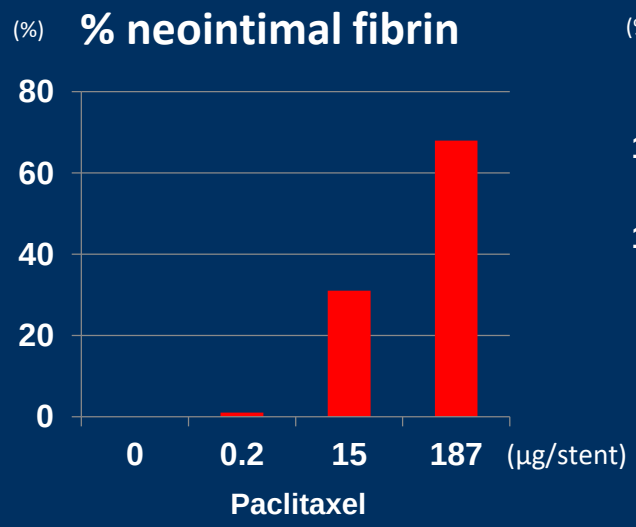
Gupta ML et al. PNAS 2003;100:6394-6397

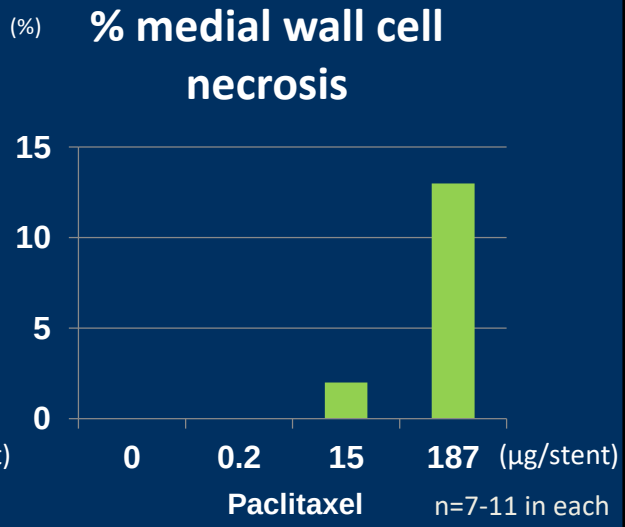
# *Dose dependent effect and toxicity of paclitaxel eluting stent in porcine coronary artery (28days)*




BMS | Paclitaxel 0.2µg/stent | Paclitaxel 15µg/stent | Paclitaxel 187µg/stent




Heldman AW, et al. Circulation. 2001;103:2289-95.

# *Sirolimus offers potential benefits over Paclitaxel*

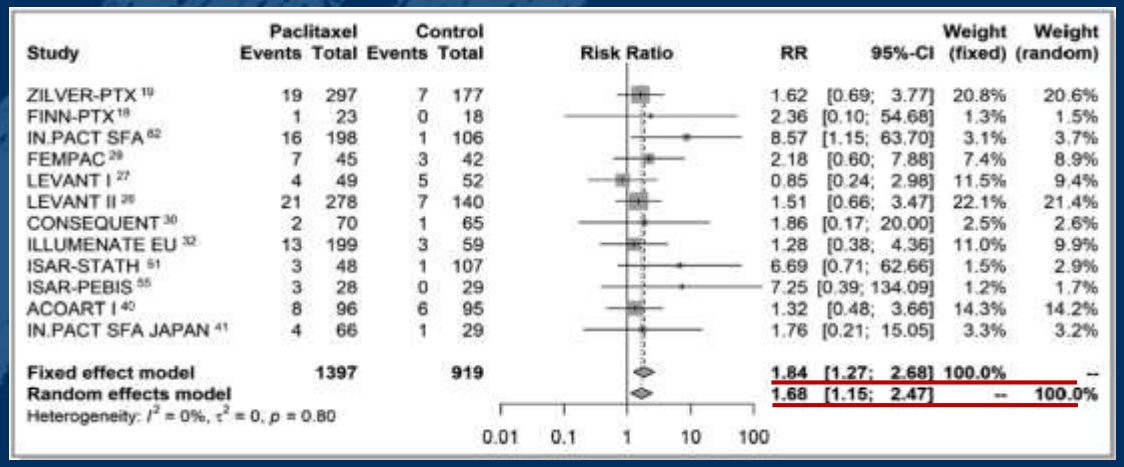
Common anti-proliferative drug for DCB is currently **PACLITAXEL**, however, **SIROLIMUS** (rapamycin) offers potential benefits over Paclitaxel.

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

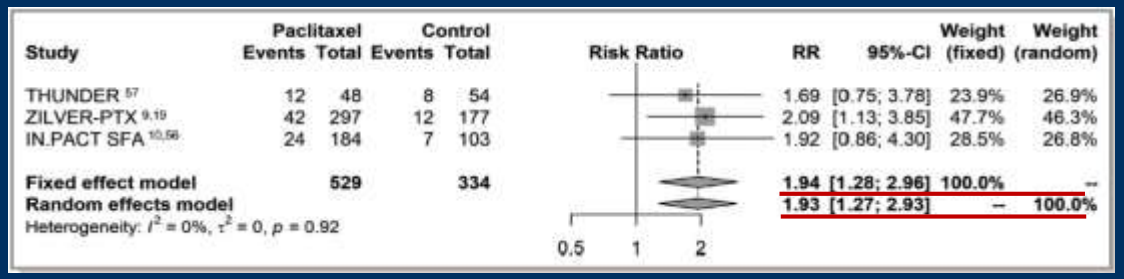
Modified Wessely R, et al. JACC 2006:47(4);708–14.

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

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




**Random effects forest plot of all-cause death at 4 to 5 years**




Meta-Analysis of RCT

**Causes of Death**

| | Paclitaxel-Coated Balloon (IN.PACT SFA) at 3 Years[10,62] | | Paclitaxel-Coated Stent (ZILVER PTX) at 2 Years[19,23] | |
|---|---|---|---|---|
| | 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

# *Sirolimus Coated Balloons – Technical challenges*

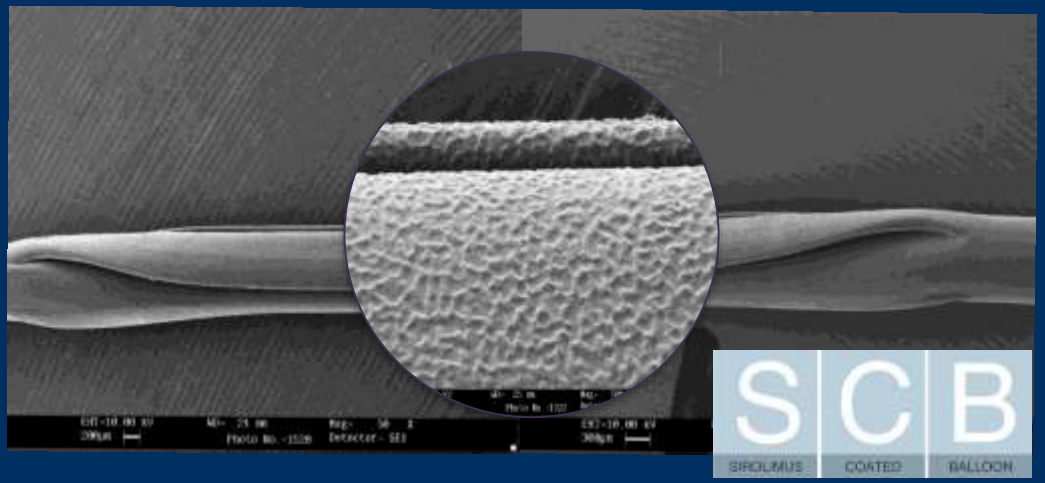
- **Enhance tissue absorption**
  - **Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of "instant glue" is required to transfer the drug from the balloon to the tissue efficiently**

- **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 particles
- Supersedes limitations of Paclitaxel
- No permanent metallic cage
- No more toxic effects
- Address many limitations of DES

**Nothing Leaves Behind**



# *Pre-clinical study 1; swine iliofemoral artery*

***Day 0***

**DCB treatment in iliofemoral arteries**

***Day 28***

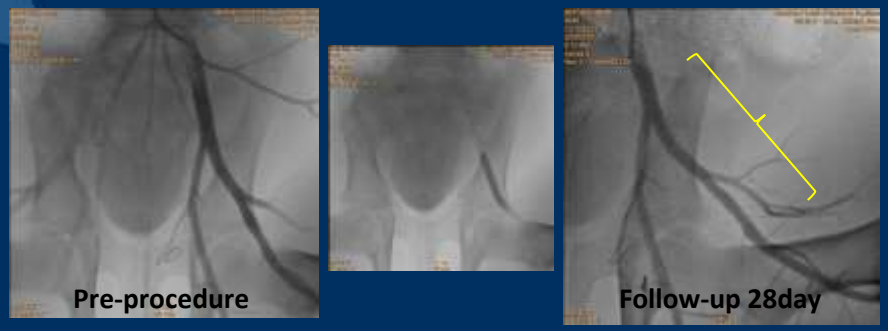
**Euthanize**

**Yorkshire domestic Swine n=2 (total 4 vessels)**

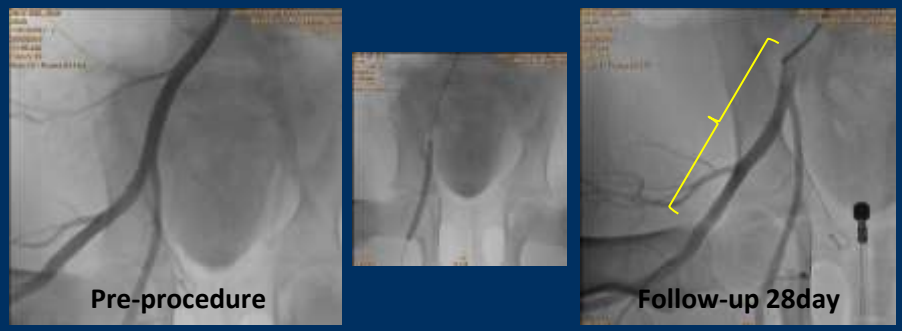
**Xtreme Touch (Magic Touch) SCB 3x**
**vs**
**Control balloon**

✓ Collect iliofemoral arteries and histopathologic analysis

***Control balloon***

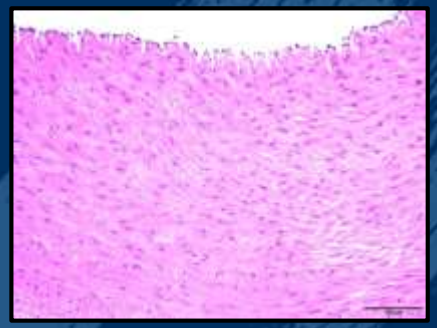


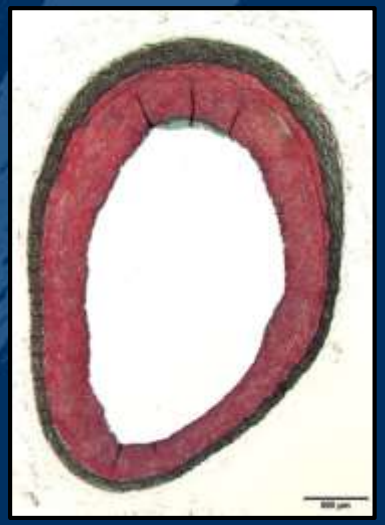

***XtremeTouch SCB 3x***



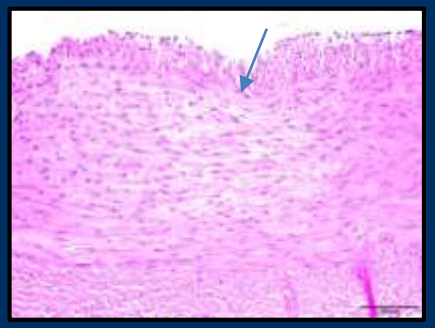
# *Histopathologic analysis for SCB treated site*

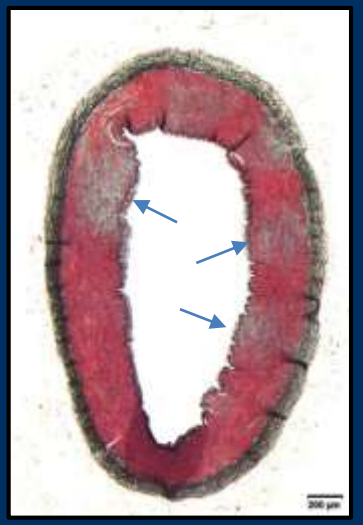
***Control balloon***



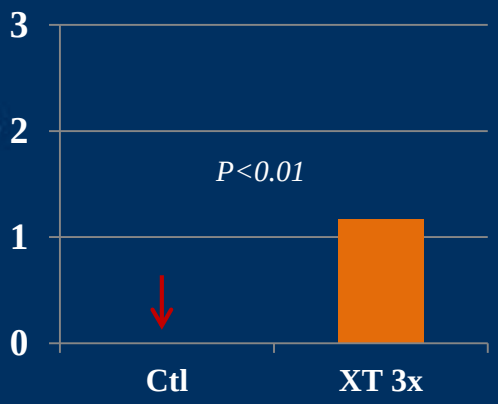


***XtremeTouch SCB 3x***

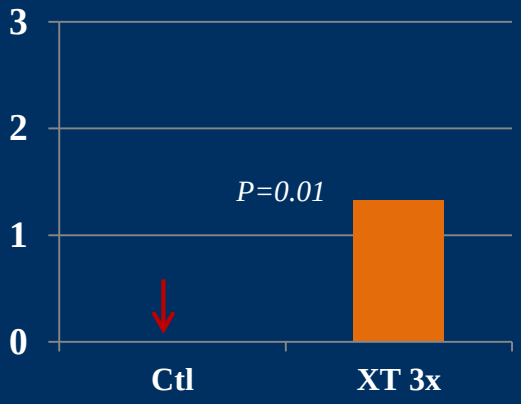




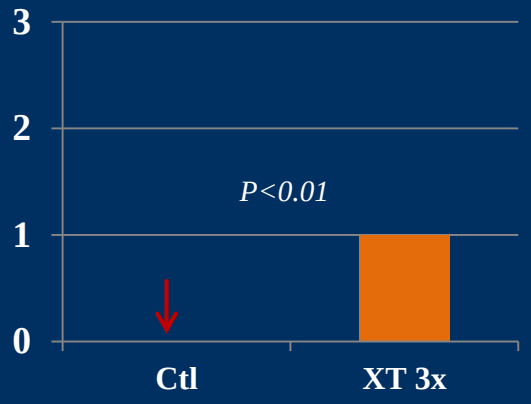
**Medial proteoglycan collagen score**




**Medial SMC loss score (Depth)**




**Medial SMC loss score (Circumf)**




N=6 sections (from 2 animal) in each * All section base analysis

# *Pre-clinical study 2; swine coronary ISR lesion*

***Day 0***

**Vessel injury and BMS implantation in coronary arteries**

***Day 28***

**Angiogram and treatment of ISR with DCB or plain balloon**

***Day 56***

**Euthanize**

**Yorkshire domestic Swine n=7 (total 16 vessels)**

**Magic Touch 1x,**
**Magic Touch 3x,**
**POBA 1x,**
**POBA 3x**

Collect
- ✓ Coronary artery
- ✓ Blood
- ✓ Tissue and Organs

↓

**Pharmacokinetics and Histopathology Analysis**

# *Pharmacokinetic data*

## Blood concentration [Sirolimus, ng/mL] in DCB 3x animal

| Baseline | 15min | 1h | 24h | 33day |
|---|---|---|---|---|
| BQL | 23.3±0.35 | 17.0±1.20 | 1.11±0.15 | BQL |

BQL: Below Quantitation Limit (0.250 ng/ml)

## Artery and surrounding myocardium [Sirolimus, ng/g] in DCB treated animal (33-day after DCB)

| Animal # | Treatment | Artery | | | Surrounding myocardium | |
|---|---|---|---|---|---|---|
| | | DCB treated section | Proximal section | Distal section | Middle of treated area | Distal of treated area |
| Animal #1 | DCB 3x (LAD) | 525 | BQL | BQL | BQL | BQL |
| Animal #2 | DCB1x (RCA) | 118 | BQL | BQL | BQL | BQL |

BQL: 50.0 ng/g

## Myocardium and other organs [Sirolimus, ng/g] in DCB treated animal (33-day after DCB)

| Animal # | Treatment | AA | AL | AP | AS | APRV | MA | ML | MP | MS | MPRV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Animal #1 | DCB 3x (LAD) | BQL | BQL | BQL | BQL | BQL | BQL | BQL | BQL | BQL | BQL |
| Animal #2 | DCB1x (RCA) | BQL | BQL | BQL | BQL | BQL | BQL | BQL | BQL | BQL | BQL |

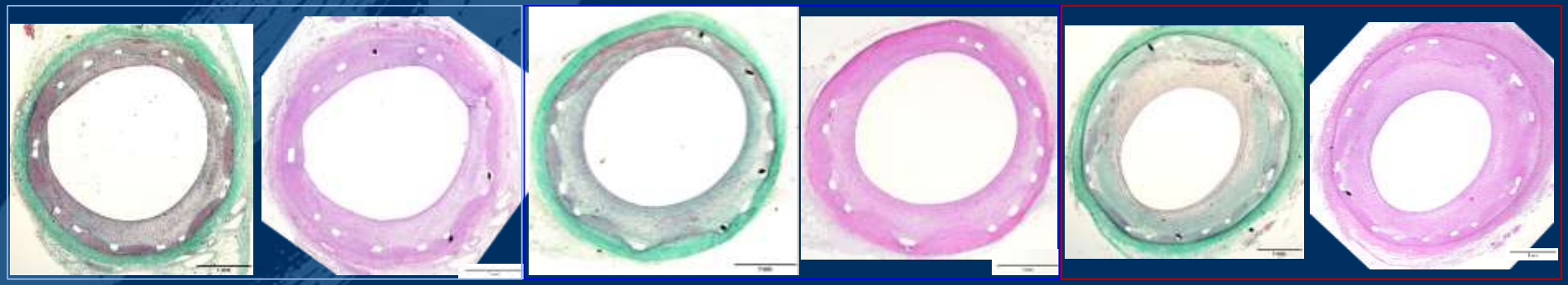
| Animal # | Treatment | Lung | Liver | Bone Marrow | Spleen | Kidney |
|---|---|---|---|---|---|---|
| Animal #1 | DCB 3x (LAD) | BQL | 2.76 | BQL | BQL | BQL |
| Animal #2 | DCB1x (RCA) | BQL | BQL | BQL | BQL | BQL |

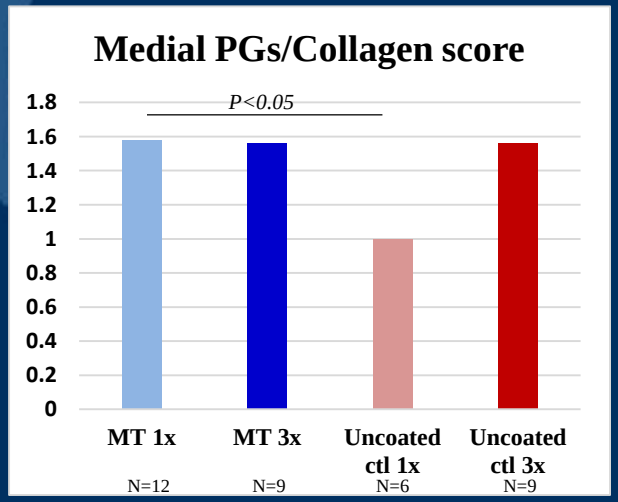
BQL: 2.5 ng/g

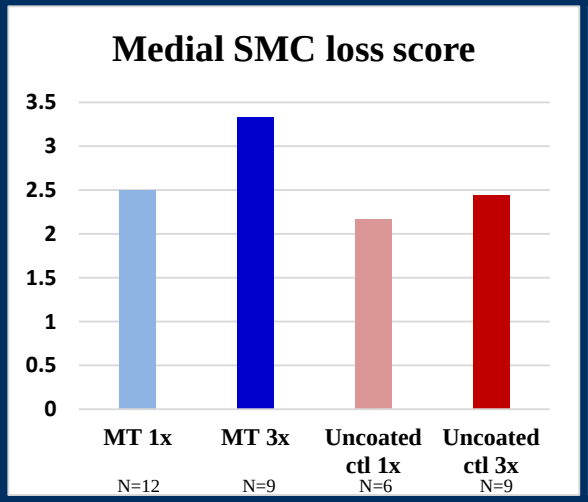
AA: apical anterior, AS: apical septum, AP: apical posterior, AL: apical lateral, ARV: apical right ventricle
MA: mid anterior, MS: mid septum, MP: mid posterior, ML: mid lateral, MRV: mid right ventricle

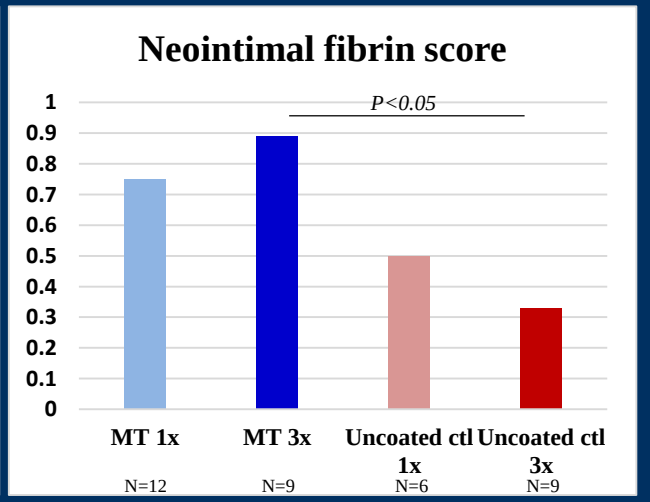
# *Histopathologic analysis for SCB vs uncoated POBA treated site*

*MagicTouch SCB 1x* | *MagicTouch SCB 3x* | *Control POBA 3x*





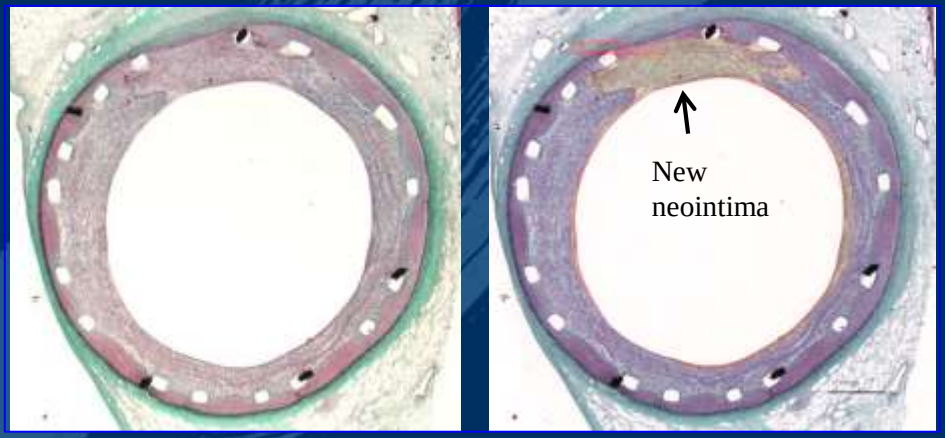



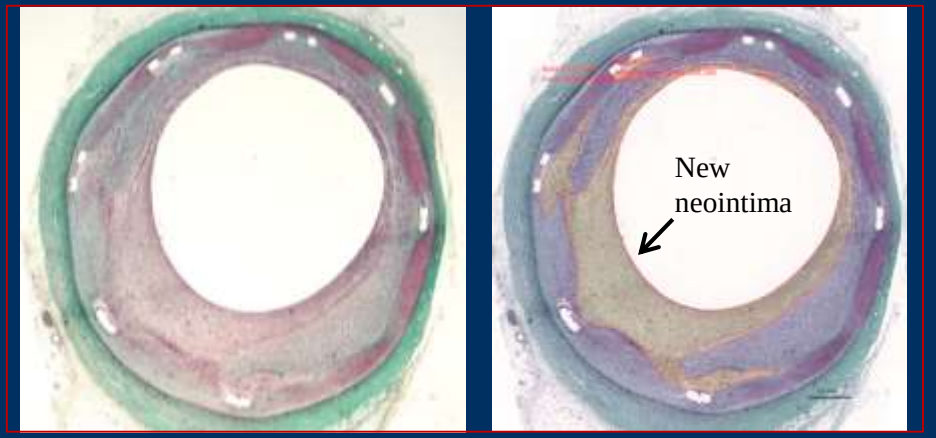

* All section base analysis

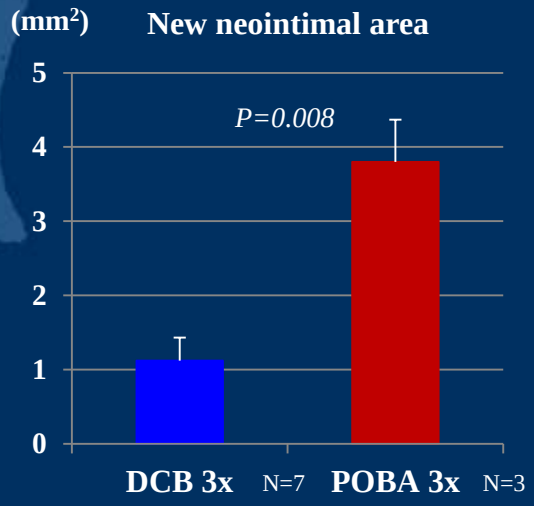
# *New neointimal growth was suppressed in SCB treatment; Major IEL disruption lesion*

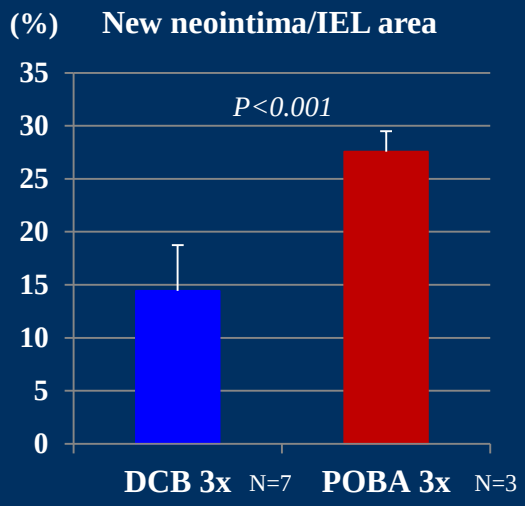
## *MagicTouch SCB 3x*

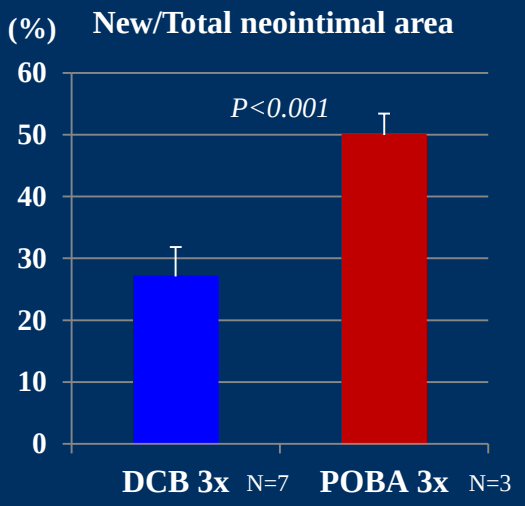



## *Control POBA 3x*




* All section base analysis

# *Summary*

- ✓ Neointimal hyperplasia is the major cause of restenosis. Pharmacologic agents used on DES and DCB mainly inhibit SMC proliferation.
- ✓ The most commonly used anti-proliferative agent for DCB is currently Paclitaxel (Ptx). However cytotoxic Ptx has narrow therapeutic window compared with sirolimus and its analogues.
- ✓ Recent meta-analysis suggested that DES and DCB using PTX associated with higher death rates at 2 to 5 years, although the mechanisms and results still remain controversial.
- ✓ MagicTouch Sirolimus DCB has novel coating technology allowing better tissue retention of sirolimus drug.
- ✓ Our pre-clinical studies support efficacy of MagicTouch Sirolimus Coated Balloons.
- ✓ Anti-restenotic effect with minimal non-target organ drug levels were observed.
- ✓ MagicTouch DCB will be an important non-paclitaxel option for peripheral and coronary intervention

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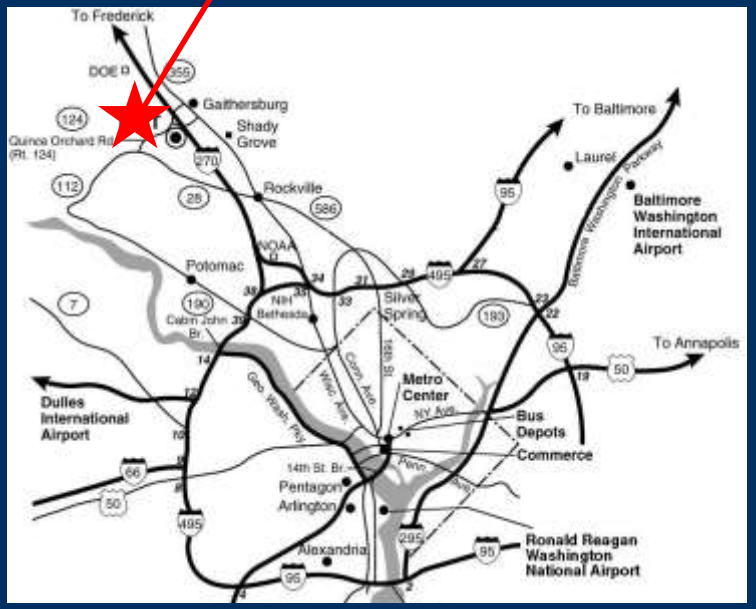
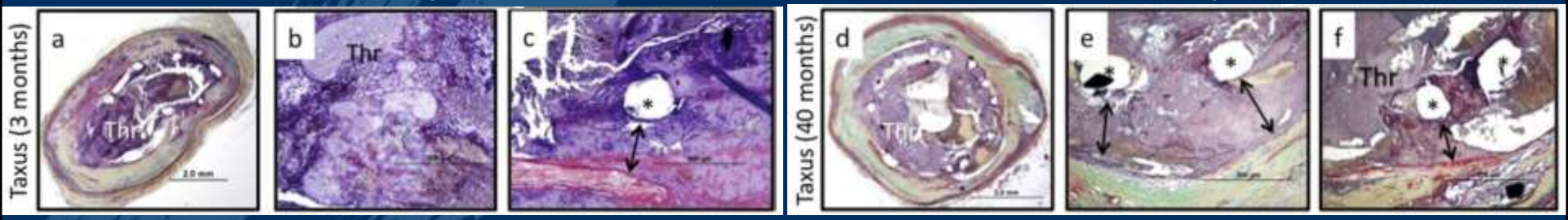



CVPATH INSTITUTE

# ≥30 days Outcomes after Paclitaxel-DES Implantation in Coronary Artery: CVPath autopsy registry

**Late stent thrombosis; 69-year old man (SVG)**

**Late stent thrombosis; 48-year old man (LAD)**




| Patients, n | 66 |
|---|---|
| Age, yrs | 60±12 |
| Male | 61 (77%) |
| Stent related cardiac death | 22 (33%) |

| Lesions, n | 94 |
|---|---|
| Duration, days | 211 (118-383) |
| Stent length, mm | 21.5 (16.0-30.0) |
| Stent outcome: Thrombosis | 25 (27%) |
| Restenosis | 5 (5%) |
| Struts with fibrin, % | 50 (36-69) |
| Uncovered struts, % | 20 (8-49) |
| Malapposition, n(%) | 18 (19%) |

## Cause of late thrombosis in PES

| Late thrombosis (≥ 30days), n | 25 |
|---|---|
| AMI, penetration/prolapse of necrotic core | 5 (20%) |
| Bifurcation | 9 (36%) |
| Long/overlapping stents | 2 (0.1%) |
| Underexpansion | 1 (0.04%) |
| Isolated uncovered struts | 1 (0.04%) |
| Localized hypersensitivity reaction | 0 (0.0%) |
| Malapposition from excessive to fibrin * | 7 (28%) |

*We have no late stent thrombosis case of sirolimus-eluting stent due to excessive fibrin around stent strut.

Nakazawa G, et al. JACC. 2011;57:390-8.

# *The Magic Touch - PTA Sirolimus Coated Balloon - Insights from pre-clinical evaluation*

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