2019 euro PCR

The Magic Touch- Sirolimus-eluting balloon: Insights from pre-clinical evaluation

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Potential conflicts of 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.

Employment in industry: No

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

Institutional grant/research support: R01 HL141425 Leducq Foundation Grant; 480 Biomedical; 4C Medical; 4Tech; Abbott; Accumedical; Amgen; Biosensors; Boston Scientific; Cardiac Implants; Celonova; Claret; Concept Medical; Cook; CSI; DuNing; Edwards; Emboline; Endotronix; Envision Scientific; Lutonix/Bard; Gateway; Lifetech; Limflo; MedAlliance; Medtronic; Mercator; Merill; Microport; Microvention; Mitraalign; Mitra assist; NAMSA; Nanova; Neovasc; NIPRO; Novogate; Occulotech; Orbus Neich; Phenox; Profusa; Protembis; Qool; Recor; Senseonics; Shockwave; Sinomed; Spectranetics; Surmodics; Symic; Vesper; W.L. Gore; Xeltis.

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 for peripheral artery

Device	Company	Coating	Drug dose (µg/mm²)
IN.PACT	Medtronic Vascular, Santa Clara, CA, USA	Paclitaxel–urea	3.5
Passeo-18 Lux®	Biotronik, Bülach, Switzerland	Paclitaxel–butyryl-tri-hexyl citrate	3.0
Lutonix® 035 DCB	BARD, Murray Hill, NJ, USA	Paclitaxel–polysorbate/sorbitol	2.0
Ranger	Boston Scientific	Paclitaxel–Acetyl Tributyl Citrate 2	2.0
Stellarex®	Covidien, Mansfield, MA, USA	Paclitaxel-polyethylene glycol	2.0
SurVeil™DCB	SurModics, MN, USA (Abbott)	Paclitaxel-proprietary photolink®	2.0

Lutonix

IN.PACT

SurModics

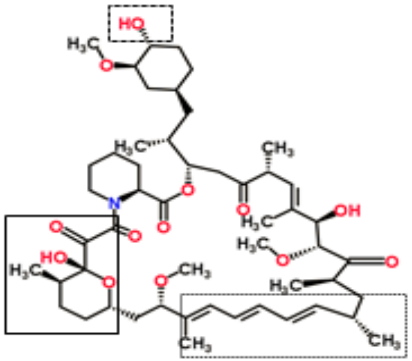
Ranger

Stellarex

Passeo-18 Lux®

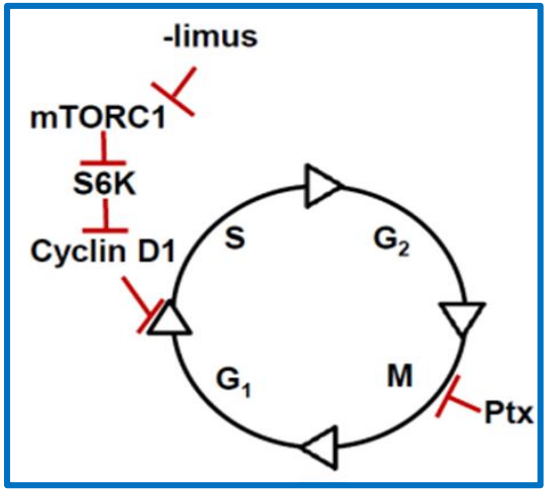
Sirolimus and Paclitaxel

Sirolimus



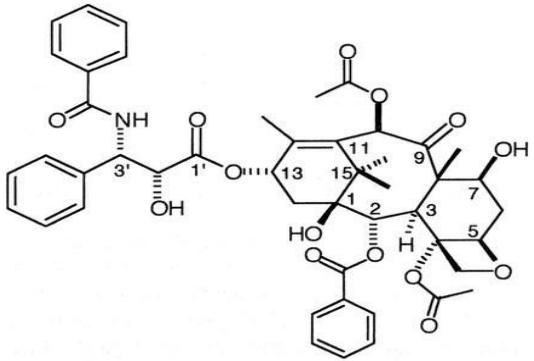
Solid line : FKBP12 binding site
Dotted line : mTOR binding site

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

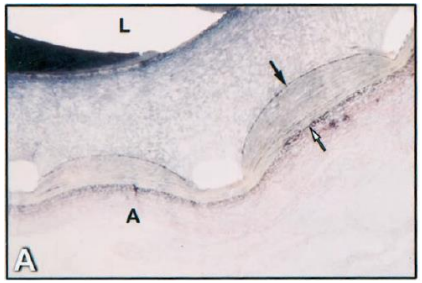
Sirolimus offers potential benefits over Paclitaxel

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

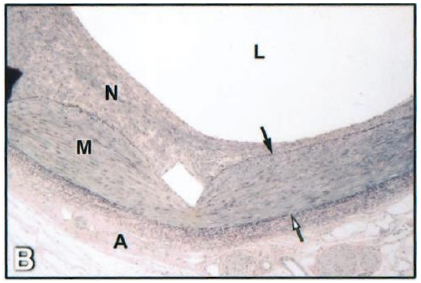
	SIROLIMUS (OR ANALOGS)	PACLITAXEL
Inhibition of SMC proliferation	+ +	+ +
Inhibition of SMC migration	+ +	+
Inhibition of EC proliferation	+ +	+ +
Pro-apoptotic effects	(+)	+ +
Therapeutic range	WIDE	NARROW
Safety margin	10,000 fold	100 fold
Anti-Restenotic impact	+ +	+
Anti-inflammatory properties	+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

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

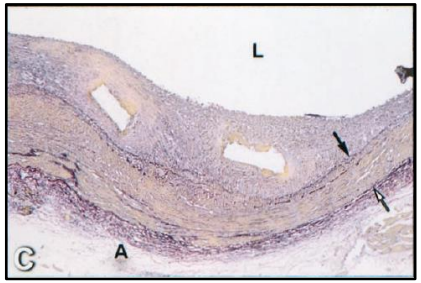
Dose dependent effect and toxicity of paclitaxel eluting stent in porcine coronary artery (28days)



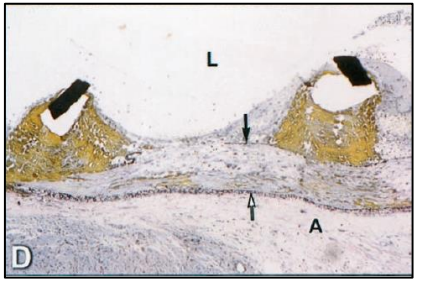
BMS



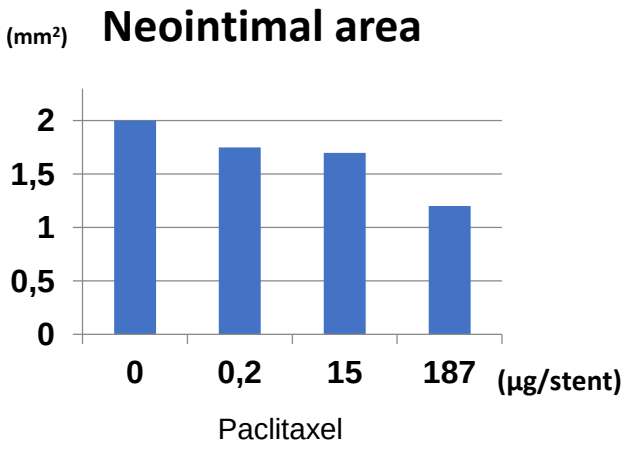
Paclitaxel
0.2µg/stent

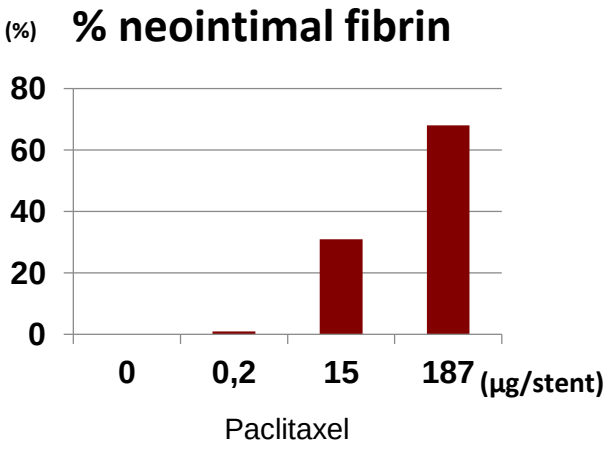


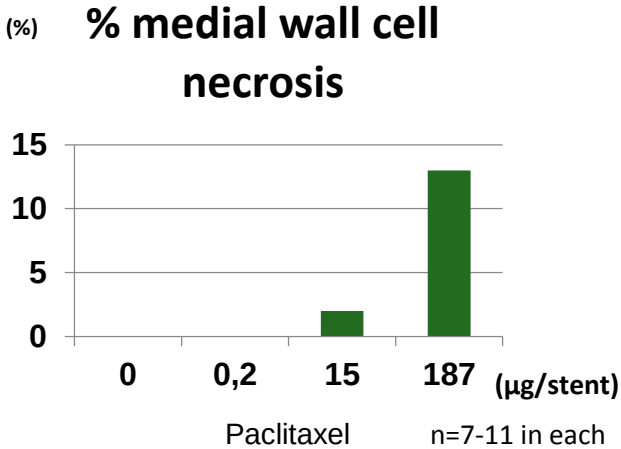
Paclitaxel
15µg/stent



Paclitaxel
187µg/stent



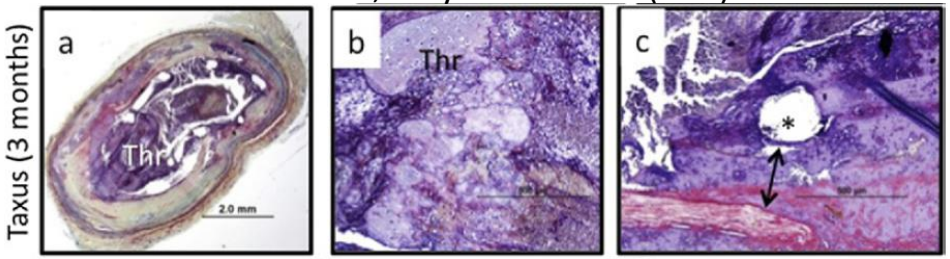




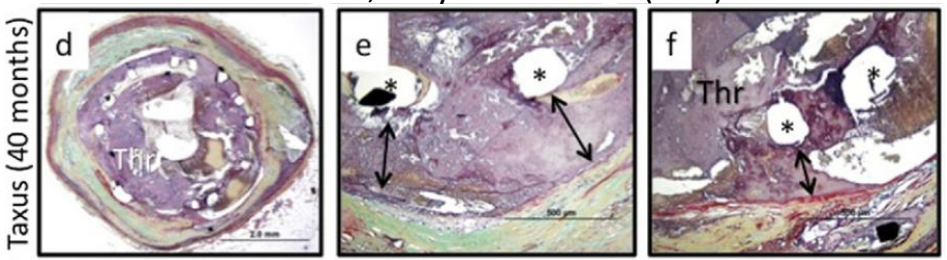
Heldman AW, et al. Circulation. 2001;103:2289-95.

≥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

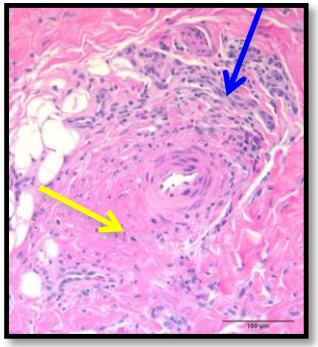
Late thrombosis (≥ 30days), n	25
AMI, penetration/prolapse of necrotic core	5 (20%)
Bifurcation	9 (36%)
Long/overlapping stents	2 (0.1%)
Underexpansion	1 (0.04%)
Isolated uncovered struts	1 (0.04%)
Localized hypersensitivity reaction	0 (0.0%)
Malapposition from excessive to fibrin *	7 (28%)

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

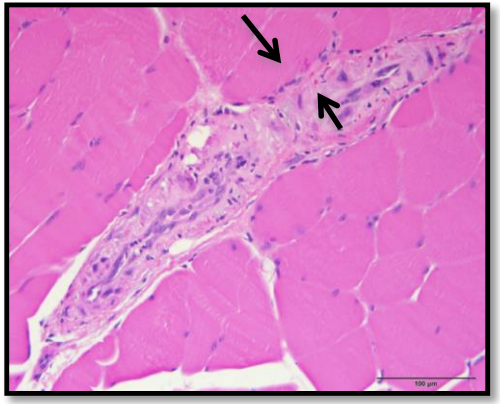
Nakazawa G, et al. JACC. 2011;57:390-8.

Downstream Findings in Porcine Skeletal Muscle (28-Day)

Lutonix (1x) Vascular Change



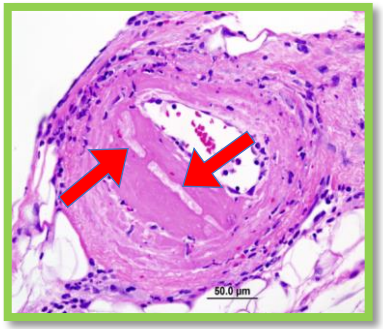
IN.PACT (1x) Vascular Change



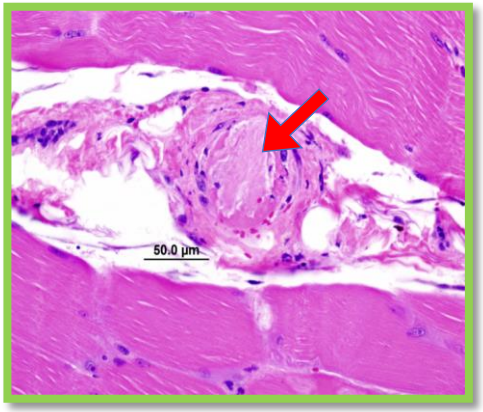
High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

IN.PACT (1x) Crystalline Material



IN.PACT (3x) Crystalline Material

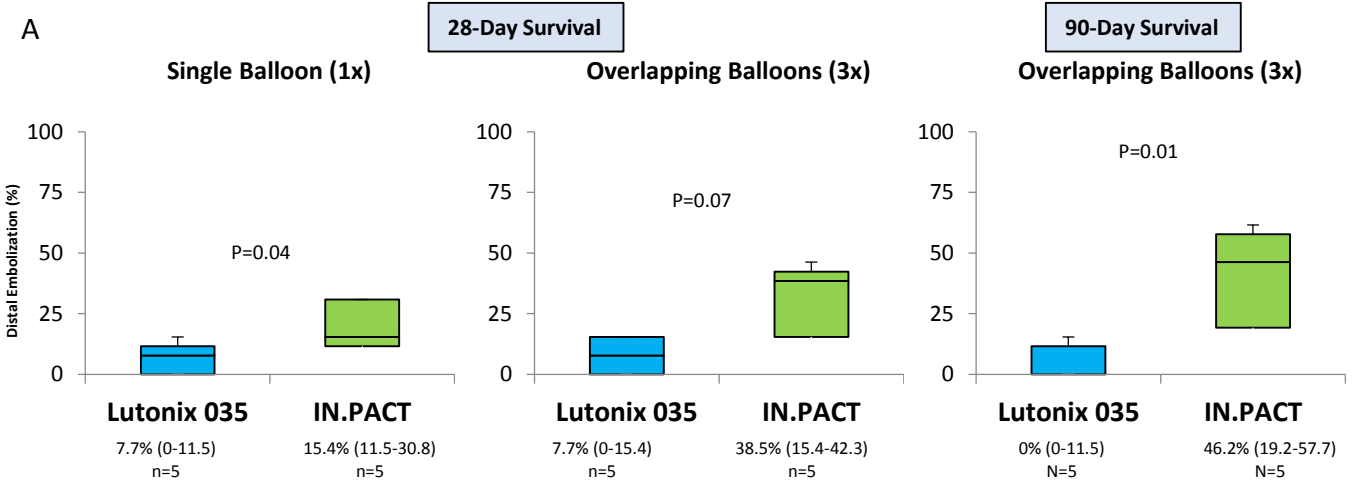


High (40x) power images of crystalline material (red arrows) at 28d

Poor Drug Transfer and Loss Of Ptx into downstream tissues

Downstream Incidence of Distal Embolization (%)

A



B

	Survival Treatment & Arteries	Lutonix 035	IN.PACT	*P*-value
Number of micro-vessels with paclitaxel- associated findings	28-day (1x, n=5)	1 (0-2)	4 (2-12)	0.03
	28-day (3x, n=5)	1 (0-12)	26 (11-34)	0.07
	90-day (3x, n=4)	0 (0-3)	11 (5-15)	0.02

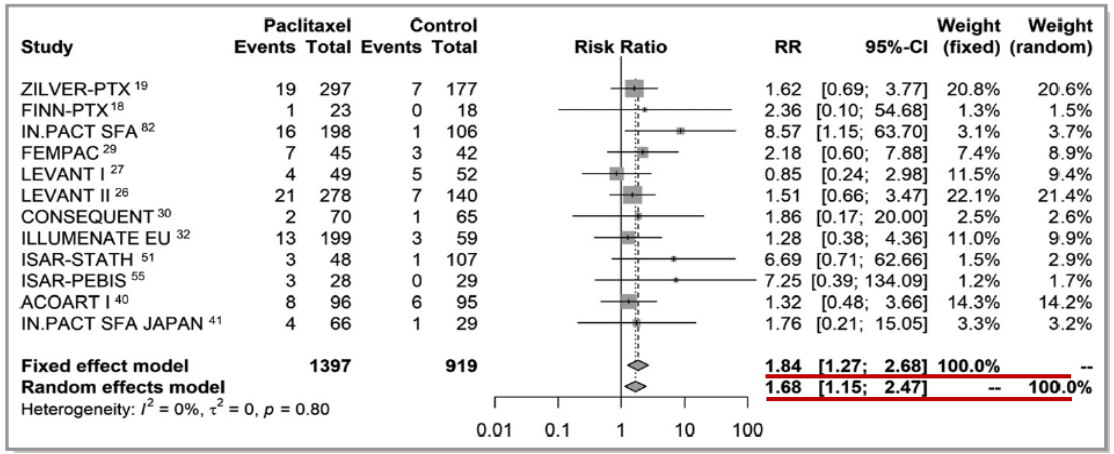
C

	Survival Treatment & Arteries	Lutonix 035		IN.PACT		*P*-value	
		Skeletal muscle	Coronary band	Skeletal muscle	Coronary band	Skeletal muscle	Coronary band
Paclitaxel concentration in downstream tissues (ng/g)	28-day (1x, n=5)	1.3 (0.6-2.3)	1.5 (1.1-65.8)	60.8 (32.6-118.1)	189.0 (134.0-700.0)	0.009	0.02
	28-day (3x, n=5)	3.7 (1.3-10.9)	31.5 (5.9-54.1)	170.9 (19.7-221.5)	871.0 (567.5-1315.0)	0.08	0.009
	90-day (3x, n=4)	0.6 (0.5-6.4)	2.7 (0.0-25.5)	16.1 (12.8-319.2)	158.0 (6.3-1178.0)	0.009	0.05

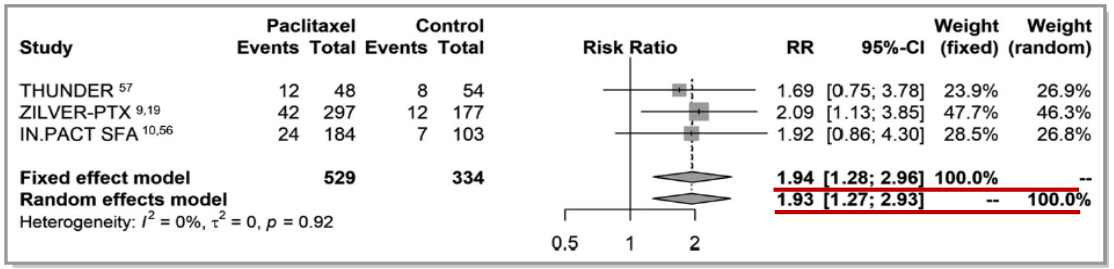
Risk of Death following Application of PES and PCB in Femoropopliteal artery

Meta-Analysis of RCT

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



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



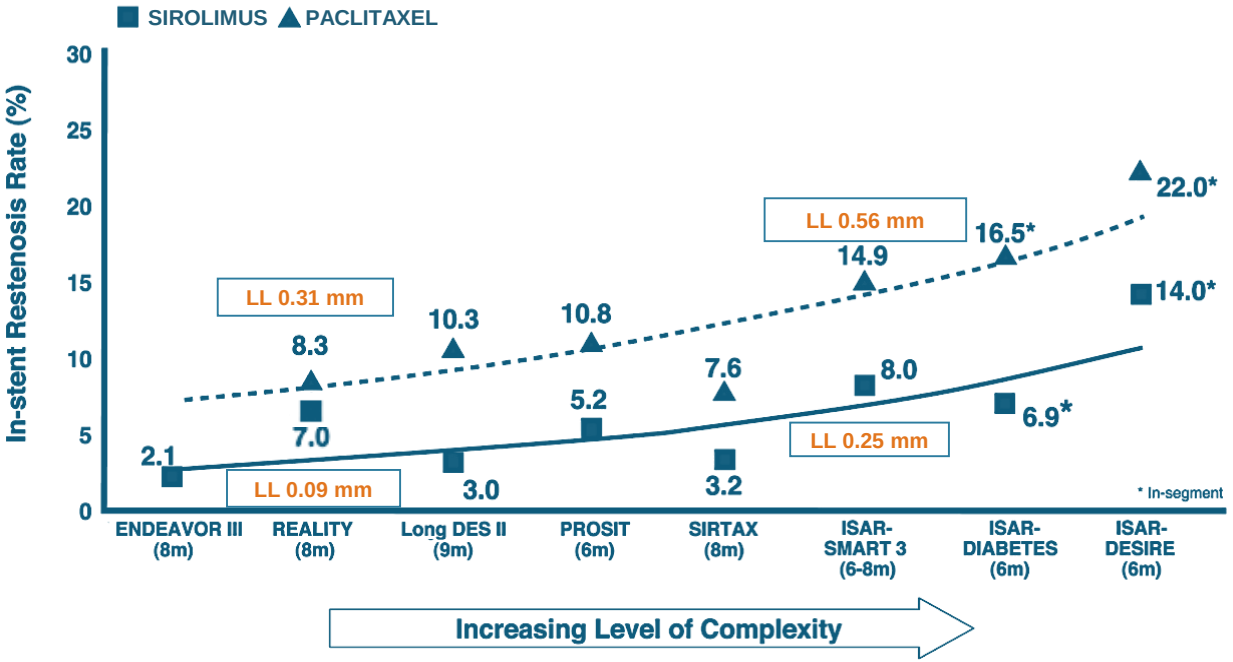
Causes of Death

	Paclitaxel-Coated Balloon (IN.PACT SFA) at 3 Years[10,82]		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

Anti-restenotic effect in coronary artery DES

In the setting of coronary DES, sirolimus is more effective than paclitaxel in terms of inhibiting proliferation.



Sirolimus Coated Balloons – technical challenges

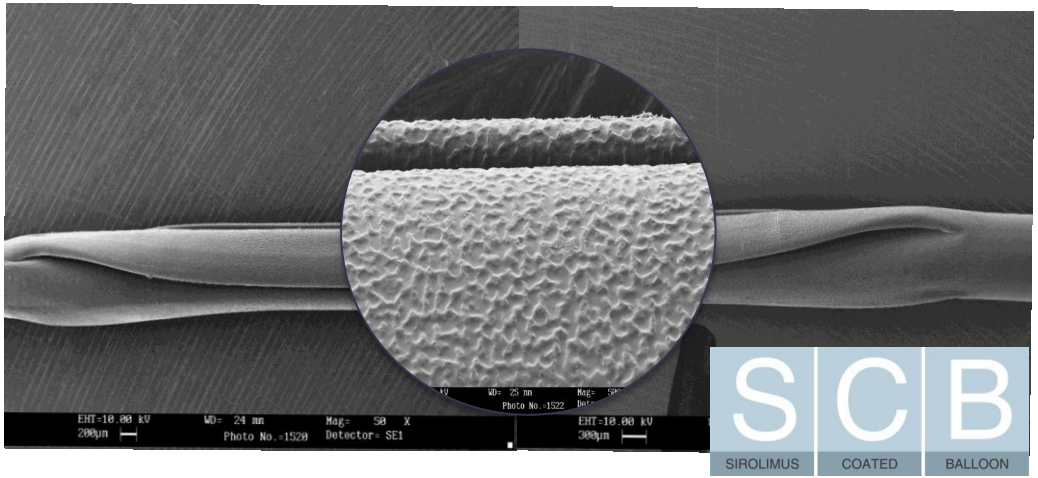
- **Enhance tissue absorption**
  - **Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently**

- **Extend tissue retention**
  - **Sirolimus must be continuously delivered over time, so some form of “time release mechanism” must be employed to maintain therapeutic levels**

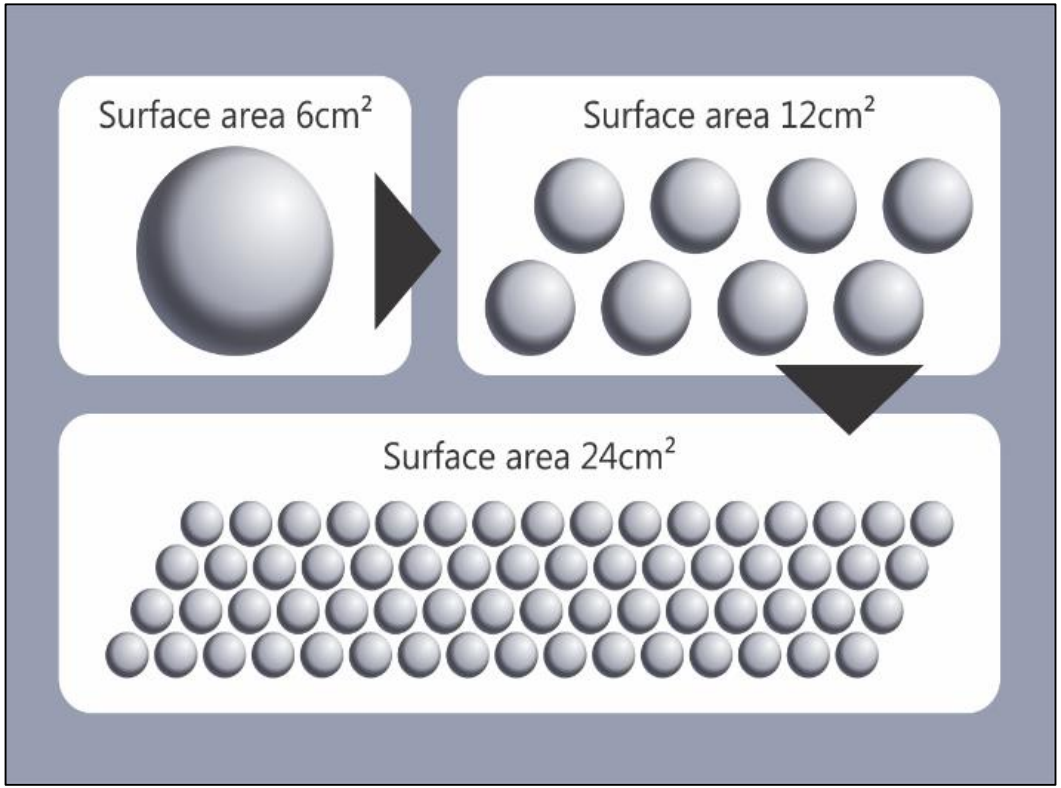
MAGIC TOUCH – Sirolimus Coated Balloon

- 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



MAGIC TOUCH – Nanotechnology Advantage



- Sub-micron gives better adhesion on balloon
- Lesser drug dose
- Easy penetration to deep layers of vessel

Pre-clinical study 1; swine native coronary artery

Day 0

DCB or POBA treatment in coronary arteries

Day 28

Euthanize

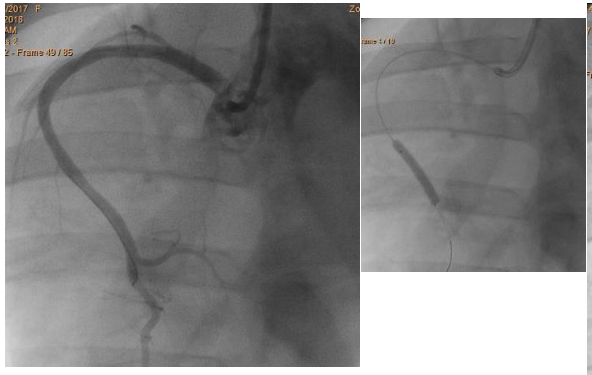
Yorkshire domestic Swine n=2 (total 6 vessels)

Magic Touch SCB 1x,
Magic Touch SCB 3x,
Uncoated control

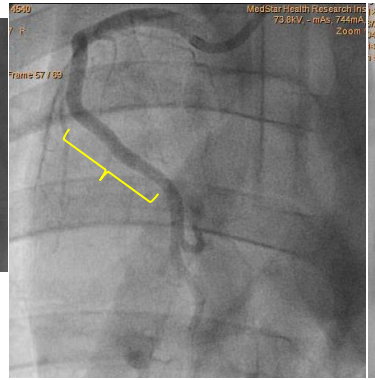
✓ Collect coronary arteries and histopathologic analysis

Angiographic result

MagicTouch SCB 1x



Pre-procedure

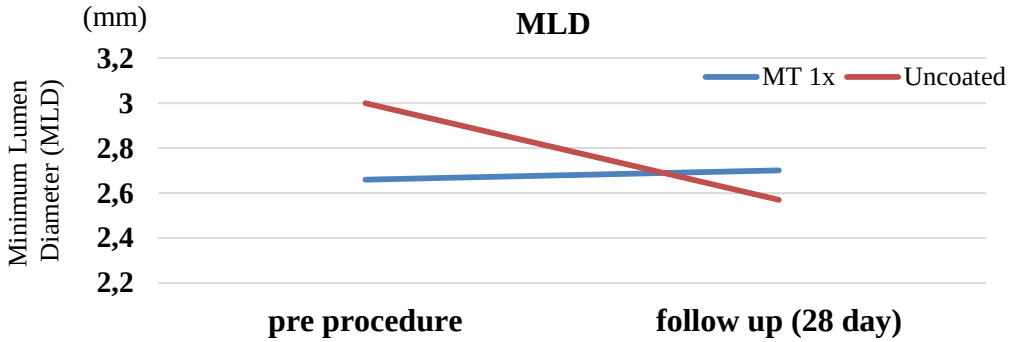


Follow-up 28day

Control POBA

Pre-procedure

Follow-up 28day



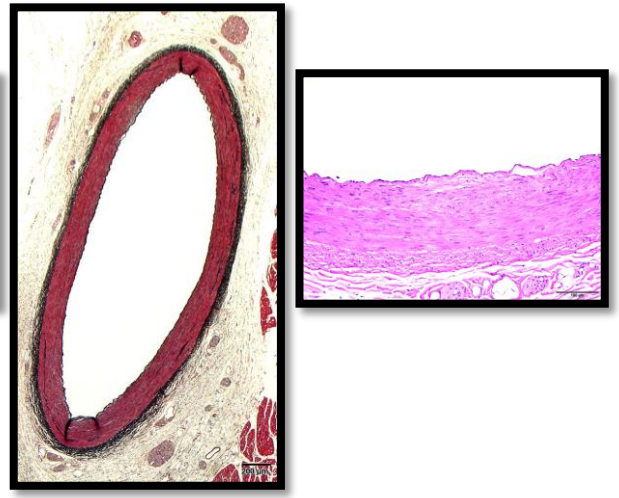
(n=2 in each)

Histopathologic analysis for SCB vs uncoated POBA treated site

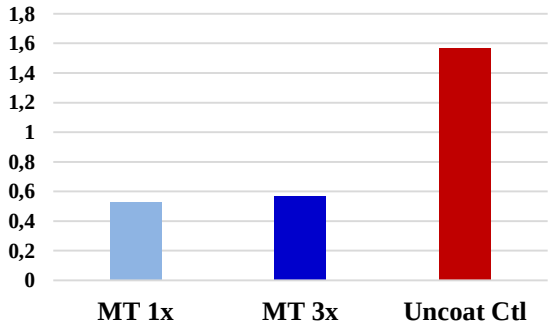
MagicTouch SCB 1x

MagicTouch SCB 3x

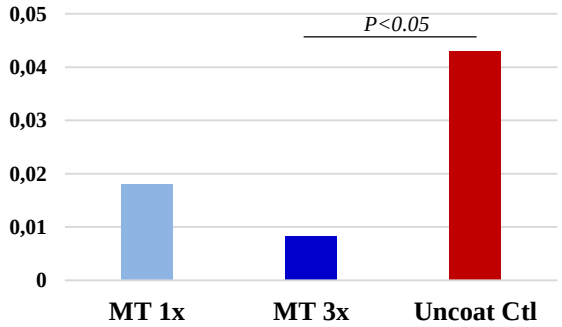
Control POBA



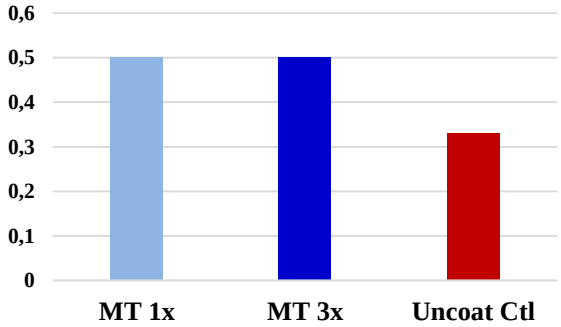
% stenosis



Neointimal area



Medial Proteoglycan/Collagen Score



N=6 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

Pharmacokinetics 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

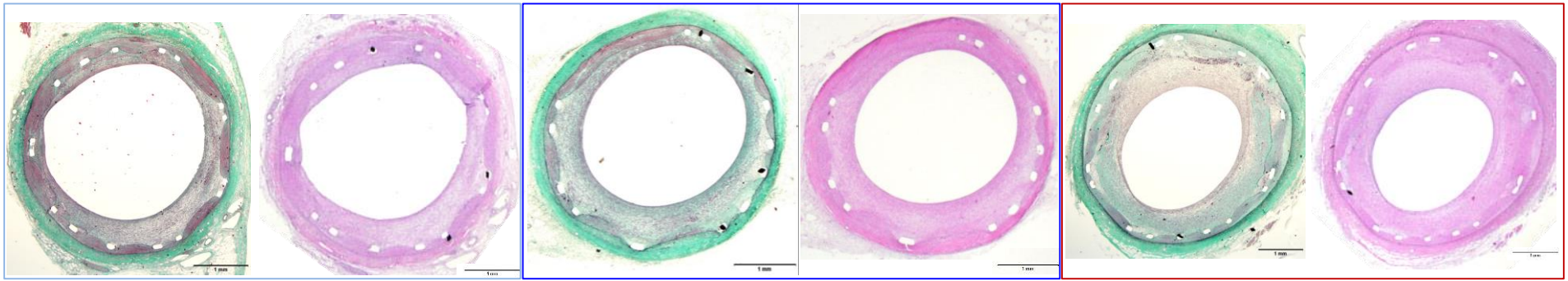
Animal #	Treatment	Lung	Liver	Bone Marrow	Spleen	Kidney
Animal #1	DCB 3x (LAD)	BQL	2.76	BQL	BQL	BQL
Animal #2	DCB1x (RCA)	BQL	BQL	BQL	BQL	BQL

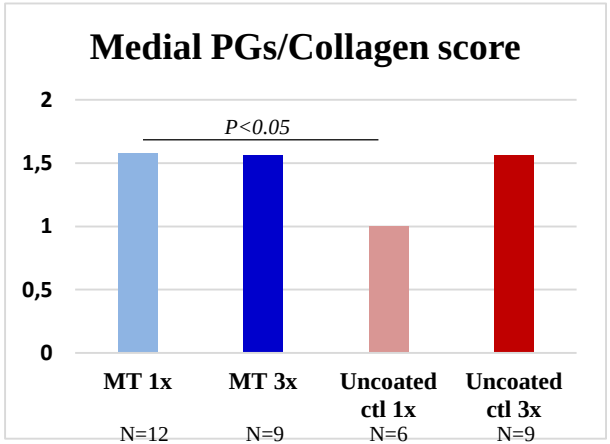
AA: apical anterior, AS: apical septum, AP: apical posterior, AL: apical lateral, ARV: apical right ventricle
MA: mid anterior, MS: mid septum, MP: mid posterior, ML: mid lateral, MRV: mid right ventricle

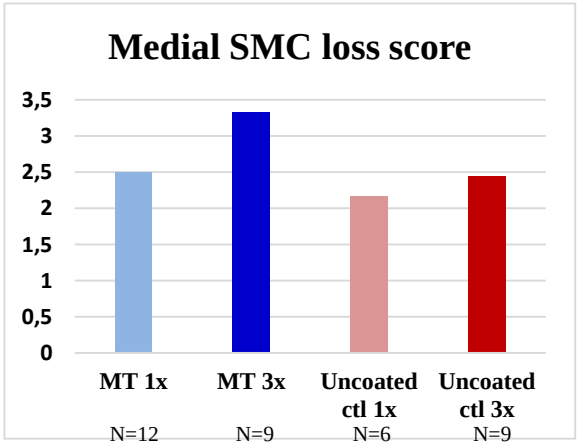
BQL: 2.5 ng/g

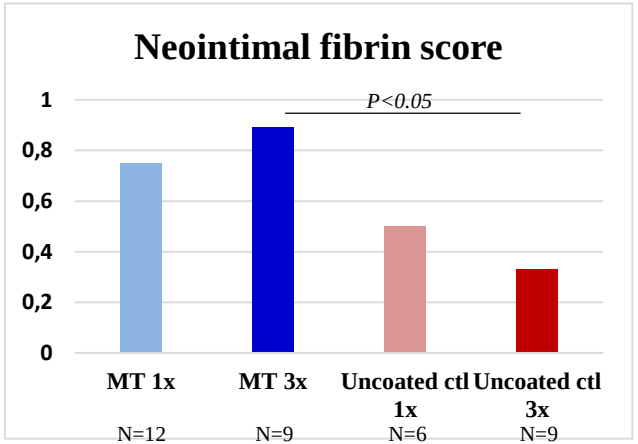
Histopathologic analysis for SCB vs uncoated POBA treated site

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





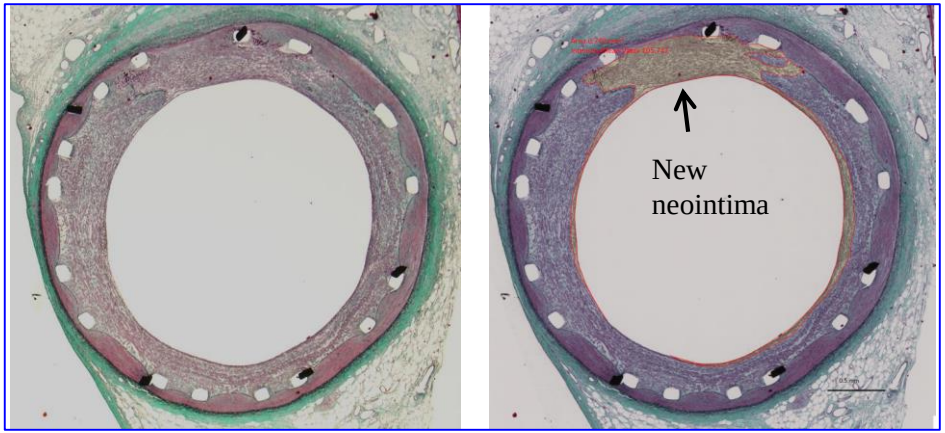




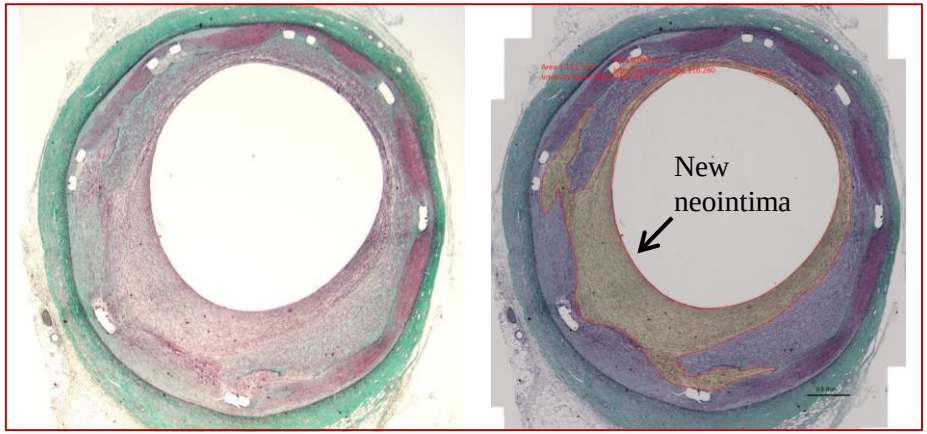
* All section base analysis

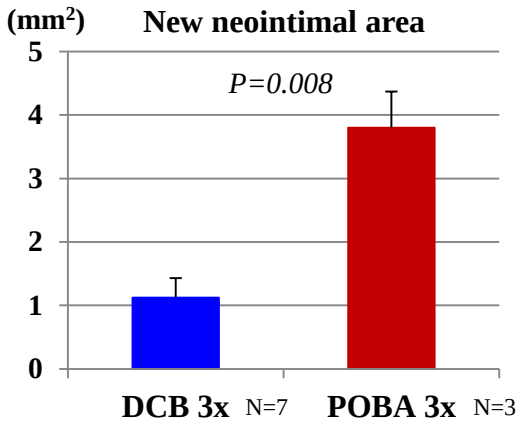
New neointimal growth was suppressed in SCB treatment; Major IEL disruption lesion

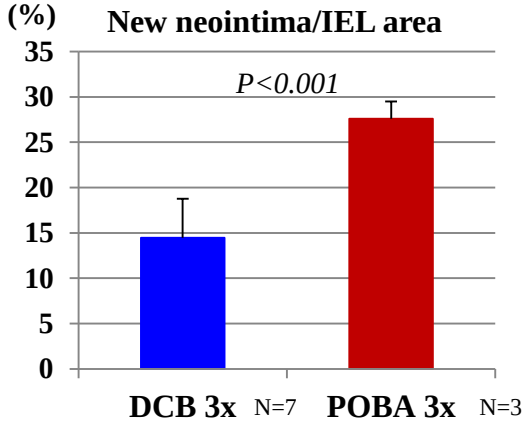
MagicTouch SCB 3x

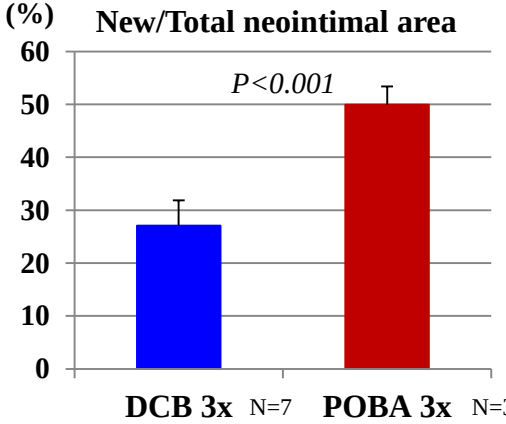


Control POBA 3x









* All section base analysis

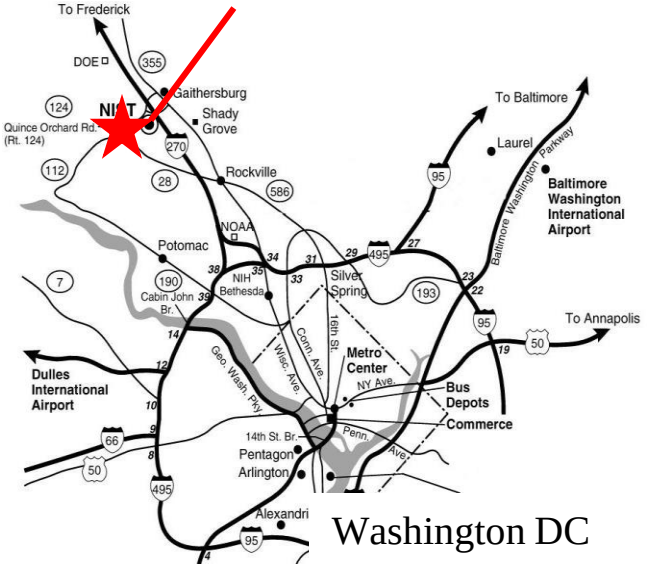
Summary

- ✓ Neointimal hyperplasia is the main cause of restenosis. Pharmacologic agents used on DES and DCB are mainly for the inhibition SMC proliferation.
- ✓ The most frequently used anti-proliferative agents for DCBs is currently Paclitaxel (PTX), however, PTX has narrow therapeutic window compared with Sirolimus and its analogues.
- ✓ A recent meta-analysis suggested that DES and DCB using PTX are associated with higher death rates at 2 to 5 years, although the mechanisms remain unclear.
- ✓ MagicTouch Sirolimus DCB has novel coating technology allowing better tissue retention of sirolimus.
- ✓ Our pre-clinical studies support safety and efficacy of MagicTouch Sirolimus Coated Balloon for clinical usage.
  - ✓ Anti-restenotic effect with minimal non-target organ drug levels seen
- ✓ MagicTouch DCB will be an important non-paclitaxel option for coronary intervention

Acknowledgments

CVPath Institute

Atsushi Sakamoto, MD
Hiroyuki Jinnouchi, MD
Yu Sato, MD
Anne Cornelissen, MD
Salome Kuntz, MD
Liang Guo, PhD
Robert Kutyz, MS
Russ Jones
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Renu Virmani, MD



Washington DC