Why Sirolimus Coated Balloons Are a Better Option for PAD and AVF Interventions

Aloke V. Finn MD

Medical Director and Chief Scientific Officer

CVPath Institute

Gaithersburg, MD

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.

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.

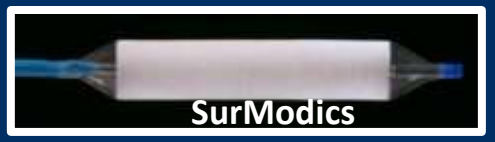
Owner of a healthcare company: No

Stockholder of a healthcare company: No

Ptx 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

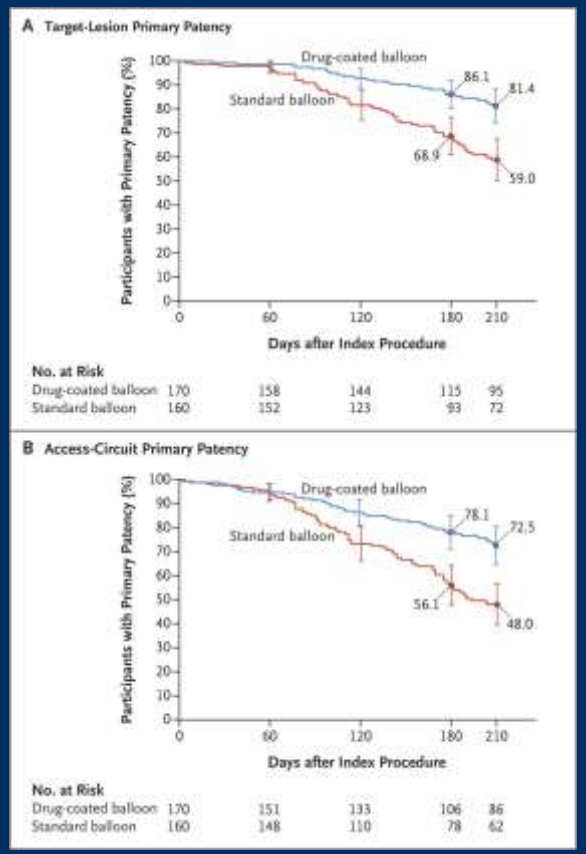
Byrne RA, Joner M. et al. Nat Rev Cardiol. 2014;11:13-23



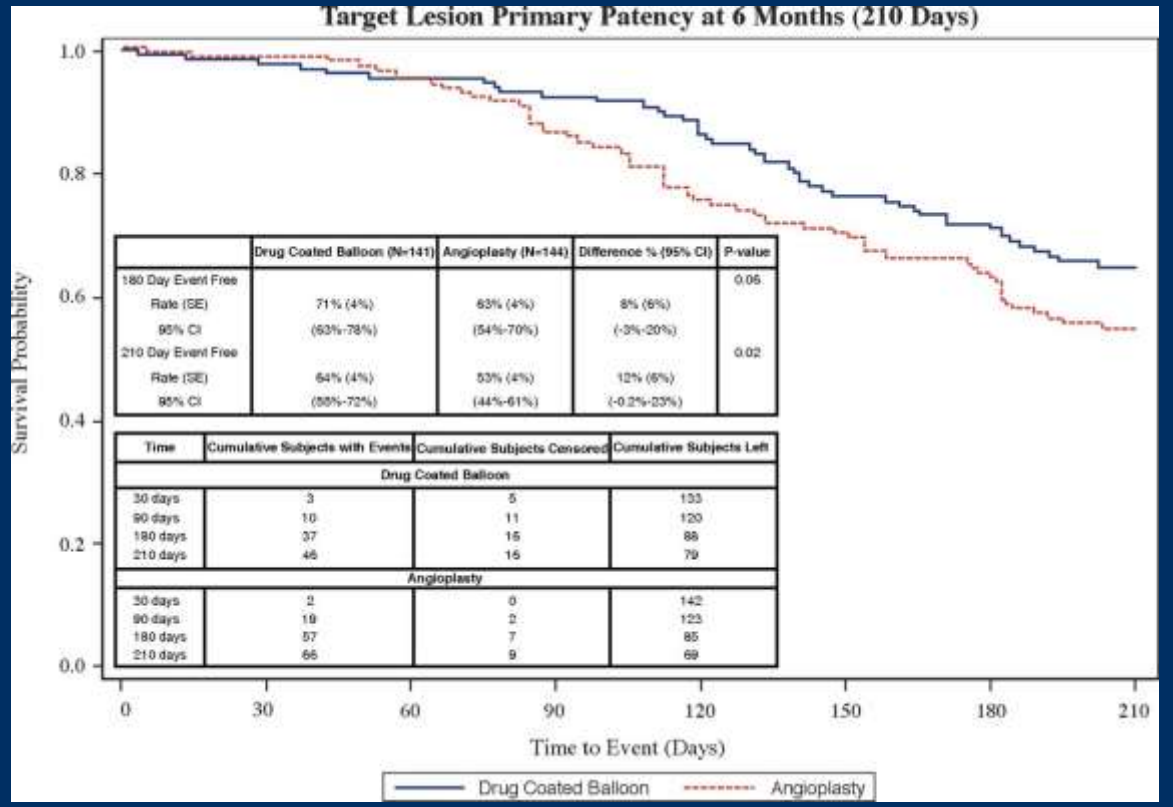
Drug Coated Balloon Devices for AVF stenosis

Device	Company	Coating	Drug dose (µg/mm²)	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

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



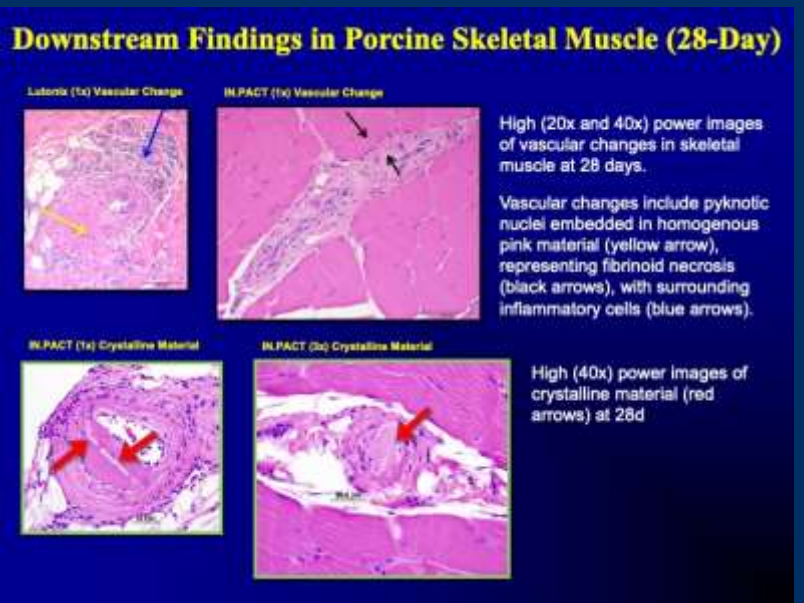
RA Lookstein et al. N Engl J Med 2020;383:733-742.

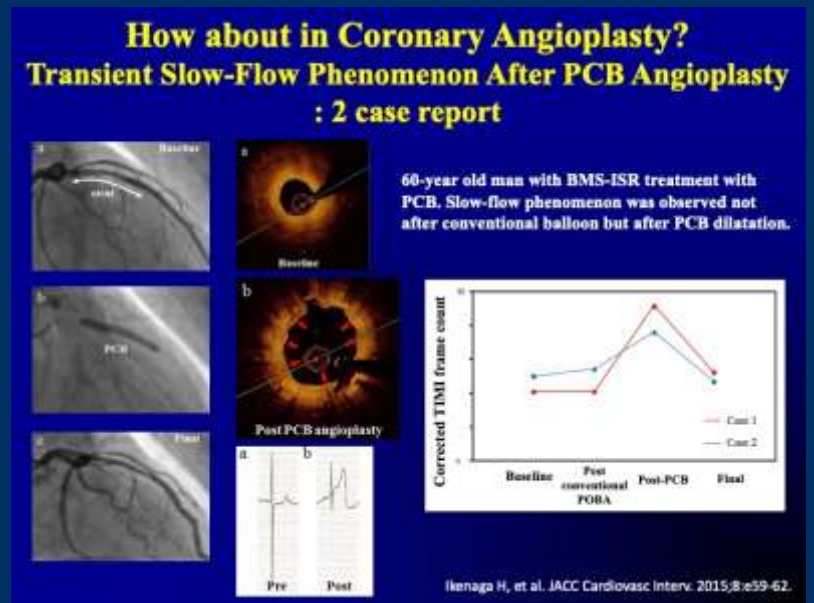


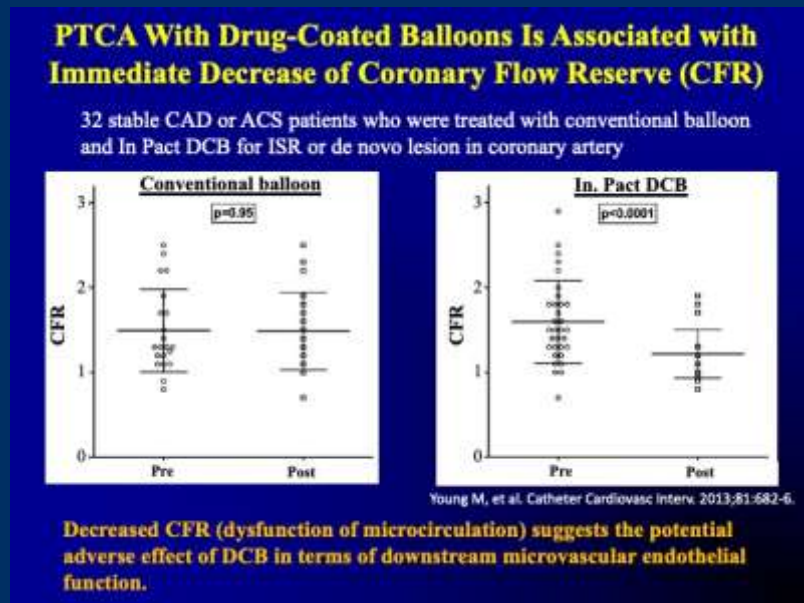
Scott O. Trerotola et al. CJASN 2018;13:1215-1224

Why 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

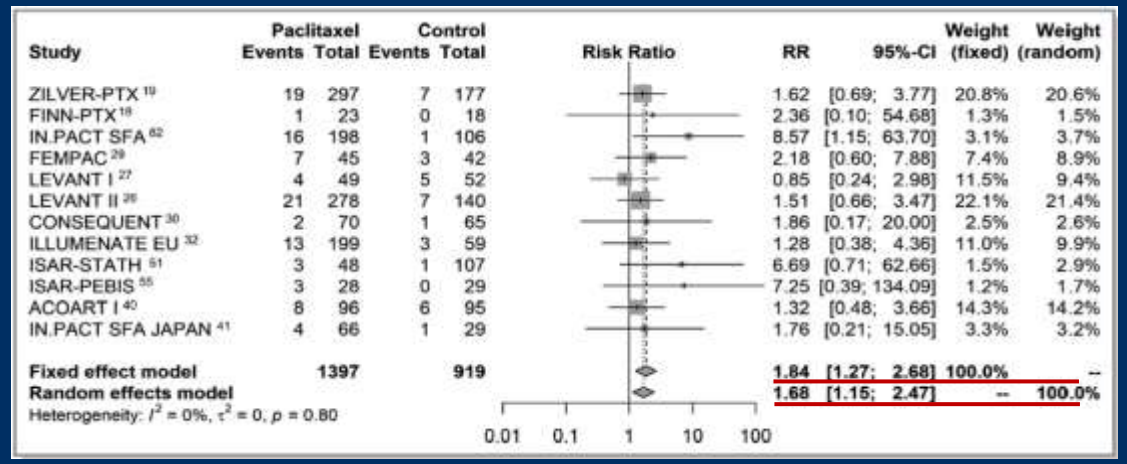




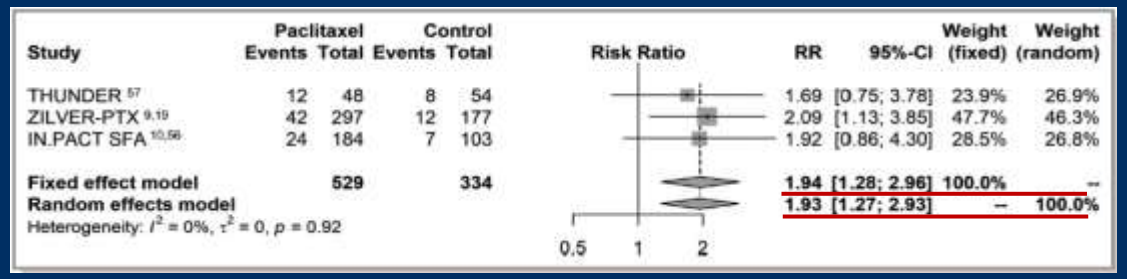


Risk of Death following Application of PES and PCB in Femoropopliteal artery

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

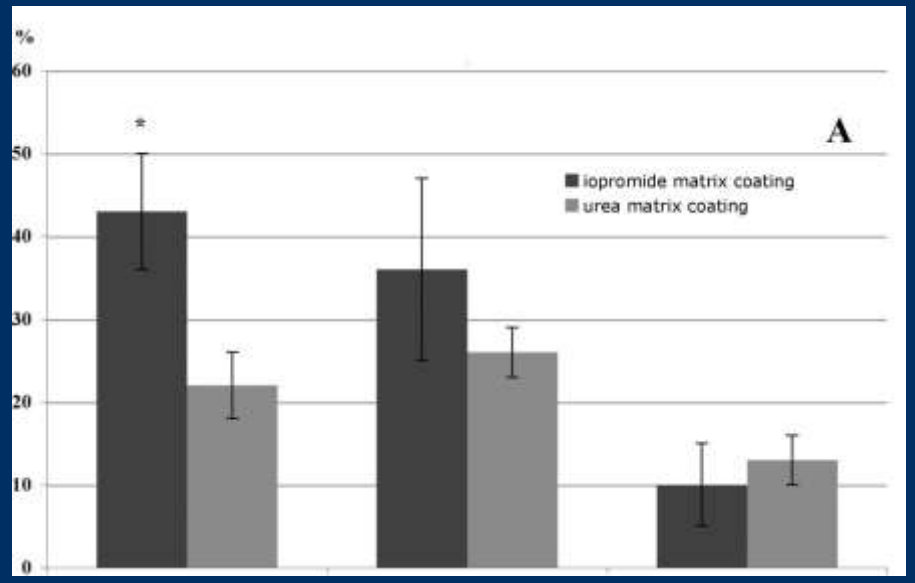
Ptx Safety Concerns Persist

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



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

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

Source: IFU for IN.PACT

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.

Sirolimus Coated Balloons – Technical challenges

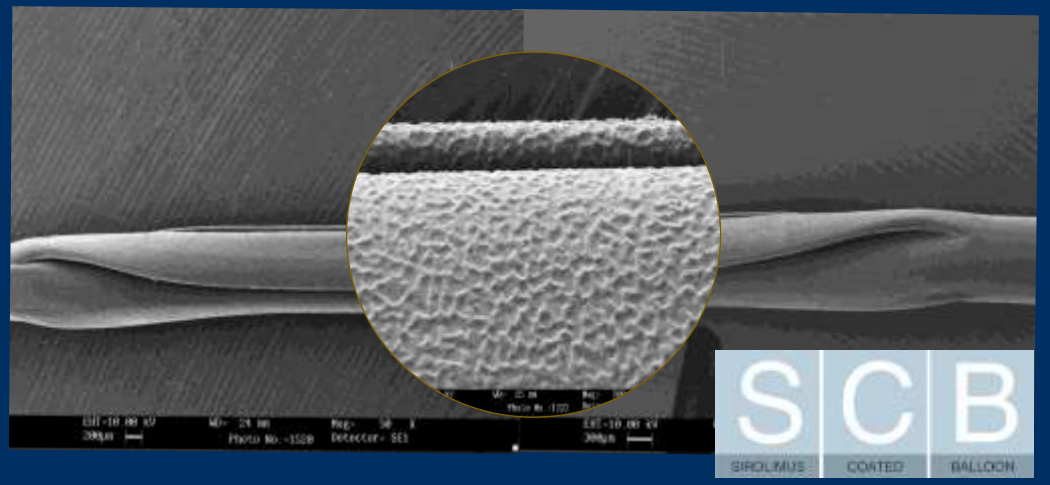
- **Enhance tissue absorption**
  - Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently

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

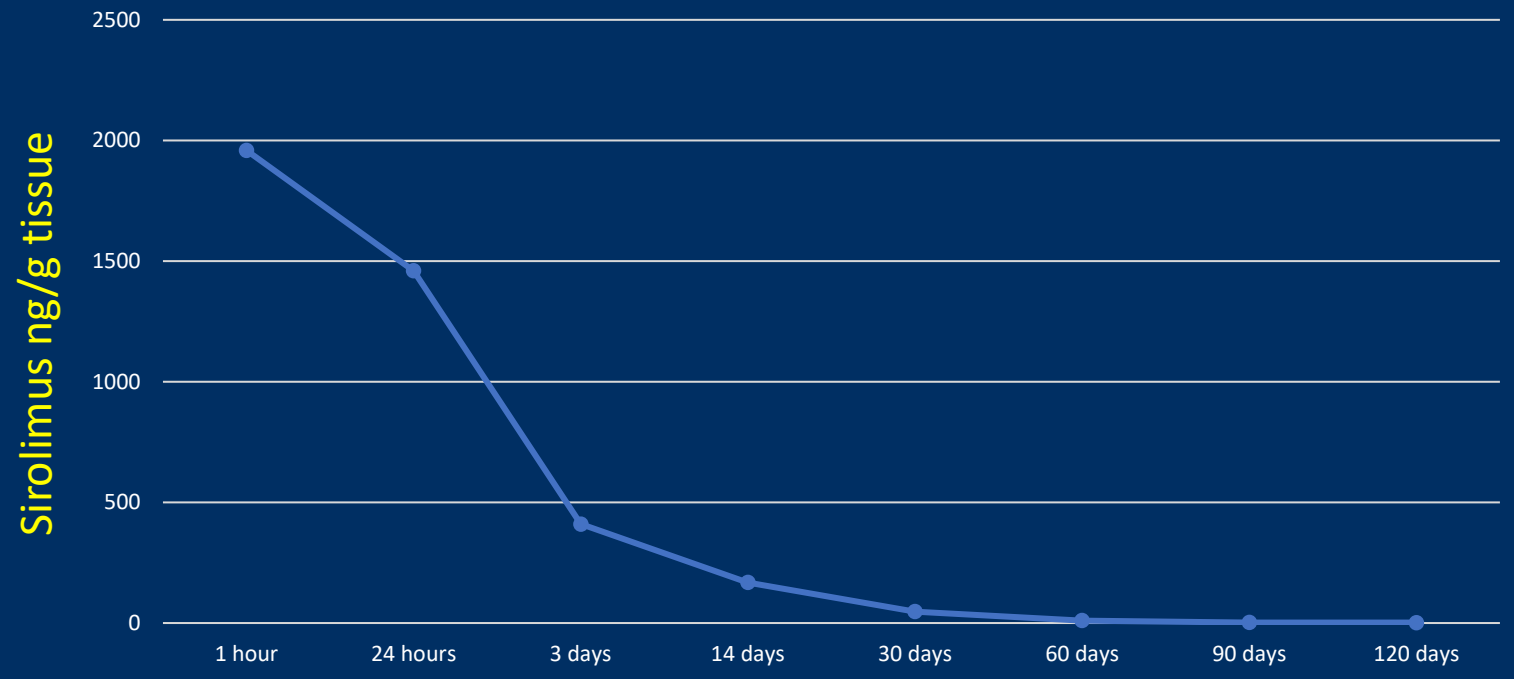
MAGIC TOUCH – Sirolimus Coated Balloon

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

Nothing Leaves Behind



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

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

Magic Touch 1x, POBA 1x,

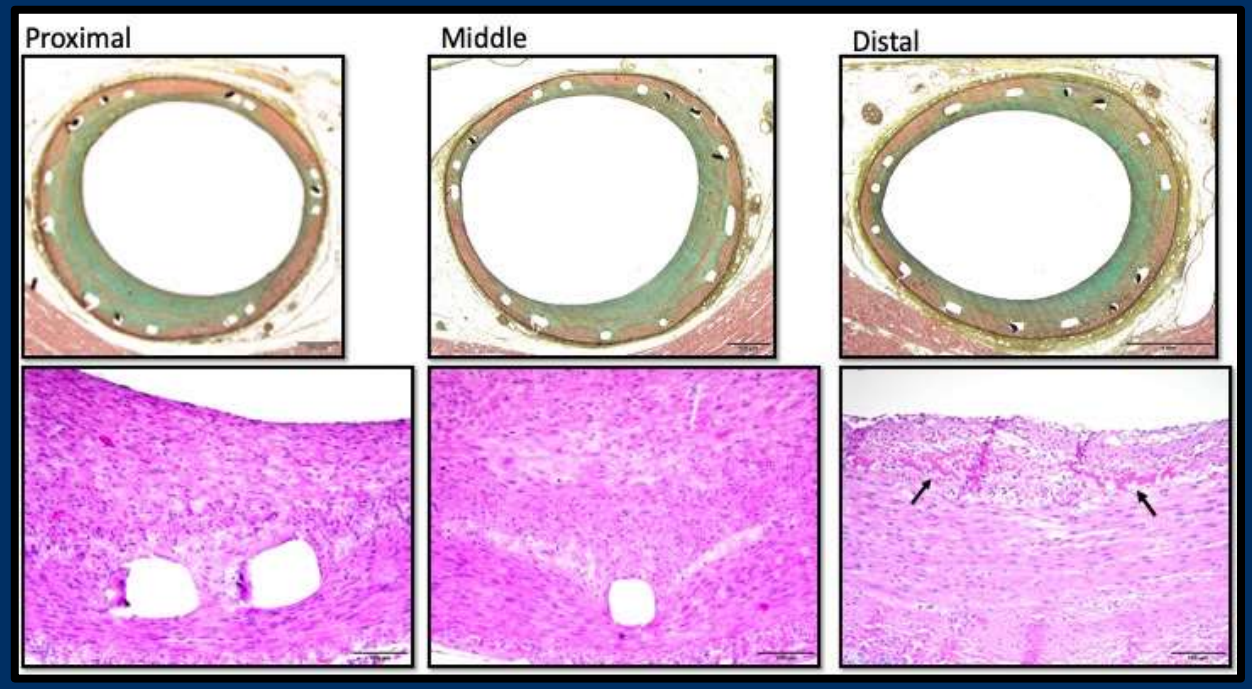
Collect

- ✓ Coronary artery
- ✓ Tissue and Organs

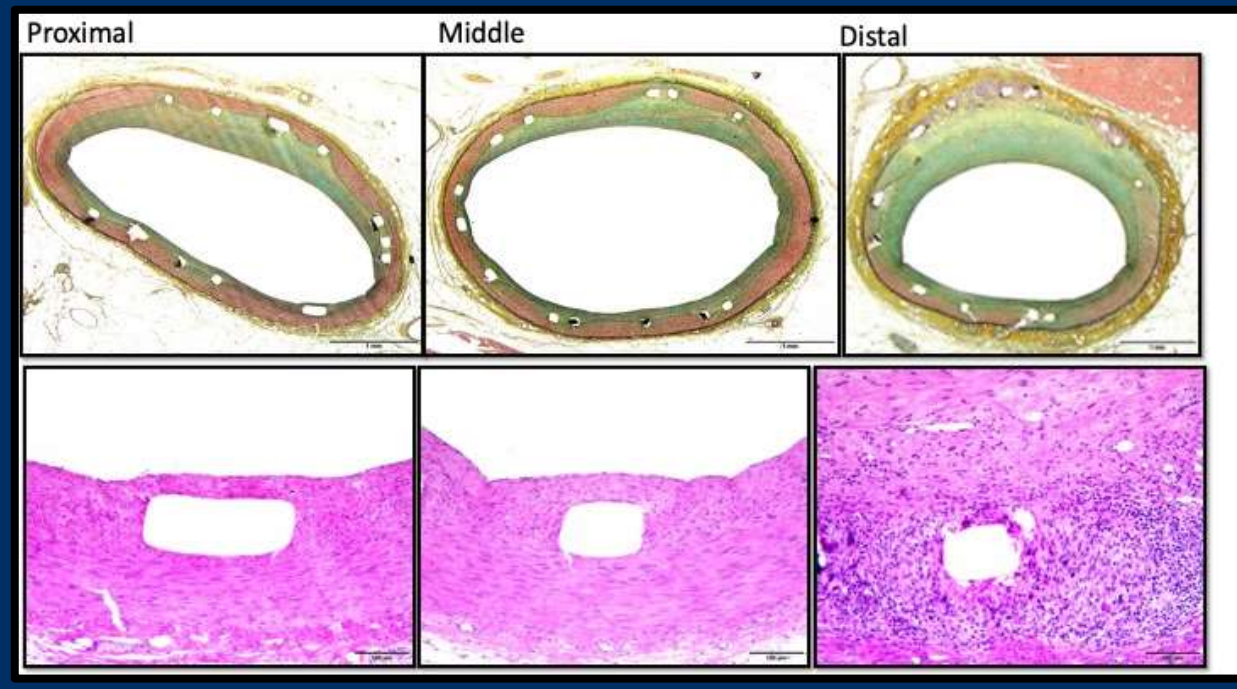
Pharmacokinetics and Histopathology Analysis

28 Day Histology

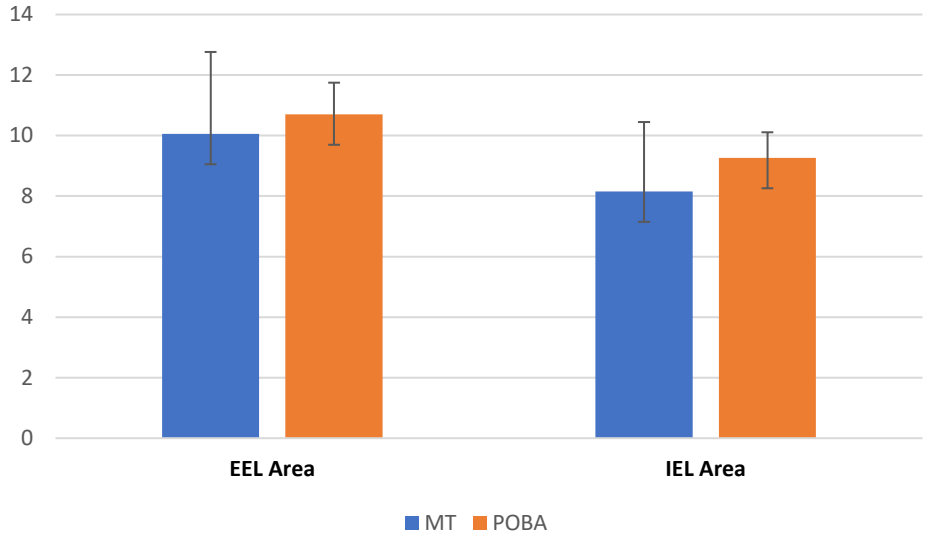
MagicTouch

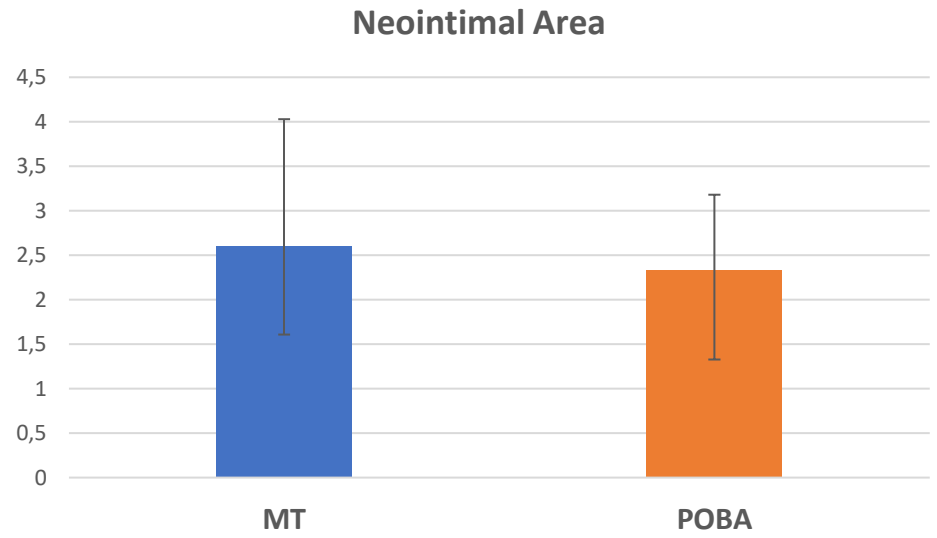


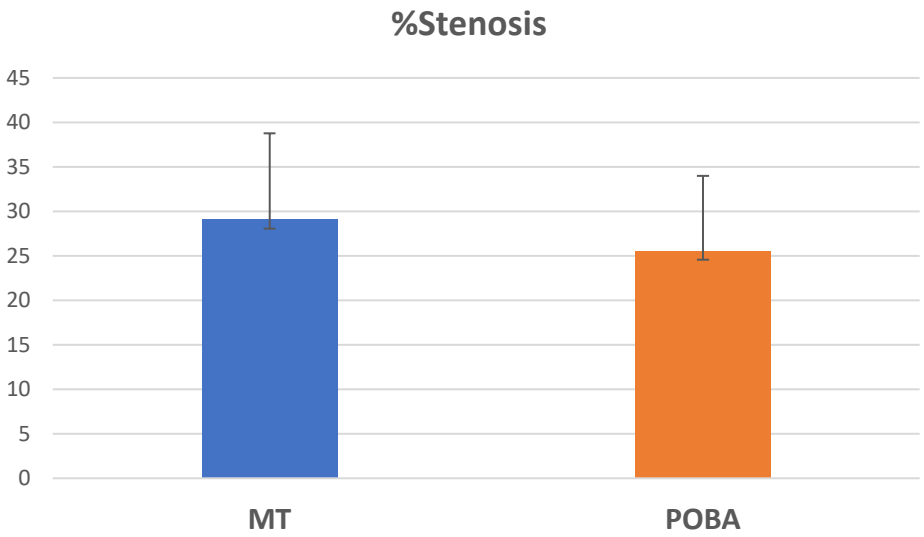
POBA

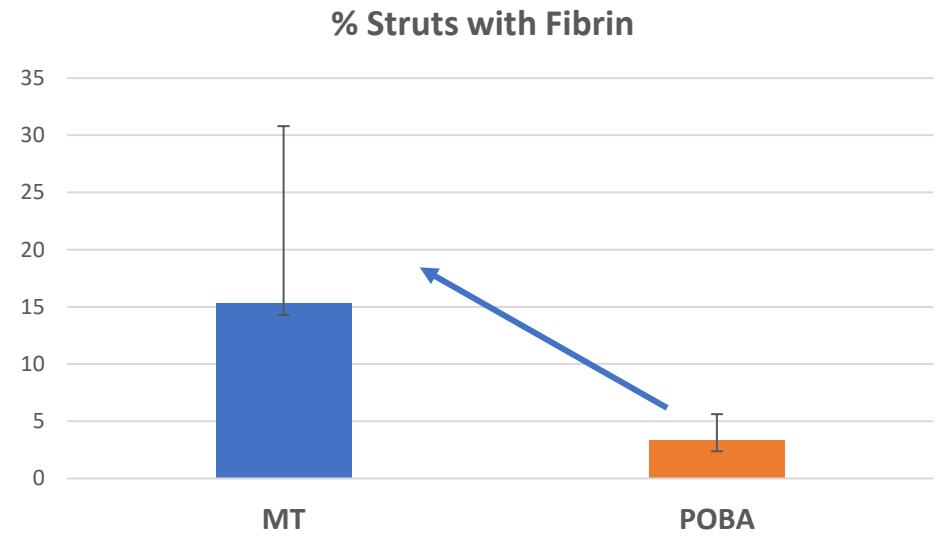


28 Day ISR Histology









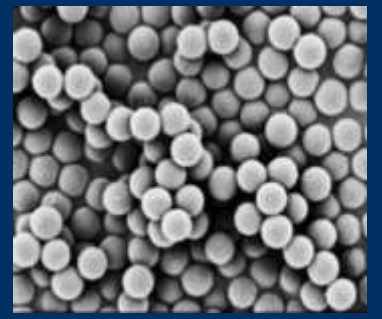
Downstream Findings

- 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

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)

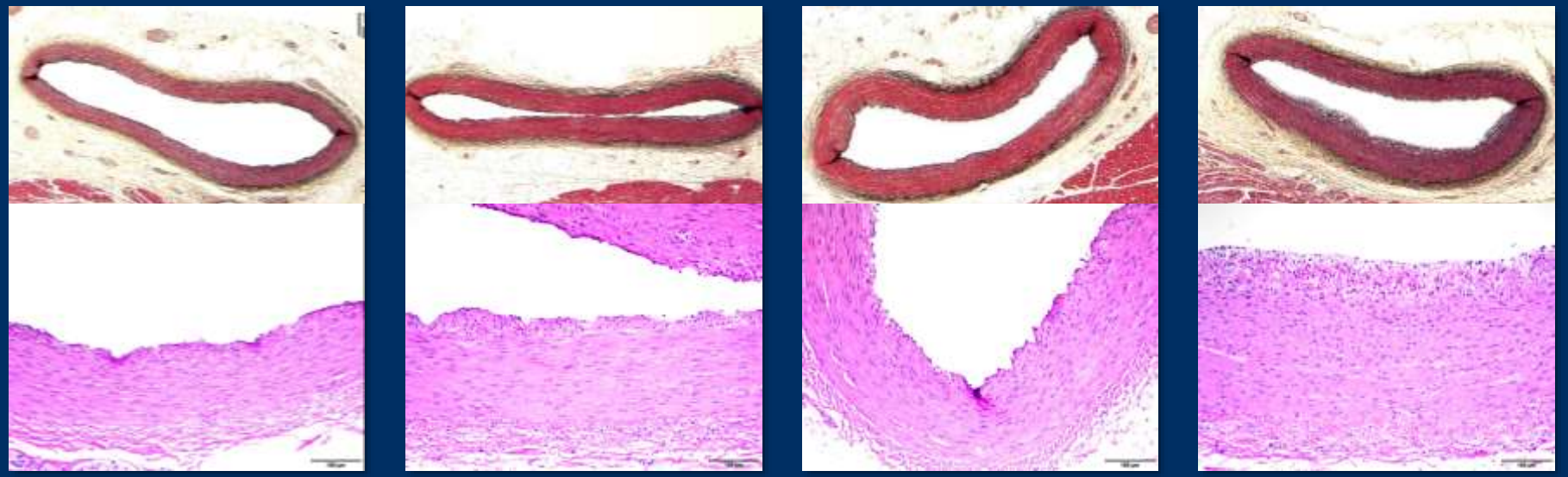
Balloon (3.0 or 3.5 × 15 mm)

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

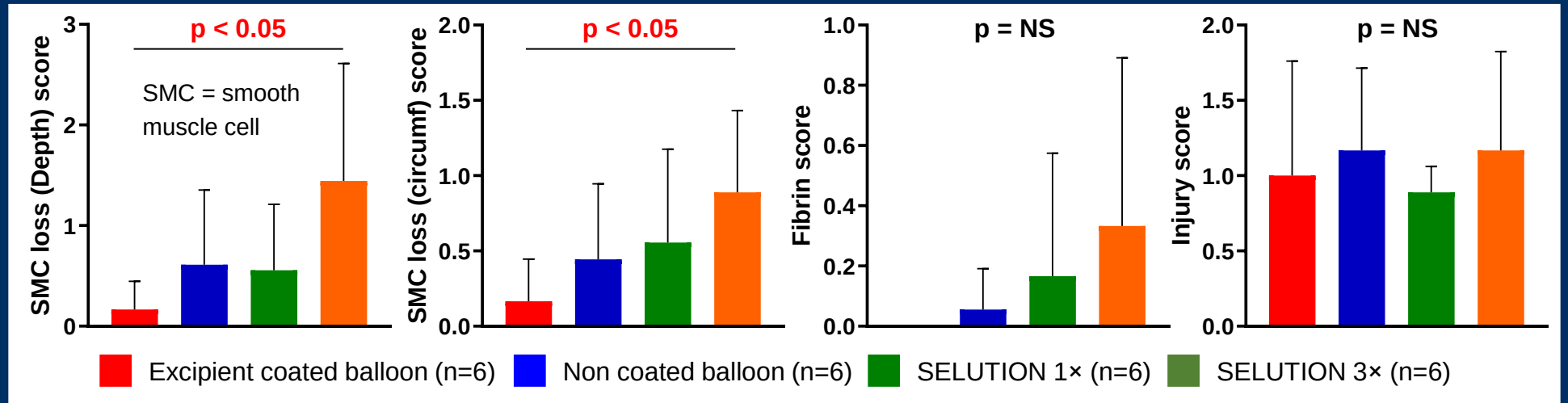
1. Anterior, lateral, posterior, septal wall and right ventricle at similar level, and surrounded treated vessels area were sampled.
2. Ischemia area, Inflammation, foreign material and Thtomboembolus were examined

30 Day Representative Histological Images

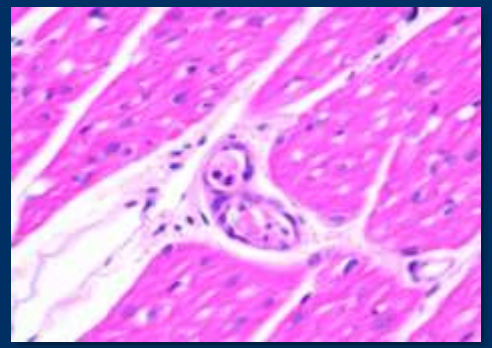


Excipient coated balloon | Non coated balloon | SELUTION 1× | SELUTION 3×

Morphometry analysis

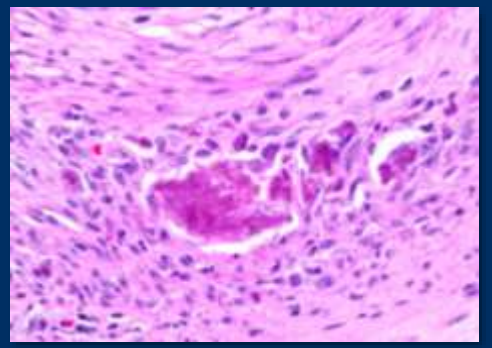


30 Day Downstream Findings in Porcine Myocardium



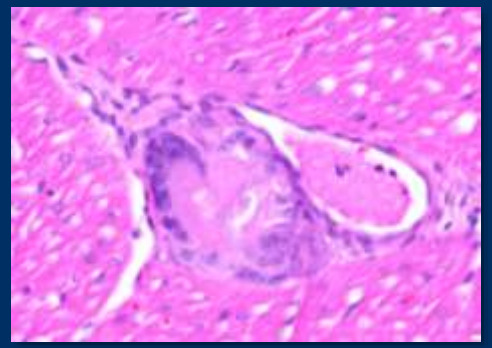
Excipient balloon

Adjacent small arterioles show embolic amorphous material.



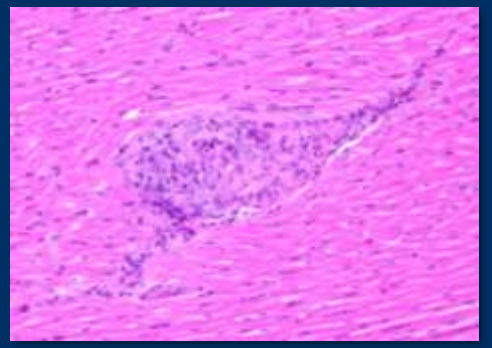
SELUTION 1×

Epicardial coronary artery shows early calcified fibrin surrounding inflammatory reaction.



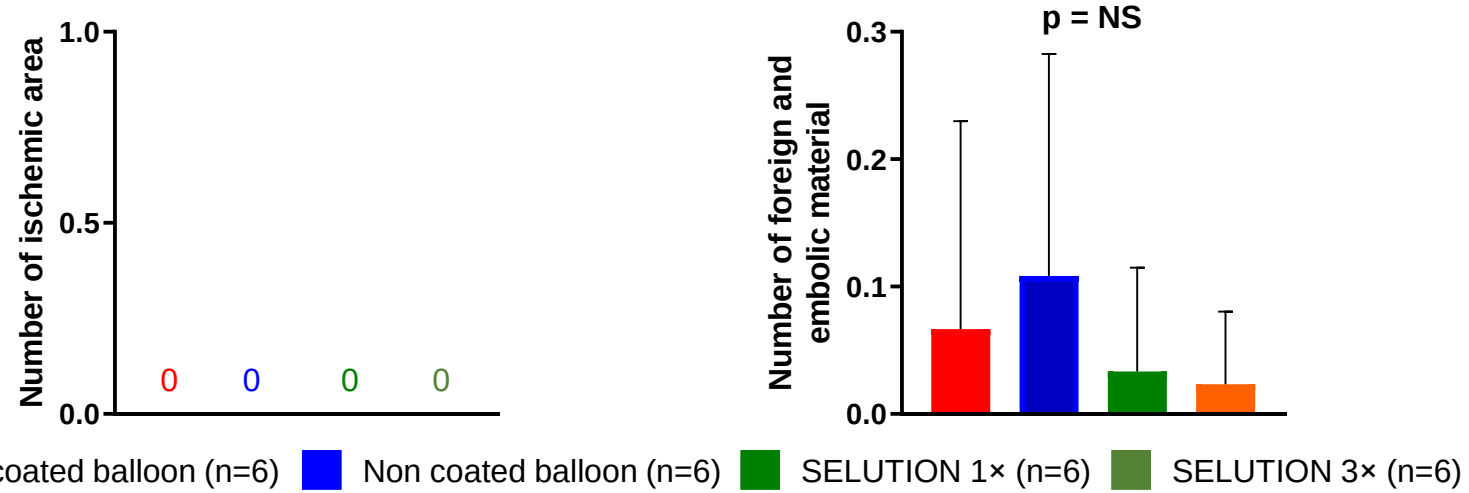
Non coated balloon

Adjacent arterioles show amorphous foreign material with inflammatory reaction.



SELUTION 3×

Giant cells surrounding a minute birefringent foreign material.



Conclusions

- Sirolimus is the preferred drug for intravascular interventions
- Ptx coated balloons are limited by high rate of distal embolization and loss of Ptx into the body-–these concerns were only heightened by the analysis of Katsanos and may be a concern with treatment of both PAD and AVF where embolization is a potential concern
- MagicTouch and Selution SCBs demonstrate successful drug transfer to the arterial wall and both have received CE Mark approval with FDA submission studies/applications ongoing
  - Safety studies in preclinical models are ongoing
  - Important to evaluate the long-term effects on the arterial wall when sirolimus is no longer present
- Sirolimus coated balloons will become an important technology for these disease in the future

Acknowledgments

CVPath Institute

Atsushi Sakamoto, MD
Kenji Kawai, MD
Yu Sato, MD
Saijat Ghosh, PhD
Robert Kutyz, MS
Russ Jones
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Maria Romero, MD
Renu Virmani, MD