

***Importance of sustained drug release
in DCB: Insight into preclinical data
for the SELUTION SLR™***

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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

60 years Coronary Progress...



DCB for Coronary Artery Disease

➤ In-Stent Restenosis

DES are recommended for ISR of BMS or DES	I	A
DCB are recommended for ISR of BMS or DES	I	A

- Both strategies are recommended in the ESC guidelines
(2018 ESC/EACTS Guidelines on myocardial revascularization)

➤ De novo small vessel lesion

Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial

- First large RCT testing DCB (SeQuent Please®) vs 2nd-G DES all-comer population.
- 758 patients with de-novo coronary stenosis (<3 mm in diameter) enrolled.
- DCB was non-inferior to 2nd-G DES regarding MACE up to 12 months.
- Potential benefits of leaving behind an intact vessel without a stent.

(Raban V Jeger, et al. Lancet 2018)

Drug Coated Balloon Devices (Coronary artery)

Common anti-restenotic drug for DCB is **Paclitaxel**

Product	Company	Drug	Drug dose ($\mu\text{g}/\text{mm}^2$)	Excipient
Elutax SV	Aachen Resonance, Luxembourg,	Paclitaxel	2.0	None
SeQuent Please	B. Braun, Melsungen, Germany	Paclitaxel	3.0	Iopromide
Biostream	Biosensors, Jalan Tukang, Singapore	Paclitaxel	3.0	Shellac
Pantera Lux	Biotronik, Buelach, Switzerland	Paclitaxel	3.0	Butyryl-tri-hexyl Citrate
Agent	Boston Scientific, Marlborough, MA, USA	Paclitaxel	2.0	Acetyl-tri-butyl Citrate
Restore / Primus	Cardionovum GmbH, Bonn, Germany	Paclitaxel	3.0	Shellac
Support C	Eucatech, Weil am Rhein, Germany	Paclitaxel	3.0	Butyryl-tri-hexyl citrate
DIOR / BioStream	Eurocor / Biosensors	Paclitaxel	3.0	Shellac
Essential	iVascular, Barcelona, Spain	Paclitaxel	3.0	Organic ester
IN.PACT Falcon	Medtronic vascular, Santa Clara, CA, USA	Paclitaxel	3.5	Urea
Danubio	Minvasys, Genn evillers, France	Paclitaxel	2.5	Butyryl-tri-hexyl Citrate
SELUTION	Med Alliance, Irvine, CA, USA	Sirolimus	1.0	Cell adherent technology
Magic Touch	Concept Medical, Surat, India	Sirolimus	1.27	Nanolute technology

**In the US, We don't have any DCBs
approved for for coronary artery applications!!**

DCB for Peripheral Artery Disease

- **In-Stent Restenosis**
- **Short segment lesions (<25cm)**

DCB may be considered for short lesion(<25cm)	IIb	A
DES may be considered in short lesion(<25cm)	IIb	B
DCB may be considered for ISR lesions	IIb	B

- Both of Drug-eluting devices are recommended in the latest ESC guidelines.
(2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases)

Drug Coated Balloon Devices (Peripheral artery)

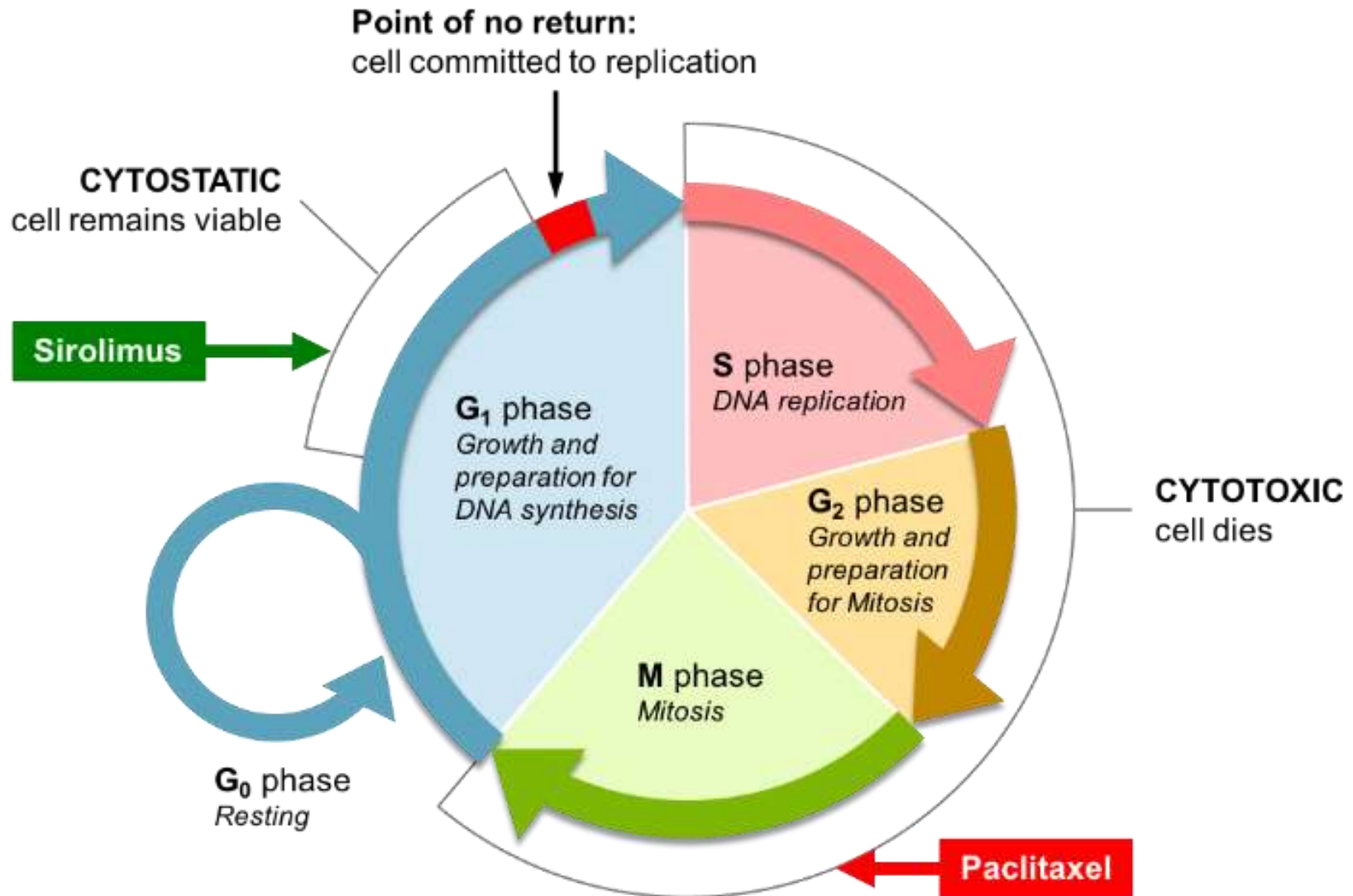
Common anti-restenotic drug for DCB is **Paclitaxel**

Product	Company	Drug	Drug dose ($\mu\text{g}/\text{mm}^2$)	Excipient
IN. PACT Admiral	Medtronic, Minneapolis, MN, USA	Paclitaxel	3.5	Urea
Lutonix	C.R. BARD, Murray Hill, NJ, USA	Paclitaxel	2.0	Polysorbate/Sorbitol
Ranger	Boston Scientific, Marlborough, MA, USA	Paclitaxel	2.0	Citrate ester
Stellarex	Philips, Amsterdam, The Netherlands	Paclitaxel	2.0	Polyethylene glycol
SeQuent Please	B. Braun, Melsungen, Germany	Paclitaxel	3.0	Resveratrol
Passeo-18 Lux	Biotronik, Buelach, Switzerland	Paclitaxel	3.0	Butyryl-tri-hexyl citrate
LEGFLOW	Cardionovum GmbH, Bonn, Germany	Paclitaxel	3.0	Shelloic acid
SurVeil	SurModics, Eden Prairie, MN, USA	Paclitaxel	3.2	Proprietary photolink
Lumior	iVascular, Barcelona, Spain	Paclitaxel	3.0	Water reduce ester
SELUTION	Med Alliance, Irvine, CA, USA	Sirolimus	1.0	Cell adherent technology
Magic Touch PTA	Concept Medical, Surat, India	Sirolimus	1.27	Nanolute technology

How about Sirolimus DCB?

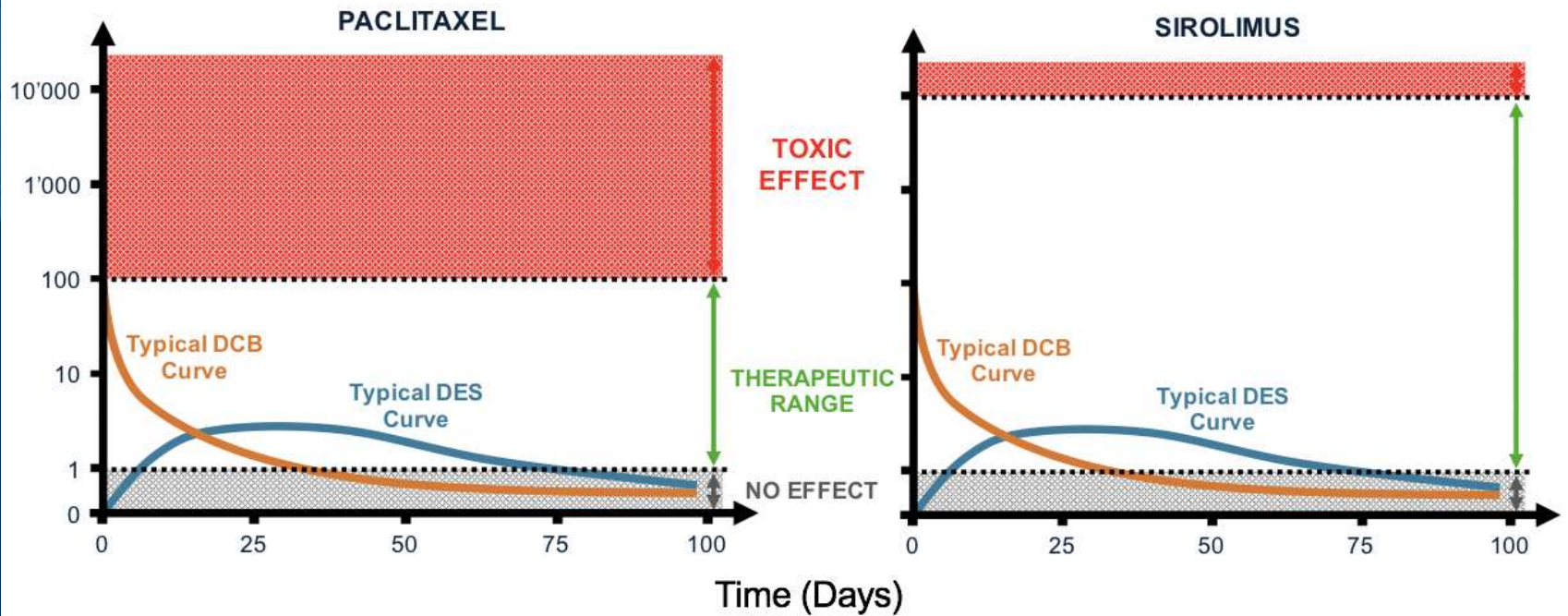
- What are the differences between sirolimus and **paclitaxel**?
- Which is the better drug of choice, sirolimus or **paclitaxel**?

Mode of Action in Sirolimus and Paclitaxel



Sirolimus Coated Balloon benefits

Arterial Drug Concentration (ug/g)



Sirolimus Drug Coated Balloons

Sirolimus offers potential benefits over Paclitaxel

Attribute	Sirolimus (or Analogs)	Paclitaxel
Mode of action	Cytostatic	Cytotoxic
Margin of safety	10'000 fold	100 fold
Therapeutic range	Wide	Narrow
Anti-restenotic	Yes – lower late lumen loss	Yes
Anti-inflammatory	Yes	No
<i>Tissue absorption</i>	<i>Slow</i>	<i>Fast</i>
<i>Tissue retention</i>	<i>Short</i>	<i>Long</i>

Sirolimus is *drug of choice* for coronary DES supported by solid clinical based evidence.

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

- **Protect**

A non-crystalline, readily-absorbed form of sirolimus from WASH-OFF during balloon delivery and from EMBOLIZATION during balloon deployment.

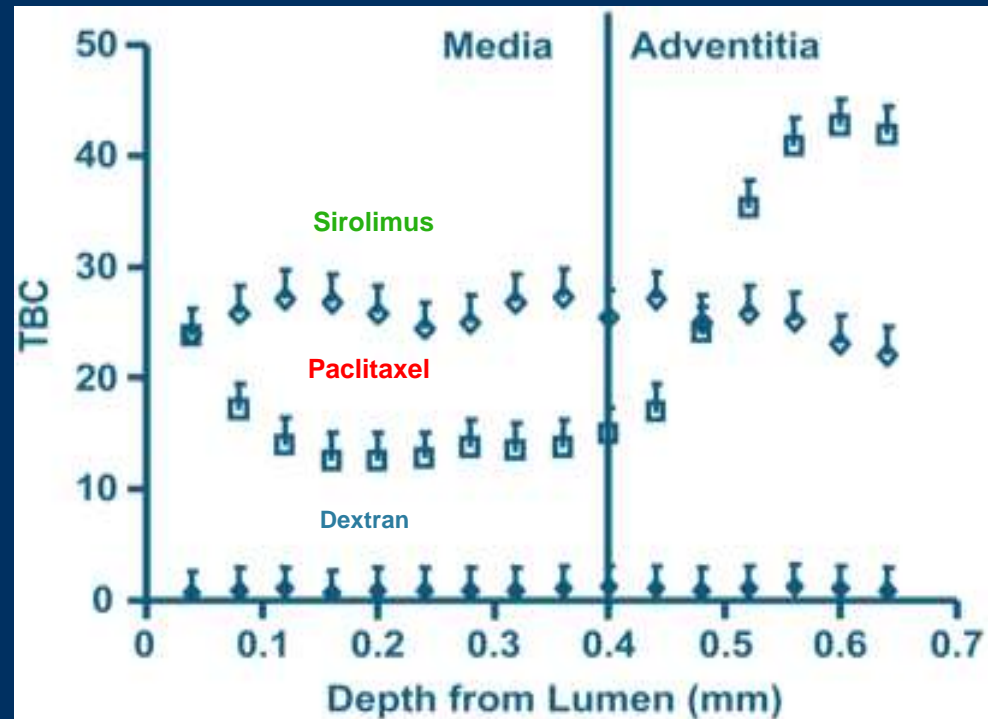
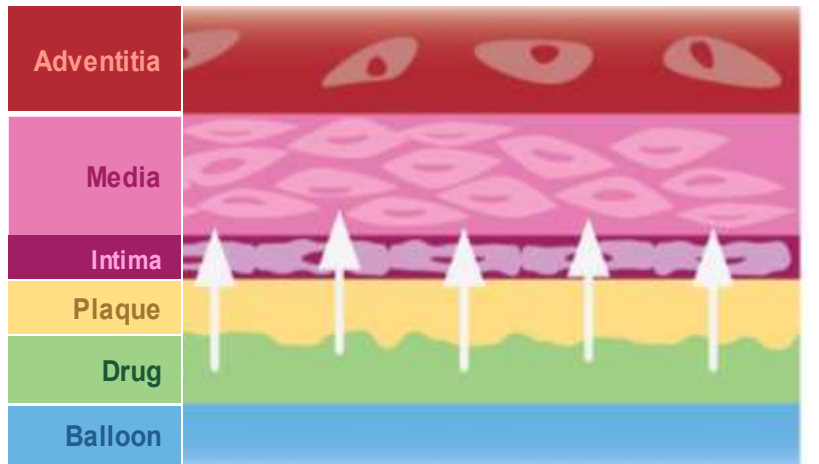
Absorption and Retention

Paclitaxel

- ▶ Tends to localize in sub-intimal space and **partitions** significantly in adventitia.

Sirolimus

- ▶ Diffuses **slowly** and spreads throughout entire artery where it **dilutes down** to sub-therapeutic levels.



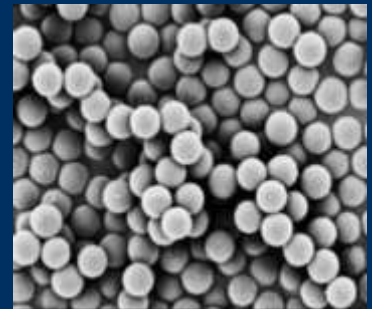
(Tissue Binding Capacity (TBC) of labeled Dextran, Paclitaxel and Sirolimus in 0.040-mm-thick bovine internal carotid tissue segments. Source: PNAS 2004)

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:

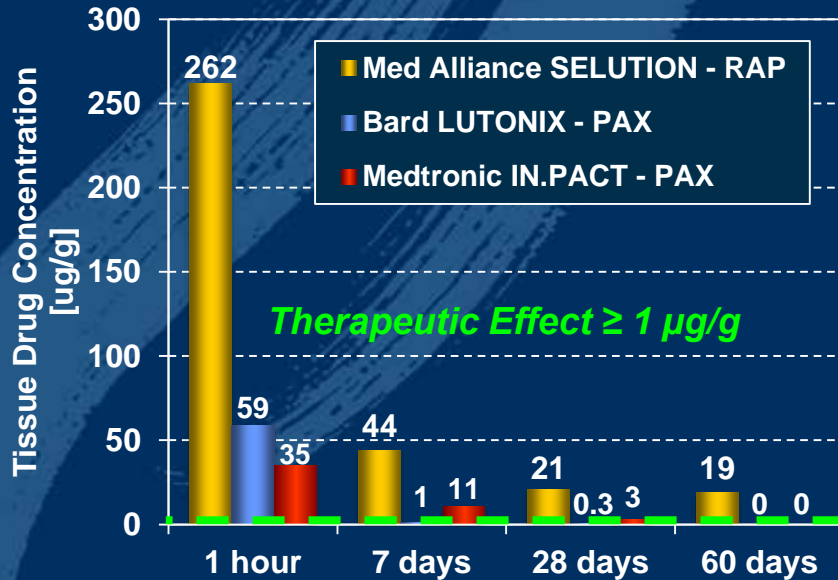
CAT transfer membrane houses and protects micro-reservoirs during balloon insertion, lesion crossing and expansion.

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

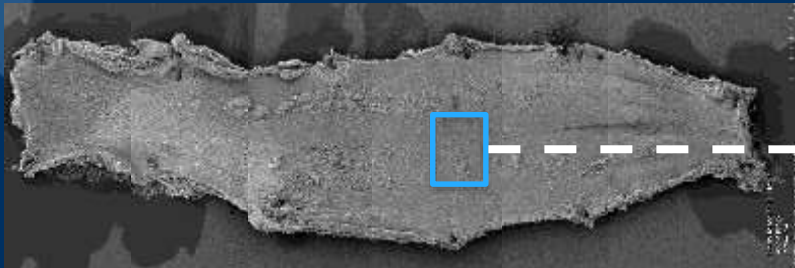
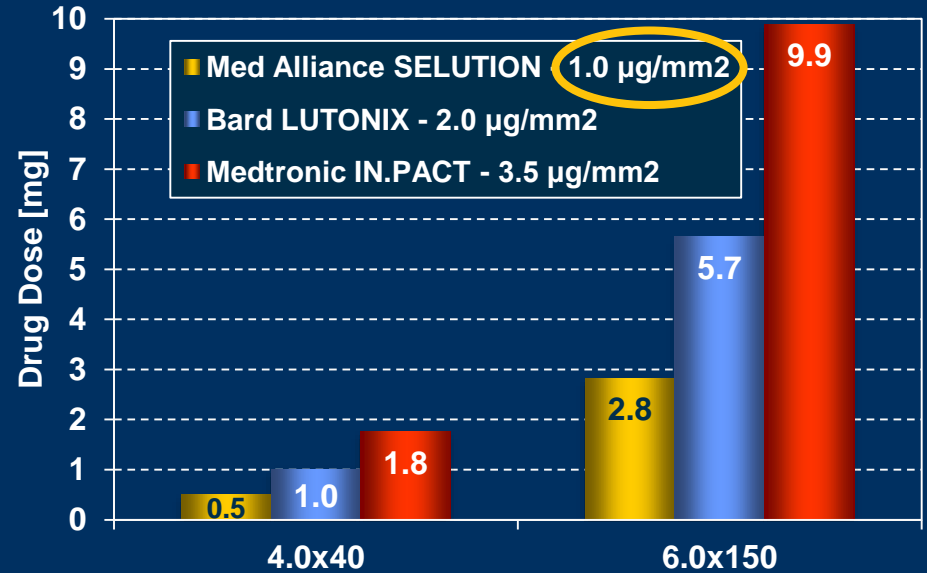


SELUTION SLR: MedAlliance

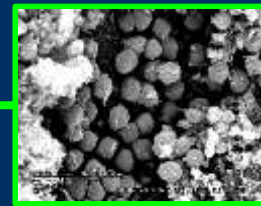
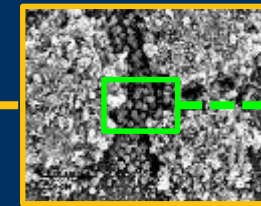
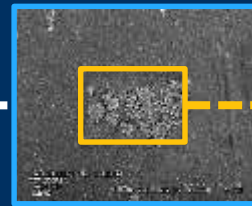
Arterial Tissue Drug Concentration
Sirolimus (RAP) versus Paclitaxel (PAX)



Drug Dose per Balloon Size



En Face Scanning Electron Microscope at 24 hours

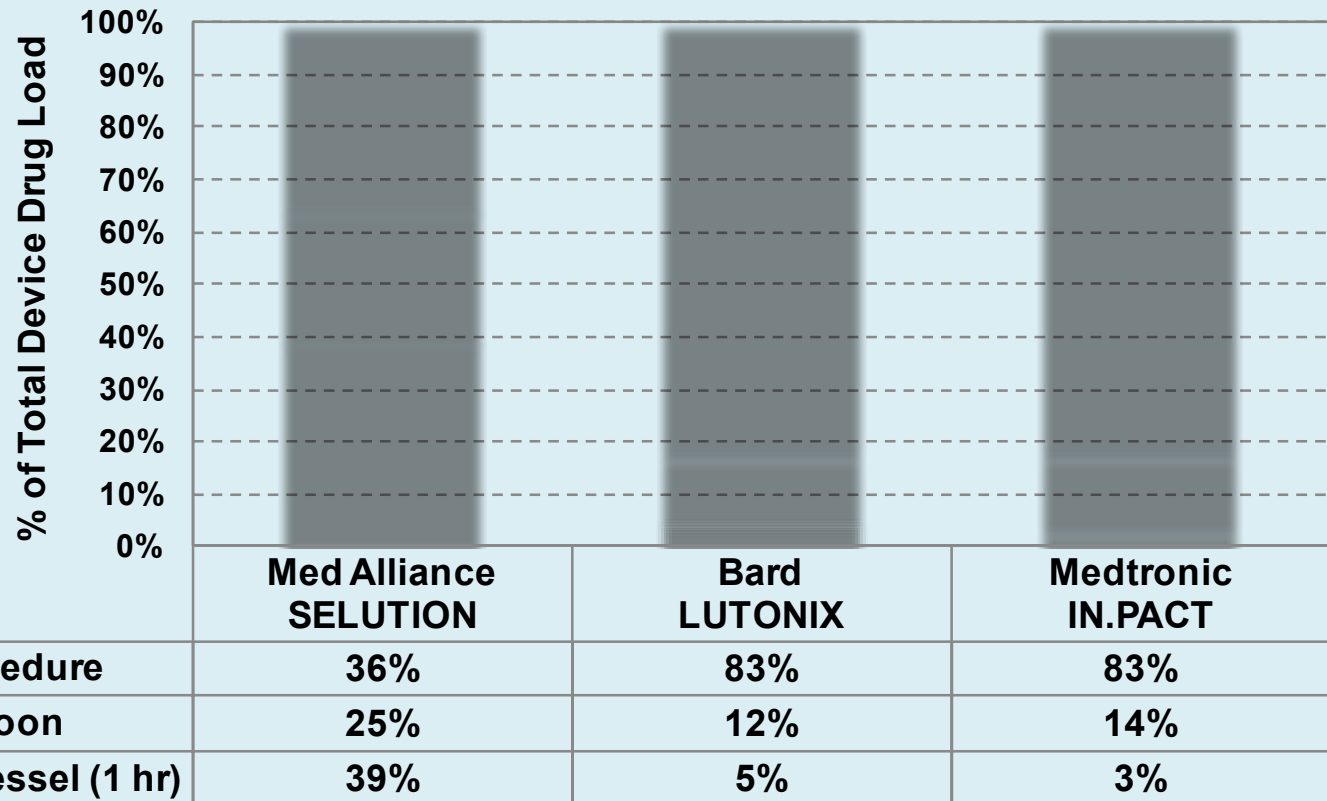


(Med Alliance – PK Study 2014-004, Medtronic – Presentation R.J. Melder LINC 2012)

(Bard – Catheterization and Cardiovascular Interventions 2014)

SELUTION SLR™ vs. Competition

Drug Transfer



Source: Med Alliance – Bench Test Data on File
 Bard-LUTONIX & Medtronic-IN.PACT – Presentation Granada at CRT 2014.

Preclinical Study (Porcine Coronary Model)



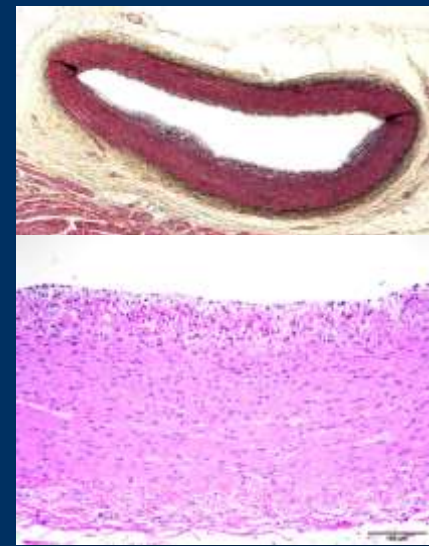
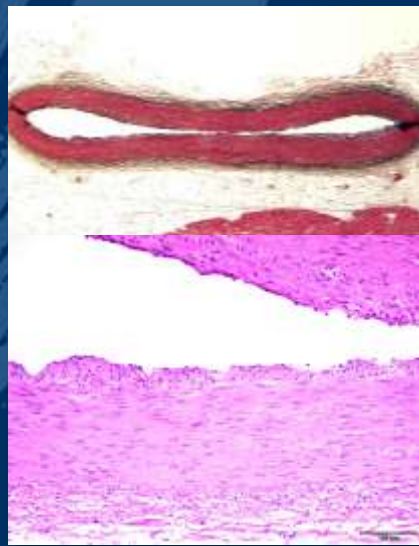
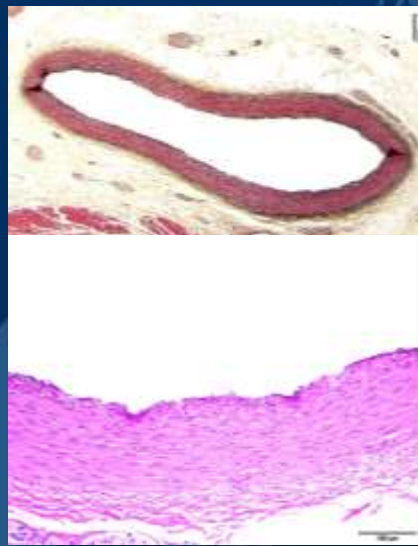
Balloon (3.0 or 3.5 × 15 mm)

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



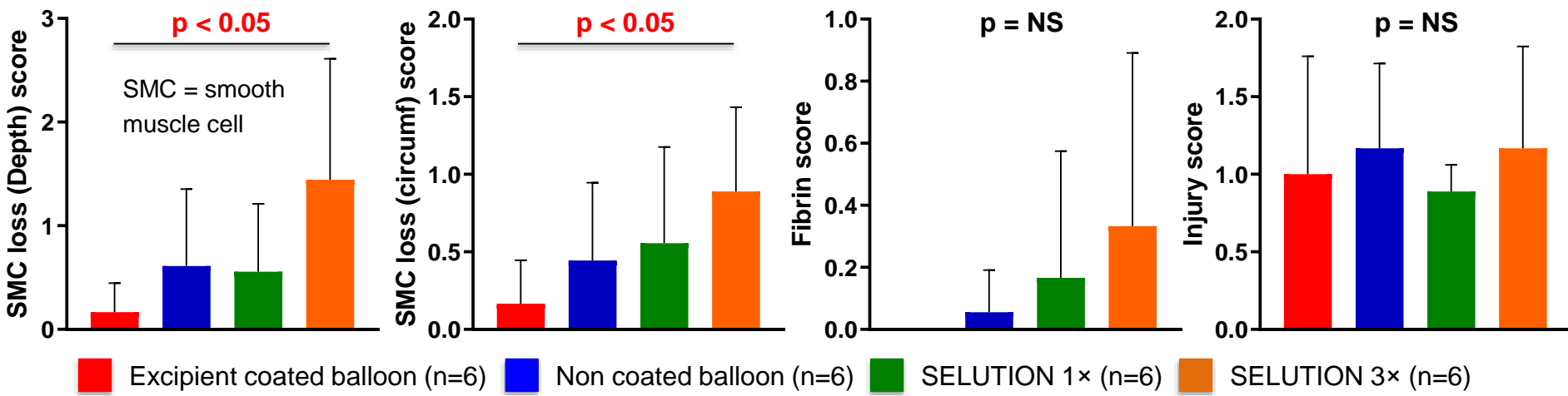
Excipient coated balloon

Non coated balloon

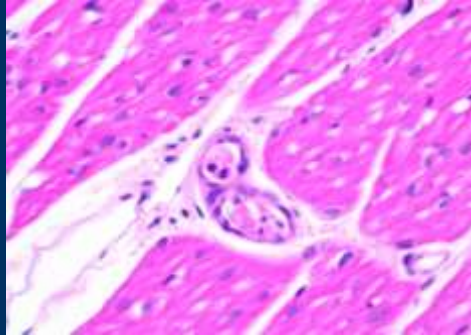
SELUTION 1x

SELUTION 3x

Morphometry analysis

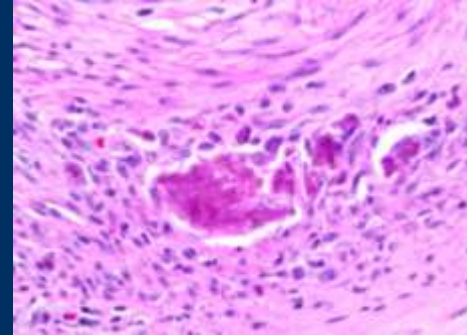


30 Day Downstream Findings in Porcine Myocardium



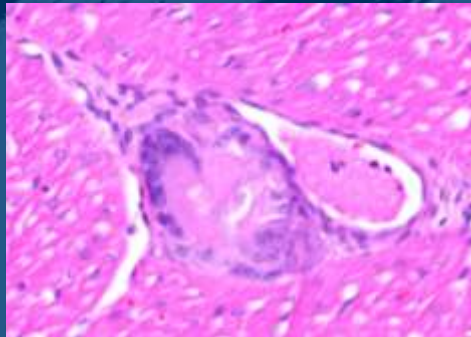
Excipient balloon

Adjacent small arterioles show embolic amorphous material.



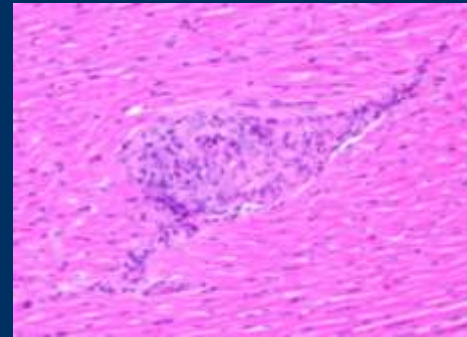
SELUTION 1x

Epicardial coronary artery shows early calcified fibrin surrounding inflammatory reaction.



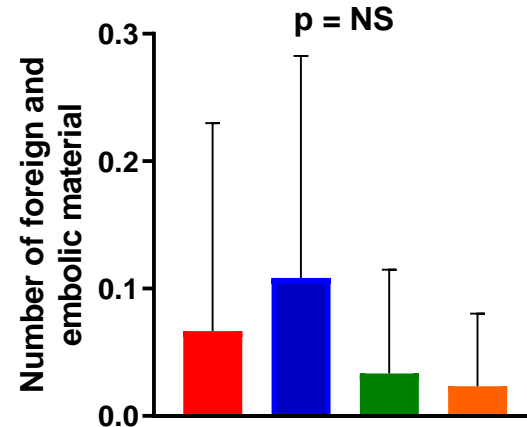
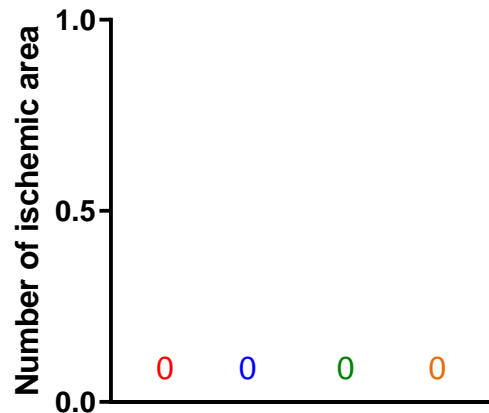
Non coated balloon

Adjacent arterioles show amorphous foreign material with inflammatory reaction.



SELUTION 3x

Giant cells surrounding a minute birefringent foreign material.

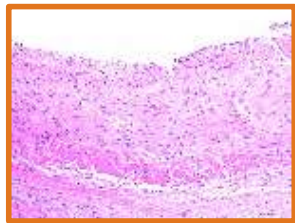


Excipient coated balloon (n=6) Non coated balloon (n=6) SELUTION 1x (n=6) SELUTION 3x (n=6)

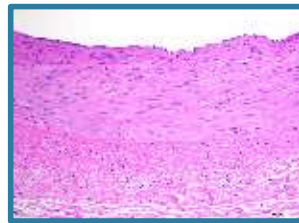
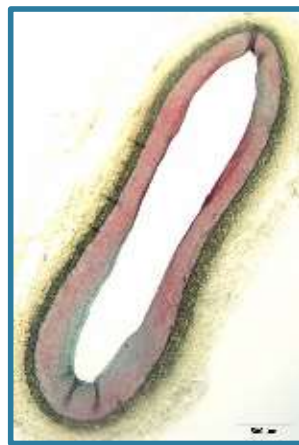
28 Days Preclinical Study in Porcine Peripheral Artery Model

Peripheral – 28 days histopathology

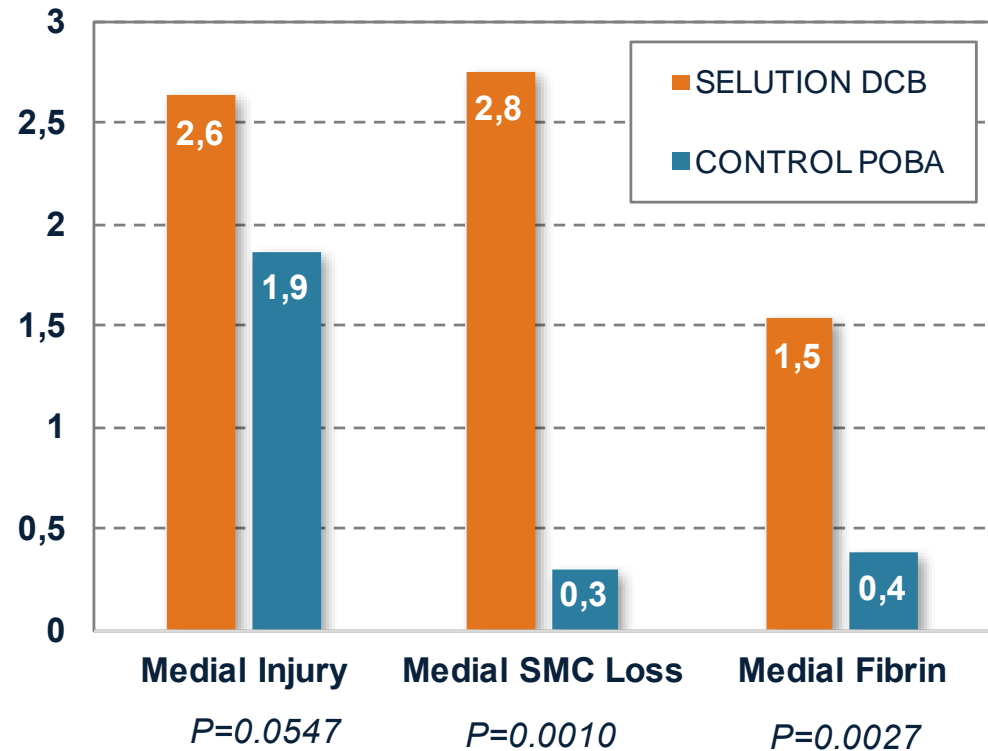
**SELUTION
DCB**



**CONTROL
POBA**



Histological Comparison – Scoring



$P \leq 0.05$ Statistically Significant

CV33054 30-138E LPFA TR E

CV33052 30-064E RSFA TR G

Source: Med Alliance – Histo Study (MEA 439-14).

Summary

- Sirolimus has higher therapeutic index (i.e. range before toxic effects) are seen as compared to paclitaxel.
- Paclitaxel has faster absorption and longer retention in tissues than sirolimus. On the other hand, sirolimus is absorbed slowly and spreads more uniformly throughout entire artery.
- Medial SMC loss and fibrin scores were relatively higher in SELUTION groups, suggesting the existence of sirolimus drug effect on the vessels wall healing process.
- The main source of embolic material is likely hydrophilic gel and plastic material derived from balloon surface coating.
- Sirolimus is drug of choice and maybe more ideal than paclitaxel for coronary and peripheral artery interventions.

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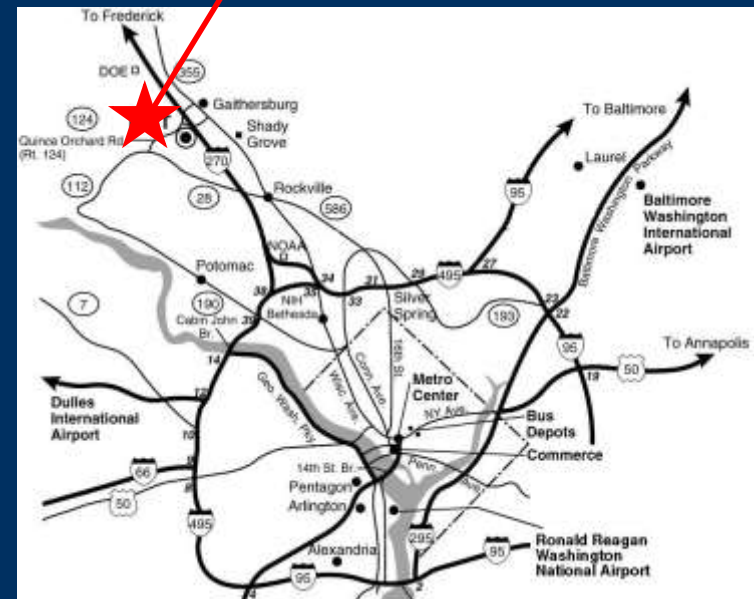
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Lila Adams, HT

Frank D Kolodgie, PhD

Renu Virmani, MD



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