Drug Eluting Technologies for PAD
From Fundamentals to Future

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Wednesday 29-Jan, 9:30 – 11:00am Main Arena 1
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- IMPORTANT INFORMATION: These materials are intended to describe common clinical considerations and procedural steps for the on-label use of referenced technologies as well as current standards of care for certain conditions. Of course, patients and their medical circumstances vary, so the clinical considerations and procedural steps described may not be appropriate for every patient or case. As always, decisions surrounding patient care depend on the physician's professional judgment in light of all available information for the case at hand.
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Fundamentals of Drug-Coated Balloons

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Disclosure

Speaker name: Ravish Sachar

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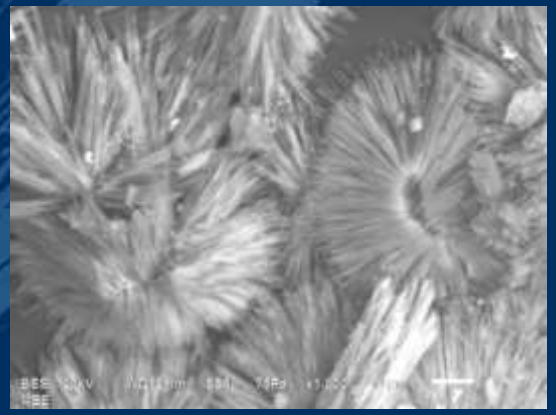
I have the following potential conflicts of interest to report:

- ☒ Consulting: Boston Scientific, Medtronic
- ☐ Employment in industry
- ☒ Stockholder of a healthcare company: Contego Medical
- ☐ Owner of a healthcare company
- ☐ Other(s)

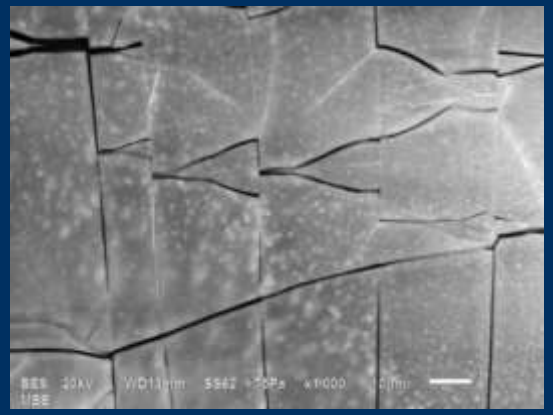
☐ I do not have any potential conflict of interest

Paclitaxel Formulation Types

Crystalline Coating



Amorphous Coating



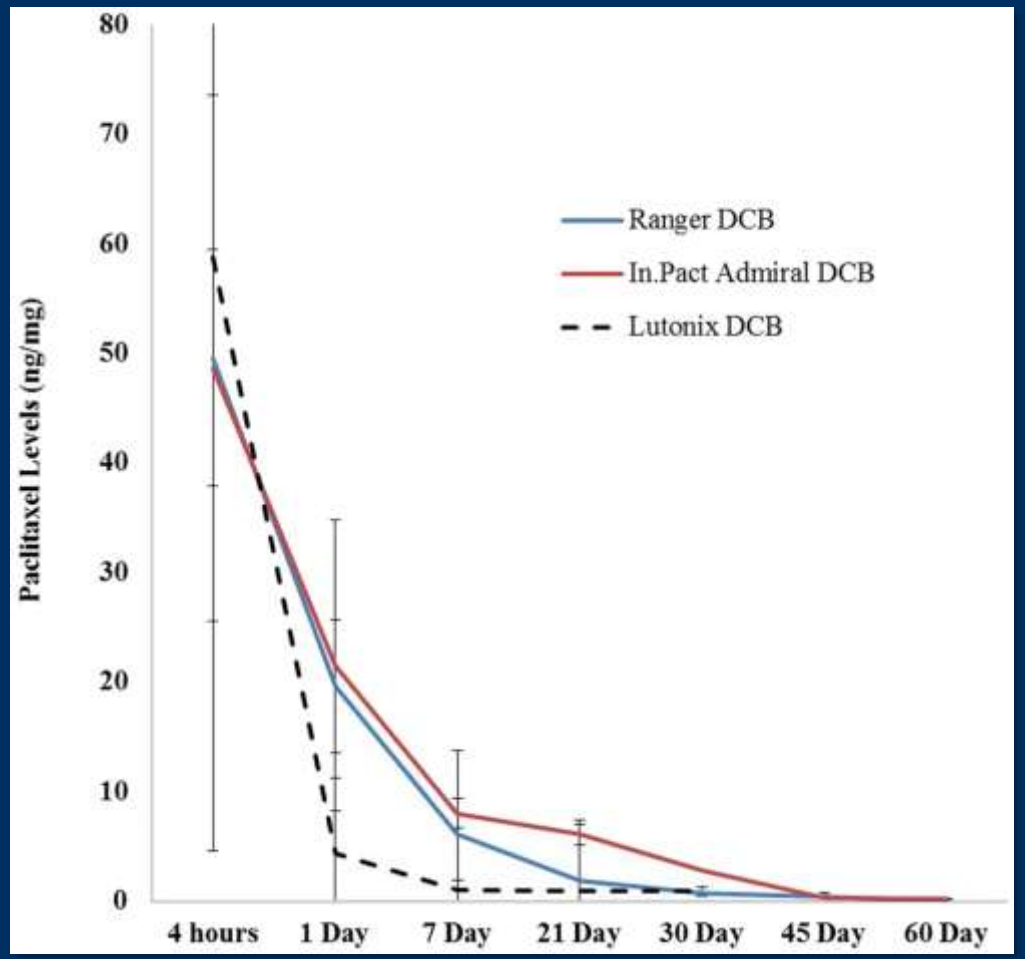
Impact on Biological Performance

	Crystalline	Amorphous
Particles Released	+++	++
Uniform Coating	++	+++
Drug Transfer to Vessel	+++	+++
Drug Retention vs. Time	+++	+
Biological Effectiveness	+++	++

Granada JF, et al. Open Heart. 2014;1(1):e000117. Tesfamariam B. J Control Release. 2016 ;238:149-156.

Local tissue uptake at lesion site

- Consistent drug tissue levels for Ranger™ achieved with 2 µg/mm² as compared with In.Pact (3.5 µg/mm²) up to 60 days in the superficial femoral artery territory of the swine
  - In.Pact 3.5 µg/mm²
  - Ranger 2 µg/mm²
  - Lutonix 2 µg/mm²

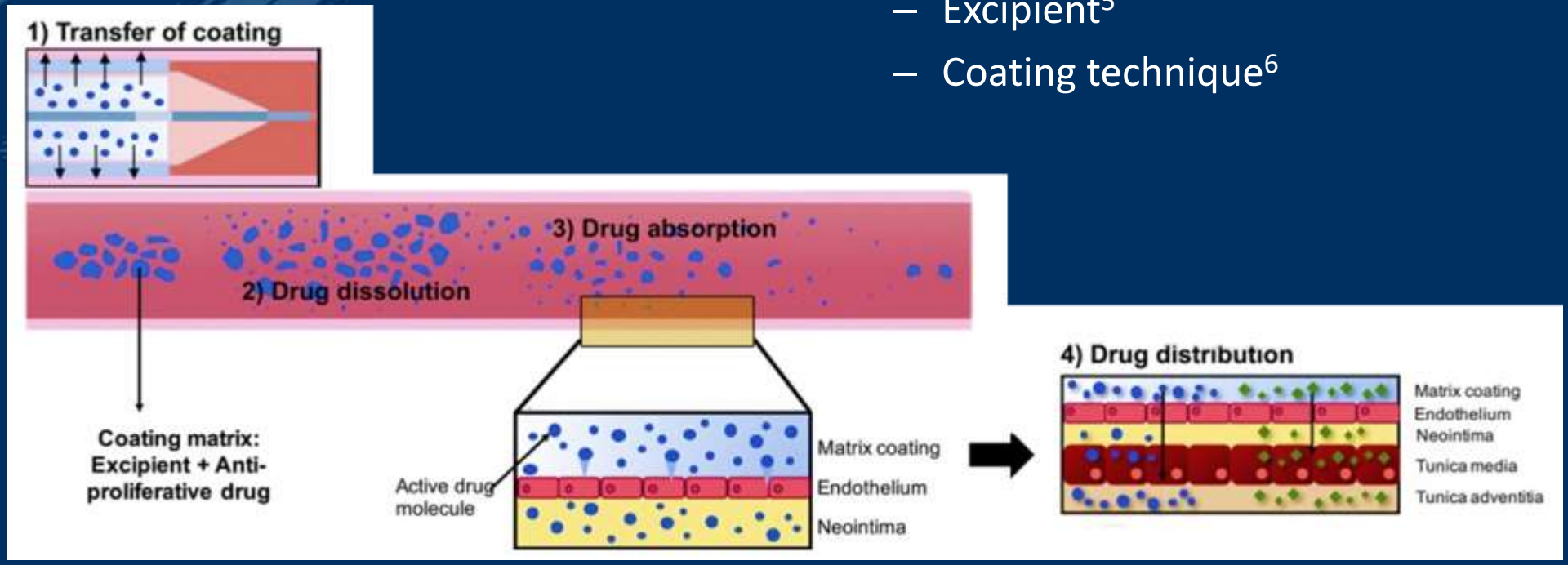


Gongora CA, et al. JACC Cardiovasc Interv. 2015;8(8):1115-1123. Preclinical results may not necessarily be indicative of clinical outcomes.
Ranger DCB is an investigational device and not available for sale in the US. Lutonix ™ Drug Coated Balloon Catheter is a trademark of C.R. Bard Inc. IN.PACT ™ is a trademark of Medtronic Inc.

Determinants of DCB Biological Effect

- **Antiproliferative agent** (Paclitaxel)
- **Initial dose/dose density**

- **Tissue transfer efficiency**
  - Coating characteristics (e.g., hydrophobicity/hydrophilicity, crystallinity/amorphous morphology)[1-4]
  - Excipient[5]
  - Coating technique[6]



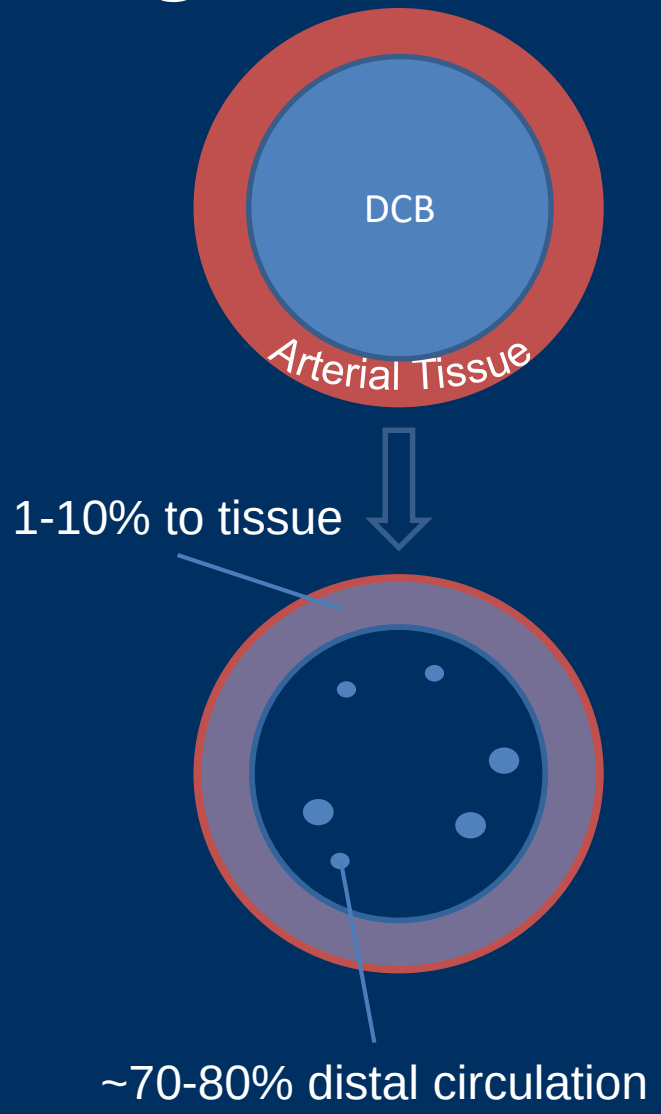
Xiong GM, et al. J Control Release. 2016;239:92-106.

1. Seidlitz et al. PLOS One 2013; DOI: 10.1371/journal.pone.0083992. 2. Afari & Granada. Endovascular Today August 2012; 53-58.
3. Granada et al. Open Heart 2014;1:e000117. 4. Creel et al. Circ Res; 2000;86:879-884. 5. Radke et al. EuroIntervention 2011;7:
730–737. 6. Buszman et al. JACC Cardiovasc Interv 2013;6(8):883-90. 7. Forrester et al. J Am Coll Cardiol 1991;17:758-769.

Determinants of DCB Biological Effect

- **Loss to circulation** (Insertion-Transit-Inflation)[1] and risk of:
  - Particulate embolization
  - Systemic effects

- **Paclitaxel tissue residency**
  - Presence in tissue during restenotic cascade[7] (duration of retention)
  - Homogeneity of distribution



1. Seidlitz et al. PLOS One 2013; DOI: 10.1371/journal.pone.0083992. 2. Afari & Granada. Endovascular Today August 2012; 53-58. 3. Granada et al. Open Heart 2014;1:e000117. 4. Creel et al. Circ Res; 2000;86:879-884. 5. Radke et al. EuroIntervention 2011;7: 730–737. 6. Buszman et al. JACC Cardiovasc Interv 2013;6(8):883-90. 7. Forrester et al. J Am Coll Cardiol 1991;17:758-769.

Granada JF, TCT 2014.
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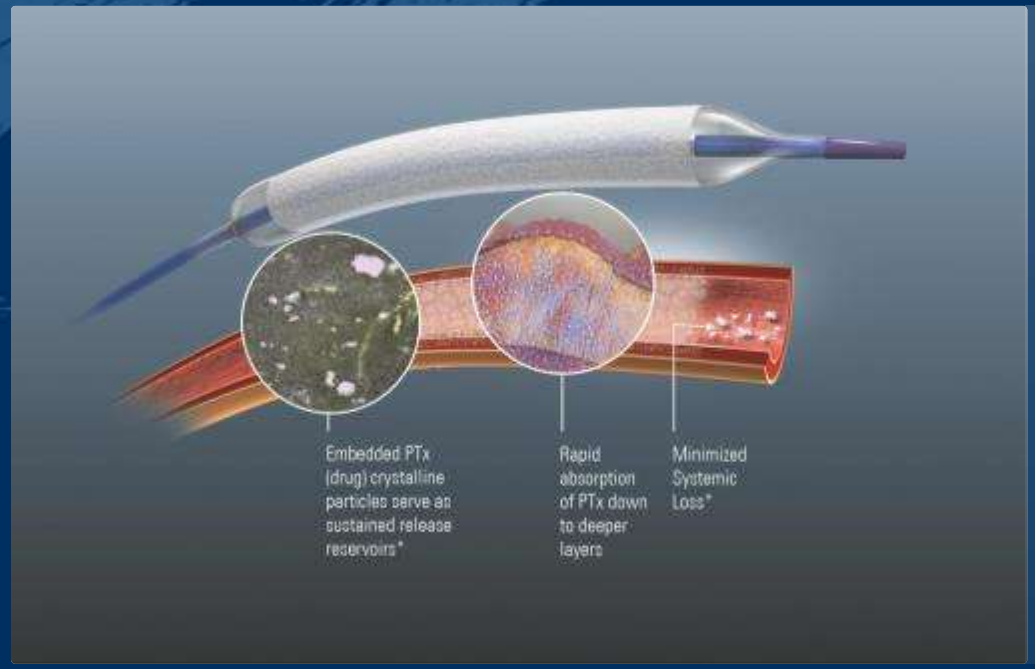
Boston Scientific Ranger™

- Sterling balloon platform
- TransPax™ coating technology
  - Paclitaxel 2 µg/mm^2
- Ranger™ DCB Loading Tool
  - Designed to protect the drug coating
- Size matrix:
  - SFA: 4-8 mm; 30-200 mm
  - BTK: 2-4 mm; up to 150 mm

Ranger DCB is an investigational device and not available for sale in the US.

Ranger™ DCB Coating Technology

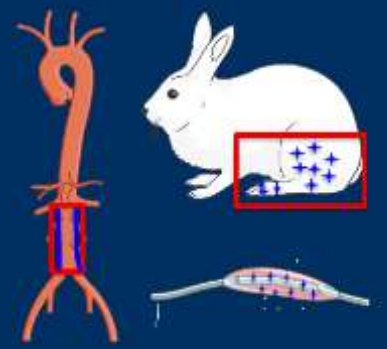
- TransPax™ Technology
  - Paclitaxel, Excipient: Citrate ester (acetyl tributyl citrate – ATBC)

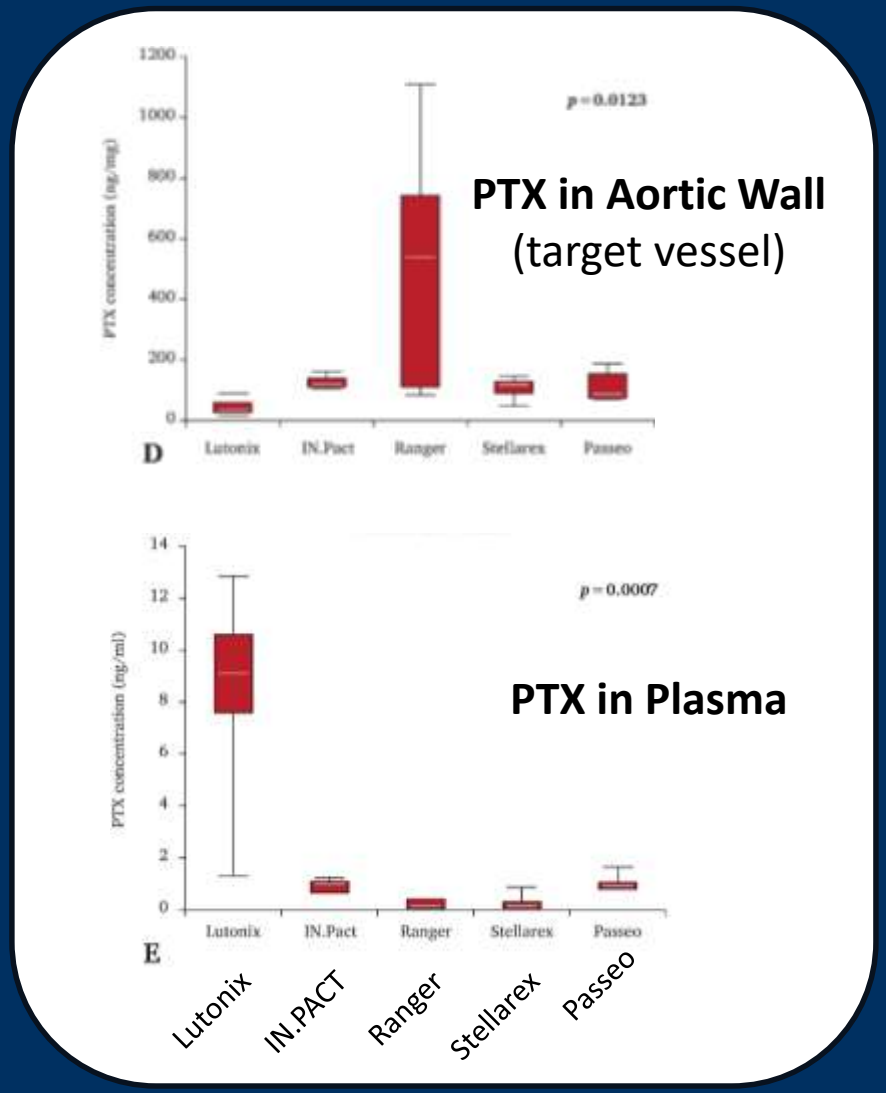


- Designed to balance hydrophilic and hydrophobic properties
- Allow adhesion to the balloon during tracking and deployment
- Allow transfer to the vessel wall during balloon inflation
- Minimize particulate loss

Local & Distal Paclitaxel Levels Recently Re-examined

- Lutonix vs In.Pact vs Ranger vs Stellarex vs Passeo-18 Lux
- Rabbit model (N=5 per DCB)
- Evaluated **paclitaxel levels** (ng/mg) in:
  - **Aorta** (target vessel)
  - **Plasma**
  - Leg Muscles (TFL, vastus lateralis, tibialis cranialis)





Boitet A, et al. Eur J Vasc Endovasc Surg. 2019. pii: S1078-5884(18)30868-2. doi: 10.1016/j.ejvs.2018.11.019. Coscas R, LINC 2018.
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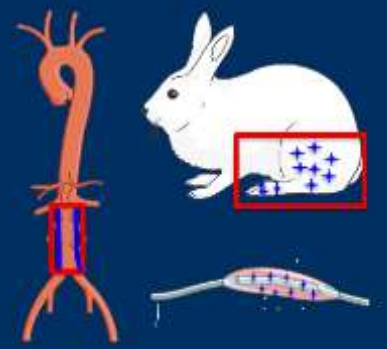

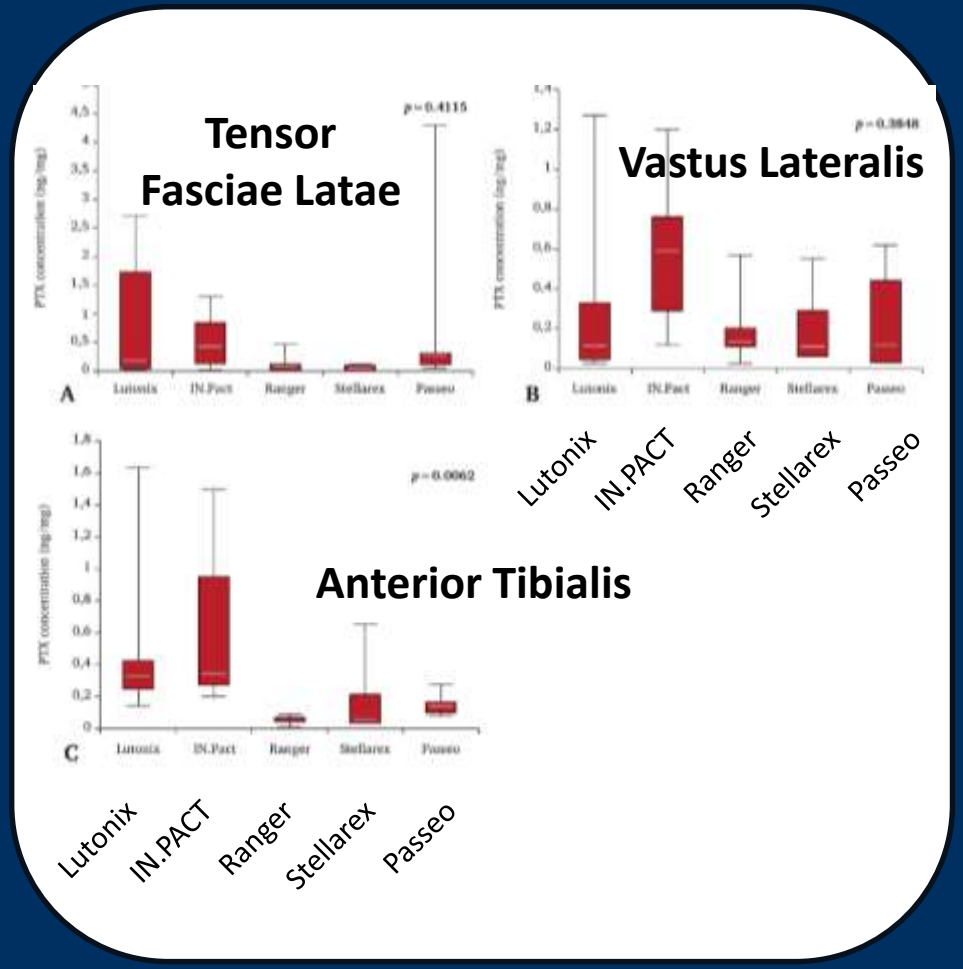

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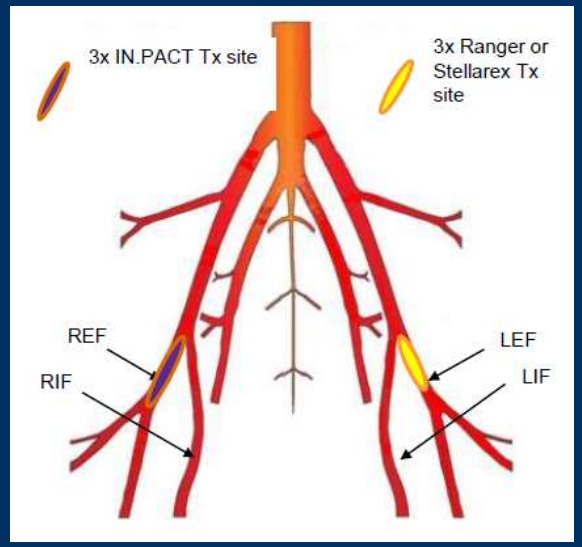
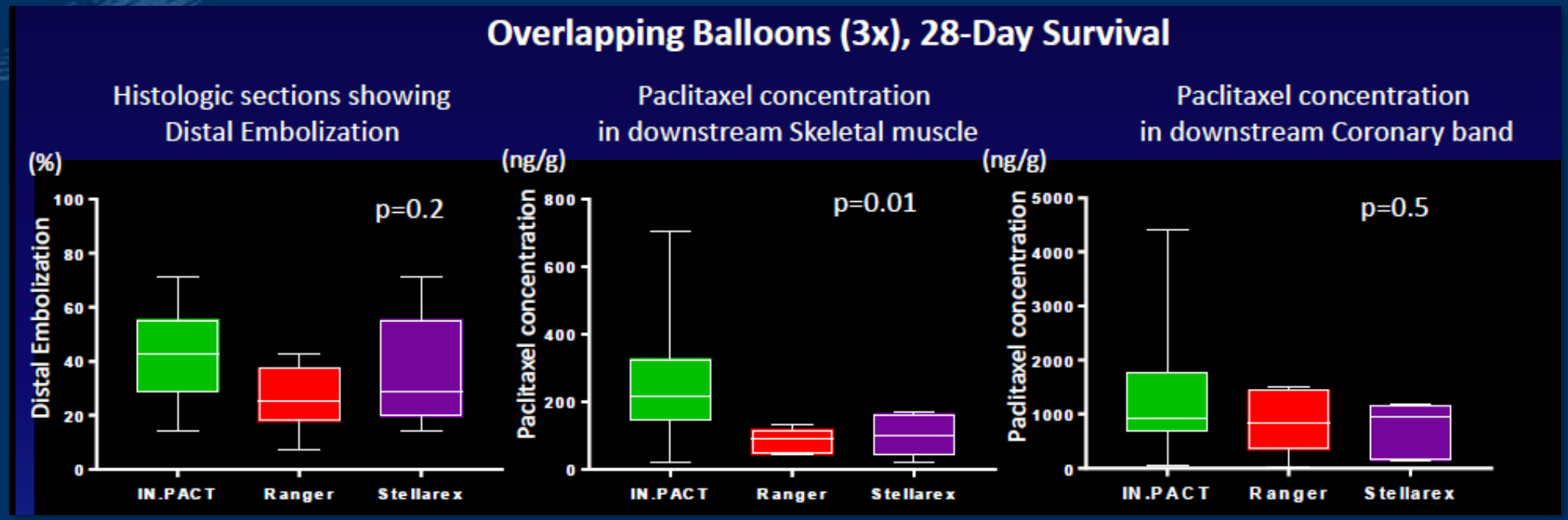
Particulate Embolization in Different DCB Formulations

- In.Pact DCB vs Ranger vs Stellarex
- Swine model – 28 day study
- 3X dose, same size DCB, 60s inflation
- Evaluated skeletal muscle and coronary band for potential embolic changes
  - Distal PTx concentration
  - Histology (distal embolization, vascular changes)





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DCB Simulated Use Testing

Anatomical basis for glass model

Tortuous anatomical model

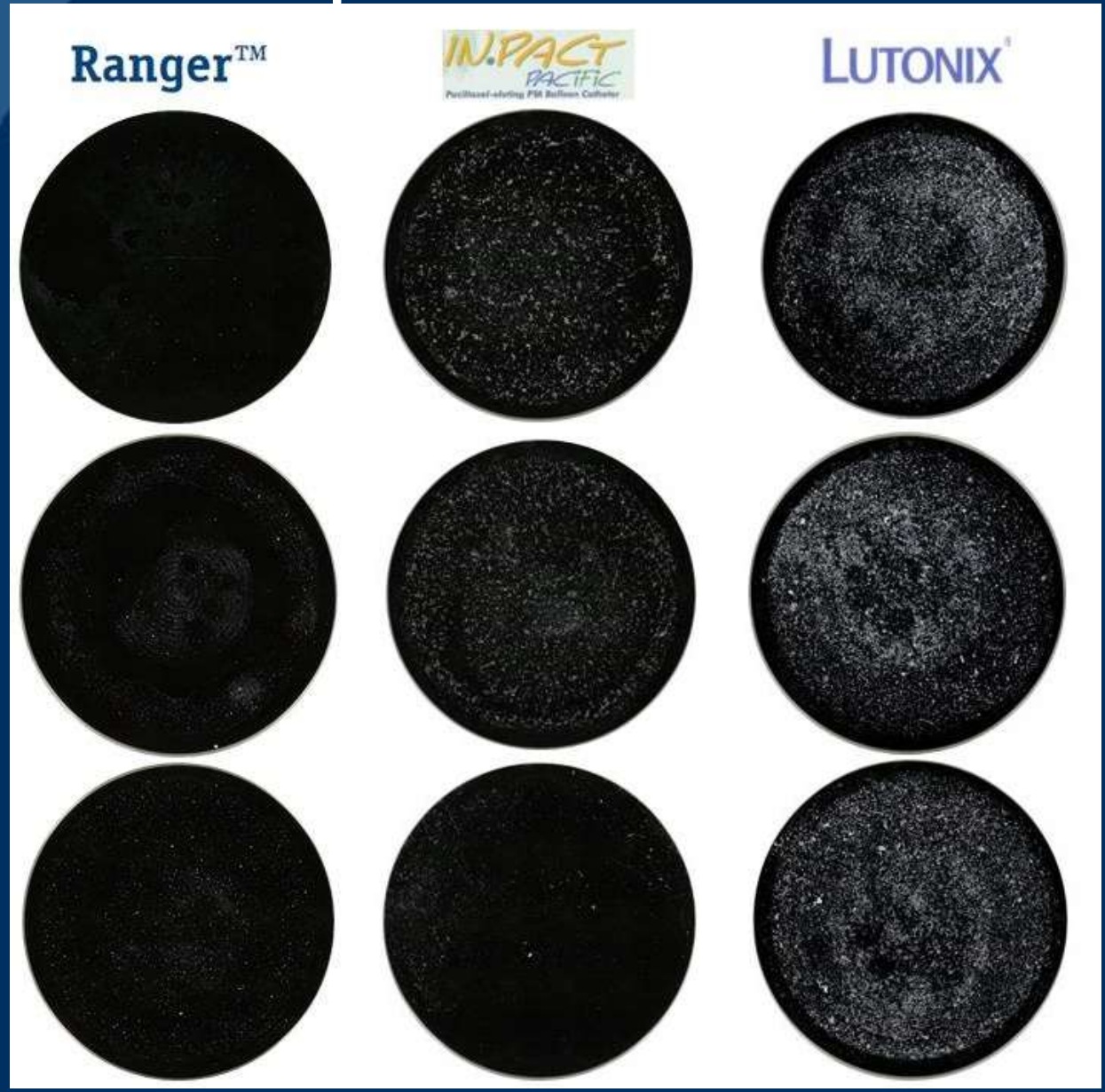
Balloon catheter tracked through a glass closed loop tortuous anatomy model with 37°C circulating water

Drug Content / Procedural Drug Loss			Particulates
Control	Tracked	Tracked & Inflated	
• Drug content assessed immediately after package removal	• Catheter tracked in model • Balloon analyzed for drug content	• Catheter tracked, inflated, and deflated in model • Balloon analyzed for drug content	The solution circulating in the closed loop passes through a particle counter
			

Bench test results may not necessarily be indicative of clinical performance. The testing was performed by or on behalf of BSC. Data on file.

Particulate Comparison

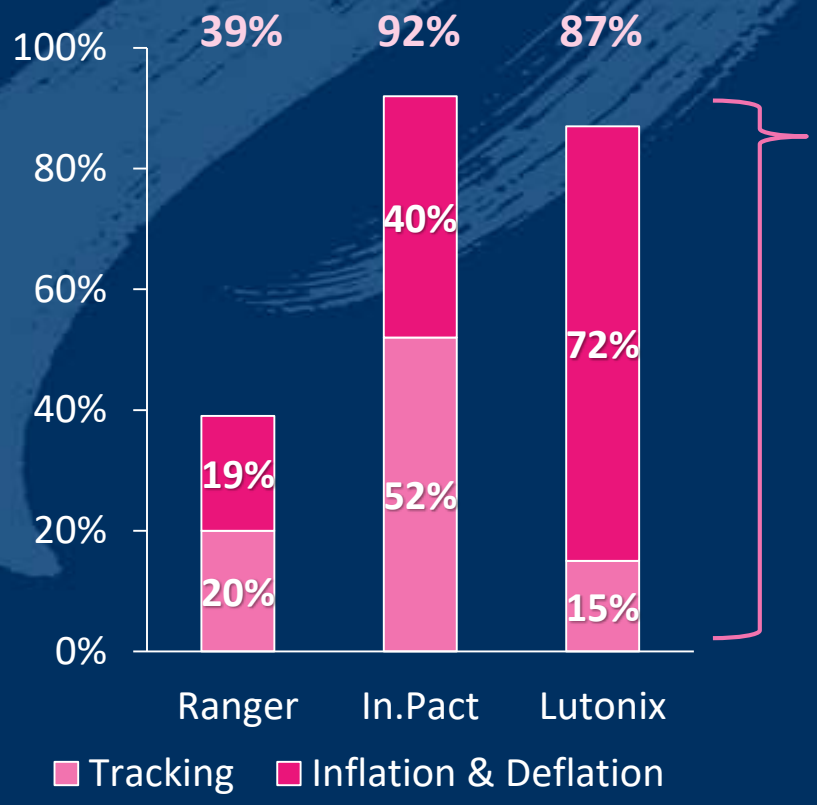
- Downstream Particulate following simulated use (Track, Inflate/Deflate)
  (Anatomical Model, Circulating Fluid at 37 ° C)
- 6.0x80 mm DCBs
- Guide Sheath used (per IFU)
  - Ranger – 5F
  - In.Pact – 6F
  - Lutonix – 5F



Solution remaining from simulated use following particle counting was filtered (5µm pore size) and imaged, N=3. 30X magnification.
Bench test results may not necessarily be indicative of clinical performance. The testing was performed by or on behalf of BSC. Data on file.

Simulated Use: Systemic Exposure

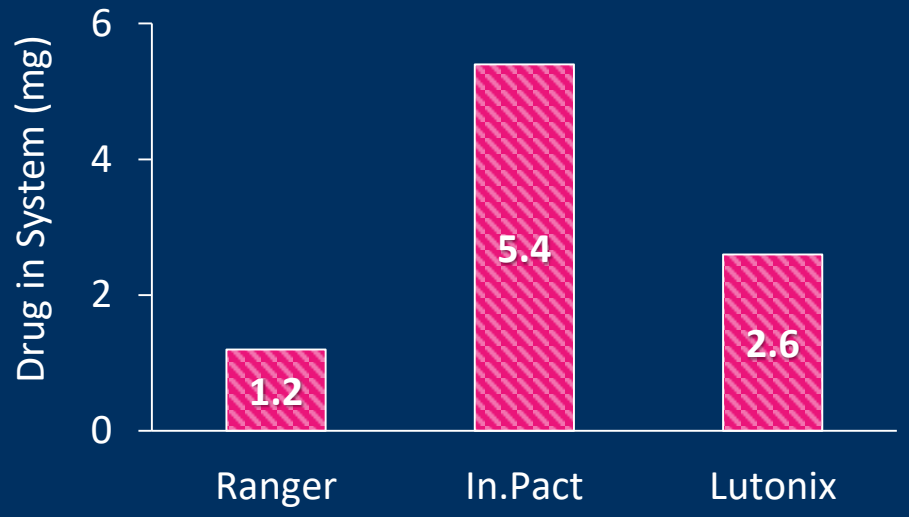
Drug Lost to Tracking, Inflation & Deflation



- Drug "lost" in simulated use approximates transfer to tissue and circulation

Drug Transferred to System

(Example 6.0x80 mm balloon)



	Ranger ($2\mu g/mm^2$)	In.Pact ($3.5\mu g/mm^2$)	Lutonix ($2\mu g/mm^2$)
Starting Drug (6.0x80 mm)	3.1 mg	5.8 mg	3.0 mg
% Drug Lost from Balloon	39%	92%	87%
Drug in System	**1.2 mg**	**5.4 mg**	**2.6 mg**

Bench Testing performed by Boston Scientific. Results not necessarily indicative of clinical performance. Data on File Boston Scientific. Drug on a 6x80 balloon per IFU of In.PACT and Lutonix and per BSC Product specifications. Catheters tracked through tortuous vessel anatomical model then balloon analyzed for drug content (Tracking) or tracked through model, inflated, deflated, and analyzed for drug content (Inflation & Deflation). Control catheters underwent no preconditioning; balloons were immediately analyzed for drug content.

RANGER II SFA Pharmacokinetics Substudy

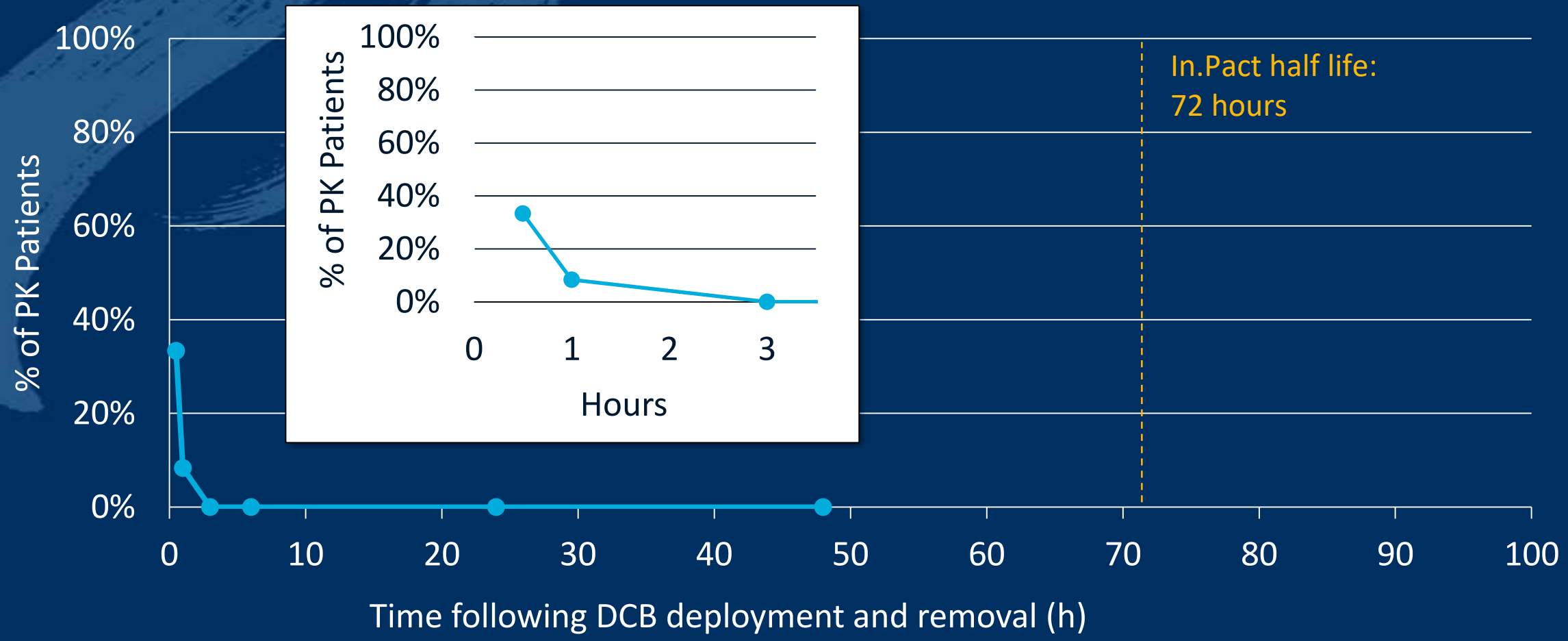
- All patients treated with Ranger DCB (N=12)
- Treated lesion length 154.2±92.8 mm, Average number of Ranger DCB used per patient: 1.75

- Plasma paclitaxel less than the limit of quantification (<1 ng/mL):
  - 11 of 12 patients by 1 hour following DCB deployment and removal
  - all patients by 3 hours

Protocol required blood draws: baseline, 10 minutes, 30 minutes, 1, 3, 6, 24 or 48 hours, 7 days and 30 days after last Ranger DCB treatment and removal.

RANGER II SFA Pharmacokinetics Substudy

Percentage of Patients with Measurable Paclitaxel (> 1 ng/mL)



Data on File Boston Scientific. In.PACT half life from In.Pact DFU.

BSC Peripheral DCB Clinical Program

Ranger II SFA Global	**Multicenter, RCT 3:1** (Ranger : PTA)	**N = 376**		12M follow up complete
COMPARE I*	**Multicenter, RCT 1:1** (Ranger : In.Pact)	**N = 414**		Pilot N=150 24M complete. N=414 Enrollment complete
RANGER SFA (FIH)	**Multicenter, RCT 2:1** (Ranger : PTA)	**N = 105**		12M follow up complete
Ranger SFA Registry*	**Multicenter, registry**	**N = 172**		12M follow up complete
Ranger DCB China	**Multicenter, single-arm**	**N = 123**		Enrolling
RANGER-BTK*	**Single center, single-arm**	**N = 30**		6M follow up complete
DCB vs PTA in CLI and Crural Arteries*	**Single center, RCT 1:1** (Ranger : PTA)	**N = 70**		Enrolling
DCB Venoplasty in AV Fistula Stenosis (DeVA)*	**Multicenter, RCT 1:1** (Ranger : PTA)	**N = 186**		Enrolling

*These investigator-sponsored studies are supported by grant funding from Boston Scientific. Boston Scientific is not responsible for the collection, analysis or reporting of these studies which remain the sole responsibility of the investigators. Information for the use in countries with applicable product registrations.
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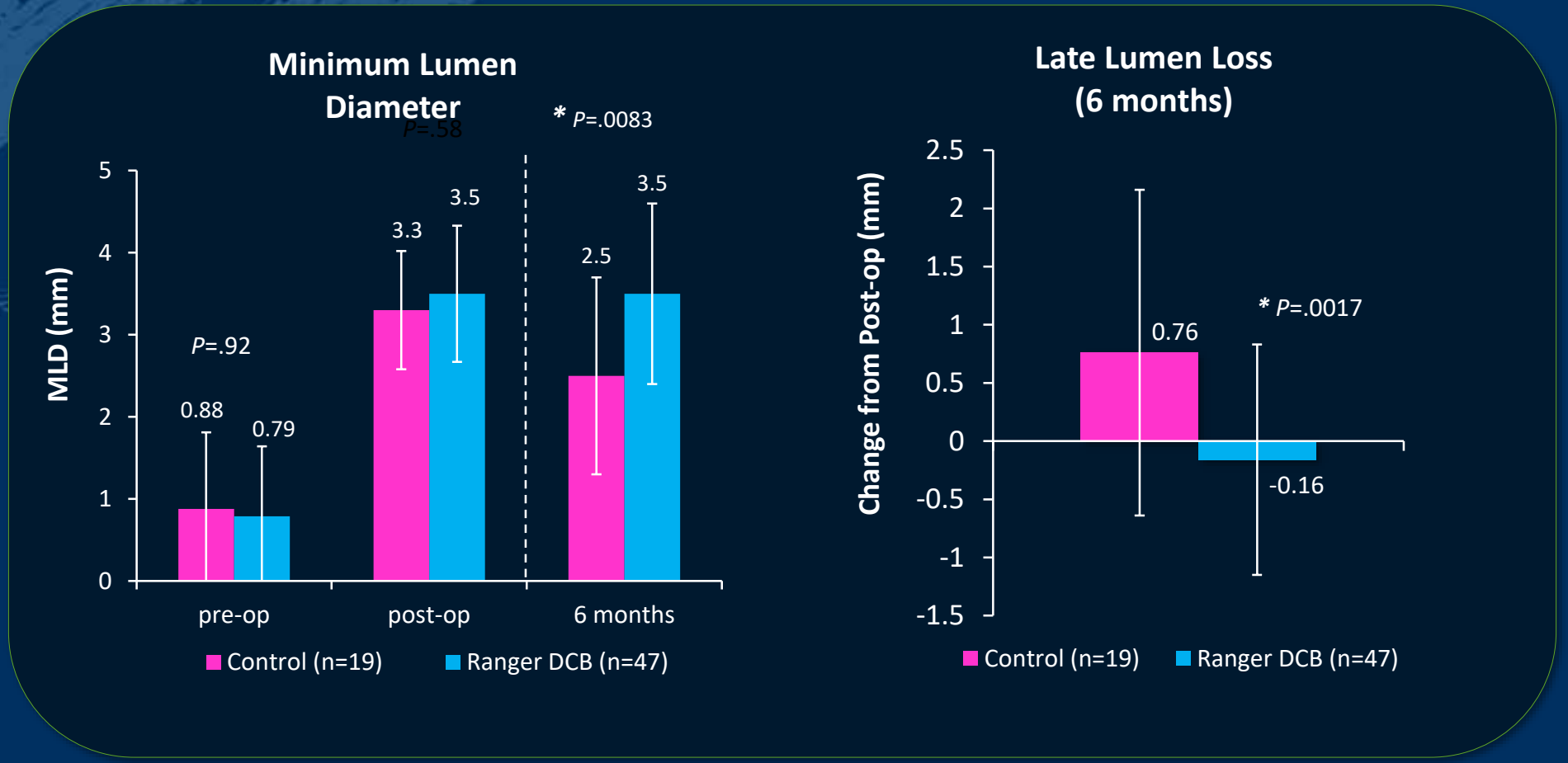
RANGER SFA

Primary Efficacy Endpoint – 6 Months

- LLL was significantly less for Ranger DCB than for control (P=.0017)



Bausback Y, et al. J Endovasc Ther. 2017;24(4):459-467.
Scheinert, D. CIRSE 2016.

Conclusions

- Fundamental differences across DCBs:
  - Paclitaxel dose
  - Paclitaxel coating (amorphous / crystalline mix)
  - Excipient
  - Particulate loss (in transit and deployment)
  - Local tissue levels
  - PK measures

Unique combinations of properties differentiate DCBs, and should be considered along with efficacy and safety profiles

Thank You!

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