AGENT™ Drug-Coated Balloon Update: Are all DCBs the Same

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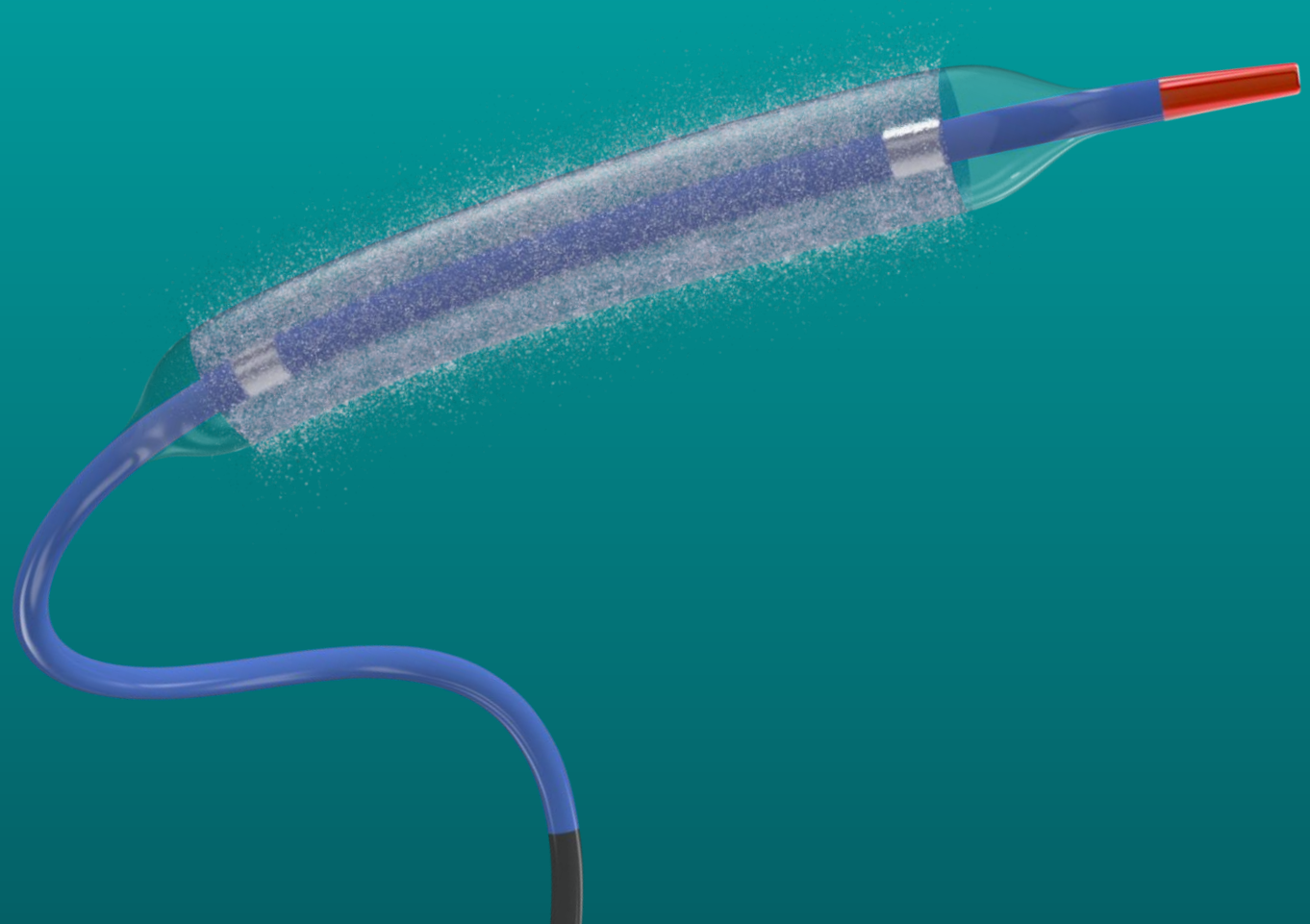
Conflict of Interest

- Employee Boston Scientific 2021-2024

- Independent Consultant to Boston Scientific

Technology and Mechanism



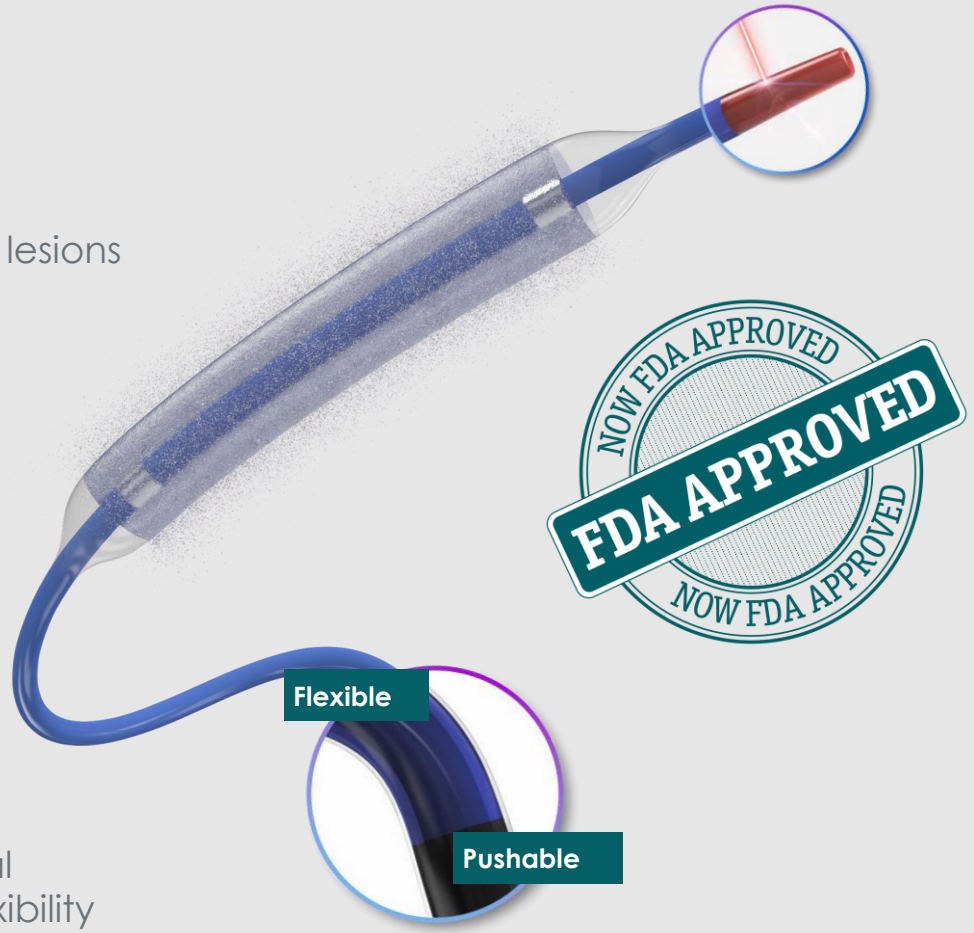
AGENT™ - The Technology

Catheter

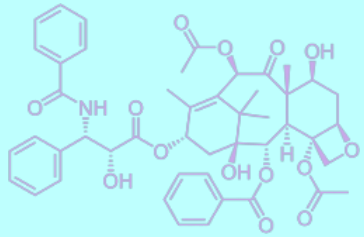
Laser Bonded Tip
Designed to improve crossability in complex lesions

Z Glide™
Lubricious coating designed to reduce friction for enhanced trackability

Bi-Segment Inner Shaft
Designed and positioned for optimal transition from proximal pushability to distal flexibility

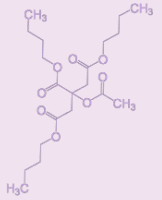


Drug
Active pharmaceutical ingredient



Paclitaxel optimal dose 2µg/mm²

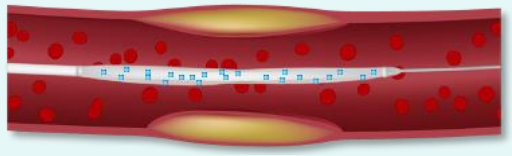
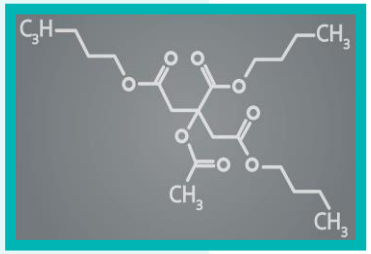
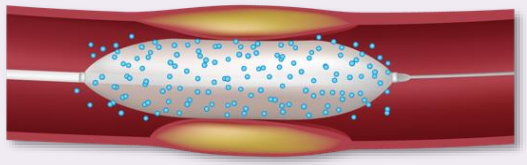
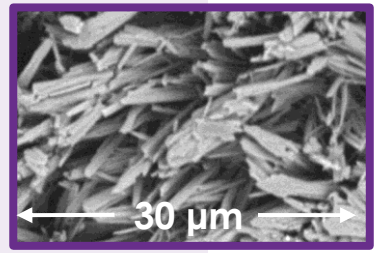
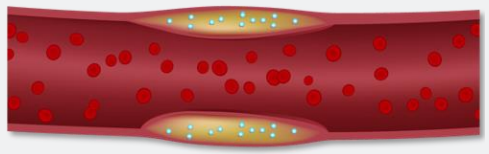
Excipient
Maintain coating integrity and facilitate drug transfer



Acetyl Tributyl Citrate (ATBC)

Three Critical Phases of Paclitaxel-DCB Drug Delivery

Following Optimal Lesion Preparation

Design Requirements	AGENT™ DCB Design Solutions		
1. Targeted Delivery 	**Hydrophobic Drug[1]** Paclitaxel is durable under hydration (stays on balloon during tracking)	**Excipient** Novel excipient minimizes drug loss in transfer and maximizes balloon-to-vessel delivery	
2. Rapid Absorption 	**Lipophilic Drug[1]** Paclitaxel has a high affinity to enter fatty tissue	**Sharp-Edge Structure** Sharp edge crystalline Paclitaxel for tissue absorption	
3. Sustained Retention 	**Uniform Crystalline Formulation** Crystalline formulation sustains therapy throughout the healing process		

1. Surapaneni, M., et al. "Designing Paclitaxel drug delivery systems aimed at improved patient outcomes: current status and challenges." International Scholarly Research Notices (2012).

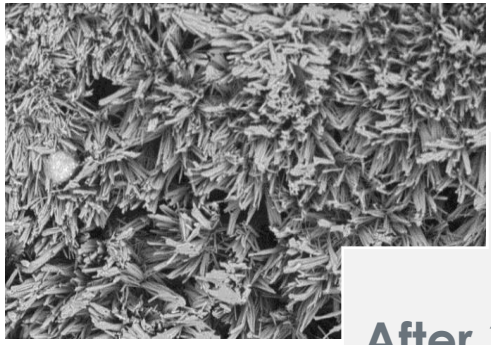
AGENT DCB is intended to be used after appropriate vessel preparation when treating in-stent restenosis (ISR)

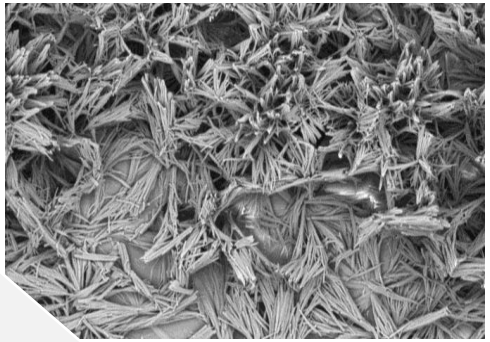
Images adapted from Brookhaven Heart

Targeted Drug Delivery

AGENT™ Crystalline Structure is Hydrophobic and Demonstrates Durability Under Hydration[1]

AGENT™
More Durable

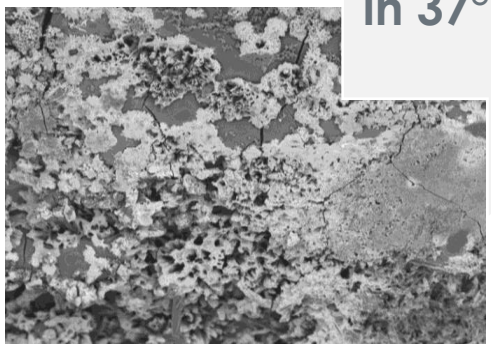


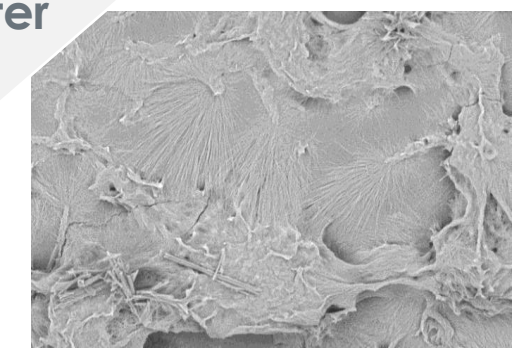


Less Particulate Loss

After 10 min
in 37°C Water

Other Amorphous PTX DCB
Less Durable





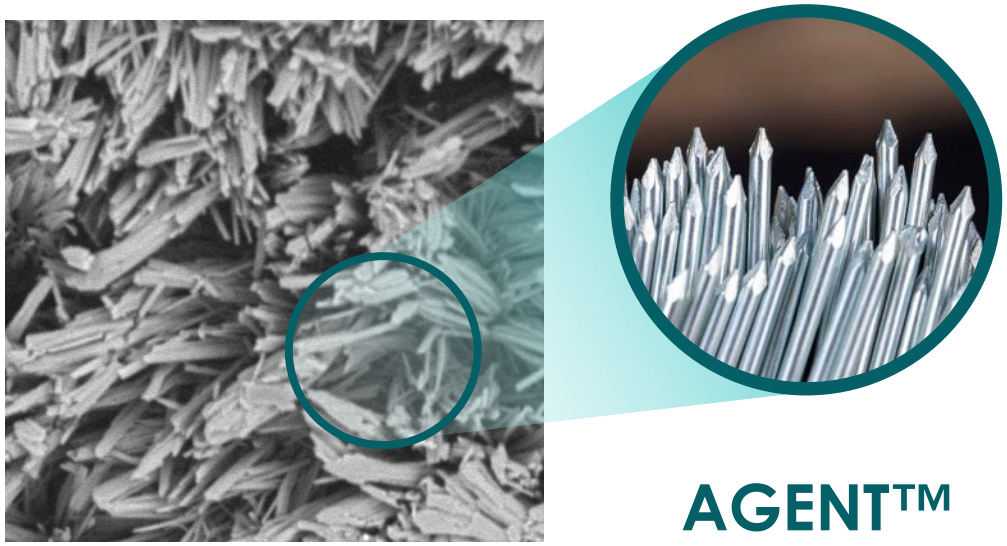
More Particulate Loss

All particulate from simulated insertion, delivery, inflation/deflation and withdrawal. Particulate capture test using a 5 µm filter.
1. BSC Internal Test. Results of internal bench studies are not representative of clinical performance. Clinical results may vary.

Rapid Drug Absorption

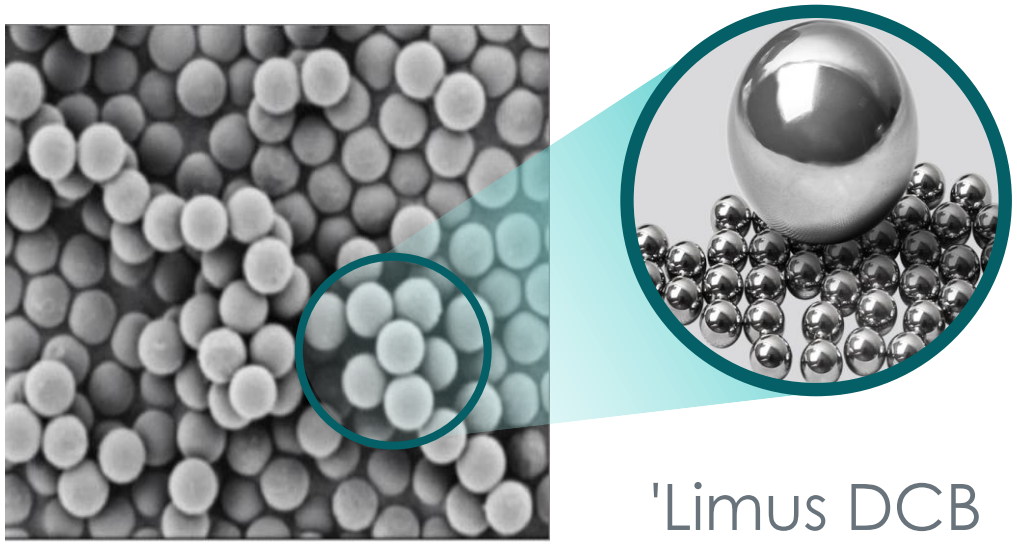
AGENT™ is Formulated With Sharp-Edge Lipophilic Paclitaxel to Accelerate Absorption

Sharp Edge Paclitaxel
(High Acute Tissue Absorption[1])



AGENT™

Rounded Structure
(Low Acute Tissue Absorption)

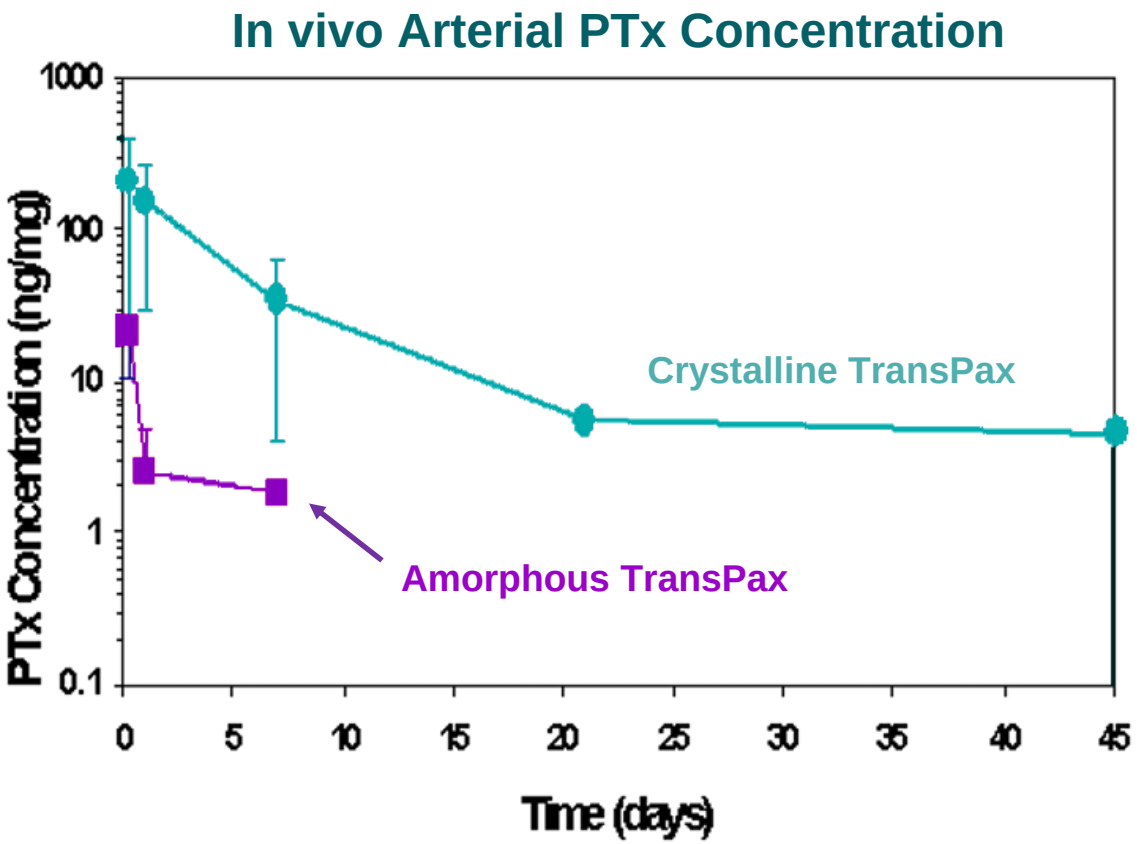


'Limus DCB

1. Chang, G., et al. Scientific Reports 9.1 (2019): 6839.
Scanning electron microscope image of microspheres with encapsulated sirolimus. from Future Medicine

Sustained Retention with Crystalline Paclitaxel

TransPax™ Coating Formulated Into a Uniform Crystalline Structure for Sustained Retention[1]

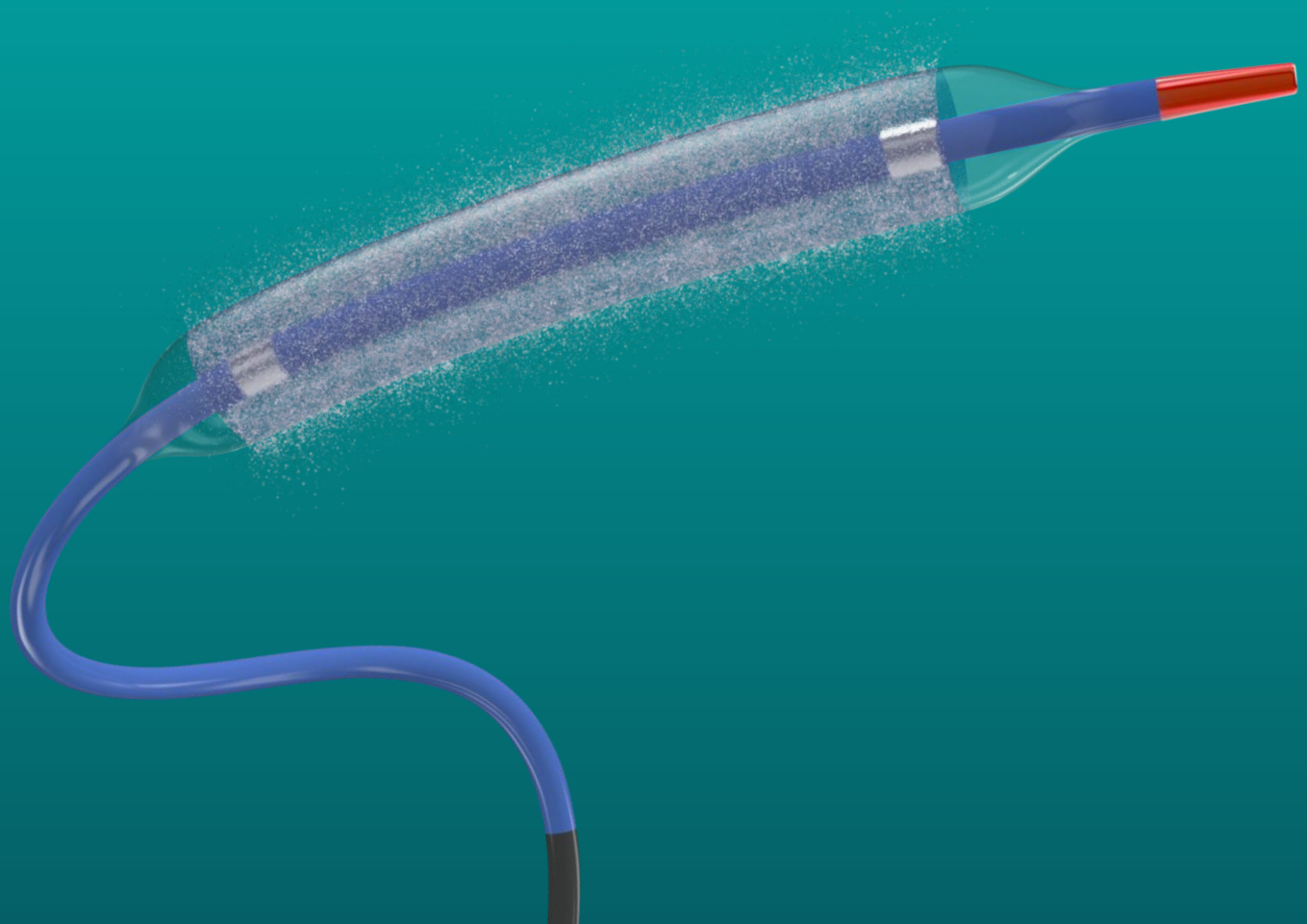


Crystalline coating morphology

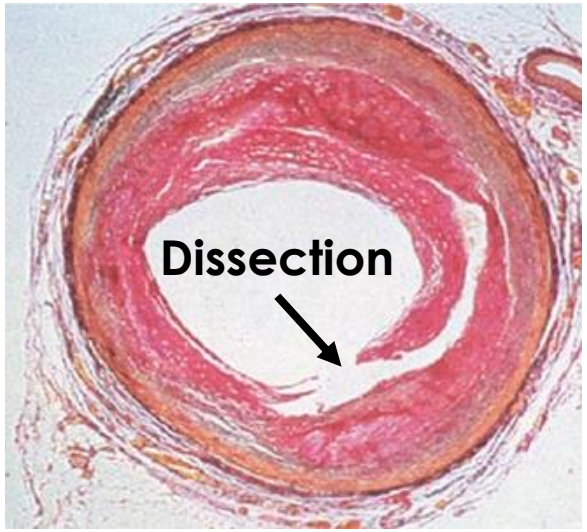
Higher and longer sustained PTx tissue levels

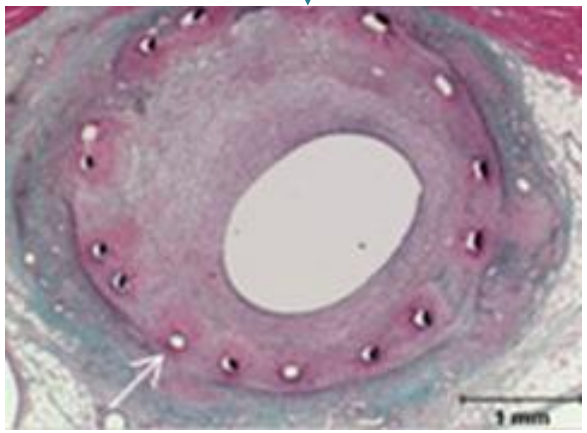
1. BSC Internal Test. Results of internal bench studies are not representative of clinical performance. Clinical results may vary.

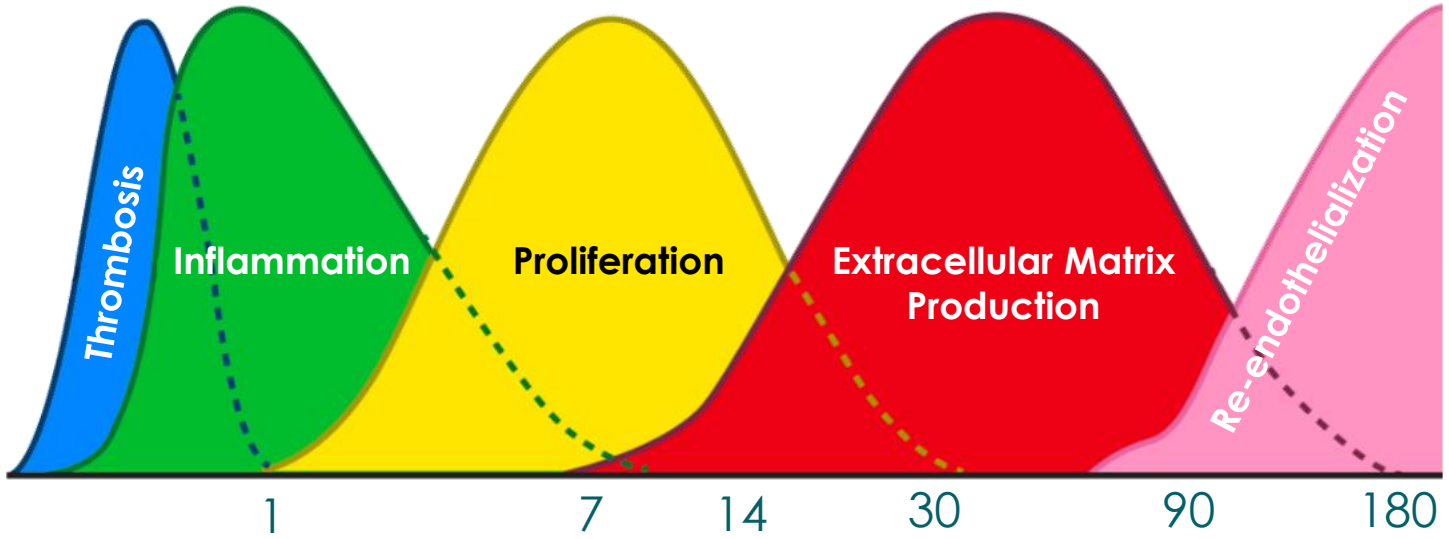
Why Paclitaxel DCB?



Neointimal Hyperplasia
Restenotic cascade following POBA







Vessel Trauma

Crush Plaque Stretch Artery
De-endothelialization

Platelet/fibrin deposition

Smooth Muscle Cell migration & division

Extracellular matrix production

Re-endothelialization

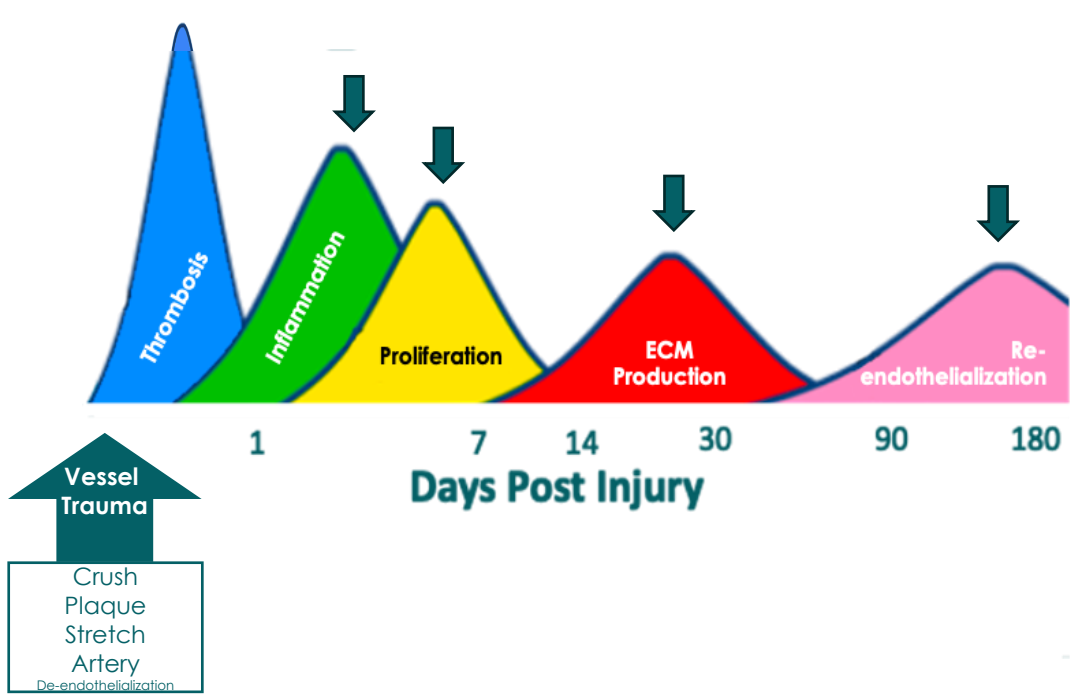
Images adapted from Basicmedical Key and Endovascular Today

Shlofmitz, E, *Circulation: Cardiovascular Interventions* 12.8 (2019): e007023.
Deloose, K, et al. Endovascular Today.

DES vs DCB Effect on the Restenotic Cascade

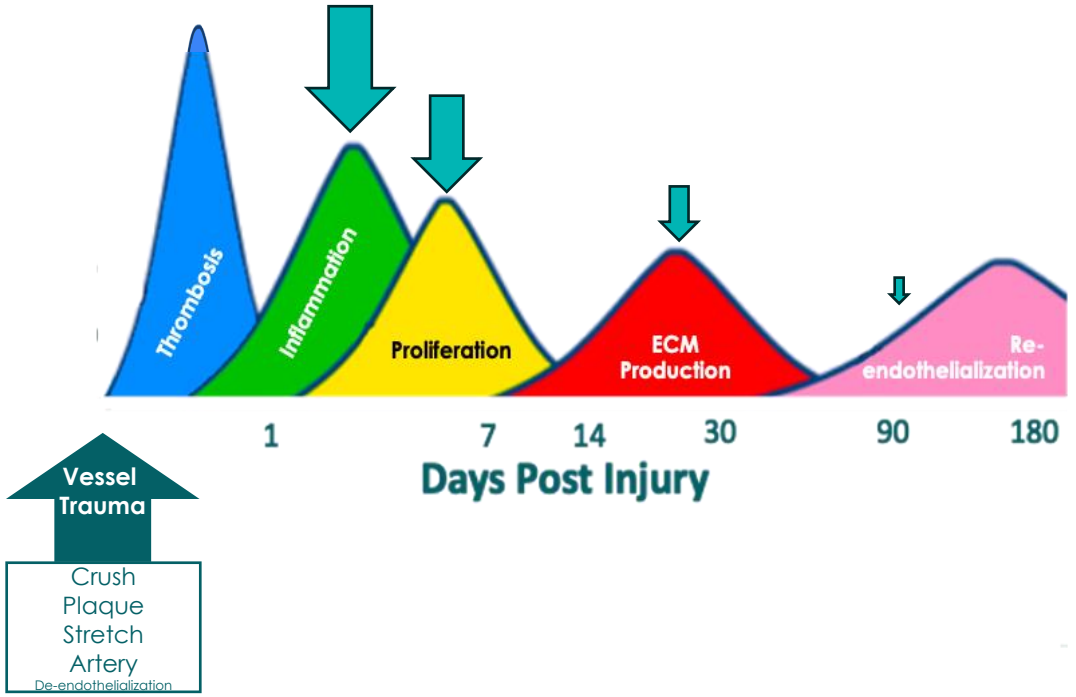
DES Drug Delivery

Sustained Drug Release Over Time



DCB Drug Delivery

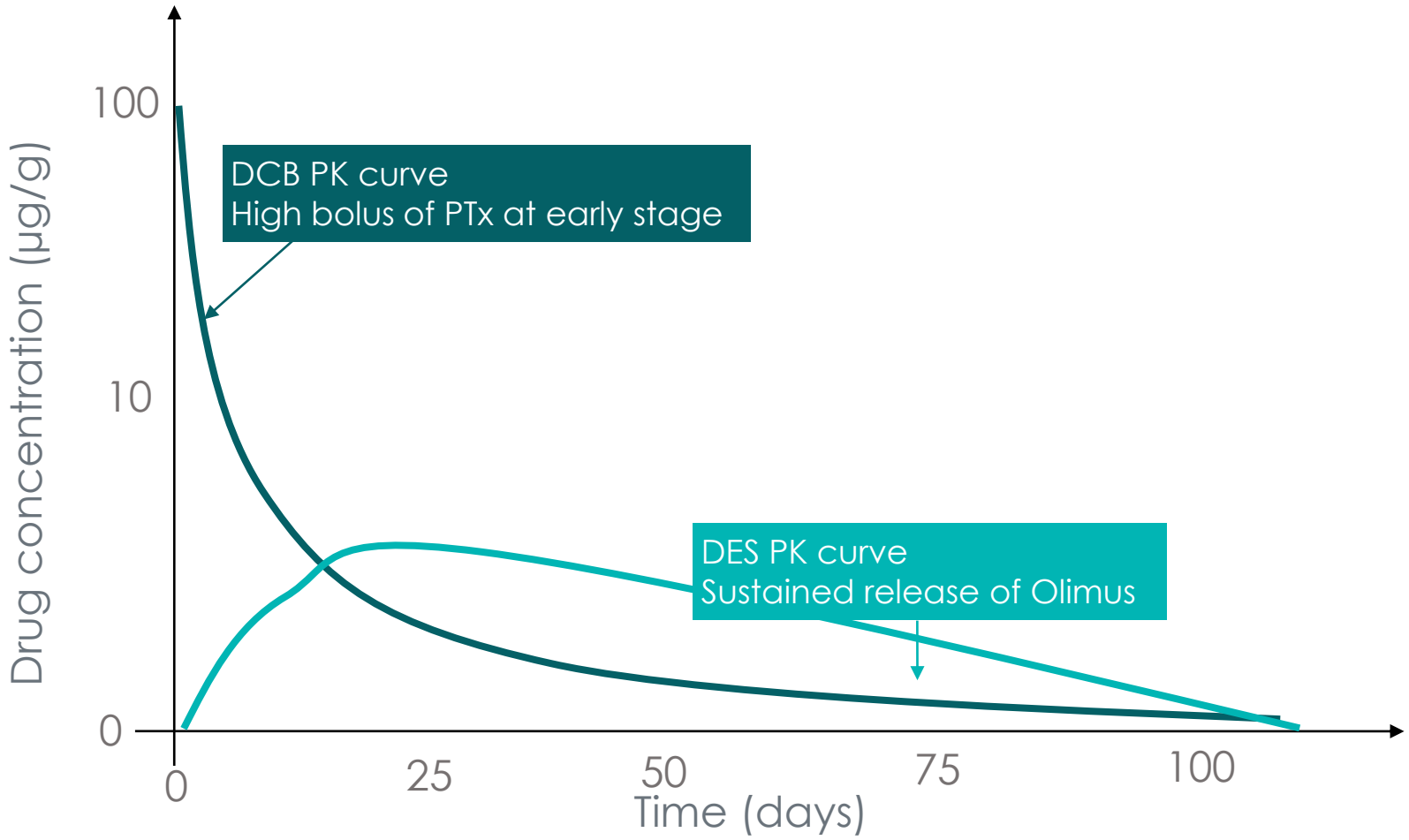
High Acute Drug Release



Conceptual Representation

Arrows Represent Magnitude of Drug Release

DCB Has Different Drug Delivery Mechanism from DES



Different technology mechanisms require different drug characteristics

Adapted from Wessely, Rainer et al. Thrombosis and hemostasis vol. 97,6 (2007): 1003-12

Paclitaxel is Better Suited for a Coronary DCB Application

Different technology mechanisms require different drug characteristics

‘Limus Coated Balloon	DCB Drug Requirement	Paclitaxel Coated Balloon
	**Durability During Tracking** • PTX repels water and dissolves slowly under hydration (hydrophobic)[1]	
	Rapid Absorption • PTX has a high affinity for fatty tissue (lipophilic), accelerating tissue absorption	
	Drug Tissue Retention • PTX has a low dissolution rate and high chemical stability that enables sustained release[2,3]	

Image adapted from Endovascular Today

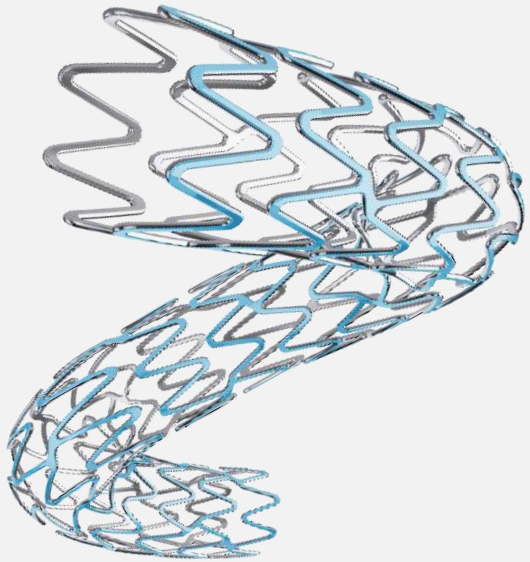
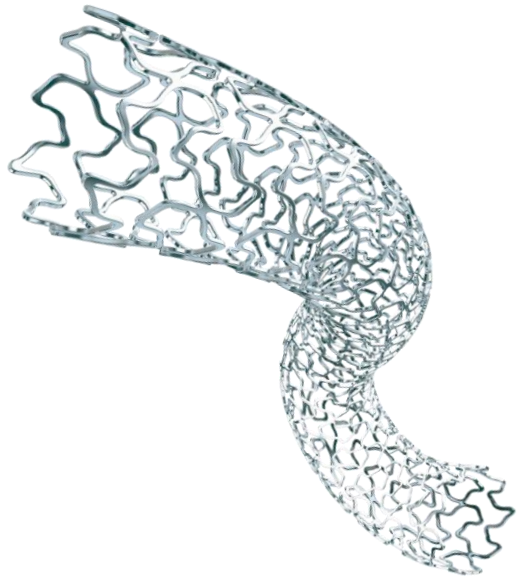
1. Surapaneni, M., et al. "Designing Paclitaxel drug delivery systems aimed at improved patient outcomes: current status and challenges." International Scholarly Research Notices (2012).

2. Tzafriri, A. et al. Journal of Controlled Release 310 (2019): 94-102.

3. Juan Granada, Endovascular Today 2017.

'Limus is Better Suited for a Coronary Stent Application

Different technology mechanisms require different drug characteristics

'Limus Eluting Stent	Stent Drug Requirement	Paclitaxel (PTX) Eluting Stent
	**Compatible with Polymer Matrix** • PTX and Everolimus can be mixed within polymer matrix **Diffusion through Polymer Matrix** • PTX is hydrophobic and tends to reside in polymer matrix[1] **Does NOT Inhibit Stent Surface Endothelization** • Long-term release of Everolimus does not inhibit endothelization[1]	

Tissue delivery of drug can be highly variable across different devices

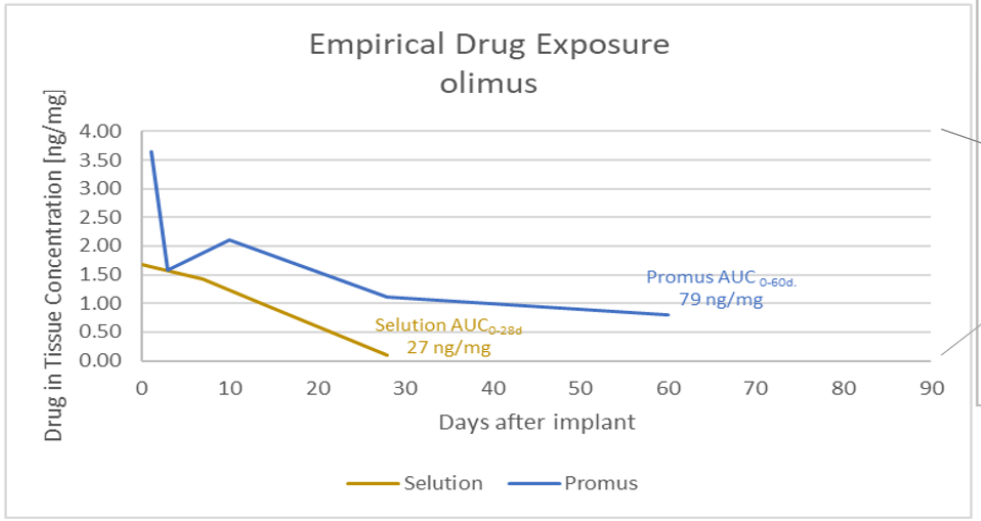
Paclitaxel in combination with DCB application transfers more drug over time

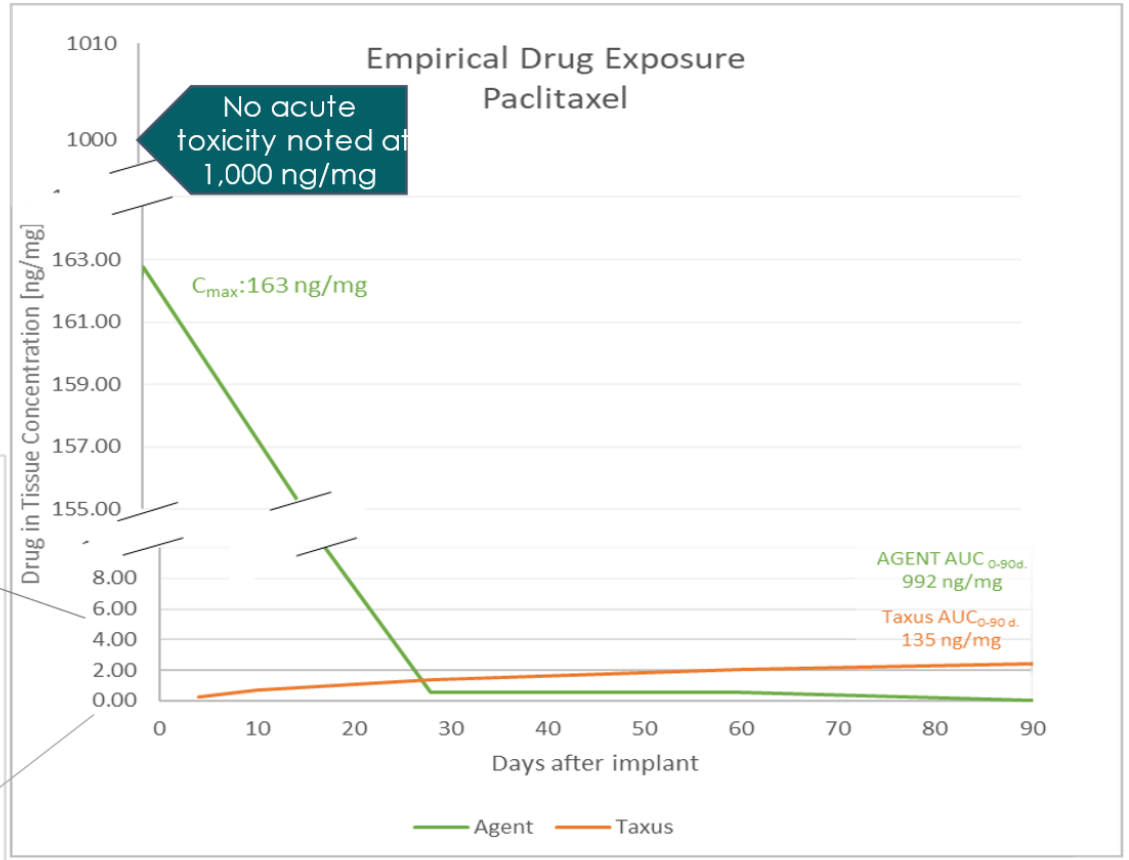
AUC*: Total Drug Exposure

	Sustained Release		Rapid Bolus Transfer	
	Taxus (Paclitaxel)	Promus (olimus)	AGENT (Paclitaxel)	Selution (olimus)
AUC $_{t0\text{-}t\ terminus}$ [ng/mg]	144	79	992	27

C_{max}*: Peak Drug Concentration

	Taxus (PTX)	Promus	AGENT (PTX)	Selution
C_{max} [ng/mg]	2.4	3.6	162.8	1.7





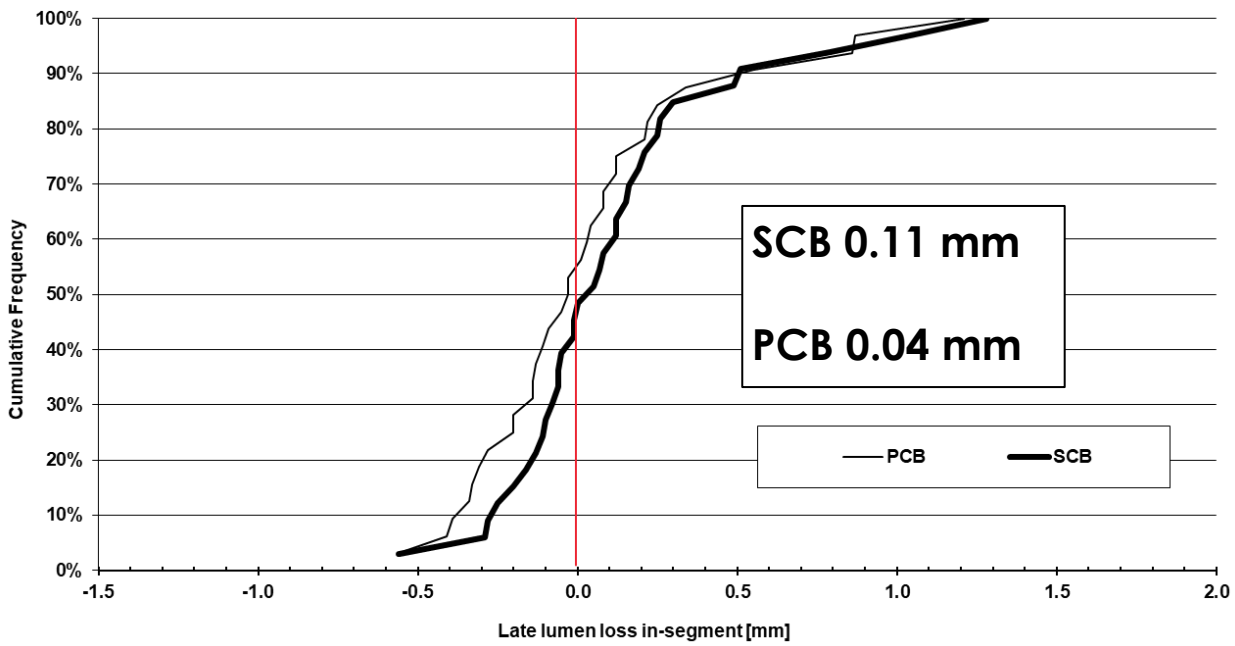
1. Data on file at BSC.

*AUC = Area under the curve (total drug exposure)
*C_{max} = Peak drug in tissue concentration

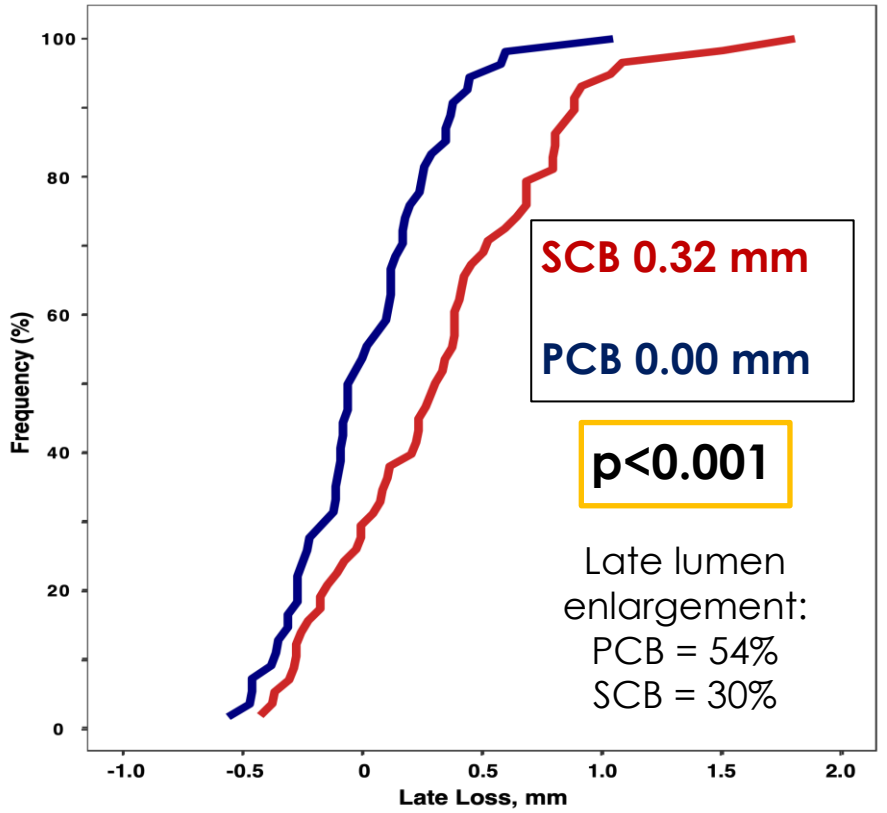
Paclitaxel- (PCB) vs. Sirolimus- (SCB) Drug Coated Balloon
de novo Lesions

PCB vs. SCB – *de novo* Late Lumen Loss

Germany, Switzerland
n=70



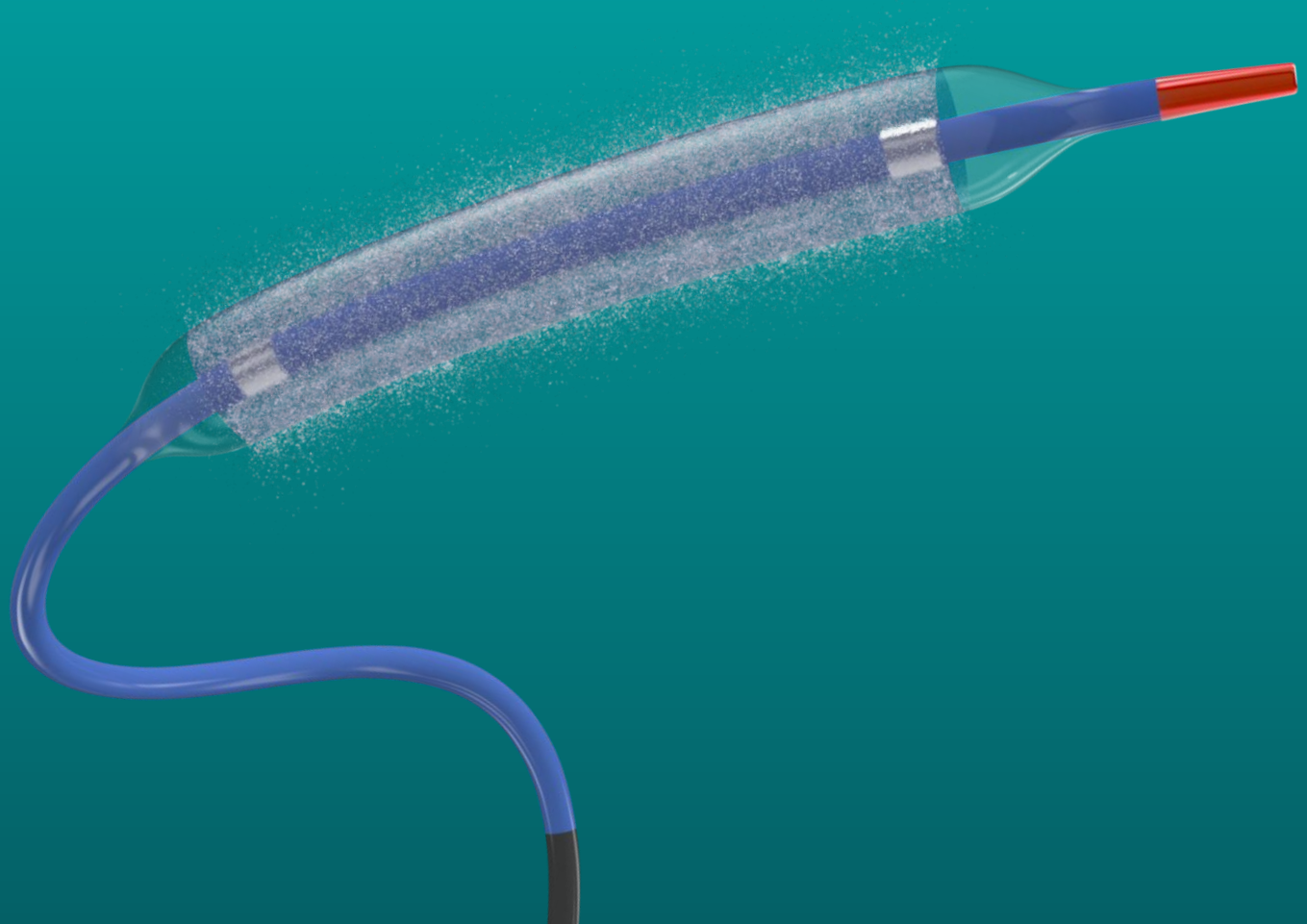
TRANSFORM I Trial - Italy, UK
n=121



Scheller B et al. presented at TCT 2023

Colombo A, et al. J Am Coll Cardiol Intv. 2023

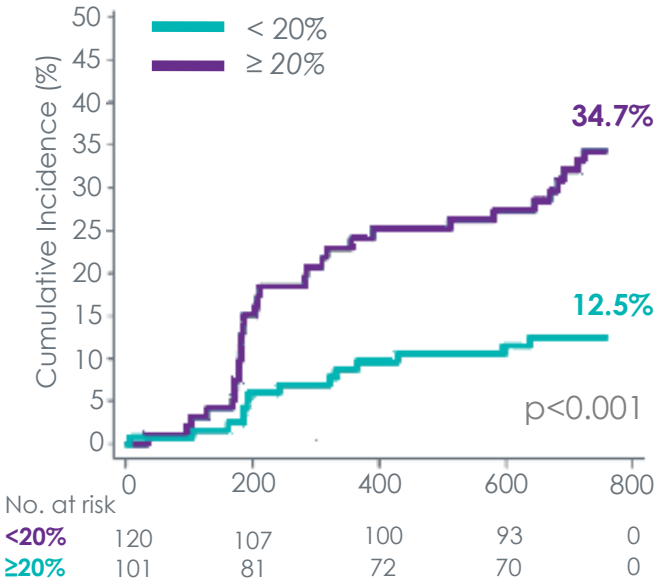
Remember: How it is done matters



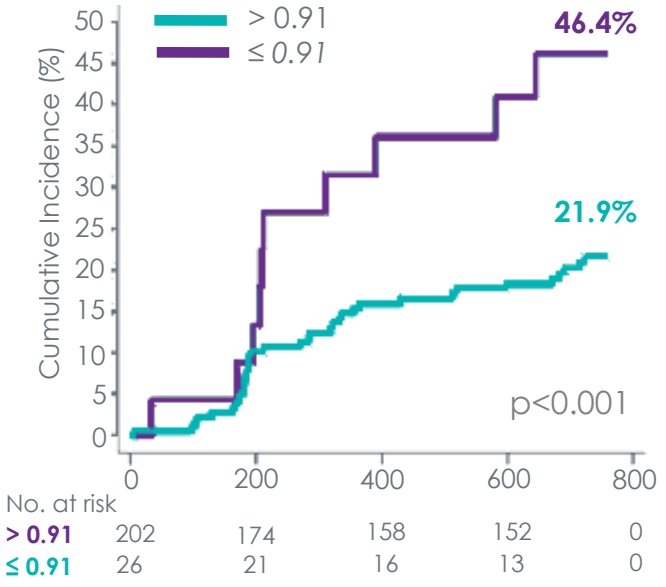
Cumulative Incidence of TLF According to Paclitaxel DCB Technique

N=256 Consecutive Patients from 4 Korean Centers

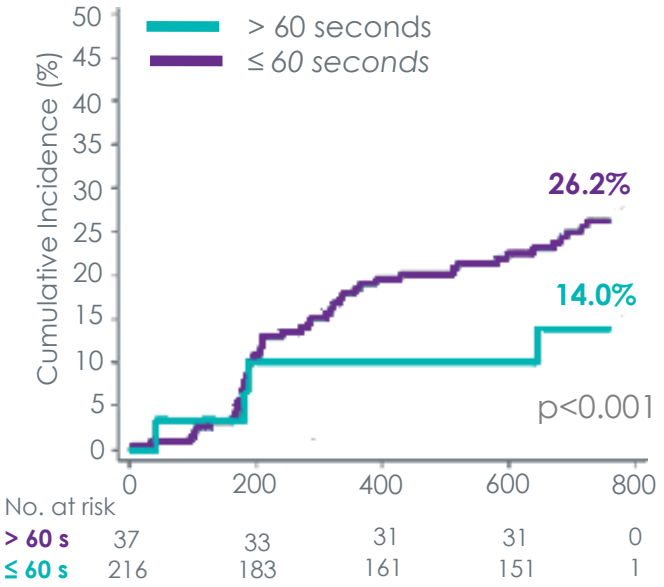
1 TLF by Lesion Prep Residual Stenosis



2 TLF by Correct DCB to Vessel Size



3 TLF by Longer DCB Inflation

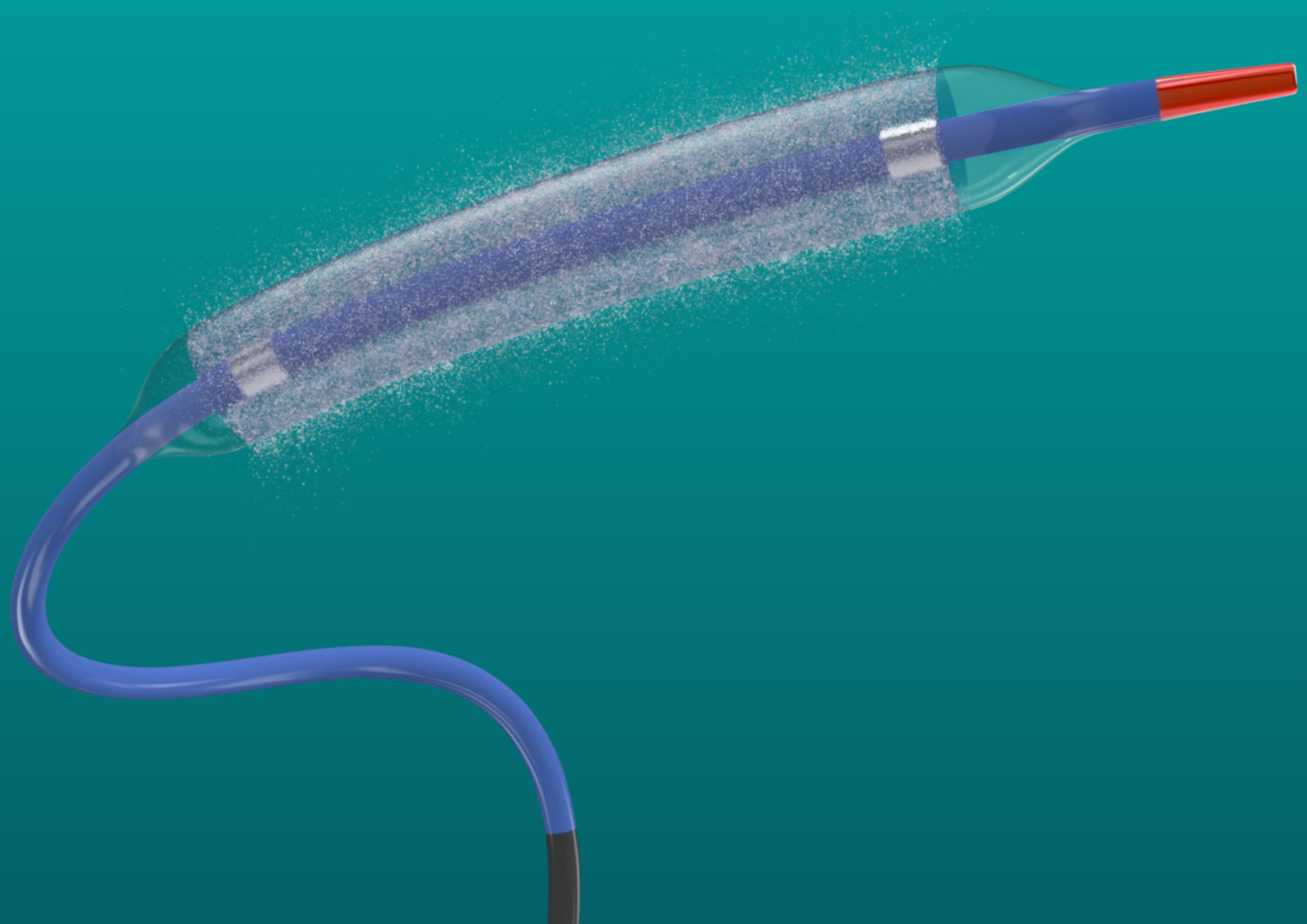


- **Fully optimized TLF 8.3%**
- **Partially optimized TLF 19.2%**
- **Non-optimized TLF 66.7%**

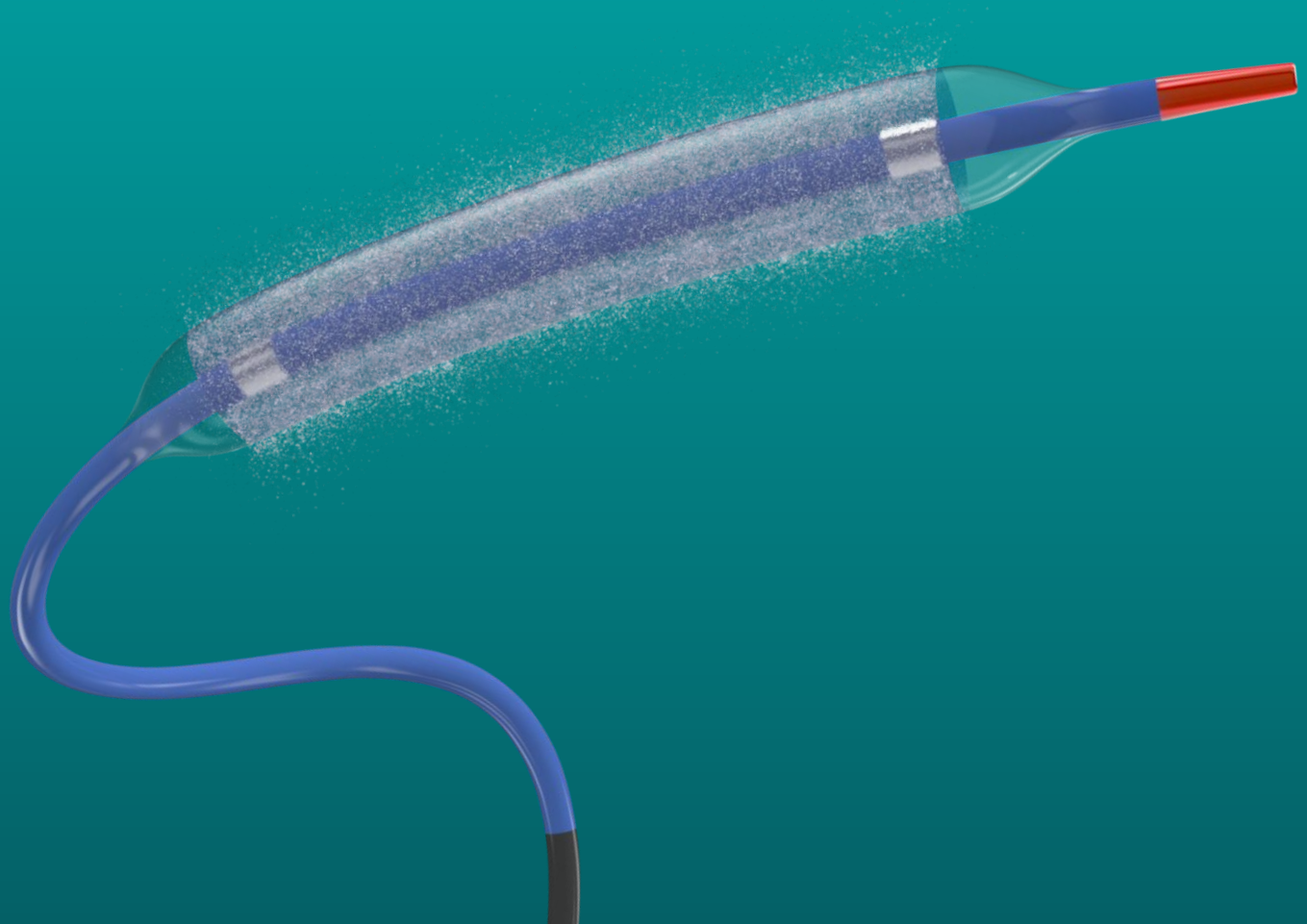
DCB Global Landscape: commonly used (amongst others)

Product(s)	AGENT	SeQuent Please (PCB 2006 & SCB 2021)	MagicTouch	SELUTION
Drug	Paclitaxel 2 µg/mm²	Paclitaxel 3 µg/mm² Sirolimus 4 µg/mm²	Sirolimus 1.27 µg/mm²	Sirolimus 1 µg/mm²
Availability	CE, Japan, Korea FDA approval – In-process	CE, Asia	CE TBD Japan	CE
Mechanism of action	Optimal dose of anti-proliferative paclitaxel designed for targeted transfer, rapid absorption and sustained retention	Matrix coating of paclitaxel and iopromide or sirolimus and BHT for effective drug release into the vessel wall.	Submicron limus particles encapsulated in phospholipid biocompatible drug carrier	90 days Limus release with advanced MicroReservoir and Cell Adherent Technology

PTX v PTX comparisons



For ISR



Learn More About IVUS + Stent Failure on EDUCARE:

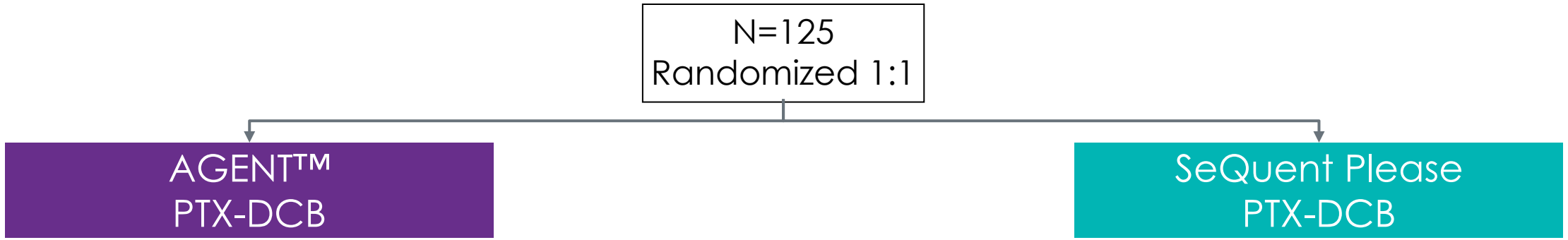
SCAN ME

AGENT™-ISR Trial

Comparison of AGENT™ and SeQuent® Please in In-Stent Restenosis

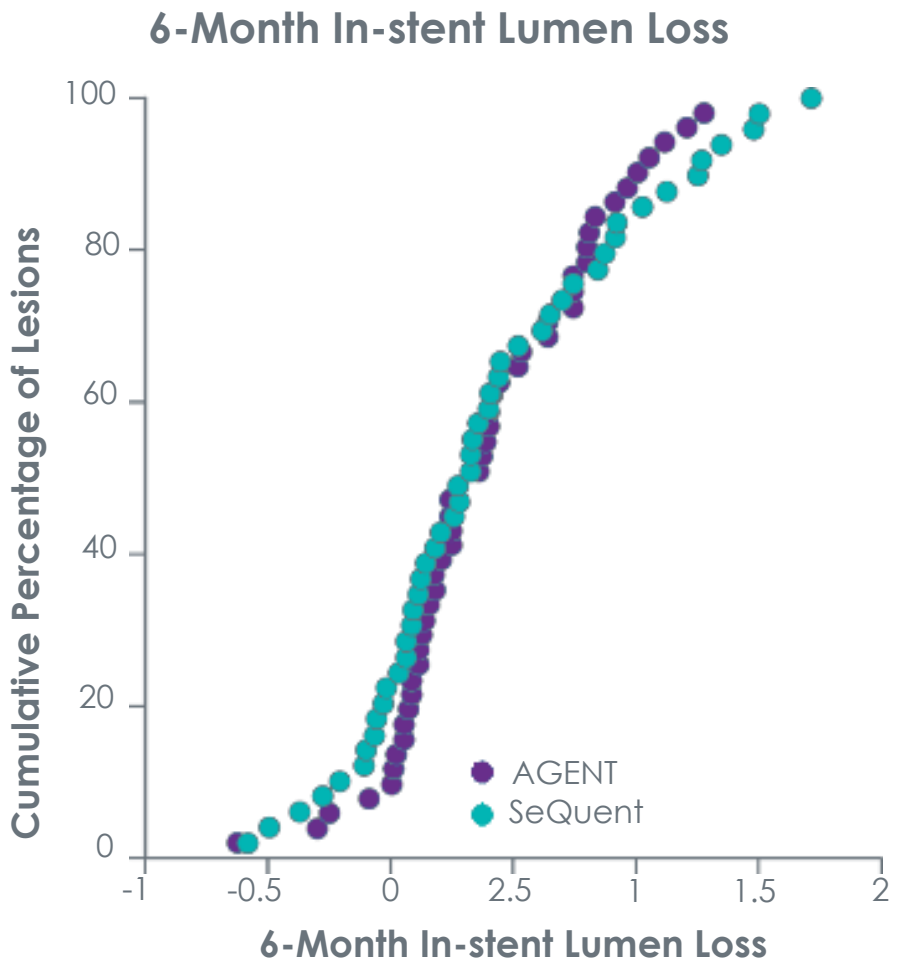
Prospective, randomized, multicenter, non-inferiority trial across 15 European sites

- **Key Inclusion Criteria:** Patients with in-stent restenosis of a lesion previously treated with BMS or DES, Lesion in native coronary artery with length ≤ 28 mm, RVD ≥ 2.0 mm ≤ 3.5, and %DS ≥ 70 < 100 if asymptomatic or %DS ≥ 50 < 100% if symptomatic
- **Key Exclusion Criteria**: Bifurcation, LM, SVG, total occlusion, recent PCI, acute MI



Primary Endpoint: In-stent late lumen loss (LLL) at 6 months Clinical follow-up through 3 years

AGENT™-ISR Trial: Primary Endpoint

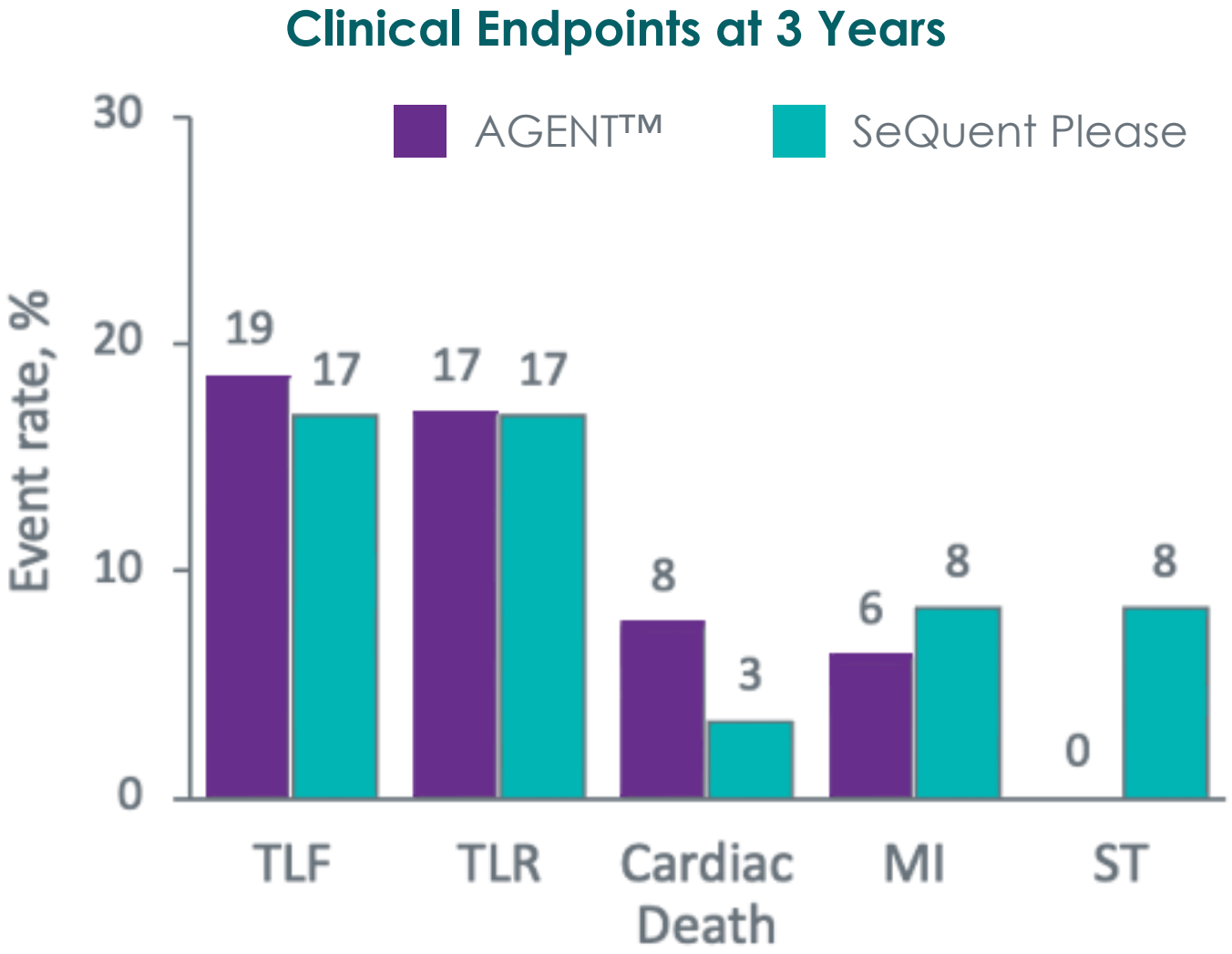


AGENT™ (N =51)	SeQuent Please (N=49)	Difference [95% CI]	Noninferiority Margin	$P_{noninferiority}$
0.397 ± 0.43	0.393 ± 0.536	0.004 [-0.189, 0.196]	0.2	0.046

Noninferiority criteria met for primary endpoint

Measured by core laboratory. Noninferiority test from a 2-sided Student t-test comparing the difference between AGENT™ and SeQuent Please to the noninferiority margin

AGENT™-ISR Trial: Clinical Endpoints at 3 Years



ISAR DESIRE AGENT 3A

Study Design

Prospective, non-randomized, single-arm study compared to a *historical control* from ISAR DESIRE 3 trial

- **Key Inclusion Criteria:** Myocardial ischemia with ≥50% restenosis of –limus DES
- **Key Exclusion Criteria**: LM, Graft, SV <2.0 mm

AGENT™
N=125

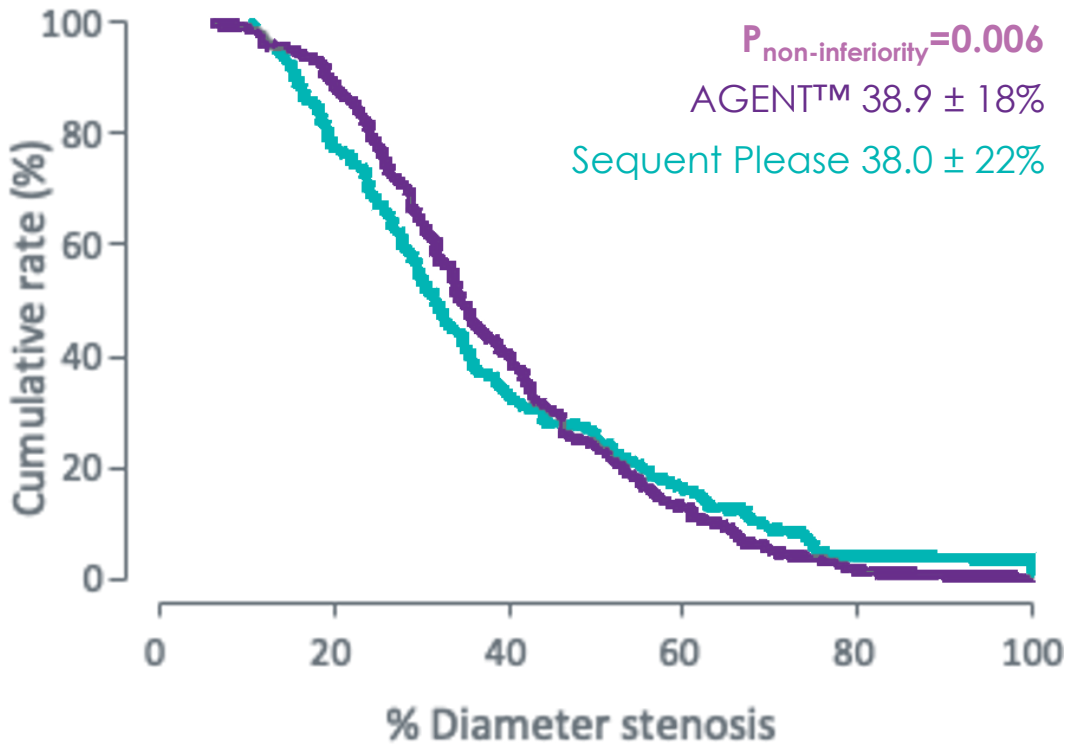
vs.

SeQuent Please
N=137
Historical Control (ISAR DESIRE 3)

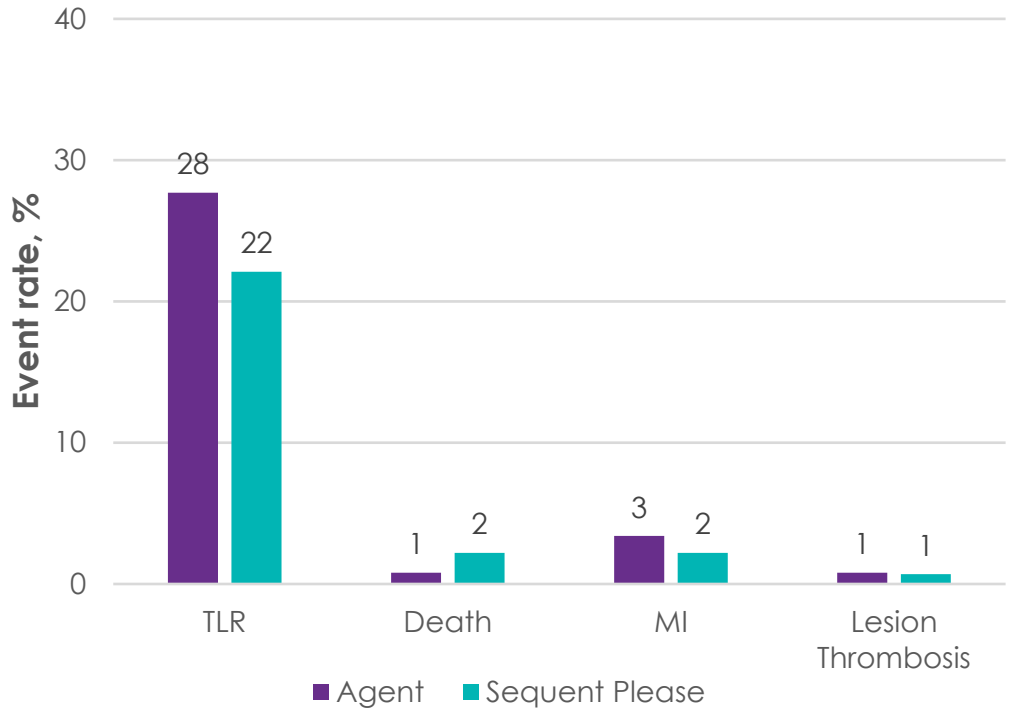
Primary Endpoint: In-stent percent diameter stenosis (%DS) at 6 to 8 months via angiography
Clinical follow-up: 1-year

ISAR DESIRE AGENT 3A
Results

6-8 Month Primary Endpoint

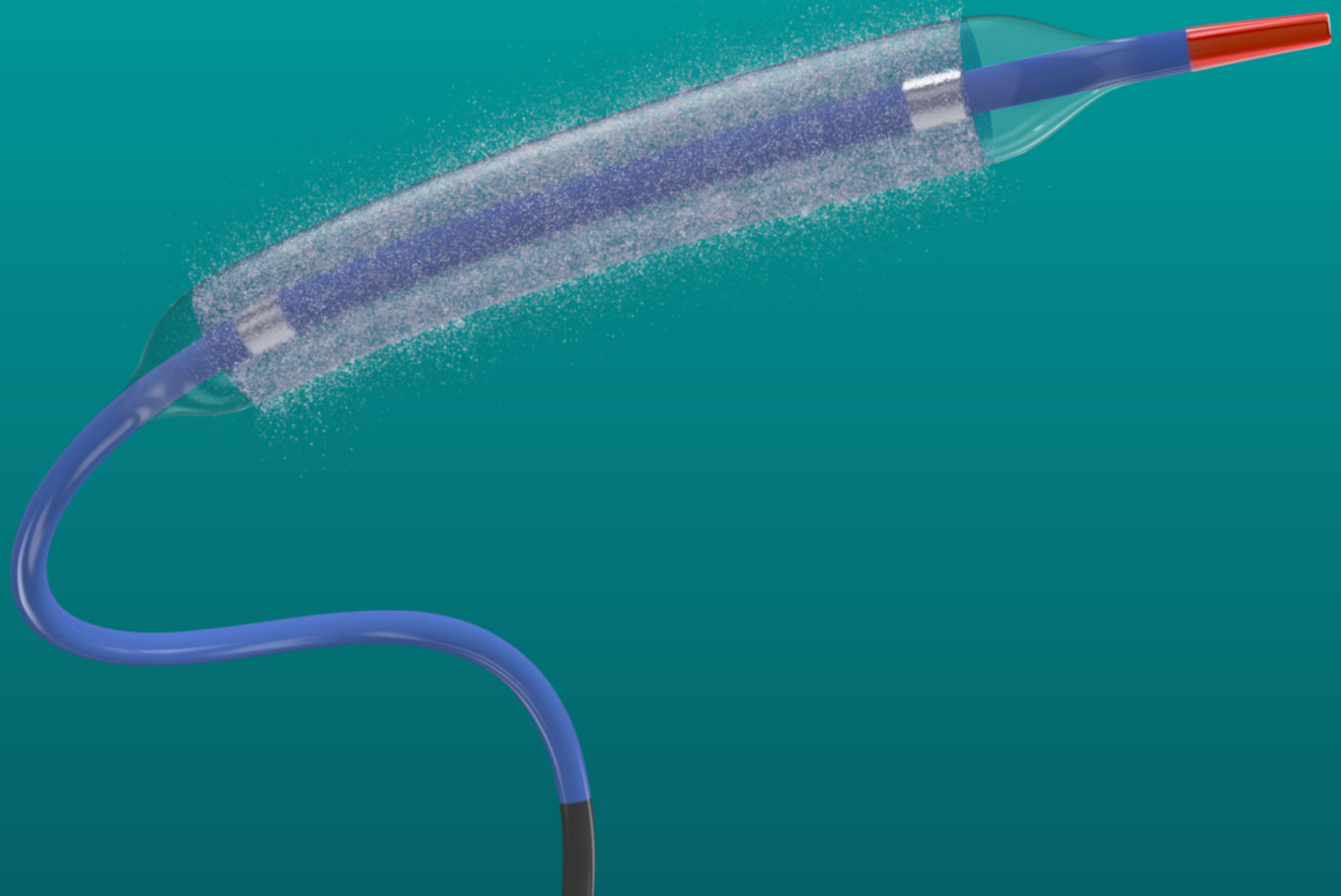


1-Year Clinical Outcomes



Non-inferiority met for In-stent percent diameter stenosis (%DS) angiographic primary endpoint

For Small Vessels



AGENT™-ISR Trial AGENT™ Japan Small Vessel

Study Design

Prospective, multicenter trial across 14 sites in Japan

- **Key Inclusion Criteria:** Lesion Length ≤ 28 mm, De Novo, RVD ≥2.00 and <3.00 mm
- **Key Exclusion Criteria**: LM Disease, Graft Disease, Complex Bifurcation, Thrombus or Severe Calcification

2:1 Randomization SV RCT

ISR sub-study

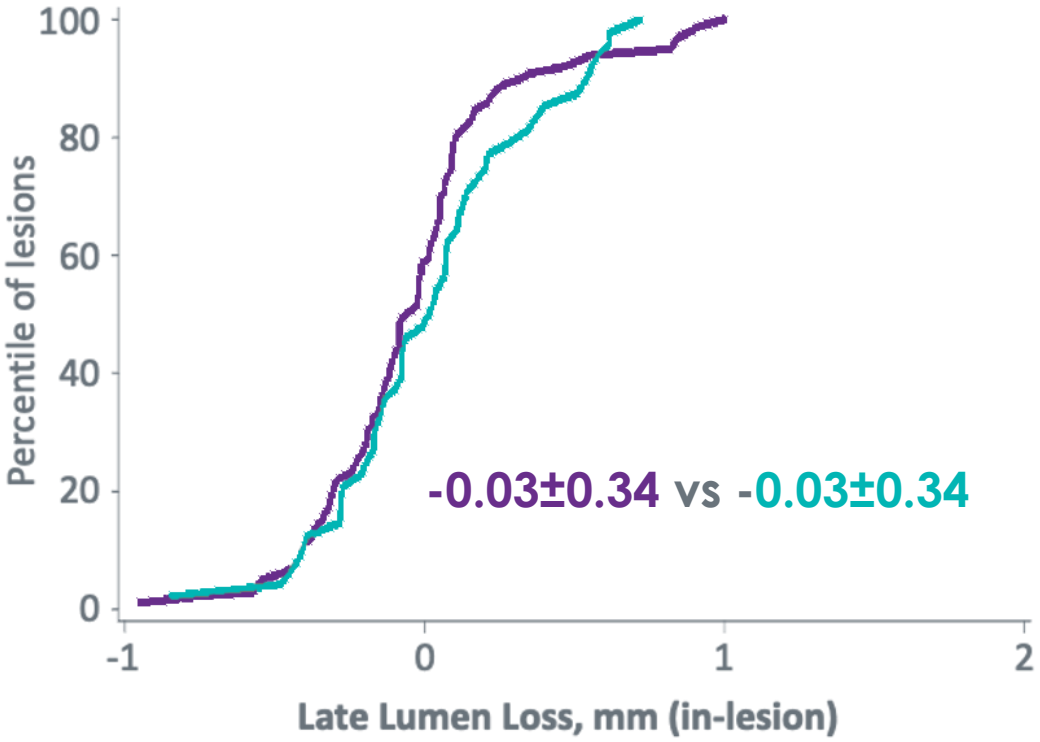
AGENT™ N=101	SeQuent Please N=49	AGENT™ N=30

Primary Endpoint: 6-month target lesion failure (composite of TLR, TV-MI, or cardiac death)
Clinical follow-up: Hospital discharge, 30 days, 6 months (angiography), 1-5 years

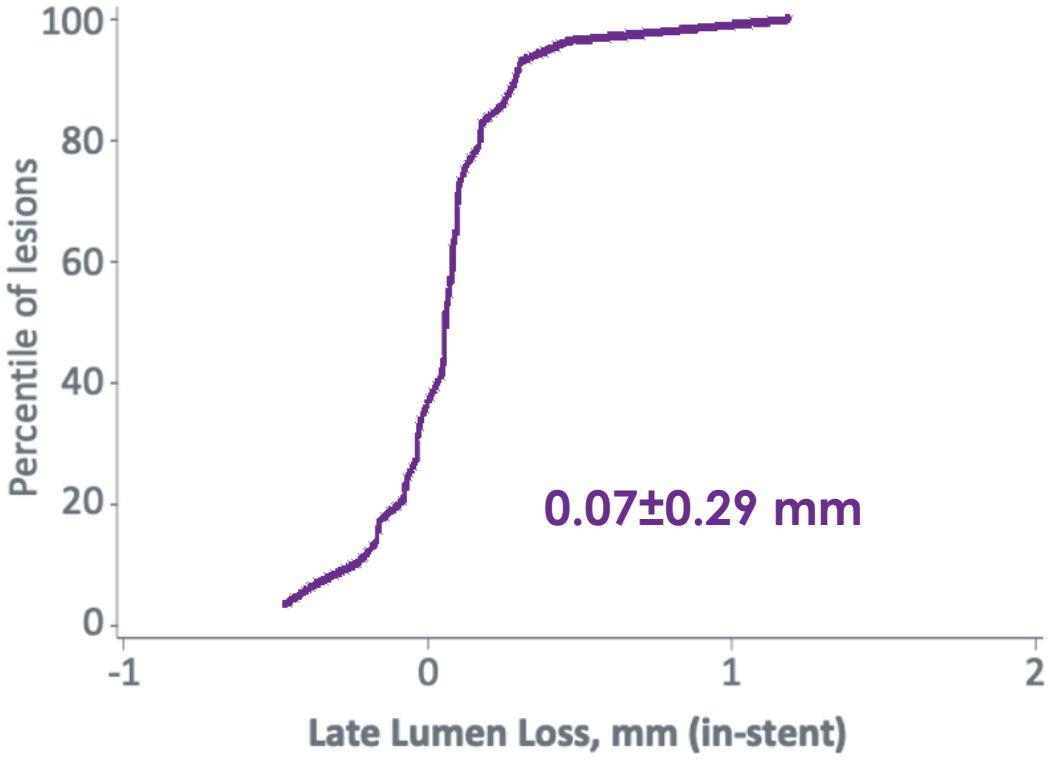
AGENT™ Japan
Angiographic Characteristics

AGENT™ SeQuent Please

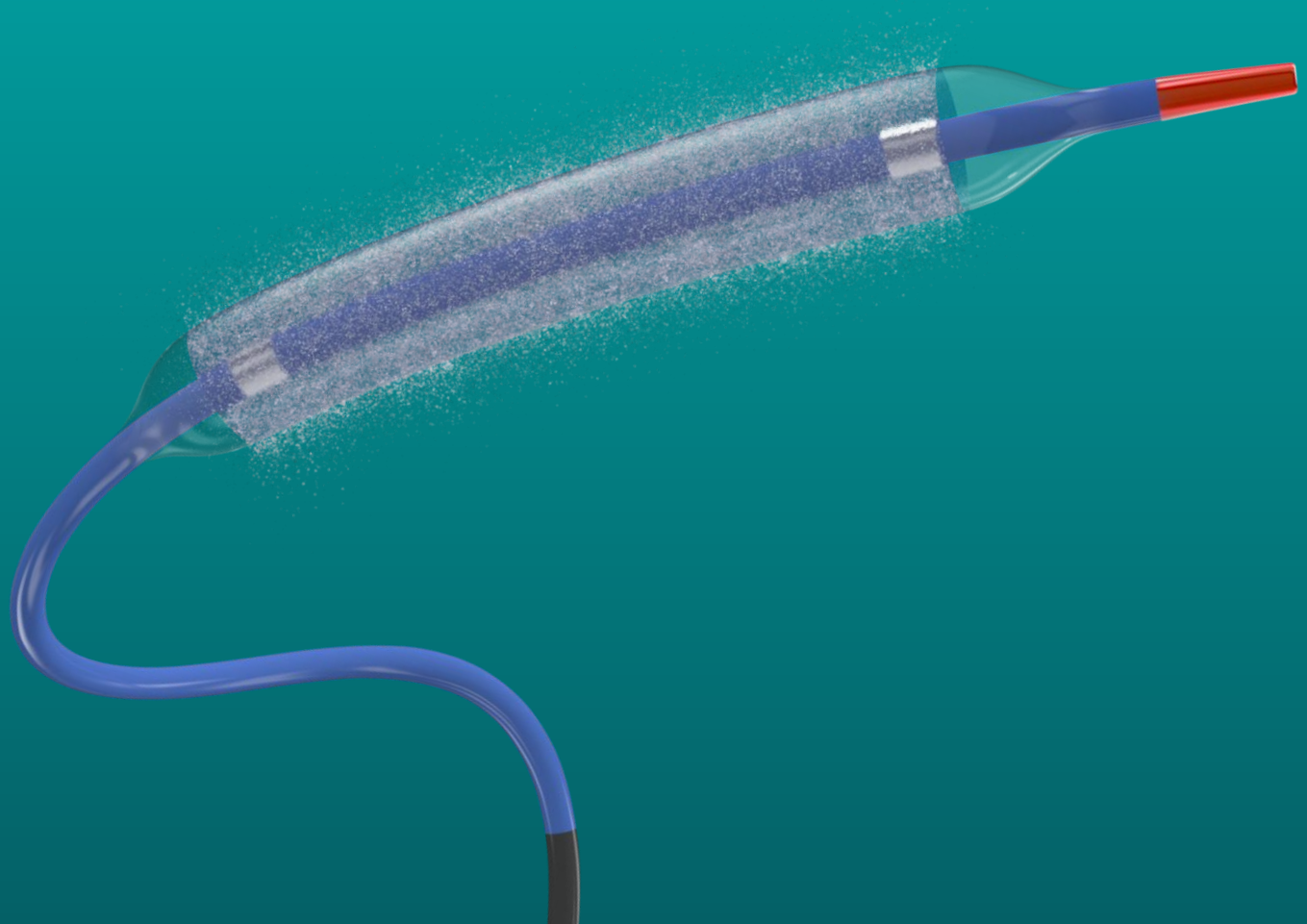
Small Vessel RCT



ISR Substudy



Other PTX v Limus Clinical Trials



Paclitaxel vs Sirolimus for DCBs – No Class Effect?

3 New Studies from TCT 2023 Comparing Angiographic Results

TRANSFORM I SV

Prospective, randomized, multicenter, open-label non-inferiority trial

Small Vessels < 2.75mm by QCA

Randomized **1:1**

- Magic Touch SCB N=61
- Sequent Please Neo N=60

Primary Endpoint: Angiographic net gain at 6-months

Sequent De Novo

Multicenter, randomized, controlled, non-inferiority trial

Randomized **1:1**

- Sequent SCB N=35
- Sequent Please Neo N=35

Primary Endpoint: Angiographic late lumen loss at 6 months

Sequent ISR

Prospective, randomized, multicenter, open-label non-inferiority trial

Randomized **1:1**

- Sequent SCB N=130
- Sequent Please Neo N=128

Primary Endpoint: Angiographic late lumen loss at 9 months

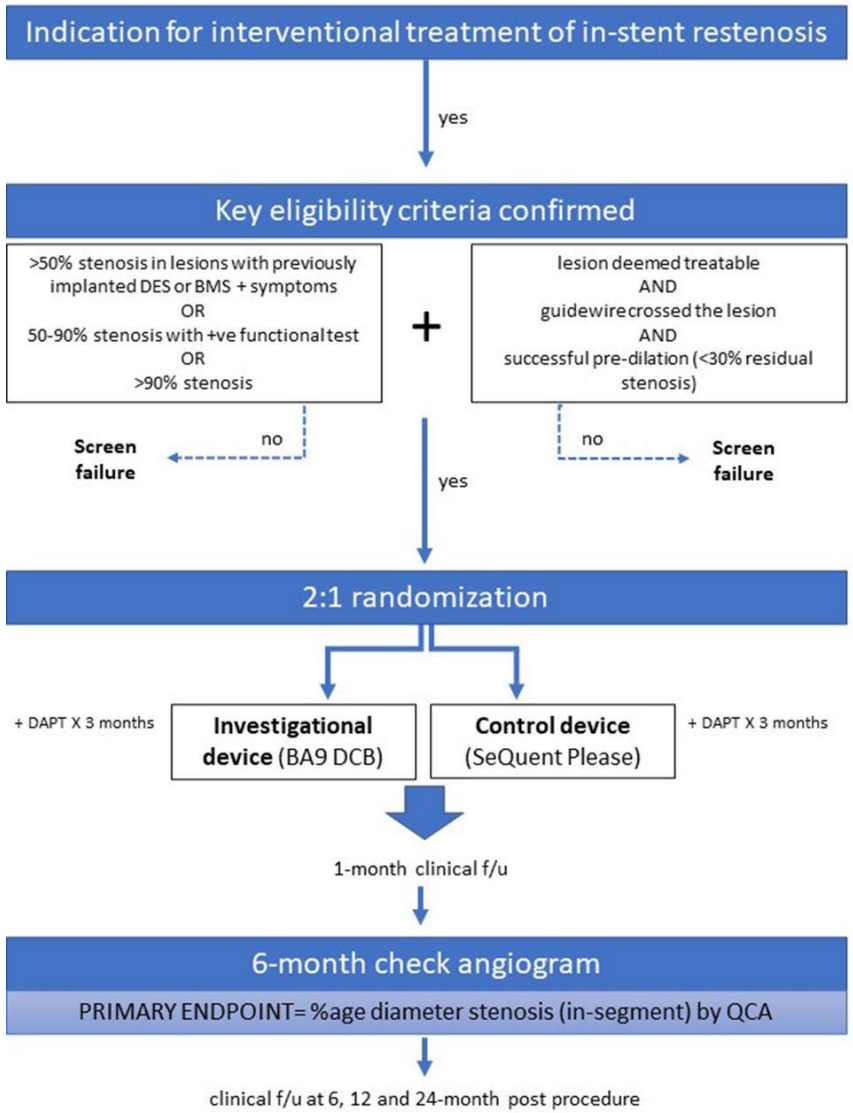
	TRANSFORM I SV		Sequent De Novo		Sequent ISR	
Signficant differences in **purple**	Magic Touch (n=61)	Sequent PCB (n=60)	Sequent SCB (n=35)	Sequent PCB (n=35)	Sequent SCB (n=130)	Sequent PCB (n=128)
Time to angiographic follow-up	6 months	6 months	6 months	6 months	9 months	9 months
Pre-PCI MLD	0.95 mm	0.88 mm	0.88 mm	0.85 mm	0.86 mm	0.94 mm
Post-PCI MLD	**1.52 mm**	**1.39 mm**	2.35 mm	2.24 mm	1.93 mm	1.94 mm
MLD at Follow-up	**1.22 mm**	**1.36 mm**	2.19 mm	2.16 mm	1.60 mm	1.65 mm
Late Lumen Loss	**0.32 mm**	**0.00 mm**	0.13 mm	0.03 mm	0.35 mm	0.31 mm
TV-MI	0%	0%	0%	0%	0.8%	0%
TLR	11.5%	6.7%	6.0%	9.0%	11.5%	10.2%

The **Sirolimus Magic Touch failed to demonstrate non inferiority** to the Paclitaxel SeQuent Please for angiographic net gain at 6 months in de novo small vessels (SCB 0.25 mm vs PCB 0.48 mm, **p=0.002**)

Sirolimus Sequent SCB was non-inferior to Paclitaxel SeQuent Please Neo for angiographic late lumen loss at 6 months in de novo vessels

Sirolimus Sequent SCB was non-inferior to Paclitaxel SeQuent Please Neo for angiographic late lumen loss at 9 months in in-stent restenosis

REFORM (ISR): Biolimus v PTX

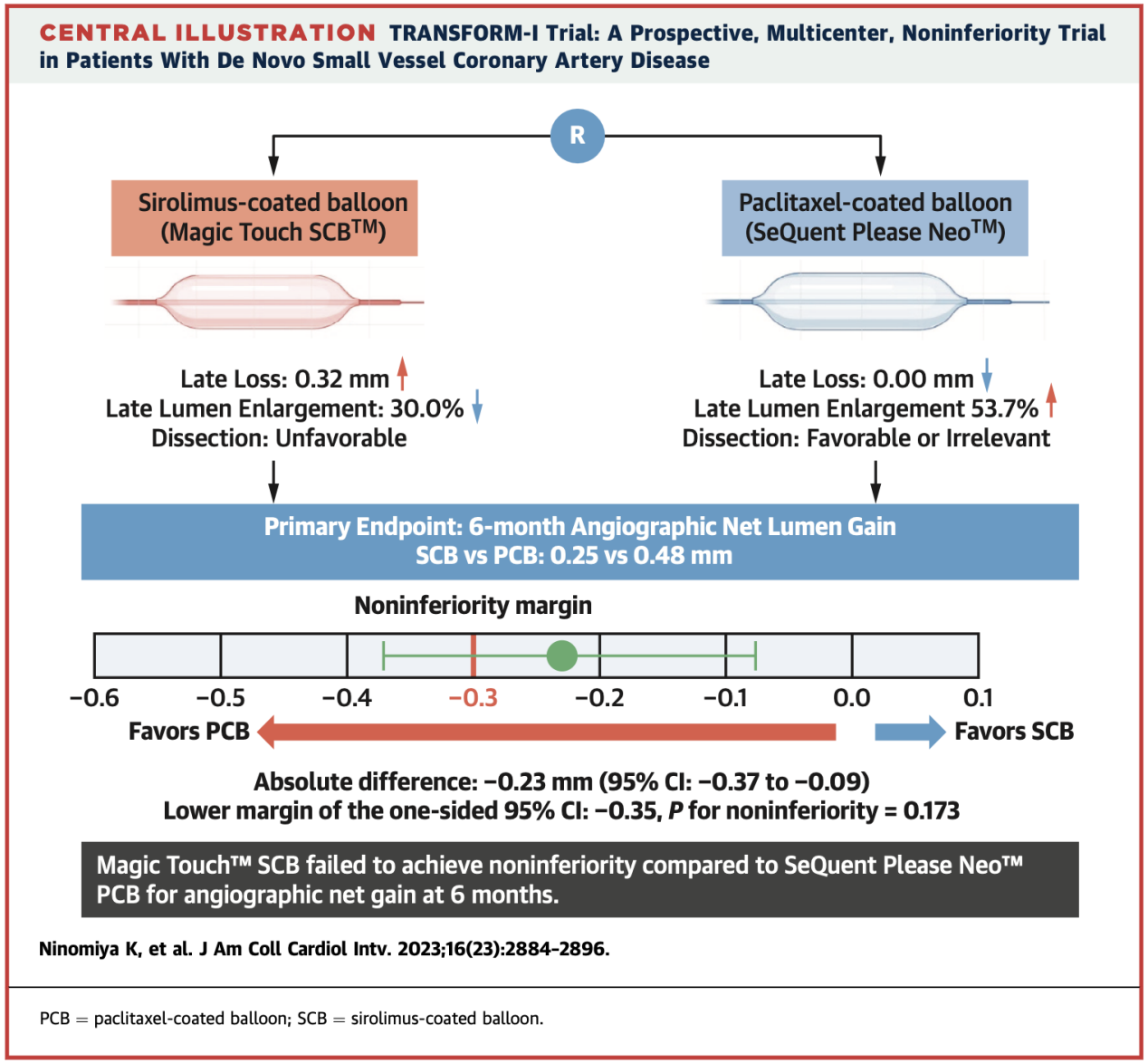


S Fitzgerald et al. Heart 2023;109:A8-A10

Key findings:

Non-inferiority was not shown by the BCB (n=135) in comparison to the PCB (n=67), with an observed %DS in the BCB group of 41.8 ± 21.3% compared to 31.2 ± 17.8% in the PCB group, a mean difference between the groups of 10.6% (95% CI 3.97–17.20) and a p-value for non-inferiority of 0.34.

TRANSFORM 1 SV: Sirolimus vs PTX



Conclusions about DCBs in 2024

- PTX appears better suited to the DCB class than the Limus analogues for drug delivery to tissue
- It is possible that Limus DCBs may prove to have lower efficacy, although larger trials are needed
- The drug formulations, excipients and tissue transfer differ across the PTX DCBs, although no definitive (or large) trials show any significant differences to date between outcomes with these devices
- Evidence to date for DCB vs DCB is typically generated from very small numbers of patients
- We should be wary over DCB vs DES data - None use IVUS optimised DES implant as the gold standard comparator (including enrolling studies) and when the current generation of larger trials report, we are still likely to be asking questions as a result