Current Update on Paclitaxel and Sirolimus Drug-ElutingTechnology

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Disclosure Statement of Financial 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.

Institutional Research Support	**Abbott Vascular, Veryan Medical, Acotec, Concept Medical, Shockwave Medical, TriReme Medical, Surmodics, Boston Scientific, MedAlliance**
Advisory Board	**Abbott, Medtronic, Boston Scientific, Cordis, R3, Philips**
Consulting	**Terumo, Abiomed, Penumbra, Canon, BD**
Equity	**Encompass Vascular, Adv NanoTherapies, eFemoral**

SFA Treatment Choices

PTA alone

Nitinol Stent – Conventional

Nitinol Stent – Vascular Mimetic Implant

Drug Eluting Stent

Drug Coated Balloon

Stent Graft

Atherectomy/Plaque Modification Alone

- Orbital vs Directional vs Rotational/Aspiration vs Laser vs IVL

Atherectomy + Stent + Drug Coated Balloon

SCAI AUC and FP PVI: 2017 Update

	PTA	BMA	DEA	DCA	LASEA	Directional Atherec	Rotational atherec	Cutting ball
RC 0-1, severe (≥70%) FP disease, focal lesion.	2	2	2	2	1	1	1	1
RC 0-1, severe (≥70%) FP disease, moderate lesion.	2	2	1	1	1	1	1	1
RC 0-1, severe (≥70%) FP diffuse lesion.	2	1	1	2	1	1	1	1
RC 0-1, severe (≥70%) FP, ISR.	2	1	2	2	1	1	1	1
RC 0-1, FP, CTO.	2	1	1	1	1	1	1	1
RC 0-1, severe (≥70%), FP, focal undilatable lesion.	1	1	1	1	1	1	2	2
RC 2-3, severe (≥70%) FP disease, focal lesion.	7	7	7	8	3	4	3	1
RC 2-3, severe (≥70%) FP, moderate lesion.	6	7	8	8	4	3	2	1
RC 2-3, severe (≥70%) FP diffuse lesion.	4	6	7	8	4	3	3	1
RC 2-3, severe (≥70%), FP, ISR.	4	5	7	8	7	3	3	3
RC 2-3, FP, CTO.	3	6	8	8	5	3	3	3
RC 2-3, severe (≥70%), FP, focal undilatable lesion.	2	2	2	2	6	3	8	7
RC 4-6, severe (≥70%) FP disease, focal lesion.	7	7	7	8	3	4	3	1
RC 4-6, severe (≥70%) FP moderate lesion.	5	7	8	8	4	3	3	1
RC 4-6, severe (≥70%) FP diffuse lesion.	4	7	8	8	4	3	3	1
RC 4-6, severe (≥70%), FP, ISR.	4	6	7	8	7	3	3	3
RC 4-6, FP, CTO.	3	6	8	8	5	3	3	3
RC 4-6, severe (≥70%), FP, focal undilatable lesion.	2	2	2	2	5	3	8	8

Appropriate
May Be Appropriate
Rarely Appropriate

Klein AJ et al. Catheter Cardiovasc Interv. 2017;90(4):E90-E110.

SCAI Consensus Guidelines for Device Selection in FP PVI Device Selection as DEFINITIVE Therapy

	PTA	Specialty balloons	BMS (Self-expanding)	DES	DCB	Covered stents	Laser atherectomy	Directional atherectomy	Orbital/ Rotational atherectomy	Excisional/aspiration atherectomy
1. CFA bifurcation lesion	IIB C-LD	IIB C-EO	IIA B-R	IIA C-EO	IIA C-EO	III H C-EO	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
2. Above knee popliteal lesion	III NB B-R	III NB C-EO	IIA A	I B-R	I A	IIB B-R	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
3. Ostial SFA lesion	IIB B-R	IIB C-EO	IIA A	I B-R	I A	IIB C-EO	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
4. Focal SFA lesion	IIB A	III NB C-LD	IIA A	I B-R	I A	IIB B-R	III NB C-LD	III NB C-LD	III NB C-LD	III NB C-LD
5. Intermediate SFA lesion	III NB B-R	III NB C-LD	IIA A	I B-R	I A	IIB B-R	III NB C-LD	III NB C-LD	III NB C-LD	III NB C-LD
6. Diffuse SFA lesion	III NB B-NR	III NB C-EO	IIA B-NR	I B-NR	I B-R	IIA B-R	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
7. Moderate to severe calcified, focal lesion	IIB B-NR	IIB C-LD	IIA C-LD	I C-LD	I C-LD	IIB C-EO	III NB C-LD	III NB C-LD	III NB C-LD	III NB C-LD
8. Moderate to severe calcified, intermediate lesion	III NB B-NR	III NB C-LD	IIA C-LD	I C-LD	I C-LD	IIB C-EO	III NB C-LD	III NB C-LD	III NB C-LD	III NB C-LD
9. Moderate to severe calcified, diffuse lesion	III NB B-NR	III NB C-LD	IIA C-EO	I C-EO	I C-LD	IIA C-EO	III NB C-EO	III NB C-EO	III NB C-EO	III NB/ C-EO
10. Chronic total occlusion, focal lesion	IIB B-R	III NB C-EO	IIA B-R	I B-R	I B-R	IIB C-LD	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
11. Chronic total occlusion, intermediate lesion	III NB B-R	III NB C-EO	IIA B-R	I B-R	I B-R	IIB B-R	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
12. Chronic total occlusion, diffuse lesion	III NB B-NR	III NB C-EO	IIA C-LD	I B-NR	I B-NR	IIA B-R	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
13. ISR, focal lesion	IIB B-R	III NB C-LD	III NB C-EO	IIB C-LD	I B-R	IIB C-LD	IIA B-R	III NB C-EO	III H C-EO	III NB C-EO
14. ISR, intermediate lesion	III NB B-R	III NB C-LD	III NB C-EO	IIA C-LD	I B-R	IIB B-R	IIA B-R	III NB C-EO	III H C-EO	III NB C-EO

Feldman DN et al. Catheter Cardiovasc Interv 2018.

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Clinical Trial Registration—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. (***J Am Heart Assoc.* 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.**)

Key Words: balloon angioplasty • paclitaxel • paclitaxel-coated balloon • paclitaxel-eluting stent

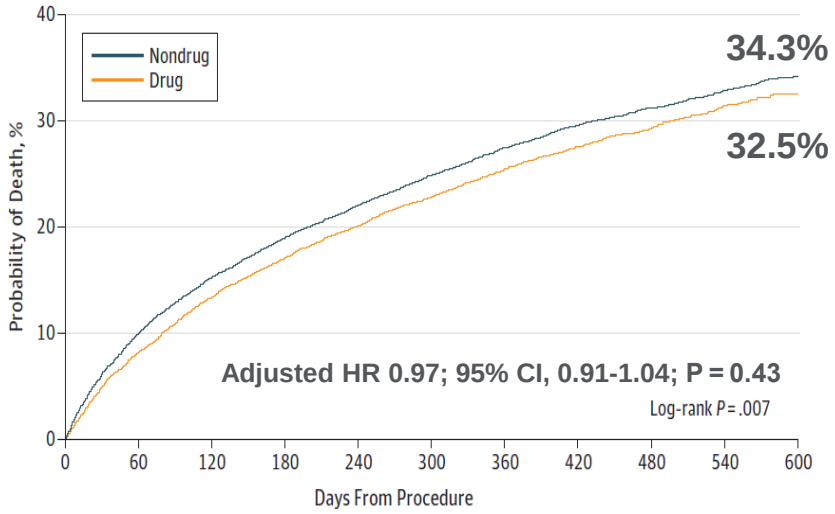
Initial Analyses of Medicare Beneficiary Data

JAMA Cardiology | Original Investigation

February 12, 2019

Association of Survival With Femoropopliteal Artery Revascularization With Drug-Coated Devices

Eric A. Secemsky, MD, MSc; Harun Kundi, MD; Ido Weinberg, MD; Michael R. Jaff, DO; Anna Krawisz, MD; Sahil A. Parikh, MD; Joshua A. Beckman, MD; Jihad Mustapha, MD; Kenneth Rosenfield, MD; Robert W. Yeh, MD

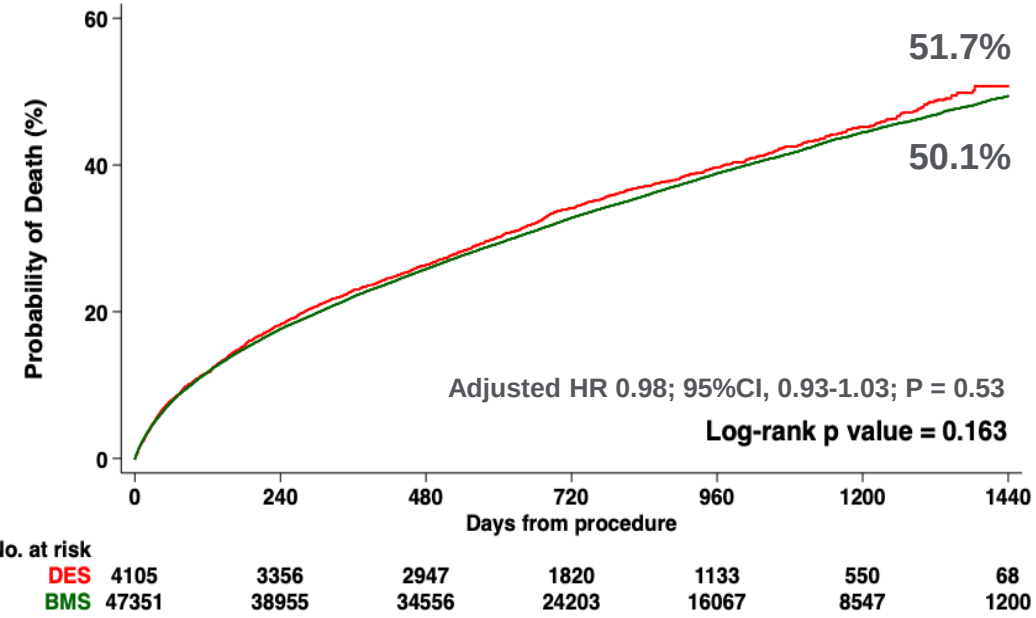


JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

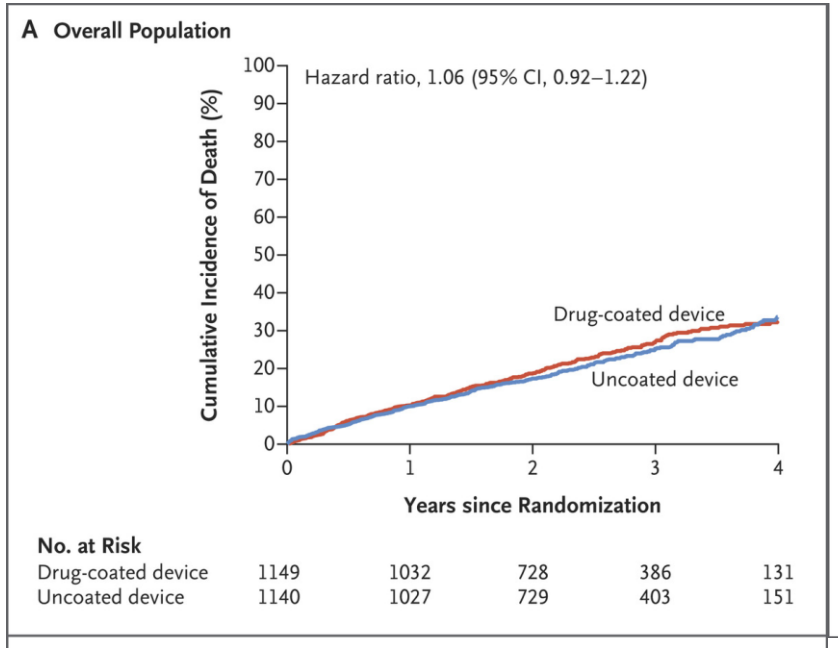
March 1, 2019

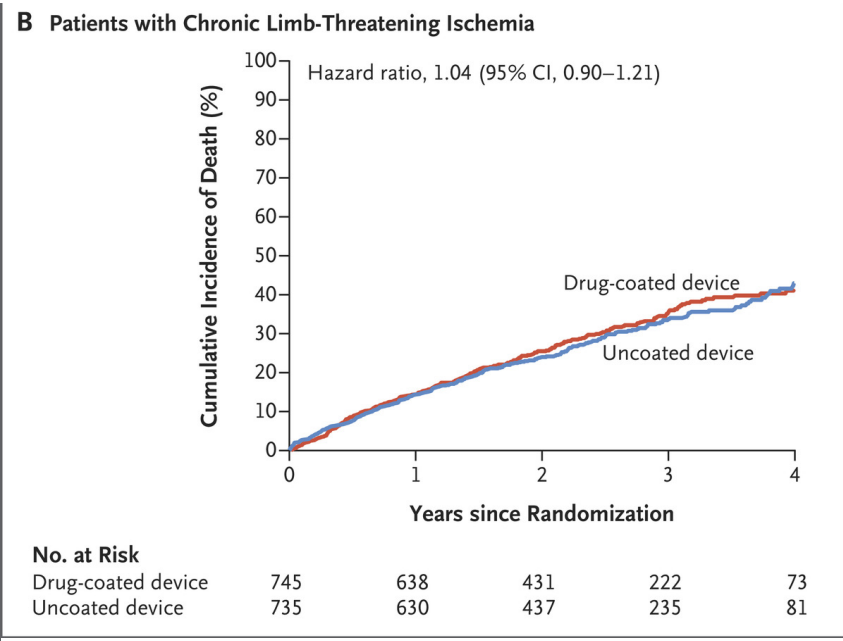
Drug-Eluting Stent Implantation and Long-Term Survival Following Peripheral Artery Revascularization

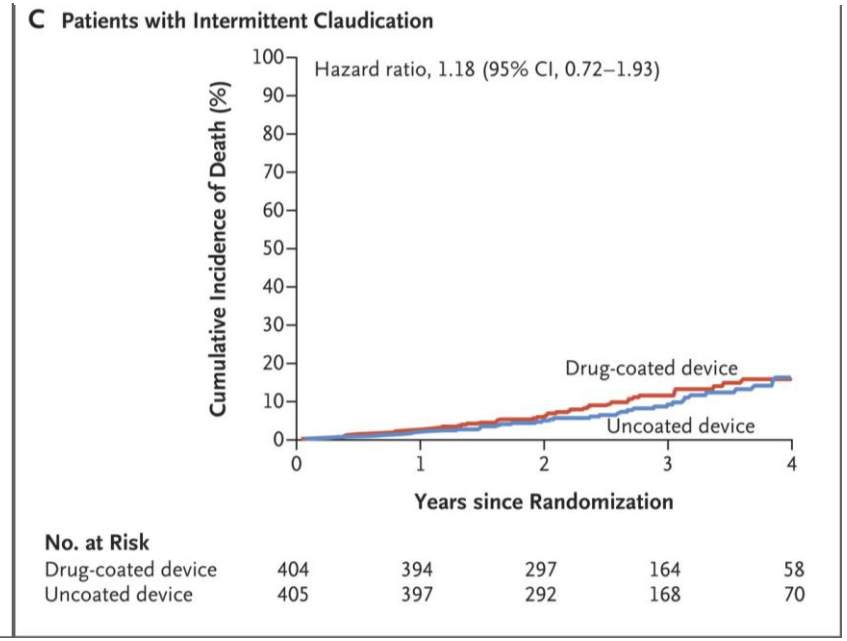
Eric A. Secemsky, Harun Kundi, Ido Weinberg, Marc Schermerhorn, Joshua A. Beckman, Sahil A. Parikh, Michael R. Jaff, Jihad Mustapha, Kenneth Rosenfield and Robert W. Yeh



SWEDEPAD:
No increased mortality in interim analysis





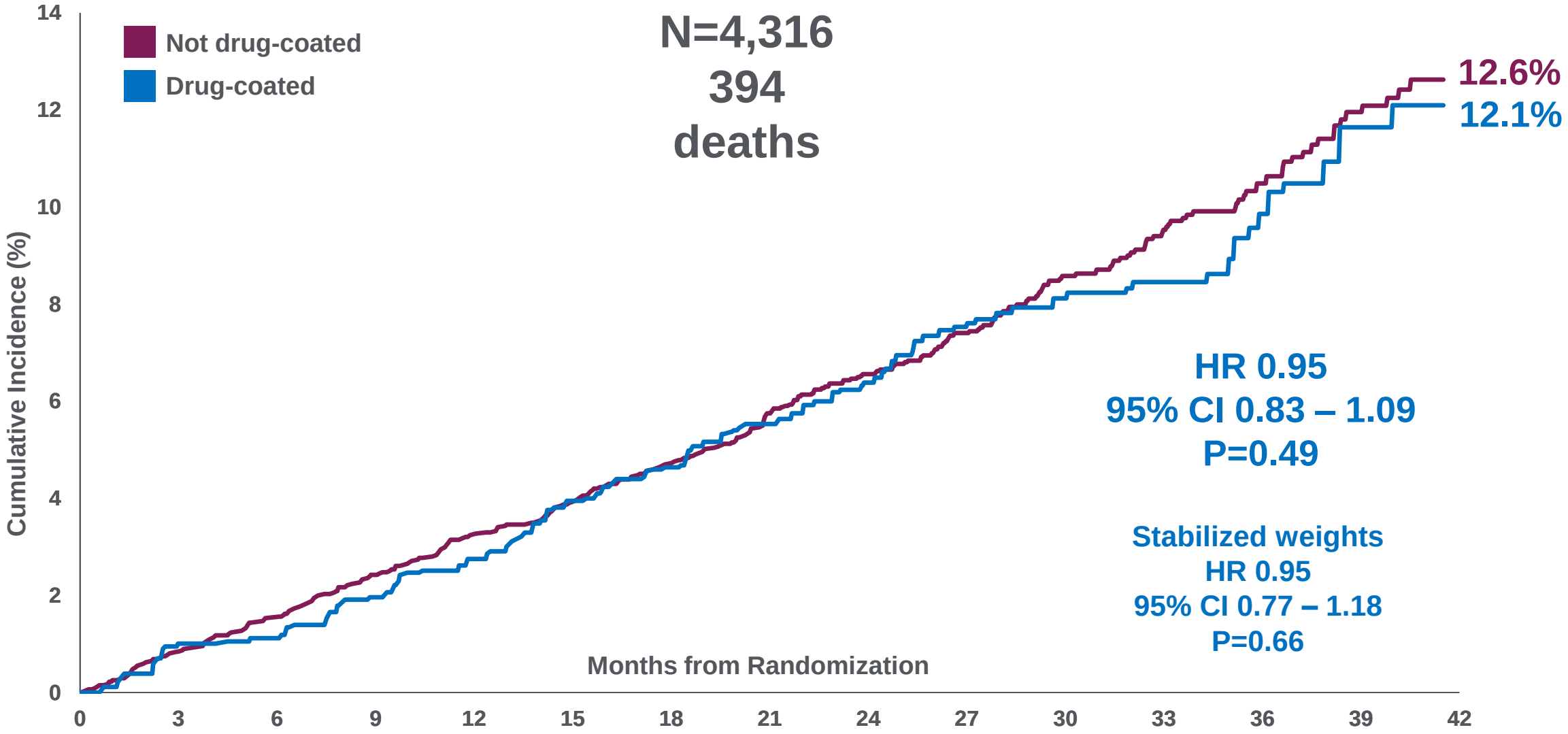


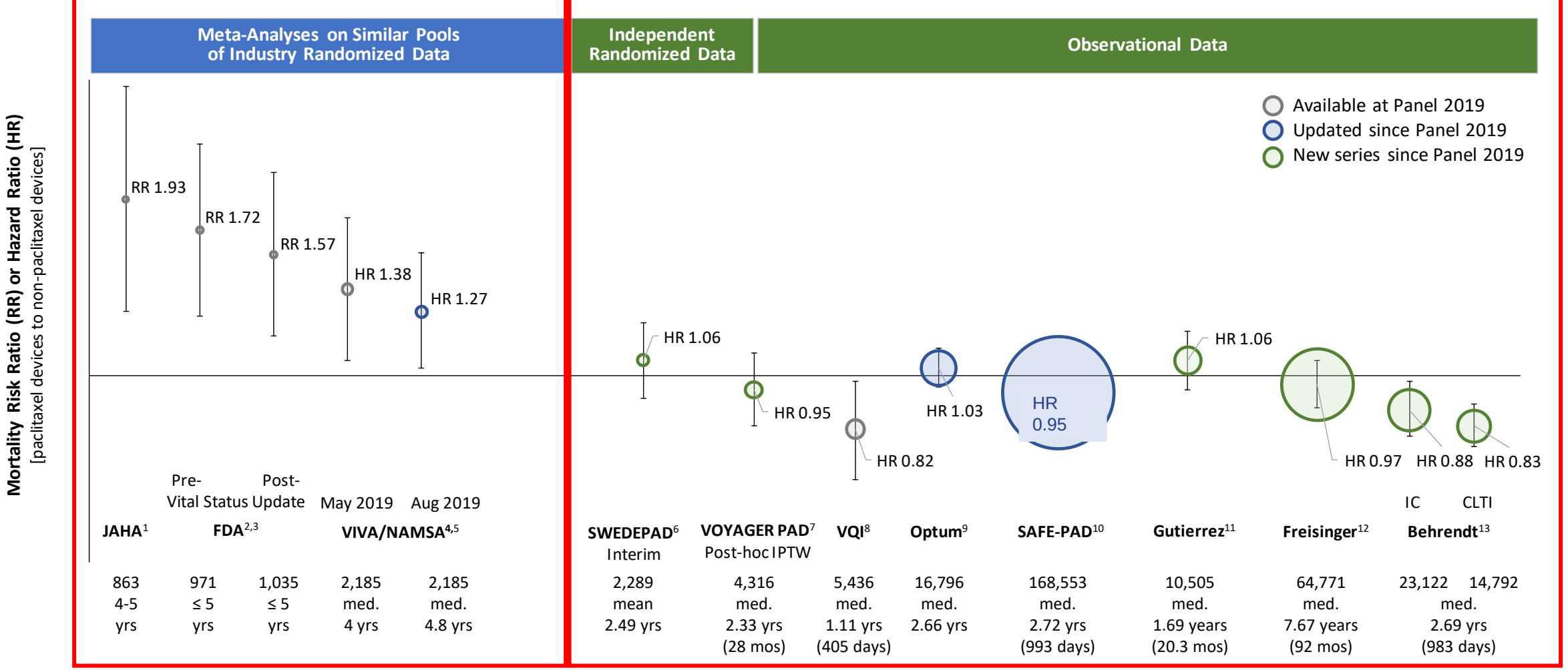
J Nordanstig et al. N Engl J Med 2020;383:2538-2546.

VOYAGER PAD

All-cause Mortality

Weighted





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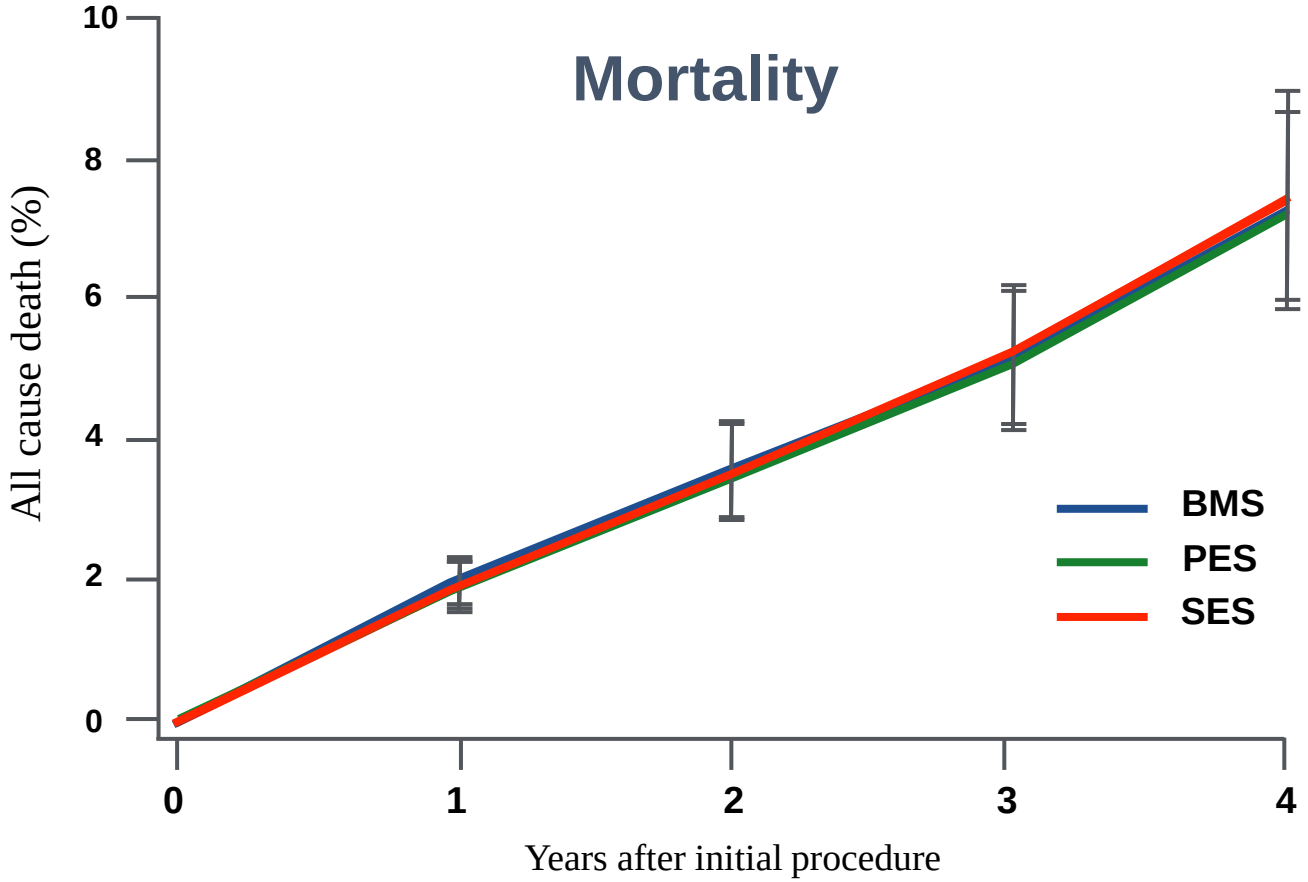
2. FDA Executive Summary, Circulatory System Devices Panel Meeting, Figure 14 June 19-20, 2019; pre vital status.
3. Whatley E, FDA presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019; post vital status.
4. Rocha-Singh KJ, et al. VIVA-NAMSA presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019.
5. Rocha-Singh KJ, et al. Circulation 2020;141:1859-69.
6. Nordanstig J, et al. New Engl J Med 2020; doi: 10.1056/NEJMoa2005206.
7. Hess C, adjusted analysis presented at TCT 2020, Oct 18, 2020.
8. Bertges DJ, et al. Circ Cardiovasc Interv. 2020;13:e008528 (combined matched analysis).
9. Secemsky EA, et al. EuroInterv 2020;doi:10.4244/EIJ-D-20-01018.
10. Secemsky EA, et al. JAMA Intern Med. 2021 Aug 1;181(8):1071-1080.
11. Gutierrez JA, et al. J Am Heart Assoc. 2021;10:e018149. DOI: 10.1161/JAHA.120.018149.
12. Freisinger E, et al. Eur Heart J 2019:ehz698 (HR at 5 year).
13. Behrendt CA, et al. Eur J Vasc Endovasc Surg 2020;59:587-96 (IC & CLTI).

No Mortality Signal was Identified Comparing Drugs

Network Meta-analysis: 38 trials, 18,023 pts



SES vs. BMS: HR 1.00 (0.82-1.25), ***p=0.89***
PES vs. BMS: HR 1.03 (0.84-1.22), ***p=0.75***
SES vs. PES: HR 0.96 (0.83-1.24), ***p=0.80***

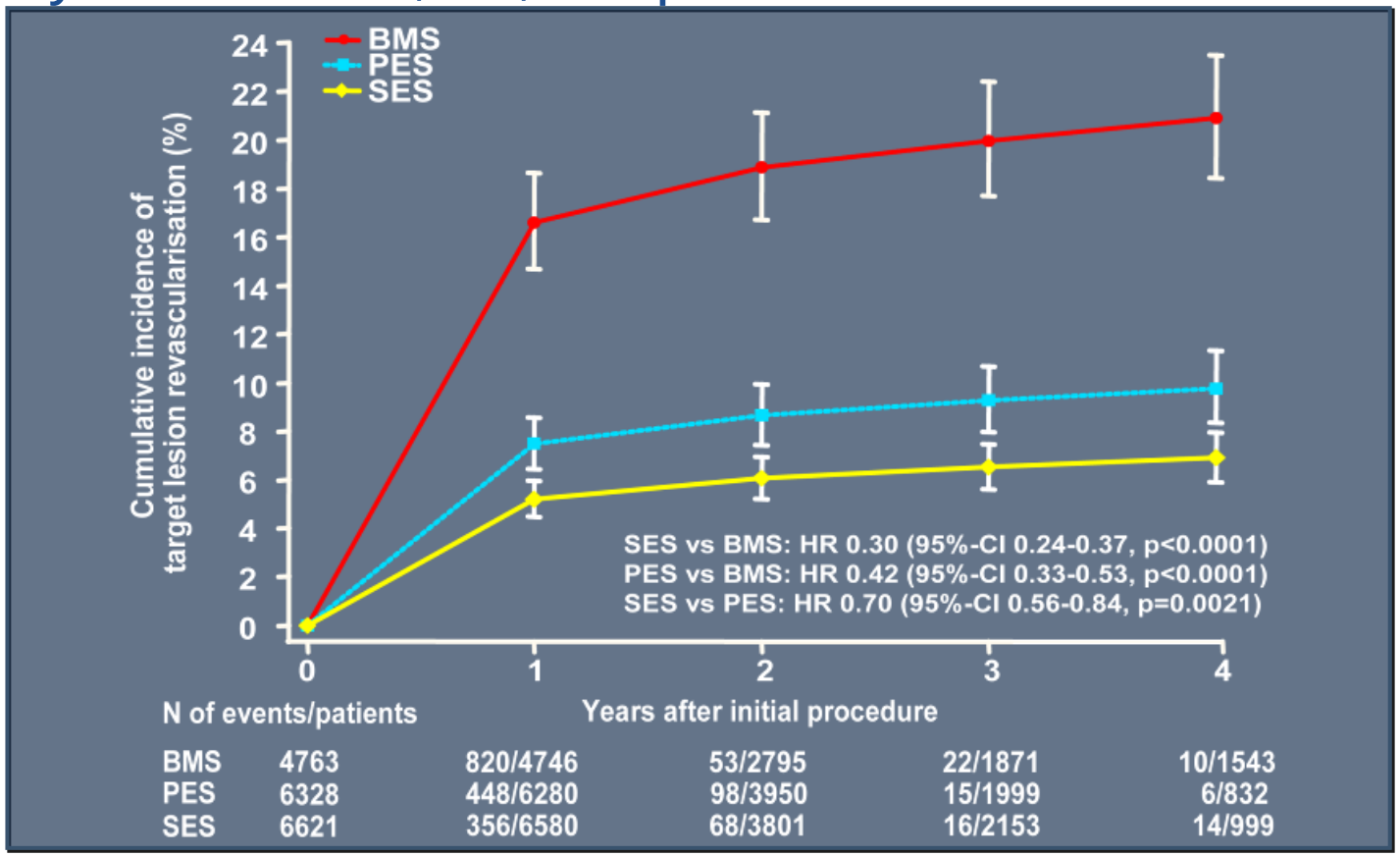
		Yr 1	Yr 2	Yr 3	Yr 4
BMS	4921	109/4904	48/3340	31/2264	44/1875
PES	6331	138/6283	78/4263	32/2187	15/869
SES	6771	139/6730	72/4041	38/2340	24/10810

Stettler C et al. Lancet 2007;370:937- 48

Limus Agents Have Been Shown to be MORE EFFECTIVE in Coronary Artery Stenting

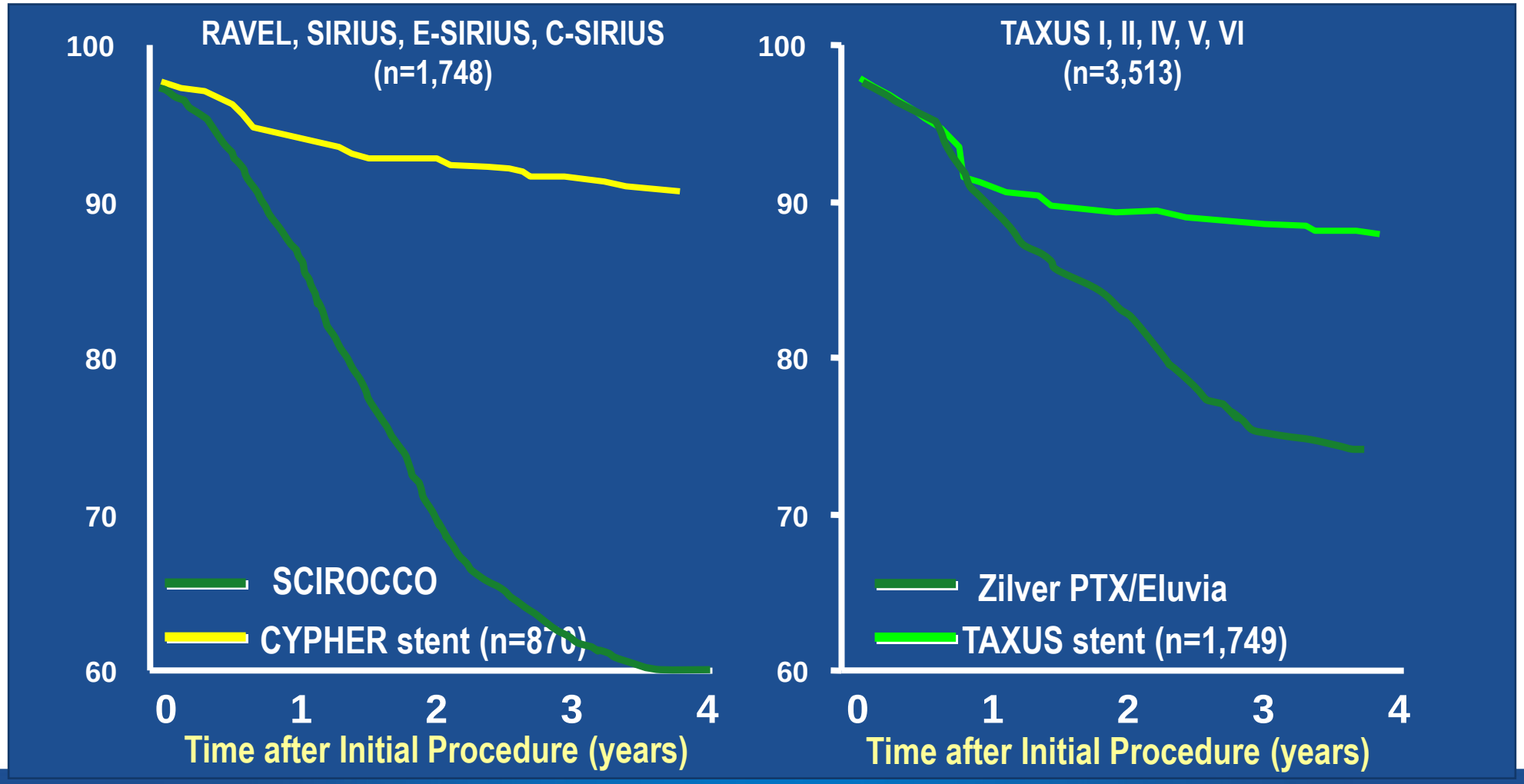
Network meta-analysis: 38 trials, 18,023 patients

TLR Frequency



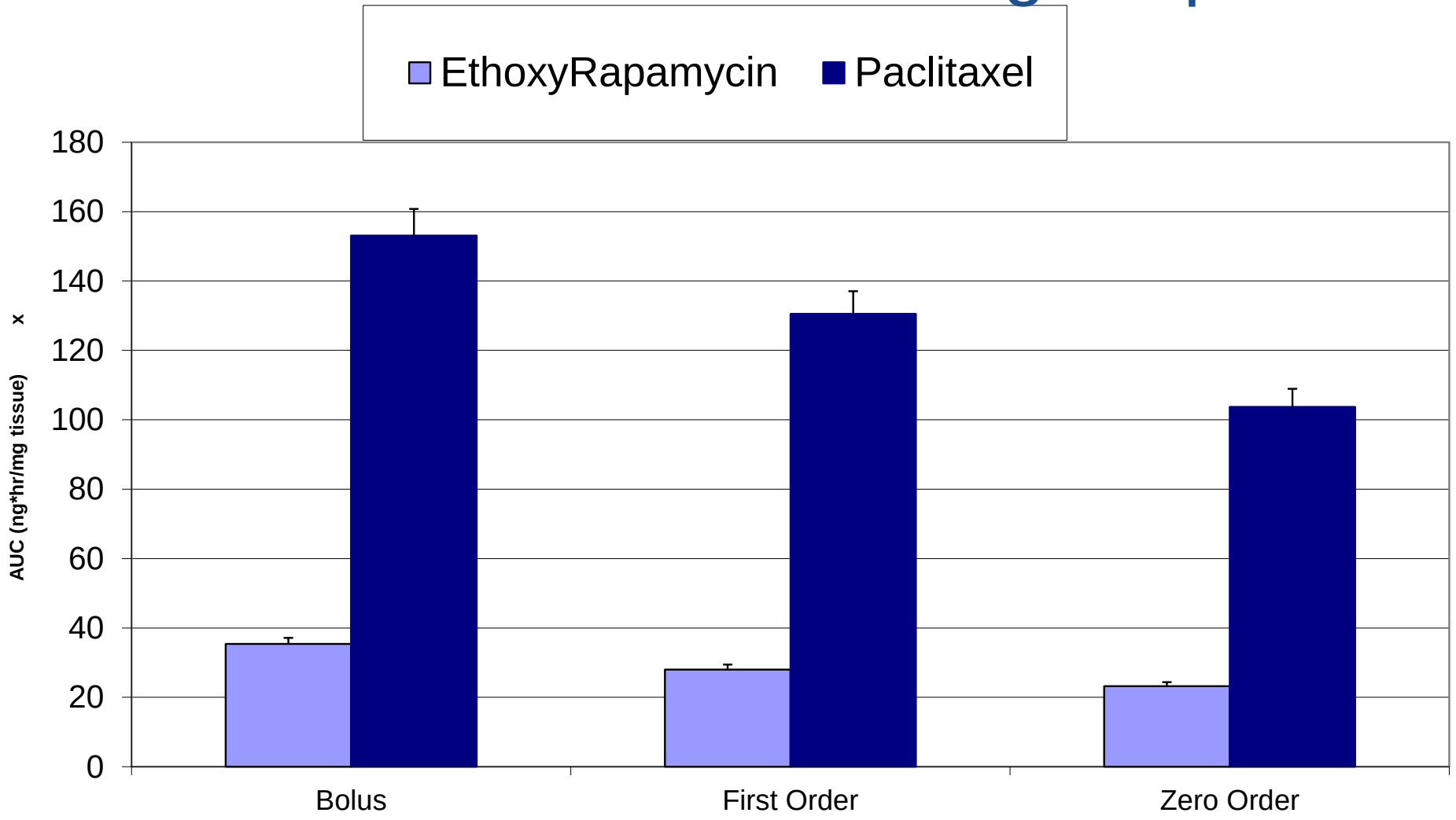
Stettler C et al. Lancet 2007;370:937- 48

TLR Rates of DES in the SFA are NOT the same as the Coronary Bed



Spaulding C et al. *N Engl J Med.* 2007;356:989-997.
Adapted from: Stone GW et al. *N Engl J Med.* 2007;356:998-1008.

Arterial Drug Uptake is a Function of Presentation Kinetics and Drug Properties

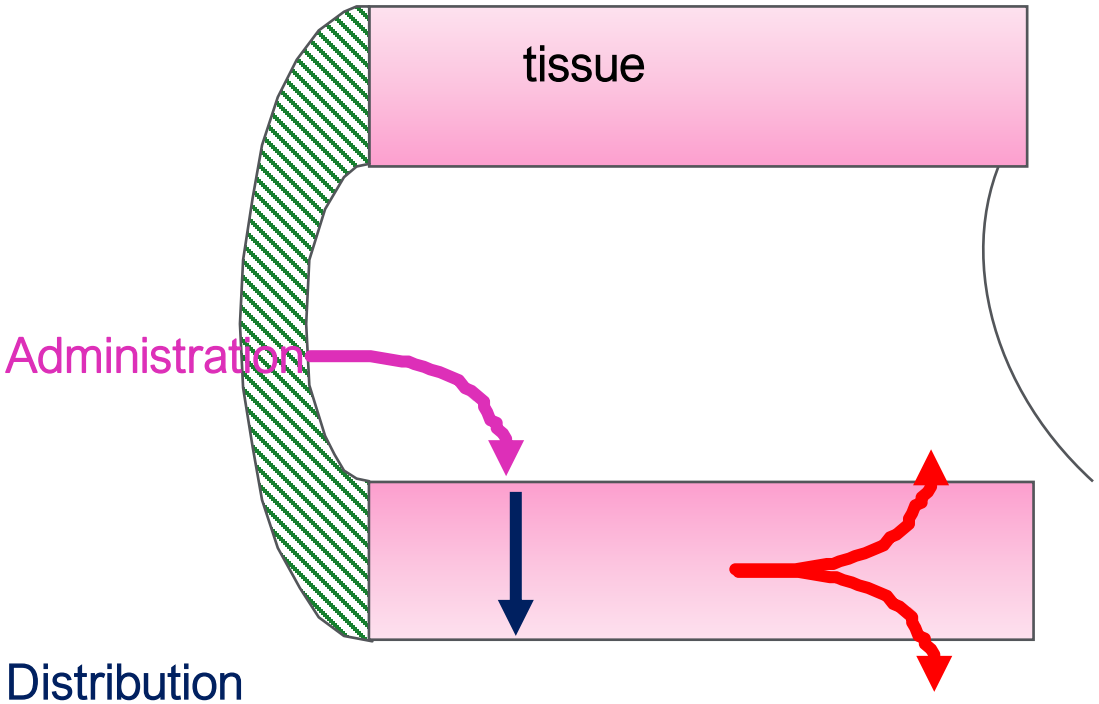


Parikh, et al. (Submitted)

Courtesy: S. Parikh, MD and E. Edelman, MD, PhD

Modes of Local Endovascular Drug Delivery

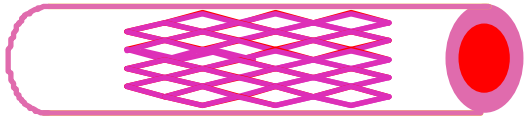
Target site



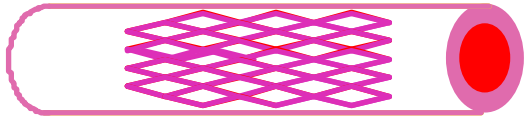
$$\int_0^t [Drug] \approx \text{EFFECT}$$

Endovascular modalities

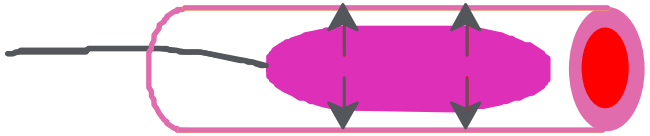
Drug release



Drug Coated Stent — FAST



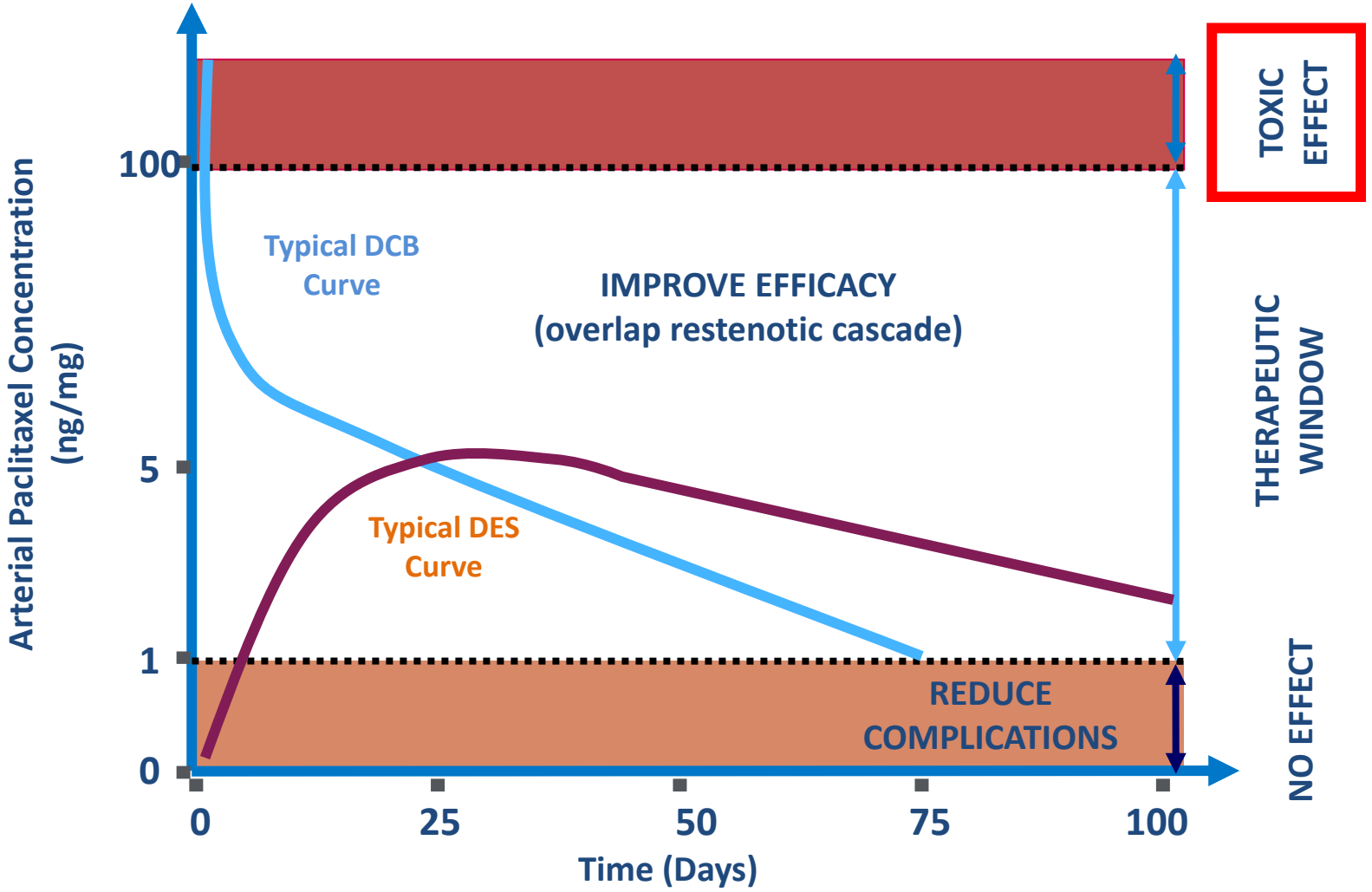
Drug Eluting Stent — CONTROLLED/ SUSTAINED



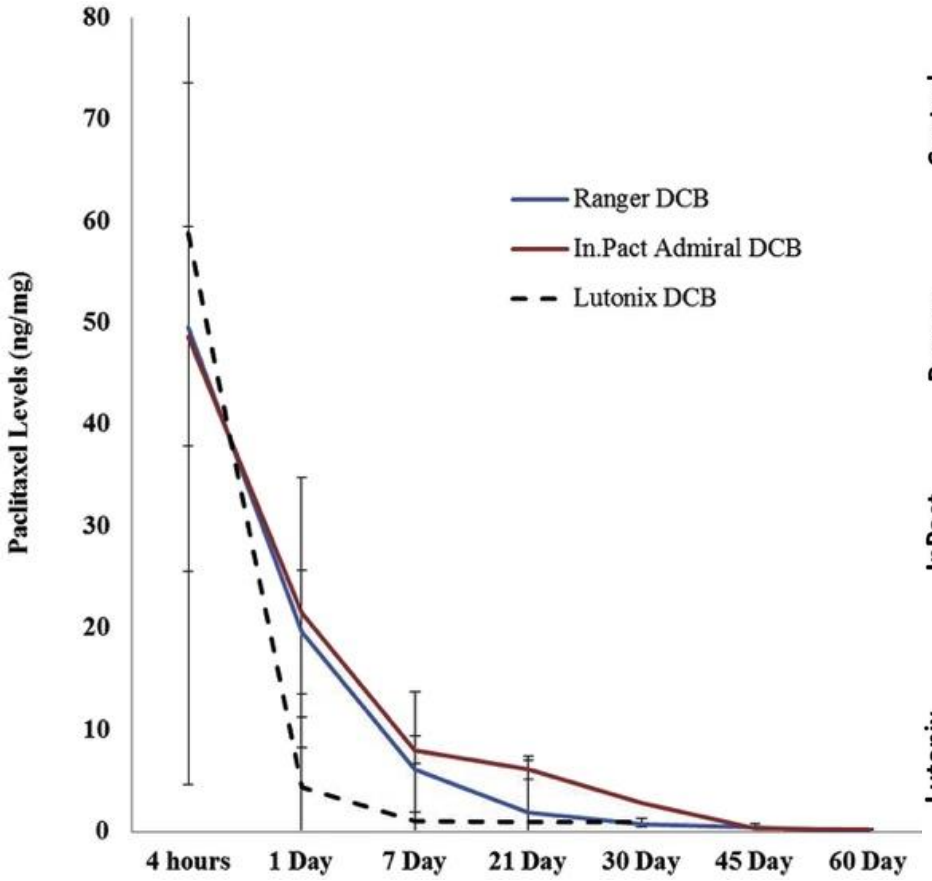
Drug Eluting Balloon — FAST

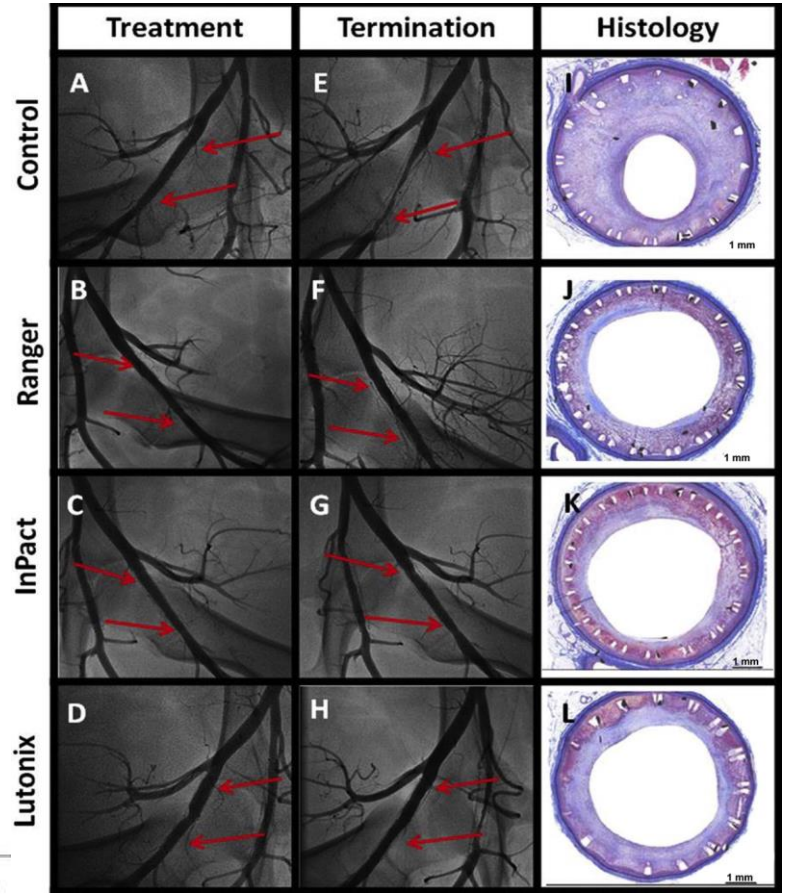
Drug “Coated” Balloon — FAST

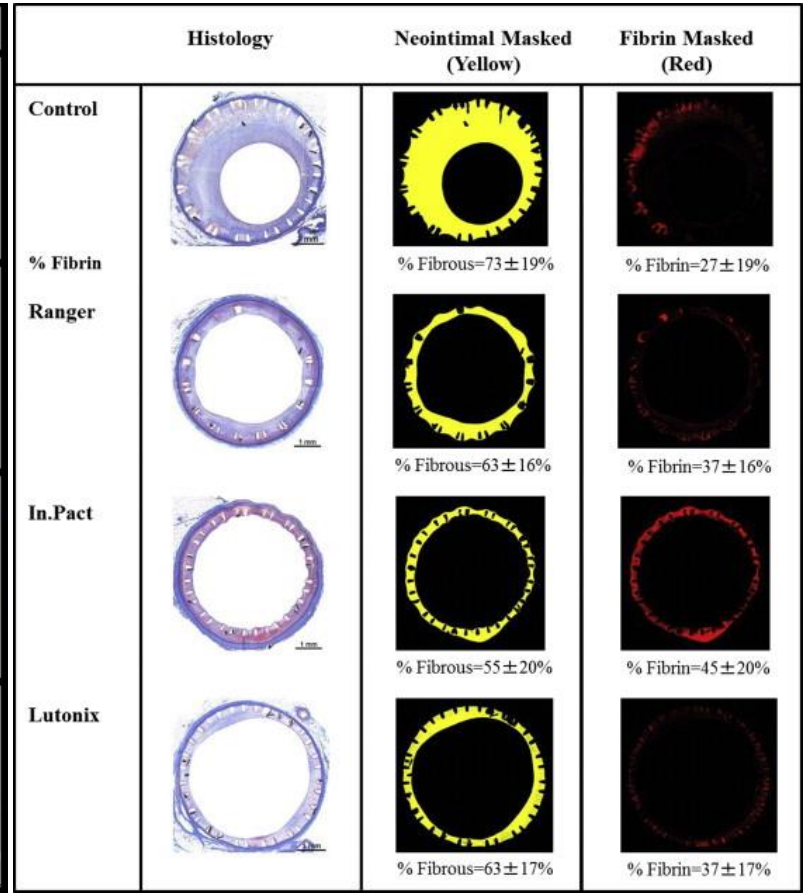
Dosing Considerations
Balancing Safety and Efficacy



Not all DCB Are Created Equal: Differential PK

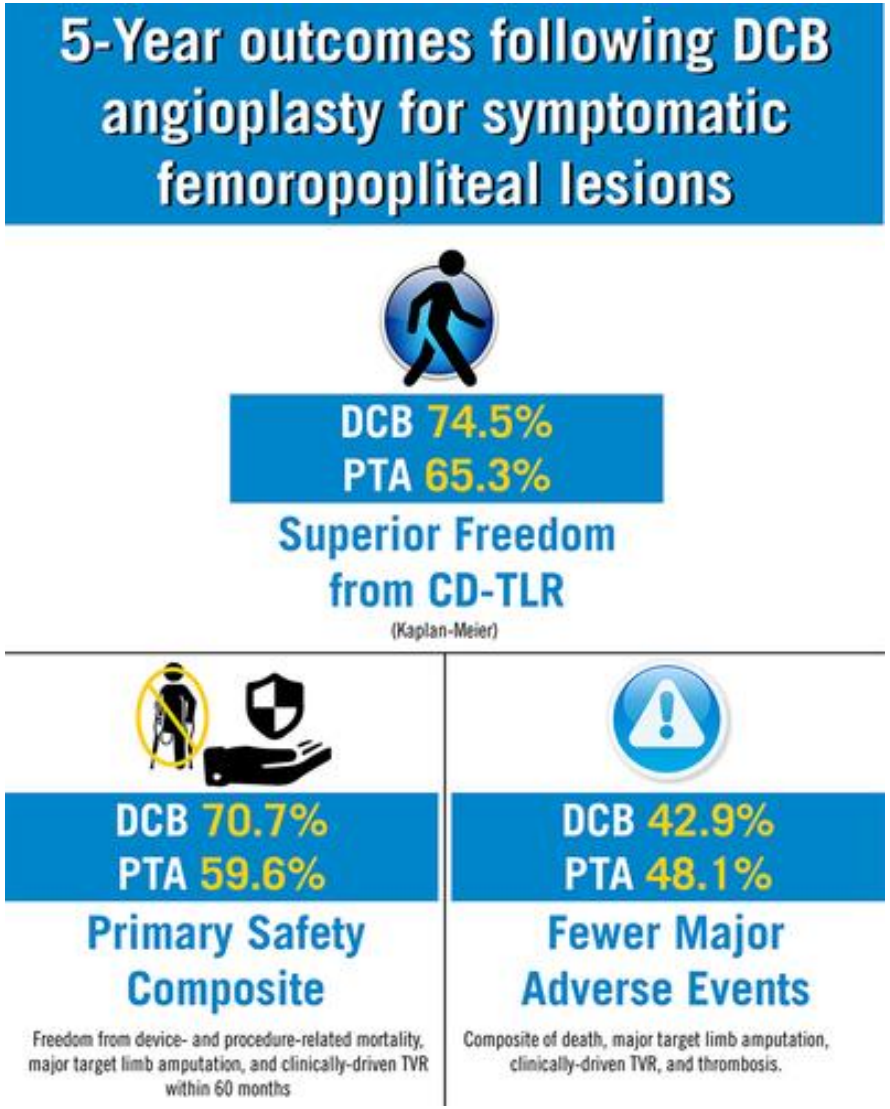






Gongora, et al. JACC: CI Volume 8, Issue 8, July 2015, Pages 1115–1123

So, if PTX is safe, what about Sirolimus? The bar is high

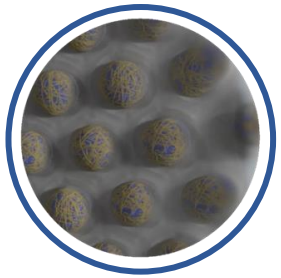


- Patency at 1 year > 80%
- Freedom from cd-TLR at 3-5y >70%
- ≤ MALE
- ≤ Mortality

John A. Laird. Circulation: Cardiovascular Interventions. Long-Term Clinical Effectiveness of a Drug-Coated Balloon for the Treatment of Femoropopliteal Lesions, Volume: 12, Issue: 6, DOI: (10.1161/CIRCINTERVENTIONS.118.007702)

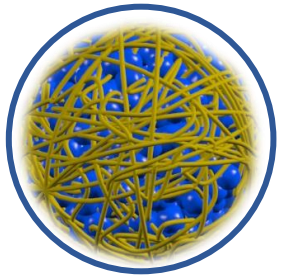
SELUTION SLR™

Sirolimus-Eluting Balloon with Sustained Release (CE-Marked)



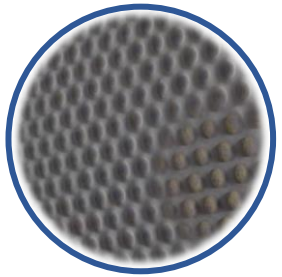
Proprietary MicroReservoir Technology

- Creation of MicroReservoirs combining sirolimus & biodegradable polymer
- Sirolimus - a proven safe & effective cytostatic drug
- Offering a wider therapeutic range



MicroReservoirs: Miniature Drug-Delivery

- Optimal size MicroReservoirs to achieve pharmaco- kinetic release profile comparable to best in class DES
- Consistent and predictable drug release
- Sustained therapeutic effect for up to 90 days[1]



Cell Adherent Technology (CAT™)

Proprietary amphipathic lipid technology which binds MicroReservoirs to the balloon surface

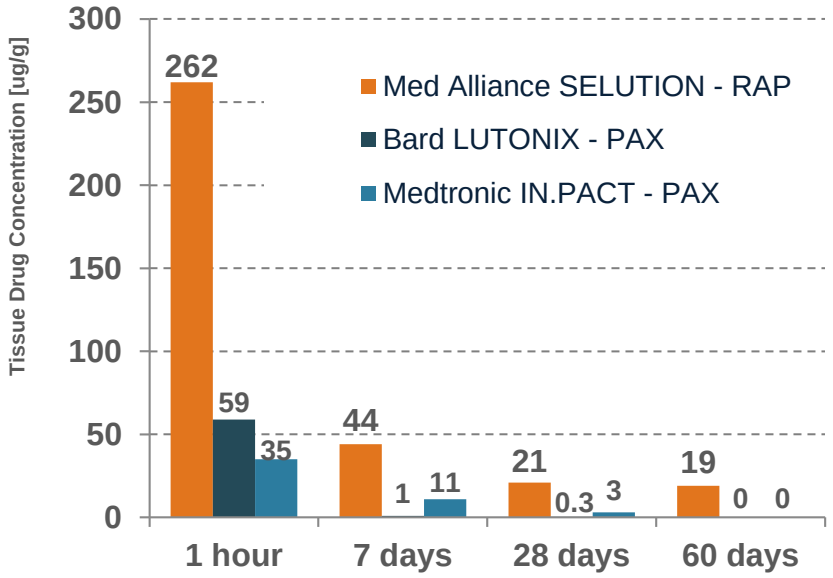
- Contains and protects micro-reservoirs during insertion and inflation
- Enhances drug retention and bioavailability, allowing for a lower drug dose concentration on the balloon surface (1 µg/mm²)
- Optimizes transfer of MicroReservoirs to the tissue and maximizes the cellular uptake of sirolimus

1.Drug concentration evident in MicroReservoirs and tissue - Data on file at M.A. Med Alliance SA

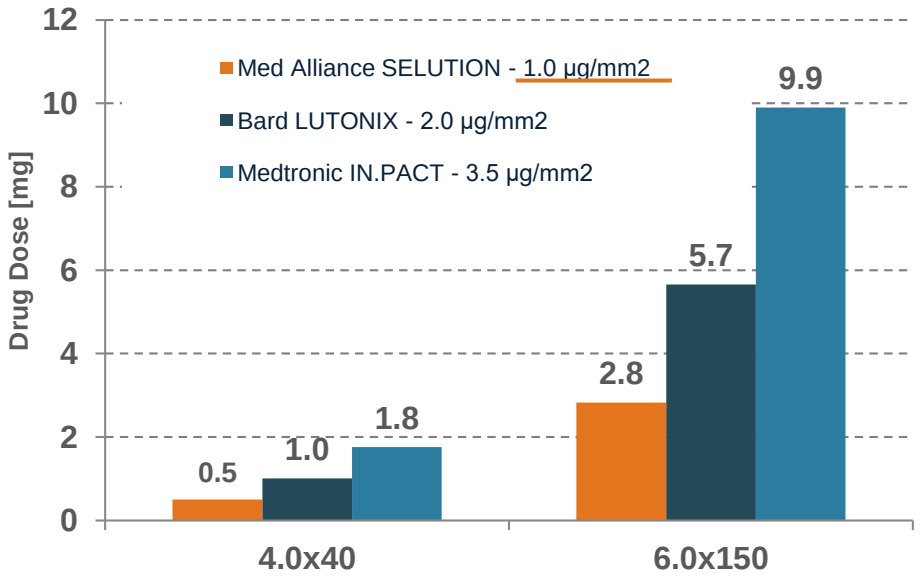
Proprietary MicroReservoir Technology
Sustained Sirolimus Release

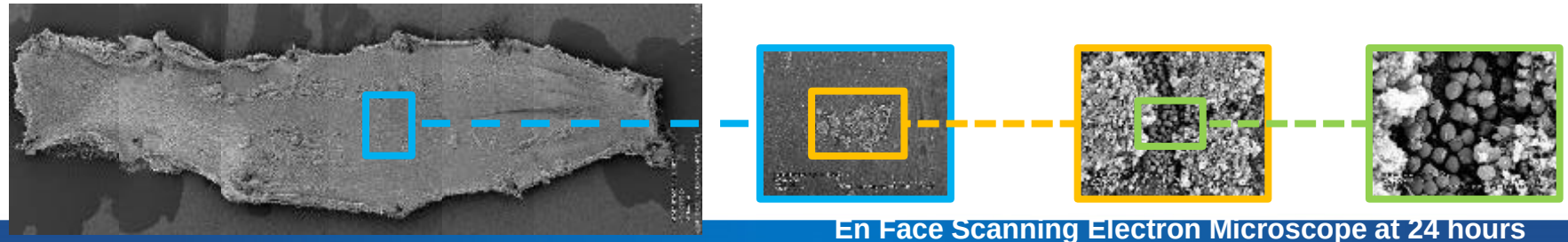
- **MicroReservoirs ensure a controlled** and **sustained** Sirolimus drug release to maintain **therapeutic effect** in tissue over long period of time and up to 90 days

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



Drug Dose per Balloon Size





En Face Scanning Electron Microscope at 24 hours

COLUMBIA NewYork-Presbyterian

MedAlliance - Tang, T. Y., et al., *The Journal of Vascular Access* (2021): 11297298211020867-11297298211020867, Medtronic – Presentation R. J. Melder (LINC 2012), Bard – Catheterization and Cardiovascular Interventions 83:132-140 (2014)

SELUTION SLR - Clinical Trial Program

Peripheral Program Enrolling Over 1900 Patients

FEMPOP Lesions Included

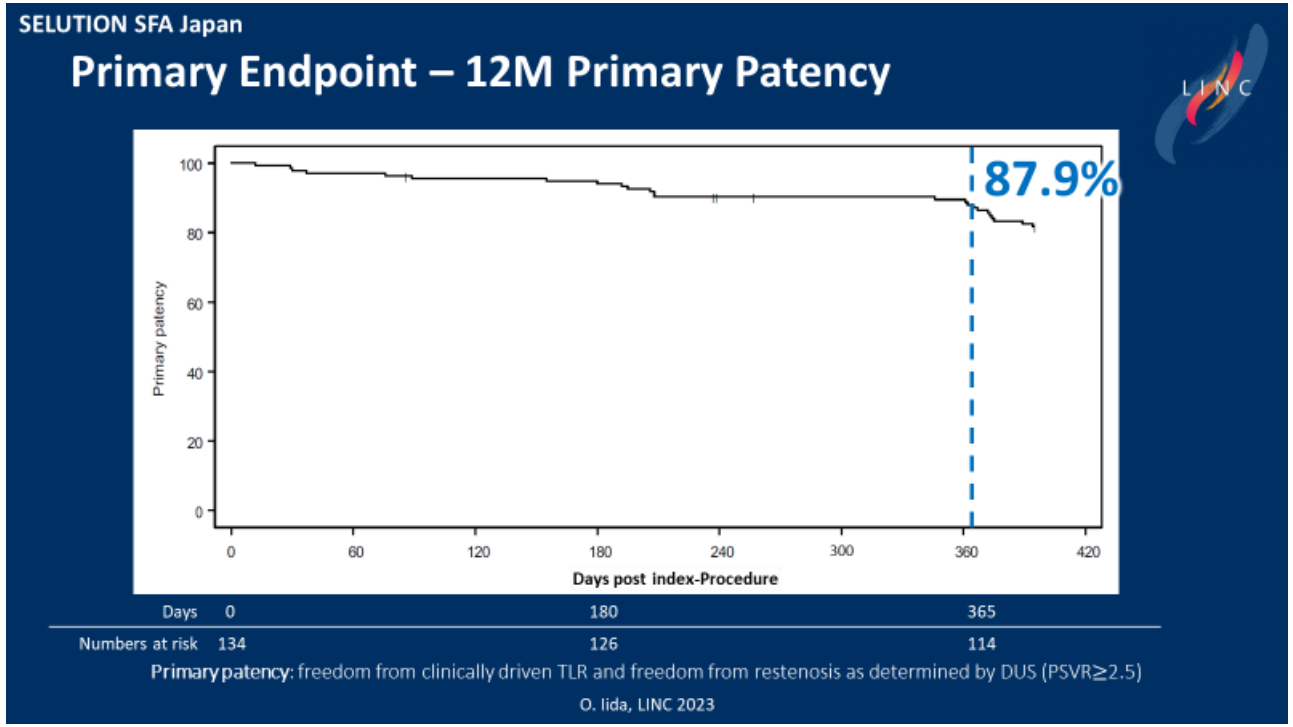
MEDALLIANCE Sponsored Trials	Indication	Patient Numbers	Region	Design	Status
SELUTION FIM	SFA/Popliteal	50	Germany	Single Arm	2 Year Data
SELUTION4SFA	SFA/Popliteal	300	Europe/US	RCT	Enrolling
JAPAN SFA	SFA/Popliteal	134	Japan	Single Arm	12 Month Data
CHINA SFA	SFA	139	China	RCT	Enrolling
SUCCESS PMS	SFA/BTK/Foot	772	Asia/Europe/LAM	Single Arm	Enrolling
SELUTION4BTK	BTK	377	Europe/US	RCT	Enrolling

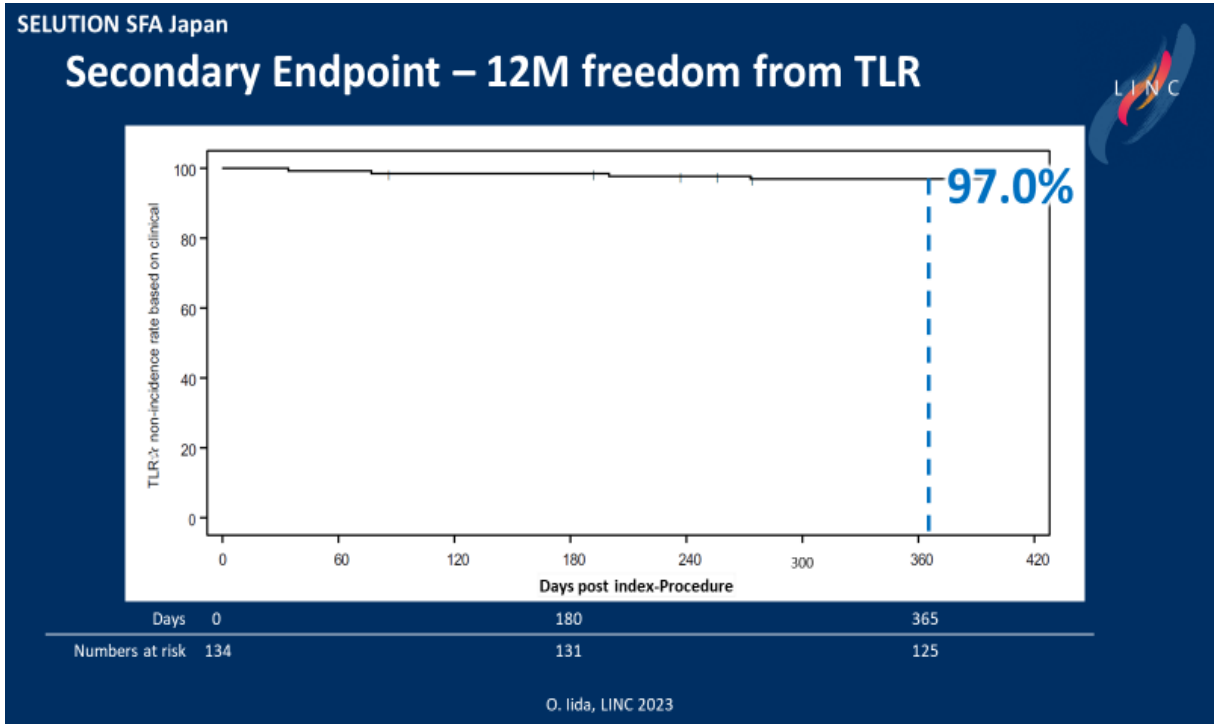
Physician-Initiated Trials	Indication	Patient Numbers	Region	Design	Status
PRESTIGE	BTK	25	Asia	Single Arm	24 Month Data
PRISTINE	BTK	75	Asia	Single Arm	12 Month Data
STEP	Foot	8	Austria	Single Arm	Completed
FLOW	SFA	70	Germany	RCT	1 Month Data

SELUTION SFA Japan (MDK-1901)
Study Design

OBJECTIVES	• To assess the safety and efficacy of the SELUTION SLR DEB in treatment of in the treatment of stenosis or occlusion of SFA and/or PA in patients with Rutherford category 2-4
DESIGN	• Prospective, controlled, multi-center, open, single-arm clinical investigation • 134 subjects in 13 sites in Japan
PRIMARY ENDPOINT	• Primary Endpoint: primary patency of the target lesion – **12M** Primary patency defined as freedom from clinically driven TLR and freedom from restenosis as determined by DUS (PSVR≥2.5)
FOLLOW-UP	• 30 days, 6, 12, 24 and 36 months post-procedure
PIs	• Osamu Iida • Yoshimitsu Soga

SELUTION SFA JAPAN- Efficacy outcomes





Iida, et al. LINC 2023

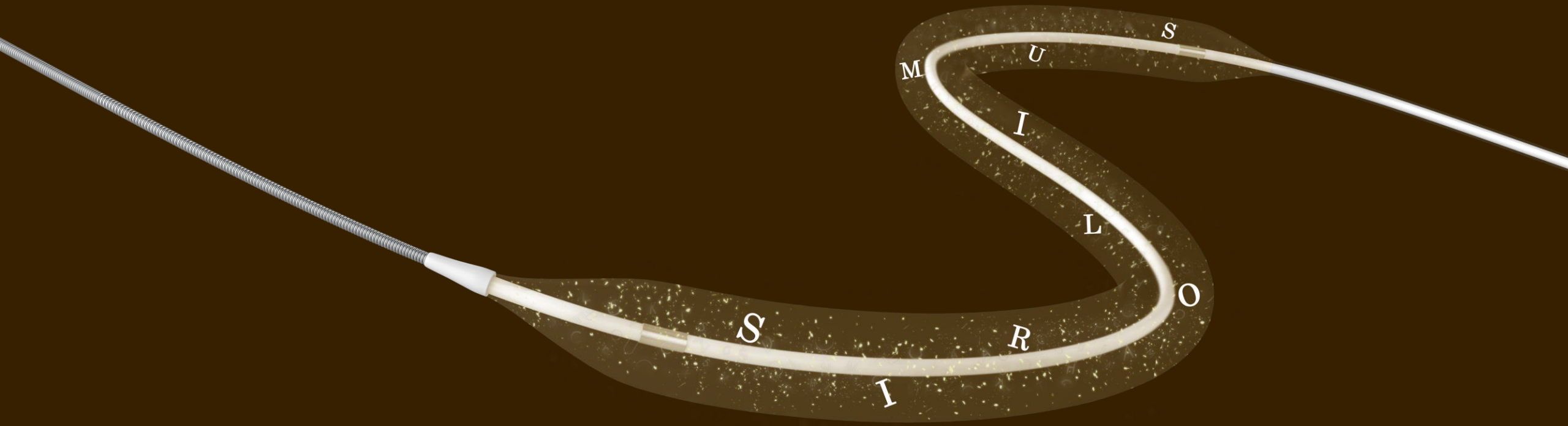
SELUTION4SFA Trial – Currently Enrolling

OBJECTIVES	➢ To demonstrate the safety and efficacy of the SELUTION SLR™ 018 DEB compared to plain (uncoated) balloon angioplasty in the treatment of PAD in the SFA and PPA artery.
DESIGN	➢ Prospective, multi-center, single blinded, randomized, controlled, superiority clinical trial ➢ 300 subjects will be enrolled at approximately 40 sites across the US, Europe, Canada and Asia.
PRIMARY ENDPOINTS	➢ Freedom from death (device and procedure related) – **30 Days** ➢ Primary patency of the target lesion – **12M**
FOLLOW-UP	➢ Subjects will be followed for 5 years post-procedure
PIs	➢ Thomas Zeller ➢ S Jay Mathews

ClinicalTrials.gov ID: NCT05132361

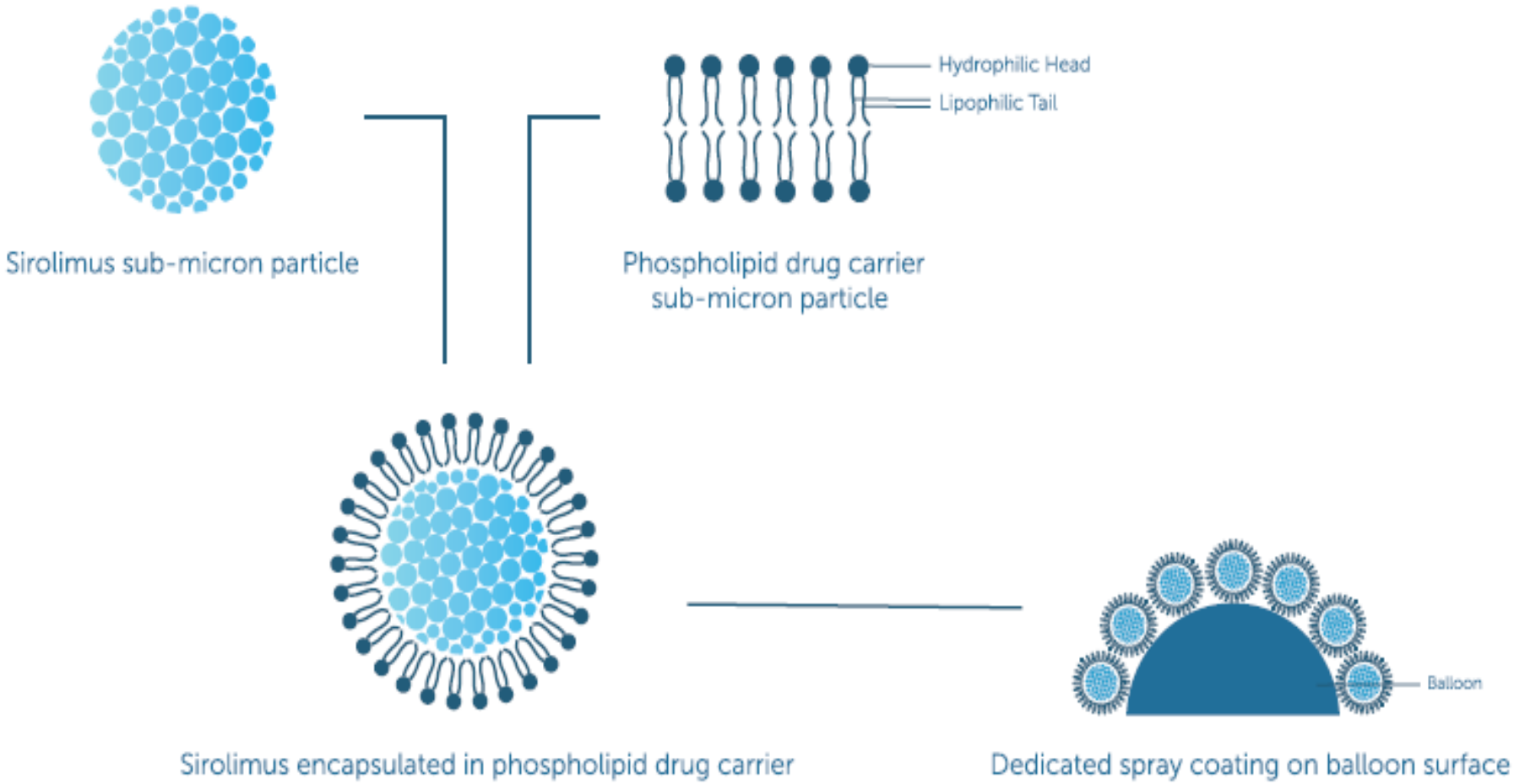
MagicTouch PTA

Sirolimus Coated Balloon

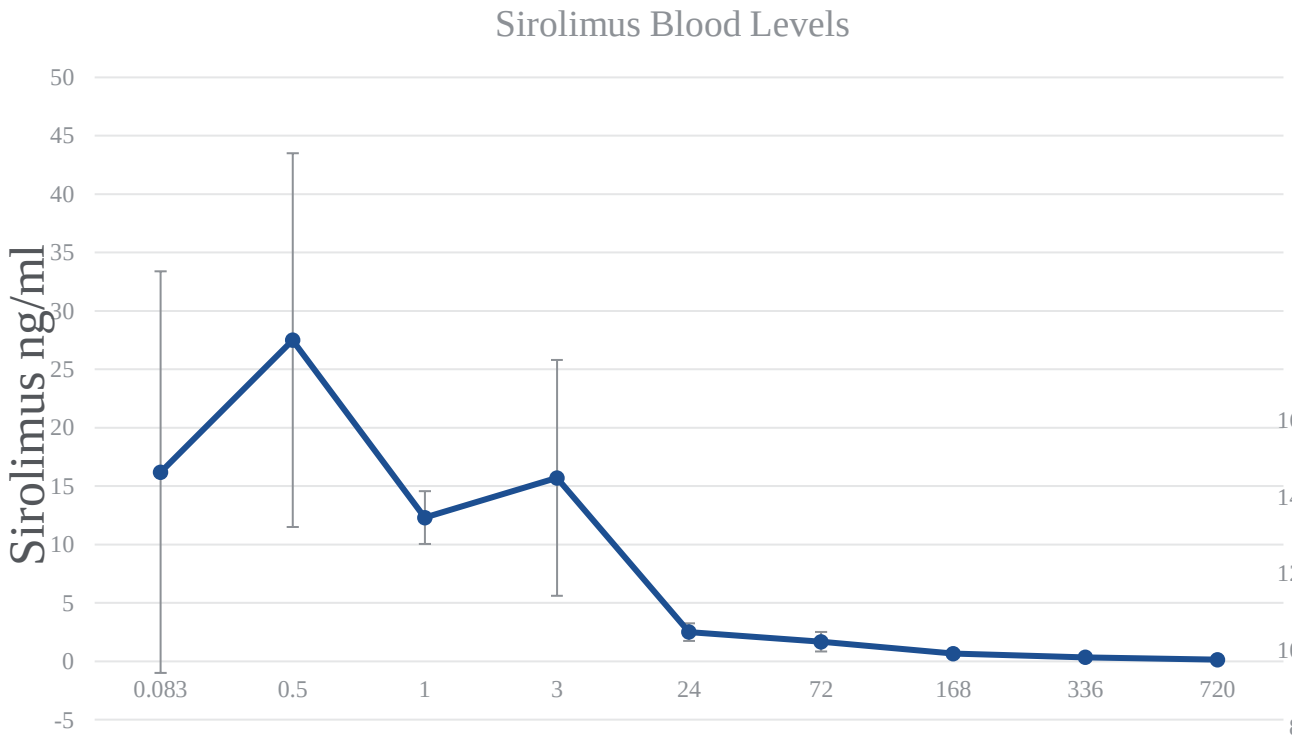


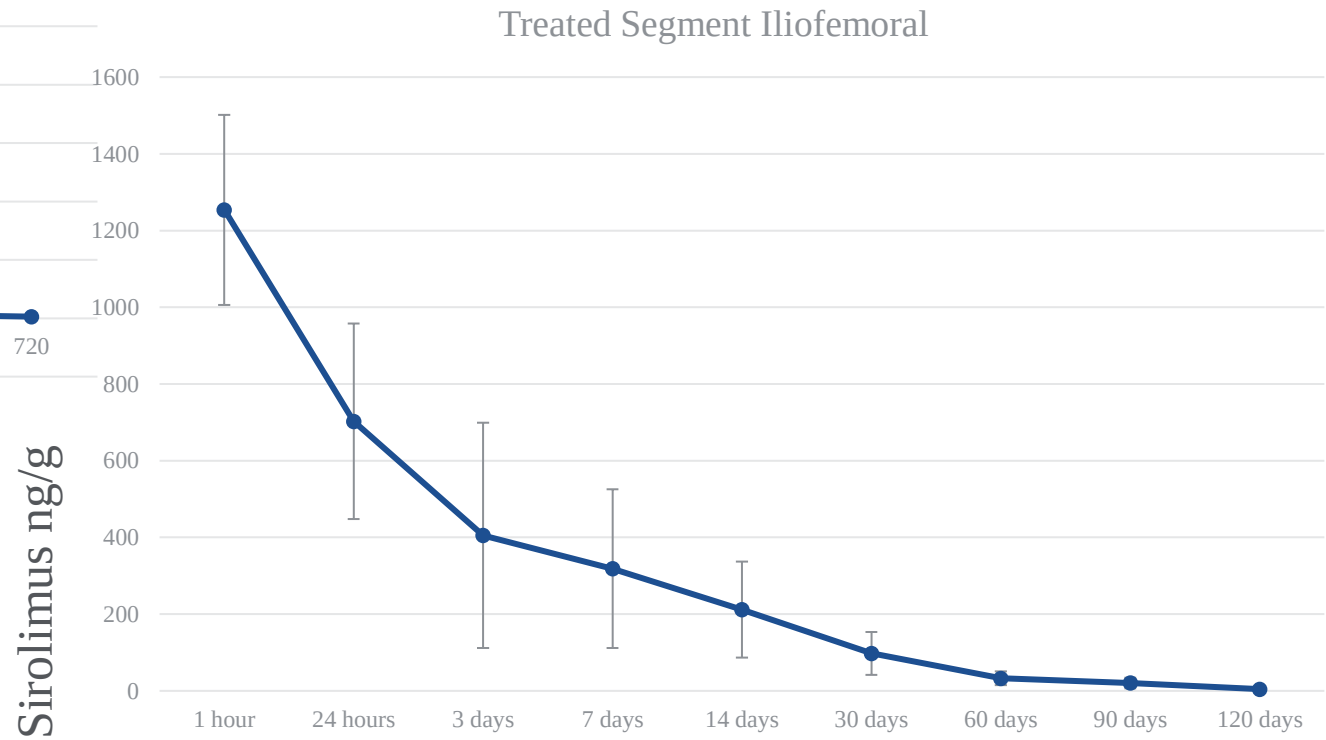
Designed by NANOLUTE TECHNOLOGY

DEPICTION OF *NANOLUTE TECHNOLOGY*



MagicTouch PK Data (Porcine Iliofemoral GLP)





Courtesy: Aloke Finn, MD

CLINICAL STUDIES - PTA

X-TOSI

PI: Prof. Edward Choke

Sponsored, Observational, Prospective, All-comers, Single Arm, Real-world To evaluate the efficacy and safety of Magic Touch in the treatment of infrainguinal peripheral arterial disease

50 Patients

Enrollment closed

BEYOND X-TOSI

PI: Prof. Edward Choke

Investigator-Initiated, Real world data for complex CLTI patients treated with MagicTouch PTA sirolimus coated balloon

216 Patients

Real World data

X-TOSI

Clinical efficacy and safety of the Magic Touch PTA Sirolimus coated balloon for SFA and BTK lesions

Primary endpoint: 6 month Primary Patency

6 month outcomes	All N=50	Femoropopliteal N=20 (% or range)	Below the knee N=30 (% or range)
Primary patency	80.0%	88.2%	74.0%

DEBATE BTK DUelL

PI: Dr. Francesco Liistro

Investigator-initiated, Randomised, Single Blind, Multicentre trial, to compare the remote patency of the sirolimus (Magic Touch) vs. paclitaxel (Lithos) release balloon, in patients undergoing tibial artery revascularization.

172
Patients
76 Patients Enrolled

FUTURE SFA- ASIA

PI: Prof. Edward Choke

Sponsored, Randomised, Double blind, Multicentres (186 SCB : 93 PTA) To determine the effectiveness (primary patency) of Magic Touch versus standard percutaneous transluminal angioplasty for the treatment of superficial and popliteal arterial disease.

279
Patients
56 Patients Enrolled

FUTURE BTK- ASIA

PI: Prof. Edward Choke

Sponsored, Randomised, Double blind, Multicentres (130 SCB : 65 PTA) To determine the effectiveness (primary patency) of Magic Touch versus standard percutaneous transluminal angioplasty for the treatment of below the knee arterial disease

219
Patients
78 Patients Enrolled

SirPAD - Zurich

PI: Prof. Nil Kucher

Investigator-initiated, Randomised, multicenter trial, to evaluate that Magic Touch is non-inferior to POBA in infra-inguinal angioplasty to prevent one-year major adverse limb events in a representative population (`all-comers`) of patients with PAD

1132
Patients
830 Patients Enrolled

SIRONA - Germany

PI: Dott. Ulf Teichgräber

Investigator-initiated, Randomised, Open Label, Multicentre trial, to investigate the safety and efficacy of Magic Touch in comparison to the most used DCBs in Germany in patients with symptomatic femoropopliteal artery disease

478
Patients
Enrollment Completed

SirPAD

Major adverse limb events in patients with femoro-popliteal and below-the-knee peripheral arterial disease treated with either sirolimus-coated balloon or standard uncoated balloon angioplasty.

Study Design

Prof. Dr. med Nils Kucher

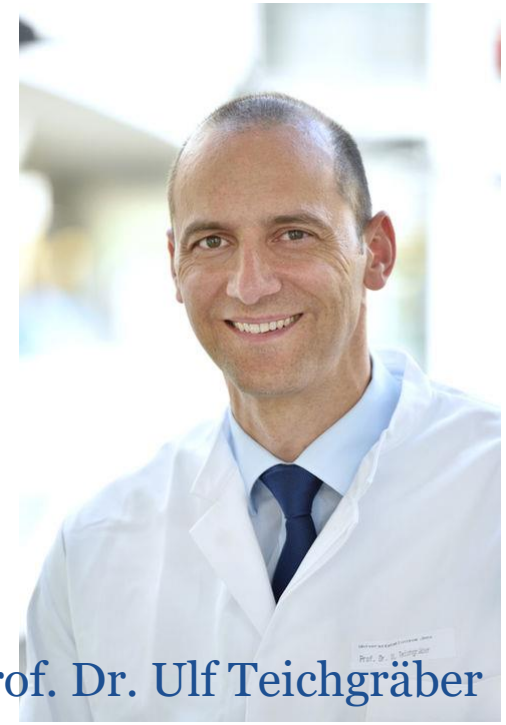
University Zurich
University Hospital Zurich
Clinic of Angiology

- Study Objective: evaluate whether the use of sirolimus-coated balloon catheters is non-inferior to uncoated balloon catheters in infra-inguinal angioplasty to prevent one-year major adverse limb events, including unplanned major amputation of the target limb and target lesion re-vascularization to treat critical limb ischemia, in a representative population (`all-comers`) of patients with PAD
- Study Design: RCT, all comers, single centre
- Study Population: 1132 patients (566 per study arm) allow to show non- inferiority of the intervention group with a power of 80% and a type I error rate of α=2.5% one-sided. Assuming a drop-out rate of approximately 5%, a total of 1200 patients will be randomized in the study.

SIRONA

Head-to-Head Comparison of **SIRO**limus versus Paclitaxel Drug-Eluting Balloo**N A**ngioplasty in the Femoropopliteal Artery

Study Design



Prof. Dr. Ulf Teichgräber

Direktor bei Universitätsklinikum Jena Institut für Radiologie

- Study Objective: investigate the safety and efficacy of a sirolimus DCB in comparison to the most used DCBs in Germany in patients with symptomatic femoropopliteal artery disease
- Study Design: prospective, multi-center, 1:1 randomized
- Stratification according to lesion length into three groups (≤ 10 cm / > 10 cm and ≤ 20 cm / > 20 cm and ≤ 30 cm)
- Study Population: 478 patients (239 per study arm) suffering peripheral artery disease ranging from intermittent claudication to critical limb ischemia

UPCOMING CLINICAL TRIALS - PTA

MAGICAL BTK - IDE FDA

PIs: Drs. Sahil Parikh, Brian Derubertis, Eric Secemsky

Sponsored, Prospective, Randomized (2 Magic Touch :1 PTA), multicenter study determine the effectiveness (primary patency) and safety of the sirolimus drug coated balloon (DCB) versus standard percutaneous transluminal angioplasty (PTA) for the treatment of below the knee arterial disease.

360 Patients

Q3 2023

MAGICAL SFA - IDE FDA

PI: Drs. Sahil Parikh, Brian Derubertis, Eric Secemsky

Sponsored, Prospective, randomized, multi-center study to compare the Magic Touch PTA Sirolimus Coated Balloon with Paclitaxel-coated DCB for treatment of high grade stenotic or occluded lesions in SFA and / or P1 segment of the popliteal artery (PA) in PAD patients.

478 Patients

Q3 2023

What about Scaffolds?

LIFE-BTK Randomized Multicenter Trial

PIVOTAL INVESTIGATION OF SAFETY AND EFFICACY OF DRS FOR BTK TREATMENT

Prospective, randomized, multicenter,
US and OUS single-blind trial
261 patients randomized
2:1 Esprit™ BTK vs. PTA

PRIMARY ENDPOINTS

Safety Endpoint @ 6 months:
MALE+POD

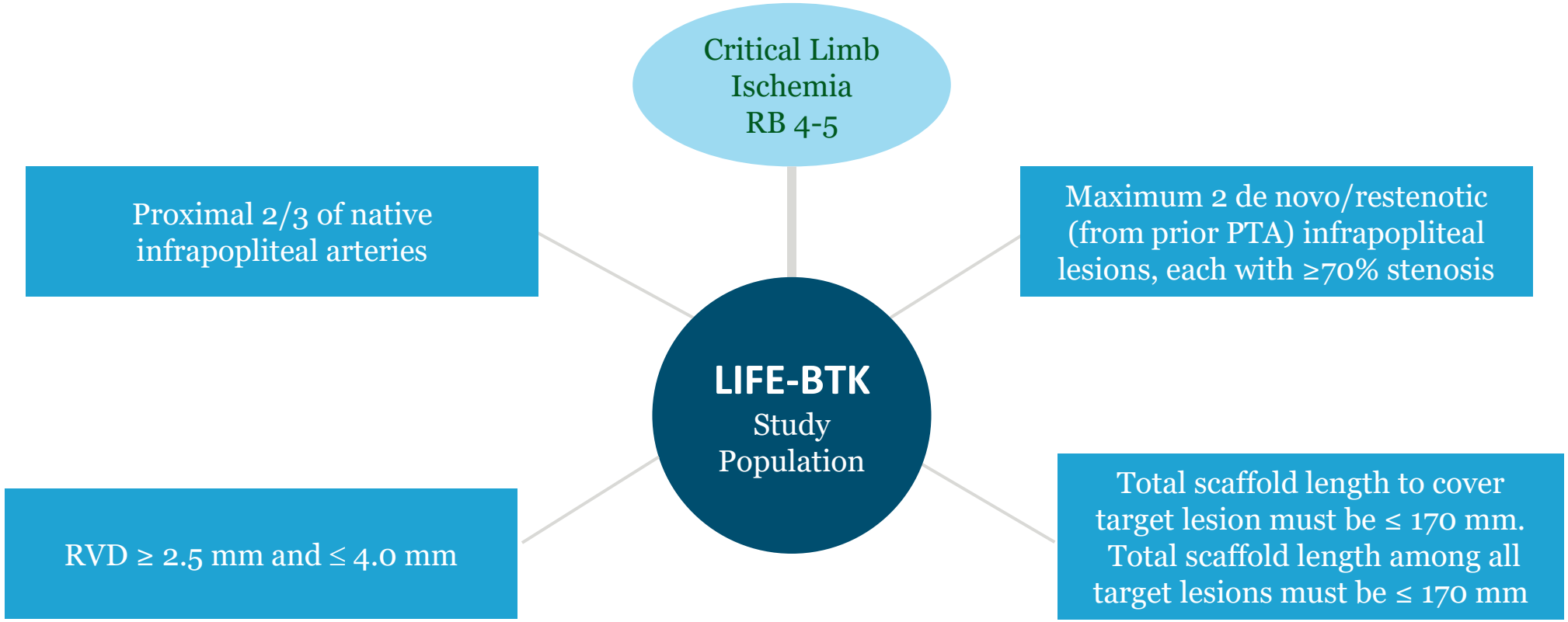
Efficacy Endpoint @ 12 months:
Primary Patency + Limb Salvage

5-YEAR FOLLOW-UP

TRIAL LEADERSHIP

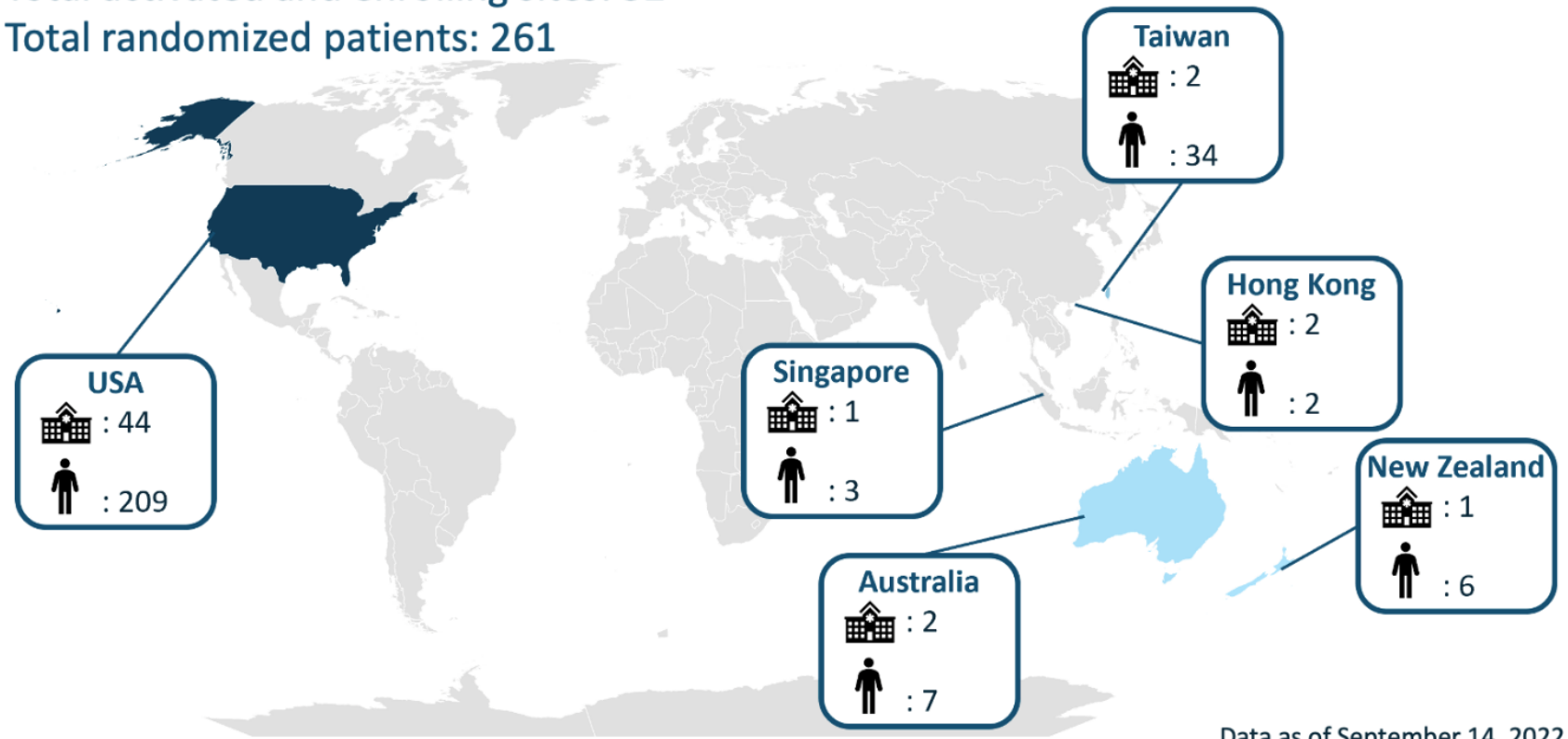
Ramon Varcoe MBBS, MS, FRACS, PhD; Sahil Parikh MD, FACC, FSCAI; Brian DeRubertis MD, FACS

LIFE-BTK Randomized Multicenter Trial



Bioresorbable Vascular Scaffolds: LIFE-BTK Trial

- Total activated and enrolling sites: 52
- Total randomized patients: 261



Data as of September 14, 2022

Bioresorbable Polymers for BRS

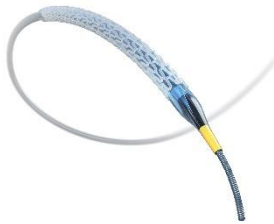
Tyrocore is the First Polymer Invented for BRS

Tyrocore Invented in Collaboration between REVA Medical & Rutgers University

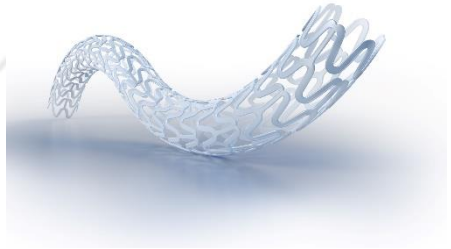
REVA

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

2nd and 3rd Generation Tyrocore BRS



Fantom



Fantom Encore & MOTIV BTK

All Other Players Use Off-the-Shelf Materials

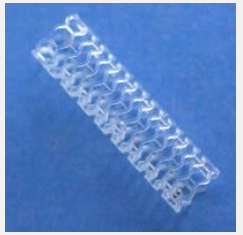
PLLA Used in Surgical Products

Bone Screws
Orthopedic Surgery

Thread
Plastic Surgery

1st Generation PLLA BRS

Absorb



DESolve

Courtesy Ehrin Armstrong, MD

MOTIV Bioresorbable Scaffold

Device Specifications Overview

MOTIV®
Sirolimus-Eluting Bioresorbable Vascular Scaffold System

Description	Bioresorbable BTK scaffold
Scaffold material	Tyrocore™
Coating material	Tyrocore
Drug	Sirolimus
Drug dose	1.97 µg/mm
Shortening	1% (lengthening)

Maximum expansion diameter

Size (mm)	Max Expansion (mm)
2.5	3.25
3.0	3.75
3.5	4.0
4.0	4.5

Catheter type		Rapid exchange
Guide catheter compatibility		6F
Working catheter length		139 cm
Scaffold lengths	*Current*	12, 18, 24 mm 36, 48, 60mm
Nominal pressure		7 atm
Rated burst pressure		18 atm
Balloon material		Nylon

Courtesy Ehrin Armstrong, MD

MOTIV™ Bioresorbable Scaffold
Preliminary Study Outcomes

- 99% Technical Success in all patients (71/72 Scaffolds)
- Primary Patency
  - **6-month final result: 90% Patency** *(N=47 patients/48 limbs)*[1]
- Clinically Driven TLR rate: 3% *(two events across all study patients)*
- Limb Salvage Rate: 97% *(across all study patients)*
  - *One patient had a lower leg amputation at ~1-month due to wound healing disorder; reported as unrelated to the MOTIV scaffold*
  - *One patient had an amputation of study limb at ~4 months due to a septic wound infection; reported as unrelated to the MOTIV scaffold*
- *8 deaths (14% of patients)*
  - *All deaths outside of 30d and **not device or procedure related***
  - *Heart & Respirtory Failure = 1, Septic Shock/Renal Failure = 4, Multi-Organ Failure = 3*

1. PSVR data for 40 patients (36/40 patent); 7 patients completed 6-month visit; no device related adverse events; PSVR not recorded
2. 29 patients have completed the 12-month follow up as of 20APR2022

Courtesy: Thomas Rand, CIRSE 2022

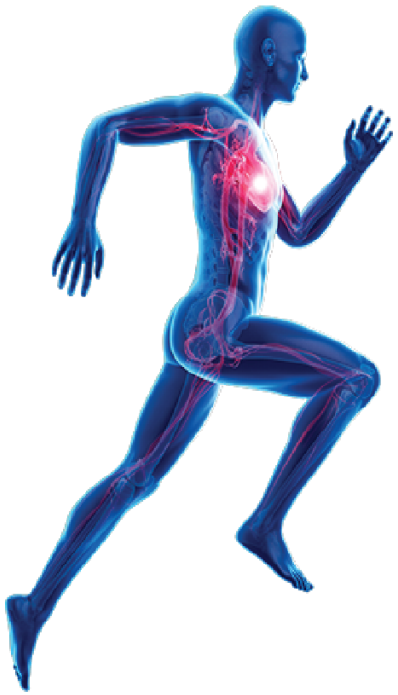
The R3 Vascular Drug-Eluting Bioresorbable Scaffold in Below the Knee Vessels: Interim Results from the RESOLV-I Trial

Prof. Marianne Brodmann, MD
Division of Angiology, Medical
University of Graz, Austria

MAGNITUDE® Sirolimus-Eluting BRS

Design Feature	Description
Polymer	Ultra High MW-Poly-L-Lactide (PLLA)
Diameters	3.0 and 3.5 mm
Lengths	18 and 38 mm
Wall Thickness	98 µm All Scaffold Sizes
Surface Coverage Area (at RBP)	22 – 27%*
Drug Coating	1:1 Poly D L-lactide:Sirolimus
Drug Content	144 – 291 µg*
Drug Density	96 µg/cm^2
Inflation Pressures	Nominal: 7 to 9 ATM* RBP: 16 ATM
Guide Catheter Size	6 French Compatible

*Depending on scaffold size



Courtesy: Marianne Brodmann, MD

6-Month Angiographic Core Lab Analysis

QCA Measurements Mean ± SD or % (Range)	*Baseline Procedure* (n = 21 Lesions)	*Post-BRS Implantation* (n = 21 Lesions)	*6-Month Follow-Up* (n = 9 Lesions)
In-Segment Analysis			
Interpolated RVD (mm)	3.20 ± 0.36 (2.47 – 3.87)	3.45 ± 0.31 (2.90 – 4.05)	2.85 ± 0.37 (2.20 – 3.26)
MLD (mm)	0.68 ± 0.37 (0 – 1.35)	2.95 ± 0.32 (2.25 – 3.45)	2.09 ± 0.68 (0.94 – 2.99)
Late Lumen Loss (mm)	---	---	0.57 ± 0.55 (-0.23 – 1.31)
Diameter Stenosis (%)	78.74 ± 10.83 (62.71 – 100)	14.31 ± 6.89 (3.90 – 27.88)	28.27 ± 16.86 (8.28 – 57.27)
Binary Restenosis (%, n)	---	---	11.1% (1)*
In-Scaffold Analysis			
MLD (mm)	---	3.07 ± 0.39 (2.25 – 3.64)	2.12 ± 0.69 (0.94 – 2.99)
Late Lumen Loss (mm)	---	---	0.62 ± 0.55 (-0.23 – 1.31)
Diameter Stenosis (%)	---	11.39 ± 7.51 (-0.83 – 27.88)	27.61 ± 17.21 (8.28 – 57.27)

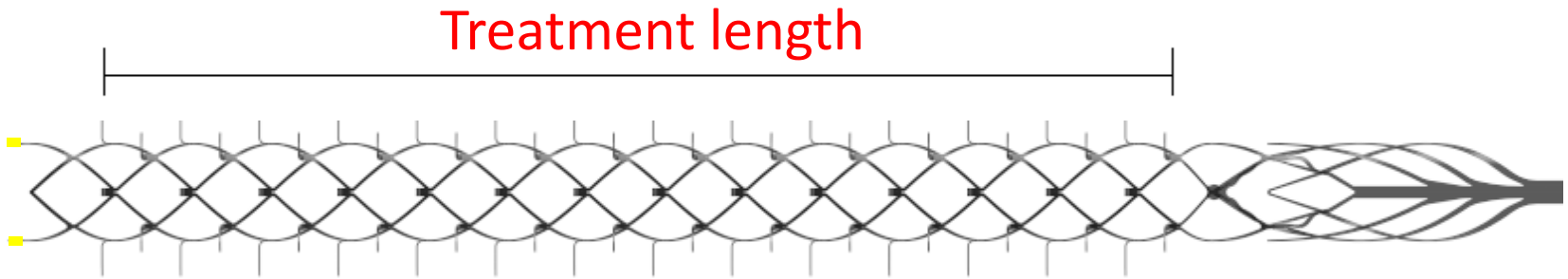
* 57% DS by core lab, asymptomatic, not treated

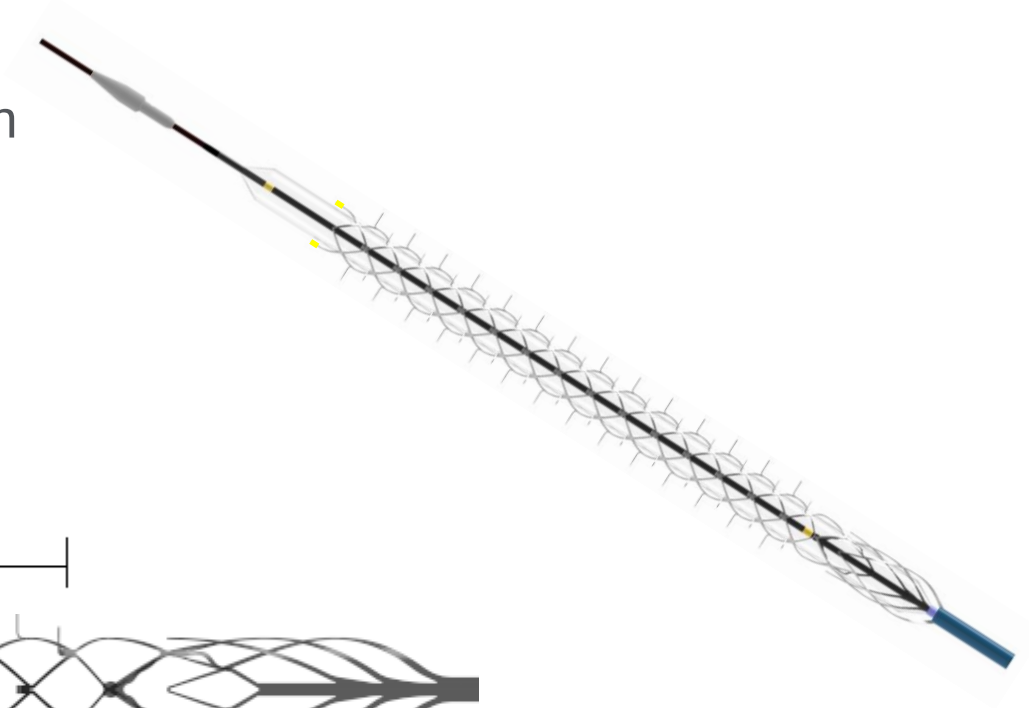
Courtesy: Marianne Brodmann, MD

Temporary Spur Stent System

SPUR Stent:

- Self Expanding Nitinol Frame w/integrated balloon
- Re-Capturable
- Available in 2 diameters (OD): 3mm, 4mm*
- Treatment Length ≈ 60mm
- Gold Radiopaque Markers



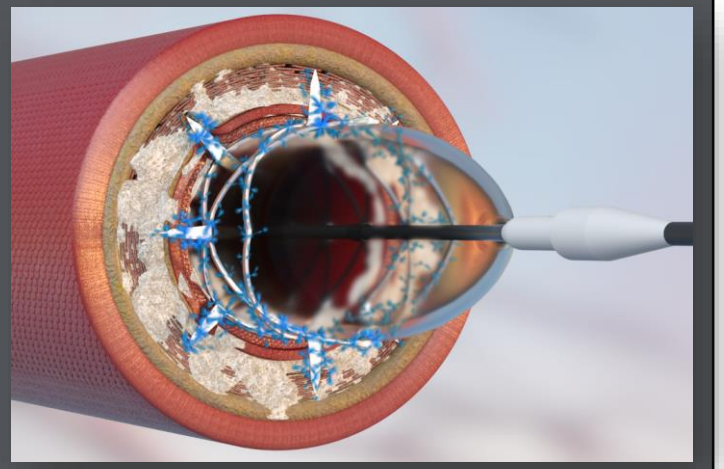


Reflow Medical's Temporary Spur Stent System*

*Under Clinical Investigation

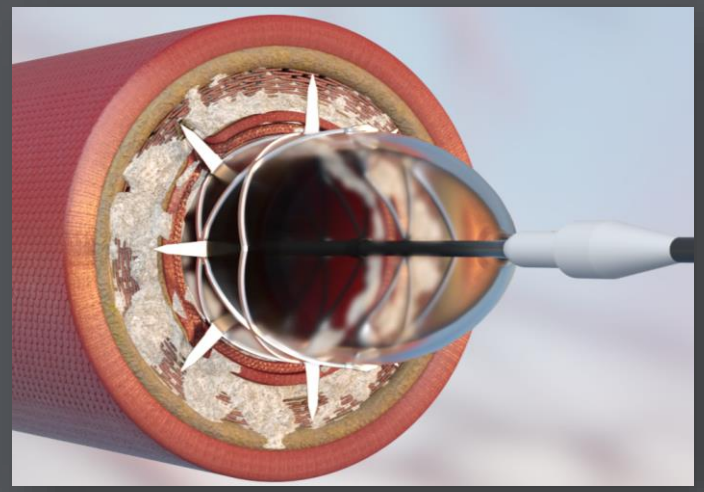
- 6F compatible sheath system
- Self-expanding temporary uncoated/drug coated nitinol stent on a balloon system
- Spikes enable controlled penetration of vessel calcification
  - Deeper drug delivery
    - **Uncoated, artery channel creation**
    - **Coated, drug deposited in artery channels**
  - Minimize recoil & dissections
- Minimal drug loss during transit (covered)
- Intended to deliver stent-like results while leaving nothing behind

Limus Drug Coated Spur Stent



Received FDA Breakthrough Designation: anticipated trial in 2022

Bare Spur Stent

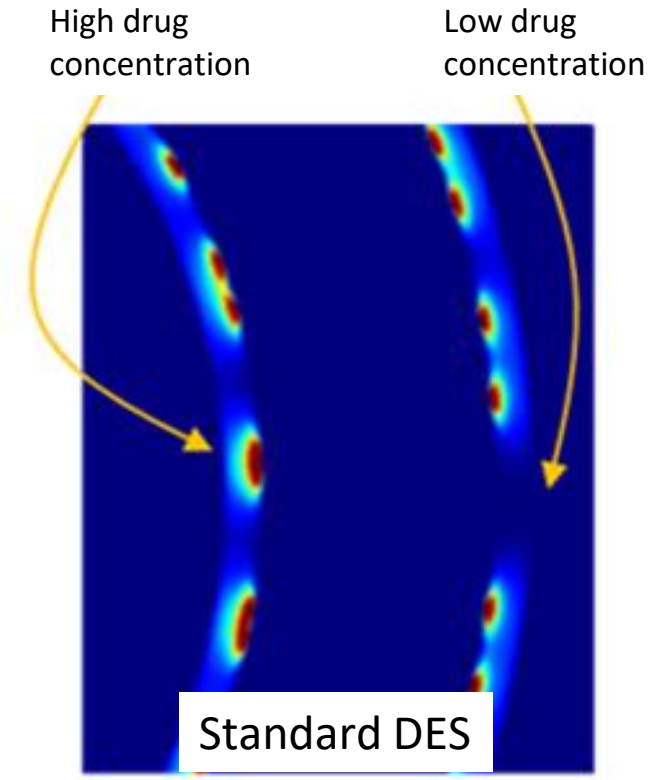


Currently being conducted OUS: DEEPER OUS and DEEPER LIMUS studies

Drug elution from stent struts

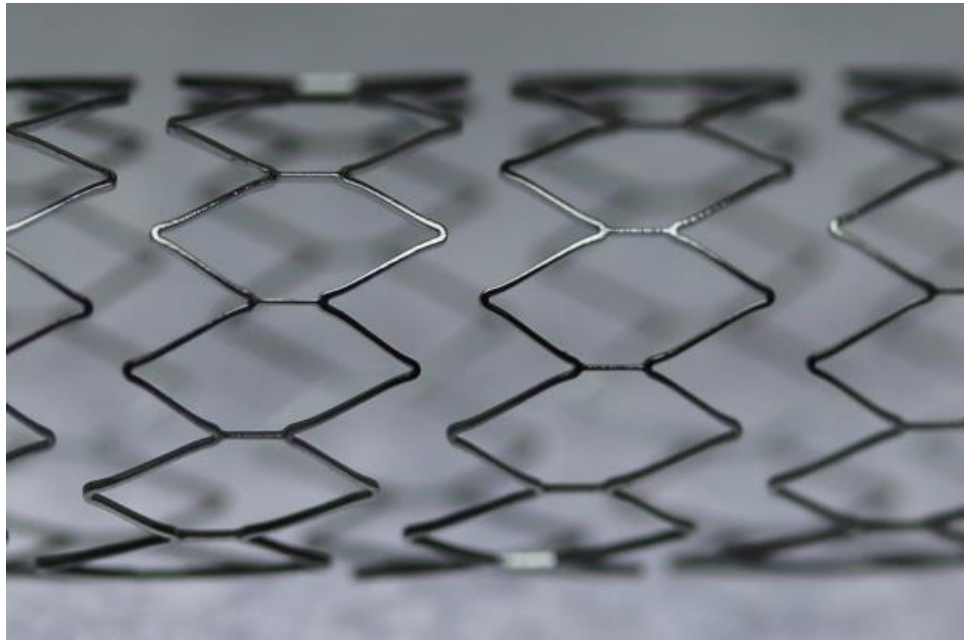
The problem: Drugs on DES (e.g. Sirolimus) have short diffusion distances

- Creates non-uniform drug distribution in vessel wall
- Requires high doses of drug that delay healing
- Sub-therapeutic drug levels in large arteries (e.g. SFA)



Courtesy: Yoram Richter, PhD, Medinol

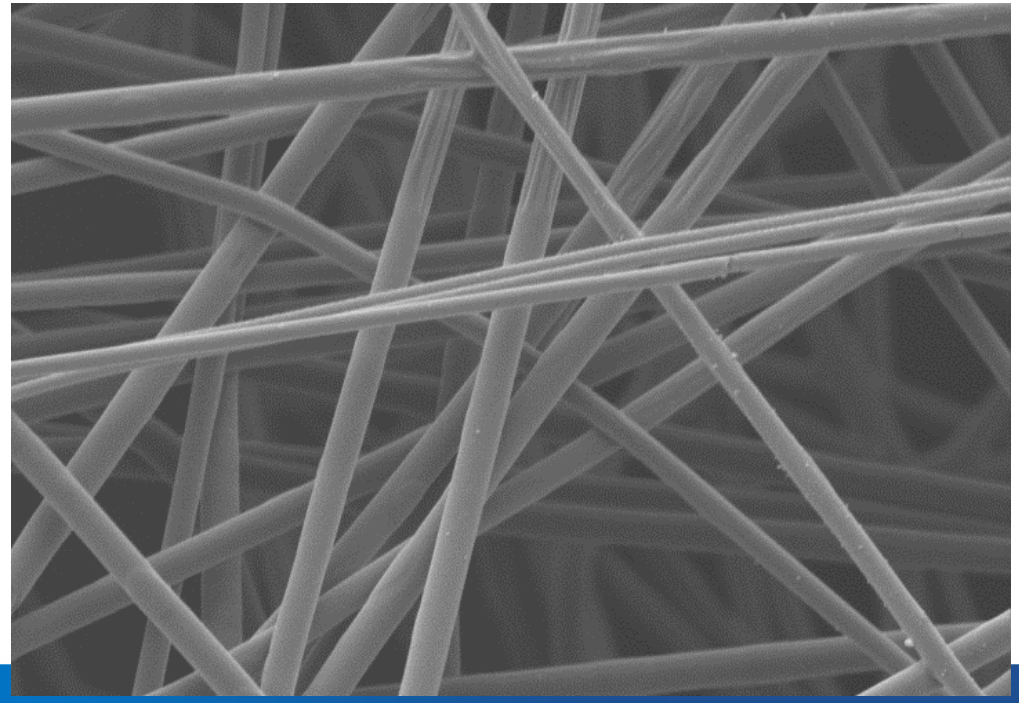
Hybrid Stent Components



Metal (NiTinol) radial structure for vessel support

- High radial strength
- Self-expanding spiral design

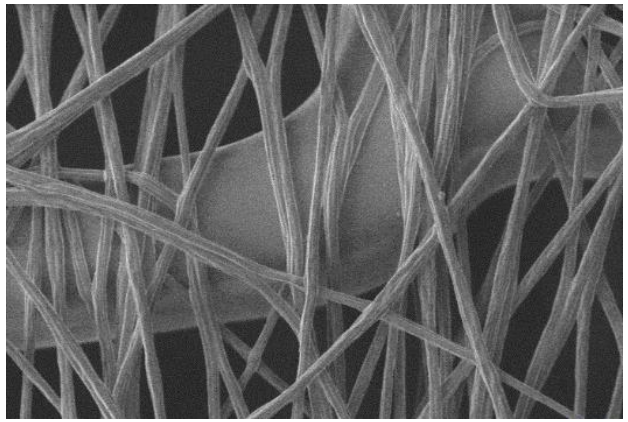
- Polymeric mesh covering for longitudinal stability
  - Infinite flexibility and fatigue resistance
  - Preservation of side branches and vessel compatibility

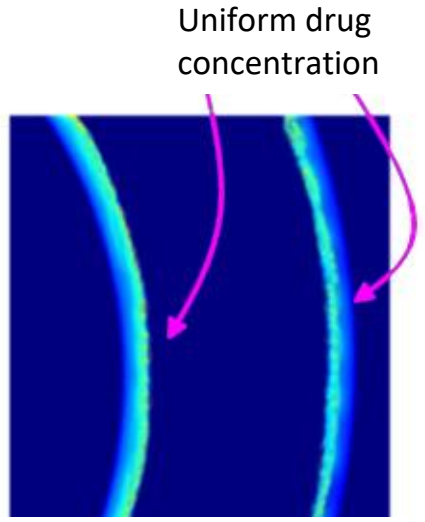


Courtesy: Yoram Richter, PhD, Medinol

Drug elution from stent envelope

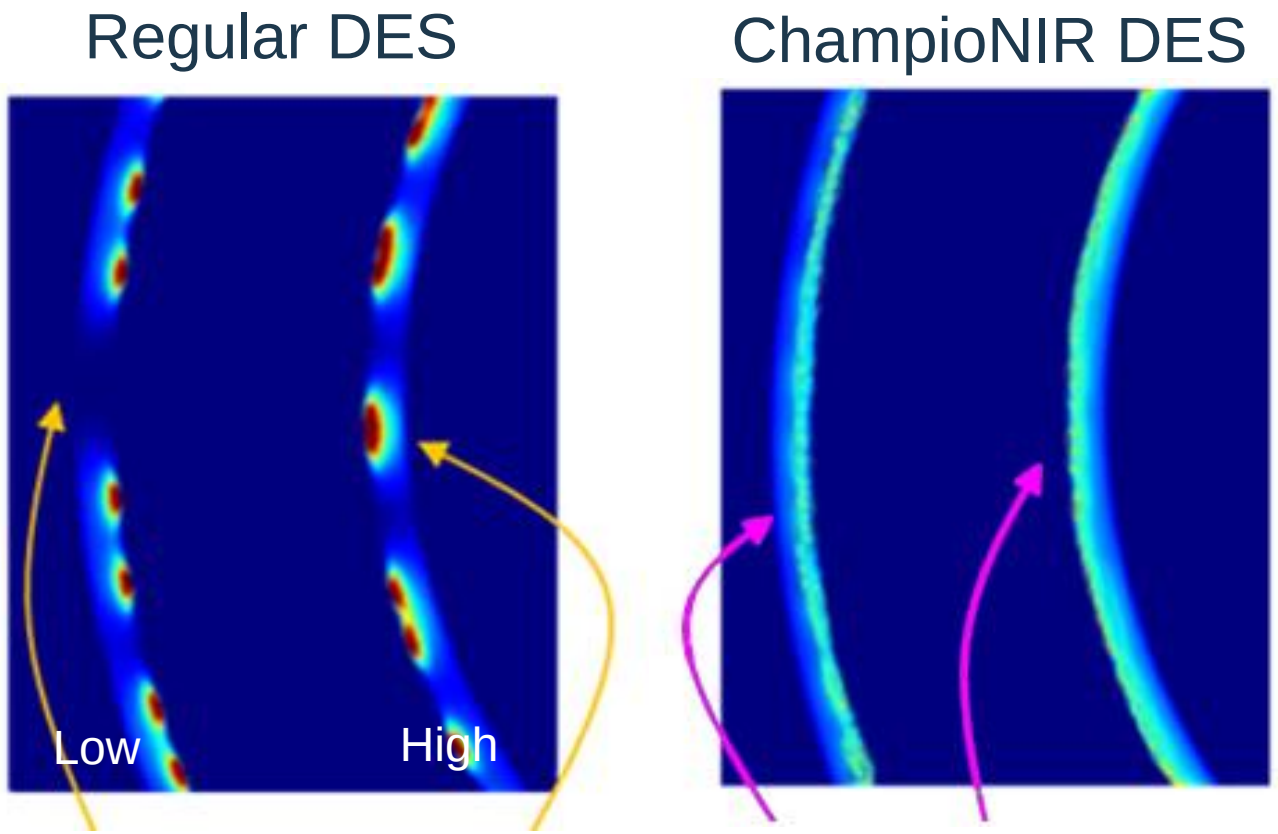
- The solution: Drug elution from fibrous mesh covering entire stent envelope
  - Short diffusion distance allows uniform drug distribution
  - Lower overall drug load
  - Therapeutic levels in every vessel size





Courtesy: Yoram Richter, PhD, Medinol

Area vs Point Elution



Spatially uniform dosing w/o regional gradients

Courtesy: Yoram Richter, PhD, Medinol

Clinical application

Coronary (IoNIR stent)

Improved local healing due to lower toxicity

4X reduction in total drug dose

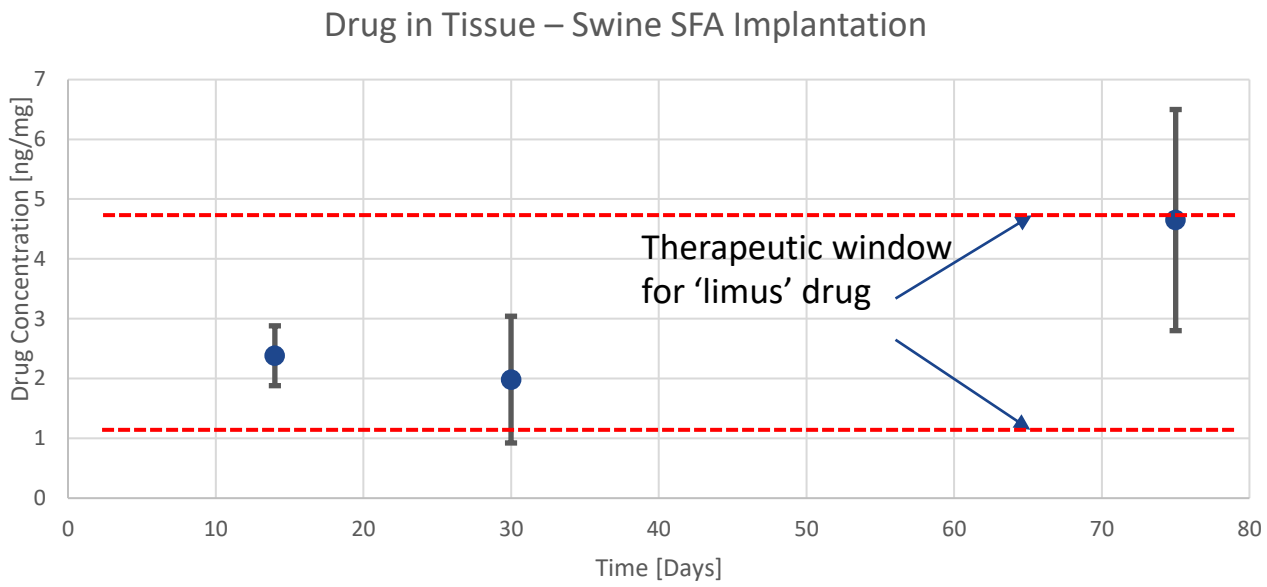
Total drug on 4.0X16mm stent [µg]	
EluNIR	115*
Synergy	125
Xience	98**
Onyx	132**
Orsiro	113**
IoNIR	31

FIM study (IonMAN) underway

* 17mm
** 15mm

Peripheral (ChampioNIR SFA stent)

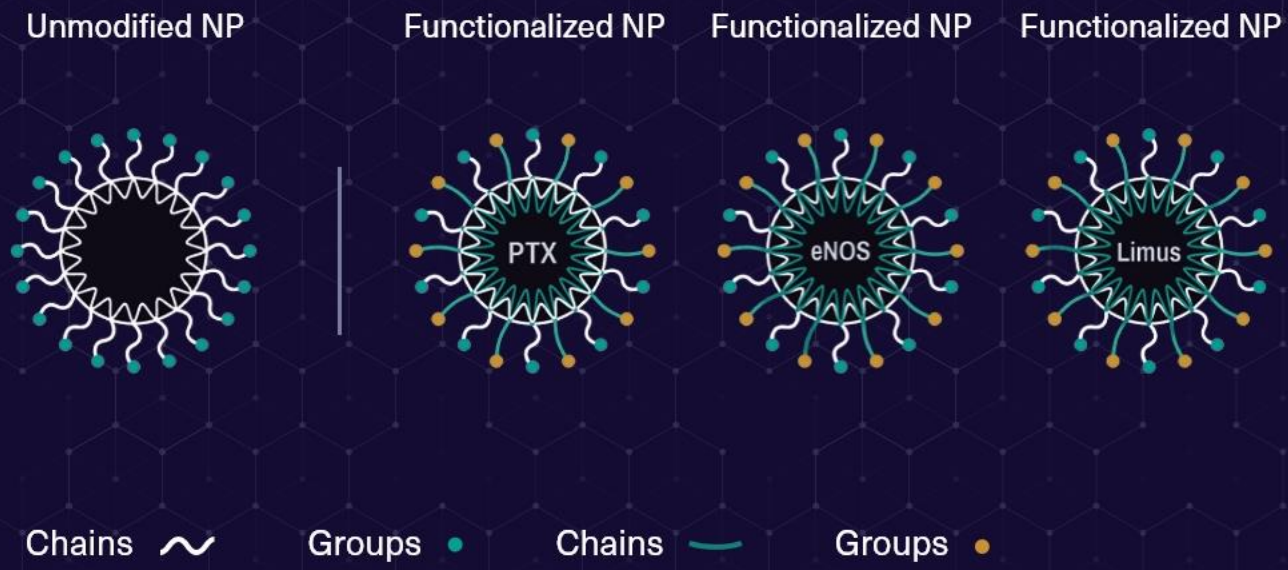
Therapeutic dosing with Sirolimus over time

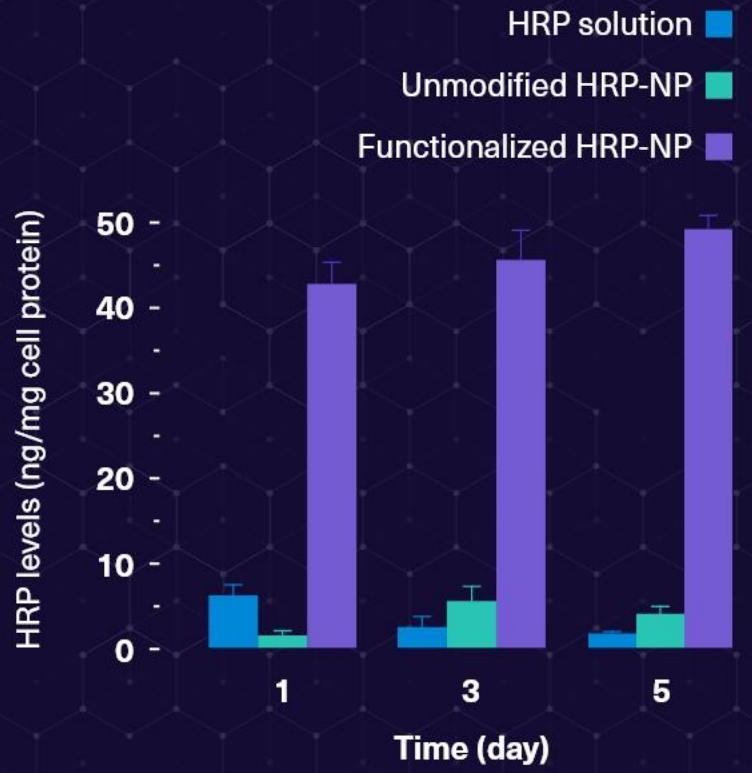


Courtesy: Yoram Richter, PhD, Medinol

Proprietary Functionalized Nanoparticle Technology

Functionalized Nanoparticle (f-NP) is a platform that enables and improves drug uptake and retention

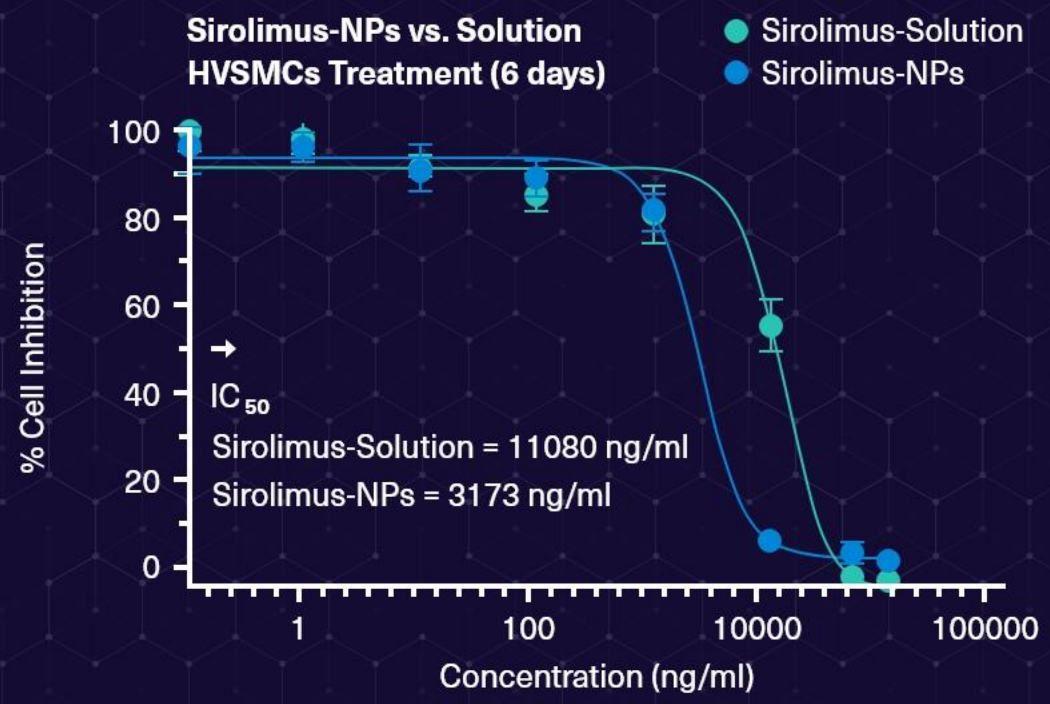


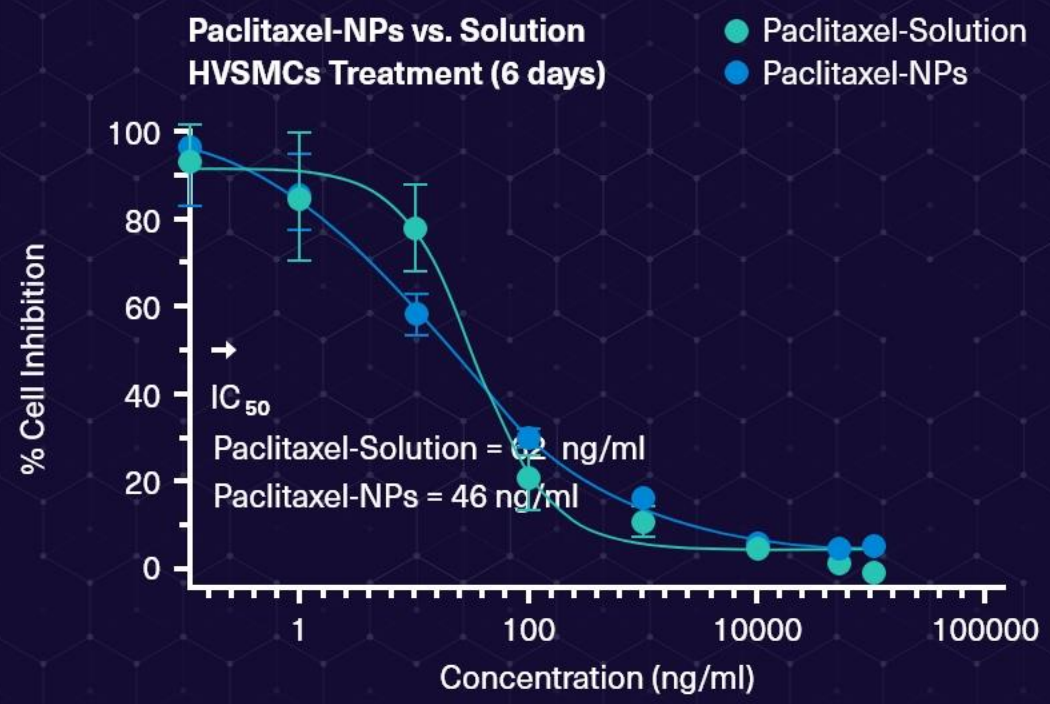


Courtesy: Mehdi Shishehbor, DO, PhD, MPH

Nanotechnology Does More With Less

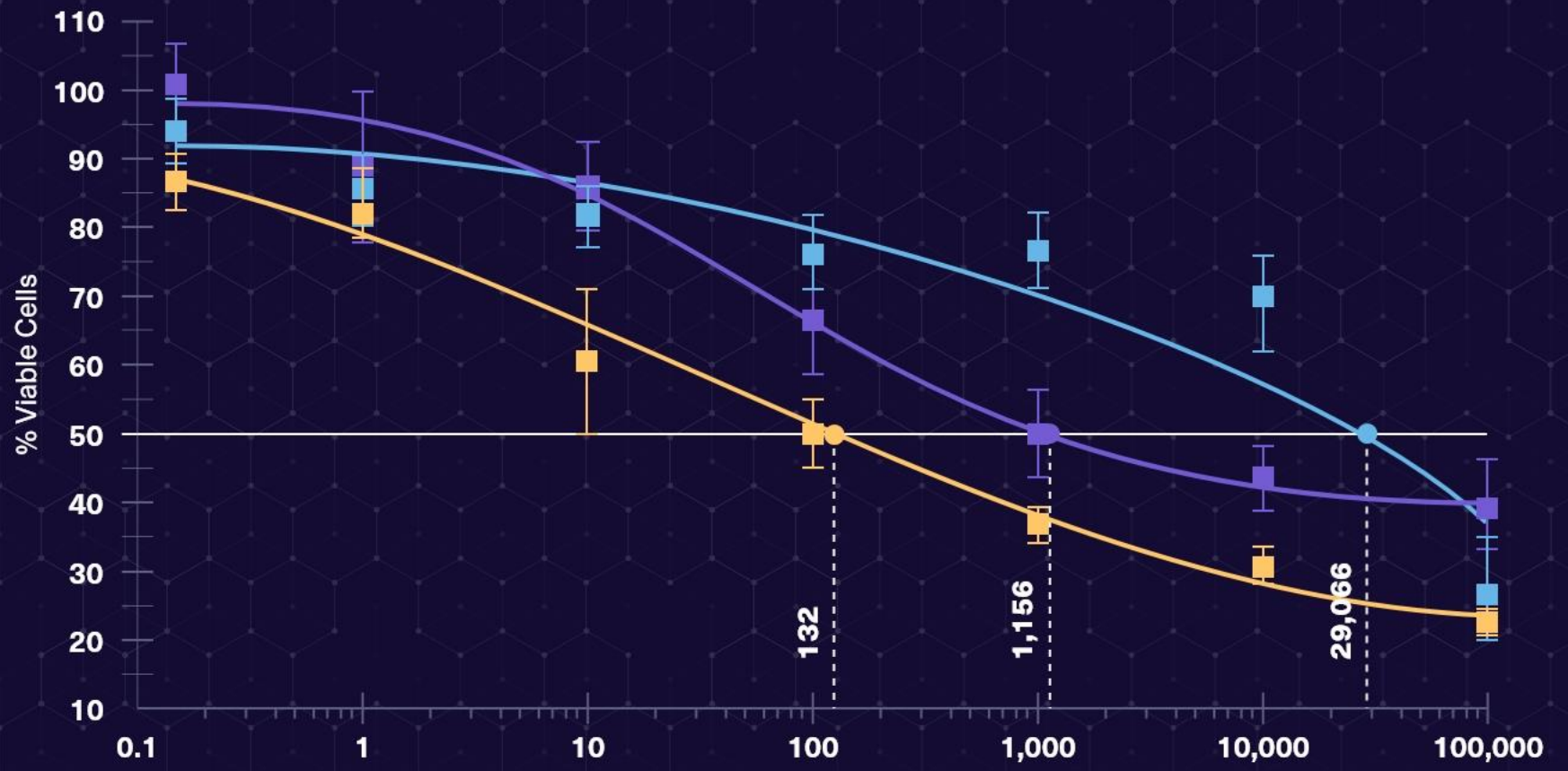
Encapsulated APIs Work Better - **encapsulated SIR and PTX have lower IC50 than in-solution**
(3x lower and 1.3x lower, respectively)





Courtesy: Mehdi Shishehbor, DO, PhD, MPH

Combination Dual Drug Treatment Demonstrates Powerful Results



Combined dual drug treatment achieves target viable cell results at lower dose than individual drugs separately

Paclitaxel

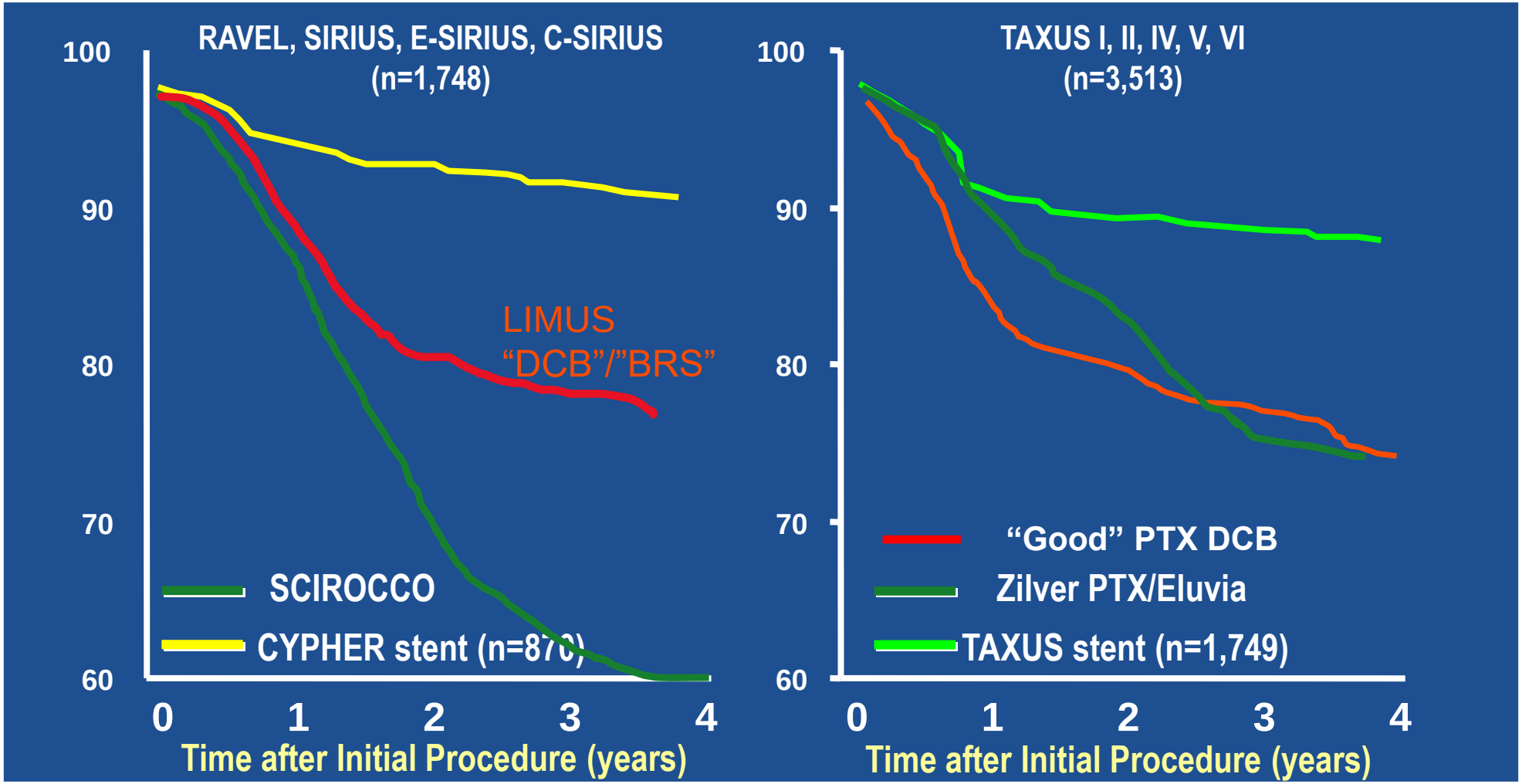
Sirolimus

SRL:PTX

*Data on graph displayed on a logarithmic scale

Courtesy: Mehdi Shishehbor, DO, PhD, MPH

Where are we with the data on Limus?



Spaulding C et al. *N Engl J Med.* 2007;356:989-997.
Adapted from: Stone GW et al. *N Engl J Med.* 2007;356:998-1008.

Summary

- Drug-eluting technologies (paclitaxel) remain the *de facto* standard of care for femoropopliteal disease
- Sirolimus and its analogues have demonstrated superior efficacy to paclitaxel in coronary intervention
- Due to differential binding and PK/PD in peripheral arteries, we've yet been unable to match these results in the SFA or BTK
- New formulations of sirolimus eluting devices have been developed for peripheral applications and are now ACTIVELY being studied against a variety of comparators – they likely represent a significant wave of innovation in local vascular drug delivery.