Cors at the Shore

June 24, 2023

Advances in Therapeutics for PAD and CLTI

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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.

Affiliation/Financial Relationship	Company
• Institutional Research Support	• Abbott, Boston Scientific, Shockwave Medical, TriReme Medical, Surmodics, Veryan Medical, MedAlliance, Concept Medical, Acotec
• Advisory Board	• Abbott, Medtronic, Boston Scientific, Cordis, Philips, BD, R3
• Consulting	• Terumo, Abiomed, Penumbra, Inari, Canon
• Equity	• Encompass Vascular, AdvancedNanotherapies, eFemoral

We will be discussing off-label applications of FDA approved and investigational devices.

Advances in Interventional Therapies for PAD

Cardiologists and PAD

Endovascular Intervention for PAD

- Anatomic Considerations
- Angioplasty & Stenting compared to Surgery

Why do Endovascular Interventions Fail?

- Restenosis Biology
- Lessons from Coronary Restenosis

Novel therapies in Peripheral Intervention

- Stent Design
- Local Drug Delivery

A Typical Case….

CC/ID: 57 yo male with prior CABG with progressive bilateral claudication

HPI: Worsening symptoms for past year now unable to keep up with his grandkids

PMH/PSH:

- CAD s/p CABGx 4 with LIMA to LAD→D1, SVG to OM, SVG to PDA
- Prior Gastric Bypass
- DM2
- HTN
- Dyslipidemia

SH: Active tobacco

FH: Mother with premature CAD, PAD

Intolerant of ASA due to gastric bypass

Meds:

- Vitamin B12 500 mcg daily
- Plavix 75 mg daily
- omeprazole 20 mg daily
- fluoxetine 40 mg daily
- iron 150 daily
- ramipril 10 mg daily
- metoprolol XL 100 mg daily
- Vytorin 80/10 mg daily

A Typical Case…. (courtesy of Dr. Barry Effron)

Physical Exam:

BP 120/70 bilaterally, HR 60, RR 12

Neck: Carotids 2+, no bruits, JVP 6

Chest: CTA&P

CVS: Quiet precordium, RRR S1 S2 no M/R/G

Abd: Soft, no bruits

Ext: dependent rubor with elevation pallor.

Pulses:	(R/L)
Femoral	1+/1+ no bruits
Popliteals	Trace/1+
DP	mono/biphasic dopplerable
PT	mono/biphasic dopplerable

Critical Reference

PAD Guideline Leadership and Structure

- Guideline Writing Committee (GWC) Leadership
  - Heather L. Gornik, MD, Chair
  - Herbert D, Aronow, MD, Vice-Chair
  - Philip P. Goodney, MD, MS, Vice-Chair
  - W. Schuyler Jones, MD, JCCPG Liaison
  - Thomas Getchius, AHA/ACC National Senior Director, Guidelines
- Broad representation of collaborating professional societies, disciplines, and specialties on the GWC
  - Vascular medicine, vascular surgery, interventional cardiology, interventional radiology, vascular nursing, cardiology/CV imaging, exercise physiology, podiatry, advanced practice nursing
  - 2 early career representatives and 2 patient representatives
- Scope of document – Atherosclerotic PAD of lower extremities
- Formal and rigorous process of disclosure and balancing the writing committee with respect to relationships with industry (RWI) and minimizing impact of RWI on guidelines (e.g., recusals from voting on relevant sections)

Coming Soon Fall '23

Courtesy: Heather L. Gornik, MD, ACC.23

Gerhard-Herman MD, et al 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease, Journal of the American College of Cardiology (2016), doi: 10.1016/j.jacc.2016.11.007.

STATE-OF-THE-ART REVIEW

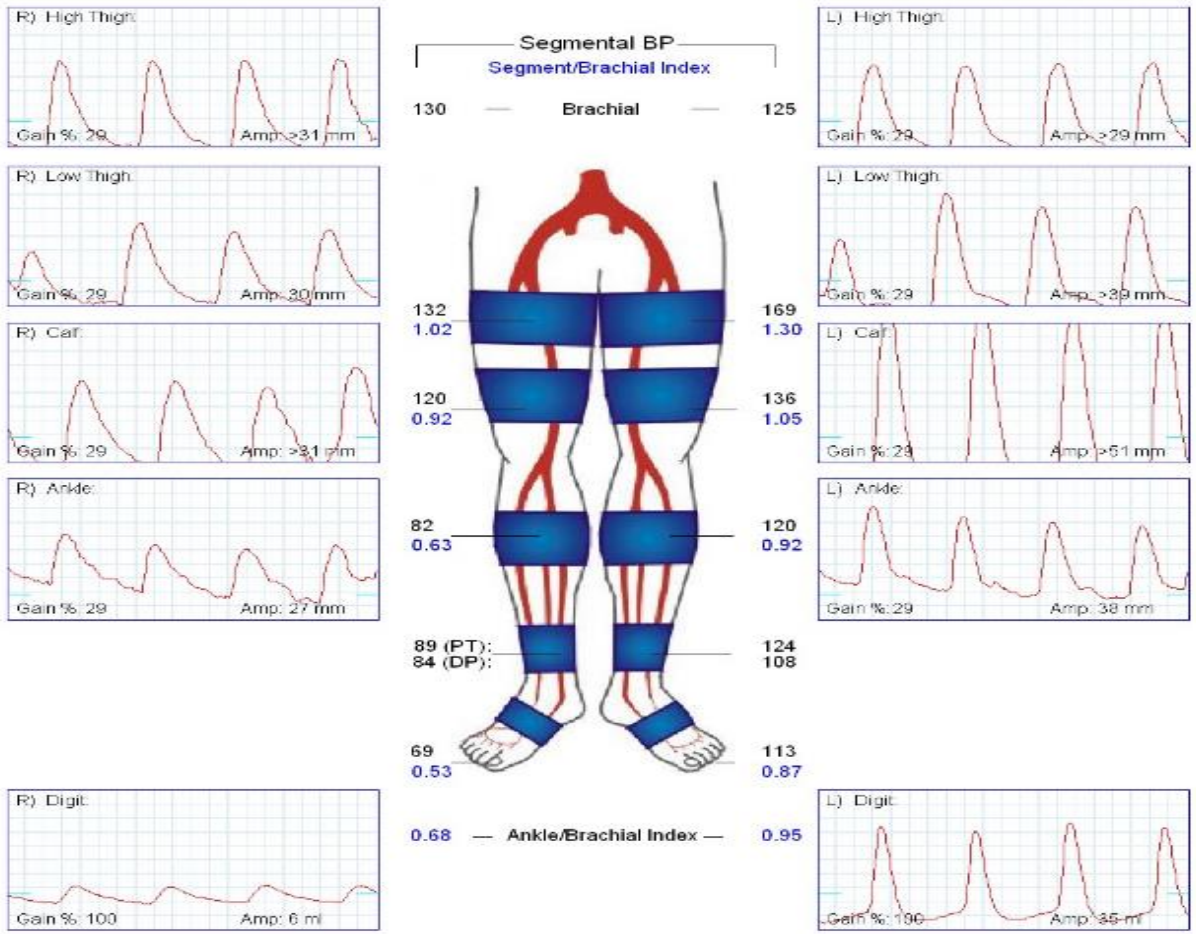
Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease

Consensus Definitions From Peripheral Academic Research Consortium (PARC)

Manesh R. Patel, MD,* Michael S. Conte, MD,† Donald E. Cutlip, MD,‡§ Nabil Dib, MD,‖ Patrick Geraghty, MD,¶ William Gray, MD,#** William R. Hiatt, MD,†† Mami Ho, MD, PhD,‡‡ Koji Ikeda, PhD,§§ Fumiaki Ikeno, MD,‖‖ Michael R. Jaff, DO,¶¶ W. Schuyler Jones, MD,* Masayuki Kawahara, MD,‡‡ Robert A. Lookstein, MD,## Roxana Mehran, MD,# ## Sanjay Misra, MD,*** Lars Norgren, MD,††† Jeffrey W. Olin, MD,## Thomas J. Povsic, MD, PhD,* Kenneth Rosenfield, MD,‡‡‡ John Rundback, MD,§§§ Fadi Shamoun, MD,‖‖‖ James Tcheng, MD,* Thomas T. Tsai, MD,¶¶¶ Yuka Suzuki, PhD,### Pascal Vranckx, MD,**** Bret N. Wiechmann, MD,†††† Christopher J. White, MD,‡‡‡‡ Hiroyoshi Yokoi, MD,§§§§ Mitchell W. Krucoff, MD*

Patel MR et al. JACC 2015

Noninvasive Evaluation: ABI, PVRs, Exercise

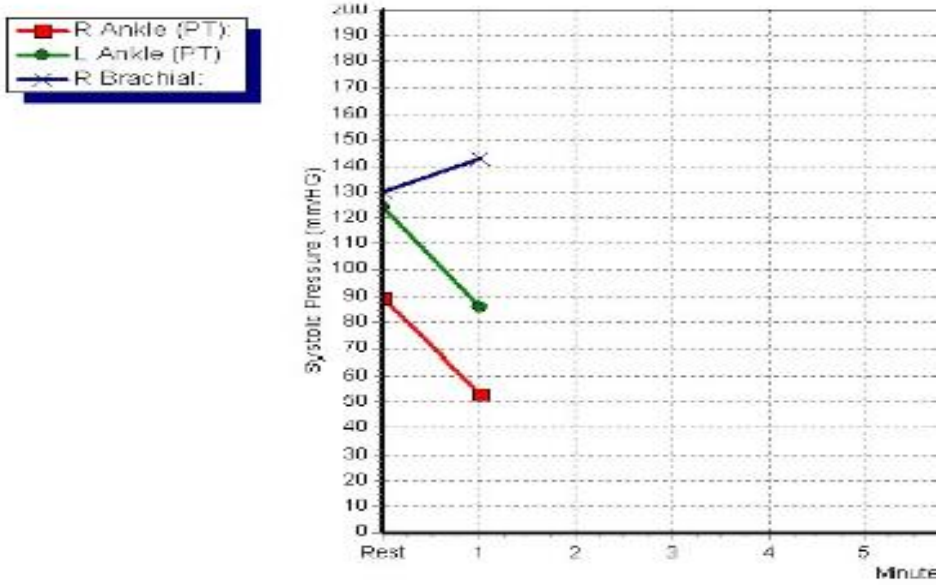


0.68→0.37

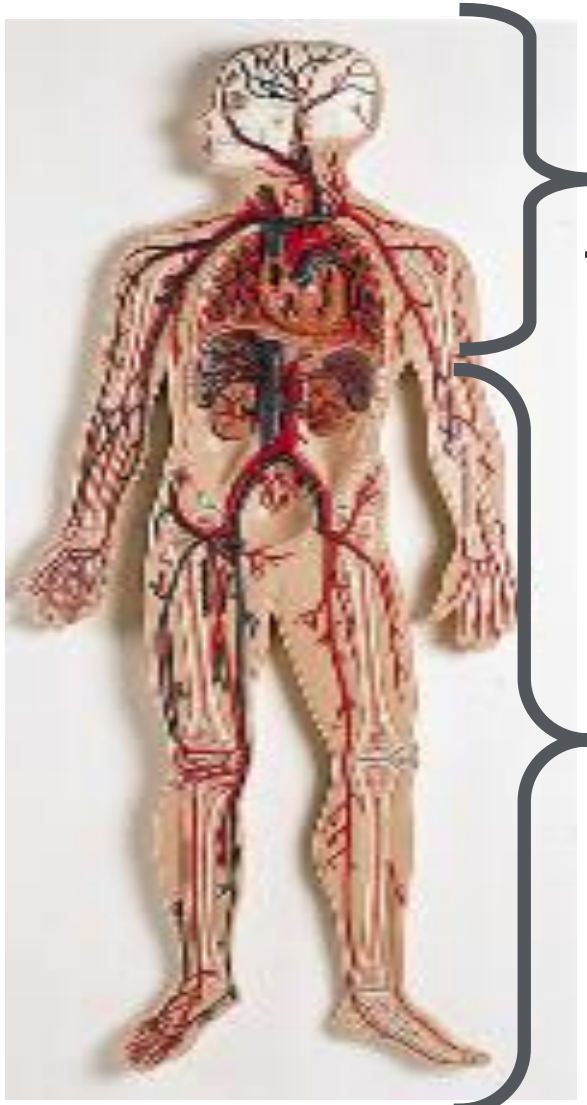
0.95→0.60

Exercise Pressure Measurement

	Rest	1	2	3	4	5
R Ankle (PT):	89	53				
L Ankle (PT):	124	86				
R Brachial:	130	143				
R ABI	0.68	0.37				
L ABI	0.95	0.60				



Therapies for PAD



Preventing Death, MI, Stroke
- Antiplatelets
- Cholesterol lowering – statins
- ACE Inhibitors

Reducing Symptoms
- Exercise
- Cilostazol
- Endovascular interventions
- Surgery

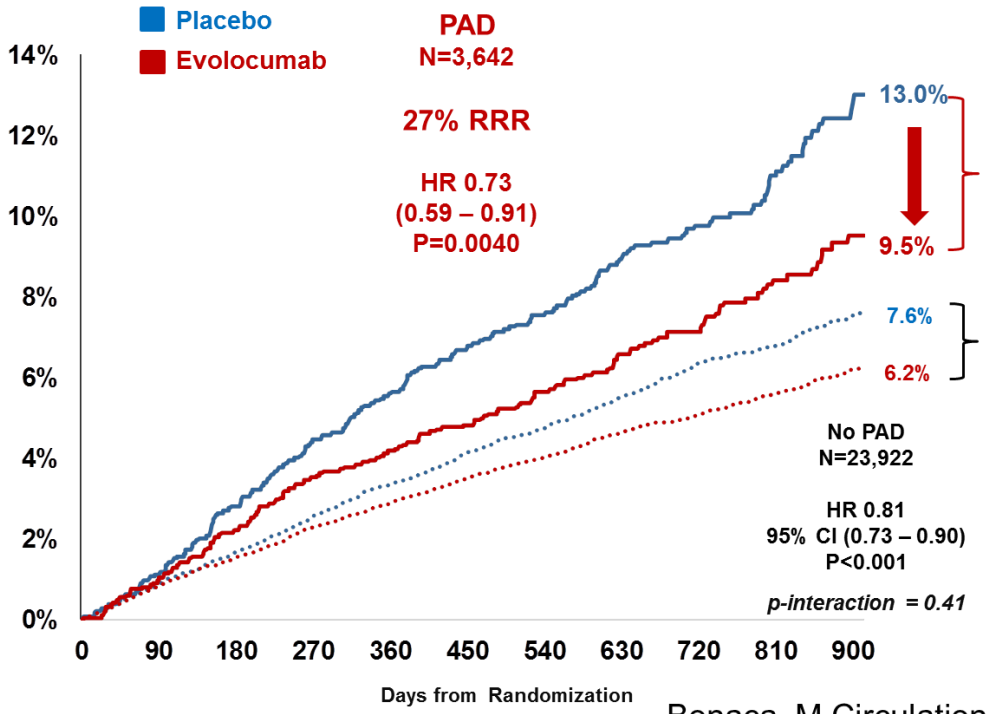
Saving Limbs
- Endovascular interventions
- Surgery

Risk Factor Guideline	Level of Evidence
Individuals should be advised by each of their clinicians to stop smoking and offered comprehensive smoking cessation interventions, including behavior modification therapy, nicotine replacement therapy, or bupropion.	I (A)
Treatment with a statin medication is indicated for all patients with PAD.	I (A)
Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death.	I (A)
Diabetes - reduce the hemoglobin A_{1C} to less than 7% may reduce microvascular complications and potentially improve cardiovascular outcomes.	II (A)
Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic/asymptomatic PAD.	I (A)/II (A)
Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.	II (B)
Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication.	I (A)
Supervised exercise training - minimum of 30 to 45 minutes, 3 times per week, minimum of 12 weeks.	I (A)

Intensification of Lipid Therapy in PAD

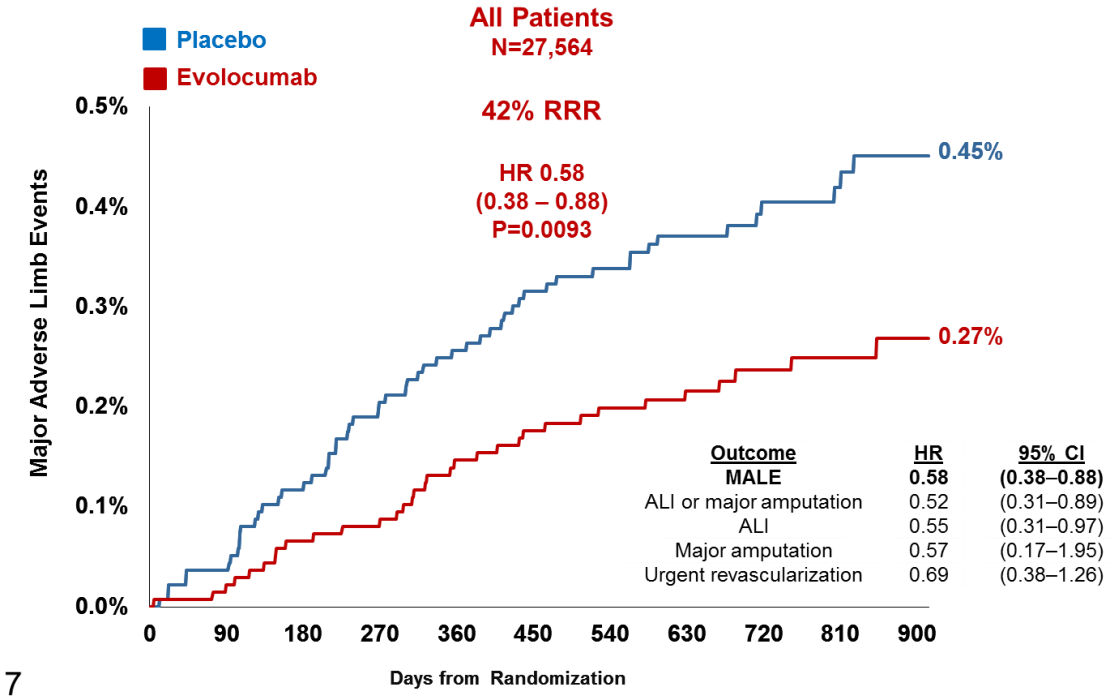
Evolocumab for LDL lowering and CV Events in PAD: Fourier Trial Analysis

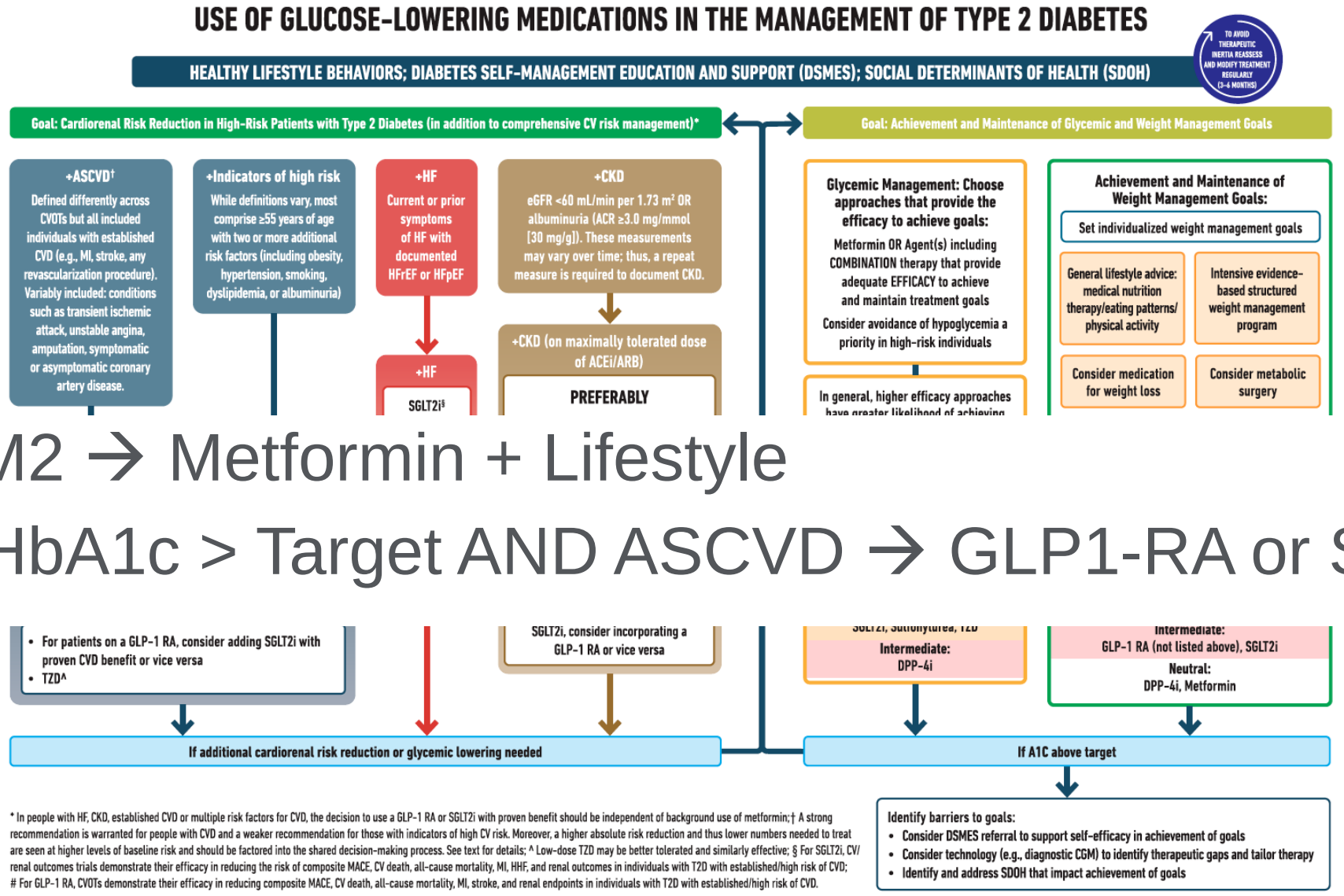
MACE



Bonaca, M Circulation 2017

MALE





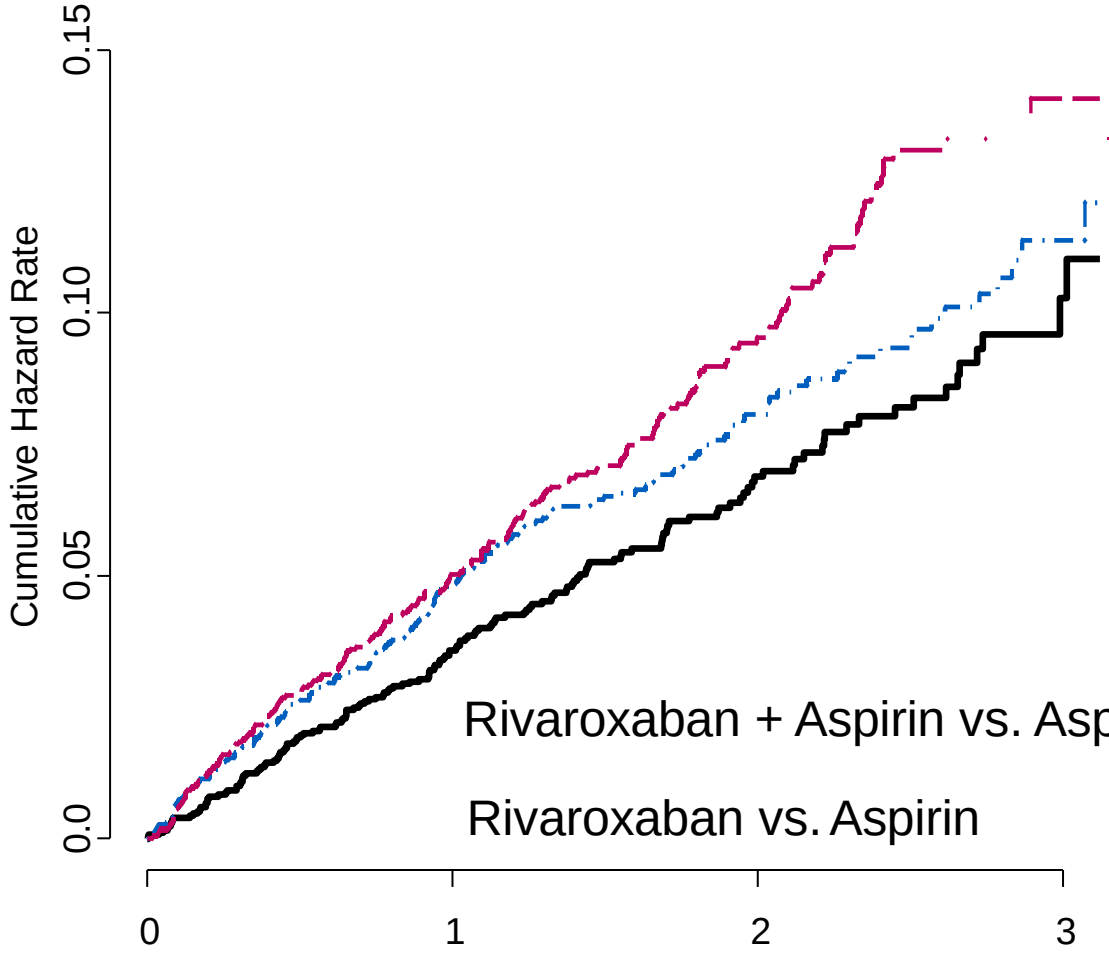
DM2 → Metformin + Lifestyle

If HbA1c > Target AND ASCVD → GLP1-RA or SGLT2

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

Diabetes Care 2023;46(Supplement_1):S140–S157
https://doi.org/10.2337/dc23-S009

MACE or MALE or Major Amputation



Rivaroxaban + Aspirin vs. Aspirin HR: 0.69 (0.56-0.85) P=0.0003

Rivaroxaban vs. Aspirin HR: 0.84 (0.69-1.02) P=0.08

No. at Risk				
Riva + ASA	2492	2069	893	124
Riva	2474	2023	864	147
ASA	2504	2034	911	113

Anand, et al. Lancet 2018; 391: 219–29

VOYAGER PAD

Trial Design

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg twice daily	*Stratified by Revascularization Approach (Surgical or Endovascular) and Use of Clopidogrel*	Placebo

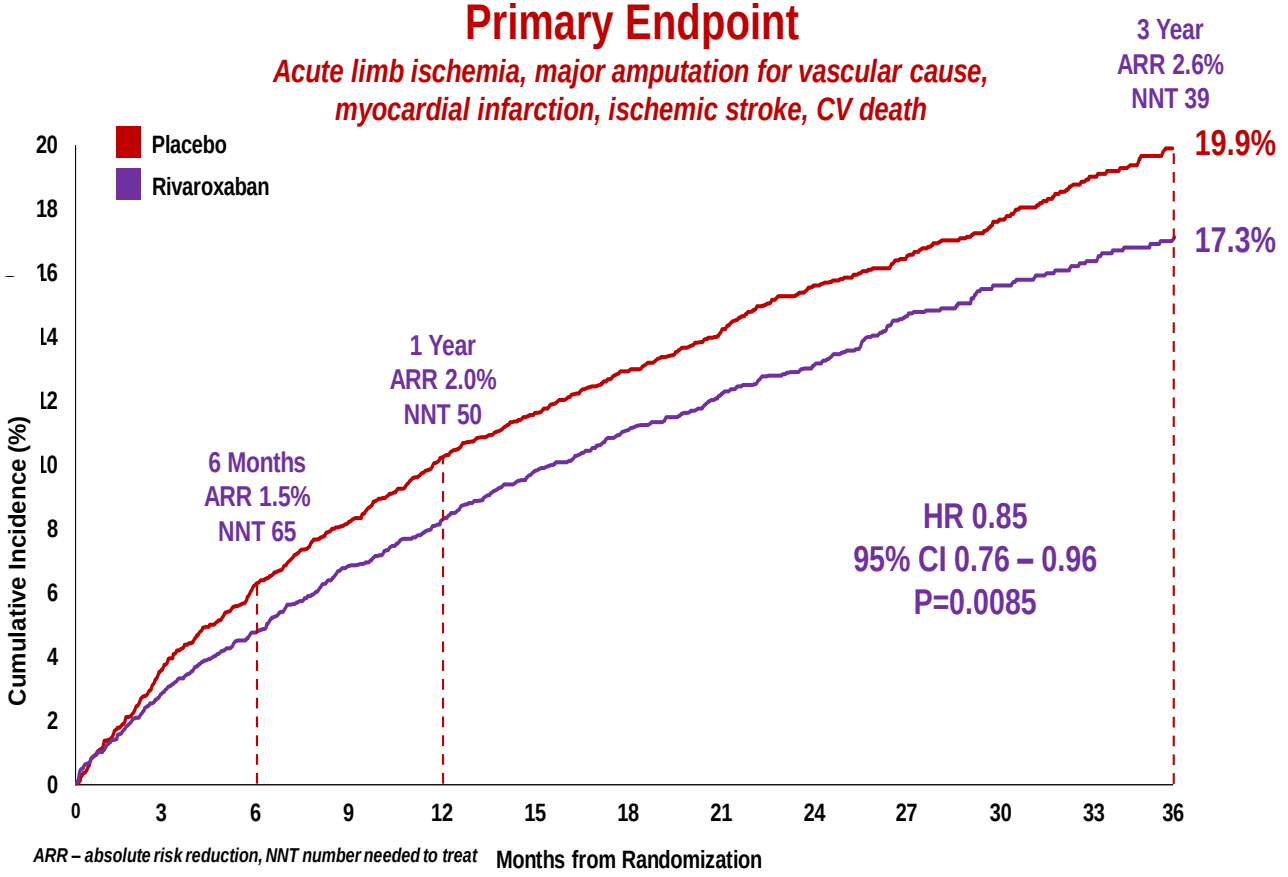
Follow up Q6 Months, Event Driven, Median f/u 28 Months

Primary Efficacy Endpoint: Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

Principal Safety Endpoint: TIMI Major Bleeding

Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



ARR – absolute risk reduction, NNT number needed to treat

Bonaca MP, et al. NEJM 2020

VOYAGER PAD

COLUMBIA NewYork-Presbyterian

Exercise Intervention is the Initial Therapy for PAD

May 2017: CMS Covers SET for PAD

4/28/2017 Insurers weigh a simpler treatment for artery disease: supervised workouts

STAT

Insurers weigh a simpler, cheaper treatment for artery disease: supervised workouts

By Eric Boodman @ericboodman

March 20, 2017

AP/Stock

When Char Zinda's doctors discovered that she had had a couple of small, undiagnosed heart attacks, their instructions were to start walking.

She was game. She tried going to the local university's indoor walking track near her house. But she couldn't even walk two tenths of a mile before her legs began to hurt — a lot. Sometimes the pain was in her ankles, sometimes in her calves, sometimes in her thighs. "It made me cry," said the 64-year-old, who lives in Morris, Minn.

That was a telltale sign of peripheral artery disease, which affects an estimated 8 million Americans. Zinda had a number of treatment possibilities, but the cheapest and least invasive has generally not been covered by insurance, despite years' worth of evidence that it can be as effective as other options.

That is on the cusp of changing, experts say, because of a long-awaited proposal from the Centers for Medicare and Medicaid Services to cover what's known as supervised exercise therapy — a program of graduated exercise with the help of an exercise physiologist, which is currently covered after certain kinds of cardiac events, but not for PAD.

- Improves exercise performance, walking ability, physical functioning, and QOL
  - Up to 180%↑PFWD (180 meters) [2,3,4]
  - 120-150%↑MWD (128 meters) in meta-analyses[2,3,4]
  - Improved quality of life SF-36 physical component summary scores[1,5]
- Highly cost-effective when compared to catheter-based revascularization[6]
- Alternate home-based approaches may overcome patient barriers
- Augments effect of intervention

[1]Stewart KJ, et al. N Engl J Med. 2002;347:1941.
[2]Gardner AW, et al. JAMA 1995;274:975.
[3]Leng GC, et al. Cochrane Review 2000. CD000990.
[4]Fakhry F, et al. J Vasc Surg 2012;56:1132.
[5]Parmenter BJ, et al. Vasc Med 2015.
[6]Treesak C, et al. Vasc Med. 2004 9:279.

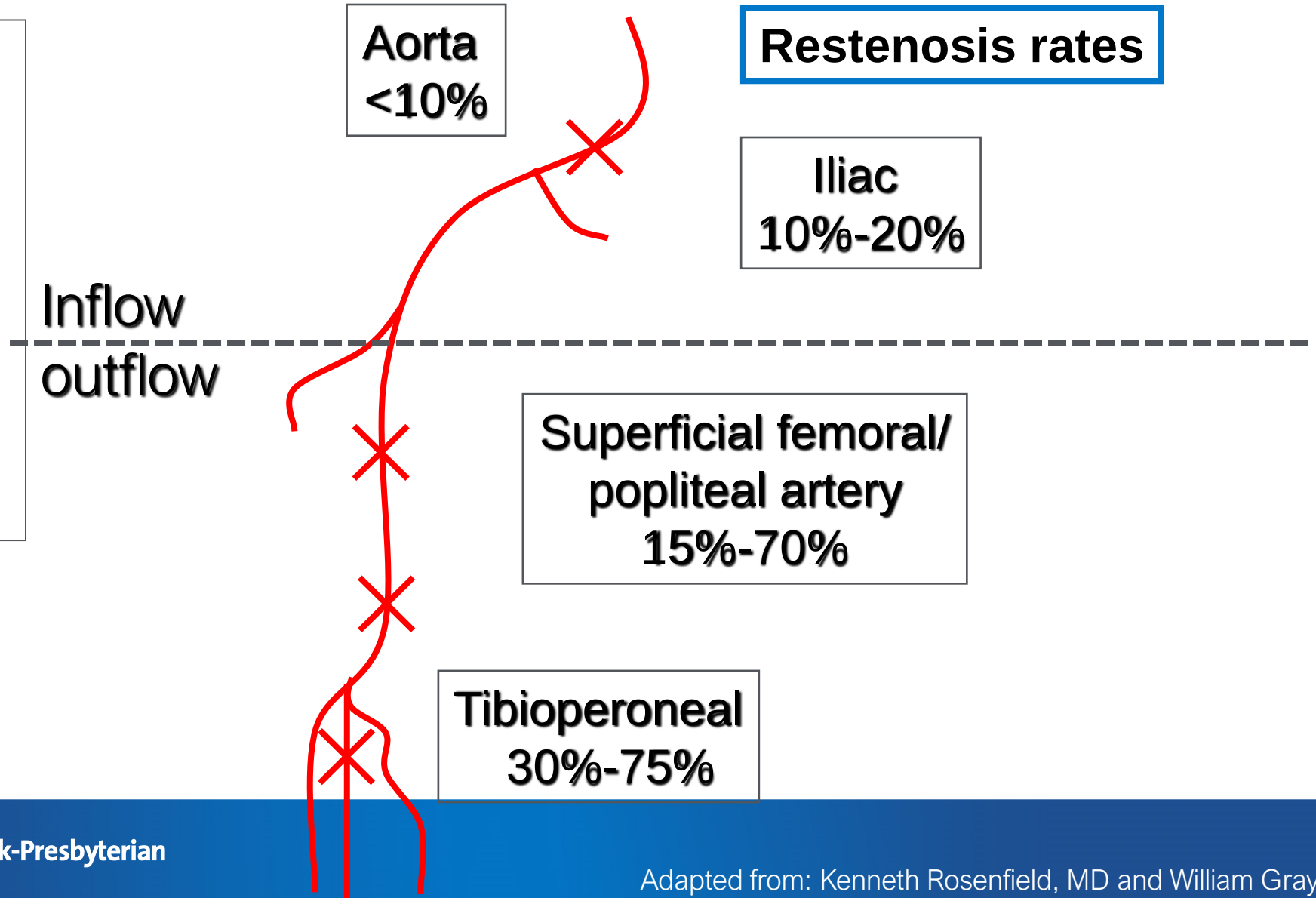
Peripheral Arterial Disease: Indications for Revascularization

	Analogy	Outcome	Urgency
Claudication • Disabling • Lifestyle limiting	ANGINA	PATENCY (QOL/WIQ)	Whenever
Chronic Limb Threatening Ischemia • Tissue loss/ischemia • Rest pain • Refractory infection	ACS	LIMB SALVAGE (AFS/Wound Healing)	NOW!!

“Inflow” versus “Outflow”
Factors influencing threshold for intervention

Principles

- Fix inflow first
- Prox revasc=
  - ⬆ Tech success
- Distal revasc=
  - ⬆ Tech difficulty
  - ⬆ Restenosis
- For healing ulcers, must restore straight-line flow to foot



Adapted from: Kenneth Rosenfield, MD and William Gray, MD

8.1. Revascularization for Claudication: Recommendation

Recommendation for Revascularization for Claudication		
COR	**LOE**	**Recommendation**
IIa	**A**	**Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to GDMT (12, 37, 38, 232, 233).**
See Online Data Supplements 35 and 36.		A minority of patients with claudication (estimated at <10% to 15% over 5 years or more) will progress to CLI (234-237). Therefore, the role of revascularization in claudication is improvement in claudication symptoms and functional status, and consequently in QoL, rather than limb salvage. Revascularization is reasonable when the patient who is being treated with GDMT (including structured exercise therapy) presents with persistent lifestyle-limiting claudication (12, 37, 38, 232, 233). Lifestyle-limiting claudication is defined by the patient rather than by any test. It includes impairment of activities of daily living and/or vocational and/or recreational activities due to claudication. There should be clear discussion with the patient about expected risks and benefits of revascularization, as well as discussion of the durability of proposed procedures.

Gerhard-Herman MD, et al 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease, Journal of the American College of Cardiology (2016), doi: 10.1016/j.jacc.2016.11.007.

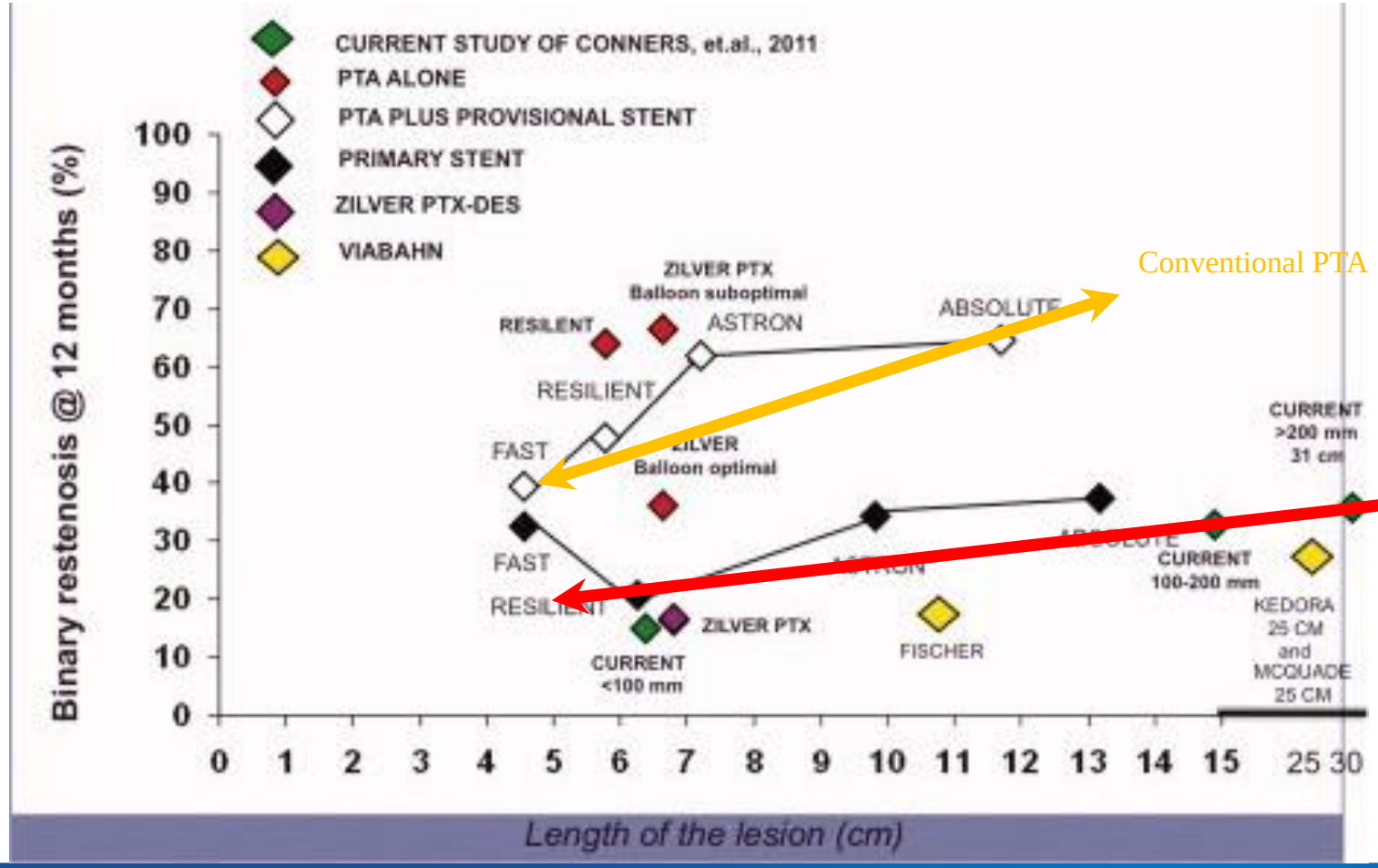
ABOVE-knee femoral popliteal bypass 5-year patency

Inter-Society Consensus for the Management of PAD

Table 3. The 5-year patency of different types of conduits	
Vein	74–76%
ePTFE Graft	39–52%

AbuRahma *et al, 1999; Green et al, 2000; Johnson and Lee, 2000; Klinkert et al, 2003*

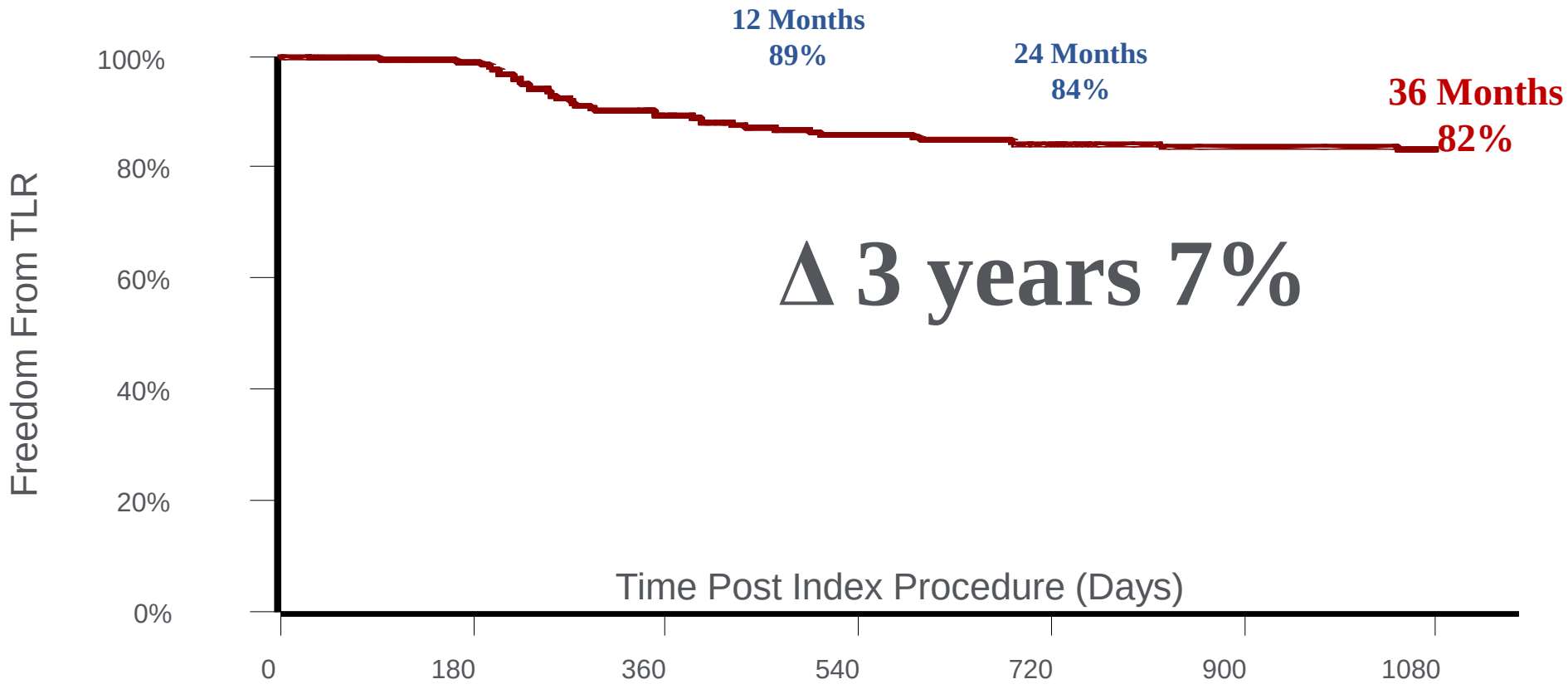
After Endovascular Intervention, SFA Patency Decreases with Lesion Length for PTA and "Conventional Stenting"



Slope of relationship between length and restenosis is steeper for PTA compared to stenting

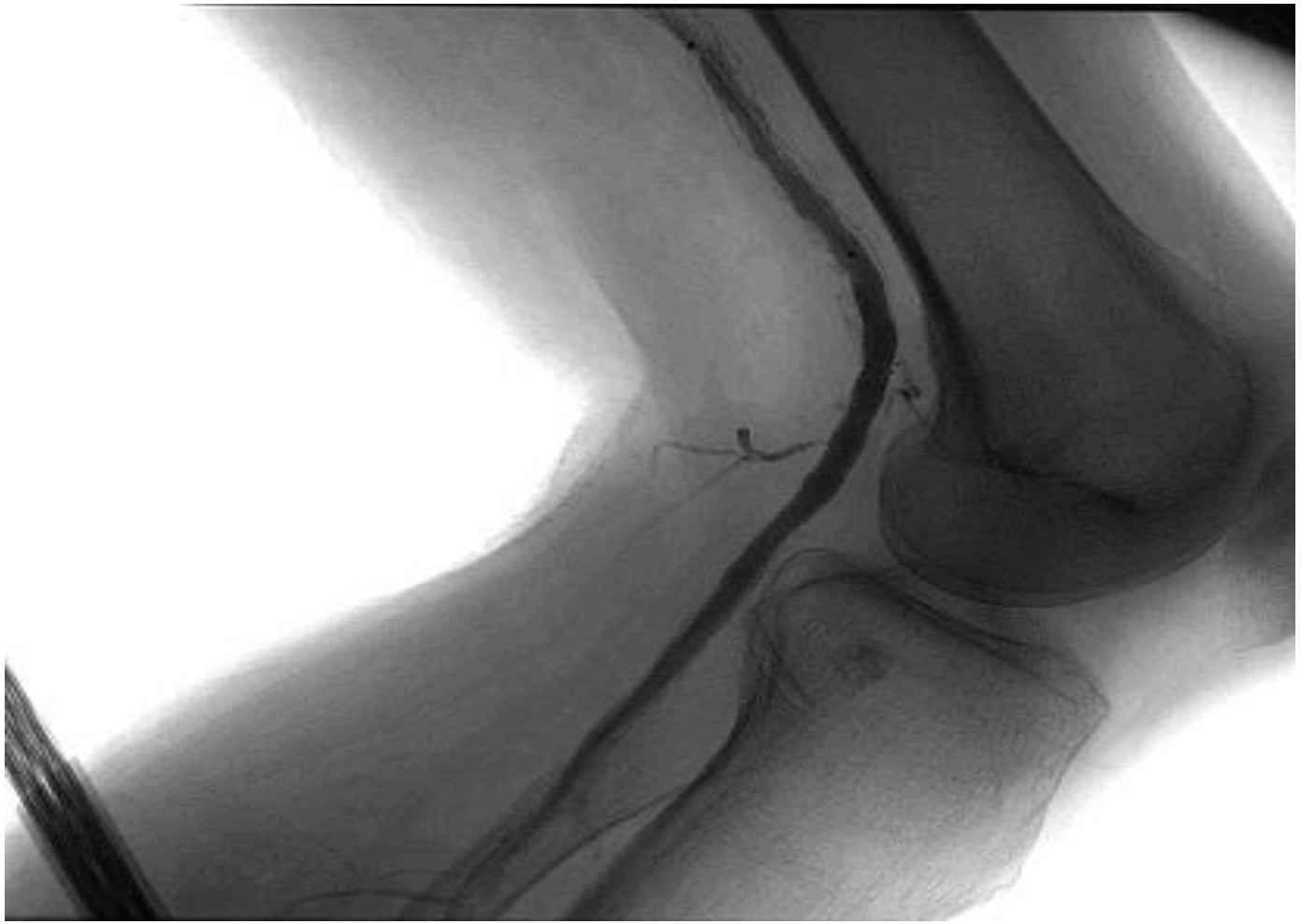
Gray B. CCI. 2011

SUPERA: Freedom From Clinically Driven TLR Through 3 Years



Courtesy: Lawrence Garcia, MD, VIVA 2014

Supera Stent: Bent Knee Lateral

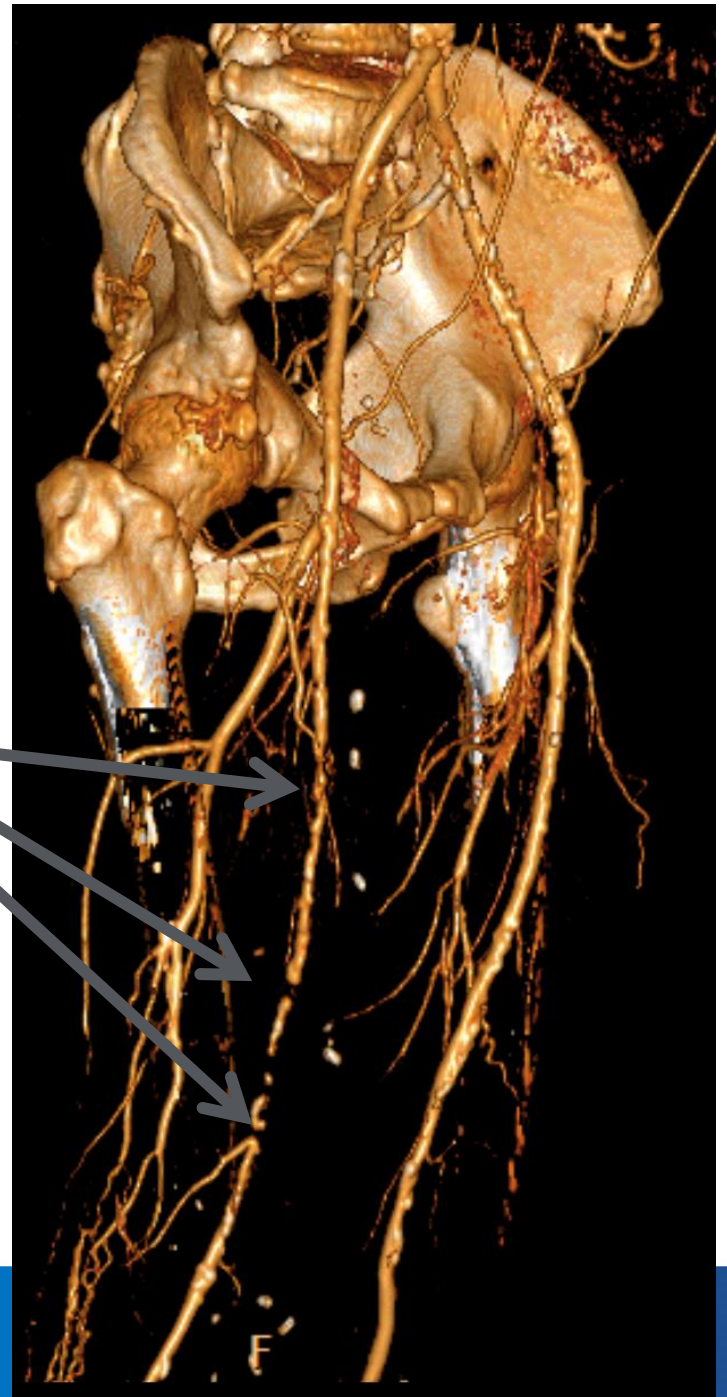


Bent knee lateral view

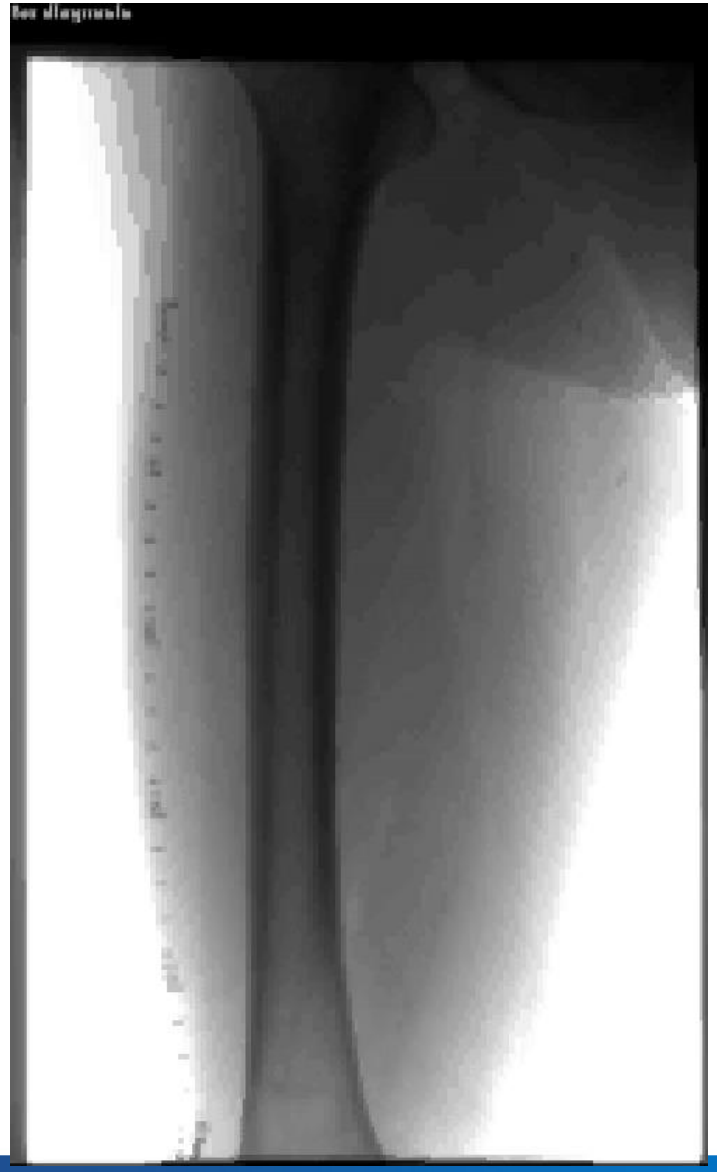
Courtesy: S. Parikh, MD, FACC, FSCAI

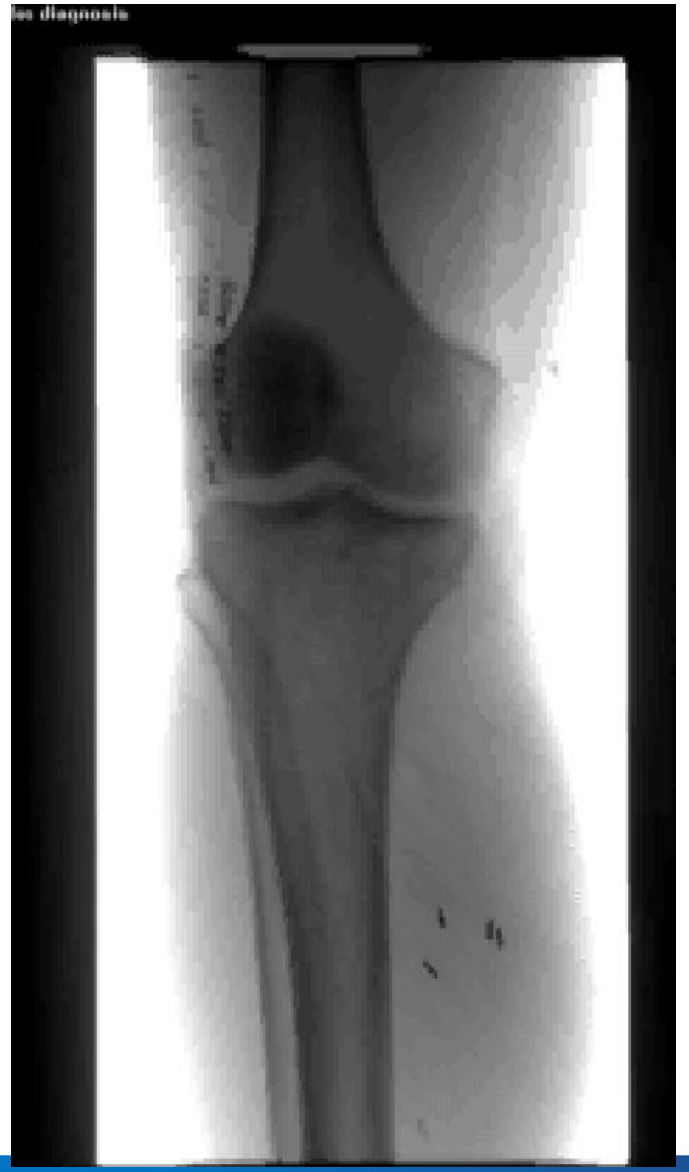
Back to our case: CT Angiogram

Segmental SFA Disease

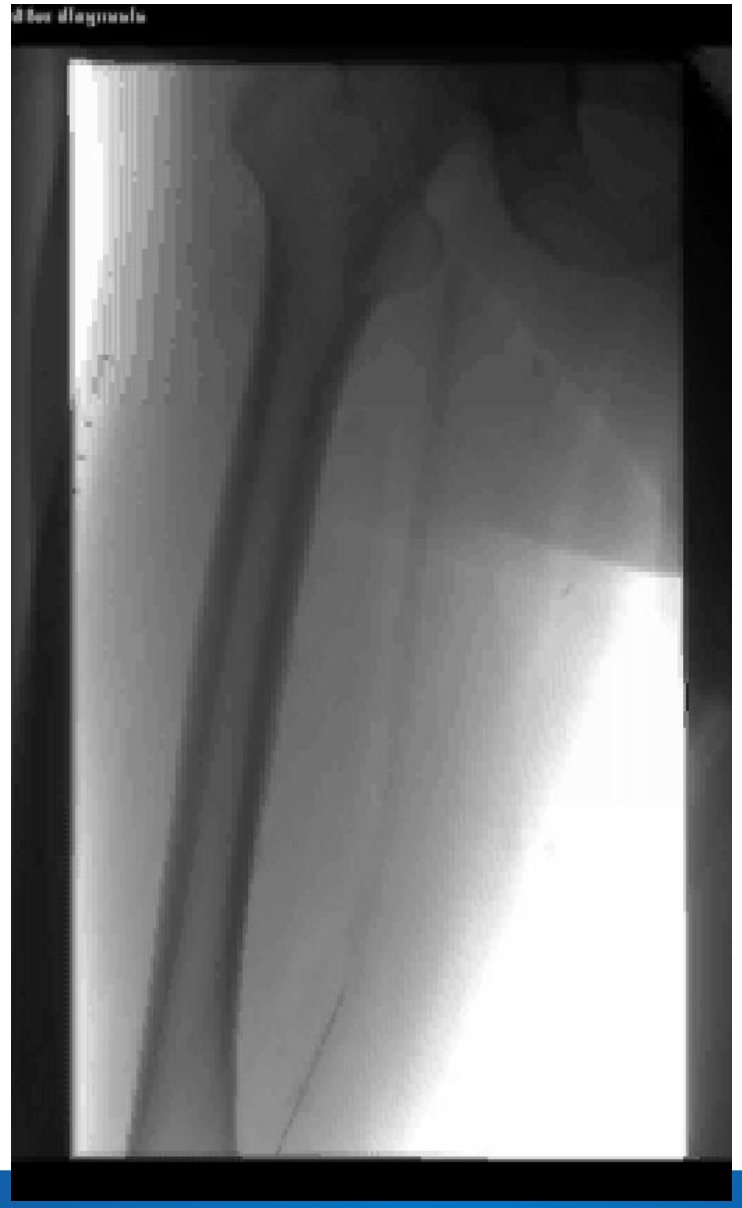


Initial RLE Angiography and Runoff



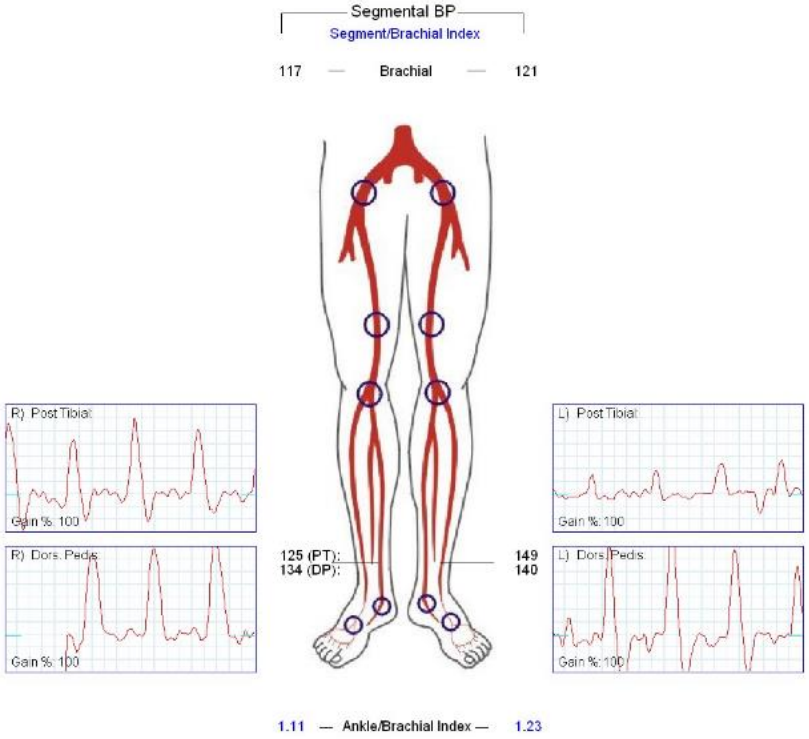


After Supera Stents



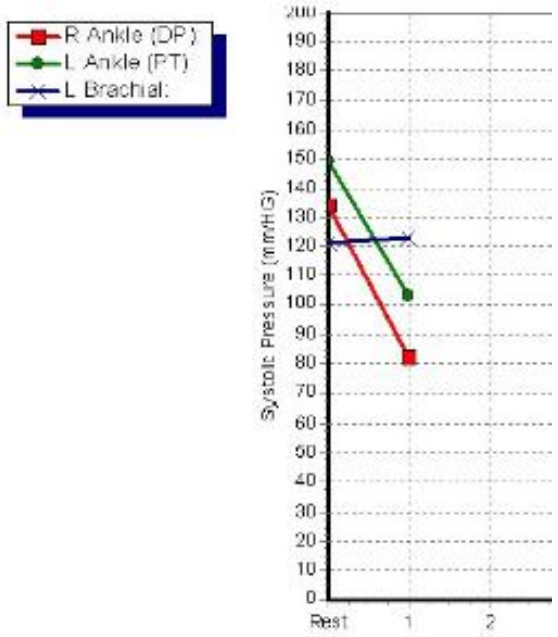
Followup ABI (2010)

Doppler



Exercise Pressure Measurement

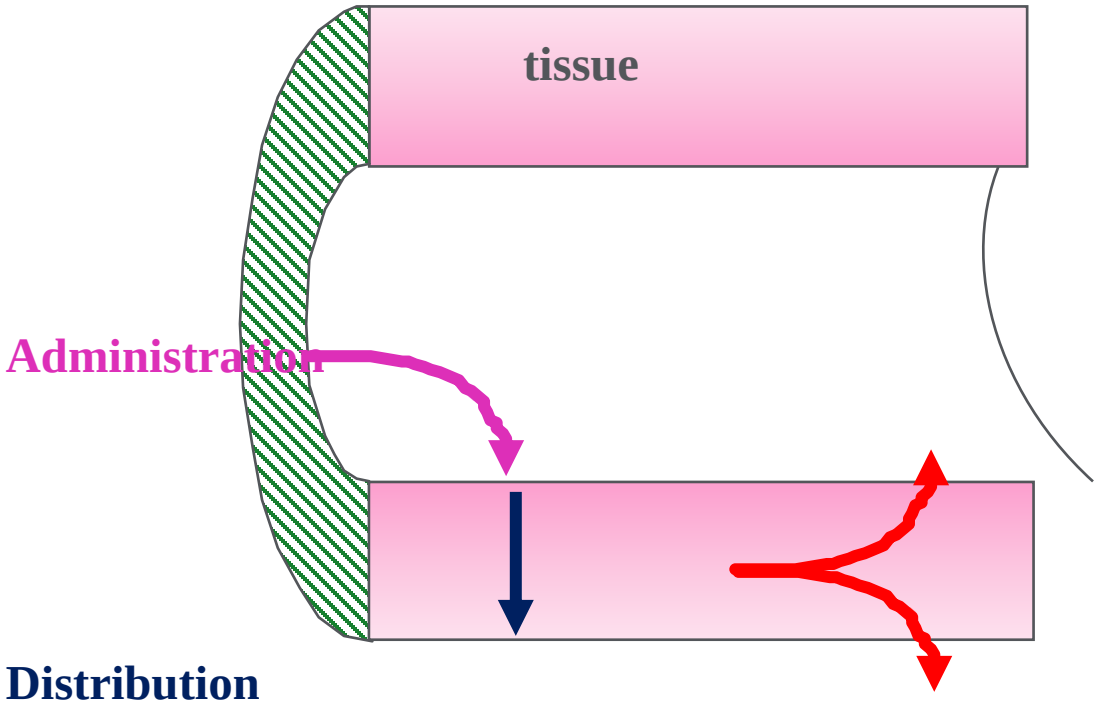
	Rest	1	2	3
R Ankle (DP):	134	82		
L Ankle (PT):	149	103		
L Brachial:	121	123		
R ABI	1.11	0.67		
L ABI	1.23	0.84		



1.11→0.67 1.23→0.84

Modes of Local Endovascular Drug Delivery

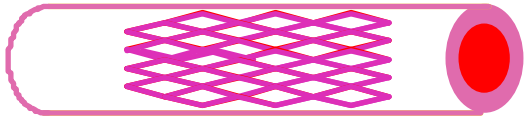
Target site



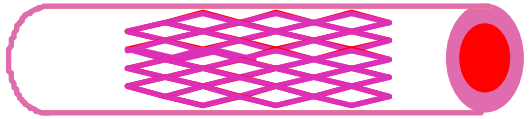
$$\int_0^t [Drug] \approx \text{EFFECT}$$

Endovascular modalities

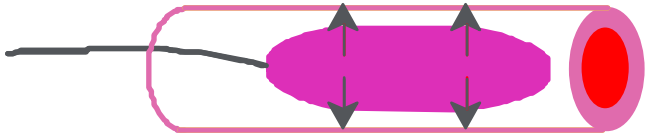
Drug release



Drug Coated Stent — FAST



Drug Eluting Stent — CONTROLLED/ SUSTAINED

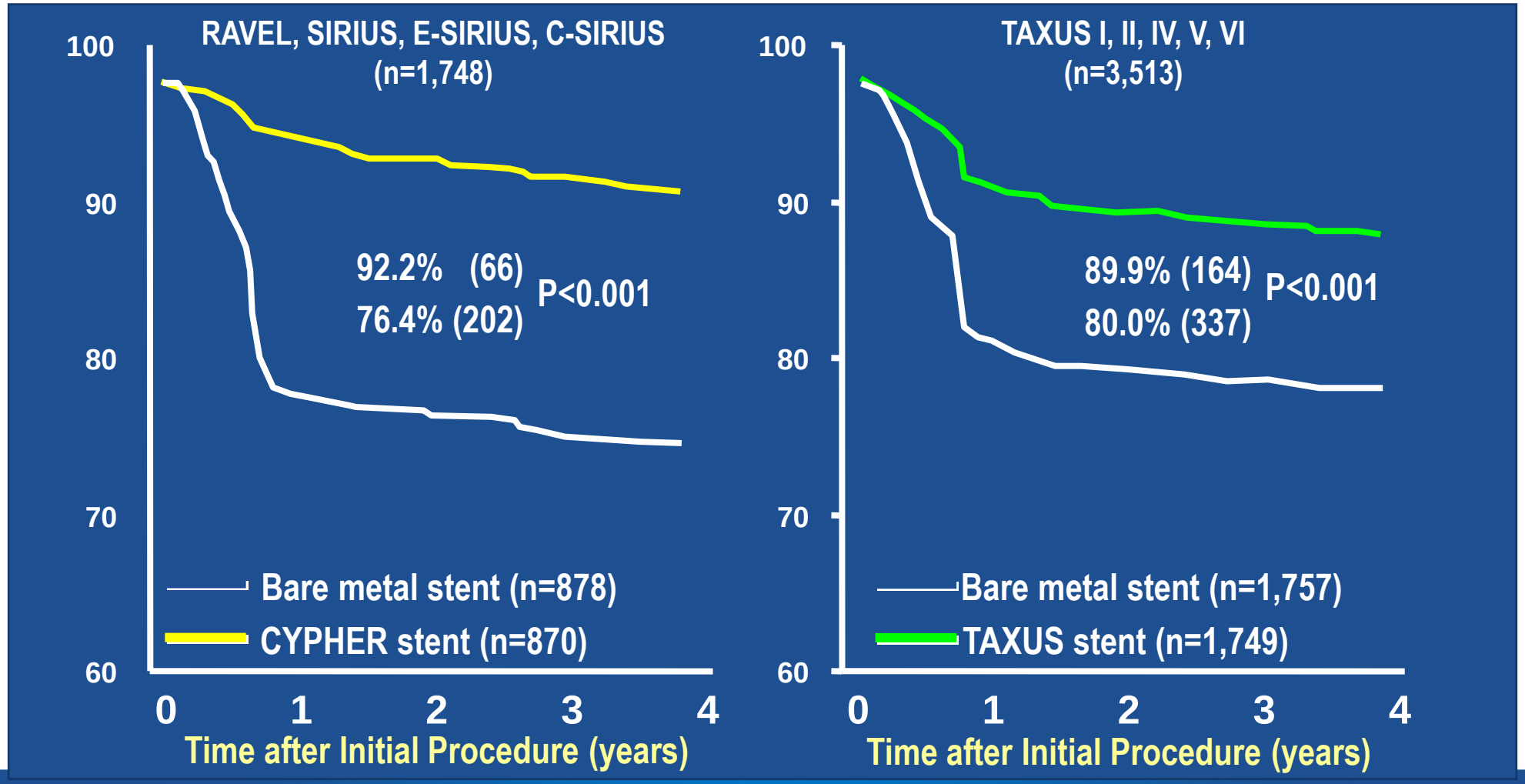


Drug Eluting Balloon — FAST

Drug “Coated” Balloon — FAST

Durable Reduction in Coronary TLR with DES

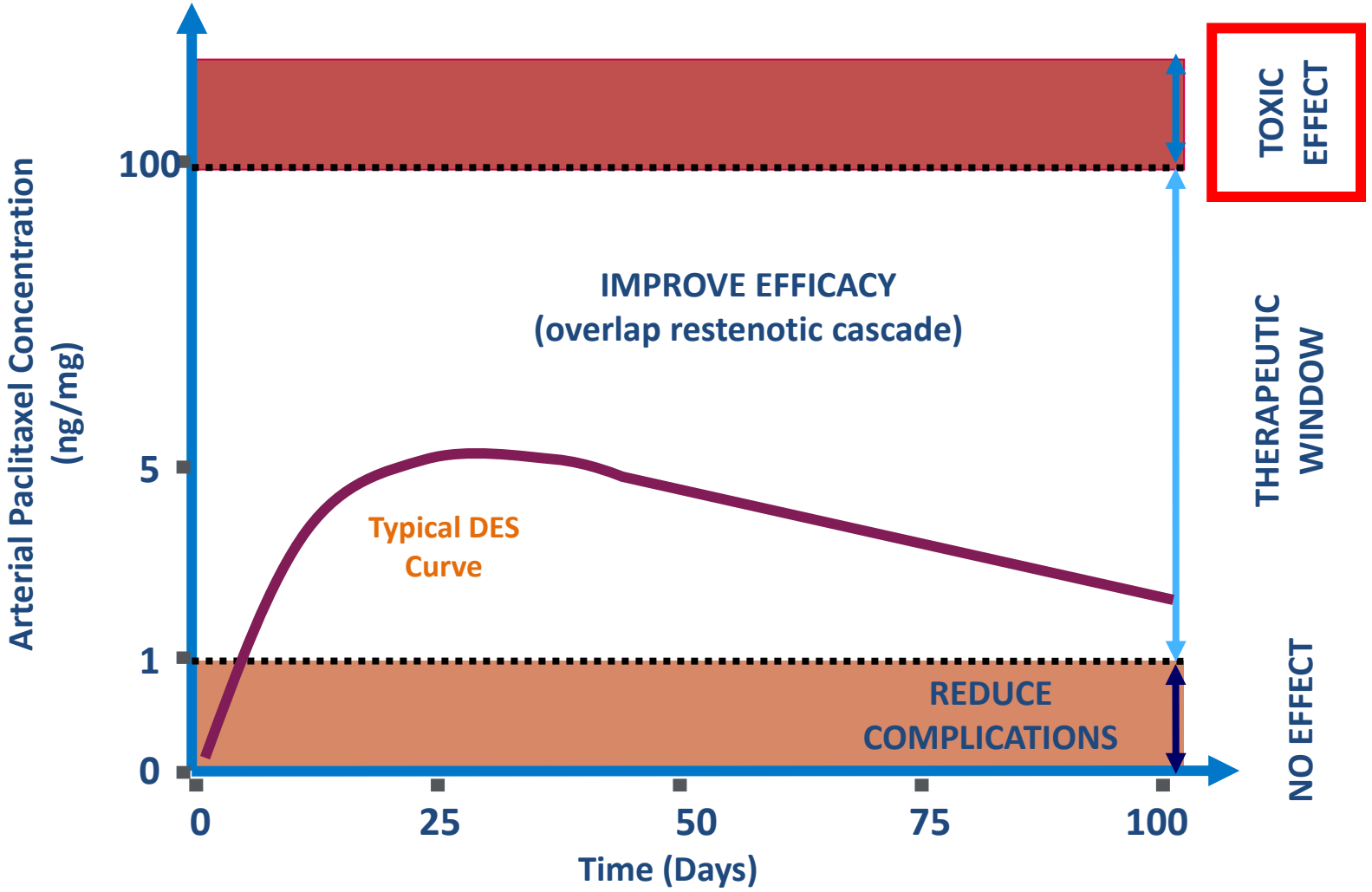
9 Prospective, Double-Blind, Randomized Trials: Freedom From Ischemic TLR ***(Meta-Analyses by CRF)***



COLUMBIA NewYork-Presbyterian

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.

Vascular Drug Dosing Considerations
Balancing Safety and Efficacy



Pivotal Peripheral Stent Studies: Zilver PTX

Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease

Twelve-Month Zilver PTX Randomized Study Results

Michael D. Dake, MD; Gary M. Ansel, MD; Michael R. Jaff, DO; Takao Ohki, MD; Richard R. Saxon, MD; H. Bob Smouse, MD; Thomas Zeller, MD; Gary S. Roubin, MD; Mark W. Burket, MD; Yazan Khatib, MD; Scott A. Snyder, PhD; Anthony O. Ragheb, PhD; J. King White, MD; Lindsay S. Machan, MD; on behalf of the Zilver PTX Investigators

Background—Sustained benefits of drug-eluting stents in femoropopliteal arteries have not been demonstrated. This prospective, multinational, randomized study was designed to compare the 12-month safety and effectiveness of a polymer-free, paclitaxel-coated nitinol drug-eluting stent (DES) with percutaneous transluminal angioplasty (PTA) and provisional bare metal stent (BMS) placement in patients with femoropopliteal peripheral artery disease.

Methods and Results—Patients were randomly assigned to primary DES implantation (n=236) or PTA (n=238). Demographics and lesion characteristics were similar between groups (eg, average lesion length, approximately 65±40 mm). One hundred twenty patients had acute PTA failure and underwent secondary random assignment to provisional DES (n=61) or BMS (n=59). Primary end points were the 12-month rates of event-free survival and patency in the primary DES and PTA groups. Compared with the PTA group, the primary DES group exhibited superior 12-month event-free survival (90.4% versus 82.6%; $P=0.004$) and primary patency (83.1% versus 32.8%; $P<0.001$), satisfying the primary hypotheses. In the secondary evaluations, (1) the primary DES group exhibited superior clinical benefit compared with the PTA group (88.3% versus 75.8%; $P<0.001$), (2) the provisional DES group exhibited superior primary patency (89.9% versus 73.0%; $P=0.01$) and superior clinical benefit (90.5% and 72.3%, $P=0.009$) compared with the provisional BMS group, and (3) the stent fracture rate (both DES and BMS) was 0.9% (4/457).

Conclusions—Femoropopliteal peripheral artery disease treatment with the paclitaxel-eluting stent was associated with superior 12-month outcomes compared with PTA and provisional BMS placement.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00120406.

(*Circ Cardiovasc Interv*. 2011;4:495-504.)

Key Words: peripheral vascular disease ■ angioplasty ■ paclitaxel-eluting stent ■ drug-eluting stent

Endovascular therapy is one option commonly used to treat patients with lifestyle-limiting intermittent claudication or critical limb ischemia caused by femoropopliteal peripheral artery disease (PAD). However, data supporting specific therapies are limited. Percutaneous transluminal balloon angioplasty (PTA) is associated with unacceptable 1-year restenosis rates (often ≥60%)[1–3] that worsen with lesion complexity. Some first-generation stents were associated with outcomes similar to PTA.[4,5] More recently, self-expanding nitinol stents have demonstrated improved patency results, yet restenosis remains a limitation, with 12-month rates between 20% and 37% reported.[3,6–8]

Editorial see p 407

Success in coronary artery intervention[9–12] led to investigation of drug-eluting stents (DES) in the superficial femoral artery (SFA). Six-month results with polymer-based sirolimus-eluting[13] and everolimus-eluting[14] stents were favorable, but benefits were not sustained.

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The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.111.962324/-/DC1.

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***Circ Cardiovasc Interv* is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.111.962324**

Vascular Medicine

OPEN

Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery

5-Year Results of the Zilver PTX Randomized Trial

Michael D. Dake, MD; Gary M. Ansel, MD; Michael R. Jaff, DO; Takao Ohki, MD; Richard R. Saxon, MD; H. Bob Smouse, MD; Lindsay S. Machan, MD; Scott A. Snyder, PhD; Erin E. O'Leary, PhD; Anthony O. Ragheb, PhD; Thomas Zeller, MD; on behalf of the Zilver PTX Investigators

Background—This randomized controlled trial evaluated clinical durability of Zilver PTX, a paclitaxel-coated drug-eluting stent (DES), for femoropopliteal artery lesions. Outcomes compare primary DES versus percutaneous transluminal angioplasty (PTA), overall DES (primary and provisional) versus standard care (PTA and provisional Zilver bare metal stent [BMS]), and provisional DES versus provisional BMS.

Methods and Results—Patients with symptomatic femoropopliteal artery disease were randomly assigned to DES (n=236) or PTA (n=238). Approximately 91% had claudication; 9% had critical limb ischemia. Patients experiencing acute PTA failure underwent secondary randomization to provisional BMS (n=59) or DES (n=61). The 1-year primary end points of event-free survival and patency showed superiority of primary DES in comparison with PTA; these results were sustained through 5 years. Clinical benefit (freedom from persistent or worsening symptoms of ischemia; 79.8% versus 59.3%, $P<0.01$), patency (66.4% versus 43.4%, $P<0.01$), and freedom from reintervention (target lesion revascularization, 83.1% versus 67.6%, $P<0.01$) for the overall DES group were superior to standard care in nonrandomized comparisons. Similarly, clinical benefit (81.8% versus 63.8%, $P=0.02$), patency (72.4% versus 53.0%, $P=0.03$), and freedom from target lesion revascularization (84.9% versus 71.6%, $P=0.06$) with provisional DES were improved over provisional BMS. These results represent >40% relative risk reduction for restenosis and target lesion revascularization through 5 years for the overall DES in comparison with standard care and for provisional DES in comparison with provisional BMS.

Conclusions—The 5-year results from this large study provide long-term information previously unavailable regarding endovascular treatment of femoropopliteal artery disease. The Zilver PTX DES provided sustained safety and clinical durability in comparison with standard endovascular treatments.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00120406.

(*Circulation*. 2016;133:1472-1483. DOI: 10.1161/CIRCULATIONAHA.115.016900.)

Key Words: angioplasty ■ drug-eluting stents ■ paclitaxel ■ peripheral artery disease ■ stents

Endovascular management of symptomatic peripheral artery disease (PAD) remains challenging despite its adoption by many as the initial preferred revascularization strategy when anatomically feasible. A wide range of percutaneous therapies using a variety of endovascular devices, including percutaneous transluminal angioplasty (PTA), atherectomy, and stent placement, have been used; however, 5-year results are confined to isolated reports.[1–5]

Editorial, see p 1435
Clinical Perspective on p 1483

In an effort to reduce restenosis rates, the most frequent cause of failure following any endovascular intervention, drug-eluting stents (DES) were developed. Their success in coronary artery intervention led to the investigation of DES in the superficial femoral artery (SFA) in hopes of providing patients

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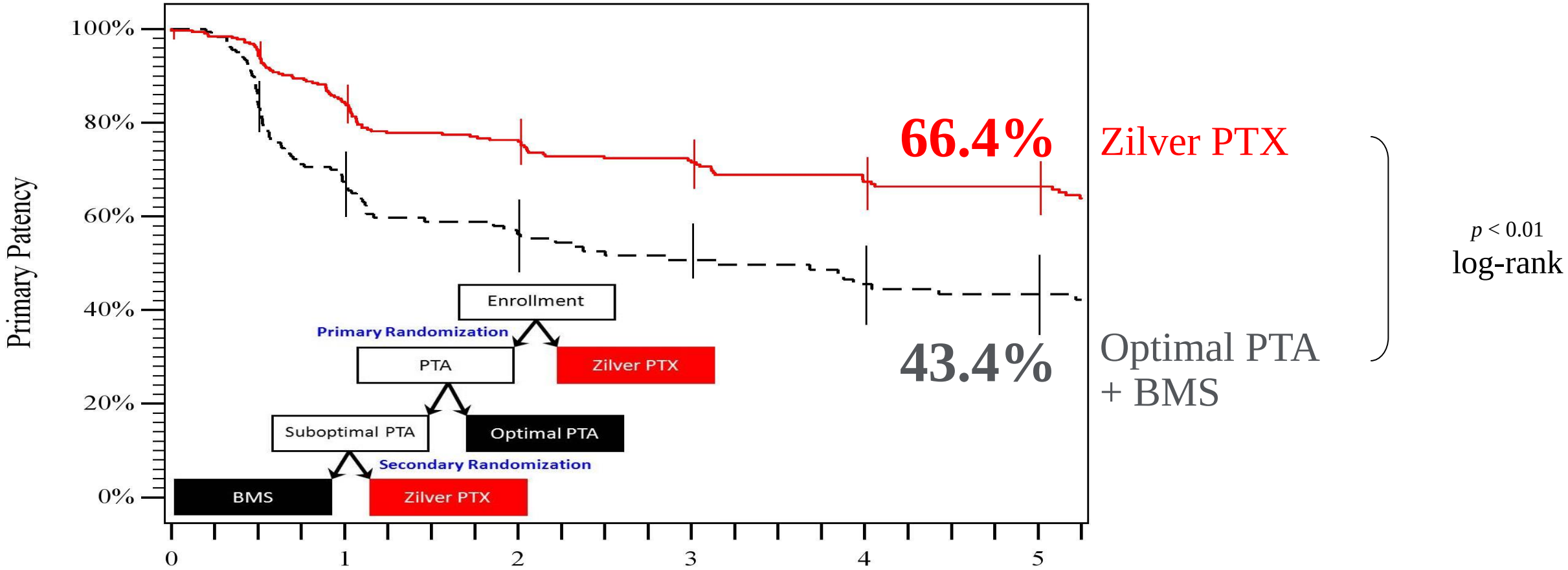
***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.115.016900**

5-year Primary Patency (PSVR < 2.0)
Zilver PTX vs. Standard Care



At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to standard care

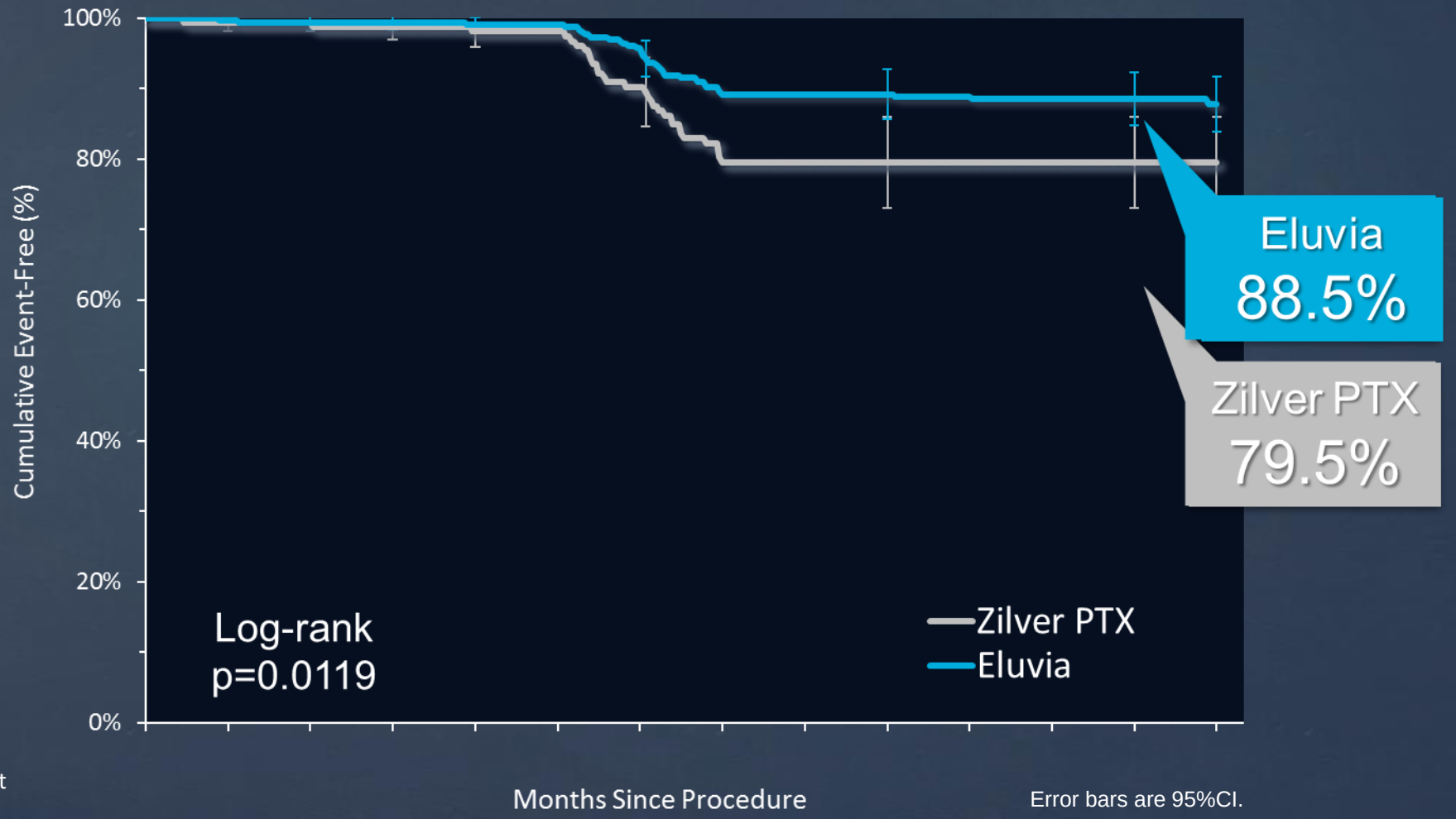
COLUMBIA NewYork-Presbyterian

Source: Dake M. The Zilver PTX randomized trial of paclitaxel-eluting stents for femoropopliteal artery disease: 5-year results. Presented at: VIVA 2014: Vascular Interventional Advances Conference; November 4-7, 2014; Las Vegas, Nevada.

Effectiveness | Primary Patency at 12 Months

Kaplan-Meier Analysis of Primary Patency

IMPERIAL CLINICAL TRIAL



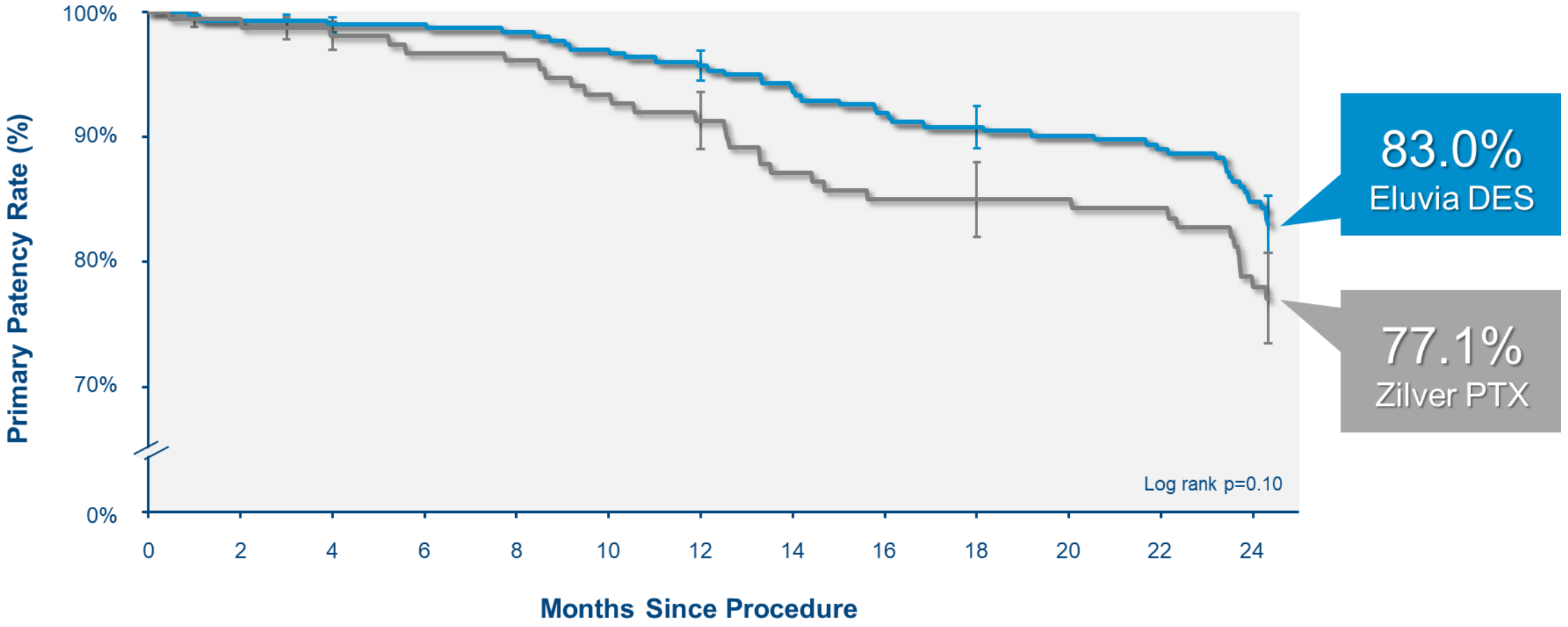
Error bars are 95%CI.

Primary patency defined as duplex ultrasound PSVR ≤2.4, in the absence of clinically-driven target lesion revascularization or bypass of the target lesion, as assessed by the DUS core lab.

Gray WA, et al. Lancet. 2018 Oct 27;392(10157):1541-1551. doi: 10.1016/S0140-6736(18)32262-1. Epub 2018 Sep 24. PMID: 30262332.

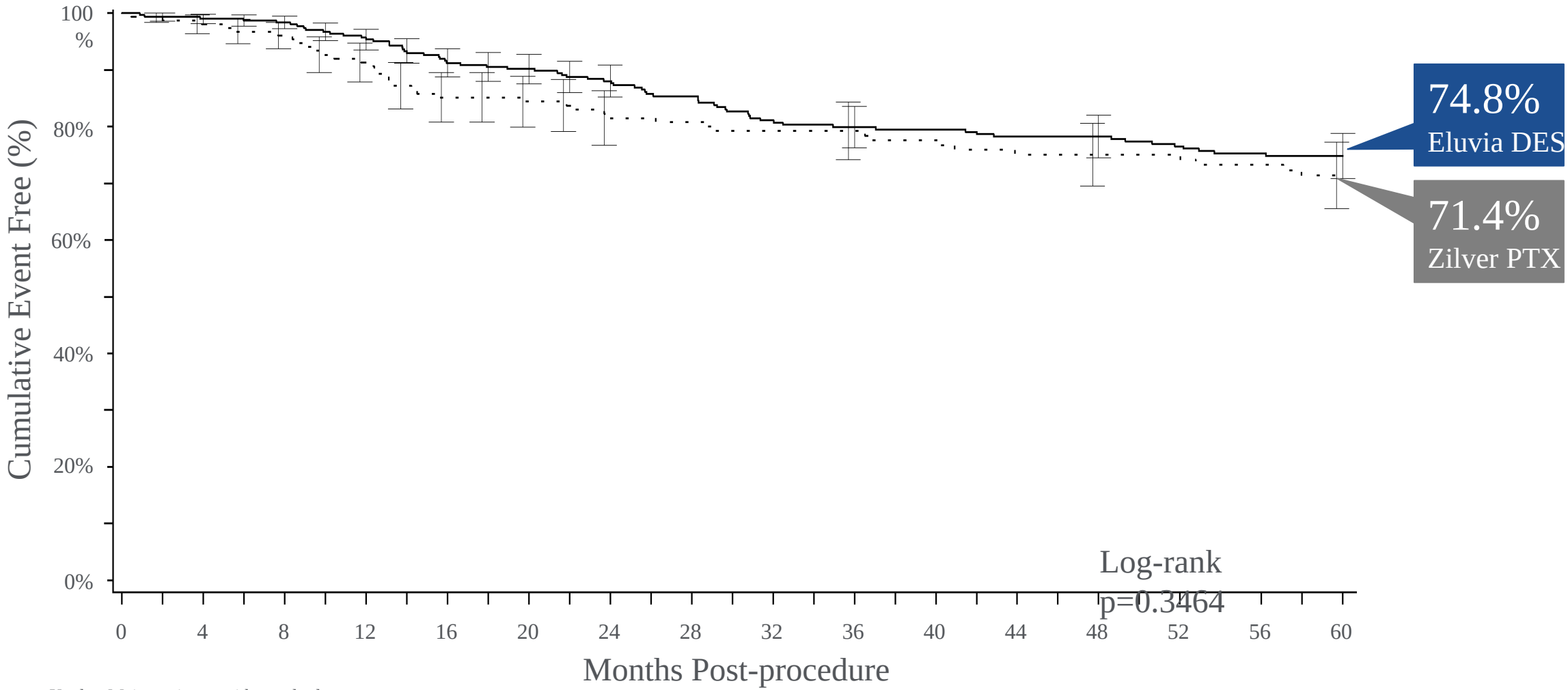
PI-549902-AB Sep2018

Effectiveness I Primary Patency at 24 Months



Iida O, VIVA 2019

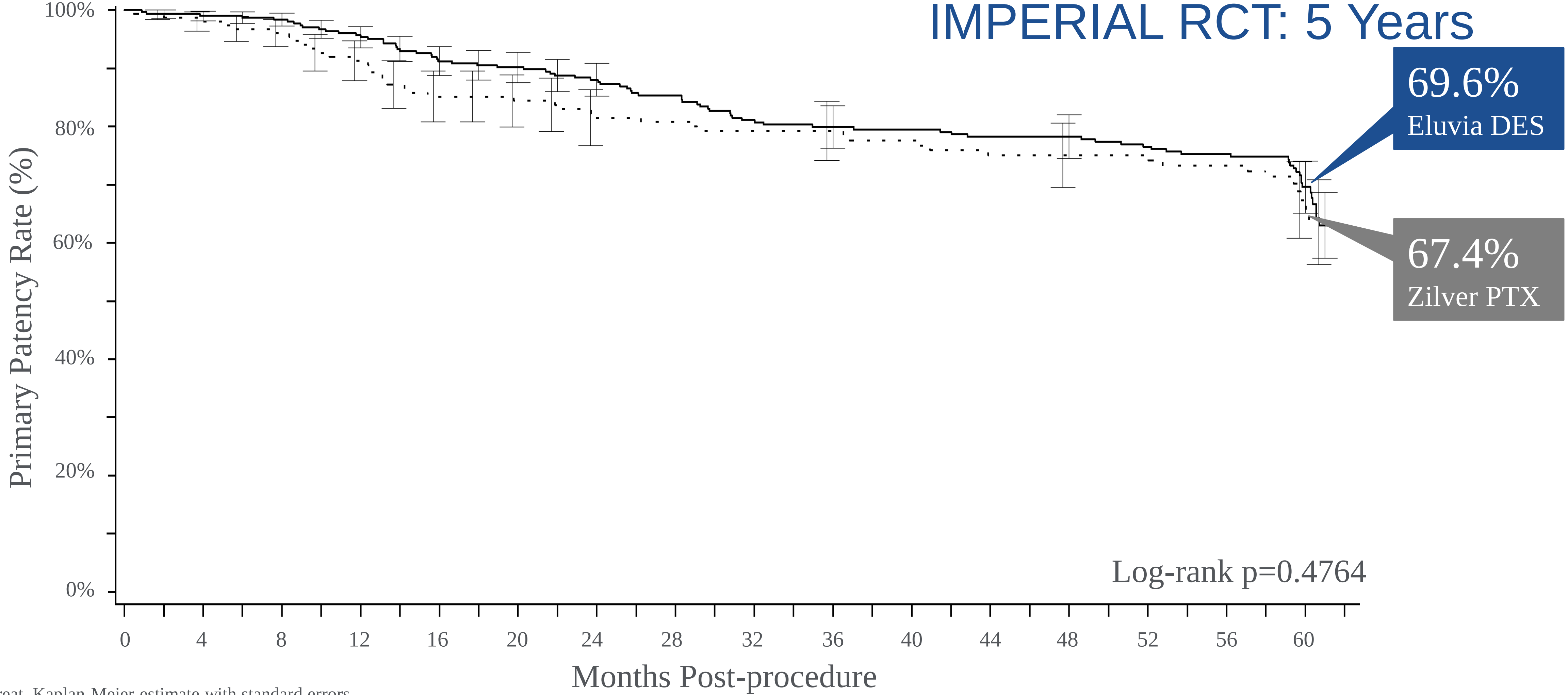
Freedom from CD-TLR
IMPERIAL RCT: 5 Years



Intention to treat. Kaplan-Meier estimate with standard errors.

Courtesy: William A. Gray, MD

Primary Patency
IMPERIAL RCT: 5 Years



Intention to treat. Kaplan-Meier estimate with standard errors.

Primary patency defined as duplex ultrasound PSVR ≤2.4, in the absence of clinically-driven target lesion revascularization or bypass of the target lesion, as assessed by the DUS core lab. Kaplan-Meier estimate utilizing time to event of clinically-driven TLR up to 1855 days and duplex ultrasound data at the 60-month visit.

Courtesy: William A. Gray, MD

EMINENT Study Overview

ClinicalTrials.gov identifier: NCT02921230

Largest industry-sponsored randomized trial of drug-eluting stents for SFA/PPA to date

Study Design	**RCT (2:1)** **N=775** **Superiority** (effectiveness) Single-blind	
Intervention	Study arm: **Eluvia DES** Control arm: **Bare nitinol stent**	N=508 N=267
Primary Endpoint	**12-month Primary Patency**	
Investigational Centers	58 centers in 10 European countries	
Principal Investigators	Prof. Dr. Yann Gouëffic Groupe Hospitalier Paris St. Joseph, Paris, France	Prof. Dr. Giovanni Torsello Sint-Franziskus-Hospital GmbH, Münster, Germany

Gouëffic, JVIVA 2021

Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings assessed by an independent core laboratory.

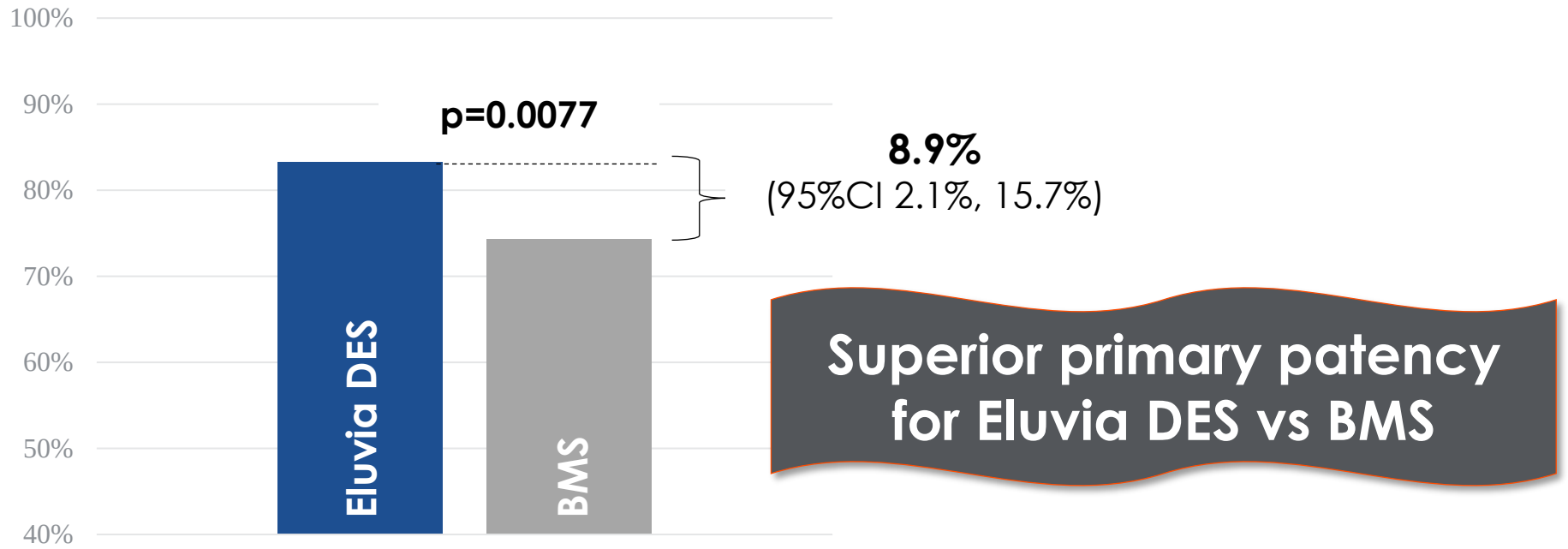
DES, drug-eluting stent; PPA, proximal popliteal artery; RCT, randomized controlled trial; SFA, superficial femoral artery.

Effectiveness: Primary Patency

Primary Endpoint

Statistically significantly greater primary patency in patients treated with Eluvia DES vs BMS

83.2% [337/405] vs 74.3% [165/222]; p=0.0077



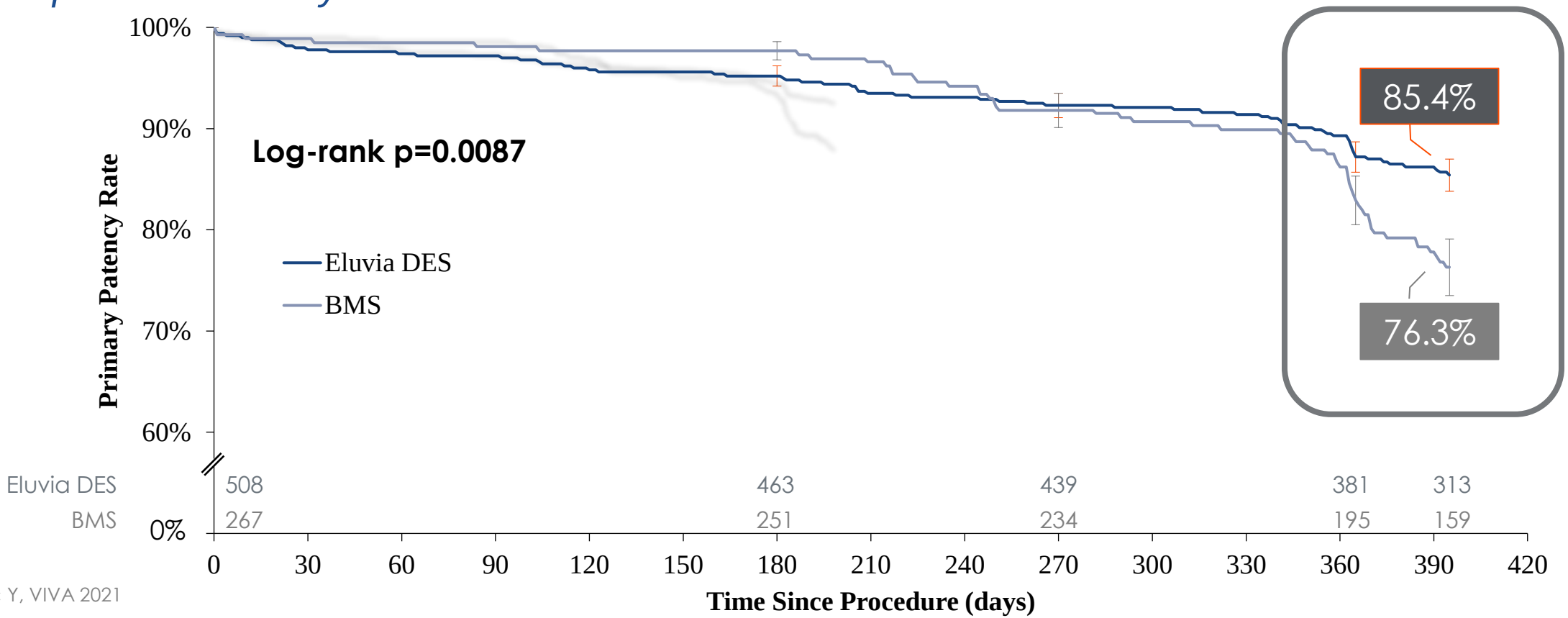
EMINENT

Gouëffic Y, VIVA 2021

Intention to treat. Primary patency defined as core-lab assessed duplex ultrasound peak systolic velocity ratio (PSVR) ≤ 2.4 at 12 months in the absence of clinically-driven TLR or bypass of the target lesion.

Effectiveness: Primary Patency

Kaplan-Meier Analysis

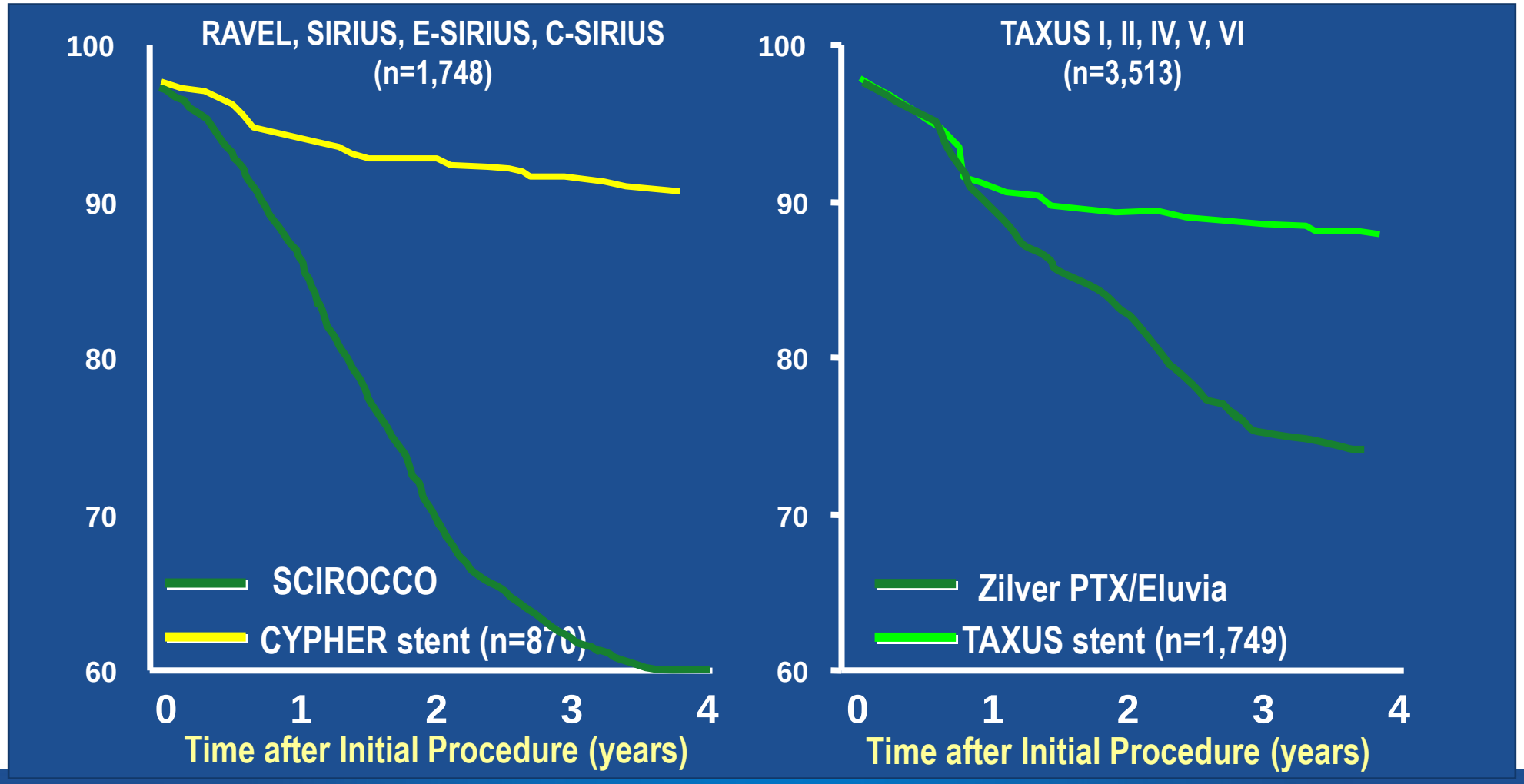


Gouëffic Y, VIVA 2021

Primary patency defined as core-lab assessed duplex ultrasound peak systolic velocity ratio (PSVR) ≤ 2.4 at 12 months in the absence of clinically-driven TLR or bypass of the target lesion.

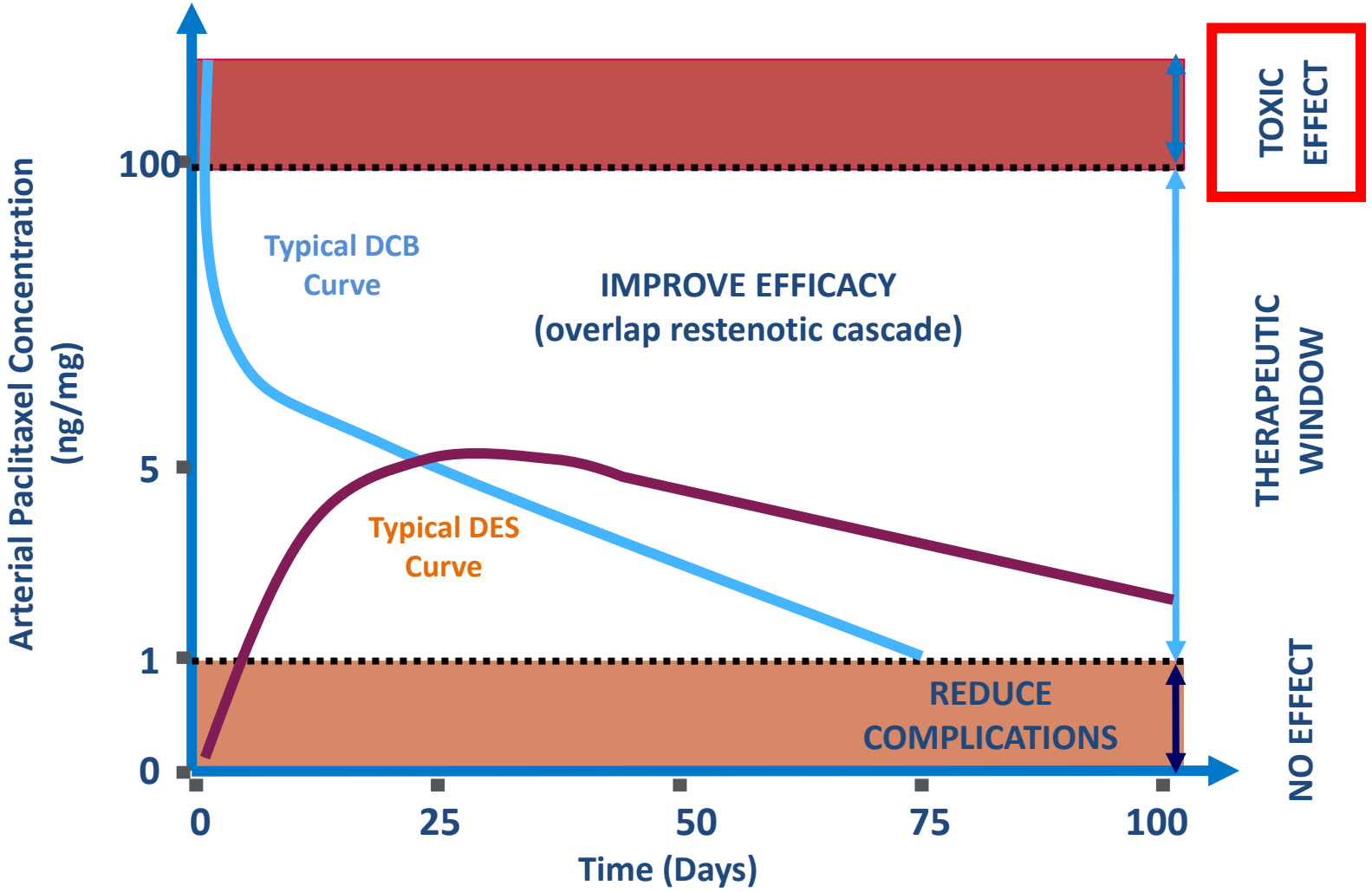
Kaplan-Meier error bars are standard error.

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.

Vascular Drug Dosing Considerations
Balancing Safety and Efficacy



Drug Coated Balloons

Ulrich Speck

Bruno Scheller

Paclitaxel Balloon Coating, a Novel Method for Prevention and Therapy of Restenosis

Bruno Scheller, MD; Ulrich Speck, PhD; Claudia Abramjuk, DVM; Ulrich Bernhardt, PhD; Michael Böhm, MD; Georg Nickenig MD

Background—Drug-eluting stents have shown promising antirestenotic effects in clinical trials. Non-stent-based local delivery of antiproliferative drugs may offer additional flexibility and also reach vessel areas beyond the immediate stent coverage. The aim of the present study was to evaluate a novel method of local drug delivery based on angioplasty balloons.

Methods and Results—Stainless steel stents (n=40; diameter, 3.0 to 3.5 mm; length, 18 mm) were implanted in the left anterior descending and circumflex coronary arteries of domestic pigs. Both conventional uncoated and 3 different types of paclitaxel-coated, percutaneous transluminal coronary angioplasty balloons (contact with vessel wall for 1 minute) were used. No difference in short-term tolerance between coated and uncoated balloons and no signs of thrombotic events were observed. Quantitative angiography and histomorphometry of the stented arteries asserted the statistical equality of the baseline parameters between the control and the 3 treatment groups. Paclitaxel balloon coating led to a marked, dose-dependent reduction of parameters characterizing in-stent restenosis (reduction of neointimal area up to 63%). Despite the marked reduction in neointimal proliferation, endothelialization of stent struts was present in all samples. There was no evidence of a significant inflammatory response in the neighborhood of the stent struts.

Conclusions—Paclitaxel balloon coating is safe, and it effectively inhibits restenosis after coronary angioplasty with stent implantation in the porcine model. The degree of reduction in neointimal formation was comparable to that achieved with drug-eluting stents. (*Circulation*. **2004;110:810-814.**)

Key Words: restenosis ■ angioplasty ■ paclitaxel

Coronary stent implantation has been proven to be an effective technique for the prevention of restenosis in native coronary vessels compared with angioplasty alone. However, the restenosis rates after bare-metal stent implantation are still as high as 20% to 40% at 6 months. Numerous initially promising approaches that included systemic antiproliferative agents have failed to prevent restenosis.[1] Coronary brachytherapy has been considered a breakthrough treatment against in-stent restenosis but depends on the availability of the radiotherapeutic armamentarium.[2]

Drug-eluting stents (DES) were shown to be safe and feasible in reducing restenosis.[3–7] However, their efficacy and safety have not been confirmed in all clinical settings, especially with regard to treating in-stent restenosis. Concerns have been raised that the polymeric matrix on the stent in which the antiproliferative drug is embedded might induce inflammation and thrombosis.[8] Another important limitation of DES is the fact that the drug concentration is highest at the stent struts, where healing is most important. On the other hand, incomplete suppression of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DES.[4]

Non–stent-based local delivery of antiproliferative drugs may offer additional flexibility and efficacy in the entire range of applications. It may also deliver drugs to vessel areas not directly covered by the stent, which could be of special interest for small and tortuous vessels. Furthermore, healing and reendothelialization of stent struts that do not carry antiproliferative agents may be facilitated.

Paclitaxel has already been investigated in previous studies that included a variety of catheter-based, local drug-delivery approaches. The "double-balloon" catheter,[9] the "porous balloon,"[10] and even intrapericardial administration[11] have been used. Although all of these approaches showed efficacy in preclinical trials, they require special and sometimes cumbersome devices, involve blockage of coronary blood flow, or induce additional vascular injury.

The aim of the present study was to test a novel method of intracoronary local drug delivery in the porcine coronary overstretch model: paclitaxel coating of conventional percutaneous transluminal coronary angioplasty (PTCA) balloon catheters with a new coating technique that allows for immediate drug release on inflation.

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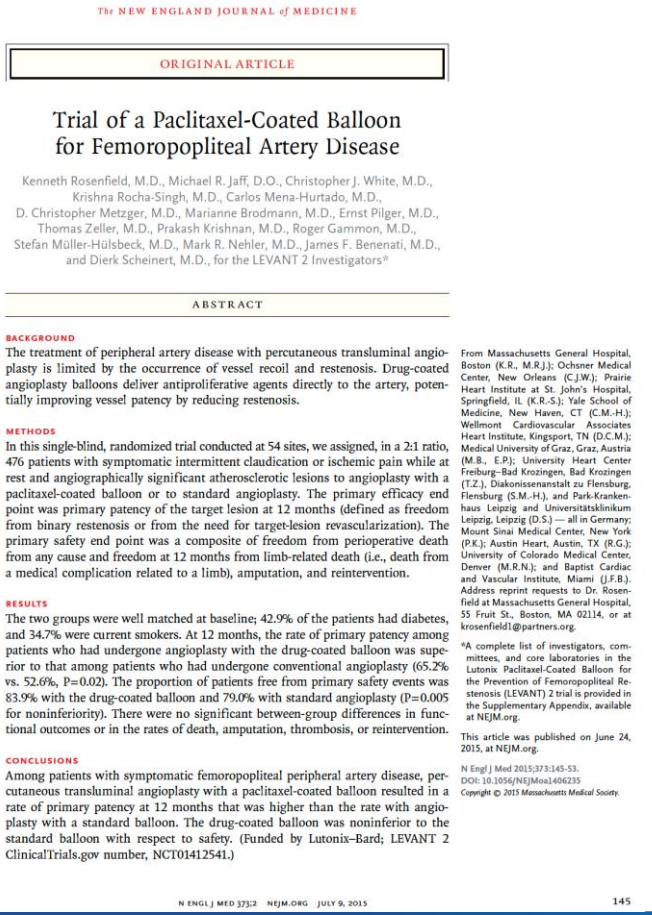
Clinical Trials Demonstrate Sustained Patency with Drug Coated Balloons



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease

Kenneth Rosenfield, M.D., Michael R. Jaff, D.O., Christopher J. White, M.D., Krishna Rocha-Singh, M.D., Carlos Mena-Hurtado, M.D., D. Christopher Metzger, M.D., Marianne Brodmann, M.D., Ernst Pilger, M.D., Thomas Zeller, M.D., Prakash Krishnan, M.D., Roger Gammon, M.D., Stefan Müller-Hülsbeck, M.D., Mark R. Nehler, M.D., James F. Benenati, M.D., and Dierk Scheinert, M.D., for the LEVANT 2 Investigators*

ABSTRACT

BACKGROUND

The treatment of peripheral artery disease with percutaneous transluminal angioplasty is limited by the occurrence of vessel recoil and restenosis. Drug-coated angioplasty balloons deliver antiproliferative agents directly to the artery, potentially improving vessel patency by reducing restenosis.

METHODS

In this single-blind, randomized trial conducted at 54 sites, we assigned, in a 2:1 ratio, 476 patients with symptomatic intermittent claudication or ischemic pain while at rest and angiographically significant atherosclerotic lesions to angioplasty with a paclitaxel-coated balloon or to standard angioplasty. The primary efficacy end point was primary patency of the target lesion at 12 months (defined as freedom from binary restenosis or from the need for target-lesion revascularization). The primary safety end point was a composite of freedom from perioperative death from any cause and freedom at 12 months from limb-related death (i.e., death from a medical complication related to a limb), amputation, and reintervention.

RESULTS

The two groups were well matched at baseline; 42.9% of the patients had diabetes, and 34.7% were current smokers. At 12 months, the rate of primary patency among patients who had undergone angioplasty with the drug-coated balloon was superior to that among patients who had undergone conventional angioplasty (65.2% vs. 52.6%, P=0.02). The proportion of patients free from primary safety events was 83.9% with the drug-coated balloon and 79.0% with standard angioplasty (P=0.005 for noninferiority). There were no significant between-group differences in functional outcomes or in the rates of death, amputation, thrombosis, or reintervention.

CONCLUSIONS

Among patients with symptomatic femoropopliteal peripheral artery disease, percutaneous transluminal angioplasty with a paclitaxel-coated balloon resulted in a rate of primary patency at 12 months that was higher than the rate with angioplasty with a standard balloon. The drug-coated balloon was noninferior to the standard balloon with respect to safety. (Funded by Lutonix–Bard; LEVANT 2 ClinicalTrials.gov number, NCT01412541.)

From Massachusetts General Hospital, Boston (K.R., M.R.J.); Ochsner Medical Center, New Orleans (C.J.W.); Prairie Heart Institute at St. John's Hospital, Springfield, IL (K.R.-S.); Yale School of Medicine, New Haven, CT (C.M.-H.); Wellmont Cardiovascular Associates Heart Institute, Kingsport, TN (D.C.M.); Medical University of Graz, Graz, Austria (M.B., E.P.); University Heart Center Freiburg–Bad Krozingen, Bad Krozingen (T.Z.), Diakonissenanstalt zu Flensburg, Flensburg (S.M.-H.), and Park-Krankenhaus Leipzig and Universitätsklinikum Leipzig, Leipzig (D.S.) — all in Germany; Mount Sinai Medical Center, New York (P.K.); Austin Heart, Austin, TX (R.G.); University of Colorado Medical Center, Denver (M.R.N.); and Baptist Cardiac and Vascular Institute, Miami (J.F.B.). Address reprint requests to Dr. Rosenfield at Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at krosenfield1@partners.org.

*A complete list of investigators, committees, and core laboratories in the Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT) 2 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 24, 2015, at NEJM.org.

N Engl J Med 2015;373:145-53.
DOI: 10.1056/NEJMoa1406235

OPEN

Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and Popliteal Peripheral Artery Disease

12-Month Results From the IN.PACT SFA Randomized Trial

Gunnar Tepe, MD; John Laird, MD; Peter Schneider, MD; Marianne Brodmann, MD; Prakash Krishnan, MD; Antonio Micari, MD; Christopher Metzger, MD; Dierk Scheinert, MD; Thomas Zeller, MD; David J. Cohen, MD, MSc; David B. Snead, PhD; Beaux Alexander, MBA; Mario Landini, MS; Michael R. Jaff, DO; for the IN.PACT SFA Trial Investigators*

Background—Drug-coated balloons (DCBs) have shown promise in improving the outcomes for patients with peripheral artery disease. We compared a paclitaxel-coated balloon with percutaneous transluminal angioplasty (PTA) for the treatment of symptomatic superficial femoral and popliteal artery disease.

Methods and Results—The IN.PACT SFA Trial is a prospective, multicenter, single-blinded, randomized trial in which 331 patients with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The primary efficacy end point was primary patency, defined as freedom from restenosis or clinically driven target lesion revascularization at 12 months. Baseline characteristics were similar between the 2 groups. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were 8.94±4.89 and 8.81±5.12 cm (P=0.82) and 25.8% and 19.5% (P=0.22), respectively. DCB resulted in higher primary patency versus PTA (82.2% versus 52.4%; P<0.001). The rate of clinically driven target lesion revascularization was 2.4% in the DCB arm in comparison with 20.6% in the PTA arm (P<0.001). There was a low rate of vessel thrombosis in both arms (1.4% after DCB and 3.7% after PTA [P=0.10]). There were no device- or procedure-related deaths and no major amputations.

Conclusions—In this prospective, multicenter, randomized trial, DCB was superior to PTA and had a favorable safety profile for the treatment of patients with symptomatic femoropopliteal peripheral artery disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique Identifiers: NCT01175850 and NCT01566461. (***Circulation***. **2015;131:495-502. DOI: 10.1161/CIRCULATIONAHA.114.011004.**)

Key Words: drug-eluting balloons ■ peripheral arterial disease ■ peripheral vascular diseases

Endovascular treatment of symptomatic atherosclerotic peripheral artery disease (PAD) has gained widespread acceptance and is now recommended as the primary revascularization strategy in many clinical and anatomic scenarios.[1–3] Percutaneous transluminal angioplasty (PTA) of the superficial femoral and popliteal artery has a high initial success rate, but restenosis occurs in up to 60% of cases.[4] Although randomized trials have demonstrated patency rates with bare metal stents and drug-eluting stents superior to those observed with PTA,[5–8] the optimal treatment for superficial femoral and popliteal artery disease remains controversial. Some practice guidelines advise against primary stenting in patients with intermittent claudication,[9] whereas others recommend primary stenting in short- or intermediate-length lesions[3] or

Clinical Perspective on p 502

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From the RodMed Klinikum, Rosenheim, Germany (G.T.); UC Davis, Sacramento, CA (J.L.); Kaiser Permanente – Moanalua Medical Center and Clinic, Honolulu, HI (P.S.); Landeskrankenhaus – Universitätsklinikum, Graz, Austria (M.B.); The Mount Sinai Medical Center, New York, NY (P.K.); GVM Care and Research, Lugo, Italy (A.M.); Maria Eleonora Hospital, Palermo, Italy (A.M.); Wellmont Holston Valley Medical Center, Kingsport, TN (C.M.); Park-Krankenhaus Leipzig, Germany (D.S.); Universitäts-Herzzentrum Freiburg - Bad Krozingen, Germany (T.Z.); Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City School of Medicine, Kansas City, MO (D.J.C.); Medtronic, Inc., Santa Rosa, CA (D.B.S., B.A., M.L.); and Massachusetts General Hospital, Boston, MA (M.R.J.).

*The principal investigators and clinical sites participating in the IN.PACT SFA Randomized Trial are listed in the online-only Data Supplement.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.011004/-/DC1.

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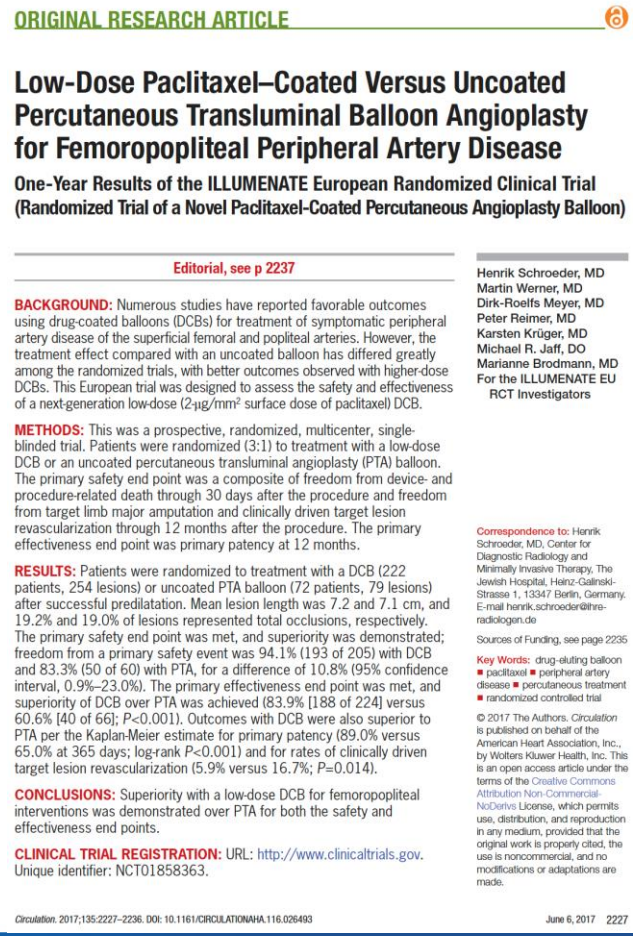


ORIGINAL RESEARCH ARTICLE

Low-Dose Paclitaxel–Coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease

One-Year Results of the ILLUMENATE European Randomized Clinical Trial (Randomized Trial of a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon)

Editorial, see p 2237

Henrik Schroeder, MD
Martin Werner, MD
Dirk-Roelfs Meyer, MD
Peter Reimer, MD
Karsten Krüger, MD
Michael R. Jaff, DO
Marianne Brodmann, MD
For the ILLUMENATE EU RCT Investigators

BACKGROUND: Numerous studies have reported favorable outcomes using drug-coated balloons (DCBs) for treatment of symptomatic peripheral artery disease of the superficial femoral and popliteal arteries. However, the treatment effect compared with an uncoated balloon has differed greatly among the randomized trials, with better outcomes observed with higher-dose DCBs. This European trial was designed to assess the safety and effectiveness of a next-generation low-dose (2-µg/mm² surface dose of paclitaxel) DCB.

METHODS: This was a prospective, randomized, multicenter, single-blinded trial. Patients were randomized (3:1) to treatment with a low-dose DCB or an uncoated percutaneous transluminal angioplasty (PTA) balloon. The primary safety end point was a composite of freedom from device- and procedure-related death through 30 days after the procedure and freedom from target limb major amputation and clinically driven target lesion revascularization through 12 months after the procedure. The primary effectiveness end point was primary patency at 12 months.

RESULTS: Patients were randomized to treatment with a DCB (222 patients, 254 lesions) or uncoated PTA balloon (72 patients, 79 lesions) after successful predilatation. Mean lesion length was 7.2 and 7.1 cm, and 19.2% and 19.0% of lesions represented total occlusions, respectively. The primary safety end point was met, and superiority was demonstrated; freedom from a primary safety event was 94.1% (193 of 205) with DCB and 83.3% (50 of 60) with PTA, for a difference of 10.8% (95% confidence interval, 0.9%–23.0%). The primary effectiveness end point was met, and superiority of DCB over PTA was achieved (83.9% [188 of 224] versus 60.6% [40 of 66]; P<0.001). Outcomes with DCB were also superior to PTA per the Kaplan-Meier estimate for primary patency (89.0% versus 65.0% at 365 days; log-rank P<0.001) and for rates of clinically driven target lesion revascularization (5.9% versus 16.7%; P=0.014).

CONCLUSIONS: Superiority with a low-dose DCB for femoropopliteal interventions was demonstrated over PTA for both the safety and effectiveness end points.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01858363.

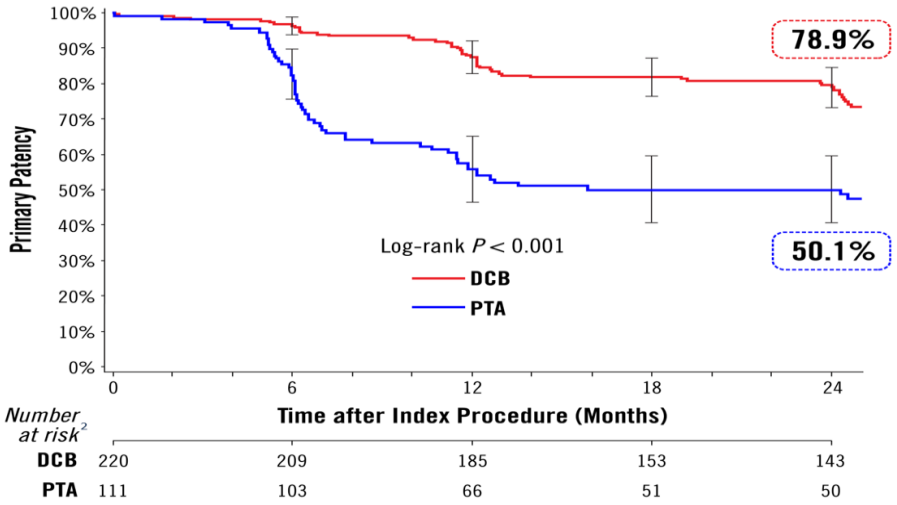
Correspondence to: Henrik Schroeder, MD, Center for Diagnostic Radiology and Minimally Invasive Therapy, The Jewish Hospital, Heinz-Galinski-Strasse 1, 13347 Berlin, Germany. E-mail henrik.schroeder@ihre-radiologen.de

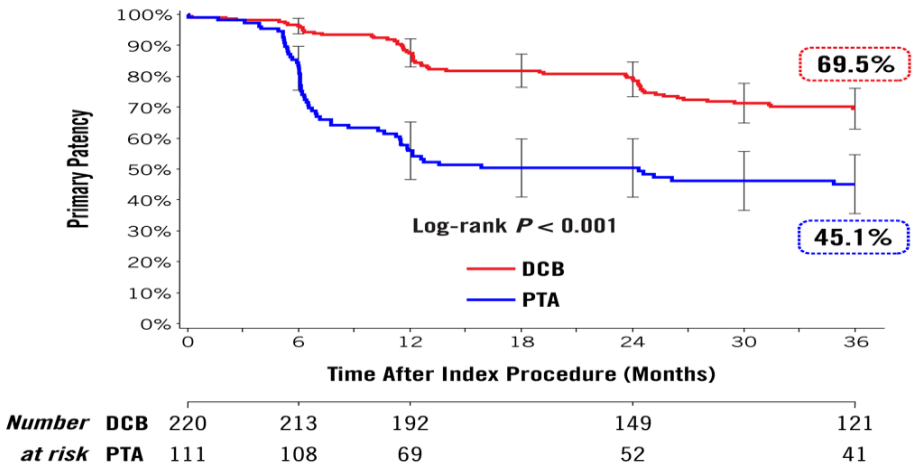
Sources of Funding, see page 2235

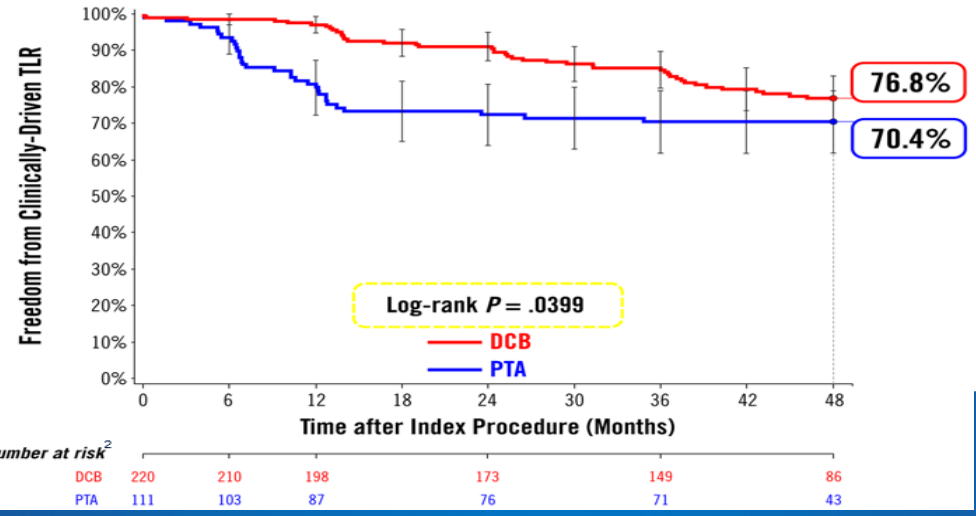
Key Words: drug-eluting balloon ■ paclitaxel ■ peripheral artery disease ■ percutaneous treatment ■ randomized controlled trial

COLUMBIA NewYork-Presbyterian

IN.PACT DCB Has Shown Superior Results Compared to PTA in Pivotal IDE Trials







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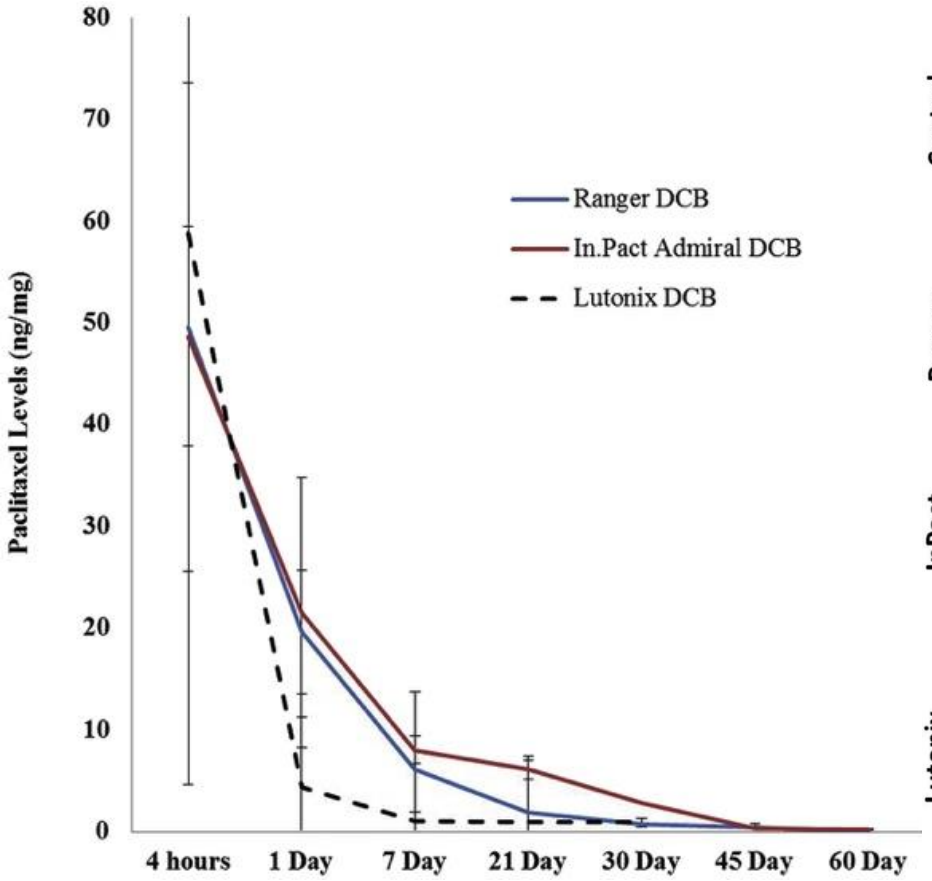
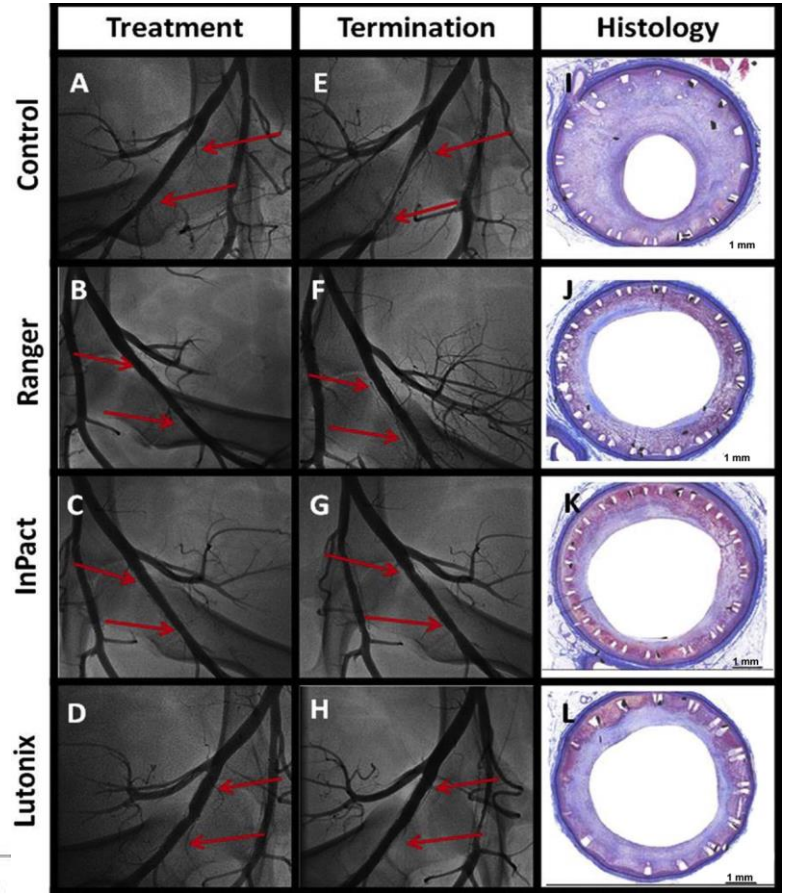
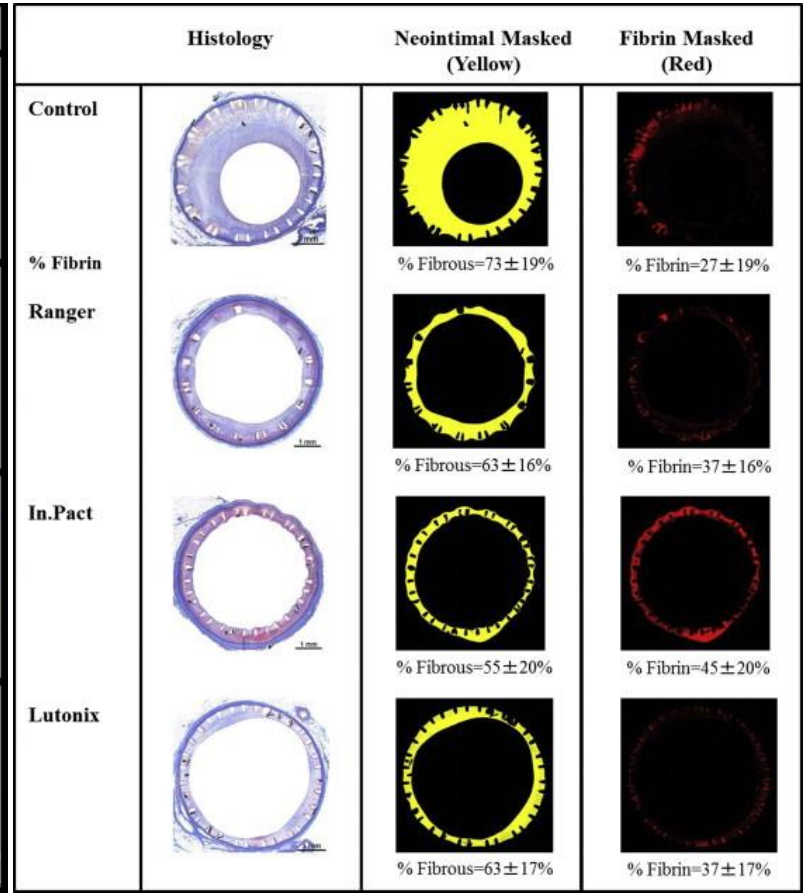
Not all DCB Are Created Equal: Differential PK

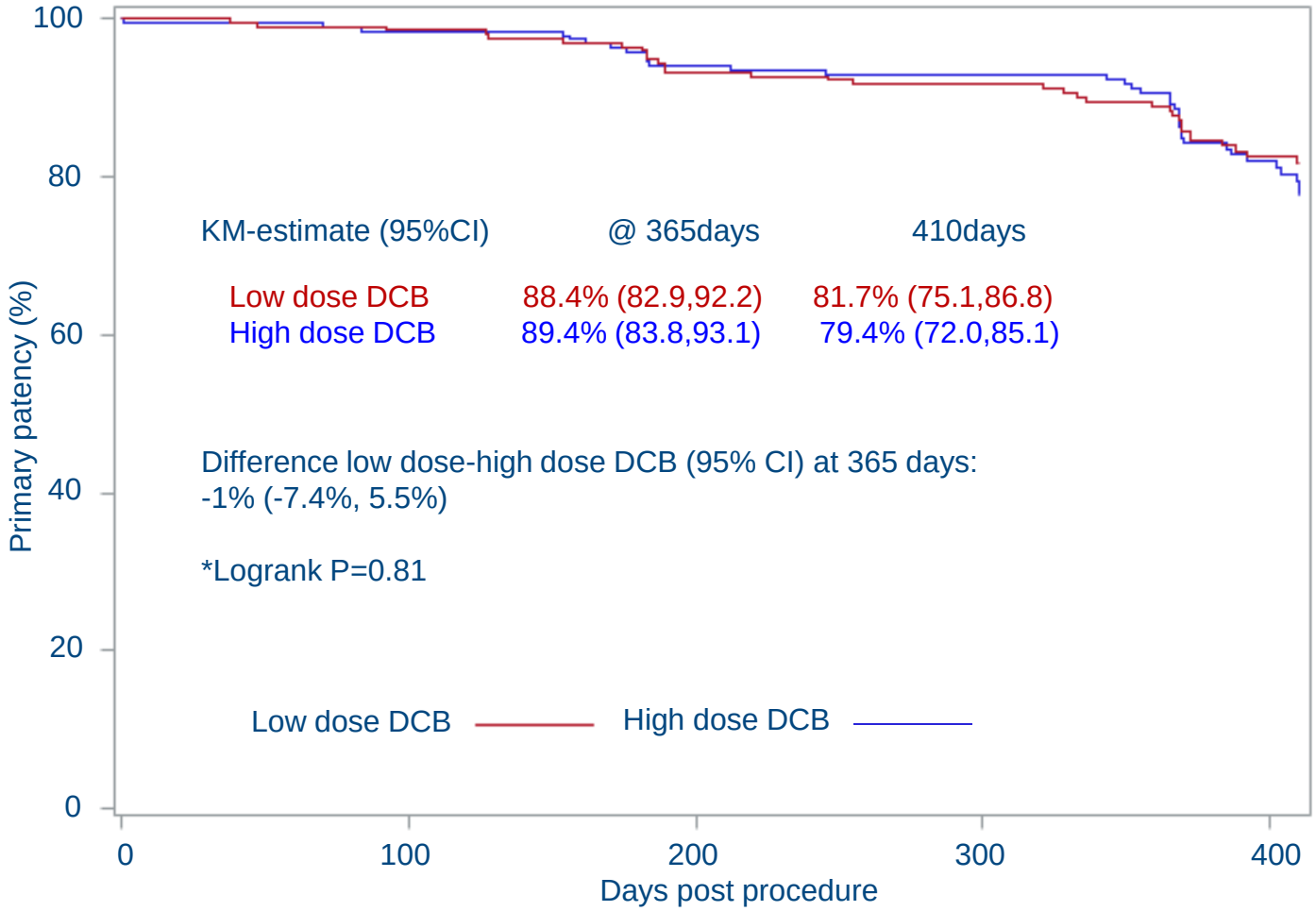






Gongora, et al. JACC: CI Volume 8, Issue 8, July 2015, Pages 1115–1123

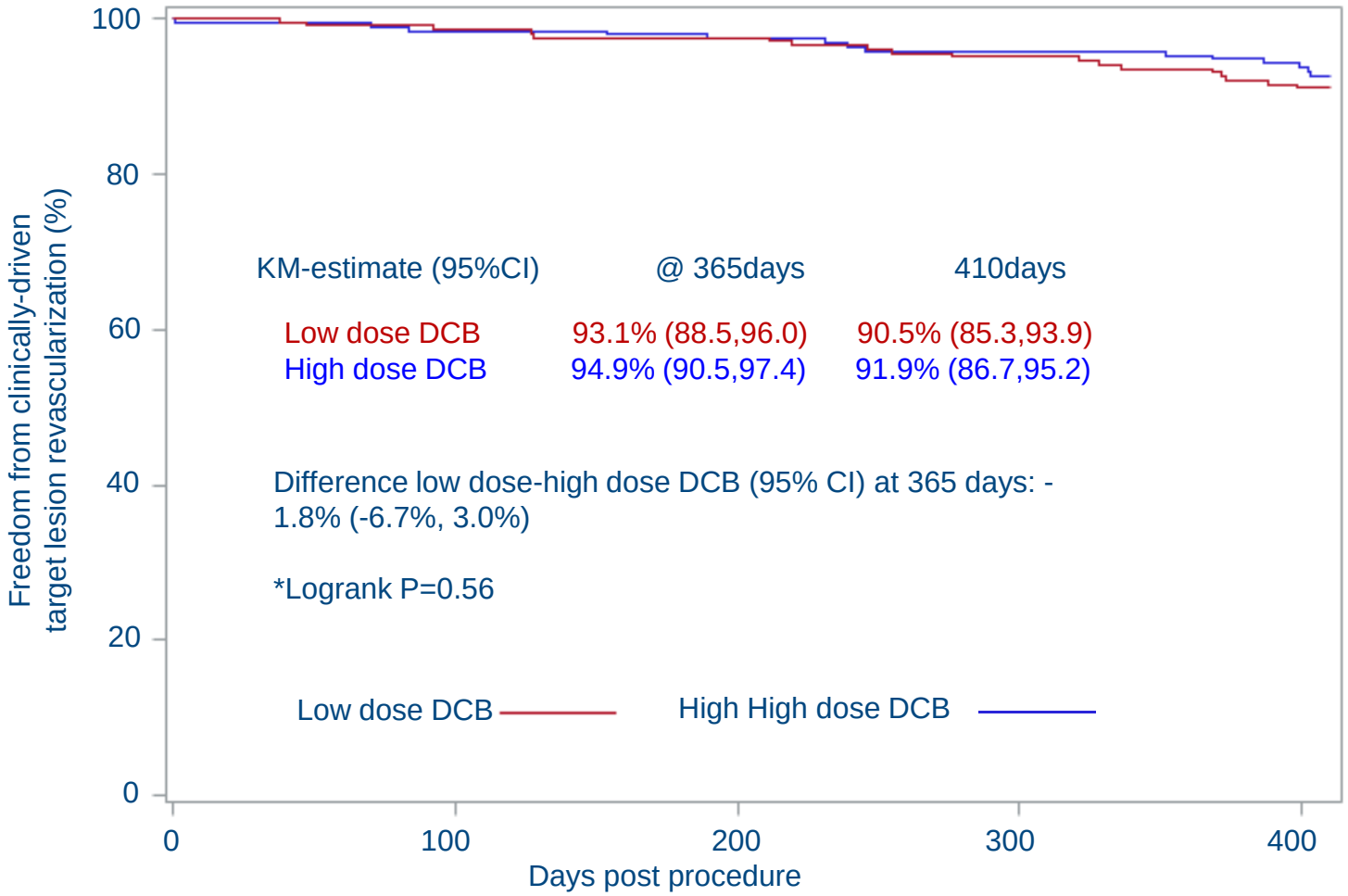
COMPARE RCT
Survival analysis: Primary Patency



Steiner S et al. Eur Heart J 2020; pre-published online Jan 28th

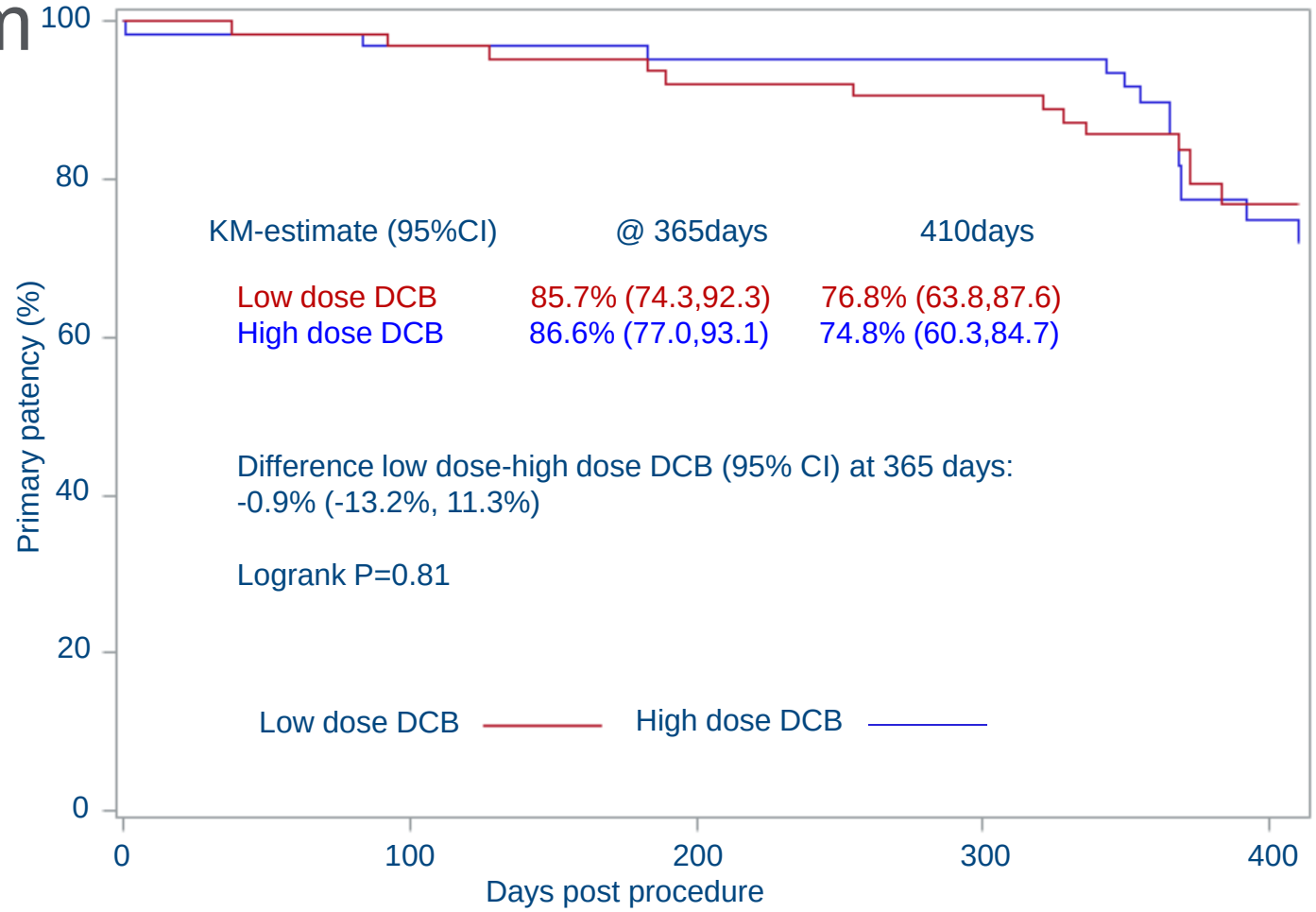
COMPARE RCT

Survival analysis: Freedom from CD-TLR



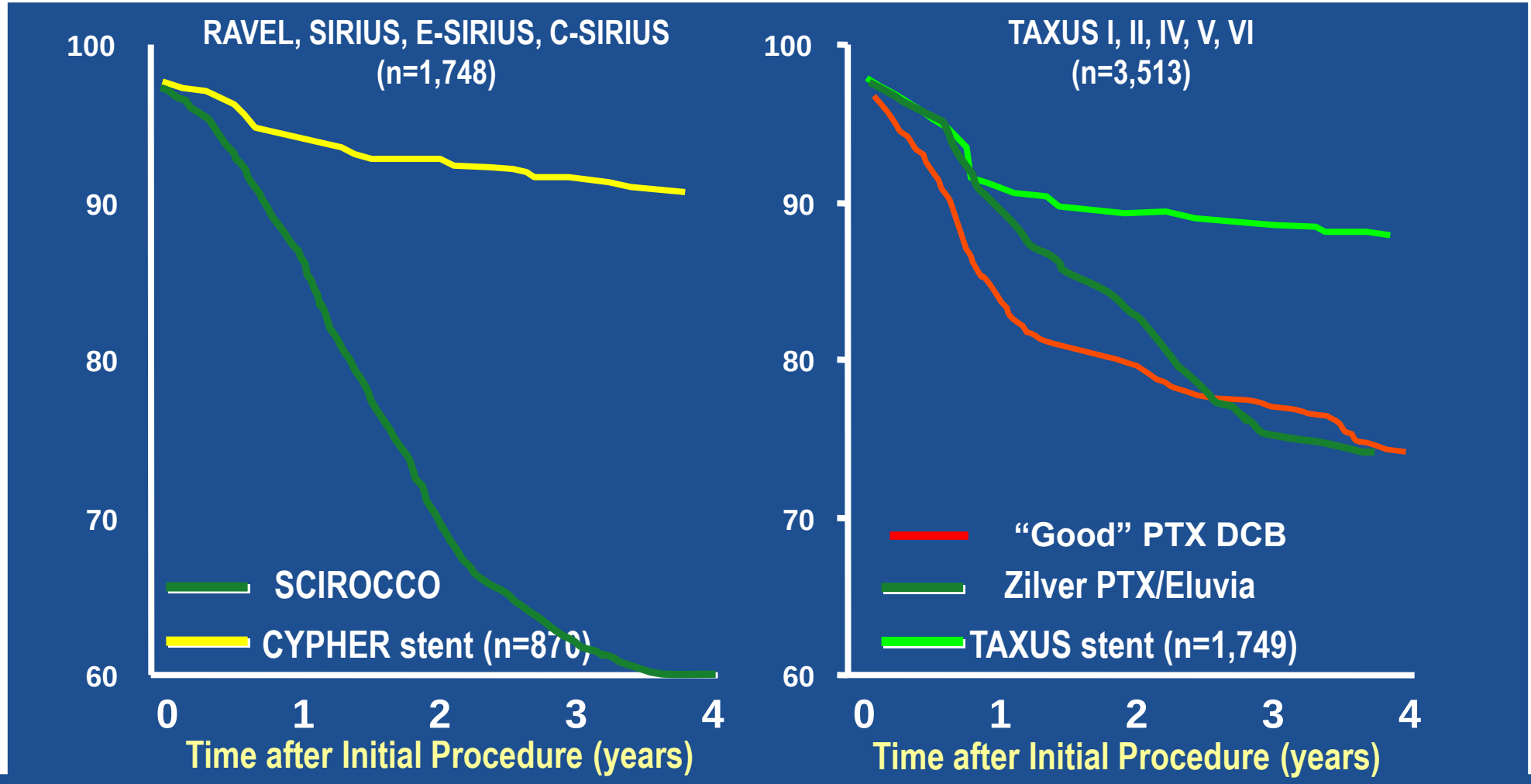
Steiner S et al. Eur Heart J 2020; pre-published online Jan 28th

COMPARE RCT: Primary patency in long lesions >20cm and ≤30cm



Steiner S et al. Eur Heart J 2020; pre-published online Jan 28th, Supplementary Data.

TLR Rates of DES and DCB 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.

Question: 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	LASER	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

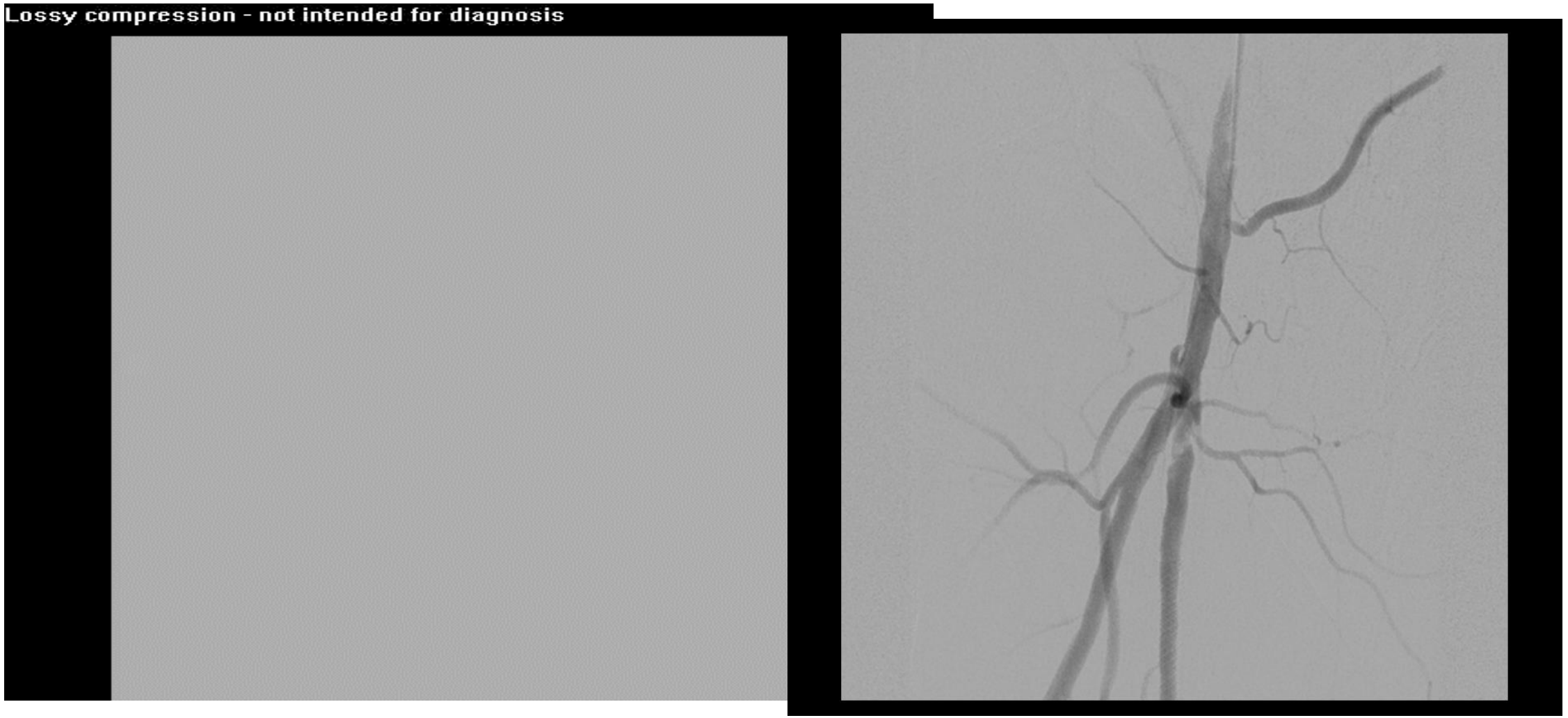
Klein AJ et al. Catheter Cardiovasc Interv. 2017;90(4):E90-E110.

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

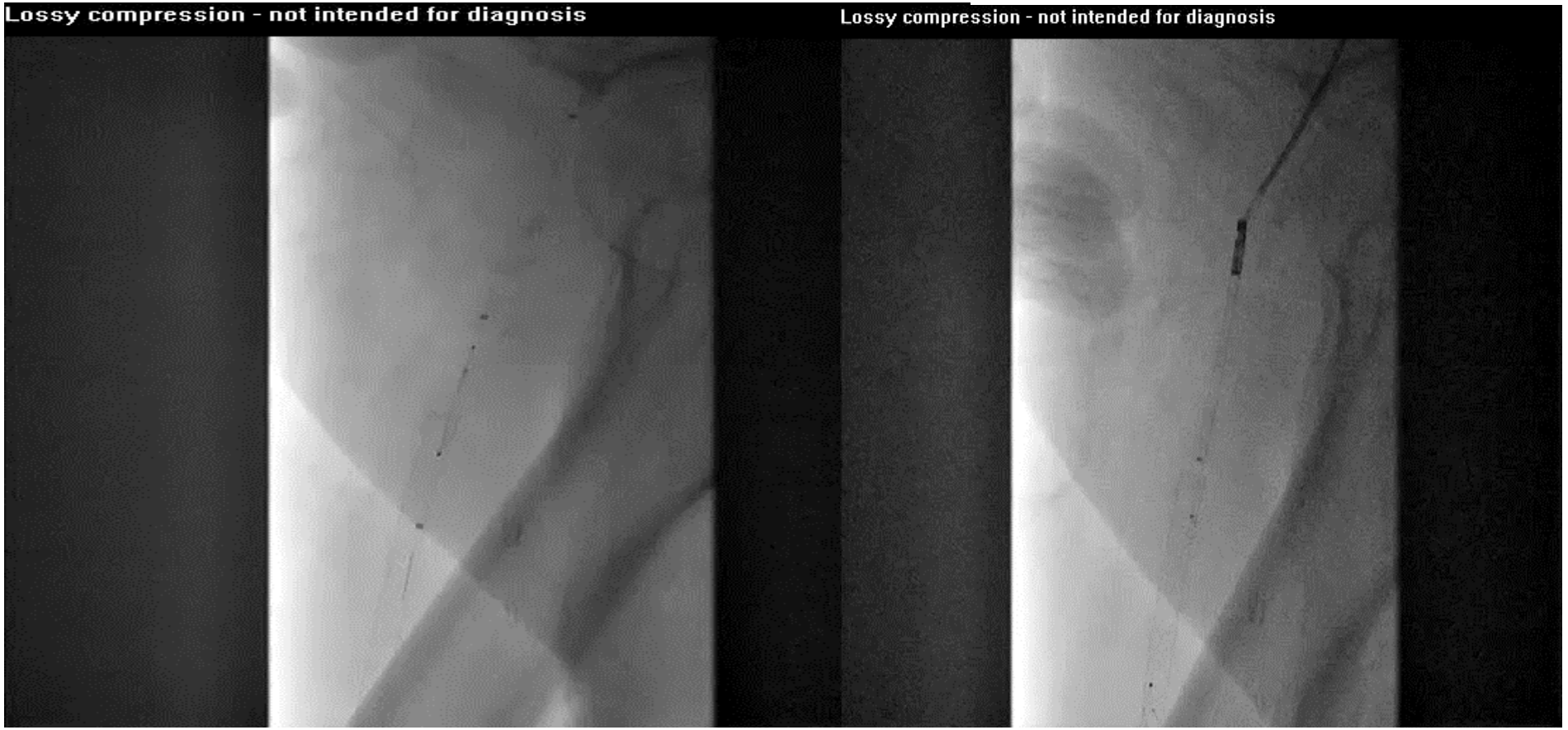
	PTA	Specialty balloons	BMS (Self-expanding)	DES	DCB	Covered stents	Laser atherectomy	Directional atherectomy	Orbital/ Rotational atherectomy	Excisional/aspiration atherectomy
1. CFA bifurcation lesion	IIB C-LD	IIB C-EO	IIA B-R	IIA C-EO	IIA C-EO	III H C-EO	III NB C-EO	III NB C-EO	III NB C-EO	III NB C-EO
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.

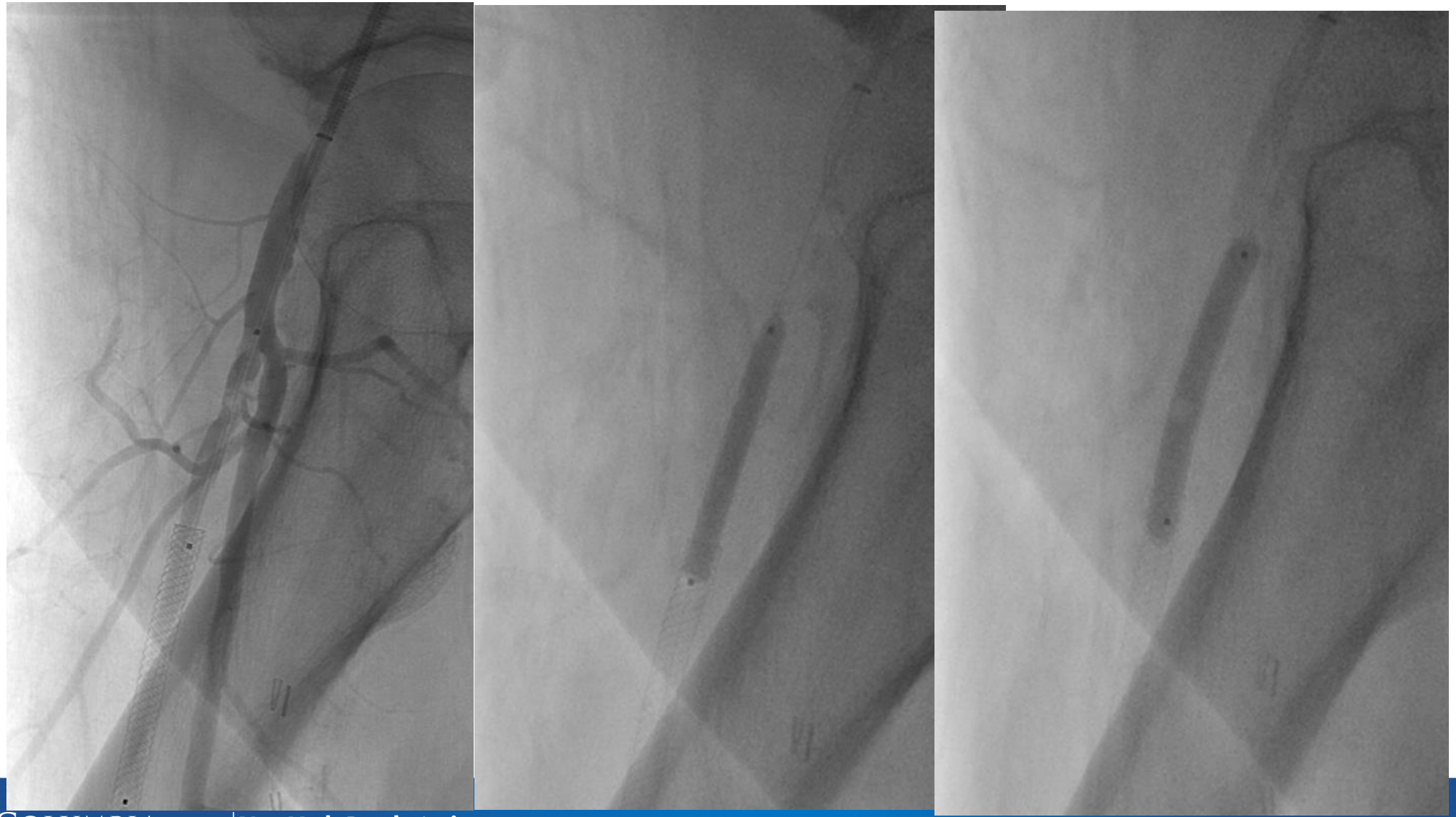
Back to our case… Two Years Later…. (2012)



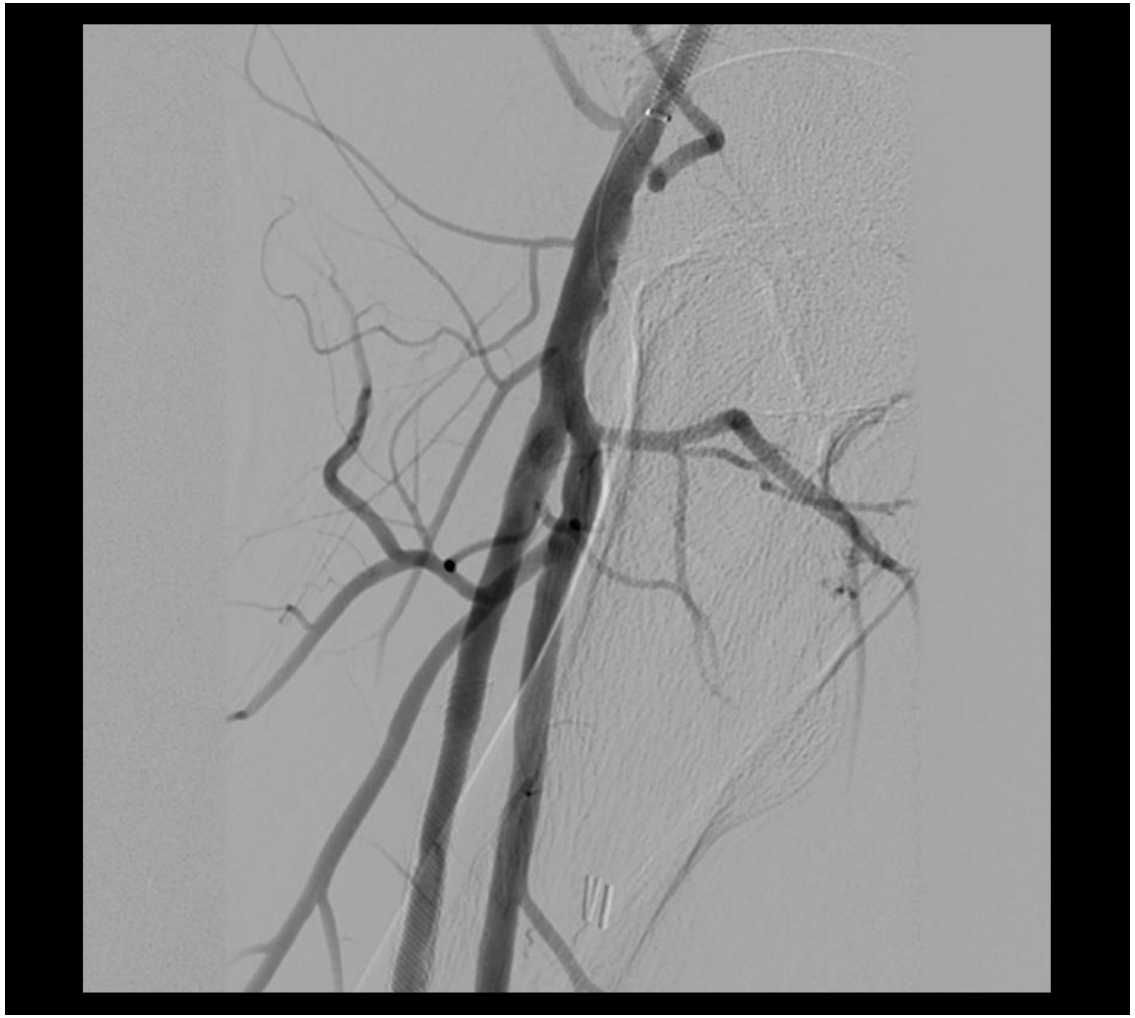
Decision to pursue directional atherectomy with filter protection



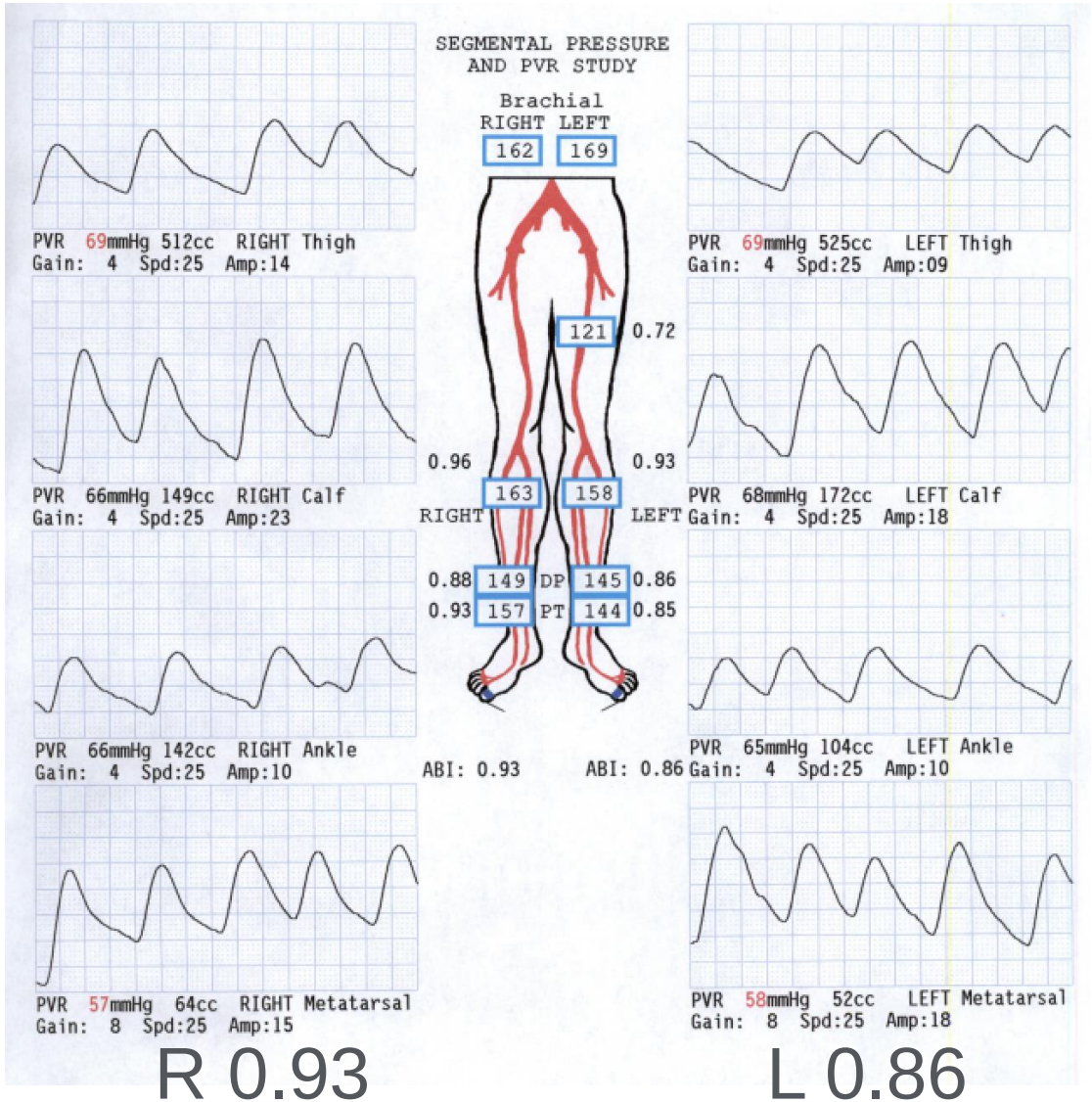
After Atherectomy



Final Angiography



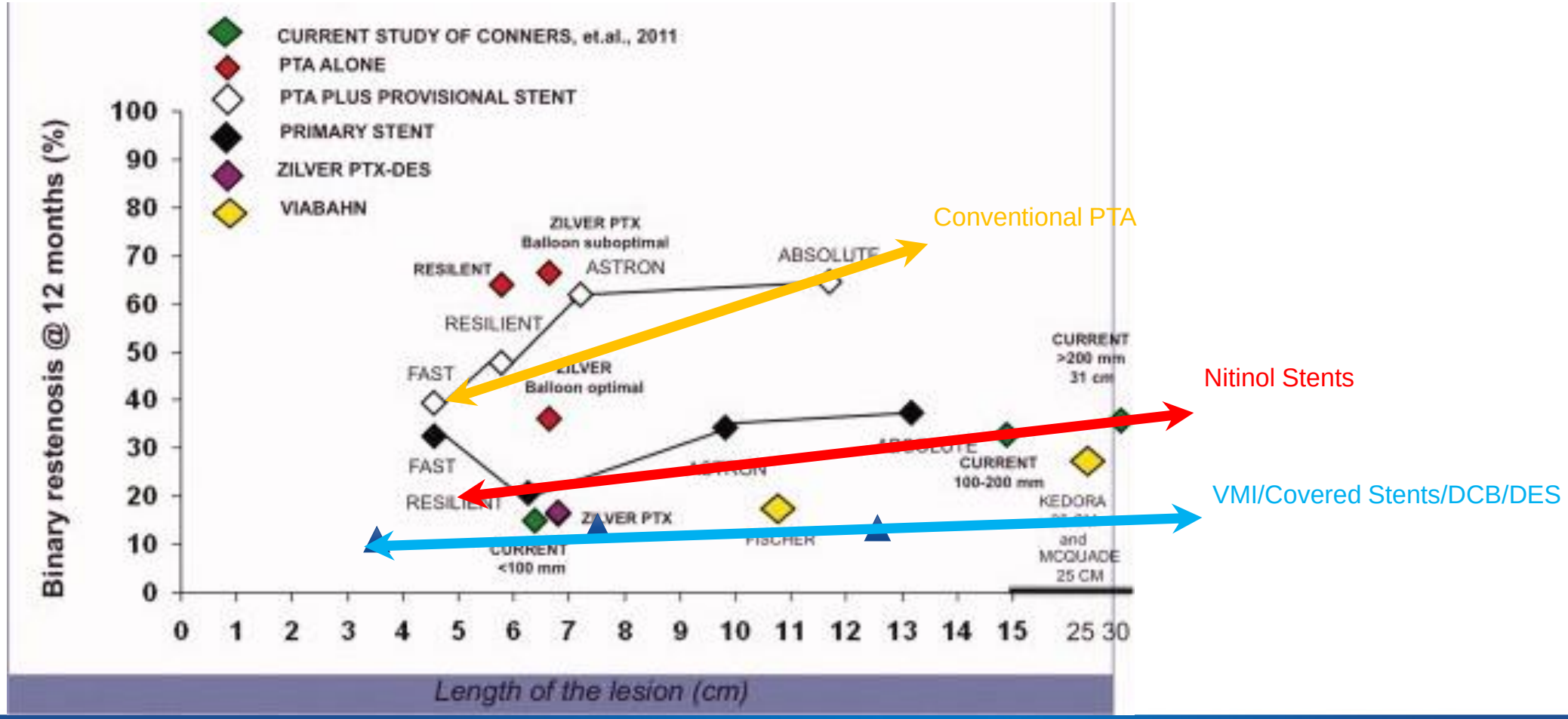
ABI 13 Years After Stent



R 0.93

L 0.86

SFA Patency Decreases with Lesion Length for PTA and "Conventional Stenting" but less so for Newer Technologies Including Novel Stent Designs and Drug Delivery Devices



Adapted from: Gray B. CCI. 2011

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

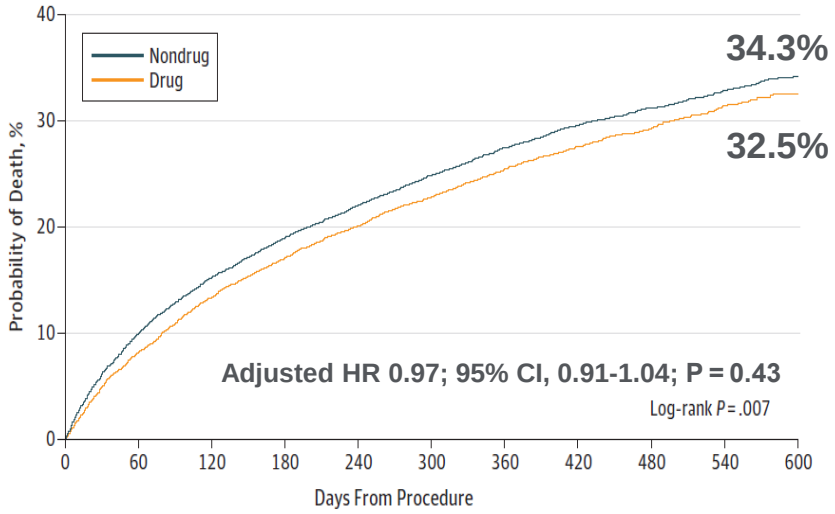
Initial Analyses of Medicare Beneficiary Data

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

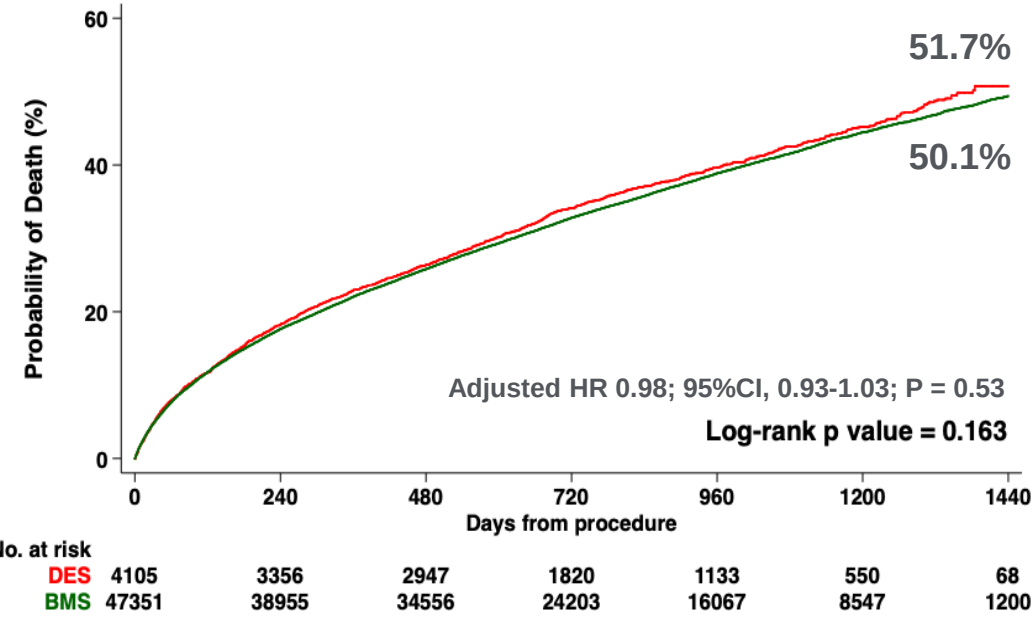


JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

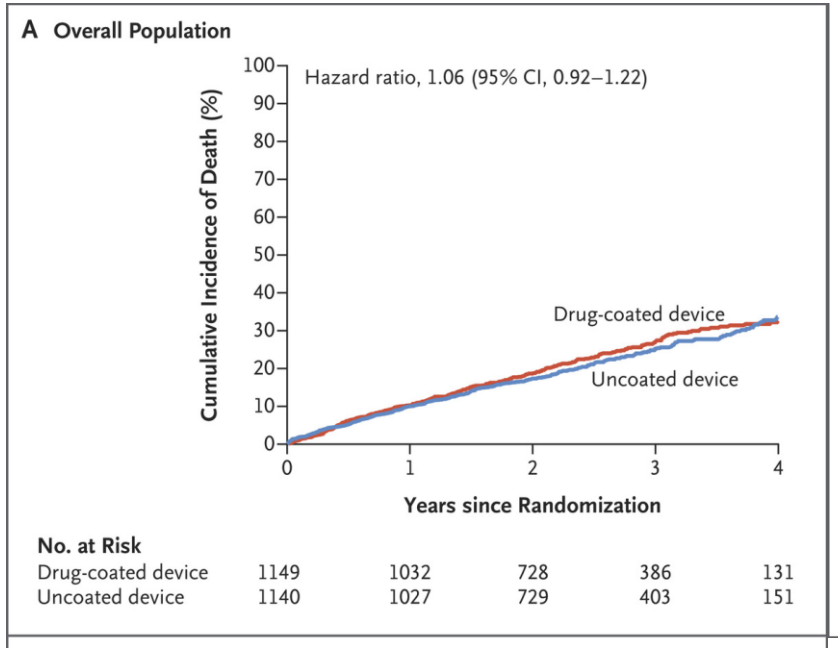
March 1, 2019

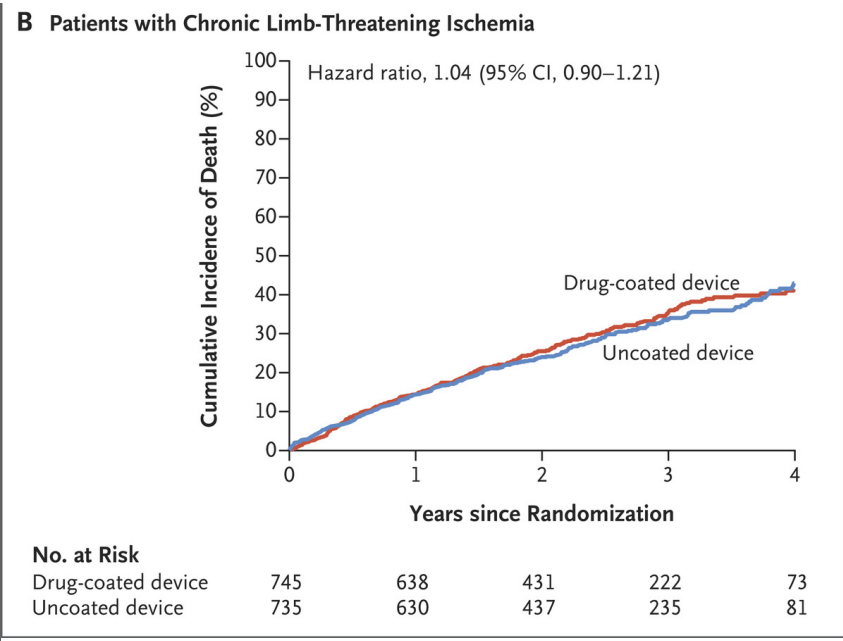
Drug-Eluting Stent Implantation and Long-Term Survival Following Peripheral Artery Revascularization

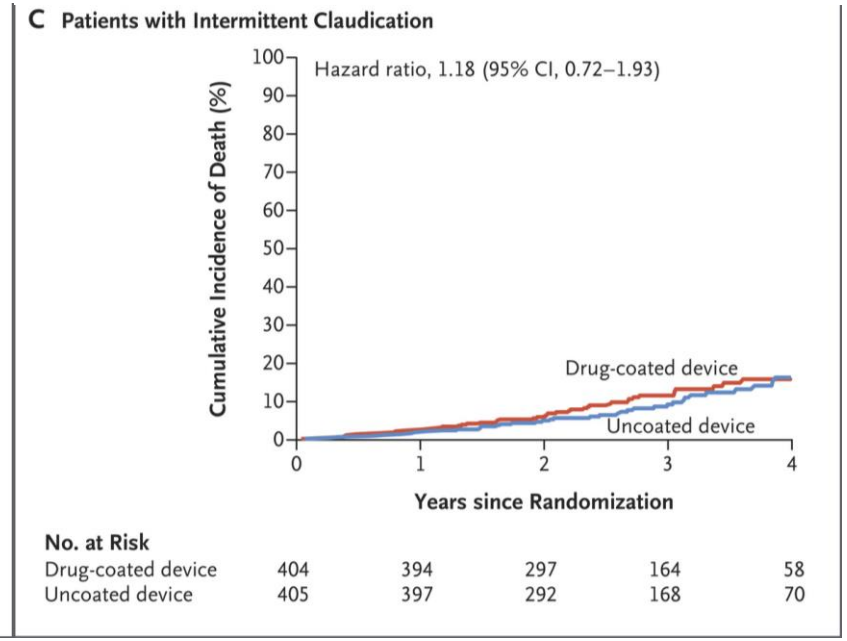
Eric A. Secemsky, Harun Kundi, Ido Weinberg, Marc Schermerhorn, Joshua A. Beckman, Sahil A. Parikh, Michael R. Jaff, Jihad Mustapha, Kenneth Rosenfield and Robert W. Yeh



SWEDEPAD:
No increased mortality in interim analysis





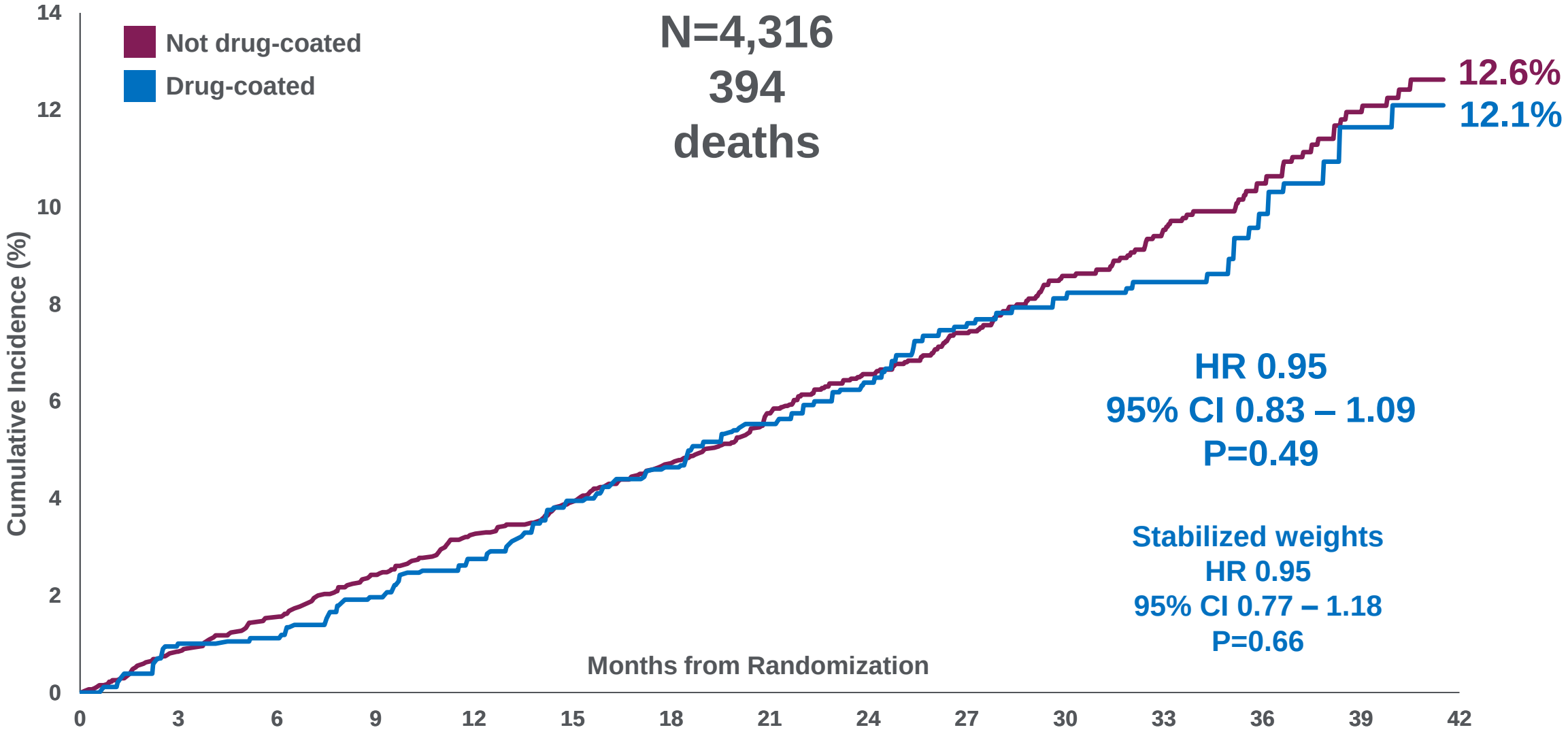


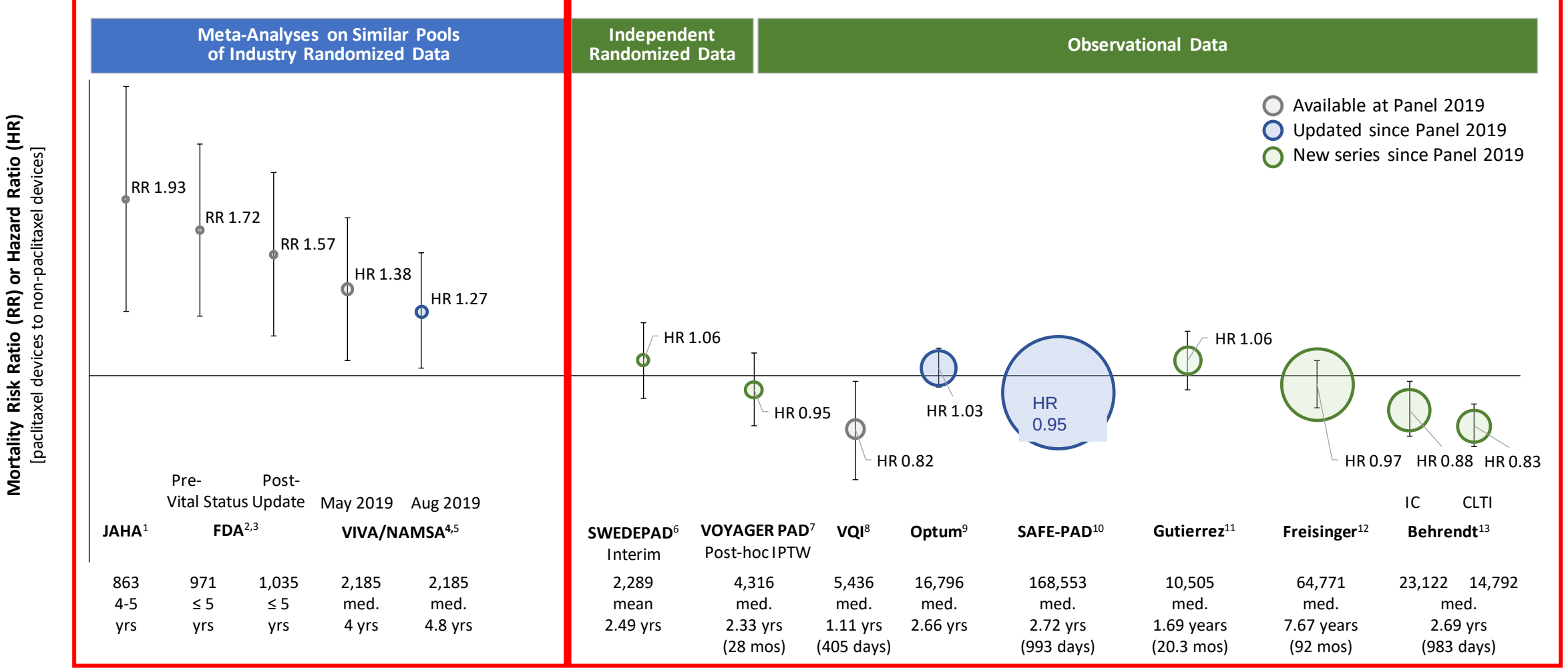
J Nordanstig et al. N Engl J Med 2020;383:2538-2546.

VOYAGER PAD

All-cause Mortality

Weighted





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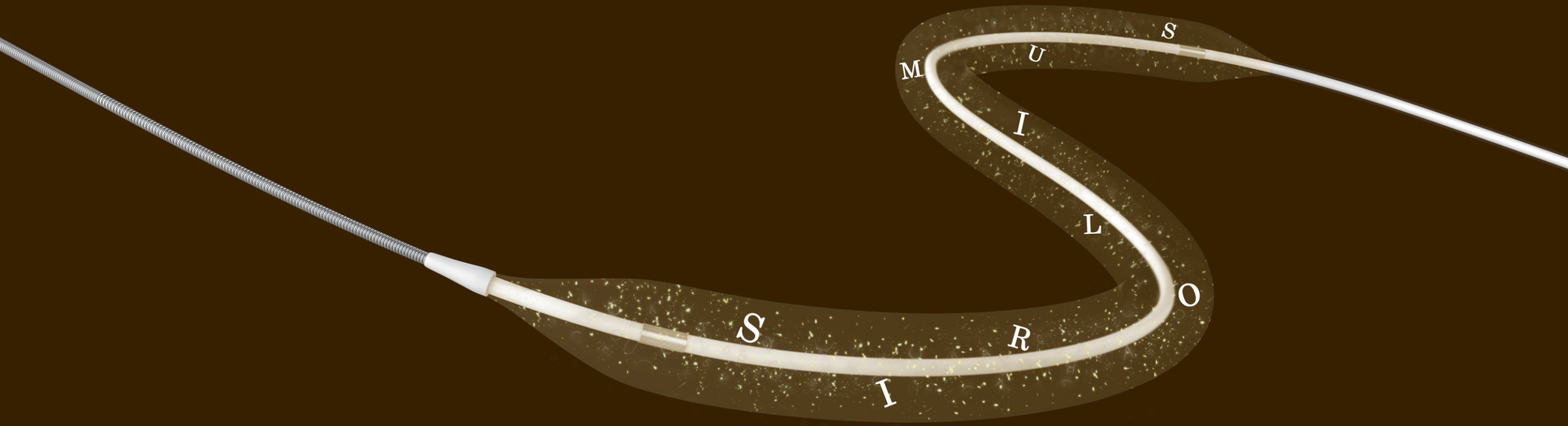
10. Secemsky EA, et al. JAMA Intern Med. 2021 Aug 1;181(8):1071-1080.

How do we do better for our patients?

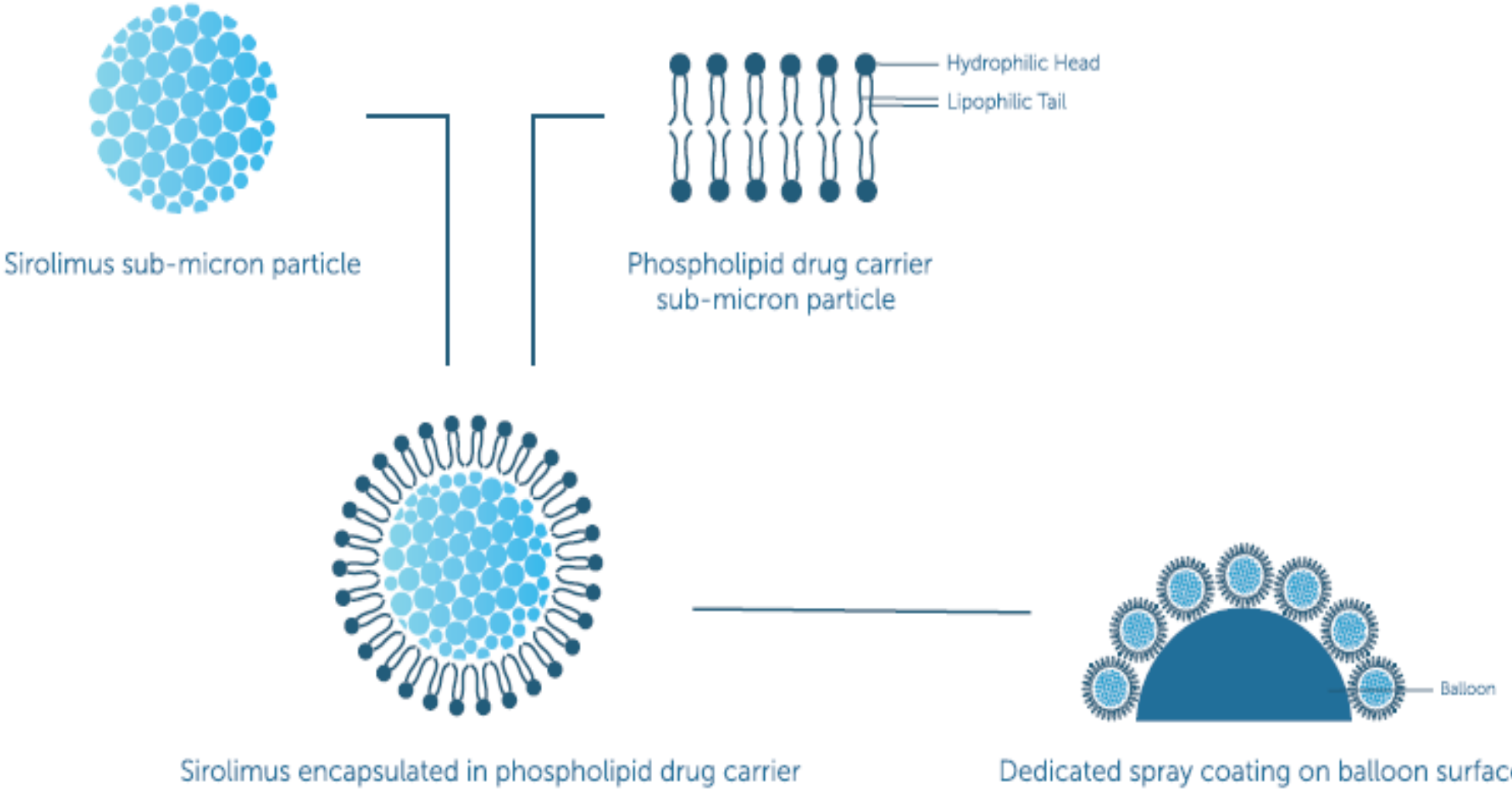
MagicTouch PTA

Sirolimus Coated Balloon



Designed by NANOLUTE TECHNOLOGY

DEPICTION OF *NANOLUTE TECHNOLOGY*



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%

FUTURE-SFA

- Subject target: 279
- Rutherford class 3-6
- SFA, P1, P2
- Single or sequential lesion, 2-20cm
- De novo or re-stenosis lesion
- No significant inflow dis
- At least 1 patent crural artery run-off to foot

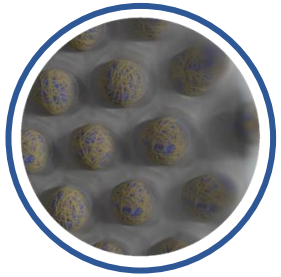
- Determine effectiveness (primary patency)
- Quadruple blinded (Participants, care provider, investigator, outcome assessor)
- 2:1 enrollment
- CRO controlled
- Core Lab adjudicated
- Follow-up 6, 12, 24 months

FUTURE-BTK

- Subject target: 219
- Rutherford class 4-6
- Proximal 20cm of BTK arteries
- Single or sequential lesion, 2-20cm
- De novo or re-stenosis lesion
- No significant inflow dis
- Target vessel has run-off to foot after Rx

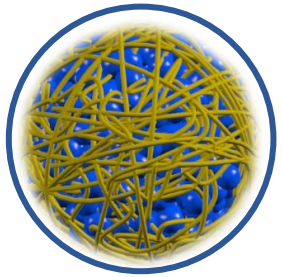
SELUTION SLR™

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



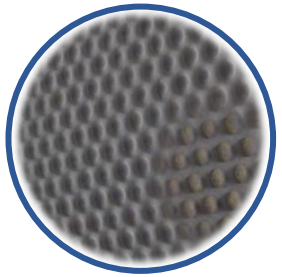
Proprietary MicroReservoir Technology

- 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

SUSTAINED LIMUS RELEASE

COLUMBIA NewYork-Presbyterian

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

SELUTION SLR - Clinical Trial Program

- Peripheral program Enrolling Over 1900 Patients

MEDALLIANCE Sponsored Trials	Indication	Patient Numbers	Region	Design	Status
SELUTION FIM	SFA	50	Germany	Single Arm	Completed 2 Year Data
SUCCESS	**SFA/BTK/Foot**	**772**	**Asia/Europe/LAM**	**Single Arm**	**Enrolling**
SELUTION 4SFA	SFA/Popliteal	300	Europe/US	RCT	In review with FDA
SELUTION 4BTK	**BTK**	**377**	**Europe/US**	**RCT**	**Enrollment expected to start in Q2 2022**
JAPAN SFA	SFA	134	Japan	Single Arm	Post-enrollment
CHINA SFA	SFA	139	China	RCT	Enrolling

Physician-Initiated Trials	Indication	Patient Numbers	Region	Design	Status
PRESTIGE	**BTK**	**25**	**Asia**	**Single Arm**	**18 Month Data**
PRISTINE	**BTK**	**75**	**Asia**	**Single Arm**	**Enrollment completed**
STEP	**Foot**	**20**	**Austria**	**Single Arm**	**Enrolling**
FLOW	SFA	70	Germany	RCT	Enrolling

Summarizing the Data for Arterial IVUS

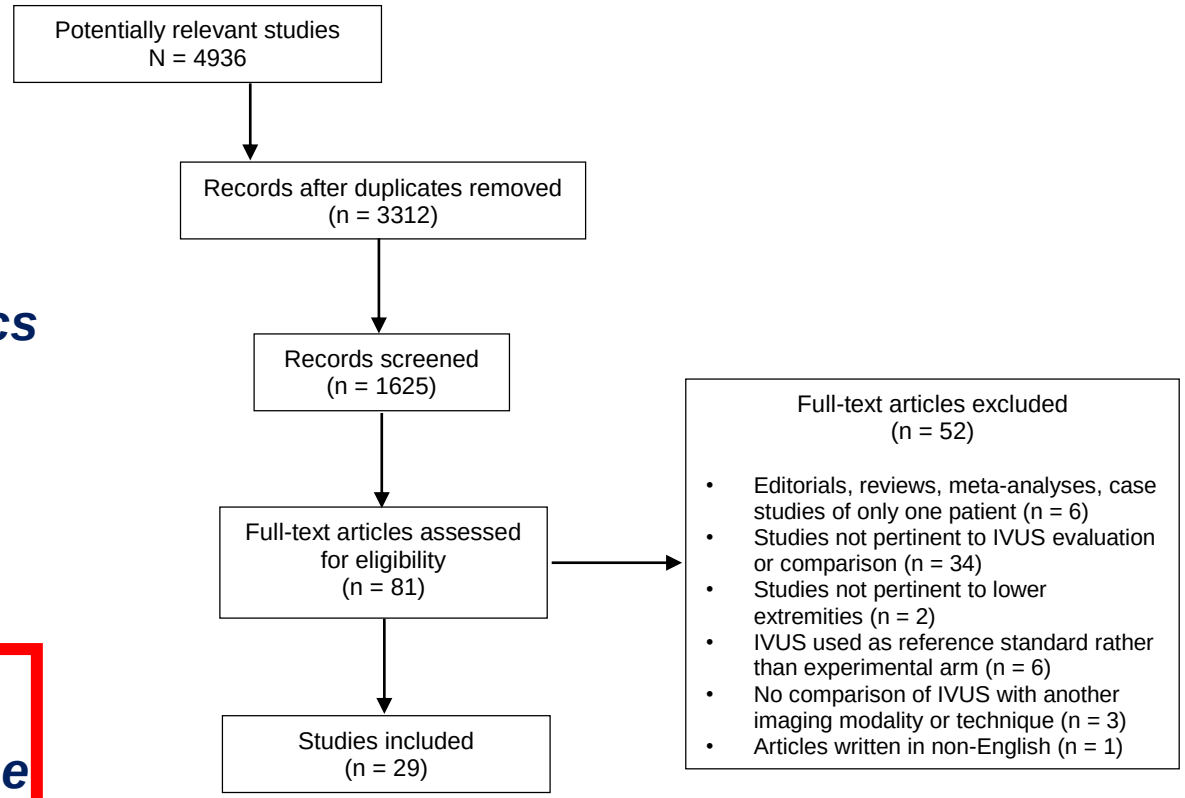
Arterial Studies (N=29):

- *25 cohort studies, 4 case-series, N=95,192 patients*
- *Studies Examined:*
  - *18/29: Device sizing, placement, and optimization*
  - *6/29:Evaluation of lesion characteristics and severity*
  - *3/29: Management of arterial dissections*
  - *2/29: Reentry of chronic total occlusions*

Grading Level of Evidence

- *23/29 (79.3%) received a Level 2b rating, the second highest level of evidence rating*

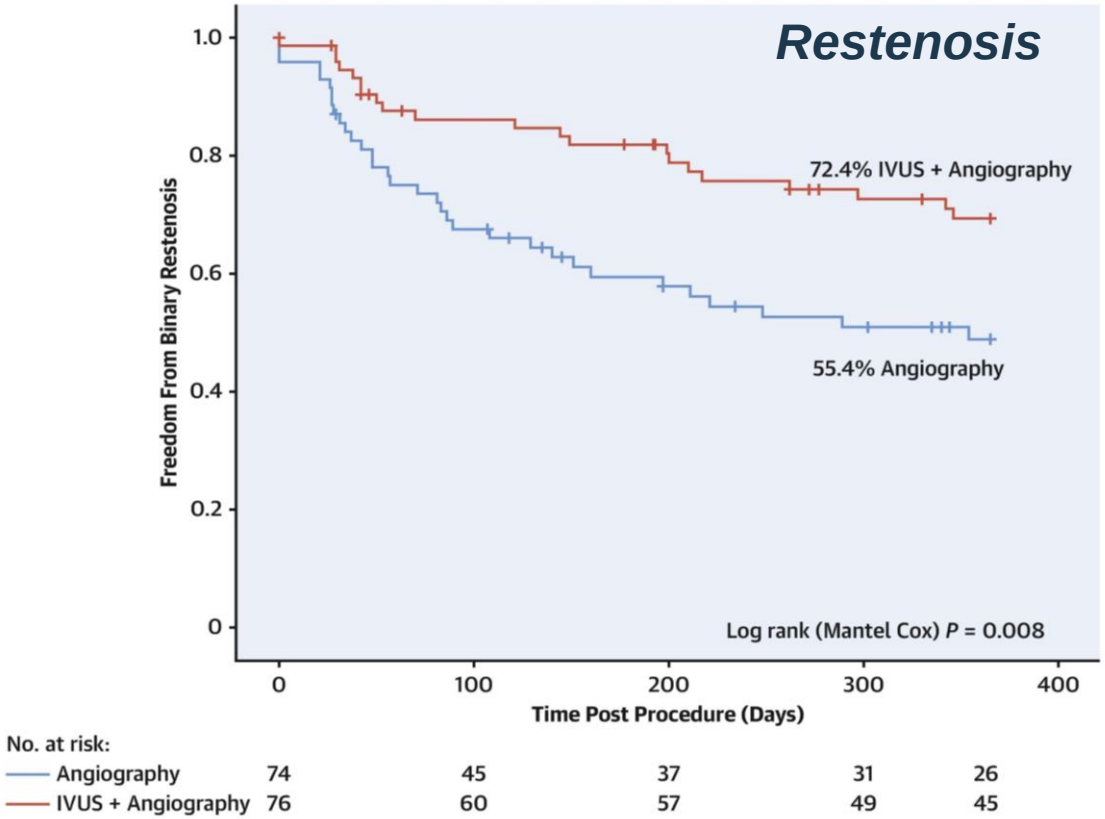
Arterial Studies



Natesan S, Mosarla RC, Parikh SA, Rosenfield K, Suomi J, Chalyan D, Jaff M, Secemsky EA. Intravascular Ultrasound in Peripheral Venous and Arterial Interventions: A Contemporary Systematic Review and Grading the Quality of Evidence. Vasc Med, 2022.

Restenosis Following Randomization to Angiographic Guidance Vs. IVUS + Angiography for Femoropopliteal Interventions

- **150 patients randomized to angiography alone vs IVUS + angiography for femoropopliteal artery intervention**



Findings driven in part by appropriate sizing of DCBs

	Control group	IVUS group	Total
No binary restenosis	25 (62.5%)	**40 (90.9%)**	P=0.004
Binary restenosis	15 (37.5%)	4 (9.1%)	

Allan RB, et al. JINT 2022.

Restenosis Following Randomization to Angiographic Guidance Vs. IVUS + Angiography for Femoropopliteal Interventions

Changes in the treatment plan due to IVUS findings

Treatment change	Number of occasions	% of total treatment changes
Changes to initial plan - total	65	78.3%
Increase in treatment length	32	38.6%
Increase in treatment device size	21	25.3%
Change in initial treatment modality	7	8.4%
Decrease in treatment length	3	3.6%
Decrease in treatment device size	2	2.4%
Changes after initial treatment	18	21.7%
Additional angioplasty due to IVUS	10	12.1%
Adjunctive stenting due to IVUS	7	8.4%
Repeat atherectomy due to IVUS	1	1.2%

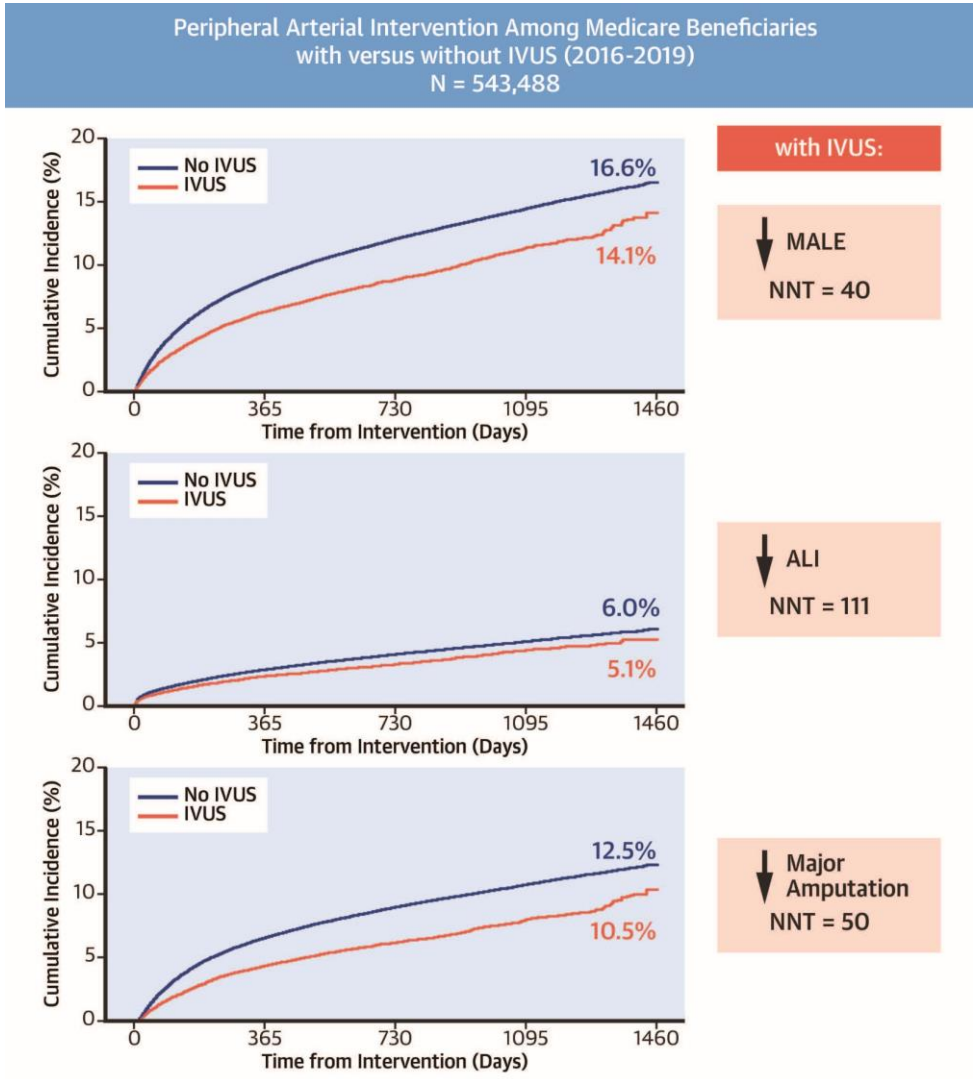
Types of disagreement in imaging findings between

Pre initial treatment	n=151
Disagreement in RVD	68 (45.0%)
Disagreement in lesion length	71 (47.0%)
Disagreement in plaque eccentricity	6 (4.0%)
Disagreement in cause of stenosis	4 (2.6%)
Disagreement in pre-treatment stent appearances	2 (1.3%)
Post initial treatment	n=34
Disagreement in the severity of dissection	16 (47.1%)
Disagreement in the severity of residual stenosis	14 (9.3%)
Disagreement in adequacy of stent expansion	4 (2.6%)

Allan RB, et al. JINT 2022.

CMS Data: Opportunities to Improve Outcomes With IVUS

- ***543,488 Medicare patients who underwent lower extremity PVI from 2016-2019***
  - ***63,372 (11.7%) treated with IVUS***
- ***Includes procedures performed in hospitals, hospital outpatient centers and ASC/OBLs***
- ***Findings stratified by:***
  - ***CLI vs Claudication***
  - ***Arterial segment (iliac, fempop, tibial)***
  - ***Procedural location***



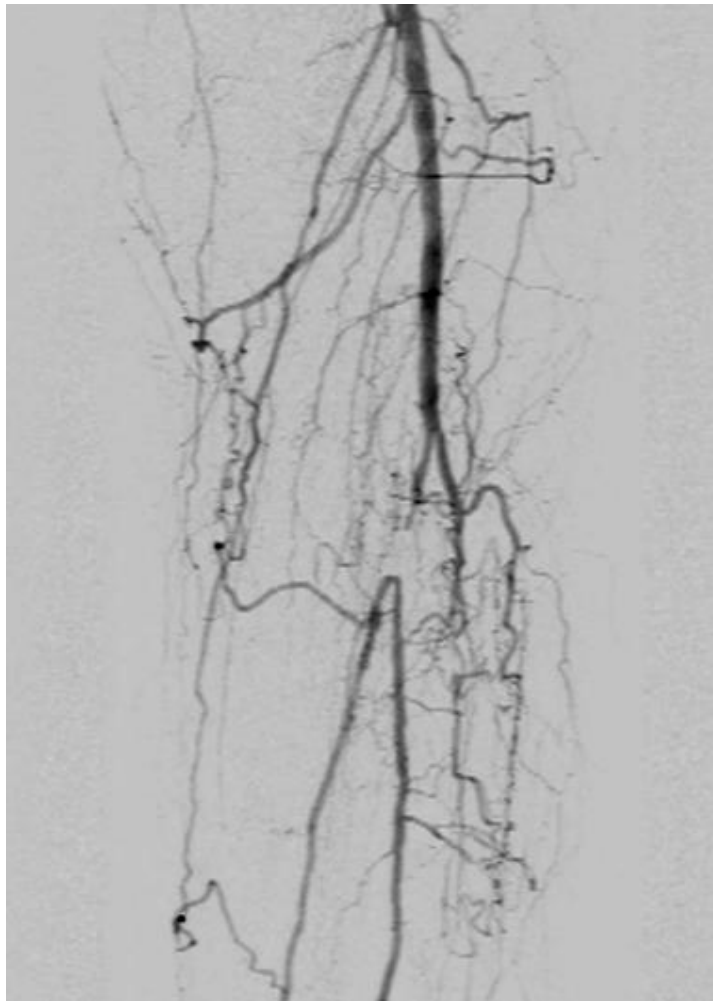
Secemsky EA, et al. JACC: Cardiovascular Interventions 2022. [In Press]

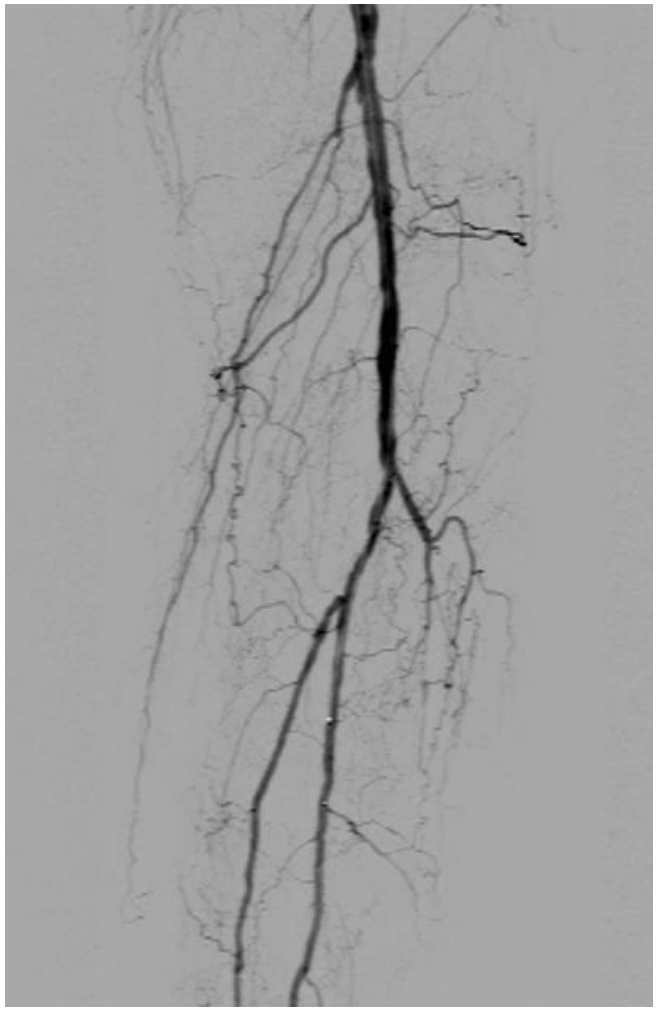
How About Below Knee Lesions?

Revascularization

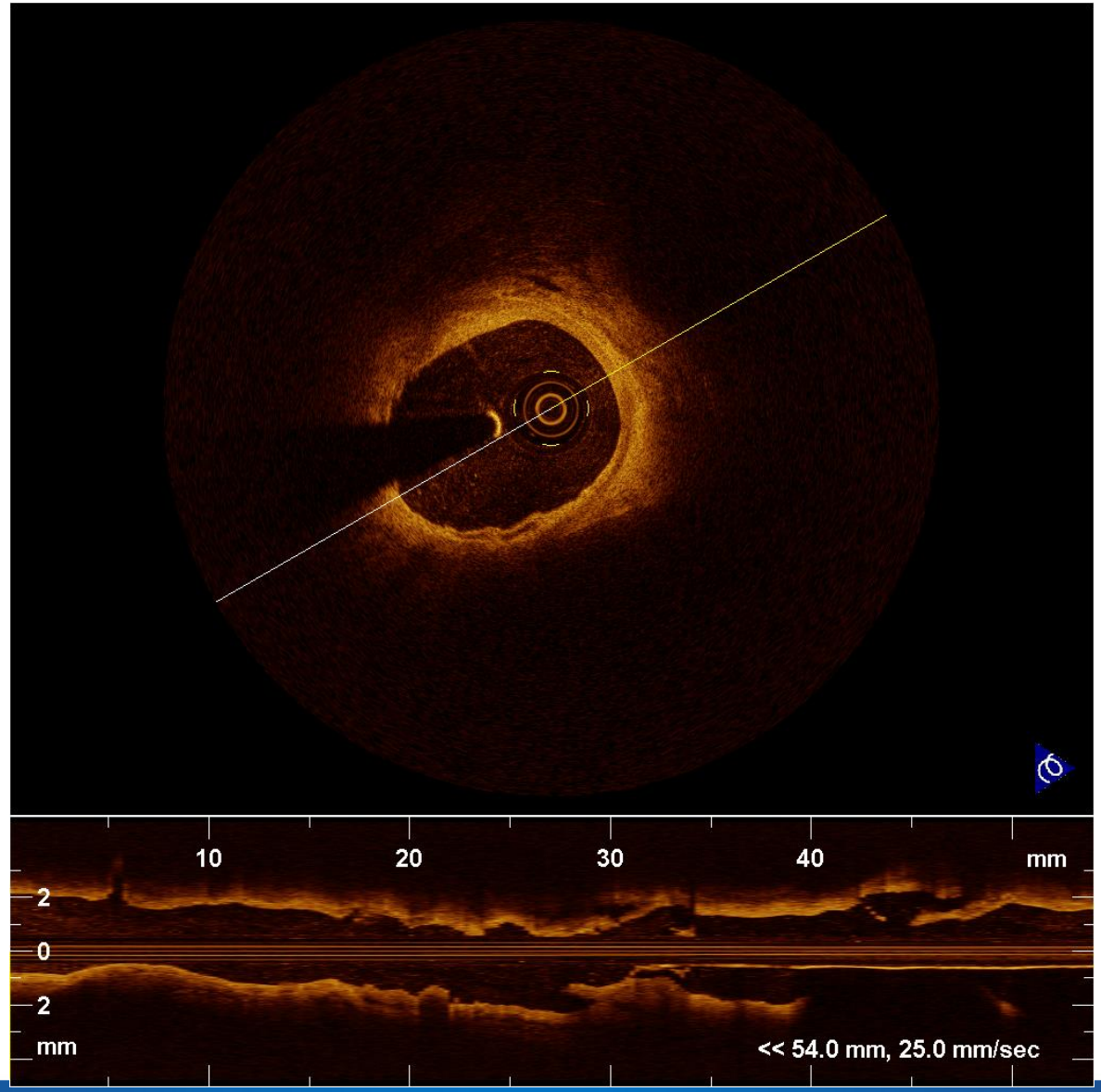
- Scaffolds → New Data – Not all good
- Drug Elution → New Trials with Sirolimus Take Flight

Short Segment Occlusion PTA: Satisfactory Angiographic Result?

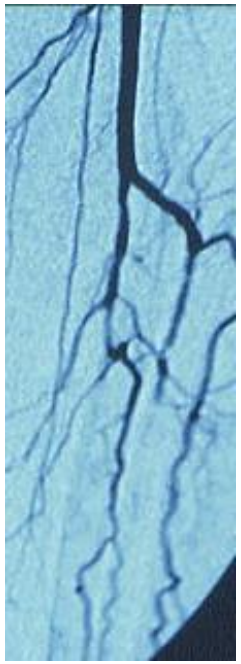
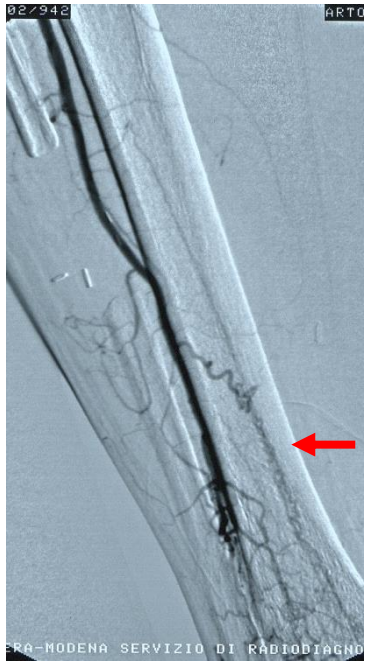
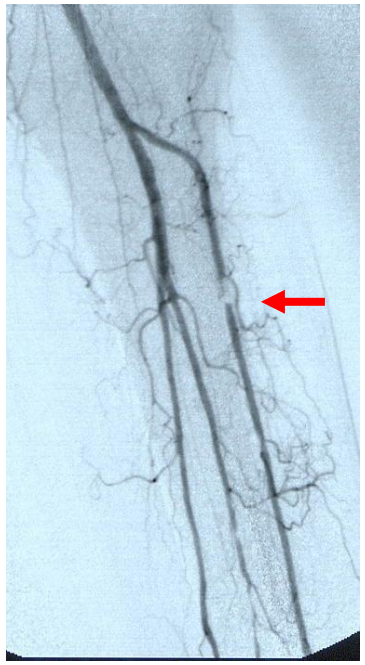
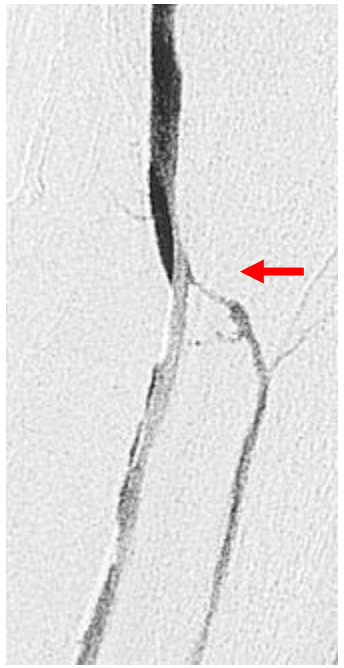




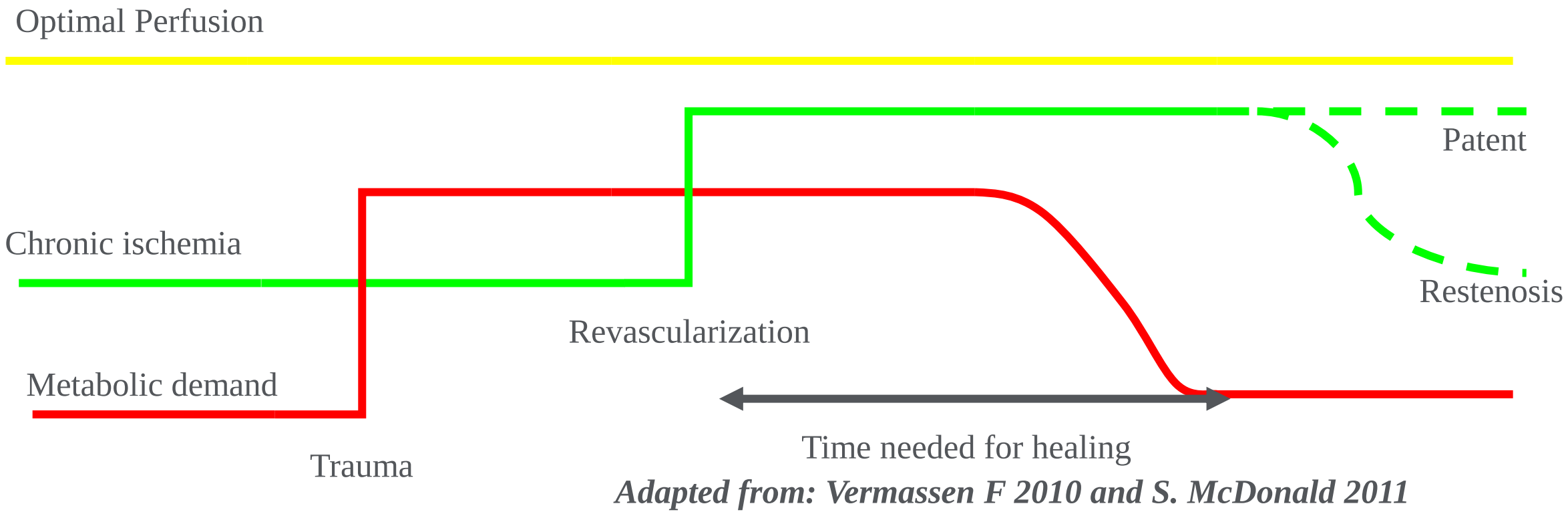
OCT of TP Trunk Post PTA



CLTI Anatomically is a Heterogenous Disease

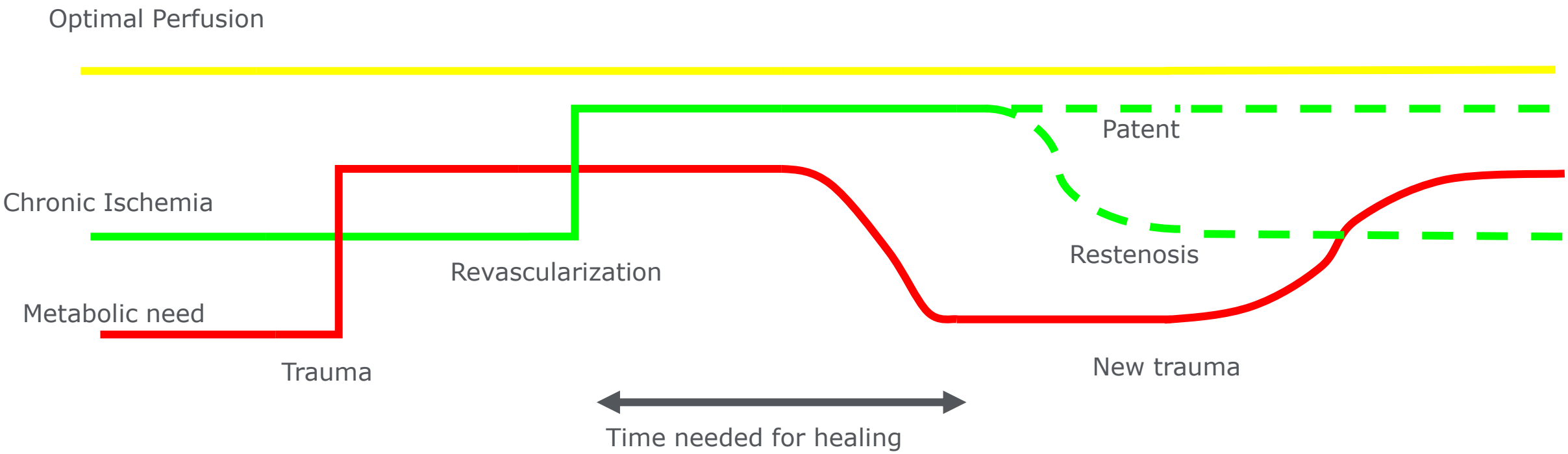
A	B	C	D
			
long occlusion	long oclusion	Short occlusion	Stenosis
3 tibial arteries	ant. + post. tibial a. + distal obstruction peroneal a.		

Is long term patency really needed for healing?



Adapted from: Vermassen F 2010 and S. McDonald 2011

Is long term patency needed for healing ?



Adapted from: Vermassen F 2010 and S. McDonald 2014

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

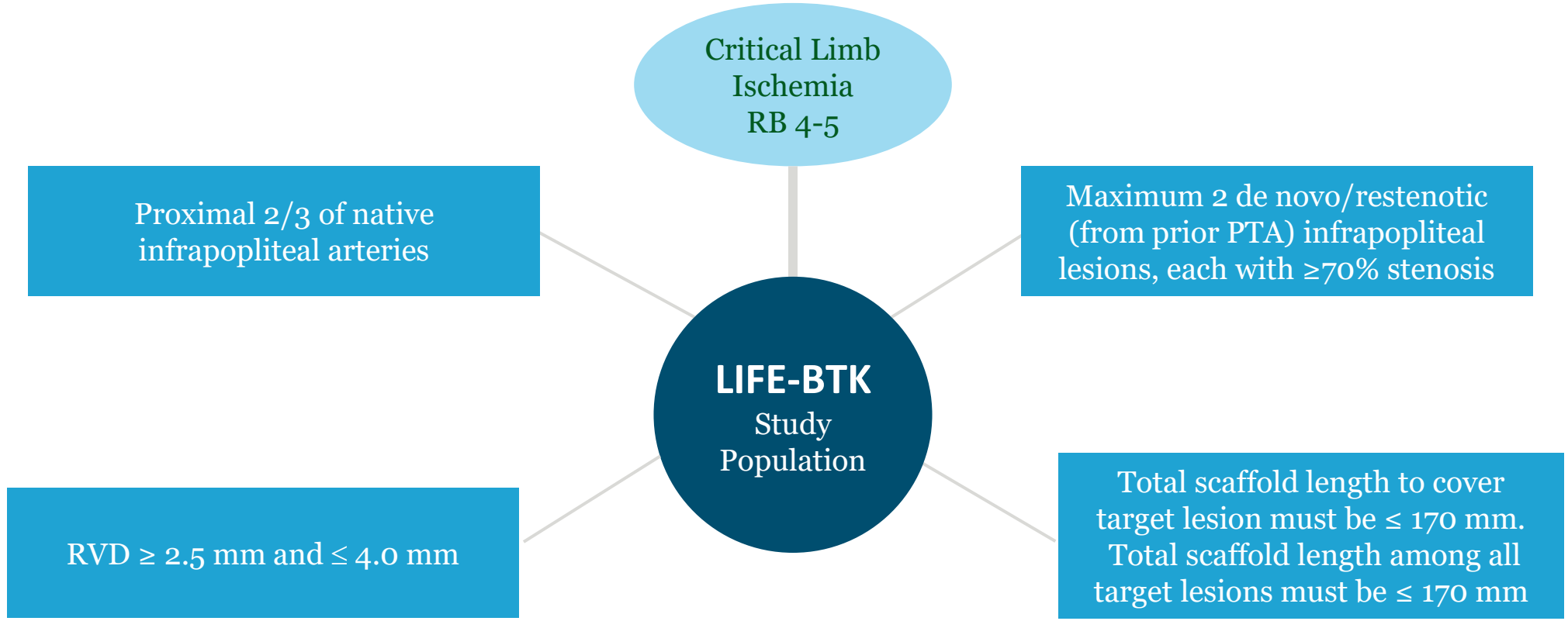
TRIAL LEADERSHIP

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

COLUMBIA NewYork-Presbyterian

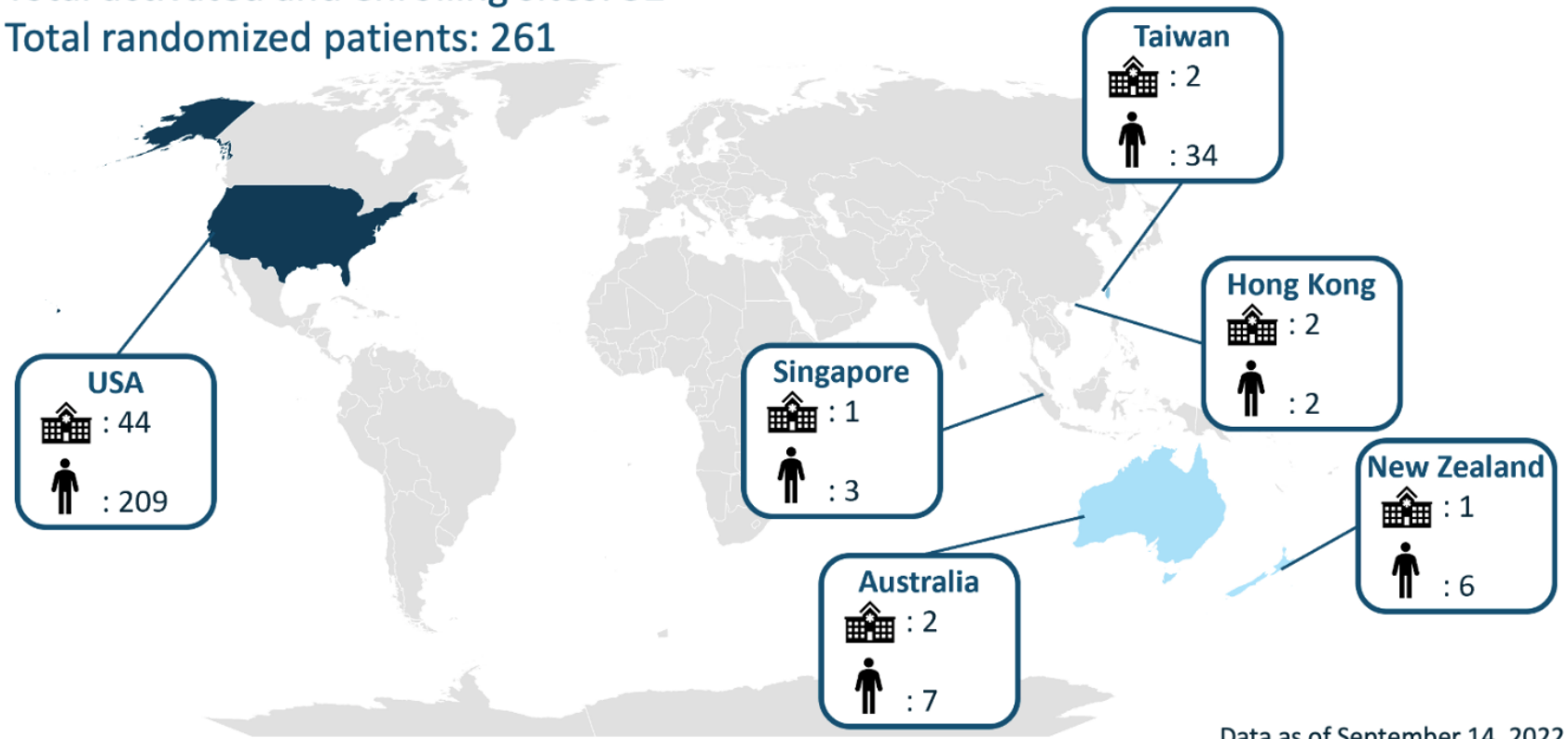
LIFE-BTK

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

LIFE-BTK Trial: Demographics

GENDER AND AGE

MALE	FEMALE
68.0% (174/256)	**32.0%** (82/256)

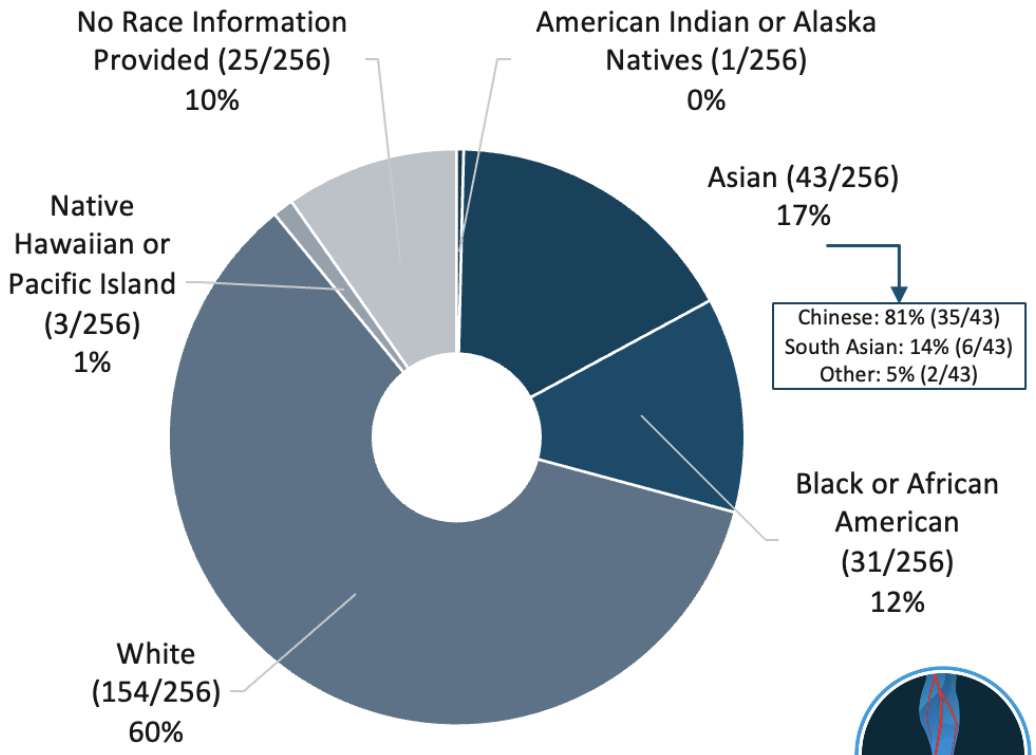
72.4 ± 10.1 years old

BMI: **28.3 ± 5.6**

ETHNICITY

80.5%	16.8%	2.7%
Not Hispanic/Latino	Hispanic/Latino	Declined/Unknown

RACE*



*One subject had 2 races entered.

Snapshot Data as of August 8, 2022.

LIFE-BTK Trial: Patient Risk Factors

Tobacco Use
53.1%
(136/256)

Hypertension
92.6%
(237/256)

Hyperlipidemia
80.9%
(207/256)

Diabetes
70.7%
(178/253)

Renal Disease
15.9%
(40/256)*

PAD Hx
80.1%
(205/256)

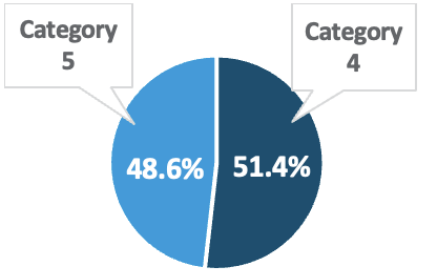
Prior MI
16.0%
(39/244)

CHF
19.8%
(50/253)

Previous PCI or CABG
34.9%
(88/252)

Prior CVA or Stroke
13.8%
(35/254)

DVT
4.3%
(11/256)



Rutherford Becker Clinical Category

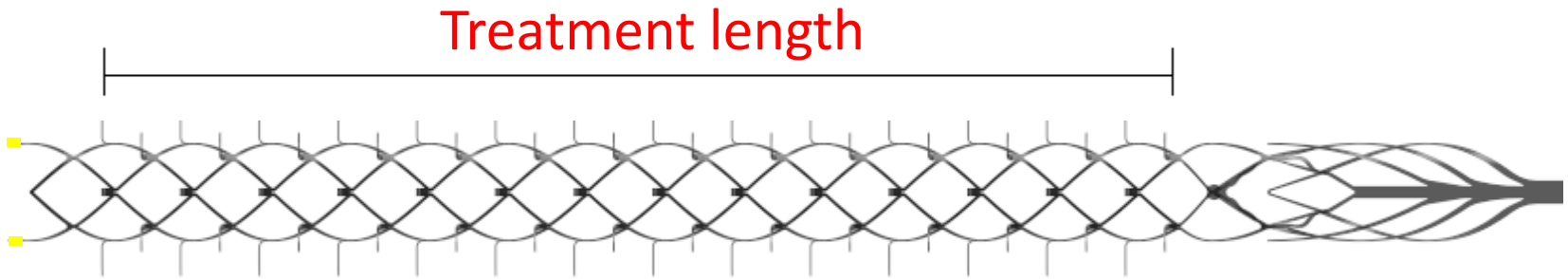
*Renal Insufficiency (Estimated GFR<30 ml/min per 1.173 m²): 7.5% (3/40).

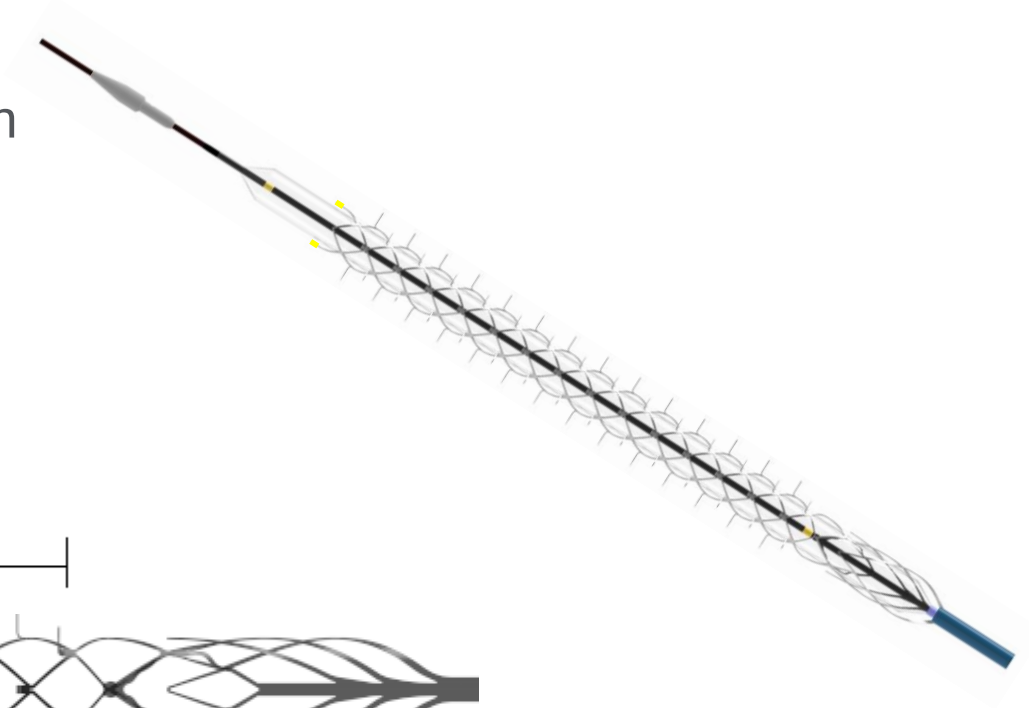
Snapshot Data as of August 8, 2022.

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

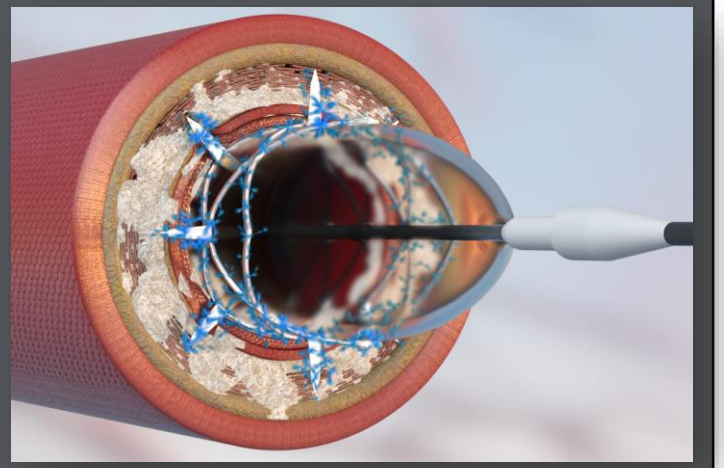




*Under Clinical Investigation

Reflow Medical's Temporary Spur Stent System*

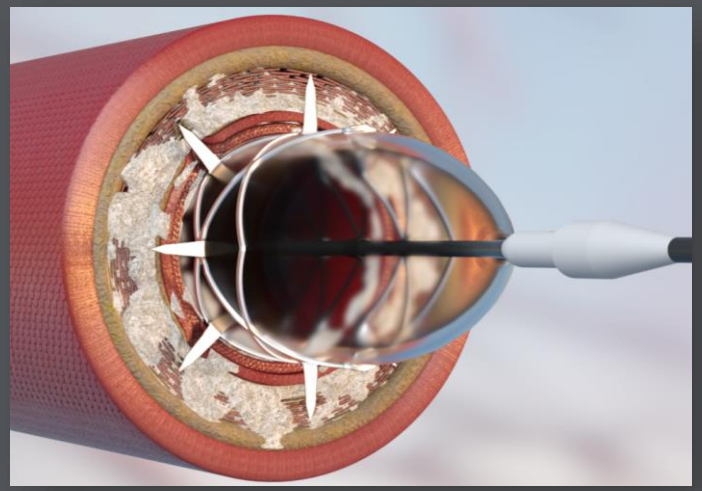
Limus Drug Coated Spur Stent



Received FDA Breakthrough Designation: an2022

- 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

Bare Spur Stent



Currently being conducted OUS: DEEPER OUS and DEEPER LIMUS studies

COLUMBIA NewYork-Presbyterian

REFLOW spur™

BEST-CLI

Best **E**ndovascular vs. Best **S**urgical **T**herapy in Patients with **C**ritical **L**imb **I**schemia

ORIGINAL ARTICLE

Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

A. Farber, M.T. Menard, M.S. Conte, J.A. Kaufman, R.J. Powell, N.K. Choudhry, T.H. Hamza, S.F. Assmann,* M.A. Creager, M.J. Cziraky, M.D. Dake, M.R. Jaff, D. Reid, F.S. Siami, G. Sopko, C.J. White, M. van Over, M.B. Strong, M.F. Villarreal, M. McKean, E. Azene, A. Azarbal, A. Barleben, D.K. Chew, L.C. Clavijo, Y. Douville, L. Findeiss, N. Garg, W. Gasper, K.A. Giles, P.P. Goodney, B.M. Hawkins, C.R. Herman, J.A. Kalish, M.C. Koopmann, I.A. Laskowski, C. Mena-Hurtado, R. Motaganahalli, V.L. Rowe, A. Schanzer, P.A. Schneider, J.J. Siracuse, M. Venermo, and K. Rosenfield, for the BEST-CLI Investigators†

CONCLUSIONS

Among patients with CLTI who had an adequate great saphenous vein for surgical revascularization (cohort 1), the incidence of a major adverse limb event or death was significantly lower in the surgical group than in the endovascular group. Among the patients who lacked an adequate saphenous vein conduit (cohort 2), the outcomes in the two groups were similar.

Critical appraisal

Case selection

- Mean age – 66 (much younger than what we typically see)
- Selection bias + operator preference; local variation
- Operators chose their preferred technique
- Operator experience - 12 cases for BTK

Enrollment

- Not required to consecutively enroll patients
- Average number of patients enrolled by the 150 sites over the 5 year study period was <10
- Only 2525 patients were assessed for eligibility, not representative of the total CLTI community.

Critical appraisal

Procedural characteristics

- Contemporary modalities not used- < 35% DCB's
- Revascularization segments
  - Tibial revascularization 1-3% for bypass and 43-51% with endo
- No Angiographic core lab to review burden of disease

Critical appraisal

Study Design

- Definitions of the outcomes → major reintervention DID NOT include endovascular interventions for secondary patency.

Data lacking

- Surgical/ endovascular complications
- Hospital readmission
- Seroma/dehiscence

HOT off the PRESS: DVA

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Transcatheter Arterialization of Deep Veins in Chronic Limb-Threatening Ischemia

Shishehbor MH et al. DOI: 10.1056/NEJMoa2212754

CLINICAL PROBLEM

Arterial revascularization is standard care for patients with chronic limb-threatening ischemia. However, up to 20% of patients are not candidates for revascularization — primarily owing to the absence of a distal runoff arterial target or lack of an appropriate conduit for surgical bypass — putting them at high risk for above-ankle amputation. Transcatheter arterialization of the deep veins is an alternative endovascular approach in which an arteriovenous fistula is created proximal to the diseased tibial arteries by means of a covered stent, allowing oxygenated blood to be diverted from the tibial arteries to the tibial veins and ultimately reaching the foot through the pedal veins. The effectiveness of this approach in patients with chronic limb-threatening ischemia without revascularization options is unclear.

CLINICAL TRIAL

Design: A prospective, single-group, multicenter study assessed the effectiveness and safety of transcatheter arterialization of the deep veins in patients with chronic limb-threatening ischemia and nonhealing ulcers with no option for revascularization.

Intervention: 105 patients were enrolled to undergo transcatheter arterialization of the deep veins. The primary end point was amputation-free survival (defined as freedom from above-ankle amputation or death from any cause) at 6 months.

RESULTS

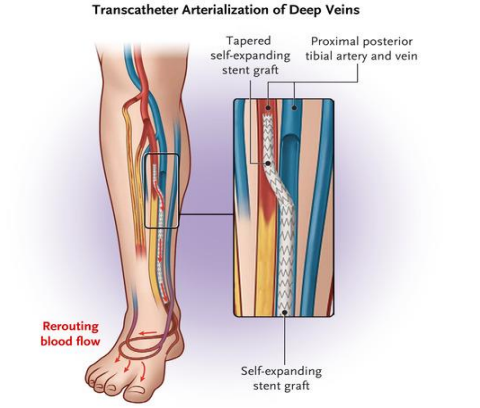
Effectiveness: The procedure was technically successful in all but one patient. The percentage of patients with amputation-free survival at 6 months was 66.1%. The probability that this outcome exceeded the performance goal of 54% exceeded the predefined success criterion.

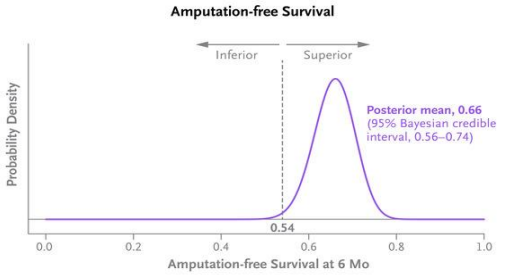
Safety: No unanticipated device-related adverse events were reported.

LIMITATIONS AND REMAINING QUESTIONS

- The study lacked a control group, although randomization of patients at high risk for amputation was not ethically feasible.
- The procedure may not be available outside specialist centers.
- Follow-up was relatively short-term.

Links: Full Article | NEJM Quick Take | Editorial

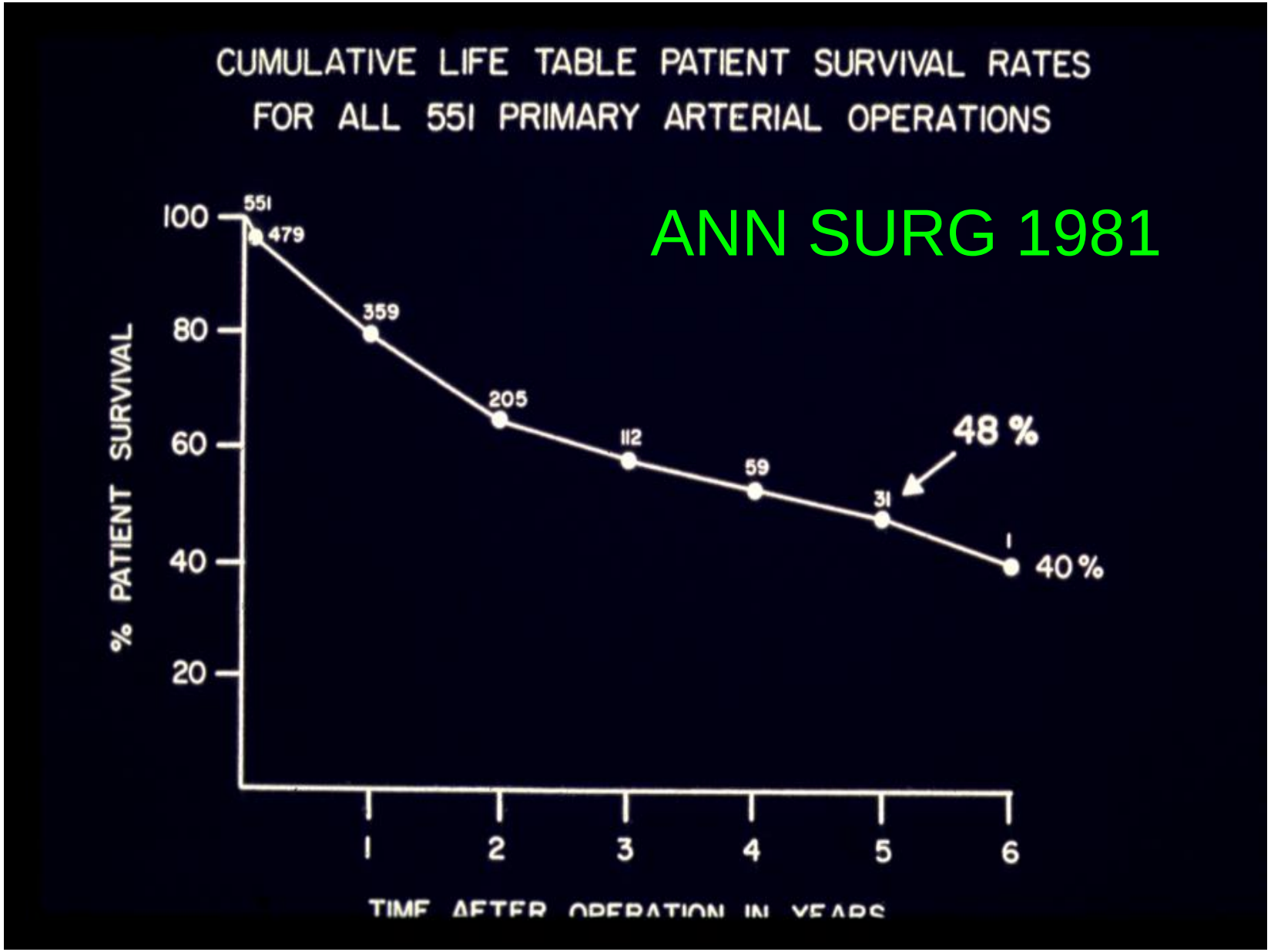




Major amputation	23/102 patients
Death	12/102 patients

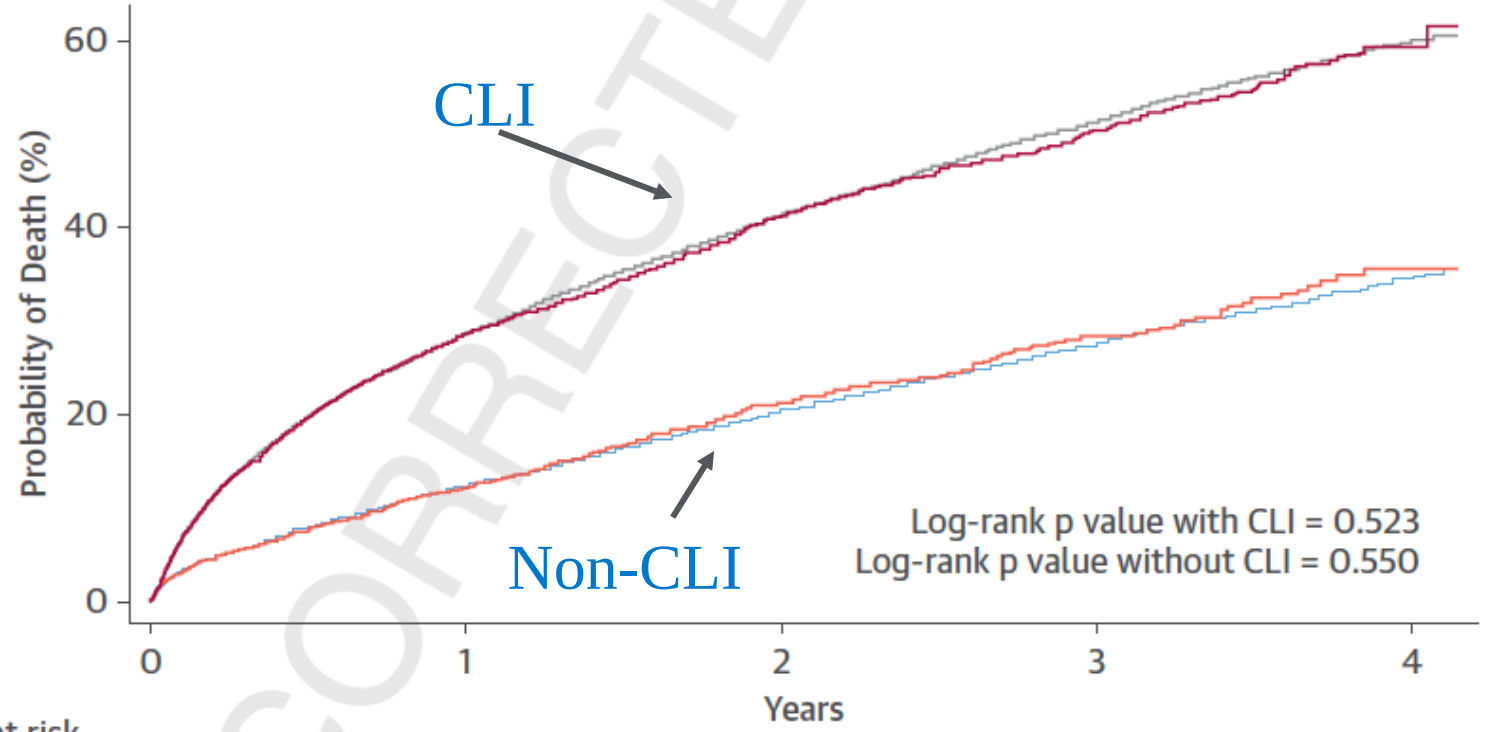
CONCLUSIONS

Among patients with chronic limb-threatening ischemia and no option for revascularization who underwent transcatheter arterialization of the deep veins, nearly two thirds were alive and free of above-ankle amputation at the 6-month follow-up, with no unanticipated safety concerns.



Courtesy: Frank Veith, MD

Long-Term Survival after Peripheral DES



No. at risk					
BMS without CLI	19,305	16,878	11,923	6,443	666
DES without CLI	1,443	1,267	800	378	35
BMS with CLI	28,046	19,996	12,280	5,570	534
DES with CLI	2,662	1,896	1,020	418	33

*No difference in survival in adjusted analyses

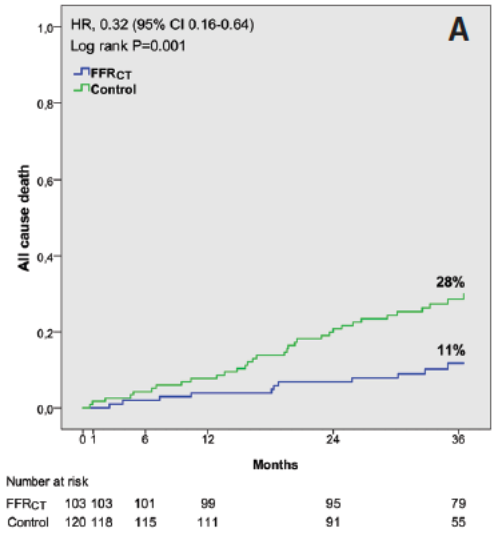
- CLI: Adjusted HR 0.97; 95%CI, 0.92-1.03; P = .32
- Non-CLI: Adjusted HR 1.01; 95%CI, 0.91-1.13; P = .80

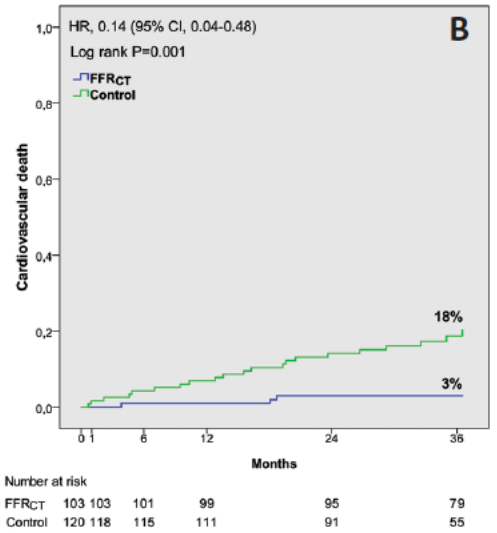
What if we just treated their coronary disease?

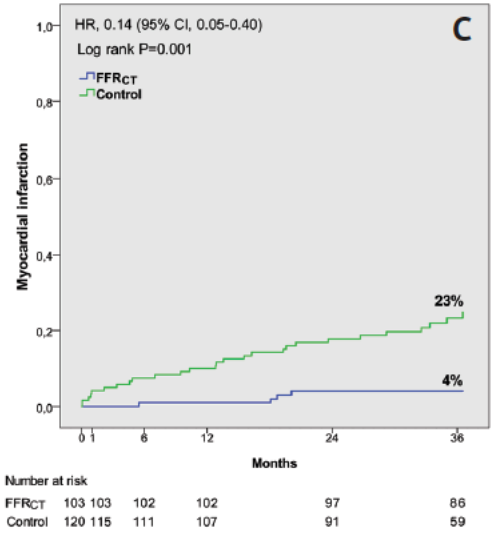
Original Contribution

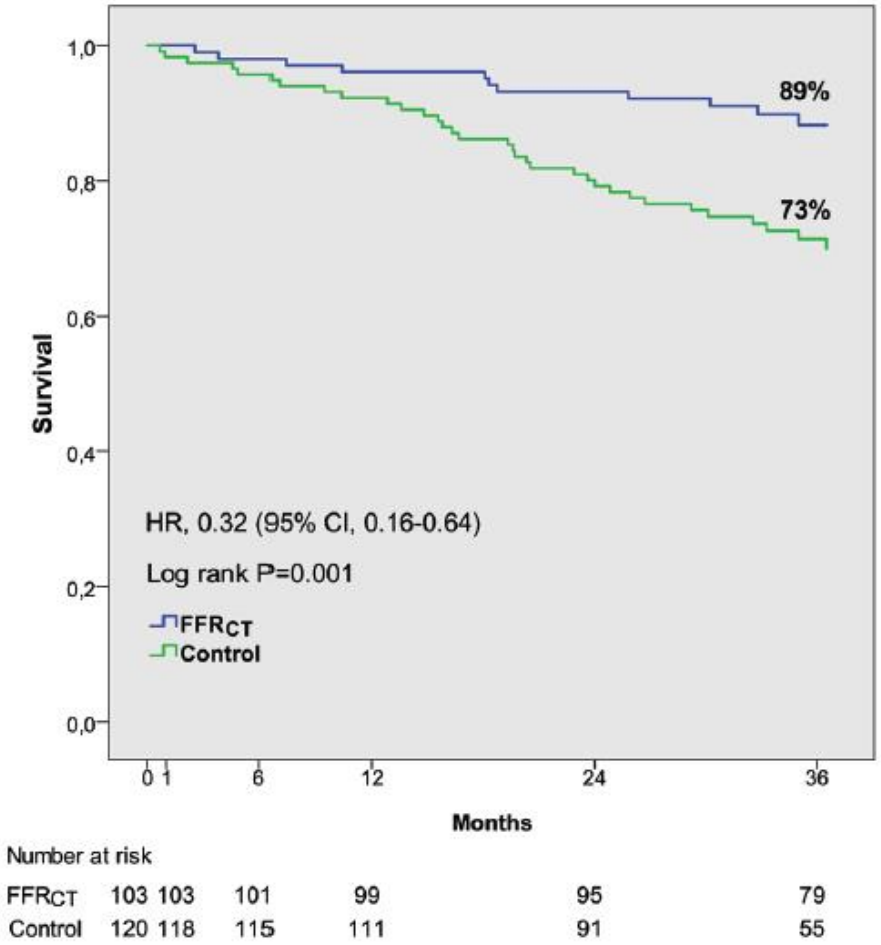
Three-Year Survival of Critical Limb-Threatening Ischemia Patients With FFRCT-Guided Coronary Revascularization Following Lower-Extremity Revascularization

Edgars Zellans[1,2]; Gustavs Latkovskis[1,2]; Christopher K. Zarins[3]; Indulis Kumsars[1,2]; Sanda Jegere[1,2]; Konstance K. Krievina[2]; Roberts Rumba[1,4]; Dainis Krievins[1,2]









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COLUMBIA NewYork-Presbyterian

Summary:

The last decade has heralded major shifts in the therapeutic options for PAD

Long term patency challenges have been addressed with:

- Novel Stent Designs
- Local Drug Delivery Approaches with DES and DCB
- New Drug Formulations

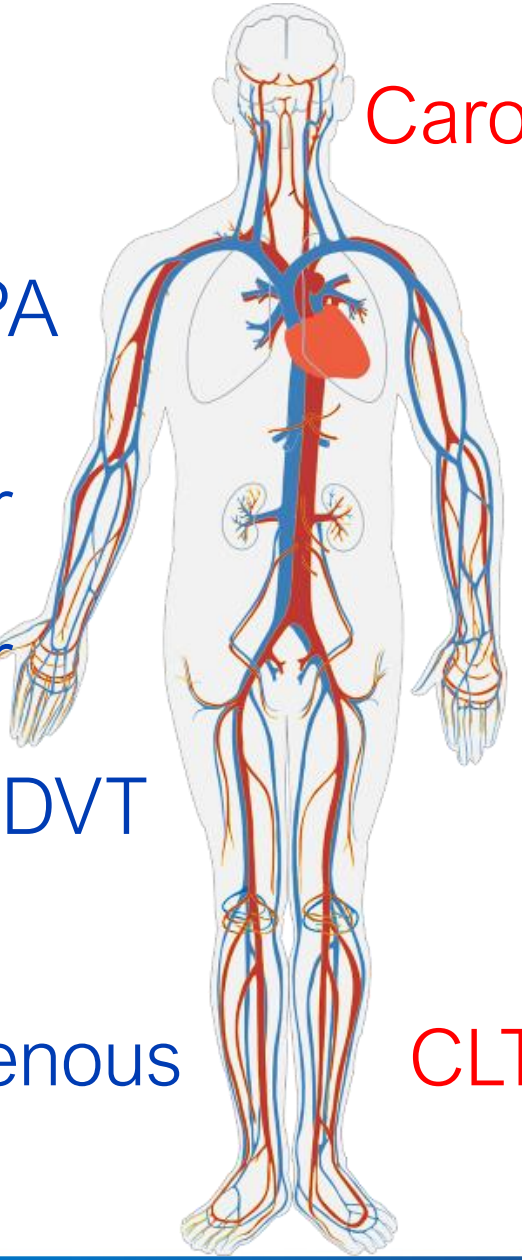
Next Generation Platforms hold promise:

- Bioresorbable Scaffolds for SFA and BTK regions
- New Scaffold Designs to Facilitate Drug Delivery
- Doing procedures “better” (e.g. using imaging)
- Better Drug:Device Combinations

CICC Endovascular Center Clinical Program Areas

Multidisciplinary Areas

- PAD/CLI – VS
- PERT – ThS
- AAA – VS, CTS
- Vascular Med – IM
- Venous – VS



Carotid

PE/BPA

Renovascular/RDN

IVC Filter

AAA

May-Thurner

PAD

DVT

Endovenous

CLTI