# Prospettive future del trattamento endovascolare: drug eluting balloon


DANIELE SAVIO

RADIOLOGIA VASCOLARE ED INTERVENTISTICA

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PRESIDENTE IESIR

ITALIAN EUROPEAN SOCIETY OF INTERVENTIONAL RADIOLOGY




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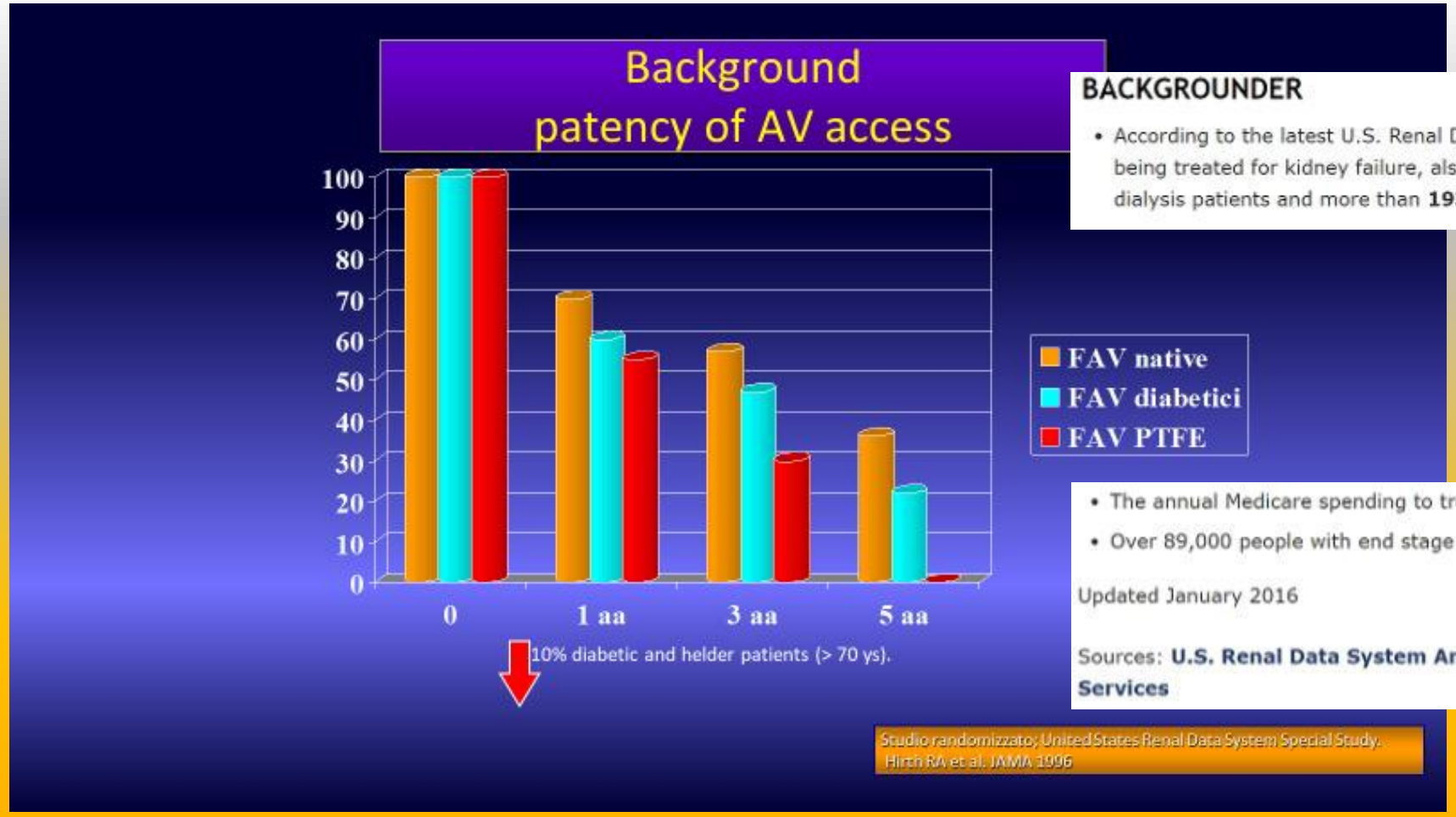



**BACKGROUNDER**

- According to the latest U.S. Renal Data System Annual Data Report, more than **660,000** Americans are being treated for kidney failure, also called end stage renal disease, or ESRD. Of these, **468,000** are dialysis patients and more than **193,000** have a functioning kidney transplant.
- The annual Medicare spending to treat kidney failure in the U.S. is approximately $31 billion.
- Over 89,000 people with end stage renal disease (kidney failure) die annually.

Updated January 2016

Sources: **U.S. Renal Data System Annual Data Report (2015), Centers for Medicare & Medicaid Services**

*Only 54.7% of AVFs were used within 4 months of placement, with maturation rates varying considerably across end-stage renal disease (ESRD) networks*

Woodside KJ, Bell S, Mukhopadhyay P, Repeck KJ, Robinson IT, Eckard AR, Dasmunshi S, Plattner BW, Pearson J, Schaubel DE, Pisoni RL, Saran R. Arteriovenous Fistula Maturation in Prevalent Hemodialysis Patients in the United States: A National Study. Am J Kidney Dis. 2018 Feb 8

# 1. Where are we in AV and NKF-K/DOQI

- Guidelines  recommend use of vascular adequacy parameters and physical examination for monitoring AVF and AVG
- **Correction of stenosis**: PTA or surgery based on center expertise
- PTA: safe and effective for failing AVFs and AVGs
- **Access stenosis should be treated if >50%** and associated with abnormalities such thrombosis episodes, elevated intra-access P, abnormal recirculation, decreased blood flow
- PTA success: **less than 30%** residual stenosis
- **50% primary patency at 6 months** after PTA
- If PTA required more than 2 times in 3 months: consider surgery
- If PTA fails: stent/covered stent:
  - unaccessible/difficult surgery access
  - controindication to surgery
  - rupture or dissection after PTAs

# 2.Where are we in AV and NKF-K/DOQI

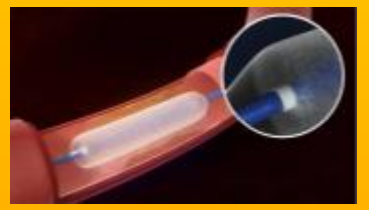
National Kidney Foundation™

*ENDOVASCULAR OPTIONS*

- 1) High pressure PTA
- 2) Cutting ballon
- 3) Bare Metal Stent

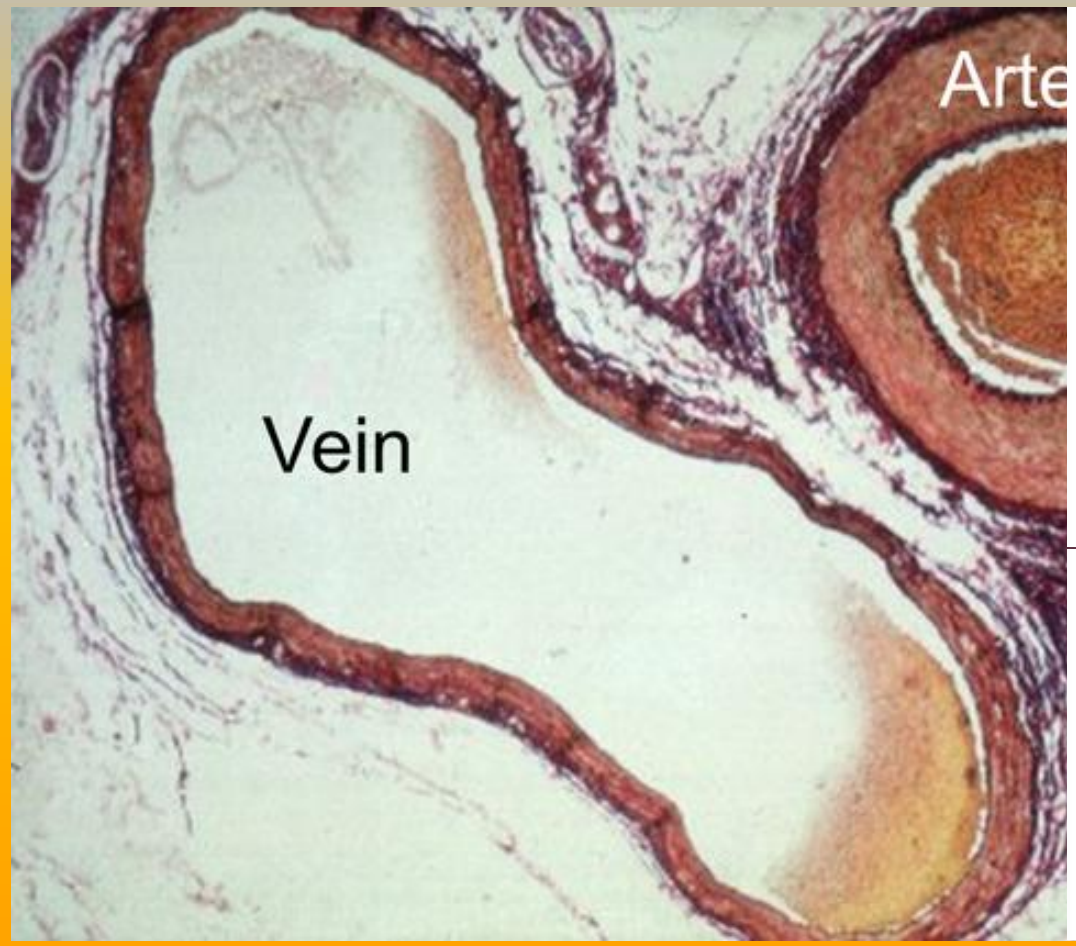
PP < 50% at 12m
HIGH NUMBER OF REINTERVENTION

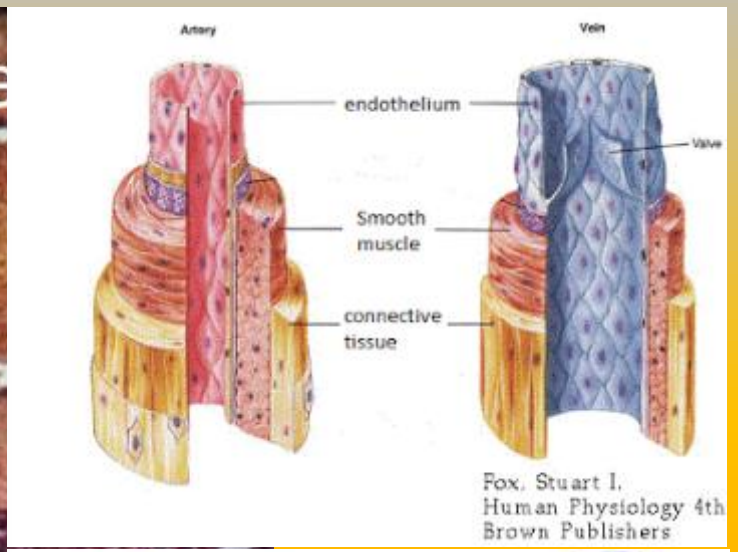
- 4) DEB  (drug eluting ballon)
- 5) Mechanical thrombectomy
- 6) endo-graft/covered stent

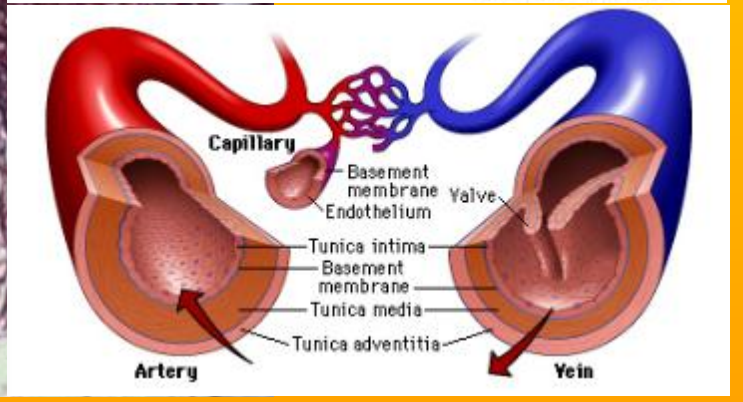


*SURGERY*

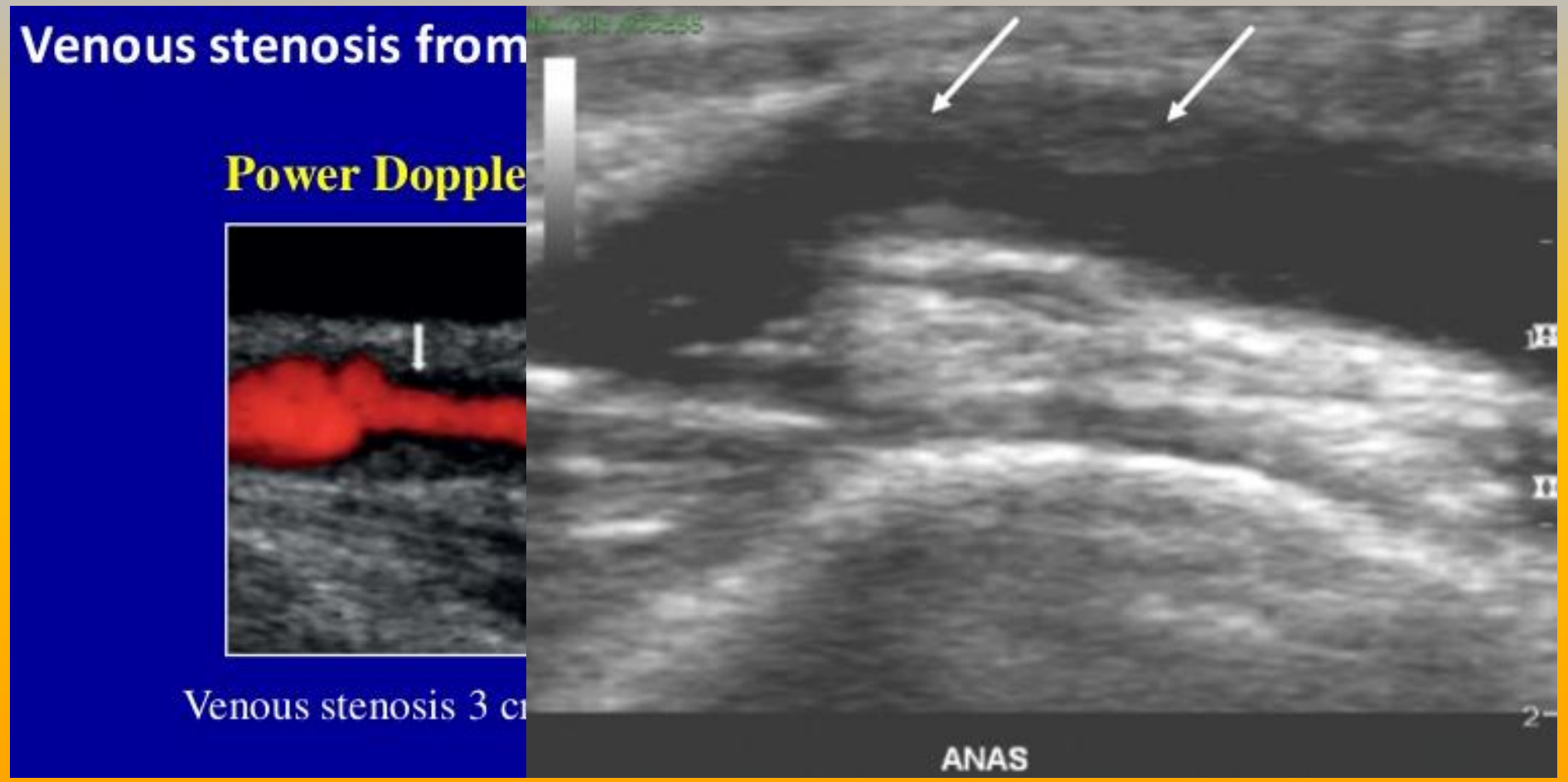
# Veins and lesion characteristics



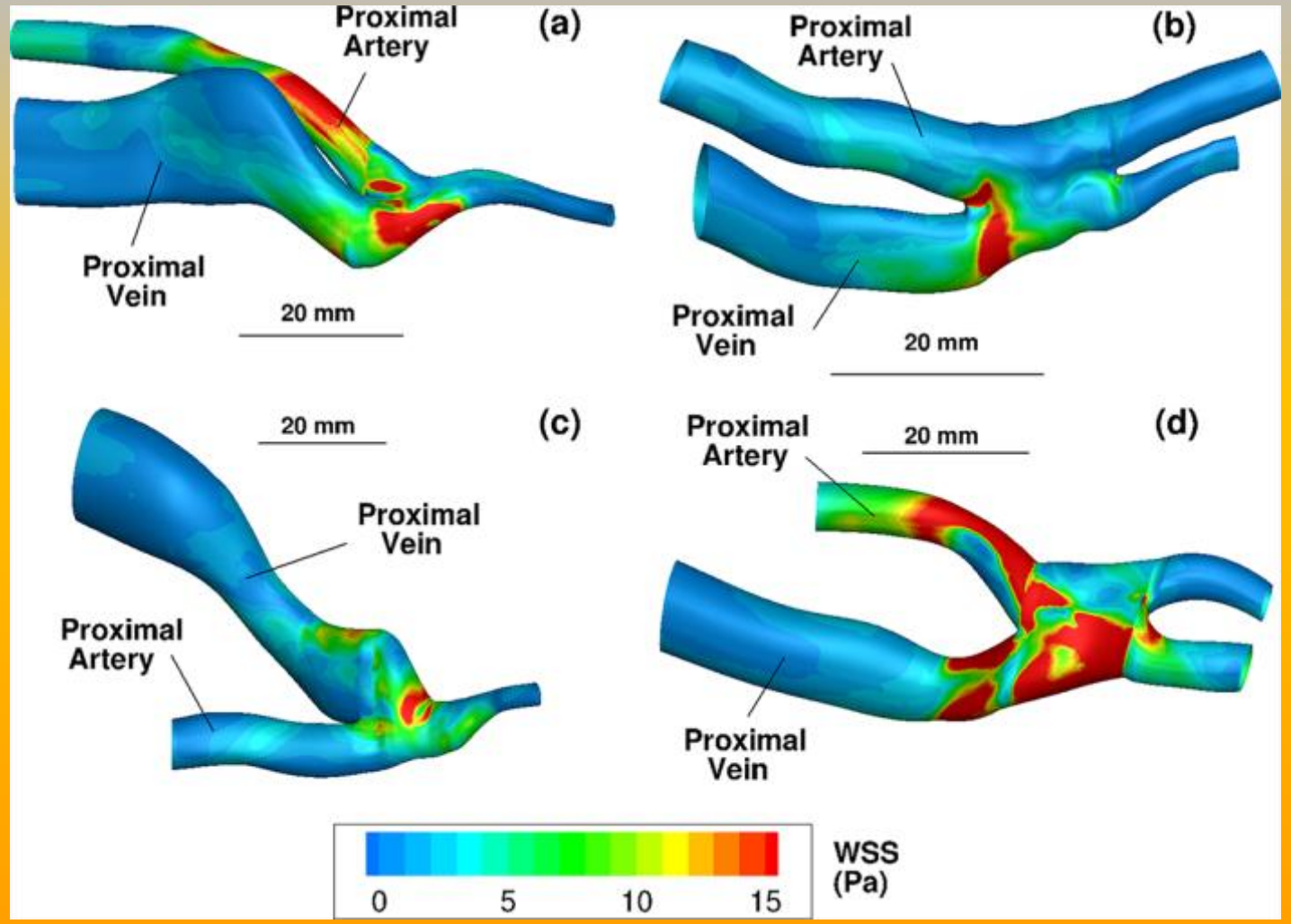



# Veins and lesion characteristics

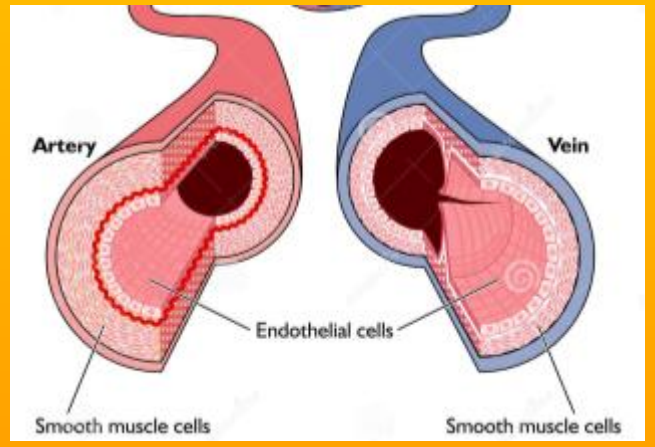


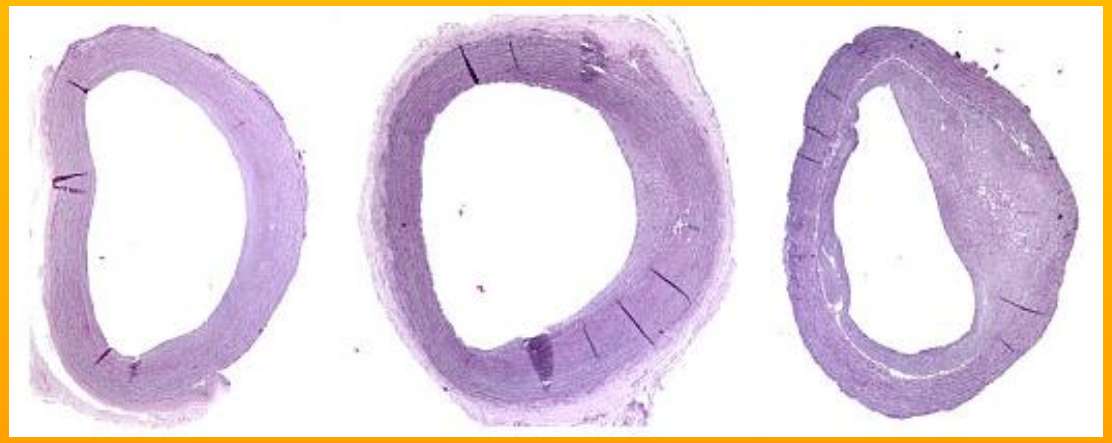
# Veins and shear stress



# Pathophysiology and lesion characteristics

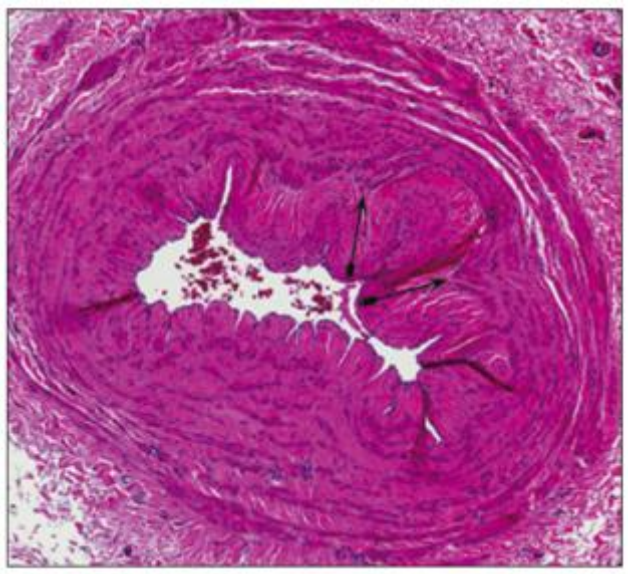
- **complex**
- cellular proliferation, microvessel formation, **cytokine expression (key factor?)** by smooth muscle cells, endothelial cells and macrophages
- cytokine result in further activation and proliferation of these cell types: **neointimal hyperplasia**

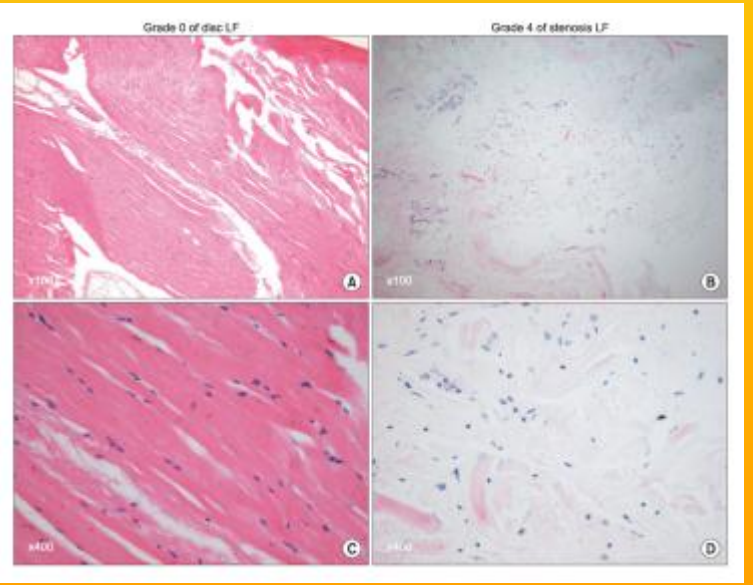


# Pathophysiology and lesion characteristics

- Potential mediators suggested to play a role in this process include basic fibroblast growth facor (**bFGF**), platelet-derived growth factor (**PDGF**), vascular endothelial growth factor (**VEGF**) and extracellular matrix (**ECM**) proteins
- Difference between stenosis an re-stenosis: **ECM**



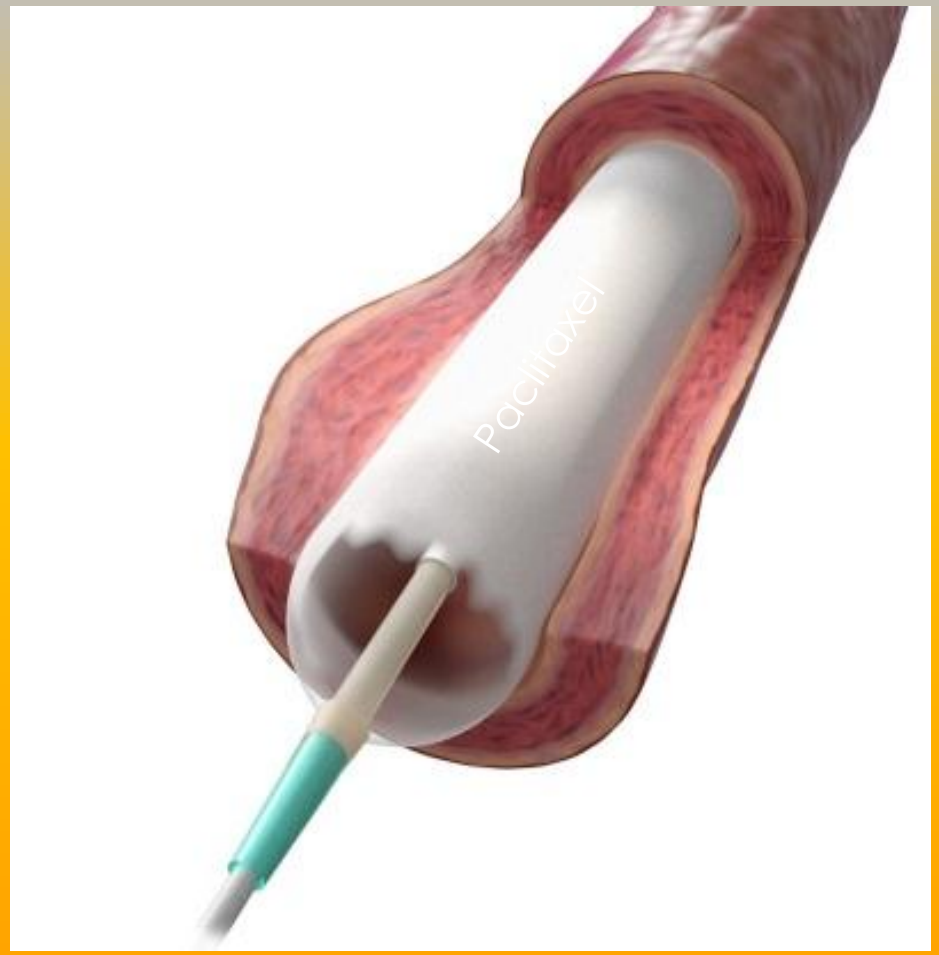


# “STATE OF ART” IN DEB USE

- When DEB?
- How my strategies change using DEB?
- Are all DEB the same?
- What should I know choosing a DEB?

# Paclitaxel (PTX) top drug for DEB

- Why Paclitaxel?
- How Paclitaxel?

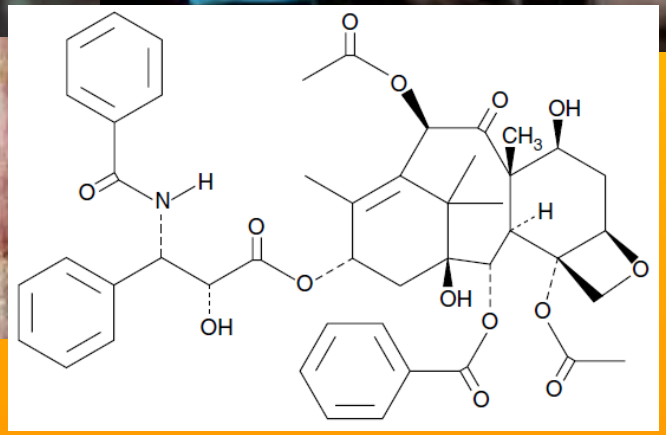


# PACLITAXEL DISCOVERY: SEARCHING FOR ANTI-CANCER DRUGS

After ‘50s until 1981 U.S. National Cancer Institute (NCI) studied 35,000 different plants with anti-cancer properties.
Paclitaxel sorted to be the one.

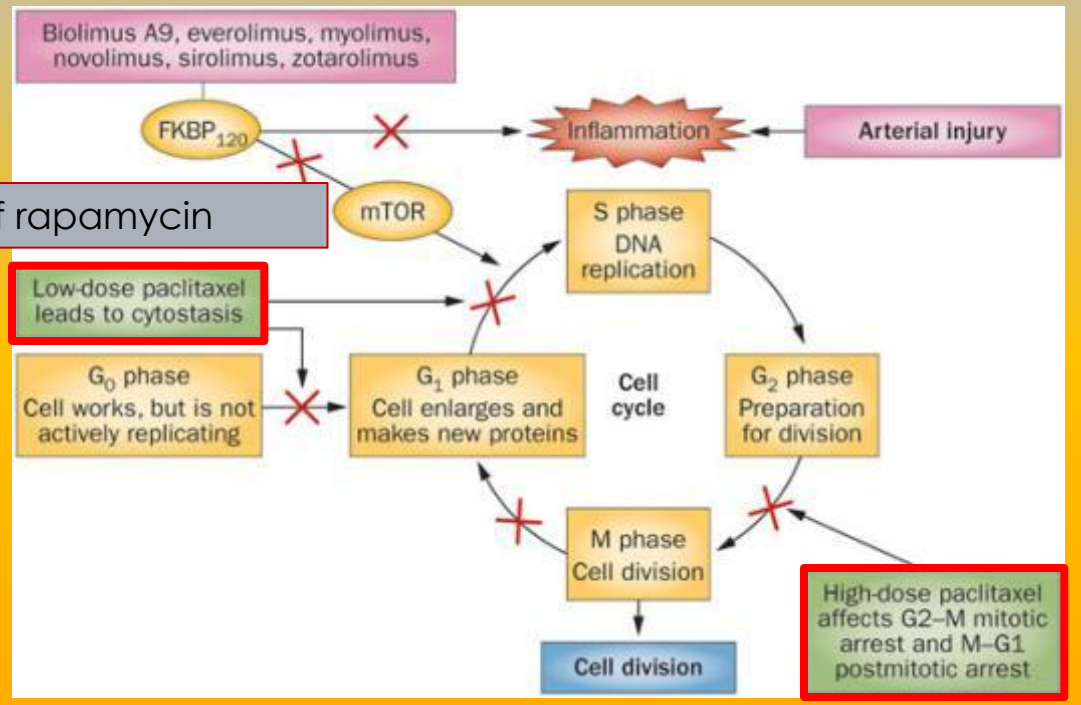


Dr. Wani
and Dr. Wall

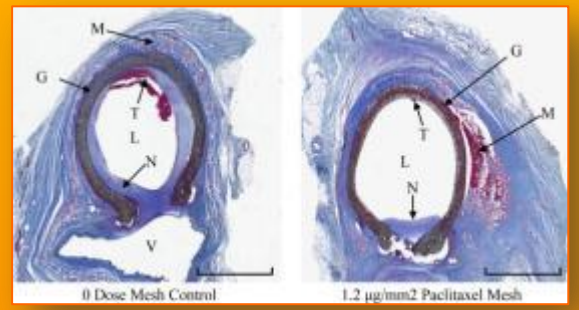


# How Paclitaxel do works?

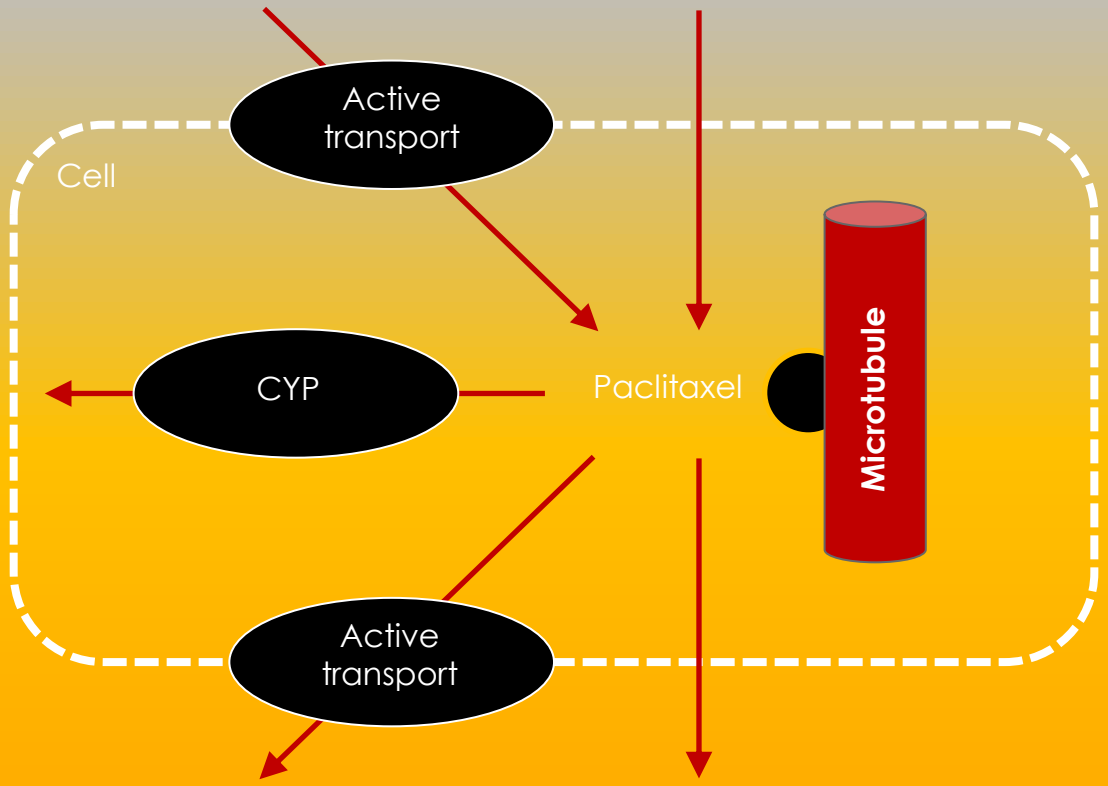
mammalian target of rapamycin




- Paclitaxel directly inhibits cellular cicle
- High doses lead to a stop of the mitotic phase
- Low doses lead to long-term antiproliferative effect

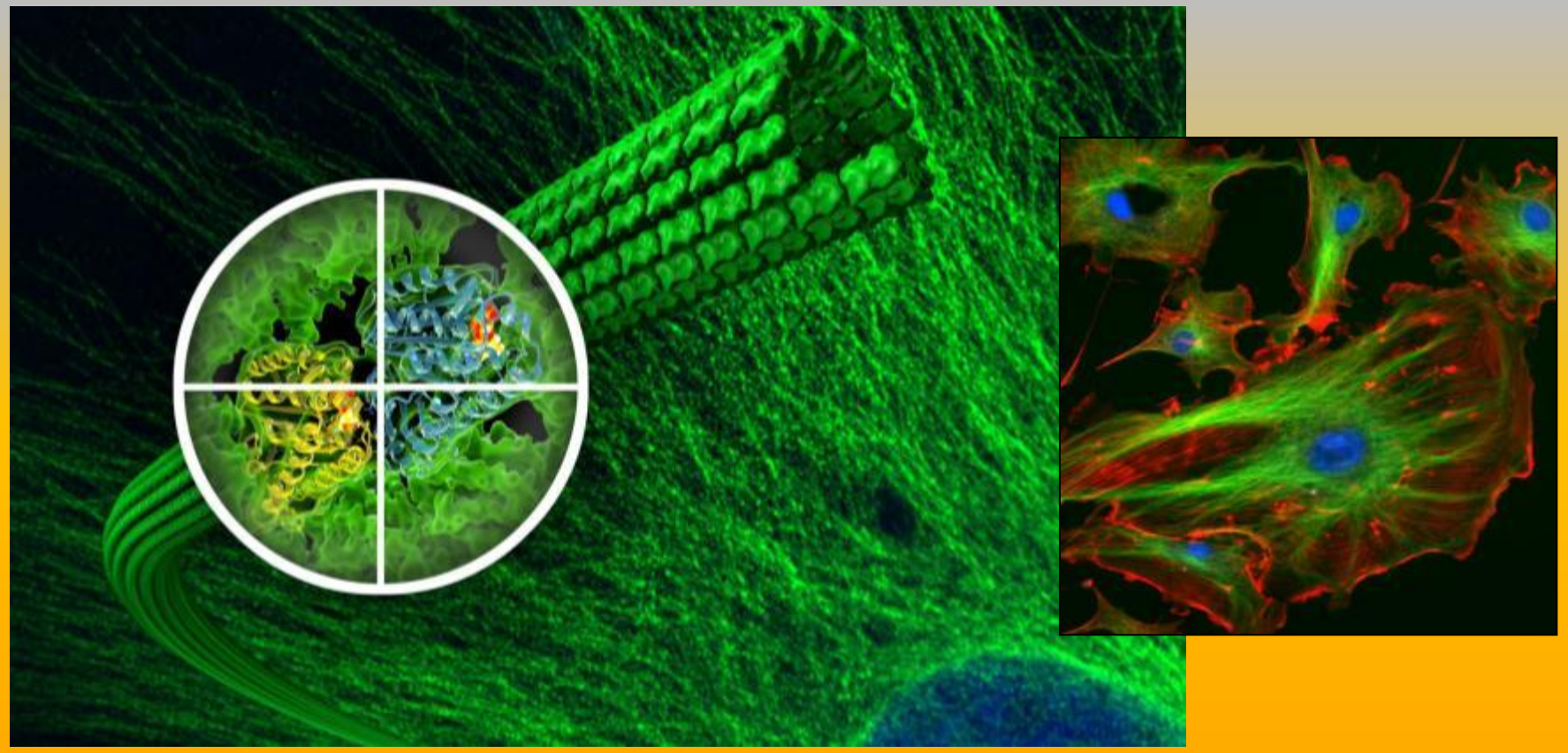


# PACLITAXEL'S PHARMACOKINETIC HELPS ITS LONG-LASTING INSIDE VESSELS CELLS WALL




- PTX moves through cells to wall's cells
- PTX reaches high intracellular levels and bonds to microtubules
- PTX has an hepatic metabolism via cytochromes

# Microtubules stabilization blocks proliferation and cell migration



- PTX links to microtubules beta-tubulin
- Microtubules stabilization inhibits proliferation/cell migration
- Microtubules steady without tissue exposition to the drug

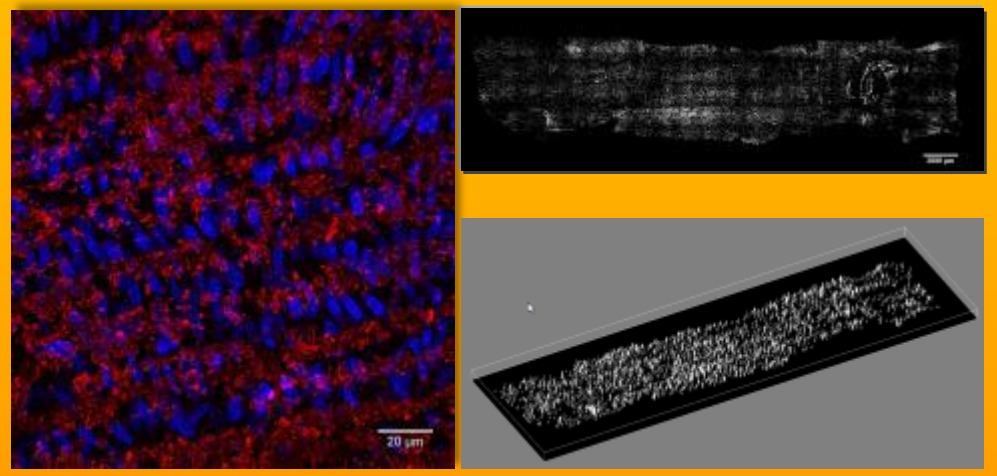
# Drug concentration and technology

- Eccipient balances drug releasing properties.
- Eccipient goal is to create an easy tissue absorbable structure (crystalline or amorphous)
- Eccipient needs to improve drug efficacy and permanence on the vessel wall.
- **Drug concentration: 2µg/mm² up to 3 - 3.5µg/mm²**
- Eccipient: hydrophobic o hydrophilic

**Spray coating**

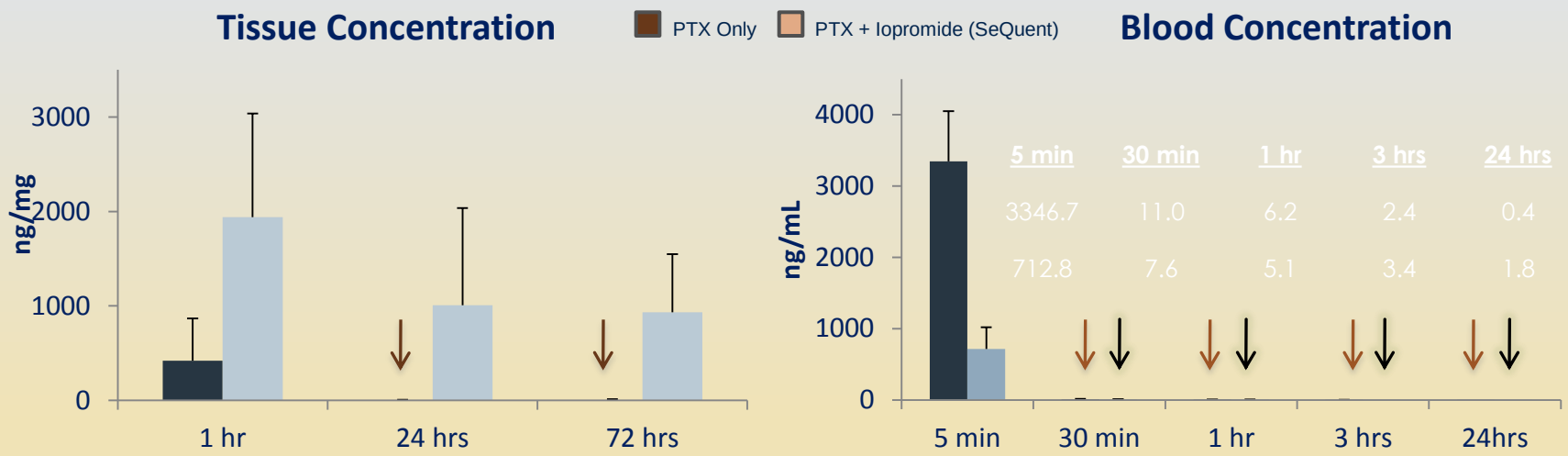
**Dip coating**

**Micro-pippeting**

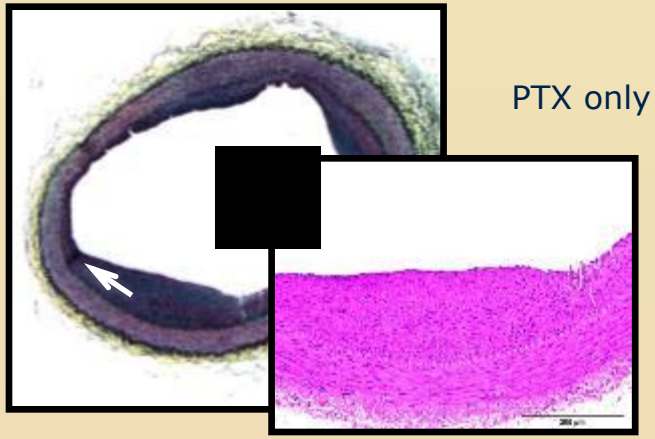



Drug distribution on artery wall

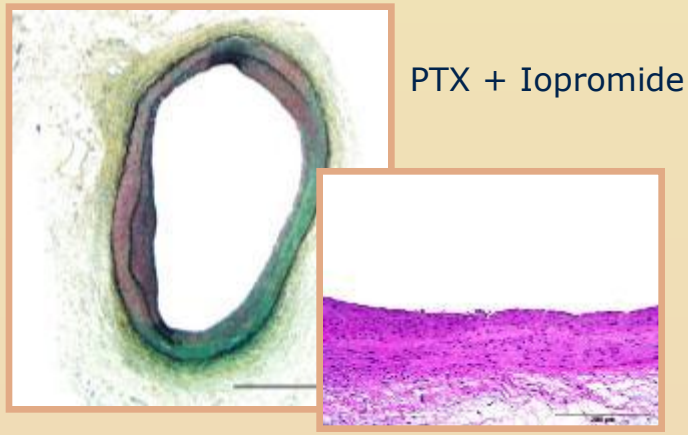
# Excipients improve tissue uptake of Paclitaxel




Non-atherosclerotic Rabbit Iliac Model – 28 days



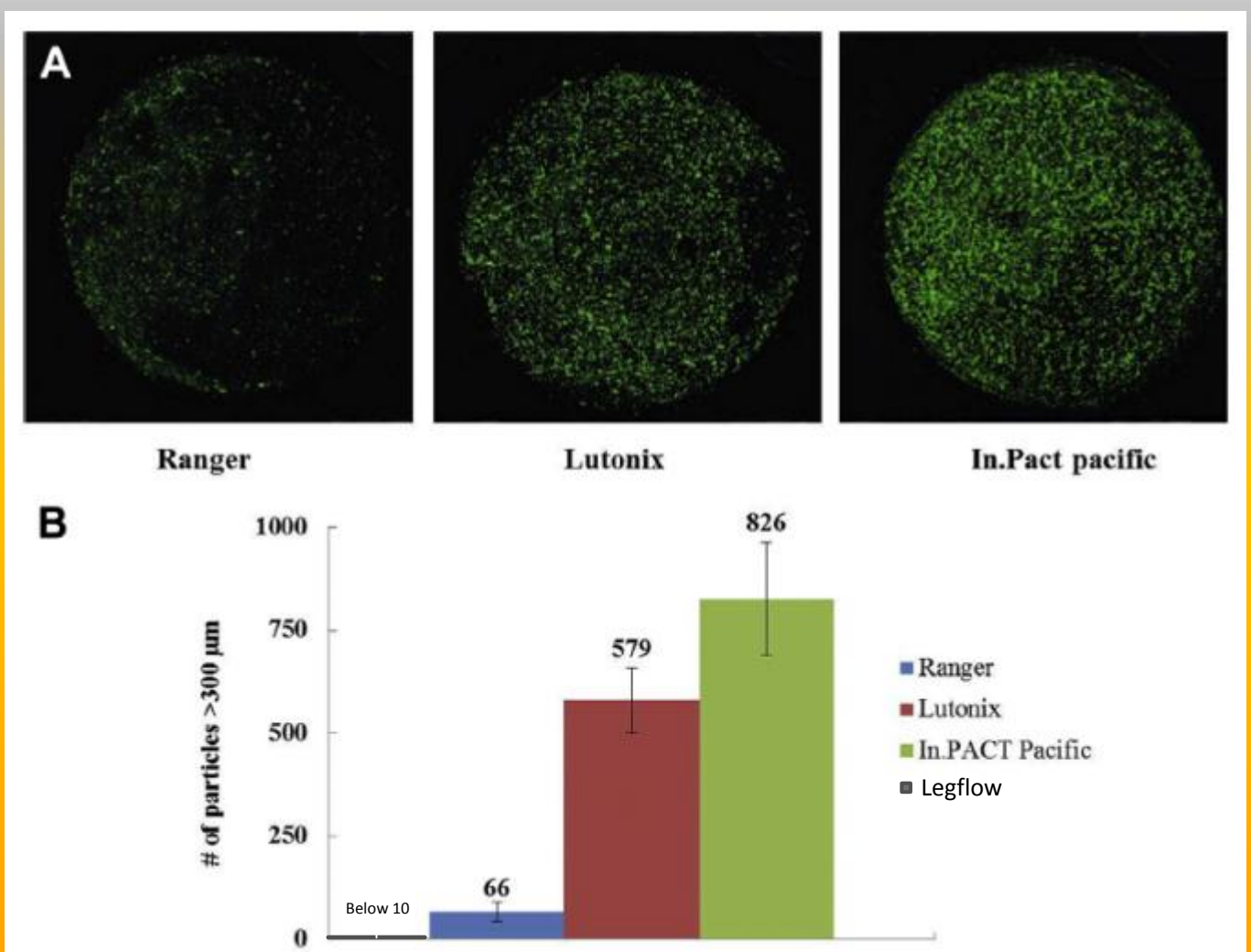
PTX only



PTX + Iopromide

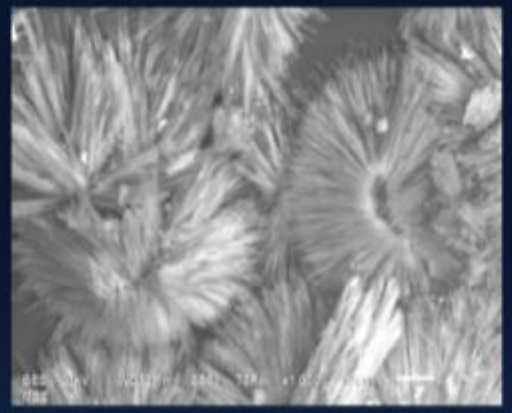
Source: Virmani, presented at Linc 2012

# PARTICLE SIZE AND NUMBER

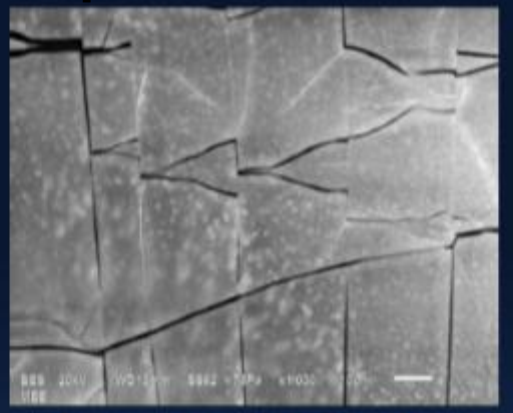



smaller particles, better drug uptake to build small but many depots!

# A crystalline morphology improves coating characteristics and performances



Crystalline Coating

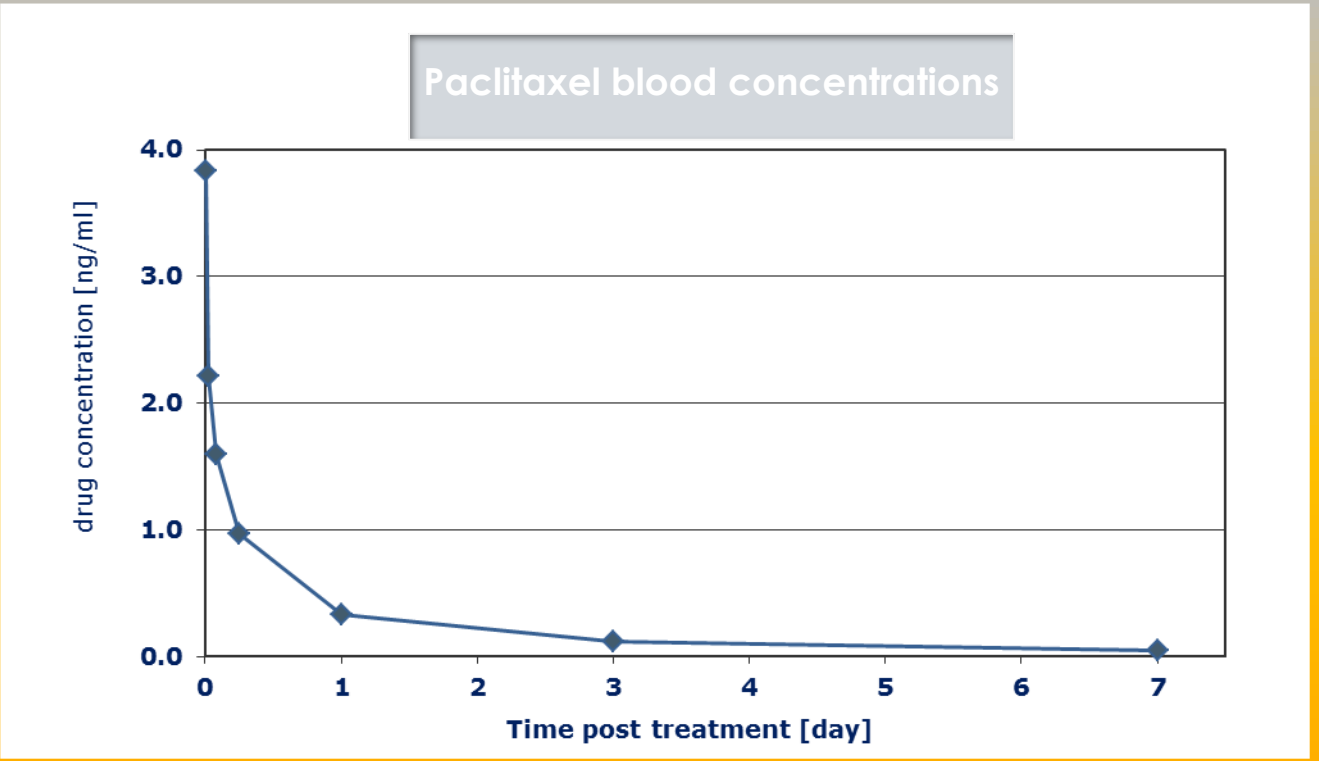


Amorphous Coating

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

Source: Gray&Granada 2010; Circulation 121; 2672-2680.

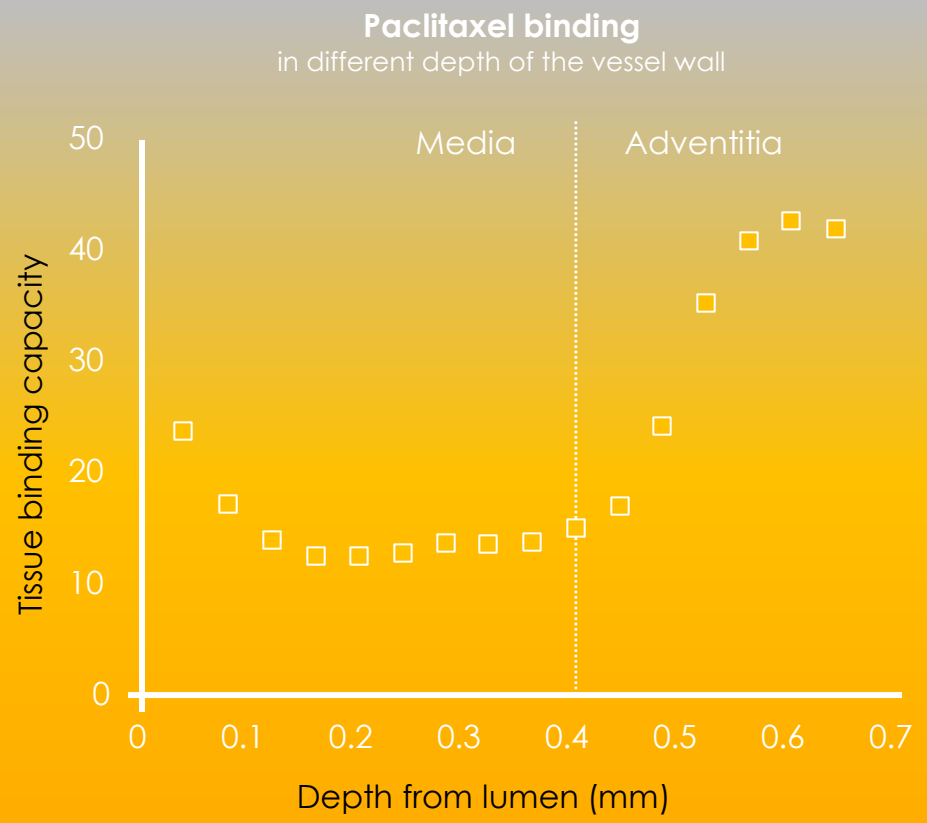
# "IN BLOOD" PTX CONCENTRATION FASTLY DECREASES AFTER TREATMENT




- Cmax 4.1 ng/ml at 5 minutes
- After 7 days 98.7% of the drug is eliminated

SFA Porcine model

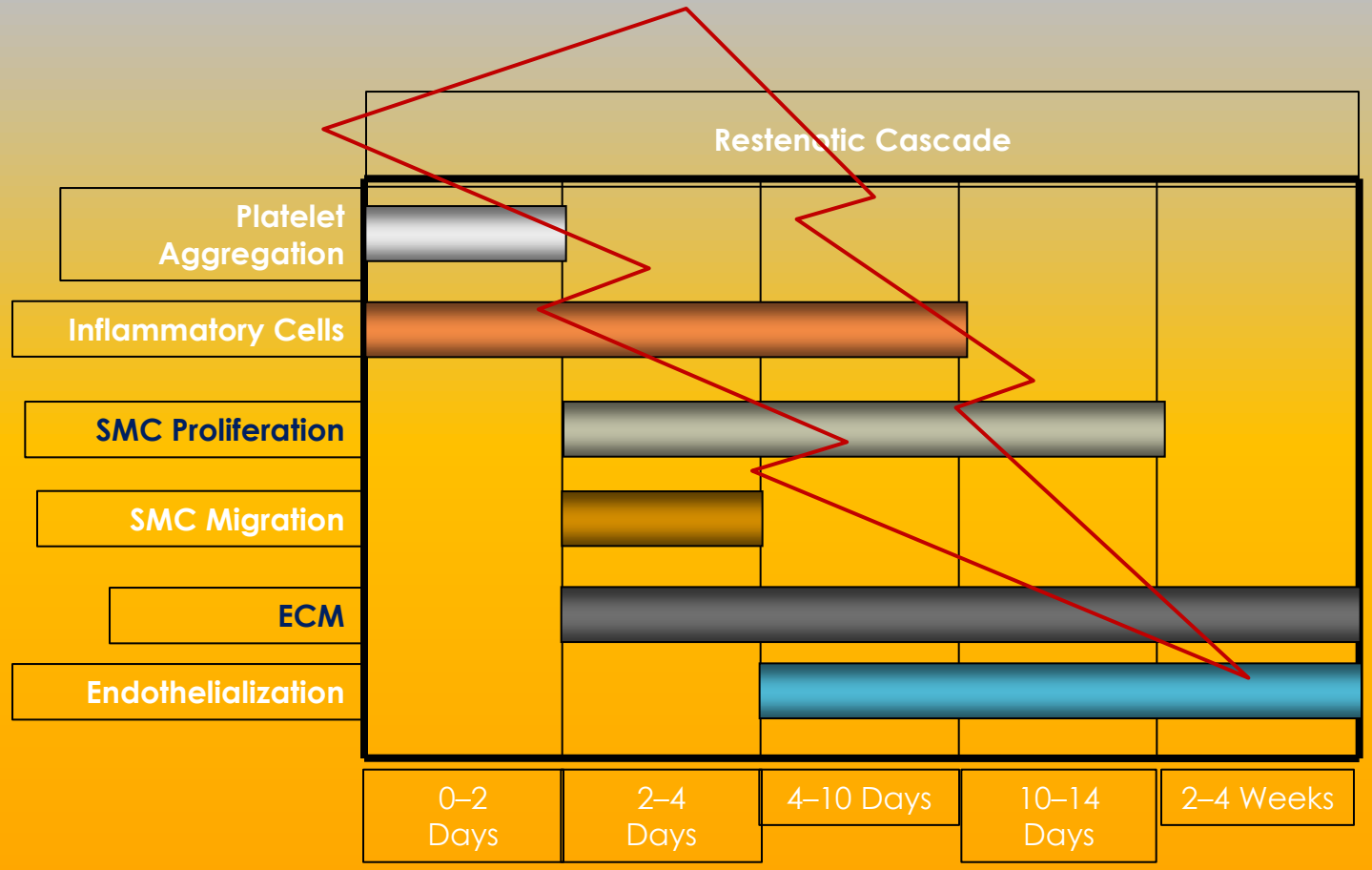
# PTX DISTRIBUTION IN VESSEL WALL LAYERS




- PTX distributes in all vessel wall layers
- Adventitia:PTX inhibits fibroblasts migration to neo-intima
- Media:PTX inhibits neointimal cells migration proliferation

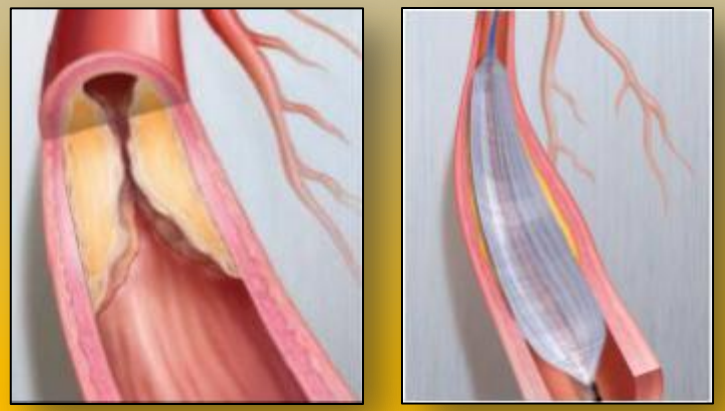
Levin et al. PNAS. 2004; 25: 9463-9467.

# CELLS PROLIFERATION AND MIGRATION INHIBITION LASTS 2 WEEKS AFTER DEB

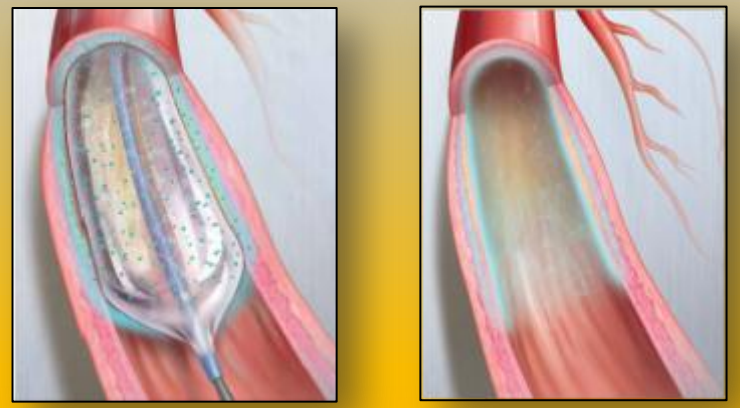


# Treatment of DENOVO STENOSIS with COMBINATION OF TWO ACTIONS

WIN THE STENOSIS
SCORING OR HPB



**Inhibits intimal Hyperplasia**
**DEB**



**Safe and effectiveness**

**1**

**3cm long high-grade stenosis involving the upper basilic vein**

**2**

**Unable to efface stenosis with standard, non-compliant balloon at 22 ATM**

**3**

**Ultra high pressure and ultra-non compliance were needed to efface lesion**

**4**

**Post angioplasty, the vessel is open and the patient can resume dialysis**

# PROCEDURAL TECHNIQUES FOR OPTIMAL DRUG DELIVERY

Observations from LEVANT 2 suggest that the Primary Patency is positively influenced by:

- ✓ Balloon Transit Time < 30 Seconds
- ✓ Balloon Inflation Pressure >7 atmosfers
- ✓ Balloon Inflation Time ≥120 Seconds
- ✓ Final % Diameter Stenosis after pre-dilation < 20%

Indicators from Levant 2 Data Analysis

# DEB OFFER PROMISING OPTION IN STENOSIS (RE-STENOSIS?)

- Encouraging results have been seen in de novo, restenotic lesions, in-stent restenosis, & in A-V access stenosis.
- Some logical indications might include:

"no-stent" zones e.g. CFA lesions

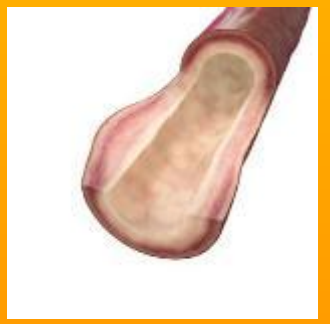
segments prone to restenosis e.g. long AK lesions

**Benefits**

- Anti-proliferative therapy while leaving nothing behind
- Broad anatomical applicability
- Easily repeatable
- Avoid stent fracture and ISR burden
- Preserve future options
- Matches patient's quality of life expectations (improvement in walking capacity, Rutherford class)

**Limitations**

- Not proven in highly calcified lesions
- When provisional stent is required= higher procedural cost



J Endovasc Ther. 2012 Apr;19(2):263-72. doi: 10.1583/11-3690.1.

**Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial**

J Vasc Interv Radiol. 2014 Apr;25(4):535-41. doi: 10.1016/j.jvir.2013.12.014. Epub 2014 Feb 12.

**Percutaneous angioplasty using a paclitaxel-coated balloon improves target lesion restenosis on inflo**

J Vasc Access. 2014 Sep-Oct;15(5):338-43. doi: 10.5301/jva.5000211. Epub 2014 Feb 10.

**Drug-eluting balloon for the treatment of failing hemodialytic radiocephalic arteriovenous fistulas: our exp**

**Paclitaxel-coated balloon fistuloplasty versus plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis (PAVE): study protocol for a randomised co**

J Vasc Access. 2017 Mar 6;18(Suppl. 1):88-91. doi: 10.5301/jva.5000663. Epub 2017 Mar 5.

**Drug eluting balloons for resistant arteriovenous dialysis access stenosis.**

Karnabatidis D[1], Kitro... P[1]

Radiol Med. 2017 Jan;122(1):69-76. doi: 10.1007/s11547-016-0680-z. Epub 2016 Sep 6.

**Usefulness of paclitaxel-releasing high-pressure balloon associated with cutting balloon angioplasty for treatment of outflow stenoses of failing hemodialysis arteriovenous shunts.**

Ierardi AM[1], Franchin M[2], Fontana F[1], Piffaretti G[2], Duka E[1], Tonolini M[3], Miele V[4], Tozzi M[2], Carrafiello G[5].

Author information

**Abstract**

**AIM:** To evaluate the technical and clinical success, primary patency (PP) and complications of angioplasty performed with paclitaxel-coated balloon (PCBs) associated with cutting balloon and for the treatment of the outflow stenoses of failing hemodialysis arteriovenous shunt.

**MATERIAL AND METHODS:** From September 2014 to September 2015, 50 patients with 66 stenoses were registered. Vascular accesses were autogenous (n = 20) and prosthetic (n = 30). Stenosis were documented during follow-up with routine echo-color Doppler, clinical evaluation and in the remaining incidentally during fistulography. Angioplasty was performed with cutting balloon and afterward with PCB. The mean follow-up time was 8 months (range 6-15 months). Technical success, clinical success, primary patency and complications were registered.

**RESULTS:** Technical success was 100 %. Clinical success was 94.7 %. Primary patency rate was 87.7 %; in five patients, a significant re-stenosis (≥50 %) was registered. A residual asymptomatic stenosis (<30 %) was registered in four cases (7 %). No major complications were registered.

**CONCLUSIONS:** A short-term patency benefit may be obtained including PCB in angioplasty treatment of failing hemodialysis arteriovenous shunts.

**KEYWORDS:** Hemodialysis arteriovenous shunt; Outflow stenoses; Paclitaxel-coated balloon

# Insubria Experience : scoring balloon+ DCB

**2016-2017 (158 PTS)**

- N° 64 SCORING BALLOON + DCB
  - 84% TL PP
  - 2 RESIDUAL STENOSIS
- N° 94 HPB + DCB
  - **79% TL PP**
  - **SHIFT TO SCORING BALLOON RECOIL 16%**
  - **10 RESIDUAL STENOSIS < 30%**

**2014-2015**

- N° 74 CUTTING BALLOON + DCB
  - **72.6% TL PP**
  - **6 ACUTE THROMBOSIS**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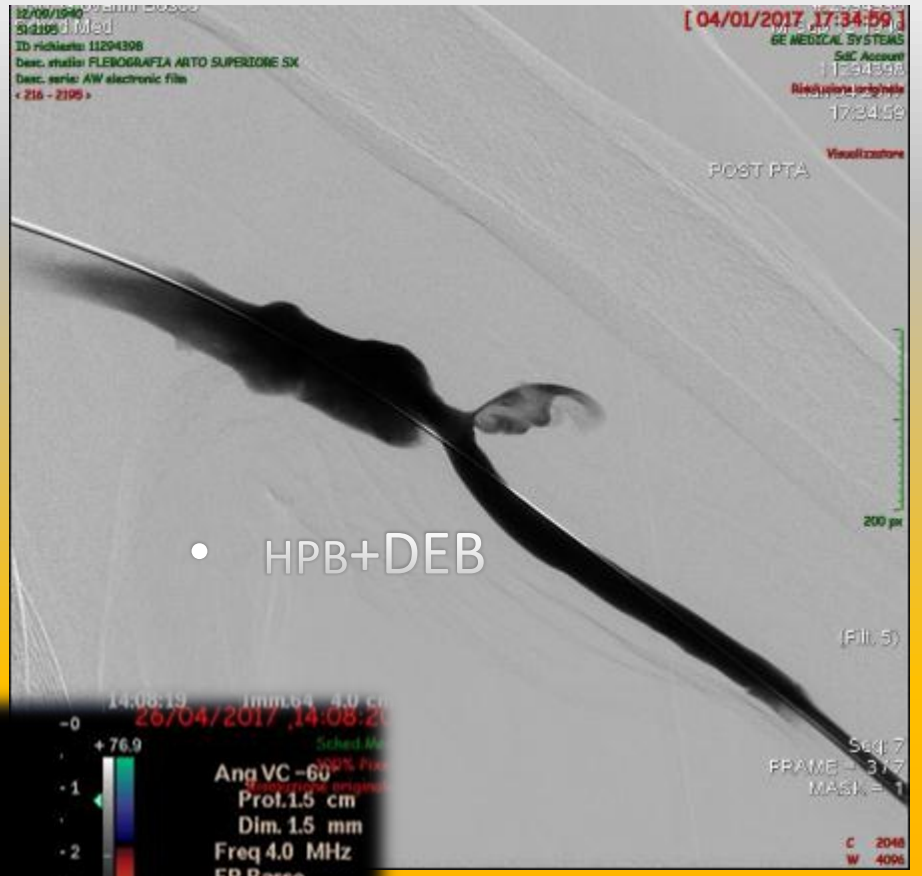
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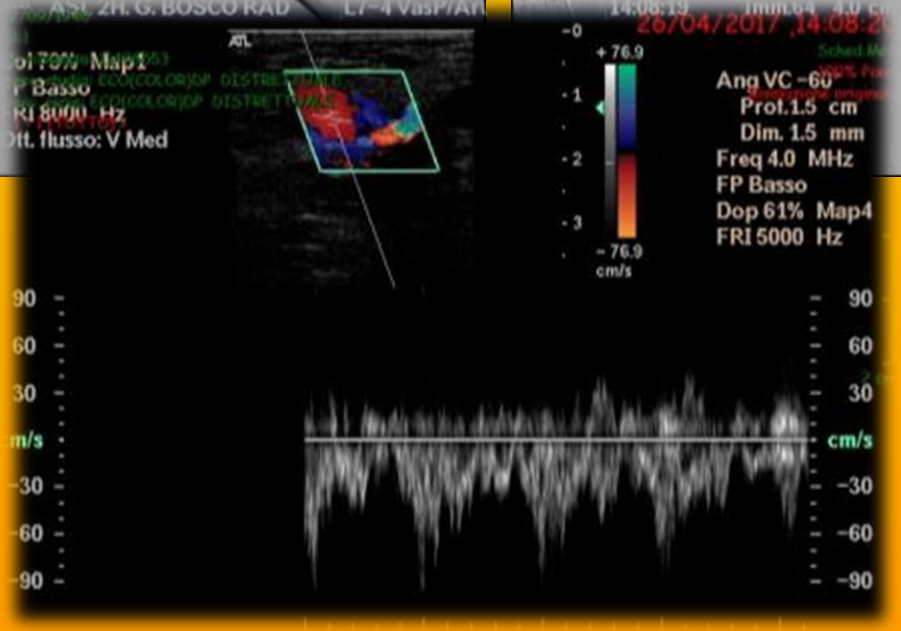
- HPB+DEB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-60
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# ECONOMIC IMPACT OF DEB

J ENDOVASC THER
2013;20:819–825



◆BUSINESS OF ENDOVASCULAR THERAPY ◆

## Cost-Effectiveness Analysis of Paclitaxel-Coated Balloons for Endovascular Therapy of Femoropopliteal Arterial Obstructions

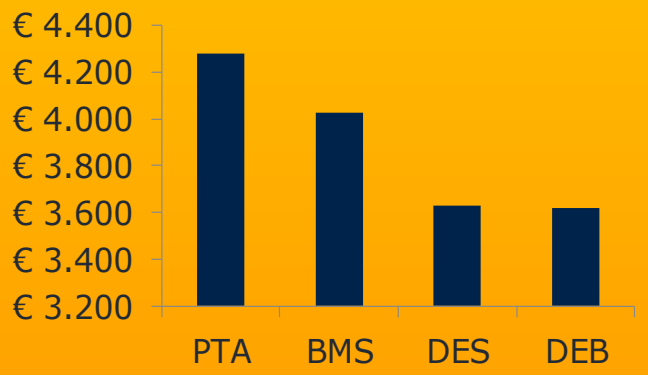
Nicolas Diehm, MD, MBA[1]; and Henrique Schneider [2]

[1]Clinical and Interventional Angiology, Swiss Cardiovascular Center, Inselspital, University Hospital Bern, Switzerland. [2]Swiss Federation of Small and Medium Enterprises, Bern, Switzerland.

**Per year:**

**DEB c. 90,000 Swiss Fr. less costly than PTA therapy due to lower repeat intervention costs, despite the greater DEB purchase costs**

**2yr Comparative Budget Impact: German Healthcare Payers.**

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Original article

## Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease

B. C. Kearns, J. A. Michaels, M. D. Stevenson and S. M. Thomas

Section of Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK
*Correspondence to:* Mr B. C. Kearns, School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK (e-mail: b.kearns@sheffield.ac.uk)

- **DEB dominated all other options by lower lifetime costs and greater effectiveness**
- **DEB represents a cost-effective alternative to PTA with bail-out BMS**

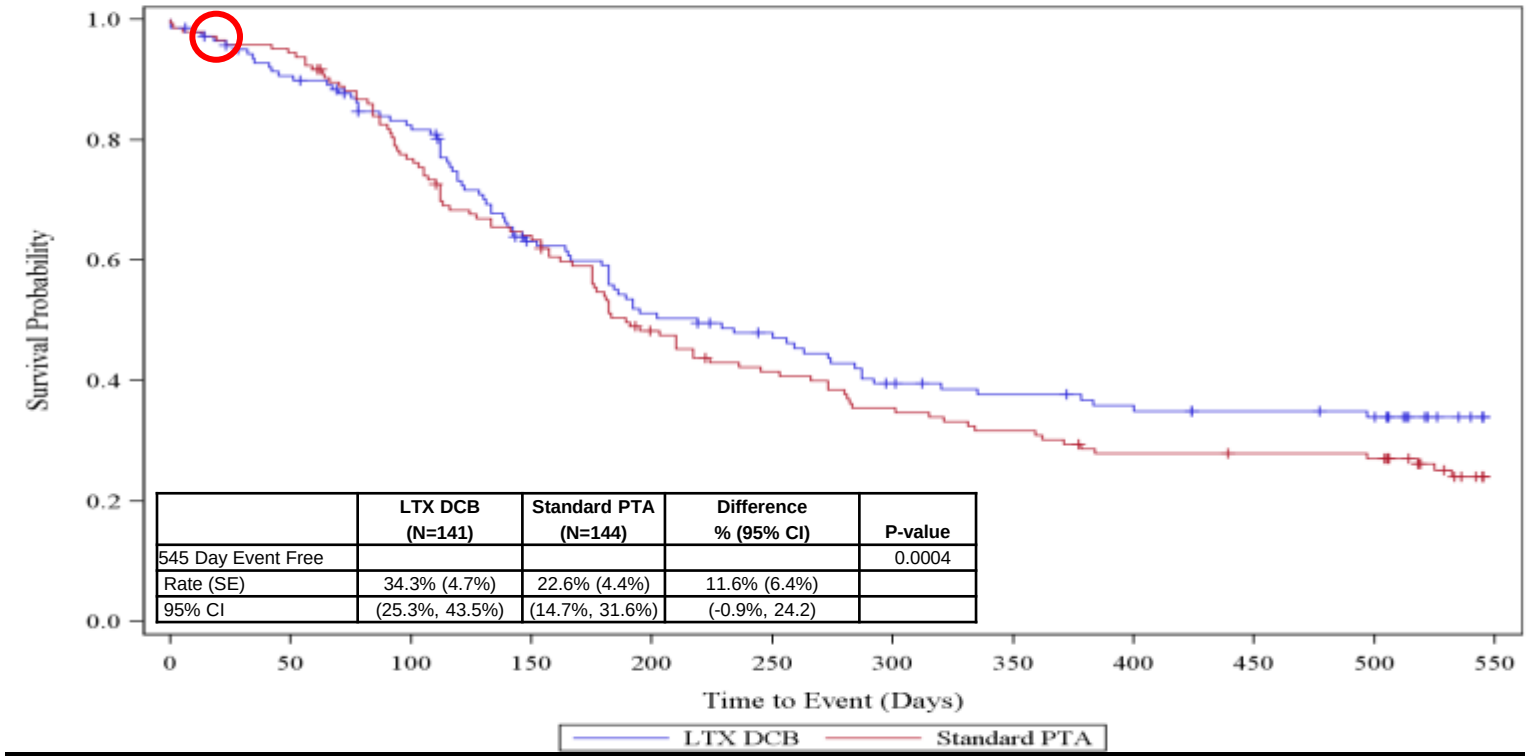
Sources: Zeller. T. LINC 2013, Diehm et al. JEVT 2013;20:819-825, Kearns BC et al. Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease. Br J Surg. 2013 Aug;100(9):1180-8

# AV IDE Trial – Study Design

| | |
|---|---|
| Study Design | Prospective, Global, Multicenter, Randomized, Core lab Blinded, Safety and Effectiveness |
| Objective | To assess the safety and effectiveness of the LUTONIX® 035 AV Drug Coated Balloon PTA Catheter in the treatment of dysfunctional AV fistulae |
| Number of Patients/Sites | 285 randomized subjects at 23 clinical sites |
| Primary Effectiveness Endpoint | Target Lesion Primary Patency (TLPP) - 6 months |
| Primary Safety Endpoint | Freedom from any serious adverse event(s) involving the AV access circuit through 30 days |
| Follow Up | 1, 3, 6, 9, 12, 18, 24 month visits |
| Status | First Subject: June 2015<br>Enrollment Completion: March 2016 |

# AV IDE Trial – Primary Safety @ 18 months

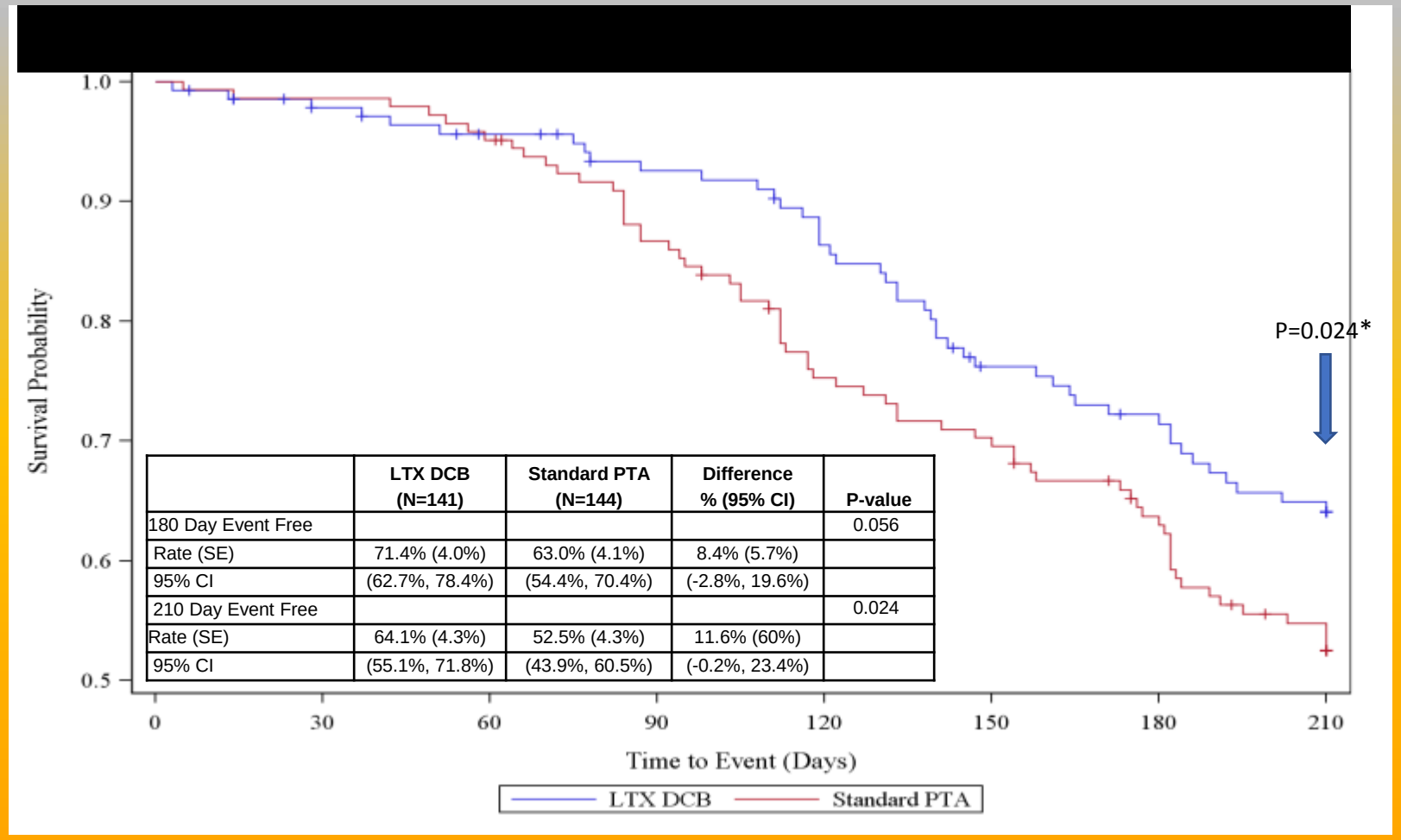
Figure 14.2.2.2.D545
Kaplan Meier Analysis of Primary Safety Endpoint at 18 Month
Modified Intent to Treat




| | LTX DCB (N=141) | Standard PTA (N=144) | Difference % (95% CI) | P-value |
|---|---|---|---|---|
| 545 Day Event Free | | | | 0.0004 |
| Rate (SE) | 34.3% (4.7%) | 22.6% (4.4%) | 11.6% (6.4%) | |
| 95% CI | (25.3%, 43.5%) | (14.7%, 31.6%) | (-0.9%, 24.2) | |

95% CI of the rate and the rate difference at each time point were calculated based on normal approximation and one-sided p-value is from test for non-inferiority, with 10% as non-inferiority margin.

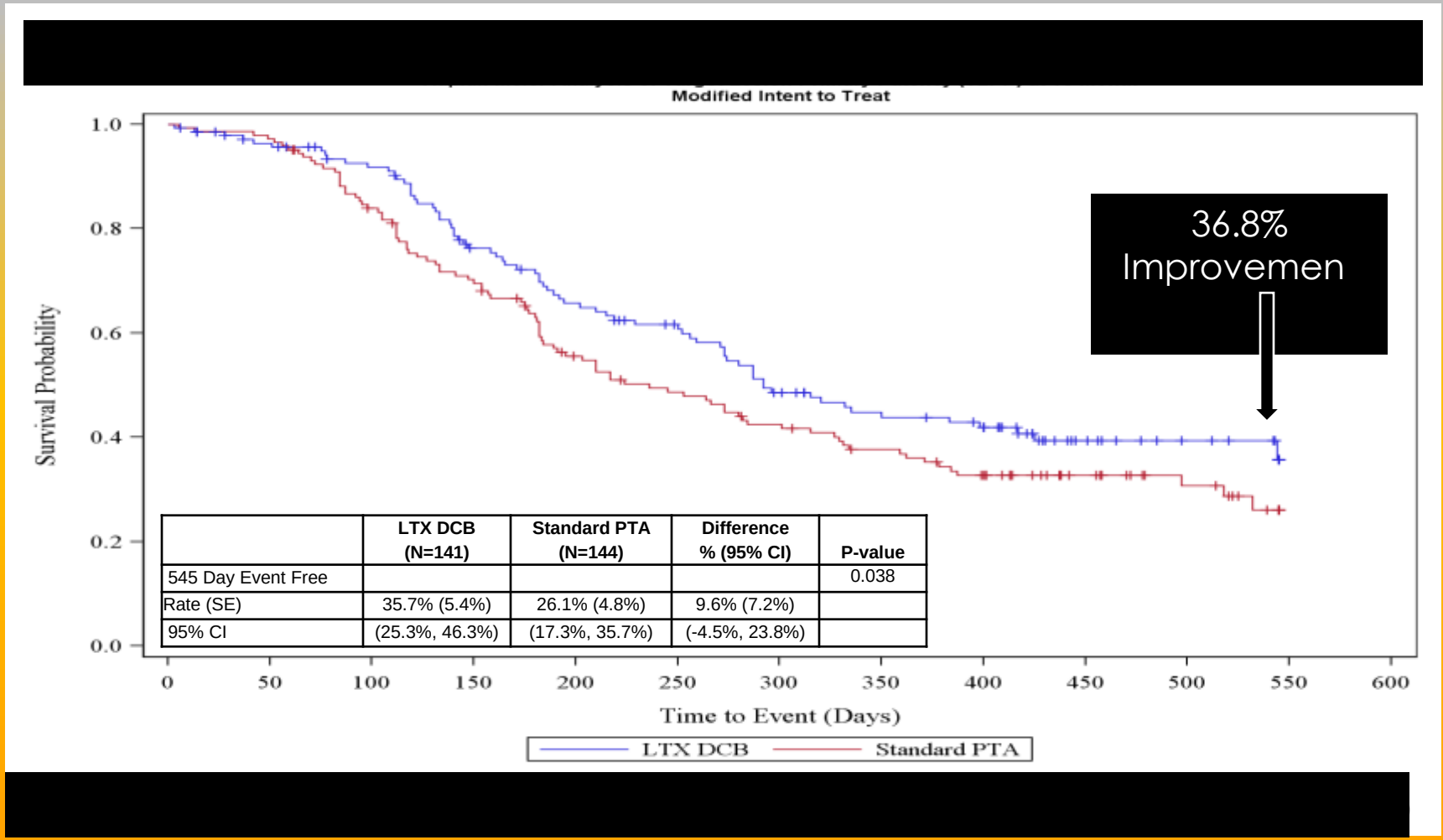
# AV IDE Trial – Target Lesion Primary Patency @ 6 Months




| | LTX DCB (N=141) | Standard PTA (N=144) | Difference % (95% CI) | P-value |
|---|---|---|---|---|
| 180 Day Event Free | | | | 0.056 |
| Rate (SE) | 71.4% (4.0%) | 63.0% (4.1%) | 8.4% (5.7%) | |
| 95% CI | (62.7%, 78.4%) | (54.4%, 70.4%) | (-2.8%, 19.6%) | |
| 210 Day Event Free | | | | 0.024 |
| Rate (SE) | 64.1% (4.3%) | 52.5% (4.3%) | 11.6% (60%) | |
| 95% CI | (55.1%, 71.8%) | (43.9%, 60.5%) | (-0.2%, 23.4%) | |

*one-sided p-value

# AV IDE Trial – Target Lesion Primary Patency @ 18 Months



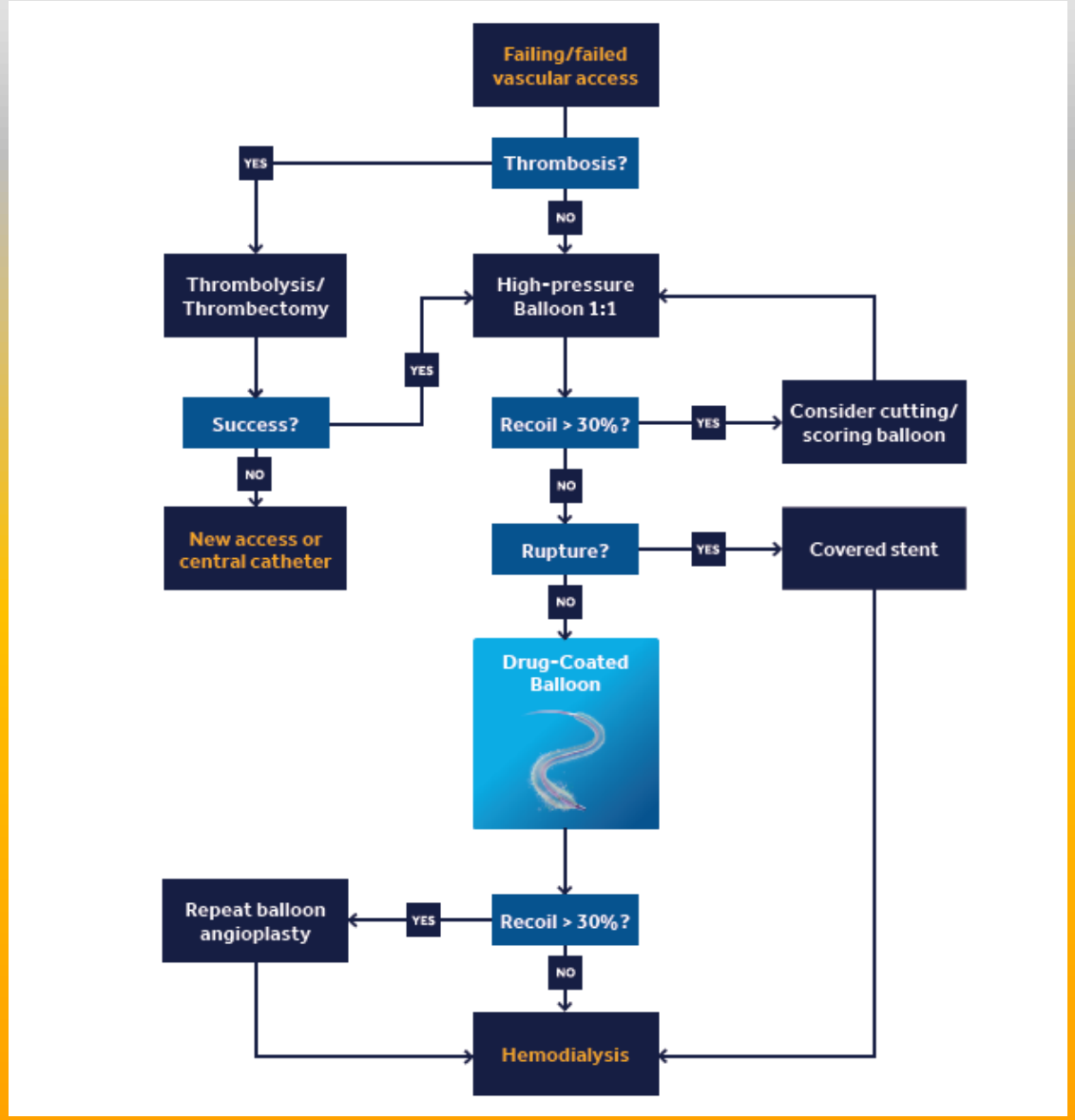

| | LTX DCB (N=141) | Standard PTA (N=144) | Difference % (95% CI) | P-value |
|---|---|---|---|---|
| 545 Day Event Free | | | | 0.038 |
| Rate (SE) | 35.7% (5.4%) | 26.1% (4.8%) | 9.6% (7.2%) | |
| 95% CI | (25.3%, 46.3%) | (17.3%, 35.7%) | (-4.5%, 23.8%) | |

*one-sided p-value

# AV IDE Trial – Summary

- First and only approved drug-coated balloon for AV fistulae in US
- Safety outcomes are non-inferior to PTA
- 71.4% target lesion primary patency (TLPP) at 6 months
- 32.6% fewer number of interventions required to maintain TLP at 6 months
- Sustained effectiveness benefit
  - ☛ 36.9% improvement in primary patency over PTA at 18m

- Limitation to the study: stenosis and re-stenosis are considered together




K. Katsanos, Vascular News Supplement, April 2016

a paradigm shift towards HP PTA + DCB?

# *THANK YOU!*


VII CONVEGNO NAZIONALE
del Gruppo di Studio degli Accessi Vascolari
Coordinator:
Giacomo Forneris
I st ITALIAN VAS CHAPTER
of Vascular Access Society
Coordinator:
Daniele Savio
Joint Event
Save the date
Turin | 15-17 november 2018

# Prospettive future del trattamento endovascolare: drug eluting balloon


DANIELE SAVIO

RADIOLOGIA VASCOLARE ED INTERVENTISTICA

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