Drug-eluting Balloon in In-Stent Restenosis

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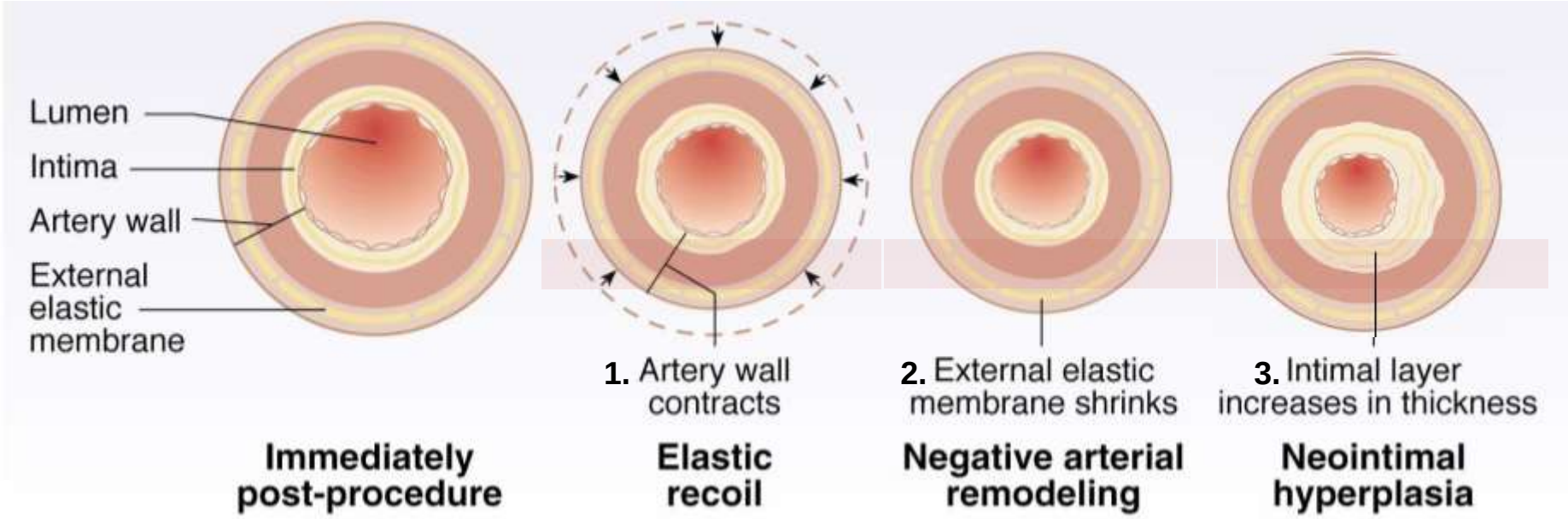
Three Mechanisms Cause Restenosis
Post Balloon Angioplasty

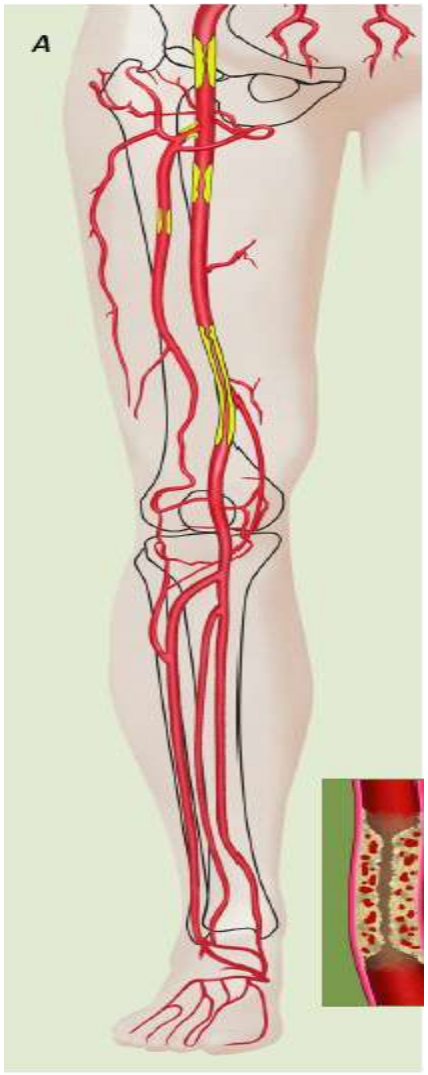
1. Elastic Recoil
2. Negative Arterial Remodeling
3. Neointimal Hyperplasia

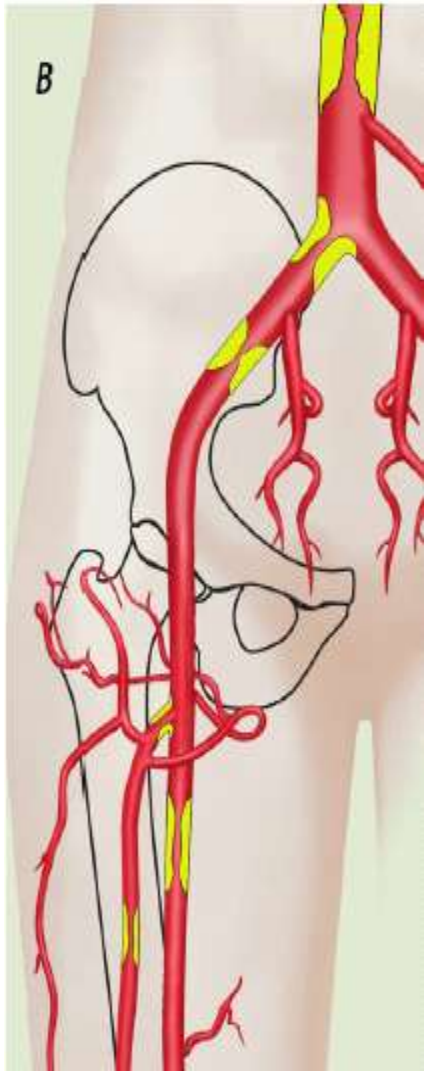
POBA Restenosis ~40–50%



J. Zidar, Restenosis & Metal Stents: The Hard Data, TCTMD.com

Disease Patterns





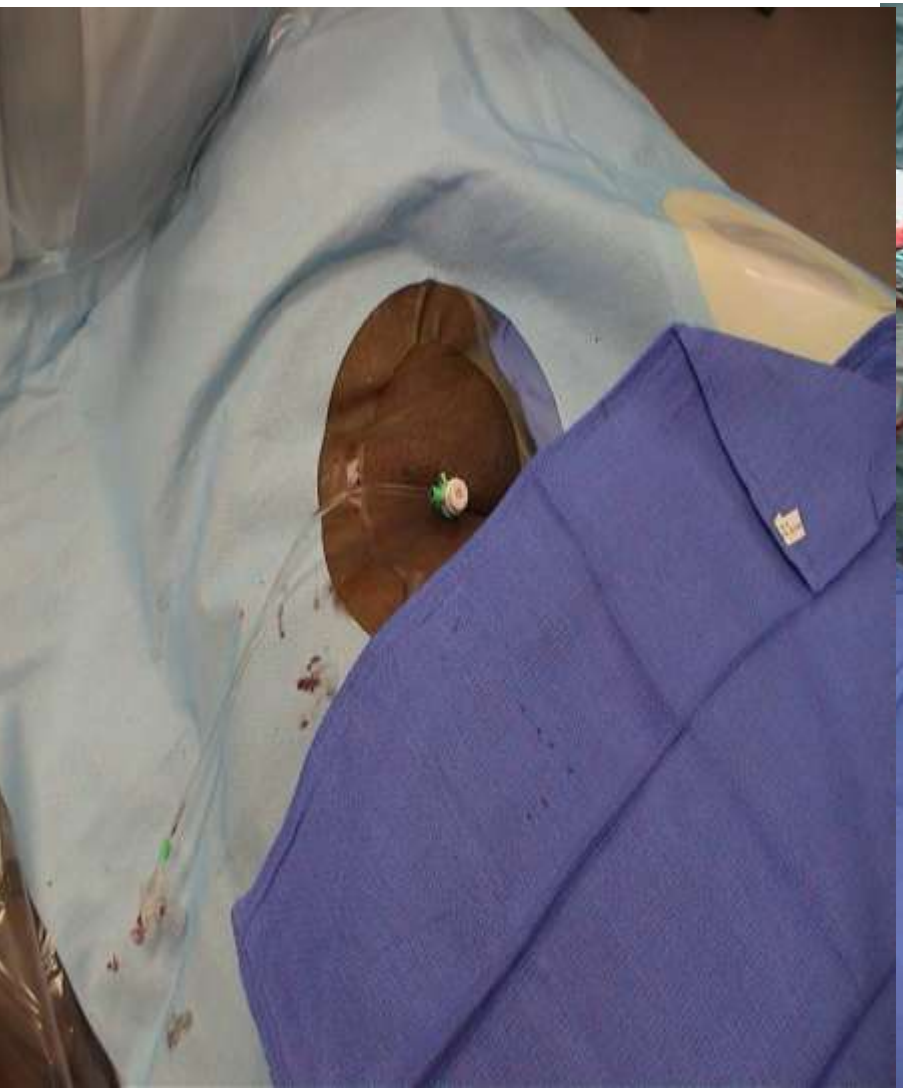
Diabetes increases risk of amputation 6X

Non-Diabetics

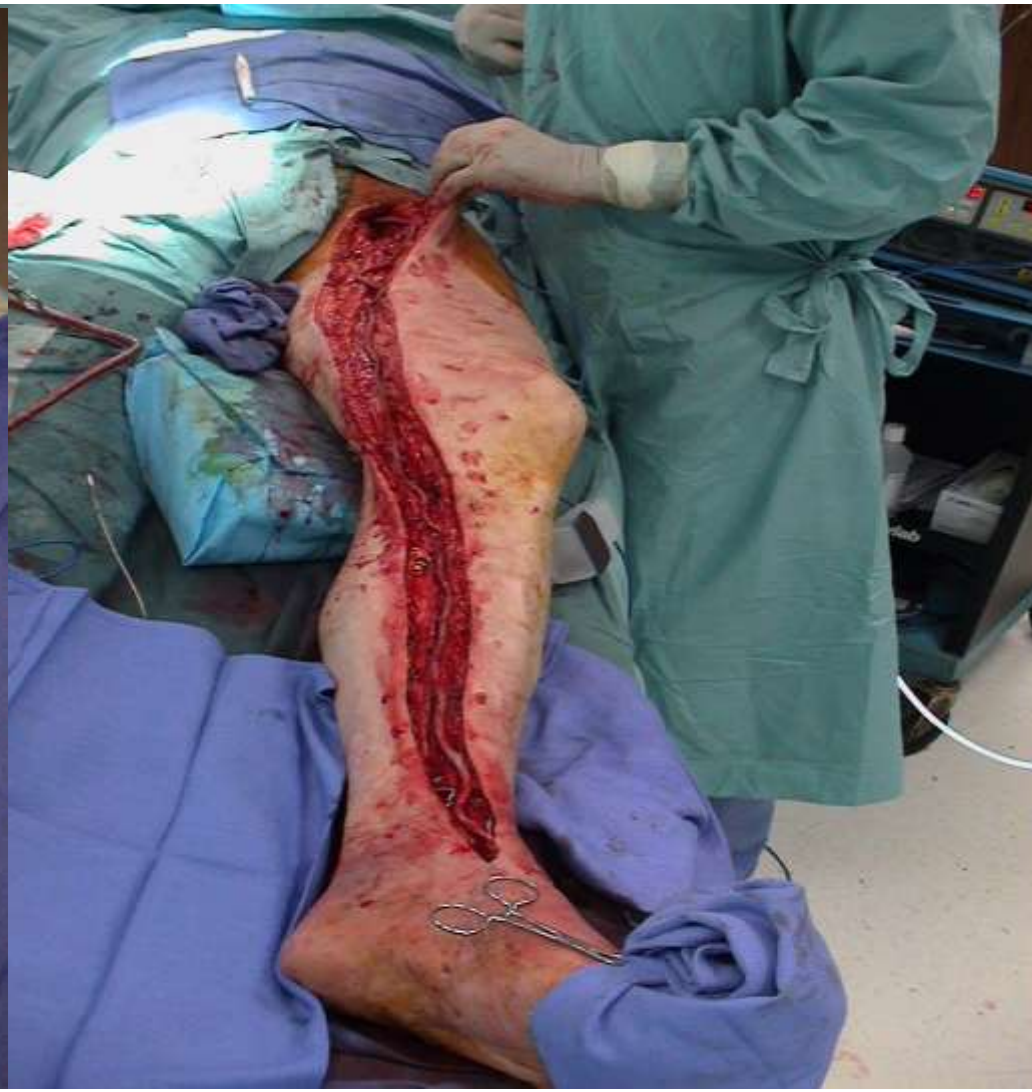
Diabetics

Patient Preference

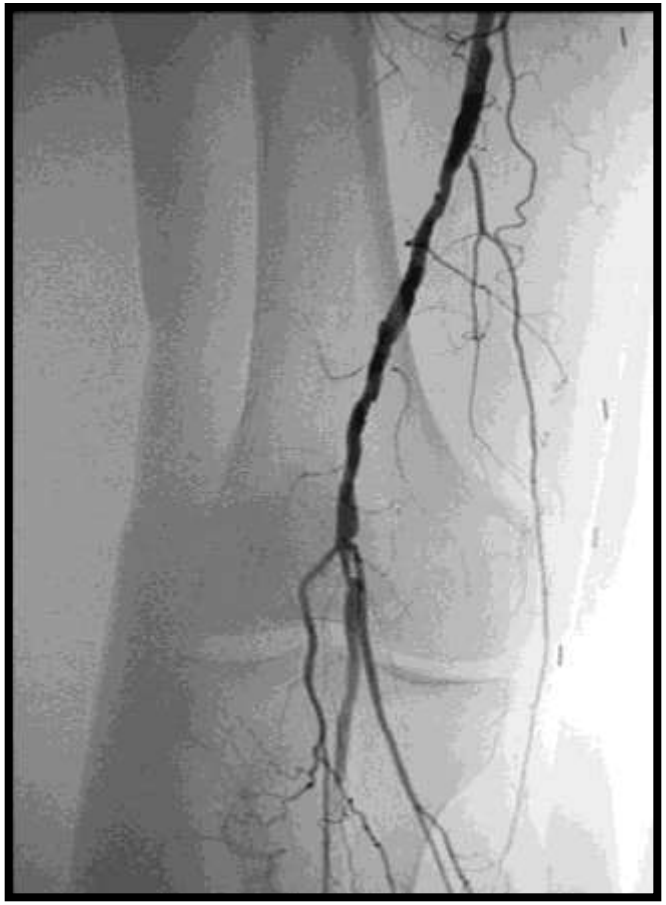
Percutaneous



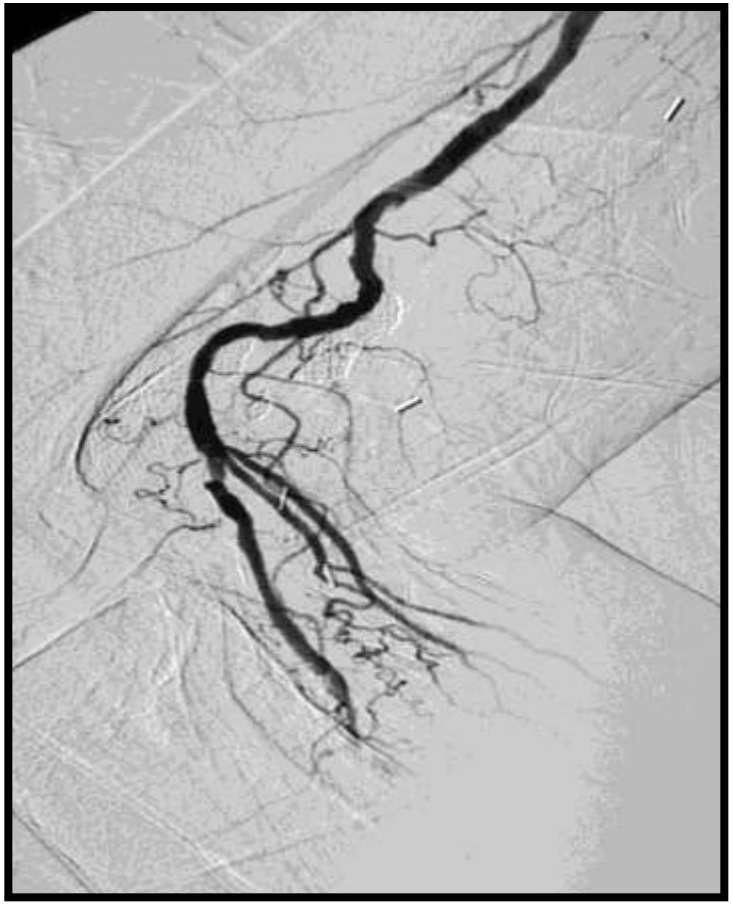
Surgical



Problems with SFA Stenting….

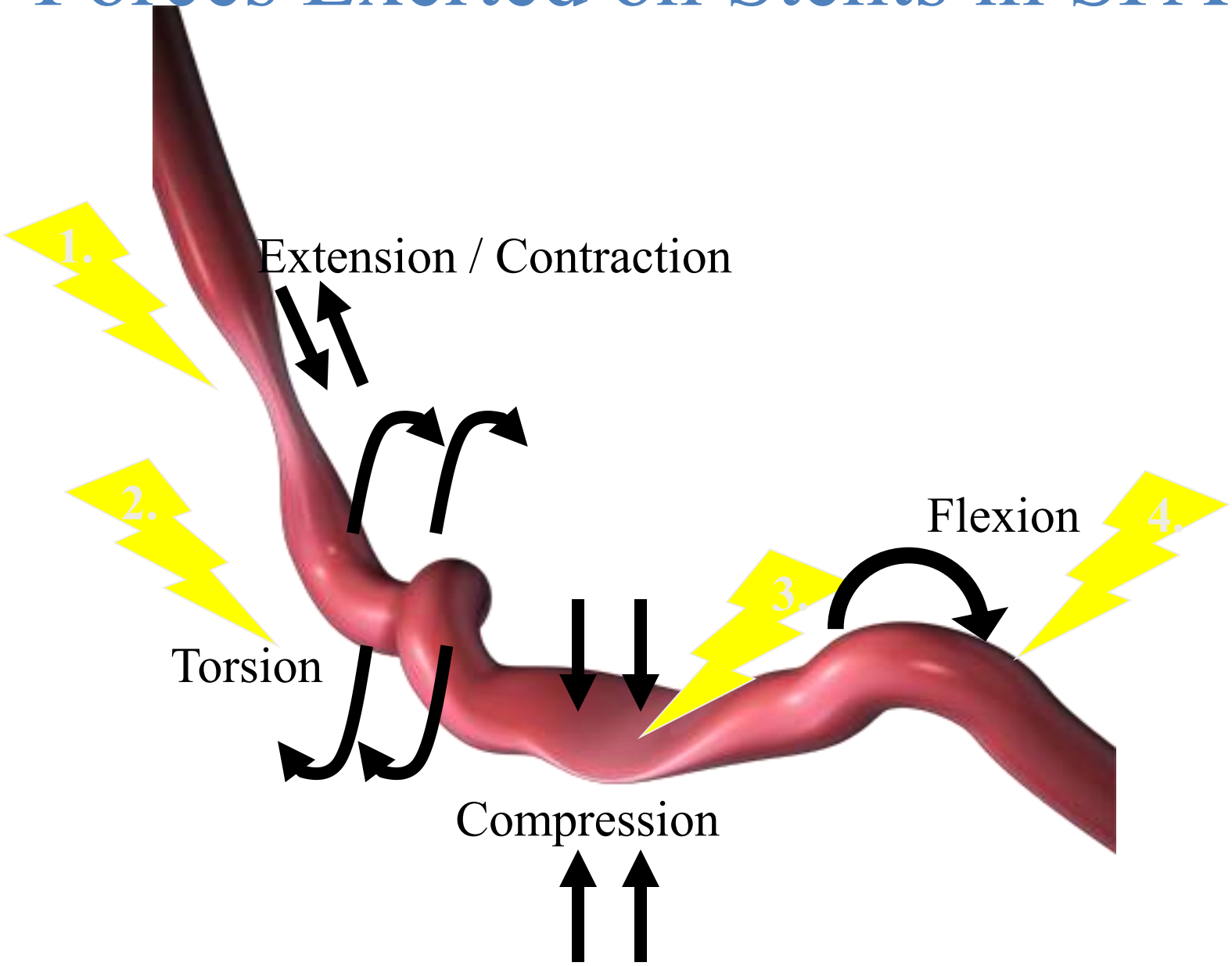


Knee Extension



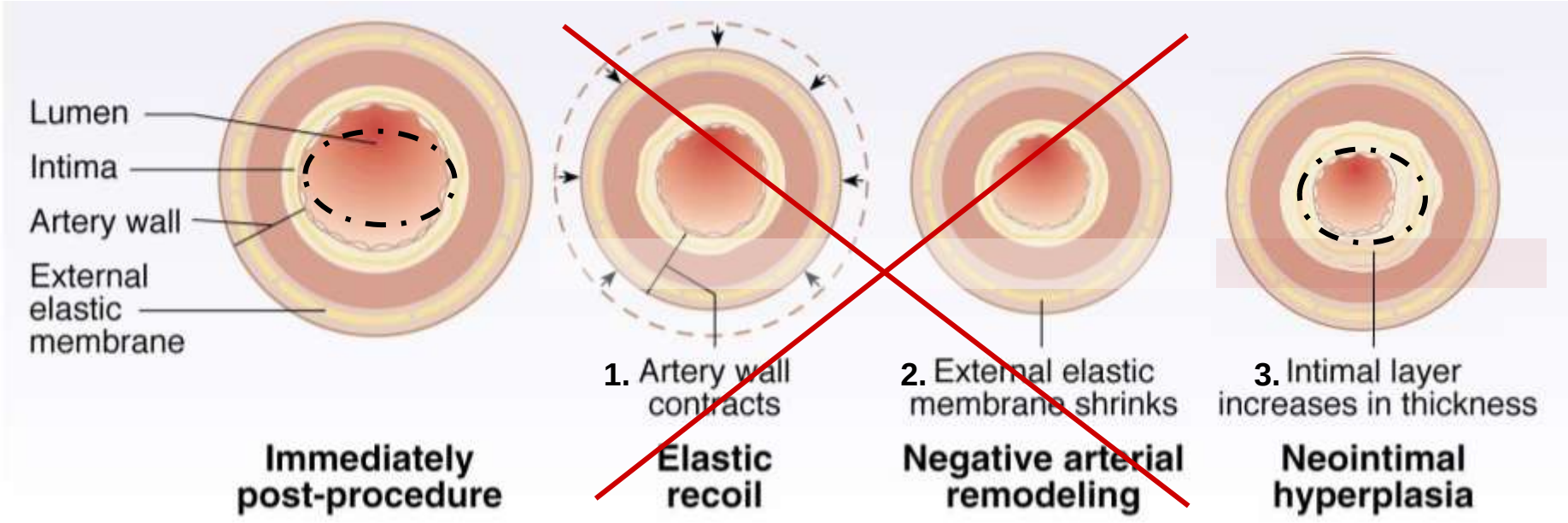
Knee Flexion

Forces Exerted on Stents in SFA

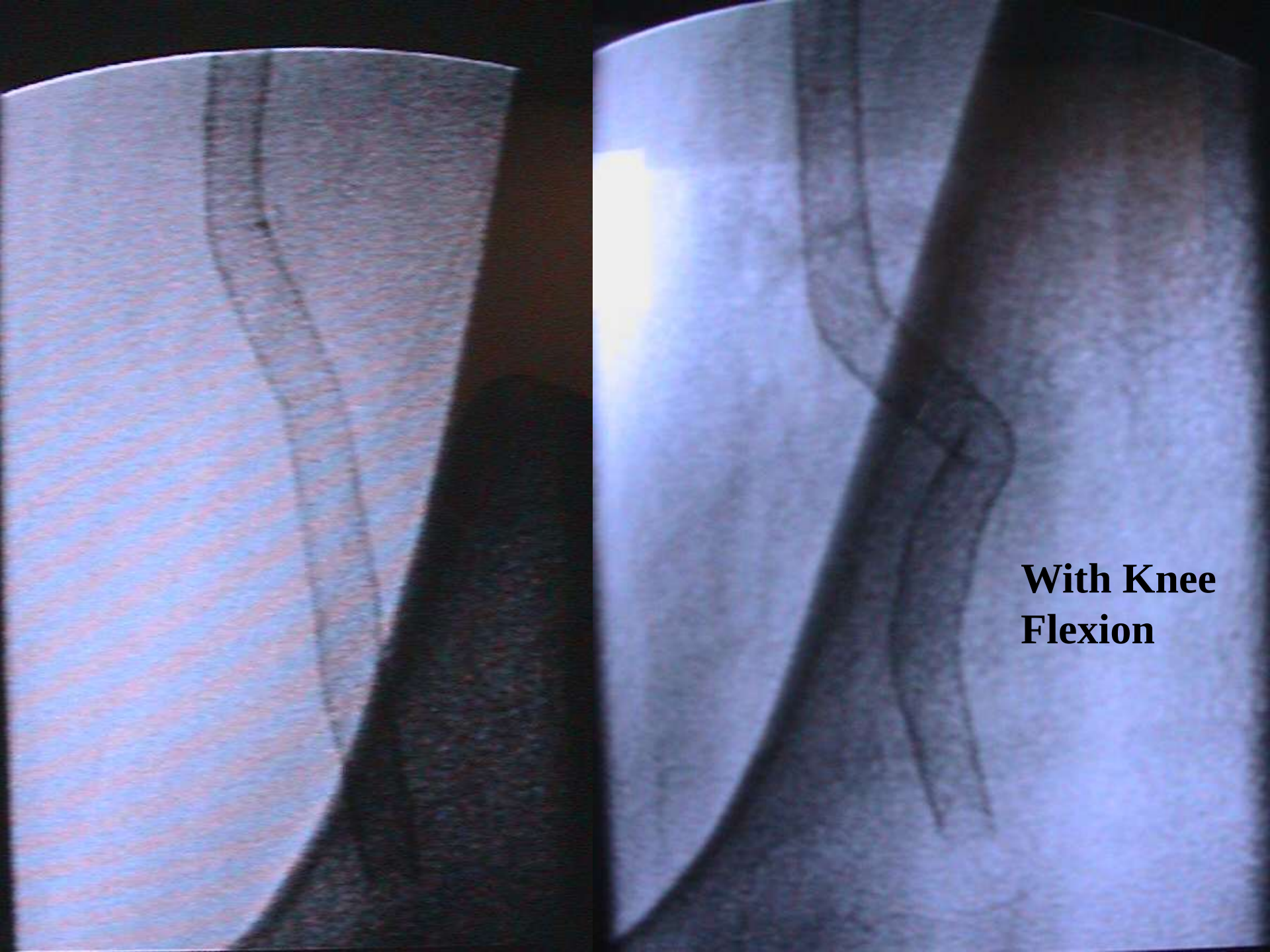


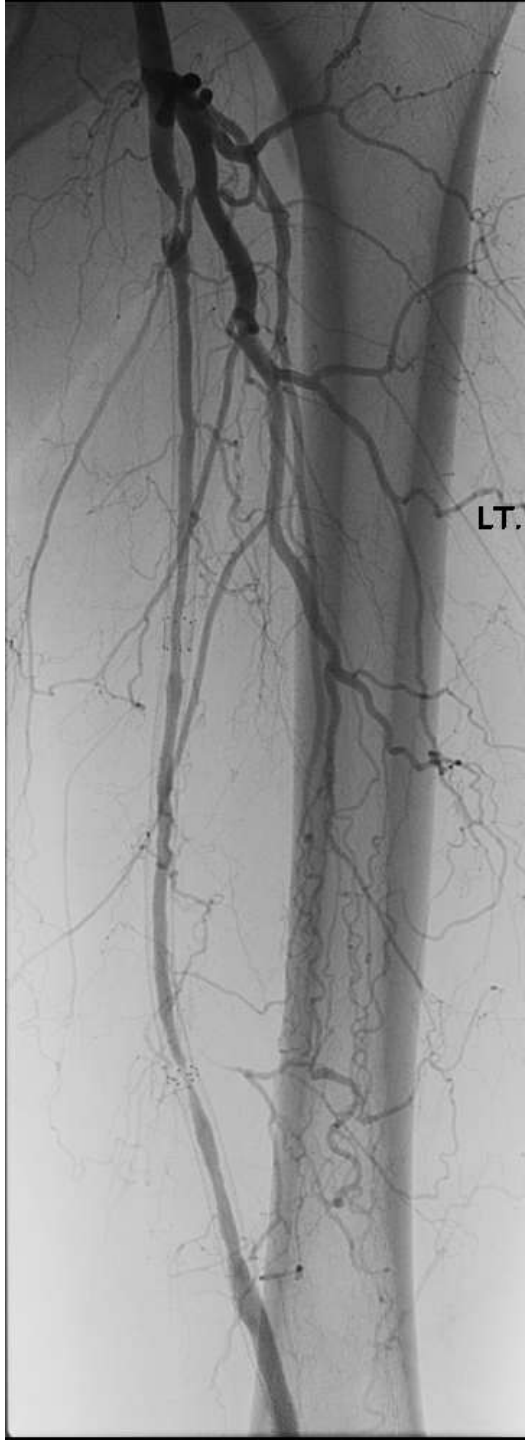
Restenosis Post-Stent:
Neointimal Growth

1. Elastic Recoil: Mitigated by stenting
2. Vascular Remodeling: Mitigated by stenting
3. Neointimal Hyperplasia: Worsened by stenting

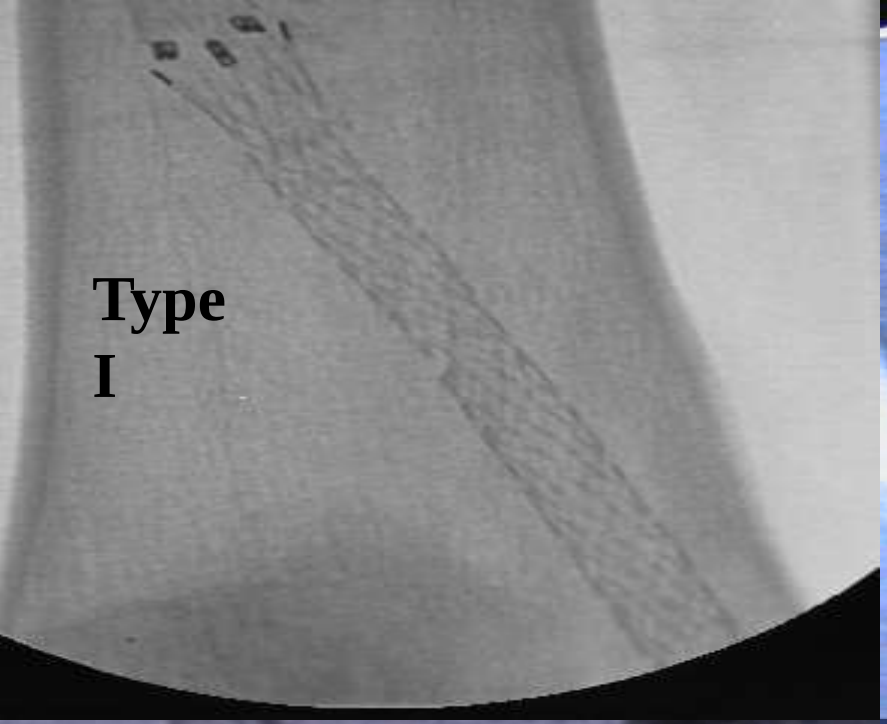


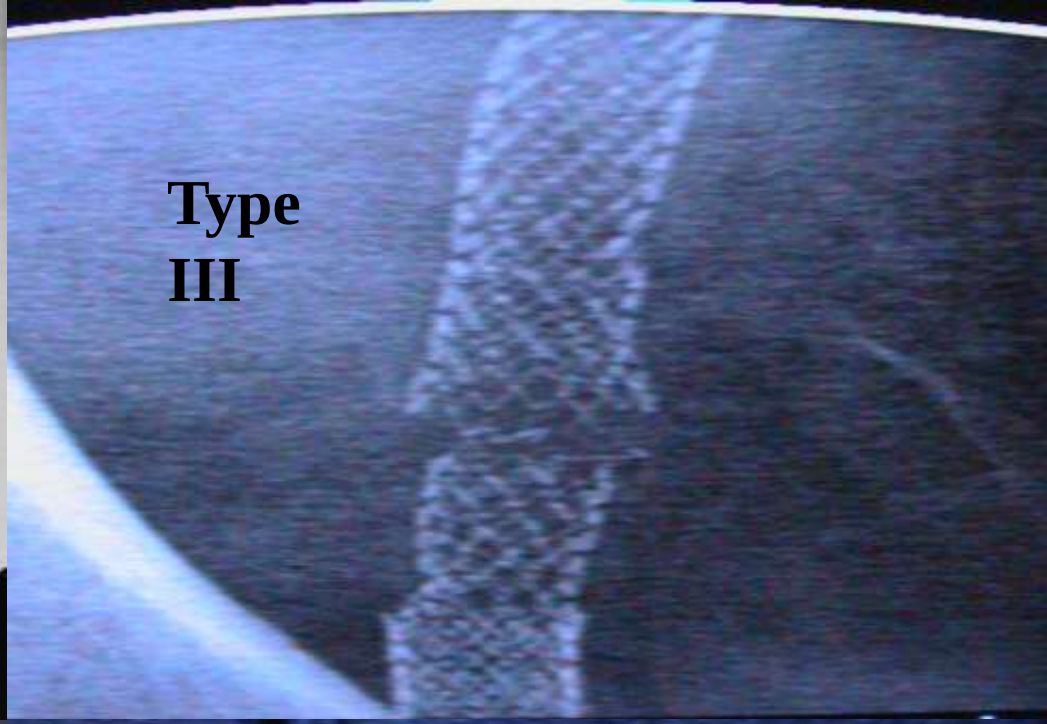
. Zidar, Restenosis & Metal Stents: The Hard Data, TCTMD.com

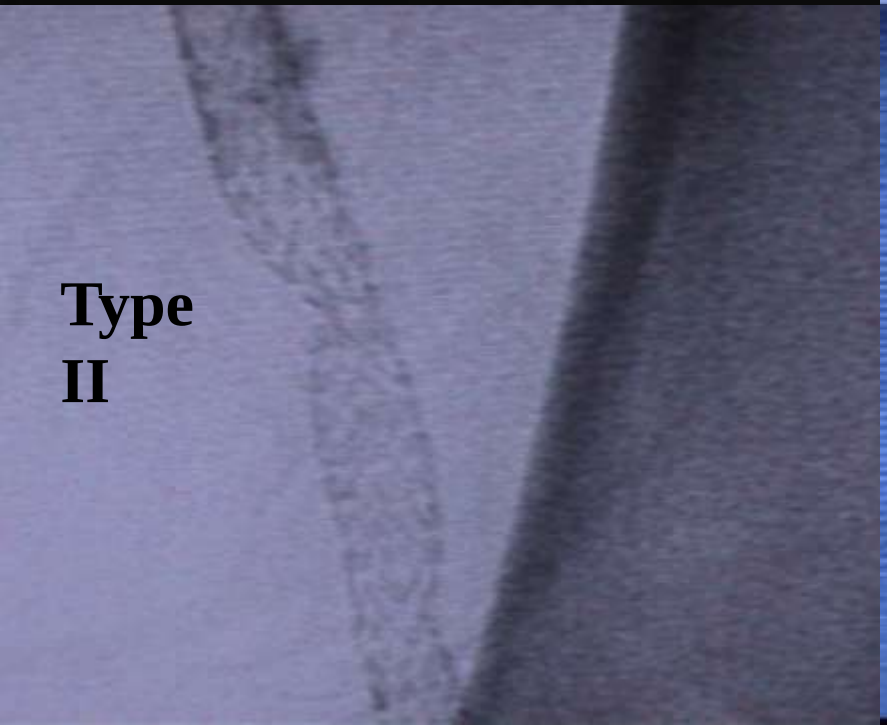

With Knee
Flexion



SFA STENT RESTENOSIS
UP TO 50%


Type
I


Type
III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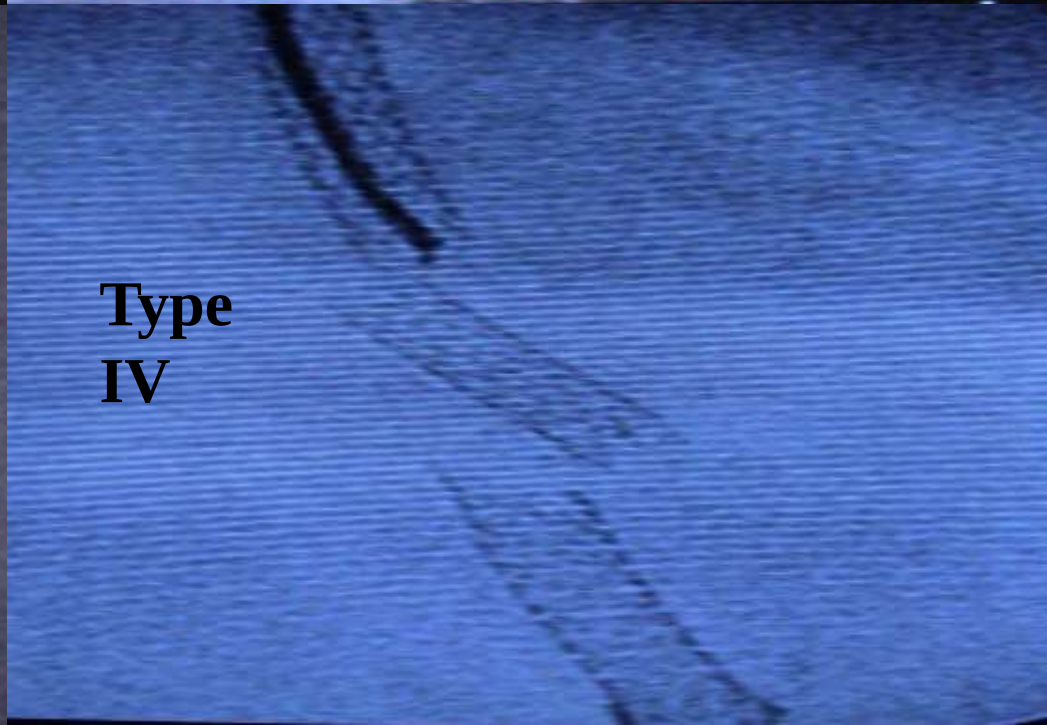
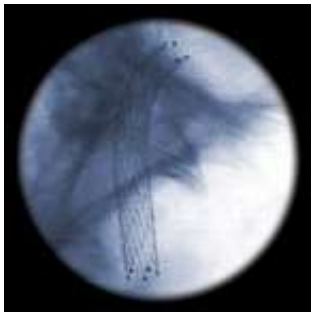

Type
IV

Endovascular Revascularization of the SFA and BTK

- Balloon only (PTA)
- Nitinol Stents
- Covered stents
- Atherectomy
  - Excisional or Laser
- "Specialized" Angioplasty Devices
  - Cutting and Scoring Balloons
- Drug coated balloons
- Drug coated stents
  - Cook Zilver PTX
- Peripheral BVS



Femoropopliteal Revascularization

Proven Benefit

Balloon angioplasty
Mechanical thrombectomy
Thrombolysis
Stent

Unproven/Failed

Cryotherapy
Brachytherapy
Laser angioplasty
Sonoangioplasty
Photoangioplasty
Drug-eluting stents
Cutting balloon
Directional atherectomy
Rotational atherectomy

Atherectomy Devices

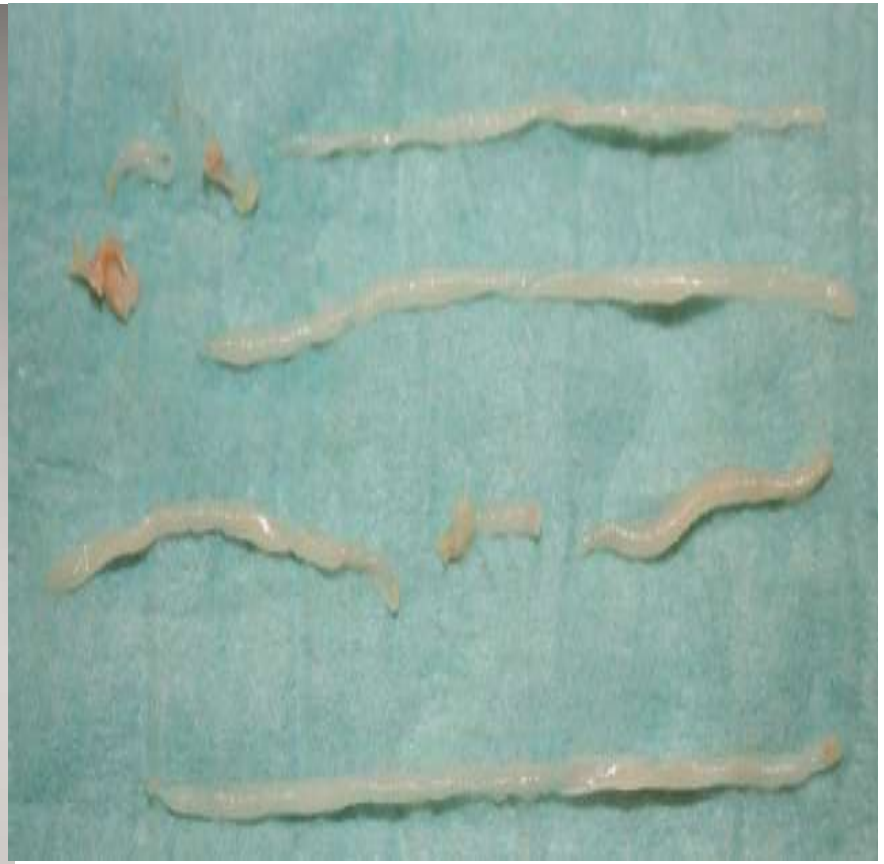
Turbo-Laser

Rotablator

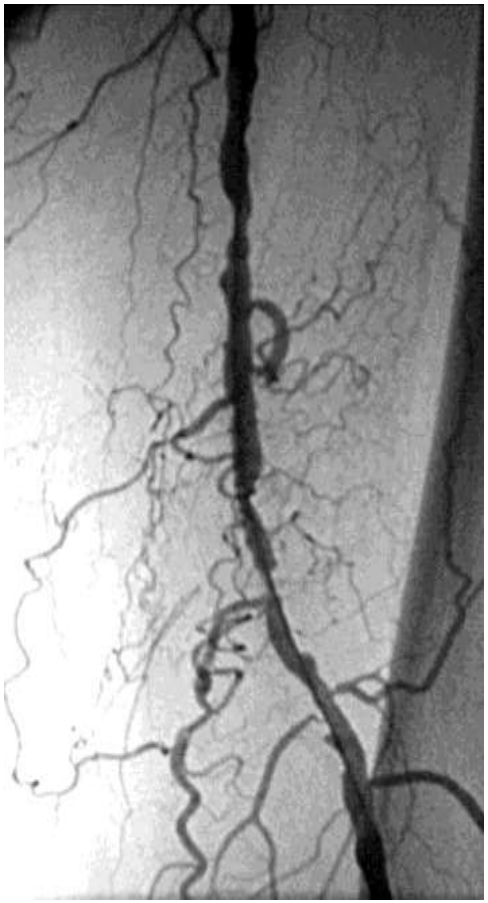
Silver Hawk

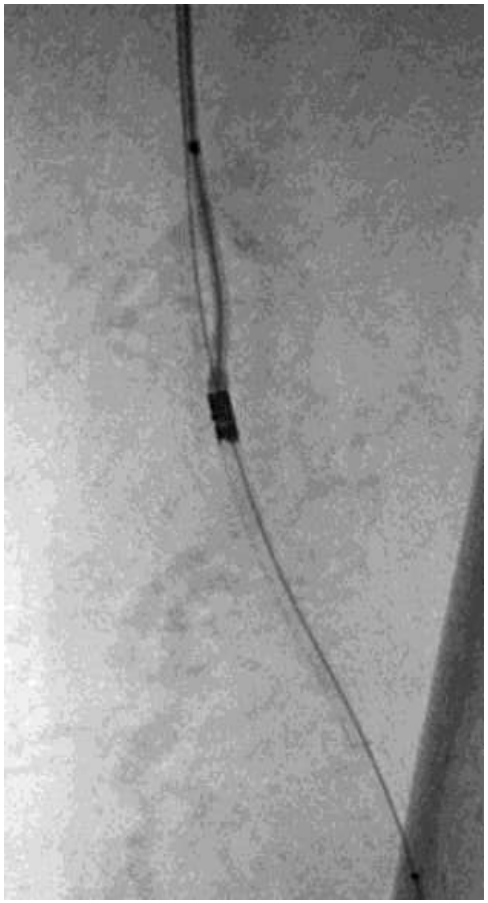
CSI 360 Orbital Atherectomy

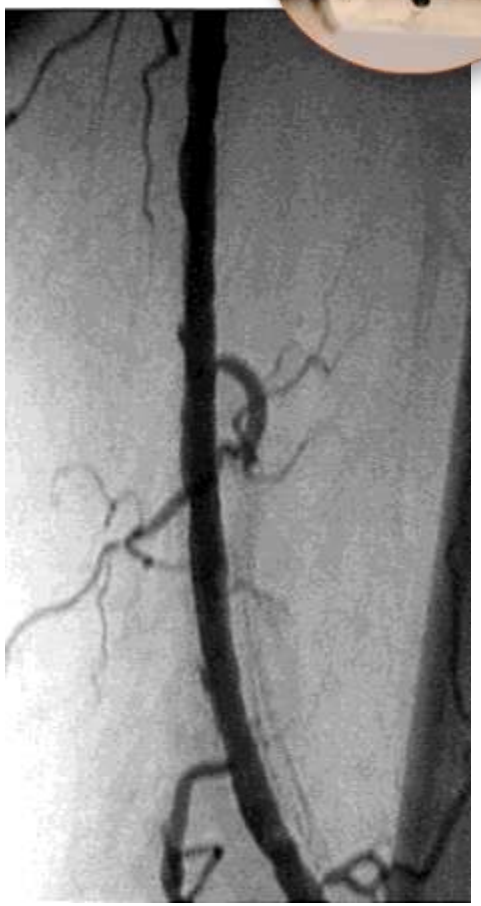
SilverHawk Plaque Excision System



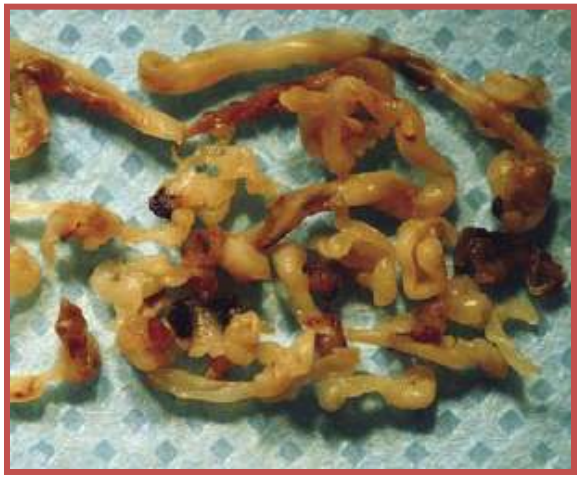
Directional Atherectomy

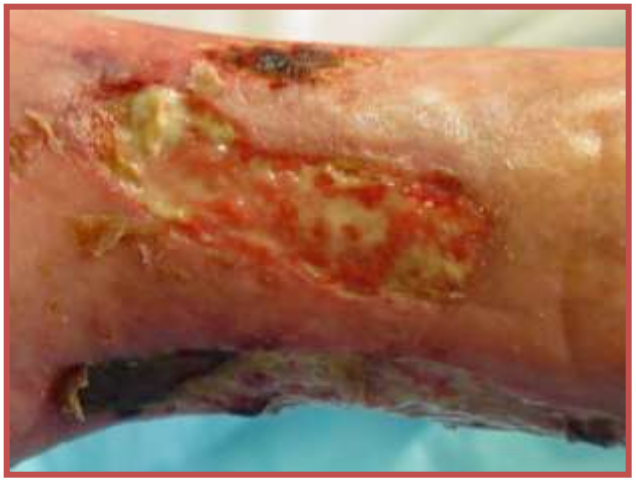




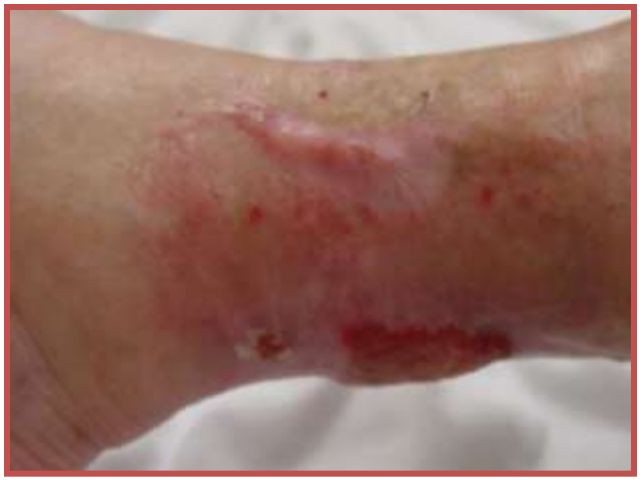


Directional Atherectomy



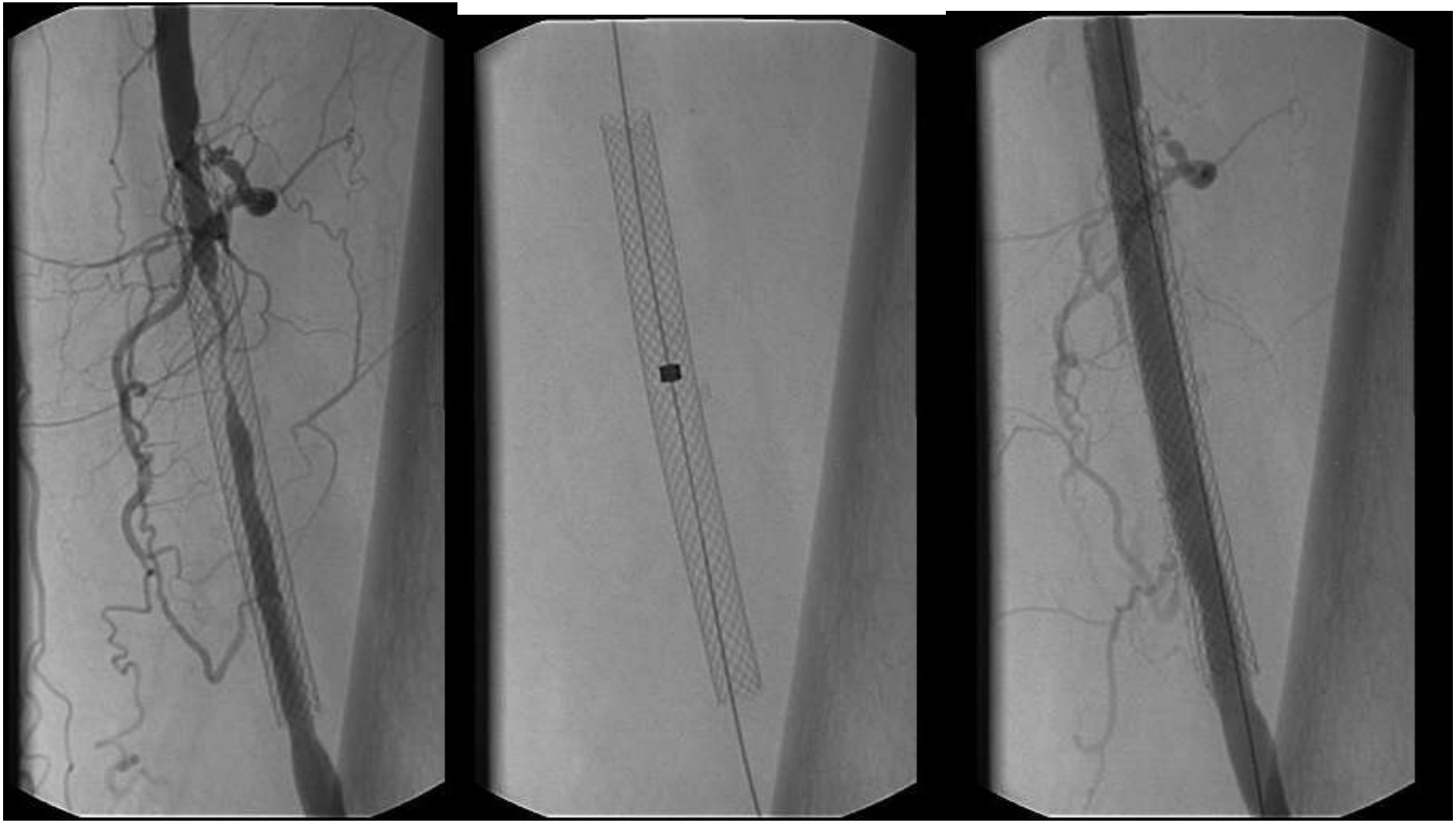


Before

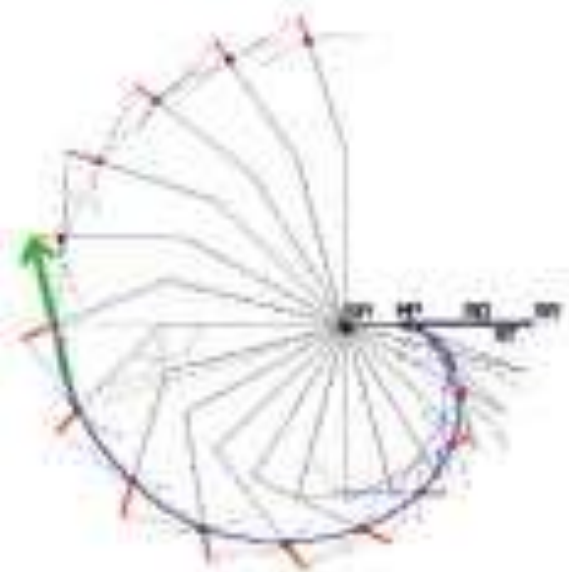


After

Laser Atherectomy



Orbital Atherectomy



CENTRIFUGAL FORCE

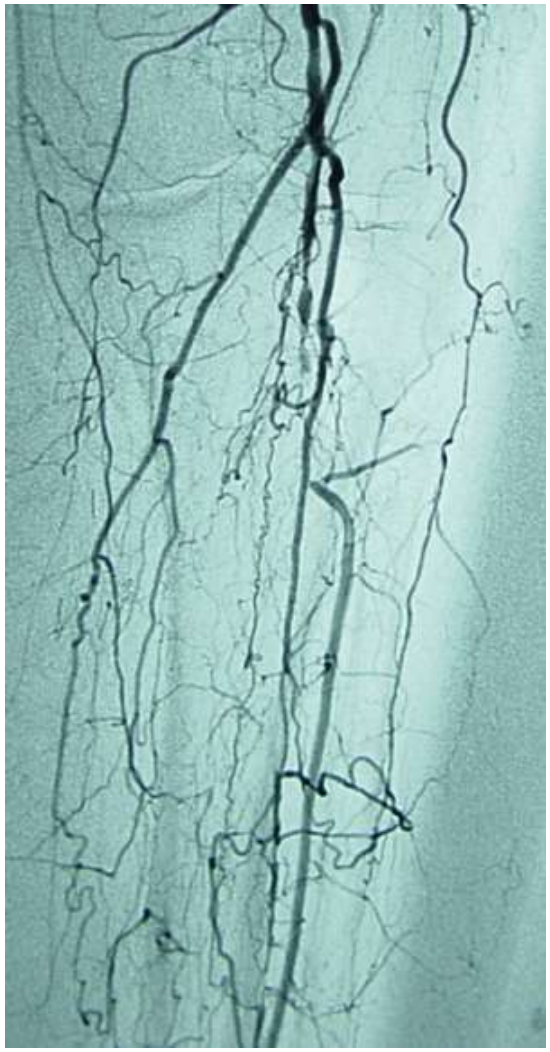
$$CF = \frac{\text{mass} * \text{rotational speed}^2}{\text{radius of the orbit}}$$

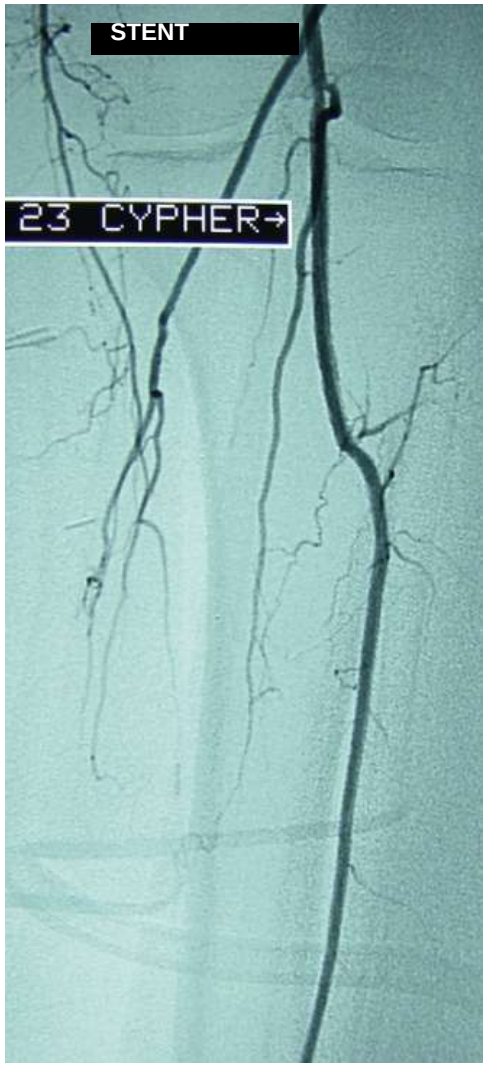
CARBON BLOCK TESTS

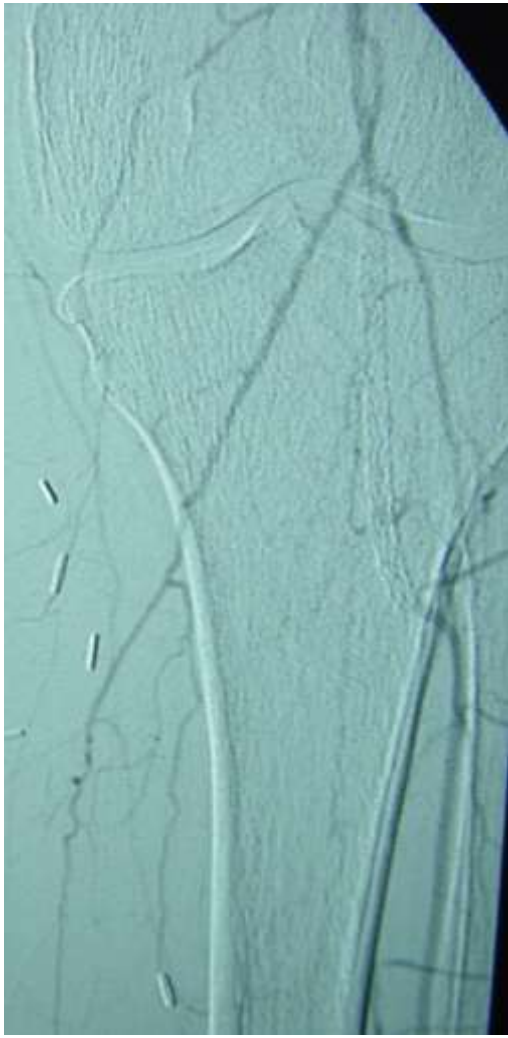
2.0MM CROWN
AT 80K RPM'S

2.0MM CROWN
AT 200K RPM'S

INFRAPOPLITEAL RESTENOSIS 50-70% in 6 months





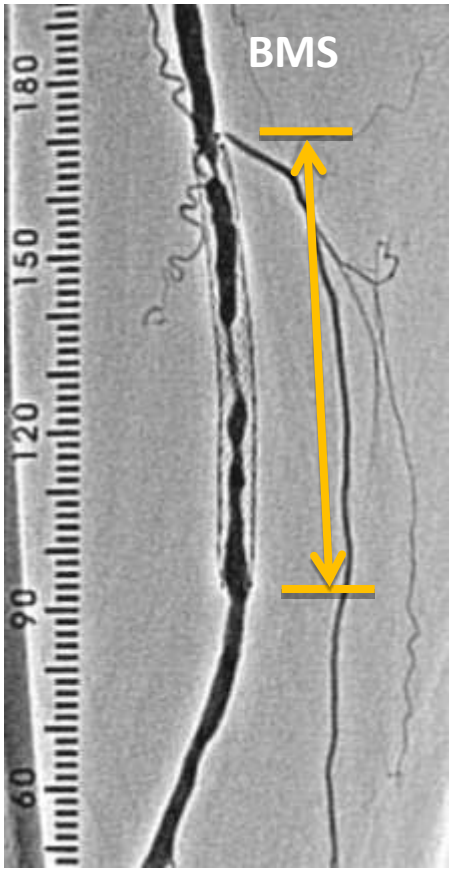


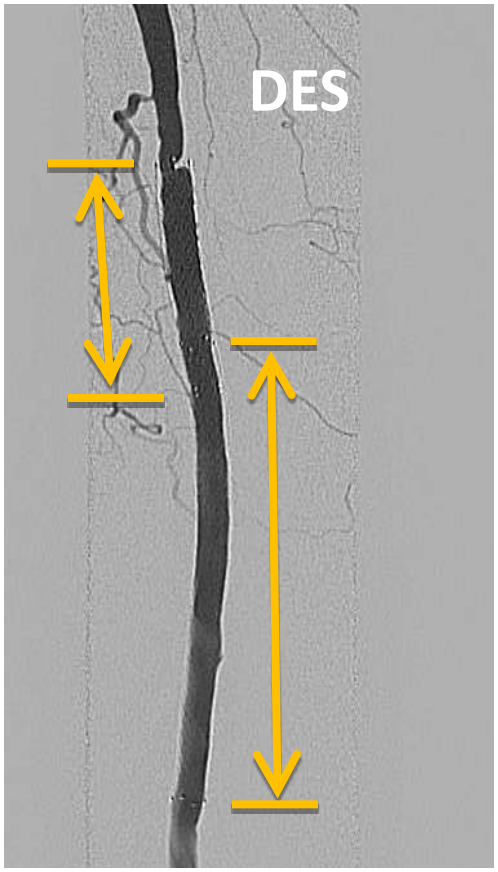
What of other devices

- Atherectomy
  - Directional - No
  - Rotational - NO
- Laser – No
- Cryoplasty – No
- Cutting balloon - ?
- Scoring ballloon - ?
- Chocolate balloon - ?

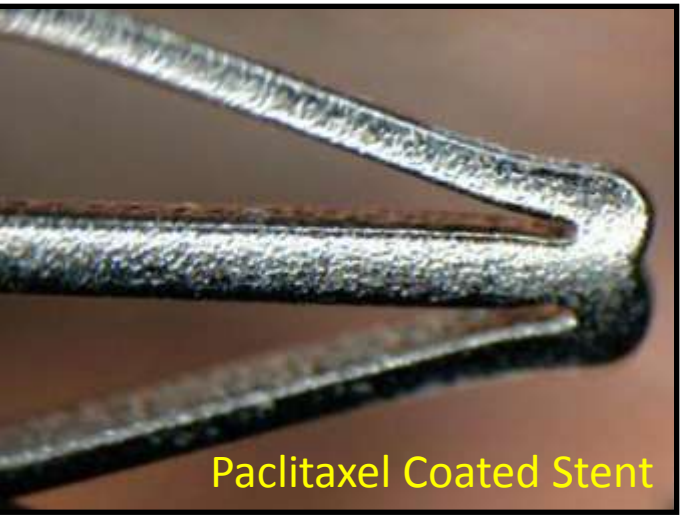
None have enjoyed the success of the coronary DES!

DES: Proof of Concept and a Paradigm Shift?

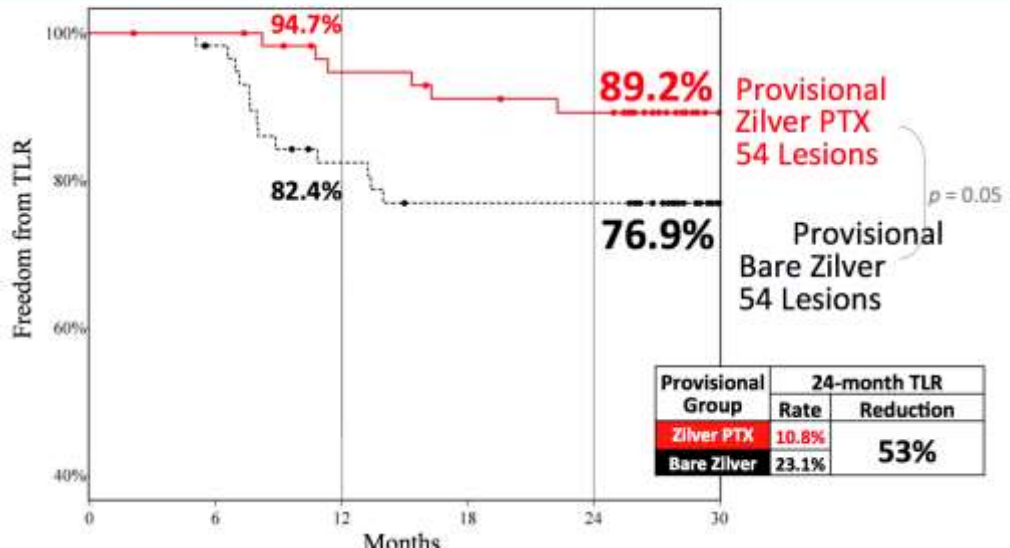




A New "Dominant" Strategy?

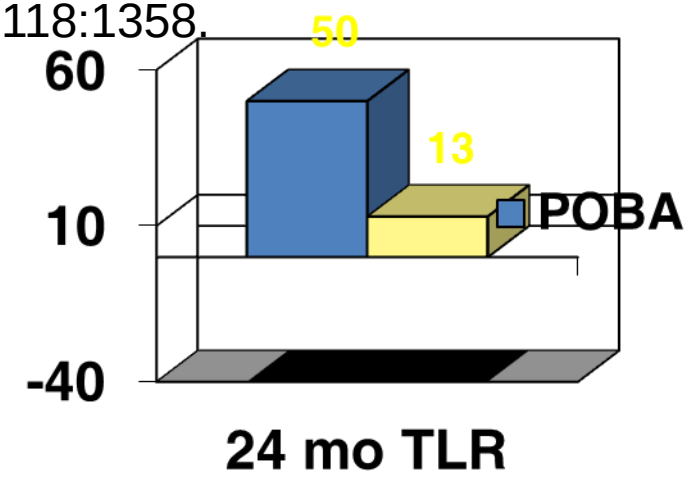


24-Month Clinical Result
Freedom from TLR: **Provisional Zilver PTX vs. BMS**



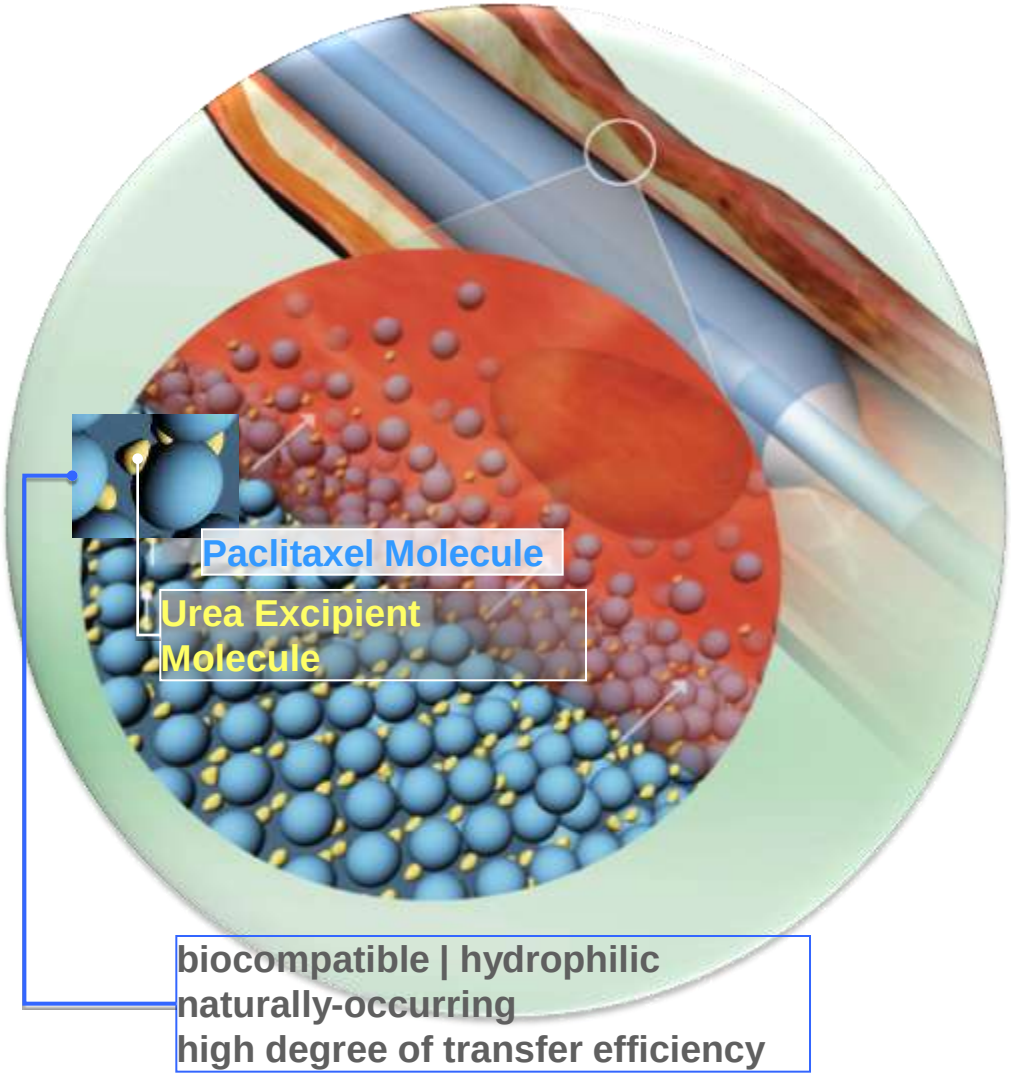
Provisional Group	24-month TLR	
	Rate	Reduction
Zilver PTX	10.8%	53%
Bare Zilver	23.1%	

FemPAC - Werk, M. Circ. 2008;118:1358.



74% Reduction in TLR

IN.PACT™ DEB with FreePac™ Coating Technology



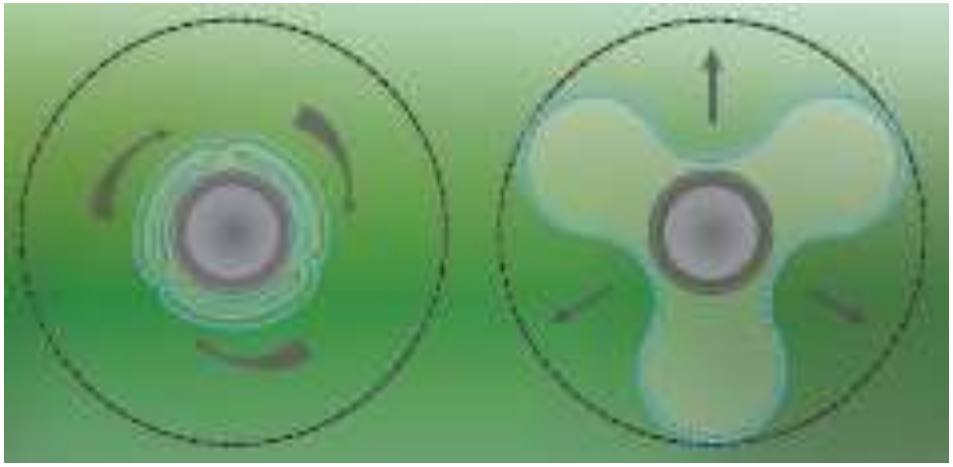
IN.PACT™

- Medtronic-Invatec DEB balloon line

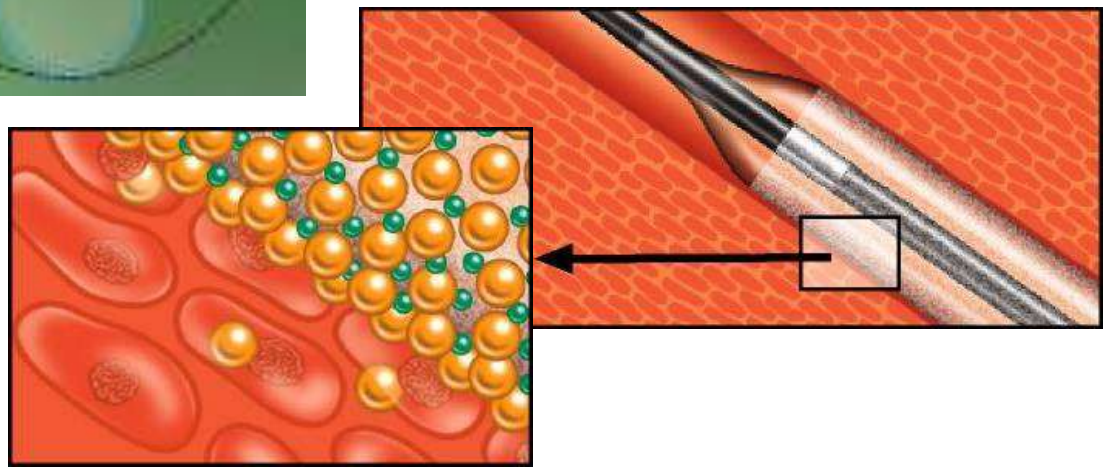
FreePac™

- Proprietary hydrophilic coating formulation
  - Urea separates Paclitaxel molecules
  - Increased drug solubility and optimal diffusion into vessel wall
  - Urea facilitates Paclitaxel absorption into the vessel wall

DEB Drug Transfer



As the balloon unwraps, the drug-excipient coating is fully exposed to the vessel wall.



Paclitaxel's hydrophobicity along with the increased solubility conferred by the excipient allows for rapid drug transfer across the vessel wall.

IN.PACT Global Clinical Study

Site Initiation Visit Presentation
CIP v2.0 dated 30 May 2012

Version 2.0, 16-Oct-2012

Protocol Synopsis

IN.PACT Global Study – Protocol Synopsis	
Title	The IN.PACT Global Clinical Study for the Treatment of Comprehensive Superficial Femoral and/or Popliteal Artery Lesions Using the IN.PACT Admiral™ Drug-Eluting Balloon
Design	Prospective, multi-centre, single-arm study
Subjects/ Sites	Maximum of 1500 at approximately 80 investigational sites globally.
Subject Population	Subjects with symptoms of intermittent claudication and/or rest pain (Rutherford Class 2-3-4) with angiographic evidence of superficial femoral and/or popliteal arterial occlusion or stenosis will be consecutively screened and enrolled based on the study inclusion and exclusion criteria
Clinical Cohort	All subjects to be evaluated for primary safety and efficacy endpoints at 12 months
Imaging Cohort	First 450 subjects to complete DUS at 12 months or earlier at the time of re-intervention: • De novo ISR cohort: 150 subjects • Long Lesion (≥ 15 cm) cohort: 150 subjects • CTO cohort (≥ 5 cm) : 150 subjects
Follow-up Schedule	30-days (phone call), 6 months, 12 months, 24 months, 36 months, 48 months (phone call) and 60 months (phone call) follow-up

Primary Endpoints

Efficacy Endpoints

- Clinical Cohort: Freedom from clinically-driven TLR within 12 months
- Imaging Cohort: Primary Patency within 12 months
  - *Defined as (1) freedom from clinically-driven TLR and (2) freedom from restenosis as determined by DUS PSVR ≤ 2.4*

Safety Endpoint

- Safety Composite Endpoint including:
  - Freedom from device- and procedure-related mortality through 30 days
  - Freedom from major target limb amputation within 12 months
  - Freedom from TLR within 12 months

Study Design

Sites need to be assessed by Corelab before they can enroll patients into the imaging cohort.

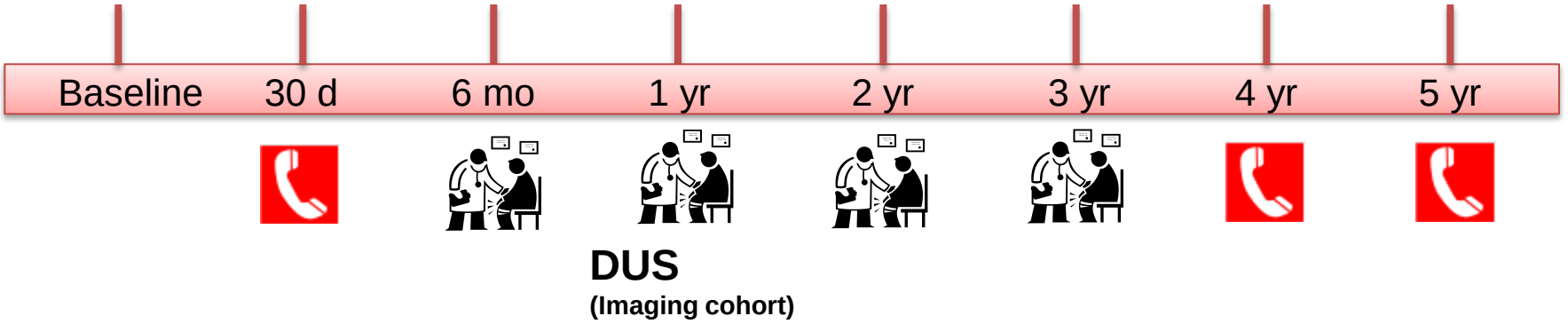
Prospective, Multi-center, Single-Arm Study

Clinical Cohort

n = 800 to 1500 patients in approx. 80 sites

Imaging Cohort

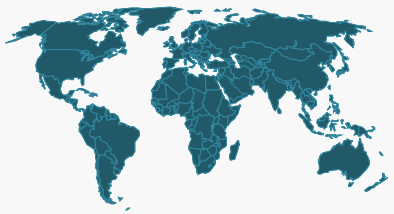
n = 450 patients
First 150 De novo ISR
First 150 LL
First 150 CTO



DUS
(Imaging cohort)

IN.PACT Global Study

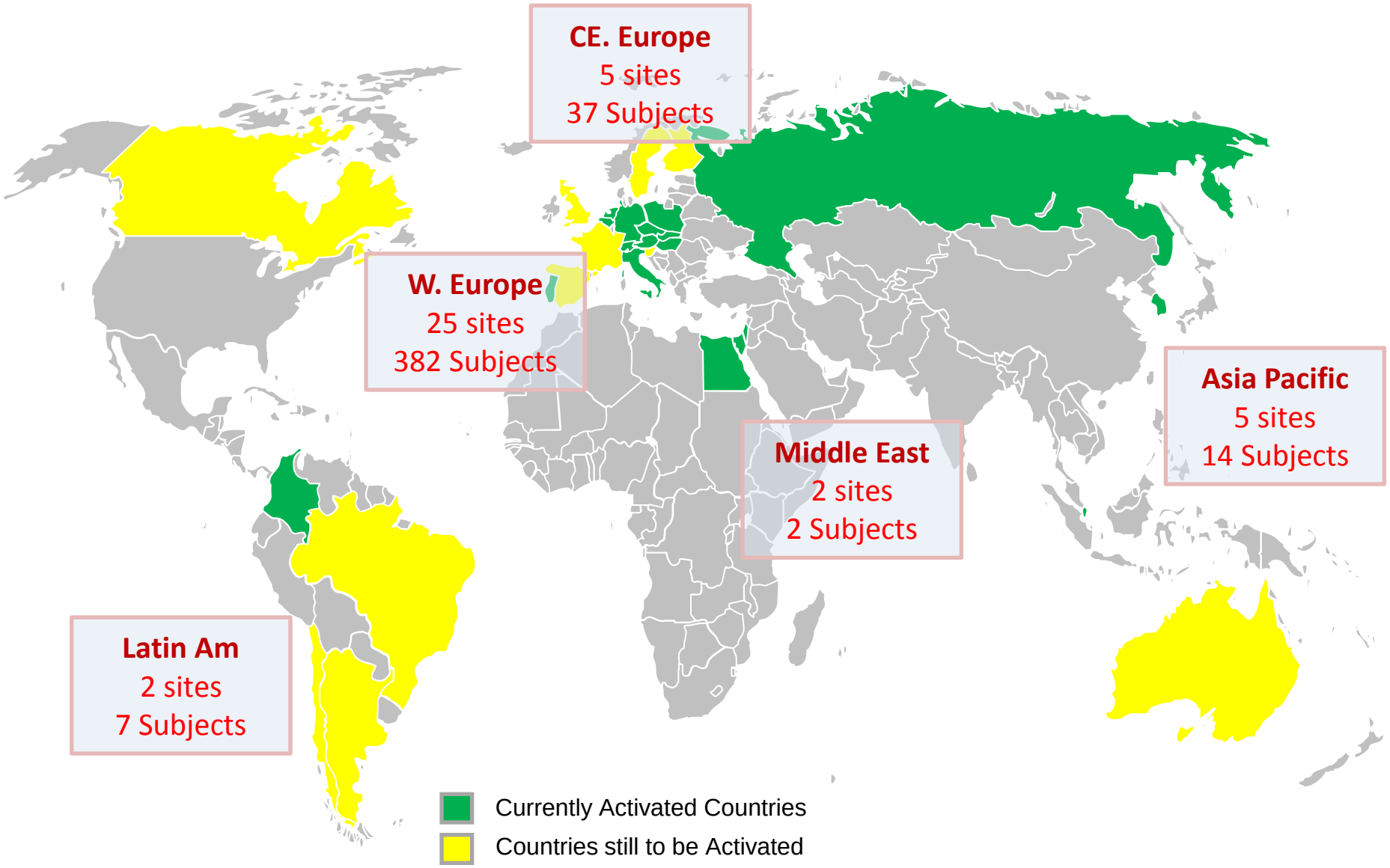
1500-patient, single arm, controlled, independently adjud. Study



- ☑ bilateral disease
- ☑ multiple lesions
- ☑ SFA and Popliteal
- ☑ TASC A
- ☑ TASC B
- ☑ TASC C
- ☑ TASC D
- ☑ Ca^{++}
- ☑ ISR

- 80 Sites (Europe, Mid-East, Latin America, Asia)
- All-comers (Claudicants + RC4)
  - **Primary Efficacy Endpoints**
    - **12m clinically driven TLR (Clinical cohort)**
    - **12m Primary Patency (450-patient Imaging Cohort):**
      1. Long lesions >15 cm (150 patients)
      2. ISR (150)
      3. CTO> 5cm (150)
  - Independent Patient Data Monitoring
  - Independent Clinical Event Committee
  - Independent DUS Corelab
  - Patient follow-Up to 5 years

Global Enrollment Distribution



* As of March 20th, 2013

Asia Pacific Enrollment

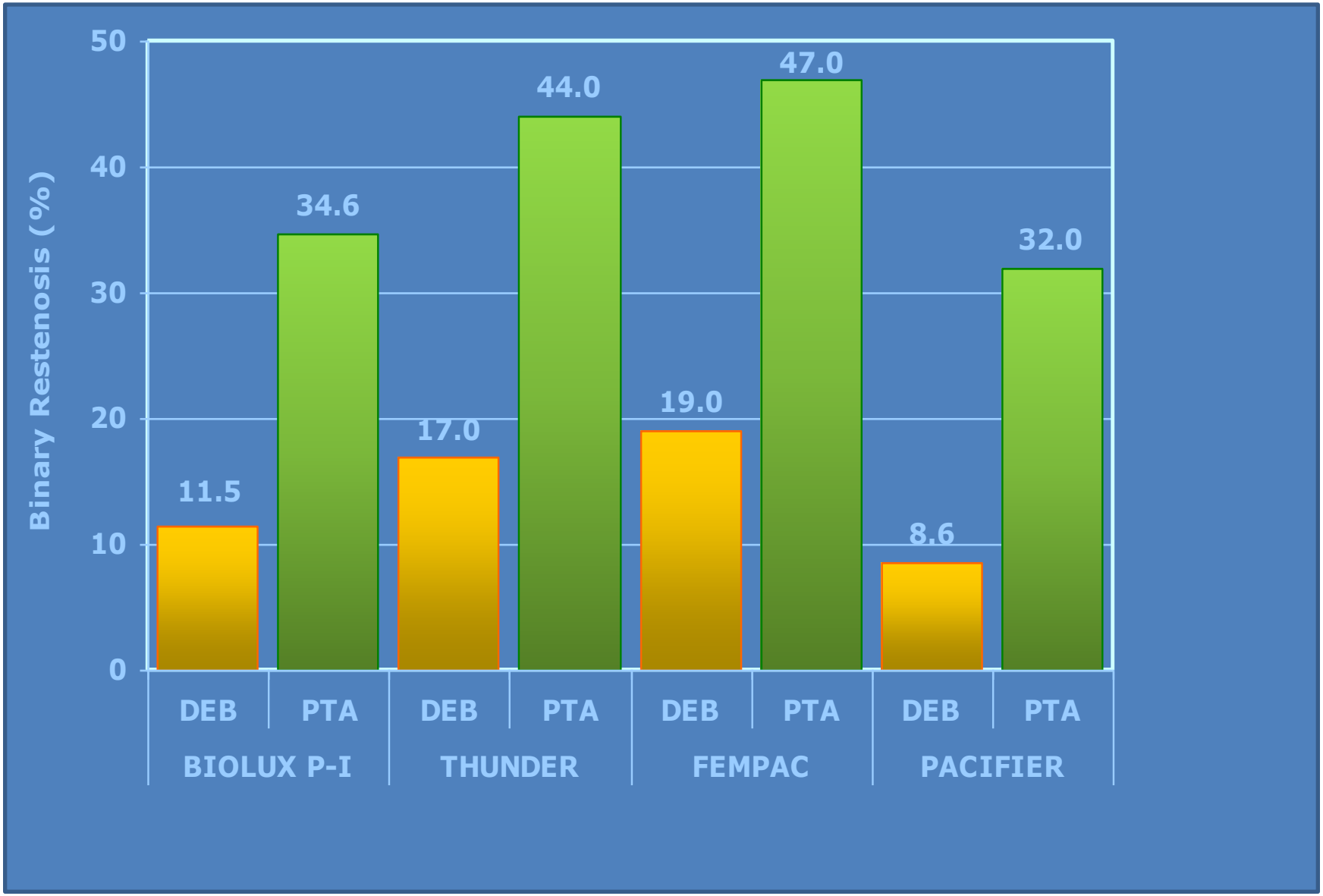
- YonSei Univ Severance Hospital (Choi DH)
- Korea Univeristy Guro Hospital (Rha SW)
- Samsung Medical Center (Do)
- Ajou University (Won)
- Asan Medical Center (Lee)

- Changi Hospital (Kum)

* As of March 20th, 2013

BIOLUX P-I in Context

6 Months Binary Restenosis



Inpact DEB Angioplasty - 2-Year Results

Kaplan Meier Curve for Primary Patency and MAEs

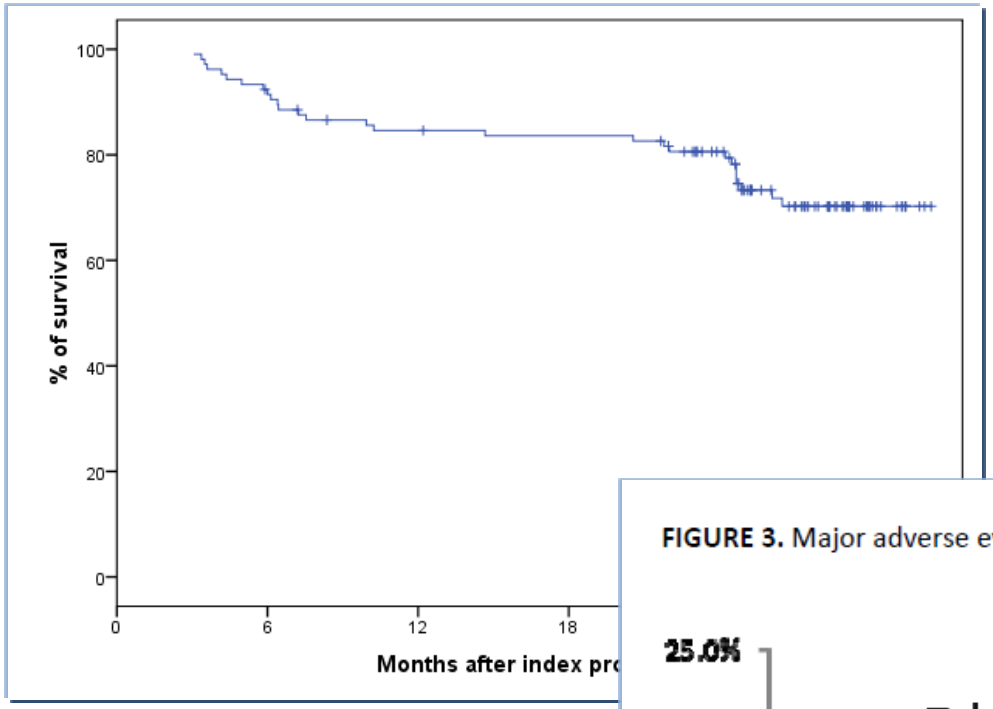
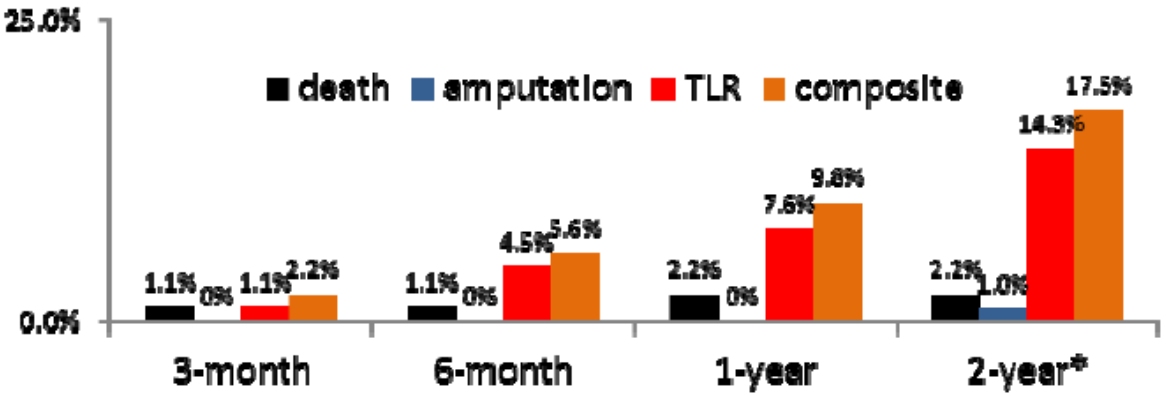


FIGURE 3. Major adverse events during follow-up.



Micari et al. JACC Cardiovasc Intervent 2012

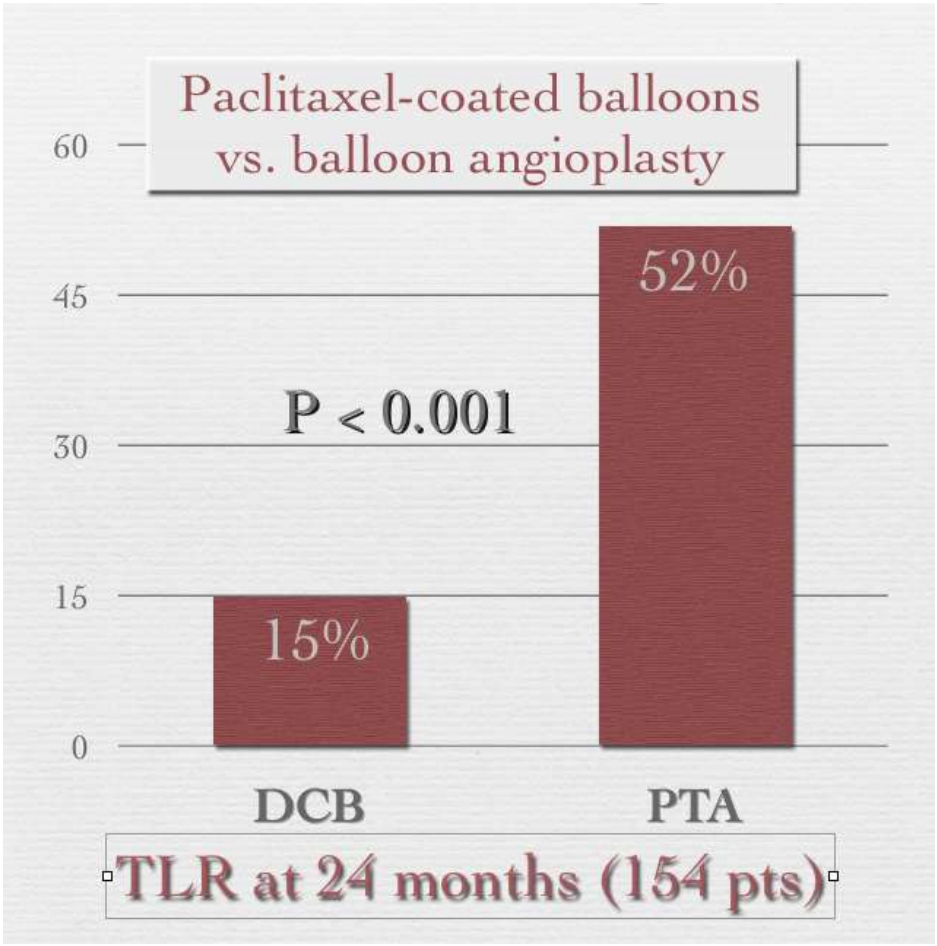
THUNDER Trial Results

- Safety
  - Comparable rates of SAE among 3 study groups
  - Low plasma levels of paclitaxel immediately and 2 hours post-procedure with maximum dosage of 3 to 19.6 mg
- Efficacy

	Paclitaxel-coated balloon (N=48)	Control Angioplasty (N=54)	Paclitaxel in contrast agent (N=52)
Late Lumen Loss - 6 months	**0.4 ± 1.2mm (P<0.001)**	1.7±1.8mm	2.2±1.6mm
TLR			
- 6 months	4% (N=2, P<0.001)	37% (N=20)	29% (N=15)
- 12 months	10% (N=5)	48% (N=26)	35% (N=18)
- 24 months	15% (N=7)	52% (N=28)	40% (N=21)

Tepe, et. al.; N Engl J Med 2008;358:689-99

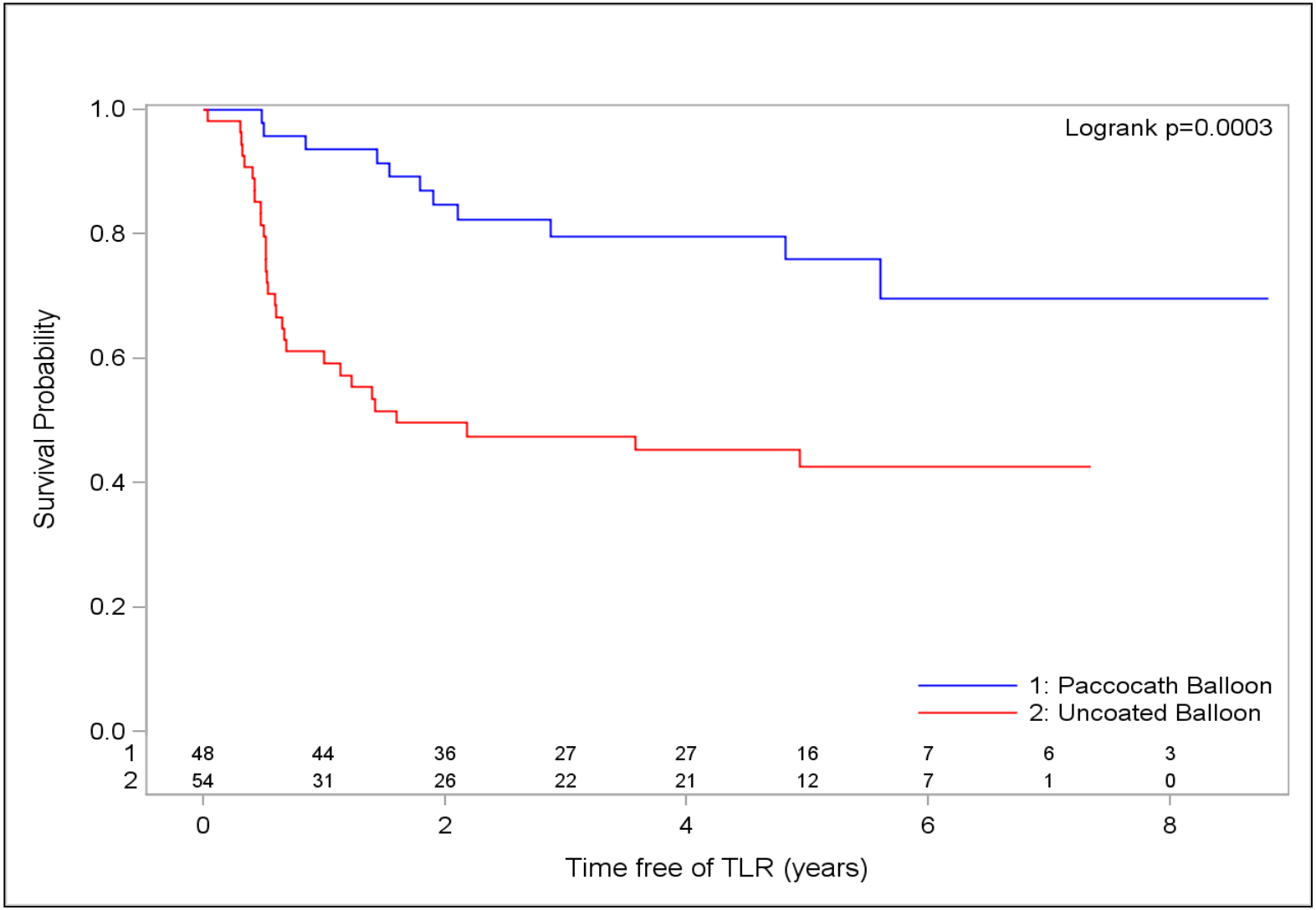
Thunder



Tepe G et al. N Engl J Med 2008;358:689-699

THUNDER

5-Year Outcomes – Freedom from TLR



Tepe, Zeller TCT 2011

My ISR Management Strategy

1. Simple balloon angioplasty using NC balloon
2. Selective atheroma modification
   1) Scoring balloon
   2) Cutting balloon
3. Debulking; Silverhawk atherectomy
4. Drug-eluting balloon /SENS or Drug-eluting stent in bail-out situation

Thank You for Your Attention!!

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