DEB will Make the Job, No Stent is Necessary in Femoropopliteal Lesions

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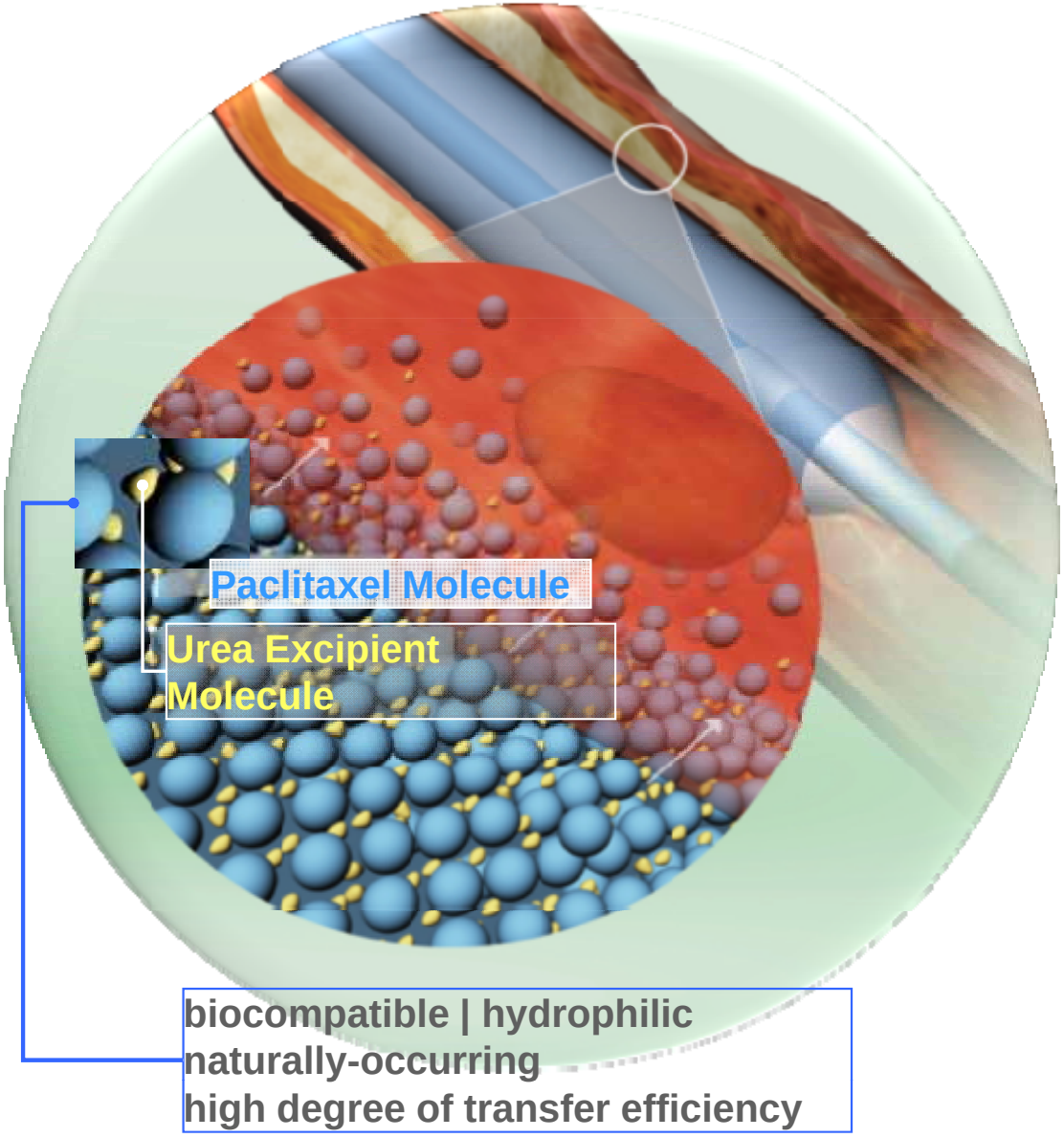
TCT AP 2013

IN.PACT™ DEB with FreePac™ Coating Technology



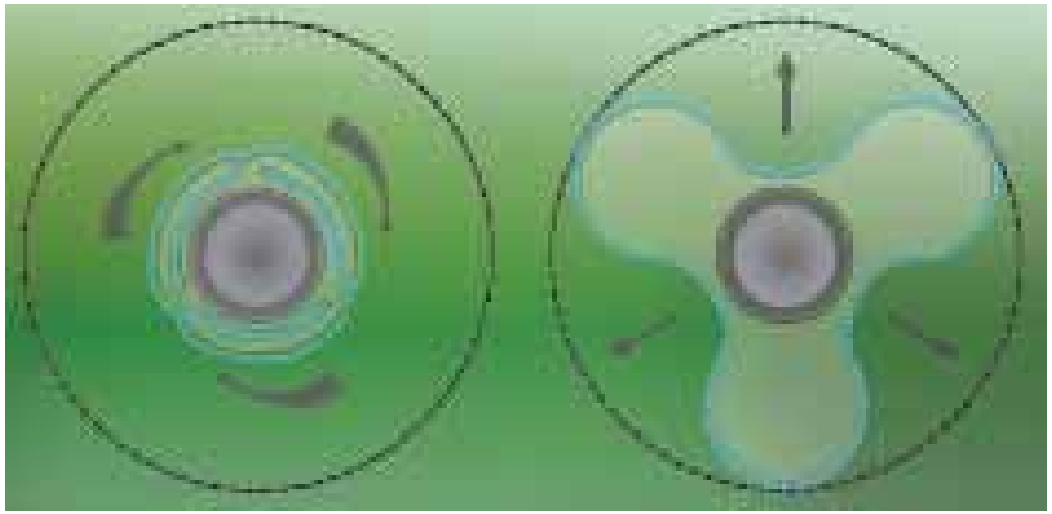
IN.PACT™

- Medtronic-Invatec DEB balloon line

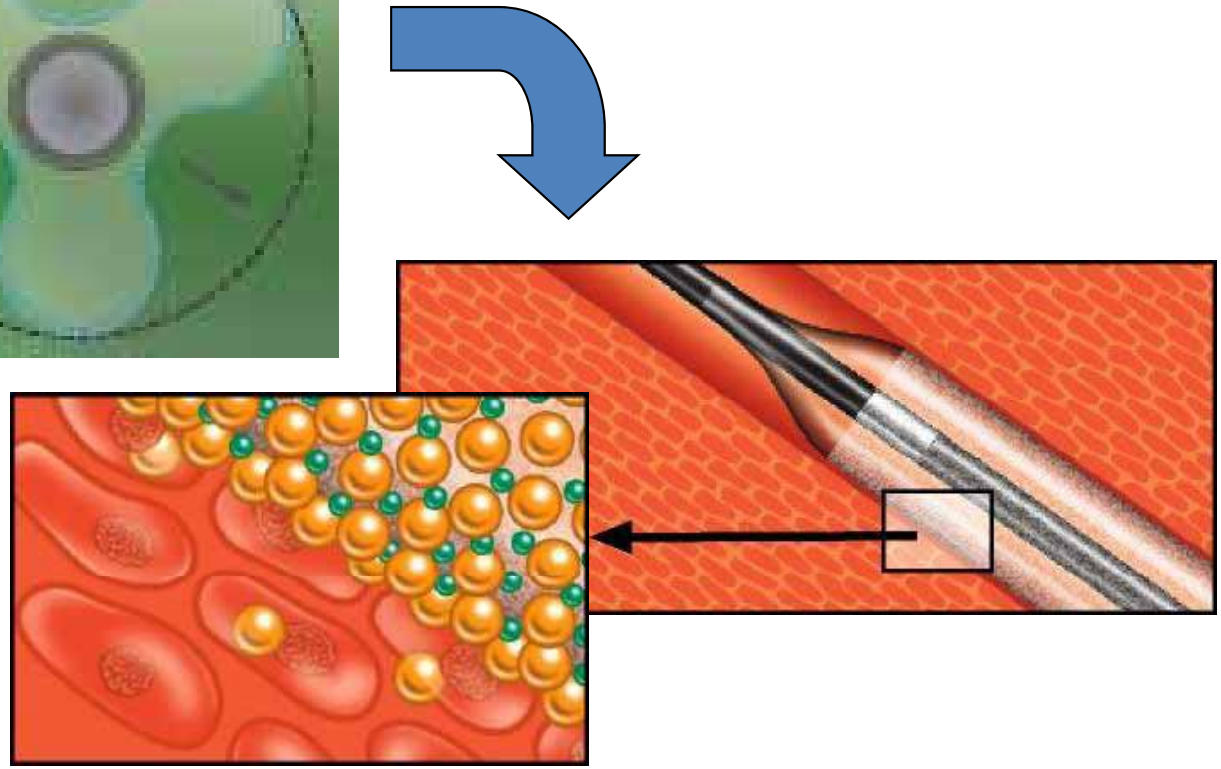
FreePac™

- 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.

Device Description

CE

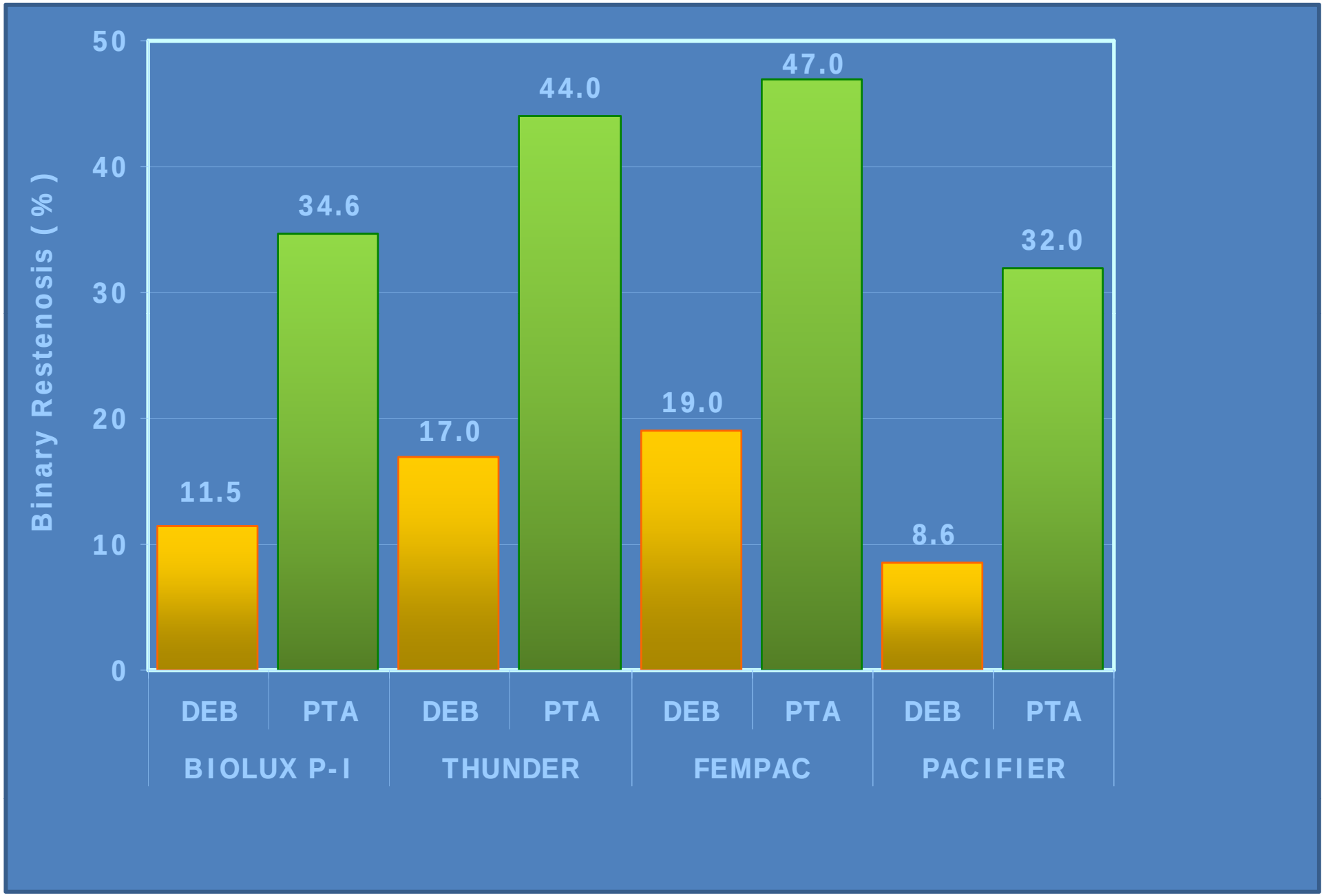
EU market release March 2009

Catheter design	Over the wire (OTW)
Diameters	4, 5, 6, 7 mm
Lengths	40, 60, 80, 120 mm
Max recommended Guide wire	0.035“
Usable shaft length	80 & 130 cm
Balloon material	FLEXITEC™ Xtreme
Coating	FreePac™
Shaft diameter	5F
Introducer sheath compatibility	5F - 6F
Nominal pressure	8 bar
RBP	up to 18 bar

REF No. (shaft length 80 cm)	REF No. (shaft length 130 cm)	Balloon Diameter (mm)	Balloon Length (mm)	Recom. Introducer sheath (F)	RBP
SBI 040 040 08P	SBI 040 040 13P	4	40	5	18
SBI 040 060 08P	SBI 040 060 13P	4	60	5	18
SBI 040 080 08P	SBI 040 080 13P	4	80	5	18
SBI 040 120 08P	SBI 040 120 13P	4	120	5	18
SBI 050 040 08P	SBI 050 040 13P	5	40	6	17
SBI 050 060 08P	SBI 050 060 13P	5	60	6	17
SBI 050 080 08P	SBI 050 080 13P	5	80	6	15
SBI 050 120 08P	SBI 050 120 13P	5	120	6	15
SBI 060 040 08P	SBI 060 040 13P	6	40	6	17
SBI 060 060 08P	SBI 060 060 13P	6	60	6	17
SBI 060 080 08P	SBI 060 080 13P	6	80	6	15
SBI 060 120 08P	SBI 060 120 13P	6	120	6	15
SBI 070 040 08P	SBI 070 040 13P	7	40	6	16
SBI 070 060 08P	SBI 070 060 13P	7	60	6	14
SBI 070 080 08P	SBI 070 080 13P	7	80	6	14

BIOLUX P-I in Context

6 Months Binary Restenosis



Inpact DEB Angioplasty - 2-Year Results

Kaplan Meier Curve for Primary Patency and MAEs

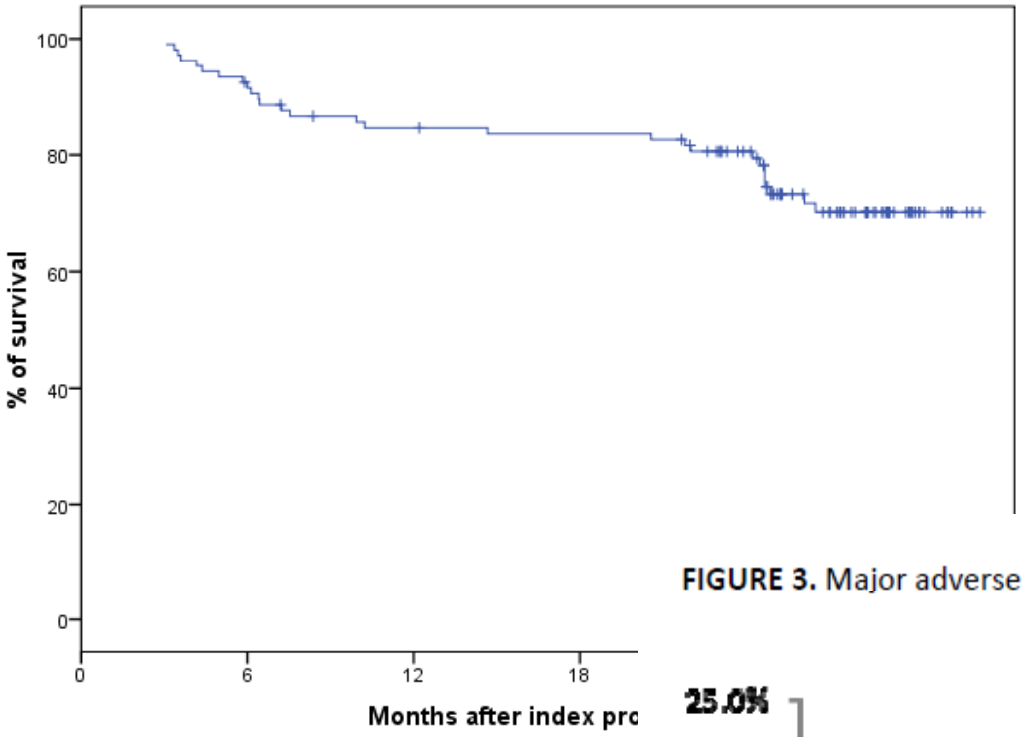
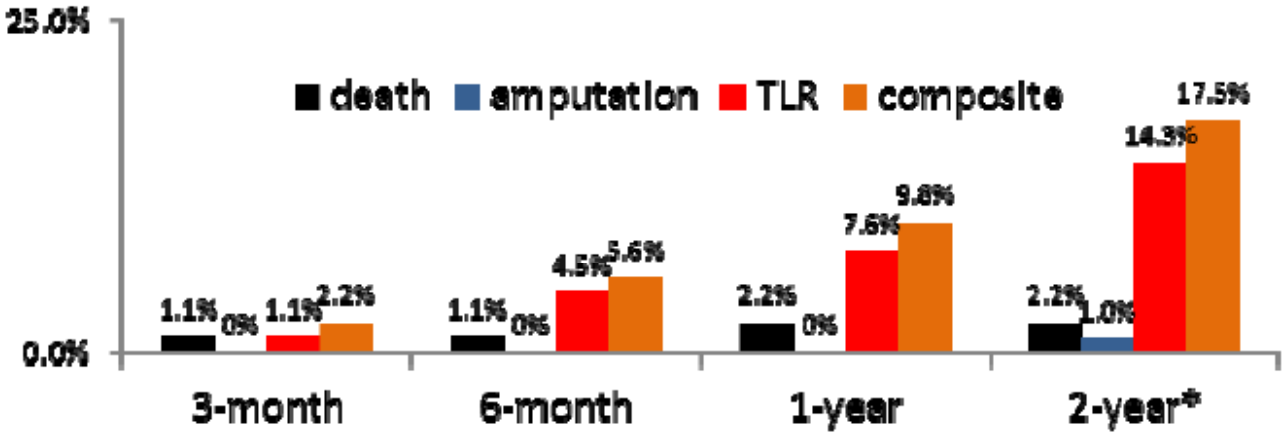


FIGURE 3. Major adverse events during follow-up.



Micari et al. JACC Cardiovasc Intervent 2012 accepted

THUNDER Trial Results

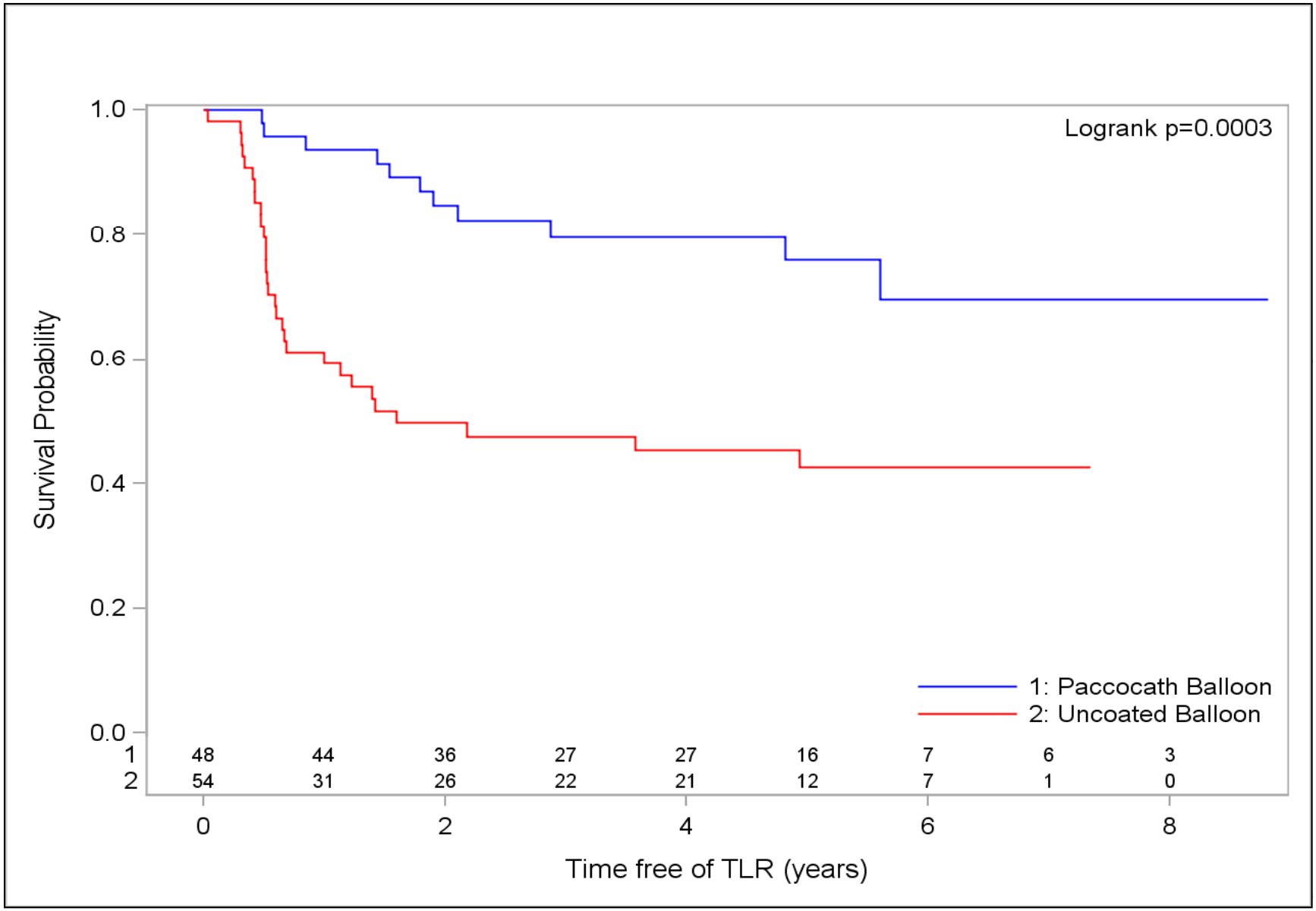
- Safety
  - Comparable rates of SAE among 3 study groups
  - Low plasma levels of paclitaxel immediately and 2 hours post-procedure with maximum dosage of 3 to 19.6 mg
- Efficacy

	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

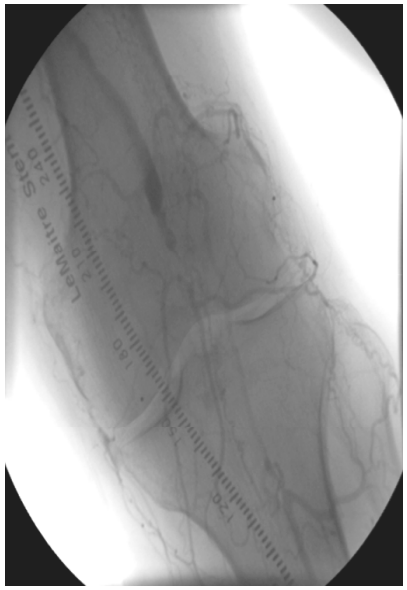
5-Year Outcomes – Freedom from TLR

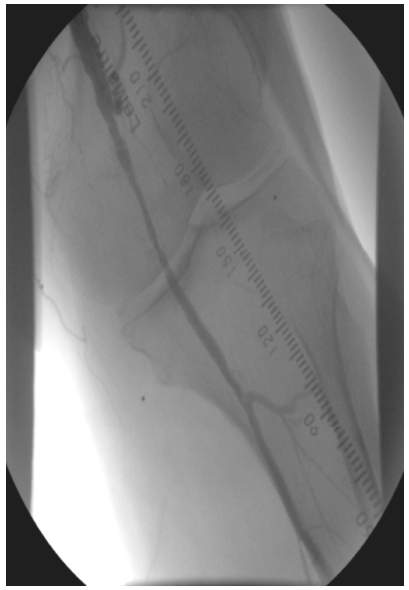


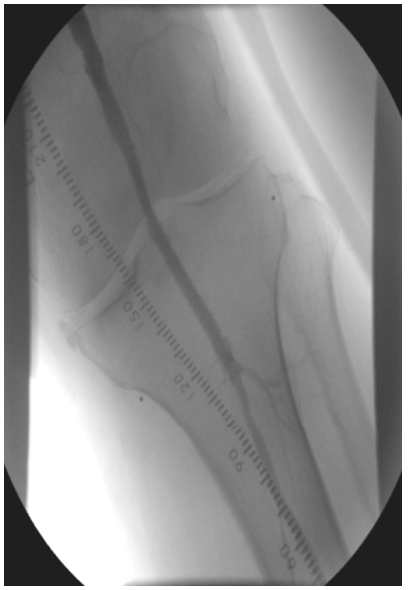
Tepe, Zeller TCT 2011

Traditional Stent Indications

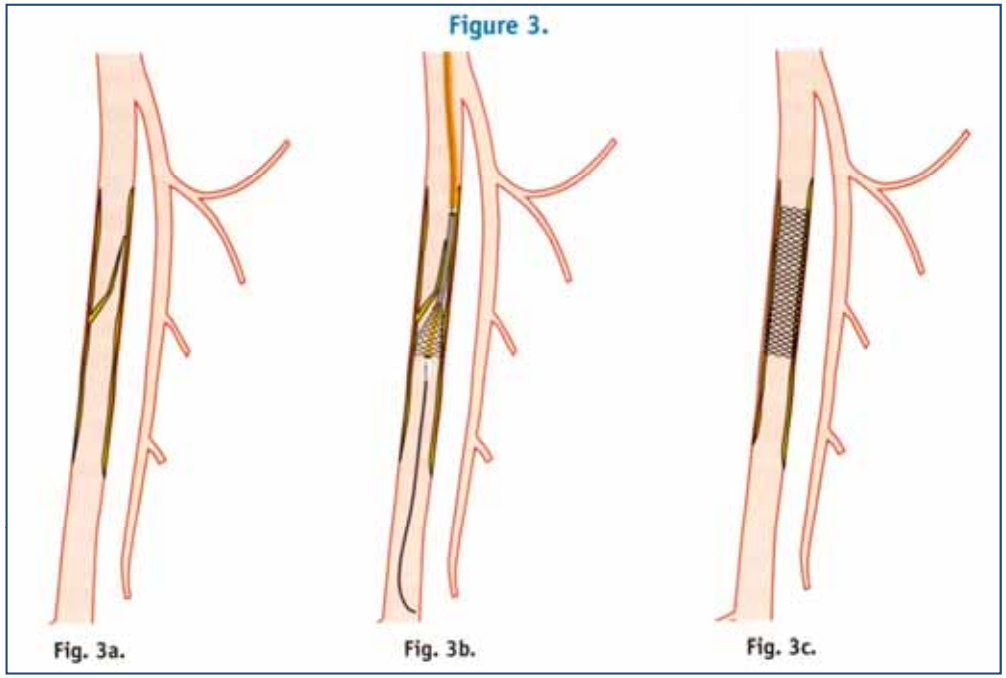
- Acute recoil





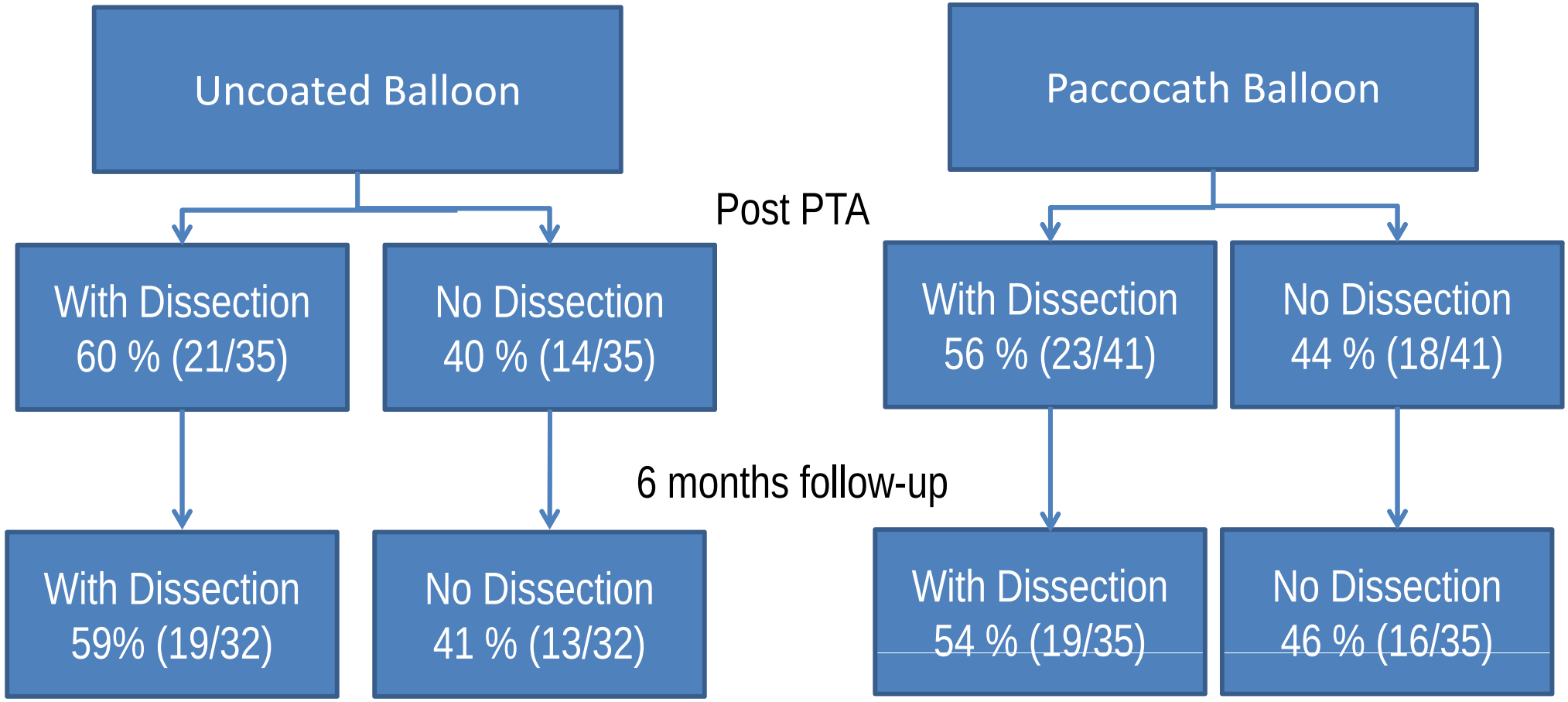


- Flow limiting dissection



THUNDER

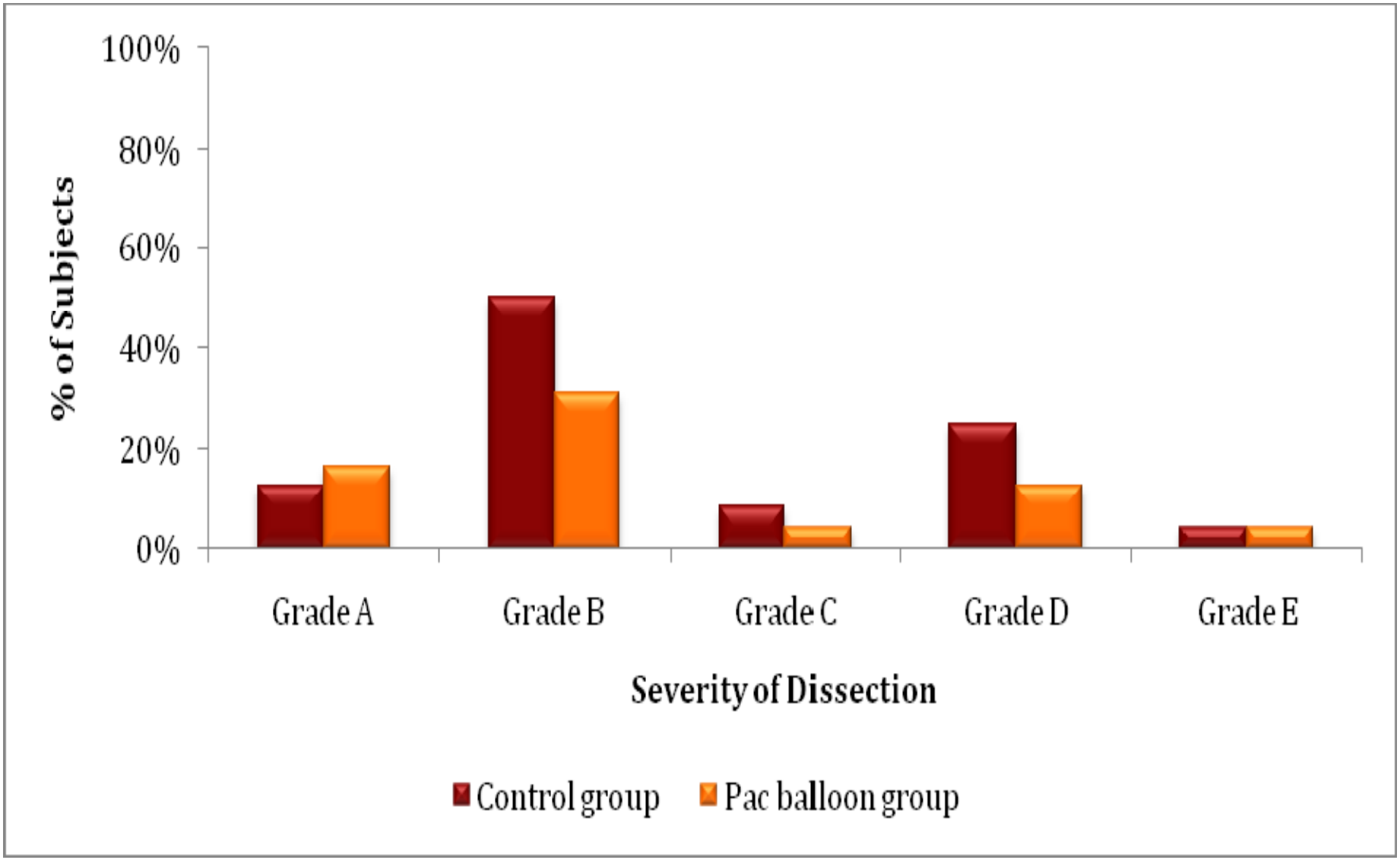
Impact of Dissections



Tepe et al. EuroIntervention in revision

THUNDER Re-Analysis

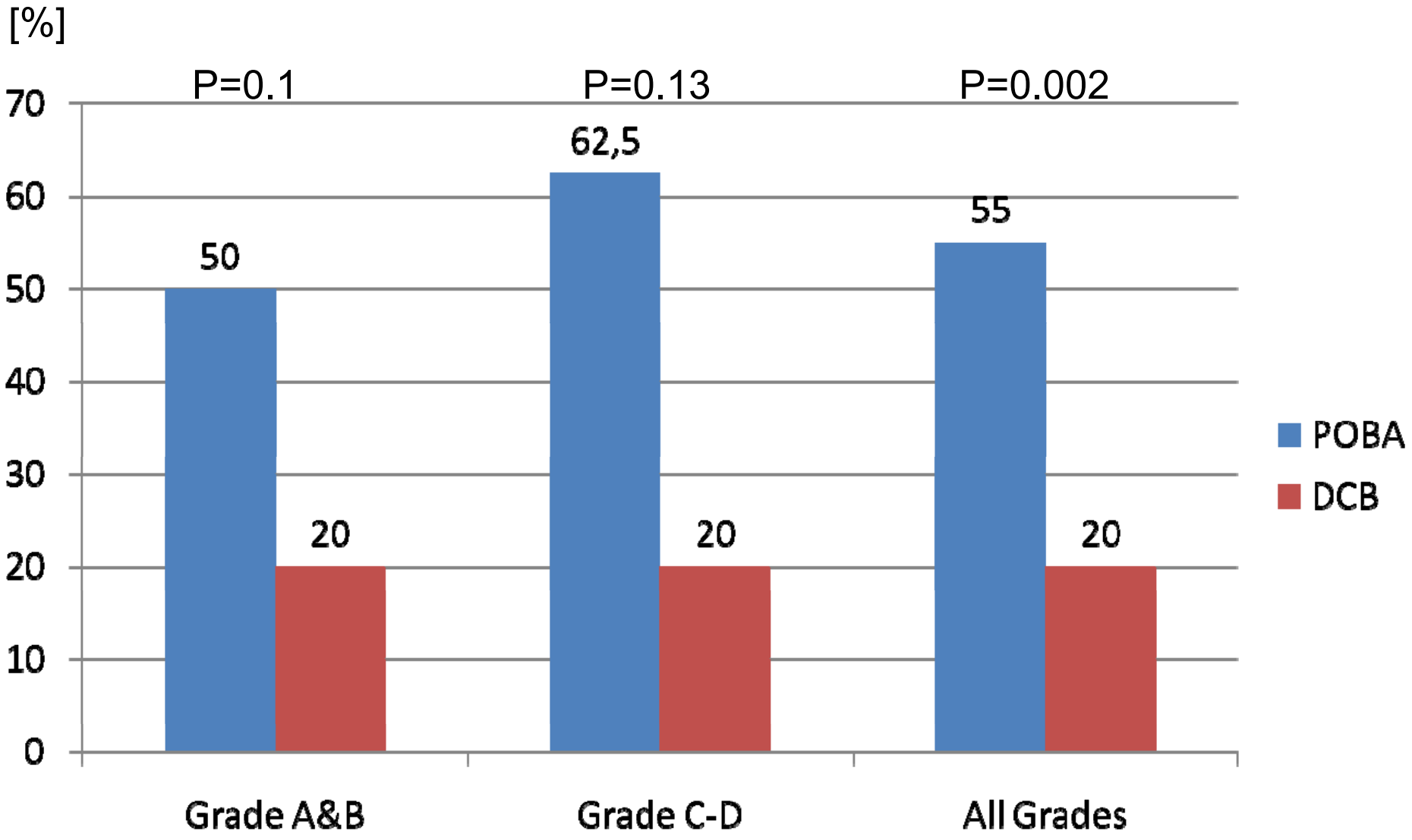
Severity of Dissection



Tepe et al. EuroIntervention in revision

6-Month Binary Restenosis

Grade of Dissection



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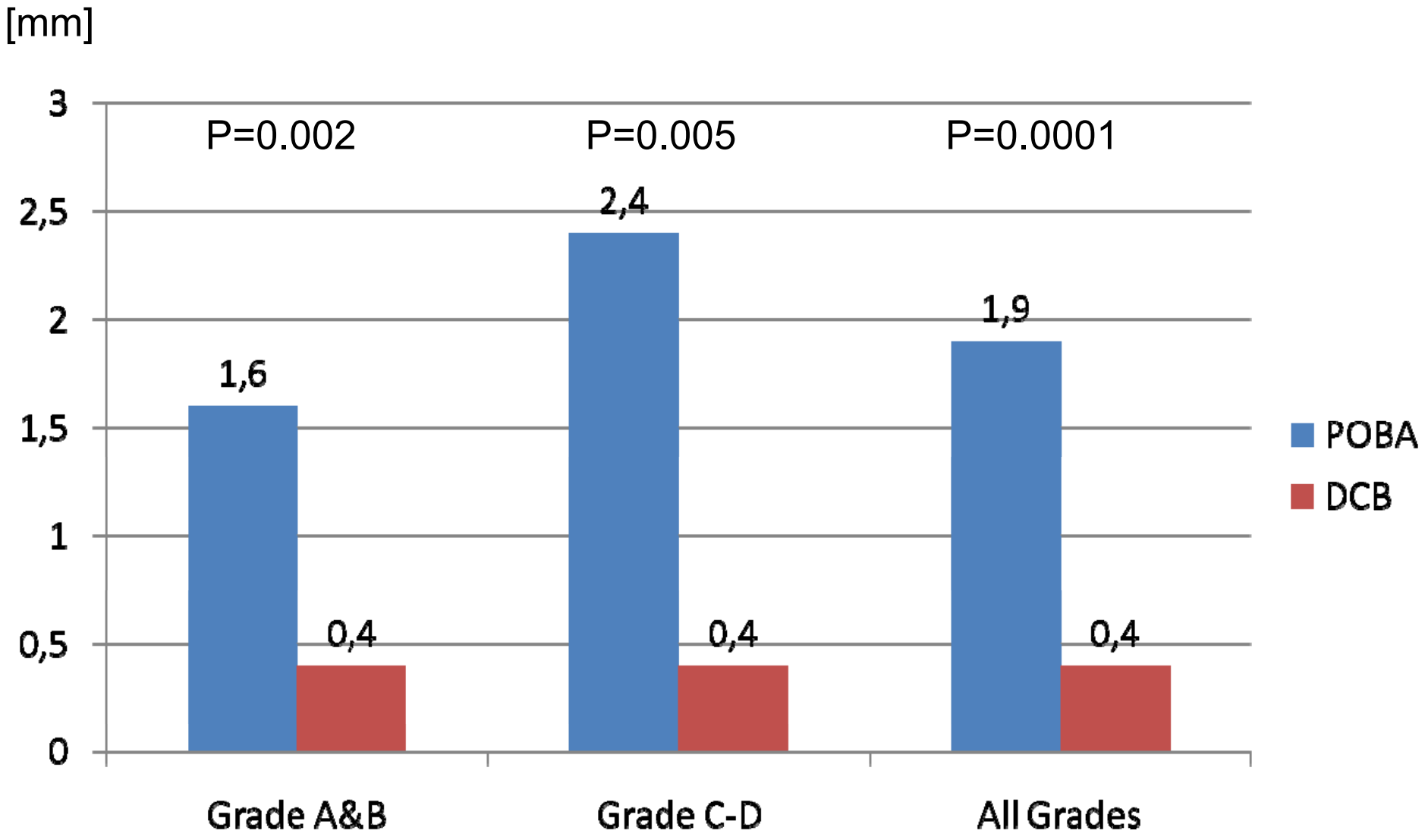
Minimum Lumen Diameter

Analysis By Dissection



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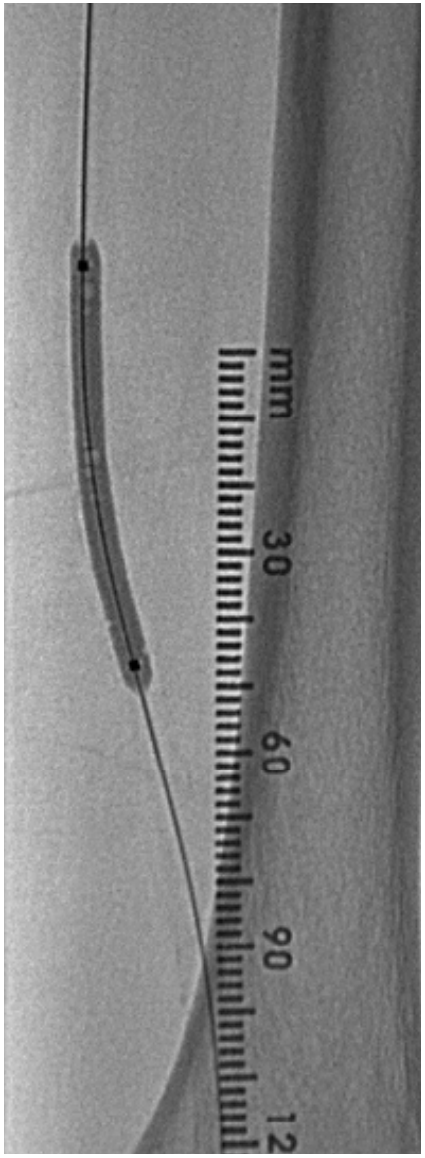
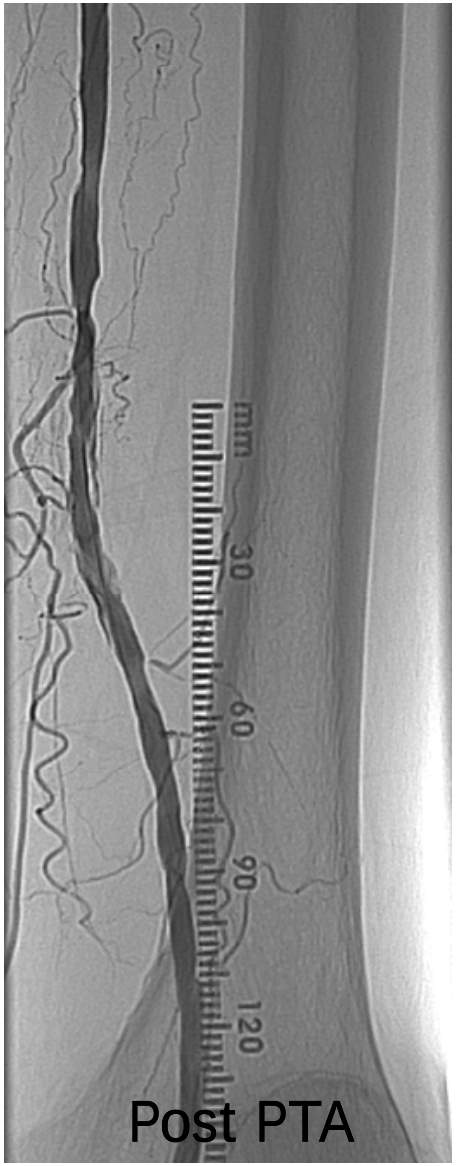
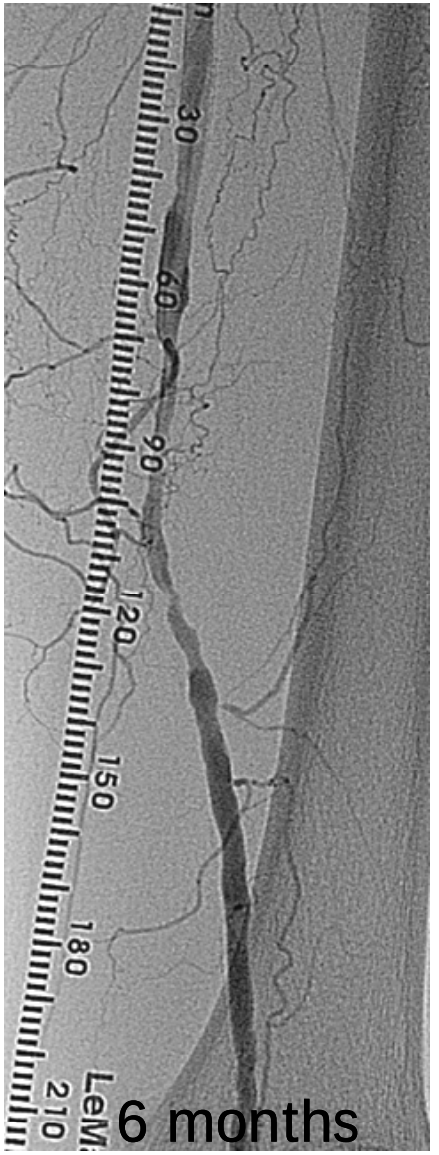
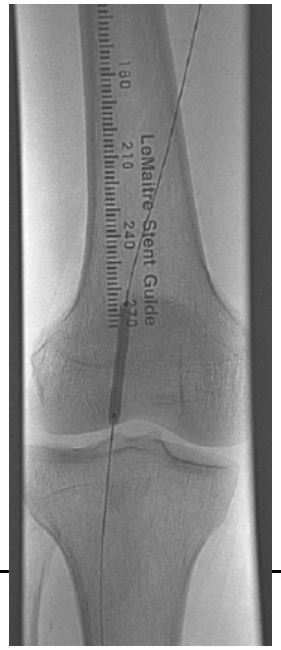
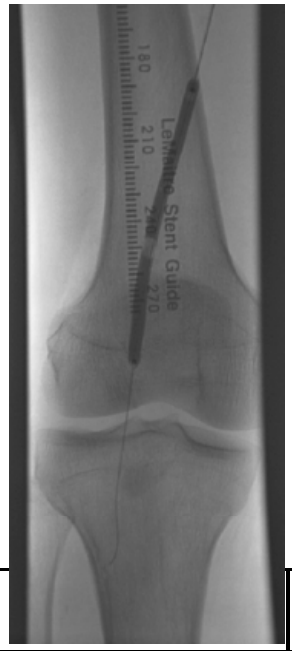
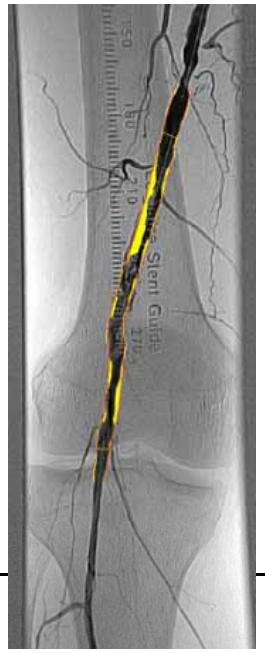
Case Example – Uncoated Balloon





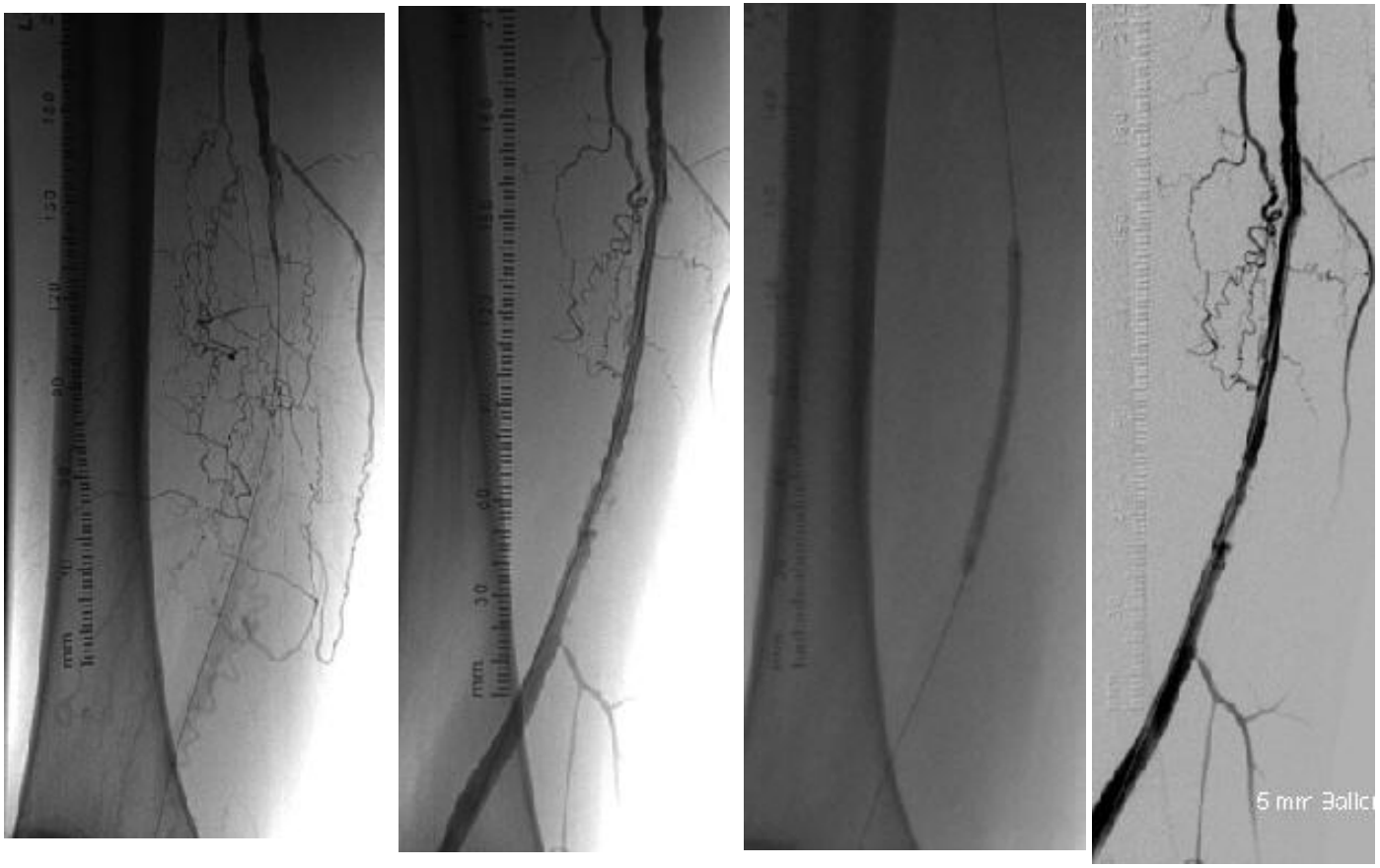


Area analyisis - Patient treated with two coated balloons and a non stented-dissection (grade E) after intervention

A	B	C	D
			
Intervention Paccocath-balloon 1 & Paccocath-balloon 2		Post intervention: Dissection grade E Residual stenosis: 64% Area analysis: 550 mm^2	6 month FUP: Stenosis: 23 % Area analysis: 780 mm^2 Difference area : 230 mm^2

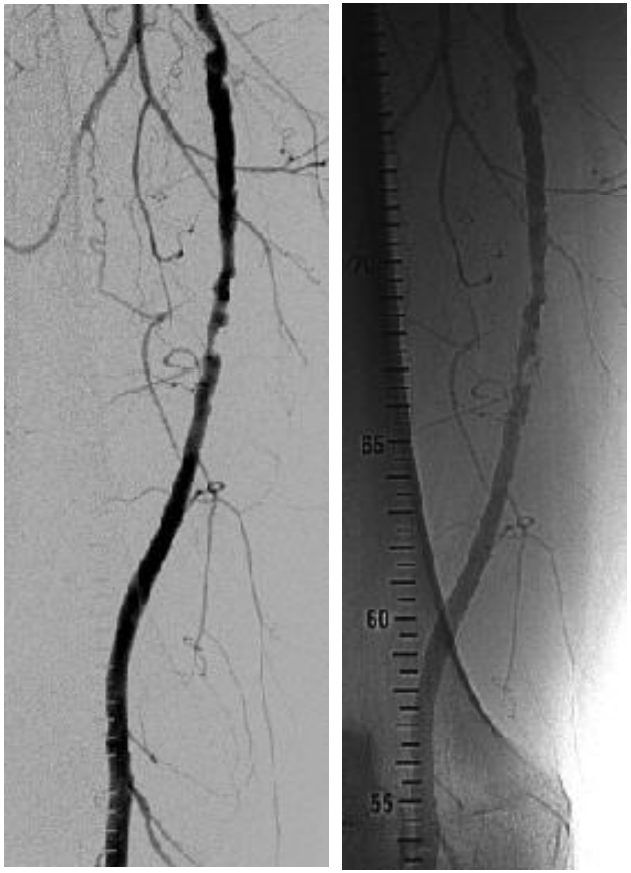
Tepe et al. EuroIntervention in revision

Sample case of restenosis following DEB administration



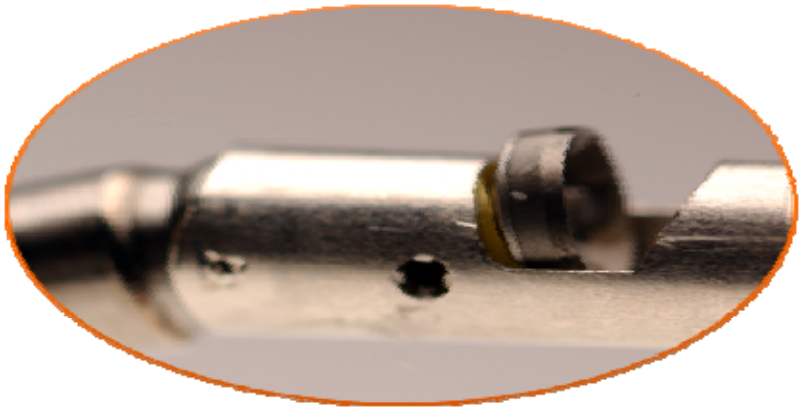
- CTO with significant calcium burden
- Efforts were made to avoid bail-out stenting, despite sub-optimal acute results

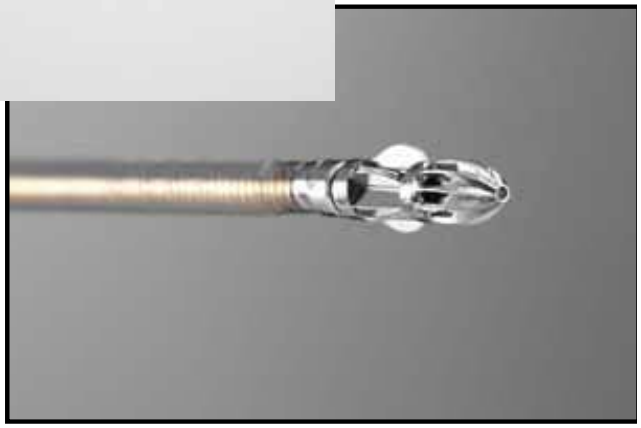
- Further progression at later time points, especially around calcified segment

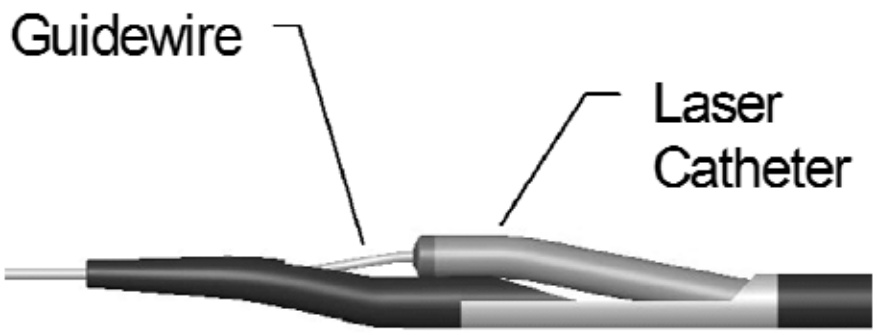


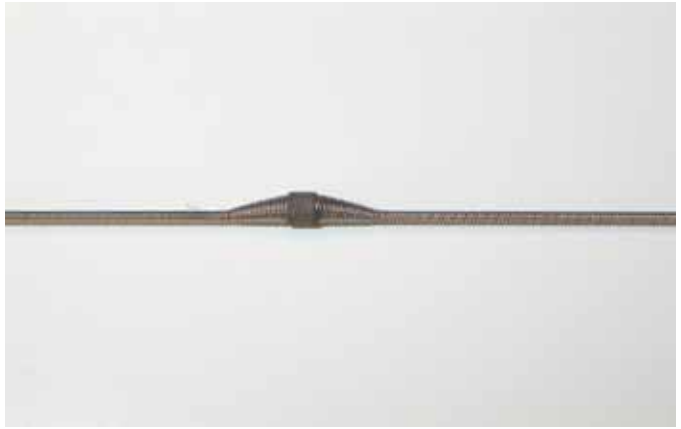
Angiograms Courtesy of Gunnar Tepe, MD

Currently Available Atherectomy Devices





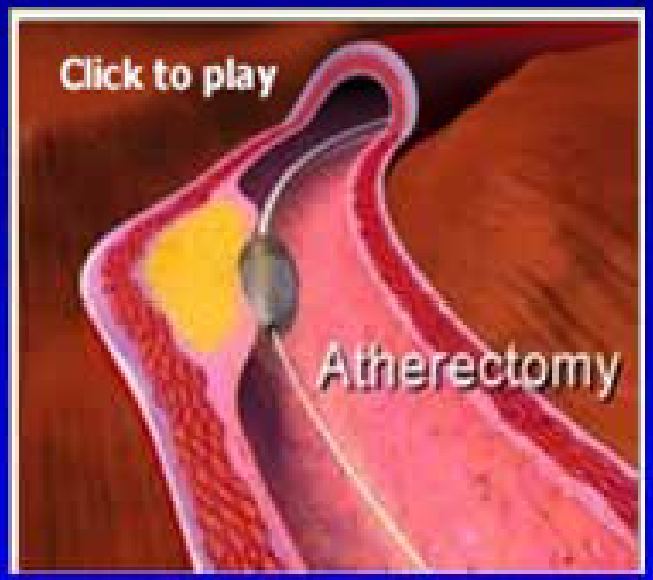




Atherectomy Devices

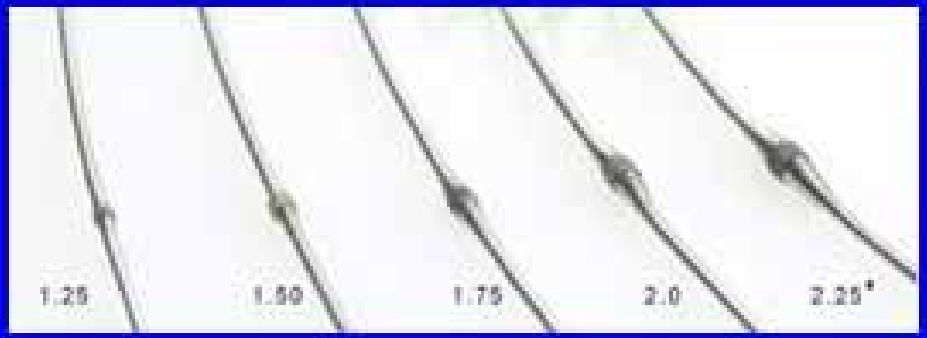
Turbo-Laser

Rotablator

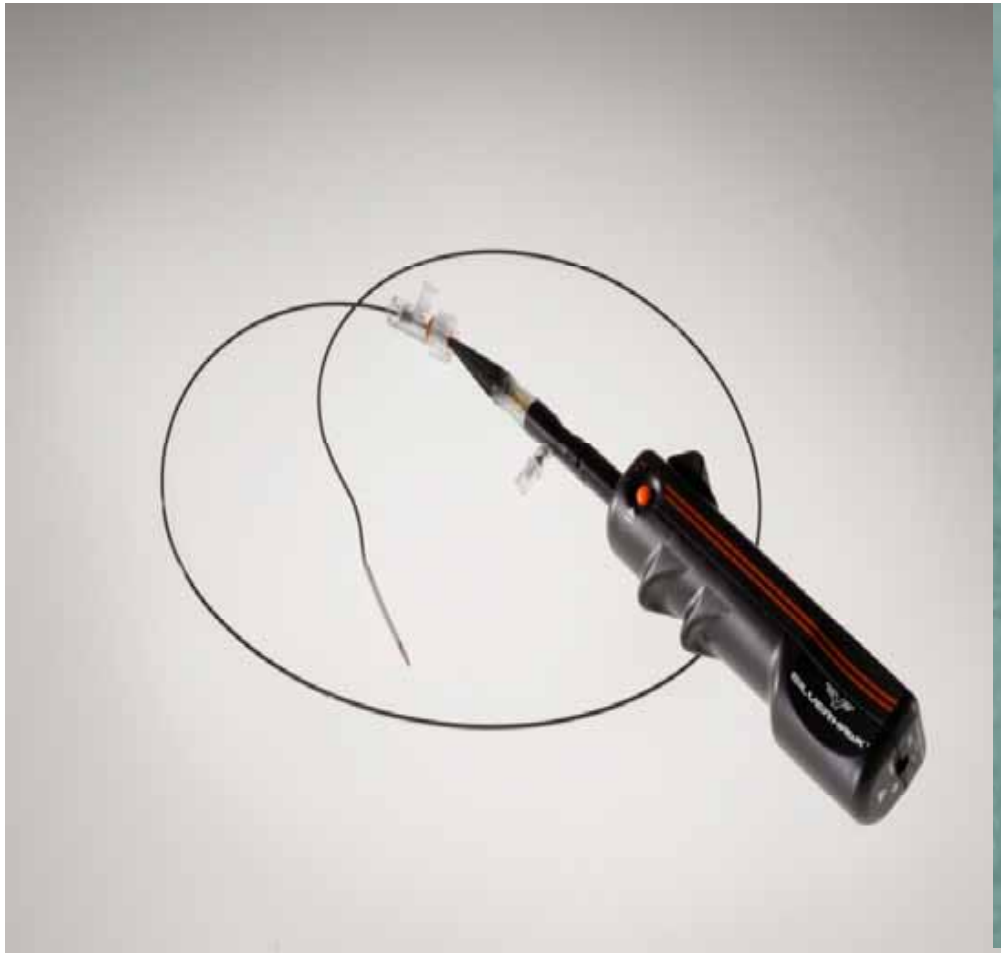


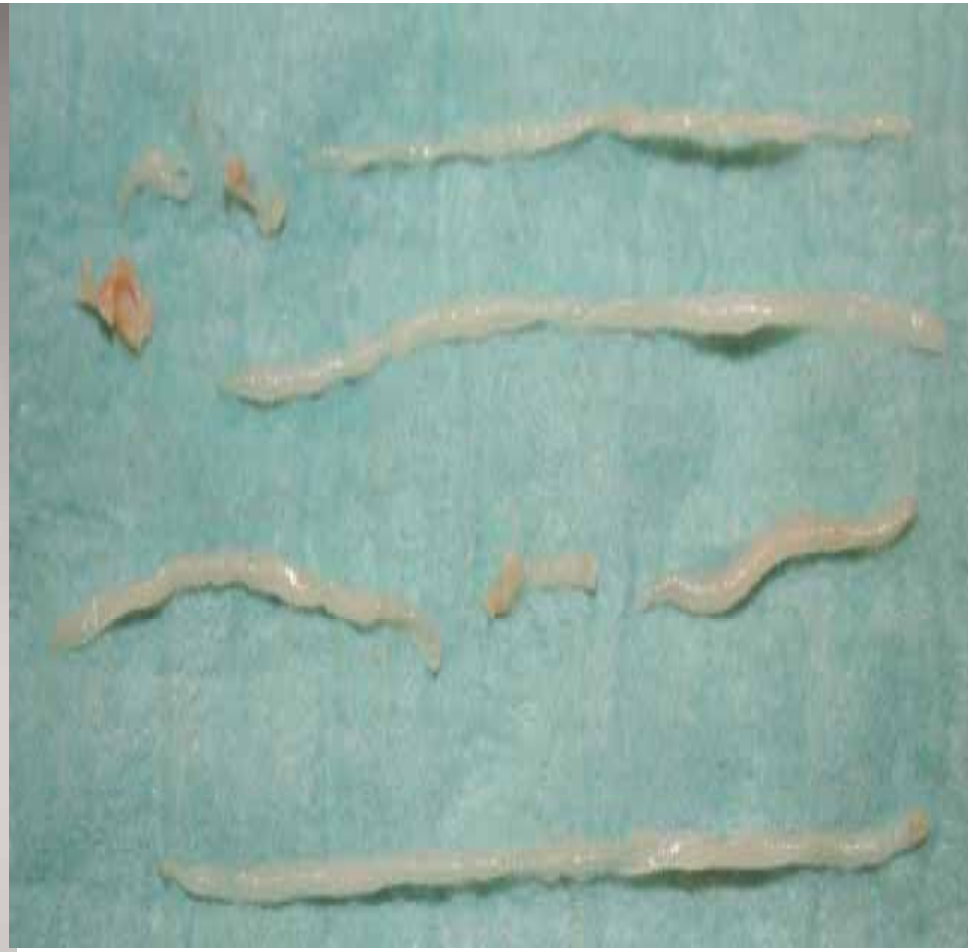
Silver Hawk

CSI 360 Orbital Atherectomy

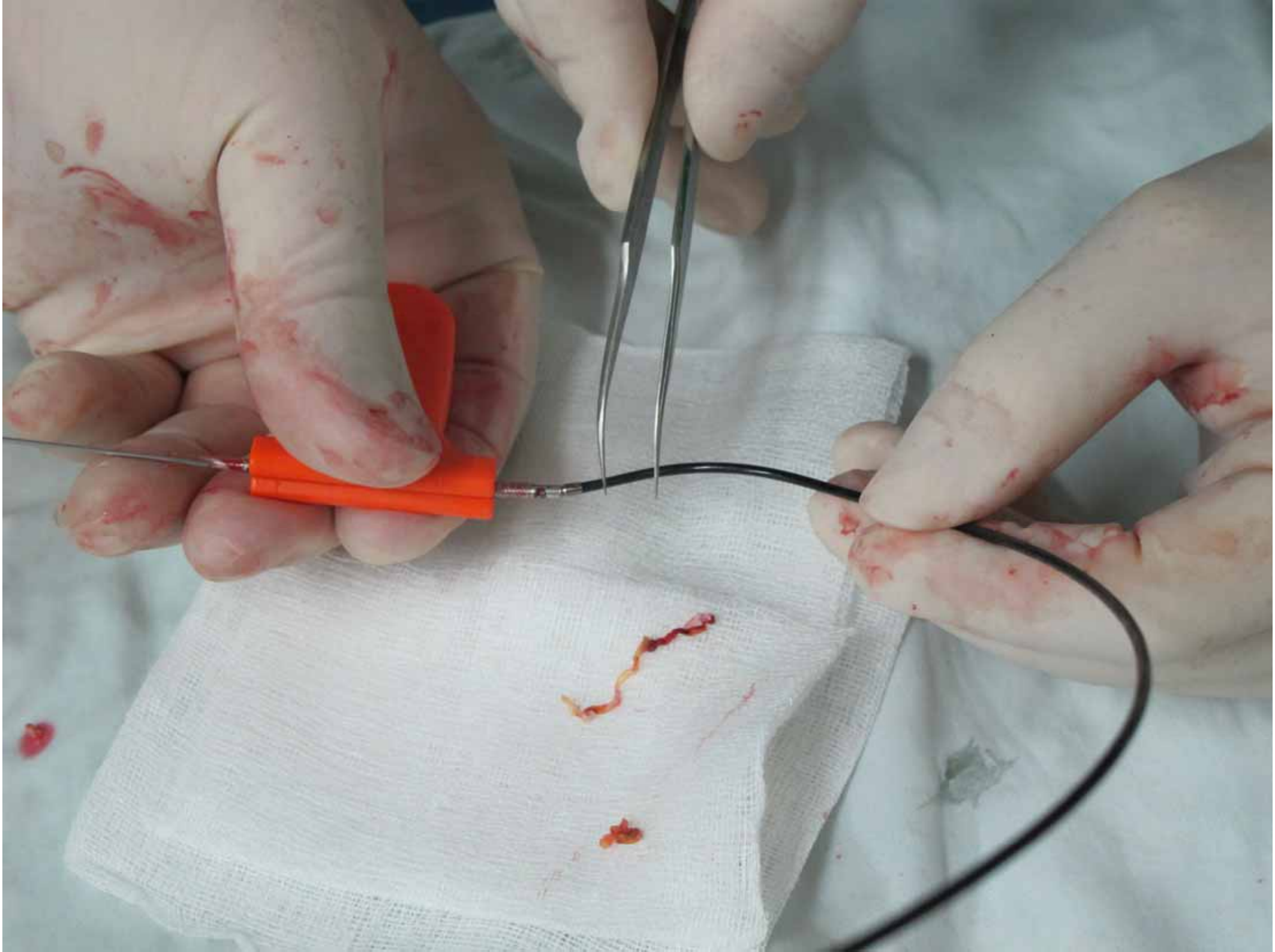


SilverHawk Plaque Excision System

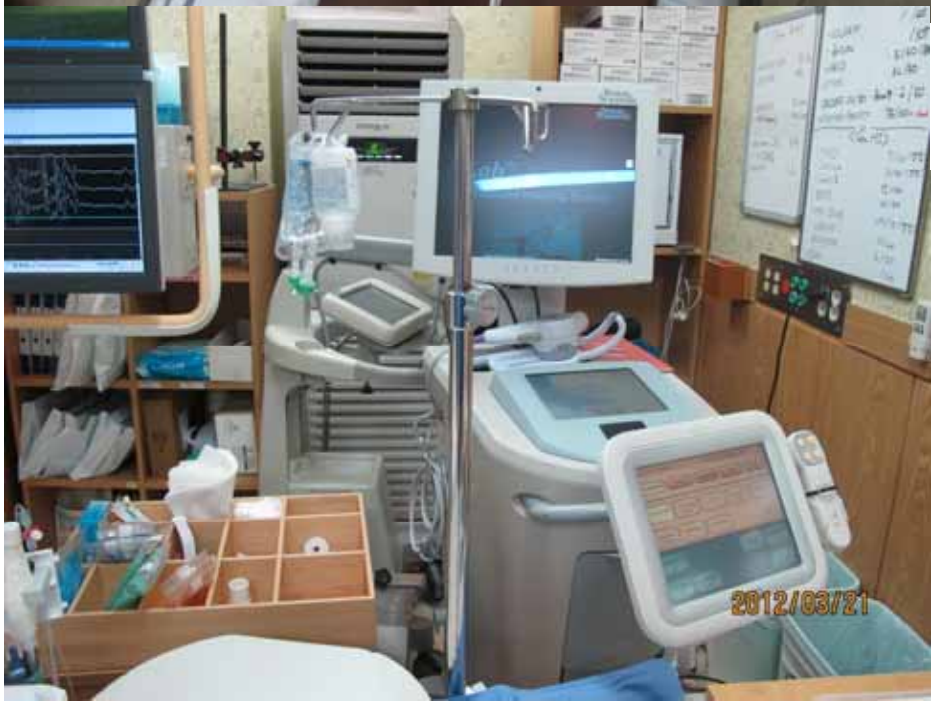




Device Overview

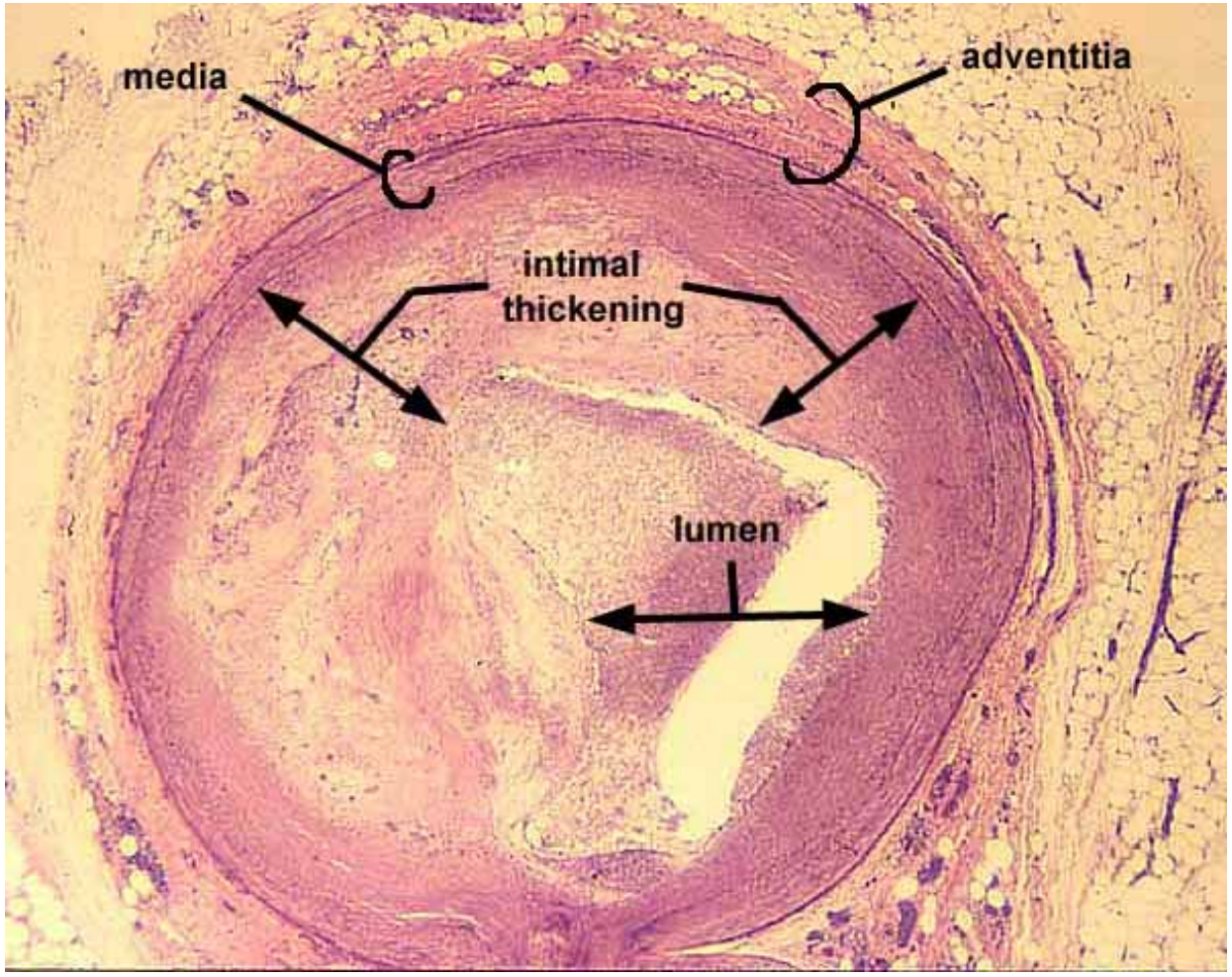


Patient Preparation for BTK Intervention (KUGH style)



Total 6 monitors and Operator friendly system

Rationale for plaque excision and drug-delivery as an essential combination



1. Mechanically re-canalize the vessel without overstretch
2. Remove the perfusion barrier – better and more homogenous drug uptake?
3. Reduce the likelihood of bail-out stenting and preserve the native vessel

SFA Highly Calcified lesions

high promising signal of safety and efficacy in combination with atherectomy to treat severly calcified SFA lesions

Contents lists available at SciVerse ScienceDirect

Cardiovascular Revascularization Medicine

ELSEVIER

Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: One-year single centre clinical results☆

Angelo Cioppa *, Eugenio Stabile, Grigore Popusoi, Luigi Salemme, Linda Cota, Armando Pucciarelli, Vittorio Ambrosini, Giovanni Sorropago, Tullio Tesorio, Alessia Agresta, Giancarlo Biamino, Paolo Rubino

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ABSTRACT

Background: The use of Directional Atherectomy (DA) for the treatment of calcified femoro-popliteal lesions seems to improve the acute procedural success, however without reducing the long term restenosis rate. Drug coated balloons (DCB) reduced restenosis rate in non heavy calcified lesions. Aim of this study was to demonstrate safety and efficacy of a combined endovascular approach using DA and DCB for the treatment of heavy calcified lesions of the femoro popliteal tract.

Methods: From January 2010 to November 2010, 240 patient underwent PTA of the femoro popliteal tract in our institution. Within this cohort a total of 30 patients had Life Limiting Claudication (LLC) (n = 18) and 12 a Critical limb Ischemia (CLI) with baseline Rutherford class 4.2 ± 1.2 underwent PTA of heavy calcified lesions with intravascular ultrasound guided DA and DCB. All procedures have been performed using a distal protection device. Stent implantation was allowed only in case of flow limiting dissections or suboptimal result (residual stenosis > 50%) by visual estimation. After the intervention patients were followed up to 12 months.

Results: Procedural and clinical success was achieved in all cases. Bail-out stenting was necessary in only two (6.5%). At twelve month follow up median Rutherford class was 2.2 ± 1.2, ABI was 0.8 ± 0.1 and Limb salvage rate was 100%. Two minor, foot finger or forefoot amputations, were performed to reach complete wound healing and/or preserve deambulation. Duplex control was performed in all the cases (n = 30). In three cases duplex scan showed a significant target lesion restenosis requiring a reintervention (TLR = 10%) leading a total one-year secondary patency rate of 100%. All the three restenosed patients were insulin dependent diabetics and none of them were smoker during the procedure.

Conclusion: The data suggest that combined use of DA and DCB may represent a potential alternative strategy for the treatment of femoro-popliteal severely calcified lesions. These very promising data and the considered hypothesis have to be confirmed in a multicentre randomised trial.

* 0= absence of calcium; 1= calcium on one side of lumen <1cm length; 2= calcium on both side <1cm length; 3=calcium on both side >1 cm length

30-patient single-center Registry

- **LLC / CLI = 6% / 94%**
- **Diabetics = 60%**
- **Mean lesion length = 115±35 mm**
- **Tot Occlusions = 13%**
- **Calcium Score* 3 = 100%**

•dist. Filter + TurboHawk + IN.PACT

- **bail-out Stenting = 7%**

•12-month results:

- Primary Patency = 90%
- TLR = 10%
- Second. Patency = 100%

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Cioppa A et al. Cardiovasc. Revasc. Medicine 2012;..:..

Overview of the DEFINITIVE™ AR Study

Objective

- Assess the effect of treating a vessel with plaque excision in combination with paclitaxel-coated balloon angioplasty compared to treatment with PTX PTA alone.

Design

- Prospective, multicenter, randomized pilot study
- 1-year follow up looking at target lesion percent stenosis
- 100 patients will be randomized and an additional 25 with severe calcification will be enrolled in a registry

Operational notes

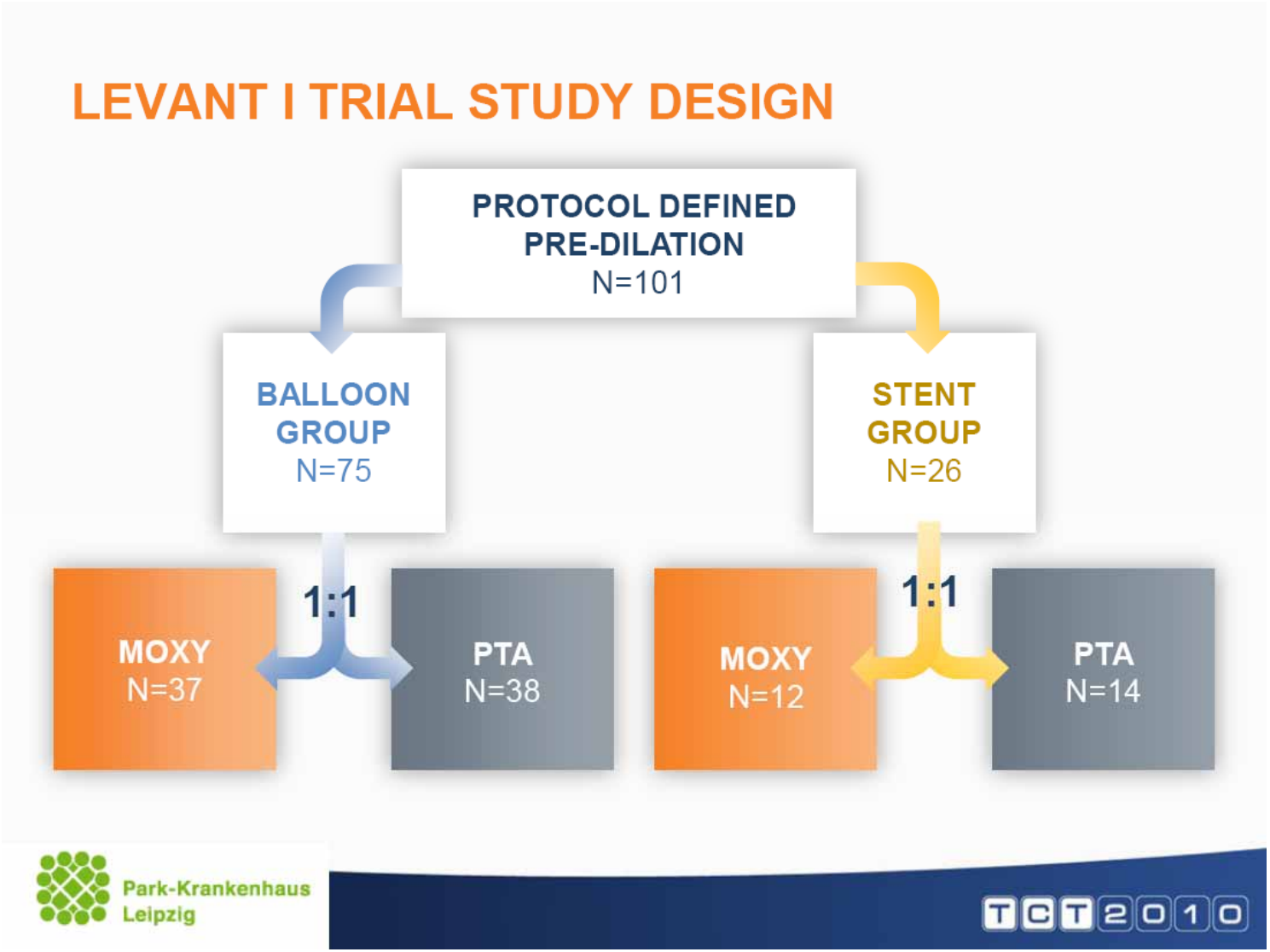
- PIs are Professors Gunnar Tepe and Thomas Zeller
- Europe-based study with enrollment started in 2nd half of 2011
- Enrollment closed December 2012

Limitations of DCB: Suboptimal Angioplasty

Is stenting the solution?

LEVANT 1

Impact of Stent Implantation



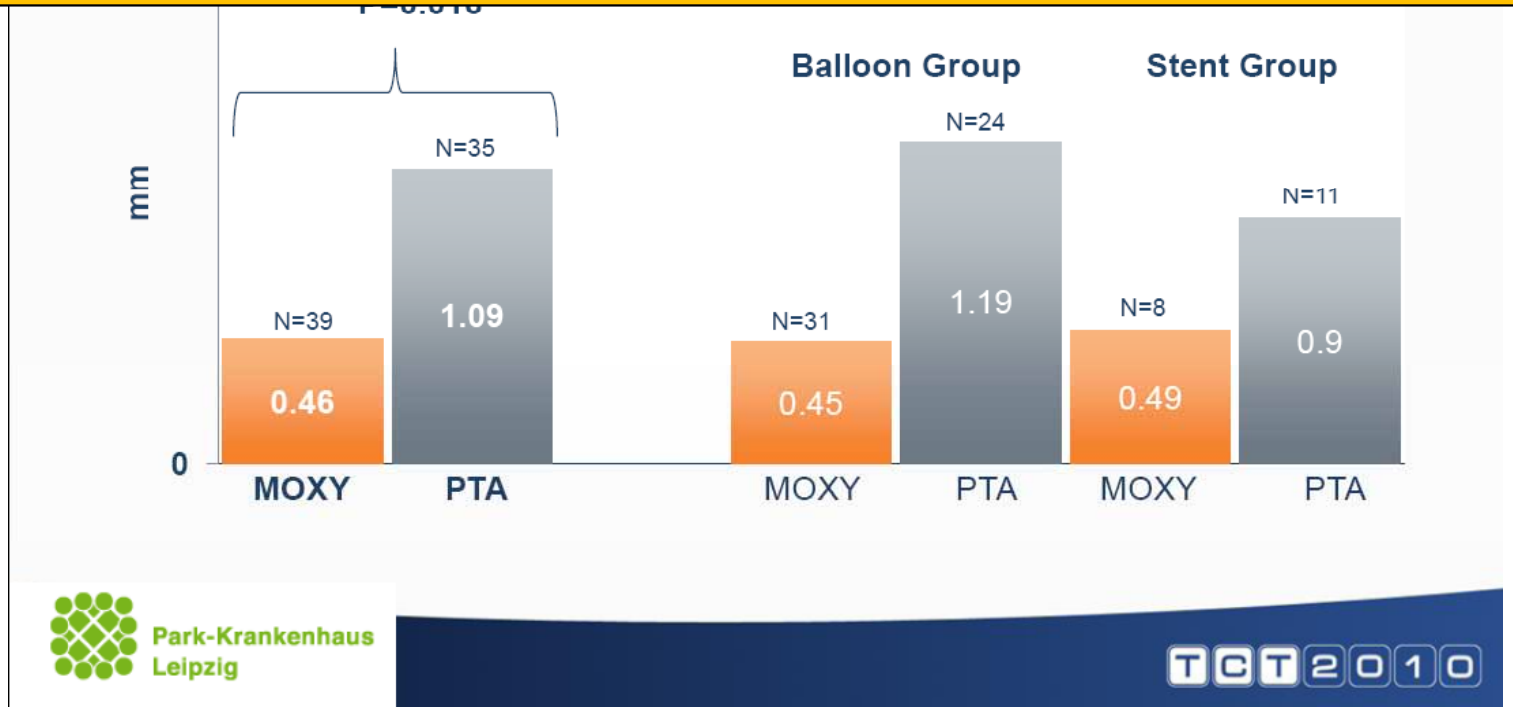
Scheinert D et al. TCT 2010

LEVANT 1

Impact of Stent Implantation

LEVANT I LATE LUMEN LOSS AT 6 MONTHS
ITT ANALYSIS

Stent coverage entire lesion length



Scheinert D et al. TCT 2010

DCB w/o Stenting in SFA Interventions

Conclusions

- Plain DCB will become to standard treatment method within 5 years
  - *Provided the large RCTs confirm the pilot trial results*
    - *Inpact SFA 1&2 and Inpact global registry*
    - *Levant 2 and Levant global registry*
- Non-flow limiting dissections are no indication for (spot-) stenting
- Following careful baseline angiography rigid material potentially resulting in recoil might be removed with atherectomy prior to DCB angioplasty

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

Secondary Endpoints

Clinical Cohort:

- Major Adverse Events (All-cause mortality, clinically-driven TVR, major target limb amputation, thrombosis at the target lesion site)
- All-cause mortality
- Clinically-driven TLR and clinically-driven TVR
- All TLR and all TVR
- Major target limb amputation
- Time to first clinically-driven TLR and all-cause mortality
- Primary and secondary sustained clinical improvement
- Immediate and sustained hemodynamic improvement
- Walking impairment evaluation (WIQ)
- Health related Quality of Life Scores (EQ5D)
- Walking distance (6MWT)
- Device, procedural and clinical success

Imaging Cohort:

- Duplex defined binary restenosis of the target lesion (PSVR > 2.0 and > 3.4)

Study Design

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

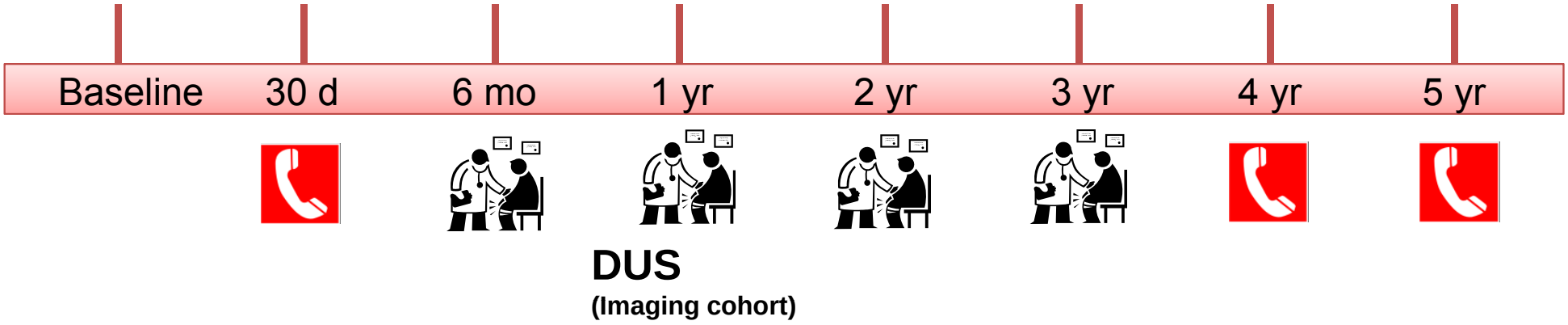
Prospective, Multi-center, Single-Arm Study

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

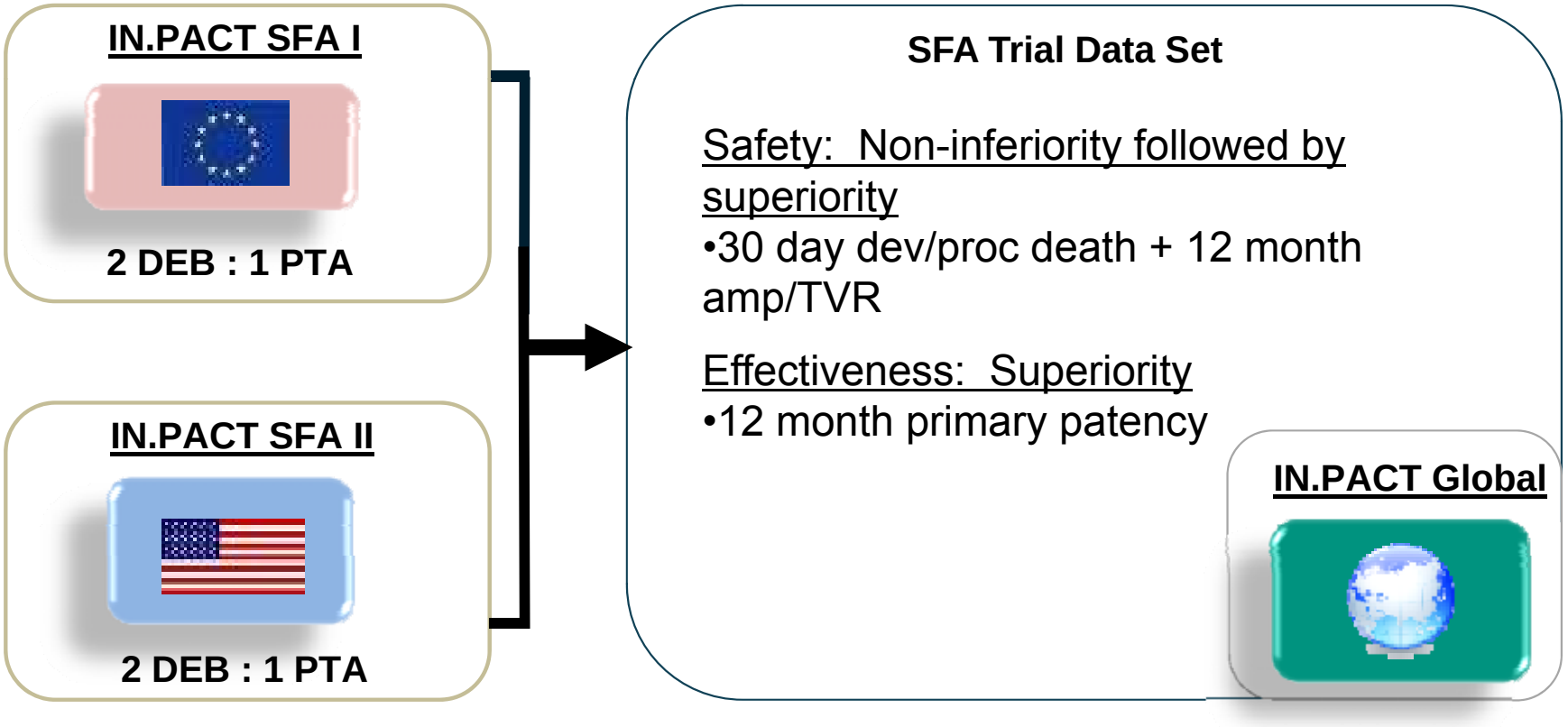


DUS
(Imaging cohort)

IN.PACT Admiral™ DEB strategy

Study Purpose: Evaluate the safety and efficacy of the IN.PACT Admiral™ paclitaxel-eluting balloon when compared to standard PTA for symptomatic PAD

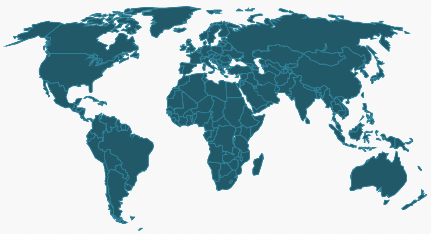
Device Approval Strategy:



** CAUTION: Investigational product. Limited by Federal (US) law to investigational use.*

IN.PACT Global Study

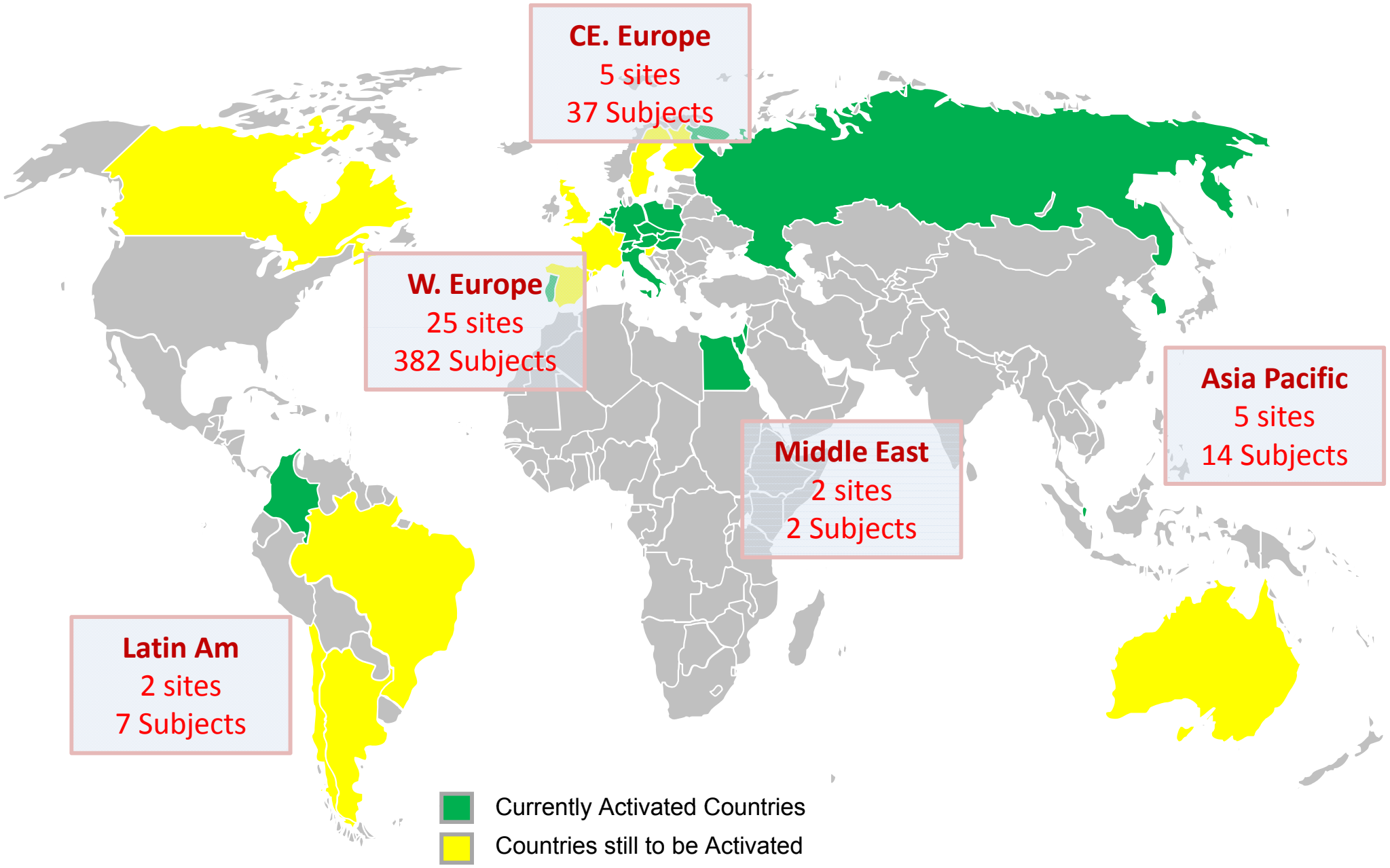
1500-patient, single arm, controlled, independently adjud. Study



- ☑ 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

- Severance Hospital (Choi): 9
- Guro Hospital (Rha): 6
- Samsung Medical Center (Do): 1
- Ajou University (Won): 0
- Asan Medical Center (Lee): NA

- Changi Hospital (Kum): 5

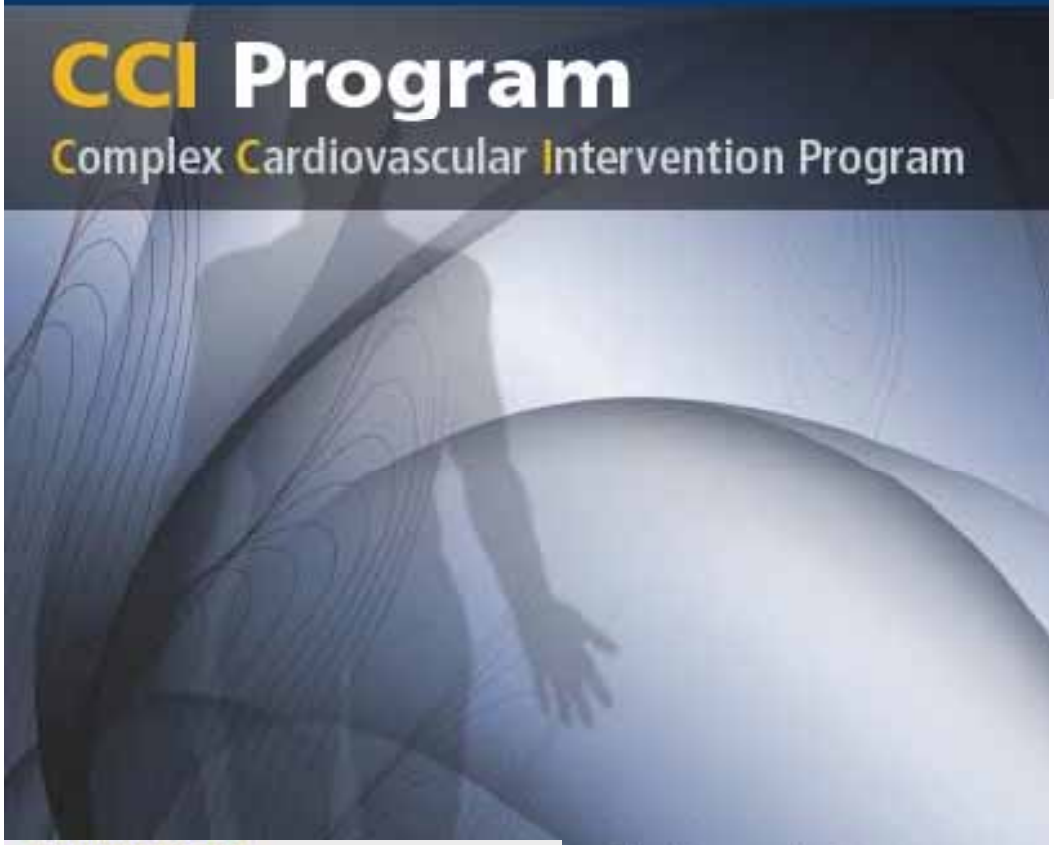
* As of March 20th, 2013

고려대학교구로병원
KOREA UNIVERSITY GURO HOSPITAL

Cordis
a Johnson & Johnson company

CCI Program

Complex Cardiovascular Intervention Program



Cardiovascular Center,
Korea Univ. Guro Hospital,
Seoul, Korea

March~, 2011

Seung-Woon, Rha MD.PhD

COURSE DIRECTOR

Seung-Woon Rha, MD., PhD.
FACC, FAHA, FSCAI, FESC, FAPSIC.

Associate Professor, Dept. of Internal Medicine, Medical College, Korea University
Director, Cardiovascular Intervention and Research,
Director, Cardiac Catheterization Laboratory,
Cardiovascular Center,
Korea University Guro Hospital, Seoul, Korea

- CTO Summit, Course Director
- TCT AP (Angioplasty Summit) and Encore Seoul, Scientific Committee & Faculty
- KSC, KSIC, CCT, CVIT, TOPIC, CTO club meeting, Faculty
- Proctor and Faculty in Korean CTO club, TRI club and VIS (Vascular Intervention Seminar)

When	Every Tuesday & Thursday for 7 Mar.11, 2011 ~
Where	Korea University Guro Hospital, Seoul, Korea
Advisory Instructo	Dong-Joo Oh MD.PhD, FACC
Course Instructor	Seung-Woon Rha MD.PhD, FACC
Invited Mentors	1. Chael-Ung Choi (Korea Univ. Guro Hospital) 2. Sang-Ho Park (Soonchunhyang Univ. Hospital Cheonan) 3. Yun-Hyeong Cho (Kwandong Univ. College Of Medicine Myongji Hospital) 4. Amro Elnagar (Banha Univ. Egypt)

COURSE OVERVIEW

1. Technical Improvement in Complex Coronary & Peripheral Intervention
2. Clinical Research in Cardiovascular Field

LEARNING OBJECTIVES

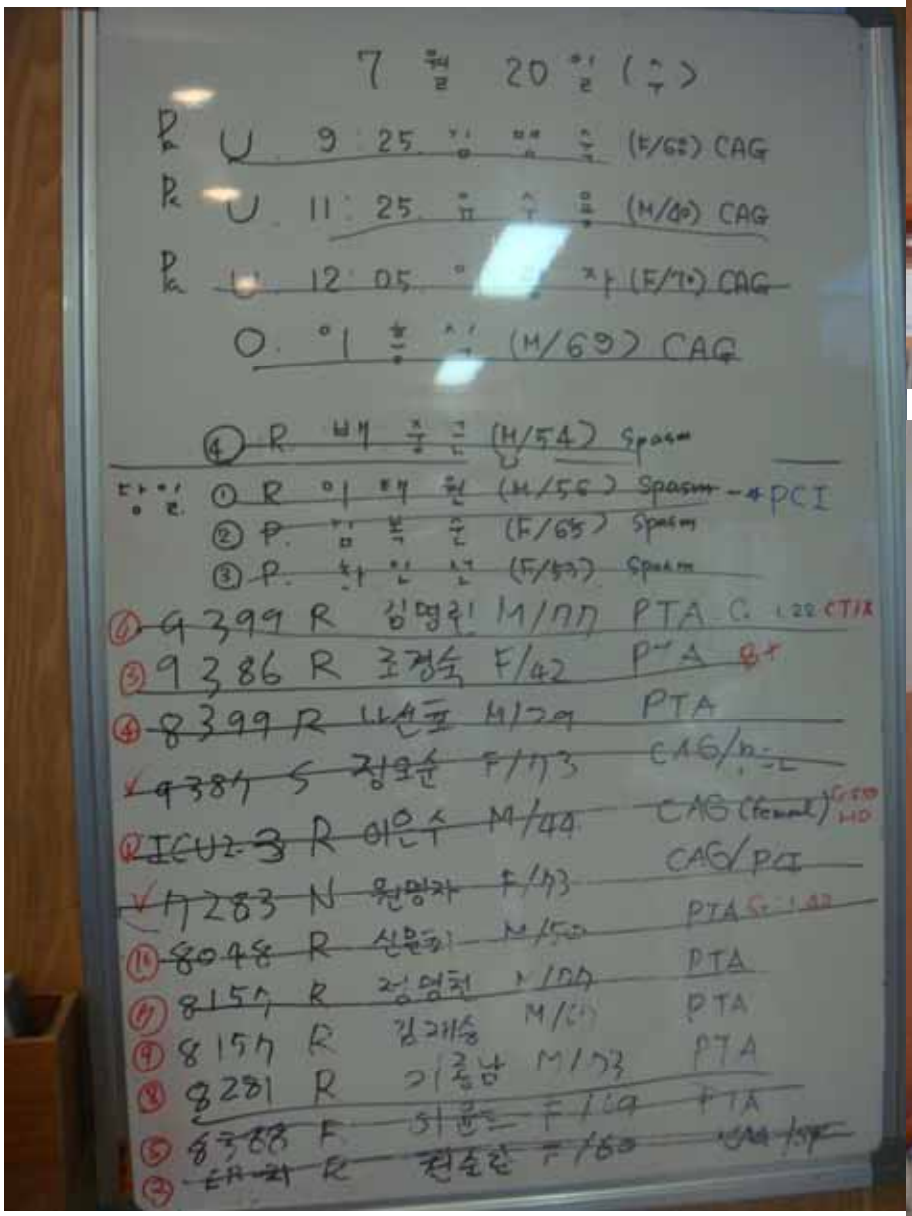
1. Complex coronary & Endovascular Intervention
   A. Complex coronary Intervention : LM, CTO, Bifurcation, Diffuse long Multi-vessel disease, Small vessel disease, FFR, Coronary Anomaly
   B. Complex Endovascular : Carotid, Subclavian, Renal, Iliofemoral, BTK, Mesentry, Vein Intervention, Aortic Aneurysm
2. Hands-on experience as an operator with mentors
3. Free discussion with experts
4. Clinical research program and paperwork
5. Visiting professors' activities : Lectures, Interesting case discussion
6. Challenging new devices and experiencing cutting edge technology
7. Improving English Proficiency

AGENDA

08:30 - 08:45	Opening Remarks & Introduction
08:45 - 12:30	TRA & TRI Session
12:30 - 13:30	Lunch
13:30 - 14:00	Round Table Meeting Topic review and Clinical Research Discussion
14:00 - 18:00	Complex Coronary & Peripheral Joint Live I
18:00 - 18:30	Dinner
18:30 - 19:00	Discussion for case of the day Meet the experts
19:00 -	Complex Coronary & Peripheral Joint Live II : Until Tired

CANDIDATE SELECTION CRITERIA

1. Current active academic position as a faculty in cardiovascular intervention field (Interventional Cardiology, Vascular Surgeon and Interventional Radiology)
2. Weekly for at least 6 – 12 months will be preferred
   1) 6-12 month : Chance of real practice
   2) <6 months : Mainly assisting job and Hand-on Experience
   3) Single Visit : Observation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To be continued from Mar 2013

1. CCI Program Schedule (Supported by Cordis)

1) Weekly CCI Program; every Tuesday (until Wed morning)

2) Intensive CCI Program (1 and ½ day course)

April 11-12 (Thursday afternoon & Friday full day)

June 25-26

Sept 26-27

Dec 19-20

2. CCI Program Contents

; intensive complex coronary and peripheral intervention joint live

(joint live, lectures, discussions and hands on…)