DEB Will Become Dominant Therapy, with DES reserved for Bail-out!

Antonio Micari, MD, PhD
GVM Care and Research
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DCB will become dominant because…….

1. Anti-proliferative therapy while leaving nothing behind
2. Broad anatomical applicability
3. Avoid stent fracture and ISR burden
4. Preserve future options
5. Matches patient's quality of life expectancy

DCB will become dominant if…….

Will show safety and efficacy in different clinical situations

DEB in fem-pop Evidence Overview

18 Trials, 2 meta-analysis, 9 DEB Peer Reviewed Publications

- 7 Proof-of-Concept: DEB vs. PTA [1-2-3-4-5-6] + 1 single arm [7]
- 1 Registry with 2-year functional outcome [8]
- 3 "Explorative" (DEB+Ather. and Calcium effect) [9-10-11]
- 2 meta-analysis: DEB vs. PTA, DEB vs. BMS (indirect) [12-13]

☑ TASC A
☑ TASC B

[1] G.Tepe et al. THUNDER, NEJM 2008; [2] M.Werk et al. FEMPAC, Circulation 2008; [3] D.Scheinert LEVANT I TCT 2012; [4] M.Werk et al. PACIFIER Circulation CI 2012; [5] D.Scheinert BIOLUX, EuroPCR 2012; [6] D.Scheinert ADVANCE PTX, LINC 2013; [7] S.Duda ILLUMENATE, EuroPCR 2013; [8] A.Micari et al. DEB SFA IT Registry, JACC CI 2013; [9] A.Cioppa et al. Card. Rev. Med. 2012; [10] S.Sixt et al. J Vasc Surg 2013 (in press); [11] F.Fanelli, LINC 2013; [12] S.Cassese et al. Circulation CI 2012; [13] M.Fusaro et al. Int J Cardiol 2013

- 4 in long SFA lesions [14-15-16-17] including 1 retrospective DEB vs. DES Trial [16] and 1 RCT DEB+BMS vs. BMS [17]

☑ TASC C
☑ TASC D

[14] F.Fanelli et al. DEBELLUM, JEVT 2012; [15] A.Schmidt LINC 2013; [16] T.Zeller Charing Cross 2013; [17] F.Liistro et al. JACC CI 2013 (in press)

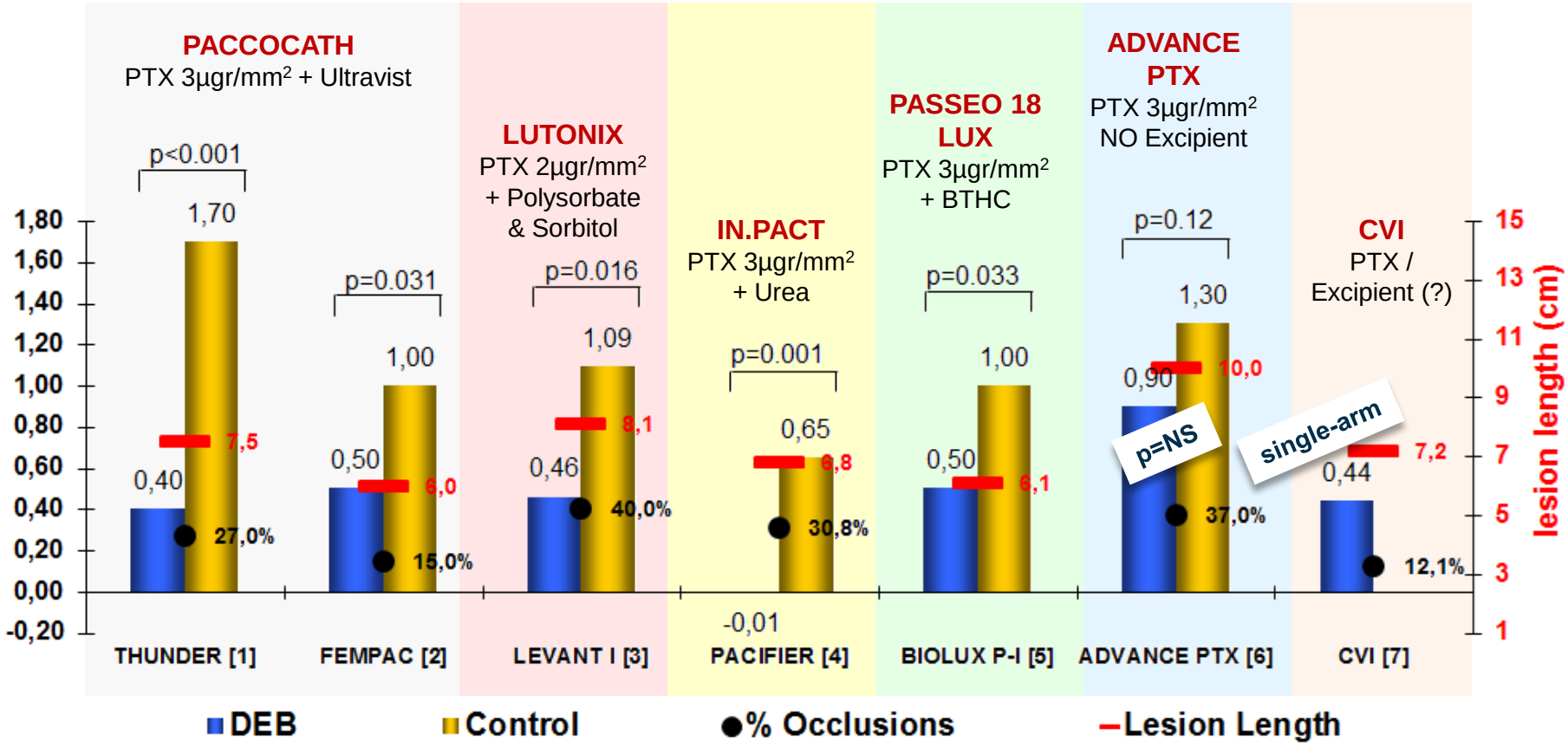
- 4 initial proof of efficacy in SFA in-Stent-Restenosis [18-19-20-21]

☑ ISR

[18] E.Stabile et al. IN.PACT ISR JACC 2012; [19] F.Liistro DEBATE ISR JEVT 2013 (in press); [20] JC Van Den Berg J Cardiovasc Surg 2012; [21] J.Lammer PACUBA preliminary results LINC 2012

DEB in SFA Evidence: Proof-of-Concept

7 Trials / 6 DEB Technologies; 6-month LLL (Primary Endpoint)



[1] G.Tepe et al. - NEJM 2008; [2] M.Werk et al. - Circulation 2008; [3] D.Scheinert - TCT 2012 oral presentation; [4] M.Werk et al. - Circulation CI 2012; [5] D.Scheinert – EuroPCR 2012 oral presentation; [6] D.Scheinert – LINC 2013 oral presentation; [7] S.Duda – EuroPCR 2013 oral presentation

DEB Italian Registry: Functional Assessment

Prospective	√
Multicenter	√
Randomized	☐
Corelab	☐
Peer-rev. Published	√

Registry, 105 Patients. Primary EP: 1y Primary Patency + Functional QoL evaluation:

- **83.7% (1y) and 72.4% (2y) Prim. Patency**
- **Sustained Walking (6mWT and WIQ) and QoL benefit at 2 years**

12.3% Stent Rate

2y Sustained QoL improvement

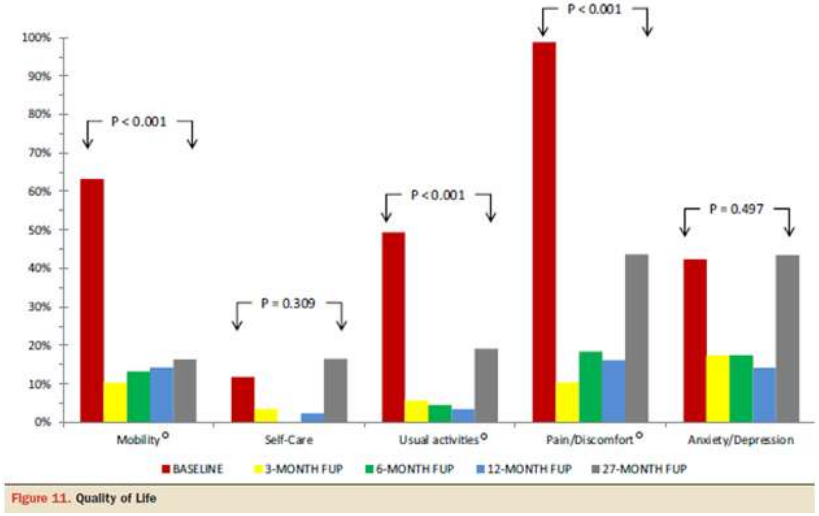


Figure 11. Quality of Life

3.5-fold ↑ in walk capacity at 2-year

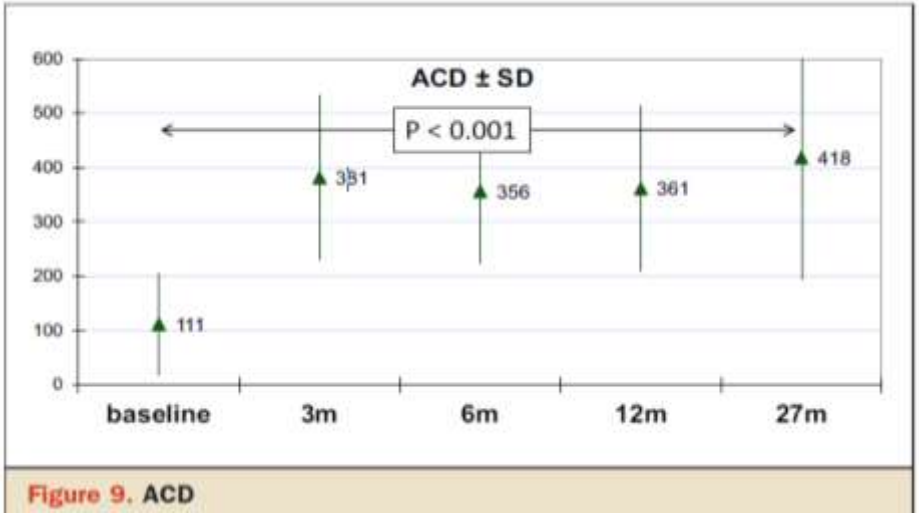


Figure 9. ACD

(Micari A et al. A.Micari J Am Coll Cardiol Intv 2013)

DEB vs. DES in Long SFA lesions

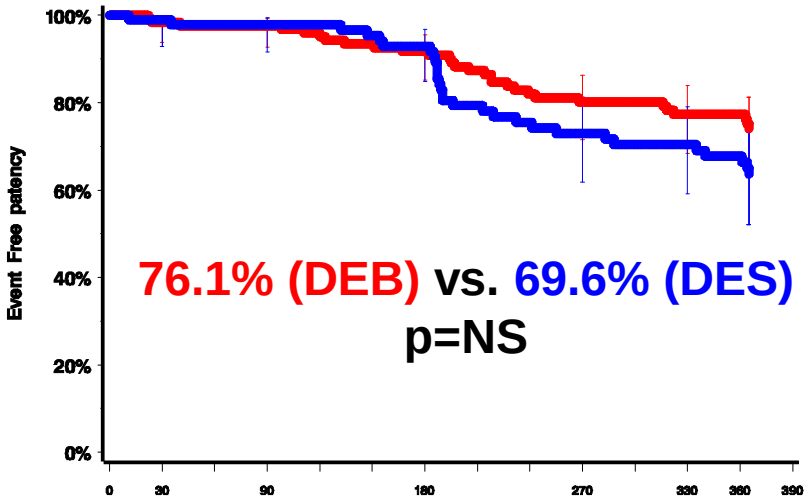
Prospective	☐
Multicenter	☑
Randomized	☐
Corelab	☐
Peer-rev. Published	☐

228-Patient retrospective – propensity score based – analysis of DEB vs. DES in long (~19 cm) SFA lesion

- **Non significant difference between IN.PACT DEB and Zilver PTX in long SFA lesions**
- **prov. Stent rate post DEB = 18.3%**

1-year freedom from loss of Primary Patency (PSVR < 2.4)

Lesions ~19 cm



(Zeller T. Charing Cross 2013)

DEB in long SFA lesions

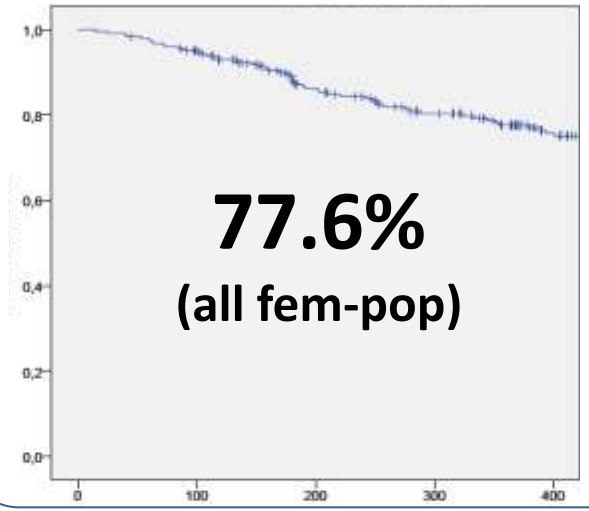
Prospective	☑
Multicenter	☐
Randomized	☐
Corelab	☐
Peer-rev. Published	☐

Real world 260-Patient Registry of complex fem-pop lesions (length ~24 cm; CTO: 65.3%; ISR: 37.2%)

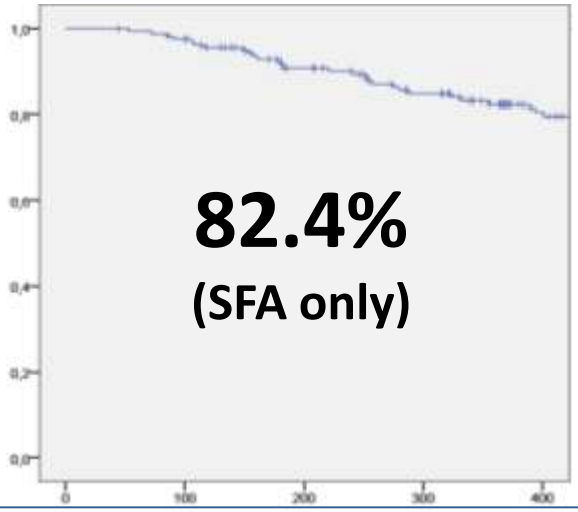
- **High Primary Patency rates achieved overall in the full cohort and subsets**
- **23.3% provisional Stent rate**

1-year freedom from loss of Primary Patency (PSVR < 2.4)

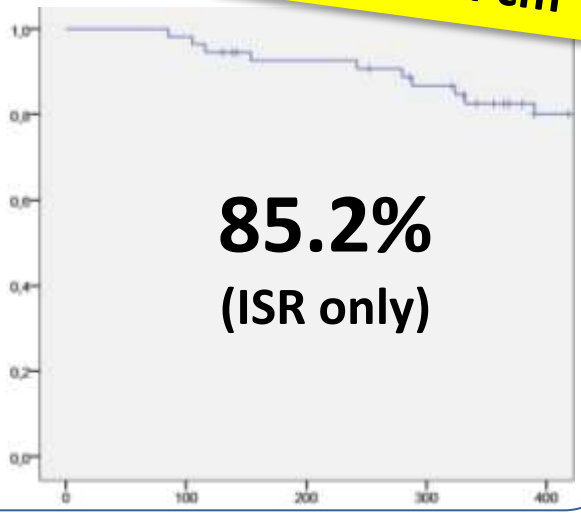
Lesions ~24 cm



77.6%
(all fem-pop)



82.4%
(SFA only)



85.2%
(ISR only)

(Schmidt. A CIRSE 2013)

Safety and efficacy of the Drug Eluting Balloon for the treatment of long lesions of the Superficial Femoral Artery ischemic vascular disease in symptomatic patients – DEB SFA-LONG

- Study design: prospective, observational, multicentre
- Study aim: to assess safety and efficacy of the DEB technology for the treatment of the SFA ischemic obstructive vascular disease in patients with long lesions
- Patients: n= 110
  - Rutherford Category 2, 3 or 4
  - Target lesion : single solitary or multiple adjacent de novo or restenotic lesions (non-in-stent) with diameter stenosis ≥ 70% by visual estimate and cumulative lesion length ≥ 15 cm
  - Target vessel is the superficial femoral artery and/or proximal popliteal artery (above the knee)
- **Primary efficacy end-point: the rate of primary patency within 12 month post index procedure**

Lesions ~26 cm

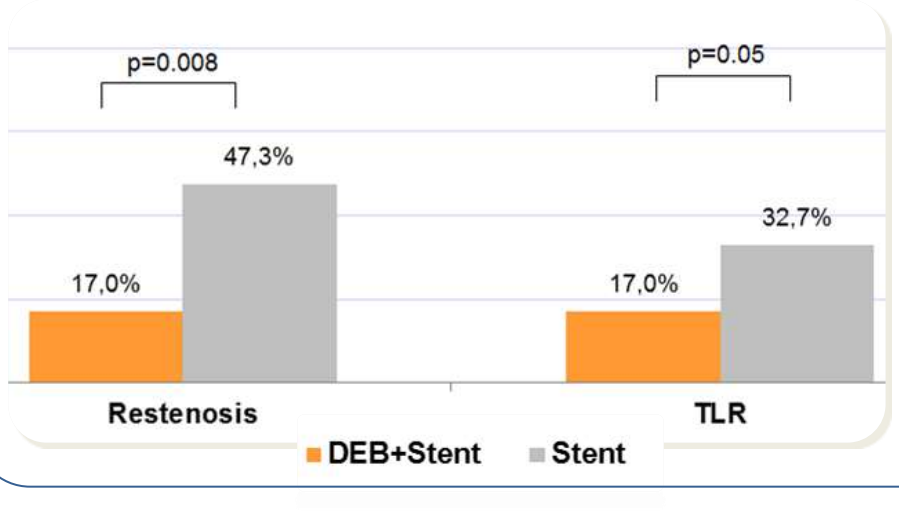
DEB+ (elective) Stent vs. Stent: DEBATE SFA

- Prospective ☑
- Multicenter ☐
- Randomized ☑
- Corelab ☐
- Peer-rev. Published ☑

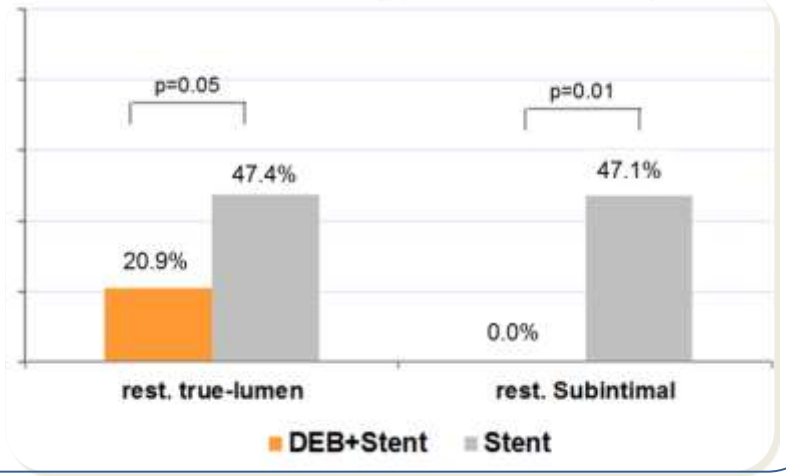
Randomized, 104 Patients (>70% CLI and Diabetics, >60% CTOs), Primary EP: 1y RR

- **DEB significantly improve Stent results**
- **Restenosis ↓↓ maintained irrespective of lesion length and recanalization technique**

1-Year Restenosis and TLR



1-Year Restenosis: subintimal vs. true lumen



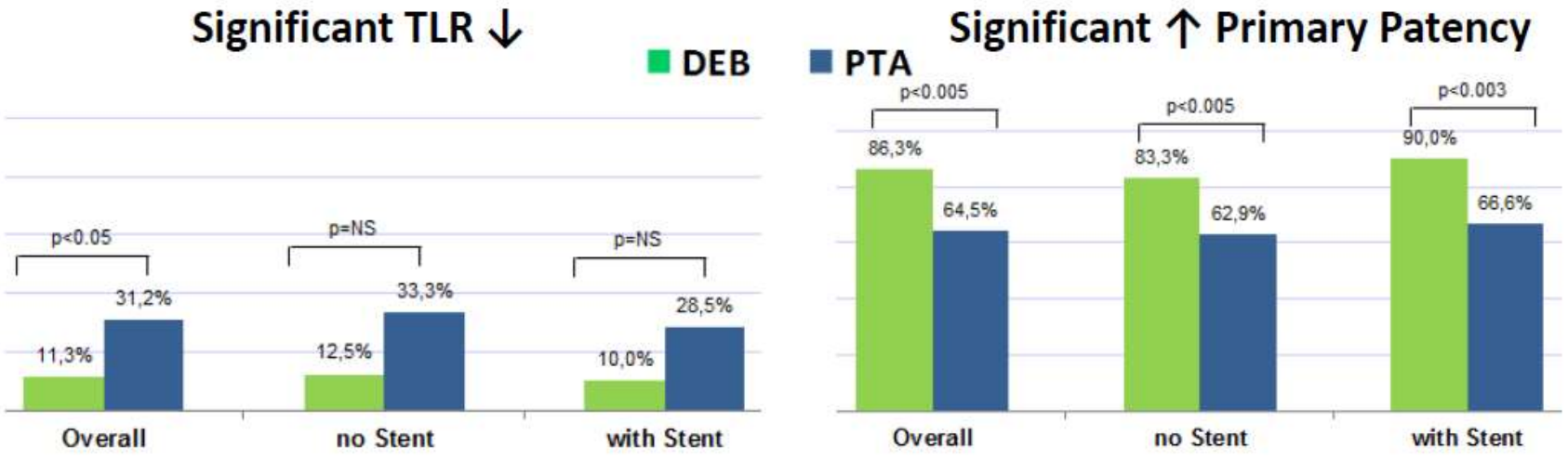
(Liistro F et al. J Am Coll Cardiol Intv 2013 – accepted)

IN.PACT ± Stent: DEBELLUM

Randomized, 50 Patients / 122 lesions (SFA and BTK):

- **Significantly ↓LLL and ↑Primary Patency vs. PTA at 6 and 12 months in SFA**
- **Stents do not compromise DEB outcomes**

IN.PACT vs. PTA in the SFA: 1-year results (with and without Stent):



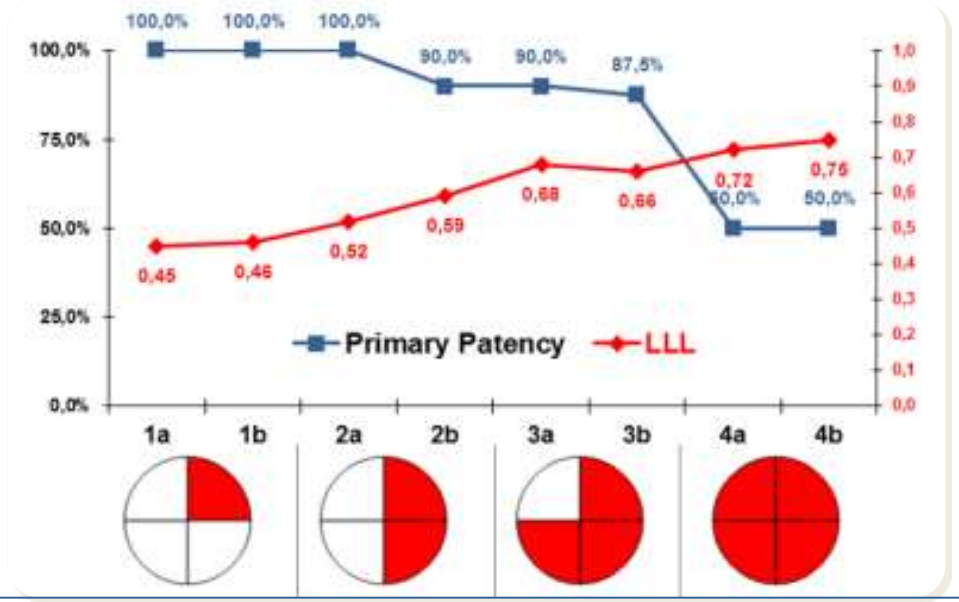
(Fanelli F et al. J Endovasc Ther. 2012)

DEB and Calcium

Prospective	☑
Multicenter	☐
Randomized	☐
Corelab	☐
Peer-rev. Published	☐

Explorative 60-patient study to assess the effect of Calcium on DEB efficacy. Primary EP: 12m LLL:

- **Calcium may proportionally impact restenosis**
- **Greater impact observed in circumferential vs. longitudinal distribution**



(Fanelli F. et al submitted)

DEB + Atherectomy in High Calcium

A.Cioppa LINC 2012

Singe center registry of IN.PACT Admiral + Atherectomy for SFA de-novo with severe calcifications

Angelo Cioppa MD

- **Primary Endpoint: 1y Prim. Patency**
- **30 patients**
  - **LLC / CLI = 6% / 94%**
  - **Diabetics = 60%**
  - **Mean lesion length = 115 ± 35 mm**
  - **Tot Occlusions = 13%**
  - **Calcium Score* 3 = 100%**
- **dist. Filter + TurboHawk + DEB**
  - **bail-out Stenting = 7%**

Initial, encouraging signals of performance in severely calcified SFA lesions with combined drug elution and debulking with nothing left behind

12-month FU

- **Primary Patency = 90%**
- **TLR = 10%**
- **Secondary Patency = 100%**

* 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

IN.PACT SFA Pivotal RCT

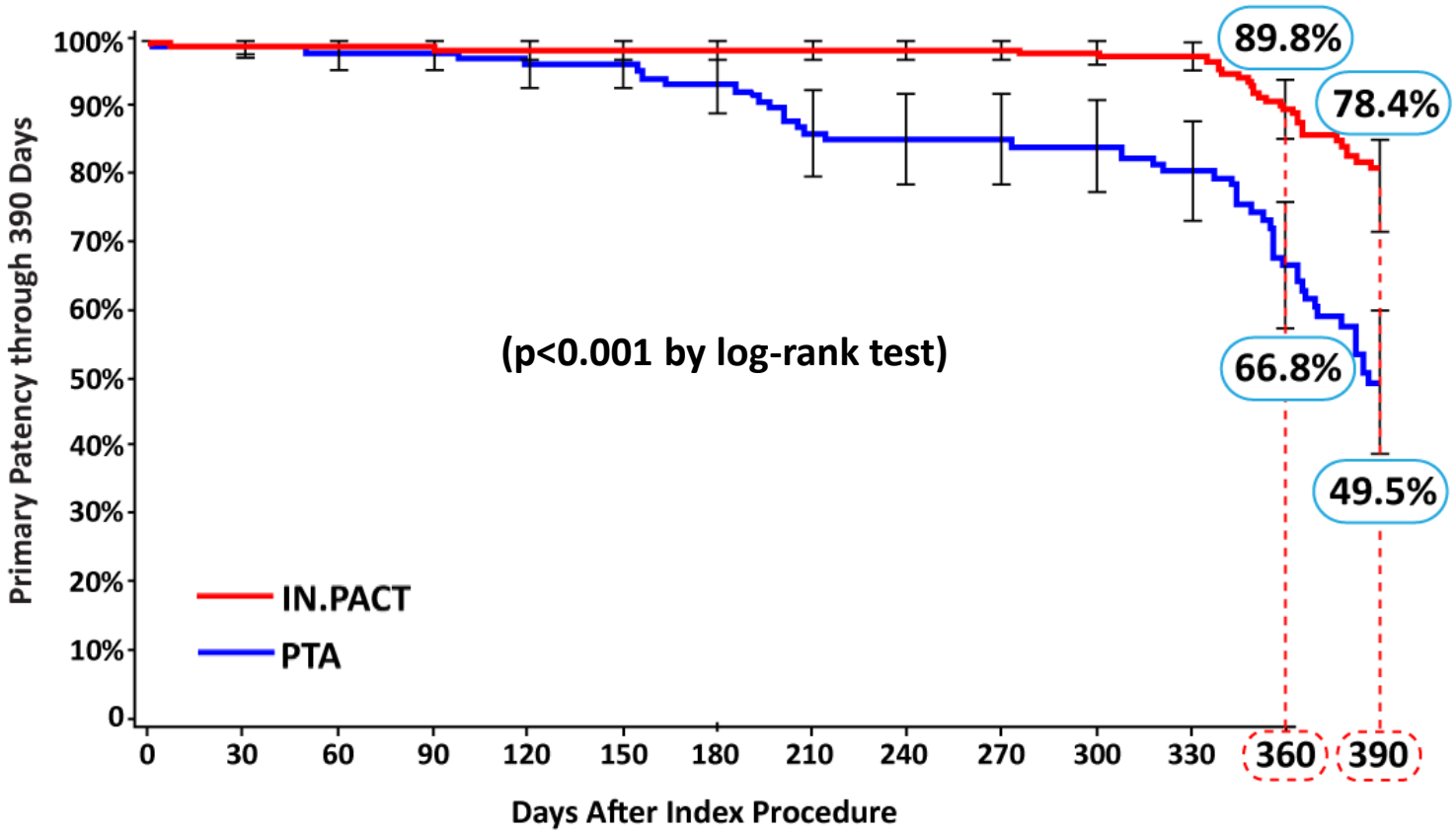
IN.PACT Admiral DCB vs. standard PTA
for the treatment of superficial femoral and proximal popliteal artery disease due to claudication and rest pain

- Prospective, multicenter EU and US, randomized (2:1), single blinded
- Independent and blinded Duplex Ultrasound Core Lab [1], Angiographic Core Lab [2], and Clinical Events Committee [3]
- Independent Data Safety Monitoring Board [3]
- External monitoring with 100% source data verification
- Subjects followed up to 5 years

Gunnar Tepe,
Charing Cross, London, UK, 4.5.2014,
on behalf of IN.PACT SFA Invesigators

IN.PACT SFA Pivotal RCT

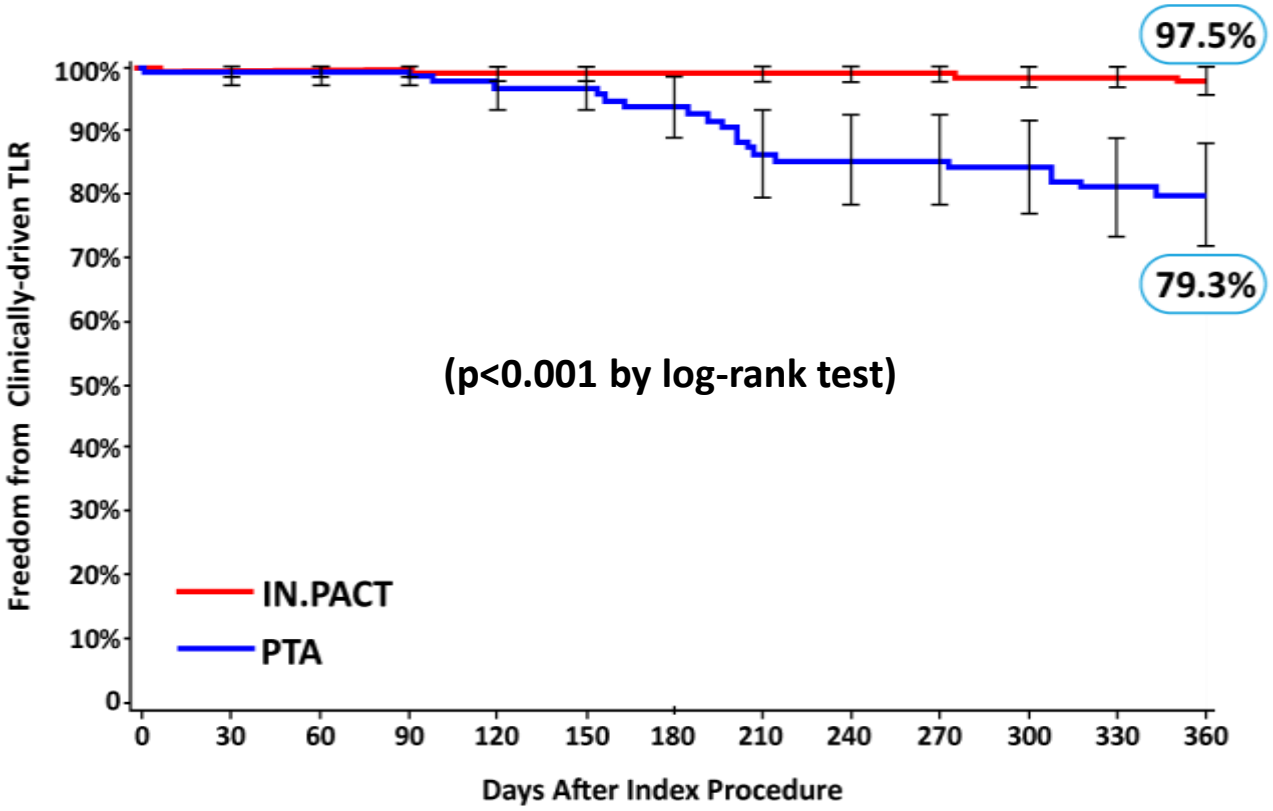
89.8% Primary Patency at 12-month



Gunnar Tepe,
Charing Cross, London, UK, 4.5.2014,
on behalf of IN.PACT SFA Invesigators

IN.PACT SFA Pivotal RCT

2.4% Clinically-driven TLR at 12-month



Gunnar Tepe,
Charing Cross, London, UK, 4.5.2014,
on behalf of IN.PACT SFA Invesigators

IN.PACT in real world: IN.PACT GLOBAL

RC-2-3-4

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

- 1500-patient, largest and rigorous all-comers single arm trial
- 67 centers WW
- Independent adjudication

1423 Patients enrolled as of March 28 (first 1-year results in Sep 2014)

Steering Committee: G.Tepe, M.Bosiers, P.Gaines, D. Dai-Do, A.Razuk, G. Ansel

DEB vs. PTA + BMS cost effectiveness analysis

40 RCTs (fem-pop and infrapop, IC and CLI) extracted by PRISMA methodology [1]

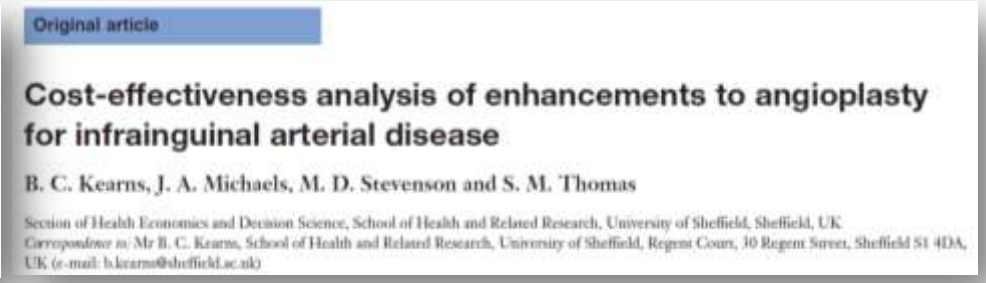
Discrete-event simulation model on cost-effectiveness from a health service perspective [2]

Systematic review

Systematic review and meta-analysis of additional technologies to enhance angioplasty for infrainguinal peripheral arterial occlusive disease

E. L. Simpson, J. A. Michaels, S. M. Thomas and A. J. Cantrell

School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK

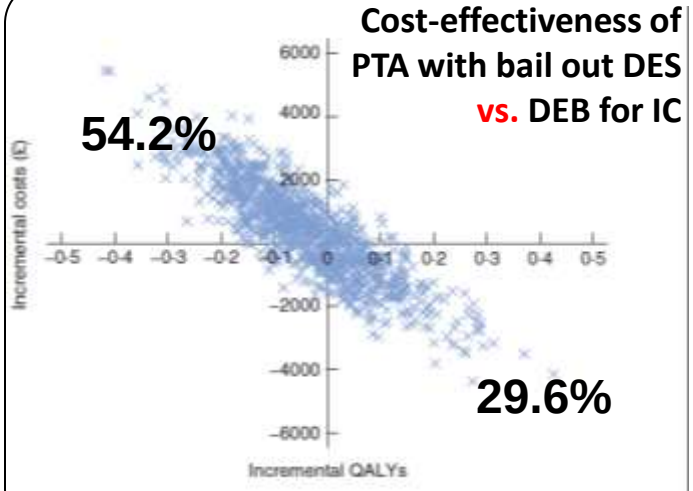


Original article

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

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

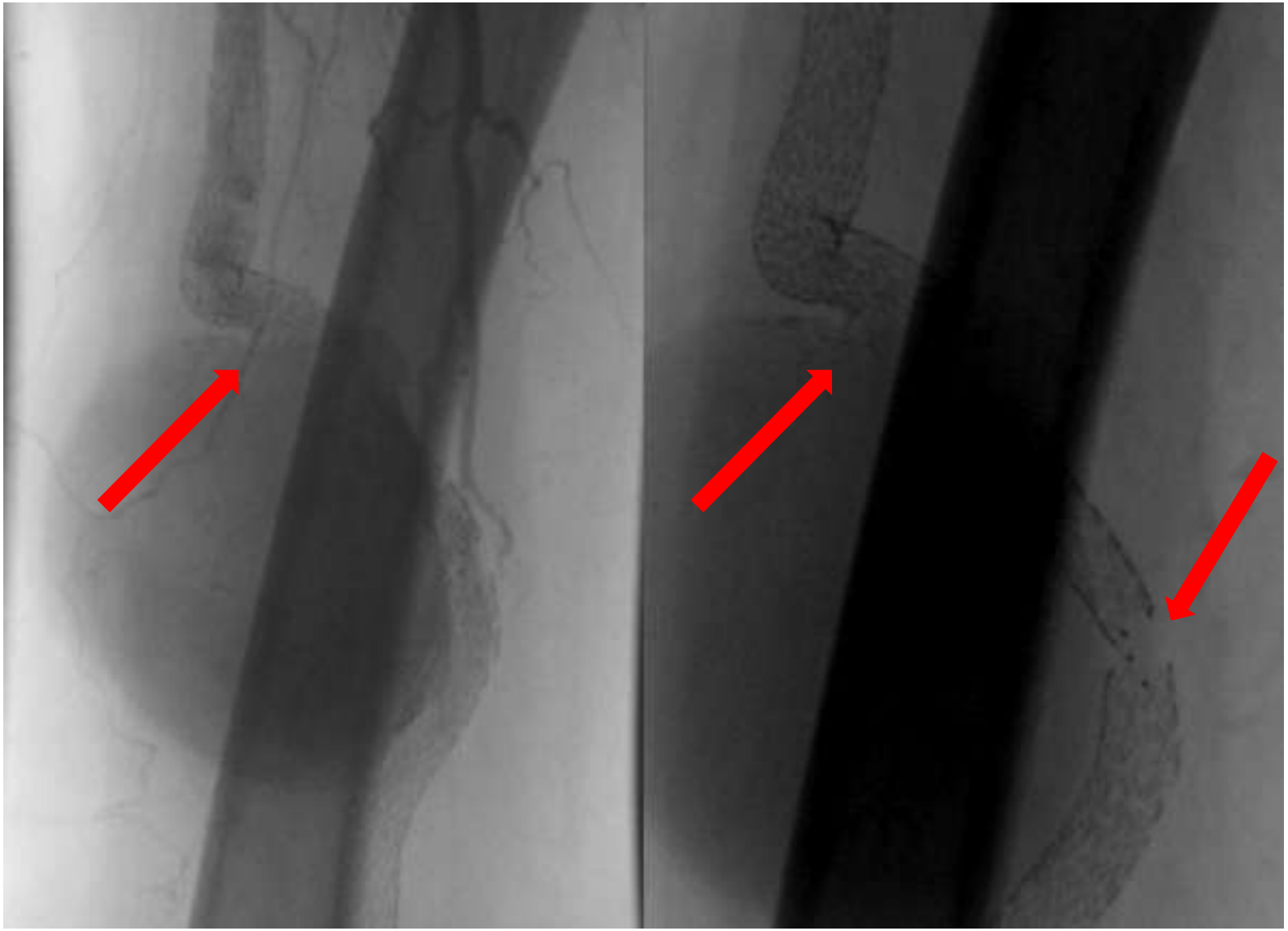
Section of Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK



8 endovasc therapies (incl. DES, DEB, BMS, Brachytherapy, Stent-grafts, Cryoplasty) vs. Standard of Care (PTA + prov. BMS)

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

1. Kearns BC et al. Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease. Br J Surg. 2013 Aug;100(9):1180-8
2. Simpson EL et al. Systematic review and meta-analysis of additional technologies to enhance angioplasty for infrainguinal peripheral arterial occlusive disease. Br J Surg. 2013 Aug;100(9):1128-37

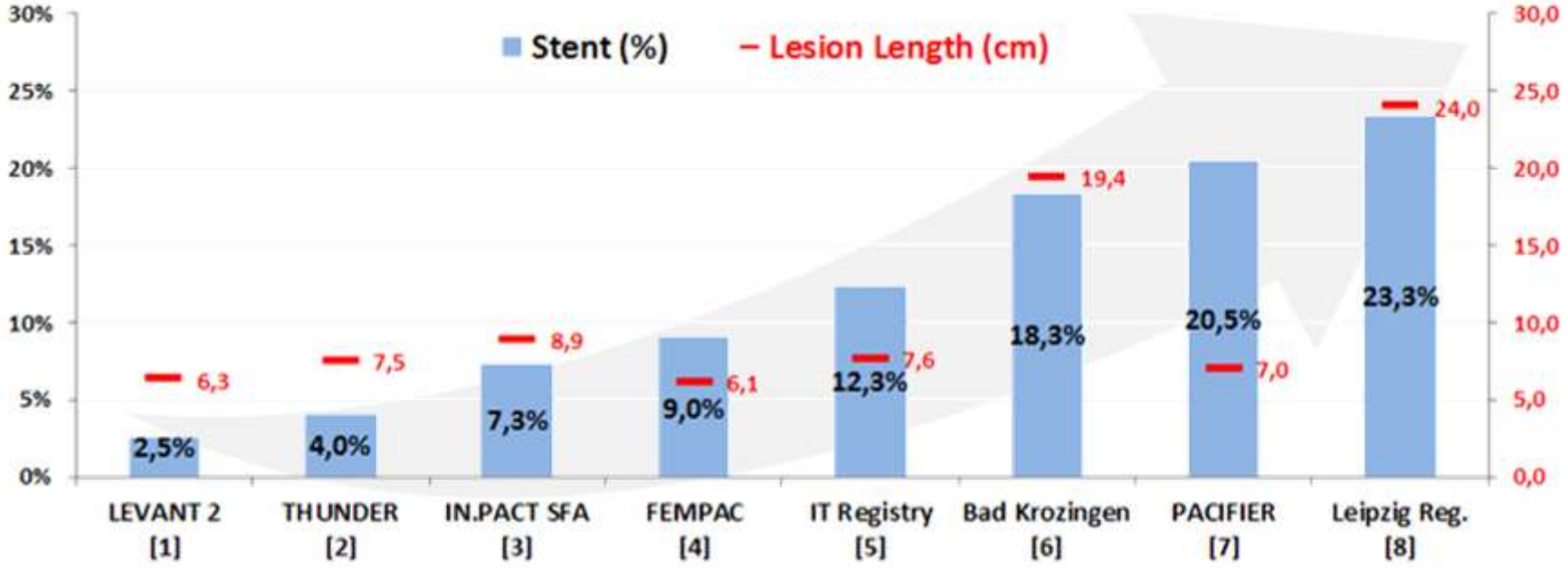


Stenting: only if we need!

(and never DES)

Scaffolds still needed, likely at rates proportional to lesion complexity

Provisional stent rates in DCB Trials are a function of lesion length



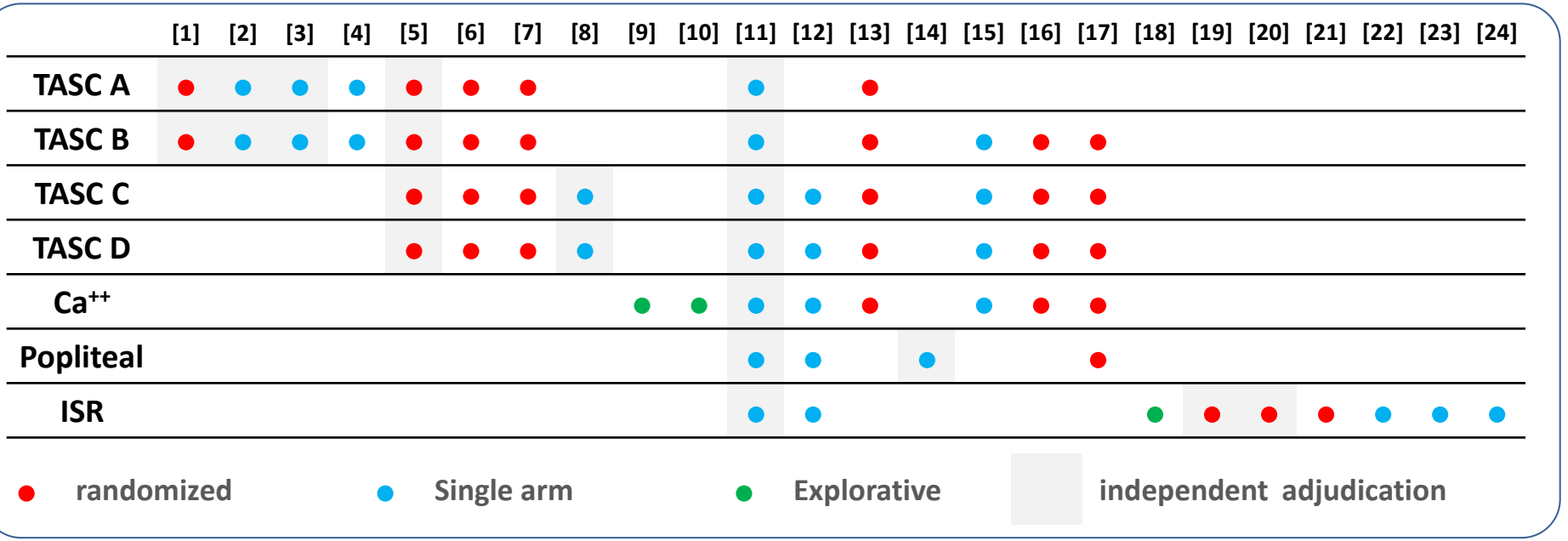
[1] Rosenfield K TCT 2013; [2] Tepe G et al. N Engl J Med 2008; [3] Tepe CX 2014; [4] Werk M et al. Circulation 2008; [5] Micari A et al. J Am Coll Cardiol Intv 2012; [6] Zeller T CX 2013 oral presentation; [7] Werk et al. Circ Cardiovasc Interv. 2012; [8] Schmidt A LINC 2013 oral presentation

Summary

- The DEB Clinical Program Evidence is showing DEB Safety and Efficacy for femoro-popliteal indications
- The opportunity to have a combination therapy (mechanical and biological) while you are “Leaving nothing behind” is unique
- Preserve future options to claudicants is a must
- DEB is a new quality standard in Clinical Evidence generation for PAD Therapies

IN.PACT DCB fem-pop Clinical Program

24 IN.PACT Trials* (10 RCT), 4200+ Patients jointly covering the full spectrum of fem-pop PAD



[1] IN.PACT SFA; [2] IN.PACT SFA Japan; [3] IN.PACT SFA China; [4] IN.PACT SFA Italian Registry; [5] PACIFIER; [6] DEBELLUM; [7] ISAR STATH; [8] IN.PACT Long Lesions; [9] IN.PACT + Ather Ca++; [10] IN.PACT Ca++; [11] IN.PACT GLOBAL; [12] IN.PACT SFA Real World Leipzig; [13] DEBATE SFA; [14] IN.PACT Flexion; [15] DEB vs. DES retrosp; [16] DEB vs. DES Italy; [17] BE Diabetic IN.PACT Trial; [18] IN.PACT SFA ISR; [19] PHOTOPAC; [20] FAIR; [21] ISAR PEBIS; [22] PLAISIR; [23], DEBATE ISR; [24] IN.PACT ISR CDN

* **Medtronic and Investigator sponsored trials**

“Easy Situations”

Prolonged balloon inflations reduce dissection entity and rates and need for stents

	Inflation Time (sec)		
	30	180	*P* Value
Major dissection (grades 3 and 4)	16	5	.010
Minor or no dissection (grades 1 and 2)	21	32	.010
Further interventions	20	9	.017
Stent	4	1	
Further dilation (prolonged dilation, dilation with larger diameter)	16	8	
Residual stenosis (>30%)	12	5	.097
Complication (embolization, thrombosis)	1	1	
Mean ankle-brachial index (before, after intervention)	0.66, 0.87	0.65, 0.84	

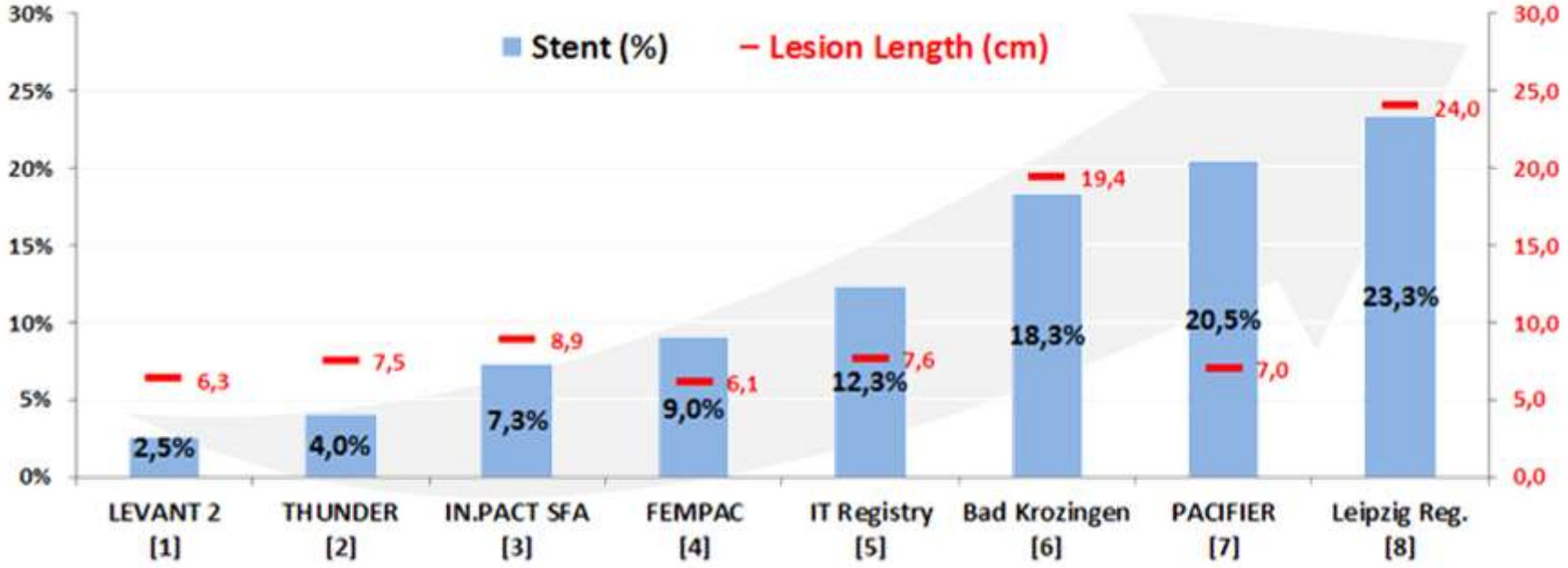
- Inflation times of 180 sec improve immediate infrainguinal PTA results vs. to a short dilation strategy
- Significantly fewer major dissections and a modest reduction of residual stenoses are observed

N. Zorger et al. Peripheral Arterial Balloon Angioplasty: Effect of Short versus Long Balloon Inflation Times on the Morphologic Results. J Vasc Interv Radiol 2002

Background: DCB and provisional Stenting

Scaffolds still needed, likely at rates proportional to lesion complexity

Provisional stent rates in DCB Trials are a function of lesion length

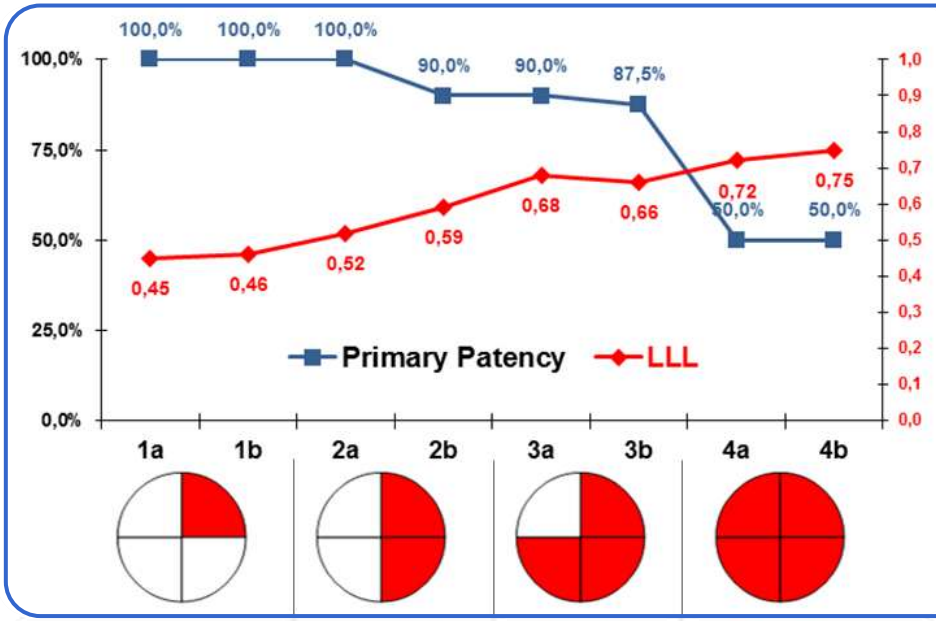


[1] Rosenfield K TCT 2013; [2] Tepe G et al. N Engl J Med 2008; [3] Tepe CX 2014; [4] Werk M et al. Circulation 2008; [5] Micari A et al. J Am Coll Cardiol Intv 2012; [6] Zeller T CX 2013 oral presentation; [7] Werk et al. Circ Cardiovasc Interv. 2012; [8] Schmidt A LINC 2013 oral presentation

Background: DCB and Calcium

GROUP	DIAMETER	LENGHT
1 a	0 – 90 °	< 3 cm
1 b		> 3 cm
2 a	90 – 180 °	< 3 cm
2 b		> 3 cm
3 a	180 – 270 °	< 3 cm
3 b		> 3 cm
4 a	270 – 360 °	< 3 cm
4 b		> 3 cm

- 60-patient registry
- SFA de-novo (~ 6 cm)
- CTO: 31.7%
- IN.PACT DCB with PTA pre-dil

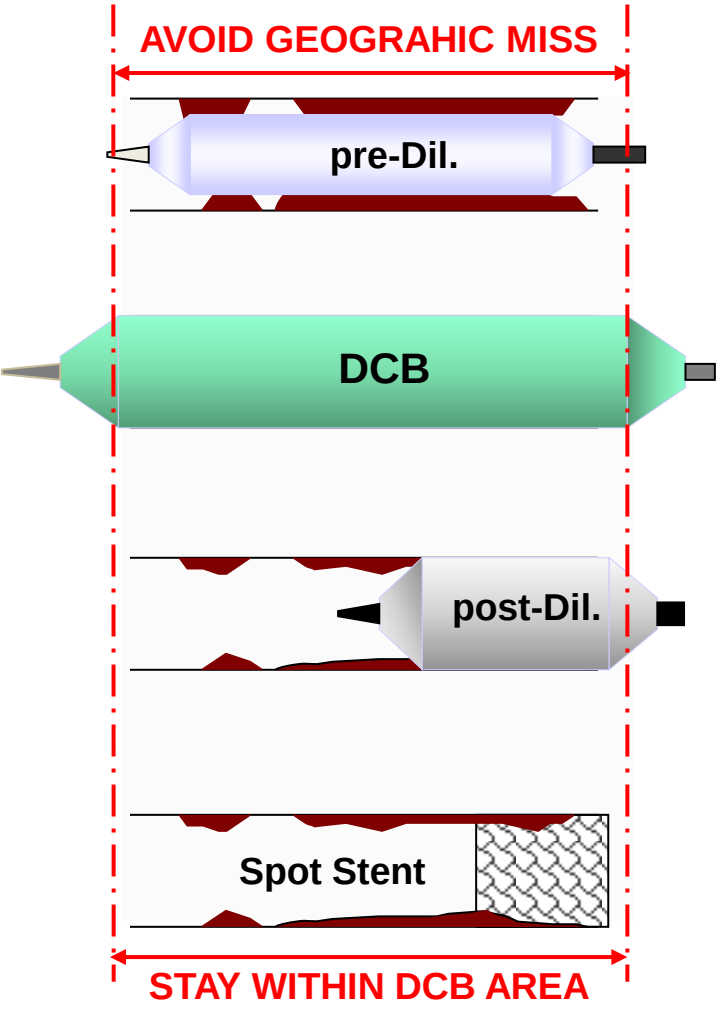


- Calcium distribution and severity affect LLL and primary patency
- Ca++ represents a barrier to optimal drug absorption

Calcium distribution evaluation by CTA (circumf.) and DSA (longitud.)

(F.Fanelli LINC 2013)

DCB and Optimal PTA



1. **Pre-dilatation (CTOs, sub-occl. lesions, Ca++)**
   a. standard PTA Ø1 mm less than RVD
   b. Balloon length>lesion length or planned DCB length, whichever is longer
   c. inflation time ~ 2 minutes
   d. inflation pressure: < RBP as needed to reach full PTA balloon expansion

2. **DCB**
   a. DCB Ø: RVD = 1:1
   b. inflation time ≥ 3min
   c. inflation pressure: <RBP as required to reach full DCB expansion

3. **Post-Dilatation if residual stenosis >50% or flow limiting dissection**
   a. standard or high pressure PTA balloon Ø 1:1 to RVD
   b. short / focal length as necessary to treat the extent of residual stenosis or dissection
   c. inflation time ≥ 3 minutes

4. **Provisional Spot Stenting for persistent residual stenosis >50% or flow liniting dissections**
   1. Min. length as necessary to fully treat the residual stenosis or dissection

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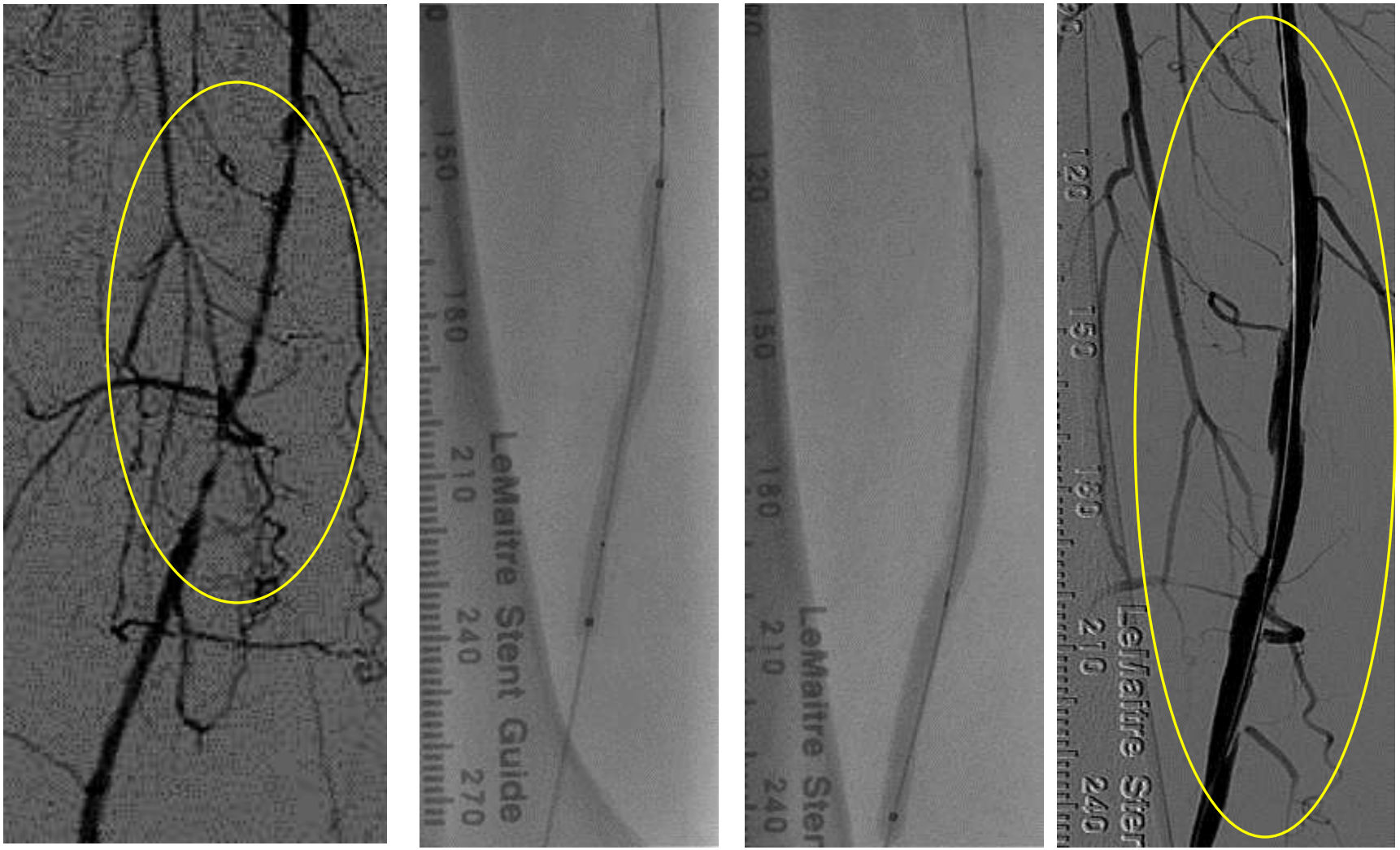
DCB and Optimal PTA:linear dissection



Pre-dilatation: Admiral 4.0-80 **DEB: In.Pact Admiral 5.0-120 mm**

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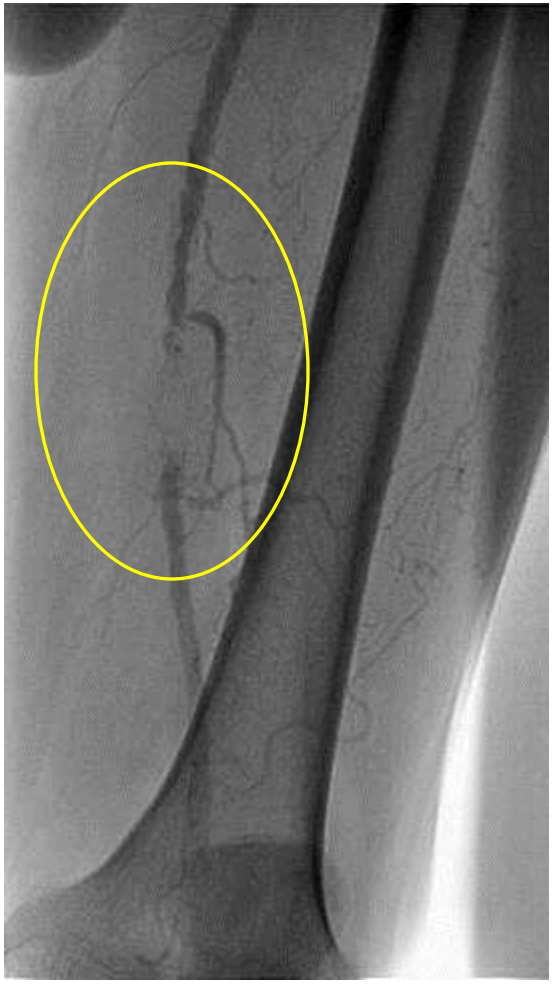
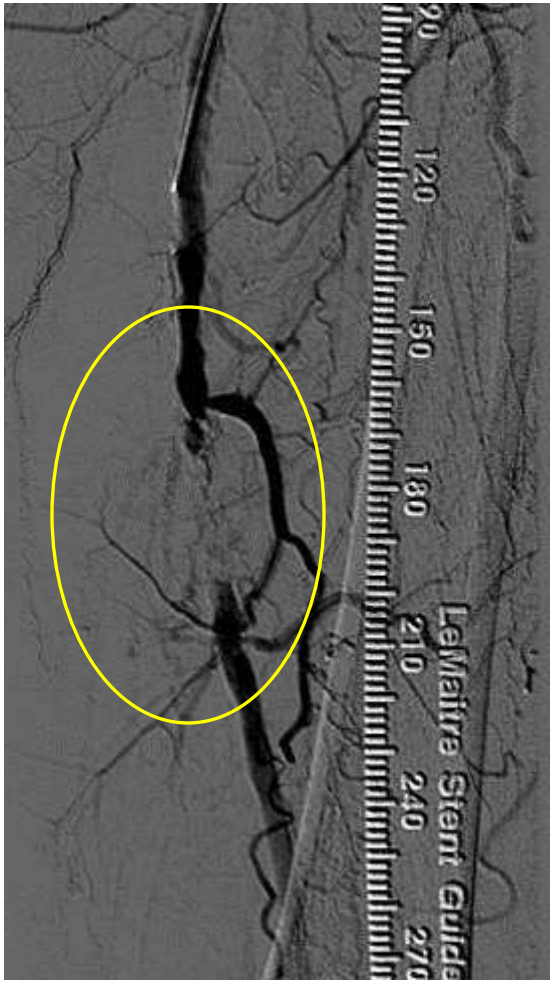
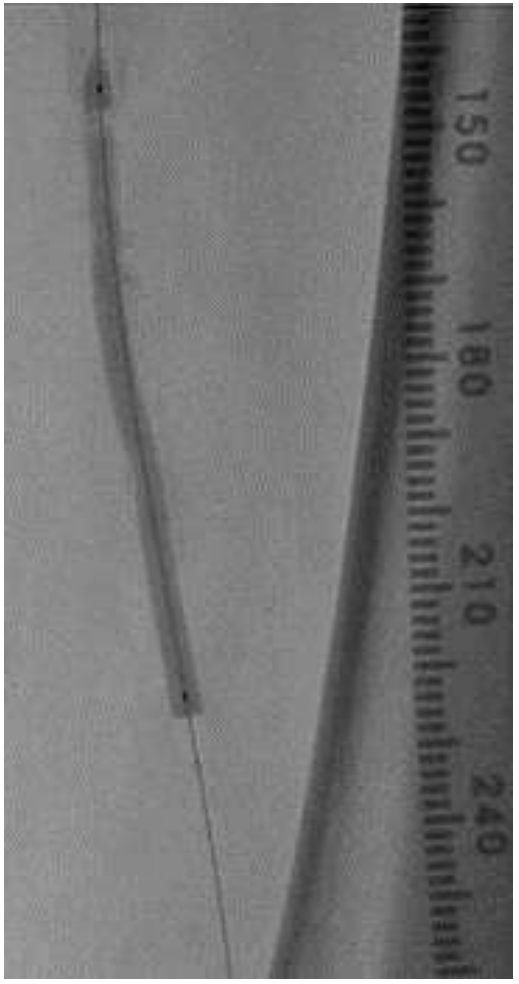
Predilation







Pre-Dilatation: Pacific 4.0-80 mm

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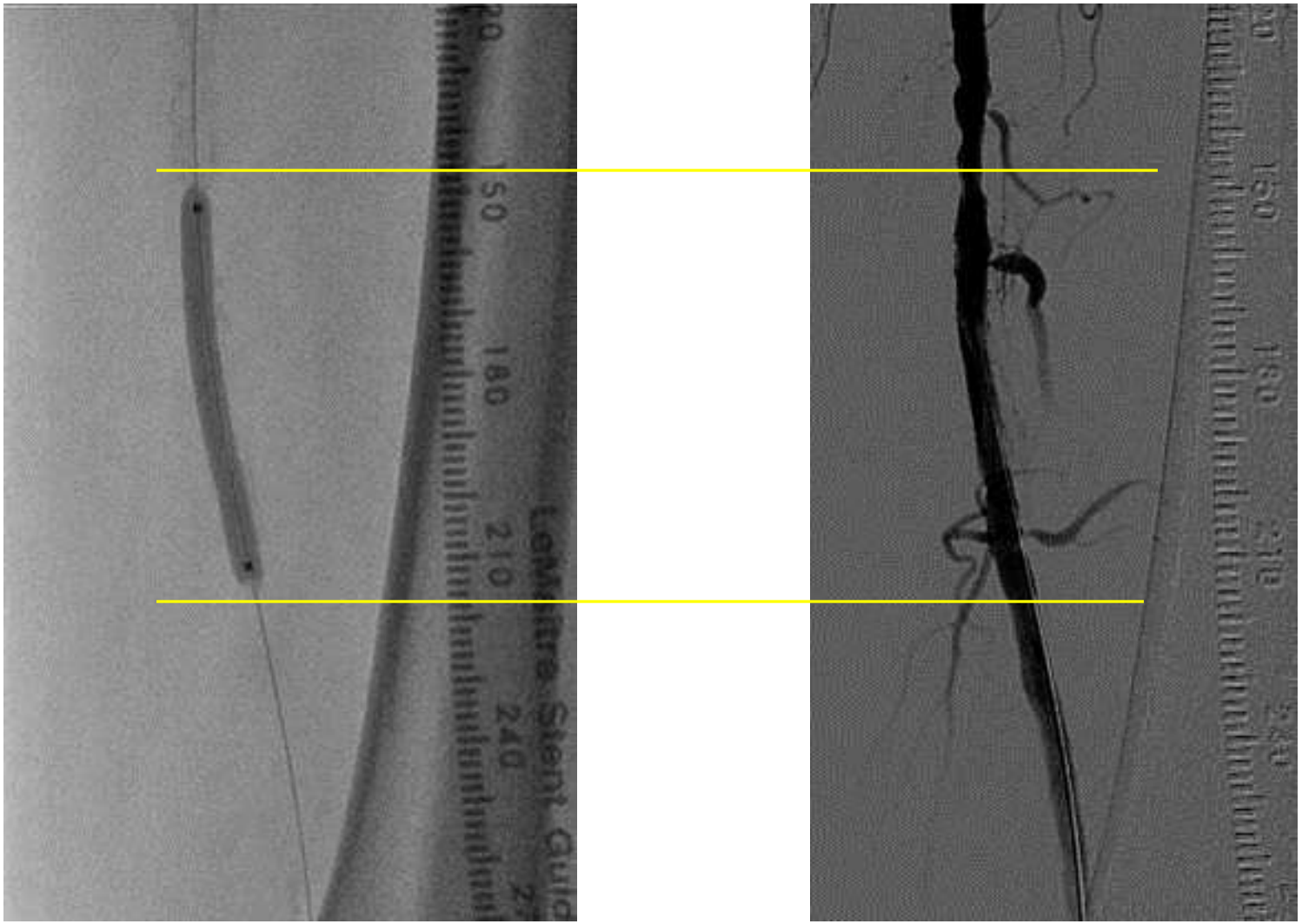
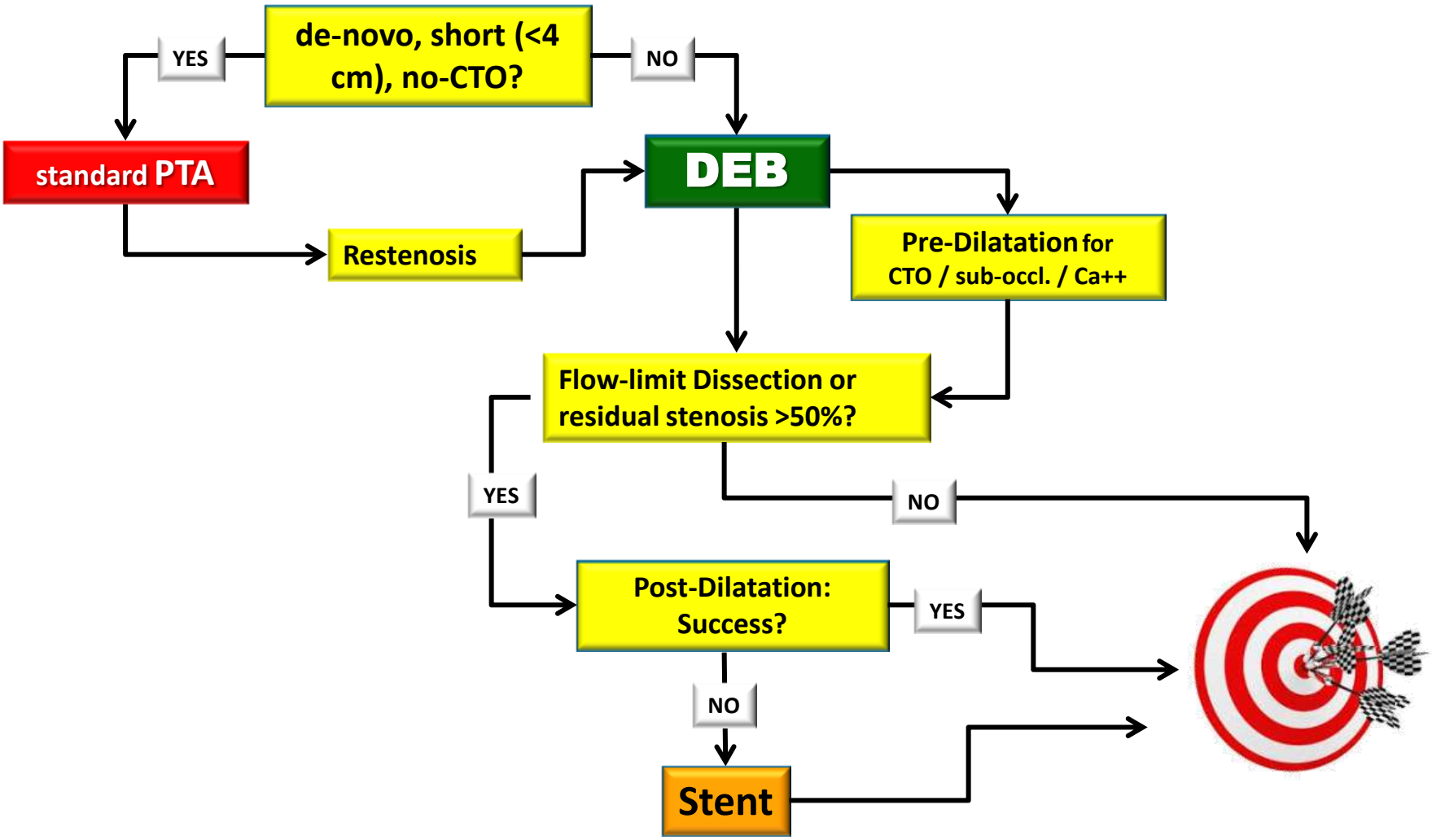
Predilation



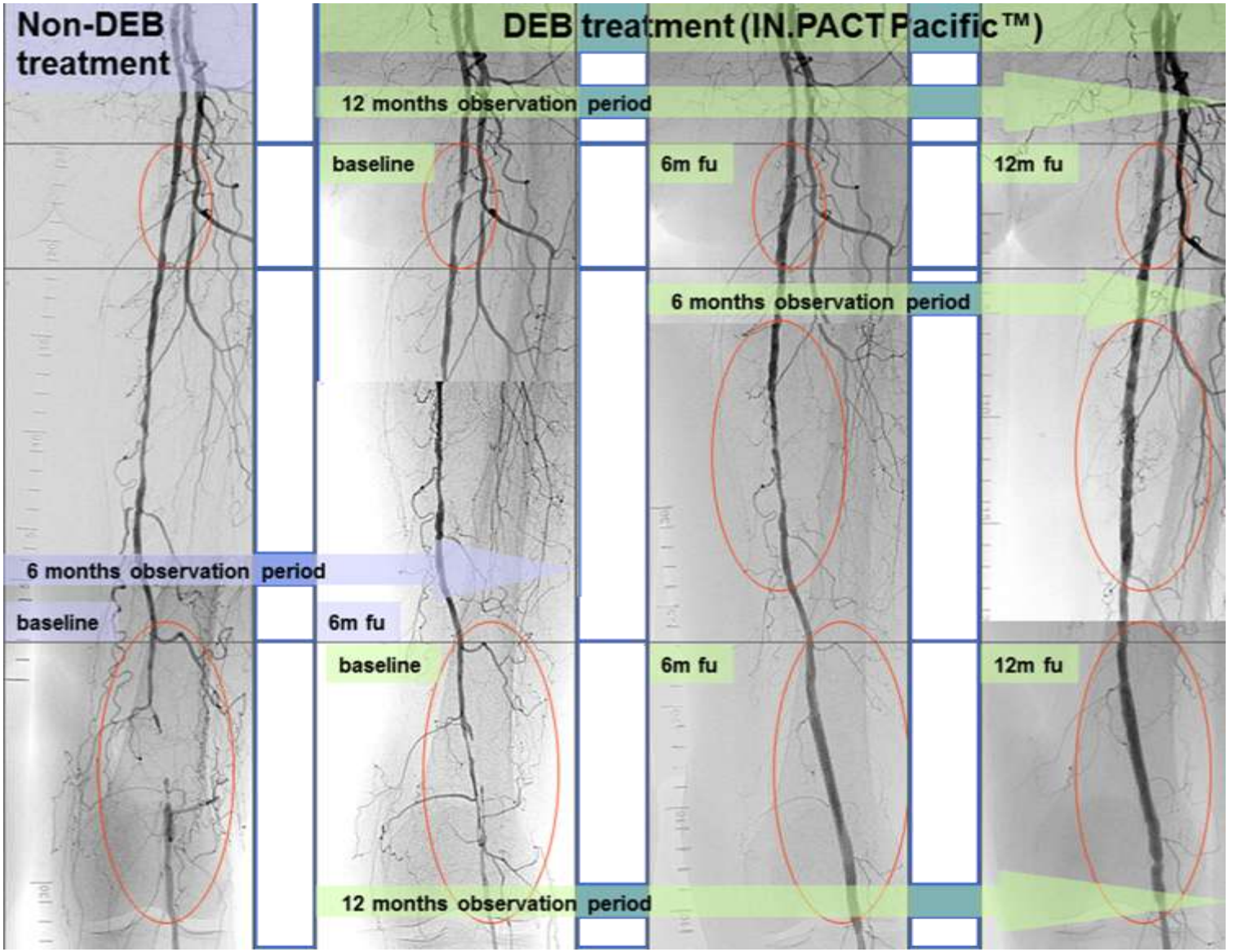
DEB: In.Pact Admiral 5.0-60 mm

Fem-pop treatment algorithm



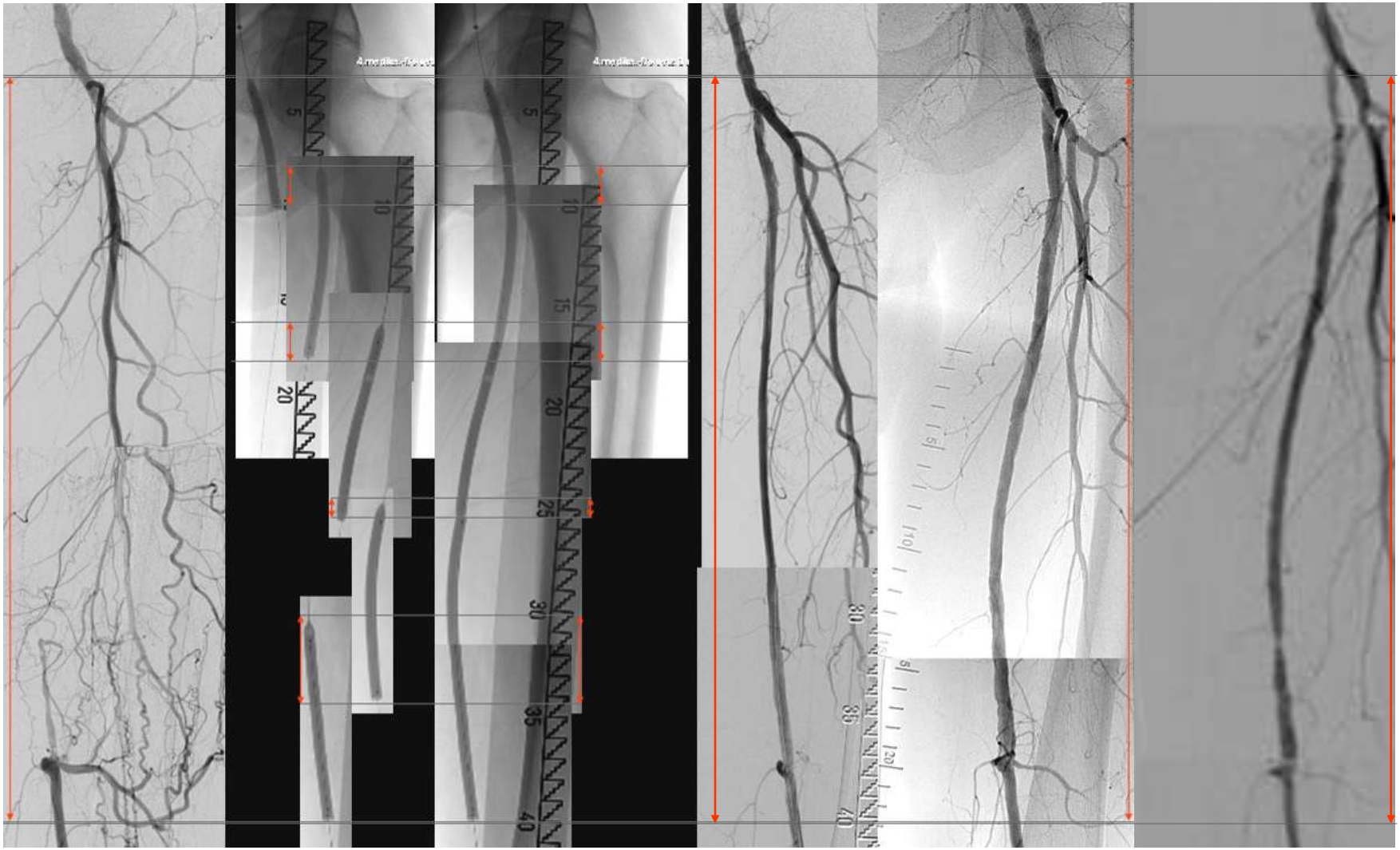
Case 1: PTA restenosis + de-novo treated by DEB

courtesy of M.Werk



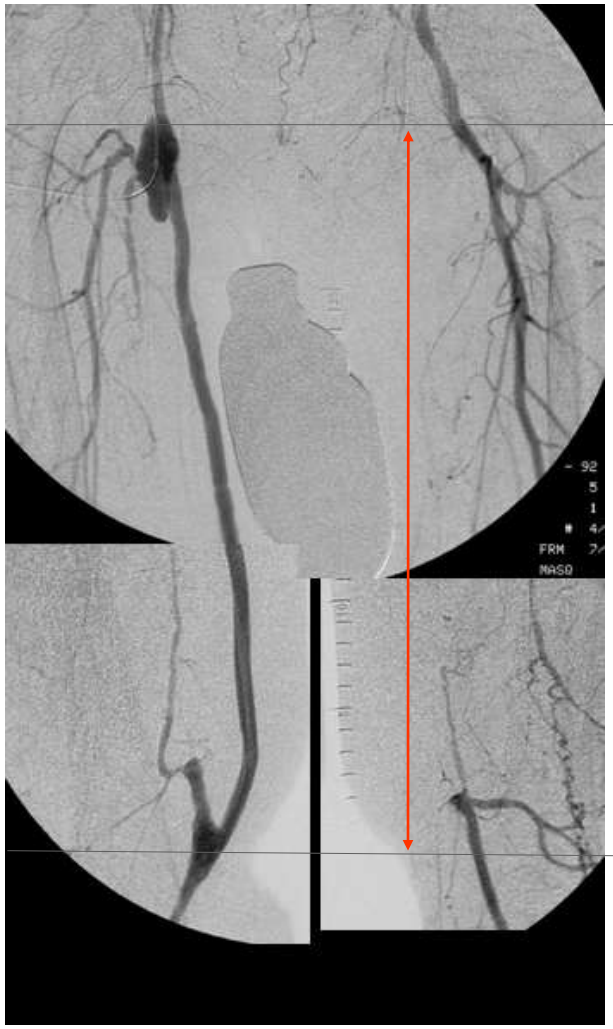
Case 2: Non-stented long occlusion

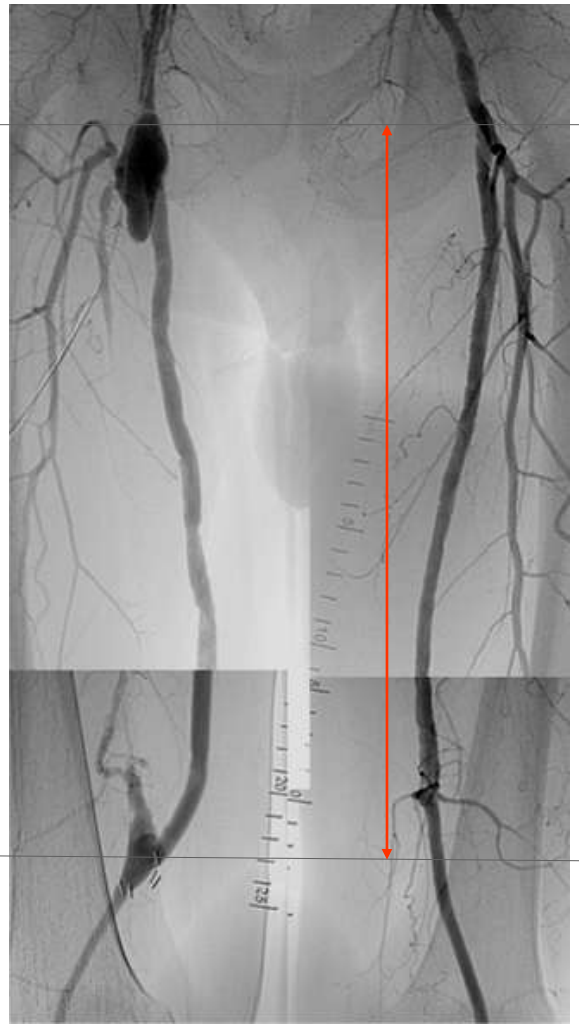
courtesy of M.Werk

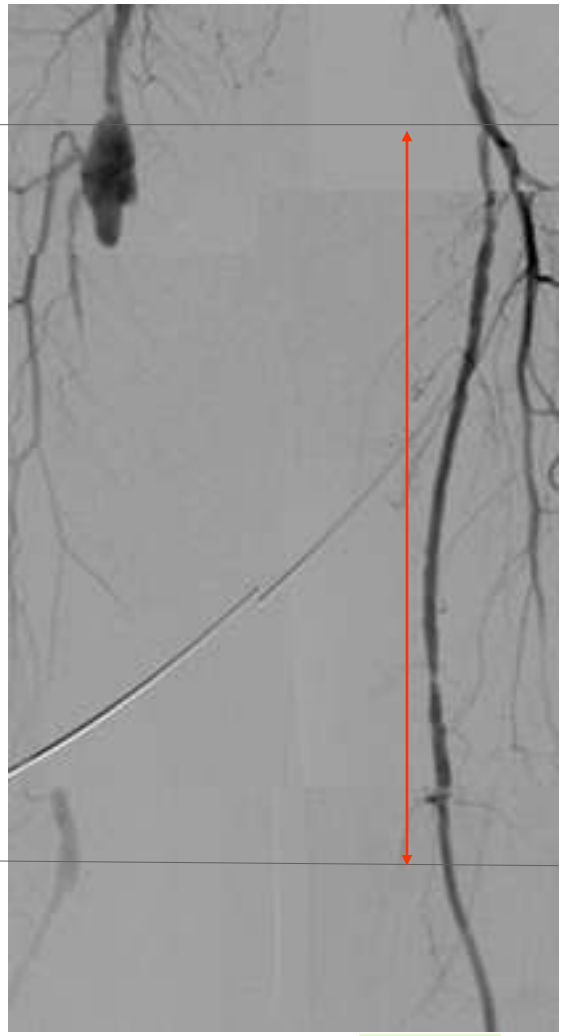


Case 3: Non-stented long occlusion

courtesy of M.Werk



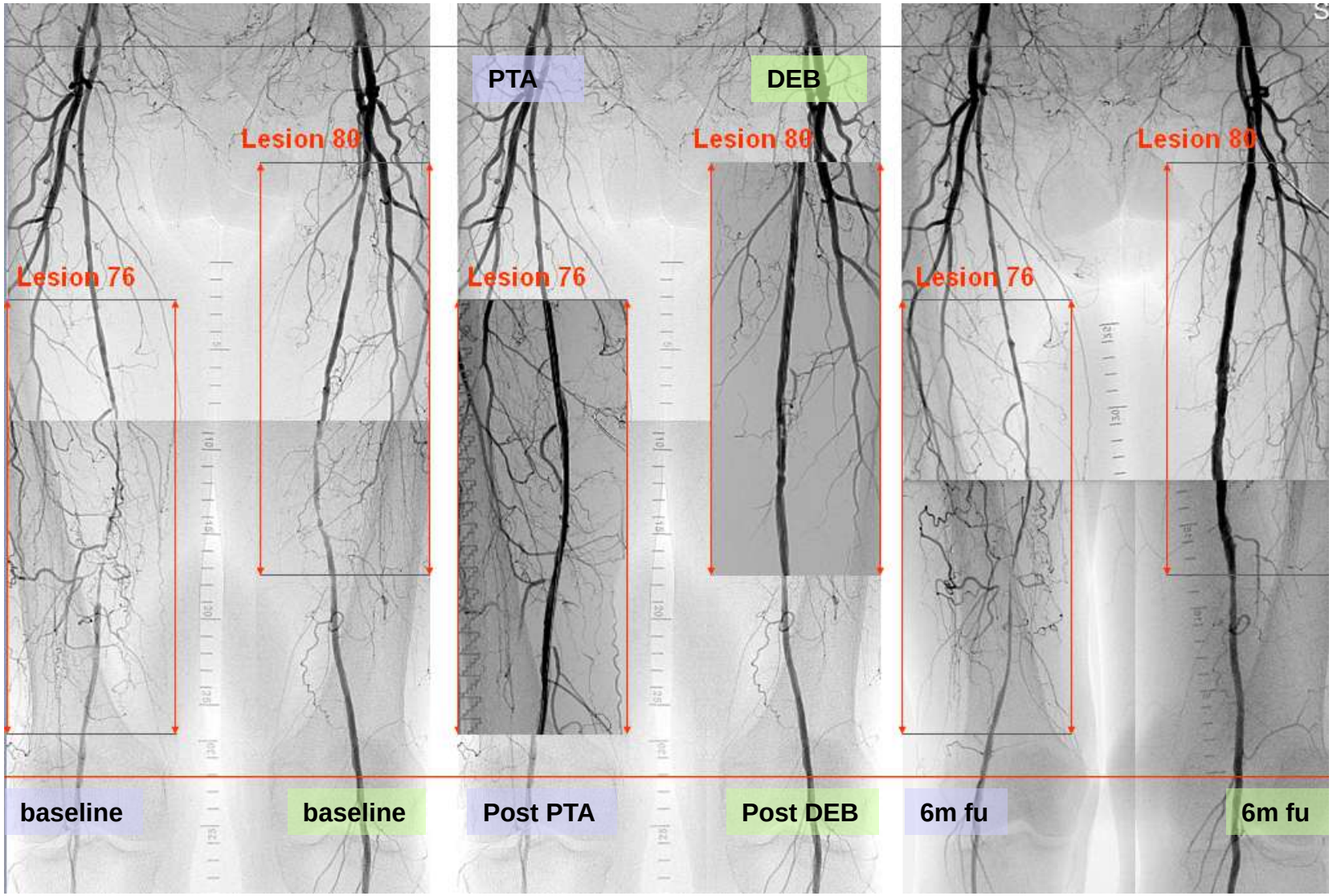




baseline **6m fu** **24m fu**

Case 4: Bilateral SFA disease

courtesy of M.Werk



IN.PACT SFA Pivotal RCT

IN.PACT Admiral DCB vs. standard PTA
for the treatment of superficial femoral and proximal popliteal artery disease due to claudication and rest pain

- Prospective, multicenter EU and US, randomized (2:1), single blinded
- Independent and blinded Duplex Ultrasound Core Lab [1], Angiographic Core Lab [2], and Clinical Events Committee [3]
- Independent Data Safety Monitoring Board [3]
- External monitoring with 100% source data verification
- Subjects followed up to 5 years

Gunnar Tepe,
Charing Cross, London, UK, 4.5.2014,
on behalf of IN.PACT SFA Invesigators