Role of DEBs For Infrainguinal Lesions (SFA/POP/BTK) In 2015 And The Future: What Is It And Will It Be In Primary And Recurrent Lesions And ISR

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Disclosure

Speaker name: .............................................. G. Biamino ..........................................................

I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☐ I do not have any potential conflict of interest

Do We need new long term concepts for peripheral infrainguinal interventions?

The SFA or the „BAD CONDUIT“

Prox Occlusion of SFA

LONG INFLATIONS TIME ( > 10 min)

Subintimal Angioplasty
EXCIMER LASER TECHNIQUE

Retrograde Approach for CTOs in Supine Patient-Position

Guidewire
Laser Catheter
Distal Marker
Orientation Band

STEP by STEP TECHNIQUE

RE-ENTRY-DEVICES

Initial Passage of a SFA Occlusion:
STILL A PROBLEM?

NO!

Crossing Success
~ 100%

The SFA or the "BAD CONDUIT"

Extension/Contraction
Flexion
Torsion
Compression
Gets worse with age
Age makes arteries longer and stiffer: shortening (up to ~25%) much better absorbed in youngers vs. elderlies

Stents and Stent’s side effects
Stents reduce vessel compliance and ability to absorb deformations

The Evidence on First and Second Generation Nitinol Stents
12 months restenosis vs. lesion length

Restenosis after SFA Stenting

Data from randomised trials

Patency (PSVR < 2.0) for Primary Zilver PTX vs. Standard Care (PTA with Provisional Bare Stenting)

Classified by visual estimate on angiography

Modified from Schillinger et al, EURO-PCR 2008

Data from randomised trials

Modified from Schillinger et al, TCT 2006

Tosaka et al, JACC 2012
Stabile E et al, JACC 2012
SFA: Bad Conduit for Implants

- Stent Fractures
  - may occur
  - may trigger restenosis
  - Long term incidence and implications remain unknown

In-Stent Restenosis
- 1-year incidence: 18 - 40%
- 2-year recurrency:
  - 49.9% in class I (focal)
  - 53.3% in class II (diffuse)
  - 84.8% in class III (occlusive)

Drug Eluting Balloon Value Proposition

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 in SFA in 2014: current evidence

7 Proof-of-Concept
1. Registry with 2-year functional outcome
2. Exploratory studies (DCB, Atherectomy, Ca++)
3. Meta-analysis

4 DCB in long lesions
- includes 1 retrospective DCB vs. DES and 1 RCT DCB/HVS vs. HVS
- IN.PACT SFA; IN.PACT SFA Japan; IN.PACT SFA China; IN.PACT SFA Italian Registry; PACIFIER; DEBELLUM; ISAR STATH; IN.PACT SFA Real World Leipzig; DEBATE SFA; IN.PACT Flexion; IN.PACT SFA ISR; PHOTOPAC; FAIR; ISAR PEBIS; PLAISIR; DEBATE ISR; IN.PACT ISR CDN

5 DCB for in-Stent-Restenosis
- includes 2 Registries and 2 RCTs
- IN.PACT fem-pop Clinical Program

DEB Proof of Concept Evidence - Overview
6 randomized controlled trials (6-month LLL Primary Endpoint)

1. G.Tape et al. - NEJM 2008
3. D.Scheiβert - TCT 2011 oral presentation
4. D.Scheiβert - EuroPCR 2011 oral presentation

IN.PACT fem-pop Clinical Program
24 IN.PACT Trials*, 4200+ Patients jointly covering the full spectrum of fem-pop PAD
IN.PACT Proof-of-Concept: PACIFIER

85 Patients RCT (Primary Endpoint 6m LLL):
- Potent inhibition of restenosis vs. PTA
- No PTX related adverse events
- Sustained TLR benefit at 2-year

(Werk M et al. Circulation CI 2012)

Metanalysis DCB vs. PTA

PacBexel-Coated Versus Uncoated Balloon Angioplasty Reduces Target Lesion Revascularization in Patients With Femoropopliteal Arterial Disease
A Meta-Analysis of Randomized Trials
Salvatore Cassese, MD; Robert A. Byrne, MD, BMS, DCB, Hyla-OH, MD; Cipri Nobile, MD; Mijajlo Nenajden, MD; Arian Karnieli, MD; Macarena Fossas, MD

4 proof of concept RCTs, 433 Patients
(median follow up: 10.3 months)
- DCBs show superior angiographic and clinical restenosis vs. PTA with comparable safety profile
  - Significant reduction of TLR, restenosis, and LLL
  - Comparable all cause mortality

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

IN.PACT ± Stent: DEBELUM

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 DCB outcomes

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

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

(Indirect) Meta-analysis DCB vs. BMS

11 RCTs: 1464 patients
Median follow up: 24m (DCB), 12m (BMS)

DCB and BMS vs. PTA
- Superior anti-restenotic efficacy
- DCB is at least as efficacious as BMS without safety tradeoffs

Fusaro M et al.  Paclitaxel-coated balloon or primary bare nitinol stent for revascularization of femoropopliteal artery: A meta-analysis of randomized trials versus uncoated balloon and an adjusted indirect comparison. Int J Cardiol. 2013 Jul 23

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

IN.PACT in long SFA lesions: Leipzig Registry

Real world 260-Patient Registry
- 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)

77.6% (all fem-pop) 82.4% (SFA only) 85.2% (ISR only)

(Schreiber A CIRSE 2013)
IN.PACT vs. DES in long SFA lesions

- Patients retrospective, propensity score analysis
- Non-significant difference between IN.PACT and Zilver PTX in long SFA lesions
- Prov. stent rate post DEB = 18.3%

IN.PACT + systematic stenting: DEBATE

- Randomized, 104 Patients, DEB+Stent vs. Stent
- DEB significantly improves stent results
- Restenosis ↓ maintain irrespective of lesion length and recanalization technique

LEVANT 2 Clinical Trial

Prospective, multicenter, randomized, controlled, single blind, comparing the
- Lutonix DCB vs. standard-balloon
In femoropopliteal lesions.
Primary endpoint: safety and primary patency at 1 y.
Clinical and Duplex FU at 6, 12, 24 months
(Blinded clinician to DUS)
N pts.: 476 randomized 2:1 / 55 global sites

Angiographic Characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>Standard PTA</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Two lesions treated</td>
<td>1.9% (6/316)</td>
<td>3.1% (5/160)</td>
<td>0.400</td>
</tr>
<tr>
<td>Total Lesion Length (mm)</td>
<td>62.9 ± 41.5 (315)</td>
<td>63.6 ± 40.3 (160)</td>
<td>0.866</td>
</tr>
<tr>
<td>Treated Length (mm)</td>
<td>107.7 ± 47.0 (316)</td>
<td>107.3 ± 49.3 (160)</td>
<td>0.933</td>
</tr>
<tr>
<td>Calcification</td>
<td>59.2% (187/316)</td>
<td>57.5% (92/160)</td>
<td>0.726</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>20.6% (65/316)</td>
<td>21.9% (35/160)</td>
<td>0.741</td>
</tr>
<tr>
<td>%DS post-treatment</td>
<td>23.4 ± 12.3 (316)</td>
<td>23.8 ± 12.3 (158)</td>
<td>0.703</td>
</tr>
<tr>
<td>Bail-out Stenting</td>
<td>2.5% (8/316)</td>
<td>6.9% (11/160)</td>
<td>0.022</td>
</tr>
<tr>
<td>Dissection</td>
<td>63.7% (200/314)</td>
<td>72.3% (115/159)</td>
<td>0.060</td>
</tr>
<tr>
<td>Procedural success</td>
<td>88.9% (281/316)</td>
<td>86.8% (138/159)</td>
<td>0.497</td>
</tr>
<tr>
<td>Device Success</td>
<td>99.5% (430/432)</td>
<td>100% (180/180)</td>
<td>0.367</td>
</tr>
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LEVANT 2 - Primary Patency

Freedom from TLR Kaplan-Meier
IN.PACT SFA Trial

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 (1:1), single blinded
- Independent and blinded Duplex ultrasound Core Lab
- Angiographic Core Lab
- Independent Data and Safety Monitoring Board
- External monitoring with 100% source data verification
- Subjects followed up to 5 years

Conclusions

• Compelling LEVEL I – Evidence supports the use of DCB as front-line therapy for femoro-popliteal revascularization
• Highest Primary Patency and lowest TLR
• Sustained QoL, functional benefit and walking improvement up to 2-year
• Encouraging evidence in long / complex SFA lesions
• NO DCB Class Effect

VASCULAR NEWS

Lutonix drug-eluting balloon receives FDA approval

The FDA has approved the Lutonix drug-eluting balloon (Bard) for the management of stenosis in the superficial femoral arteries or in the popliteal arteries. This is the first time that the agency has approved such a device for this indication in the USA.

VASCULAR NEWS

IN.PACT Admiral drug-eluting balloon (Medtronic) receives FDA approval

In the IN.PACT SFA trial, the device demonstrated the lowest clinically-driven target lesion revascularisation rate (2.4%) ever reported for an interventional treatment of peripheral arterial disease in the superficial femoral artery.
Sustained Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA

John R. Laird, MD; Peter A. Schneider, MD; Gunnar Tepe, MD; Marianne Brodmann, MD; Thomas Zeller, MD; Christopher Metzger, MD; Prakash Krishnan, MD; Dierk Scheinert, MD; Antonio Micari, MD, PhD; David J. Cohen, MD, MSc; Hong Wang, MD, MPH; Melissa S. Hasenbank, PhD; Michael R. Jaff, DO


Methods: 331 patients (2 to 4) with femoropopliteal lesions up to 18 cm in length were enrolled. Patients were randomly assigned in a 2:1 ratio to treatment with DCB or PTA.

The 24-month assessments included primary patency, freedom from (CD-TLR), major adverse events, and quality of life and functional outcomes as assessed by the EuroQOL-5D quality-of-life questionnaire, walking impairment questionnaire, and 6-min walk test.

Results: At 24 months, patients treated with DCB showed significantly higher primary patency when compared with PTA (78.9% vs. 50.1%; p < 0.001). The rates of CD-TLR were 9.1% and 28.3% (p < 0.001) for the DCB and PTA groups, respectively.

Both groups showed similar functional improvement at 2 years, although DCB patients achieved this level of function with 58% fewer reinterventions.

Potential Dimensions of the Problem:

SFA-In-Stent-Restenoses

- USA: Estimated Number of Transcutaneous Interventions in the Femoropopliteal Tract in 2014: 220,000
- 55-60% Stenting = 121,132.00
- > 65,000 In-Stent-Restenoses / y

Millenium Research Group, 2014

Drug-Eluting Balloon for Treatment of Superficial Femoral Artery In-Stent Restenosis

- 92.2% Primary Patency rate at 1 yrs
- 70.3% Primary Patency rate at 2 yrs

Virga V et al., JACC Cardiovasc Int 2014

Tosaka et al, JACC 2012

Stabile E et al., JACC 2012
One-year outcomes from the IN.PACT Global Study in complex ISR lesions in the SFA

This single-arm, multicenter, prospective study: with independent core laboratory and clinical events committee adjudication included 131 patients with pure de novo ISR lesions. The one-year primary patency rate for this patient subgroup was 88.7%.

Considering the mean lesion length of $17.2 + 10.5$ cm the CD-TLR rate was with 7.3% very low.

DCB is a proven primary therapy for SFA disease.

The latest clinical results demonstrating consistency, safety, efficacy and cost-effectiveness will continue to drive a paradigm shift in SFA interventions.

**DCB and Optimal PTA**

1. Pre-dilatation (CTOs, sub-occl. lesions, Ca++)
   a. Invasive PTA if needed to re-enter RND
   b. Balloon length = lesion length + planned DCB length, whichever is longer
   c. Inflation pressure = RBP as needed to reach full PTA balloon expansion

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

3. Post-Dilatation if residual stenosis >50% or flow limiting dissection
   a. Invasive or high pressure PTA balloon Ø 1:1 to RVD
   b. Inflation time = ≥ 3 minutes
   c. Inflation pressure = <RBP as needed to reach full PTA balloon expansion

4. Provisional Spot Stenting for persistent residual stenosis >50% or flow limiting dissections
   a. Standard or high pressure PTA balloon Ø 1:1 to RVD
   b. Spot Stent length = necessary to fully treat the residual stenosis or dissection
   c. Inflation time = ≥ 3 minutes

**Angioplasty with Uncoated Balloons (POBA)**

**Leipzig Experience with DEB BTK**

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<tr>
<th></th>
<th>POB BTK</th>
<th>DEB BTK</th>
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<tbody>
<tr>
<td>Lesion-length</td>
<td>183 mm</td>
<td>173 mm</td>
</tr>
<tr>
<td>Restenosis &gt;50 % @ 3 Mo</td>
<td>69 %</td>
<td>27 %</td>
</tr>
<tr>
<td>% restenosis reduction</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Length of restenosis</td>
<td>155 mm</td>
<td>64 mm</td>
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**DEB vs. PTA in BTK (RCT)**

- **DEBATE BTK** randomized Trial - IN.PACT vs. PTA
  - Lesion length 12.8 cm (DEB) / 13.0 cm (PTA)
  - 12-m TLR = 18.5% (DEB) vs. 43.3% (PTA) (p=0.003)
  - 12-m Wound Heal. Rate (WHR) 86% (DEB) vs. 67% (PTA) (p=0.01)

- 59% TLR $p=0.003$
- 28% WHR $p=0.01$
DEB vs. PTA in BTK (RCT)
*Impact deep - Medtronic Press Release*

- No biological efficacy (identical LLL)
- Trend towards more major amputations in the DEB cohort

**What to do now in long lesions?**
- Continue with new studies using alternative coating technologies

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**Follow – Re-interventions**

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<th>N=220</th>
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<tbody>
<tr>
<td>BTK re-intervention</td>
<td>22.7</td>
</tr>
<tr>
<td>(including pre-planned secondary interventions), %</td>
<td></td>
</tr>
<tr>
<td>Time to 1st re-intervention (months), mean± std</td>
<td>7.6±4.8</td>
</tr>
<tr>
<td>Target lesion revascularization, %</td>
<td>15.9</td>
</tr>
<tr>
<td>Time to 1st target lesion revascularization (months), mean± std</td>
<td>8.1±4.7</td>
</tr>
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Courtesy of S.Steiner

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**Freedom from target lesion revascularization**

- 6 months: 89%
- 12 months: 77%

Courtesy of S.Steiner

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**Discrepancy between limb salvage (LS) and wound healing (WH) rate**

- Approximately 20% CLI patients are free from death and amputation without complete wound healing.

Courtesy of O.Iida

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The End