Role of Drug Coated Balloon, Drug Eluting stent and Lithoplasty

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Disclosures

I have had a financial interest/arrangement or affiliation with the organizations(s) listed below

• Advisory  
  – NONE

• Training  
  – NONE

• Royalties  
  – NONE

• Research  
  – NONE

• Stock  
  – NONE

• Other  
  – NONE
Evaluation of intervention
Evaluation of intervention
Balloon Angioplasty

- Early vascular recoil
- Negative vascular remodeling
- Excessive neointimal proliferation
- Occlusive plaque dissection
Bare Metal stent

In-stent restenosis due to

• Initial vascular injury
• Metallic prosthesis leading to excessive neointimal proliferation.
Drug eluting stent

In-stent thrombosis

• Delay vascular healing initially due to anti proliferative effect
• Hypersensitivity reaction to drug, polymer coating or combine
PTA Vs BMS in PAD
Restenosis rates at 12 months after balloon angioplasty vs primary stent implantation in the superficial femoral artery in 4 randomized, controlled trials using nitinol self-expanding stents.

Schillinger M, and Minar E Circulation. 2012;126:2433-2440
Drug Coated Balloon
Two FDA Approved Drug Coated Balloon

- LUTONIX (Brad peripheral vascular)
- IN.PACT admiral/IN.PACT pacific (medtronic)
Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease

Kenneth Rosenfield, M.D., Michael R. Jaff, D.O., Christopher J. White, M.D., Krishna Rocha-Singh, M.D., Carlos Mena-Hurtado, M.D., D. Christopher Metzger, M.D., Marianne Brodmann, M.D., Ernst Pilger, M.D., Thomas Zeller, M.D., Prakash Krishnan, M.D., Roger Gammon, M.D., Stefan Müller-Hülsbeck, M.D., Mark R. Nehler, M.D., James F. Benenati, M.D., and Dierk Scheinert, M.D., for the LEVANT 2 Investigators*
LEVANT 2 Trial

To check primary patency and safety of LUTONIX 0.35” (Paclitaxel coated) DCB Vs standard angioplasty at end of 12 months.

- **Prospective, randomized (2:1), multicenter, single blinded trial**
- **Total of 476 enrolled**
  - 316 to LUTONIX 0.35” and 160 Balloon PTA
- **Subject to 12 months follow up**
Primary Patency

Figure 1. Kaplan–Meier Curves for Primary Patency at 12 Months.
Primary patency was defined as the absence of target-lesion restenosis (defined by core-laboratory adjudication) and target-lesion revascularization (adjudicated by the clinical-events committee).

LEVANT 2 Trial
Figure 2. Kaplan–Meier Curves for the Composite Safety Outcome at 12 Months.

The safety outcome was a composite of freedom from perioperative death from any cause (≤30 days after the procedure) and freedom at 12 months from index-limb amputation, index-limb revascularization, or index-limb–related death.
Conclusion

• Among the symptomatic femoropopliteal peripheral artery disease, PTA with a paclitaxel-coated balloon (DCB) resulted in a rate of primary patency at 12 months that was higher than the rate with angioplasty with a standard balloon.

• The drug-coated balloon was noninferior to the standard balloon with respect to safety.
INPACT SFA trial
IN.PACT SFA Trial

To assess safety and efficacy of IN.PACT Admiral ECB to PTA in SFA and proximal popliteal artery due to IC and rest pain

- **Prospective, randomized** (2:1), multicentre, single blinded trial

- Total of 331 enrolled
  - IN.PACT DCB (n=220) Vs PTA (n=111)

- Subjects followed **for 5 years**
Primary Patency

Log-rank $P < 0.001$

- **DCB**
- **PTA**

Time After Index Procedure (Months)

- **Number at risk**
  - DCB: 220, 213, 192, 149, 121
  - PTA: 111, 108, 69, 52, 41

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤ 2.4) and clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)
2. Number at risk represents the number of evaluable subjects at the beginning of the each 30-day window
Log-rank $P < 0.001$

**Freedom from Clinically-driven Target Lesion Revascularization**

- **DCB** (Red Line): 84.5%
- **PTA** (Blue Line): 70.4%

<table>
<thead>
<tr>
<th>Time After Index Procedure (Months)</th>
<th>DCB</th>
<th>PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>220</td>
<td>111</td>
</tr>
<tr>
<td>6</td>
<td>215</td>
<td>108</td>
</tr>
<tr>
<td>12</td>
<td>205</td>
<td>93</td>
</tr>
<tr>
<td>18</td>
<td>175</td>
<td>78</td>
</tr>
<tr>
<td>24</td>
<td>153</td>
<td>70</td>
</tr>
</tbody>
</table>

1. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.
Conclusion

• **Superior** and **durable** (for **3 years**) effect of paclitaxel-coated balloon **DCB** Vs **PTA** with significant high primary patency rate

• Similar functional status improvement with fewer repeat intervention with **DCB** Vs **PTA**
IN.PACT Global Study

- **Real world**, prospective, multicenter, single arm study for IN.PACT Admiral balloon for femoropopliteal study
- Total of 1535 enrolled
- Including **CTOs ≥ 50 mm**, **ISR**, **long lesion ≥ 15 cm**, **calcified lesion**
- Including pt treated with **DCB of 150 mm**
**Objective:** Expand clinical evidence of the IN.PACT™ Admiral™ DCB in the treatment of a real-world patient population

**Clinical Cohort:**
- **1416 Subjects**

**Pure Imaging Cohorts:**
- **de novo ISR 131 Subjects**
  - VIVA 2015 M. Brodmann
- **Long Lesion (≥15 cm) 157 Subjects**
  - EuroPCR 2015 D. Scheinert
- **CTO (≥25 cm) 126 Subjects**
  - Charing Cross 2016 G. Tepe

**150 mm DCB Cohort:**
- **119 Subjects**

**1535 Subjects Enrolled**
IN.PACT Global Clinical Cohort
Primary Endpoint: Freedom from CD-TLR through 1 Year

Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.
Conclusion

• Real world experience of **efficacy** of the IN.PACT Admiral DCB in **diverse groups** of patient at 1 year

• Not randomized
Case Study

- 64 years female with HTN, DM, Dyslipidemia. H/o Atherectomy followed by BMS for CTO of distal left SFA
Case Study
Case Study
Drug Coating Stent
Drug Coated Stent

Zilver® PTX®: drug-eluting stent.
Zilver PTX® stent

- FDA approved for femoropopliteal lesion
- Scaffold + Anti proliferative drug
  Scaffold: Zilver Flex 35® platform
  Drug: Paclitaxel
    With out polymer or binder
    3 microgram/ mm² dose density
Zilver PTX Trial

• **Prospective, randomized, multicenter**

• Reference vessel diameter **4-9 mm**

• Symptomatic *de novo* or restenotic **femoropopliteal** lesion above the knee

• Follow up to the **5 years**
Zilver PTX Study Design

Primary Randomization

Enrollment
N= 479

PTA
N= 238

Failed PTA
N= 118

Successful PTA
N= 120

Secondary Randomization

Provisional
BMS
N= 59

Provisional
Zilver PTX
n= 61

63% patient received Zilver PTX
5-year Freedom from TLR

Zilver PTX vs. Standard Care

83.1% Zilver PTX

67.6% Optimal PTA + BMS

At 5 years, Zilver PTX demonstrates a 48% reduction in reintervention compared to standard care
5-year Primary Patency (PSVR < 2.0)

Zilver PTX vs. Standard Care

At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to standard care.

<table>
<thead>
<tr>
<th>Years (LESIONS)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zilver PTX</strong></td>
<td>At Risk</td>
<td>318</td>
<td>246</td>
<td>199</td>
<td>163</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>Failed</td>
<td>1</td>
<td>48</td>
<td>71</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td><strong>Standard Care</strong></td>
<td>At Risk</td>
<td>183</td>
<td>108</td>
<td>64</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Failed</td>
<td>0</td>
<td>57</td>
<td>73</td>
<td>79</td>
<td>84</td>
</tr>
</tbody>
</table>

$p < 0.01$ log-rank
Conclusion

• Zilver PTX (DES) provide **sustained safety** and **clinical durability**

• **5 year data** for zilver PTX vs Standard of care (PTA or BMS)
  - More then 40% reduction in restenosis and reintervention
  - Durable effect **with out “late catch up”**
## Case Study

### Zilver PTX results

<table>
<thead>
<tr>
<th>Preimplantation</th>
<th>Postimplantation</th>
<th>12-month follow-up</th>
<th>12-month IVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
DCB Vs DES
DCB Vs DES

- **Retrospective**, dual center study
- Total of 282 randomized
  - IN.PACT Admiral/ Pacific (DCB) 177 Vs Zilver PTX (DES) 105
- ≥ **100 mm lesions** were treated

J Endovasc Ther. 2014;21:359–368
DCB Vs DES

A

Freedom from TLR, %

0 1 3 6 9 11 12

DCB DES

Months

B

Event-Free Survival, %

0 1 3 6 9 11 12

DCB DES

At risk

Months 0 1 3 6 9 11 12
DCB 131 125 123 118 109 93 85
DES 97 97 94 82 76 66 61

J Endovasc Ther. 2014;21:359–368
Conclusion

• DCB and DES equally better for endovascular treatment for femoropopliteal lesion ≥ 10 cm

• Both modality better then tradition endovascular treatment (PTA or BMS)
What we learn: Drug elusion works

• Both DCB and DES showed positive drug effect then traditional PTA or BMS

• How long the drug effect last
  - 3 years data for DCB
  - 5 years data for DES
Issue with DES

- Liming future revascularization option
- Anatomical limitation
  - Ostial lesion
  - Lesion at or below the knee
  - Small vessels
- Stent fracture
Issue with DCB

• Calcium- hard plaque => Elastic recoil
• Calcium => dissection
## Existing Atherectomy + DCB Data

Few reports – Two single-center studies and one randomized feasibility study

<table>
<thead>
<tr>
<th>Study (* Core Lab)</th>
<th>Type</th>
<th>Patients</th>
<th>Lesions</th>
<th>Dissection$^4$</th>
<th>BO Stent</th>
<th>30-day MAE</th>
<th>1-year</th>
<th>&gt;1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>*DEFINITIVE AR$^1$</td>
<td>DCB$^+$</td>
<td>54</td>
<td>54</td>
<td>19% (10/54)</td>
<td>3.7% (2/54)</td>
<td>NR</td>
<td>89.6%</td>
<td>93.4%</td>
</tr>
<tr>
<td></td>
<td>DAART$^+$</td>
<td>48</td>
<td>48</td>
<td>2% (1/48)</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DAART-Ca</td>
<td>19</td>
<td>19</td>
<td>0%</td>
<td>5.3% (1/19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cioppa$^2$</td>
<td>DAART</td>
<td>30</td>
<td>30</td>
<td>6.7% (2/30)</td>
<td>6.7% (2/30)</td>
<td>13% (4/30) (1-year)</td>
<td>90%</td>
<td>?</td>
</tr>
<tr>
<td>Stavroulakis$^3$</td>
<td>DAART</td>
<td>21</td>
<td>26</td>
<td>NR</td>
<td>NR</td>
<td>14% (3/21)</td>
<td>95%</td>
<td>90% (18-mo)</td>
</tr>
</tbody>
</table>

1. “DEFINITIVE AR: A Pilot Study of Antirestenosis Treatment. 12-month Results: Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency” presented by Zeller T, VIVA Las Vegas 2014. † Randomized arms included DCB and directional atherectomy plus DCB (DAART). A non-randomized arm, “DAART-Ca”, was also enrolled in DEFINITIVE AR, but DUS patency is unavailable for the 19 subjects in this arm.


4. Zeller, et al., defined dissection as ≥ Grade C while Cioppa, et al., defined dissection via chroma-flow involving more than 60% of cross-sectional diameter with blood flow in the false lumen.
Conclusion

• **Vessel preparation** is a critical step in enhancing DCB effectiveness

• While **PTA** best practices may be adequate in **non-calcified lesions**, **atherectomy** may be indicated in **calcified lesions**

• The **marriage** of **atherectomy** and **DCB** may bring together the best of two worlds – effective plaque modification / debulking paired with sustained drug presence

• More studies, such as the recently initiated REALITY study, may shed more light on this combination approach to femoropopliteal artery lesions
REALITY Study

• Study is sponsored by the VIVA Physician Organization and funded in part by an external research project grant from Medtronic plc

• The REALITY Study evaluates patient outcomes with adjuctive use of Medtronic HawkOne™ or Medtronic TurboHawk™ and Medtronic IN.PACT™ Admiral™ drug-coated balloon.

• The multi-center, international, prospective, single-arm study will enroll up to 250 subject at up to 15 sites.
  – Co-PI: Krishna Rocha-Singh, MD, Prairie Heart Institute of Illinois
  – Co-PI: Brian DeRubertis MD, FACS, UCLA Division of Vascular Surgery
  – 10 US sites enrolling patients with lesions up to 18cm
  – 3 German sites enrolling patients with lesions up to 25cm

• Primary Endpoints
  – Primary Effectiveness: Primary patency of patients with long, moderate and severely calcified femoropopliteal artery lesions at 12 months
  – Primary Safety: Freedom from major adverse events and clinically-driven target vessel revascularization through 30 days

• Follow-up through 24-months
  – Angiographic and duplex ultrasound core lab adjudication of primary patency at 12 months
  – Clinically-driven target lesion revascularization (CD-TLR) evaluated through 24 months
Algorithm for drug elusion

Modify the plaque + Low pressure PTA

- Sub optimal and failed PTA
  - Need Scaffold (DES)
- Optimal PTA
  - DEB
    - If flow limiting dissection then
      - BMS
Paradigm shift of peripheral intervention

• Open aortic valve replacement to endo vascular aortic valve replacement

• Coronary stenting moved to drug elution

• Peripheral intervention moved to drug elution
Lithoplasty
• Litho (stone) + Tripsy (break) = lithotripsy
• Lithotripsy + Angioplasty = Lithoplasty
Litho plastic

- Intermittent pulsatile mechanical energy to disrupt the internal and external calcium then low pressure balloon inflation
## Safety and Acute performance

<table>
<thead>
<tr>
<th></th>
<th>1 Months (n=95)</th>
<th>6 Months (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency surgical revascularization</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Major amputation</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombus or distal emboli</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Peroration or Major dissection (≥D)</td>
<td>1.1%(1)</td>
<td>1.1%(1)</td>
</tr>
</tbody>
</table>

**Graph:**
- Pre-Proc: 77.8%
- Post-Proc: 23.8%
Lithoplasty

• Currently under investigation
Thank you