The importance of scientific evidence

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Disclosure

Speaker name:

.........I. Baumgartner..............................................................

I have the following potential conflicts of interest to report:

☐ Consulting

☐ Employment in industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

☐ X Other(s)

- educational grant COOK

☐ I do not have any potential conflict of interest
Understanding strengths and shortcomings of each trial ... is more important and challenging than ever

Prof. M. Jaff
~ all DCBs passed «Proof-of-Concept» Test

6-month LLL from 7 Trials / 6 DCB Technologies

Class Effect? NO!
just a signal of ~consistent biologic response

6. D.Scheinert – LINC 2013 oral presentation
Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs

Review: Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs
Comparison: 2 Drug-eluting balloon (DEB) versus uncoated balloon angioplasty at twelve months
Outcome: 5 Target lesion revascularization

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Drug-eluting balloons n/N</th>
<th>Uncoated balloons n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOLUX P-I</td>
<td>4/33</td>
<td>10/35</td>
<td>4.5 %</td>
<td>0.34 [0.10, 1.24]</td>
</tr>
<tr>
<td>BIOLUX P-II</td>
<td>10/50</td>
<td>10/55</td>
<td>4.0 %</td>
<td>1.13 [0.42, 2.98]</td>
</tr>
<tr>
<td>DEBATE:BTK 2013</td>
<td>12/65</td>
<td>29/67</td>
<td>12.2 %</td>
<td>0.30 [0.13, 0.65]</td>
</tr>
<tr>
<td>DEBELLEUM 2012</td>
<td>5/35</td>
<td>17/40</td>
<td>7.1 %</td>
<td>0.23 [0.07, 0.70]</td>
</tr>
<tr>
<td>FemPac 2006</td>
<td>6/45</td>
<td>21/42</td>
<td>9.9 %</td>
<td>0.15 [0.05, 0.44]</td>
</tr>
<tr>
<td>IN.PACT DEEP 2014</td>
<td>27/239</td>
<td>15/119</td>
<td>9.3 %</td>
<td>0.88 [0.45, 1.73]</td>
</tr>
<tr>
<td>IN.PACT SFA 2015</td>
<td>5/220</td>
<td>22/111</td>
<td>15.0 %</td>
<td>0.09 [0.03, 0.26]</td>
</tr>
<tr>
<td>LEVANT I 2014</td>
<td>13/37</td>
<td>14/36</td>
<td>4.7 %</td>
<td>0.93 [0.36, 2.39]</td>
</tr>
<tr>
<td>LEVANT II 2015</td>
<td>35/316</td>
<td>24/160</td>
<td>14.8 %</td>
<td>0.71 [0.40, 1.23]</td>
</tr>
<tr>
<td>PACIFIER 2012</td>
<td>3/44</td>
<td>15/47</td>
<td>7.1 %</td>
<td>0.16 [0.04, 0.59]</td>
</tr>
<tr>
<td>THUNDER 2006</td>
<td>5/48</td>
<td>23/54</td>
<td>11.5 %</td>
<td>0.13 [0.04, 0.38]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1132 768 100.0 % 0.40 [0.31, 0.51]

Total events: 125 (Drug-eluting balloons), 203 (Uncoated balloons)
Heterogeneity: Chi² = 35.95, df = 10 (P = 0.00009); I² = 72%
Test for overall effect: Z = 7.19 (P < 0.00001)
Test for subgroup differences: Not applicable
Scientific evidence

Trials had differences in the way in which they inserted the balloons, and in the type and duration of additional antiplatelet (anticlotting) therapy, leading to downgrading of the quality of the evidence.
Why you can’t compare trials: Trial Design

Zilver PTX Randomized Trial

DCB Trial Designs

Included in PTX Trial

Excluded in DCB Trials
Why you can’t compare trials: PSVR threshold

<table>
<thead>
<tr>
<th>Zilver PTX</th>
<th>Supera 500</th>
<th>In.Pact Admiral</th>
<th>Lutonix</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSVR</td>
<td>2.0</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

PSVR ≥ 2.0
(≥~40% stenosis)

PSVR ≥ 2.5
(≥~50% stenosis)

Why you can’t compare trials: PSVR threshold

11% DROP IN PATENCY!

Secondary Effectiveness Endpoints
12-Month Patency – PSVR Levels

<table>
<thead>
<tr>
<th>Threshold for Binary Restenosis</th>
<th>Test DCB</th>
<th>Control PTA</th>
<th>Difference % [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUS PSVR 2.5 (per original protocol)</td>
<td>64.0%</td>
<td>52.6%</td>
<td>12.6% [0.015]</td>
<td>✓</td>
</tr>
<tr>
<td>DUS PSVR 2.0</td>
<td>53.2%</td>
<td>8.2%</td>
<td>45.0% [0.130]</td>
<td>❌</td>
</tr>
</tbody>
</table>

Patency endpoint significant at PSVR of 2.5 and 3.0. Patency endpoint not significant at PSVR 2.0.
So, if we don’t compare trials, what’s the basis for device selection?

Two things:
1. Long-term performance in RCTs (Level 1 data).
2. Consistent performance across multiple trials.
Global Clinical Program

Pre-Market Studies

- **RCT**
  - Moderate lesions
  - PTA
    - Optimal n=118
    - Sub-optimal
      - Zilver Flex n=56
      - Zilver PTX n=63
      - Zilver PTX n=787
- **SAS**
  - More complex lesions
  - Zilver PTX n=242
- **China**
  - Similar lesions to RCT
  - Zilver PTX n=178

Post-Market Studies

- **Japan**
  - PMS All-comers
  - Zilver PTX n=905
- **US PAS**
  - Similar lesions to RCT
  - Zilver PTX n=200
- **EU**
  - Longer Lesions
  - Zilver PTX n=45
- **XPEDITE**
  - Next Generation Coating
  - Zilver PTX n=150

More than 2500 patients included in current Zilver PTX clinical program
At 5 years, Zilver PTX demonstrates a 48% reduction in reintervention compared to standard care.
At 5 years, Zilver PTX demonstrates a 47% reduction in reintervention compared to BMS.
Long-term performance in RCTs (Level 1 data)

4-Year Primary Patency (PSVR 2.0)
Zilver PTX in Diabetic Patients

Zilver PTX results are similar in diabetic and non-diabetic patients

- Non-Diabetics: 69.3%
- Diabetics: 65.9%

$p = 0.50$ (log-rank test)
### Long-term performance in RCTs (Level 1 data)
Consistent performance across multiple trials

<table>
<thead>
<tr>
<th>Key Study Criteria</th>
<th>Zilver PTX RCT</th>
<th>Zilver PTX SAS</th>
<th>Zilver PTX Japan PMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No significant untreated inflow tract stenosis</strong></td>
<td></td>
<td></td>
<td>ALL patients treated with Zilver PTX enrolled (up to enrollment limit), NO exclusion criteria</td>
</tr>
<tr>
<td><strong>At least one patent runoff vessel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum 2 Zilver PTX stents per lesion</strong></td>
<td></td>
<td><strong>Maximum 4 Zilver PTX stents per patient</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Lesion length ≤ 14 cm</strong></td>
<td></td>
<td><strong>No exclusions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>One lesion per limb</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No prior stent in SFA</strong></td>
<td><strong>ISR included</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Excluded if serum creatinine &gt; 2.0, renal failure, or dialysis</strong></td>
<td></td>
<td><strong>No exclusions</strong></td>
<td></td>
</tr>
</tbody>
</table>

| **Antiplatelets** | Clopidogrel or ticlopidine recommended for 60 days, aspirin indefinitely |
| **Follow-up** | 5 years | 2 years | 5 years |
| **Patency** | DUS core laboratory analysis | DUS site analysis |
| **Stent Integrity** | X-ray core laboratory analysis |

Increasingly complex patients and lesions

*These studies included previously stented lesions that are outside of the approved indication for use in the US.*
### Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>SAS</th>
<th>Japan PMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>247</td>
<td>900</td>
<td>1080</td>
</tr>
<tr>
<td>Lesion length (cm)</td>
<td>6.6 ± 3.9 *</td>
<td>10.0 ± 8.2 *</td>
<td>14.6 ± 9.6</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>81 ± 16 *</td>
<td>85 ± 16 *</td>
<td>92 ± 11</td>
</tr>
<tr>
<td>Total occlusions</td>
<td>30% *</td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>0% *</td>
<td>15%*</td>
<td>19%</td>
</tr>
<tr>
<td>Patent runoff vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0%*</td>
<td>0%*</td>
<td>7%</td>
</tr>
<tr>
<td>1</td>
<td>22%*</td>
<td>19%*</td>
<td>32%</td>
</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td>9%*</td>
<td>11%*</td>
<td>21%</td>
</tr>
<tr>
<td>ABI</td>
<td>0.67 ± 0.20*</td>
<td>0.64 ± 0.28</td>
<td>0.63 ± 0.18</td>
</tr>
</tbody>
</table>

* p < 0.01 compared to Japan PMS

- p-value for patent runoff vessels calculated based on 0 to 3 vessels
- p-value for CLI based on all reported Rutherford values (1 to 6)
Consistent performance across multiple trials

Demographics & Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>SAS</th>
<th>Japan PMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>236</td>
<td>787</td>
<td>905</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>$68 \pm 10 ,*$</td>
<td>$67 \pm 10 ,*$</td>
<td>$74 \pm 9$</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>66%</td>
<td>73%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>50% *</td>
<td>36% *</td>
<td>59%</td>
</tr>
<tr>
<td><strong>High cholesterol</strong></td>
<td>76% *</td>
<td>58%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>89%</td>
<td>80% *</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Pulmonary disease</strong></td>
<td>19% *</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
<td>10% *</td>
<td>11% *</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>0% *</td>
<td>Not assessed</td>
<td>35%</td>
</tr>
</tbody>
</table>

* $p < 0.01$ compared to Japan PMS

*a* eGFR < 60 mL/min/1.73m² and/or on dialysis
Consistent performance across multiple trials

**Freedom from TLR**

TLR rate consistent despite more complex lesions

<table>
<thead>
<tr>
<th>Years</th>
<th>Freedom from TLR (n=patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT (n=305)</td>
</tr>
<tr>
<td>1</td>
<td>91.6%</td>
</tr>
<tr>
<td>2</td>
<td>85.7%</td>
</tr>
<tr>
<td>3</td>
<td>83.3%</td>
</tr>
<tr>
<td>4</td>
<td>82.8%</td>
</tr>
</tbody>
</table>
Chronic Renal Failure

eGFR < 60mL/min/1.73m² and/or dialysis

• Higher incidence of diabetes (69% vs. 53%) in the CRF group
• Lower rate of total occlusions (34% vs. 45%) in the CRF group
• No other significant demographic or lesion differences
Consistent performance across multiple trials

Subgroup Analyses

Chronic Renal Failure

Freedom from TLR rates are similar through 2 years

\[ p = 0.24 \]
Patients who did not have any continuous patent runoff vessels to the foot

- Higher incidence of CLI (45% vs. 20%) in the no runoff group
- No other significant demographic or lesion differences

Japan PMS
n = 905

- No runoff vessels
  n = 54 (7%)
- ≥1 runoff vessel
  n = 846
Consistent performance across multiple trials

Subgroup Analyses

No Patent Runoff Vessels

Freedom from TLR rates are similar through 2 years

\[ p = 0.87 \]
In-stent restenosis is outside of the approved indication for use in the US

- Higher incidence of hypercholesterolemia (70% vs. 59%) and lower ABI (0.59 vs. 0.64) in the ISR group
- Longer lesion length (17.8 vs. 14.0 cm) in the ISR group
- No other significant demographic or lesion differences

Consistent performance across multiple trials

Subgroup Analyses

In-Stent Restenosis

Japan PMS
n = 905

ISR
n = 175
(19%)

Non ISR
n = 730
In-Stent Restenosis

Consistent performance across multiple trials

Subgroup Analyses

Nearly similar outcomes for ISR and non-ISR patients

p = 0.05
Conclusion

- Long-term, level I RCT evidence as well as consistent results across “real-world” registries are needed to aid in clinical decision making
  - Zilver PTX shows promising results through 5-year in the randomized control trial
  - Despite having more “real-world” patients and lesions, the Zilver PTX SAS and JPMS studies show similar results to the RCT
The importance of scientific evidence

Prof. I. Baumgartner
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