Paclitaxel-Eluting Balloon Valvuloplasty to Prevent Restenosis in an Animal Model of Aortic Stenosis

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- I have the following potential conflicts of interest to report:
  - Research contracts
  - 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
BAV and Restenosis components

- **Recoil**
  - Immediate in ~20% of patients no acute improvement (no change or ≤0.1 cm² ↑ in AVA)
  - Late (12h to 30 days) conflicting data

- **Hyperplastic reaction**
  Histologic changes in restenosed valves differ from those seen initially in calcific AS and they exhibit:
  - Zones of active capillary growth
  - Zones of cellular proliferation
  - Granulation tissue
  - Fibrosis
  - Ossification
The scarring component of restenosis is evident as early as a few days post-BAV. Young scar tissue gradually fills up splits between commissures, small tears or lacerations in the collagenous valve stroma and fractures in calcifications.

Paclitaxel-eluting valvuloplasty balloon

DIOR II™ Technology (Eurocor GmbH)

- Paclitaxel loading/balloon surface: 3 µg/mm²
- Coating method: directly on balloon surface, 1:1 mixture of aleuritic & shellolic acid with Paclitaxel
- Complete drug release @ 30 sec
Paclitaxel-eluting balloon valvuloplasty in healthy pigs: Tissue concentrations

- 8 healthy domestic pigs
- BAV with 22/24 mm paclitaxel-eluting balloons (3 µg/mm², DIOR technology)
- Randomly 2 or 4 X 15-second inflations

<table>
<thead>
<tr>
<th>Location</th>
<th>µg/ml</th>
<th>2 inflations</th>
<th>4 inflations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao root</td>
<td>µg/ml</td>
<td>0.13±0.09</td>
<td>0.32±0.26</td>
</tr>
<tr>
<td>AV leaflets</td>
<td>µg/ml</td>
<td>0.34±0.05</td>
<td>1.48±1.86</td>
</tr>
<tr>
<td>LVOT</td>
<td>µg/ml</td>
<td>0.06±0.03</td>
<td>0.07±0.01</td>
</tr>
</tbody>
</table>

Spargias et al, JOIC 2009, 22:291-8
Study protocol based on an animal model of AS

• Cholesterol-rich diet (0.5% cholesterol) + 50000 IU/day Vit. D2*

  3 months

• General anaesthesia, TTE
• Access: right carotid artery, Aortography
• Pressure measurements of the ascending aorta and left ventricle
• BAV randomly with coated or uncoated balloon (8.0/20 mm, 3x10 sec)

3 weeks

• General anaesthesia, TTE
• Access: right femoral artery, Aortography
• Pressure measurements of the ascending aorta and left ventricle

• Histology (Masson’s trichrom in all, PCNA in last 16)

*Drolet et al, JACC 2003;41:1211
53 rabbits started the diet

13 died

20 assigned to paclitaxel-coated balloon

6 died

14 completed study
14 for analysis
8 full histology

20 assigned to uncoated balloon

6 died

14 completed study
14 for analysis
8 full histology
Echocardiography: thickened sclerotic aortic valve
## Invasive and echocardiographic data

<table>
<thead>
<tr>
<th></th>
<th>Uncoated</th>
<th>Paclitaxel-coated</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=14</td>
<td>n=14</td>
<td></td>
</tr>
<tr>
<td>Pressure gradient* Baseline (mm Hg)</td>
<td>5.7±4.6</td>
<td>7.0±7.6</td>
<td>0.59</td>
</tr>
<tr>
<td>Pressure gradient Post-BAV (mm Hg)</td>
<td>1.5±2.5</td>
<td>1.5±2.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Pressure gradient Follow-up (mm Hg)</td>
<td>7.7±7.7</td>
<td>3.6±3.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Aortic valve area Baseline (cm²)</td>
<td>0.63±0.14</td>
<td>0.58±0.17</td>
<td>0.42</td>
</tr>
<tr>
<td>Aortic valve area Post-BAV (cm²)</td>
<td>0.62±0.16</td>
<td>0.58±0.19</td>
<td>0.55</td>
</tr>
<tr>
<td>Aortic valve area Follow-up (cm²)</td>
<td>0.58±0.22</td>
<td>0.83±0.49</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Mean transvalvular pressure gradients

Blue lines: baseline, green lines: post-BAV, brown lines: follow-up. *0.01, **0.02, §0.004, ¶0.15
Aortic valve area post-BAV and at follow-up

Uncoated

$p=0.32$

Paclitaxel-coated

$p=0.04$
# Echocardiographic data

<table>
<thead>
<tr>
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<th>Uncoated n=14</th>
<th>Paclitaxel-coated n=14</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVS diastolic (cm)</strong></td>
<td>0.30±0.04</td>
<td>0.29±0.06</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>IVS systolic (cm)</strong></td>
<td>0.42±0.09</td>
<td>0.44±0.08</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>PW diastolic (cm)</strong></td>
<td>0.38±0.12</td>
<td>0.37±0.09</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>PW systolic (cm)</strong></td>
<td>0.49±0.08</td>
<td>0.52±0.06</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>EDD (cm)</strong></td>
<td>1.46±0.31</td>
<td>1.35±0.39</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>ESD (cm)</strong></td>
<td>0.92±0.16</td>
<td>0.83±0.13</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>EDV (mL)</strong></td>
<td>6.00±3.05</td>
<td>5.45±3.41</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>ESV (mL)</strong></td>
<td>1.77±1.02</td>
<td>1.60±1.25</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>SV (mL)</strong></td>
<td>3.67±1.89</td>
<td>4.14±2.18</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>FS (%)</strong></td>
<td>31.9±4.71</td>
<td>37.3±7.02</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>69±6.85</td>
<td>74±9.58</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Extracellular matrix deposition on AV leaflets post BAV: Masson`s trichrom staining

Uncoated balloon

Paclitaxel-coated balloon

*Quantitative analysis pending*
Cell proliferation post BAV
PCNA staining

Paclitaxel-Coated
Uncoated
Maiats trichrom (left) and PCNA (right) stainings

Uncoated

Paclitaxel coated
AV leaflet thickness post-BAV

According to Rajamannan et al, Circulation 2005;112:I229
**Histology data**

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</tr>
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<tbody>
<tr>
<td>Leaflet thickness (mm)</td>
<td>0.71±0.17</td>
<td>0.60±0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>PCNA grade</td>
<td>2.88±1.55</td>
<td>1.88±1.72</td>
<td>0.24</td>
</tr>
</tbody>
</table>

n=16; 8 each group

PCNA: Proliferating Cell Nuclear Antigen staining
Drug-eluting balloon valvuloplasty development

- The results of this study support a preventative effect of the paclitaxel-coated balloon on restenosis

- FIM pilot studies with clinical and ECHO FU for safety, efficacy (ongoing)

- Randomized studies vs. plain BAV balloon for comparative efficacy (clinical outcomes)

- Consider and test other potential drugs (such as antiproliferative, ossification inhibitors)

- Determine clinical use in triaging AS patients in the era of PAVR
Patient risk and treatment options

- TAVI
- Surgery
- BAV or No Rx
- DEBAV

Risk

# Patients

Graph showing the distribution of patients across different treatment options based on risk.