Increased outward force of self-expanding BMS in the SFA could be a significant risk factor for restenosis (COF evaluation of BIOFLEX-I study)

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I have the following potential conflicts of interest to report:

- Consulting: Abbott, BD, Biotronik, Boston Scientific, Cook, CTI vascular, iVascular, Medtronic, Philips, Terumo, CyndRX, Profusa
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

I do not have any potential conflict of interest
**CHRONIC OUTWARD FORCE**

**COF**: the force exerted on a vessel wall by a self-expanding stent

COF depends on:
- **OPERATOR**
- **LESION**
- **STENT**
Chronic Outward Force (COF) exerted by a nitinol stent on vessel wall

- Is the lesion sufficiently predilated?

- Average reference vessel diameter of SFA is 5 mm
- Most commonly used stent diameter in SFA is 7 mm

Reference Vessel Diameters from SFA trials

<table>
<thead>
<tr>
<th>RVD (mm)</th>
<th>RESILIENT</th>
<th>DURABILITY II</th>
<th>ZILVER PTX</th>
<th>STROLL</th>
<th>SUPERB1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.1</td>
<td>4.8</td>
<td>5.1</td>
<td>4.9</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Source: Garcia L. Superb Trial 12 Month Results. Presented at TCT 2012, Miami, FL

Stent Diameter Use in SFA, %

- 5 mm
- 6 mm
- 7 mm
- 8 mm
Chronic Outward Force (COF) exerted by a nitinol stent on vessel wall

Expansion force increases with decreasing diameter

Bent Leg: vessel diameter range: 5.02 - 2.98 mm : 6mm stent

- 100N
- 60N
- 40N

Outward Force (N) vs Stent Diameter (mm)
Chronic Outward Force (COF) exerted by a nitinol stent on vessel wall
High COF shows increase of neointimal proliferation
Pre-clinical study on stent oversizing by Zhao

14 Yucatan swine
6 month follow-up

«... Severe oversizing (stent-to-artery ratio[1.4:1]) results in a profound long-term histological response including exuberant neointimal proliferation, medial disruption by stent struts, higher injury scores and luminal stenosis.»
High COF shows increase of neointimal proliferation
Pre-clinical study on low vs high COF stents by Vienna University

28 days:
- Astron Pulsar (low COF): 10 stents
- LifeStent (high COF): 8 stents

90 days:
- Astron Pulsar (low COF): 8 stents
- LifeStent (high COF): 8 stents

Presented at CIRSE 2017 by Pr Martin Funovic, Medical University of Vienna
High COF shows increase of neointimal proliferation
Pre-clinical study on low vs high COF stents by Vienna University

Low COF stent shows significantly smaller neointima area than High COF stent
High COF shows increase of neointimal proliferation
Case experiences with high COF stents

Source: Goverde P, Presented at LINC 2015 - Consequences of SFA stenting and how to overcome them
High COF shows increase of neointimal proliferation

-> Supporting clinical data

Zilver PTX global clinical program, Cox proportional hazards model

<table>
<thead>
<tr>
<th>Factors with Moderate Impact on TLR from Classification Tree</th>
<th>p-value$^1$</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent oversizing</td>
<td>0.043</td>
<td>• Oversizing (&gt;30%) may impact TLR</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.64</td>
<td>• No significant impact on TLR</td>
</tr>
<tr>
<td>Patent runoff vessels</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Stent diameter</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

$^1$ joint p-value; not univariate

* Data presented at LINC 2019: “Insights from Global Zilver PTX Experience: What are the Predictors for Clinical Failure and TLR” by Michael D. Dake, MD

TLR: Target Lesion Resvascularization
High COF shows increase of neointimal proliferation. Are there clinical data available to support this statement?

**BIOFLEX-I study**

- Prospective, international, multicenter, IDE trial investigating 302 subjects in 38 clinical sites in US (29), Canada (2) and Europe (7)
- PI’s: MW. Burket (US/Canada) & M. Brodmann (EU)

*Pulsar* stents: Astron Pulsar and Pulsar-18 stents

- **Angio**
  - 30-Day FUP
  - 6-Month FUP
  - 12-Month FUP

- **DUS**
  - 24 & 36 Month FUP

Each individual stent (over)sizing determined by angiography

PSVR measurements@1, 6, 12 months

Correlated to stent radial outward force as measured with bench tests

** independent core lab adjudicated – independent CEC
High COF shows increase of neointimal proliferation
Are there clinical data available to support this statement?

**BIOFLEX-I study**

<table>
<thead>
<tr>
<th></th>
<th>radial outward force</th>
<th>1/PSVR at 1 month</th>
<th>1/PSVR at 6 months</th>
<th>1/PSVR at 12 months</th>
<th>PSVR at 1 month/PSVR at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pearson Correlation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial outward force</td>
<td>1</td>
<td>.129***</td>
<td>-.052</td>
<td>-.161</td>
<td>-.196</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.046</td>
<td>.444</td>
<td>.020</td>
<td>.008</td>
</tr>
<tr>
<td>N</td>
<td>456</td>
<td>240</td>
<td>216</td>
<td>208</td>
<td>183</td>
</tr>
</tbody>
</table>

@ 1 month
Statistically significant
The higher COF -> the lower PSVR

@ 6 month
Statistically not significant
The higher COF -> the higher PSVR

@ 12 month
Statistically significant
The higher COF -> the higher PSVR

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
High COF shows increase of neointimal proliferation
Are there clinical data available to support this statement?

**BIOFLEX-I study**

@ 1 month
Statistically significant
The higher COF -> the lower PSVR

@ 12 month
Statistically significant
The higher COF -> the higher PSVR
High COF shows increase of neointimal proliferation
Are there clinical data available to support this statement?

**BIOFLEX-I COF as risk factor: linear regression model**

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>1 (Constant)</td>
<td>1.124</td>
<td>.169</td>
<td></td>
<td>.000</td>
<td>.791</td>
</tr>
<tr>
<td>radial outward force</td>
<td>-2.970</td>
<td>1.299</td>
<td>-.169</td>
<td>.024</td>
<td>-5.536</td>
</tr>
</tbody>
</table>

Dependent Variable: PSVR at 1 month/PSVR at 12 months

COF is the most significant predictor for worsening of PSVR in the multivariate analysis
Conclusions

Based on the data available (preclinical, cases, BIOFLEX1), we see the following trends:

➢ At 12 months high COF is a significant risk factor for restenosis (high PSVR), reversing the early (1 month) results

➢ Long term low COF seems to result in less restenosis and potentially less re-interventions

➢ Further research is needed to clarify the relation between stent forces and clinical outcome. BIOFLEX COF RCT will provide more insights how COF influences clinical outcome in patients with SFA disease.
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