Investigation of catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications: Three-month results from the randomized, sham-controlled, proof of concept SPYRAL HTN-OFF MED Trial

Prof. Dr. Michael Böhm

Disclosures
• Consultant – Abbott/St. Jude, Astra, Medtronic, Servier, Vifor
• Grant support – Medtronic, Servier, German Research Foundation (DFG)
SPYRAL HTN Clinical Program

Background

• Up to one-third of adults have hypertension
  – Increased risk of cardiovascular events and stroke
  – Many patients remain uncontrolled

• Renal denervation therapy (RDN) targets the sympathetic nervous system

• SYMPLICITY HTN-3 trial failed to demonstrate a significant blood pressure lowering effect of RDN

• Sub-analyses suggested:
  – Variance in medication adherence
  – Incomplete denervation of the renal arteries
  – Inclusion of patients with isolated systolic hypertension
SPYRAL HTN – OFF MED
Study Design

Randomized, sham-controlled, single-blinded trial

**Screening visit 1**
- Office BP
- Drug naïve or medications D/C

**Screening visit 2**
- Office BP (Baseline)
- 24-hr ABPM
- Drug testing

2-week safety check*

- OSBP ≥ 180
- Screen failure

**Renal denervation**

**Sham control**

Randomization / Procedure

Follow-up every 2 weeks

- ABPM Office BP
- Drug testing

Unblinding

**Drug titration until OSBP < 140**

Follow-up 6M

*Only for patients discontinuing anti-hypertensive medications
**SPYRAL HTN – OFF MED**

**Blood Pressure Change from Baseline to 3 Months**

<table>
<thead>
<tr>
<th>Baseline BP (mmHg)</th>
<th>24-hr SBP</th>
<th>24-hr DBP</th>
<th>Office SBP</th>
<th>Office DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>154</td>
<td>152</td>
<td>162</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>101</td>
</tr>
<tr>
<td>n = 35</td>
<td>n = 35</td>
<td>n = 35</td>
<td>n = 37</td>
<td>n = 41</td>
</tr>
<tr>
<td>n = 36</td>
<td>n = 36</td>
<td>n = 36</td>
<td>n = 41</td>
<td>n = 41</td>
</tr>
</tbody>
</table>

**Δ -5.0 mmHg**
(-9.9, -0.2)  
P = 0.04

**Δ -4.4 mmHg**
(-7.2, -1.6)  
P = 0.002

**Δ -7.7 mmHg**
(-14.0, -1.5)  
P = 0.002

**Δ -2.3 mmHg**
(-6.1, 1.6)  
P = 0.24

**Δ -4.9 mmHg**
(-8.5, -1.4)  
P = 0.008

**Δ -0.4 mmHg**
(-2.2, 1.4)  
P = 0.65

**Δ -5.5 mmHg**
(-9.1, -2.0)  
P = 0.003

**Δ -4.4 mmHg**
(-7.0, -2.6)  
P = 0.001

**Δ -7.7 mmHg**
(-14.0, -1.5)  
P = 0.02

**Δ -0.3 mmHg**
(-2.9, 2.2)  
P = 0.81

**BP Change from baseline to 3 months (mmHg)**

- RDN
- Sham
## SPYRAL HTN – OFF MED
### Safety Results at 3 Months

<table>
<thead>
<tr>
<th>%</th>
<th>RDN (n = 38)</th>
<th>Sham Control (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New myocardial infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding (TIMI¹)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New onset end stage renal disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serum creatinine elevation &gt;50%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Significant embolic event resulting in end-organ damage</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization for hypertensive crisis/emergency</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New stroke</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

¹TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure.
## SPYRAL HTN Clinical Program

### Advances of SPYRAL HTN Compared to SYMPLICITY HTN-3

<table>
<thead>
<tr>
<th></th>
<th>Symplicity HTN-3</th>
<th>Spyral HTN off Med</th>
</tr>
</thead>
</table>
| **Medications** | 5.1 prescribed anti-HTN drugs at randomization  
No drug adherence testing | No anti-HTN drugs at time of randomization  
Drug adherence testing by serum and urine |
| **Patients**   | Resistant hypertension patients (OSBP $180 \pm 16$)  
No diastolic cutoff | Moderate hypertension patients (OSBP $162 \pm 7$)  
Excluding ISH patients (ODB $101 \pm 7$) |
| **Procedure**  | Mono-electrode, sequential ablation system  
Mostly inexperienced operators without proctoring  
Main artery RDN only  
Ablations per pt: $11.2 \pm 2.8$ | Four-electrode, simultaneous ablation system  
Highly experienced operators with proctoring  
Main + branches RDN  
Ablations/pt: $43.8 \pm 13.1$ |
SPYRAL HTN – OFF MED

Conclusions

• **Biologic proof of principle** for the efficacy of renal denervation

• **Clinically meaningful blood pressure reductions** at 3 months
  – In mild to moderate hypertensive patients treated with RDN
  – In the absence of anti-hypertensive medications compared to sham control

• **No major safety events**
  – Despite a more complete denervation procedure that extended into renal artery branch vessels

• **The results of this feasibility study will inform the design of a larger pivotal trial**
Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial


Townsend et al, Lancet. Published online 28 Aug, 2017
We thank patients, investigators, committee members and staff for their outstanding contribution!

Thank you for your attention!
### SPYRAL HTN – OFF MED
#### Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Mean ± SD or % (N)</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>55.8 ± 10.1</td>
<td>52.8 ± 11.5</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>68.4% (26/38)</td>
<td>73.8% (31/42)</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td>29.8 ± 5.1</td>
<td>30.2 ± 5.1</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td>88.8 ± 16.6</td>
<td>90.9 ± 19.1</td>
</tr>
<tr>
<td><strong>Diabetes (type 2)</strong></td>
<td>2.6% (1/38)</td>
<td>7.1% (3/42)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>10.5% (4/38)</td>
<td>23.8% (10/42)</td>
</tr>
<tr>
<td><strong>Obstructive sleep apnea</strong></td>
<td>7.9% (3/38)</td>
<td>7.1% (3/42)</td>
</tr>
<tr>
<td><strong>Peripheral artery disease</strong></td>
<td>2.6% (1/38)</td>
<td>0% (0/42)</td>
</tr>
<tr>
<td><strong>Coronary artery disease(^†)</strong></td>
<td>0% (0/38)</td>
<td>4.8% (2/42)</td>
</tr>
<tr>
<td><strong>Stroke and transient ischemic attack(^†)</strong></td>
<td>2.6% (1/38)</td>
<td>0% (0/42)</td>
</tr>
<tr>
<td><strong>Myocardial infarction / acute coronary syndrome(^†)</strong></td>
<td>0% (0/38)</td>
<td>2.4% (1/42)</td>
</tr>
</tbody>
</table>

\(^†\)These events occurred >3 months before randomization.  
\(P = NS\) for differences in all baseline characteristics.
### SPYRAL HTN – OFF MED

#### Baseline Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>RDN</th>
<th>Sham Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office SBP (mm Hg)</td>
<td>162.0 ± 7.6</td>
<td>161.4 ± 6.4</td>
</tr>
<tr>
<td>Office DBP (mm Hg)</td>
<td>99.9 ± 6.8</td>
<td>101.5 ± 7.5</td>
</tr>
<tr>
<td>Office heart rate (bpm)</td>
<td>71.1 ± 11.0</td>
<td>73.4 ± 9.8</td>
</tr>
<tr>
<td><strong>24-hour measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 24-hour SBP (mm Hg)</td>
<td>153.4 ± 9.0</td>
<td>151.6 ± 7.4</td>
</tr>
<tr>
<td>Mean 24-hour DBP (mm Hg)</td>
<td>99.1 ± 7.7</td>
<td>98.7 ± 8.2</td>
</tr>
<tr>
<td>Mean 24-hour heart rate (bpm)</td>
<td>72.3 ± 10.9</td>
<td>75.5 ± 11.5</td>
</tr>
</tbody>
</table>

\[ P = \text{NS for differences in all baseline characteristics.} \]