After Symplicity-HTN 3:

Is there a future for catheter-based therapies Hypertension?

M. Böhm
Innere Medizin III (Kardiologie / Angiologie / Internistische Intensivmedizin)
Universitätsklinikum des Saarlandes
Homburg/Saar

michael.boehm@uks.eu
Catheter-based Renal Denervation: Staged Clinical Evaluation

First-in-Man ✓

Series of Pilot studies ✓

Symplicity HTN-1
Extended follow-up

Symplicity HTN-2
Initial Randomized Clinical Trial

Symplicity HTN-3
US PMA Randomized Clinical Trial (ACC LBCT, NEJM)

Global Symplicity Registry (ACC LBCT)
Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study

Henry Krum, Markus P Schlaich, Michael Böhm, Felix Mahfoud, Krishna Rocha-Singh, Richard Katholi, Murray D Esler

Time course of office BP change

RDN
\[ \Delta \text{ from Baseline (mmHg)} \]

Control
\[ \Delta \text{ from Baseline (mmHg)} \]

![Graph showing changes in systolic and diastolic blood pressure over time for RDN and Control groups.](image)

- **RDN**
  - 1M: -20, **p<0.0001**
  - 3M: -24, **p=0.002**
  - 6M: -32, **p=0.005**

- **Control**
  - Baseline: 0
  - 1M: 0
  - 3M: -4
  - 6M: 1

† p<0.0001 for between-group comparisons
‡ p=0.002 for between-group comparisons
‡‡ p=0.005 for between-group comparisons

Two-way repeated measures ANOVA, p=0.001

Primary safety endpoint

Performance Goal = 9.8%

P < 0.001

Major Adverse Event (MAE) Rate

0% 2% 4% 6% 8% 10%

Bhatt DL, NEJM 2014
Primary efficacy endpoint

-2.39 (-6.89, 2.12), $P = 0.255$ (Primary analysis with 5 mm Hg superiority margin)

- Did not meet primary efficacy endpoint
Global SYMPLICITY Registry – Current Activated Site Locations

Böhm et al., submitted 2014, ACC Hotline, Hypertension, 2015
Change in Office SBP at 6 Months for GSR and SYMPLICITY HTN-3 Patients

- **GSR HTN3-like cohort**: N=244
- **RDN**: N=353
- **HTN-3**: N=171

<table>
<thead>
<tr>
<th>Change in Office SBP (mm Hg)</th>
<th>GSR HTN3-like cohort</th>
<th>RDN</th>
<th>HTN-3</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean # anti-HTN drugs at baseline</td>
<td>4.7 (1.2)</td>
<td>5.1 (1.4)</td>
<td>5.2 (1.4)</td>
<td>-11.7</td>
</tr>
</tbody>
</table>

Böhm et al., submitted 2014, ACC Hotline, Hypertension, 2015, online
Blood pressure lowering evidence

- SYMPLECTIC HTN 1, N=163
- SYMPLECTIC HTN 2, N=102
- Global Symplicity Registry, N=613
- ENCOREd, N=109
- ABPM Meta Analysis, N=346
- Heidelberg Registry, N=63
- EnlightHTN 1, N=46
- REDUCE-HTN, N=46
- RAPID, N=47
- REDUCE, N=15

Published Sources:
1. Lancet 2009
2. Lancet 2010
3. TCT 2013
4. Journal of Human Hypertension 2013
5. Circulation 2013
8. Eur Heart J 2013
9. TCT 2013
10. EuroIntervention 2013
11. EuroIntervention 2013
Uncertainties

- **Subgroups** - Afro-Americans, women

- **Procedural Aspects** – 4-Quadrant, numbers

- **Stability of Treatment** – 40-50 % unstable

- **Hawthorne** – Placebo - unknown
Change in Office Blood Pressure through 12-Months Post-Procedure

P<0.001 at all time points
Error Bars= 1.96 SE

Baseline SBP (mm Hg) | 180 | 179 | 184*
Baseline DBP (mm Hg) | 96  | 95  | 102*

*Baseline = time of RDN procedure

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

RDN 6 Months: n=350
- Baseline SBP (mm Hg): 180
- Baseline DBP (mm Hg): 96
- Change in SBP: -15.3 mm Hg
- Change in DBP: -18.9 mm Hg
- P<0.001 at all time points
- Error Bars= 1.96 SE

RDN 12 Months: n=320
- Baseline SBP (mm Hg): 179
- Baseline DBP (mm Hg): 95
- Change in SBP: -7.8 mm Hg
- Change in DBP: -7.1 mm Hg
- P<0.001 at all time points
- Error Bars= 1.96 SE

Crossover 6 Months: n=92
- Baseline SBP (mm Hg): 184*
- Baseline DBP (mm Hg): 102*
- Change in SBP: -7.1 mm Hg
- Change in DBP: -17.7 mm Hg
- P<0.001 at all time points
- Error Bars= 1.96 SE

*Baseline = time of RDN procedure

Bakris et al., ESC CTU, 2014

Error Bars

Sham vs non Sham not different

SBP
DBP
Change in Mean 24-hour Ambulatory Blood Pressure through 12 Months

Sham vs non Sham not different

Baseline SBP (mm Hg) | 159 | 158 | 163*  
Baseline DBP (mm Hg) | 87  | 86  | 94*  

*Baseline = time of RDN procedure

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

Subjects unblinded

Non-Crossover 6 Months

Non-Crossover 12 Months

Δ 6 to 12 months = +11.5/+5 mmHg

P<0.001 at all time points

Error Bars=1.96 SE

Baseline SBP (mm Hg) | 176 | 176
Baseline DBP (mm Hg) | 94 | 94

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

Non-Crossover 6 Months

Subjects unblinded

Non-Crossover 12 Months

Baseline SBP (mm Hg) | 176 | 176
Baseline DBP (mm Hg) | 94 | 94

Δ 6 to 12 months = +11.5/5 mmHg

P<0.001 at all time points
Error Bars=1.96 SE

Bakris et al., ESC CTU, 2014
Discuss. Böhm
Change in Mean 24-hour Ambulatory Blood Pressure through 12 Months

Subjects unblinded

Non-Crossover 6 Months

Non-Crossover 12 Months

Δ 6 to 12 months = +4.9/+3.7 mmHg

Baseline SBP (mm Hg) | 151 | 151
Baseline DBP (mm Hg) | 86 | 86

P=0.02
P=0.03
P=NS

Error Bars=1.96SE

Bakris et al., ESC CTU, 2014 Discuss. Böhm
The future... What has to be done?
Classical Study Design: RDN on top of medication

Randomize 1:1

8 week stable Medication

Sham Control Group

Primary Endpoint:
Safety
SBP by ABPM and office
Drug-Naïve Hypertensives

Drug Titration

- Sham Group
- Efficacy off-meds & Procedural Safety
- RDN Group
- Improved Sensitivity of Drug Treatment
- Medication
4-week run-in period with administration of standardized triple combination therapy (Diuretic + ACE inhibitor + CCB)

Optimal and stepped-care antihypertensive treatment + RDN versus Optimal and stepped-care antihypertensive treatment

Azizi et al., Lancet, 2015, online
Changes in daytime and nighttime ambulatory BP at 6-month follow up

Azizi et al., Lancet, 2015, online
Changes in daytime and nighttime ambulatory BP at 6-month follow up

Primary efficacy endpoint was met

Azizi et al., Lancet, 2015, online
Changes in daytime and nighttime ambulatory BP at 6-month follow up

Azizi et al., Lancet, 2015, in press
- **Subgroups**
  - Non or Low Response: Vasodilator use, Isolated systolic hypertension, Afro-Americans (?), assure high baseline BP

- **Procedural Aspects**
  - Adequate RDN (more intense, periphery), novel device, experienced investigators

- **Stability of Treatment**
  - Stable therapy, no drop ins and outs, Evaluation of drug combinations
Thank you!

M. Böhm
Innere Medizin III (Kardiologie / Angiologie / Internistische Intensivmedizin)
Universitätskliniken des Saarlandes
Homburg/Saar
michael.boehm@uks.eu
After Symplicity-HTN 3:

Is there a future for catheter-based therapies Hypertension?

M. Böhm
Innere Medizin III (Kardiologie / Angiologie / Internistische Intensivmedizin)
Universitätsklinikum des Saarlandes
Homburg/Saar

michael.boehm@uks.eu