LINC 2016

The next step in the interventional treatment of hypertension: SPYRAL HTN global clinical trial program

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I have the following potential conflicts of interest to report:

Research grants:
- Deutsche Hochdruckliga
- Deutsche Gesellschaft für Kardiologie
- Saarländisches Ministerium für Wissenschaft und Forschung
- Medtronic, St. Jude

Consultant/Lecture fee:
- Medtronic, St. Jude
Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design

Felix Mahfoud1*, Michael Böhm1, Michel Azizi2,3,4, Atul Pathak5, Isabelle Durand Zaleski6, Sebastian Ewen1, Kostantinos Tsioufis7, Bert Andersson8, Peter J. Blankestijn9, Michel Burnier10, Gilles Chatellier2,11, Sameer Gafoor12,13, Guido Grassi14, Michael Joner15, Sverre E. Kjeldsen16,17, Thomas Felix Lüscher18, Melvin D. Lobo19, Chaim Lotan20, Gianfranco Parati21, Josep Redon22, Luis Ruijope23, Isabella Sudano18, Christian Ukena1, Evert van Leeuwen24, Massimo Volpe25, Stephan Windecker26, Adam Witkowski27, William Wijns28, Thomas Zeller29, and Roland E. Schmieder30

ASH Scientific Statement
Detection, evaluation, and treatment of severe and resistant hypertension

Proceedings from an American Society of Hypertension Interactive Forum held in Bethesda, MD, USA, October 10th 2013
William B. White, MD, FASH, FAHA, FACPa,*, J. Rick Turner, PhDb, Domenic A. Sica, MD, FASHc, John D. Bisognano, MD, PhD, FASHd, David A. Calhoun, MD, FASHe, Raymond R. Townsend, MD, FASHf, Herbert D. Aronow, MD, MPH, FACC, FSCAIg, Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAIh, and George L. Bakris, MD, FASHi
Confounding factors

Medication  
Study population  
Procedure
SPYRAL HTN
Global Clinical Trial Program

HTN-3 Factor Identified

Medication
What to learn from Symplicity HTN-3?

Antihypertensive drugs may have been maximized but may not have be stabilized.

Kandzari D, Eur Heart J 2014
What to learn from Symplicity HTN-3?

Antihypertensive drugs may have been maximized but may not have been stabilized.

Proportion of patients with medication changes

Kandzari D, Eur Heart J 2014
Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis.

Blood pressure reduction after 6 months

N=100

<table>
<thead>
<tr>
<th></th>
<th>Office</th>
<th>Ambulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BP</td>
<td>167/88</td>
<td>154/86</td>
</tr>
<tr>
<td>SBP Reduction</td>
<td>-15</td>
<td>-8</td>
</tr>
<tr>
<td>DBP Reduction</td>
<td>-5</td>
<td>-4</td>
</tr>
</tbody>
</table>

p<0.001 p<0.001 p<0.001 p=0.001

Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis.

**Responder office SBP**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Drugs taken (%)</td>
<td>81.7</td>
<td>79.2</td>
</tr>
</tbody>
</table>

$p=0.174$
Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis.

**Responder office SBP**

- Baseline: 81.7%
- 6 months: 79.2%

- p = 0.174

**Non-responder office SBP**

- Baseline: 90.6%
- 6 months: 83.4%

- p = 0.006
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HTN-3 Factor Identified

Medication

Solution

• Obtain off-meds data
• Standardize meds
• No max dose titration
• Measure adherence
• Less severe HTN
SPYRAL HTN
Global Clinical Trial Program

HTN-3 Factor Identified

Medication

Study Population

Solution

- Obtain off-meds data
- Standardize meds
- No max dose titration
- Measure adherence
- Less severe HTN
Who is the ideal candidate?
Sympathetic activity in different hypertensive populations

Rate of spillover of noradrenaline from the kidneys to plasma (ng/min)

- Normal BP
- 20-39 years
- 40-59 years
- 60-79 years

Essential Hypertension

Esler M, J Hypertension 1990
Sympathetic activity in different hypertensive populations

Rate of spillover of noradrenaline from the kidneys to plasma (ng/min)

Normal BP

20-39

40-59

60-79 years

Essential Hypertension

Esler M, J Hypertension 1990
Office systolic BP change at 6 months

**HTN-3**

**RDN**
- Change in blood pressure (mm Hg): -17.9 ± 24.3
- n=225
- CH: -10.7 ± 22.6
- ISH: -7.21 (-12.42, -2.01)
- P=0.007

**Sham**
- Change in blood pressure (mm Hg): -12.1 ± 27.2
- n=121
- CH: -9.2 ± 24.5
- ISH: -2.92 (-11.83, 6.00)
- P=0.52

**Combined hypertension (CH):**
- SBP >140 mmHg, DBP >90 mmHg

**Isolated systolic hypertension (ISH):**
- SBP >140 mmHg, DBP <90 mmHg

Mahfoud F, ACC 2015
Office systolic BP change at 6 months

Pooled dataset (HTN-3 + GSR)

Change in blood pressure (mm Hg)

-18.7
-10.8
-8.0 [-10.6, -5.3]

P < 0.001

Combined hypertension (CH):
- SBP > 140 mmHg, DBP > 90 mmHg

Isolated systolic hypertension (ISH):
- SBP > 140 mmHg, DBP < 90 mmHg

n = 680
n = 445

Mahfoud F, ACC 2015
**SPYRAL HTN**
Global Clinical Trial Program

**HTN-3 Factor Identified**

- **Medication**
  - Obtain Off-meds data
  - Standardize Meds
  - No Max Dose Titration
  - Measure adherence

- **Study Population**
  - No isolated systolic hypertension
  - Less severe HTN
  - Focus on ABPM
  - Avoid changing patient behavior

**Alternative**
# SPYRAL HTN Global Clinical Trial Program

## HTN-3 Factor Identified

**Medication**
- Obtain Off-meds data
- Standardize Meds
- No Max Dose Titration
- Measure adherence

**Study Population**
- No isolated systolic hypertension
- Less severe HTN
- Focus on ABPM
- Avoid changing patient behavior

**Procedural**
- Experienced proceduralists

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**Alternative**
- Main + Branch vessel treatment
Treatment strategies
Treatment strategies?
Optimization of the treatment methodology

RF treatment of the **Main Artery**

RF treatment of each **Branch**

RF treatment of the **Main Artery and Branches**

*Mahfoud F, JACC 2015*
Branch & main artery treatment highly effective in reducing renal NE

Group I

N  12  12

NE Concentration (pg/mg)

[Graph showing scatter plot and box plots with 71% reduction indicated.]

Mahfoud F, JACC 2015
Branch & main artery treatment highly effective in reducing renal NE

Group I  Group V

N 12  12  12  12

NE Concentration (pg/mg)

71%

83%

Mahfoud F, JACC 2015
Branch & main artery treatment highly effective in reducing renal NE

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>NE Concentration (pg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>12</td>
<td>*</td>
</tr>
<tr>
<td>Group V</td>
<td>12</td>
<td>*</td>
</tr>
<tr>
<td>Group Y</td>
<td>12</td>
<td>€</td>
</tr>
</tbody>
</table>

Mahfoud F, JACC 2015
Do we need to revise the treatment recommendation?
Medication

- Obtain Off-meds data
- Standardize Meds
- No Max Dose Titration
- Measure adherence

Study Population

- HTN-3 Factor Identified
- No isolated systolic hypertension
- Less severe HTN
- Focus on ABPM
- Avoid changing patient behavior

Procedural

- Multielectrode catheter
- Main + Branch vessel treatment
- Experienced proceduralists

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SPYRAL HTN Global Clinical Program

Phase A

- Off Meds
- Sham

RDN 3M

3M Titrate Meds

3M 6M

6M
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Phase A

Off Meds → RDN → 3M → 6M

Phase A

On Meds → Sham → 3M → 6M

On Meds → RDN → 3M → 6M

On Meds → Sham → 3M → 6M

Titrate Meds
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Phase A
- Off Meds
  - RDN
  - Sham
- On Meds
  - RDN
  - Sham

Phase B
- Titrate Meds
  - 3M
  - 6M

Kandzari DE, Am J Card in press
Vielen Dank!

PD Dr. Felix Mahfoud, FESC

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