Why the Renal Denervation RCTs Have Not Shown A Positive Effect: Does The Treatment Concept Have a Future?

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Polypharmacy Strategy Is Failing to Achieve Goals for Hypertension Control

- Despite steady prevalence of hypertension, the proportion of patients who achieve “control” has plateaued or decreasing in recent years

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DENER HTN: Drug Titration Algorithm

- Iteration and refinement
- What we know

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SYMPLICITY HTN-3: One Trial in Larger Scientific Context

- Preclinical evidence supports RDN hypothesis
- Renal nerves play a role in hypertension
- Early, but abandoned, experience with surgical sympathectomy and nephrectomy for reducing BP
- Elevated sympathetic tone contributes to hypertension

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Conflicts of Interest

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DENER HTN Daytime and Nighttime ABPM From Randomization to 6 Months

- New Generation of RDN Trials
- SYMPLICITY HTN intercepted analysis
- Global SYMPLICITY Registry
- Independent panel recommendations
- SYMPLICITY HTN-3 did not meet efficacy EP

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**Evolving Perspective on Renal Nerve Distribution**

Renal nerves may have a positional bias on radial distance from arterial lumen: distal nerves are closer and may be poised as more accessible therapeutic target.

**Current concept – Non-uniform radial distribution**

Distal

Proximal

**Prior concept – Uniform radial distribution**

Distal

Proximal

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**Preclinical Study of Combined Branch and Main Artery Treatment Reduction in Norepinephrine Content**

**REINFORCE Trial Design**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>100 pts with moderate uncontrolled HTN (office systolic blood pressure (OSBP) ≥ 150 mmHg and ≤ 180 mmHg) at 15 US centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective, multicenter, mask/single blinded, randomized (2:1 treatment:control), pilot study</td>
</tr>
<tr>
<td>Test Device</td>
<td>Vessix™ Renal Denervation System: Vessix Reduce™ Catheter - 4mm, 5mm, 6mm, 7mm, Vessix™ Generator</td>
</tr>
<tr>
<td>Primary Efficacy</td>
<td>Mean reduction in average 24-hour ambulatory systolic blood pressure (ASBP) at 8 weeks post randomization in subjects treated with renal denervation (Test) as compared to subjects treated with masked procedure (Control)</td>
</tr>
</tbody>
</table>

**Selected Secondary Endpoints and Safety Assessments**

- All-cause death
- Renal failure
- Myocardial infarction
- Stroke
- Procedure-related complications
- Significant new renal artery stenosis
- Mean number of medications

**Pharmacology Placebo in Hypertensive Trials**

**SPYRAL HTN Global Clinical Trial Program**

**Spyral HTN Global Clinical Trial Program**

- Consistent four-quadrant ablation pattern
- 4Fr catheter profile
- 6Fr guide catheter compatible
- 0.014" over-the-wire rapid exchange delivery
- 60-second simultaneous energy delivery

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**Symplicity Spyral Multi-Electrode Renal Denervation Catheter**

- Consistent four-quadrant ablation pattern
- 4Fr catheter profile
- 6Fr guide catheter compatible
- 0.014" over-the-wire rapid exchange delivery
- 60-second simultaneous energy delivery

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**Spyral HTN Global Clinical Trial Program**

**First Phase Includes Two Parallel Trials**

**SPYRAL HTN-OFF MED**

- 100 patients, OSBP 150-180, ABPM 140-170, DBP ≥ 90
- Sham RCT (1:1)
- Main body and branch ablation
- No specific medication requirement
- Focus on ASBP change at 3 months QOL data to be measured

**SPYRAL HTN-ON MED**

- 100 patients, OSBP 150-180, ABPM 140-170, DBP ≥ 90
- Sham RCT (1:1)
- Main body and branch ablation
- No max tolerated dose
- Focus on ASBP change at 3 months QOL data to be measured

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**Second Phase**

**SPYRAL HTN Pivotal**

Based on OFF/MED trial results: Cost Effectiveness Data/QOL to be measured

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**DeFelice et al.**

**J Hum Hypertens. 2008 22(10): 659–668.**

This analysis reveals no objective reason to conclude that the use of placebo in short-term antihypertensive trials should be discontinued.

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**Henegar et al.**

**Am J Hypertens. 2015; doi:10.1093/ajh/hpu258**

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**Evolution Perspective on Renal Nerve Distribution**

- Distal nerves are closer and may be poised as more accessible therapeutic target

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**Preclinical Study of Combined Branch and Main Artery Treatment Reduction in Norepinephrine Content**

- Reduction in Norepinephrine Content Areas of Renal Denervation

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**REINFORCE Trial Design**

- Patient Population: 100 pts with moderate uncontrolled HTN (office systolic blood pressure (OSBP) ≥ 150 mmHg and ≤ 180 mmHg) at 15 US centers

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**Placebo in Antihypertensive Trials**

- **PHARM: Placebo in Hypertension Adverse Reaction Meta-analysis**

  Meta-analysis conducted by FDA shows that randomization to placebo is not associated with detectable irreversible harm (cardiovascular accident, myocardial infarction, death)

  - **Drug Event Rate/1000 Patient Years**
    - **Placebo Event Rate/1000 Patient Years**
    - **p-Value for Relative Risk**
  
    | Event Type            | Drug Event Rate | Placebo Event Rate | p-Value for Relative Risk |
    |-----------------------|-----------------|--------------------|---------------------------|
    | Serious cardiac events | 23.5            | 24.8               | 0.96                      |
    | Irreversible harm      | 12.3            | 13.7               | 0.86                      |

  DeFelice et al. 2008. 22(10): 659–668
The Carotid Sinus Baroreflex

Mobius HD
Interim Results of the First-in-Man Clinical Study Evaluating the MobiusHD Device for the Treatment of Resistant Hypertension
Malcolm Foster, MD
Turkey Creek Medical Center
Knoxville, Tennessee

MobiusHD™ Baroreflex Modulation
1. MobiusHD is passive implant designed to reshape the carotid sinus, delivered using standard percutaneous techniques and angiographic visualization
2. MobiusHD is designed to exert just enough radial force to reshape it in the diastolic phase, and prevent migration in the systolic phase
3. Reshaping the vessel increases the differential strain, and therefore the stretch, measured by the baroreceptors with every pulsatile wave, concentrated in the windows of the device

CALM-FIM Studies
• Controlling and Lowering Blood Pressure with the MobiusHD – A Prospective Multicenter Safety Study
  • 20 patient safety study in the US
  • Concurrent equivalent 30 patient study in Europe
  • Patients with stage 2 resistant hypertension
    - ≥160 mmHg office cuff BP on ≥3 drugs

CALM Office Cuff BP, n = 25

Does Sympathetic Modulation Have a Future?
• Issue is not whether enough evidence exists for RDN as a routine therapy but instead is there enough evidence to support further study
  - Oversimplification to assume a singular therapy to uniformly treat a heterogeneous disease condition
• HTN 3 presented an unexpected opportunity to revisit physiology and identify practical measures of effective sympathetic interruption
• A new momentum is resurging for novel RDN technologies and non-HTN indications
• Forthcoming evaluation of RDN for HTN require careful trial design that:
  - Demonstrates biologic efficacy in context of on and off medications, and
  - Differentiates potential confounders of observer and patient bias
  - Focus on less variable and more independent endpoints (eg, ABPM)
  - Explore opportunities for more effective ablation based on technology and anatomy