Renal Denervation: is the concept still alive?

Philipp Lurz
Approximately 44% of patients were partially non-adherent, while roughly 17% were totally nonadherent to antihypertensive medications.

Adherence worsens with:
- Male Gender
- Younger age
- More prescribed drugs
- Certain Drugs (e.g. diuretics)
Poorly controlled hypertensive patients were randomized to a smartphone adherence app vs. standard of care

Medisafe app includes reminder alerts, adherence reports, and optional peer support

Self reported medication adherence (Morisky medication adherence scale) improved from 6.0 to 6.4 in the intervention arm and remained 5.7 in the control group (P=0.01 between groups).

SBP decreased by 10.6 mmHg among intervention participants and 10.1 mmHg among controls (P=NS)

Renal Denervation for Blood Pressure Control

Modulation of **PHYSIOLOGICAL PATHWAYS**

RDN is an interventional rather than a pharmacological way to treat hypertension.

The kidney modulates sympathetic tone via the renal nerves to control blood pressure.

Hypertension medication may modulate parts of the renin-angiotensin-aldosterone system, adjust blood volume, or affect heart rate.
Effectiveness of RDN in controlled trials

- **HTN 3 2014**
- **DENER-HTN 2015**
- **TREND 2015**
- **SPYRAL-OFF 2017**
- **SPYRAL-ON 2018**
- **SOLO 2018**
- **TRIO 2019?**
Results of Symplicity HTN-3

Office Systolic Blood Pressure at 6 Months, 5-mm Superiority Margin

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

<table>
<thead>
<tr>
<th></th>
<th>RDN</th>
<th>Control</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP</td>
<td>179.7</td>
<td>180.2</td>
<td>0.765</td>
</tr>
<tr>
<td>6-Month SBP</td>
<td>165.6</td>
<td>168.4</td>
<td>0.260</td>
</tr>
<tr>
<td>Change</td>
<td>-14.1</td>
<td>-11.7</td>
<td>0.255</td>
</tr>
</tbody>
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40% (n = 211) of trial subjects required medication changes between baseline and primary efficacy endpoint assessment:

- 69% of first medication changes were medically necessary
- 121 patients had a medication change due to an adverse event
- 80 patients had a medication change due to a drug side effect
- 69% were changes in drugs at maximally-tolerated doses

Renal nerves generally originate from the aorta and arborise towards the kidney.

Nerve fibers do not completely converge on the renal artery until beyond the main bifurcation.

Accessory arteries, when present, have similar anatomical innervation patterns that mimic the main renal arteries.
Radiofrequency Based Renal Denervation

- Symplicity spiral catheter
- Multi-electrode catheter with quadrantic vessel contact
- Simultaneous ablation in 4 electrodes
- Ablations delivery to renal main artery and branches
Ultrasonic Heating + Water Cooling \rightarrow Thermal Profile

- Paradise endovascular ultrasound ablation catheter
- Ring of ablative energy (depth of 1-6 mm)
- Endothelial cooling by water circulating through balloon
- 2-3 ablations delivered to each main renal artery
RDN superior to sham in drug naive patients

**SPYRAL-HTN ON MED**
Change in 24 h systolic ABPM

<table>
<thead>
<tr>
<th></th>
<th>RDN</th>
<th>Sham</th>
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</thead>
<tbody>
<tr>
<td>Baseline BP (mmHg)</td>
<td>152</td>
<td>151</td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

**Primary Efficacy Endpoint (ITT):**
Change in Daytime Ambulatory Systolic BP at 2 Months
Between Group

- **RDN:** 95% CI: -10.6 to -6.3
- **Sham:** 95% CI: -4.5 to 0.2

Between Group Difference Adjusted for Baseline BP

- **RDN:** 95% CI: -10.6 to -6.3
- **Sham:** 95% CI: -4.5 to 0.2

**RADIANCE-HTN SOLO**
Change in daytime systolic ABPM

- **RDN:** -6.3 mm Hg (95% CI, -9.4 to -3.1)
- **Sham:** -2.2 mm Hg

Kandzari DE et al. Lancet 2018, 9;391:2346-2355
Azizi M et al. Lancet 2018, 9;391:2335-2345
Renal Denervation - ‘always on’ therapy

RDN

Sham Control

24-hr Systolic Blood Pressure from Baseline to 6 Months

Dashed line represents the 24-hr mean at baseline (blue) and 6 months (red)

Graphs based on actual clock times. Similar results were observed when 24-hour BP patterns were normalized to patient reported time of waking.

Significant number of non-responders

How to Explain Variability of Response?
- Variability of measurement
- Differences due to procedure
- Differences due to patients
MRI-Markers of Aortic Stiffness

Aortic distensibility (AAD)

\[ \text{AAD} = \frac{(A_{o_{\text{max}}} - A_{o_{\text{min}}})}{PP \times A_{o_{\text{min}}}} \]

AUC 0.78
\( p = 0.027 \)

AUC 0.83
\( p = 0.004 \)

Fengler F, Lurz P et al. CRIC 2018
Summary

• Three randomized, sham-controlled studies have demonstrated the safety and efficacy of renal denervation.

• Taken together, these results strongly suggest that the neutral results of the earlier SYMPPLICITY HTN-3 trial were likely due to uncontrolled changes in drug therapy, leading to unexpectedly large pressure drops in the sham control group.

• The ongoing randomized sham-controlled SPYRAL PIVOTAL and SPYRAL HTN-ON MED extension trials will confirm the safety and efficacy of the Spyral system.

• Numerous published clinical trials, including prospective randomized sham controlled trials, non-sham RCTs, active comparator randomized trials, and single armed trials highlight the safety and efficacy of renal denervation in the broad hypertensive population.
  – These trial cohorts, cumulatively amounting to almost 6000 patients, include isolated systolic hypertension, combined hypertension, resistant hypertension, diabetics, obstructive sleep apnea, the elderly, etc.
An Alternative to Life-long Poly-pharmacy!
Thank you

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Regression to the mean

Baseline blood pressure strongest predictor for change

Blood Pressure Change from Baseline to 6 Months

**24-hr SBP**
- Baseline BP (mmHg): 152, 151
- n: 36, 36
- Change: -1.6 mmHg, P=NS

**24-hr DBP**
- Baseline BP (mmHg): 97, 98
- n: 36, 36
- Change: -1.9 mmHg, P=NS

**Office SBP**
- Baseline BP (mmHg): 165, 163
- n: 38, 40
- Change: -2.6 mmHg, P=NS

**Office DBP**
- Baseline BP (mmHg): 100, 102
- n: 38, 40
- Change: -1.7 mmHg, P=NS

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