Renal Denervation For Hypertension: Status Update
Disclosures

- Speaker’s Panel – Medtronic, Abbott Vascular, Penumbra
- Clinical Instructor – Bard, Medtronic

Some devices discussed are not approved by the FDA or currently available in the United States.
Outline

• “Resistant Hypertension” Prevalence and Impact
• Denervation Mechanism
• Current Technology
• Denervation literature
• Future Technology
Age-specific and age-adjusted prevalence of hypertension among adults aged 18 and over: US, 2009–2010

Age-adjusted awareness, treatment, and control of hypertension among adults with hypertension: US, 2007–2010
Impact of Hypertension

• **Framingham Heart Study**
  - CHF related mortality 2.3-3x in Pt’s with HTN

• **Multiple Risk Factor Intervention Trial**
  - $\uparrow$RR 2.3-6.9 - CAD mortality
  - $\uparrow$RR 3.6 to 19.2 – stroke

• **JNC-7 - Benefit for anti-Hypertensive's:**
  - 35-40% reduction in CVA
  - 20-25% reduction in MI
  - >50% reduction in CHF
Global Impact

- Prevalence of adult HTN: 30.4% (66.9 million)
- Uncontrolled HTN: 53.5% of HTN patients (35.8 million)
- 85.2% of uncontrolled HTN patients had health insurance
- Worldwide Burden of Hypertension:
  - 7.6 million premature deaths each year attributed to high blood pressure
  - About 54% of stroke and 47% of ischemic heart disease attributable to high blood pressure
### Table 2. Dates of Discovery of Antihypertensive Drugs or Drug Classes

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Antihypertensive Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Sodium thiocyanate</td>
</tr>
<tr>
<td>1931</td>
<td>Reserpine</td>
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<tr>
<td>1947–1950</td>
<td>Ganglion blocking drugs</td>
</tr>
<tr>
<td>1958</td>
<td>Thiazide-type diuretics</td>
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<tr>
<td>1950s</td>
<td>Hydralazine</td>
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<tr>
<td>1950s</td>
<td>Guanethidine</td>
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<tr>
<td>1957</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>1960</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>1973</td>
<td>$\beta$-Receptor blockers (eg, propranolol)</td>
</tr>
<tr>
<td>1970s</td>
<td>Central $\alpha_2$ agonists (eg, clonidine)</td>
</tr>
<tr>
<td>1975</td>
<td>Peripheral $\alpha_1$ receptor blockers (eg, prazosin)</td>
</tr>
<tr>
<td>1977</td>
<td>ACE inhibitors (eg, captopril)</td>
</tr>
<tr>
<td>1977</td>
<td>Calcium channel blockers (eg, verapamil, nifedipine)</td>
</tr>
<tr>
<td>1993</td>
<td>Angiotensin II receptor blockers (eg, losartan)</td>
</tr>
<tr>
<td>2000</td>
<td>Renin inhibitors (eg, aliskiren)</td>
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</table>

ACE indicates angiotensin-converting enzyme. Data derived from Freis.\(^{39}\)
Renal Sympathetic Innervation and Hypertension

Splanchnicectomy for Essential Hypertension

Results in 1,266 cases

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston
Catheter Based Renal Sympathetic Denervation – **Syplicity (Medtronic)**

- 4-6 two minute treatments per artery
- $800 million

[Image of catheter-based renal sympathetics denervation equipment and medical illustration]
Catheter Based Renal Sympathetic Denervation – **Syplicity (Medtronic)**
Baseline BP (mm Hg) | 176/98 ± 17/15
---|---
# of anti-HTN meds (mean) | 5.1 ± 1.4

- 19 centers in Australia, Europe, and the United States
- 153 patients with catheter-based renal sympathetic denervation
Symplicity HTN-1 Results

BP change (mm Hg)

1 M (n=138)  3 M (n=135)  6 M (n=86)  12 M (n=64)  18 M (n=36)  24 M (n=18)
Prospective, randomized trial in 24 centers in Europe, Australia and New Zealand

106 patients randomized

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=52)</th>
<th>Control (n=54)</th>
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</thead>
<tbody>
<tr>
<td>Baseline BP (mm Hg)</td>
<td>178/97</td>
<td>178/98</td>
</tr>
<tr>
<td># of Anti-HTN Meds</td>
<td>5.2 ±1.5</td>
<td>5.3 ±1.8</td>
</tr>
</tbody>
</table>
• 84% of RDN patients had ≥ 10 mmHg reduction in SBP
• 10% of RDN patients had no reduction in SBP
<table>
<thead>
<tr>
<th>Preclinical</th>
<th>First-in-Man Trial</th>
<th>CE Mark Approval</th>
<th>Clinical Trials USA</th>
<th>FDA Approval</th>
<th>Post Marketing Trial Data</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Radio Frequency</td>
<td>Symplicity™</td>
<td></td>
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</table>
Prospective, double blinded study

Randomization is accomplished at the time of angiogram
- 535 patients
- 88 sites in the United States

<table>
<thead>
<tr>
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<th>RDN (n=364)</th>
<th>Sham (n=171)</th>
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<tbody>
<tr>
<td># of Anti-HTN Meds</td>
<td>5.1 ±1.4</td>
<td>5.2 ±1.4</td>
</tr>
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March 29, 2014
Results of Simplicity HTN-3

Figure 1. Primary Efficacy End Point.
A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.
Explanations

• **137 Operators**
  – 111 operators who did at least one procedure (31% did only 1 procedures)
  – 26 operators who did ≥5 procedures

• **Good medical care**
  – Without a control group, the observed treatment effect may have been a result of trial participation
  – Reduction in SBP could be due to good care and a high degree of adherence to antihypertensive therapy as a result of close follow-up (i.e., the Hawthorne effect)
Renal Denervation
Predictors of Response: RDN Device?

**EnligHTN** *(St. Jude Medical)*

- **EnligHTN-1**: (n = 46)
  - ΔoSBP at 6 month: -26mmHg
  - Response Rate: 76%

**OneShot** *(Covidien)*

- **RHAS**: (n = 8)
  - ΔoSBP at 6 month: -42mmHg
  - ΔoDBP at 6 month: -15mmHg

**Vessix V2** *(Boston Scientific)*

- **ReduceHTN**: (n = 10)
  - ΔoSBP at 1 month: -30mmHg
  - ΔoDBP at 1 month: -11mmHg
  - Response Rate: 100% at 1 month

**Paradise** *(ReCor)*

- **REALISE**: (n = 20)
  - Δ BP at 6 month: -21/9mmHg
  - Δ ABP at 6 month: -9/4mmHg
Downstream effects of “HTN-3”

*Cordis Renlane*
10 patient German study, removed from market

*Covidien OneShot*
Discontinued product in 2014 due to slow market development

*Terumo Iberis*
2 case reports in 2013, no ongoing studies
EnligHTN – St. Jude
EnligHTN – St. Jude

**Office BP Reduction from Baseline**

EnligHTN therapy delivers a rapid significant reduction in Office BP that is sustained through the 24-month timeframe.

**EnligHTN III: Twelve-Month Clinical Data**

Office BP Reduction from Baseline

<table>
<thead>
<tr>
<th>Month</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
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<tbody>
<tr>
<td>Month 1</td>
<td>-19</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>-26</td>
<td>-7</td>
</tr>
<tr>
<td>Month 6</td>
<td>-9</td>
<td>-9</td>
</tr>
<tr>
<td>Month 12</td>
<td>-7</td>
<td>-7</td>
</tr>
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</table>

95% CI

<table>
<thead>
<tr>
<th>Month</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Month 3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Month 6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Month 12</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**EnligHTN I: 24-Month Clinical Data**

- Systolic BP
- Diastolic BP
Vessix
Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension (REDUCE HTN:REINFORCE)

- Randomized, sham-controlled, multicenter study
- The primary efficacy assessment is the mean reduction in average 24-hour ambulatory systolic blood pressure (ASBP) at eight weeks post randomization.

<table>
<thead>
<tr>
<th>Estimated Enrollment:</th>
<th>100</th>
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<tbody>
<tr>
<td>Study Start Date:</td>
<td>April 2015</td>
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<tr>
<td>Estimated Study Completion Date:</td>
<td>March 2021</td>
</tr>
<tr>
<td>Estimated Primary Completion Date:</td>
<td>February 2018 (Final data collection date for primary outcome measure)</td>
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ReCor Medical Paradise System
A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN)

- Randomized, double-blind, sham controlled
- Primary Outcome Measures: Mean reduction in average daytime ambulatory systolic BP: from baseline to 2 months post procedure

Estimated Enrollment: 292
Study Start Date: March 2016
Estimated Study Completion Date: August 2021
Estimated Primary Completion Date: August 2018 (Final data collection date for primary outcome measure)
baseline to 6 months was analyzed for all patients and renal function; a cohort with severe hypertension ≥135 mm Hg; and ≥3 antihypertensive medication safety events. Six-month outcomes for 998 patients, baseline office systolic BP was 163.5±24.0 mm Hg corresponding baseline 24-hour mean systolic BPs with office and 24-hour systolic BPs were −11.6±25.3 and −8.9±16.9 mm Hg for those with severe hypertension rates of adverse events. After the procedure through hospitalization for a hypertensive emergency. In office and 24-hour BPs with a favorable safety profile baseline pressures.

Clinical Trial Registration—URL: www.clinicaltrials.gov (Hypertension. 2015;65:766-774. DOI: 10.1161/HYPERTENSIONAHA.114.06791)

Key Words: denervation • hypertensive emergency

**Abstract**

The benefit of renal nerve ablation in patients with severe hypertension was analyzed in the HALT-II trial. A total of 998 patients with severe hypertension were randomly assigned to renal nerve ablation or sham procedure. The primary endpoint was a composite of mortality, hospitalization for a hypertensive emergency, or a ≥20 mm Hg increase in office systolic blood pressure (SBP). The primary analysis was revised to include ≥3 antihypertensive medication safety events.

The study was stopped early due to an increased risk of mortality, hospitalization, or ≥20 mm Hg increase in office SBP, and ≥3 antihypertensive medication safety events. The results were consistent across all subgroups, including patients with baseline renal function impairment. The findings suggest that renal nerve ablation may be a viable treatment option for patients with severe hypertension, particularly those with multiple antihypertensive medication safety events.
Figure 2. The next-generation Symplicity Spyral™ catheter is 6 French compatible, 0.014” wire monorail technology that allows the electrode energy delivery and reduced ablation times.
The SPYRAL HTN Global Clinical Trial Program: Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications
SPYRAL HTN-ON MED Study

Patients to be treated with a consistent triple therapy antihypertensive regimen

SPYRAL HTN-OFF MED Study

3- to 4-week drug washout period followed by a 3-month efficacy and safety end point in the absence of antihypertensive medications

- Primary Outcome Measures:
  - Major Adverse Events
  - Change in SBP

<table>
<thead>
<tr>
<th>Estimated Enrollment:</th>
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<th>120</th>
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<tbody>
<tr>
<td>Study Start Date:</td>
<td>June 2015</td>
<td>June 2015</td>
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<tr>
<td>Estimated Study Completion Date:</td>
<td>July 2020</td>
<td>July 2020</td>
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<tr>
<td>Estimated Primary Completion Date:</td>
<td>July 2017 (Final data collection date for primary outcome measure)</td>
<td>July 2017 (Final data collection date for primary outcome measure)</td>
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A Prospective, Post-marketing, Single-arm, Open Label, Multi-center Clinical Study to Evaluate the Safety and Efficacy of the ReDy™ Renal Denervation System in the Treatment of Patients With Uncontrolled Hypertension

Estimated Enrollment: 55
Study Start Date: April 2016
Estimated Study Completion Date: August 2017
Estimated Primary Completion Date: April 2017 (Final data collection date for primary outcome measure)

Primary Outcome Measures: Device-related adverse events at 1-month follow-up post treatment
Annual Publications on "Renal Sympathetic Denervation" from PubMed
Conclusions

• Uncontrolled hypertension is a global epidemic that, for a significant portion of the population, is inadequately managed

• Future studies on Renal Denervation are necessary for mainstream use

• The saga continues...