Renal Denervation for Resistant Hypertension

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Disclosures
- Advisory Board
  - Abbott Vascular, Access Closure
- Speakers Bureau
  - Abbott Vascular, Eli Lilly, Astra-Zeneca
- Clinical Research Trials
  - Medtronic, Abbott Vascular
Agenda

- Define Resistant Hypertension
- Role of Sympathetic Nervous System in HTN
- Renal Denervation as therapy
- Summary of prior investigations
- Symplicity HTN-3 clinical study design
- Upcoming Clinical Studies
- Future Applications

Resistant Hypertension & Overview of the Sympathetic Nervous System in Hypertension
Definition of Resistant Hypertension

**Uncontrolled Hypertension**
- Includes all patients who lack BP control on treatment, including those on inadequate treatment regimens, those with poor adherence, those with undetected secondary hypertension, as well as those with true treatment resistance.¹

**Resistant Hypertension**
- BP that remains above goal in spite of compliance with full doses of ≥3 antihypertensive medications of different classes; ideally, 1 of the 3 agents should be a diuretic.²
- The treatment plan must include attention to lifestyle measures.²
- Includes those patients who achieve BP control but require ≥4 antihypertensive agents to do so.¹

What is the prevalence of resistant HTN you see in your practice?
- A) 5%
- B) 10%
- C) 20%
- D) 30%
- E) > 50%

Prevalence of Resistant Hypertension
- Exact prevalence of resistant hypertension is unknown.¹
- Small studies estimate the prevalence at approximately
  - 5% in general practice
  - ≥50% in nephrology clinics.²
- NHANES estimated prevalence of resistant hypertension (15,968 pts)
  - 8.9% of all adults with hypertension
  - 12.8% of all drug-treated hypertensive adults in the US.³

Cardiovascular Mortality Risk Doubles With Each 20/10 mm Hg Increase in BP *

**Cardiovascular** Mortality Risk

- SBP/DBP: mm Hg
- CV M: Cardiovascular; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.
- *In individuals aged 40 to 69 years (10-year study period), starting at BP 115/75 mm Hg.
- Meta analysis: 61 studies, 1 million pts

Consequences of Hypertension

- Pre-hypertension
- Severe hypertension
- Proteinuria
- Nephrosclerosis
- Left ventricular hypertrophy
- Atrial fibrillation
- Systolic/diastolic dysfunction
- Chronic renal failure
- Left ventricular tachycardia/fibrillation
- Stroke
- Congestive heart failure
- End-stage renal disease
- Hypertensive encephalopathy
- Insulin resistance
- Binswanger lesions
- Retroperitoneal fibrosis
- Ischemic heart disease
- Myocardial infarction
- Dementia
- Transient ischemic attack
- Congestive heart failure
- Death

Even Small Reductions in BP Reduce Risk of CV Mortality

- Meta-analysis of 61 prospective, observational studies
- 1 million adults (40-89 years; 70% Europe, 20% North America or Australia, 10% Japan or China)
- 12.7 million person-years
- 2 mm Hg decrease in mean office SBP
- 10% reduction in risk of stroke mortality
- 7% reduction in risk of ischemic heart disease mortality

SBP= Systolic Blood Pressure.
Drivers of Arterial Blood Pressure

- Extracellular fluid volume
- Blood volume
- Cardiac output
- Peripheral resistance
- Arteriovenous compliance
- Resistance to venous return

\[ \text{Arterial pressure} = \text{Peripheral resistance} \times \text{Cardiac output} \]


The Sympathetic Nervous System

- The SNS supplies catabolic signals to the body, acting whenever rapid response to the environment is needed
- Functions include:
  - Accelerating the heart
  - Dilating coronary vessels
  - Increasing arterial BP
  - Emptying blood reservoirs
  - Dilating bronchi
  - Releasing glucose
  - Inhibiting GI activity

The Sympathetic Nervous System

Epinephrine—adrenal glands
Norepinephrine—kidney

GI=gastrointestinal.

Adapted from Campbell WW. DeJong’s The Neurologic Examination: Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. 6th ed. 2005.

Afferent (not Efferent) Renal Sympathetics send signals from the Kidneys to the CNS?

- A) True
- B) False
Effect of Afferent Renal Nerves on Sympathetic Activity

The kidney is a source of central sympathetic activity, sending signals to the CNS.


Renal Nerves and the SNS

Effect of Efferent Renal Nerves on Sympathetic Activity

Sympathetic signals from the CNS modulate the physiology of the kidneys.


Crosstalk Between Renal Nerves and CNS

↑ Neurohormones

↑ Blood Pressure

Amplifies central, or systemic, sympathetic outflow

Kidney impairment, or dysfunction, no change


Sympathetic Imbalance

Acute Adrenergic Stimulation is critical for survival

Chronic Adrenergic Stimulation is maladaptive
Central Sympathetic Drive in Hypertension

- Sympathetic drive is elevated in multiple types of hypertension

![Graph showing sympathetic drive in various types of hypertension](image)

- s-MSNA=single-unit efferent sympathetic nerve activity.
- LVH=left ventricular hypertrophy.

* P < 0.05 Compared with borderline hypertension.
† P < 0.05 Compared with white coat hypertension.
‡ P < 0.05 Compared with normal pressure.
§ P < 0.05 Compared with high-normal pressure.
¶ P < 0.05 Compared with essential hypertension-stage 1.
# P < 0.05 Compared with essential hypertension-stage 2/3.


Sympathectomy: An Early Surgical Option

Dr. Reginald H. Smithwick

Surgical Sympathectomy in Essential Hypertension Provided Beneficial Effect on Survival

![Graph showing survival rates after surgical sympathectomy](image)

However, surgical sympathectomy was associated with significant morbidity: postural hypotension, orthostatic tachycardia, intestinal disturbances, ED, palpitations.

Methodology of Catheter-Based Renal Denervation

Renal Denervation

↑ Neurohormones

↑ Blood Pressure

Disrupt the renal nerves, break the cycle
Simultaneously reduce both efferent & afferent effects


Renal Sympathetic-Nerve Ablation for Uncontrolled Hypertension

New Engl J Med Case Study

59-year-old patient, resistant hypertension on 7 BP meds, had renal sympathetic-nerve activity modulated by catheter-based radiofrequency (RF) ablation

Reduced Sympathetic-Nerve Activity After Catheter-Based RDN*  
*New Engl J Med Case Study

<table>
<thead>
<tr>
<th></th>
<th>MSNA (burst/min)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>56</td>
<td>161/107</td>
</tr>
<tr>
<td>1 Month</td>
<td>41</td>
<td>141/90 (-20/-17)</td>
</tr>
<tr>
<td>12 Months</td>
<td>19</td>
<td>127/81 (-34/-26)</td>
</tr>
</tbody>
</table>


Improvement in cardiac baroreflex sensitivity after RDN (7.8 → 11.7 msec/mm Hg)

Targeting Renal Nerves

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia

Renal Nerve Anatomy Allows a Catheter-Based Approach

- Access achieved using standard interventional technique
- 4-6 120-second treatments per artery
Investigational Symplicity™ Renal Denervation System

- Generator will automatically control RF energy delivery:
  - Power automatically ramped and maintained (3-8W)
  - Continuously monitors temperature and impedance
  - Automatically shuts off after 120 seconds or when either impedance or temperature exceed program limits

Flexible Tip (self-orienting)

Deflectable Shaft

Six Month Post-Procedure Histology (Porcine Model)

Movat’s Pentachrome Stain

- An area of medial injury (yellow) is located between the arrows on the left. An enlargement of the boxed region is shown on the right.
  - Findings: minimal intimal thickening and minimal internal elastic lamina injury overlying areas of mild full thickness medial fibrosis (yellow [fibrosis]) with green [proteoglycan deposition] and adventitial fibrosis (yellow)


Six Month Post-Procedure Nerve Histology (Porcine Model)

H&E

- Nerve from untreated vessel: Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium)
- Nerve from treated vessel: Periarterial nerve bundle has a hypervascular appearance and the perineurium has a thickened and fibrotic appearance.

The Symplicity HTN Trials

Symplicity Staged Evaluation in Hypertension and Beyond

- **Symplicity HTN-1**
  - First-in-Man
  - Series of Pilot Studies

- **Symplicity HTN-2**
  - EU/AU Randomized Clinical Trial

- **Symplicity HTN-3**
  - US Randomized Clinical Trial (enrolling)
  - Approved Geographies
  - Other Areas of Research
  - Global SYMPLICITY Registry


**Symplicity HTN-2 Design**

**Purpose:** To demonstrate the effectiveness of catheter-based renal denervation (RDN) for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial

- **Patients:** 196 patients with drug-resistant hypertension randomized 1:1 to treatment with RDN vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand
- **Primary Endpoint:** Office systolic BP change from baseline at 6 months
Patient Population

Inclusion Criteria:
- Office SBP ≥160 mm Hg (≥150 mm Hg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:
- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR <45 mL/min/1.73m² (MDRD formula)
- Type 1 diabetes mellitus
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months


Symplicity HTN-2 Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Symplicity RDN Group (n=52)</th>
<th>Control Group (n=54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>58 ± 12</td>
<td>58 ± 12</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>35</td>
<td>50</td>
<td>0.12</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>98</td>
<td>96</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (%)</td>
<td>40</td>
<td>28</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>12</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>52</td>
<td>52</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Mean eGFR ± SD (mL/min/1.73m²)</td>
<td>77 ± 19</td>
<td>86 ± 20</td>
<td>0.013</td>
</tr>
<tr>
<td>eGFR 45-60 mL/min/1.73m² (%)</td>
<td>21</td>
<td>11</td>
<td>0.19</td>
</tr>
</tbody>
</table>

2. Data on file, Medtronic.

Symplicity HTN-2 Trial: Baseline Characteristics (cont)

<table>
<thead>
<tr>
<th></th>
<th>Symplicity RDN Group (n=52)</th>
<th>Control Group (n=54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline SBP ± SD (mm Hg)</td>
<td>176 ± 18</td>
<td>176 ± 14</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean baseline DBP ± SD (mm Hg)</td>
<td>96 ± 16</td>
<td>96 ± 17</td>
<td>0.89</td>
</tr>
<tr>
<td>Mean number of antihypertensive medications ± SD</td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>69</td>
<td>91</td>
<td>0.76</td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>17</td>
<td>17</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Direct vasodilator (%)</td>
<td>98</td>
<td>94</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Betablocker (%)</td>
<td>55</td>
<td>66</td>
<td>0.13</td>
</tr>
<tr>
<td>Calcium-channel blocker (%)</td>
<td>79</td>
<td>83</td>
<td>0.62</td>
</tr>
<tr>
<td>Central acting sympatholytic (%)</td>
<td>52</td>
<td>52</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Vasodilator (%)</td>
<td>15</td>
<td>17</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Alpha-1 blocker (%)</td>
<td>33</td>
<td>19</td>
<td>0.12</td>
</tr>
</tbody>
</table>

2. Data on file, Medtronic.
At 6-month follow up what was average drop in BP in treatment arm?

- A) None
- B) 10/5 mmHg
- C) 20/10 mmHg
- D) 30/10 mmHg
- E) 40/15 mmHg

Primary Endpoint: 6-Month Office BP

![BP Graph]

- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

RDN Procedural Safety

Adverse events (n = 52)

- 1 femoral artery pseudoaneurysm treated with manual compression
- 1 post-procedural drop in BP resulting in a reduction in medication
- 1 urinary tract infection
- 1 prolonged hospitalization for evaluation of paraesthesias
- 1 back pain treated with pain medications & resolved after one month

6-month renal imaging (n = 43)

- No vascular abnormality at any RF treatment site
- 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)
Primary Endpoint reached.

Randomization

Office BP 18 months Post Procedure

Baseline 6M Baseline 6M Post RDN 12M Baseline 12M Post RDN 18M Baseline 18M Post RDN

RDN

Control Crossover

Stolic BP (mmHg)

Patients randomized to control were offered RDN following the primary endpoint assessment. Only patients still meeting entry criteria (SBP ≥ 160 mmHg) were included in this analysis (n=37).

Renal Function Over Time

Stage I

Stage II

Stage III

Stage IV

ESRD

Stage V

Stage II

Stage III

Stage IV

Stage V

Baseline 6M post-RDN 12M post-RDN
### Other Safety: 0-6 Months Post Randomization

<table>
<thead>
<tr>
<th>Event</th>
<th>Symplicity RDN Group (n=49)</th>
<th>Control Group (n=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CV Events</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hypertensive event unrelated to non-adherence to medication</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other CV events</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Other Serious AEs

<table>
<thead>
<tr>
<th>Event</th>
<th>Symplicity RDN Group (n=49)</th>
<th>Control Group (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive event after abruptly stopping clonidine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive episode resulting in reduction of medications</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Coronary stent for angina</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Temporary nausea/edema</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>


### Symplicity HTN-2 Trial: Medication Changes

<table>
<thead>
<tr>
<th>Medication dose decrease (%)</th>
<th>Symplicity RDN Group (n=49)</th>
<th>Control Group (n=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=10)</td>
<td>20</td>
<td>5</td>
<td>0.04</td>
</tr>
<tr>
<td>(n=4)</td>
<td>8</td>
<td>12</td>
<td>0.74</td>
</tr>
</tbody>
</table>

- Censoring BP data (after medication increases)
  - Among those who had no drug increases, the absolute difference between groups after 6 months was 3.7/11 mm Hg (P=0.0001)

**SYMPLICITY HTN-3: Overview**

- **Design**
  - Multicenter (90 sites in the United States), prospective, randomized, blinded, controlled study
- **Population**
  - 530 patients with treatment-resistant hypertension
- **Treatment**
  - Treatment group (endovascular catheter-based RDN with the Symplicity™ renal denervation system plus baseline antihypertensive medications)
  - Control group (sham procedure* plus baseline antihypertensive medications)

**Primary Outcome Measures**

- Change in office SBP from baseline to 6 months
- Safety


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**SYMPLICITY HTN-3 Trial: Inclusion Criteria**

- **Average SBP ≥160 mm Hg** (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80 years

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**SYMPLICITY HTN-3 Trial: Exclusion Criteria**

- Hemodynamically or anatomically significant renal artery abnormalities or stenosis (>50%) or prior renal artery intervention
- eGFR <45 mL/min/1.73m² (MDRD formula)
- In-patient hospitalization for HTN Crisis in past year
- 24-hour average ABPM SBP <135 mm Hg
- Type 1 diabetes mellitus
- Symptomatic orthostatic hypotension in past year
- Stenotic valvular heart disease for which ↓BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months
- Planned surgery or CV intervention within the next 6 months
- Known primary pulmonary HTN
- Known pheochromocytoma, Cushing’s disease, coarctation of the aorta, hyperthyroidism or hyperparathyroidism
- Known alcohol or drug abuse

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SYMPLICITY HTN-3 Trial: Study Design

What is the inclusion criteria for Symplicity HTN-3?

- A) SBP>180, >=3 BP meds
- B) SBP>180, >=3 BP meds with one a Diuretic
- C) SBP>160, >=3 BP meds
- D) SBP>160, >=3 BP meds with one a Diuretic
- E) SBP>160, >=3 BP meds plus a Diuretic

SYMPLICITY HTN-3: Summary

- Office SBP ≥160 mm Hg
- ≥3 antihypertensive medications (one must be a diuretic)
- On stable, ≥3 full tolerated dose antihypertensive medication regimen for at least 2 weeks
- No significant renal insufficiency (eGFR <45 mL/min)
- Meets inclusion/exclusion criteria by general medical review
- No known renal artery anatomy exclusion (i.e. dual renal arteries, known RA stenosis ≥50%)
- Until 6-month primary endpoint:
  - Patients must remain blinded
  - No changes in medication unless medically necessary
- After 6-month endpoint, control patients can crossover if still meet all initial criteria
**Baylor University Medical Center Experience**

- First Patient Screened: March 2012
- First Patient Randomized: May 2012
- Prescreened: 177 pts
- Screened: 57 pts (1st out of 88 sites)
- Screen Failures: 34 (4 based on anatomy)
- Angiogram: 27 pts
  - 1 renal cell carcinoma
- Randomized: 23 pts (1st out of 88 sites)
- Cross-over Treatment: 3 pts

**Special Thanks**

- Cara East
- BHVH Cath Lab Team
- Robert Stoler
- Jeff Schussler
- George Feghali
- Andrew Fenves
- Venkata Ram

**Upcoming HTN Trials**
SYMPLICITY HTN-4

- **Objective:** To demonstrate that catheter-based renal denervation is an effective and safe treatment for uncontrolled hypertension.

- **Population:** SBP ≥140 and <160mmHg or 3 or more maximum tolerated doses of anti-hypertension medications of 3 different classes, one of which must be a thiazide/thiazide-like diuretic (unless approved by medical monitor).

- **Design:**
  - Up to 100 study centers
  - Enrollment of approximately 2000 subjects to reach 530 randomized
  - 6 Month blinding requirement
  - 2:1 randomization (treatment/control)
  - Stratification by race (African American vs. other) and by study center
  - 5 year follow up

Vessix (Boston)

- Unipolar: less energy
- Multiple burns at once

HTN trial:
- SBP>160
- SBP 140-160
- Not randomized

2nd Generation Devices

EnligHTN (St Jude) OneShot (Covidien)
Future Applications

- ESRD
- Systolic CHF
- Aflb
- Ventricular Tachycardia
- Metabolic Syndrome/Insulin resistance
- Polycystic Ovarian Disease
- Obstructive Sleep Apnea