RENAL DENERVATION THERAPY FOR RESISTANT HYPERTENSION

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CONSULTANT PHYSICIAN
PAMELA YOUDE NETHERSOLE EASTERN HOSPITAL

HA Convention, 7 May 2014
DRUGS: MAINSTAY OF TREATMENT FOR HYPERTENSION
RENAL DE-NERVATION THERAPY FOR RESISTANT HYPERTENSION
FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

A Need of Change
HYPERTENSION: A MAJOR PUBLIC HEALTH BURDEN

**CVD Mortality Risk Doubles with Each 20/10 mm Hg BP Increment**

*Individuals aged 40-69 years, starting at BP 115/75 mm Hg.*
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure
JNC VII. JAMA. 2003.
BENEFITS OF BP CONTROL IN REDUCING COMPLICATIONS

Meta-analysis of 61 prospective, observational studies which involve 1 million adults

Blood Pressure reduction of 2 mmHg decreases the risk of cardiovascular events by 7-10%

DRUGS WORK, BUT NOT AS WELL AS YOU MAY THINK

- Current approach failing:
  - Physician inertia
  - Patient compliance
  - Resistant HTN

Renal denervation (RDN) = potentially a compliance-independent therapy
FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

A Basis for Change
RENAL DENERVATION
WELL-ESTABLISHED SCIENTIFIC FOUNDATION

- Roles of kidneys and sympathetic nervous system in development and progression of HTN is well established
- Pharmaceuticals modify physiology at intermediate steps in pathway
- RDN attempts to break the cycle at its source
RENAL SYMPATHETIC NERVE ACTIVITY: KIDNEY AS ORIGIN & RECIPIENT OF CENTRAL SYMPATHETIC DRIVE

- Vasoconstriction
- ↑ Contractility
- • ↑ Heart rate
- Afferent Nerves
- Efferent Nerves
- Blood Pressure
- ↑ Renin Release → RAAS activation
- ↑ Sodium Retention
- ↓ Renal Blood Flow

RENAL SYMPATHETIC NERVE ACTIVITY:
KIDNEY AS ORIGIN & RECIPIENT OF CENTRAL SYMPATHETIC DRIVE

• Vasoconstriction
• Atherosclerosis

• ↑ Contractility
• ↑ Heart rate
• Hypertrophy
• Arrhythmia
• Heart Failure

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
↓ Kidney function

Blood Pressure
+ Increase co-morbidities

RENAL SYMPATHETIC NERVE ACTIVITY:
RDN DISRUPTS RENAL NERVES, LOWERING SNS ACTIVITY

Afferent Nerves
- ↑ Contractility
- ↑ Heart Rate
- Hypertrophy
- Arrhythmia
- Heart Failure
- ↑ Renin Release → RAAS activation
- ↑ Sodium Retention
- ↓ Renal Blood Flow
- ↓ Kidney function

Efferent Nerves
- ↑ Contractility
- ↑ Heart Rate
- Hypertrophy
- Arrhythmia
- Heart Failure

Blood Pressure
- Decrease comorbidities

→ Renal Denervation (RDN) →

Effective, but significant, morbidity
Sympathectomy in Hypertension: Effects on survival, but side effects and complications

Denervating lower half of the body produced:
- Mortality benefit
- Inconsistent BP results
- Significant morbidity including orthostatic hypotension, bowel & bladder dysfunction

Smithwick RH, J Am Med Assoc. 1953;152:1501-1504
FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

A Way to Change
RENAL ANATOMY ALLOWS A CATHETER-BASED APPROACH

- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent and afferent nerves travel together
VASCULAR SAFETY PREDICTED BY PRECLINICAL STUDIES

- Extensive research in >300 swine
- Angiography and pathology at 7, 30, 60 and 180 days
- No stenosis or luminal reduction seen in treated arteries
- RF generator algorithm optimized to minimize vascular injury
COMMERCIALLY AVAILABLE
RENAL DENERVATION SYSTEM
MEDTRONIC SYMPlicity

- Low-profile, electrode tipped catheter
- Delivers RF energy to treatment site
- Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
- Standard interventional technique
- 40 minutes from first to last RF delivery
PROCEDURE OVERVIEW
Example Treatment Locations in a Right Renal Artery
FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

An Effect from the Change
CLINICAL RESULTS
SYMPLICITY Clinical Trial Programs: over 5000 patients across multiple indications

First-in-Man (AU)

Series of Pilot Studies (EU, US & AU)

Symplicity HTN-2
Initial RCT (EU & AU)

SYMPLICITY HTN-3
US Pivotal Trial (US)

Global SYMPLICITY Registry (Approved Regions)

Expand HTN Indication (Approved Regions)

Pilot Studies in New Indications (Approved Regions)

SYMPLICITY HF
**Key Inclusion Criteria**

- Office SBP ≥160 mmHg
- Stable drug regimen of 3+ more anti-HTN medications (including diuretic)
- eGFR ≥45 mL/min/1.73m²

**Non-randomized**

**Initial cohort:** 45 patients

**Expanded cohort:** 153 patients

36-month follow-up

## BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>57 ± 11</td>
<td></td>
</tr>
<tr>
<td>Gender (female) (%)</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Race (noncaucasian) (%)</td>
<td>5</td>
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</table>

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th></th>
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<tbody>
<tr>
<td>Diabetes mellitus type 2 (%)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>CAD (%)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>83 ± 20</td>
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</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th></th>
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<tbody>
<tr>
<td>Baseline BP (mmHg)</td>
<td>176/98 ± 17/15</td>
<td></td>
</tr>
<tr>
<td>Number of anti-HTN meds (mean)</td>
<td>5.0 ± 1.4</td>
<td></td>
</tr>
</tbody>
</table>

- ACE/ARB (%): 90
- Beta blocker (%): 82
- Calcium channel blocker (%): 75
- Vasodilator (%): 19
- Diuretic (%): 95
- Spironolactone (%): 21

SIGNIFICANT, SUSTAINED BLOOD PRESSURE REDUCTIONS TO AT LEAST 3 YEARS

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

$P < 0.01$ for $\Delta$ from baseline for all time points
BRIEF PROCEDURE WITH A LOW COMPLICATION RATE

- 38-minute median time from first to last ablation
  - Average of 4 ablations per artery
- Intravenous narcotics and sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- Minor complications 4/153
  - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  - 3 access site complications, treated without further sequelae

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)
SYMPLECTICITY Clinical Trial Programs:
over 5000 patients across multiple indications

First-in-Man (AU)

Series of Pilot Studies (EU, US & AU)

Symplicity HTN-2
Initial RCT (EU & AU)

Symplicity HTN-1

SYMPLICITY HTN-3
US Pivotal Trial (US)

Global SYMPLICITY Registry (Approved Regions)

Expand HTN Indication (Approved Regions)

Pilot Studies in New Indications (Approved Regions)

Post-Market Registry (US)

SYMPLICITY HF
Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators*
SYMPLECTICITY HTN-2: RANDOMISED CONTROLLED TRIAL

• Patients: 106 patients randomised 1:1 to treatment with RDN vs. control
• Clinical sites: 24 centres in Europe, Australia and New Zealand

Key Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Office SBP ≥160 mmHg (≥150 mmHg with type 2 diabetes mellitus)</td>
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<tr>
<td>– Stable drug regimen of 3+ more anti-HTN medications</td>
</tr>
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<td>– Age 18–85 years</td>
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<table>
<thead>
<tr>
<th>Exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention</td>
</tr>
<tr>
<td>– eGFR &lt;45 mL/min/1.73m² (MDRD formula)</td>
</tr>
<tr>
<td>– Type 1 diabetes mellitus</td>
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<tr>
<td>– Contraindication to MRI</td>
</tr>
<tr>
<td>– Stenotic valvular heart disease for which reduction of BP would be hazardous</td>
</tr>
<tr>
<td>– MI, unstable angina or CVA in the past 6 months</td>
</tr>
</tbody>
</table>

*Lancet 2010; 376: 1903–09;* Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)
SYMPLICITY HTN-2: RDN SUPERIOR TO MEDICAL MANAGEMENT

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

Latest Follow-up:
- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)
SYMPPLICITY HTN-2: BP REDUCTIONS SUSTAINED TO 3 YEARS

Sustained Reductions in the Pooled (RDN and Crossover) Group*

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
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<tbody>
<tr>
<td>6 Months</td>
<td>-28</td>
<td>-10</td>
</tr>
<tr>
<td>12 Months</td>
<td>-26</td>
<td>-10</td>
</tr>
<tr>
<td>18 Months</td>
<td>-31</td>
<td>-12</td>
</tr>
<tr>
<td>24 Months</td>
<td>-30</td>
<td>-11</td>
</tr>
<tr>
<td>30 Months</td>
<td>-34</td>
<td>-13</td>
</tr>
<tr>
<td>36 Months</td>
<td>-33</td>
<td>-14</td>
</tr>
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</table>

*P <0.01 at all time points

*Crossover patients only had 30 months post-procedure data.

Whitbourn, TCT 2013
PROCEDURAL SAFETY (EXPANDED COHORT)

• One renal artery dissection from injection of contrast into renal artery wall during dye angiography. The lesion was stented without further consequences.

• One hospitalization prolonged in a crossover patient due to hypotension following the RDN procedure. IV fluids administered, anti-hypertensive medications decreased and patient discharge without further incident.

• No radiofrequency-related renal artery stenosis or aneurysm occurred in either Randomised group.

• Minor adverse events (full cohort)
  • 1 femoral artery pseudoaneurysm treated with manual compression
  • 1 postprocedural drop in BP resulting in a reduction in medication
  • 1 urinary tract infection
  • 1 prolonged hospitalisation for evaluation of paraesthesias
  • 1 back pain treated with pain medications and resolved after 1 month

*Lancet 2010; 376: 1903–09; Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)*
SYMPPLICITY Clinical Trial Programs: over 5000 patients across multiple indications
Global Symplicity Registry (GSR)

Consecutive patients treated in real-world population 5000 patients

GREAT Registry  N = 1000
Korea Registry*  N = 102
South Africa Registry*  N = 400
Canada and Mexico*  
Rest of GSR  N ≈ 3500

Follow-up schedule:
3M  6M  1Y  2Y  3Y  4Y  5Y

* Limited to resistant hypertension only
Change in Office Systolic BP for All Patients and Subgroups

-25 -20 -15 -10 -5 0 5 10 15 20

All Patients*

<140 mm Hg*

140-159 mm Hg †

≥160 mm Hg*

N=769  N=751  N=94  N=96  N=227  N=222  N=448  N=433

-10.0 -11.9 12.9 14.2 -2.0 -4.6 -18.9 -21.4

*P<0.0001 for both 3 and 6 month change from baseline
†P=0.14 at 3 months and P=0.0006 at 6 months
Distribution of SBP in Patients With Office SBP ≥160 mm Hg and Ambulatory SBP ≥135 mm Hg* at Baseline

*with ≥3 antihypertensive medication classes
Multiple Devices Developed for Renal Denervation Therapy
MULTIPLE UNBLINDED TRIALS SHOW RDN LOWERS BLOOD PRESSURE

Published Sources:
1. Lancet 2009
2. Lancet 2010
3. TCT 2013
4. Journal of Human Hypertension 2013
5. Circulation 2013
8. Eur Heart J 2013
9. TCT 2013
10. Eurointervention 2013
11. EuroIntervention 2013
Expert consensus document from the European Society of Cardiology on catheter-based renal denervation

Felix Mahfoud\textsuperscript{1*}, Thomas Felix Lüscher\textsuperscript{2}, Bert Andersson\textsuperscript{3}, Iris Baumgartner\textsuperscript{4}, Renata Cifkova\textsuperscript{5}, Carlo DiMario\textsuperscript{6}, Pieter Doesvendans\textsuperscript{7}, Robert Fagard\textsuperscript{8}, Jean Fajadet\textsuperscript{9}, Michel Komajda\textsuperscript{10}, Thierry LeFèvre\textsuperscript{11}, Chaim Lotan\textsuperscript{12}, Horst Sievert\textsuperscript{13}, Massimo Volpe\textsuperscript{14,15}, Petr Widimsky\textsuperscript{16}, William Wijns\textsuperscript{17}, Bryan Williams\textsuperscript{18}, Stephan Windecker\textsuperscript{19}, Adam Witkowski\textsuperscript{20}, Thomas Zeller\textsuperscript{21}, and Michael Böhm\textsuperscript{1}

- Office-based systolic BP $\geq 160$ mmHg ($\geq 150$ mmHg diabetes type 2)
- $\geq 3$ antihypertensive drugs in adequate dosage and combination (incl. diuretic)
- Lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudo-resistance using ABPM (average BP $> 130$ mmHg or mean daytime BP $> 135$ mmHg)
- Preserved renal function (GFR $\geq 45$ ml/min/1.73 m$^2$)
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization
RENAL DENERVATION BEYOND HYPERTENSION
RENAL DENERVATION BEYOND HYPERTENSION

- Vasoconstriction
- Atherosclerosis

↑ Contractility
↑ Heart rate
Hypertrophy
Arrhythmia
Heart Failure

Blood Pressure
+ Increase co-morbidities

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
↓ Kidney function

RENAL DENERVATION BEYOND HYPERTENSION

• ↑ Contractility
• ↑ Heart rate
• Hypertrophy
• Arrhythmia
• Heart Failure

Afferent Nerves

• Vasoconstriction
• Atherosclerosis

• ↑ Gluconeogenesis
• Insulin resistance

Efferent Nerves

• ↑ Renin Release → RAAS activation
• ↑ Sodium Retention
• ↓ Renal Blood Flow
• ↓ Kidney function

RDN REDUCES LV HYPERTROPHY & INCREASES CARDIAC FUNCTION IN RHTN PATIENTS
LEFT VENTRICULAR MASS

Figure 2  Impact of RD on LV Mass

(A) Left ventricular (LV) mass/height\(^{2.7}\) and (B) end-diastolic interventricular septum thickness (IVSTD) measured in renal sympathetic denervation (RD) and control patients at baseline, 1 month, and 6 months. While there was a steady decrease in the average left ventricular (LV) mass and IVSTD after RD, these parameters slightly increased in control patients. In the treatment group, p for statistical trend was \(p = 0.004\) for LV mass/height\(^{2.7}\) (A), \(p = 0.007\) for IVSTD (B). (C) Differential effect of RD on LV mass regression depends on the degree of left ventricular hypertrophy (LVH) at baseline. LV mass/height\(^{2.7}\) regression by RD was significantly greater in those patients with LVH at baseline. Values are presented as mean ± standard error. (D) Regression of LV mass after RD in individual patients with a LVH at baseline (n = 29). LVM = left ventricular mass index.
RDN IMPROVES GLUCOSE METABOLISM

Fasting Glucose

- Change in fasting glucose (mg/dl)
  - 1 month: -8.9 (p=0.043)
  - 3 months: -9.4 (p=0.039)
- Renal denervation (n=37)
- Control (n=13)

Fasting Insulin

- Change in fasting insulin (μU/ml)
  - 1 month: -8.7 (p=0.036)
  - 3 months: -11.6 (p=0.006)
- Renal denervation (n=37)
- Control (n=13)

Fasting C-Peptide

- Change in fasting C-peptide (ng/ml)
  - 1 month: -2.0 (p=0.006)
  - 3 months: -2.3 (p=0.002)
- Renal denervation (n=37)
- Control (n=13)

Insulin Sensitivity

- Change in HOMA-IR (ng/ml)
  - 1 month: -3.1 (p=0.008)
  - 3 months: -3.7 (p=0.001)
- Renal denervation (n=37)
- Control (n=13)

RENAL DENERVATION THERAPY FOR RESISTANT HYPERTENSION IN TYPE 2 DIABETES MELLITUS (HTN2DM STUDY)

ClinicalTrials.gov Identifier: NCT01887067

PI: Dr. Tsui Kin Lam (Pamela Youde Nethersole Eastern Hospital)
Renal Denervation Therapy for Resistant Hypertension in Type 2 Diabetes Mellitus

**HTN2DM Study Design**

- Office systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mmHg
- Stable regimen of 3 or more anti-hypertensive medications of different classes at fully tolerated dosage, including a diuretic
- Type 2 diabetes mellitus

**Symplicity Catheter**

- 15 patients
- 1 site (Pamela Youde Nethersole Eastern Hospital)

**Office Systolic & Diastolic BP**

<table>
<thead>
<tr>
<th></th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>2 yr</th>
<th>3 yr</th>
</tr>
</thead>
</table>

**Primary endpoint:**
- Change in office systolic & diastolic blood pressure from baseline to 6 months

**Secondary endpoints:**
- Change in office systolic and diastolic blood pressure up to 3 years
- Fasting glucose, HbA1c level, OGTT and spot urine albumin to creatinine ratio before and after renal denervation at 3-month, 12-month, and 36-month; HOMA-IR index before and after renal denervation at 3-month and 12-month
RENAL DENERVATION:
RENAL DENERVATION: THE ROAD TURNS BUMPY
Press Release

Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint

MINNEAPOLIS - January 9, 2014 - Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPLECTICITY HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

"SYMPLECTICITY HTN-3 met its primary safety endpoint related to the incidence of major adverse events one month following randomization and renal artery stenosis to six months," said Deepak L. Bhatt, M.D., M.P.H., executive director, Interventional Cardiovascular Programs, Brigham and Women’s Hospital Heart and Vascular Center, professor of medicine, Harvard Medical School, and co-principal investigator of SYMPLECTICITY HTN-3. "Importantly, however, the trial did not meet its primary efficacy endpoint."
SYMPLICITY Clinical Trial Programs: over 5000 patients across multiple indications

- **SYMPPLICITY HTN-3**
  - US Pivotal Trial (US)
  - Post-Market Registry (US)

- **Global SYMPPLICITY Registry**
  - (Approved Regions)

- **Expand HTN Indication**
  - (Approved Regions)

- **Pilot Studies in New Indications**
  - (Approved Regions)

- **SYMPPLICITY HF**
A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O’Neill, M.D., Ralph D’Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D.,

for the SYMPLECTICITY HTN-3 Investigators*

Key Inclusion/Exclusion Criteria

Key Inclusion:

- Stable medication regimen including full tolerated doses of 3+ anti-hypertensive medications of different classes, including a diuretic
- Office SBP ≥160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit

Key Exclusion:

- ABPM 24 hour average SBP <135 mm Hg
- eGFR of <45 mL/min/1.73 m²
- Main renal arteries <4 mm diameter or <20 mm treatable length
TRIAL OBJECTIVES

• SYMPLICITY HTN-3 is the first prospective, multi-center, randomized, blinded, sham controlled study to evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant hypertension.

• The trial included 535 patients enrolled by 88 participating US centers.

SYMPPLICITY HTN-3 TRIAL DESIGN

2 weeks

Home BP & HTN med confirmation

Screening Visit 1
• Office SBP ≥160 mm Hg
• Full doses ≥3 meds
• No med changes in past 2 weeks
• No planned med changes for 6 M

Screening Visit 2
• Office SBP ≥160 mm Hg
• 24-h ABPM SBP ≥135 mm Hg
• Documented med adherence

Renal Denervation

Sham Procedure

Renal angiogram; Eligible subjects randomized

Primary endpoint

2 weeks

Home BP & HTN med confirmation

1 M 3 M 6 M

12-60 M

• Patients, BP assessors, and study personnel all blinded to treatment status
• No changes in medications for 6 M

EFFICACY ENDPOINTS

Primary Effectiveness Endpoint:
• Comparison of office SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

\[
\text{Endpoint} = (\text{SBP}_{\text{RDN 6 month}} - \text{SBP}_{\text{RDN Baseline}}) - (\text{SBP}_{\text{CTL 6 month}} - \text{SBP}_{\text{CTL Baseline}})
\]

• Superiority margin of 5 mm Hg

Powered Secondary Effectiveness Endpoint:
• Comparison of mean 24-hour ambulatory (ABPM) SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

• Superiority margin of 2 mm Hg

**PRIMARY EFFICACY ENDPOINT**

\[ \Delta = -2.39 \text{ (95% CI, -6.89 to 2.12)} \]

\[ P=0.26^* \]

\[ \Delta = -14.1 \pm 23.9 \]

\[ P<0.001 \]

\[ \Delta = -11.7 \pm 25.9 \]

\[ P<0.001 \]

*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

POWERED SECONDARY EFFICACY ENDPOINT

\[ \Delta = -1.96 \text{ (95\% CI, -4.97 to 1.06)} \]

\[ P=0.98^* \]

\[ \Delta = -6.8\pm15.1 \]

\[ P<0.001 \]

\[ \Delta = -4.8\pm17.3 \]

\[ P<0.001 \]

\*P value for superiority with a 2 mm Hg margin; bars denote standard deviations.

**PRIMARY SAFETY ENDPOINT**

Major Adverse Event Rate (MAE)

Performance Goal = 9.8%

- **Renal Denervation (N=364)**: 1.4% (5/361)
- **Sham Procedure (N=171)**: 0.6% (1/171)

**Difference [95% CI]**: 0.8% [-0.9%, 2.5%]  

*P* = 0.67

---

HTN-3 RESULTS: POTENTIAL FACTORS

The Patient

- **Patient behavior** (improved or modified lifestyle and drug adherence) may change due to being enrolled and closely monitored in a clinical trial ("Hawthorne effect")

The Trial

- Patient demographics
- Medication adherence and medication change
- Duration of primary endpoint may have been too short

The Doctor

- Greater variation in procedural experience
HTN-3 RESULTS: POTENTIAL FACTORS

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- **Patient demographics**
- Medication adherence and medication change
- Duration of primary endpoint may have been too short

The Doctor

- Greater variation in procedural experience
## RESULTS: POPULATION DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Renal Denervation (N=364)</th>
<th>Sham Procedure (N=171)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.9 ± 10.4</td>
<td>56.2 ± 11.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>59.1</td>
<td>64.3</td>
<td>0.26</td>
</tr>
<tr>
<td>Office systolic blood pressure (mm Hg)</td>
<td>180±16</td>
<td>180±17</td>
<td>0.77</td>
</tr>
<tr>
<td>24 hour mean systolic ABPM (mm Hg)</td>
<td>159±13</td>
<td>160±15</td>
<td>0.83</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.2 ± 6.5</td>
<td>33.9 ± 6.4</td>
<td>0.56</td>
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<tr>
<td>Race* (%)</td>
<td></td>
<td></td>
<td>0.57</td>
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<tr>
<td>African American</td>
<td>24.8</td>
<td>29.2</td>
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<tr>
<td>White</td>
<td>73.0</td>
<td>69.6</td>
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<td>Medical history (%)</td>
<td></td>
<td></td>
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<tr>
<td>Renal insufficiency (eGFR&lt;60 ml/min/1.73m²)</td>
<td>9.3</td>
<td>9.9</td>
<td>0.88</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>1.4</td>
<td>2.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>25.8</td>
<td>31.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Stroke</td>
<td>8.0</td>
<td>11.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>47.0</td>
<td>40.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Hospitalization for hypertensive crisis</td>
<td>22.8</td>
<td>22.2</td>
<td>0.91</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>69.2</td>
<td>64.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Current smoking</td>
<td>9.9</td>
<td>12.3</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Race also includes Asian, Native American, or other

## RESULTS: PRESPECIFIED SUBGROUP ANALYSES

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th></th>
<th>Difference (95% CI)</th>
<th>Interaction P Value</th>
<th>P Value for superiority with margin of 5 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Denervation</td>
<td>Sham</td>
<td>mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>353</td>
<td>171</td>
<td>-2.39 (-6.89 - 2.12)</td>
<td>0.26 *</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>169</td>
<td>68</td>
<td>-4.53 (-11.51 - 2.46)</td>
<td>0.20</td>
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</tr>
<tr>
<td>No</td>
<td>181</td>
<td>101</td>
<td>-3.46 (-9.55 - 2.62)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>208</td>
<td>108</td>
<td>-2.30 (-7.63 - 3.03)</td>
<td>0.40</td>
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<tr>
<td>Female</td>
<td>142</td>
<td>61</td>
<td>-6.64 (-14.94 - 1.65)</td>
<td>0.12</td>
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<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>85</td>
<td>49</td>
<td>2.25 (-7.27 - 11.78)</td>
<td>0.64</td>
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<tr>
<td>No</td>
<td>264</td>
<td>120</td>
<td>-6.63 (-11.81 - 1.44)</td>
<td>0.01</td>
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</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>91</td>
<td>42</td>
<td>-2.77 (-11.47 - 5.93)</td>
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<tr>
<td>≥30 kg/m²</td>
<td>259</td>
<td>126</td>
<td>-4.36 (-9.76 - 1.03)</td>
<td>0.11</td>
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<tr>
<td>On AA at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>76</td>
<td>47</td>
<td>-8.05 (-17.63 - 1.52)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>274</td>
<td>122</td>
<td>-3.24 (-8.42 - 1.93)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 mL/min/1.73 m²</td>
<td>68</td>
<td>38</td>
<td>0.54 (-8.29 - 9.37)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>≥60 mL/min/1.73 m²</td>
<td>282</td>
<td>131</td>
<td>-5.22 (-10.51 - 0.06)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>246</td>
<td>128</td>
<td>-5.73 (-11.06 - 0.40)</td>
<td>0.04</td>
<td></td>
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<tr>
<td>≥65 yr</td>
<td>104</td>
<td>41</td>
<td>0.09 (-8.80 - 8.99)</td>
<td>0.99</td>
<td></td>
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<tr>
<td>Any medication change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>132</td>
<td>70</td>
<td>-5.41 (-13.49 - 2.67)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>218</td>
<td>99</td>
<td>-3.44 (-8.83 - 1.96)</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

* P value for superiority with margin of 5 mm Hg

HTN-3 RESULTS: POTENTIAL FACTORS

The Patient

• **Patient behavior** (improved or modified lifestyle and drug adherence) may change due to being enrolled and closely monitored in a clinical trial ("Hawthorne effect")

The Trial

• **Patient demographics**

• **Medication adherence and medication change**

• **Duration of primary endpoint may have been too short**

The Doctor

• **Greater variation in procedural experience**
Medication Adherence and Medication Change

• Drug adherence not measured by blood levels, but adherence was measured by patient diaries at baseline and 6 months.
Protocol mandated maximum doses and **no** medication changes

~40% of patients (n = 211) in the trial required medication changes

- 69% of first medication changes were medically necessary
HTN-3 RESULTS: POTENTIAL FACTORS

The Patient

- Patient behavior (improved or modified lifestyle and drug adherence) may change due to being enrolled and closely monitored in a clinical trial (“Hawthorne effect”)

The Trial

- Patient demographics
- Medication adherence and medication change
- Duration of primary endpoint may have been too short

The Doctor

- Greater variation in procedural experience
HTN-3 RESULTS: POTENTIAL FACTORS

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- Medication adherence and medication change
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The Doctor

- Greater variation in procedural experience
HTN-3: PROCEDURAL EXPERIENCE

<table>
<thead>
<tr>
<th></th>
<th>HTN-1</th>
<th>HTN-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of operators</td>
<td>20</td>
<td>112</td>
</tr>
<tr>
<td>No. of procedures per operator</td>
<td>6.0</td>
<td>3.3</td>
</tr>
<tr>
<td>No. of procedures per site</td>
<td>8.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

a) 5X more operators vs HTN-1
b) Greater heterogeneity of operator experience vs. HTN-1 and HTN-2
c) Case proctoring was different and not comparable

>50% of interventionalists performed ≤2 RDN procedures in SYMPLICITY HTN-3
HTN-3: CONTINUING AREAS OF INVESTIGATION

- Patient Demographics
- Medication Changes or Adherence
- Hawthorne Effect
- Regression to Mean
- Placebo Effect
- Trial Conduct
- Catheter Design
- Heterogeneity of US Operator Experience

[Diagram showing overlapping circles for each area of investigation]
FUTURE DIRECTION

Further study / data
- Longer term follow-up
- Effects of medication change
- Any means to predict response

Define appropriate treatment populations
- Key subgroups

Reinforce medication adherence
- Before and after procedure

Operator experience
- Optimal training and proctoring
SUMMARY

- Resistant hypertension is associated with high rates of cardiovascular complications
- Sympathetic nervous system appears to play an important role in resistant hypertension
- Renal denervation therapy (RDN) has emerged as a potential therapy for resistant hypertension
- Effectiveness of RDN was shown in non-randomized studies and randomized, unblinded trials
- However, the latest blinded, randomized, sham-controlled trial confirmed the safety of RDN but not the efficacy
- The optimal clinical use of RDN needs to be defined