MHIF FEATURED STUDY: SPYRAL-HTN

DESCRIPTION:
The aim of the study is to test the hypothesis that renal denervation is safe and reduces systolic blood pressure (SBP) in patients with uncontrolled hypertension compared to a sham controlled population, in the absence of antihypertensive medications (OFF MED) or uncontrolled hypertension on one, two, or three standard antihypertensive medications (ON-MED).

PARTIAL CRITERIA LIST/ QUALIFICATIONS:
Inclusion
- Office systolic blood pressure (SBP) ≥150mmHg and <180mmHg and an office diastolic blood pressure (DBP) ≥90mm Hg with or without meds

Exclusion:
- Main renal artery < 3 mm or > 8 mm ; eGFR <45 ml/min
*Screen failure if OSBP > or = 180 mm Hg

CONDITION: Hypertension
PI: Yale Wang, MD
RESEARCH CONTACT: Carina Benson
Carina.Benson@allina.com | 612-863-6288
SPONSOR: Medtronic

OPEN AND ENROLLING: Please Refer Patients!
**Minneapolis Heart Institute Foundation® Cardiovascular Grand Rounds**

**Title:** Renal Denervation Update 2019  
**Speaker(s):** Yale Wang, MD, FACC, FSCAI  
Senior Consulting Cardiologist  
Minneapolis Heart Institute® at Abbott Northwestern Hospital  
Researcher  
Minneapolis Heart Institute Foundation®

**Date:** September 23, 2019  
**Time:** 7:00 – 8:00 AM  
**Location:** Minneapolis Heart Institute Building, Suite 100, Learning Center

**OBJECTIVES**
At the completion of this activity, the participants should be able to:

1. Appreciate the burden of systemic hypertension.  
2. Understand the inadequacies of current management strategies.  

**ACCREDITATION**

**Physician** - Allina Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**Nurse** - This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.0 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

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The **ACCME defines a commercial interest** as “any entity” producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests - unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest.

**Moderator(s)/Speaker(s)**
Dr. Wang, MD has disclosed that he DOES NOT have any real or apparent conflicts with any commercial interest as it relates to presenting the content in this activity/course.

**Planning Committee**
Dr. Alex Campbell, Jake Cohen, Jane Fox, Dr. Kevin Harris, Dr. Kasia Hryniewicz, Rebecca Lindberg, Amy McMeans, Dr. Michael Miedema, Dr. JoEllyn Moore, Pamela Morley, Dr. Scott Sharkey, Maia Hendel and Jolene Bell Makowesky have
disclosed that they DO NOT have any real or apparent conflicts with any commercial interest as it relates to the planning of this activity/course. Dr. Mario Gössl has disclosed the following relationships – Edwards Life Sciences: Grant/Research Support; Abbott Vascular, Caisson: Consultant; Speaker’s Bureau: Edwards Lifesciences. Dr. David Hurrell has disclosed the following relationship –Boston Scientific: Chair, Clinical Events Committee.

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We would like to thank the following company for their generous support of our activity.

ReCor Medical

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**Maintaining these details are the responsibility of the individual.**

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| Signature:__________________________________________________________________________ |
| My signature verifies that I have attended the above stated number of hours of the CME activity. |

Allina Health - Learning & Development - 2925 Chicago Ave - MR 10701 - Minneapolis MN 55407
Disclosures

- ReCor: research, consultant
- Medtronic: research, consultant
- Boston Scientific: consultant
- Denervx: consultant
- QX Medical: consultant
Will Renal Denervation for Hypertension Rise Again?

"There's once again excitement about renal artery denervation and... it's justified," says one cardiologist, while another hopes for FDA approval next year, and a third is "still not 100% convinced."

Read Now

MORE ON RENAL DENERVATION
Hypertension

The most common diagnosis you will make

Risks of Hypertension Result from Target Organ Damage

Hypertension Remains The Leading Global Risk Factor For Death

Total annual number of deaths by risk factor, measured across all age groups and gender - 2016

Foreman et al. Lancet 2018; 392: 2052–90

Source: WHO, Global Burden of Disease (GBD)

CC BY-SA

Hypertension is the #1 Cause of Global Disease Burden and Projected to Remain the Top Cause in 2040
Small Reductions in Blood Pressure Reduce Risk of Cardiovascular Mortality

- 10% Reduction in Risk of Stroke Mortality
- 7% Reduction in Risk of Ischemic Heart Disease 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

SBP = systolic blood pressure


SPRINT: Systolic Blood Pressure Intervention Trial Showed Lower Risk and Improved Mortality with More Aggressive BP Targets

9361 Patients with HTN
Exclusions: DM, prior stroke
Inclusion: age >50 and CAD, CKD, ≥75 (~25%) or Framingham risk ≥15% over 10 years

SBP Goal <120
chlorthalidone, amlodipine, lisinopril

SBP Goal <140

Primary endpoint: MI, CV death, ACS, heart failure, stroke
25%

Secondary endpoint: all-cause mortality
27%

Pharmacology - HTN

Beta Blockers
- Acebutolol (Sectral)
- Atenolol (Tenormin)
- Betaxolol (Kerlone)
- Bisoprolol fumarate (Zebeta)
- Carteolol HCL (Cartrol)
- *Metoprolol tartrate (Lopressor)
- *Metoprolol succinate (Toprol XL)
- *Nadolol (Corgard)
- Penbutolol (Levatol)
- *Pindolol (Visken)
- *Propranolol HCL (Inderal, Inderal LA)
- Sotalol HCL (Betapace)
- *Timolol maleate (Blocadren)

Combined
- Atenolol and Chlorthalidone (Tenoretic)
- Bisoprolol fumarate and HCTZ (Ziac)
- Metoprolol tartrate and HCTZ (Loperssor HCT)
- Nadolol and bendroflumethiazide (Corzide)
- Propranolol HCL and HCTZ (Inderide)
- Propranolol HCL and HCTZ extended release (Inderide LA)
- Timolol and HCTZ (Timolide)

ACE Inhibitors (ACEi)
- Benazepril HCL (Lotensin)
- *Captopril (Capoten)
- *Enalapril maleate (Vasotec)
- Fosinopril sodium (Monopril)
- *Lisinopril (Prinivil, Zestril)
- Perindopril (Aceon)
- Moexipril (Univasc)
- Quinapril HCL (Accupril)
- Ramipril (Altace)
- Trandolapril (Mavik)

Angiotensin II Receptor Blockers (ARB)
- Candesartan (Atacand)
- Eprosartan mesylate (Teveten)
- Irbesartan (Avapro)
- Losartan potassium (Cozaar)
- Telmisartan (Micardis)
- Valsartan (Diovan)

Direct Renin Inhibitor
- Aliskiren (Tekturna)

Diuretics
- *Chlorthalidone (Hygroton)
- Chlorthiazide (Diuril)
- *HCTZ (Esidrix, Hydrodiuril, Microzide)
- Indapamide (Lozol)
- Metolazone (Mykrox, Zaroxolyn)

Potassium sparing
- *Amiloride hydrochloride (Midamar)
- *Spironolactone (Aldactone)
- *Triamterene (Dyrenium)
- Eplerenone (Inspra)

Combination
- Amiloride hydrochloride + HCTZ (Moduretic)
- Spironolactone + HCTZ (Aldactazide)
- Triamterene + HCTZ (Dyazide, Maxzide)

Calcium Channel Antagonists
- Bepridil (Vasocor)
- *Diltiazem HCL (Cardiazem CD/SR, Dilacor XR, Tiazac)
- Mibefradil (Posicor)
- *Verapamil (Isoptin SR, Calan SR, Verelan, Covera HS)

Dihydropyridines
- *Amlodipine (Norvasc)
- Felodipine (Plendil)
- Isradipine (DynaCirc, CR)
- Nicardipine (Cardene SR)
- *Nifedipine (Procardia XL, Adalat CC)
- Nisoldipine (Sular)

Combined Calcium Antagonists and ACEi
- Amlodipine besylate and Benazepril HCL (Lotrel)
- Diltiazem HCL and Enalapril maleate (Teczem)
- Verapamil HCL and Trandolapril (Tarka)
- Felodipine and enalapril maleate (Lexxel)

Combined ARB and Diuretic
- Losartan potassium and HCTZ (Hyzaar)

Combined ACEi and Diuretic
- Benazepril HCL and HCTZ (Lotensin HCT)
- Captopril and HCTZ (Capozide)
- Enalapril maleate and HCTZ (Vaseretic)
- Lisinopril and HCTZ (Prinzide, Zestoretic)

Other Combinations
- *Hydralazine HCL and HCTZ (Apresoline)
- Minoxidil (Loniten)

Association Between Antihypertensive Medication Adherence and Mortality of Cardiovascular Disease, or All-Cause Death

Lifelong Polypharmacy is Failing as a Therapy Strategy for Hypertension

- US Hypertension prevalence remains steady at about 29%.
- Overall hypertension control rates have plateaued at about 50%, despite increasing from 1999–2010.

Up to 30% of Adults Would Rather Die Early than Submit to Lifelong Polypharmacy

Hutchins et al. Circ Cardiovasc Qual Outcomes. 2015;8:00-00. DOI: 10.1161/CIRCOUTCOMES.114.001240

High blood pressure now defined as 130/80 mm Hg compared to prior definition of 140/90 mm Hg

<table>
<thead>
<tr>
<th>SBP</th>
<th>DBP</th>
<th>JNC 7</th>
<th>2017 ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Normal BP</td>
<td>Normal BP</td>
</tr>
<tr>
<td>120-129</td>
<td>&lt;80</td>
<td>Prehypertension</td>
<td>Elevated BP</td>
</tr>
<tr>
<td>130-139</td>
<td>80-89</td>
<td>Prehypertension</td>
<td>Stage 1 hypertension</td>
</tr>
<tr>
<td>140-159</td>
<td>90-99</td>
<td>Stage 1 hypertension</td>
<td>Stage 2 hypertension</td>
</tr>
<tr>
<td>≥160</td>
<td>≥100</td>
<td>Stage 2 hypertension</td>
<td>Stage 2 hypertension</td>
</tr>
</tbody>
</table>
Prevalence of Hypertension & Control Rates

<table>
<thead>
<tr>
<th></th>
<th>JNC-7</th>
<th>2017 ACC/AHA Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence Among US Adults</td>
<td>72.2 million</td>
<td>103.3 million</td>
</tr>
<tr>
<td>Rate of Control in Patients on Meds</td>
<td>31.9%</td>
<td>45.6%</td>
</tr>
<tr>
<td></td>
<td>53.4%</td>
<td>39.0%</td>
</tr>
</tbody>
</table>

Change in BP guidelines increased prevalence of hypertension by 43% while rate of patients under control on medication decreased by 14.4%.

History of HTN Management


- Surgical Sympathectomy
- Nephrectomy for hypertension with a small kidney
- Central acting drugs, ganglion-blocking agents
- 1st RCT showing benefit of Rx of HTN
- Prospective trials: Med Rx vs. Stent CORAL ASTRAL STAR RAVE
- ACE inhibitor Rx
- Ca++ blockers
- PTRA introduced
- Improved Surgery
- ARB Rx
- Statin Rx
- Stents
- Renal Denervation

History of HTN Management

- Cooperative study of renovascular hypertension

Change in BP guidelines increased prevalence of hypertension by 43% while rate of patients under control on medication decreased by 14.4%.
Central Sympathetic Drive in Hypertension

Baseline activity (normotensives)

- 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.


Surgical Sympathectomy: Basis for RDN

Surgical Series—The surgical series consists of 1,066 patients. This represents a 90% five-year follow-up of the total patients originally operated on. Forty-seven per cent were men and 53% women. The average age of this group was 43 years. Surgery consisted of thoracoabdominal splanchic sympathectomy, carried out in two stages 10 days apart, through the bed of the 13th or the 11th and 12th ribs, using a retroperitoneal, retroperitoneal transdiaphragmatic approach. The sympathetic trunks were exposed from the right or left dorsal vertebra through the first or second lumbar vertebrae, inclusive, and the great splanchic nerves were removed from the celiac ganglia in the mid thoracic level. The adrenals, renal in-
teracts, and kidneys were inspected, and renal biopsies were taken in all cases. The operative mortality has been distinctly lowered postoperatively. One year after the 45% of living operated patients have a significant lowering of final blood pressure values in the early years (1 to 5) after splanchic sympathectomy, and 55% have no change or show an increase in blood pressure.

Crosstalk Between Renal Nerves and CNS

↑ Neurohormones  ↓ RBF/GFR

↑ Vasoconstriction  ↓ Renin  ↓ Na+/Volume

↑ Blood Pressure  ↑ Contractility/Rate

Amplifies central, or systemic, sympathetic outflow

Kidney impairment, or dysfunction = ↑ afferent activity


Renal Sympathetic Nerve Distribution

Adapted from Atherton DS. Et al Clinical Anatomy, 2011
Representative Pre-Clinical Histology

- Porcine model, 7-days
  - 7-second ultrasound emissions delivered in main renal artery
- Renal Arterial Wall protected from thermal injury
- Significant Renal Nerve Injury at site of each ultrasound emission
- Target ablation region of 1mm-6mm achieved

Symplicity Investigational Catheter Device

- **Generator will automatically control RF energy delivery:**
  - Power automatically ramped and maintained (5-8W)
  - Continuously monitors temperature and impedance
  - Automatically shuts off after 2 min or when either impedance or temperature exceed program limits
Symplicity Staged Evaluation in Hypertension and Beyond

First-in-Man1 ✓

Series of Pilot Studies ✓

Symplicity HTN-2 ✓

EU/AU Randomized Clinical Trial

USA

Symplicity HTN-34

US Randomized Clinical Trial

EU/AU

Other Areas of Research:4

Insulin Resistance,
HF/Cardiorenal,
Sleep Apnea, More

Sources:

Initial Cohort – Reported in the Lancet 2009
- First-in-man, non-randomized study conducted in Europe and Australia
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- All patients received bilateral renal denervation with the Symplicity Renal Denervation System
- Primary endpoint: change in office BP; 1, 3, 6, 9 and 12 months post-procedure

Expanded Cohort – Symplicity HTN-1:
- Expanded cohort of patients (n=153) from 19 sites (US, Europe, and Australia)
- 24 and 36-month follow-up of safety and effectiveness
Symplicity HTN-1 Trial: Key Inclusion/Exclusion Criteria*

**Inclusion Criteria**
- >18 years of age
- Elevated office systolic blood pressure (SBP) ≥160 mm Hg
- ≥3 antihypertensive medications (including 1 diuretic)

**Exclusion Criteria**
- Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m²
- Type 1 diabetes mellitus
- Known secondary cause of hypertension other than sleep apnea or chronic kidney disease
- Significant renovascular abnormalities

*Inclusion/exclusion criteria in the trial settings were stringent and conservative in order to ensure a homogenous population – in clinical practice, individual patient characteristics and physician judgment should guide patient selection


Symplicity HTN-1: Significant, Sustained Blood Pressure Reductions to at Least Three Years*

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>-18</td>
<td>-13</td>
</tr>
<tr>
<td>(n = 144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Year</td>
<td>-18</td>
<td>-14</td>
</tr>
<tr>
<td>(n = 132)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Years</td>
<td>-19</td>
<td>-16</td>
</tr>
<tr>
<td>(n = 105)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Years</td>
<td>-20</td>
<td>-16</td>
</tr>
<tr>
<td>(n = 34*)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01 for Δ from baseline for all time points.
+ Number of patients represents data available at time of data-lock.

*Expanded results presented at the Transcatheter Cardiovascular Therapeutics Annual Meeting 2012 (Schlaich M).
Assessed for Eligibility (n=190)

- Excluded During Screening, (n=84)
  - BP < 160 at Baseline Visit (after 2-weeks of medication compliance confirmation) (n=36; 19%)
  - Ineligible anatomy (n=30; 16%)
  - Declined participation (n=10; 5%)
  - Other exclusion criteria discovered after consent (n=8; 4%)  

Randomized (n=106)

- Allocated to RDN
  - n=52 Treated; n=49 Analyzable

- Allocated to Control
  - n=54 Control; n=51 Analyzable

- Crossover n=46
  - Not-Protocol† (Crossover) n=9
  - *Crossed-over with ineligible BP (<160 mmHg)

12-month Post RDN

- 12-month Post RDN n=47
- 12-month Post RDN (Crossover) n=35

30-month Post RDN

- 30-month Post RDN n=37
- 30-month Post RDN (Crossover) n=7

Symplicity HTN-2 Patient Disposition 30M Post-RDN*

*Expanded results presented at the American Society of Hypertension annual meeting 2013

Symplicity HTN-2 Trial: 1-, 3-, and 6-Month Office BP Reduction*

*P≤0.005 for changes in SBP and DBP at all time points between Symplicity RDN and control groups; error bars represent 95% CIs.

Global SYMPLICITY Registry: Real-World Clinical Outcomes

Worldwide evaluation of the safety and efficacy of treatment with the Symplicity™ renal denervation system in real world uncontrolled hypertensive patients

Consecutive patients treated in real world population ~ 5000 patients

Follow-up schedule
3mo 6mo 1yr 2yr 3yr 4yr 5yr

~ 200 Global Sites
Minimum 10% randomly assigned to 100% monitoring
30% monitoring to date

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

Worldwide evaluation of the safety and efficacy of treatment with the Symplicity™ renal denervation system in real world uncontrolled hypertensive patients

Significant Reductions in Office BP for Patients with Uncontrolled Hypertension

3 Months
-13 -17 -8 -8 -18

6 Months
-28 -30

*Results Presented at EuroPCR 2013 annual meeting

n=274 n=220 n=36 n=135 n=114 n=17

p=0.0002 for SBP BL >=180 at 6 months
p=0.0008 for DBP BL >=180 at 6 months
p<0.0001 all other groups

*Results Presented at EuroPCR 2013 annual meeting
**Office BP Reduction from Baseline**

Mean reduction in office-based BP was -24.6/-10.3 mmHg at 6 months and significant reductions were sustained through 12 months.

**REDUCE-HTN PMS – Interim Analysis**

*Significant Office Blood Pressure Reduction*

Mean reduction in office-based BP was -24.6/-10.3 mmHg at 6 months and significant reductions were sustained through 12 months.

*P < 0.0001 for each timepoint vs baseline*

*Error bars represent 95% confidence bounds*
The OneShot™ System is a balloon-based RF system using a mounted spiral electrode with a unique feature of irrigation of the vessel lumen during treatment. The non-compliant balloon is inflated under low pressure (1 atm) in the renal artery. The electrode delivers RF energy to ablate adjacent nerve bundles with a single 2-minute treatment. A first-in-man feasibility study to evaluate the OneShot™ System was performed. These are the six month data for the RHAS (Renal Hypertension Ablation System) trial.

Eligible patients had:

- Office systolic blood pressure (SBP) ≥160 mmHg (≥150 if diabetic)
- A drug regimen that included two or more antihypertensive medications, including a diuretic
- Renal artery sizes were 4-7 mm

Endpoints:

- Primary: delivery of RF energy using the OneShot™ RF Balloon Catheter into each renal artery
- Secondary: Office blood pressure and procedure time

The OneShot™ System procedure time (min) was on average 19.9 minutes (IQR 13.4-24.3)

Endpoints:

- Primary: delivery of RF energy using the OneShot™ RF Balloon Catheter into each renal artery
- Secondary: Office blood pressure and procedure time

Procedural Variables Median (Interquartile Range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Procedure Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OneShot ™ System procedure time</td>
<td>19.9 (13.4-24.3)</td>
</tr>
<tr>
<td>Tool procedure time</td>
<td>16.6 (10.2-23.0)</td>
</tr>
<tr>
<td>Fluoroscopy time</td>
<td>7.1 (6.4-9.9)</td>
</tr>
<tr>
<td>Contrast volume used (mL)</td>
<td>134 (98-198)</td>
</tr>
</tbody>
</table>

In the RHAS trial the OneShot™ RF Balloon Catheter produced in the 8 treated patients a substantial and significant reduction in the office SBP (p≤0.006) that improved over time. There were no significant complications. Only 2 minutes of treatment are required on each side, so the procedure is shorter and therefore less painful than some technologies.

**Hypertension Devices**

- **Radiofrequency**
  - Medronic Symplicity™
  - St. Jude EnlightN™
  - BSC Vessix V2
  - Covidien-Mayo OneShot

- **Ultrasound**
  - ReCor PARADISE®
  - CVRx® Barostim neo™
  - Mobius

- **Baro-receptor Modulation**
  - A-V Fistula (afterload)
  - Ablative Solutions (ethanol)
  - Mercator Bullfrog® (Guanethidine)

- **Chemical**
  - Kona Medical
  - ROX Coupler
  - Median Nerve Stimulator

**MN360x1 | Effective date: 11/1/2022**
**Symplicity HTN-3**

**Overview**

- **Design**
  - Multicenter (60 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

*The renal angiogram also acts as the sham procedure for patients in the control group.

Data on file, Medtronic.

---

**Symplicity HTN-3 Trial: Study Design**

**Initial Screening**
- 2 weeks

**Confirmatory Screening**
- 2 weeks

**Renal Angiogram**
- 2 weeks

**Treatment**
- 1M 3M 6M
- Home BP & Med Confirmation

**Control**
- 1M 3M 6M
- Home BP & Med Confirmation

**Main Differences**
- ABPM
- Sham-blinded study

Patient and Research staff assessing BP are blinded to treatment status
No changes in medications for 6 months
Follow-up to 5 years
Ambulatory Blood Pressure Monitoring (ABPM) May Offer Advantages Over Traditional Office Measurement

**Office BP**
- Point-in-time “snapshot” of BP
- Highly Variable
  - May overestimate due to white-coat HTN

**ABPM**
- Measures BP at regular intervals over a 24-hour period, including both day and night
- Enables determination of BP variability and nighttime “dipping” or “nondipping” patterns


High ABPM Is Associated with Increased CV Risk Independent of Office BP

![Bar chart showing the incidence of cardiovascular events associated with different ABPM levels and office systolic blood pressure levels.](chart.png)

- **24-HOUR AMBULATORY SYSTOLIC BLOOD PRESSURE:**
  - <135 mm Hg
  - ≥135 mm Hg

- **OFFICE SYSTOLIC BP (mm Hg):**
  - <140
  - 140–159
  - ≥160

Note: Numbers above the bars are the number of patients in the specific subgroup with a cardiovascular event over the total number of patients in that subgroup.

PAMELA Study

Ambulatory Blood Pressure Reductions Are Associated with Greater Risk Reduction than Office BP Reductions


Symplicity HTN-3

“Victory Lap”
"In God we trust; all others must bring data."

W. Edwards Deming

"We are disappointed that the clinical trial failed to meet its primary efficacy endpoint,"

Primary Safety Endpoint
January 8, 2019

The data and evidence from the trial were insufficient to support the primary endpoint—a reduction in the rate of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke—within the specified time frame.
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., Mingli Li, Ph.D., Laura Muiatt, M.D., Manuela Negoiță, 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. Beller, M.D., for the SYMPLECTIC HTN-3 Investigators

Symplicity 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 reach a test of superiority with a margin of 5 mm Hg. The 1 bars indicate standard deviations.

**Figure 2. Secondary Efficacy End Point.**
A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The 1 bars indicate standard deviations.
Why Did SYMPLICITY HTN-3 Fail?
Possible Interpretations

- Renal nerve ablation does not work
- Statistical power was not sufficient
- Renal nerve ablation was not properly performed
  - Majority of US operators did 1-2 cases
- Patients were not stabilized medically
- Patients were medically overtreated
- The wrong patient population was treated
- Other factors

Procedural Variability - Correlation with # of ablations and Correlation with 4-quadrant ablation pattern

David E. Kandzari et al. EuroPCR 2014
Critical Neuro-Anatomical Differences: Normal vs. Chronic Hypertensive Patient

1. Sympathetic nerve proliferation
2. Much deeper nerve location

Our View of Renal Nerve Distribution Has Changed

Sakakura K et al. JACC. 2014;64:634–643.
Medication Changes During Trial

- ~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 med change due to an adverse event
  - 80 patients had a med change due to a drug side-effect
  - ~69% were changes in drugs at maximally-tolerated dose
Renal Denervation - Lessons Learned

- Need Improved Technology
  - Better understanding of renal nerve anatomy
  - Robust preclinical science

- Need Reproducible Procedures
  - Safe, easy access, reduced operator variability
  - Consistent denervation

- Need Robust Clinical Study Design
  - Standardization of BP measures
  - Standardization of medication management
  - Need improved understanding of patient selection
DENER-HTN: Baseline-Adjusted Changes in Daytime and Nighttime Ambulatory BP from Randomisation to 6 Months

- **Daytime**
  - ∆: −5.9 mm Hg
  - (95% CI: −11.3 to −0.5)
  - \( p = 0.0329 \)

- **Nighttime**
  - ∆: −6.3 mm Hg
  - (95% CI: −12.0 to −0.6)
  - \( p = 0.0296 \)

Primary endpoint


**SPYRAL HTN Clinical Program**

*Study Device: Symplicity Spyral™ Catheter*

- Multi-electrode catheter with quadrantic vessel contact for simultaneous ablation in up to 4 electrodes
- 60-second simultaneous energy delivery
- Vessel diameter range: 3 – 8 mm
- Flexible catheter allows branch treatment
- 6F guiding catheter compatible
Combined Branch and Main Artery Treatment

Effective in Reducing Renal NE in Normotensive Pigs

AREAS OF RENAL DENERVATION

Ostium

Main artery

Branches

RENAL NOREPINEPHRINE LEVELS

Control

RD

Ostium

Main Artery

Branches

Note: Preclinical data may not be representative of human data.

SPYRAL HTN – OFF MED

Study Design

- Randomized, sham-controlled, (patient and assessor) blinded, proof-of-concept trial
- 25 sites in Germany, UK, Austria, Greece, Japan, Australia and USA

SCREENING

Inclusion criteria:
- Office SBP ≥120 to ≤180
- Patient is either drug naïve OR permitting discontinuation of antihypertensive medications

VISIT 1 - 5.4 months
- Drug naïve or stop medications
- 2-week safety/washout

VISIT 2 - 1.2 months
- Drug testing
  - Office SBP: ≥120 to ≤180
  - DBP: ≤90
  - Randomized drug allocation
  - Drug naïve or stop medications

TREATMENT

Sham Control
- Office BP
- DNP
- 24-hr ABPM

Renal Denervation
- Office BP
- DNP
- 24-hr ABPM

Study medications. 1. Drug naïve (stopping antihypertensive medications). 2. Drug naïve (stopping antihypertensive medications at 20 and 30 months). 3. Patients permitted to continue DNP ≥120.
OFF MED: Key Inclusion/Exclusion Criteria

**Inclusion**
- Individual is willing to discontinue current antihypertensive medications between Screening visit 1 and postprocedure visit at 3 months.
- Office SBP: ≥ 150 and < 180 mm Hg
- Office DBP: ≥ 90 mm Hg
- Systolic 24-hour mean ABPM following witnessed antihypertensive drug ingestion: ≥ 140 and < 170 mm Hg
- Age: 20–80 years

**Exclusion**
- Ineligible renal artery anatomy
- eGFR: < 45 mL/min/1.73m²
- Type 1 diabetes mellitus or type 2 diabetes mellitus with HbA1C > 8.0%
- Secondary causes of hypertension

---

SPYRAL HTN – ON MED

**Study Design**

- Randomized, sham-controlled, (patient and assessor) blinded, proof-of-concept trial
- 25 sites in Germany, UK, Austria, Greece, Japan, Australia and USA
## ON MED: Key Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| 1. Patient is prescribed 1, 2 or 3 antihypertensive medications at least 50% of the maximum dosage;  
  - Thiazide-type diuretic  
  - Dihydropyridine calcium channel blocker  
  - ACE-I/ARB  
  - Beta Blocker  | 1. Ineligible renal artery anatomy  |
| 2. Office SBP: ≥ 150 mm Hg and < 180 mm Hg  | 2. eGFR < 45 mL/min/1.73m²  |
| 3. Office DBP ≥ 90 mm Hg  | 3. Type 1 diabetes mellitus or type 2 diabetes mellitus with HbA1C > 8.0%  |
| 4. Systolic 24-hour mean ABPM following witnessed antihypertensive drug ingestion:  
  ≥ 140 mm Hg and < 170 mm Hg  | 4. Secondary causes of hypertension  |
| 5. Age: 20-80 years  | 5.  |

---

**SYMPLECTICITY OFF MED**

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**Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial**

Raymond F Taveras, Fabio Whitehead, Daniel Kandrac, Kazuhiro Goto, Stuart Peacock, Michael A Moler, Sebastian Cers, Konstantinos Tsatsopoulos, Stavros Tzoukias, Andrew F Ishop, Anthony J Westenhofer, Edith Schmidlin, Janel Lafford, James V Chu, Carol Dava, Anthony Mathen, Ingmar Hagen, Stéphane Cahan, Robert Mmekepwa, David Y Lee, Adrian Isac, Chandran K Pratap, Jean-Francois Philip, Paul-Yves Le, Abd Almagid, Justin Curtain, Neil Chapman, Sadiqa Ruhana, Rebecca Delbar, Martin Hickey, David D Jones, Martin Rothensee, Michael Moler, on behalf of the SPYRAL HTN-OFF MED trial investigators

*Lancet 2017; 390:2160-70*
**MHIF CV Grand Rounds – Sep. 23, 2019**

**SPYRAL HTN – OFF MED**

Blood Pressure Change from Baseline to 3 Months


**SPYRAL HTN – OFF MED**

24-hr Systolic Blood Pressure from Baseline to 3 Months


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

#### Safety Results at 3 Months

<table>
<thead>
<tr>
<th>Event</th>
<th>RDN (n = 38)</th>
<th>Sham Control (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New myocardial infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding (TIMI&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New onset end stage renal disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serum creatinine elevation &gt;50%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Significant embolic event resulting in end-organ damage</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization for hypertensive crisis/emergency</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New stroke</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup> TIMI: TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days after procedure.


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### SYMPLECTICITY OFF MED

Lancet 2017; 390:2160-70

[Graphs and data related to SYMPLECTICITY OFF MED study]
**SYMPLICITY ON MED**

Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial


*Lancet* 2018; 391:2346-2355.

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**SPYRAL HTN – ON MED**

Blood Pressure Change from Baseline to 6 Months

![Graph showing blood pressure change from baseline to 6 months](image)

SPYRAL HTN – ON MED
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.

SPYRAL HTN – ON MED
Medication Adherence

Drug testing of urine and serum by tandem HPLC and mass spectroscopy. Medication adherence defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected.

- Baseline:
  - Adherent: 62.5% (N=38)
  - Incomplete or Non-Adherent: 37.5% (N=24)
  - Missing: 6.5% (N=2)

- 3M:
  - Adherent: 55.0% (N=37)
  - Incomplete or Non-Adherent: 42.5% (N=22)
  - Missing: 12.5% (N=2)

- 6M:
  - Adherent: 62.5% (N=38)
  - Incomplete or Non-Adherent: 36.3% (N=20)
  - Missing: 11.1% (N=2)

SPYRAL HTN – ON MED
24-Hr ABPM – Progressive Change Over Time

Systolic

Diastolic

ANCOVA adjusted analysis

RDN Lowered Blood Pressure in 2 Sham-Controlled Pilot Trials
With and Without Meds

* Between group difference
**SPYRAL HTN Pivotal**  
**RANDOMIZED, SHAM-CONTROLLED TRIAL**

**SCREENING**

- **VISIT 1**
  - Office BP
  - Drug testing
  - 2-week safety check
  - 3-4 weeks

- **VISIT 2**
  - Office BP (baseline)
  - 3M

**TREATMENT**

- **SHAM CONTROL**
  - Follow-up every 2 weeks
  - 1-2 weeks
  - 3M
  - 4M
  - 6M

- **RENAI DENERVATION**
  - Follow-up every 2 weeks
  - 3M
  - 4M
  - 6M
  - 12-36M

- **Primary endpoint**
  - Unblinding and optional crossover to RDN

1 Only for patients discontinuing anti-hypertensive medications. 2 According to scheduling. 3 Drug testing to ensure no medications are present. 4 Optional follow up at weeks 6 and/or 10 if the patient is not controlled. 5 Only for patients with BP ≥140 mmHg at 3M. 6 Drug testing to ensure prescribed medications are present (if on drug). 7 6 and 12 month renal imaging.

---

**Paradise® RDN System**  
ReCor Medical

- **Cool** – protect the renal artery from the inside
- **Heat** – ablate the renal nerves on the outside
RADIANCE-HTN Key Study Eligibility

**SOLO Cohort**
- Essential HTN on ≤2 HTN meds
- OPB < 180/110 mmHg while on 1-2 meds or OBP ≥ 140/90 and <180/110 mmHg while on no meds
- Daytime ABP ≥ 135/85 mmHg and <170/105 mmHg after 4-week period off meds
- No history of CVA
- No repeat hospitalization for hypertensive crisis within prior 12 months

**TRIO Cohort**
- Resistant HTN on ≥3 HTN meds
- OBP ≥ 140/90 while on stable regimen of 3-4 meds
- Daytime ABP ≥ 135/85 mmHg after 4-week stabilization period on single pill, fixed dose, triple medication
- No history of CVA within 3 months
- No evidence of secondary hypertension

**Suitable anatomy per renal CTA or MRA**
- Main renal artery diameter 4-8mm and length >25mm
- Accessory renal artery diameter <2mm or 4-8mm
- No evidence of renal artery stenosis ≥30%
- No prior renal artery intervention

---

RADIANCE-HTN SOLO Design: Blinded, Sham-Controlled, Powered to Demonstrate BP Lowering Effectiveness at 2 Months

**Key Entry Criteria:**
- Hypertension controlled on 1-2 anti-HTN meds or uncontrolled on 0-2 meds
- Off-medication daytime ABP ≥135/85 and <170/105 mmHg
- Age 18-75 years
- No prior cardiovascular or cerebrovascular events
- No Type I or uncontrolled Type II diabetes
- Eligible renal artery anatomy (bilaterial diameter 4-8mm, length >25mm, and no stenosis ≥30%)
RADIANCE SOLO

Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial


The RADIANCE-HTN SOLO randomized trial was designed to demonstrate efficacy of RDN vs. Sham Control at 2 months among hypertensive patients subjected to medication washout.

Per-Protocol


MKT-0121(B), DCO 0993, Effective Date: May 15, 2019
Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control Following Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial


MKT-0123(B), DCO-0993, Effective Date: May 15, 2019
RADIANCE-HTN SOLO: Blinded Medication Titration Protocol During Months 2-5

2, 3, 4, & 5 Month Visits
BP Control Achieved (1-week Home BP <135/85)?

Add Medications

No Change

Resolution
Recommended drugs
Step | Medication
--- | ---
1 | Amlodipine 5 mg
2 | ARB: Telmisartan 80 mg; Olmesartan 20-40 mg
3 | ACEi: Ramipril 10-20 mg; Lisinopril 20-40 mg
4 | HCTZ 12.5 mg
5 | HCTZ 25 mg
6 | Amlodipine 10 mg

6-Month Follow-Up:
Medication Burden, Ambulatory, Home, and Office BP

Yes
No
No
Change
Escalation

Percentage on 0, 1, 2 or ≥ 3 Antihypertensive Meds Each Month Through 6M in RDN (n=69) and Sham (n=71)
MHIF CV Grand Rounds – Sep. 23, 2019

Overall between-group difference -6.9 mm Hg, 95% CI [-9.6, -4.1], p<0.001 from linear mixed model including visit x arm interaction term, adjusted for number of meds

Home Systolic BP Values and Changes from Baseline to 2, 3, 4, 5 and 6 Months

Ambulatory, Home & Office BP Control Rates at 6 Months

## Safety Events at 6 Months (complete cohort)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Renal Denervation (n=73)</th>
<th>Sham Procedure (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute renal failure within 30 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death or embolic event resulting in end-organ damage within 30 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive crisis within 30 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New renal artery stenosis of more than 70% within 6 months†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other Prespecified Safety Events Through 6 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Embolic event resulting in end-organ damage</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive crisis within 30 days</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hypotensive emergency</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroke, transient ischemic attack, cerebrovascular accident</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction (STEMI/non-STEMI)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New renal stenosis of greater than 50% within 6 months</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Need for renal artery angioplasty or stenting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>New orthostatic hypotension (transient)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* One patient in the renal denervation group had an episode of transient renal artery stenosis of ≥70% and underwent stenting which measured ≥70% prior to abrupt closure at 6 months.

† One patient in the renal denervation group had unrecognized pre-existing renal artery stenosis of 44% and underwent stenting for the lesion which measured 57% prior to stent placement at 6 months.

---

### Conclusions

1. The BP lowering effect of endovascular ultrasound RDN was maintained at 6 months with less prescribed antihypertensive medications compared with a sham control.

2. Taken together, the 2- and 6-month data demonstrate the efficacy of endovascular RDN both in the absence (2 months) and presence (6 months) of background antihypertensive medications.

3. If corroborated by additional data from the ongoing trials in the RADIANCE program, these data suggest that endovascular ultrasound RDN may have a clinical role as adjunctive therapy or even an alternative to starting/uptritrating antihypertensive medications in patients with uncontrolled systolic-diastolic blood pressure.
ReCor Multicenter Sham-Controlled RCTs

**RADIANCE-HTN**
(N=292)
US & EU
- Multicenter, blinded, randomized (1:1), sham control
- Patients on 0-2 meds
- Off meds screening and primary analysis period
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: daytime systolic ABP @ 2 months

**RADIANCE II**
(N=225)
US & EU
- Multicenter, blinded, randomized (2:1), sham control
- Patients on 0-2 meds
- Off meds screening and primary analysis period
- Standardized denervation procedure
- Powered for efficacy & safety
- 1º Endpoint: daytime systolic ABP @ 2 months

**SOLO**
(N=146)
- Multicenter, blinded, randomized (1:1), sham control
- Patients on 0-2 meds
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: daytime systolic ABP @ 2 months

**SOLO**
(N=146)
- Multicenter, blinded, randomized (1:1), sham control
- Patients on 0-2 meds
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: daytime systolic ABP @ 2 months

**TRIO**
(N=146)
- Multicenter, blinded, randomized (1:1), sham control
- Patients on ≥3 meds
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: daytime systolic ABP @ 2 months

**TRIO**
(N=146)
- Multicenter, blinded, randomized (1:1), sham control
- Patients on ≥3 meds
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: daytime systolic ABP @ 2 months

**N=140**
- Multicenter, blinded, randomized (1:1), sham control
- Patients on ≥3 meds
- Meds stabilized for screening/analysis period
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: 24-hour systolic ABP @ 3 months

**N=140**
- Multicenter, blinded, randomized (1:1), sham control
- Patients on ≥3 meds
- Meds stabilized for screening/analysis period
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: 24-hour systolic ABP @ 3 months


MHIF CV Grand Rounds – Sep. 23, 2019

Three Separate Multicenter, Blinded, Randomized, Sham-Controlled Trials Establish Efficacy of RDN

**SOLO**
2 months
Daytime systolic BP
- 100
- 105
- 110

**OFF Med**
3 months
24-h systolic BP
- 100
- 105
- 110

**ON Med**
6 months
24-h systolic BP
- 100
- 105
- 110

Each Study Demonstrated a Statistically Significant Drop in BP

RADIANCE-HTN
Ad Campaign and Referral Process

- Online ads placed on site-by-site basis
- Ads run for approximately 2 weeks at a time
- Ads targeted based on geography/demographics
- Ads direct patients to study-specific, patient information website
- Interested patients can pre-screen to see if they might qualify
- All interested, pre-screened patients referred directly (real-time) to site via Galen Gateway®

Minneapolis Heart
RADIANCE-HTN (SOLO & TRIO)
Facebook Campaign Results 2017 & 2018

Facebook 'Impressions'
500,000 + potential patients reached

16,000+ patients clicked on ad

3,950+ potential patients started online questionnaire

Passed Criteria
820 referrals contacted

*111 consented
(66 SOLO/ 35 TRIO)

*15 Randomized
(14 SOLO, 1 TRIO)

*Global Leader in SOLO consents and randomizations (42 sites)
**RADIOSOUND-HTN: Study Design**

Objective: To compare the effects of renal denervation using 3 treatments in patients with resistant hypertension

1. **Radiofrequency main renal artery ablation**
2. **Radiofrequency main and branch renal artery ablation**
3. **Ultrasound main renal artery ablation**

- **Design:** Prospective, single-blind, single-center, three-arm randomized trial (1:1:1)
- **Population:** Patients aged 18-75 years with resistant hypertension despite treatment with ≥3 drug classes at ≥50% maximum dosage including ≥1 diuretic
- **Primary endpoint:** Between-group difference in 3 Mo ∆ in Daytime Systolic ABPM

**Inclusion:**
- Antihypertensive medication stable for at least 4 weeks
- Daytime ABPM systolic >135 mmHg
- Screening office BP measurements
- Renal duplex ultrasound and renal angiography

**Exclusion:**
- Secondary hypertension
- Lab testing for hyperaldosteronism in all
- Further diagnostics as appropriate
- Stenosis, unsuitable anatomy, main artery <4mm diameter
- RF main & branch renal artery
- Ultrasound main renal artery

**Objective:**
To compare the effects of renal denervation using 3 treatments in patients with resistant hypertension

1. Radiofrequency main renal artery ablation
2. Radiofrequency main and branch renal artery ablation
3. Ultrasound main renal artery ablation

**Fengler et al. Circulation. 2019 Jan 29;139(5):590-600.**

**Circulation 2019;139:590-6--. DOI:10.1161/CIRCULATIONAHA.118.037654**
Summary

• Hypertension is a significant public health issue
• Effective blood pressure control leads to better CV outcomes
• Medication non-adherence remains a large issue
• The results of SPYRAL ON MED, SPYRAL OFF MED, and RADIANCE HTN SOLO create renewed optimism for the field of renal sympathetic denervation.
• Early data would suggest that RDN may have a role as an adjunctive therapy in the management of HTN
• Still, much remains to be learned.

Limitations of RDN

• No actual or surrogate marker of effective renal sympathetic nerve ablation
• Identifying responders vs non-responders
• Mechanism and timeline of action
  – Afferent vs efferent vs both?
  – Neurohumoral?
  – Instant vs gradual?
• Best technology?
• Long term durability?
• Long term safety?
Progress in Neuromodulation

CVRx® Receives FDA Approval for World’s First Heart Failure Neuromodulation Device

BAROSTIM NEO™ provides significant clinical benefit to heart failure patients

MINNEAPOLIS, Aug. 16, 2019 /PRNewswire/ -- CVRx, Inc., a private medical device company, announced today that it has received Premarket Approval (PMA) from the United States Food and Drug Administration (FDA) to market its BAROSTIM NEO device for heart failure in the United States. The FDA’s Center for Devices and Radiological Health (CDRH) approved the Company’s submission after a thorough review of the clinical trial data from the Barostim Activation Therapy for Heart Failure Pivotal Trial (BatHT).

• RADIANCE HTN SOLO
  - Completed, top enroller in the world
• RADIANCE HTN TRIO
• RADIANCE 2 Pivotal Trial
  - Currently top enroller in the world

• SPYRAL HTN OFF MED Pivotal Trial
• SPYRAL HTN ON MED Pivotal Trial
Special Thanks

Research Coordinators
- Rose Peterson
- Carmen Chan-Tram
- Amy McMeans
- JoAnne Goldman
- Kalia Yang
- Carina Benson
- Holly MacDonald
  (SYMPLECTIC HTN-3)

Co-investigators
- Rob Schwartz
- Des Jay
- Nedaa Skeik
- Richard Bae
- Nick Burke
- Santiago Garcia

- MHI Advanced Imaging
- Renal duplex section