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!
Disclosures

- ReCor: research, consultant
- Medtronic: research, consultant
- Boston Scientific: consultant
- Denervx: consultant
- QX Medical: consultant
Will Renal Denervation for Hypertension Rise Again?
From Cardiology  September 15, 2015

"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

Adapted from Messerli FH et al. The Lancet. 2007;370:591–593.
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. Lancer 2018, 392: 2052–90

Hypertension is the #1 Cause of Global Disease Burden and Projected to Remain the Top Cause in 2040

Foreman et al. Lancer 2018, 392: 2052–90
Small Reductions in Blood Pressure Reduce Risk of Cardiovascular Mortality

- 2-mm Hg decrease in mean office SBP
- 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
  Exclusion: DM, prior stroke
  Inclusion: age ≥50 and CAD, CKD, ≥75 (~25%) or Framingham score ≥15% over 10 years
  SBP Goal <120
  chlorthalidone, amlodipine, lisinopril
  SBP Goal <140

- Primary endpoint: MI, CV death, ACS, heart failure, stroke
- Secondary endpoint: all-cause mortality

- 25%
- 27%

Alpha-Blockers
- Doxazosin (Cardura)
- Prazosin HCL (Minipress)
- Terazosin (Hytrin)

Beta-Antagonists
- 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)
- 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)
- Loop
  - *Bumetanide (Bumex)
  - Ethacrynic acid (Edecrin)
  - *Furosemide (Lasix)
  - Torsemide (Demadex)
  - 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
- Non-Dihydropyridines
  - Bepridil (Vasocor)
  - *Diltiazem HCL (Cardiazem CD/SR, Dilacor XR, Tiazac)
  - Mibebradil (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 (Prinizide, Zestoretic)

Other Combinations
- Guanadrel (Hylorel)
- Guanethidine monosulfate (Ismelin)
- *Reserpine (Serpasil)
- *Hydralazine HCL (Apresoline)
- *Minoxidil (Loniten)
- *Hydralazine HCL and HCTZ (Apresazide)
- * Methyldopa (Aldomet)
- *Doxazosin and HCTZ (Atapril)
- *Nifedipine and HCTZ (Procardia XL Extended release)

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Good Adherence</th>
<th>Intermediate Adherence</th>
<th>Poor Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>12316</td>
<td>742</td>
<td>10568</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>12316</td>
<td>50</td>
<td>10568</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>12316</td>
<td>65</td>
<td>10568</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>12316</td>
<td>23</td>
<td>10568</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>12316</td>
<td>34</td>
<td>10568</td>
</tr>
<tr>
<td>Stroke</td>
<td>12316</td>
<td>98</td>
<td>10568</td>
</tr>
</tbody>
</table>

Adjusted for age group, sex, income, Charlson comorbidity score, area of residence, use of drugs taken, diabetes mellitus, and dyslipidemia. CI indicates confidence interval; and HR, hazard ratio.

Blood pressure medication recall expands again to include losartan

Google Blood pressure medications

MHIF CV Grand Rounds – Sep. 23, 2019

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.

2017 BP Guidelines

<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>

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

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

CD Owens, ICT 2011
Central Sympathetic Drive in Hypertension

Sympathetic drive is elevated in multiple types of hypertension

- **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

*Sympathetic innervation of the kidney*

Crosstalk Between Renal Nerves and CNS

↑ Neurohormones  ➔ Blood Pressure

↑ Vasoconstriction  ➔ Contractility/Rate

Kidney impairment, or dysfunction = ↑ afferent activity

Amplifies central, or systemic, sympathetic outflow

Kidney impairment, or dysfunction = ↑ afferent activity

↑ RBF/GFR

↑ Renin

↑ Na+/Volume

Ang II

Aldo


Renal Sympathetic Nerve Distribution

Atherton DS. Et al Clinical Anatomy. 2017
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**

**Symplicity HTN-1**
- First-in-Man\(^1\)
- Series of Pilot Studies\(^2\)
- **Symplicity HTN-2**\(^2\)
- EU/AU Randomized Clinical Trial

**US**
- **Symplicity HTN-3**\(^4\)
- 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*

![Graph showing blood pressure reductions over time](image)

- *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-Per Protocol* (Crossover) n=9

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
- GREAT Registry N=1000
- Korea Registry* N=152
- South Africa Registry* N=400
- Canada and Mexico* N=152
- Rest of GSR N~3500

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

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

### Significant Reductions in Office BP for Patients with Uncontrolled Hypertension

#### 3 Months

<table>
<thead>
<tr>
<th>BP Change (mmHg)</th>
<th>n=274</th>
<th>n=220</th>
<th>n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>-13</td>
<td>-17</td>
<td>-28</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 6 Months

<table>
<thead>
<tr>
<th>BP Change (mmHg)</th>
<th>n=135</th>
<th>n=114</th>
<th>n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>-15</td>
<td>-18</td>
<td>-16</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.0002 for SBP BL >=180 at 6 months
*p = 0.0003 for DBP BL >=115 at 6 months
*p<0.0001 all other groups

*Results Presented at EuroPCR 2013 annual meeting
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.

Signific\* I. H. Treatment

Error bars represent 95% confidence bounds.
OneShot™ Renal Denervation System Six Month Data

Results for RHAS Trial

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: to deliver RF energy using the OneShot™ RF Balloon Catheter into each renal artery
• Secondary: Office blood pressure and procedure time

Endpoints:
• Primary: to deliver RF energy using the OneShot™ RF Balloon Catheter into each renal artery
• Secondary: Office blood pressure and procedure time

Procedural Variables Median (Interquartile Range)
- Median OneShot™ System procedure time (min)* 10 (9, 11)
- Median tool procedure time (min) 16 (14, 18)
- Median fluoroscopy time (min) 7 (3, 10)
- Median contrast volume used (mL) 34 (19, 46)

*Comparable median Symplicity™ RDN System procedure time: 38 min from initiation to completion of radiofrequency delivery (Source: Lancet, 2009; 373: 1275-1281)

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.
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.

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**Symplicity HTN-3 Trial:**

**Study Design**

<table>
<thead>
<tr>
<th>Initial Screening</th>
<th>2 weeks</th>
<th>Confirmatory Screening</th>
<th>Renal Angiogram</th>
<th>2 weeks 6M</th>
<th>1M 3M 6M 12 36M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home BP &amp; Med Diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1M 3M 6M 12 36M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Patient and Research staff assessing BP are blinded to treatment status
No changes in medications for 6M
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

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

<table>
<thead>
<tr>
<th>Office Systolic BP (mm Hg)</th>
<th>Incidence of Cardiovascular Events (no./1000 person-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤140</td>
<td>14/376</td>
</tr>
<tr>
<td>140–159</td>
<td>23/284</td>
</tr>
<tr>
<td>≥160</td>
<td>26/284</td>
</tr>
</tbody>
</table>

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
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., Mingjie Liu, Ph.D., Laura Maunt, 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. Beller, M.D.,

for the SYMPLICITY HTN-3 Investigators

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 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 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
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.
Relationship Between Office SBP Changes and Number of Ablations Attempted for Combined* RDN Subjects at 6 Months

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

---

David E. Kandzari et al. EuroPCR 2014

David E. Kandzari et al. EuroPCR 2014
Hypertension Devices

- Radiofrequency
- Ultrasound
- Baro-receptor Modulation
- Chemical

- Medtronic Symplicity™
- St. Jude Enlight™
- BSC Vessix V2
- Covidien-Maya OneShot
- ReCor PARADISE®
- CVRx® Barostim neo™
- Mobius
- Mercator Bullfrog®
- Ablative Solutions (ethanol)
- Median Nerve Stimulator
- ROX Coupler
- Kona Medical
- A-V Fistula (afterload)
- Ethanol
- (Guanethidine)
- (Vincristine)

A-V Fistula (afterload)
Median Nerve Stimulator

Hypertension Devices

- Radiofrequency
- Ultrasound
- Baro-receptor Modulation
- Chemical

- Medtronic Symplicity™
- St. Jude Enlight™
- BSC Vessix V2
- Covidien-Maya OneShot
- ReCor PARADISE®
- CVRx® Barostim neo™
- Mobius
- Mercator Bullfrog®
- Ablative Solutions (ethanol)
- Median Nerve Stimulator
- ROX Coupler
- Kona Medical
- A-V Fistula (afterload)
- Ethanol
- (Guanethidine)
- (Vincristine)


**Hypertension Devices**

- Radiofrequency
- Ultrasound
- Baro-receptor Modulation
- Chemical
- A-V Fistula (afterload)

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**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**

<table>
<thead>
<tr>
<th></th>
<th>Denervation</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP Change</td>
<td>-5.9 mm Hg</td>
<td>-6.3 mm Hg</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>-11.3 to -0.5</td>
<td>-12.0 to -0.6</td>
</tr>
<tr>
<td>p</td>
<td>0.0329</td>
<td>0.0296</td>
</tr>
<tr>
<td><strong>Nighttime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP Change</td>
<td>-5.5 mm Hg</td>
<td>-6.3 mm Hg</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>-11.3 to -0.3</td>
<td>-12.0 to -0.6</td>
</tr>
<tr>
<td>p</td>
<td>0.0329</td>
<td>0.0296</td>
</tr>
</tbody>
</table>

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
**AREAS OF RENAL DENERVATION**

Combined Branch and Main Artery Treatment

Effective in Reducing Renal NE in Normotensive Pigs

**RENAL NOREPINEPHRINE LEVELS**

- **Control**
- **RD**

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-naive OR permitting discontinuation of antihypertensive medications

**VISIT 1**

- 3-4 months
- Office SBP
- DBP
- Drug naïve or stop meds
- 2-week safety/week 2

**VISIT 2**

- Drug testing
- Office SBP
- DBP
- sham
- Randomized drug intake
- 24-hr ABPM
- DBP 2 to 4 mm Hg

**TREATMENT**

- Sham Control
- Renal Denervation

- Drug testing
- Office SBP
- Furosemide drug intake
- 24-hr ABPM

Clinicaltrials.gov NCT02439749

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

**Screening**

- Inclusion criteria:
  - Office SBP ≥ 150 and < 180
  - Stable on 1, 2, or 3 antihypertensive drugs for 6 weeks
  - Thiazide diuretic
  - Calcium channel blocker
  - ACE/ARB
  - Beta blocker

**Visit 1**

- Office SBP: SBP ≥ 180 ≤ 190
- DBP ≥ 100

**Visit 2**

- Drug naïve
- Office BP: SBP ≤ 180 ≤ 190
- DBP ≥ 100 ≤ 110
- Witnessed drug intake
- 24 hr ABPM

**Screening if CSSP > 180**

**Treatment**

- Sham Control + Medications
- Renal Denervation + Medications

- 1M
- 3M
- 6M
- 12M

- Office BP
- Witnessed drug intake
- 24 hr ABPM
## ON MED: Key Inclusion/Exclusion Criteria

### Inclusion
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
2. Office SBP: ≥ 150 mm Hg and < 180 mm Hg
3. Office DBP: ≥ 90 mm Hg
4. Systolic 24-hour mean ABPM following witnessed antihypertensive drug ingestion:
   - ≥ 140 mm Hg and < 170 mm Hg
5. Age: 20-80 years

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

---

### SYMPPLICITY OFF MED

**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**


*Lancet 2017; 390:2160-70*
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

### 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)</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>

1TIMI definition: Intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure.


### SYMPLICITY OFF MED

Lancet 2017; 390:2160-70
**SYMPLECTICITY 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

David I. Kandzari, Michael Bihn, Fola Mafloju, Raymond E. Townsend, Michael A. Weber, Stuart Pocock, Konstantinos Tousoulis, Dimitris Tousoulis, Jiyong H. Oh, Carol Eust, Sandip Banerjee, Siddhaik Cohen, Martin Fisch, Garrett Hickey; Executive Co- or on behalf of the SPYRAL HTN-ON MED Trial Investigators

*Lancet* 2018; S0140-6736(18)30951-6

---

**SPYRAL HTN – ON MED**

Blood Pressure Change from Baseline to 6 Months

![Graph showing blood pressure change from baseline to 6 months for SPYRAL HTN-ON MED trial.](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.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3M</th>
<th>6M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherent</td>
<td>62.5% (N=38)</td>
<td>55.0% (N=37)</td>
<td>62.5% (N=50)</td>
</tr>
<tr>
<td>Incomplete or Non-Adherent</td>
<td>37.5% (N=24)</td>
<td>42.5% (N=22)</td>
<td>36.3% (N=25)</td>
</tr>
<tr>
<td>Missing</td>
<td>n=10</td>
<td>n=7</td>
<td>n=12</td>
</tr>
<tr>
<td></td>
<td>n=8</td>
<td>n=12</td>
<td>n=1</td>
</tr>
</tbody>
</table>

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

Systolic

Diastolic

Change in 24-hour SBP (mmHg)

Change in 24-hour DBP (mmHg)

Baseline 3 Months 6 Months
Baseline 3 Months 6 Months

Sham control
RDN

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

SPYRAL HTN-OFF MED¹
(change from baseline to 3 months)

24-hour SBP
n=35
n=35

24-hour DBP
n=35
n=35

SPYRAL HTN-ON MED²
(change from baseline to 6 months)

24-hour SBP
n=36
n=36

24-hour DBP
n=36
n=36

Δ Baseline
Δ3 Months
Δ6 Months
Δ Baseline
Δ3 Months
Δ6 Months

-5.5
-4.8
-4.5
-9.0
-6.0

-0.5
-0.4
-1.9

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

SCREENING

VISIT 1
- Office BP
- Drug naïve or medications discontinued
- 2-week safety check

VISIT 2
- Office BP (baseline) DBP ≥100 to <110
- 24-h ABPM SBP ≥130 to <170
- Drug testing

Follow-up every 2 weeks

3M

SHAM CONTROL

TREATMENT

Visit every 2 weeks

3M

4M

6M

12-36M

RENAL 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
- OBP < 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 4-8 mm and length >25 mm
- Accessory renal artery diameter <2 mm or 4-8 mm
- 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 (bilateral diameter 4-8 mm, length >25 mm, and no stenosis ≥30%)

### Antihypertensive Medication Washout - 4 weeks

### Office BP Baseline
- Daytime ABP ≥ 135/85 and <170/105 mmHg

### CTA / MRA, Renal Duplex, Renal Angiography

### Systolic BP

### Primary Efficacy Endpoint @ 2 Months
- Daytime Ambulatory Systolic BP

---

The PARADISE® system is approved for sale in markets regulated by the CE mark.

Investigational Device in the US. Limited by U.S. Federal Law to Investigational Use Only in the United States

Data presented at ACC 2019. Published in Circulation 2019 Mar 17, Azizi, M., et. al. https://doi.org/10.1161/CIRCULATIONAHA.119.040451

MKT-0121(B), DCO 0993, Effective Date: May 15, 2019
RADIANCE SOLO

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


Lancet 2018; S0140-6736(18)31082-1

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.

The PARADISE® system is approved for sale in markets regulated by the CE mark. Investigational Device in the US, Limited by US Federal Law to Investigational Use Only in the United States.


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

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Data presented at ACC 2019. Published in Circulation 2019 Mar 17, Azizi, M., et. al. https://doi.org/10.1161/CIRCULATIONAHA.119.040451

MKT-0121(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)?**

- **Yes**
  - **Add Medications**
  - **Resolution Step**
    - **Recommended drugs**
      - 1: Amlodipine: 5 mg
      - 2: ARB: Valsartan 160-320 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

- **No Change**

#### 6-Month Follow-Up:

- **Medication Burden, Ambulatory, Home, and Office BP**
- **Yes**
- **No**
  - **Change**
  - **Escalation Step Recommended drugs**
    - 0: No A
    - 1: Amlodipine: 5 mg
    - 2: ARB: Valsartan 160-320 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

---


---

### Percentage on 0, 1, 2 or ≥ 3 Antihypertensive Meds Each Month Through 6M in RDN (n=69) and Sham (n=71)

- **Renal Denervation**
- **Sham Procedure**

---

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.

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=72)</th>
<th>Sham Procedure (n=70)</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>Acute kidney injury requiring dialysis within 30 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal or other vascular complication requiring intervention within 30 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension 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>Acute kidney injury requiring dialysis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal or other vascular complication requiring intervention</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension crisis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive 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 artery stenosis of greater than 50%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New onset renal stenosis of greater than 50%</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>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* One patient in the renal denervation group had uncontrolled primary hypertension with renal artery stenosis of 44% and underwent stenting for the lesion which measured 57% prior to stent placement at 6 months.
† One patient had a vasovagal episode that is not counted here.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Renal Denervation (n=72)</th>
<th>Sham Procedure (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conclusions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. The BP lowering effect of endovascular ultrasound RDN was maintained at 6 months with less prescribed antihypertensive medications compared with a sham control.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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/updating antihypertensive medications in patients with uncontrolled systolic-diastolic blood pressure.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ReCor Multicenter Sham-Controlled RCTs

**RAIDANCE-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

**RAIDANCE 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
- Off meds screening and primary analysis period
- 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 $\geq 3$ meds
- Standardized meds for screening/analysis period
- Standardized denervation procedure
- Powered for efficacy
- 1º Endpoint: daytime systolic ABP @ 2 months

**REQUIRE**
(N=140)
Japan & Korea
- 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

2-month endpoint met
6-month data complete
Ongoing FU through 3 years
Ongoing
Anticipate Results in 2020
Study Initiated
Anticipate Results in 2020

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Data presented at ACC 2019. Published in Circulation 2019 Mar 17; Azizi, M., et. al. [10.1161/CIRCULATIONAHA.119.040451]

MKT-0121(B), DCO 0993, Effective Date: May 15, 2019

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

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 APBM

- **Inclusion:** 1 or more renal artery ≥5.5 mm diameter
- **Exclusion:** stenosis, unsuitable anatomy, main artery <4mm diameter

**Screening office BP measurements**
- Antihypertensive medication stable for at least 4 weeks
- Daytime ABPM systolic >135 mmHg
- Exclusion of secondary hypertension; lab testing for hyperaldosteronism in all; further diagnostics as appropriate
- MRA, renal duplex, renal angiography
- Inclusion: 1 or more renal artery ≥25.5 mm diameter
- Exclusion: stenosis, unsuitable anatomy, main artery <4mm diameter

**Primary endpoint @ 3 months between group difference of change in systolic daytime ABPM**

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 (BARHT).
Special Thanks

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

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

• MHI Advanced Imaging
• Renal duplex section