Renal Denervation in the Presence of Antihypertensive Medications: Six-month Results from the Randomized, Blinded, Sham-controlled SPYRAL HTN-ON MED Trial

Dr. David E. Kandzari
Piedmont Heart Institute, Atlanta, USA
and
Michael Böhm, Felix Mahfoud, Ray Townsend, Michael Weber, Stuart Pocock, Kazuomi Kario on behalf of the SPYRAL HTN-ON MED Trial Investigators
# Disclosure

**Speaker’s Name: David Kandzari**

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional Grant/Research Support</td>
<td>Biotronik, Boston Scientific, Medtronic CardioVascular, Medinol, Orbus Neich</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria</td>
<td>Biotronik, Boston Scientific Corporation, Medtronic CardioVascular, Cardinal Health</td>
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<tr>
<td>Major Stock Shareholder/Equity</td>
<td>None</td>
</tr>
<tr>
<td>Royalty Income</td>
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<tr>
<td>Ownership/Founder</td>
<td>None</td>
</tr>
<tr>
<td>Intellectual Property Rights</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial Benefit</td>
<td>None</td>
</tr>
</tbody>
</table>
Background

• Up to 1/3 of adults have hypertension
  – Increased risk of cardiovascular events and stroke
  – Many patients remain uncontrolled

• Renal denervation therapy targets the sympathetic nervous system to lower blood pressure

• Recently the SPYRAL HTN – OFF MED trial provided proof of principle for the efficacy of renal denervation in the absence of antihypertensive medications

• The current SPYRAL HTN – ON MED study evaluated the effect of renal denervation on blood pressure in the presence of prescribed antihypertensive medications
Background: SPYRAL HTN – OFF MED at 3 Months

RCT with Hypertensive Patients Off Medications


**24-hr SBP**

<table>
<thead>
<tr>
<th>Baseline BP (mmHg)</th>
<th>RDN</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>-5.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>n=35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Office SBP**

<table>
<thead>
<tr>
<th>Baseline BP (mmHg)</th>
<th>RDN</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td>-10.0</td>
<td>-2.3</td>
</tr>
<tr>
<td>n=37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP Change at 3 months (mmHg)

Δ -5.0 mmHg

P=0.04

Δ -7.7 mmHg

P=0.02

RDN  Sham
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
# Key Patient Eligibility Criteria

## INCLUSION

1. **Patients on 1-3 anti-hypertensive medications:**
   - Thiazide diuretic
   - Calcium channel blocker
   - ACE-I / ARB
   - Beta-Blocker
   Prescribed at minimum 50% of maximum recommended dosage*
   Stable regimen for ≥6 weeks

2. **Office SBP** ≥ 150 and < 180 mm Hg

3. **Office DBP** ≥ 90 mm Hg

4. **Systolic 24-hour mean ABPM** ≥ 140 and < 170 mm Hg

## EXCLUSION

1. **Ineligible renal artery anatomy** (accessory arteries allowed)

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**

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*In Japan, patients could be prescribed less than 50% of maximum manufacturer’s recommended dosage of a thiazide-type diuretic per standard of care.*

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 \(\geq 150\) to \(< 180\)
- Stable on 1, 2, or 3 antihypertensive drugs for 6 weeks
  - Thiazide diuretic
  - Calcium channel blocker
  - ACE/ARB
  - Beta blocker

**Visit 1**
- Office BP
  - SBP \(\geq 150\) to \(< 180\)
  - DBP \(\geq 90\)

**Visit 2**
- Drug testing
- Office BP
  - SBP \(\geq 150\) to \(< 180\)
  - DBP \(\geq 90\)
- Witnessed drug intake
- 24-hr ABPM
  - SBP \(\geq 140\) to \(< 170\)

Screen failure if OSBP \(\geq 180\)

**Treatment**

- Renal Denervation
  - Medications
- Sham Control
  - Medications

1-2 weeks

1-2 weeks

1-2 weeks

1-2 weeks

1-2 weeks

**R**

**Screening**

**Visit 1**
- Office BP
  - SBP \(\geq 150\) to \(< 180\)
  - DBP \(\geq 90\)

**Visit 2**
- Drug testing
- Office BP
  - SBP \(\geq 150\) to \(< 180\)
  - DBP \(\geq 90\)
- Witnessed drug intake
- 24-hr ABPM

Screen failure if OSBP \(\geq 180\)

3M Renal Denervation + Medications

1M 3M 6M 12-36M

1M 3M 6M 12-36M

**Unblinding**

1-2 weeks

1-2 weeks

1-2 weeks

1-2 weeks

1-2 weeks

**According to scheduling**

Clinicaltrials.gov NCT02439775

# Study Organization

<table>
<thead>
<tr>
<th>Executive Committee</th>
<th>Data Safety Monitoring Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI: Michael Böhm, MD (Homburg/Saar, Germany)</td>
<td>Chairman: Bernard J. Gersh, MB, ChB, DPhil, FRCP (Rochester, MN, USA)</td>
</tr>
<tr>
<td>PI: David E. Kandzari, MD (Atlanta, GA, USA)</td>
<td>John A. Ambrose, MD (Fresno, CA, USA)</td>
</tr>
<tr>
<td>PI: Kazuomi Kario, MD (Tochigi, Japan)</td>
<td>Phyllis August, MD, MPH (New York, NY, USA)</td>
</tr>
<tr>
<td>PI: Raymond R. Townsend, MD (Philadelphia, PA, USA)</td>
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<td>Felix Mahfoud, MD (Homburg/Saar, Germany)</td>
<td></td>
</tr>
<tr>
<td>Stuart Pocock, PhD (London, United Kingdom)</td>
<td>Clinical Event Committee</td>
</tr>
<tr>
<td>Michael A. Weber, MD (Brooklyn, NY, USA)</td>
<td>Chairman: Clive Rosendorff, MD, FRCP, FACC (Bronx, NY, USA)</td>
</tr>
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<td></td>
<td>Ladan Golestaneh, MD (Bronx, NY, USA)</td>
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<tr>
<td>Study Sponsor</td>
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<td>Medtronic</td>
<td>Steven Marx, MD (New York, NY, USA)</td>
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<td></td>
<td>Michele H. Morkrzycki, MD (Bronx, NY, USA)</td>
</tr>
<tr>
<td></td>
<td>Joel Neugarten, MD, PhD, DSc (Bronx, NY, USA)</td>
</tr>
</tbody>
</table>
Participating Centers

USA
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  Hattiesburg, MS
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  Dallas, TX
- Dr. Cohen
  Philadelphia, PA
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- Dr. David
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  Lübeck, Germany
- Dr. Zeller
  Bad Krozingen, Germany

Japan
- Dr. Aoki
  Tokyo, Japan
- Dr. Kario
  Tochigi, Japan

Australia
- Dr. Walton
  Melbourne, Australia
SPYRAL HTN – ON MED

Patient Flowchart

Enrollment July 2015 – June 2017

467 patients enrolled and assessed for eligibility

428 patients at screening visit 1

219 patients at screening visit 2

80 patients randomized

39 patients did not meet all eligibility criteria

42 patients at 6-month follow up

209 excluded:
- 194 with office BP out of range
- 15 miscellaneous

RDN group
N = 38 patients (ITT)

38 patients at 6-month follow up

Office BP Measurement
n = 38/38 (100%)

24-hour BP Measurement
n = 37/38 (97.4%)

Sham control group
N = 42 patients (ITT)

42 patients at 6-month follow up

Office BP Measurement
n = 41/42 (97.6%)

24-hour BP Measurement
n = 40/42 (95.2%)

139 excluded:
- 53 with office BP out of range
- 71 with ABPM out of range or invalid
- 8 with ineligible renal anatomy
- 7 miscellaneous
### Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Mean ± SD or % (n)</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.9 ± 8.7</td>
<td>53.0 ± 10.7</td>
</tr>
<tr>
<td>Male</td>
<td>86.8 (33)</td>
<td>81.0 (34)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 ± 6.4</td>
<td>32.5 ± 4.6</td>
</tr>
<tr>
<td>Diabetes (type 2)</td>
<td>13.2 (5)</td>
<td>19.0 (8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>21.1 (8)</td>
<td>26.2 (11)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>5.3 (2)</td>
<td>23.8 (10)*</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Coronary artery disease†</td>
<td>2.6 (1)</td>
<td>2.4 (1)</td>
</tr>
<tr>
<td>Stroke and transient ischemic attack†</td>
<td>0 (0)</td>
<td>2.4 (1)</td>
</tr>
<tr>
<td>Myocardial infarction / acute coronary syndrome†</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*These events occurred > 3 months before randomization

*P = NS for differences in all baseline characteristics, except for OSA (P = 0.03)
### Baseline Blood Pressure

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office SBP (mm Hg)</td>
<td>164.6 ± 7.1</td>
<td>163.5 ± 7.5</td>
</tr>
<tr>
<td>Office DBP (mm Hg)</td>
<td>99.6 ± 6.9</td>
<td>102.7 ± 8.0</td>
</tr>
<tr>
<td>Office heart rate (bpm)</td>
<td>75.6 ± 11.8</td>
<td>73.5 ± 10.4</td>
</tr>
<tr>
<td><strong>24-hour measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 24-hour SBP (mm Hg)</td>
<td>152.1 ± 7.0</td>
<td>151.3 ± 6.8</td>
</tr>
<tr>
<td>Mean 24-hour DBP (mm Hg)</td>
<td>97.2 ± 6.9</td>
<td>97.9 ± 8.4</td>
</tr>
<tr>
<td>Mean 24-hour heart rate (bpm)</td>
<td>75.3 ± 11.3</td>
<td>75.6 ± 10.7</td>
</tr>
</tbody>
</table>

*P = NS for differences in all baseline measurements*
### Baseline Medications

#### Number of anti-hypertensive medication classes

<table>
<thead>
<tr>
<th>% (n)</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>2.2 ± 0.9</td>
<td>2.3 ± 0.8</td>
</tr>
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</table>

#### Prescribed medication classes

<table>
<thead>
<tr>
<th>Medication class</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>28.9 (11)</td>
<td>21.4 (9)</td>
</tr>
<tr>
<td>2</td>
<td>18.4 (7)</td>
<td>26.2 (11)</td>
</tr>
<tr>
<td>3</td>
<td>52.6 (20)</td>
<td>52.4 (22)</td>
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#### Medication class

<table>
<thead>
<tr>
<th>Medication class</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretic</td>
<td>57.9 (22)</td>
<td>59.5 (25)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>71.1 (27)</td>
<td>73.8 (31)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>81.6 (31)</td>
<td>83.3 (35)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>10.5 (4)</td>
<td>14.3 (6)</td>
</tr>
</tbody>
</table>

*P = NS for differences in all baseline medications*
## Procedural Details

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>RDN (N = 38)</th>
<th>Sham Control (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of main renal arteries treated per patient</td>
<td>2.3 ± 0.5</td>
<td>NA</td>
</tr>
<tr>
<td>Number of branches treated per patient</td>
<td>5.8 ± 2.2</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total number of ablations per patient</strong></td>
<td>45.9 ± 13.7</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Main artery ablations</strong></td>
<td>19.3 ± 8.9</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Branch ablations</strong></td>
<td>26.6 ± 11.7</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>60.8 ± 25.3</td>
<td>NA</td>
</tr>
<tr>
<td>Contrast volume used (cc)</td>
<td>270.8 ± 101.6</td>
<td>86.0 ± 50.0</td>
</tr>
<tr>
<td>Serum creatinine change (baseline – discharge, mg/dL)</td>
<td>-0.03 ± 0.14</td>
<td>-0.01 ± 0.12†</td>
</tr>
<tr>
<td>eGFR change (baseline – discharge, ml/min/1.73 m²)</td>
<td>6.76 ± 14.83</td>
<td>0.69 ± 12.00‡</td>
</tr>
</tbody>
</table>

*P = NS  
†*P = 0.047
SPYRAL HTN – ON MED

24-Hr ABPM Change from Baseline to 6 Months

**Systolic**

- Baseline BP (mmHg):
  - RDN: 152
  - Sham: 151

- Change from baseline to 6 months:
  - RDN: -9.0 (-12.7, -5.3) \( P<0.001 \)
  - Sham: -1.6 (-5.2, 2.0) \( P=0.37 \)

**Diastolic**

- Baseline BP (mmHg):
  - RDN: 97
  - Sham: 98

- Change from baseline to 6 months:
  - RDN: -6.0 (-8.5, -3.5) \( P=0.005 \)
  - Sham: -1.9 (-4.7, 0.9) \( P=0.17 \)

**Change from Baseline**

- RDN: -7.4 mmHg (-12.5, -2.3) \( P=0.005 \)

- Sham: -4.1 mmHg (-7.8, -0.4) \( P=0.03 \)

**Legend**

- RDN
- Sham
Office Blood Pressure Change from Baseline to 6 Months

**Systolic**
- Baseline BP (mmHg):
  - RDN: 165 (n=38)
  - Sham: 163 (n=40)
- Change from baseline to 6 months (mmHg):
  - RDN: -2.6 (-6.7, 1.6) P=0.22
  - Sham: -5.2 (-7.7, -2.7) P<0.001

**Diastolic**
- Baseline BP (mmHg):
  - RDN: 100 (n=38)
  - Sham: 102 (n=40)
- Change from baseline to 6 months (mmHg):
  - RDN: -1.7 (-4.2, 0.9) P=0.19
  - Sham: -5.2 (-7.7, -2.7) P<0.001

**Chart Title**

- Δ -6.8 mmHg
  - RDN: (-12.5, -1.1) P=0.02
  - Sham: (-13.5, -5.3) P<0.001
- Δ -3.5 mmHg
  - RDN: (-7.0, -0.0) P=0.048
24-Hr ABPM – Progressive Change Over Time

**Systolic**

Baseline: -0.7
3 Months: -4.3
6 Months: -1.8

**Diastolic**

Baseline: -0.8
3 Months: -4.2
6 Months: -1.8

Change in 24-hour SBP (mmHg)

-4.3
-8.8

Change in 24-hour DBP (mmHg)

-4.2
-6.1

ANCOVA adjusted analysis
Dashed line represents the 24-hr mean at baseline (blue) and 6 months (red)
W = Self reported wake time or 7:00 AM if not reported
## Safety Results at 6 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>
<tr>
<td>New renal artery stenosis &gt; 70%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

• Study design did not include prospective statistical power estimates

• **Adherence to prescribed antihypertensive medications was ~60% and dynamic**, despite patient education and awareness of drug testing
  – Rates of adherence were similar to several contemporary trials
  – Adherence rates similar between groups and results directionally consistent
  – Office measurements performed before and ABPM measurements after witnessed pill intake

• Enrolled patients who were taking **1-3 classes of anti-hypertensive drugs**

• **Results may not be generalizable** to other RDN technologies, other clinical populations and alternative medication classes

• **No practical methods to verify nerve ablation**
  – Number of ablations and procedural technique similar to SPYRAL OFF MED
Conclusions

- Renal denervation with the Symplicity Spyral™ system resulted in **statistically significant and clinically relevant blood pressure reductions** at 6 months
  - In uncontrolled hypertensive patients compared with sham control
  - In the presence of commonly prescribed anti-hypertensive medications
- Blood pressure after renal denervation **continued to decrease** between 3 and 6 months
- Blood pressure reductions following renal denervation were present **throughout the day and night** ("always on" effect)
- **No major safety events** despite a more complete denervation procedure that extended into renal artery branch vessels
- Non-adherence to antihypertensive medications was common (~40%) and dynamic
- Larger **SPYRAL HTN PIVOTAL trial in an off med population** is ongoing
  - Recent IDE approval from FDA
  - As part of the global clinical program, this trial will further inform the safety and effectiveness of RDN for the treatment of uncontrolled hypertension
- Study design for a **larger trial** in the presence of antihypertensive therapy is in development
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 E Kandzari, Michael Böhm, Felix Mahfoud, Raymond R Townsend, Michael A Weber, Stuart Pocock, Konstantinos Tsioufis, Dimitrios Tousoulis, James W Choi, Cara East, Sandeep Brar, Sidney A Cohen, Martin Fahy, Garrett Pilcher, Kazuomi Kario on behalf of the SPYRAL HTN-ON MED Trial Investigators

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