Renal Sympathetic Denervation for Treatment of Resistant Hypertension: 18-Month Results from the Symplicity HTN-2 Randomized Controlled Trial

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Baker IDI Heart and Diabetes Institute, Melbourne

On behalf of Henry Krum, Markus Schlaich, Roland Schmieder, Michael Böhm, Paul Sobotka and the Symplicity HTN-2 Investigators
Disclaimer

Speaker is the Chief Investigator of the multi-centre randomized international trial of therapeutic endovascular renal denervation with the Symplicity™ renal denervation system in drug-resistant hypertension (HTN-2 trial), and is a recipient of research grant, travel and consultancy funding from Medtronic and Ardian Inc. He holds no stock or shares in either company, or patent rights for renal denervation.
Differentiation of Treatment-Resistant Hypertension

Uncontrolled Hypertension
Patients who lack BP control including:
- Inadequate treatment regimens
- Poor adherence
- Undetected secondary hypertension
- True treatment resistance

Controlled Hypertension
Patients who achieve current BP control rates of SBP <140 mm Hg and DBP <90 mm Hg (or lower if there are other complications).

BP remains above goal with ≥3 antihypertensive medications\(^1,3\)
- Therapeutic plan should include lifestyle measures\(^3\)

BP controlled but requires ≥4 antihypertensive medications\(^1\)

BP=blood pressure; DBP=diastolic blood pressure; SBP=systolic blood pressure.
Catheter-Based Radiofrequency Renal Nerve Ablation

- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms
Activation of the Renal Sympathetic Nerves in Patients with Essential Hypertension¹

“Renal Denervation Delays or Prevents Development of Many Experimental Forms of Hypertension”²

1. M Esler, G Lambert, G Jennings J Hypertension 1990;8: S53-S57 (Updated)
2. G F DiBona Physiol Rev 1997;77:75-197
Participating Centers: HTN-2 Randomized Controlled Trial

- Universitätsklinikum des Saarlandes Homburg, Germany (Michael Böhm)
- CardioVascular Center Frankfurt Frankfurt, Germany (Horst Sievert)
- Universitätsklinikum Düsseldorf Düsseldorf, Germany (Lars Christian Rump)
- Universität Erlangen-Nürnberg Erlangen, Germany (Roland Schmieder)
- Barts and The London London, UK (Mel Lobo)
- Pauls Stradins Clinical University Hospital Riga, Latvia (Andrejs Erglis)
- L'Hôpital Européen Georges Pompidou Paris, France (Guillaume Bobrie)
- John Hunter Hospital Newcastle, Australia (Suku Thambar)
- Cliniques Universitaires Saint-Luc Brussels, Belgium (Alexandre Persu)
- Universitätsklinikum Schleswig-Holstein Lübeck, Germany (Heribert Schunkert)
- Universität zu Köln Köln, Germany (Uta Hoppe)
- The Alfred Hospital Melbourne, Australia (Henry Krum)
- Universitität Leipzig – Herzzentrum Leipzig, Germany (Dierk Scheinert)
- Allgemeines Krankenhaus der Stadt Wien Vienna, Austria (Thomas Binder)
- Samodzielna Pracownia Hemodynamiczna Warsaw, Poland (Andrzej Januszewicz & Adam Witkowski)
- Hospital 12 de Octubre Madrid, Spain (Luis Ruilope)
- St. Vincent's Hospital Melbourne, Australia (Robert Whitbourn)
- Universitätsklinikum Essen Essen, Germany (Heike Bruck)
- Kent and Canterbury Hospital Canterbury, UK (Mark Downes)
- University Hospital Zurich Zurich, Switzerland (Thomas Lüscher)
- University of Glasgow Glasgow, UK (Alan Jardine)
- Auckland City Hospital Auckland, New Zealand (Mark Webster)
- Herz-Zentrum Bad Krozingen Bad Krozingen, Germany (Thomas Zeller)
- The John Paul II Hospital Krakow, Poland (Jerzy Sadowski)

Patient Population

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

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

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
- 6-month Per Protocol Post RDN (Crossover) n=35
- Not-Per Protocol*, (Crossover) n=9

Patient Disposition

* Crossed-over with ineligible BP (<160 mmHg)
### Symplicity HTN-2 Pre-Procedure Demographics

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=49)</th>
<th>Cross-Over (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office Systolic Blood Pressure (mm Hg)</strong></td>
<td>178.2 ± 17.1</td>
<td>190.9 ± 19.6</td>
</tr>
<tr>
<td><strong>Office Diastolic Blood Pressure (mm Hg)</strong></td>
<td>97.0 ± 15.8</td>
<td>101.4 ± 16.2</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>58.2 ± 11.9</td>
<td>57.3 ± 13.1</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td>34.6%</td>
<td>59.5%</td>
</tr>
<tr>
<td><strong>Race (% Caucasian)</strong></td>
<td>98.1%</td>
<td>97.3%</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>30.9 ± 5.1</td>
<td>31.1 ± 5.4</td>
</tr>
<tr>
<td><strong>Type II DM</strong></td>
<td>40.4%</td>
<td>29.7%</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td>19.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td><strong>Heart Rate (bpm)</strong></td>
<td>75 ± 15</td>
<td>73 ± 15</td>
</tr>
</tbody>
</table>

Standard deviations are presented unless otherwise specified
<table>
<thead>
<tr>
<th>% usage</th>
<th>Renal Denervation Group (n=49)</th>
<th>Crossover Group (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>51.0% (25/49)</td>
<td>48.6% (17/35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Angiotensin Receptor blocker</td>
<td>67.3% (33/49)</td>
<td>82.9% (29/35)</td>
<td>0.136</td>
</tr>
<tr>
<td>Calcium Channel blocker</td>
<td>77.6% (38/49)</td>
<td>77.1% (27/35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diuretic</td>
<td>89.8% (44/49)</td>
<td>91.4% (32/35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>18.4% (9/49)</td>
<td>22.9% (8/35)</td>
<td>0.784</td>
</tr>
<tr>
<td>Centrally-acting sympatholytics</td>
<td>51.0% (25/49)</td>
<td>42.9% (15/35)</td>
<td>0.511</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>16.3% (8/49)</td>
<td>22.9% (8/35)</td>
<td>0.575</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>81.6% (40/49)</td>
<td>62.9% (22/35)</td>
<td>0.078</td>
</tr>
<tr>
<td>Alpha-adrenergic blocker</td>
<td>8.2% (4/49)</td>
<td>2.9% (1/35)</td>
<td>0.396</td>
</tr>
<tr>
<td>Direct-acting vasodilators</td>
<td>8.2% (4/49)</td>
<td>2.9% (1/35)</td>
<td>0.396</td>
</tr>
</tbody>
</table>
*Patients randomized to control were offered RDN following the primary endpoint assessment. Only patients still meeting entry criteria (SBP ≥ 160 mmHg) were included in this analysis (n=37)
Change in Office Blood Pressure Through 18 Months*

P-values < 0.01 at each time point compared to pre procedure values for each group

*Post Procedure follow up
Renal Function Over Time

**RDN eGFR***

- Pre Procedure (n=52): 76.7
- 6 months (n=49): 77.1
- 12 months (n=45): 78.2

**Crossover eGFR***

- Pre Procedure (n=37): 88.6
- 6 months (n=35): 85.2
- 12 months (n=31): 81.2

Renal function parameters were not obtained beyond 12 months follow up

*eGFR mL/min/1.73m²
Change in Pulse Pressure
Post Procedure

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN*</td>
<td>-19,9</td>
<td>-18,3</td>
<td>-19,8</td>
</tr>
<tr>
<td>N=49</td>
<td>N=35</td>
<td>N=47</td>
<td>N=33</td>
</tr>
<tr>
<td>Crossover*</td>
<td>-15,3</td>
<td>-13,8</td>
<td>-17,6</td>
</tr>
<tr>
<td>N=47</td>
<td>N=33</td>
<td>N=43</td>
<td>N=31</td>
</tr>
</tbody>
</table>

*P<.01 from pre procedure values at all time points
Heart Rate Over Time

All p-values at each time point are compared to pre procedure HR

* p < .01 (6, 12m), p = .02 (18m)
† p = NS (6, 18m), p < .01 (12m)
Physicians were allowed to change medication following the 6-month primary endpoint.

Reasons for medication changes were unknown and may be related to a variety of confounding factors.

Increase: if both meds/dose increase, or if meds no change and dose increase, or if dose no change and meds increase.

Decrease: if both meds/dose decrease, or if meds no change and dose decrease, or if dose no change and meds decrease.

Indeterminate: All other combinations.
Safety Update: 12 to 18 months Post Procedure

• 3 hypertensive events requiring hospitalization in the initially treated group
• 1 hypotensive event which required hospitalization
• 1 mild transient acute renal failure
  o Admitted with elevated $K^+$, meds temporarily d/c’d (Co-Amilofruse, perindopril, metformin). IV fluids administered; $K^+$ decreased. Patient discharged and remained off perindopril.
• 2 deaths unrelated to the device or therapy

No clinically significant changes in eGFR compared to pre procedure values and no renal vascular events reported
Conclusions

- Subjects in both groups had blood pressure reductions which were significant and sustained through 18 months of follow up.
- Physicians were allowed to change medications following the 6-month primary endpoint. Reasons for changes were mostly unknown but may be related to a variety of confounding factors.
- Pulse pressure improved and heart rate was stable or dropped following treatment with the Symplicity™ renal denervation system.
- At 18 months follow-up there are no device-related serious adverse effects and no detrimental effects on the renal vasculature following treatment.