Recent Update of Renal Denervation Therapy

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Yonsei University College of Medicine, Seoul, Korea
Renal denervation therapy for resistant hypertension

Catheter-based renal sympathetic denervation has shown remarkable and durable BP reduction in patients with resistant hypertension through the staged clinical studies.

**Symplicity HTN-1, Cohort study**
Significant BP reduction started at 1 month ... Sustained at 12 & 24 months

**Symplicity HTN-2 Trial**
Primary Endpoint: 6-Month Office BP

First-in-Man
Series of Pilot studies

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

33/11 mmHg
difference between RDN and Control
(P<0.0001)

✓ 84% of RDN patients had ≥ 10 mmHg reduction in SBP
153 patients with resistant hypertension were enrolled in the Symplicity HTN-1 study, of whom 88 patients had complete data at 36 months.

At 36 months, significant BP changes; SBP (–32.0 mm Hg), DBP (–14.4 mm Hg)

Rates of SBP-drop ≥10 mm Hg;
- 1, 6, 12, 24, and 36 months, 69%, 81%, 85%, 83%, and 93%
Prospective, single-blind, randomized, sham-controlled trial.
Trial Design

- 2:1 randomization, blinded and sham-controlled
- 535 subjects randomized out of 1441 enrolled at 88 sites in US (63% screen failure rate)
- 2-week screening process, including **maximum** tolerated doses of antihypertensive medications

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

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

**Sham Procedure**
- Renal angiogram; Eligible subjects randomized

**Renal Denervation**
- Home BP & HTN med confirmation

1 mo 3 mo 6 mo 12-60 mo

- Patients, BP assessors, and study personnel all blinded to treatment status
- No changes in medications for 6 M
A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Lakkis, Ralph E. D’Agostino Jr., Michael J. Riley, Martin B. Scheinman, Sidney A. Cohn, David B. Grines, Daniel Parise, Joseph T. Guglielmi, R. Scott Wright, Rolf M. Krum, Sandeep Mistry, and the Symplicity HTN-3 Investigators

Methods
We designed the study with several enrollment criteria, including a systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of at least 90 mm Hg, and a reduction of at least 10 mm Hg in systolic blood pressure. The study was the largest randomized controlled trial designed to evaluate the safety and efficacy of renal denervation for the treatment of resistant hypertension.

Results
A total of 364 patients were randomized to the intervention group and 353 to the sham control group. The mean change in systolic blood pressure from baseline to 6 months in the intervention group was -2.39 mm Hg, while in the sham control group it was -1.96 mm Hg. The between-group difference was not statistically significant (P = 0.26).

Conclusions
This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLECTIC HTN-3 ClinicalTrials.gov number, NCT01418261.)
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 L. Steiner, M.D., Sidney Smiley, M.D.

RESULTS
A total of 1,138 participants were randomly assigned in a 1:1 ratio to receive renal denervation (n=569) or a sham procedure (n=569), after which they were followed for 6 months. The mean change in systolic blood pressure at 6 months was -12.1 mm Hg lower in the renal denervation group than in the sham group (P<0.001). There were also statistically significant differences in the change in diastolic blood pressure (P=0.03). The proportion of patients whose systolic blood pressure was <140 mm Hg at 6 months was significantly greater in the renal denervation group (67%) than in the sham group (50%) (P<0.001). There were no serious adverse events that were possibly or probably related to the procedure.

CONCLUSION
This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLECTICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)
After SYM-3 publication

From 2014 EuroPCR meeting
Predictors of blood pressure response in the SYMPLICITY HTN-3 trial

David E. Kandzari¹*, Deepak L. Bhatt², Sandeep Brar³, Chandan M. Devireddy⁴, Murray Esler⁵, Martin Fahy³, John M. Flack⁶, Barry T. Katzen⁷, Janice Lea⁴, David P. Lee⁸, Martin B. Leon⁹, Adrian Ma⁸, Joseph Massaro¹⁰, Laura Mauri²,¹⁰, Suzanne Oparil¹¹, William W. O’Neill¹², Manesh R. Patel¹³, Krishna Rocha-Singh¹⁴, Paul A. Sobotka¹⁵, Laura Svetkey¹³, Raymond R. Townsend¹⁶, and George L. Bakris¹⁷

¹Piedmont Heart Institute, Atlanta, GA, USA; ²Brigham and Women’s Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA; ³Medtronic, Inc., Santa Rosa, CA, USA; ⁴Emory University School of Medicine, Atlanta, GA, USA; ⁵Baker IDI Heart and Diabetes Institute, Monash University, Melbourne, Australia; ⁶Wayne State University and the Detroit Medical Center, Detroit, MI, USA; ⁷Baptist Cardiac and Vascular Institute, Miami, FL, USA; ⁸Stanford Hospital and Clinics, Palo Alto, CA, USA; ⁹New York Presbyterian Hospital, Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY, USA; ¹⁰Harvard Clinical Research Institute, Boston, MA, USA; ¹¹University of Alabama at Birmingham, Birmingham, AL, USA; ¹²Division of Cardiology, Henry Ford Hospital, Detroit, MI, USA; ¹³Duke University Medical Center, Durham, NC, USA; ¹⁴Prairie Heart Institute, Springfield, IL, USA; ¹⁵The Ohio State University, Columbus, OH, USA; ¹⁶Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; and ¹⁷The University of Chicago Medicine, Chicago, IL, USA

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Background & Objective

**Key factors**, for the **greater than expected** BP-drop after sham-procedure and the **less than expected** BP-drop after RDN

Based on the results of **multivariable analysis for the predictors of SBP change**, and **analysis of pre-specified and post hoc subgroups** to identify “potential confounding factors” that may have affected the trial results, three areas of investigation were pursued:

i. outcomes in selected subgroups, and

ii. detailed assessment of procedural data that may have impacted the delivery of effective RDN.
Multivariable predictors of SBP reduction at 6 months

Positive Predictors

Control
-12.003 | Alpha-1 blocker use
-11.975 | African American race
-8.004 | Baseline Office SBP at ≥180

RDN
-9.774 | Aldosterone Antagonist

Estimate (mmHg/attempt)

Negative Predictors

Vasodilator
7.551

P value
0.044
0.003
0.064
0.005
0.002
0.04
0.0001

Univariate P < 0.2 required to enter the model.
Sub-group analysis of SYMPPLICITY HTN-3

Unlike previous SYMPPLICITY trials, SYMPPLICITY HTN-3 enrolled a substantial number of African-American patients who represent a significant proportion of hypertensive patients in U.S.
Change in Office SBP at 6 Months for Non-African American and African American Subgroups

<table>
<thead>
<tr>
<th>Change in Office Systolic BP at 6 Months (mm Hg)</th>
<th>Non-African American</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=264</td>
<td>N=120</td>
<td>N=85</td>
</tr>
<tr>
<td>-15.2</td>
<td>-8.6</td>
<td>-15.5</td>
</tr>
<tr>
<td>P=0.012</td>
<td></td>
<td>P=0.641</td>
</tr>
</tbody>
</table>

Baseline SBP, mm Hg | 179.5 | 178.6 | 180.6 | 183.9

SEVERANCE CARDIOVASCULAR HOSPITAL
YONSEI UNIVERSITY COLLEGE OF MEDICINE
Procedural Variability

- Correlation with # of ablations?
- Correlation with 4-quadrant ablation pattern?

Patients were categorized by delivery of 4-quadrant ablations into 1) 2 Four-quadrant ablation pattern (both sides), 2) 1 Four-quadrant ablation pattern (either right or left), or 3) 0 Four-quadrant ablation.
Impact of “number of ablation attempts” on difference in 6-month change in office SBP (A) and 24-h ABPM, SBP (B) after propensity scored matching

There was no increase in safety events corresponding to the increasing number of renal artery ablations (no MAEs occurred in patients receiving ≥13 ablations).
Systolic BP Change at 6 Months According to the Ablation Pattern

**Baseline SBP Measurements (mm Hg)**

<table>
<thead>
<tr>
<th></th>
<th>Office</th>
<th>ABPM</th>
<th>Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 four-quadrant tx*</td>
<td>179.6</td>
<td>158.7</td>
<td>168.5</td>
</tr>
<tr>
<td>1 Four-quadrant tx</td>
<td>178.8</td>
<td>161.2</td>
<td>171.3</td>
</tr>
<tr>
<td>2 four-quadrant tx</td>
<td>186.9</td>
<td>159.9</td>
<td>170.4</td>
</tr>
</tbody>
</table>

*1 superior, 1 inferior and 2 anterior/posterior

**P value for trend**
- **Office:** 0.10
- **ABPM:** 0.24
- **Home:** 0.58
Catheter-Based Renal Denervation Is No Simple Matter
Lessons to Be Learned From Our Anatomy?

Felix Mahfoud, MD,† Elazer R. Edelman, MD, PhD,‡§ Michael Böhm, MD†
FIGURE 1  Distribution and Density of Renal Sympathetic Nerves

Distribution of nerves stratified according to total number (each green dot represents 10 nerves), relative number as percent per segment, and distance from the lumen in relative (A) proximal, (B) middle, and (C) distal location. Figure prepared using raw data from Sakakura et al. (4), and from raw data provided by M. Joner, of CVPath Inc.
Predictors of nonresponse to renal denervation in a real world population of patients with uncontrolled hypertension: Analysis of the Global SYMPLICITY Registry

non-response to RDN defined as Office SBP reduction $<10$ mm Hg from baseline

Felix Mahfoud, MD
on behalf of the GSR Investigators
Universitätskliniken des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany
Global SYMPLICITY Registry

Consecutive patients treated in real world population
5000 patients

GREAT Registry
N=1000

Korea Registry*
N=102

South Africa Registry*
N=400

Canada and Mexico*

Rest of GSR
N~3500

231 international sites in 37 countries
40% randomly assigned to 100% monitoring

Follow-up schedule
3M  6M  1Y  2Y  3Y  4Y  5Y
Change in Office SBP at 6 Months

N=751

N=244

GSR All Pts

GSR (≥160 office /≥135 ABPM)*

-11.9 ± 24.5

-20.2 ± 21.8

P<0.0001 for change from baseline for both

*with ≥3 antihypertensive medication classes

Error bar is ± 1.96 SE
Change in Ambulatory SBP at 6 Months

Change in Mean 24-Hour SBP (mm Hg)

N=404

N=176

GSR All Pts

GSR (≥160 office /≥135 ABPM) *

-7.9 ± 17.7

-9.1 ± 16.4

P<0.001 for change from baseline for both

*with ≥3 antihypertensive medication classes

Error bar is ± 1.96 SE
Predictors of non-response in office systolic BP: all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>342 non-responders/ 408 responders in both models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline office SBP (mm Hg)</td>
<td>0.95 [ 0.94, 0.96]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 or more comorbidities</td>
<td>0.69 [ 0.50, 0.97]</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- **Higher baseline office SBP** and **presence of 2 or more comorbidities** was associated with a response to renal denervation.

- ✓ **Relatively lower baseline SBP** and **lower risks** was associated with non-response.
Predictors of non-response in office systolic BP: HTN-3 like cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>77 non-responders/ 167 responders in model with standard covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of attempts</td>
<td>0.91 [ 0.84, 0.99]</td>
<td>0.032</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.46 [0.24, 0.87]</td>
<td>0.018</td>
</tr>
<tr>
<td>Baseline office SBP</td>
<td>0.94 [ 0.91, 0.96]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of anti-HTN drugs</td>
<td>1.26 [0.97, 1.63]</td>
<td>0.078</td>
</tr>
</tbody>
</table>

- Higher baseline office SBP, male sex and increasing number of ablation attempts were associated with a response to renal denervation.
- Number of anti-hypertensive medications at baseline was associated with non-response.
Changes of Ambulatory BP
# 24-h ABPM: Analysis on technically sufficient (>70% of readings) paired baseline & 6-month

- **RDN (n=20):** -11 / -7 mmHg  
  (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)

- **Control (n=25):** -3 / -1 mmHg  
  (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)
Ambulatory Blood Pressure Changes After Renal Sympathetic Denervation in Patients With Resistant Hypertension

Felix Mahfoud, MD; Christian Ukena, MD; Roland E. Schmieder, MD; Bodo Cremers, MD; Lars C. Rump, MD; Oliver Vonend, MD; Joachim Weil, MD; Martin Schmidt, MD; Uta C. Hopp, MD; Thomas Zeller, MD; Anel Rupp, MD; Christian Otto, MD; Erwin Blessing

**Background**—Catheter-based renal sympathetic denervation (RDN) is an emerging solution to high cardiovascular risk in patients with resistant hypertension. Pseudoresistant hypertension is defined as resting systolic blood pressure (SBP) <130 mm Hg on 24-hour ambulatory monitoring, despite elevated office SBP.

**Methods and Results**—The RDN System (Medtronic, Minneapolis, MN) was used to treat 346 patients (303 true resistant hypertension; 43 pseudoresistant hypertension) in a prospective, single-arm, multicenter trial. Ambulatory BP monitoring was done at 3, 6, and 12 months. At 12 months, office SBP and DBP were reduced by 8.9/9.5/11.7 mm Hg, 8.3/9.0/11.6 mm Hg, and 8.1/9.4/11.1 mm Hg among patients with true resistant hypertension (n=303), pseudoresistant hypertension (n=43), and minimum SBP >130 mm Hg, respectively. The 12-month changes in SBP and DBP were similar between the groups and correlated with the patients' baseline characteristics.

**Conclusions**—RDN is an effective and safe solution to high cardiovascular risk in resistant hypertension, with similar results in patients with true resistant hypertension and those with pseudoresistant hypertension.

**Changes in Office DBP and SBP and ABP in Patients With True Treatment-Resistant Hypertension and Those With Pseudoresistant Hypertension**

Oslo RDN trial

Fadl Elman
Sverre Heggelund

Abstract—We conducted a randomized trial of renal denervation (RDN) versus standard medical therapy in patients with baseline uncontrolled hypertension (SBP ≥135 mm Hg, DBP ≥85 mm Hg) and diabetes, despite maximal medical therapy. RDN was delivered using the catheter system, because RDN was associated with lower systolic and diastolic BP, respectively (160±14/88±10 mm Hg vs. 161±16/89±16 mm Hg, P=0.004). In the adjusted drug treatment group, the investigators excluded patients with SBP ≥135 mm Hg, DBP ≥85 mm Hg, and P=0.004.

Figure 2. Illustration shows the flow chart of the present study. BP indicates blood pressure.
Our data suggest that **adjusted drug treatment has superior BP lowering effects** compared with RDN in patients with true TRH.
Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label.

<table>
<thead>
<tr>
<th>Renal denervation group</th>
<th>Control group</th>
<th>Mean baseline-adjusted difference (95% CI) between the two groups at 6 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomisation (mean ± SD)</td>
<td>6 months (mean ± SD)</td>
<td>Mean baseline-adjusted difference (95% CI)</td>
</tr>
<tr>
<td></td>
<td>n=48</td>
<td>n=48</td>
<td>155.5±16.1</td>
</tr>
<tr>
<td></td>
<td>n=53</td>
<td>n=53</td>
<td>139.1±17.8</td>
</tr>
<tr>
<td>ABP, mm Hg</td>
<td>139.1±17.8</td>
<td>129.4±21.0</td>
<td>92.9±15.0</td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
<td>82.9±13.7</td>
</tr>
<tr>
<td></td>
<td>141.4±17.3</td>
<td>126.7±18.5</td>
<td>135.5±14.3</td>
</tr>
<tr>
<td></td>
<td>82.0±16.1</td>
<td>73.1±13.3</td>
<td>79.4±10.5</td>
</tr>
<tr>
<td>Night-time</td>
<td>151.6±16.2</td>
<td>135.5±17.6</td>
<td>146.8±15.2</td>
</tr>
<tr>
<td></td>
<td>90.0±15.2</td>
<td>80.1±13.0</td>
<td>88.8±10.6</td>
</tr>
</tbody>
</table>

The randomisation sequence was generated by computer, and stratified by centres. For SSAHT, after randomisation, spironolactone 25 mg per day, bisoprolol 10 mg per day, prazosin 5 mg per day, and rilmenidine 1 mg per day were sequentially added from months two to five in both groups if home blood pressure was more than or equal to 135/85 mm Hg. The primary endpoint was the mean change in daytime systolic blood pressure from baseline to 6 months as assessed by ambulatory blood pressure monitoring. The primary endpoint was analysed blindly. The safety outcomes were the incidence of acute adverse events of the renal denervation procedure and the change in estimated glomerular filtration rate from baseline to 6 months. This trial is registered with ClinicalTrials.gov, number NCT01570777.
Sub-group analysis of SYMPLICITY HTN-3

Unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 enrolled a substantial number of African-American patients who represent a significant proportion of hypertensive patients in U.S.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Denervation no. of patients</th>
<th>Sham no. of patients</th>
<th>Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>353</td>
<td>171</td>
<td>-2.39 (-6.89 to 2.12)</td>
<td>0.26</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>169</td>
<td>68</td>
<td>-4.53 (-11.51 to 2.46)</td>
<td>0.20</td>
<td>0.82</td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>101</td>
<td>-3.46 (-9.55 to 2.62)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Male</td>
<td>208</td>
<td>101</td>
<td>-2.30 (-7.63 to 3.03)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>142</td>
<td>61</td>
<td>-6.64 (-14.94 to 1.65)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Yes</td>
<td>85</td>
<td>49</td>
<td>2.25 (-7.27 to 11.78)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>264</td>
<td>120</td>
<td>-6.63 (-11.81 to -1.44)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Body-mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>&lt;30</td>
<td>91</td>
<td>42</td>
<td>-2.77 (-11.47 to 5.93)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>259</td>
<td>126</td>
<td>-4.36 (-9.76 to 1.03)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Receiving aldosterone antagonist at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Yes</td>
<td>76</td>
<td>47</td>
<td>-8.05 (-17.63 to 1.52)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>274</td>
<td>122</td>
<td>-3.24 (-8.42 to 1.93)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>&lt;60 ml/min/1.73 m²</td>
<td>68</td>
<td>38</td>
<td>0.54 (-8.29 to 9.37)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>≥60 ml/min/1.73 m²</td>
<td>282</td>
<td>131</td>
<td>-5.22 (-10.51 to 0.06)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>246</td>
<td>128</td>
<td>-5.73 (-11.06 to -0.40)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>104</td>
<td>41</td>
<td>0.09 (-8.80 to 8.99)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Any medication change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Yes</td>
<td>132</td>
<td>70</td>
<td>-5.41 (-13.49 to 2.67)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>218</td>
<td>99</td>
<td>-3.44 (-8.83 to 1.96)</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>
How about the treatment **Outcome after** RDN in Asian population?

Outcomes of Korean population

Data of Global Symplicity Korean registry
Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension in an Asian Population: Results from the Global SYMPLICITY Registry in South Korea (GSR Korea)

Byeong-Keuk Kim*, Michael Boehm, Felix Mahfoud, Giuseppe Mancia, Sungha Park, Myeong-Ki Hong, Hyo-Soo Kim, Seung-Jung Park, Chang Gyu Park, Ki Bae Seung, Hyeon-Cheol Gwon, Dong-Ju Choi, Tae Hoon Ahn, Chong Jin Kim, Hyuck Moon Kwon, Murray Esler, Yangsoo Jang

*Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea
Global Symplicity Registry
Clinical Trial Design

Prospective, open-label, single-arm, all-comer observational registry

5000 consecutive “real-world” patients treated with Symplicity™ renal denervation system for uncontrolled hypertension and/or conditions associated with sympathetic nervous system activation

**Primary objective**: assess peri-procedural and long-term safety of RDN in a real world population
**Min. 10% randomly assigned to 100% monitoring**
**Key GSR inclusion criteria**: any candidate for renal denervation by the Symplicity™ catheter
**Key GSR-Korea inclusion criteria**: office systolic BP ≥160 mmHg (or ≥150 mmHg for diabetes mellitus type-2) while receiving ≥3 antihypertensive medications
**Key GSR-Korea exclusion criteria**: prior renal artery intervention, main renal artery diameter <4mm or length <20mm, hemodynamically or anatomically significant renal artery abnormalities

GREAT Registry
N=1000

Korea Registry
N=102

South Africa Registry
N=400

Canada & Mexico

Rest of GSR
N≈3500

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

1000 GSR Patients

1 Limited to resistant hypertension only

NCT01534299
Patient Flowchart

GSR (N=1000)

GSR, Asia Pacific countries (n=252)
  - GSR, Australia, New Zealand (n=126)
  - GSR, other Asia Pacific countries (n=24)

GSR Korea (n=102 at baseline)
  - 1 Withdraw
  - 2 Missed visits
  - 1 BP not measured
  - 6 months (n=98)
  - 2 Missed visits
  - 3 BP not measured
  - 12 months, matched population
    Baseline, 6-month, and 12-month BP recorded (n=93)

GSR, outside Asia Pacific (n=748)
  - Patients of non-African descent (n=728)
  - Patients of African descent (n=20)

GSR Caucasian
Inclusion/exclusion criteria similar to GSR Korea (n=432 at baseline)

12 months, matched population
Baseline, 6-month, and 12-month BP recorded (n=169)
# Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>% or mean ± SD</th>
<th>GSR Korea (N=93)</th>
<th>GSR Caucasian (N=169)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office systolic blood pressure, mm Hg</td>
<td>168.3 ± 13.9</td>
<td>176.1 ± 15.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Office diastolic blood pressure, mm Hg</td>
<td>95.5 ± 12.8</td>
<td>94.5 ± 14.5</td>
<td>0.403</td>
</tr>
<tr>
<td>Age, years</td>
<td>55.9 ± 13.4</td>
<td>61.8 ± 10.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>72.0</td>
<td>62.7</td>
<td>0.127</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5 ± 4.3</td>
<td>31.2 ± 5.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Obesity (≥ 30 kg/m²)</td>
<td>10.8</td>
<td>38.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>46.2</td>
<td>36.3</td>
<td>0.117</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>88.9 ± 25.3</td>
<td>80.9 ± 18.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Renal insufficiency (eGFR &lt;60 ml/min/1.73 m²)</td>
<td>5.4</td>
<td>13.6</td>
<td>0.039</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>5.4</td>
<td>11.3</td>
<td>0.112</td>
</tr>
<tr>
<td>History of sleep apnea</td>
<td>2.2</td>
<td>21.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>72.3 ± 11.5</td>
<td>69.0 ± 14.2</td>
<td>0.016</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.2</td>
<td>3.0</td>
<td>&gt; 0.999</td>
</tr>
</tbody>
</table>
# Antihypertensive Medications

## Baseline

<table>
<thead>
<tr>
<th>% (n)</th>
<th>GSR Korea (N=93)</th>
<th>GSR Caucasian (N=169)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of anti-hypertensive medication classes</td>
<td>3.7 ± 0.9</td>
<td>4.7 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>8.6 (8)</td>
<td>38.5 (65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>88.2 (82)</td>
<td>69.2 (117)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>84.9 (79)</td>
<td>78.1 (132)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diuretics</td>
<td>83.9 (78)</td>
<td>78.1 (132)</td>
<td>0.26</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>8.6 (8)</td>
<td>18.3 (31)</td>
<td>0.03</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>0.0 (0)</td>
<td>12.4 (21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>79.6 (74)</td>
<td>79.9 (135)</td>
<td>0.95</td>
</tr>
<tr>
<td>Alpha-adrenergic blocker</td>
<td>11.8 (11)</td>
<td>37.3 (63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Direct-acting vasodilators</td>
<td>4.3 (4)</td>
<td>16.6 (28)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Office BP Change
6- and 12 Months

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=93</td>
<td>-19.4</td>
<td>-27.2</td>
</tr>
<tr>
<td>N=169</td>
<td>-20.9</td>
<td>-27.2</td>
</tr>
<tr>
<td>p=0.547</td>
<td>p=0.004</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=93</td>
<td>-10.9</td>
<td>-20.1</td>
</tr>
<tr>
<td>N=169</td>
<td>-7.0</td>
<td>-7.6</td>
</tr>
<tr>
<td><strong>p=0.006</strong></td>
<td><strong>p&lt;0.001</strong></td>
<td></td>
</tr>
</tbody>
</table>

p<0.001 for all changes vs baseline
Results presented as mean ± standard error.
Office Systolic BP
≥ 10- and 20 mmHG Reduction

<table>
<thead>
<tr>
<th></th>
<th>GSR Korea</th>
<th>GSR Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 mmHg</td>
<td>69.9</td>
<td>68.6</td>
</tr>
<tr>
<td>p=0.834</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 20 mmHg</td>
<td>50.5</td>
<td>48.5</td>
</tr>
<tr>
<td>p=0.755</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 mmHg</td>
<td>87.1</td>
<td>65.7</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 20 mmHg</td>
<td>65.6</td>
<td>46.7</td>
</tr>
<tr>
<td>p=0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Determinants for Office Systolic BP Change Multivariate Analysis

### 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korean (vs Caucasian)</td>
<td>-2.4</td>
<td>(-7.14, 2.29)</td>
<td>0.315</td>
</tr>
</tbody>
</table>

### 12 Months

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korean (vs Caucasian)</td>
<td>-11.8</td>
<td>(-16.85, -6.73)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Safety Outcomes at 12 Months

<table>
<thead>
<tr>
<th>%</th>
<th>GSR Korea (n = 93/93)</th>
<th>GSR Caucasian (n=165/169)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure-related vascular complications</td>
<td>0.0</td>
<td>0.0 ¹</td>
<td>³</td>
</tr>
<tr>
<td>Death</td>
<td>0.0</td>
<td>0.0 ²</td>
<td>³</td>
</tr>
<tr>
<td>Spontaneous myocardial infarction</td>
<td>0.0</td>
<td>0.6</td>
<td>1.00</td>
</tr>
<tr>
<td>Serum creatinine elevation &gt; 50%</td>
<td>0.0</td>
<td>0.0 ¹</td>
<td>³</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.1</td>
<td>0.0</td>
<td>0.36</td>
</tr>
<tr>
<td>Atrial fibrillation requiring hospitalization</td>
<td>2.2</td>
<td>0.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>0.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertensive crisis requiring hospitalization</td>
<td>1.1</td>
<td>1.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>0.0</td>
<td>1.2</td>
<td>0.54</td>
</tr>
</tbody>
</table>

¹ For vascular complications and serum creatinine elevation >50%, 12-month data available on all 169 matched patients
² There was no deaths in the total GSR population (N=432)
³ P-value cannot be calculated when there are no events in both arms
Conclusions

✓ RDN in the GSR Korea substudy provided a **significant reduction** in **office systolic BP** at 6 and 12 months compared to baseline.

✓ As compared to the GSR Caucasian subset, the reduction in systolic BP in GSR Korea was **similar at 6 months but higher at 12 months** (fewer medications and a lower systolic BP in baseline; contrary to prior studies that consistently indicated a relationship between baseline systolic BP and RDN BP-lowering response).

✓ In multivariate analysis, **Korean patients** remained **more likely** to have a **larger reduction** in 12-month **systolic BP**

→ A larger role of **Sympathetic tone** in the pathogenesis of hypertension of **Asian patients** compared to Caucasian patients? **Ethnic difference** by RDN?

✓ Finally, **RDN with the Symplicity™** still showed **favorable safety results**.
RDN is not dead...

Why?

REMAIN OPTIMISTIC
A large and significant unmet need remains for patients with uncontrolled hypertension. Other definite methods for uncontrolled true resistant hypertension?

The safety profile for current catheter-based RDN

Pre-clinical data and post-hoc analyses from HTN-3 continue to instill new confidence in the therapy

Therapeutic roles of RDN are not confined to the treatment of resistant hypertension. Beyond BP-lowering effects of RDN.
For the successful RDN therapy for resistant hypertension

1. “Proper patients-selection” will be the most important.

- Before the selection of patients for RDN, the following factors first should be met.

1) ABPM for excluding pseudo-resistant hypertension
2) Proper full doses medications including diuretics, especially aldosterone antagonists
3) Good drug-adherence
For the successful RDN therapy for resistant hypertension

2.

As for technical issues ...

“Grater No. of ablation” and “Even ablations of 4-quadrants of renal artery” will be important.

How to?
Upcoming “Next-generation RDN device”

; Multi-electrode system, one shot system

EnligHTN™ Ablation Catheter; designed with an expandable electrode basket with four Platinum–Iridium (Pt–Ir) ablation electrodes.

Symplicity Spyral™ Multi-Electrode Renal Denervation Catheter
Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial

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**Aims**

Catheter-based renal artery sympathetic denervation has emerged as a novel therapy for treatment of patients with drug-resistant hypertension. Initial studies were performed using a single electrode radiofrequency catheter, but recent advances in catheter design have allowed the development of multi-electrode systems that can deliver lesions with a pre-determined pattern. This study was designed to evaluate the safety and efficacy of the EnligHTN™ multi-electrode system.

**Methods and results**

We conducted the first-in-human, prospective, multi-centre, non-randomized study in 46 patients (67% male, mean age 60 years, and mean baseline office blood pressure 176/96 mm Hg) with drug-resistant hypertension. The primary efficacy objective was change in office blood pressure from baseline to 6 months. Safety measures included all adverse events with a focus on the renal artery and other vascular complications and changes in renal function. Renal artery denervation, using the EnligHTN™ system significantly reduced the office blood pressure from baseline to 1, 3, and 6 months by −28/10, −27/10 and −26/10 mm Hg, respectively (P < 0.0001). No acute renal artery injury or other serious vascular complications occurred. Small, non-clinically relevant, changes in average estimated glomerular filtration rate were reported from baseline (87 ± 19 mL/min/1.73 m²) to 6 months post-procedure (82 ± 20 mL/min/1.73 m²).

**Conclusion**

Renal sympathetic denervation, using the EnligHTN™ multi-electrode catheter results in a rapid and significant office blood pressure reduction that was sustained through 6 months. The EnligHTN™ system delivers a promising therapy for the treatment of drug-resistant hypertension.
Renal artery denervation with a new simultaneous multi-electrode catheter for treatment of resistant hypertension: 6-month safety results from the SYMPLICITY Spyral FIM Study

SympliCity Spyral Feasibility Study: Change in Office BP through 6 months

-14  -7  -8  -7

Preparing for sham-controlled clinical study (already submitted to FDA)

P < 0.001 for all values compared to baseline
Error bars: ± 1.96 SE
BP reduction have been shown even with controversies after SYMPLICITY HTN-3.

... outcome data on hard CV endpoints are missing!

→ the game will be over if the clinical outcomes following RDN could be improved irrespective of BP reduction.
Never forget the proven roles of RDN beyond BP lowering! ... Can Sham-group do these?

- Hypertrophy
- Arrhythmia
- Oxygen consumption
- Vasoconstriction
- Atherosclerosis
- Afferent Nerves
- ↑ Renin release → RAAS activation
- ↑ Sodium retention
- ↓ Renal blood flow
- ↓ Kidney function

RAAS = renin-angiotensin-aldosterone system.

RDN therapy is “not the End” … However, we need a more concrete data … we should await future studies…
Thank you for your attention