Renal Sympathetic Denervation for Resistant Hypertension

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SNU Bundang Hospital, Cardiovascular Center
Drugs Work, But Not as Well as You May Think

Current approach failing

- Physician inertia
- Patient compliance
- Resistant HTN

Renal Denervation (RDN) = Potentially a compliance-independent therapy

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WELL ESTABLISHED
SCIENTIFIC FOUNDATION
: Why renal denervation?
Renal Sympathetic Connection

- Role of kidneys & sympathetic nervous system in development & progression of HTN is well established
- Pharmaceuticals modify physiology at intermediate steps in pathway
- RDN attempts to break the cycle at its source

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Renal Sympathetic Nerve Activity: Kidney as Origin & Recipient of Central Sympathetic Drive

- Vasoconstriction
- Renin Release → RAAS activation
- Sodium Retention
- Renal Blood Flow
- ↑ Contractility
- ↑ Heart rate
- ↓ Renal Blood Flow

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Renal Sympathetic Nerve Activity:
Kidney as Origin & Recipient of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis

Blood Pressure
- Increase co-morbidities

↑ Renin Release → RAAS activation
- Sodium Retention
- Renal Blood Flow
- Kidney function

- ↑ Contractility
- ↑ Heart rate
- Hypertrophy
- Arrhythmia
- Heart Failure

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Renal Sympathetic Nerve Activity: Kidney as Origin & Recipient of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis

Blood Pressure
- Decrease co-morbidities

Efferent Nerves

Afferent Nerves

• ↑ Contractility
• ↑ Heart rate
• Hypertrophy
• Arrhythmia
• Heart Failure

• ↑ Renin Release → RAAS activation
• ↑ Sodium Retention
• ↓ Renal Blood Flow
• ↓ Kidney function

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7 - Decrease co-morbidities
+ Increase co-morbidities

The concept is validated by surgical history. The concept is to remove the sympathetic chain from at least T8 to L2-3.

- Effective
- But significant morbidity

Today it is only performed for the treatment of Hyperhidrosis and Raynaud-Syndrome.

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A common question ...

How will the kidney function without sympathetic control?

- Transplanted kidneys lack innervation
- Yet effectively maintain fluid and electrolyte balance
- Establishes that sympathetic component of control represents “overdrive” system, rather than foundation of basic renal function
A SIMPLER, MORE ELEGANT SOLUTION

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Renal Anatomy Allows a Catheter-Based Approach

- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent & afferent nerves travel together

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Symplicity® Catheter System™

- Low profile, electrode tipped catheter
- Delivers RF energy to treatment site
- Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
- Standard interventional technique
- 40-minutes from first to last RF delivery

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Vascular Safety Predicted by Preclinical Studies

- Extensive research in >300 swine
- Angiography and pathology at 7, 30, 60 & 180 days
- No stenosis or luminal reduction seen in treated arteries
- RF Generator algorithm optimized to minimize vascular injury
SCIENTIFIC PROOF OF CONCEPT

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Quantifying Human SNS Activity

Central Sympathetic Nerve Activity

Muscle Sympathetic Nerve Activity (MSNA)
recording postganglionic nerve traffic

Renal Sympathetic Nerve Activity

Norepinephrine Spillover
measuring transmitter release from sympathetic nerves to plasma

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Proof of Principle: Direct Measurement of Reduced Central Sympathetic Nerve Activity

Denervation of Patient w/ Essential HTN:

<table>
<thead>
<tr>
<th></th>
<th>MSNA (burst/min)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>56</td>
<td>161/107</td>
</tr>
<tr>
<td>1 mo</td>
<td>41 (-27%)</td>
<td>141/90 (-20/-17)</td>
</tr>
<tr>
<td>12 mo</td>
<td>19 (-66%)</td>
<td>127/81 (-34/-26)</td>
</tr>
</tbody>
</table>

* 59 year old male on 7 HTN meds

Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 → 11.7 msec/mmHg)

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### Proof of Principle:
**Related Changes in Underlying Physiology**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 mo</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office BP (mmHg)</strong></td>
<td>161/107</td>
<td>141/90</td>
<td></td>
</tr>
<tr>
<td><strong>Renal NE spillover (ng/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- left kidney</td>
<td>72</td>
<td>37</td>
<td>-48%</td>
</tr>
<tr>
<td>- right kidney</td>
<td>79</td>
<td>20</td>
<td>-75%</td>
</tr>
<tr>
<td><strong>Total body NE spillover (ng/min)</strong></td>
<td>600</td>
<td>348</td>
<td>-42%</td>
</tr>
<tr>
<td><strong>Plasma Renin (µg/l/hr)</strong></td>
<td>0.3</td>
<td>0.15</td>
<td>-50%</td>
</tr>
<tr>
<td><strong>Renal Plasma flow (ml/min)</strong></td>
<td>719</td>
<td>1126</td>
<td>57%</td>
</tr>
</tbody>
</table>

LV Mass (cMRI) dropped 7% (from 78.8 to 73.1 g/m²) from baseline to 12 months

**Consistent with Expected Effects of Denervation**

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Renal Norepinephrine Spillover: 10 cases

- Mean total renal norepinephrine spillover $\downarrow$ 47%, $p=0.023$ (95% CI: 28–65%)
- Mean total body NE spillover $\downarrow$ 28%, $p=0.043$ (95% CI: 4–52%)

**Example Case:**
Left: 75% reduction
Right: 85% reduction

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YU ET M/71 15845438

- 2007, HTN
- 2010, DM
- 2010, CAOD 2VD -> PCI at mRCA

Medications:
- Astrix 100mg cap (Aspirin enteric coated)
- Clopidogrel 72mg tab
- Vaxar 2mg tab (Lacidipine)
- Dichlozid 25mg tab (Hydrochlorothiazide)
- Cozaar 50mg tab (Losartan)
- Janumet 50/850mg (Sitagliptin/Meformin)

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ECG (2012-04-16)
Non-Invasive Tests

• TTE (2010-07-09)
  1. Normal LV cavity size (EDD=51mm) and systolic function; EF=64%
  2. Normal valvular structure and function
CAG & PCI (2008.12.08)

Pre stenting

Post stenting

Endeavor (3.0*18mm)

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DSA of both renal arteries (2012.04)

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Rt. renal a. ⇐ Ablation ⇒ Lt. renal a.

#1 Inferior

#2 Lateral

#3 Superior

#4 Superior - Anterior

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Renal Angiogram after Denervation

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Renal Angiogram after Denervation: Edematous lesions
BP during admission

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CLINICAL DATA
Staged Clinical Evaluation

First-in-Man ✓
Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

Symplicity HTN-1
Series of Pilot studies ✓

Symplicity HTN-3
US Randomized Clinical Trial (upcoming)

EU/AU
Other Areas of Research:
Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

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Symplicity HTN-1

Initial Cohort – Reported in the Lancet, 2009:
- First-in-man, non-randomized
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- 12-month data

Expanded Cohort – This Report (Symplicity HTN-1):
- Expanded cohort of patients (n=153)
- 24-month follow-up

Lancet. 2009;373:1275-1281

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## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age (years)</th>
<th>57 ± 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gender (% female)</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>Race (% non-Caucasian)</td>
<td>5%</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>Diabetes Mellitus II (%)</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>CAD (%)</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia (%)</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>eGFR (mL/min/1.73m²)</td>
<td>83 ± 20</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Baseline BP (mmHg)</td>
<td>176/98 ± 17/15</td>
</tr>
<tr>
<td></td>
<td>Number of anti-HTN meds (mean)</td>
<td>5.0 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>ACE/ARB (%)</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Beta-blocker (%)</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blocker (%)</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Vasodilator (%)</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>Diuretic (%)</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Spironolactone (%)</td>
<td>21%</td>
</tr>
</tbody>
</table>

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Procedure Detail & Safety

• 38 minute median time from first to last ablation
  – Average of 4 ablations per artery
• Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
• No catheter or generator malfunctions
• No major complications
• Minor complications 4/153:
  – 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  – 3 access site complications, treated without further sequelae
Chronic Safety

- 81 patients with 6-month renal CTA, MRA, or Duplex
  - No vascular abnormalities at any site of RF delivery
  - One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- Two deaths within the follow-up period; both unrelated to the device or therapy
- No orthostatic or electrolyte disturbances
- No change in renal function ($\Delta$ eGFR)
  - 12 Months: -2.9 mL/min/1.73m$^2$ (n.s.)
Significant, Sustained BP Reduction

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BP change (mmHg)

-20 -10 -24 -11 -25 -11 -23 -11 -26 -14 -32 -14

1 M (n=138) 3 M (n=135) 6 M (n=86) 12 M (n=64) 18 M (n=36) 24 M (n=18)

Systolic  Diastolic
Significant, Sustained Blood Pressure Reductions to at Least 3 Years

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

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Percentage Responders Increases Over Time

Responser was defined as an office SBP reduction ≥10 mmHg
Symplicity HTN-1: Response Rate Among 1-Month Non-responders (n=45)*

*Non-responder defined as a SBP reduction of <10 mmHg

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

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**Symplicity HTN-2**

*Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial*

*Symplicity HTN-2 Investigators*

*Lancet.* 2010. Published electronically on November 17, 2010

- **Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)
## Symplicty HTN-2 Trial

### Key Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>Exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Office SBP $\geq 160$ mmHg ($\geq 150$ mmHg with type 2 diabetes mellitus)</td>
<td>- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention</td>
</tr>
<tr>
<td>- Stable drug regimen of 3+ more anti-HTN medications</td>
<td>- eGFR $&lt; 45$ mL/min/1.73m² (MDRD formula)</td>
</tr>
<tr>
<td>- Age 18–85 years</td>
<td>- Type 1 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>- Contraindication to MRI</td>
</tr>
<tr>
<td></td>
<td>- Stenotic valvular heart disease for which reduction of BP would be hazardous</td>
</tr>
<tr>
<td></td>
<td>- MI, unstable angina or CVA in the past 6 months</td>
</tr>
</tbody>
</table>
Patient Disposition

Assessed for Eligibility (n=190)

Excluded During Screening, Prior to Randomisation (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%)

Randomised (n=106)

Allocated to RDN
- n=52 Treated
- n=49 Analysable

Allocated to Control
- n=54 Control
- n=51 Analysable

Crossover
- n=46

12-month post-RDN
- n=47

Per protocol, 6-mo Post-RDN (Crossover)
- n=35

Not-per-protocol*, 6-mo Post-RDN (Crossover)
- n=9

* Crossed-over with ineligible BP (<160 mmHg)

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### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RDN (n = 52)</th>
<th>Control (n = 54)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline systolic BP (mmHg)</td>
<td>178 ± 18</td>
<td>178 ± 16</td>
<td>0.97</td>
</tr>
<tr>
<td>Baseline diastolic BP (mmHg)</td>
<td>97 ± 16</td>
<td>98 ± 17</td>
<td>0.80</td>
</tr>
<tr>
<td>Number anti-HTN medications</td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Age</td>
<td>58 ± 12</td>
<td>58 ± 12</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender (female) (%)</td>
<td>35%</td>
<td>50%</td>
<td>0.12</td>
</tr>
<tr>
<td>Race (Caucasian) (%)</td>
<td>98%</td>
<td>96%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>31 ± 5</td>
<td>31 ± 5</td>
<td>0.77</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>40%</td>
<td>28%</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>19%</td>
<td>7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>52%</td>
<td>52%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>eGFR (MDRD, ml/min/1.73m^2)</td>
<td>77 ± 19</td>
<td>86 ± 20</td>
<td>0.013</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Urine alb/creat ratio (mg/g)^*</td>
<td>128 ± 363</td>
<td>109 ± 254</td>
<td>0.64</td>
</tr>
<tr>
<td>Cystatin C (mg/L)^†</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 15</td>
<td>71 ± 15</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* †n=42 for RDN and n=43 for Control, Wilcoxon rank-sum test for two independent samples used for between-group comparisons of UACR
††n=39 for RDN and n=42 for Control

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# Baseline Medications

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=52)</th>
<th>Control (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Anti-HTN medications</td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>% patients on HTN meds &gt;5 years</td>
<td>71%</td>
<td>78%</td>
<td>0.51</td>
</tr>
<tr>
<td>% percent patients on ≥5 medications</td>
<td>67%</td>
<td>57%</td>
<td>0.32</td>
</tr>
<tr>
<td>% patients on drug class:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>96%</td>
<td>94%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Direct renin inhibitor</td>
<td>15%</td>
<td>19%</td>
<td>0.80</td>
</tr>
<tr>
<td>Beta-adrenergic blocker</td>
<td>83%</td>
<td>69%</td>
<td>0.12</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>79%</td>
<td>83%</td>
<td>0.62</td>
</tr>
<tr>
<td>Diuretic</td>
<td>89%</td>
<td>91%</td>
<td>0.76</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>17%</td>
<td>17%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>15%</td>
<td>17%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Alpha-1 adrenergic blocker</td>
<td>33%</td>
<td>19%</td>
<td>0.12</td>
</tr>
<tr>
<td>Centrally acting sympatholytic</td>
<td>52%</td>
<td>52%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Primary Endpoint: 6-Month Office BP

- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

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Medication Changes

Despite protocol guidance to maintain medications, some medication changes were required:

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=49)</th>
<th>Control (n=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Med Dose Decrease (%)</td>
<td>10 (20%)</td>
<td>3 (6%)</td>
<td>0.04</td>
</tr>
<tr>
<td># Med Dose Increase (%)</td>
<td>4 (8%)</td>
<td>6 (12%)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Censoring BP after medication increases:

• Renal Denervation → Reduction of 31/12 ± 22/11 mmHg (p<0.0001 for SBP & DBP)
• Control → Change of 0/-1 ± 20/10 mmHg (p=0.90 & p=0.61 for SBP & DBP, respectively)
Office Systolic BP Distribution

- **RDN Baseline**: 39% ≥ 180 mmHg, 43% 160-179 mmHg, 10% 140-159 mmHg, 10% < 140 mmHg
- **RDN 6 Months**: 6% ≥ 180 mmHg, 35% 160-179 mmHg, 4% 140-159 mmHg, 6% < 140 mmHg
- **Control Baseline**: 51% ≥ 180 mmHg, 61% 160-179 mmHg, 4% 140-159 mmHg, 18% < 140 mmHg
- **Control 6 Months**: 45% ≥ 180 mmHg, 31% 160-179 mmHg, 6% 140-159 mmHg, 6% < 140 mmHg

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24-h ABPM:
• Analysis on technically sufficient (>70% of readings) paired baseline and 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)
Time Course of Office BP Change

RDN
Δ from Baseline (mmHg)

Control
Δ from Baseline (mmHg)

† p<0.0001 for between-group comparisons
†† p=0.002 for between-group comparisons
††† p=0.005 for between-group comparisons
Two-way repeated measures ANOVA, p=0.001

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Procedural Safety

- No serious device or procedure related adverse events (n=52)
- Minor adverse events
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 6-month renal imaging (n=43)
  - No vascular abnormality at any RF treatment site
  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

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## Renal Function

<table>
<thead>
<tr>
<th>∆ Renal Function (baseline - 6M)</th>
<th>RDN Mean ± SD (n)</th>
<th>Control Mean ± SD (n)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (MDRD) (mL/min/1.73m²)</td>
<td>0 ± 11 (49)</td>
<td>1 ± 12 (51)</td>
<td>-1 (-5, 4)</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.0 ± 0.2 (49)</td>
<td>0.0 ± 0.1 (51)</td>
<td>0.0 (-0.1, 0.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Cystatin-C (mg/L)</td>
<td>0.1 ± 0.2 (37)</td>
<td>0.0 ± 0.1 (40)</td>
<td>0.0 (-0.0, 0.1)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

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## Other Safety

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=49)</th>
<th>Control (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite CV Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive event unrelated to non-adherence to medication</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other CV events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other Serious AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive event after abruptly stopping clonidine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypotensive episode resulting in reduction of medications</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Coronary stent for angina</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Temporary nausea/edema</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Simplicity HTN-2 : Conclusions at 2010

• Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.
• The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality.
• The technique was applied without major complications.
• This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of BP in patients with hypertension.
• Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Cardiovascular Center, Seoul National University Bundang Hospital
Symplicity HTN-2: RDN Superior to Medical Management, Reductions Sustained to 12M

Primary Endpoint:
- 84% of RDN patients had ≥10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Latest Follow-up:
- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)

Cardiovascular Center, Seoul National University Bundang Hospital
## ACC 2012: Medication Changes at 6 and 12 Months Post-Renal Denervation

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=47)</th>
<th>6 month</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease (# Meds or Dose)</td>
<td>20.9% (9/43)</td>
<td>27.9% (12/43)</td>
<td></td>
</tr>
<tr>
<td>Increase (# Meds or Dose)</td>
<td>11.6% (5/43)</td>
<td>18.6% (8/43)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Crossover (n=35)</th>
<th>6 months post-RDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease (# Meds or Dose)</td>
<td>18.2% (6/33)</td>
<td></td>
</tr>
<tr>
<td>Increase (# Meds or Dose)</td>
<td>15.2% (5/33)</td>
<td></td>
</tr>
</tbody>
</table>

*Physicians were allowed to make changes to medications Once the 6 month primary endpoint was reached*

*Further analysis of Medications is ongoing*

Cardiovascular Center, Seoul National University Bundang Hospital
RENAL DENERVATION & INSULIN RESISTANCE

Cardiovascular Center, Seoul National University Bundang Hospital
Effects of Renal Denervation on Glucose Handling in Patients with Resistant HTN

- 25 Treatment, 11 Control
- Age 56.9 ± 10 years
- BMI 31.4 ± 5.5 kg/m²
- Type 2 DM on oral medication, n=15
- No patients on insulin treatment
- Baseline BP: 178/94 ± 16/13 mmHg
- 5.6 ± 1.4 antihypertensive meds

Mahfoud et al. European Society of Cardiology. 2010.
Reduction in HOMA Index at 1 & 3 Months following Renal Denervation

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Fasting Glucose (mg/dl)</th>
<th>Fasting Insulin (mU/l)</th>
<th>C-peptide (µg/l)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (25)</td>
<td>118 ± 20</td>
<td>20.7 ± 11.8</td>
<td>6.1 ± 3.6</td>
<td>6.1 ± 4.3</td>
</tr>
<tr>
<td>1 month (25)</td>
<td>110 ± 14*</td>
<td>12.9 ± 7.3*</td>
<td>3.3 ± 1.5*</td>
<td>3.5 ± 1.8*</td>
</tr>
<tr>
<td>3 months (25)</td>
<td>106 ± 12*</td>
<td>11.1 ± 4.8*</td>
<td>3.1 ± 1.1*</td>
<td>2.9 ± 1.3*</td>
</tr>
</tbody>
</table>

*significant reduction (p<0.05) compared to baseline

HOmeostasisModelAssessment-InsulinResistance (HOMA-IR) = (FPI x FPG)/405

Symplicity HTN-1 Three year and Symplicity HTN-2 Full year Summary

• **Sustained BP Reductions to Three Years**
  • First Symplicity HTN-1 patient treated June 2007
  • Three year reporting shows no diminishment of effect and impressive long term safety
  • For patients that have completed 3 year follow up, 100% have been classified as responders (>10 mmHg reduction), while at 6 months 71% of patients were classified as responders.

• **Superior Results Confirmed in Randomised Study**
  • Symplicity HTN-2 treatment population shows sustained treatment effect at 12 month follow-up
  • Control cross-over patients also show significant BP reduction

**Only the Symplicity™ renal denervation system has proven safe, superior and sustained BP reductions**

Cardiovascular Center, Seoul National University Bundang Hospital
Comprehensive SYMPLICITY Clinical Trial Program follows over 5000 patients across multiple indications

This report

- **First-in-Man (AU)**
- **Series of Pilot Studies (EU, US & AU)**
- **Symplicity HTN-2 Initial RCT (EU & AU)**

**Symplicity HTN-1**

**SYMPLICITY HTN-3**
- US Pivotal Trial (US)
- Post-Market Registry (US)

**Global SYMPLICITY Registry (Approved Regions)**

**Expand HTN Indication (Approved Regions)**

**Pilot Studies in New Indications (Approved Regions)**

**SYMPLICITY HF**

**Trials under way**

Cardiovascular Center, Seoul National University Bundang Hospital