Transcatheter Renal Denervation

AMC Experience
SYMPLICITY Registry

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Hypertension Epidemiology

- Single largest contributor to death worldwide
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Only half of all treated hypertensive patients are controlled to established BP targets
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025
- Resistant HTN : 5-30%

Effects of Increased Sympathetic Tone

Causes of increased afferent signaling from the kidney to central integrative structures:
- Adenosine
- Acidosis
- Oxidative stress
- Inflammation
- Endothelial factors
- Angiotensin II
- Ischemia

Factors that might contribute to increased renal afferent signaling:
- Remodeling
- Hypertrophy
- Arrhythmias
- Ischemia
- Apoptosis

Consequences of increased efferent sympathetic outflow to the kidney and other organs:
- Medial hyperplasia
- Arterial compliance ↓
- Endothelial dysfunction
- Na⁺ / H₂O retention
- Reduced renal blood flow
- Activation of the RAAS
- Proteinuria
- Glomerulosclerosis

Renal injury / Renal ischemia

Renal denervation
Renal Nerves as a Therapeutic Target

• Arise from ~ T10-L2
• Follow the renal artery to the kidney
• Primarily lie within the adventitia
Generator

- Energy maximum 8 Watt
- It automatically switches off if
  - temperature increases too fast or too slowly
  - temperature is higher than 75 °C
- Impedance does not decrease sufficiently
Simplicity™ Catheter

- Radiofrequency electrode tip
- Handle allows bending of the tip and rotation
- Compatible with a 6 F guiding catheter
 Treatment Strategy

Focal ablations
spaced along vessel

Multiple focal ablations
↑ circumferential coverage
Procedural details

• Premedication
  - Aspirin 100 mg/day (to be continued for 1 week)
  - 10-20 mg morphin + sedatives
  - 5,000 U heparin
  - Nitro i.a.
• 6 F femoral sheath
• 6 F renal guiding catheter
• Angiography of all renal arteries
• Introduce radiofrequency catheter
• 4-8 ablations, 2 min each
The Symplicity HTN Clinical Trial Program

Symplicity HTN-1
First-in-Man, and Expanded Cohort (N=153)\(^1,2\)

Symplicity HTN-2
Randomized, Controlled Trial (N=106)\(^3\)

Symplicity HTN-3
Randomized, Blinded, Controlled Trial (N~530)\(^4\)

Shading on bars indicates clinical trial enrollment periods. Enrollment period for HTN-3 is estimated.

Global Program for Uncontrolled Hypertension

First-in-Man (AU)

Pilot Studies (EU, US & AU)

Symplicity HTN-2 Initial RCT (EU & AU) (n=106)

Symplicity HTN-1 Single arm (n=153)

Symplicity HTN-3 (n=530)

Post-Market Global Registry (n=5,000)

Other Geographic Studies

Korea Study (n=102)
Patients & Centers

Study Population
- Approximately 5000 patients will be enrolled in Global SYMPLICITY Registry
- All consecutive patients who undergo the renal denervation procedure are candidates to be enrolled
- Patients should be treated according to routine hospital care

Centers
- Approximately 200 centers world-wide
Korea Patients and Centers

Study Population
- Approximately 200 patients will be enrolled in the Global SYMPLICITY Registry in Korea
- Focus in Korea is on resistant hypertension patient population for purposes of Health Technology Assessment submission

Centers
- Approximately 10 centers in Korea
# Korea Centers and Principal Investigators

<table>
<thead>
<tr>
<th>Site</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asan Medical Center</td>
<td>Seung-Jung Park</td>
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<tr>
<td>Gachon University Gill Hospital</td>
<td>Tae-Hoon Ahn</td>
</tr>
<tr>
<td>Gangnam Severance Hospital</td>
<td>Hyuck-Moon Kwon</td>
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<tr>
<td>Korea University Guro Hospital</td>
<td>Chang-Gyu Park</td>
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<tr>
<td>Kyung Hee University Hospital</td>
<td>Chong-Jin Kim</td>
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<tr>
<td>Samsung Medical Center</td>
<td>Hyeon-Cheol Gwon</td>
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<tr>
<td>Seoul National University Bundang Hospital</td>
<td>Dong-Ju Choi</td>
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<tr>
<td>Seoul National University Hospital</td>
<td>Hyo-Soo Kim</td>
</tr>
<tr>
<td>Seoul Saint Mary's Hospital</td>
<td>Ki-Bae Seung</td>
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<tr>
<td>Severance Hospital</td>
<td>Yang-Soo Jang</td>
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Key Inclusion Criteria

• Age ≥ 18 years

• Systolic blood pressure ≥ 160 mmHg (≥ 150 mmHg for type 2 diabetics) based on an average of 3 office blood pressure readings.

• Patient is adhering to a stable drug regimen including 3 or more antihypertensive medications (with no changes for a minimum of 2 weeks prior to enrollment)
Key Exclusion Criteria

• Ineligible anatomy:
  Main renal arteries < 4 mm in diameter
  Main renal arteries < 20 mm length
  Renal artery abnormality or stenosis

• History of prior renal artery intervention

• eGFR of < 45mL/min/1.73m²
Clinical Data Measures

- **Key measures:**
  - Patient demographics
  - Medical health history
  - Office Blood Pressure
  - Heart rate
  - Renal artery imaging (prior to procedure)
  - Medications Log
  - EQ5D Quality of Life
Recommended Follow-up assessments will be performed at:

- 3 months ± 30 days
- 6 months ± 30 days
- 1 year ± 60 days
- 2 year ± 60 days
- 3 year ± 60 days
- Possibly 4 year ± 60 days
- Possibly 5 year ± 60 days
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Symplicity HTN-2 (n=52)</th>
<th>AMC (n=13)</th>
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<tbody>
<tr>
<td>Baseline Systolic BP (mmHg)</td>
<td>178 ± 18</td>
<td>179.9 ± 16.6</td>
</tr>
<tr>
<td>Baseline Diastolic BP (mmHg)</td>
<td>97 ± 16</td>
<td>100.3 ± 15.9</td>
</tr>
<tr>
<td>Age</td>
<td>58 ± 12</td>
<td>54 ± 13.5</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>35%</td>
<td>23.1%</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>31 ± 5</td>
<td>26.4 ± 3.7</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>40%</td>
<td>28%</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>19%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>52%</td>
<td>100%</td>
</tr>
<tr>
<td>eGFR (MDRD, ml/min/1.73m$^2$)</td>
<td>77 ± 19</td>
<td>68.2 ± 13.2</td>
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<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.0 ± 0.3</td>
<td>0.97 ± 0.3</td>
</tr>
<tr>
<td>Urine Alb/Creat Ratio (mg/g)†</td>
<td>128 ± 363</td>
<td>1125.9 ± 1173.9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 15</td>
<td>73.8 ± 7.2</td>
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# Baseline Medications

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<tr>
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<th>Symplicity HTN-2 (n=52)</th>
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<tr>
<td>Number Anti-HTN medications</td>
<td>5.2 ± 1.5</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>% patients on HTN meds &gt;5 years</td>
<td>71%</td>
<td>72.7%</td>
</tr>
<tr>
<td>% percent patients on ≥5 medications</td>
<td>67%</td>
<td>15.4%</td>
</tr>
<tr>
<td>% patients on drug class:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>96%</td>
<td>92.3%</td>
</tr>
<tr>
<td>Direct renin inhibitor</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>Beta-adrenergic blocker</td>
<td>83%</td>
<td>92.3%</td>
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<tr>
<td><strong>Calcium channel blocker</strong></td>
<td><strong>79%</strong></td>
<td><strong>66.7%</strong></td>
</tr>
<tr>
<td>Diuretic</td>
<td>89%</td>
<td>81.8%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>17%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>15%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Alpha-1 adrenergic blocker</td>
<td>33%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Centrally acting sympatheolytic</td>
<td>52%</td>
<td>-</td>
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Primary Endpoint: 6-Month Office BP

Symplicity HTN-2 (n=49)

- Systolic: -32
- Diastolic: -12

AMC (n=11)

- Systolic: -38
- Diastolic: -15

Δ from Baseline to 6 Months (mmHg)

Change in Office BP : AMC

△ from Baseline to 6 Months (mmHg)

-41
-38
-38
-47

N=13
N=12
N=11
N=3

1 Month  3 Months  6 Months  1 Year

AMC Data
Procedural Safety

- Procedure time: 81 ± 4.5 minutes
- Amount of Contrast Medium: 63.9 ± 6.8 cc
  - 1 patient: Cr 0.90 -> 1yr later: 1.21 DM with Nephropathy
- Ablation Points
  - Right: 11.5 ± 3.8
  - Left: 13.1 ± 4.5
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- No Minor complications
AMC Cases - RAS

- 65/ M, 170cm, 68kg
- HTN, variant angina
- Exforge 5/160mg, dilatrend 25mg, atacand plus 1T qd.
- Initial BP: 178/122, HR 87/min
- Cr 0.9
- Procedure time; 120 min
- Contrast medium ; Visipaque, 90 cc
Successful Ablation in Right Renal Artery

Totally, 14 ablations were done in Right Renal Artery
And Then, Left Renal Artery....

Additionally, 14 ablations were done in Left Renal Artery.

Palmaz 5.0*15

Stering 4.0*20
Follow Up

- No procedure related complication
- Discharge 1 day later
- 1 month follow up: 140/80 mmHg, HR 70
- 3 months: 139/89 mmHg, HR 68
AMC Cases

- 53/ M, 171cm, 78kg
- HTN, DM
- Caduet 5/20mg, cadura XL 1T, dichlozid 25mg, exforge 5/160mg, tenormin 50mg qd
- Initial BP: 167/88
- Cr 0.97
- Procedure time; 80min
- Contrast medium ; Visipaque, 70 cc
Successful Ablation in Left Renal Artery

Totally, 14 ablations were done in Left Renal Artery
And Then, Right Renal Artery....

Additionally, 14 ablations were done in Right Renal Artery.
Follow Up

- No procedure related complication
- Discharge 1 day later
- 1 month follow up: 155/85 mmHg, HR 78
- 3 months: 145/85 mmHg, HR 77
- 6 months: 135/78 mmHb, HR 65
Unmet Needs in RND?

- No Sham Control Group – Symplicity HTN-3
- 24 ABPM was available in a small portion
- Long term effect during nerve regeneration
- Exclusion: dual renal artery, accessory artery, no data on unilateral RND
- Lack of preprocedural marker
- No clinical applicable technique
- No data; less severe HTN, hard end points
- Cost-benefit studies
- Standardized certification of RND centers
Future Directions for Research

- Chronic activation of renal nerves is common in multiple conditions/disease states\(^1,2\)
- Future research may be warranted in disease states characterized by hyperactive afferent and efferent renal nerves

RAAS = renin-angiotensin-aldosterone system.
Transcatheter Renal Denervation results in significant reductions in BP
• The procedure seems to be very safe
• The effect is sustained up to 1 year
• It may also be beneficial in patients with diabetes, sleep apnea, heart failure and other diseases
• However, we still need to be under the strict indication, such as true resistant hypertension