Transcatheter Renal Denervation and Hong Kong Experience

Dr. Steven Li Siu-lung
FACC, FESC, FRCP, FACP

Director, Heart Centre, Union Hospital
President, Hong Kong Society of Congenital and Structural Heart Diseases
A Major Public Health Burden

• Astonishing prevalence
  – 1 in 3 adults
  – 1 B people worldwide → 1.6 B by 2025

• Single largest contributor to death

• Dramatically increases risk of heart attack, stroke, heart failure, kidney failure & insulin resistance
Current approach failing

- Physician inertia
- Patient compliance
- Resistant HTN

Renal Denervation (RDN) = Potentially a compliance-independent therapy
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
Renal Sympathetic Nerve Activity: Kidney as Origin & Recipient of Central Sympathetic Drive

- **Afferent Nerves**
  - Vasoconstriction
  - ↑ Renin Release → RAAS activation
  - ↑ Sodium Retention
  - ↓ Renal Blood Flow

- **Efferent Nerves**
  - ↑ Contractility
  - ↑ Heart rate

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

- Vasoconstriction
- Atherosclerosis

Efferent Nerves

- ▲ Contractility
- ▲ Heart rate
- Hypertrophy
- Arrhythmia
- Heart Failure

Afferent Nerves

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

Blood Pressure

+ Increase co-morbidities

Renal Sympathetic Nerve Activity: RDN Disrupts Renal Nerves, Lowering SNS Activity

Afferent Nerves
- Vasoconstriction
- Atherosclerosis

↑ Contractility
↑ Heart rate
Hypertrophy
Arrhythmia
Heart Failure

Vasoconstriction
Atherosclerosis

Blood Pressure
- Decrease co-morbidities
+ Increase co-morbidities

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

VALIDATION OF PHYSIOLOGY
Proof of Principle

- Central Sympathetic Nerve Activity
- Muscle Sympathetic Nerve Activity (MSNA)
- Renal Sympathetic Nerve Activity
- Norepinephrine Spillover
Reduction of Renal Contribution to Central Sympathetic Drive: MSNA in Resistant Hypertension Patient

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

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

Schlaich et al. NEJM. 2009; 36(9): 932-934.
### 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</strong></td>
<td>161/107</td>
<td>141/90</td>
<td></td>
</tr>
<tr>
<td><strong>Renal NE spillover</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</strong></td>
<td>600</td>
<td>348</td>
<td>-42%</td>
</tr>
<tr>
<td><strong>Plasma Renin</strong></td>
<td>0.3</td>
<td>0.15</td>
<td>-50%</td>
</tr>
<tr>
<td><strong>Renal Plasma flow</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.

Schlaich et al. NEJM. 2009; 36(9): 932-934.
Renal Norepinephrine Spillover: 10 cases

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

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

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

*From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

THE BRITISH JOURNAL OF SURGERY

1952

SYMPATHECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT HYPERTENSION

A REVIEW OF 76 PATIENTS

BY C. J. LONGLAND AND W. E. GIBB

THE JOURNAL

of the American Medical Association

Published Under the Auspices of the Board of Trustees

CHICAGO, ILLINOIS

Copyright, 1953, by American Medical Association

AUGUST 15, 1953

SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.

and

Jesse E. Thompson, M.D., Boston

Effective, but significant morbidity
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
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
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
Renal Denervation: Preclinical Evidence
Renal Denervation
Preclinical Efficacy and Safety

- Extensive research in >300 swine
- Effectiveness:
  - Significant reduction in renal tissue NE
- Safety:
  - Verification testing included angiography, gross pathology, histopathology, & clinical pathology at 7, 30, 60, and 180 days
  - Intact endothelium by 7 days
  - Vascular healing observed at 30 and 60 days; by 180 days, arteries were well healed (no inflammatory cells) – treatment sites were considered sterile and stable
  - No stenosis or luminal reduction seen in any treated artery through 180 days

Data on file. Medtronic, Inc.
Vascular Safety Documented by Preclinical Studies

- Studied 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
Six Month Post-Procedure Nerve Histology (Porcine Model)

H&E

- Nerve from untreated vessel: Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium)
- Nerve from treated vessel: Periarterial nerve bundle has a hypercellular appearance and the perineurium has a thickened and fibrotic appearance.

Staged Clinical Evaluation

- **Symplicity HTN-1**
  - First-in-Man ✓
  - Series of Pilot studies ✓
  - **Symplicity HTN-2 ✓**
    - EU/AU Randomized Clinical Trial

**Other Areas of Research:**
- Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

**Symplicity HTN-3**
- US Randomized Clinical Trial (upcoming)
Relevant studies

**THE LANCET**

Volume 371, Number 9611, Pages 1215-1216, April 16-22, 2008

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre, single-arm, open-label cohort study

Henry Kiem, Markus Schlach, Rob Whithers, Peter Steyer, Soke Theme, William T AI

**The NEW ENGLAND JOURNAL of MEDICINE**

Renal Sympathetic Denervation

**Hypertension**

Renal Denervation as a Therapeutic Approach for Hypertension: Novel Implications

Markus P. Schlach, Paul A. Armstrong, Anthony J. DePasquale

**THE LANCET**

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

SymplicityHTN-2 Investigators

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

Expanded Cohort – This Report (Symplicity HTN-1):
- Expanded cohort of patients (n=153)
- 24 and 36-month follow-up
Baseline Patient Characteristics (n=153)

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>39%</td>
</tr>
<tr>
<td>Race (% non-Caucasian)</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus II (%)</td>
<td>31%</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>22%</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>68%</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>83 ± 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BP (mmHg)</td>
<td>176/98 ± 17/15</td>
</tr>
<tr>
<td>Number of anti-HTN meds (mean)</td>
<td>5.1 ± 1.4</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>95%</td>
</tr>
<tr>
<td>Aldosterone blocker (%)</td>
<td>22%</td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>91%</td>
</tr>
<tr>
<td>Direct Renin Inhibitor</td>
<td>14%</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>82%</td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>75%</td>
</tr>
<tr>
<td>Centrally acting sympatholytic (%)</td>
<td>33%</td>
</tr>
<tr>
<td>Vasodilator (%)</td>
<td>19%</td>
</tr>
<tr>
<td>Alpha-1 blocker</td>
<td>19%</td>
</tr>
</tbody>
</table>

Procedure Detail & Safety (n=153)

- 38 minute median procedure time
  - 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

Change in Office BP Through 36 Months

BP change (mmHg)

P<0.01 for ∆ from BL for all time points

Sobotka P, ACC 2012
Distribution of SBP Change at Baseline, 1, 12, 24, and 36 Months

<table>
<thead>
<tr>
<th>Time</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (N=150)</td>
<td></td>
</tr>
<tr>
<td>1 Mo (N=143)</td>
<td></td>
</tr>
<tr>
<td>12 Mo (N=130)</td>
<td></td>
</tr>
<tr>
<td>24 Mo (N=59)</td>
<td></td>
</tr>
<tr>
<td>36 Mo (N=24)</td>
<td></td>
</tr>
</tbody>
</table>

- ≥ 180 mmHg
- 160-179 mmHg
- 140-159 mmHg
- < 140 mmHg

Sobotka P, ACC 2012
Response Rate Among 1-Month Non-responders (n=45)

Responder was defined as an office SBP reduction ≥ 10 mmHg

- 1 Month (N=45): 58%
- 3 Months (N=45): 57%
- 6 Months (N=44): 64%
- 12 Months (N=39): 82%
- 24 Months (N=17): 100%
- 36 Months (N=8): 100%

Sobotka P, ACC 2012
Change in Office BP by Age

<table>
<thead>
<tr>
<th></th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 yr</td>
<td>-27</td>
<td>-33</td>
<td>-34</td>
</tr>
<tr>
<td>≥ 65 yr</td>
<td>-26</td>
<td>-16</td>
<td>-19</td>
</tr>
<tr>
<td>N</td>
<td>97</td>
<td>44</td>
<td>21</td>
</tr>
</tbody>
</table>

SBP change (mmHg)
Change in Office BP in Diabetic and Non-Diabetic Patients

<table>
<thead>
<tr>
<th></th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (N=44)</td>
<td>-11</td>
<td>-11</td>
<td>-17</td>
</tr>
<tr>
<td>Non-DM (N=86)</td>
<td>-15</td>
<td>-32</td>
<td>-33</td>
</tr>
<tr>
<td>DM (N=17)</td>
<td>-27</td>
<td>-38</td>
<td>-31</td>
</tr>
<tr>
<td>Non-DM (N=42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM (N=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DM (N=16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sobotka P, ACC 2012
Change in Office BP by Baseline Renal function

<table>
<thead>
<tr>
<th>Baseline Renal Function</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 45-60 (N=9)</td>
<td>-30</td>
<td>-41</td>
<td>-40</td>
</tr>
<tr>
<td>eGFR &gt;60 (N=115)</td>
<td>-27</td>
<td>-22</td>
<td>-10</td>
</tr>
<tr>
<td>eGFR 45-60 (N=5)</td>
<td>-23</td>
<td>-16</td>
<td>-19</td>
</tr>
<tr>
<td>eGFR &gt;60 (N=51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 45-60 (N=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &gt;60 (N=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP change (mmHg)

Sobotka P, ACC 2012
Renal Function Over Time

<table>
<thead>
<tr>
<th>Time (M)</th>
<th>Value (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>143</td>
</tr>
<tr>
<td>3 M</td>
<td>131</td>
</tr>
<tr>
<td>6 M</td>
<td>141</td>
</tr>
<tr>
<td>12 M</td>
<td>128</td>
</tr>
<tr>
<td>18 M</td>
<td>53</td>
</tr>
<tr>
<td>24 M</td>
<td>35</td>
</tr>
<tr>
<td>30 M</td>
<td>11</td>
</tr>
<tr>
<td>36 M</td>
<td>3</td>
</tr>
</tbody>
</table>

eGFR (MDRD calculation)
Chronic Safety Out to 3 Years

- One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- One new moderate stenosis which was not hemodynamically relevant and no treatment
- 3 deaths within the follow-up period; all unrelated to the device or therapy
- No hypotensive events that required hospitalization
- There were no observed changes in mean electrolytes or eGFR to 18 months

Sobotka P. Hypertension. 2011;57:911-917.
Conclusions from Symplicity HTN-1

• The magnitude of clinical response is significant and sustained through 3 years.

• Increasing responder rates indicate:
  – no loss of treatment effect out to 36 months
  – BP non-response at 6 months does not predict failure to respond at 12 months or later

• The treatment effect was consistent across subgroups (age, diabetes status, and baseline renal function)

• No late adverse events were seen
• **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)
Symplicity HTN-2 Trial

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
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

*MDRD, ml/min/1.73m²

Patient Disposition

Assessed for Eligibility (n=190)

Excluded Prior to Randomization (n=84)
- BP<160 after 2-weeks of 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)

No Six-Month Primary Endpoint Visit (n = 3)
Reasons:
- Withdrew consent (n=1)
- Missed visit (n=2)

Analyzed (n = 49)

Allocated to Control (n = 54)

No Six-Month Primary Endpoint Visit (n = 3)
Reasons:
- Withdrew consent (n=2)
- Lost to follow-up (n=1)

Analyzed (n = 51)

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

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

Home & 24 Hour Ambulatory BP

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)

Procedural Safety

• One renal artery dissection from injection of contrast into renal artery wall during dye angiography. The lesion was stented without further consequences

• One hospitalization prolonged in a crossover patient due to hypotension following the RDN procedure. IV fluids administered, anti-hypertensive medications decreased and patient discharge without further incident

• No radiofrequency-related renal artery stenosis or aneurysm occurred in either Randomised group

• Minor adverse events (full cohort)
  – 1 femoral artery pseudoaneurysm treated with manual compression
  – 1 postprocedural 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 and resolved after 1 month

• 6-month renal imaging (n=43) showed no vascular abnormalities at any RF treatment site

  • 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)
Office BP 18 months Post Procedure

*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*

**RDN Group**
- 6 months: N=49
- 12 months: N=47
- 18 months: N=43

**Crossover Group**
- 6 months: N=35
- 12 months: N=33
- 18 months: N=31

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

*Post Procedure follow up

Esler M, ESC 2012
Renal Function Over Time

RDN eGFR*

<table>
<thead>
<tr>
<th>Pre Procedure (n=52)</th>
<th>6 months (n=49)</th>
<th>12 months (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76.7</td>
<td>77.1</td>
<td>78.2</td>
</tr>
</tbody>
</table>

Crossover eGFR*

<table>
<thead>
<tr>
<th>Pre Procedure (n=37)</th>
<th>6 months (n=35)</th>
<th>12 months (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88.6</td>
<td>85.2</td>
<td>81.2</td>
</tr>
</tbody>
</table>

Renal function parameters were not obtained beyond 12 months follow up

*eGFR mL/min/1.73m²

Esler M, ESC 2012
Change in Pulse Pressure
Post Procedure

N=49  N=35
N=47  N=33
N=43  N=31

*P<.01 from pre procedure values at all time points

Esler M, ESC 2012
Heart Rate Over Time

*B < .01 (6, 12m), p = .02 (18m)

†p = NS (6, 18m), p < .01 (12m)

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

Esler M, ESC 2012
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

Esler M, ESC 2012
Safety Through 18 months Post Procedure

- No device-related SAEs
- No vascular complications at any site of RF delivery
- No clinically significant changes to eGFR for RDN or crossover groups at 12 months post RDN*
- 2 hypotensive events that required hospitalization: 1 in crossover cohort and 1 in RDN cohort
- 10 hypertensive events (in 8 patients) requiring hospitalization through 18 months post RDN in combined cohort
- 1 mild transient acute renal failure
  - Patient admitted with elevated K+, meds temporarily discontinued (Co-Amilofruse, perindopril, metformin). IV fluids administered and K+ decreased. Patient discharged and remained off perindopril
- 2 deaths within the follow-up period; all unrelated to the device or therapy

*Renal function parameters were not obtained beyond 12 months follow up
### Symplicity HTN-2 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>

Symplicity HTN-2 Medication Changes at 6 months

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)

## Symplicity HTN-2 Renal Function (6 months)

<table>
<thead>
<tr>
<th>Δ 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>

Symplicity HTN-2 Other Safety (6 months)

<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</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>unrelated to non-adherence to medication</td>
<td></td>
<td></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</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>after abruptly stopping clonidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotensive episode</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>resulting in reduction of medications</td>
<td></td>
<td></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>

Symplicity HTN-2 Trial
Distribution of Office SBP Post-RDN

Treated with RDN

Crossover group Treated after 6 M follow up

- Baseline
- 6 M RDN
- 12 M RDN

- Baseline
- Pre-RDN
- 6 M post RDN

- ≥180 mmHg
- 160-179 mmHg
- 140-159 mmHg
- <140 mm Hg

Esler M, ACC 2012
## Medication Change Analysis to 18 Months Post Procedure

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=47)</th>
<th>Crossover (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 month</td>
<td>12 months</td>
</tr>
<tr>
<td>Decrease (# Meds or Dose)</td>
<td>18.6% (8/43)</td>
<td>23.3% (10/43)</td>
</tr>
<tr>
<td>Increase (# Meds or Dose)</td>
<td>9.3% (4/43)</td>
<td>9.3% (4/43)</td>
</tr>
<tr>
<td>No Change</td>
<td>67.4% (29/43)</td>
<td>53.5% (23/43)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>4.7% (2/43)</td>
<td>14.0% (6/43)</td>
</tr>
<tr>
<td></td>
<td>6 months post-RDN</td>
<td>12 months post-RDN</td>
</tr>
<tr>
<td>Decrease (# Meds or Dose)</td>
<td>15.2% (5/33)</td>
<td>24.2% (8/33)</td>
</tr>
<tr>
<td>Increase (# Meds or Dose)</td>
<td>12.1% (4/33)</td>
<td>30.3% (10/33)</td>
</tr>
<tr>
<td>No Change</td>
<td>66.7% (22/33)</td>
<td>27.3% (9/33)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>6.1% (2/33)</td>
<td>18.2% (6/33)</td>
</tr>
</tbody>
</table>

- 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
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
Equipment and Lab Setup
Equipment Set-up

- Symplicity Catheter and Generator
  - Dispersive electrode (Ground pad)
- 6 Fr Renal guide catheter (45-55cm) (RDC or LIMA) and introducer sheath
- Guidewire (0.014”, non-hydrophilic)
- Tuohy (RHV)
- Non-ionic contrast (dilute to 50:50)
- Heparinized saline flush bag (pressurized)
- Radiopaque ruler

Common medications to have available:
- Heparin
- Fentanyl / Morphine or similar
- Midazolam (Dormicum, Versed) or similar
- Nitroglycerine
- Atropine
Catheter Tip Features

Flexible Tip (self-orienting)

Deflectable Shaft

5mm

12mm
Catheter Handle Features

Shaft & electrode can rotate independent from handle body
- Handle rotator has tactile “click” every 45°
- Dot on rotator gives relative rotational reference

Deflect tip by pulling lever towards back of handle

Straighten tip by pushing lever towards front of handle
Assessing Renal Anatomy
Renal Angiogram

Eligible Anatomy:
• Absence of flow limiting obstructions
• Diameter ≥ 4mm in targeted area
• Length ≥ 20mm
Renal Angiogram

- Prudently limit contrast dye exposure
  - 50/50 dilution of contrast and use of DSA or biplane may help
- Verify entire kidney fills with contrast

Unfilled kidney sections may indicate multiple main arteries

Lower Pole Not Completely Filling on Selective Injection

Accessory Vessel Partially Supplies Lower Portions of the Kidney
Oblique Angiographic Views

- Changing from AP to oblique and cranial views can provide optimal assessment of artery length

AP projection

~20% LAO projection
Guide Catheter Selection

Typical: RDC-1

Alternate: LIMA

- Once suitable anatomy is confirmed, upsize to 6Fr (or larger) introducer and guide
- Consider guide shape based on renal anatomy (LIMA for inferior takeoffs)
Intra-Procedural Patient Management and Monitoring
Patient Management

• Premedication
  • Aspirin 100-300mg on the day of procedure, then for one month after operation

• Anxiolytic and Amnesic
  – Midazolam (*Dormicum*, Versed) or similar recommended, often administered before groin access. 3-5mg or more may be required.

• Anticoagulation
  – *Heparin*: target ACT >250 sec
  – Continuously flush guide catheter with heparinized saline during the procedure

• Pain Management
  – Patients may experience transient visceral pain during each ablation
  – Fentanyl or *Morphine* (or similar) 2-5 minutes before first ablation; as needed thereafter. 10-20mg may be required.

• Vasodilatation
  – IA *nitroglycerine* through renal guide is recommended before treating each artery
Vital Signs During Procedure

- **Blood Pressure**
  - Pain medications, nitroglycerine, valsalva maneuvers during therapy, and changes of heart rate can all reduce BP during procedure
    - Fluid resuscitation for hypotension
    - Atropine for bradycardia or block associated with hypotension

- **Heart Rate**
  - Pain medications, valsalva maneuvers during therapy, and pain can cause bradycardia
    - Atropine for bradycardia or block associated with hypotension

- **Oxygenation**
  - Pain medications and anxiolytic may reduce quality of respiration and oxygenation
  - Monitor respiratory rate and pulse oximetry
Symplicity Catheter & Generator
Targeting Renal Nerves

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia
Targeting Renal Nerves

- Treat distal to proximal
- 4-6 focal treatments
  - 2 min per treatment
  - $\geq 5$ mm between locations
  - Stable, unique locations
  - Circumferential coverage
- Common strategy (dependent on renal anatomy):
  - Distal: Inferior and inferolateral locations
  - Proximal: Superior and superolateral locations
  - Avoid purely lateral treatments (possible electrode movement with respiration)
- PULL, ROTATE, ASSESS new location and prior treatment site
Delivering Symplicity Catheter

- Fully straighten tip of catheter. NEVER advance the catheter while the tip is deflected
- DO NOT cross recently treated sites
- Deliver Symplicity Catheter through the renal guide catheter

Use the catheter shaft (not handle) to position catheter within vessel

Position electrode ≥5mm proximal to renal bifurcation
Positioning Catheter

• With electrode advanced to most distal treatment site, use handle lever to deflect catheter tip against vessel wall

• Good wall contact is important for the proper delivery of energy
  – First deflect slightly
  – Rotate to superior or inferior hemisphere
  – Continue to deflect until electrode is well apposed to the vessel wall
  – May not need to use handle lever to deflect tip in tortuous anatomy or proximal locations
Wall Contact

Sufficient Wall Contact

Excessive Wall Contact
(avoid distending vessel wall with electrode)
Example Treatment Sites

Because of added guide catheter support, proximal locations may require less deflection to achieve vessel wall contact.

Distal locations in straight vessels may require more deflection to achieve vessel wall contact.
Optimizing Treatment Sites: Impedance

- Impedance may be used to confirm stable wall contact:
  - Higher impedance may indicate better wall contact
  - Stable impedance over a respiratory cycle (Δ < 15-20 ohms) may indicate consistent wall contact
  - Abnormally high impedance may indicate electrode is in a side-branch

* Impedance varies by patient and vessel. Care should be taken to notice range of available impedance readings within each vessel.
Initiate First Treatment

• Meds:
  • IA nitroglycerine
  • Fentanyl or morphine (or similar)
  • Sufficient anticoagulation (confirm ACT > 250)

• Document each treatment site using cine

• **Initiate energy delivery:**
  – Stabilize catheter – do not move during treatment
  – Press foot pedal (or RF button) once to activate catheter
  – Do not inject contrast during active treatment (alters impedance)

• Generator will automatically control RF energy delivery:
  – Power automatically ramped and maintained (5-8W)
  – Continuously monitors temperature and impedance
  – Automatically shuts off after 2 min or when either impedance or temperature exceed program limits
  – To manually stop RF delivery, depress foot pedal or press RF button once
Repeat for Additional Treatment Sites

- Reposition electrode for next treatment:
  - Retract Symplicity Catheter proximal (using catheter shaft)
  - If needed, straighten catheter tip using handle lever
  - Deflect electrode to make contact with vessel wall, using visual and impedance feedback
  - Rotate electrode to appropriate treatment location
  - Optionally, using physician discretion, the tip may remain deflected while positioning electrode for next treatment (rotating and retracting)

- Allow ≥ 5 mm between treatment sites (~3 electrode lengths)
  - Secondary shaft marker may help identify 5mm spacing
Switching Sides / Ending Procedure

- Straighten tip, then remove Symplicity Catheter from patient
- Perform renal artery angiogram (cine) of treated artery
  - Prudently limit dye exposure
- If coagulum or clot are present on electrode, gently wipe with a sterile gauze pad dampened with sterile saline
- Confirm ACT > 250 sec
- Repeat entire procedure on opposite renal artery if required
- After treating both kidneys:
  - Remove ground pad from patient
Areas to Avoid

- There is no clinical experience treating near any areas of visible atherosclerosis, calcification, or fibromuscular dysplasia. Avoid treating areas of visible disease.
- There is no clinical experience treating in vessels with renal artery aneurysms.

**Atherosclerosis (Ostial Stenosis)**

- Avoid treating in segment with stenosis.

**Calcification**

- Avoid energy delivery to area with visible calcification.

**Fibromuscular Dysplasia (FMD)**

- Avoid treating in segment with FMD.
Angiographic Appearance: Typical

Pre-Procedure

Acute Post-Procedure

1 Month Follow-Up
Angiographic Appearance: Less Common

* Increased vessel reactivity, such as spasm, may be encountered when treating in areas with reduced blood flow, such as dual renal arteries or beyond significant renal artery branch points
Multiple sites of edema and spasm
Post-Procedure Care

• Manage femoral access site per standard protocol
  – Be attentive to preventing groin access complications

• Be attentive to radiocontrast nephropathy prophylaxis (hydrate well)
Expanding Indications of TRENDD
RENAL DENERVATION & INSULIN RESISTANCE
RDN and Insulin Resistance

• Three separate publications with data on changes of IR post denervation
  – Schlaich – Euglycemic clamp in 2 resistant HTN patients with polycystic ovarian syndrome
  – Warsaw – HOMA + HgbA1c in 10 patients with resistant HTN with sleep apnea
  – Homburg – HOMA in 37 patients with resistant HTN

Improvement in Fasting Plasma Glucose and Insulin Sensitivity in 2 patients with rHTN + PCOS

Insulin Resistance and HgbA1c

• Significant decrease in plasma glucose concentration 2 hours after glucose challenge at 6 months
  – BL median: 7.0 mmol/dL at baseline (IQR: 5.8-12.0)
  – 6-month median: 6.4 mmol/dL (IQR: 4.1-10.1)
  – $P<0.05$

• Significant decrease in HgbA1C level at 6 months
  – BL median: 6.1% (IQR: 5.9%-6.7%)
  – 6-month median: 5.6% (IQR: 5.4%-6.5%)
  – $P<0.05$

### Hypertension

**Effect of Renal Sympathetic Denervation on Glucose Metabolism in Patients With Resistant Hypertension**

A Pilot Study

Felix Mahfoud, MD; Markus Schlüch, MD; Ingrid Kindermann, MD; Christian Ukena, MD; Bodo Cremers, MD; Mathias C. Brandt, MD; Urs C. Hoppe, MD; Oliver Vonend, MD; Lars C. Rump, MD; Paul A. Sobotta, MD; Henry Krum, MBBS, PhD; Murray Ester, MBBS, PhD, FRACP; Michael Böhm, MD

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=50)</th>
<th>Renal Denervation Group (n=37)</th>
<th>Control Group (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>59.7±1.4</td>
<td>58.7±1.6</td>
<td>62.5±2.9</td>
<td>0.228</td>
</tr>
<tr>
<td><strong>Sex (female), n (%)</strong></td>
<td>13 (26)</td>
<td>8 (21)</td>
<td>5 (38)</td>
<td>0.281</td>
</tr>
<tr>
<td><strong>Type 2 diabetes mellitus, n (%)</strong></td>
<td>20 (40)</td>
<td>13 (35)</td>
<td>7 (54)</td>
<td>0.327</td>
</tr>
<tr>
<td><strong>On medication, n (%)</strong></td>
<td>16 (32)</td>
<td>12 (32)</td>
<td>4 (31)</td>
<td>0.441</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>31.2±0.8</td>
<td>31.3±0.9</td>
<td>30.7±1.7</td>
<td>0.752</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>94.0±2.8</td>
<td>96.5±3.1</td>
<td>93.2±5.8</td>
<td>0.220</td>
</tr>
<tr>
<td><strong>eGFR, mL • min⁻¹ 1.72 m⁻²</strong></td>
<td>76.6±3.1</td>
<td>75.1±3.3</td>
<td>81.0±7.6</td>
<td>0.413</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td>70.9±2.1</td>
<td>69.7±2.0</td>
<td>74.1±5.5</td>
<td>0.354</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>178±3</td>
<td>177±3</td>
<td>184±6</td>
<td>0.235</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td>96±2</td>
<td>96±6</td>
<td>94±4</td>
<td>0.668</td>
</tr>
<tr>
<td><strong>Antihypertensive drugs, n</strong></td>
<td>5.6±0.2</td>
<td>5.8±0.2</td>
<td>5.0±0.4</td>
<td>0.098</td>
</tr>
<tr>
<td><strong>Fasting glucose, mg/dL</strong></td>
<td>121±4</td>
<td>118±3</td>
<td>129±12</td>
<td>0.246</td>
</tr>
<tr>
<td><strong>Glucose level at 60 min, OGTT, mg/dL</strong></td>
<td>219±10</td>
<td>221±10</td>
<td>215±25</td>
<td>0.804</td>
</tr>
<tr>
<td><strong>Glucose level at 120 min, OGTT, mg/dL</strong></td>
<td>186±11</td>
<td>184±13</td>
<td>190±21</td>
<td>0.831</td>
</tr>
<tr>
<td><strong>Impaired fasting glycemia, OGTT, n (%)</strong></td>
<td>8 (16)</td>
<td>5 (13)</td>
<td>3 (23)</td>
<td>0.413</td>
</tr>
<tr>
<td><strong>Impaired glucose tolerance, OGTT, n (%)</strong></td>
<td>18 (36)</td>
<td>15 (40)</td>
<td>3 (23)</td>
<td>0.328</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, OGTT, n (%)</strong></td>
<td>8 (16)</td>
<td>5 (13)</td>
<td>3 (23)</td>
<td>0.241</td>
</tr>
<tr>
<td><strong>Hemoglobin A₁c, %</strong></td>
<td>6.0±0.1</td>
<td>5.8±0.1</td>
<td>6.3±0.3</td>
<td>0.072</td>
</tr>
<tr>
<td><strong>Insulin, µIU/mL</strong></td>
<td>19.3±2.5</td>
<td>20.8±3.0</td>
<td>14.8±4.5</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>C peptide, ng/mL</strong></td>
<td>4.9±0.5</td>
<td>5.3±0.6</td>
<td>3.9±0.4</td>
<td>0.179</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>5.7±0.7</td>
<td>6.0±0.9</td>
<td>4.9±1.5</td>
<td>0.489</td>
</tr>
<tr>
<td><strong>ISQUICKI</strong></td>
<td>0.32±0.01</td>
<td>0.32±0.01</td>
<td>0.33±0.01</td>
<td>0.273</td>
</tr>
</tbody>
</table>

- Treatment-resistant HTN population
- 37 RDN, 13 Control
- Age 60 years
- BMI 31 kg/m²
- 16% with Diabetes
- 52% either impaired fasting glucose or impaired glucose tolerance
- RDN and Control groups generally well-matched

RDN Group Showed Improvements In Several Key Insulin Resistance Markers

**Fasting Glucose**

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in fasting glucose (mg/dL)</td>
<td>17.5</td>
<td>15.0</td>
</tr>
<tr>
<td>p for interaction (ANOVA)</td>
<td>0.043</td>
<td>0.039</td>
</tr>
</tbody>
</table>


**Fasting C-peptide**

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in fasting C-peptide (ng/mL)</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>p for interaction (ANOVA)</td>
<td>0.006</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Fasting Insulin**

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in fasting insulin (mIU/mL)</td>
<td>15.0</td>
<td>10.0</td>
</tr>
<tr>
<td>p for interaction (ANOVA)</td>
<td>0.036</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**HOMA-IR**

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HOMA-IR (ng/mL)</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>p for interaction (ANOVA)</td>
<td>0.008</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Change in Status from Baseline to 3 months:
1) Diabetes
2) Impaired Glucose Tolerance or Impaired Fasting Glucose (IGT/IFG)
3) Normal Glucose Tolerance (NGT)

Possible Physiologic Explanations?

• Sympathetic hyperactivity:
  – Shifts blood from striated skeletal muscle to visceral tissue
  – Visceral tissue is less insulin sensitive than striated muscle
  – Sympathetic activity increases glucagon secretion

• Inhibition of the sympathetic nervous system by moxonidine has been shown to improve glucose metabolism

RENAL DENERVATION & Heart Failure
RDN and Heart Failure

• A recent publication with data on changes to LVH post denervation
  – Mathias Brandt et al Evaluated BP and cardiac structure and function following renal denervation.
Renal Sympathetic Denervation Reduces Left Ventricular Hypertrophy and Improves Cardiac Function in Patients With Resistant Hypertension

Mathias C. Brandt, MD,*† Felix Mahfoud, MD,§ Sara Reda, MD,*† Stephan H. Schirmer, MD, PhD,§ Erland Erdmann, MD,† Michael Böhm, MD,§ Uta C. Hoppe, MD*†‡

Salzburg, Austria; and Cologne and Homburg/Saar, Germany

**Table 1** Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation (n = 46)</th>
<th>Control (n = 18)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>63.1 ± 10.2</td>
<td>63.0 ± 15.3</td>
<td>0.977</td>
</tr>
<tr>
<td>Male</td>
<td>31 (67%)</td>
<td>11 (61%)</td>
<td>0.771</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.6 ± 3.4</td>
<td>28.1 ± 3.8</td>
<td>0.595</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20 (44%)</td>
<td>7 (39%)</td>
<td>0.785</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (15%)</td>
<td>2 (11%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (17%)</td>
<td>4 (22%)</td>
<td>0.726</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>21 (46%)</td>
<td>7 (39%)</td>
<td>0.781</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>32 (70%)</td>
<td>10 (56%)</td>
<td>0.382</td>
</tr>
<tr>
<td>Smoking</td>
<td>14 (30%)</td>
<td>3 (17%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Number of antihypertensive drugs</td>
<td>4.7 ± 0.5</td>
<td>4.8 ± 2.5</td>
<td>0.979</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). Statistical differences between groups, where applicable, are indicated in the far-right column.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index (kg/m²).

- Treatment-resistant HTN population
- 46 RDN, 18 Control
- Evaluated BP and cardiac structure and function via echo and baseline, 1 mo & 6 mo
- RDN Group:
  - Mean age 63 years
  - BMI 28.6 kg/m²
  - 46% with Diabetes
  - 4.7 mean anti-htn meds
- Incidence LVH 63% by echo

RDN Group:
↓ in SBP, DBP, & Pulse Pressure at 1 & 6 Mo

A
RDN – SBP Histogram at 1 & 6 mo

B
RDN & Control – SBP at 1 & 6 Mo

C
RDN & Control – DBP at 1 & 6 Mo

D
RDN & Control – PP at 1 & 6 Mo
**RDN Impact on Cardiac Structure & Fxn:**

1. **↓ LV Mass Index**
2. **↑ EF**
3. **Improved Diastolic Dysfunction**
   - Myocardial Relaxation
   - End-Diastolic Pressures – E/E' & LA size

---

### Echocardiographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=46)</th>
<th>1 Month</th>
<th>6 Months</th>
<th>p for Trend</th>
<th>Control (n=18)</th>
<th>1 Month</th>
<th>6 Months</th>
<th>p for Trend</th>
<th>RD vs. Control Differential Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial diameter (mm)</td>
<td>45.2 ± 6.1</td>
<td>43.0 ± 5.3</td>
<td>42.5 ± 5.0</td>
<td>&lt;0.001</td>
<td>44.7 ± 5.3</td>
<td>44.5 ± 4.2</td>
<td>46.0 ± 5.5</td>
<td>0.495</td>
<td>0.021</td>
</tr>
<tr>
<td>IVSTd (mm)</td>
<td>14.1 ± 1.9</td>
<td>13.4 ± 2.1</td>
<td>12.5 ± 1.4</td>
<td>0.007</td>
<td>14.2 ± 1.9</td>
<td>14.2 ± 1.6</td>
<td>14.2 ± 1.9</td>
<td>0.815</td>
<td>0.032</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>46.5 ± 5.4</td>
<td>47.7 ± 4.7</td>
<td>47.3 ± 6.0</td>
<td>0.232</td>
<td>44.5 ± 8.5</td>
<td>48.3 ± 6.8</td>
<td>46.4 ± 7.6</td>
<td>0.417</td>
<td>0.097</td>
</tr>
<tr>
<td>PWtd (mm)</td>
<td>11.1 ± 2.7</td>
<td>9.9 ± 3.3</td>
<td>9.3 ± 2.8</td>
<td>&lt;0.001</td>
<td>12.0 ± 3.4</td>
<td>11.7 ± 2.1</td>
<td>11.3 ± 3.0</td>
<td>0.676</td>
<td>0.019</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>87.0 ± 28.5</td>
<td>87.1 ± 28.7</td>
<td>84.6 ± 45.4</td>
<td>0.635</td>
<td>85.9 ± 36.5</td>
<td>86.0 ± 40.7</td>
<td>84.0 ± 37.8</td>
<td>0.966</td>
<td>0.783</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>32.8 ± 16.1</td>
<td>27.7 ± 13.5</td>
<td>25.6 ± 12.5</td>
<td>&lt;0.001</td>
<td>31.1 ± 18.2</td>
<td>30.6 ± 16.1</td>
<td>31.8 ± 19.5</td>
<td>0.811</td>
<td>0.015</td>
</tr>
<tr>
<td>LVEF Simpson (%)</td>
<td>63.1 ± 8.1</td>
<td>69.1 ± 7.5</td>
<td>70.1 ± 11.5</td>
<td>&lt;0.001</td>
<td>64.3 ± 7.2</td>
<td>63.9 ± 8.9</td>
<td>62.9 ± 8.1</td>
<td>0.487</td>
<td>0.048</td>
</tr>
<tr>
<td>LV mass/body surface area (g/m²)</td>
<td>112.4 ± 33.9</td>
<td>103.6 ± 30.5</td>
<td>94.9 ± 29.8</td>
<td>0.004</td>
<td>114.8 ± 41.6</td>
<td>115.3 ± 23.3</td>
<td>118.7 ± 30.1</td>
<td>0.634</td>
<td>0.004</td>
</tr>
<tr>
<td>LV mass/height² (g/m²)</td>
<td>53.9 ± 15.6</td>
<td>47.0 ± 14.2</td>
<td>44.7 ± 14.9</td>
<td>&lt;0.001</td>
<td>55.7 ± 15.3</td>
<td>55.8 ± 17.4</td>
<td>58.6 ± 16.1</td>
<td>0.369</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral valve E’ max (cm/s)</td>
<td>74.2 ± 21.0</td>
<td>70.3 ± 17.0</td>
<td>74.3 ± 24.4</td>
<td>0.708</td>
<td>74.7 ± 31.4</td>
<td>74.2 ± 26.4</td>
<td>76.5 ± 22.5</td>
<td>0.892</td>
<td>0.987</td>
</tr>
<tr>
<td>Mitral valve A’ max (cm/s)</td>
<td>85.8 ± 23.7</td>
<td>79.7 ± 17.6</td>
<td>79.6 ± 21.7</td>
<td>0.028</td>
<td>78.6 ± 50.9</td>
<td>83.6 ± 27.6</td>
<td>85.6 ± 28.8</td>
<td>0.609</td>
<td>0.048</td>
</tr>
<tr>
<td>Mitral valve E/ A ratio</td>
<td>0.89 ± 0.29</td>
<td>0.90 ± 0.27</td>
<td>1.12 ± 0.88</td>
<td>0.183</td>
<td>0.88 ± 0.21</td>
<td>0.87 ± 0.25</td>
<td>0.90 ± 0.25</td>
<td>0.878</td>
<td>0.587</td>
</tr>
<tr>
<td>Mitral valve E deceleration time (ms)</td>
<td>227.2 ± 66.5</td>
<td>211.3 ± 57.6</td>
<td>185.2 ± 67.1</td>
<td>0.003</td>
<td>236.0 ± 115.0</td>
<td>253.9 ± 70.4</td>
<td>233.4 ± 89.0</td>
<td>0.745</td>
<td>0.008</td>
</tr>
<tr>
<td>Mitral valve lateral E’ (cm/s)</td>
<td>8.1 ± 2.8</td>
<td>9.5 ± 2.4</td>
<td>9.9 ± 2.7</td>
<td>0.001</td>
<td>6.6 ± 2.5</td>
<td>6.1 ± 2.5</td>
<td>6.3 ± 1.7</td>
<td>0.541</td>
<td>0.023</td>
</tr>
<tr>
<td>Mitral valve lateral E'/E'</td>
<td>9.9 ± 4.0</td>
<td>7.9 ± 2.2</td>
<td>7.4 ± 2.7</td>
<td>&lt;0.001</td>
<td>10.9 ± 3.0</td>
<td>12.3 ± 4.2</td>
<td>12.1 ± 3.8</td>
<td>0.495</td>
<td>0.001</td>
</tr>
<tr>
<td>Isovolumic relaxation time (ms)</td>
<td>109.1 ± 21.7</td>
<td>93.0 ± 22.4</td>
<td>85.6 ± 24.4</td>
<td>0.002</td>
<td>119.4 ± 26.3</td>
<td>111.8 ± 14.0</td>
<td>111.6 ± 40.7</td>
<td>0.615</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>22.8 ± 6.1</td>
<td>24.9 ± 5.8</td>
<td>25.75 ± 6.8</td>
<td>0.009</td>
<td>21.9 ± 8.9</td>
<td>22.6 ± 11.9</td>
<td>22.2 ± 7.6</td>
<td>0.949</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Brandt et al.  *J Am Coll Cardiol.* 2012;59:901–9
LVMI Reduction after RDN

Effect driven by LVMI reduction among patients with LVH at baseline (no appreciable change in LVMI in patients without LVMI at baseline)
LVMI decreases in every group, but correlates with magnitude of BP reduction.

“LV mass regression occurred also in 5 of 6 RD ‘nonresponders’, supporting the notion of BP-independent effects of RD on LVH”
**Goal**
Evaluate safety of the *Symplicity Catheter System* and efficacy of renal denervation for improving cardiac & renal function in patients who have Chronic Heart Failure with Renal impairment

**Study Design**
Multicenter prospective, non-randomized, open-label study

**Enrollment**
40 subjects NYHA Class II-III, EF<40%, eGFR 30-75 mL/min/1.73m²
~ 8 sites in Australia and Europe

**Major Assessments:**
- Cardiac ventricular function by Echocardiography - 6 & 12 months
- Renal function by GFR - 1, 3, 6, & 12 months
Objectives:

- Assess procedural and long term safety of renal denervation
- Evaluate effectiveness of renal denervation on clinical outcomes
- Establish procedural benchmarking & physician practice patterns
- Evaluate the effect of geographical variations in patients and procedural characteristics on clinical outcomes
- Perform Quality of Life analysis

Scope:

- Over 200 sites worldwide; at least 5000 patients
- Prospective, single-arm, open-label, non-interventional registry
- In accordance with Instructions For Use
- Geographies with commercial availability of Medtronic Symplicity Renal Denervation System

First enrollment
February 2nd, 2012
SYMPPLICITY HTN-3

- **Study Design**
  - Multi-center, prospective, blinded, randomized controlled trial

- **Study Objective**
  - To demonstrate that catheter-based renal denervation is a safe and effective treatment for uncontrolled hypertension

- **Study Population**
  - Uncontrolled hypertension population
    - SBP ≥160 mmHg despite maximally tolerated doses of ≥3 antihypertensive medication classes
    - Without significant renal impairment (eGFR > 45mL/min)
  - 530 randomized subjects at 90 sites
    - Randomization (2:1)
    - All patients maintained on baseline meds for 6 months

- This study is actively enrolling patients
Conclusions

- Transcatheter renal denervation, 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.
- Transcatheter renal denervation is the latest breakthrough in the area of non-pharmaceutical treatment of essential hypertension.
- It produces significant reductions in BP in patients with treatment-resistant essential hypertension,
- The magnitude of BP reduction is predictable.
- The technique was applied without major complications.
Conclusions

• At present, this therapy is mainly reserved for those patients whose blood pressure cannot be controlled (SBP >160mmHg) with three or more medications

• And in those whose blood pressure cannot be controlled due to intolerance of anti-hypertensive drugs

• Its role in milder forms of hypertension remains to be explored
Conclusions

• Its long term results and its application in other areas still require more studies and long term follow-up but its initial results are very encouraging.

• Good drug compliance and modification of life style (diet, exercise, body weight control) are the most important elements for good blood pressure control in all patients with essential hypertension.