What We've Learned from Simplicity HTN-1,2, and Registries

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CardioVascular Center Frankfurt, Frankfurt, Germany
The Renin-Angiotensin-System
Renal Sympathetic Efferent Nerves
Kidney as the recipient of central sympathetic signals

Renal efferent nerves

Renin release ↑
NaCl- retention ↑
Renal blood flow ↓
Renal Afferent Nerves
Kidney as the origin of central sympathetic drive

- Vasoconstriction
- Arteriosclerosis
- Insulin Resistance ↑
- Renin-release ↑
- NaCl-retention ↑
- Renal blood flow ↓
- Hypertrophy
- Arrhythmia
- O₂ consumption
- Heart failure
The Renal Nerves

- 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
Example Treatment Locations in a Right Renal Artery

Treatment #1

Treatment #2

Treatment #3

Treatment #4

Treatment #5

Treatment #6
TREND ASIA-PACIFIC
SEPTEMBER 29, 2012 | HONG KONG

 Neuro-Humoral Interventions
Catheter and Device Based Treatment of Hypertension and Heart Failure
Transcatheter Renal Denervation

www.csi-trend.org

TREND Frankfurt, Germany, Frankfurt, March 1-2. 2013
Reduction of sympathetic activity:
**MSNA in a patient with resistant hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 M FU</th>
<th>12 M FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>161/107 mmHg</td>
<td>141/90 mmHg</td>
<td>127/81 mmHg</td>
</tr>
<tr>
<td><strong>MSNA</strong></td>
<td>56 bursts/min</td>
<td>41 bursts/min</td>
<td>19 bursts/min</td>
</tr>
</tbody>
</table>

Improvement in cardiac baroreflex sensitivity after renal denervation (from 7.8 to 11.7 msec/mmHg).

Schlaich et. al. NEJM pending
Effects of renal denervation on renal and total body NA spillover

Mean office blood pressure
161/107 141/90

47% reduction in renal noradrenaline spillover (p<0.05)

28% reduction in total body NA spillover (p<0.05)

Esler et al. ESH 2009
Clinical studies

Renal denervation
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
Baseline Patient Characteristics

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

Sievert et al. European Society of Cardiology. 2010.
Symplicity HTN-1
Significant, Sustained BP Reduction through 3 yrs

P<0.01 for Δ from BL for all time points

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Symplicity HTN-1
Change in Office Blood Pressure for 24 Pts with 3 yrs Follow-up

<table>
<thead>
<tr>
<th>Time</th>
<th>BP change (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>-19</td>
</tr>
<tr>
<td>3 M</td>
<td>-23</td>
</tr>
<tr>
<td>6 M</td>
<td>-31</td>
</tr>
<tr>
<td>12 M</td>
<td>-26</td>
</tr>
<tr>
<td>18 M</td>
<td>-24</td>
</tr>
<tr>
<td>24 M</td>
<td>-16</td>
</tr>
<tr>
<td>30 M</td>
<td>-30</td>
</tr>
<tr>
<td>36 M</td>
<td>-33</td>
</tr>
</tbody>
</table>

P<0.01 for ∆ from BL for all time points

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Distribution of SBP Change at BL, 1, 12, 24, and 36 Months

Baseline, 1 Mo, 12 Mo, 24 Mo, 36 Mo

(N=150) (N=143) (N=130) (N=59) (N=24)

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HTN-1: Adverse Events 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
Symplicity HTN-2

- **Study design:** 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
Symplicity HTN-2 Trial

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

Exclusion Criteria:
- 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

## 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>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/m²)</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/1.73m²)</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>eGFR 45-60 (% patients)</td>
<td>21%</td>
<td>11%</td>
<td>0.19</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

## 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
- Only 10% of RDN patients had no reduction in SBP

How does this compare to medical treatment?
Randomized Trials in Resistant Hypertension
Mean Reduction in Systolic BP

- Darusentan\textsuperscript{2} (-12 mmHg)
- Spironolactone\textsuperscript{3} (-16 mmHg)
- ISMN + Sildenafil\textsuperscript{4} (-22 mmHg)
- Renal Denervation\textsuperscript{1} (-32 mmHg)

\textsuperscript{1}Lancet. 2010
\textsuperscript{3}Hypertension. 2010 Jan;55(1):147-52
\textsuperscript{4}Hypertension. 2010 Jul;56(1):22-3.
Adverse events

• No serious device or procedure related adverse events (n=52)
• Minor adverse events (all unrelated to RF)
  • 1 femoral artery pseudoaneurysm → 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)

No Change in Renal Function

<table>
<thead>
<tr>
<th>Δ Renal Function</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>

Subgroup analyses

- Age
- Gender
- Diabetes

→ no differences
6-month Office BP Change by Age (≥65, <65)

RDN
Δ from Baseline (mmHg)

≥ 65 y.o.
-32 -13
N=18

< 65 y.o.
-31 -11
N=31

Control
Δ from Baseline (mmHg)

6 1
N=20

-2 -1
N=31

All between-age p-values = NS

Scheinert. LINC 2011
6-month Office BP Change by Gender

**RDN**

- **Female**
  - Systolic: -35 mmHg
  - Diastolic: -14 mmHg
  - N=16

- **Male**
  - Systolic: -30 mmHg
  - Diastolic: -11 mmHg
  - N=33

**Control**

- **Female**
  - Systolic: 5 mmHg
  - Diastolic: 1 mmHg
  - N=26

- **Male**
  - Systolic: -3 mmHg
  - Diastolic: -1 mmHg
  - N=25

All between-gender p-values = NS

Scheinert. LINC 2011
6-month Office BP Change by DM Status

Diabetes type II only

RDN

\[ \Delta \text{ from Baseline (mmHg)} \]

DM - Type II

N=21

-28

-9

Systolic

Diastolic

No DM

N=28

-35

-14

Systolic

Diastolic

Control

\[ \Delta \text{ from Baseline (mmHg)} \]

N=15

7

3

Systolic

Diastolic

N=36

-2

-2

Systolic

Diastolic

All between-DM group p-values = NS

Scheinert. LINC 2011
Does it work in less severe resistant hypertension?
Renal Denervation in Borderline Hypertension - Mean Office BP

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>3M FU</th>
<th>6M FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>148.4</td>
<td>142.7</td>
<td>135.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83.0</td>
<td>82.4</td>
<td>78.0</td>
</tr>
</tbody>
</table>

Mean Office blood pressure at baseline, 3M FU and 6M FU after denervation.
Other potential indications

• Sleep apnea syndrome
• Heart failure
• Ventricular arrhythmias
• Diabetes
Sleep apnea syndrome

- ... is considered to be a causal factor for hypertension
- Frequent in resistant hypertension
- Sympathetic activity is increased

- Renal denervation
  - reduces sympathetic activity
  - may be beneficial in sleep apnea syndrome
Sleep apnea syndrome

- 10 patients with sleep apnea who participated in the Simplicity trial

- AHI (Apnea-Hypopnea Index) before and at 3 and 6 months after denervation

Witkowski A et al, Hypertension 2011
Results (2): AHI before and at 3 and 6 months after denervation. Data of individual cases

AHI 3 and 6m (median): p=NS and 16.3 vs 4.5 (events/hour; ), p=0.059, respectively

Witkowski et al, Hypertension 2011; 58: 559-65
Impact of Type 2 Diabetes Mellitus on Sympathetic Neural Mechanisms in Hypertension

Robert J. Huggett, MD, DS; Eleanor M. Scott, DM, DS, MD; Stephen G. Gilbey, BA, MD; John B. Stoker, BSc, MB, ChB; Alan F. Mackintosh, MA, MD; David A.S.G. Mary, MB, ChB, PhD

Sympathetic Activity (impulses/100 beats)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Activity (impulses/100 beats)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT (n=17)</td>
<td>53</td>
</tr>
<tr>
<td>DM2 (n=17)</td>
<td>78</td>
</tr>
<tr>
<td>HTN (n=17)</td>
<td>69</td>
</tr>
<tr>
<td>HTN + DM2 (n=17)</td>
<td>97</td>
</tr>
</tbody>
</table>

NT: normo tensive controls; DM: diabetes; HTN: hypertension; HTN+DM: hypertension+diabetes

F. Mahfoud et al, Trend Asia Pacific, 2011
RD improves insulin sensitivity

F. Mahfoud et al, Trend Asia Pacific, 2011

Mahfoud F et al., Circulation 2011
RD improves glucose tolerance

Glucose tolerance test, 75 g glucose per os

Renal denervation

3 months

-9
-27*

60-min glucose level
120-min glucose level

*significant reduction (p<0.05) compared to baseline

F. Mahfoud et al, Trend Asia Pacific, 2011

Mahfoud F et al., Circulation 2011
Take Home Messages

- Transcatheter Renal Denervation results in significant reductions in BP
- The procedure seems to be very safe
- The effect is sustained up to 3 years
- It may also be beneficial in patients with diabetes, sleep apnea, heart failure and other diseases