Renal Sympathetic Denervation in the Treatment of Resistant Hypertension: Current Clinical Evidence, Patient Selection, Real life data

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Kostadin Kichukov, MD, PhD
Department cardiology, angiology and electrophysiology
City Clinic - Sofia
“The greatest danger to anyone with high blood pressure (BP) lies in its discovery, because then some fool is certain to try to reduce it”

John Hay, 1931

“For mild benign hypertension, or BP below 200/100 mmHg, there is no indication for use of hypertensive drugs”

Friedberg C. K., 1949
Despite the development of multiple classes of antihypertensive drugs over the last 40 years, improvements in their efficacy and tolerance and the use of combination therapies, target BP is not achieved in a significant proportion of hypertensive patients. BP control rates of 30–50% have been reported in the hypertensive population from the United States and Europe.

This poor control of hypertension remains a major public health issue, because it directly influences prognosis, target-organ damage and cardio- and cerebrovascular morbidity and mortality.

Resistant hypertension (RH)

Definition and scope of the problem

- **Resistant hypertension** is a blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes
- One of the 3 agents should be a (thiazide) diuretic and all agents should be prescribed at optimal dose amounts
- **Treatment-resistant hypertension**
  - BP remains above goal on more than 3 medications
  - BP controlled but requires >4 medications
- **Prevalence**
  - General population 5%-9%
  - Clinical trials: ALLHAT 15-27%, CONVINCE 18%; VALUE 15%
- Prevalence of resistant hypertension **is expected to increase**, owing to the aging population and increasing trends in obesity, sleep apnea, and chronic kidney disease

Calhoun Circulation 2008;117:e510-e526
Mancia G Eur H J 2007; 28:1462-1563
Uncontrolled Hypertension is not equal to Resistant Hypertension!

What we have to look for?

- White coat hypertension
- Secondary hypertension
- Inaccurate measurement
- Inappropriate drug combinations
- Interfering substances
- Non compliance with drug regimen or lifestyle modification
- Sleep apnoea
Obstructive sleep apnoea causing Hypertension peaks

Prof. Klaus Weber, Doz. Jan Borgel, RHC
2013
**Real life data – Utrecht registry.**

**Referral for RDN – 66% dropouts. Why?**

<table>
<thead>
<tr>
<th><strong>Results:</strong> Excluded patients (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Pressure</strong></td>
</tr>
<tr>
<td>- Office SBP&lt;160 mmHg</td>
</tr>
<tr>
<td>- Mean 24-h ABPM &lt; threshold</td>
</tr>
<tr>
<td><strong>Secondary cause of hypertension</strong></td>
</tr>
<tr>
<td>- Primary hyperaldosteronism</td>
</tr>
<tr>
<td>- Primary hyperparathyroidism</td>
</tr>
<tr>
<td>- Pseudo-hyperaldosteronism</td>
</tr>
<tr>
<td>- Coarctatio aortae</td>
</tr>
<tr>
<td><strong>Ineligible renal artery anatomy</strong></td>
</tr>
<tr>
<td>- Renal artery stent</td>
</tr>
<tr>
<td>- Renal artery stenosis</td>
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<tr>
<td><strong>Co-morbidity</strong></td>
</tr>
<tr>
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<tr>
<td><strong>Options for pharmacological treatment</strong></td>
</tr>
<tr>
<td></td>
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<td><strong>Other reasons</strong></td>
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<td></td>
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</tbody>
</table>
True resistant hypertension is a significant predictive factor for CV events.

- Responder Hypertension: 0.87
- Masked Hypertension: 2.42
- False Resistant Hypertension: 1.2
- True Resistant Hypertension: 4.1
Control of Central Sympathetic Drive

- Chemosensors (carotid body)
- Mechanosensors (baroreceptor)

- HTN & Insulin Resistance
- Vasoconstriction
- Hypertrophy Arrhythmia
- Dyspnea, Exercise Intolerance, Central Sleep Apnea
- Central Chemoreceptor Sensitivity
- Renin, AngII, Aldo Sodium Retention Renal Blood Flow
- Splanchnic Venous Capacitance
- Congestion Acute HF
Viewing a stressful soccer match more than doubles the risk of an acute cardiovascular event.”
Cardiovascular Events during World Cup Soccer

Ute Wilbert-Lampen, M.D., David Leistner, M.D., Sonja Greven, M.S., Tilmann Pohl, M.D., Sebastian Sper, Christoph Völker, Denise Güthlin, Andrea Plasse, Andreas Knez, M.D., Helmut Küchenhoff, Ph.D., and Gerhard Steinbeck, M.D.

BACKGROUND

The Fédération Internationale de Football Association (FIFA) World Cup, held in Germany from June 9 to July 9, 2006, provided an opportunity to examine the relation between emotional stress and the incidence of cardiovascular events.

METHODS

Cardiovascular events occurring in patients in the greater Munich area were prospectively assessed by emergency physicians during the World Cup. We compared those events with events that occurred during the control period: May 1 to June 8 and July 10 to July 31, 2006, and May 1 to July 31 in 2003 and 2005.

RESULTS

Acute cardiovascular events were assessed in 4279 patients. On days of matches involving the German team, the incidence of cardiac emergencies was 2.66 times that during the control period (95% confidence interval [CI], 2.33 to 3.04; P<0.001); for men, the incidence was 3.26 times that during the control period (95% CI, 2.78 to 3.84; P<0.001), and for women, it was 1.82 times that during the control period (95% CI, 1.44 to 2.31; P<0.001). Among patients with coronary events on days when the German team played, the proportion with known coronary heart disease was 47.0%, as compared with 29.1% of patients with events during the control period. On those days, the highest average incidence of events was observed during the first 2 hours after the beginning of each match. A subanalysis of serious events during that period, as compared with the control period, showed an increase in the incidence of myocardial infarction with ST-segment elevation by a factor of 2.40 (95% CI, 1.39 to 4.13).
Animal models

- Increased renal sympathetic nerve activity (RSNA) is known to be a factor capable of decreasing renal excretory function. The renal effects of increased RSNA include increased renal tubular sodium reabsorption leading to renal sodium retention; decreased renal blood flow and glomerular filtration rate with renal vasoconstriction and increased renal vascular resistance; and increased renin release leading to angiotensin II production. Each of these renal functional alterations can decrease renal excretory function.

- In a large number of diverse animal models of experimental hypertension, bilateral renal denervation prevents the development of or attenuates the magnitude of hypertension. For example, in the obesity model of canine hypertension, bilateral renal denervation completely prevents the development of hypertension in association with a marked reduction in renal sodium retention.

Effect of renal sympathetic denervation on muscle sympathetic nerve activity (MSNA) over 12 months of follow-up (FU).

Surgical experience to reduce sympathetic tone

• In the 1950s, surgical renal denervation was shown to be a highly effective treatment for resistant hypertension, but the procedure was abandoned because of intolerable side effects such as bladder dysfunction and orthostasis.

• More recently, carotid baroreceptor surgery for resistant hypertension was investigated; results were encouraging, but this currently remains a surgical procedure.²

DEEPAK L. BHATT. The promise of renal denervation
Cleveland Clinic Journal of Medicine July 2012 vol. 797 498-500
End Results of Thoracolumbar Sympathectomy for Advanced Essential Hypertension

J., William Hinton, M.D., New York City

In a six-year period from February 1942 to February 1948, 473 patients (185 males and 288 females) were operated upon for essential hypertension and most of them were in advanced stages of hypertensive disease. Patients were selected or rejected for operation on the basis of a set of rules drawn to guide clinical judgment.

I.H. Page, G.J. Heuer
A surgical treatment of essential hypertension
J Clin Invest, 14 (1935), pp. 22–26
Surgical sympathectomy- efficient to control resistant hypertension, but:
High price of complications:
Mortality  6-10%
Severe hypotension  5-15%
Incontinence  15-25%
Renal denervation during surgery for aortic aneurysms and occlusive disease

Friday, 10 Jan 2014 11:06

By Juan Parodi
Ambulatory blood pressure monitoring during 24 hours: under treatment with three drugs, the preoperative blood pressure was 152/95mmHg; after three months under treatment with one drug, the blood pressure average was 134/83mmHg. Sodium excretion in urine for 24h was 164meq in the pre-operative measurement and 251.1meq after three months.

/www.cxvascular.com
Catheter based RF renal nerve ablation SYMPLICITY catheter (Medtronic)

- Interventional technique
- 6F Femoral artery approach
- Single electrode catheter with deflectable tip
- 4-6 two minute treatments per artery
- RF generator
Efficacy data: Symplicity HTN-1

- Blood pressure reduction sustained over 3Y

Baseline BP (mmHg) - 176/98±17/15
Number of anti-HTN meds - 5,0±1,4
Symplicity HTN-2

Crossover Group

RDN Group

SBP

DBP

6 months N=35  12 months N=33  18 months N=31

6 month N=49  12 months N=47  18 months N=43

(mm Hg)
Renal denervation in 2014:
7 commercially available devices
## Renal Denervation Technologies

<table>
<thead>
<tr>
<th></th>
<th>BSC Vessix</th>
<th>MDT Symplicity</th>
<th>MDT Spyral</th>
<th>STJ EnlightN</th>
<th>COV OneShot</th>
<th>ReCor Gen-2 Paradise</th>
<th>JNJ ThermoCool</th>
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<tbody>
<tr>
<td><strong>CE Mark</strong></td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td></td>
</tr>
<tr>
<td><strong>Catheter Design</strong></td>
<td>Balloon catheter 4-8 electrodes</td>
<td>Catheter with single electrode</td>
<td>Pigtail Catheter 4 electrodes</td>
<td>Basket with four electrodes</td>
<td>Balloon catheter helical electrode and cooling</td>
<td>Balloon catheter; internal cooling; <strong>Circumferential treatment</strong></td>
<td>Pigtail catheter with 5 electrodes and cooling</td>
</tr>
<tr>
<td><strong>Balloon</strong></td>
<td>✓</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td><strong>Guidewire</strong></td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>Bipolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Ultrasound</td>
<td>Monopolar RF</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>~1W</td>
<td>8W</td>
<td>8W</td>
<td>6W</td>
<td>25W</td>
<td>~12W</td>
<td>15W</td>
</tr>
<tr>
<td><strong>Energy Delivery Time</strong></td>
<td>30 sec.</td>
<td>2 min.</td>
<td>1 min.</td>
<td>90 sec</td>
<td>2 min.</td>
<td>30 sec.</td>
<td>Unknown</td>
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<tr>
<td><strong>Total Treatment Time</strong></td>
<td>2 min.</td>
<td>16-24 min.</td>
<td>2 min.</td>
<td>24 min.</td>
<td>4 min.</td>
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None of these devices are available for sale in the US.

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<td>24 min.</td>
<td>4 min.</td>
<td>3 min.</td>
<td>Unknown</td>
</tr>
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</table>
RF Energy Devices – Consistent Data

EnligHTN


Verheyse S, TCT 2013

Symplicity HTN-1

Symplicity HTN-2 RCT

Symplicity Spyral

16/7 mm Hg

p < 0.001

p = 0.002
### Recor Study: Office Blood Pressure
![BP Chart]

#### Cardiosonic TIVUS™ ABPM
3 Month Follow-up (n=10)

- **BP Mm Hg**
  - **Systolic**
  - **Diastolic**

#### Kona: External Ultrasound
Wave 1 study

- **Change from Baseline (mm Hg)**
  - 3-week SBP
  - 6-week SBP
  - 12-week SBP
  - 24-week SBP

External ultrasound energy delivered to renal nerves

- **Non-Focused, High Intensity Ultrasonic Catheter**

- **Ultrasound tranudcer inside 6 F balloon**
- **Ultrasound creates heat**
- **Cooled water in the balloon to protect**

None of these devices are available for sale in the US.
SYMPLICITY HTN-3 complicated the future of renal denervation. Many ongoing similar trials were stopped. WHY?

MINNEAPOLIS - January 9, 2014 - Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPPLICITY HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

"SYMPPLICITY HTN-3 met its primary safety endpoint related to the incidence of major adverse events one month following randomization and renal artery stenosis to six months," said Deepak L. Bhatt, M.D., M.P.H., executive director, Interventional Cardiovascular Programs, Brigham and Women's Hospital Heart and Vascular Center, professor of medicine, Harvard Medical School, and co-principal investigator of SYMPPLICITY HTN-3. "Importantly, however, the trial did not meet its primary efficacy endpoint."

George Bakris, M.D., professor of medicine and director of the ASH Comprehensive Hypertension Center at the University of Chicago Medicine, past-president of the American Society of Hypertension, and co-principal investigator of SYMPPLICITY HTN-3 stated. "While it's disappointing the trial did not meet its primary efficacy endpoint. This is the most rigorous renal
### SYMPLICITY HTN-3

Trial design was different

<table>
<thead>
<tr>
<th></th>
<th>HTN-3</th>
<th>HTN-2</th>
<th>HTN-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinding</strong></td>
<td>• Sham procedure in control group (included renal angiogram)</td>
<td>• No sham procedure in control group</td>
<td>• No control group</td>
</tr>
<tr>
<td></td>
<td>• Patients blinded to study arm</td>
<td>• No blinding</td>
<td>• No sham procedure</td>
</tr>
<tr>
<td></td>
<td>• Blinding of clinicians monitoring subjects’ hypertension</td>
<td></td>
<td>• No blinding</td>
</tr>
<tr>
<td></td>
<td>• Blinding of study management</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ABPM</strong></td>
<td>• Inclusion criteria—designed to exclude white-coat syndrome</td>
<td>• Not part of inclusion criteria</td>
<td>• Not part of inclusion criteria</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>• Full tolerated doses of 3+ anti-HTN medications of different classes</td>
<td>• 3+ anti-HTN medications</td>
<td>• 3+ anti-HTN medications, including a diuretic</td>
</tr>
<tr>
<td></td>
<td>including a diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vasodilator use</strong></td>
<td>• 36.8% in RDN group</td>
<td>• 15% in RDN group</td>
<td>• 21% in RDN group</td>
</tr>
<tr>
<td></td>
<td>• 45.0% Sham control</td>
<td>17% in control</td>
<td></td>
</tr>
<tr>
<td><strong>Evaluable Sample Size</strong></td>
<td>• N=535 patients</td>
<td>• N=106 patients</td>
<td>• N=153 patients</td>
</tr>
<tr>
<td></td>
<td>• Powered for both safety and efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>• 25% African American</td>
<td>• &gt; 95% Caucasian</td>
<td>• &gt; 95% Caucasian</td>
</tr>
</tbody>
</table>

SYMPLECTICITY HTN-3 Trial Design

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

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

2 weeks
Home BP & HTN med confirmation

1 M
3 M
6 M

Sham Procedure
Renal angiogram; Eligible subjects randomized
Renal Denervation

1 M
3 M
6 M
2 weeks

Home BP & HTN med confirmation

12-60 M
Primary endpoint

2 weeks

• Patients, BP assessors, and study personnel all blinded to treatment status
• No changes in medications for 6 M


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Primary Efficacy 6-Month Endpoint: Office Systolic BP

Δ = -2.39 (95% CI, -6.89 to 2.12)
P = 0.26*

Δ = -14.1±23.9  
P < 0.001

Δ = -11.7±25.9  
P < 0.001

*P value for superiority with a 5 mm Hg margin; bars denote ±1 standard deviation


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Patient Disposition: 6 Months to 1 Year

Crossover subjects were denervated after unblinding at 6 months if blood pressure criteria for treatment were met and subjects elected to proceed.

Denervation Group
361 Subjects

- 4 died
- 3 withdrew

- 354 eligible for 12M follow-up
- 322 Subjects (91%) 12M post-RDN follow-up

Crossover Group
101 Subjects

- 2 died
- 3 withdrew

- 96 eligible for 6M post-RDN follow-up
- 93 Subjects (96.9%) 6M post-RDN follow-up

Non-Crossover Group
70 Subjects

- 2 died
- 6 withdrew

- 96 eligible for 12M follow-up
- 48 Subjects (77%) 12M follow-up

Sham Control Group
171 subjects

- 2 died

- 6M post-RDN follow-up
Change in Office Blood Pressure through 12 Months Post-Procedure

![Graph showing changes in blood pressure before and after a procedure.](image)

**Change in Blood Pressure (mm Hg)**

<table>
<thead>
<tr>
<th>Group</th>
<th>6 Months</th>
<th>12 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denervation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=350</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>-15.3</td>
<td>-6.6</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td>-7.8</td>
<td></td>
</tr>
<tr>
<td>Crossover*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>-17.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>-7.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Changes are vs. patient baseline, not RDN vs Control. Error Bars = 1.96SE

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### Change in Office SBP at 6 Months With and Without Aldosterone Antagonist Use

<table>
<thead>
<tr>
<th></th>
<th>Non-African American on AAs</th>
<th>African American on AAs</th>
<th>Non-African American Not on AAs</th>
<th>African American Not on AAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline SBP (mm Hg)</strong></td>
<td>183</td>
<td>181</td>
<td>181</td>
<td>191</td>
</tr>
<tr>
<td><strong>Change in Office Systolic Blood Pressure (mm Hg)</strong></td>
<td>-11.8 [-23.5, 0.01] p=0.05</td>
<td>-18.7 [-20.6]</td>
<td>-5.6 [-11.4, 0.15] p=0.06</td>
<td>-17.3 [4.0 [-7.7, 15.7] p=0.50</td>
</tr>
</tbody>
</table>

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Procedural Variability

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

4-quadrant ablation pattern

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Relationship Between SBP Changes and Number of Ablations Attempted for Denervation Group at 6 Months

Number of ablations remains significant after adjustment for baseline blood pressure
Systolic Blood Pressure Change at 6 Months According to Ablation Pattern

**RDN Only**

- **Office**
  - n=253, Change: -14.2
  - n=68, Change: -17.2
  - n=19, Change: -24.3

- **ABPM**
  - n=236, Change: -6.3
  - n=62, Change: -7.7
  - n=17, Change: -10.3

- **Home**
  - n=248, Change: -7.3
  - n=66, Change: -8.2
  - n=19, Change: -9.0

**RDN + Crossover**

- **Office**
  - n=314, Change: -14.6
  - n=83, Change: -16.7
  - n=27, Change: -27.3

- **ABPM**
  - n=289, Change: -6.4
  - n=76, Change: -8.2
  - n=24, Change: -12.1

- **Home**
  - n=308, Change: -7.5
  - n=82, Change: -8.2
  - n=27, Change: -10.6

Four quadrants = 1 superior, 1 inferior, and 2 posterior

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...to summarize

- The 12-month results of SYMPPLICITY HTN-3 are consistent with the 6-month findings previously reported. The safety of the procedure is maintained but blood pressure reductions are similar to a sham procedure.

- The positive correlation of the total number of ablations and the circumferential pattern of ablations on systolic BP drop is maintained and enhanced when the 6-month data from the crossover subjects are added.

- These *post hoc* observations suggest hypotheses concerning optimization of the denervation procedure that may inform the design of future renal denervation trials.
There could be many answers

- Heterogeneity of US Operator Experience
- Catheter Design
- Trial Conduct
- Placebo Effect
- Regression to Mean
- Hawthorne Effect
- Medication Changes or Adherence
- Patient Demographics

Manesh Patel, EuroPCR 2014
During denervation one of the strong markers for future success is the notching of the renal artery. Usually you can see most of the notches (around 3-4 per artery)

In the Symplicity HTN-3 above 60% percent of the patients had 0-1 notch.

<table>
<thead>
<tr>
<th># notches</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denervation (%)</td>
<td>(41.4)</td>
<td>(21.4)</td>
<td>(15.8)</td>
<td>(8.3)</td>
<td>(7.5)</td>
<td>(2.5)</td>
<td>(1.4)</td>
<td>(1.1)</td>
<td>(0.3)</td>
<td>(0.3)</td>
<td>360</td>
</tr>
</tbody>
</table>

Global SYMPLICITY Registry – Current Activated Site Locations

Michael Böhm, MD
on behalf of the GSR Investigators
March 30, 2014
The Global SYMPPLICITY Registry includes the following registries:

- **GREAT Registry** (N=1000)
- **Korea Registry** (N=102) *
- **South Africa Registry** (N=400) *
- **Canada and Mexico** *
- **Rest of GSR** (N~3500)

The registry consists of 5000 consecutive patients treated in a real-world population. There are 231 international sites in 37 countries with a minimum of 10% randomly assigned to 100% monitoring.

The follow-up schedule includes visits at 3M, 6M, 1Y, 2Y, 3Y, 4Y, and 5Y.

* Limited to resistant hypertension only
## Safety in HTN-3 and GSR

<table>
<thead>
<tr>
<th>Event</th>
<th>HTN-3 RDN arm (N=364)</th>
<th>GSR All Patients (N=1000)</th>
<th>GSR OSBP≥160 and ABPM≥135* (N=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAE</strong></td>
<td>1.4%</td>
<td>0.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>At 6 month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.6%</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>New onset end stage renal disease</td>
<td>0.0%</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Significant embolic event resulting in end-organ damage</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Renal artery re-intervention</td>
<td>0.0%</td>
<td>0.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hypertensive crisis/emergency</td>
<td>2.6%</td>
<td>1.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>New renal artery stenosis &gt; 70%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*With ≥3 antihypertensive medication classes*
Change in Office Systolic BP for All Patients and Subgroups

<table>
<thead>
<tr>
<th>All Patients*</th>
<th>&lt;140 mm Hg*</th>
<th>140-159 mm Hg †</th>
<th>≥160 mm Hg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=769</td>
<td>N=751</td>
<td>N=94</td>
<td>N=96</td>
</tr>
<tr>
<td>-10.0</td>
<td>-11.9</td>
<td>12.9</td>
<td>14.2</td>
</tr>
<tr>
<td>N=227</td>
<td>N=222</td>
<td>-2.0</td>
<td>-4.6</td>
</tr>
<tr>
<td>N=448</td>
<td>N=433</td>
<td>-18.9</td>
<td>-21.4</td>
</tr>
</tbody>
</table>

*P<0.0001 for both 3 and 6 month change from baseline
†P=0.14 at 3 months and P=0.0006 at 6 months
Change in Office SBP at 6 Months for GSR and SYMPPLICITY HTN-3 Patients

- GSR All Pts: N=751, Change in Office SBP = -11.9 mm Hg
- GSR (≥160 office/≥135 ABPM): N=244, Change in Office SBP = -20.2 mm Hg
- GSR (≥160 office/≥135 ABPM)*: N=62, Change in Office SBP = -17.3 mm Hg

*with ≥3 antihypertensive medication classes
† with ≥3 antihypertensive meds at maximum tolerated dose
Change in Office SBP at 6 Months for GSR and SYMPLICITY HTN-3 Patients

- **GSR All Pts**: N=751, Change in Office SBP = -11.9 mm Hg
- **GSR (≥160 office/≥135 ABPM)**: N=244, Change in Office SBP = -20.2 mm Hg
- **GSR (≥160 office/≥135 ABPM)†**: N=62, Change in Office SBP = -17.3 mm Hg
- **HTN-3 RDN**: N=353, Change in Office SBP = -14.1 mm Hg
- **HTN-3 Sham**: N=171, Change in Office SBP = -11.7 mm Hg

* with ≥3 antihypertensive medication classes
† with ≥3 antihypertensive meds at maximum tolerated dose
Change in Office SBP at 6 Months for GSR and Non-African American Patients in SYMPLICITY HTN-3

-20.2

-17.3

-15.2

-8.6

* with ≥3 antihypertensive medication classes
† with ≥3 antihypertensive meds at maximum tolerated dose
...to summarize Global Simplicity

- Excellent procedural and clinical safety profile in the largest dataset of real world RDN patients to date

- Significant reductions in both office and ambulatory BP from baseline
  - Differences with SYMPLICITY HTN-3 include randomization, blinding, sham control, BP inclusion criteria, antihypertensive-drug treatment intensity, and African-American inclusion in HTN-3
  - Despite the limitations of comparing a registry with a randomized, blinded, controlled study, the reduction in blood pressure is numerically larger in the GSR at 6 months after treatment
  - Due to the registry nature of the GSR, it is difficult to account for the magnitude of a possible placebo effect.
Future Research

• Define appropriate treatment populations
  – Key subgroups
  – Optimal BP inclusion criteria
• Interaction with drug treatments
• Time course
• Technical issues
• Operator experience
  – Optimal training and proctoring
Design Goals

- Deliver consistent simultaneous ablation pattern
- Enhance ease of access
- Conform to a wide variety of anatomies
- Reduce total procedural time
Change in Office Blood Pressure

Change in Systolic Office Blood Pressure

SBP

P < 0.001 for all values compared to baseline. Error bars: ± 1.96 SE
Change in 24-hr Mean Ambulatory Blood Pressure

P < 0.05 for all values compared to baseline

Error bars: ± 1.96 SE
Our view of renal nerve distribution has changed: Can we do better with new methodological approaches to denervation with the existing technology?

- Histological analysis by Sakakura¹ and others²,³ suggest that a more distal approach could increase the frequency of successful ablations.
- Distal ablation strategies can be executed with the existing catheters.

Renal nerves may have a positional bias: distal nerves are closer to the arterial lumen.

¹Sakakura K et al. J Am Coll Cardiol. 2014 Aug 19;64(7):635-43.
²Tzafiri ARJ Am Coll Cardiol. 2014 Sep 16;64(11):1079-87.
³Mahfoud F EuroPCR2014
Optimization of the Treatment Methodology: a combined target approach to renal denervation

1. RF treatment of the Main Artery
2. RF treatment of each Branch
3. RF treatment of the Main Artery and Branches
Necropsy and histology indicate Branch Artery and Main Renal Artery treatment appear to show similar safety profile as conventional RF treatment in the main artery with minimal non-target involvement.
First RDN in Bulgaria 15.03.2012

Ivo Petrov MD, PhD and team:
Kostadin Kichukov MD, PhD
Christo Dimitrov, MD

Currently three active
RDN centres in Bulgaria
City Clinic, Lozenetz, Sv. Anna (Pat. N>100)
Mostly treated with Symplicity system
Patient Selection

- Office SBP $\geq 160$ mmHg ($\geq 150$ mmHg with type II diabetes mellitus)
- ABPM – above thresholds for day/night; 24H BP
- Stable drug regimen of 3+ more anti-HTN medications
- Age $>18$ years
- Suitable renal vessels - Length $>20$mm, Diameter $>4$mm.
- Without hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR $> 45$ mL/min/1.73m$^2$ (MDRD formula)
Renal denervation is not a procedure – it is a program

- Started on March 15, 2012 (FIB)
- 2012 – 20 patients undergone the procedure
- 2013 – 41 patients
- 2014 – 47 up to 08.09.2014.
Total 108 pts
- All procedures performed with the Medtronic Symplicity system
- A dedicated team for patient management
Pre-procedure and in-hospital assessment

- All patients are well known with initial ABPM readings – 100%.
- Clinical physical exam
- ECG
- EchoCG
- Doppler ultrasound of renal arteries
- Baseline laboratory panel
- Careful observation (BP) after procedure
- Control doppler and creatinine before discharge
Follow-up scheme?
You need a team!

- Tailored for individual patient’s needs, e.g. associated co-morbidities treated
- Control physical exams at M1, M3, M6, M12
- Control ABPM – M1, M3, M6, M12
- Control Lab – sCrea, sUric Acid, sK, sNa,
- Control cardiac Echo – M12
- Control Doppler of the renal arteries – M1, M3.
## Pre-procedure antihypertensive treatment

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>% Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE - I</td>
<td>34%</td>
</tr>
<tr>
<td>ARB</td>
<td>66%</td>
</tr>
<tr>
<td>CCB</td>
<td>71%</td>
</tr>
<tr>
<td>Duiretic</td>
<td>100%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>27%</td>
</tr>
<tr>
<td>Centrally acting sympatholytics</td>
<td>57%</td>
</tr>
<tr>
<td>DRI</td>
<td>11%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>92%</td>
</tr>
<tr>
<td>Alfa blockers</td>
<td>43%</td>
</tr>
</tbody>
</table>

Average number of drug classes 4.7 (3-7)
Results over office BP

P<0.05

SBP
DBP

P<0.05
Other variables during FU

• **eGFR** – Without significant change between BL, M01, M03, M06.
  - With 2 exclusions. 1 Pt with early CIN (72h), successfully treated. 1 patient with CKD – had dialysis on the day of procedure and the day after. After that case all patients with ESRD have planned dialysis the same manner.
  - 2 patients had gradual deterioration of kidney function at M06 – Consulted with nephrologist+biopsy (Both with DM type 2>15years). Dg: Diabetic Nephropathy.

• **Heart Rate** – Without significant change between BL, M01, M03, M06
  - Explanation: First type of medication withdrawn are usually centrally acting sympathicolytics

• **Responder rate** – by the Symplicity HTN criteria:
  - At M03 – 67%, at M06 – 82%
Other variables during FU

• Antihypertensive Medication
  - Average No. of antihypertensive classes dropped from 4,7 (3-7) to 3,8 (2-6) at M03. There were exclusions.

• Off-Label Use
  - RDN in 4 patients with CKD on dialysis with malignant hypertension with perfect outcome during FU – More than 25mm drop in SBP, 14mm Drop in DBP. Safe and sound!

• Responder vs non-responder
  - Up to now we do not have predictors of success. Optimal response in unilateral RDN vs poor response in bilateral x6-7.
We cautiously change therapy at Mo 3 following this advice.

Discontinue, as BP control permits:

1. Centrally-acting agent
2. \(\alpha\)-blocker
3. \(\beta\)-blocker
4. spironolactone
5. CCA or thiazide-like diuretic

Consider maintaining ACEI, statin and aspirin.

Plouin, RHC 2013
Invasive Procedure (1)

- Femoral / Brachial artery access 6/5 Fr
- Up to 08/09/14 – 35 patients had RDN via Brachial 5 Fr access
- Renal angiogram
  - Absence of flow limiting stenoses
  - Diameter >4mm in target vessel
  - Length >20mm
  - Guide catheter selection
    - RDC, IMA, MP
- Areas to avoid
  - Atherosclerosis, calcification, FMD
Invasive Procedure (2)

- Remember – Treat all suitable vessels!
- Never rely on 4 ablations!
- Conscious sedation and analgesia
  - Midazolam – uptitration to 5mg; Fentanyl – up to 6ml
  - Tip: Lidocaine – 50-100mg ia in the renal artery before/during ablation session
- Careful monitoring of pulse oxymetry
- Anticoagulation – Heparine 7500-10000IU
- All patients pretreated with 100-325mg ASA
## Procedure – specific details

City Clinic data (up to sep/2013)

<table>
<thead>
<tr>
<th>Renal ablation procedural details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural success</td>
<td>100%</td>
</tr>
<tr>
<td>Procedure time</td>
<td>69±35 min</td>
</tr>
<tr>
<td>X ray time</td>
<td>16 min</td>
</tr>
<tr>
<td>Number of ablations per artery</td>
<td>5.8</td>
</tr>
<tr>
<td>Bilateral ablation</td>
<td>94.5%</td>
</tr>
<tr>
<td>Combined with coronary intervention</td>
<td>23%</td>
</tr>
<tr>
<td>Combined with renal intervention</td>
<td>6.8%</td>
</tr>
<tr>
<td>Contrast volume</td>
<td>145 ± 67 ml</td>
</tr>
<tr>
<td>GC used</td>
<td></td>
</tr>
<tr>
<td>IMA</td>
<td>38%</td>
</tr>
<tr>
<td>RDC 2</td>
<td>58%</td>
</tr>
<tr>
<td>Guiding sheath 5/6Fr</td>
<td>4%</td>
</tr>
<tr>
<td>Double GW use</td>
<td>18%</td>
</tr>
<tr>
<td>Telescopic technique</td>
<td>12%</td>
</tr>
</tbody>
</table>
Procedural safety
City Clinic Data - 73 patients treated

- Minor bleeding at puncture site - 2 pt
- 1 pt transient haematuria with on D1 with full resolution
- 3 pt with hypotension within hospital period
- 1 case of renal artery dissection, successfully stented
- **No cases of renal artery blood flow compromise** (assessed by doppler) during FU
Case 1- KTK History (FIB)

• 53 YO Male
• History of severe uncontrolled hypertension since 2005
• Dyslipidemia on statin therapy
• Hyperuricaemia
• Evidence of Target organ Damage:
  o LV Hypertrophy - ECG and Echo criteria
  o No evidence of angina at effort
• Drug regimen
  o Lercanidipine - 2x10mg
  o HCTZ - 25mg
  o Candesartan - 32mg
  o Metoprolol Succinate - 150mg
  o Doxazosine - 4mg
  o Moxonidine - 0,4mg
Case 1 - KTK - ABPM readings 09-10/03/2012
Case 1- KTK - Clinical and lab findings

13/03/12

- Physical exam - unremarkable; BP - 180/100
- ECG - sinus rhythm, criteria for LVH
- Cardiac Echo:
  - Preserved LV systolic function - EF-65%
  - LVH - IVS/LVPW - 14/14mm;
  - LVd Mass A-L – 191g
  - Impaired LV relaxation; E/e’ - 10,660
- Peripheral Echo Doppler:
  - No evidence of carotid, mesenteric or renal stenoses. Renal arteries - solitary bilaterally, with diameter 6mm, length >30mm.
- Lab - CrCl - 112,77ml/min
KTK - Procedure
Lercanidipine - 2x10mg
HCTZ - 25mg
Candesartan - 32mg
Metoprolol Succinate - 150mg
Doxazosine - 4mg
Moxonidine - 0,4mg
Case 2 VPS – Challenging, state of the art procedure
Expanding indications

Heart failure
LV Hypertrophy
Sleep apnoea
Insulin resistance
Chronic kidney disease/ESRD
Atrial fibrillation
Take home messages

- Careful selection of candidates for RDN is essential.
- Inform patients not to expect immediate results and be patient up to M06.
- But be prepared for immediate drops in BP!
- Expect results in most of the cases around M03.
- Try to keep BP-lowering therapy unchanged until M03, except in cases of hypotension.
- **You never know who will be responder of the procedure, because we do not have reliable predictors of success. That’s why do your best!**
Now we know that renal denervation success is not in the believing, but in doing it right
Paradigm Shift

Innovation

Unbridled enthusiasm

Harsh realities

Thoughtful adaptations

Ultimate applicability

SAFETY + EFFICACY

Time

Efficacy

ST
Thank you for your attention!