The concept of renal artery denervation: dead or alive?

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Disclosures

• Presenter: Dariusz Dudek
  Research grant, speakers from Medtronic
How common is true resistant hypertension?

Resistant HT confirmed in ABPM – 62.5% (7.6% all pts)

Resistant HT in office BP measurements – 12.2%

68,045 pts with HT
Renal denervation – ready for prime time?

Dariusz Dudek
Institute of Cardiology, Krakow, Poland

The European Association of Percutaneous Cardiovascular Interventions (EAPCI)
Chair, Scientific Programme Committee
Staged Clinical Evaluation

Symplicity HTN-1

First-in-Man ✓
Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

USA
Symplicity HTN-3
US Randomized Clinical Trial (enrolling)

Approved Geographies

Other Areas of Research:
Global SYMPLICITY Registry,
Insulin Resistance, HF,
Sleep Apnea, others
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kupelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

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 – 24 months report (Symplicity HTN-1):
- Expanded cohort of patients (n=153)
- 24-month follow-up

Sievert et al. European Society of Cardiology, 2010
Purpose: To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial.

Patients: 106 patients randomized 1:1 to treatment with renal denervation vs. control.

Clinical Sites: 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence).
The magnitude of blood pressure reduction can be predicted to have a meaningful effect on cardiovascular mortality and numerous known sequelae of hypertension.

but we need more data due to

a) Sympathetic nerve regrowth might mitigate effect (however, 2 years follow up till now with no loss !)

b) Artery spasm?, Renal artery stenoses ?, aneurysmal dilatation ?,
plaques progression of underlying atherosclerosis (no major problems at 6 months f-up, but only 52 procedures in this study)

we need to prove clinical benefit in larger study
Renal denervation – ready for prime time?

Not fully, but almost ready
Change in ABPM

<table>
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P<0.005

LINC 2013/2014, Leipzig

RDN-POL Registry
**IDENTIFICATION OF RESPONDERS**

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<tr>
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<th>non-responders</th>
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<td><strong>Age</strong></td>
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<tr>
<td><strong>Sex F (%)</strong></td>
<td>56</td>
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<td><strong>BMI (kg/m2)</strong></td>
<td>31.1</td>
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<tr>
<td><strong>Baseline SBP</strong></td>
<td>165 mmHg</td>
<td>173 mHg</td>
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<td><strong>Non-dippers (%)</strong></td>
<td>44</td>
<td>33</td>
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<tr>
<td><strong>No of RDN applications</strong></td>
<td>5.2</td>
<td>5.3</td>
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</table>

*LINC 2013/2014, Leipzig*
Change in Office SBP for All Patients and SBP Subgroups

Baseline Office SBP

Baseline SBP (mmHg) | 164 ± 24 | 150 ± 6 | 167 ± 6 | 196 ± 14

Change in Office Systolic Blood Pressure (mm Hg)

All Patients

n=790 n=784 n=740

-9.9* -11.6* -13.0*

140-159 mmHg

n=234 n=231 n=214

-1.9† -4.7‡ -4.3‡

160-179 mmHg

n=280 n=286 n=264

-13.0* -14.6* -16.3*

≥180 mmHg

n=179 n=166 n=162

-27.7* -31.8* -33.9*

*P<0.0001
†P<0.05
‡P=NS

Error Bars=1.96 SE

F. Mahfoud @ TCT 2014
SYMPPLICITY HTN-3, 2014

- SYMPPLICITY HTN-3 is the first randomized, blinded, sham-controlled clinical trial of renal denervation for uncontrolled hypertension.

- Initial results confirmed the safety of renal denervation but did not achieve the 6-month primary efficacy endpoint.
Primary Endpoints at 6 Months

**SAFETY**

MAE Rate at 6 Months (%)

- RDN (n=361): 1.4%
- Sham Control (n=171): 0.6%

Performance Goal = 9.8%

P < 0.001

**EFFICACY**

SBP at 6 Months

- RDN (n=353): -14.1
- Sham Control (n=171): -11.7

P < 0.001

**ΔSBP: -2.39 (-6.89, 2.12), p=0.26**

(Primary analysis with 5 mm Hg superiority margin)

Baseline SBP

- RDN: 179.7
- Sham Control: 180.2

6-Month SBP

- RDN: 165.6
- Sham Control: 168.4

MAE is a composite of major adverse events, defined as death from any cause, endstage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months.

Ambulatory Systolic Blood Pressure Through 24-Months Post-Randomization (Matched Data)

- **RDN (n=160)**
- **Crossover (n=44)**
- **Non-crossover (n=28)**

Non-crossover patients were matched at baseline and 24 months only.
Renal denervation – dead or ....?

not fully, but almost dead

with current technology & clinical approach

and

we need new concepts, new technologies and more scientific research
– let`s check clinical status, pharmacological treatment and technique of renal denervation
Multivariate Predictors of Systolic Blood Pressure Change at 6 Months

Presented at EuroPCR 2014

Univariate $P<0.2$ required to enter the model
Relationship Between Office SBP Changes and Number of Ablations Attempted for Combined* RDN Subjects at 6 Months

Baseline SBP (mm Hg)

<table>
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<tr>
<th>Baseline SBP</th>
<th>≥ 8</th>
<th>≥ 9</th>
<th>≥ 10</th>
<th>≥ 11</th>
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<td>440</td>
<td>400</td>
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<td>161</td>
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<td>71</td>
<td>48</td>
<td>31</td>
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*Denervation and crossover subjects combined

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use. Not available for sale in the United States.
The new **SPYRAL-HTN** trial - renal denervation in patients with uncontrolled hypertension, was designed to directly address the potential confounding factors identified in the current SYMPLICITY HTN-3 study.

The **SPYRAL-HTN** trial is currently enrolling patients
External Energy vs Internal Energy

Energy Maximum at the Vessel Wall

Symplicity® and others

Maximum Energy At Vessel Wall

Energy Maximum is Outside Vessel

Kona Medical

Energy Surrounds Vessel
Potential Advantages of Non-Invasive Therapy

- Expand patient population
  - Moderate hypertensives
  - Patients contraindicated for catheterization
  - Improve access to RDN therapy / geography
- Lower cost
- Fewer complications
- No contrast, radiation, or groin/femoral access required
- Repeat treatments or dose escalation
Renal artery denervation and beyond

- Renal denervation works in real life in true resistance hypertensive patients (Global Simplicity Registry 1,000 pts).
- Renal denervation does not work in randomized HTN-3 trial with sham treatment. Possible confounding factors in HTN-3:
  - Drug changes and variable patient adherence
  - Study population
  - Procedural experience and variability
- The continuation of research is needed to explore all aspects related to the renal denervation
- In meantime we have new other promising applications of renal denervation and other endovascular devices….

...... but extensive research is needed