Renal Denervation:

The jury is still out!

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Effects of Increased Sympathetic Tone

Factors that might contribute to increased renal afferent signaling:

- Adenosine
- Acidosis
- Oxidative stress
- Inflammation
- Endothelial factors
- Angiotensin II
- Ischemia

Consequences of increased efferent sympathetic outflow to the kidney and other organs:

- Remodeling
- Hypertrophy
- Arrhythmias
- Ischemia
- Apoptosis

- Medial hyperplasia
- Arterial compliance ↓
- Endothelial dysfunction

Renal denervation

- Renal injury / Renal ischemia
- Na⁺ / H₂O retention
- Reduced renal blood flow
- Activation of the RAAS
- Proteinuria
- Glomerulosclerosis
End organ Damage Induced by Sympathetic Activation

- LV remodelling
- Heart Failure
- Atrial remodelling
- Arrhythmias
- ↑ Heart rate
- ↑ O₂ consumption
- Ischemia
- ↑ Wall thickness
- ↓ Distensibility
- ↑ Sodium retention
- ↑ RAAS
- ↓ Renal blood flow
- Chronic kidney disease
- ↑ Wall thickness
- ↓ Distensibility
- ↑ Heart rate
- ↑ O₂ consumption
- Ischemia
- ↑ Wall thickness
- ↓ Distensibility
Endorgan Damage Induced by Sympathetic Activation

SYMPATHETIC OVERDRIVE

DM Type II

↑ Sodium retention
↑ RAAS
↓ Renal blood flow
Chronic kidney disease

LV remodelling
Heart Failure
Atrial remodelling
Arrhythmias
↑ Heart rate
↑ O$_2$ consumption
Ischemia

↑ Wall thickness
↓ Distensibility

Renal ischemia
Adenosine ↑

LV remodelling
Heart Failure
Atrial remodelling
Arrhythmias
↑ Heart rate
↑ O$_2$ consumption
Ischemia

↑ Wall thickness
↓ Distensibility
End organ Damage Induced by Sympathetic Activation

- LV remodelling
- Heart Failure
- Atrial remodelling
- Arrhythmias

- DM Type II

- RESISTANT HYPERTENSION
- Wall thickness
- Distensibility

- Sympathetic Overdrive
- DM Type II

- Renal ischemia
- Adenosine ↑

- Sodium retention
- RAAS
- Renal blood flow
- Chronic kidney disease

- Wall thickness
- Distensibility

- Heart rate
- O₂ consumption
- Ischemia
Role of the SNS Activation in the Cardiovascular Continuum

Grassi G, Am J Hypertens 2010
Catheter-based Renal Denervation: Staged Clinical Evaluation

First-in-Man ✓

Series of Pilot studies ✓

Symplicity HTN-2
Initial Randomized Clinical Trial

Symplicity HTN-3
US PMA Randomized Clinical Trial (completed)

Registries, Symplicity GLOBAL, ACC, LBCT

Symplicity HTN-1
Extended follow-up
Catheter-based Renal Denervation: Staged Clinical Evaluation

- Symplicity HTN-1
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Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study

Henry Krum, Markus P Schlaich, Michael Böhm, Felix Mahfoud, Krishna Rocha-Singh, Richard Katholi, Murray D Eisler

Catheter-based Renal Denervation: Staged Clinical Evaluation

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Symplicity HTN-3
- US PMA Randomized Clinical Trial (ACC LBCT, NEJM)

Global Symplicity Registry (ACC LBCT)
Time course of office BP change

RDN
\(\Delta \text{ from Baseline (mmHg)}\)

Control
\(\Delta \text{ from Baseline (mmHg)}\)

![Graph showing time course of office BP change with RDN and Control groups. The graph indicates a significant decrease in both systolic and diastolic BP for RDN compared to Control over 1M, 3M, and 6M. The decrease is marked by bars indicating the change from baseline for each time point.]

### Systolic and Diastolic Blood Pressure Changes

- **RDN**
  - 1M: -20 \(^\dagger\), -7 \(^{\ddagger\ddagger}\)
  - 3M: -24 \(^\dagger\)
  - 6M: -32 \(^\dagger\)

- **Control**
  - 1M: 0
  - 3M: -4
  - 6M: 1

† p<0.0001 for between-group comparisons
\(^{\ddagger\ddagger}\) p=0.002 for between-group comparisons
\(^{\ddagger\ddagger\ddagger}\) p=0.005 for between-group comparisons

Two-way repeated measures ANOVA, p=0.001

Catheter-based Renal Denervation: Staged Clinical Evaluation

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Primary safety endpoint

Performance Goal = 9.8%

$P < 0.001$

Major Adverse Event (MAE) Rate

Bhatt DL, NEJM 2014
Primary efficacy endpoint

-2.39 (-6.89, 2.12), $P = 0.255$ (Primary analysis with 5 mm Hg superiority margin)

- Did not meet primary efficacy endpoint
Secondary efficacy endpoint

-1.96 (-4.97, 1.06), $P = 0.979$ (ITT analysis with 2 mm Hg superiority margin)

- Did not meet secondary efficacy endpoint
- Subgroups
- Procedural Aspects
- Stability of Treatment
- Subgroups

- Procedural Aspects

- Stability of Treatment
Change in Blood Pressure in African-Americans vs Non-African-Americans

Kandzari et al., 2014 submitted (Symplicity HTN-3), Hotline EurpPCR
- Subgroups
- Procedural Aspects
- Stabliity of Treatment
What was the distribution of procedures among operators?

- N = 111 operators from 88 sites
- Median cases per operator = 2.6
Angiographic “notches” as evidence of biological effect of the procedure

Table S8. SYMPLICITY HTN-3: Notching Following Renal Denervation

<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(41.4)</td>
<td></td>
<td></td>
<td>(15.8)</td>
<td></td>
<td>(8.3)</td>
<td></td>
<td>(7.5)</td>
<td></td>
<td>(2.5)</td>
<td>(1.4)</td>
<td></td>
</tr>
<tr>
<td>(21.4)</td>
<td></td>
<td></td>
<td>(11.1)</td>
<td></td>
<td>(1.1)</td>
<td></td>
<td>(0.3)</td>
<td></td>
<td>(0.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean # number of notches in the denervated group: 1.41 ± 1.7.
ABPM Response by Number of Ablation Attempts

Kandzari et al., Eur Heart J, online 2014 (Symplicity HTN-3)
Electrode Effects are Additive

- Efficacy requires more than 3 electrodes
- Implies axial additively

Data on file, Cordis Corporation. 2013

*Edelman E, F. Mahfoud, EuroPCR 2014*
Procedural Variability

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

Cross-section of artery

Lesion

Inferior

Anterior

Superior

Posterio

4 quadrant ablation pattern
Renal denervation in 2014 – 7 CE-marked devices
Sweet spots to target?

Mahfoud F, Böhm M, Edelman E JACC Int, 2014
Sweet spots to target?

Proximal Superior

Distal Superior

Mahfoud F, Böhm M, Edelman E, JACC Int, 2014
Sweet spots to target?

Proximal

Distal

Mahfoud F, Böhm M, Edelman E; JACC Int, 2014
Predictibility of lesions is limited
- Subgroups
- Procedural Aspects
- Stability of Treatment
Antihypertensive drugs may have been maximized but may not have been stabilized appropriately.

**Initial Screening**
- Office SBP ≥ 160 mmHg
- Full tolerated doses of ≥ 3 meds
- No HTN med changes in past 2 weeks
- No plan to change meds for 6 M

**2 weeks**

**Home BP & Med Confirmation**

**Confirmatory Screening**
- Office SBP ≥ 160 mmHg
- Documented compliance on meds
- Lab work
- 24 hr ABPM SBP ≥ 135
Did many patients change antihypertensive drug regimens shortly before qualifying?

~80% of patients were on stable medication regimes for at least 6w prior to inclusion
Were there frequent drug changes between baseline and 6 months of follow up?

Protocol mandated:

- **Maximum** doses and
- **No** medication changes

~40% of patients *underwent medication changes*

69% of first medication changes were medically necessary

*Changes included class or dose*
Change in Office Blood Pressure through 12-Months Post-Procedures

Baseline SBP (mm Hg) | 180 | 179 | 184*  
Baseline DBP (mm Hg) | 96 | 95 | 102*  

P<0.001 at all time points
Error Bars= 1.96 SE

*Baseline = time of RDN procedure

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

- **Baseline SBP (mm Hg):**
  - RDN 6 Months: 180
  - RDN 12 Months: 179
  - Crossover 6 Months: 184*

- **Baseline DBP (mm Hg):**
  - RDN 6 Months: 96
  - RDN 12 Months: 95
  - Crossover 6 Months: 102*

*Baseline = time of RDN procedure

Sham vs non Sham not different

P<0.001 at all time points

Error Bars = 1.96 SE

Bakris et al., ESC CTU, 2014
Change in Mean 24-hour Ambulatory Blood Pressure through 12 Months

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

Subjects unblinded

Baseline SBP (mm Hg) | 176 | 176
Baseline DBP (mm Hg) | 94  | 94

Δ 6 to 12 months = +11.5/+5 mmHg

P<0.001 at all time points

Error Bars=1.96 SE

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

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Δ 6 to 12 months = +11.5/+5 mmHg

Baseline SBP (mm Hg) | 176 | 176
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Error Bars=1.96 SE

Bakris et al., ESC CTU, 2014
Discuss. Böhm
Change in Mean 24-hour Ambulatory Blood Pressure through 12 Months

Subjects unblinded

Baseline SBP (mm Hg) | 151 | 151
Baseline DBP (mm Hg) | 86 | 86

Δ 6 to 12 months = +4.9/+3.7 mmHg

P=0.02

P=NS

P=0.03

P=NS

Error Bars=1.96SE

Bakris et al., ESC CTU, 2014 Discuss. Böhm
Catheter-based Renal Denervation: Staged Clinical Evaluation

- First-in-Man ✓
- Series of Pilot studies ✓

Symplicity HTN-1
Extended follow-up

Symplicity HTN-2
Initial Randomized Clinical Trial

Symplicity HTN-3
US PMA Randomized Clinical Trial (ACC LBCT)

Global Simplicity Registry (ACC LBCT)
Global SYMPLICITY Registry – Current Activated Site Locations

LA: 6
CA: 5
MEA: 11
WE: 116
ANZ: 11
C&EEU: 10
ASEAN: 10
Korea: 10

Böhm et al., submitted 2014, ACC Hotline, Mahfoud el al., 2014 ESC CTRU
<table>
<thead>
<tr>
<th></th>
<th>GSR HTN3-like cohort</th>
<th>RDN</th>
<th>HTN-3</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>244</td>
<td>353</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>Change in Office SBP (mm Hg)</td>
<td>-20.2</td>
<td>-14.1</td>
<td>-11.7</td>
<td></td>
</tr>
<tr>
<td>Mean # anti-HTN drugs at baseline</td>
<td>4.7 (1.2)</td>
<td>5.1 (1.4)</td>
<td>5.2 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>

Böhm et al., submitted 2014, ACC Hotline, Mahfoud et al., 2014 ESC CTRU
2013 ESH/ESC Guidelines for the management of arterial hypertension

Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.
How Should a Trial Look Like: Lessons From Symplicity HTN-3

- **Subgroups**
  - Non or Low Response: Vasodilator use, Isolated systolic hypertension, Afro-Americans (?), assure high baseline BP

- **Procedural Aspects**
  - Adequate RDN (more intense, periphery), novel device, experienced investigators

- **Stability of Treatment**
  - Stable therapy, no drop ins and outs, Evaluation of drug combinations
Thank you!

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