Hypertension lecture 3:

Catheter-Based Renal Denervation (RDN)

Adapted from slides prepared by Dr IOEBRAHIM, UNITAS HOSPITAL and others
Hypertension Epidemiology

- Single largest contributor to death worldwide
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Only half of all treated hypertensives are controlled to established BP targets
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025

What is resistant hypertension?

The ESC / ESH defines Hypertension as **resistant** when a therapeutic strategy that includes

- lifestyle measures
- plus a diuretic
- and two other antihypertensive drugs, belonging to different classes

fails to lower BP below 140/90mmHg.

¹Not necessarily including a mineralocorticoid antagonist

Patients with resistant Hypertension – typical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Old Age; especially &gt;75yrs</td>
</tr>
<tr>
<td>High Baseline Blood Pressure and chronic Uncontrolled Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Atherosclerotic vascular disease</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Black African Patients</td>
</tr>
<tr>
<td>Target organ damage: LVH and/or CKD</td>
</tr>
<tr>
<td>Aortic stiffening</td>
</tr>
<tr>
<td>Excessive dietary sodium</td>
</tr>
</tbody>
</table>
Renal Sympathetic Activation: Efferent Nerves
Kidney as Recipient of Sympathetic Signals

Renin Release $\rightarrow$ RAAS activation
$\uparrow$ Sodium Retention
$\downarrow$ Renal Blood Flow
Renal Sympathetic Activation: Afferent Nerves
Kidney as Origin of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis
- Insulin Resistance
- Sleep Disturbances
- Hypertension
- Arrhythmia
- Oxygen Consumption

↑ Renin Release ➔ RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
Renal Nerve Anatomy

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia
Renal Nerve Anatomy Allows a Catheter-Based Approach

- Renal artery access via standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF generator
  - Automated
  - Low power
  - Built-in safety algorithms
SYMPLICITY Clinical Trial Program follows over 5000 patients across multiple indications

- **First-in-Man (AU)**
- **Series of Pilot Studies (EU, US & AU)**
  - **Symplcity HTN-1**
    - Initial RCT (EU & AU)
  - **Symplcity HTN-2**
    - Expand HTN Indication (Approved Regions)
    - Pilot Studies in New Indications (Approved Regions)
  - **Global Symplcity Registry (Approved Regions)**
  - **SYMPPLICITY HF**
- **SYMPPLICITY HTN-3**
  - US Pivotal Trial (US)
  - Post-Market Registry (US)

**SA Heart / SAHS Lecture Series – Hypertension**
SA Heart /SAHS Lecture Series – Hypertension

**Simplicity 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 (Simplicity HTN-1):**
- Expanded cohort of patients (n=153)
- 36-month follow-up

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*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)*
## Baseline Patient Characteristics (n=153)

### Demographics
- Age (years): 57 ± 11
- Gender (% female): 39%
- Race (% non-Caucasian): 5%

### Co-morbidities
- Diabetes Mellitus II (%): 31%
- CAD (%): 22%
- Hyperlipidemia (%): 68%
- eGFR (mL/min/1.73m²): 83 ± 20

### Blood Pressure
- **Baseline BP (mmHg)**: 176/98 ± 17/15
- **Number of anti-HTN meds (mean)**: 5.1 ± 1.4
  - Diuretic (%): 95%
  - Aldosterone blocker(%): 22%
  - ACE/ARB (%): 91%
  - Direct Renin Inhibitor: 14%
  - Beta-blocker (%): 82%
  - Calcium channel blocker (%): 75%
  - Centrally acting sympatholytic (%): 33%
  - Vasodilator (%): 19%
  - Alpha-1 blocker: 19%
Brief Procedure with a Low Complication rate (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

Symplicity HTN-1: BP Reductions through 3 years

BP change (mmHg)

-19  -21  -22  -26  -26  -33  -33  -33

P<0.01 for Δ from BL for all time points

1 M (n=143)  3 M (n=148)  6 M (n=144)  12 M (n=130)  18 M (n=107)  24 M (n=59)  30 M (n=24)  36 M (n=24)

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)
Symplicity HTN-1: Percentage Responders Over Time

Responder was defined as an office SBP reduction ≥ 10 mmHg

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)
Symplicity HTN-1: Response Rate Among Non-responders at 1 Month (n=45)

Responder was defined as an office SBP reduction ≥ 10 mmHg

- 1 Month: 58%
- 3 Months: 57%
- 6 Months: 64%
- 12 Months: 82%
- 24 Months: 100%

*(Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)*
Symplicity HTN-1: 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

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)*
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.
Rev. A Heart /SAHS Lecture Series

**Simplicity HTN-2**

**THE LANCET**

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

Simplicity HTN-2 Investigators


- **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

- Treatment-resistant HTN population
- BL OBP 178/97 mmHg
- 49 RDN, 51 Control
- Age 58 years
- BMI 31 kg/m²
- 40% with Diabetes
- eGFR 77*
- Avg # meds 5.2
- RDN and Control groups generally well-matched

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

**Symplicity HTN-2: Patient disposition**

- **Screening**
  - Assessed for Eligibility (n=190)

- **Excluded During Screening, Prior to Randomisation** (n=84)
  - BP < 160 at Baseline Visit (after 2-weeks of medication compliance confirmation) (n=36; 19%)
  - Ineligible anatomy (n=30; 16%)
  - Declined participation (n=10; 5%)
  - Other exclusion criteria discovered after consent (n=8; 4%)

- **Randomised** (n=106)
  - Allocated to RDN
    - n=52 Treated
    - n=49 Analysable
  - Allocated to Control
    - n=54 Control
    - n=51 Analysable

- **6-month Primary End-Point**
  - 12-month post-RDN
    - n=47
  - Per protocol, 6-mo Post-RDN (Crossover)
    - n=35
  - Not-per-protocol*, 6-mo Post-RDN (Crossover)
    - n=9

- **Crossover**
  - n=46

  2 LTFU

* Crossed-over with ineligible BP (<160 mmHg)
RDN and Control Populations Well-matched, Severe Treatment Resistant Hypertensives
<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 B (mmHg)</td>
<td>97 ± 16</td>
<td>98 ± 17</td>
<td>0.80</td>
</tr>
<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>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>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.
Symplicity HTN-2: 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 hospitalisation for evaluation of paraesthesias
  - 1 back pain treated with pain medications and resolved after 1 month

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)
Primary Endpoint:

• 84% of RDN patients had ≥10 mmHg reduction in SBP
• 10% of RDN patients had no reduction in SBP

Latest Follow-up:

• Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

p < 0.01 for difference between RDN and Control

p < 0.01 for Δ from baseline

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)
### Symplicity HTN-2: Medication Changes at 6 and 12 Months Post-Renal Denervation

<table>
<thead>
<tr>
<th>RDN (n=47)</th>
<th>6 month</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease (# Meds or Dose)</td>
<td>20.9% (9/43)</td>
<td>27.9% (12/43)</td>
</tr>
<tr>
<td>Increase (# Meds or Dose)</td>
<td>11.6% (5/43)</td>
<td>18.6% (8/43)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crossover (n=35)</th>
<th>6 months post-RDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease (# Meds or Dose)</td>
<td>18.2% (6/33)</td>
</tr>
<tr>
<td>Increase (# Meds or Dose)</td>
<td>15.2% (5/33)</td>
</tr>
</tbody>
</table>

*Physicians were allowed to make changes to medications Once the 6 month primary endpoint was reached*

*Further analysis of Medications is ongoing*
Symplicity HTN-2: Renal Function Results

**Treated at Randomisation**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 month</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RDN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>76.9 ± 19.3 (n= 49)</td>
<td>77.1± 18.8 (n=49)</td>
<td>78.2± 17.4 (n=45)</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.91± 0.25 (n=38)</td>
<td>0.98± 0.36 (n=40)</td>
<td>0.98± 0.30 (n=38)</td>
</tr>
</tbody>
</table>

**Crossover**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 month</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>88.8 ± 20.7 (n = 35)</td>
<td>89.3± 19.5 (n = 35)</td>
<td>85.2±18.3 (n = 35)</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.78± 0.17 (n=27)</td>
<td>0.82±0.16 (n=26)</td>
<td>0.89±0.20 (n=26)</td>
</tr>
</tbody>
</table>

Symplicity HTN-2: Lancet Conclusions

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.
- The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality.
- The technique was applied without major complications.
- This therapeutic innovation, 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.
- Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.
Critique and further research

Questions around the high response rates— is all resistant hypertension really driven by sympathetic overdrive?

Issues of patient selection - where the patients truly resistant to drug treatment?

Is there a placebo effect of the treatment? – no real control group

Why was ABPM not used to measure efficacy and why when used did the ABPM response seem much less than the office BP response?

Critique led to the next step:

SYMPLICITY HTN-3, the first prospective, multi-center, randomized, blinded, sham controlled study to evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant hypertension.

The trial included 535 patients enrolled by 88 participating US centers.
SYMPPLICITY HTN-3 is One Trial in a Larger Scientific Context

Other studies demonstrate efficacy
HTN-3 subgroup analysis
Real-world data demonstrates efficacy
Independent Panel recommendations

HTN-3 *did not* meet efficacy EP

HTN-2 demonstrated efficacy in RCT
HTN-1 demonstrated human safety/feasibility

Preclinical evidence supported RDN hypothesis
Renal nerves played a role in hypertension
Surgical sympathectomy and nephrectomy reduced BP
Elevated sympathetic tone contributed to hypertension

Iterate & Refine
Medication Adherence Continues to be a Problem in Hypertension

ORIGINAL ARTICLE
High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis

Maciej Tomaszewski,¹,² Christobelle White,¹,² Prashanth Patel,³ Nicholas Masca,¹,² Ravi Damani,¹ Joanne Hepworth,³ Nilesh J Samani,¹,² Pankaj Gupta,¹,³ Webster Madira,³ Adrian Stanley,¹,³ Bryan Williams⁴

• 25% of patients were totally or partially non-adherent to antihypertensive treatment (total non-adherence 10.1%, partial non-adherence 14.9%)
An early Surgical option **Sympathectomy**: Mortality Reduction but Significant Morbidity

![Graph showing survival rates and comparison between surgical and medical treatments.](image)

Groups are based on Smithwick classification of hypertension patients. Higher group numbers represent increasing amount of cardiovascular disease.

Smithwick et al. JAMA 1953;152(16):1501-1504
SYMPPLICITY HTN–3: Areas of Investigation

- patient demographics
- heterogeneity of US operator experience
- medication changes or adherence
- catheter design
- trial conduct
- placebo effect
- hawthorne effect
- regression to mean
2 weeks

Home BP & HTN med confirmation

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

Sham Procedure
- Renal angiogram; Eligible subjects randomized

Renal Denervation
- Home BP & HTN med confirmation

Primary endpoint
- Home BP & HTN med confirmation

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

Change in Mean 24–hour Ambulatory SBP for HTN3–Like Patients in Global SYMPLICITY Registry

All patients

HTN3-like patients*

<table>
<thead>
<tr>
<th>Change in Systolic Blood Pressure (mm Hg)</th>
<th>n=432</th>
<th>n=390</th>
<th>n=55</th>
<th>n=64</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-7.9 ± 17.5</td>
<td>-8.3 ± 17.8</td>
<td>-9.5 ± 14.7</td>
<td>-11.4 ± 17.9</td>
</tr>
</tbody>
</table>

P<0.0001 for all vs. Baseline
Error bars=1.96 SE

*Patients with baseline office SBP≥160 mm Hg and mean 24-hr SBP≥135 mm Hg and prescribed ≥3 antihypertensive medication classes

Mahfoud, ESC 2014
SYMPPLICITY HTN–3 Results: Primary Safety Endpoint Exceeded Expectations

**Safety Measures**

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation (n=364)</th>
<th>Sham Procedure (n=171)</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAE</td>
<td>1.4% (5/361)</td>
<td>0.6% (1/171)</td>
<td>0.8% (-0.9%, 2.5%)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Bhatt, ACC 2014
**SYMPLECTIVITY HTN–3 Results: 12 Month Safety Events Remain Low Across All Groups**

<table>
<thead>
<tr>
<th></th>
<th>Denervation n=364</th>
<th>Crossover* n=101</th>
<th>Non-Crossover n=70</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>To 6 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite Safety to 6M (%)</td>
<td>3.6 (13/358)</td>
<td>5.2 (5/96)</td>
<td>2.9 (2/70)</td>
</tr>
<tr>
<td>Death</td>
<td>0.6</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>New-onset end-stage renal disease</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Sig. embolic event resulting in end-organ damage</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vascular complication</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>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertensive crisis/emergency</td>
<td>2.5</td>
<td>3.1</td>
<td>1.4</td>
</tr>
<tr>
<td>New renal artery stenosis &gt;70%</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>To 12 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite Safety to 12M (%)</td>
<td>6.8 (24/355)</td>
<td>5.3 (5/95)</td>
<td>7.2 (5/69)</td>
</tr>
<tr>
<td>Death</td>
<td>1.8</td>
<td>n/a</td>
<td>3.6</td>
</tr>
<tr>
<td>New-onset end-stage renal disease</td>
<td>0.3</td>
<td>n/a</td>
<td>0.0</td>
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<td>0.0</td>
</tr>
<tr>
<td>Renal artery re-intervention</td>
<td>0.6</td>
<td>n/a</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertensive crisis/emergency</td>
<td>4.8</td>
<td>n/a</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*Safety from time of crossover procedure*
Three main areas were identified for Additional Investigation

Pre-specified and post-hoc analyses of SYMPLICITY HTN-3 have identified potentially confounding factors that include:

- **Drug Changes and Variable Patient Adherence**
  - Driving adherence to multiple anti-hypertensive medications and at maximally tolerated doses did not result in uniform drug use throughout the trial
  - Aldosterone antagonist use at baseline was a predictor of systolic blood pressure reduction; conversely, baseline vasodilator use was a negative predictor of blood pressure reduction

- **Study Population**
  - The population studied was different from other SYMPLICITY studies, which may have led to the large drop in the control arm
  - African American ethnicity was associated with substantial blood pressure reduction in sham control patients
Three main areas were identified for Additional Investigation continued

- **Procedural experience and variability**
  - SYMPLICITY HTN–3 included a greater number of trial sites and proceduralists compared to SYMPLICITY HTN–1 and HTN–2, which may have led to greater procedural variability.
  - Increasing reductions in systolic blood pressure were associated with increasing numbers of ablations and the delivery of ablations in 4-quadrants of the renal artery.
  - We continue to explore all aspects related to the procedure.
Medication Changes During SYMPLICITY HTN–3 Put Into Question Resistant Hypertension Concept

- ~40% (n = 211) of trial subjects required medication changes between baseline and primary efficacy endpoint assessment:
  - 69% of first medication changes were medically necessary
  - 121 patients had a med change due to an adverse event
  - 80 patients had a med change due to a drug side-effect
  - ~69% were changes in drugs at maximally-tolerated dose

HTN-3 showed how difficult it is to study this patient population and put into question this concept of resistant hypertension

Kandzari, EuroPCR 2014
SYMPPLICITY HTN–3 Showed Different Outcomes in African American Sham Population

Changes in Office Systolic Blood Pressure at 6 months (mm Hg)

- Non-African American
  - n=264
  - n=120
  - P=0.012

- African American
  - n=85
  - n=49
  - P=0.641

Baseline SBP, mm Hg
- Non-African American: 179.5
- African American: 180.6

Kandzari, EuroPCR 2014
Procedural Variability
Correlation with number of ablations
Correlation with 4-quadrant ablation pattern

Kandzari, EuroPCR 2014
SYMPPLICITY HTN–3: Impact of Number of Ablation Attempts on Change in Office Systolic Blood Pressure: Matched Cohort Analysis

Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients.

*P value change in SBP for RDN compared with sham

Data presented are mean (SD)

Kandzari, EuroPCR 2014
**SYMPLECTICITY HTN–3: Impact of Number of Ablation Attempts on Change in Ambulatory Blood Pressure: Matched Cohort Analysis**

<table>
<thead>
<tr>
<th>Change in Systolic BP (mmHg)</th>
<th>Denervation</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8</td>
<td>-6.1</td>
<td>N=149</td>
</tr>
<tr>
<td>≥9</td>
<td>-6.5</td>
<td>N=138</td>
</tr>
<tr>
<td>≥10</td>
<td>-6.9</td>
<td>N=119</td>
</tr>
<tr>
<td>≥11</td>
<td>-6.8</td>
<td>N=108</td>
</tr>
<tr>
<td>≥12</td>
<td>-10.5</td>
<td>N=66</td>
</tr>
<tr>
<td>≥13</td>
<td>-10.3</td>
<td>N=40</td>
</tr>
<tr>
<td>≥14</td>
<td>-12.2</td>
<td>N=24</td>
</tr>
<tr>
<td>≥15</td>
<td>-14.3</td>
<td>N=16</td>
</tr>
<tr>
<td>≥16</td>
<td>-21.2</td>
<td>N=8</td>
</tr>
</tbody>
</table>

*P value change in SBP for RDN compared with sham

Data presented are mean (SD)

Kandzari, EuroPCR 2014
SYMPPLICITY HTN–3: Systolic Blood Pressure Change at 6 Months According to Ablation Pattern

Baseline SBP Measurements (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Office</th>
<th>ABPM</th>
<th>Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 four-quadrant tx</td>
<td>179.6</td>
<td>158.7</td>
<td>168.5</td>
</tr>
<tr>
<td>1 Four-quadrant tx</td>
<td>178.8</td>
<td>161.2</td>
<td>171.3</td>
</tr>
<tr>
<td>2 Four-quadrant tx</td>
<td>186.9</td>
<td>159.9</td>
<td>170.4</td>
</tr>
</tbody>
</table>

Four quadrants = 1 superior, 1 inferior, and 2 posterior/anterior
SYMPLICITY HTN–3: Procedural Experience

<table>
<thead>
<tr>
<th></th>
<th>HTN-1</th>
<th>HTN-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of operators</td>
<td>20</td>
<td>112</td>
</tr>
<tr>
<td>No. of procedures per operator</td>
<td>6.0</td>
<td>3.3</td>
</tr>
<tr>
<td>No. of procedures per site</td>
<td>8.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

>50% of interventionalists performed ≤2 RDN procedures in SYMPLICITY HTN-3
Global SYMPLICITY Registry: Operator Experience

59% of interventionists performed >15 RDN procedures

Mahfoud, ESC 2014
SYMPLICITY HTN–3: Change in 24h Ambulatory Blood Pressure at 6 and 12 Months for Denervation Subjects

**Denervation 6 Months**
- Baseline SBP: 158 mm Hg
- Baseline DBP: 95 mm Hg
- Change in SBP: -6.4 mm Hg
- Change in DBP: -7.6 mm Hg
- n=247

**Denervation 12 Months**
- Baseline SBP: 163 mm Hg
- Baseline DBP: 94 mm Hg
- Change in SBP: -4.7 mm Hg
- Change in DBP: -4.9 mm Hg
- n=247

**Crossover 6 Months**
- Baseline SBP: 
- Baseline DBP: 
- Change in SBP: -9.2 mm Hg
- Change in DBP: 
- n=92

*Baseline = time of RDN procedure
Note: BP changes are vs. patient baseline, not RDN vs Control. Error Bars = 1.96SE

Bhatt, TCT 2014
SA Heart / SAHS Lecture Series – Hypertension

SYMPLICITY HTN–3: Change in Mean 24–hour Ambulatory Blood Pressure through 12 Months

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

Note: BP changes are vs. patient baseline, not RDN - Control

Bakris, ESC 2014

Subjects unblinded

Non-Crossover 6 Months

Non-Crossover 12 Months

Change in Blood Pressure (mm Hg)

Δ 6 to 12 months SBP = +4.9/+3.7 mm Hg

P=NS

Error bars=1.96 SE
SYMPPLICITY HTN–3: Change in 24–hour SBP in African American and Non–African American Subgroups

Baseline SBP (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>African American</th>
<th></th>
<th>Non-African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>160</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>6m</td>
<td>159</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td>12m</td>
<td>166</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>6m</td>
<td>156</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>12m</td>
<td>150</td>
<td>151</td>
<td></td>
</tr>
</tbody>
</table>

*Unblinded at 6 months

ΔBP = 14.8 mm Hg

Flack, TCT 2014
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered. The European Society of Hypertension believes that although in the Symplicity HTN-3 study use of an appropriate control group makes the results less open to confounders than those of previous studies, the conclusion that renal denervation is ineffective is not justified.

“There is, from these data, no singular factor that led to the lack of efficacy of renal denervation in the trial. But at the same time, these data take us many steps further in identifying the factors that led to the negative result.” – Dr. Kandzari

“We’re learning that this is much more complicated than we originally thought...this [technology] is too young and too promising to stop now.” – Dr. Mahfoud

Dr. George Bakris presented an ABPM analysis from SYMPLICITY HTN-3, which was concurrently published in JACC.

Global SYMPLICITY Substudy Teases out Reasons for Non-response in Real-World Patients
Global Symplicity Study

This study aimed to assess the safety and effectiveness of renal denervation using the Symplicity system in realworld patients with uncontrolled hypertension.

The Global SYMPLICITY Registry is a prospective, open-label, multicentre registry. Office and 24-hour ambulatory blood pressures (BPs) were measured.

Change from baseline to 6 months was analysed for all patients and for subgroups based on baseline office systolic BP, diabetic status, and renal function;

a cohort with severe hypertension (office systolic pressure, ≥160 mm Hg; 24-hour systolic pressure, ≥135 mm Hg; and ≥3 antihypertensive medication classes) was also included.

(Böhm, M et al Hypertension. 2015;65:00-00. DOI:10.1161/HYPERTENSIONAHA.114.05010.)
Global Symplicity Study

The analysis included protocol-defined safety events. Six-month outcomes for 998 patients, including 323 in the severe hypertension cohort, are reported.

Mean baseline office systolic BP was 163.5±24.0 mm Hg for all patients and 179.3±16.5 mm Hg for the severe cohort; the corresponding baseline 24-hour mean systolic BPs were 151.5±17.0 and 159.0±15.6 mm Hg.

At 6 months, the changes in office and 24-hour systolic BPs were −11.6±25.3 and −6.6±18.0 mm Hg for all patients (P<0.001 for both) and −20.3±22.8 and −8.9±16.9 mm Hg for those with severe hypertension (P<0.001 for both).

Renal denervation was associated with low rates of adverse events. After the procedure through 6 months, there was 1 new renal artery stenosis >70% and 5 cases of hospitalization for a hypertensive emergency. In clinical practice, renal denervation resulted in significant reductions in office and 24-hour BPs with a favorable safety profile.

Greater BP-lowering effects occurred in patients with higher baseline pressures.

(Böhm, M et al Hypertension. 2015;65:00-00. DOI:10.1161/HYPERTENSIONAHA.114.05010.)
Table 2. Office and Ambulatory Blood Pressure at Baseline and 6 Months After Renal Denervation

<table>
<thead>
<tr>
<th>BP, mm Hg</th>
<th>All Patients</th>
<th>Severe HTN Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP</td>
<td>n=998</td>
<td>n=323</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>163.5±24.0</td>
<td>179.3±16.5</td>
</tr>
<tr>
<td>DBP</td>
<td>89.0±16.6</td>
<td>94.7±15.9</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>151.9±21.9</td>
<td>159.0±21.5</td>
</tr>
<tr>
<td>DBP</td>
<td>84.7±15.1</td>
<td>87.4±15.4</td>
</tr>
<tr>
<td>24-h ambulatory BP</td>
<td>n=506</td>
<td>n=221</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>151.5±17.0</td>
<td>159.0±15.6</td>
</tr>
<tr>
<td>DBP</td>
<td>85.3±13.0</td>
<td>88.9±13.1</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>144.6±17.4</td>
<td>150.0±18.0</td>
</tr>
<tr>
<td>DBP</td>
<td>81.4±12.9</td>
<td>84.0±13.0</td>
</tr>
</tbody>
</table>

Values are mean±SD. BP indicates blood pressure; DBP, diastolic BP; HTN, hypertension; and SBP, systolic BP.

(Böhm, M et al *Hypertension*. 2015;65:00-00. DOI:10.1161/HYPERTENSIONAHA.114.05010.)
Perspectives

RDN has provided BP-reducing effects in multiple clinical studies. This is the first large scale study to demonstrate that in ≈1000 patients from around the world the procedure is safe and significantly reduces office and ambulatory BP in a real life setting.

RDN provides additional BP reduction on top of intensive pharmacological therapies in patients with uncontrolled hypertension with a great level of short-term safety.

The BP-lowering effect directly related to the height of BP at baseline.

(Böhm, M et al Hypertension. 2015;65:00-00. DOI:10.1161/HYPERTENSIONAHA.114.05010.)
The Global SYMPLICITY registry provides further evidence that radiofrequency RDN safely reduces BP in patients with uncontrolled hypertension requiring complex multidrug antihypertensive therapy.

Potential roles for RDN are not yet clearly defined but the procedure might provide an add-on technique to improve BP control in a broad population of hypertensive patients.

Further studies to better define appropriate patient populations and clarify the optimal procedural technology and technique for RDN are warranted.

(Böhm, M et al Hypertension. 2015;65:00-00. DOI:10.1161/HYPERTENSIONAHA.114.05010.)