Review Team

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FDA Presentation

Section 1: Introduction
Section 2: Hypertension Background
Section 3: Overview of Device Anatomical Targets
Section 4: Evolution of Clinical Evidence
Section 5: Clinical Study Design Elements
Section 6: Safety Endpoints
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Section 8: Pre/Post Market Balance
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Panel Purpose

• FDA is requesting panel recommendations on:
  – Indications for use
  – Critical clinical study design elements
  – Safety endpoints
  – Effectiveness endpoints
  – Device and population based benefit and risk balance
  – Pre/Post market balance
Overview of Discussion

• We will discuss:
  – Current treatment of hypertension
  – Anatomical targets of device based therapies
  – Clinical evidence supporting device therapies
  – Clinical study design elements
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## Current Guidelines: Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Office Blood Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2003 JNC 7 / 2014 JNC 8</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159 OR 90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥ 160 OR ≥ 100</td>
</tr>
<tr>
<td><strong>2017 ACC/AHA</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130-139 OR 80-89</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥ 140 OR ≥ 90</td>
</tr>
<tr>
<td><strong>2018 AAFP/ACP</strong></td>
<td></td>
</tr>
<tr>
<td>JNC 8 &amp; Initiate treatment ≥ 60 y.o. if SBP ≥150 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

BP Link to CV Outcomes

# Hypertension Treatment Guidelines

<table>
<thead>
<tr>
<th>Elevated Blood Pressure 120-129 / &lt;80 mmHg</th>
<th>Lifestyle Changes (e.g. weight loss, healthy diet, physical activity) &amp; Periodic Reassessment (i.e. 3-6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 Hypertension 130-139/80-89 mmHg</td>
<td>Lifestyle Changes &amp; Periodic Reassessment</td>
</tr>
<tr>
<td>Stage 2 Hypertension ≥ 140/90 mmHg</td>
<td>10 yr Cardiovascular risk ≥ 10% OR Cardiovascular disease, diabetes mellitus, chronic kidney disease</td>
</tr>
</tbody>
</table>

Antihypertensive Medication Therapy

Antihypertensive Medication Therapy

2 Agents Different Classes

Pharmacotherapy Treatment

• Relative risk of total major cardiovascular events are reduced by the antihypertensive medication regimens, with no significant differences in events between drug classes as determined by large clinical trials (e.g. ALLHAT)

• Pharmaceuticals are indicated for treatment of hypertension as sole agents and/or in combination with other antihypertensive drugs for more severe forms of hypertension

• Role for devices with or without drug therapy remains unclear

J Hypertens. 1998;16(2):127-37
Jama. 2002;288(23):2981-97
Pharmacotherapy Treatment (cont.)

• Treatment strategy depends on a variety of factors (e.g. age, comorbidities, drug interactions, etc.)

• Poor medication adherence
  – Failure to fill (28%)
  – Omission of Dose (10%)
  – Discontinuation of treatment w/in first year (40%)

• Medication adherence may impact evaluation of device effectiveness

Vrijens B, et. al. Front Pharmacol. 2017;8:100
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Devices Target Mechanisms of BP Regulation

Section 4: Evolution of Clinical Evidence
First Sham Controlled RCT
Renal Denervation

• Early RCT studies were positive, but the results had some limitations

• HTN-3 Study Design Features:
  – Randomized, sham controlled
  – Subjects with drug-resistant hypertension
  – Office SBP & ABPM collected
  – Primary Effectiveness Endpoint: Δ Office SBP at 6 months (5 mmHg superiority margin)
### Symplicity HTN-3 Results

**Office Systolic Blood Pressure (mm Hg)**

- **Baseline**
  - Denervation: (N=364)
  - Sham: (N=353)
- **6 Months**
  - Denervation: (N=171)
  - Sham: (N=171)

**Difference in change**

- Office Systolic Blood Pressure:
  - Baseline: $-14.13\pm23.93$ mm Hg ($P<0.001$)
  - 6 Months: $-11.74\pm25.94$ mm Hg ($P<0.001$)
  - Change: $-2.39$ mm Hg (95% CI, $-6.89$ to $2.12$) ($P=0.26$)

**Ambulatory 24-Hr Average Systolic Blood Pressure (mm Hg)**

- **Baseline**
  - Denervation: (N=360)
  - Sham: (N=329)
- **6 Months**
  - Denervation: (N=167)
  - Sham: (N=162)

**Difference in change**

- Ambulatory 24-Hr Average Systolic Blood Pressure:
  - Baseline: $-6.75\pm15.11$ mm Hg ($P<0.001$)
  - 6 Months: $-4.79\pm17.25$ mm Hg ($P<0.001$)
  - Change: $-1.96$ mm Hg (95% CI, $-4.97$ to $1.06$) ($P=0.98$)

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Potential Confounders

– Medication adherence
– Procedural technique variations for complete denervation
– Ethnic subgroups
– Regression to the mean
RDN: Shift to a Distal Target


2014 American Society of Hypertension (ASH) Recommendations

• Phase II Clinical Trial (Medication “OFF”)
  – Obtain clear proof of principle
  – Demonstrate effectiveness in medication OFF population

2014 ASH Recommendations (cont.)

• Phase III Clinical Trial (Medication “ON”)
  – Demonstrate device effectiveness in presence of medications
  – Allows evaluation in real-world population

Run-in Period (6-8 weeks)

## Comparison of Current Studies

### Commonalities
- Randomization
- Sham control
- Double blinding
- Measurement of Office and Ambulatory BP

### Differences
- Severity of HTN
- Medication presence / absence
- Adherence evaluation method
- Endpoints
  - BP measurement type
  - Timing

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Categorizing the Patient Population

• The hypertensive population is complex, definitions for “hypertension” are continuously revised

• Unclear which patients may benefit from device based therapies
  – Severe Hypertension
  – Uncontrolled Resistant Hypertension
  – Controlled by Medications
  – Medication Naive
Minimization of Confounders

Placebo Effect → Sham-controlled

Medication Use & Compliance → Medication Washout & Adherence Testing

BP Variability & Regression to the Mean → Run-in Period & Multiple BP Measurements
Considerations for Study Designs

Medication OFF

Value:
- Isolate device effect from medication confounders

Potential Confounding Factors:
- Safety concerns limit severity of hypertension studied
- Limited study of durability of device effect

Medication ON

Value:
- Evaluate device function with real world medication use

Potential Confounding Factors:
- Medication adherence
- Discerning device and medication effect
Additional Study Features

• Pre-specified Interim Analysis
  – May stop for futility, conclude early success, and/or conduct sample size re-estimation
  – Sufficient sample size needs to be ensured for safety evaluation when study is stopped early for effectiveness

• Patient Crossover
  – May help facilitate patient enrollment
  – Equipoise for study should be maintained
  – May limit dataset for long term comparisons of safety and effectiveness
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Analysis of Adverse Events

• Safety profile of a device is assessed by adverse events (AE)

• AE are impacted by:
  – Device design
  – Means required to evaluate subject suitability
  – Techniques used to achieve therapeutic benefit
  – Anatomic location of the treatment
  – Whether an implant is left behind
Safety Endpoints

- **Procedural Safety**: Captures serious procedure or system-related adverse events occurring within 30 days of treatment, expressed as the event free rate.
- **Treatment Safety**: Captures adverse events related to therapy like drug reactions, hypertensive crisis and any therapy specific AE.
- **Device Safety**: the event-free rate for all major hypertension-related and serious device-related adverse events occurring beyond 30 days post-treatment.
Methods of Safety Analysis

- **RCT:** Compare AE severity and rates between the control and experimental groups
- **Single arm study:** Performance goals (PG) need to be derived on safety data from comparable populations undergoing similar therapies.
- Establishing a meaningful PG and safety margin can be challenging when a device is truly novel
Example: Potential Risks of Carotid Devices

Potential Complications

- Cerebral angiography
- Distal emboli
- Vascular changes from altered geometry & flow
- Need to assess acute and chronic local and downstream effects: carotid duplex scan & brain imaging
- Not easily removable

Example: Potential Risks of Peripheral AV Fistulas

Potential Complications

- Combined arterial and venous access
- Predicatable venous stenosis known to develop in AVF
- Adverse hemodynamic effects of the AVF on the cardiopulmonary system
- Device not easily removable

FIGURE: https://www.medgadget.com/2015/01/coupler-device-shows-promise-hypertension-control-video.html
Example: Risks of Renal Denervation

Potential Complications

- Vascular access site complications
- Renal artery injury:
  - Acute dissection
  - Late stenosis
- Impact on longer term glomerular filtration rate (GFR)

Figure 1. Functional anatomy of renal sympathetic innervation.

# Catheter based RD Safety

<table>
<thead>
<tr>
<th>STUDY</th>
<th>HTN-1</th>
<th>HTN-2</th>
<th>HTN-3</th>
<th>Enlig-HTN</th>
<th>Reduce-HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Number</td>
<td>153</td>
<td>52</td>
<td>364</td>
<td>46</td>
<td>146</td>
</tr>
<tr>
<td>Final Safety Subject Number</td>
<td>88</td>
<td>70</td>
<td>364</td>
<td>46</td>
<td>146</td>
</tr>
<tr>
<td>Device</td>
<td>Symplicity</td>
<td>Symplicity</td>
<td>Symplicity</td>
<td>Enlighten</td>
<td>Vessix</td>
</tr>
<tr>
<td>Months of F/U</td>
<td>36</td>
<td>36</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Imaging Modality</td>
<td>US or CT or MR</td>
<td>US or CT or MR</td>
<td>US or CT or MR</td>
<td>US</td>
<td>US</td>
</tr>
<tr>
<td>Access Site Complications</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Acute Renal Artery Issues</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Last RAS &gt; 70% or stent</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Worse renal function</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

# Renal Artery Imaging

<table>
<thead>
<tr>
<th>METHOD</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| Duplex Scan | • Cost effective  
  • No radiation                                                            | • Operator dependent  
  • Distal visualization challenging  
  • Poor grading of degree of stenosis                                        |
| CT Angio  | • High accuracy  
  • Multiplanar resolution, even of branch vessels                          | • Higher cost  
  • Exposure to radiation & iodinated contrast                                 |
| MR Angio  | • No radiation  
  • Accurate in detecting proximal lesions                                      | • Gadolinium exposure  
  • Less accurate for branch vessels  
  • Higher cost                                                                   |
Safety Evaluation of Devices

• To properly assess safety, trials of devices used to treat hypertension require:
  – Meaningful safety endpoints,
  – Appropriate imaging to be able to accurately capture all relevant events, and
  – Adequate study duration to assess the potential for device related adverse events

• Primary safety hypothesis remains important for device safety evaluation
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BP as a Surrogate Endpoint

- Framingham Heart Study: Elevated SBP is associated with increased risk of CV events, with greater risk with advancing age
- Medications: Relative risk of total major CV events reduced with treatment; no significant difference by drug class
- Surrogate endpoint of BP is appropriate if the reduction in BP is associated with morbidity and/or mortality outcomes
- Unclear whether BP lowering by devices will lead to same CV benefits as established by current medications

## Comparison of Methods of BP Measurement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Office BP</th>
<th>Home Daytime BP</th>
<th>ABPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicts CV outcomes</td>
<td>Poor-Moderate</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Detects nighttime dipping</td>
<td>Poor</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Captures 24 h activity</td>
<td>Poor</td>
<td>Depends on number of readings</td>
<td>High</td>
</tr>
<tr>
<td>Allows risk stratification</td>
<td>Poor</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Easy to perform</td>
<td>Yes</td>
<td>Depends on number of readings</td>
<td>No</td>
</tr>
<tr>
<td>Identifies WC or masked HTN</td>
<td>No</td>
<td>Maybe</td>
<td>Yes</td>
</tr>
<tr>
<td>Observer bias</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Defining Clinically-Meaningful BP Reduction

The relationship between BP and risk for future CV events is well established, but the BP levels likely vary according to methodology of measurement:

- **Lassere**: Meta-analysis; BP measurement modality not defined or variable: Showed that the threshold for stroke was ≥7.1 mmHg SBP/2.4 DBP
- **Verdecchia**: Meta-analysis; BP measurement modality not defined or variable: Showed that the threshold for CV events was ≥4.6 mmHg SBP/2.2 DBP
- **Stevens**: Meta-analysis; BP measurement modality variable: Showed an increased risk for CV events with elevated BP

Stevens, et al. BMJ. 2016;354:i4098
## Efficacy of Anti-Hypertensive Medications for BP Reduction

<table>
<thead>
<tr>
<th>Medication</th>
<th>No of Trials</th>
<th>No. of Patients</th>
<th>SBP* Reduction</th>
<th>DBP* Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>36</td>
<td>1898</td>
<td>12.5±5.3</td>
<td>9.5±3.4</td>
</tr>
<tr>
<td>Alpha Blocker</td>
<td>15</td>
<td>1849</td>
<td>15.5±4.8</td>
<td>11.7±1.3</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>18</td>
<td>908</td>
<td>14.8±4.9</td>
<td>12.2±2.2</td>
</tr>
<tr>
<td>Calcium-channel Blocker</td>
<td>34</td>
<td>3727</td>
<td>15.3±5.0</td>
<td>10.5±2.8</td>
</tr>
<tr>
<td>Thiazides</td>
<td>18</td>
<td>1657</td>
<td>15.3±5.4</td>
<td>9.8±3.6</td>
</tr>
<tr>
<td>Loop Diuretics</td>
<td>17</td>
<td>366</td>
<td>15.8±7.8</td>
<td>8.2±4.7</td>
</tr>
<tr>
<td>Average</td>
<td>137</td>
<td>10405</td>
<td>14.8±1.1</td>
<td>10.5±1.0</td>
</tr>
</tbody>
</table>

*Sitting or supine BP

Measuring Durability of Effect

- Recent feasibility studies have established short-term effectiveness around 2-3 months for RDN.
- Short-term results may not predict long-term success.
- Relationship of BP reduction to reduced CV events is based on a sustained effect of the pharmacological intervention.
- Concomitant medication use during the trial may confound treatment effect.
Methods for Statistical Comparison

• RCT: Comparison of primary effectiveness between control and treatment arms.

• Demonstration of an outcome driven difference in mean BP reduction:

  **Superiority**  \[ \text{Device} - \text{Control} > 0 \]

  **Super Superiority**  \[ \text{Device} - \text{Control} > \text{Clinically Meaningful Margin} \]

• Non-inferiority may provide value after approval of device based therapies.
Additional Endpoints to Consider

• Patients preference information (PPI)
  – Weigh risk tolerance and benefits
  – Quality of Life (QoL) measurements

• Patient reported outcome measures may be considered for certain secondary safety endpoints

• Assessment of changes in medication burden
  – Type, dosage, frequency
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Pre / Post Market Balance

**Premarket**
Assurance of safety & effectiveness

**Postmarket**
Opportunities to gather additional clinical data and real-world evidence
Pre / Post Market Balance (cont.)

• Patient Population
  – Specific versus Generalizable
  – Identification of responders

• Identification of longer term safety concerns

• Evaluating the durability of the treatment effect with real world medication use
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Conclusions

• Device based therapies may be an important option for different hypertensive populations
• Establish reasonable benefit-risk profile and population
• Future clinical studies should answer key questions for safety and effectiveness
Recap of Panel Purpose

• FDA is requesting panel recommendations on:
  – Indications for use
  – Critical clinical study design elements
  – Safety endpoints
  – Effectiveness endpoints
  – Device and population based benefit and risk balance
  – Pre/Post market balance
Thank you