ReCor Medical Presentations

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Current State of Hypertension and Renal Denervation

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Paradise Renal Denervation System – RADIANCE Clinical Trial Program

Michael Bloch, MD, FASH FAHA, FACP, FNLA, FSVM
Clinician and Patient Perspective on Potential of Renal Denervation
Current State of Hypertension and Renal Denervation

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Michael A. Weber, MD, Disclosures

- Research/Clinical Trial Steering Committees/Consulting: Medtronic, Boston Scientific, ReCor Medical, Ablative Solutions, Abbvie, J&J, Astellas

- Note: The products discussed in this talk are all investigational in the United States and are not FDA approved.
Highlights of the RDN Program

• New hypertension guidelines

• Evolution of device trial design to a drug model

• Sham controlled trials: RDN “alone” and RDN + drugs

• Clinical practice experience with RDN

• Patient adherence to drug treatment: issues revealed in RDN trials

• Patient preference: key in evaluating new therapy

• Unfinished business

• Where we are heading
Dominating Presence of SPRINT

A landmark NHLBI-sponsored clinical trial completed before the ACC/AHA and ESC/ESH Guidelines were produced.
Examine effect of more intensive high blood pressure treatment vs. standard treatment in high risk patients

Randomized Controlled Trial
Target Systolic BP

Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg

SPRINT design details available at:
- ClinicalTrials.gov (NCT01206062)
Systolic BP During Follow-up

**Figure 1: Mean Systolic BP (95% CI)**

- **Year 1**
  - **Mean SBP**: 136.2 mm Hg
  - **Mean SBP**: 121.4 mm Hg

- **Average SBP (During Follow-up)**
  - Standard: 134.6 mm Hg
  - Intensive: 121.5 mm Hg

- **Average number of antihypertensive medications**
- **Number of participants**
Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to prevent a primary outcome = 61
Cardiovascular (CV) Outcomes by Treatment Group in SPRINT in Patients Aged >75 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Treatment (n=1317)</th>
<th>Standard Treatment (n=1319)</th>
<th>H.R. (95% CI)</th>
<th>← Favors Intensive Treatment</th>
<th>Favors → Standard Treatment</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CV Outcome*</td>
<td>102</td>
<td>148</td>
<td>0.66 (0.51, 0.85)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>37</td>
<td>53</td>
<td>0.69 (0.45, 1.05)</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>ASC not resulting in MI</td>
<td>17</td>
<td>17</td>
<td>1.03 (0.52, 2.04)</td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>Stroke</td>
<td>27</td>
<td>34</td>
<td>0.72 (0.43, 1.21)</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Heart failure</td>
<td>35</td>
<td>56</td>
<td>0.62 (0.40, 0.95)</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>CV disease mortality</td>
<td>18</td>
<td>29</td>
<td>0.60 (0.33, 1.09)</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>73</td>
<td>107</td>
<td>0.67 (0.49, 0.91)</td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
</tbody>
</table>

* Primary outcome includes nonfatal MI, acute coronary syndrome not resulting in an MI, nonfatal stroke, nonfatal acute decompensated heart failure, and death from CV causes.

SPRINT, Systolic Blood Pressure Intervention Trial; CI, confidence interval

Highlights of Guidelines

• U.S. (ACC/AHA) treatment target for all patients: < 130/80 mmHg

• European target: < 140/90 mmHg, then carefully “approach” 130/80 mmHg

• U.S. and European guidelines used virtually identical analyses of RCT evidence on CV outcomes -- independent of SPRINT – to establish recommendations

• Target of 140/90 mmHg used and planned in device trials (mean patient age <60) is highly appropriate for development of new therapies and consistent with all guidelines
On to RDN . . .

• Past studies – lessons learned
• Improved RDN Study Designs
• Recent RDN study results – what do they mean?
• Who should be treated, in what conditions
Change in Office BP in Treatment Resistant Hypertension: Symplicity 2 (controlled, open-label trial)

**BP change (mmHg)**

- **SBP mmHg**
  - 1 mo (n=143): -19
  - 3 mo (n=148): -21
  - 6 mo (n=144): -22
  - 12 mo (n=132): -27
  - 24 mo (n=105): -29
  - 30 mo (n=44): -34
  - 36 mo (n=34)*: -31

- **DBP mmHg**
  - 1 mo (n=143): -9
  - 3 mo (n=148): -10
  - 6 mo (n=144): -10
  - 12 mo (n=132): -14
  - 24 mo (n=105): -14
  - 30 mo (n=44): -17
  - 36 mo (n=34)*: -16

*Number of patients represents data available at time of data-lock

Reported as mean with 95% confidence intervals

P<0.01 for ∆ from BL for all time points

Schlaich M, TCT 2012
Symplicity HTN-3: RDN vs. Sham in Treatment Resistant HTN

\[ \Delta = -2.39 \text{ (95\% CI, -6.89 to 2.12) \ P=0.26}^* \]

\[ \Delta = -14.1 \pm 23.9 \ \text{P<0.001} \]

\[ \Delta = -11.7 \pm 25.9 \ \text{P<0.001} \]

*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

Bhatt et al. NEJM. 2014
Renal Denervation for the Treatment of Hypertension: Making a New Start, Getting It Right

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An RDN study strategy based on the widely followed protocol for antihypertensive drug development:

– Demonstrate safety and efficacy of RDN as a single therapy
– Demonstrate safety and added efficacy of RDN when combined with BP-lowering drugs

Why is it Important to Study RDN in the Absence of BP Medications?

1. This is the most precise way to measure the effects of RDN on BP

2. RDN will often be added to BP drug therapy. Since patient adherence to drugs is highly variable it is important to establish that in the absence of medications RDN is safe and able to sustain an antihypertensive effect
Focused Protocols for Renal Denervation in Hypertension

Patient Selection

No BP meds at baseline (any previous meds D/C’d)

Randomization
(Blinded to patients and observers)

Primary BP Efficacy Endpoint

ABPM

Sham Procedure

Renal Denervation

Systematic addition of drugs needed to achieve BP control

Long-term BP Efficacy Endpoint

ABPM

4-Week “Wash-Out” Period

8-Week “Off-Meds” Period†

4-Month Continuing Treatment Period

- Clinic systolic BP 140-180 mmHg and ABPM systolic BP 135-170 mmHg
- †Can be extended with careful patient oversight
Blood Pressure Change from Baseline to 3 Months
(24-Hr ABPM)

**Systolic**

- **Baseline BP (mmHg):**
  - 154 (n=35)
  - 152 (n=36)

- **Δ:** -5.5 mmHg
  - (-9.1, -2.0)
  - *P*=0.003

**Diastolic**

- **Baseline BP (mmHg):**
  - 100 (n=35)
  - 99 (n=36)

- **Δ:** -4.4 mmHg
  - (-7.2, -1.6)
  - *P*=0.002

- **Δ:** -4.8 mmHg
  - (-7.0, -2.6)
  - *P*=0.04

- **Δ:** -0.4 mmHg
  - (-2.2, 1.4)
  - *P*=0.65

- **Δ:** -0.5 mmHg
  - (-3.9, 2.9)
  - *P*=0.76

RADIANCE-HTN SOLO - Primary Efficacy Endpoint

Change in Daytime Ambulatory Systolic BP at 2 Months, ITT

<table>
<thead>
<tr>
<th>Renal Denervation (N=74)</th>
<th>Sham Procedure (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-8.5 mm Hg</td>
<td>-2.2 mm Hg</td>
</tr>
</tbody>
</table>

Between Group Difference Adjusted for Baseline BP

-6.3 mm Hg

(95% CI, -9.4 to -3.1)

P<0.001

Azizi et al. Lancet 2018; 391:2335
Off-Meds Results in Sham-Controlled RDN Trials of Hypertensive Patients

- Two randomized controlled trials (Medtronic & ReCor) utilizing radiofrequency or ultrasound energy have demonstrated statistically significant BP reductions vs. sham control in hypertensive patients not taking BP medications

- The reductions in office BP in these trials would be predicted to reduce CV events by 20% in hypertensive patients (Ettehad et al. Lancet 2016; 387:957-967)
Focused Protocols for Renal Denervation: Adding Denervation to Drug Therapy

Patient Selection

Strictly-defined 1 or 2 or 3+ drug regimen at baseline

Randomization (Blinded to patients and observers)

ABPM

Renal Denervation

Sham Procedure

Patients with inclusion BP* confirmed by clinic and ABPM measurements

4-Week Medication Stabilization Period

8-Week Stable Medication Period

Primary BP Efficacy Endpoint

ABPM

Systematic addition of drugs needed to achieve BP control

4-Month Continuing Treatment Period

Long-term BP Efficacy Endpoint

ABPM

* Clinic systolic BP 140-180 mmHg and ABPM systolic BP 135-170 mmHg

DENER-HTN: The First Successful *Controlled* Trial of Renal Denervation in Treatment Resistant Hypertension

**Primary endpoint**

Daytime ABPM: 
- \( \Delta: -5.9 \text{ mm Hg} \) (95% CI: -11.3 to -0.5)
- \( p = 0.0329 \)

Nighttime ABPM: 
- \( \Delta: -6.3 \text{ mm Hg} \) (95% CI: -12.0 to -0.6)
- \( p = 0.0296 \)

1416 referred resistant patients needed to yield 106 eligible for the trial (1:13)

DENER HTN: Compliance with Drug Therapy

Azizi et al. Circulation 2016; 134:847-857
**24-Hr ABPM Change from Baseline to 6 Months**

**Systolic**
- Baseline BP (mmHg): 152 (n=36)
- Change: -9.0 (-12.7, -5.3) 
P<0.001

**Diastolic**
- Baseline BP (mmHg): 97 (n=36)
- Change: -1.9 (-4.7, 0.9) 
P=0.17

RDN vs Sham:
- Δ -7.4 mmHg 
  (-12.5, -2.3) 
P=0.005
- Δ -4.1 mmHg 
  (-7.8, -0.4) 
P=0.03

Drug testing of urine and serum by tandem HPLC and mass spectroscopy. Medication adherence defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected.

Major On-Medication RDN Trials Underway or Imminent

- **RADIANCE-HTN TRIO**, actively recruiting
  - Sham-controlled study of ReCor Paradise Ultrasound System in patients with uncontrolled hypertension despite receiving 3+ drugs in optimized 1-pill combination

- Additional “On-Meds” ultrasound studies (ReCor) now in detailed planning (in addition to approved pivotal trial)

- Expansion of Medtronic On-Meds protocol has been approved & now getting under way

- The Spyral, RADIANCE-HTN SOLO, and RADIANCE II pivotal trials will study blinded effects of addition of meds to RDN following initial short periods of 3 months (Spyral) or 8 weeks (RADIANCE II) treatment with RDN alone

- On meds trial of Ablative Solutions’ Peregrine catheter (alcohol neurolysis) soon to start (FDA CDER Cardio-Renal)
Medtronic Global Symplicity Registry

Results in almost 3000 hypertensive patients demonstrate highly meaningful reductions in BP measured by office and ABPM methods
3 MAJOR SOURCES OF EVIDENCE

1. Low patient adherence to drugs, despite education, outreach, family support and rigorous monitoring appears strongly indicative of many patients seeking alternatives to drugs.

2. Enormous response (>1,000,000) to social media RDN clinical trial recruitment message from ReCor that implied a possible alternative to drugs. Medtronic reports similar experience.

3. Rigorous patient survey by professional medical survey company (RTI, contracted by Medtronic) – protocol to undergo FDA review – will measure patient responses & choices when they are accurately informed about risks of hypertension & the risks and benefits of drug vs. interventional therapy.
Where is RDN At This Moment?

• Safety
  – In trials so far, no major renal artery effects (under continuing long term scrutiny) or procedural effects, no evidence for adverse kidney or CV outcomes

• BP-lowering Efficacy in RCTs
  – Significant effect of RDN as single therapy
  – Additional BP effect when RDN added to drugs
  – Additional BP effect when drugs added to RDN

• Clinical Experience
  – Meaningful and sustained (for over 3 years) BP reductions in almost 3000 patients in Global Symplicity Registry

• Unanswered Questions – Trial-Excluded Patients and Durability
  – Isolated systolic HTN (re-analysis of HTN 3 and GSR, is RDN effective in ISH?)
  – Type 1 DM
  – Variant renal artery anatomy
  – Long term data: durability of efficacy & safety --- U.S. post-marketing registries
Renal Denervation and Hypertension: Indication and Use

[This procedure] is indicated in patients with hypertension to reduce blood pressure when used alone or combined with drug therapy.

[This procedure] can be considered for treating hypertension in:
- Patients with uncontrolled hypertension despite being prescribed BP drugs
- Patients who are poorly adherent to drugs
- Patients who are physically or emotionally intolerant to drugs
- Patients who express a strong preference for the procedure

Whatever the reason, patients with uncontrolled hypertension are at high risk of CV and stroke events.

- No anticipated exclusions on basis of age, race, gender or other demographic features