Baroreflex Activation Therapy: Integrated Autonomic Neuromodulation for Heart Failure and Hypertension

Robert S. Kieval, VMD, PhD
Founder & Chief Technology Officer, CVRx, Inc.
Financial Disclosure

I, Robert Kieval, am an employee of CVRx, Inc.
Autonomic Dysregulation in Heart Failure

Progressive Autonomic Imbalance

Adapted from Robinson et al, 1966
The Baroreflex Provides Integrated Autonomic Neuromodulation

Adapted from Floras, J Am Coll Cardiol 2009

Heitz and Brody, 1973

Vagus Nerve

Parasympathetic

Sympathetic

Adverse Cardiac Effects

Heart Rate

Renal Sympathetic Nerves

Na\(^+\) Reabsorption

Renin

Renal Vascular Resistance

Stiffness and Peripheral Vascular Resistance

Arterial Baroreceptors

CNS

Baroreceptor Afferents

Efferents
A Unique Therapeutic Target for Heart Failure and Hypertension

Programmable Baroreceptor Activation

Brain

Autonomic Nervous System
- Reduced Sympathetic Activity
- Enhanced Parasympathetic Activity

Heart
- Heart rate
- Irritability

Vessels
- Vasodilation
- Stiffness
- Venous capacitance

Kidneys
- Diuresis
- Natriuresis
- RAAS activity

myocardial work and oxygen consumption
neurohormonal activation
arrhythmogenesis
excessive blood pressure
The Barostim *neo* Technology Platform

- **2 mm Electrode**
- **Wireless Programmer**
- **Baroreflex Activation Lead**
- **Implantable Pulse Generator**

**Total Patients Treated with BAT**
### Effects of Baroreflex Activation

Dose-related and reversible

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 Volt</th>
<th>2 Volts</th>
<th>3 Volts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>71</td>
<td>56</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>210 / 96</td>
<td>168 / 73</td>
<td>156 / 72</td>
<td>144 / 66</td>
</tr>
</tbody>
</table>

63 yo female

The Baroreflex remains intact and responsive during therapy

\[ 	ext{CSN} \rightarrow \text{stimulation} \]

Muscle work

Respiration

Forearm Muscle Symp. Nerve Activity

\[ \text{BP} \]

* Isometric hand exercise

Delius et al, 1973
Cardiac and Peripheral Vascular Effects

Heusser et al, 2010

Georgakopoulos et al, 2011

Wustmann et al, 2009

Hasenfuss et al, 2011
<table>
<thead>
<tr>
<th>Stage</th>
<th>Heart Failure: CE-Approved</th>
<th>Hypertension: CE-Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Rationale</td>
<td>Georgakopoulos et al, J Cardiac Fail 2012</td>
<td>Ram VS, <em>J Clin Hypertension</em> 2010</td>
</tr>
<tr>
<td></td>
<td>Sabbah et al, Circ Heart Failure 2011</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bakris et al, <em>JASH</em> 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hoppe et al, <em>JASH</em> 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>de Leeuw et al, <em>Hypertension</em> 2014</td>
</tr>
<tr>
<td>US Phase III Pivotal</td>
<td>− Clinical trial fully FDA-approved</td>
<td>− Clinical trial fully FDA-approved</td>
</tr>
<tr>
<td></td>
<td>− Randomized, controlled clinical trial; n = 480</td>
<td>− RCT; n = 240</td>
</tr>
<tr>
<td></td>
<td>− Composite of CV death and HF hospitalization</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Results in Resistant Hypertension

Safety of the Barostim neo

Sham-controlled results of BAT at 6 months

$\text{€ 7.800 per QALY gained}$

Bakris et al, 2014

Borisenko et al, 2013

Hoppe et al, 2012
Heart Failure: US & European Randomized, Controlled, Clinical Trial

- $n = 146$
- NYHA III
- LVEF ≤35%

**6-month results in all patients**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Difference</th>
<th>p value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA (% improved)</td>
<td>31</td>
<td>&lt; 0.01</td>
<td>Barostim</td>
</tr>
<tr>
<td>MLWHF QoL Score (points)</td>
<td>20</td>
<td>&lt;0.001</td>
<td>Barostim</td>
</tr>
<tr>
<td>6-MHW Distance (m)</td>
<td>58</td>
<td>&lt;0.01</td>
<td>Barostim</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL, median)</td>
<td>342</td>
<td>0.02</td>
<td>Barostim</td>
</tr>
<tr>
<td>LVEF (absolute %)</td>
<td>2.5</td>
<td>0.15</td>
<td>Barostim</td>
</tr>
<tr>
<td>Hospitalization Days for Worsening HF</td>
<td>6.4</td>
<td>0.05</td>
<td>Barostim</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Prospectively-defined non-CRT vs. CRT analysis**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>p value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLWHF QoL Score (points)</td>
<td>12</td>
<td>0.040</td>
<td>Non-CRT</td>
</tr>
<tr>
<td>6MHWD (meters)</td>
<td>69</td>
<td>0.010</td>
<td>Non-CRT</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>841</td>
<td>0.59</td>
<td>Non-CRT</td>
</tr>
<tr>
<td>LVEF (absolute %)</td>
<td>5.5</td>
<td>0.022</td>
<td>Non-CRT</td>
</tr>
<tr>
<td># HF Hospitalization Days</td>
<td>8.1</td>
<td>0.09</td>
<td>Non-CRT</td>
</tr>
</tbody>
</table>

Abraham et al, 2015

Prospectively-defined non-CRT vs. CRT analysis

MANCE

97% event free
2 pocket hematomas

Event-free Rate (%)
Regulatory Status in Heart Failure

- NYHA functional Class III
- Left ventricular ejection fraction ≤35%

*Despite guideline-directed therapy*

- Narrow QRS
- Concomitant treatment with CRT
- Concomitant ICD
- Atrial Fibrillation

- FDA-approved Phase III Pivotal Clinical Trial
- Morbidity & mortality design
- Expedited Access Pathway designation

- NYHA III, LVEF ≤35%
- Non-CRT eligible or treated
- Concomitant ICD
- Atrial Fibrillation
Summary of Barostim Therapy

- Targeted and specific with favorable procedural and therapy safety
- Provides integrated autonomic neuromodulation: SNS + PNS
- Demonstrated mechanisms of action and physiologic effects
- Positive 5-year clinical results in resistant hypertension
- Positive 146-patient RCT in heart failure; outcomes trial approved
  - A new treatment alternative for CRT-ineligible patients

The Barostim neo System is CE Marked for the treatment of heart failure and for the treatment of resistant hypertension