Neurostimulation for the Treatment of HFrEF: Vagal Nerve Stimulation, Spinal Cord Stimulation, Renal Denervation, and Baroreflex Activation Therapy

Luanda Grazette MD, MPH, FACC, Associate Professor of Medicine Director, Heart Failure and Cardiomyopathy Keck School of Medicine of USC
Disclosures

CVRx
Cardio-Neural Dysfunction in the Pathophysiology of Heart Failure

Central Nervous System

↑ Sympathetic activation
↑ Parasympathetic Inhibition

Heart
↑ Heart Rate
↑ Wall stress
↑ Myocyte Hypertrophy, Myocyte death
↑ Eccentric remodeling
↑ MVO2, ischemia
↑ Arrhythmogenesis

Vasculature
↑ Endothelin and Vasopressin
↑ Vasoconstriction
↑ Vascular Remodeling

Kidney
↑ RAAS
↑ Renal Vascular Resistance
↓ Renal Blood Plasma Blood Flow
↑ Sodium and Water Retention

Altered Signaling in HF
Arterial Baroreceptors
Arterial chemoreceptors
Cardiopulmonary reflexes
Renal Afferents
Muscle reflexes
The Goal of Neuromodulation is Restoration of Favorable Neuro-Cardiac Signaling

Standardized approach using:
- Pulse amplitude
- Pulse width
- Frequency

Achieve maximum efficacy by:
- Maximizing therapeutic dose
- Minimizing patient discomfort
- Maintaining patient safety

The outcome of neuromodulation depends on the stimulation parameters and the location within the cardioneural axis where the therapy is applied.

Hanna et al. Cardiac Failure Review 2018
Vagal Nerve Stimulation

- FDA approved for epilepsy since 1997 and refractory depression since 2005
- Device composed of a pulse generator and bipolar lead that delivers biphasic current and cycles on and off to stimulate vagus
- In animal models, increased survival, decreased inflammation postulated "cholinergic anti-inflammatory reflex"
Vagal Nerve Stimulation: Cardiofit System Pilot

- N = 32
- Open label, single arm
- NYHA Class II and III
- Titration over 4 weeks
- 7.1 ± 4.8 mA

No Significant Adverse Events, Improvement in NYHA class, 6MW and LV volume indices and QOL
Vagal Nerve Stimulation
ANTHEM HF Trial, Autonomic Regulation Therapy via Left or Right Cervical Vagus Stimulation in Patients with Chronic Heart Failure

N = 60
Randomized Open Label
NYHA class II, III
EF < 40%
10 week titration
Average 2.0 ± 0.6 mA
6 month follow up

4.5% Increase in EF, Improved NYHA class and QOL

Byku and Mann JACC: Basic to Translational Science.1:3, 2016:9 5 – 1 0 6
Vagal Nerve Stimulation, INOVATE-HF, Increase of Vagal Tone in Heart Failure

N=730
Randomized Open Label
12 Month follow up
NYHA class III, LVEF <40%
LV end-diastolic size 50 to 80 mm
Stimulation over 4 weeks to achieve 3.5 to 5.5 mA

Primary Composite Endpoint death from any cause or a worsening heart failure

Quality of life, NYHA functional class and 6-min walking distance were favorably affected by VNS
The ventricular remodeling effects seen in the pilot were not replicated
The primary efficacy outcome, with 202 of the 362 anticipated endpoints had occurred in 30.3% in the VNS group compared with 25.8% in the control group (hazard ratio: 1.14; 95% confidence interval: 0.86 to 1.53; p = 0.37).
The trial was stopped on the recommendation of the DSMB for projected futility
# Vagal Nerve Stimulation

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>N</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CardioFit (NCT00461019)</td>
<td>Nonrandomized Open label</td>
<td>32</td>
<td>1. Occurrence of all system and/or procedure-related adverse events (6 months)</td>
<td>No significant adverse events</td>
</tr>
<tr>
<td></td>
<td>NYHA functional classes II and III EF &lt;35%</td>
<td></td>
<td>2. NYHA functional class, 6MWD, LVE SV, MLHFQ QoL scores</td>
<td>Significant improvement in NYHA functional class, 6MWD, LVE SV, and QoL scores</td>
</tr>
<tr>
<td>NECTAR-HF (NCT01385176)</td>
<td>Randomized Double blind</td>
<td>96</td>
<td>1. LVESD (6 months)</td>
<td>No sig change in LVESD</td>
</tr>
<tr>
<td></td>
<td>NYHA functional classes II and III EF ≤35%</td>
<td></td>
<td>2. NYHA functional class, V o₂ max, SF-36 and MLHFQ QoL scores, pro-BNP</td>
<td>Significant improvement in NYHA functional class and QoL scores</td>
</tr>
<tr>
<td></td>
<td>LVESD &gt;5.5 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>QRS interval &lt;130 ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANTHEM-HF (NCT01823887)</td>
<td>Randomized Open label</td>
<td>60</td>
<td>1. Change in EF and LVESV (6 months)</td>
<td>Significant increase in EF</td>
</tr>
<tr>
<td></td>
<td>NYHA functional classes II and III EF ≤40%</td>
<td></td>
<td>2. NYHA functional class, 6MWD, MLHFQ QoL scores, LVESD, HRV, BNP</td>
<td>(4.5%); no change in LVESV</td>
</tr>
<tr>
<td></td>
<td>QRS interval &lt;150 ms</td>
<td></td>
<td></td>
<td>Significant improvement in NYHA functional class and QoL score</td>
</tr>
<tr>
<td>INOVATE-HF (NCT01303718)</td>
<td>Randomized Open label</td>
<td>730</td>
<td>1. Composite all-cause mortality/ HF hospitalizations (end of study); freedom from procedure-system-related complications (90 days); all-cause death or complications (12 months)</td>
<td>No significant difference in all-cause mortality and HF hospitalizations; significant improvement in 6MWD, KCCQ QoL; no safety issues identified</td>
</tr>
<tr>
<td></td>
<td>NYHA functional class III EF ≤40% LVESD 5-8 cm</td>
<td></td>
<td>2. LVESV index, 6MWD, KCCQ QoL scores, hospitalization-free days</td>
<td></td>
</tr>
</tbody>
</table>
Spinal Cord Stimulation
In use for over 40 years as treatment for pain

In animal models of MI, preemptive SCS resulted in infarct size reduction, and reduced tachycardia (VT)/VF.

Subsequent studies using the same animal model showed that SCS was superior to carvedilol and ramipril.
### TABLE 2 Spinal Cord Stimulation

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>N</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCS HEART (NCT01362725)</td>
<td>Nonrandomized Open label NYHA functional classes III and IV EF 20% to 35%</td>
<td>17</td>
<td>1. Safety and efficacy (composite of change in NYHA functional class, ( V_{O_2} ) max, LVESV, EF) (6 months) 2. Long-term safety (24 months)</td>
<td>Significant improvement in &gt; 4 of 6 efficacy parameters, without significant adverse events No significant long-term complications</td>
</tr>
<tr>
<td>DEFEAT-HF (NCT01112579)</td>
<td>Randomized Single blind NYHA functional class III EF ≤ 35% LVESD 5.5-8 cm QRS interval &lt; 120 ms</td>
<td>66</td>
<td>1. LVESV index (6 months) 2. ( V_{O_2} ) max, pro-BNP</td>
<td>No significant change in LVESV index No significant change in ( V_{O_2} ) max or pro-BNP level</td>
</tr>
<tr>
<td>Methodist SCS (NCT01124136)</td>
<td>Randomized Double blind NYHA functional classes III and IV EF ≤ 30%</td>
<td>9</td>
<td>Safety (composite of worsening HF, hospitalizations, arrhythmia, device-device interaction) and efficacy (change in EF, ( V_{O_2} ) max, BNP, QoL scores) (2 yrs)</td>
<td>No adverse events and no interference with ICD No significant change in EF or BNP</td>
</tr>
<tr>
<td>TAME-HF (NCT01820130)</td>
<td>Nonrandomized Open label NYHA functional class III EF ≤ 40% LVESD 5-8 cm</td>
<td>0</td>
<td>1. Change in LVEDV, NYHA functional class, and 6MWD (6 months) 2. Safety, QoL scores, ( V_{O_2} ) max, LV systolic and diastolic function</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

DEFEAT-HF = Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure; ICD = implantable cardioverter-defibrillator; LVEDV = left ventricular end-diastolic volume; Methodist SCS = Neurostimulation of Spinal Nerves That Affect the Heart; SCS = spinal cord stimulation; SCS HEART = Spinal Cord Stimulation for Heart Failure; TAME-HF = Trial of Autonomic Neuromodulation for Treatment of Chronic Heart Failure; other abbreviations as in Table 1.
Renal Denervation

CENTRAL ILLUSTRATION: Renal Denervation Protects the Failing Heart via Reduced Neprilysin Activity and RAS Inhibition

Brain
Failing Heart
Coronary Arteries

- Brain
- Failing Heart
- Coronary Arteries

- Renal Afferent Sympathetic Activity
- Renal Efferent Sympathetic Activity
- Fibrosis
- LV Function
- Coronary Vascular Function

- Kidney
- Radiofrequency Ablation of Renal Sympathetic Nerves
- Renal Norepinephrine
- Renal Neprilysin Activity

- B-Type Natriuretic Peptide
- Angiotensin I & II

# Renal Denervation in HFrEF

<table>
<thead>
<tr>
<th>Renal Denervation Studies</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reach Pilot</td>
<td>Open label, non-randomized safety trial, first in man, bilateral renal denervation</td>
<td>NYHA III-IV OMT</td>
<td>7</td>
<td>Increase in 6 mw and improvement in patient reported symptoms</td>
</tr>
<tr>
<td>Olomouc Pilot</td>
<td>Single Center Randomized Controlled Trial RDN +OMT vs OMT</td>
<td>NYHA III, EF &lt; 35% , OMT</td>
<td>51</td>
<td>preliminary data increase in EF, decrease in LV volumes, decrease in NT BNP</td>
</tr>
<tr>
<td>RDT-PEF</td>
<td>Single Center Randomized open controlled RDN vs OMT</td>
<td>NYHA II-IV HFpEF, OMT</td>
<td>25</td>
<td>No sig difference in BNP, EF, E/e VO2 max, LA volume I, LV mass</td>
</tr>
</tbody>
</table>
The Baroreflex as Therapeutic Target

"Unloading of high-pressure baroreceptors in the left ventricle, carotid sinus, and aortic arch generates afferent signals that orchestrate the neurohormonal response to heart failure.” Schrier and Abraham, NEJM 1999

Integrated Autonomic Nervous System Response
- Inhibits **Sympathetic** Activity
- Enhances **Parasympathetic** Activity

- ↓ HR
- ↓ Remodeling
- ↑ Vasodilation
- ↓ Elevated BP
- ↑ Diuresis
- ↓ Renin secretion
• First successful clinical trial completed in mid 60s
• Bilateral CSN stimulation for intractable myocardial ischemia and angina
• Activation shows immediate cessation of pain and increased duration of exercise intolerance
• CABG becomes widely available, Phase III trials never completed
### TABLE 3  Baroreflex Activation Therapy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Characteristics</th>
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<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheos DHF (NCT00718939)</td>
<td>EF &gt;45% Elevated BNP or pro-BNP</td>
<td>6</td>
<td>1. LVMI; safety (occurrence of all adverse events) (6 months) 2. Change in blood pressure, BNP or pro-BNP, QoL scores</td>
<td>Pending</td>
</tr>
<tr>
<td>Barostim neo HF (NCT01471860) and Barostim HOPE4HF (NCT01720160)</td>
<td>NYHA functional class III EF ≤35%</td>
<td>146</td>
<td>1. Safety (system and procedure-related adverse event) 2. Efficacy (change in NYHA functional class, QoL scores, 6MWD) (6 months)</td>
<td>No significant adverse events Significant improvement in 6MWD, NYHA functional class, QoL scores, pro-BNP level</td>
</tr>
<tr>
<td>BeAT-HF (NCT02627196)</td>
<td>NYHA functional class III EF ≤35%</td>
<td>800</td>
<td>1. Cardiovascular mortality and HF morbidity (5 yrs); MANCE (6 months)</td>
<td>Pending (estimated 2021)</td>
</tr>
</tbody>
</table>

BeAT-HF = Barostim Therapy for Heart Failure; DHF = Rheos Diastolic Heart Failure Trial; HOPE4HF = Barostim Hope for Heart Failure Study; LVMI = left ventricle mass index; MANCE = major adverse neurological and cardiovascular events; other abbreviations as in Table 1.
The BAROSTIM NEO Technology Platform

Carotid Sinus Nerve Stimulation
Hand exercise

Forearm Sympathetic Nerve Traffic
Blood Pressure

Source: R. R. Baliga, William T. Abraham: Color Atlas and Synopsis of Heart Failure Copyright © McGraw-Hill Education. All rights reserved.
BeAT-HF Outcomes Trial Design

**A** Cohort A, n=271
- April 2018: Initial Unblinding
- October 2018: 6-month Follow-up
- April 2019: Primary Safety Endpoint
  - MANCE free rate
- Primary Effectiveness Endpoints
  - 6MHW
  - MLWHF-QOL
  - NT-proBNP

**B** Cohort B, n=162 of 271 (NT-proBNP<1600 pg/ml, hypothesis generating cohort)
- 6-month Follow-up

**C** Cohort C, n=102 of 137 (Augmented, Confirmatory, SAP prospectively defined, Intended Use Population)
- 6-month Follow-up
- Second Unblinding
- Primary Safety Endpoint
  - MANCE free rate
- Primary Effectiveness Endpoints
  - 6MHW
  - MLWHF-QOL
  - NT-proBNP

**D** = **B** + **C** Cohort D, n=264 of 408 (for illustration and labeling use)
- Cohort B, n=162
- 6-month Follow-up
- Cohort C, n=102
- 6-month Follow-up

**Cohort D Analysis**
- Primary Effectiveness Endpoints
  - 6MHW
  - MLWHF-QOL
  - NT-proBNP
- Primary Safety Endpoint
  - MANCE free rate

**FDA Expedited Access Pathway**
BAT Significantly Improves Exercise Capacity and Functional Status

6 Month 6MHW (change from Baseline)

Cohort D

BAT Control Diff

60 49 -8

6 Month NYHA Classes (% of patients changed class from baseline)

Cohort D

BAT Control

13% 52% 29% 2%

65% Improved

p<0.001

31% Improved
BAT Significantly Reduces NT-proBNP and Improves Quality of Life

Cohort D

<table>
<thead>
<tr>
<th></th>
<th>BAT</th>
<th>Control</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP Improvement</td>
<td>-21%</td>
<td>-25%</td>
<td>3%</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cohort D

<table>
<thead>
<tr>
<th></th>
<th>BAT</th>
<th>Control</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLWHF Improvement</td>
<td>-21</td>
<td>-14</td>
<td>-6</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
</tbody>
</table>

Data = Mean ± 95% confidence interval, all differences analyzed using Log10 transformed NT-proBNP by ANCOVA adjusted for baseline values
The BAROSTIM NEO® System is indicated for the improvement of symptoms of heart failure – quality of life, six-minute hall walk and functional status, for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction ≤ 35%, a NT-proBNP < 1600 pg/ml and excluding patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines.
The Goal of Neuromodulation is Restoration of Favorable Neuro-Cardiac Balance
So, how does it work?

- Baroreflex acts as a negative feedback loop
- Stimulation of Baroreflex, by distention or electrical stim, propagates via Carotid Sinus (Hering) Nerve through CN IX to the ipsilateral NTS
- Via series of interneurons, an excitatory signal is transmitted to the caudal ventrolateral medulla
- Results in inhibited activity in the rostral ventrolateral medulla (RVLM), which is the principal site of sympathetic outflow from the brain stem
Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction

William Abraham, MD1, Michael Zile, MD2, Fred Weaver, MD3, Christian Butter, MD4, Anique Ducharme, MD5, Marcel Halbach, MD6, Didier Klug, MD7, Eric Lovett, PhD8, Jochen Müller-Ehmsen, MD9, Jill Schafer, MS10, Michele Senni, MD11, Vijay Swarup, MD12, Rolf Wachter, MD13, William Little, MD14; on behalf of the BAT for HFrEF Study Group

1Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; 2Medical University of South Carolina, Charleston, South Carolina; Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina, USA; 3Division of Vascular Surgery and Endovascular Therapy, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; 4Department of Cardiology, Immanuel Heart Center Bernau - Medical School Brandenburg, Bernau, Germany; 5Montréal Heart Institute, University of Montréal, Montreal, Quebec, Canada; 6Department of Internal Medicine III, University Hospital of Cologne, Cologne, Germany; 7Department of Cardiology A, University Hospital, Lille, France; 8Department of Research, CVRx, Inc., Minneapolis, Minnesota, USA; 9Department of Medicine #, Asklepios Klinik Altona, Hamburg, Germany; 10Department of Statistics, NAMSA, Inc., Minneapolis, Minnesota, USA; 11Cardiovascular Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy; 12Department of Electrophysiology, Arizona Heart Hospital, Phoenix, Arizona, USA; 13Clinic for Cardiology and Pneumology, University Medicine Götingen and German Cardiovascular Research Center (DZHK), Götingen, Germany; 14Division of Cardiology, University of Mississippi Medical Center, Jackson, Mississippi, USA
Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction:

Safety and Efficacy in Patients Without Cardiac Resynchronization Therapy

Michael Zile, MD, William Abraham, MD, Fred Weaver, MD, Christian Butter, MD, Anique Ducharme, MD, Marcel Halbach, MD, Didier Klug, MD, Eric Lovett, PhD, Jochen Müller-Ehmsen, MD, Jill Schafer, MS, Michele Senni, MD, Vijay Swarup, MD, Rolf Wachter, MD, William Little, MD
Placement Procedure