Baroreceptor Stimulation: A Novel Approach for the Treatment of Heart Failure

Christina Economides, MD, MM, FSCAI
Cardiology & Cardiovascular Intervention
Disclosures

CVRx – Speakers Bureau, Consultant
Objectives

- Review the unmet need in the treatment of HFrEF
- Review the role of the Autonomic Nervous System (ANS) and baroreflex in heart failure
- Review the clinical evidence for Baroreflex Activation Therapy (BAT) in HFrEF
- Implant and system overview
- Patient selection and case experience
Unmet Need in the Treatment of Heart Failure
GDMT Improves Heart Failure Morbidity and Mortality

2022 AHA/ACC/HFSA HF Guidelines

**ARNI**
- 20% decrease in sudden death, 21% decrease in VA, ICD shock or resuscitated cardiac arrest in PARADIGM-HF

**MRA**
- 23% decrease in sudden death in RALES, EPHESUS, EMPHASIS-HF

**B-Blockers**
- 31% decreased in sudden death based on meta-analysis of trials

**SGLT2i**
- 21% decrease in VA, resuscitated cardiac arrest or sudden death in DAPA-HF

1.4 - 6.3 years

Estimated aggregate mortality benefit of comprehensive quadruple therapy in HFrEF

---

CRT is Only Indicated for 30% of HFrEF Patients

GDMT Produces Modest Improvements in Exercise Capacity

Adapted from Lewis G et al, Developments in Exercise Capacity Assessment in Heart Failure Clinical Trials and the Rationale for the Design of METEORIC-HF. Circ Heart Fail. 2022 May; 15(5):510-524..
Patient Goals in the Treatment of Heart Failure

Survival

35%

“35% preferred treatments that prolonged survival time”¹,²

Quality of Life

65%

“65% favored strategies that improved quality of life but reduced survival time”¹,²

Role of the Autonomic Nervous System (ANS) and Baroreflex in Heart Failure
Autonomic Nervous System (ANS) & Cardiovascular Hemostasis

Klabunde, PhD, Richard E. Cardiovascular Physiology Concepts, Arterial Baroceptors.
Arterial Baroreceptor Reflexes

Autonomic Nervous System in Heart Failure

Decreased Baroreceptor Signaling

Imbalance in Autonomic Nervous System

- Heart Rate Remodeling
- Diuresis Renin Secretion
- Vasodilation Blood Pressure

Baroreflex Sensitivity is Reduced in Heart Failure Patients

HF patients have less change in systolic BP in response to changes in pressure on carotid baroreceptors

Baroreflex Sensitivity and Heart Failure Symptoms

Decreased baroreflex sensitivity is associated with worsening survival

Mortara A. Circulation. 1997;96:3450–3458
Clinical Evidence for Baroreflex Activation Therapy (BAT) in HFrEF
Baroreflex Activation Therapy (BAT): Proof of Concept

BAT Increases Baroreflex Sensitivity

BAT Decreases Sympathetic Tone

Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction

Michael R. Zile, MD,a,b JoAnn Lindenfeld, MD,c Fred A. Weaver, MD,d Faiez Zannad, MD,e Elizabeth Galle, MPH,f Tyson Rogers, MS,g William T. Abraham, MDh
Multicenter, prospective, controlled trial
Patients randomized 1:1
- Baroreflex Activation Therapy (BAT) + optimal medial management (BAT group)
- Optimal medical management alone (control group)

Inclusion Criteria:
- NYHA Functional Class III or NYHA Class II with recent history of functional class III
- Left ventricular ejection fraction ≤35%
- Six-minute hall walk distance: 150-400m
- Elevated NT-proBNP or previous HF hospitalization
- Stable optimal medical therapy ≥4 weeks

CRT-eligible subjects were excluded
No restriction on AF, QRS width or concomitant devices
Effectiveness endpoints:
- Change from baseline to 6 months in 6-min hall walk distance (6MHW)
- Minnesota Living with HF Questionnaire quality-of-life (QOL) score
- N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels

Safety endpoint:
- Major adverse neurological or cardiovascular system or procedure-related event rate (MANCE)
### Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Barostim (n=130)</th>
<th>Control (n=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62 ± 11</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Gender female</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>Race: Caucasian</td>
<td>75%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Heart failure and physical status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>MLWHF QOL score</td>
<td>53 ± 24</td>
<td>52 ± 24</td>
</tr>
<tr>
<td>6MHW (m)</td>
<td>316 ± 58</td>
<td>294 ± 73</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>75 ± 10</td>
<td>75 ± 11</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 17</td>
<td>121 ± 16</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73 ± 10</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27 ± 7</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) (IQR)</td>
<td>731 (475,1021)</td>
<td>765 (479,1052)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>64 ± 17</td>
<td>62 ± 20</td>
</tr>
<tr>
<td>QRS interval</td>
<td>109 ± 18</td>
<td>111 ± 26</td>
</tr>
<tr>
<td>Previous HF hospitalization</td>
<td>42%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Co-Morbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>62%</td>
<td>69%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>29%</td>
<td>43%</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetes Type II</td>
<td>45%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Heart failure treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of meds</td>
<td>3.9 ± 1.2</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td>ACE-I/ARB/ARNI</td>
<td>89%</td>
<td>84%</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>MRA</td>
<td>49%</td>
<td>42%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>85%</td>
<td>87%</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>2.3%</td>
<td>4.5%</td>
</tr>
<tr>
<td>ICD</td>
<td>78%</td>
<td>79%</td>
</tr>
</tbody>
</table>

BeAT-HF Results: Symptom Improvement at 6 months

**Exercise capacity (6MHW)**
- **Barostim Control Diff**:
  - 60 Meters
- **Clinically Meaningful**
  - 25 Meters
- **49**
- **-8**

**Quality of Life (MLWHF)**
- **Barostim Control Diff**:
  - -14 Points
- **Clinically Meaningful**
  - -5 Points
- **-21**
- **-14**

**NYHA class**
- **Barostim Control Diff**:
  - 13%
  - 52%
  - 2%
  - 29%
- **34% Improve**
- **Improved 2 NYHA Classes**
- **Improved 1 NYHA Class**
Improvements in Exercise Capacity in HFrEF

BeAT-HF Results: Reduction in NT-proBNP

-25% reduction

Clinically meaningful 10% relative reduction

Change to 6 Month NT-proBNP (% Change from baseline)

-30% -35% -40% -25% -20% -15% -10% -5% 0 5% 10%

BAT Control Diff

p=0.004
# BeAT-HF Safety

## 6-month MANCE (System or Procedure-Related)

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Events</th>
<th>Number of Subjects</th>
<th>Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Acute Decompensated HF</td>
<td>1</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hypertensive Crisis</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Severe Complication of HF Treatment</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Systemic and Pulmonary Thromboembolism</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Infection Requiring Explant</td>
<td>2</td>
<td>2</td>
<td>1.6%</td>
</tr>
<tr>
<td>Cranial Nerve Damage</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Non-Elective Major Restorative Procedures</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
<td><strong>4</strong></td>
<td><strong>3.2%</strong></td>
</tr>
</tbody>
</table>
BeAT-HF Trial

Optimize & Stabilize Medications ≥ 1 month

Baseline

1:1 Randomization

FDA Approval
- 6MHW
- QOL (MLWHF)
- NT-proBNP
- MANCE

Post-Market Phase
- CV Mortality
- HF Morbidity

FDA Approval
August 2019

~2023

MEDICAL MANAGEMENT

BAROSTIM + MEDICAL MANAGEMENT

Implant

3

6

Follow-up

Months post-activation

Highlights of the data presented by Dr. Zile include:

- **Safety** - Major Adverse Neurological or Cardiovascular (MANCE) system or procedure-related event-free rate
  - MANCE-free rate of 97% (p<0.001)

- **Long-term symptom improvement for Barostim Baroreflex Activation Therapy (BAT) vs. Control:**
  - 6 Minute Hall Walk improved by 44 meters at 12 months (nominal p<0.001)
  - Quality of Life improved by 10 points in Minnesota Living with Heart Failure Questionnaire at 24 months (nominal p<0.001)
  - NYHA Class improved in 27% more BAT patients at 24 months (nominal p<0.001)

- **Mortality** (cardiovascular death, LVAD, heart transplant) and **morbidity** (HF hospitalizations, ER visits) – primary endpoint
  - No statistically significant difference [Rate Ratio 0.94, (95% Confidence Interval 0.57, 1.57); p=0.82]

- **All-cause mortality** (all-cause death, LVAD, heart transplant)
  - 34% relative reduction in BAT vs. Control [Hazard Ratio 0.66 (95% CI 0.44, 1.007); nominal p=0.054]

- **Hierarchical composite of cardiovascular death, LVAD, heart transplant, HF hospitalization, and Quality of Life using Win Ratio**
  - Win Ratio of 1.26 favored BAT vs. Control [95% CI 1.02, 1.58; nominal p=0.04]
Composite Endpoint vs Win Ratio Analysis

**Traditional Composite**
- All events equally weighted
- Only patients who experienced an event are considered (~40% in BeAT-HF)
- Does not include patient-centric metrics, such as Quality of Life

**Win Ratio Analysis**
- Events are prioritized by severity
- Evaluates experience of 100% of the patients in the study
- Allows for the inclusion of Quality of Life metric
Calculating a Win Ratio in BeAT-HF

BeAT-HF Win Ratio Analysis

Each Barostim patient (n=163) vs. Each control Patient (n=160)

- Mortality: Did one patient survive vs. the other? Yes = Winner
- LVAD/Transplant: Did one patient avoid LVAD or transplant vs. the other? Yes = Winner
- HF Hospitalization: Did one patient have fewer hospitalizations vs. the other? Yes = Winner
- Quality of Life: Did one patient have better symptomatic outcomes vs. the other? Yes = Winner

Total wins for treatment arm / Total wins for control arm

Win Ratio =

Value > 1 favors Barostim

Win Ratio analysis concept from the BeAT-HF Trial
# BeAT-HF Summary of Key Evidence

## Description

**Primary endpoint**

- **Composite CV Mortality and HF Morbidity**
  - Rate Ratio = 0.94

- **CV Mortality** (CV death, LVAD, heart transplant)
  - Hazard Ratio = 0.73

- **HF Morbidity** (Heart failure hospitalization, ER/ED visit)
  - Rate Ratio = 1.08

**Additional Analyses**

- **All-cause Mortality** (death, LVAD, heart transplant)
  - Hazard Ratio = 0.86

- **Hierarchical Win Ratio** (CV mortality, HF morbidity, QOL)
  - Win Ratio = 1.26

## Long-term Safety

**Related MANCE-free Rate***

| Rate | 96.9% |

*Major Adverse Neurologic and Cardiac Events

## Long-term Symptom Improvement

- **Quality of Life – MLWHF**
  - (6 / 12 / 24 Month)
  - -13 / -8 / -10

- **Exercise Capacity – 6MHW**
  - (6 / 12 Month)
  - +55 / +44

- **Functional Status – NYHA Class % Improved**
  - (6 / 12 / 24 Month)
  - 30% / 32% / 27%

---

This summary is adapted from Dr. Michael Zile's presentation at THT 2020 on March 21, 2020 entitled "Baroreflex Activation Therapy (BAT) in Patients With Heart Failure and a Reduced Ejection Fraction (BeAT-HF): Long-Term Outcomes". These data have not yet been peer-reviewed or published in a peer-reviewed medical journal. Access to full THT presentation and symposium are available at THT.com.
Implant and System Overview
**Carotid Sinus Lead**

Create a small incision to access the carotid bifurcation and secure the 2mm electrode and lead.

**Implantable Pulse Generator (IPG)**

Tunnel the lead over the collarbone and connect to IPG in a standard device pocket.

**Extravascular - no leads in the heart or vasculature**

MRI-compatible
**Programming goal:** Maximum stimulation that is well tolerated by the patient

**Recommended follow-up schedule:**
- Activation approximately 2-3 weeks post-implant
- Optimization at 3 months and 6 months
- Follow-up visits every 6 months based on each patient’s medical need

**Average battery life 6 years, no charging required**
Patient Selection and Case Experience
Patients to Consider for BAT

**BAT Indications from BeAT-HF**

- NYHA III or NYHA II w/ recent history of NYHA III on GDMT*
- LVEF ≤ 35%
- NNT-proBNP < 1600 pg/mL
- Not indicated for CRT**

**Patients to consider for BAT**

- ICD patient – symptomatic despite GDMT
- CRT non-responders
- Hospitalized for CHF or recurrent hospitalizations
- High-risk indicators: syncope, ventricular arrhythmias, CVA
- Difficulties performing meaningful daily activities due to heart failure symptoms:
  - Showering
  - Making the bed
  - Cooking
  - Climbing stairs
  - Walking a few blocks, or to doctor’s office
  - Shopping
  - Playing with children / grandchildren
  - Golfing, Gardening, Traveling

---

*Guideline directed medical therapy (GDMT) according to 2022 AHA/ACC/ESC guidelines.
**Or not receiving adequate response from existing CRT device.
Homeostasis is a Synergistic Balance between the Autonomic Branches

- ‘Rest, Heal & Digest’: Parasympathetic activity dominates.
- ‘Fight or Flight’: Sympathetic activity dominates.
74 yo man: Ischemic CDM – 20 year course

CAD s/p MI 2001, MI in 2012 s/p RCA PCI with LAD CTO, Isch CDM, EF 25, BiV/ICD, P A-fib, HTN, HL, DM, CKD

2013: NYHA Class III, 9 CHF admissions/15 mos, 4 thoracenteses
2014: LAD CTO, viability present, CABG LIMA to LAD, post-op EF 40%, NYHA Class I-II
2019: NYHA Class III, EF 30%, LV thrombus, 6 CHF admissions/19 mos, 8 thoracenteses, EF 20%
10/2021: Syncope admission, hypotension, head CT negative, EF 20%
- Cath: LIMA-LAD ok, mod CFX/R PDA dz, negative FFR, RCA stents, LVEDP 12mmHg
- Meds: Amiodarone, Coreg 3.125mg bid, Digoxin, Lasix 40mg bid, KCl, Synthroid, Spironolactone 25mg daily, Metolazone daily, Simvastatin, Coumadin, Plavix
- **Barostim implant 10/2021**

2 weeks post: Decreased SOB, feels improved, no Metolazone since implant
2 mos post: Decreased SOB, improved energy, Lasix daily, no CHF admissions
9 mos post: No CHF admissions, COVID admission, NYHA Class I-II
1 ½ yrs post: No CHF admissions Lasix daily, Metolazone prn, NYHA Class I-II
77 yo woman: Nonischemic CDM

Case

Dilated NCDM, EF 10-15%, NYHA Class III, CRT-D 2016, HTN, HL, CVA, Breast Ca s/p R mastectomy 2000, Depression, Mild Dementia

- Multiple CHF admissions over 5 years at different hospitals
- Intolerant to meds and max doses, hypotension, on/off CKD
- Meds: Corlanor 7.5mg bid, Entresto low dose, Lasix 40mg bid, Eliquis, Zoloft
- Barostim implant 7/2021

Follow up

- 2 weeks post: Decreased SOB and edema
- 2 mos post: EF 20-25%, No LV thrombus
- 1 year 9 mos post: 4 CHF admissions, all secondary to patient noncompliance

- Per family, patient feels so well she thinks she’s cured and stops taking meds, also with progression of dementia
GDMT has shown significant improvements in morbidity and mortality, but only modest improvements in exercise capacity.

CRT significantly improves exercise capacity, but only in specific patient populations (QRS ≥ 150/LBBB), only 30% of the HFrEF population.

When baroreflex sensitivity is decreased, the ANS becomes unbalanced (increased sympathetic tone, decreased parasympathetic tone) which exacerbates HF symptoms.

Direct electrical stimulation of carotid baroreceptors up-regulates the baroreflex, rebalances the autonomic nervous system, and improves heart failure symptoms.

BeAT-HF study showed significant improvements in symptomatic outcomes with BAT above GDMT (6MHW, QOL and NYHA Class) and decreases in NT-proBNP.

BAT is a novel device option for improvement of symptoms in patients with HFrEF who are refractory to GDMT and/or CRT, and who are not indicated for CRT.
Thank you.