Evidence of Baroreflex Activation Therapy’s Mechanism of Action

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Agenda

• Baroreflex Activation Therapy Background
• Proof of Concept Investigation
• Confirmatory Data from the Randomised Controlled Trial
• BAROSTIM THERAPY™ Long-term Durability
• Leveraging Baroreflex Activation Therapy in Management of HFrEF Patients
Baroreflex Sensitivity (BRS) and HF Mortality: PREDICTIVE VALUE PRESERVED WITH $\beta$ BLOCKADE

Kaplan-Meier survival curves according to dichotomized baroreceptor-heart rate reflex sensitivity (BRS) in patients (A) taking and (B) not taking beta-blockers.

La Rovere MT JACC 2011
Is the baroreceptor a valuable target for HF treatment?

1. Preserved MSNA pulse-synchronicity
2. Immediate reflex augmentation of MSNA burst amplitude and duration in response to the long diastolic period following a ventricular ectopic complex
3. Post-extrasystolic suppression of MSNA proportional to the diastolic pressure overshoot
4. MSNA tracks reflexively pulsus alternans
5. Reflex reduction in MSNA when diastolic pressure rises modestly upon left or biventricular pacing
6. Similar inhibition of MSNA by aortic and ventricular mechanoreceptor stimulation in subjects with normal and impaired ventricular systolic function
7. Similar reflex increases in TNES in patients and control subjects with nitroprusside infusion to achieve comparable baroreceptor unloading
8. Similar gain, in subjects with and without HF, of the cross-spectral transfer function between BP and MSNA across all frequency bands.
The baroreflex is a therapeutic target

Carotid Baroreceptor Stimulation

Integrated Autonomic Nervous System Response
Inhibits Sympathetic Activity
Enhances Parasympathetic Activity

↓ HR Remodeling
↑ Vasodilation
↓ Elevated BP
↑ Diuresis
↓ Renin secretion
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Proof of Concept Investigation: DESIGN

- Single-center, open label study conducted in Milan, Italy

- Optimal, Stable Medical Therapy:
  - Prescribed $\beta$-blocker, diuretic and ACE-Inhibitor/ARB unless contraindicated
  - No more than a 50% increase or a 50% decrease in dose of any medication & post-titration of all HF drugs

**Diagram:**
- MSNA
- SCREENING 1-MONTH STABILITY
- DEVICE ON
- LONG-TERM FOLLOW-UP

**Months:**
- -0.5
- 0
- 1
- 2
- 3
- 4
- 6

**Barostim Therapy Summit:** September 30th, 2017 • Radisson Blu, Berlin, Germany
Proof of Concept Investigation:

MAIN INCLUSION CRITERIA

- NYHA Class III
- Left Ventricular EF ≤ 40%
- 6-minute Hall Walk 150-450 m
- eGFR ≥ 30 mL/min/1.73m²
- Heart Rate 60-100 bpm
- BMI ≤ 40 kg/m²
- Not receiving cardiac resynchronization
- No autonomic neuropathy or baroreflex failure
# Proof of Concept Investigation:
**HF POPULATION BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic (N=11)</th>
<th>N (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, Caucasian</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>History of Atrial Fibrillation</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>31 ± 7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HF Medication</th>
<th>N (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-Inhibitor or ARB</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>Diuretic – loop</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Diuretic – thiazide</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Diuretic – other</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (64%)</td>
</tr>
</tbody>
</table>
BAT showed a positive impact on Muscle Sympathetic Nerve Activity (MSNA)

Gronda E et al. EJHF 2014

N=11; Mean ± SE; †p < 0.005, §p < 0.001 vs. Baseline
Baroreflex Sensitivity was restored & mirrored by a striking reduction in hospital admission rates

N=11; Mean ± SE; * $p < 0.05$, § $p < 0.001$ vs. Baseline

Gronda E et al. EJHF 2014
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- Baroreflex Activation Therapy Background
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- Confirmatory Data from the Randomised Controlled Trial
- BAROSTIM THERAPY™ Long-term Durability
- Current Baroreflex Activation Therapy Placement in HFrEF Patient Management
BAT for HFrEF Randomised Controlled Trial: EFFICACY ENDPOINTS

• Change from baseline to 6 months in
  • New York Heart Association Functional Class Rank
  • Minnesota Living with Heart Failure Quality of Life Score
  • Six-Minute Hall Walk (6-MHW) Distance
  • Serum Biomarker (NT-proBNP)
  • Left Ventricular Ejection Fraction
  • Hospitalizations (Days) for Worsening Heart Failure*

*Baseline defined as 6 months prior to enrollment
# BAT for HFrEF Randomised Controlled Trial: BASELINE DEMOGRAPHICS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>BAT (N=71)</th>
<th>MED MGMT (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race: Caucasian</td>
<td>82%</td>
<td>90%</td>
</tr>
<tr>
<td>Gender: Female</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>NYHA: Class III</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 11</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115 ± 18</td>
<td>119 ± 17</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 11</td>
<td>73 ± 11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73 ± 11</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>24 ± 7</td>
<td>25 ± 7</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>58 ± 21</td>
<td>59 ± 19</td>
</tr>
<tr>
<td>NT-pro BNP (pg/mL)*</td>
<td>1422 [455, 4559]</td>
<td>1172 [548, 2558]</td>
</tr>
<tr>
<td>6 Minute Hall Walk (m)</td>
<td>297 ± 79</td>
<td>308 ± 85</td>
</tr>
<tr>
<td>MN Living with HF QOL†</td>
<td>51 ± 21</td>
<td>43 ± 22</td>
</tr>
<tr>
<td>Number of Meds</td>
<td>4.8 ± 1.6</td>
<td>4.4 ± 1.9</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>66%</td>
<td>68%</td>
</tr>
<tr>
<td>History of Atrial Fibrillation</td>
<td>45%</td>
<td>44%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td>HF hospitalizations prior 6 Mo (days/pt/year)</td>
<td>7.0 ± 21</td>
<td>2.4 ± 9</td>
</tr>
</tbody>
</table>

*Median [IQR]; †p<0.05 between groups
### BAT for HFrEF Randomised Controlled Trial: BASELINE MEDICATIONS

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<th>VARIABLE</th>
<th>BAT (N=71)</th>
<th>MED MGMT (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Meds</td>
<td>4.8</td>
<td>4.4</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>87%</td>
<td>85%</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Diuretic†</td>
<td>93%</td>
<td>78%</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>MRA</td>
<td>59%</td>
<td>50%</td>
</tr>
<tr>
<td>CRT</td>
<td>34%</td>
<td>30%</td>
</tr>
<tr>
<td>ICD</td>
<td>89%</td>
<td>86%</td>
</tr>
</tbody>
</table>

†p≤0.05 between groups
BAT significantly reduces NT-proBNP levels

Difference = -342 pg/mL
p=0.02

<table>
<thead>
<tr>
<th></th>
<th>BAT n=43</th>
<th>Med Mgmt n=40</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1422 [455, 4559]</td>
<td>1172 [548, 2558]</td>
</tr>
</tbody>
</table>

Non-parametric (median [IQR])

Abraham WT JACC-HF 2015
Concordance of results supports BAT efficacy in HFrEF

<table>
<thead>
<tr>
<th></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>BAT</td>
</tr>
<tr>
<td>MLWHF QoL Score (points)</td>
<td>20</td>
<td>&lt;0.001</td>
<td>BAT</td>
</tr>
<tr>
<td>6-MHW Distance (m)</td>
<td>58</td>
<td>&lt;0.01</td>
<td>BAT</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)*</td>
<td>342</td>
<td>0.02</td>
<td>BAT</td>
</tr>
<tr>
<td>LVEF (absolute %)</td>
<td>2.5</td>
<td>0.15</td>
<td>BAT</td>
</tr>
<tr>
<td>Hospitalization Days for</td>
<td>6.4</td>
<td>0.05</td>
<td>BAT</td>
</tr>
<tr>
<td>Worsening HF (days/pt/yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abraham WT et al. JACC-HF 2015

* Median
Are blood pressure results consistent across HFrEF and resistant hypertension?

HFrEF

SBP SIGNIFICANTLY INCREASED IN BAT ARM

MSNA TRAFFIC IS SIGNIFICANTLY GREATER IN HYPERTENSIVE SUBJECTS

rHTN

RHEOS HYPERTENSION PIVOTAL TRIAL ACTION ON BP (N.111)

BAROSTIM THERAPY SUMMIT • September 30th, 2017 • Radisson Blu, Berlin, Germany
The Dose-Response Concept: TOLERANCE TO STIMULATION INCREASES WITH LOWER FREQUENCY

BETTER TRENDS NOTICED IN PATIENTS WITH NO CRT, RECEIVING HIGHER CURRENTS (ACC 2015)

Smith S et al. Int J Cardiol 2016

Abraham WT JACC HF 2015
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BAT in HF Proof of Concept Investigation showed sustained effects after 21 & 42 months.

**AFTER 21 MONTHS**

**MSNA, BRS**

Gronda E J Hypertension 2016

**HF HOSPITALIZATION DAYS/MONTH**

Gronda E JH 2015

**AFTER 42 MONTHS**

**MSNA**

Dell’Oro R J Hypertension 2017

**BRS**

Gronda E ESC-HF 2017
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HF patients with NT-proBNP > 1000 pg/ml after 1 month of GDMT are under great risk…

Zile M et al. JACC 2016
...therefore it is important to assess and treat them rapidly...

WHERE BAT IS AN EXCELLENT TREATMENT OPTION

- Symptomatic, Systolic HF
- NYHA Class III, despite GDMT

Assess eligibility for CRT

- Eligible
  - Consider CRT
- Not eligible
  - Consider BAT
Thank you.