Symptomatic endpoint responder rates to BAROSTIM Therapy

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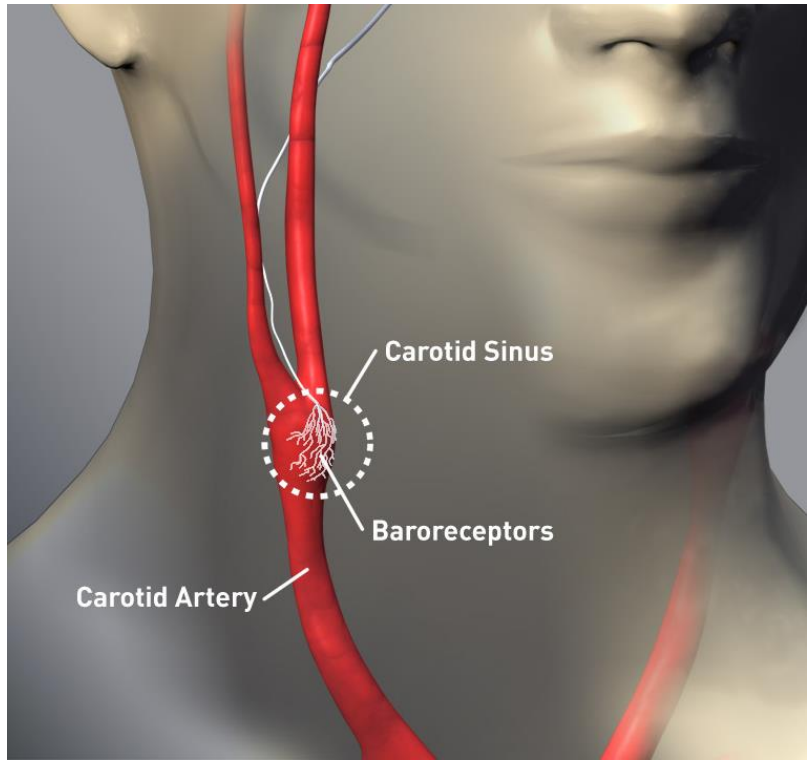
Presenter Disclosure Information

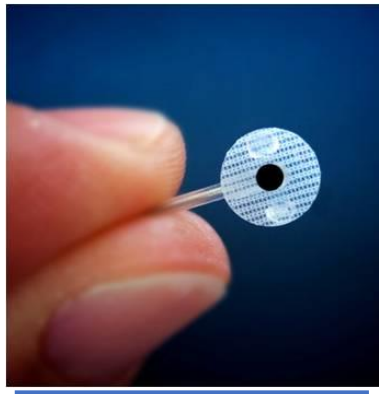
- The presenter has previously received consulting fees from CVRx, as a member of the HOPE4HF and BeAT-HF Executive Committees

Presentation Goals

- Determine the proportion of clinically relevant responders and super responders to Baroreflex Activation Therapy (BAT) in HFrEF from the BeAT-HF randomized clinical trial

Device Design





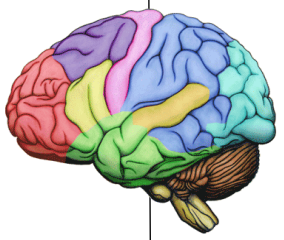
2 mm electrode
7mm silicone backer
Unipolar design

4-5 year longevity
RF telemetry
Programming flexibility

8.7 mA amplitude
125 ms duration
40 pps frequency

Mechanism of BAT in HFrEF

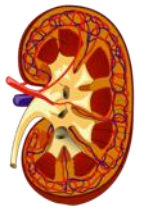
Carotid Baroreceptor Stimulation
Afferent Signaling



Integrated Autonomic Nervous System Response
Inhibits Sympathetic Activity
Enhances Parasympathetic Activity

↓ **Heart Rate**
↓ **Remodeling**

↑ **Vasodilation**
↓ **Elevated BP**

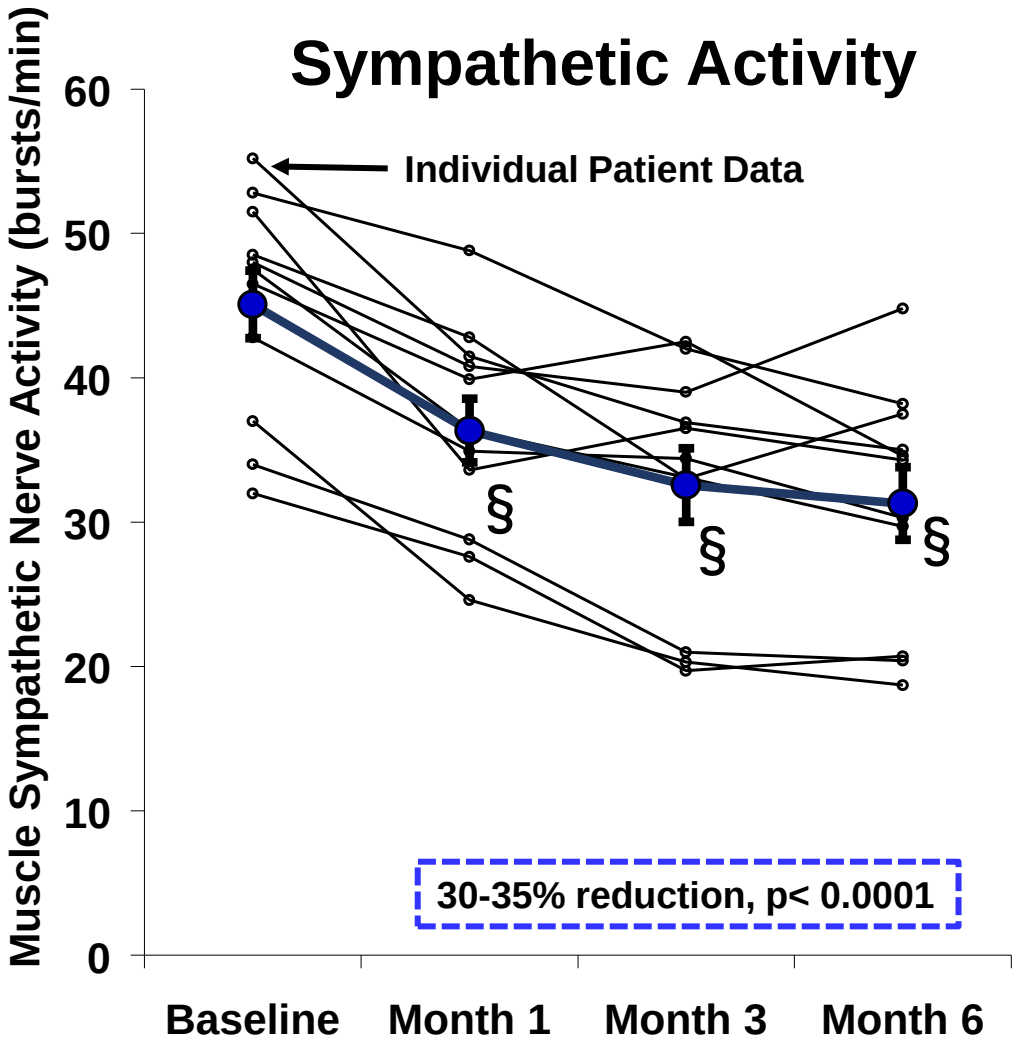


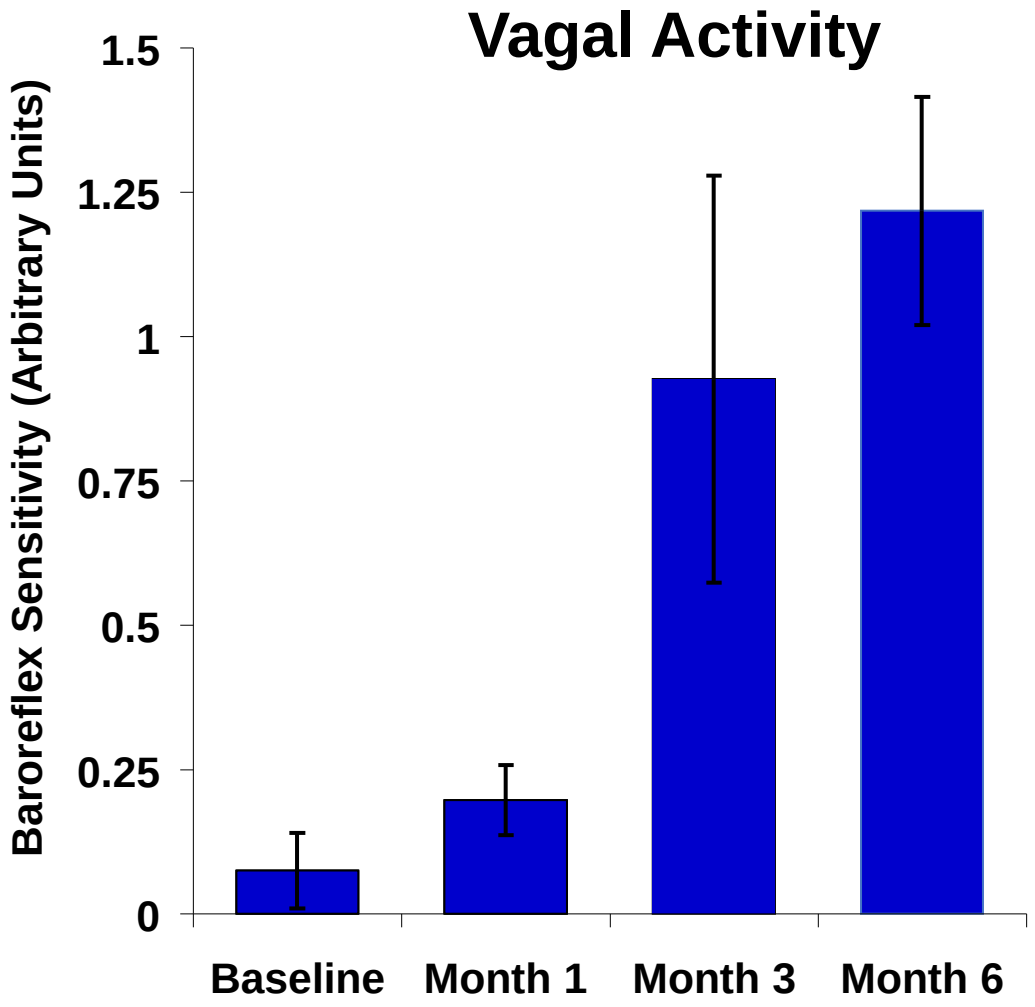
↑ **Diuresis**
↓ **Renin secretion**

Clinical Evidence Development in Heart Failure

	Phase I: BAT in HF 1st Enrollment 12/2011	Phase II: HOPE4HF 1st Enrollment 5/2012	Pivotal: BeAT-HF 1st Enrollment 4/2016
Objective	• Assess safety • Demonstrate mechanism of action with GDMT	• Assess safety and Effectiveness	• Demonstrate safety and effectiveness, including morbidity & mortality • Assess health economics
Study Subjects	• n = 11	• n = 146	• n = 408
Outcomes	• BAROSTIM Therapy is safe • Mechanism of action demonstrated through muscle sympathetic nerve activity & HR Variability	• BAROSTIM Therapy is safe and effective in heart failure • CE Mark Approval	• BAROSTIM Therapy is a safe, effective and an economically attractive solution for heart failure patients • FDA Approval

Effect of BAT in HFrEF on Sympatho-Vagal Balance





All Rx GDMT (> 90% ACE-I/ARB, β-blker, MRA)
Replicated using High, Low HR Variability Studies

Gronda et al Eur J HF 16: 977-983, 2014

A Phase III Randomized, Controlled Trial of Baroreflex Activation Therapy (BAT) in Patients with Heart Failure and Reduced Ejection Fraction (HFrEF)

BeAT-HF

(ClinicalTrial.gov Identifier: NCT02627196)

The BeAT-HF Executive Steering Committee

Michael R. **Zile**, MD, William T. **Abraham**, MD, JoAnn **Lindenfeld**, MD, Fred A. **Weaver**, MD, Faiez **Zannad**, MD

Sponsor

CVRx, Inc.

Zile MR, et.al Am Heart J. 2018 Jul 22; 204:139-150.

BeAT-HF Pivotal Phase III Study

Purpose:

- Demonstrate safety and effectiveness of BAT in HFrEF patients using the FDA Breakthrough Devices Program

Design:

- Multicenter, prospective, randomized controlled trial
- Randomized 1:1 to receive BAT plus optimal medical management (“BAT”) or optimal medical management alone (“Control”)

Zile MR, et.al Am Heart J. 2018 Jul 22; 204:139-150.

BeAT-HF Key Eligibility Criteria

- NYHA Functional Class III
- Left ventricular ejection fraction ≤ 35%
- Six-minute hall walk distance (6MHW) 150 – 400 m
- Elevated NT-proBNP or previous Heart Failure Hospitalization
- Stable optimal medical therapy ≥ 4 weeks
- Subjects not indicated for CRT
- No restriction on AF, QRS width or concomitant devices

Zile MR, et.al Am Heart J. 2018 Jul 22; 204:139-150.

BeAT-HF Baseline Demographics

Variable	BAT (n=130)	Control (n=134)
Age (years)	62 ± 11	63 ± 10
Gender: Female	19%	22%
Race: Caucasian	75%	72%
NYHA: Class III	93%	95%
MLWHF QOL Score	53 ± 24	52 ± 24
6 Minute Hall Walk Distance (m)*	316 ± 68	294 ± 73
HR (bpm)	75 ± 10	75 ± 11
SBP (mmHg)	120 ± 17	121 ± 16
DBP (mmHg)	73 ± 10	73 ± 10
LVEF (%)	27 ± 7	28 ± 6
NT-pro BNP (pg/mL, Median [IQR])	731 [475, 1021]	765 [479, 1052]
eGFR (mL/min)	64 ± 17	62 ± 20
QRS Interval	109 ± 18	110 ± 26
History of Atrial Fibrillation	29%	43%
History of Coronary Artery Disease	62%	69%
Previous HF hospitalization	42%	51%

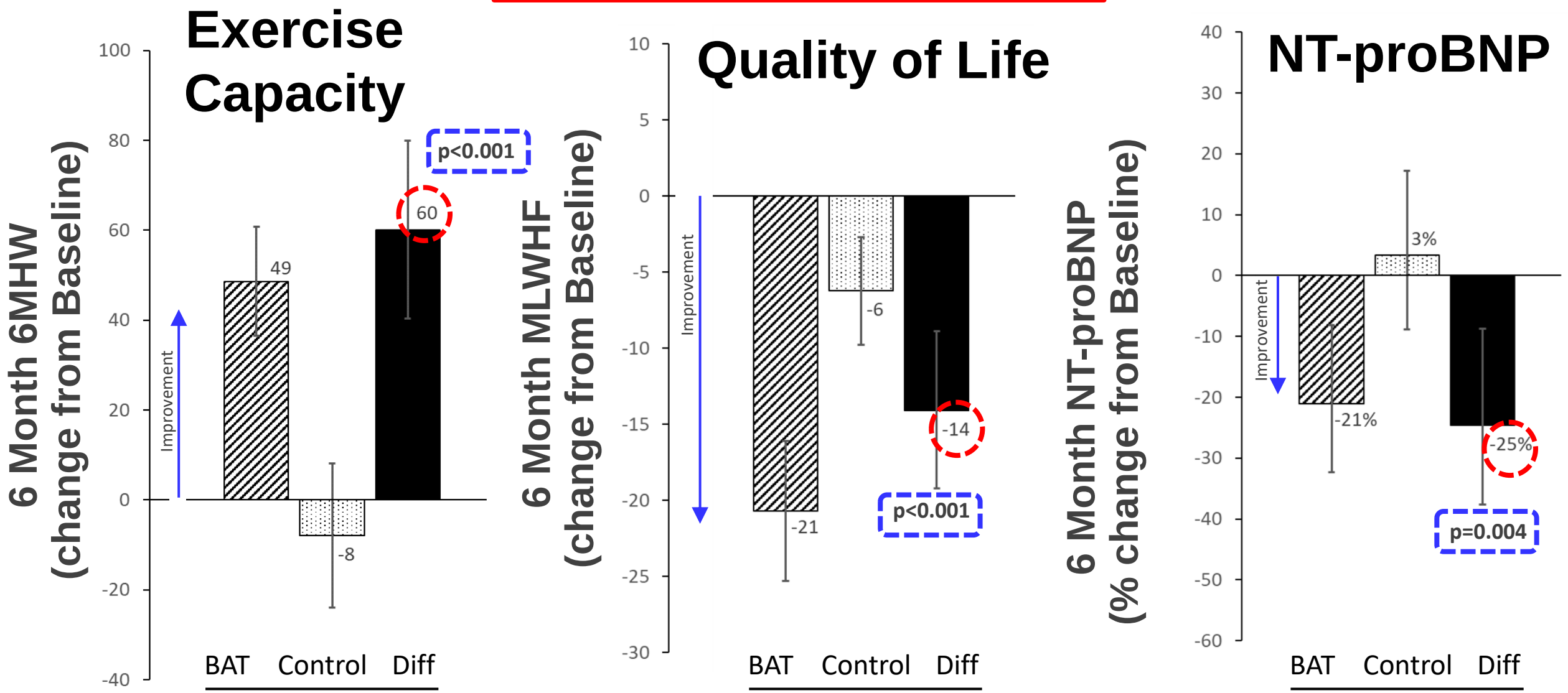
No significant difference between BAT and Control: none below 0.01, 6MHW p=0.015, AF p=0.03, all others > 0.05

BeAT-HF Baseline Therapies

Variable	BAT (n=130)	Control (n=134)
Number of Meds	3.9 ± 1.2	4.1 ± 1.4
ACE-I/ARB/ARNI	89%	84%
Beta-Blocker	95%	95%
MRA	49%	42%
Diuretic	85%	87%
Ivabradine	2%	5%
ICD	78%	79%

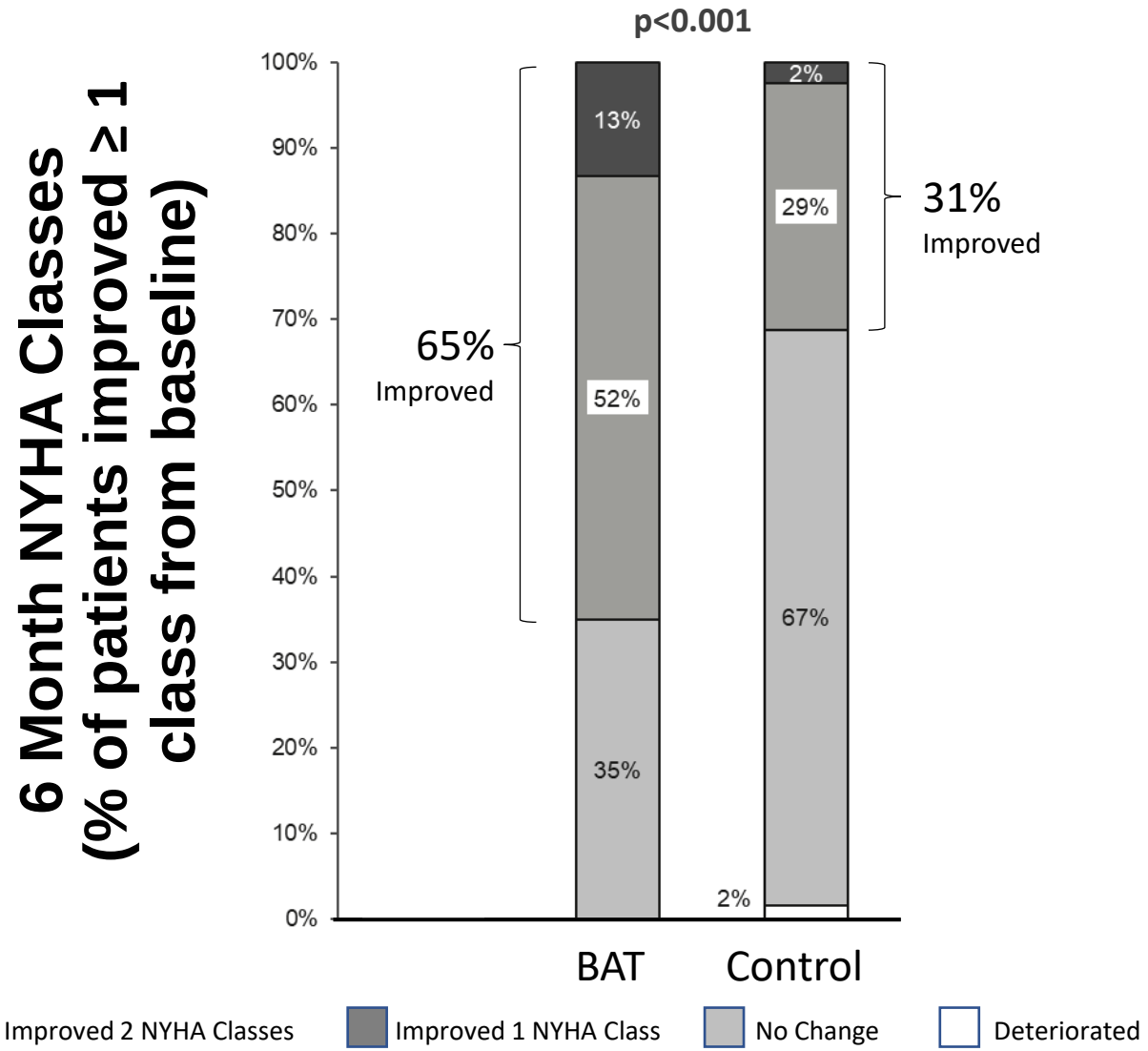
No significant difference between BAT and Control

BeAT-HF Top-Line Results



BeAT-HF Top-Line Results

Functional Status



Responder Definitions at Six Months

Clinically Relevant Responder:

- 6MHW > 10% meter improvement
- QoL > 5 points improvement
- NYHA ≥ 1 Class improvement

Super Responder:

- 6MHW > 20% meter improvement
- QoL > 10 points improvement
- NYHA improved to Class 1

Clinically Relevant Responders at Six Months

Clinically Relevant Responder	BAT N=120	Control N=125
6MHW>10%	73 (62%)	37 (31%)
NYHA Improve≥1 Class	78 (65%)	39 (31%)
QOL>5 Points	82 (68%)	55 (44%)
No clinically relevant response	7 (6%)	35 (29%)
Clinically relevant response in ≥ 2	85 (72%)	35 (29%)
Clinically relevant response in all 3	35 (30%)	10 (8%)

All p-value < 0.03

Super Responders at Six Months

Super Responder	BAT N=120	Control N=125
6MHW>20%	40 (34%)	22 (18%)
NYHA Improve to Class I	19 (16%)	3 (2.4%)
QOL>10 Points	73 (61%)	45 (36%)
No super response	25 (21%)	62 (52%)
Super response in ≥ 2	33 (28%)	12 (10%)
Super response in all 3	5 (4%)	0 (0.0%)

All p-value < 0.03

Results

- Both clinically relevant responders and super responders were significantly higher in BAT versus Control subjects for all symptomatic endpoints.
- In BAT subjects, 72% had clinically relevant improvements in ≥2 endpoints compared to 29% of Control subjects ($p<0.001$), and 28% of BAT subjects had super responder improvements in ≥2 endpoints versus 10% of Control subjects ($p<0.001$).

Conclusions

- Among subjects with symptomatic HFrEF, treatment with BAT resulted in clinically relevant responder and super responder rates. The BAT clinically relevant responder and super responder rates are similar to those seen with CRT, in CRT-indicated patients.

FDA Approval 8/16/2019 : Instruction For Use

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.