Response to Baroreflex Activation Therapy (BAT) By Atrial Fibrillation Status

Presenter: Michael R. Zile, MD

Charles Ezra Daniel Professor of Medicine, Medical University of South Carolina

Chief, Division of Cardiology, RHJ Department of Veterans Affairs MC

Charleston, South Carolina, USA

Co-Authors:

JoAnn Lindenfeld, MD, Vanderbilt Heart and Vascular Institute
William T. Abraham, MD, The Ohio State University
Fred A. Weaver, MD, University of Southern California
Faiez Zannad, MD, Inserm Centre d'Investigation
Elizabeth Galle, MPH, CVRx Inc.
Tyson Rogers, MS, NAMSA Inc.
Vijendra Swarup, MD, Arizona Heart Rhythm Center

Presenter Disclosure Information

I will discuss research examining the development of new therapies in my presentation.

I have financial relationships to disclose:

Employee of:

Department of Veterans Affairs, Medical University of SC

Consultant for:

Abbott, Boston Scientific, Corvia, CVRx, Cyclerion, EBR, Endotronics, Eli Lilly, Janssen, Medtronic, Merck, Myokardia, Novartis, ReCor, V Wave

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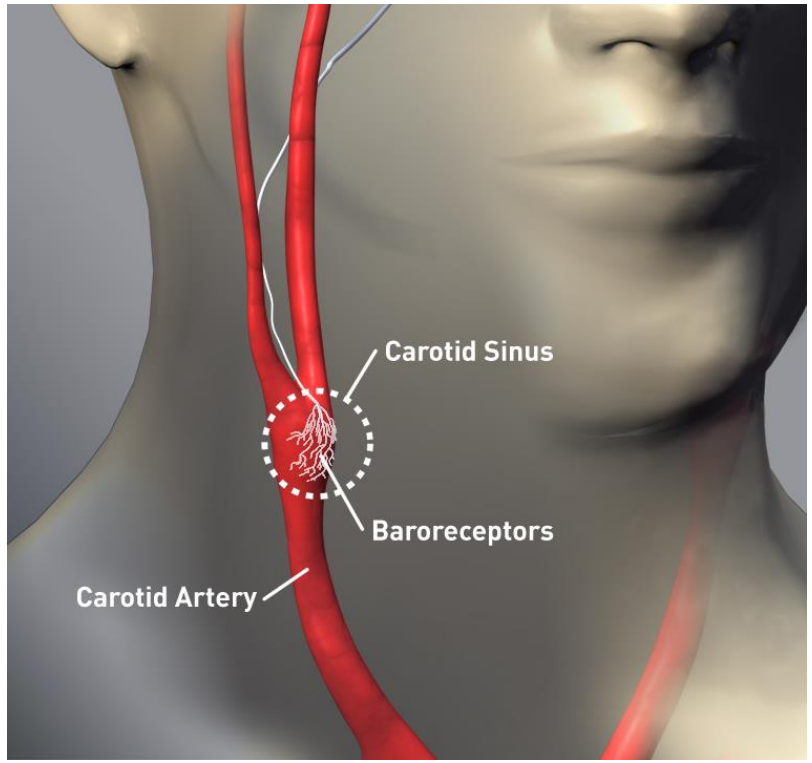
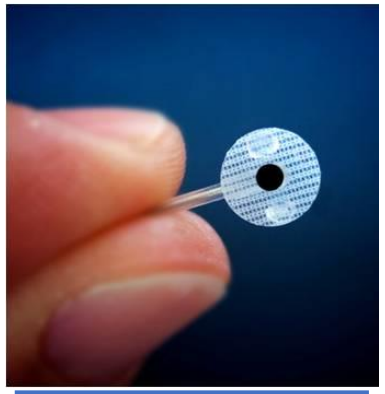
NHLBI, VA, DOD, CVRx, Medtronic, Novartis

Presentation Goals

- Device Design, Mechanism of Action
- Clinical Evidence Development in Heart Failure
- BeAT-HF Trial Data
- Response to BAT By Atrial Fibrillation Status
- Patients who should be considered for BAT

Device Design





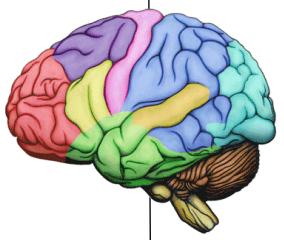
2 mm electrode
7mm silicone backer
Unipolar design

4-5 year longevity
RF telemetry
Programming flexibility

8.7 mA amplitude
125 ms duration
40 pps frequency

Mechanism of BAT in HFrEF

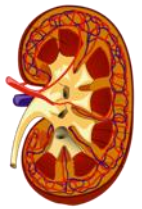
Carotid Baroreceptor Stimulation
Afferent Signaling



Integrated Autonomic Nervous System Response
Inhibits Sympathetic Activity
Enhances Parasympathetic Activity

↓ **Heart Rate**
↓ **Remodeling**

↑ **Vasodilation**
↓ **Elevated BP**

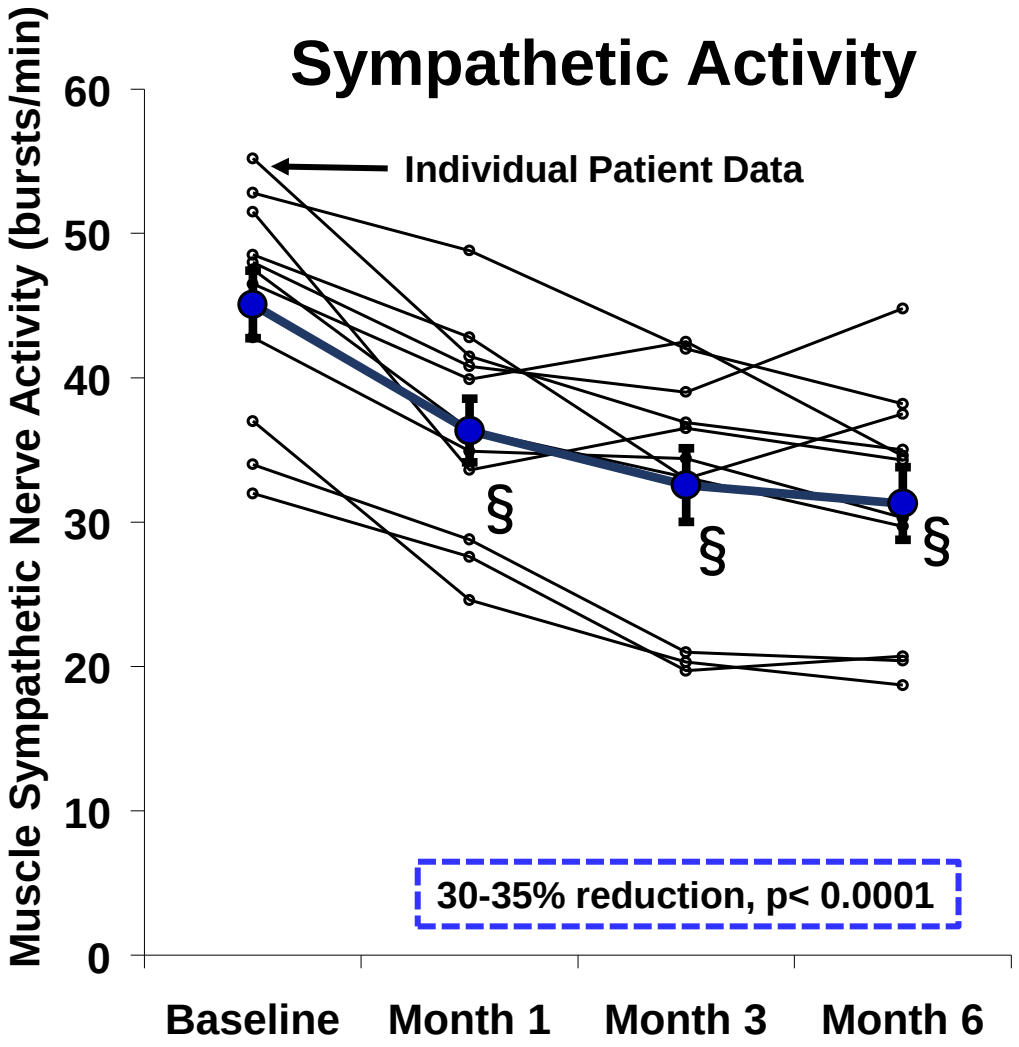


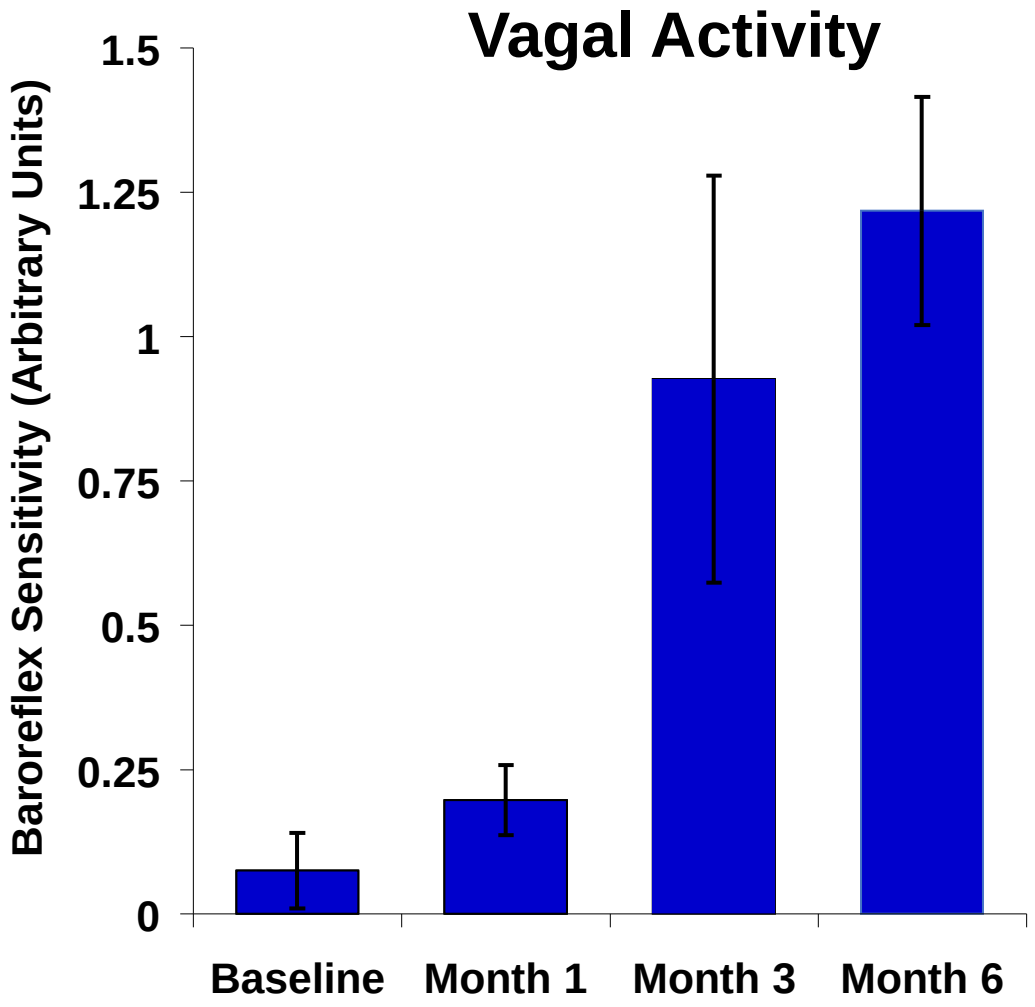
↑ **Diuresis**
↓ **Renin secretion**

Clinical Evidence Development in Heart Failure

	Phase I: BAT in HF 1st Enrollment 12/2011	Phase II: HOPE4HF 1st Enrollment 5/2012	Phase III: 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 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%

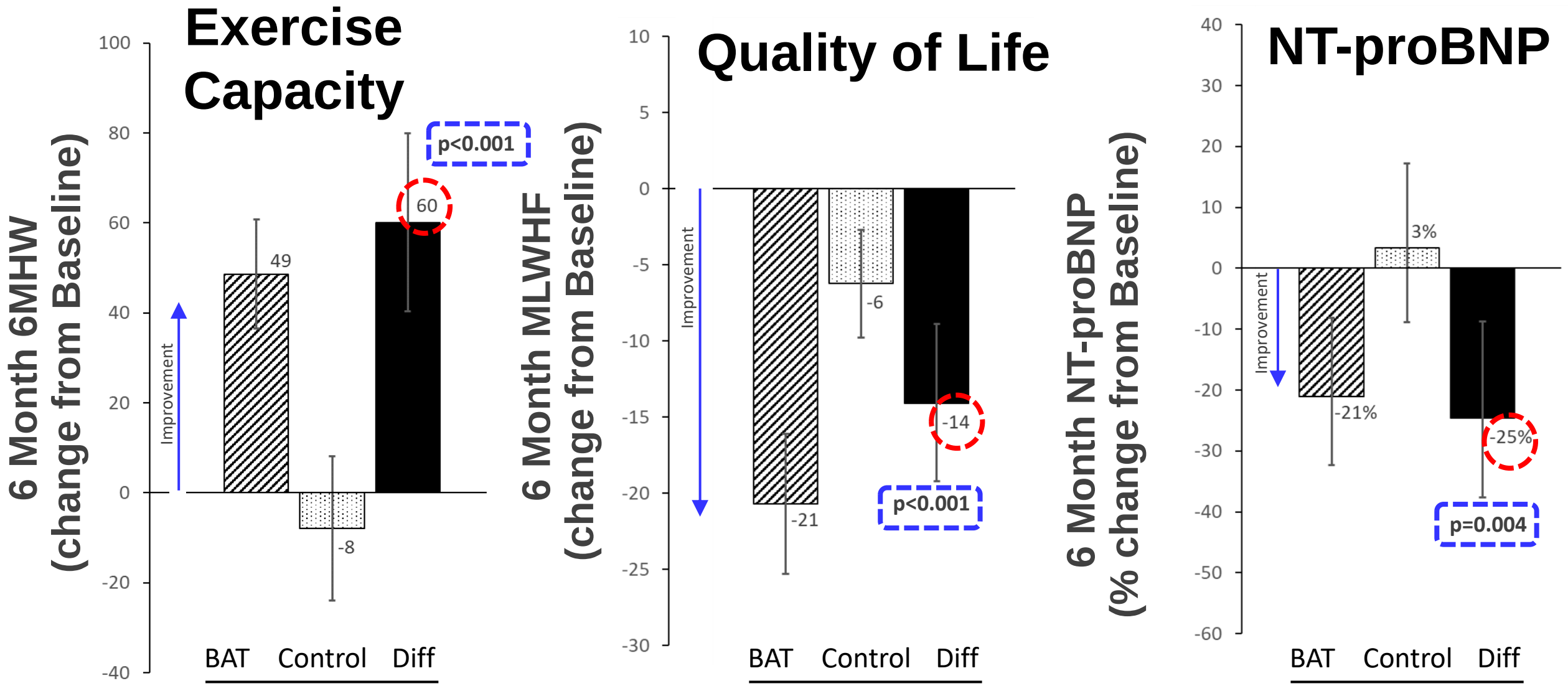
No significant difference between BAT and Control: none below 0.01, 6MHW p=0.015, AF p=0.03, all others > 0.05

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%

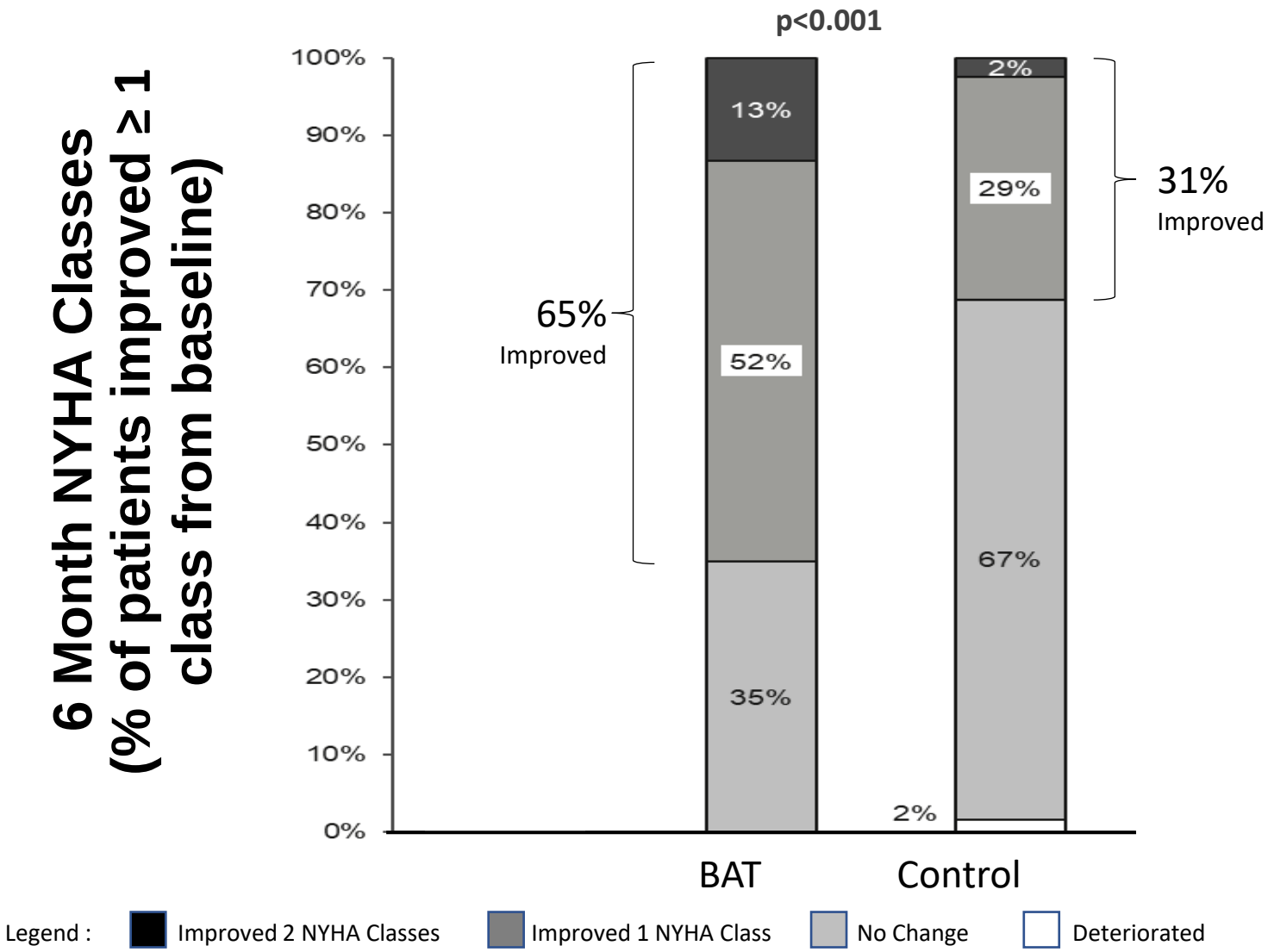
No significant difference between BAT and Control

BeAT-HF Top-Line Results



BeAT-HF Top-Line Results

Functional Status



Baseline AF Status

- Medical history form asked for history of atrial fibrillation (AF) and, if yes, was it paroxysmal, persistent or permanent
- 95 / 264 (36%) randomized subjects indicated a history of AF

Variable	N (%)
No AF	169 (64.0%)
Paroxysmal	63 (23.9%)
Permanent	8 (3.0%)
Persistent	22 (8.3%)
Unknown	2 (0.8%)

Baseline Demographics by AF Status

Variable Mean ± SD or N (%)	History of AF N=95	No History of AF N=169	P-value
Race: White	74 (77.9%)	119 (70.4%)	0.197
Female	17 (17.9%)	36 (21.3%)	0.631
Age at Screening (years)	64 ± 10	61 ± 11	0.014
BMI (kg/m2)	31 ± 5	31 ± 5	0.406
SBP (mmHg)	121 ± 18	120 ± 16	0.744
DBP (mmHg)	74 ± 11	73 ± 10	0.627
HR (bpm)	75 ± 11	75 ± 11	0.749
LVEF (%)	28 ± 5	27 ± 6	0.022
Core Lab NT-proBNP (pg/mL)*	847 (594, 1128)	658 (414, 956)	0.002
NYHA: Class III	89 (93.7%)	159 (94.1%)	1.000
6 Minute Walk (m)	298 ± 72	308 ± 71	0.280
QOL	49 ± 23	55 ± 24	0.064
QRS Interval	114.3 ± 26.2	107.1 ± 18.9	0.011
At Least One HF Hospitalization	46 (48.4%)	76 (45.0%)	0.609

* = Median (interquartile range)

Baseline Co-Morbidities by AF Status

Co-Morbidity	History of A Fib N=95 Mean ± SD or N (%)	No History of A Fib N=169 Mean ± SD or N (%)	P-value
Coronary Heart Disease			
Coronary Artery Disease	62 (65.3%)	110 (65.1%)	1.000
Myocardial Infarction	61 (64.2%)	93 (55.0%)	0.155
CABG	25 (26.3%)	37 (21.9%)	0.451
PCI	35 (36.8%)	80 (47.3%)	0.121
Cardiac Arrhythmia			
Bradycardia	10 (10.5%)	17 (10.1%)	1.000
Tachycardia	35 (36.8%)	54 (32.0%)	0.420
Atrial Fibrillation	95 (100.0%)	0 (0.0%)	<.001
Stroke or TIA	27 (28.4%)	27 (16.0%)	0.025
Chronic Kidney Disease	24 (25.3%)	40 (23.7%)	0.767
Diabetes			
Type I	0 (0.0%)	2 (1.2%)	0.538
Type II	45 (47.4%)	81 (47.9%)	1.000

Baseline Treatments by AF Status

Treatment	History of A Fib N=95 Mean ± SD or N (%)	No History of A Fib N=169 Mean ± SD or N (%)	P-value
Number of Meds	4.1 ± 1.4	4.0 ± 1.3	0.362
ACE-I/ARB	55 (57.9%)	99 (58.6%)	1.000
Beta-Blocker	92 (96.8%)	159 (94.1%)	0.388
Diuretic	81 (85.3%)	146 (86.4%)	0.854
Ivabradine	1 (1.1%)	8 (4.7%)	0.163
MRA	39 (41.1%)	80 (47.3%)	0.368
ARNI	25 (26.3%)	51 (30.2%)	0.572
ACE/ARB or ARNI Use	79 (83.2%)	149 (88.2%)	0.267
ICD	78 (82.1%)	129 (76.3%)	0.350
Pacemaker (non-ICD)	1 (1.1%)	2 (1.2%)	1.000
CRT	5 (5.3%)	2 (1.2%)	0.102

Outcomes by Baseline AF Status

	BAT		Control		Difference*	
	N	Mean±SD	N	Mean±SD	Δ Means	p-value
Six Minute Hall Walk						
AF	32	50.0 ± 56.5	53	-8.3 ± 97.4	66.5	<0.001
No AF	86	48.1 ± 69.9	67	-7.6 ± 81.3	57.4	<0.001
Quality of Life						
AF	33	-19.8 ± 24.3	54	-7.6 ± 17.6	-12.0	0.002
No AF	87	-21.0 ± 26.0	71	-5.2 ± 21.8	-15.9	<0.001
Log10 NT-proBNP (% change)**						
AF	33	-24.1% ± 0.3	53	-1.0% ± 0.3	-23.4%	0.10
No AF	87	-20.0% ± 0.4	70	6.7% ± 0.3	-25.4%	0.02
NYHA (% Improved)						
AF	33	20 (61%)	54	18 (33%)	28%	0.015
No AF	87	58 (67%)	71	21 (30%)	37%	<0.001
Freedom from procedure/system-related MANCE						
AF	36	92%				
No AF	89	99%				

*Difference evaluated based on ANCOVA model adjusting for baseline value.**Results modeled parametrically log10 scale. Results converted to % change

There were no significant interaction P-values for AF vs no AF for any parameter measured, all > 0.05

Conclusions

- A total of 95 (36%) of the 264 subjects enrolled in BeAT-HF had a history of atrial fibrillation when enrolled.
- BAT significantly improved patient-centered symptomatic endpoints
  - quality of life score
  - exercise capacity, and
  - functional status.
- These results were supported by objective evidence of significant reduction of NT-proBNP.
- BAT is equally safe and effective in patients with or without Atrial Fibrillation

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.