Does Neuromodulation Using Baroreflex Activation Therapy (BAT) have Potential Application in HFpEF?

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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

Stockholder in: N/A

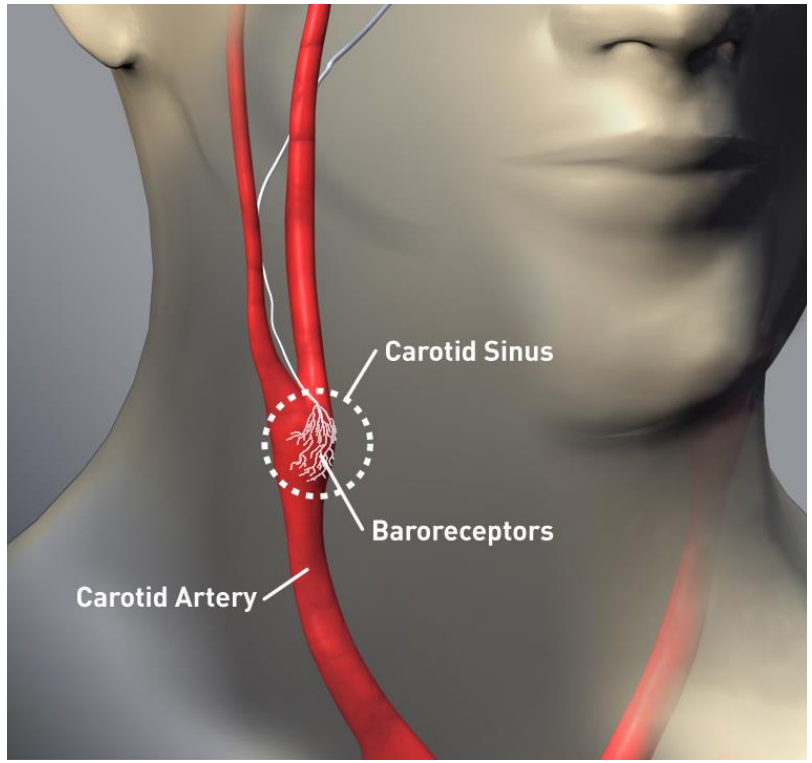
Research support from:

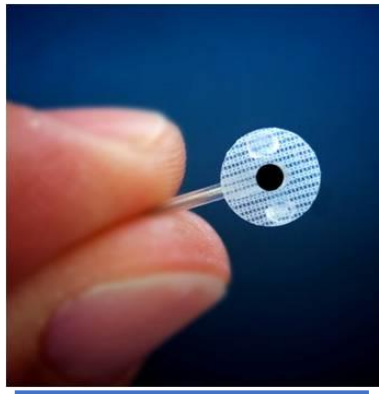
NHLBI, VA, DOD, CVRx, Medtronic, Novartis

Presentation Goals

- Device Design, Mechanism of Action
- Clinical Evidence Development in Heart Failure
- BeAT-HF Trial Data
- BeAT-HF vs other studies
- FDA approval 8/16/19
- Application to HFpEF
- Patients who should be considered for BAT

Device Design





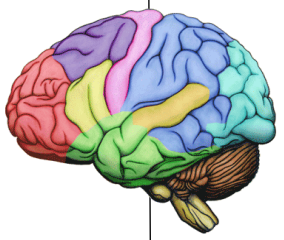
2 mm electrode
7mm silicone backer
Unipolar design

4-5 year longevity
RF telemetry
Programming flexibility

8.7 mA amplitude
125 ms duration
40 pps frequency

Mechanism of BAT in HFrEF

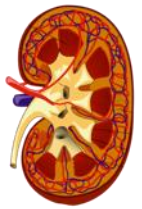
Carotid Baroreceptor Stimulation
Afferent Signaling



Integrated Autonomic Nervous System Response
Inhibits Sympathetic Activity
Enhances Parasympathetic Activity

↓ **Heart Rate**
↓ **Remodeling**

↑ **Vasodilation**
↓ **Elevated BP**

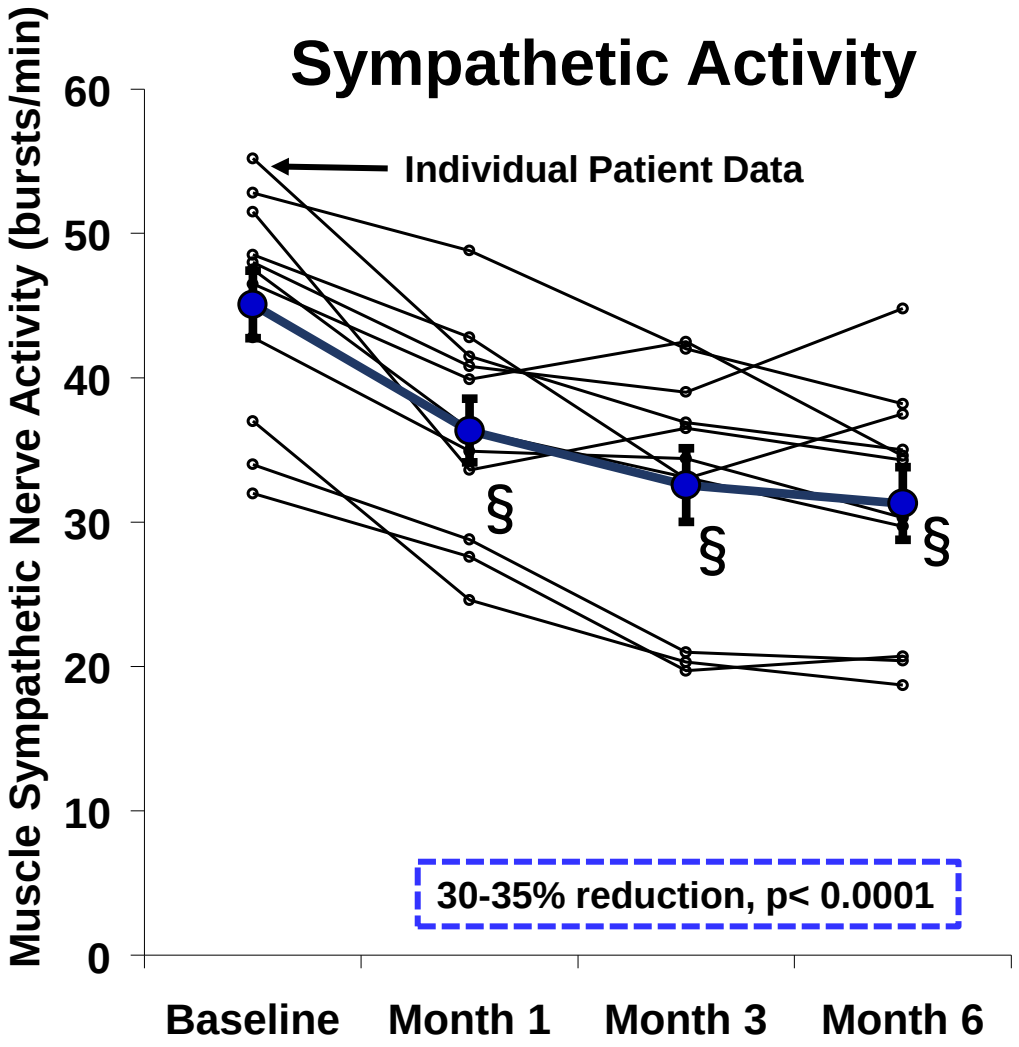


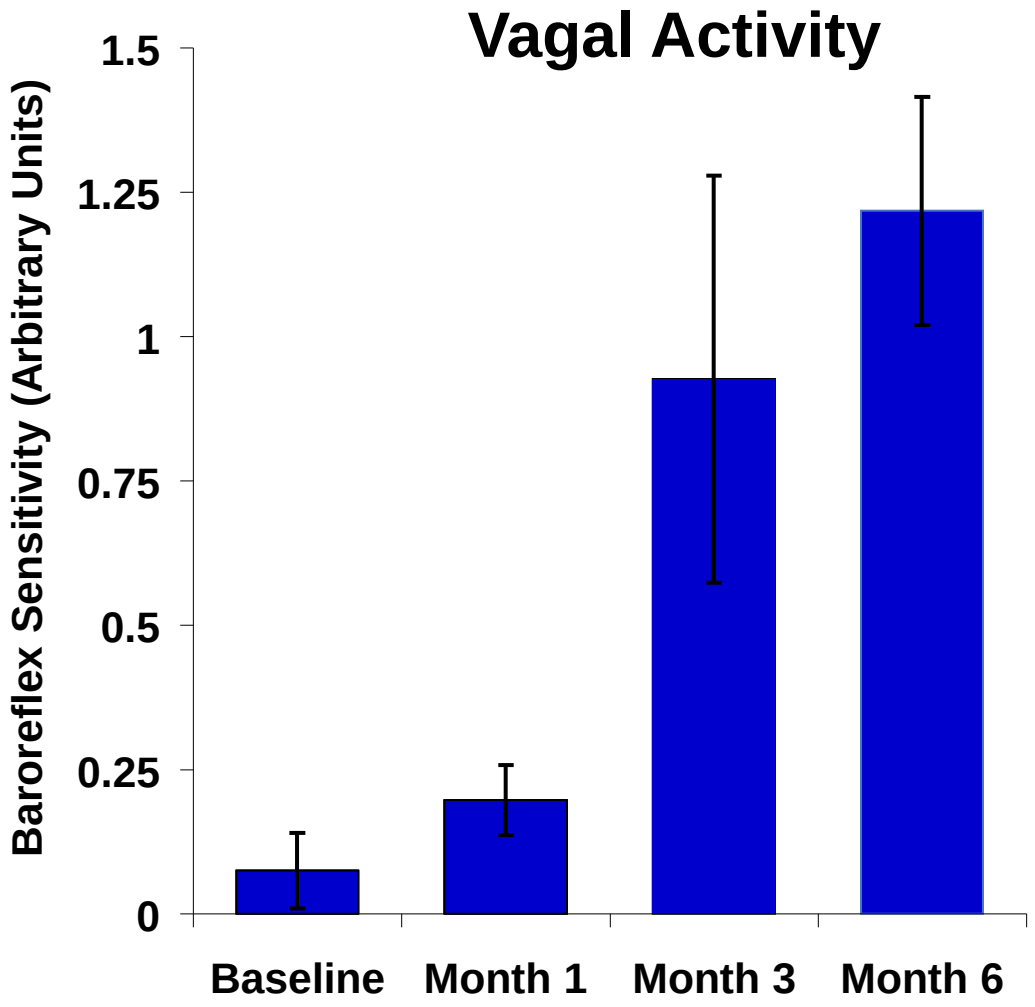
↑ **Diuresis**
↓ **Renin secretion**

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

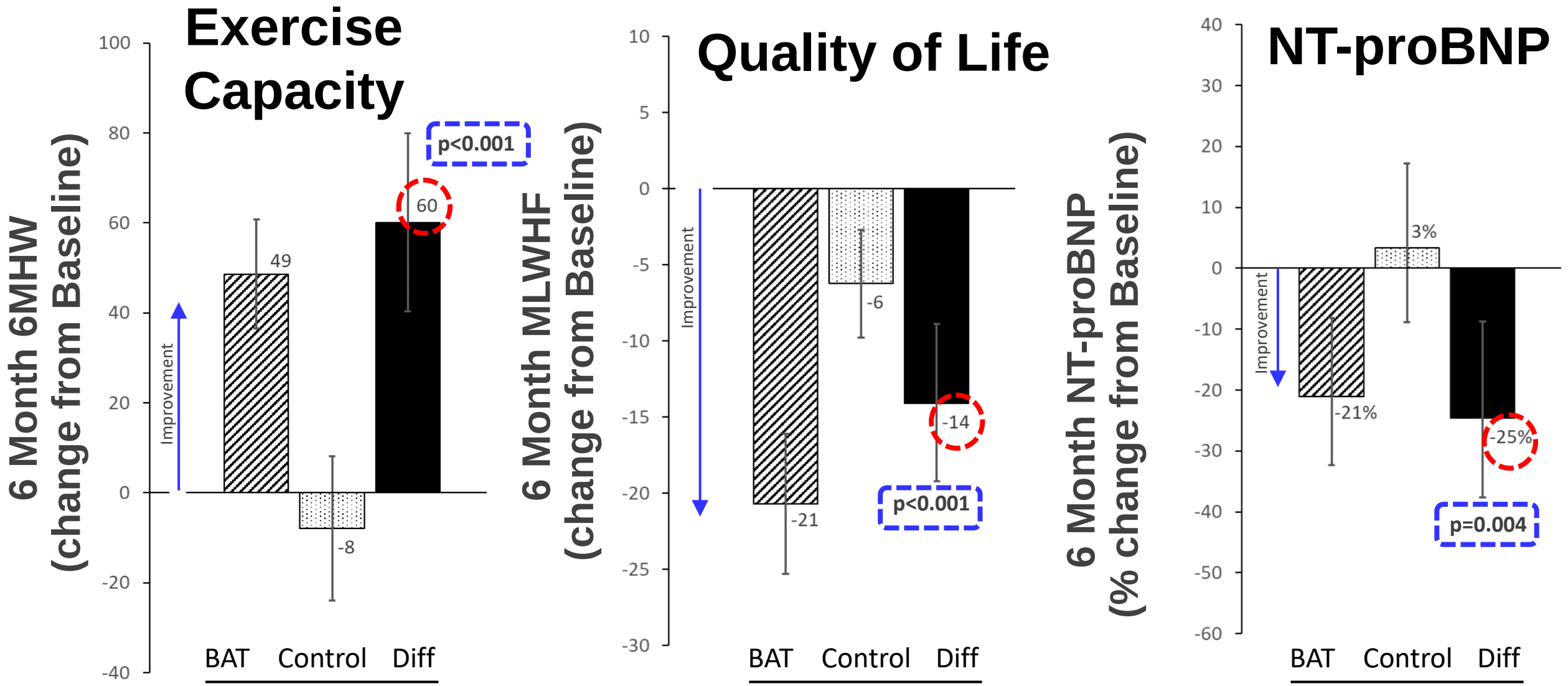
BeAT-HF 6 Month Results: MANCE Safety

System or procedure related Major Adverse Neurological and Cardiovascular Events (MANCE)

MANCE-free rate : 97% (121/125)

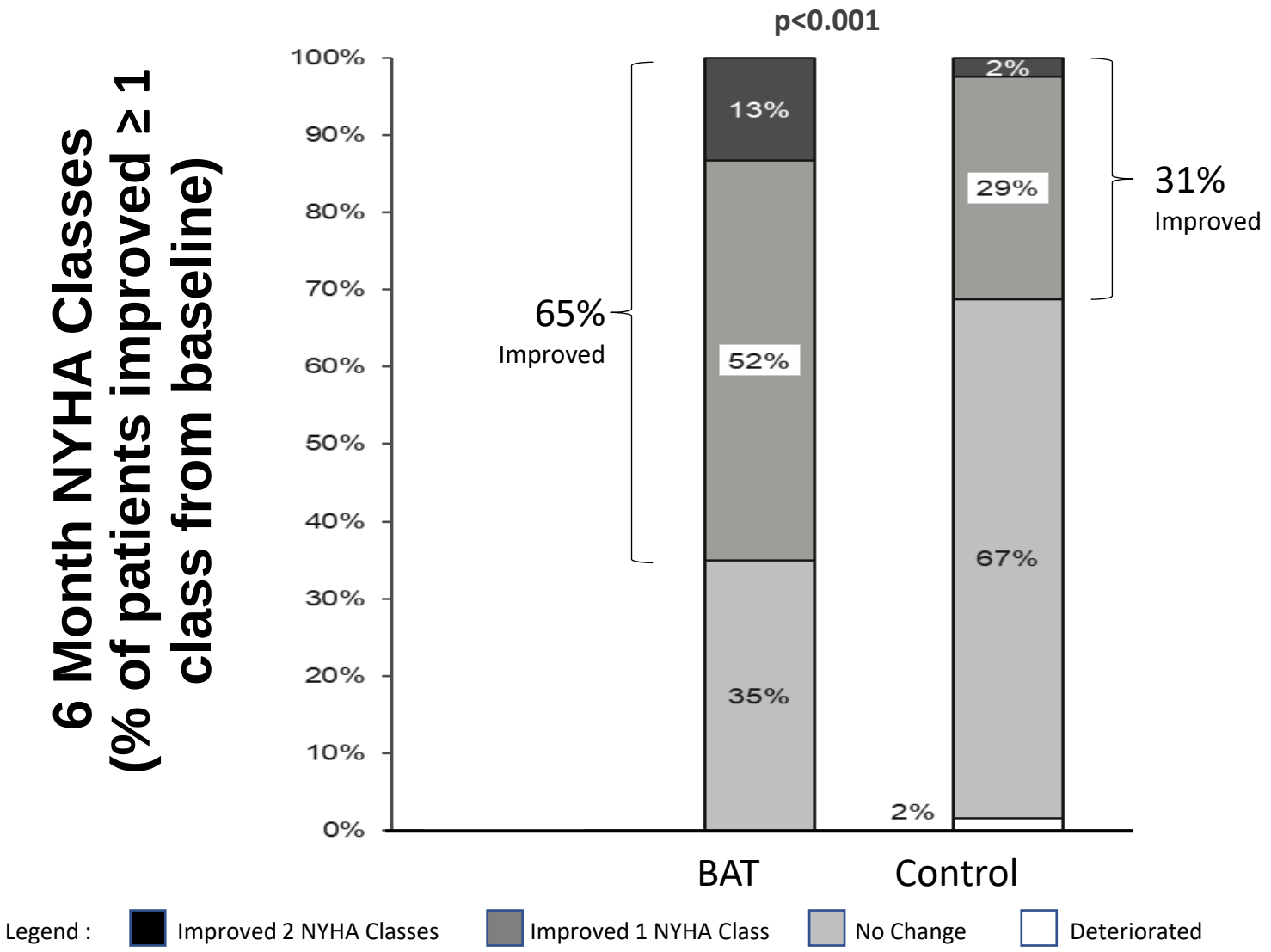
Event	Days since Implant	Outcome	Procedure Related	System Related
Acute decompensated heart failure	1	Recovered, no residual effects	Related	Not related
Postoperative Wound Infection Requiring Explant	6	Recovered, no residual effects	Related	Related
Device Infection Requiring Explant	25	Recovered, no residual effects	Related	Related
Acute left-sided CVA	11	Recovered, with residual effects	Related	Not related

BeAT-HF Top-Line Results



BeAT-HF Top-Line Results

Functional Status



BeAT-HF Medication Changes

- **These significant differences in treatment effect were observed despite an increase in the number medication in the control arms**

Variable	BAT (N=120)	CONTROL (N=125)	Increase in Control
Subjects with new classes of drugs added	21 (18%)	36 (29%)	**+11%***
Subjects with newly added ARNI	5 (4%)	20 (16%)	**+12%***
Subjects with doubling of dose of medications	40 (33%)	44 (35%)	+2%
Subjects with halving of dose of medications	17 (14%)	19 (15%)	+1%

***p-value<0.05**

The number of subjects used (BAT N=120 and Control N=125) is the number of subjects who completed their 6-month visits

Placing Results of BeAT-HF In Context with Other HFrEF Therapies

Name of Trial		BeAT-HF	Miracle	Contak CD	Rhythm ICD	Paradigm-HF
Intervention		BAT	CRT	CRT	CRT	Sac/Val vs Enal
Eligibility Criteria		NYHA III (or II) LVEF≤35% NTproBNP<1600 CRT Not indicated	NYHA III LVEF≤35% QRS≥130ms	NYHA III or IV LVEF≤35% QRS≥120ms	NYHA III or IV LVEF≤35% QRS>150ms	NYHA II - IV LVEF≤40% NT-proBNP≥600 or HF hosp & NT-proBNP≥400
Change in 6-minute walk distance in meters)	Mean	60		39	28 (ns)	
	Median	52	29			
Change in Quality of Life (points)	Mean	-14		-11	-11	
	Median	-17	-9			
NYHA Class Improvement	%	34	30	20		13
	Diffs	-0.5			-0.2	
NT-proBNP	% ↓	-25				-26

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.

BeAT-HF Conclusions

- Baroreflex Activation Therapy is safe in HFrEF patients.
- BAT significantly improves patient-centered symptomatic endpoints
  - quality of life score
  - exercise capacity, and
  - functional status.
- These results are supported by objective evidence of significant reduction of NT-proBNP.
- Success of BeAT-HF was critically dependent upon Breakthrough Devices Program, adaptive design, and FDA collaboration.

Patients who should be considered for Baroreflex Activation Therapy

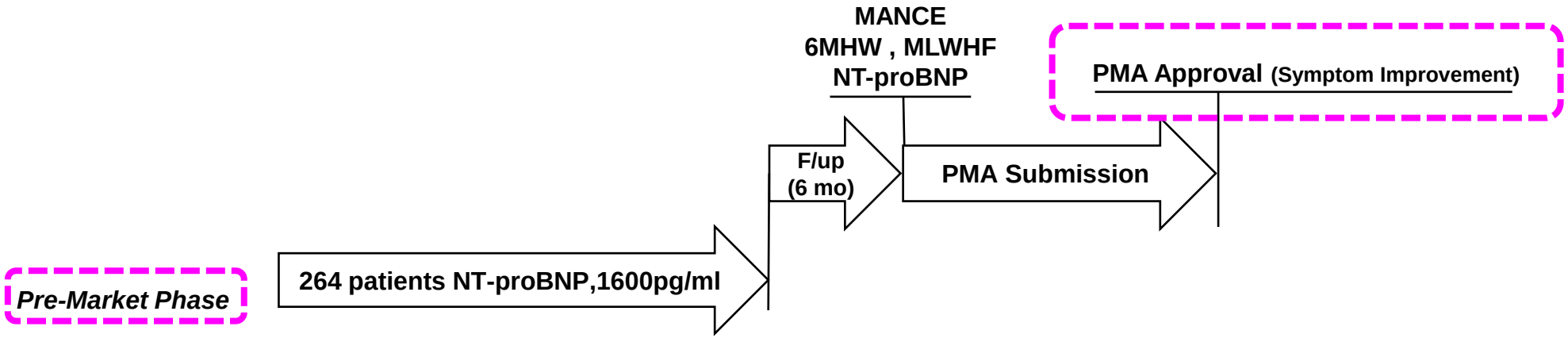
- Any Ejection Fraction ≤ 35%
- NSR or Atrial Fibrillation
- NYHA Class III, or Class II who were recently Class III
- NT-proBNP < 1600 pg/ml
- Not indicated for CRT (59% indicated below in green)

PURPOSE	TYPE	TREATMENT OPTIONS FOR PATIENTS WITH NYHA CLASS II OR III, LVEF ≤ 35%			
		QRS < 120ms	QRS 120-150 w/o LBBB	QRS > 150 w/o LBBB or 120-150 w/ LBBB	QRS > 150 w/ LBBB
Prevent Sudden Cardiac Death	DEVICE	ICD			
Improve HF Symptoms and Outcomes	DRUG	GUIDELINE DIRECTED MEDICAL THERAPY			
	DEVICE	NOT INDICATED FOR CRT 59%	CRT COR IIb "may be considered" 11%	CRT COR IIa "is probably indicated" 16%	CRT COR I "is indicated" 14%

Yancy CW et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Endpoint Strategy: Breakthrough Devices Program Approved Approach

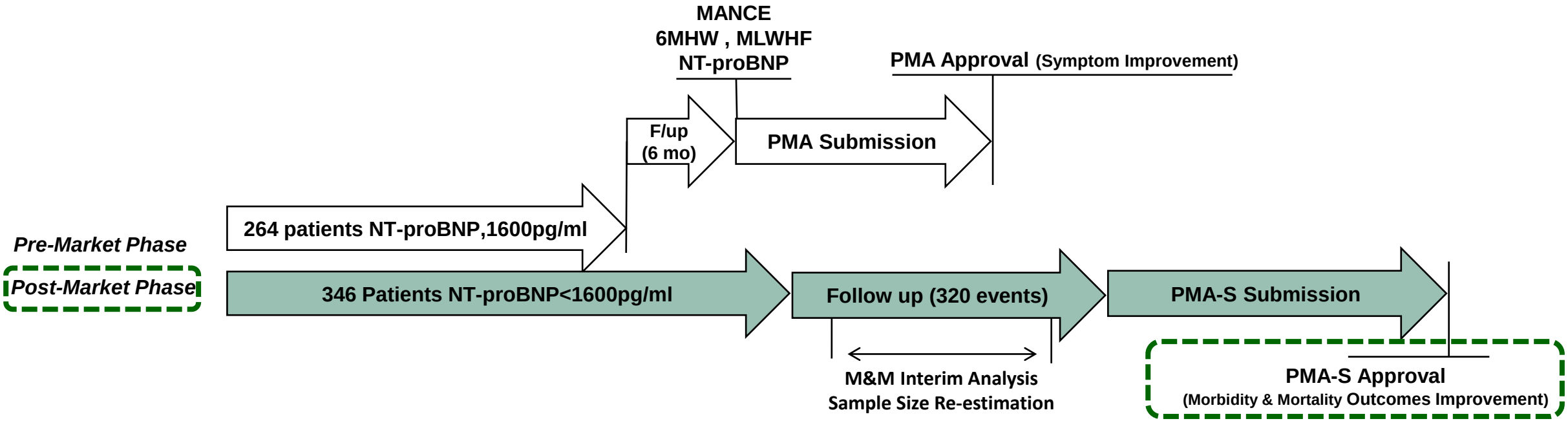
-- Completed



	Sample Size	Analysis Timing	Clinical Evidence
Pre-Market Phase	N = 264 randomized subjects	N = 264 complete 6 months follow-up	• Safety evaluation (MANCE) • NT-proBNP • Six minute hall walk • Minnesota living with heart failure (QOL)

Endpoint Strategy: Breakthrough Devices Program Approved Approach

-- Ongoing



	Sample Size	Analysis Timing	Clinical Evidence
Pre-Market Phase	N = 264 randomized subjects	N = 264 complete 6 months follow-up	• Safety evaluation (MANCE) • NT-proBNP • Six minute hall walk • Minnesota living with heart failure (QOL)
Post-Market Phase	N = 336 randomized subjects (N=264 subjects from Pre-Market Phase + additional N=72 new subjects)	Sufficient morbidity and mortality data collected on all subjects (320 events collected)	• Full morbidity and mortality • Heart Failure Hospitalization • CV Death • Totality of evidence

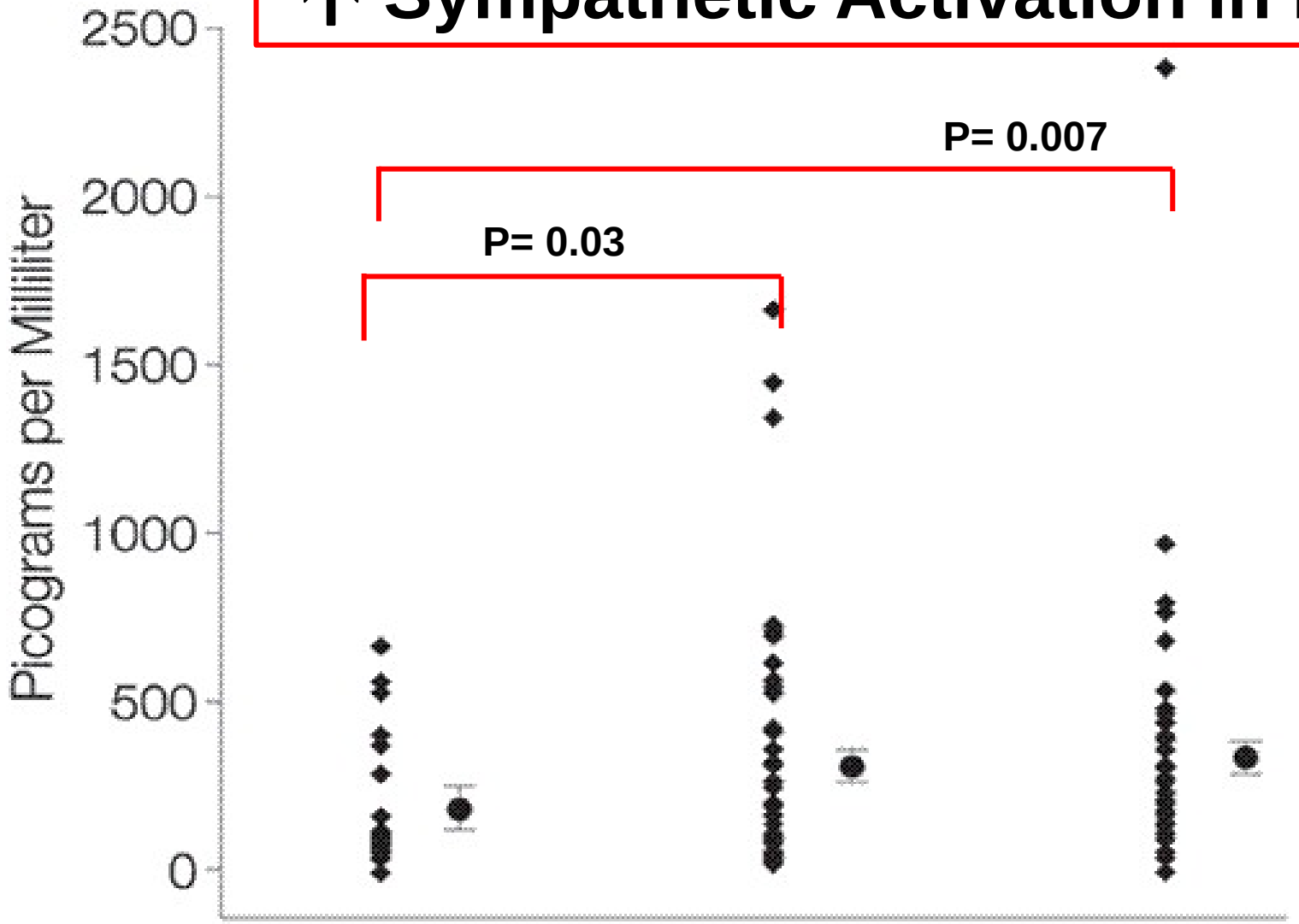
Neuromodulation Using BAT in HFpEF

- Autonomic dysfunction occurs in HFpEF
  - ↑ Sympathetic Activity
  - ↓ Parasympathetic Activity

- HFpEF Data
  - Rheos Hope-4 HF
  - European Hypertension Registry

- Future Applications of BAT
  - Hypertension
  - HFpEF
  - HFpEF in patients with hypertension

Plasma Norepinephrine:
↑ Sympathetic Activation in HFpEF



JAMA 288: 2144-2150, 2002

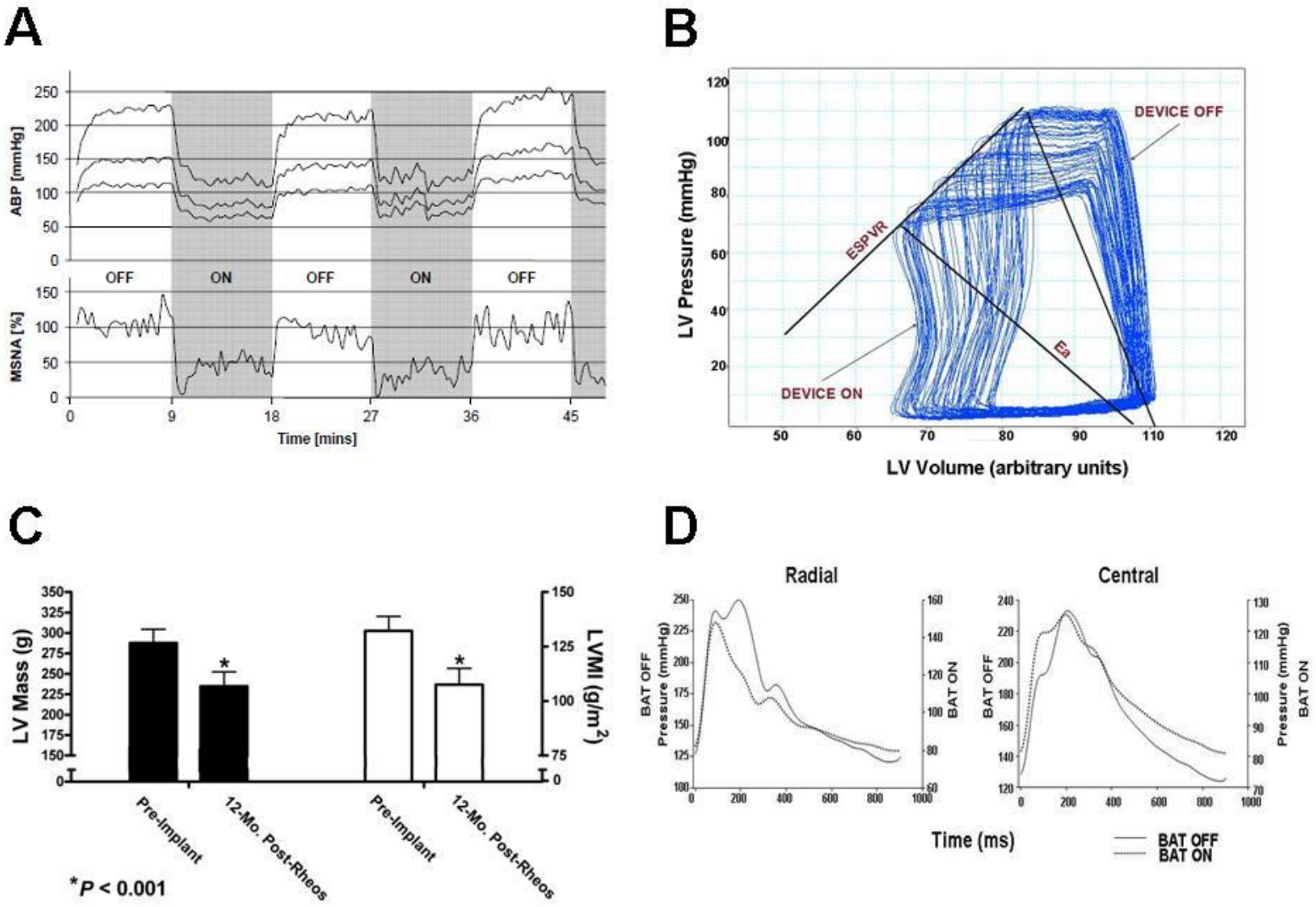
Heart Rate Variability Analysis: ↓ Parasympathetic Activity

	HFrEF	HFpEF	Normal	P Value HFpEF vs Normal
Time Domain				
Average NN	825.8 ± 219.6	825.7 ± 112.4	765.7 ± 195.2	0.63
SDNN	94.4 ± 33	121.9 ± 31*	137.8 ± 32.9	0.03
pNN50%	3.4 ± 3.5	6.5 ± 8.2	18.2 ± 10.6	0.001
ASDNN	38.8 ± 12.0	46.3 ± 18.6	65.1 ± 20.8	0.01
SDANN	80.6 ± 26.5	106.5 ± 33.1	120.2 ± 32.9	0.046
Frequency Domain				
5 min (total)	1739.3 ± 852	2587.2 ± 2901.4	4437 ± 2425	0.087
5 min LF	373.5 ± 282.3	606.2 ± 1022.3	1143 ± 806.8	0.17
5 min HF	210.4 ± 178.5	493.2 ± 1233.5	835.9 ± 661.2	0.42
5 min LF/HF	2.7 ± 1.9	2.9 ± 2.4	1.7 ± 1.2	0.36
24 hours (total)	4872.4 ± 2686.3	10385.3 ± 5249.5†	17512 ± 10294	0.001
ULF	4284.9 ± 1684.1	7837.5 ± 4551‡	12892 ± 7893	0.006
VLF	890.6 ± 468.8	1278.8 ± 886.9	2111 ± 1307	0.03
24 hour LF	329.6 ± 260.2	648.2 ± 1111.6	1214 ± 807	0.14
24 hour HF	171.6 ± 168.4	538.3 ± 1287.4	1041 ± 1039	0.26
24 hour LF/HF	2.9 ± 1.9	3.1 ± 3.1	1.6 ± 1.0	0.32

Time and Frequency domain variables reduced in HFpEF compared to controls
↓ HRV, suggesting = disturbed sympathetic-parasympathetic balance

PACE 2004, 27:299-303

Rationale for BAT in HFpEF



A. Acute impact of BAT on muscle sympathetic nerve activity, showing rapid reductions in sympathetic traffic concomitant with pressure reduction induced by activation of BAT.

B. Acute effects of BAT on cardiac pressure-volume relationships, demonstrating preserved contractility, reduced filling pressure, reduced arterial stiffness, and greater stroke volume.

C. Chronic effects of BAT on left ventricular mass, showing significant reductions in LV mass and mass index.

D. Impact of acute BAT on central pressure waveform derived from radial tonometry, demonstrating reduction in augmentation index and prolonged diastolic pressure decay by attenuation of reflected wave amplitude and improved arterial stiffness. Note that the left axes represent pressures when BAT is off and the right axes represent pressures with BAT on.

Georgakopoulos et al, Journal of Cardiac Failure, 2010:1-12

HFpEF Clinical Studies: Effects of BAT

HFpEF Registry (Germany)	RHEOS HOPE4HF
CE-Mark approved indications: resistant hypertension	
○ Systolic blood pressure ≥ 140 mmHg AND	Systolic blood pressure ≥ 140 mmHg & ≤ 180 mmHg
○ Resistance to max tolerated therapy with a diuretic and two other anti-hypertension medications	On ≥3 antihypertensive medications, including a diuretic
Left ventricular ejection fraction ≥ 50%	Left ventricular ejection fraction ≥ 40%
On stable, maximally-tolerated, guideline-directed cardiovascular medications	On stable anti-hypertensive therapy
Hospitalization for heart failure within 12 months prior to enrollment **OR** Echocardiographic evidence of diastolic dysfunction (LA Volume Index >34 ml/m2 OR E/e >13) within 30 days prior to enrollment **OR** NTproBNP > 220 pg/mL or BNP > 80 pg/mL (in atrial fibrillation, NTproBNP > 600 pg/mL or BNP > 200 pg/mL) within 30 days prior to enrollment	Symptomatic HFpEF, NYHA Class II-IV **AND** Heart failure event within 12 months prior to randomization and BNP ≥ 125 pg/mL or NT-proBNP ≥ 500 pg/mL **AND** BNP ≤ 1250 pg/mL or NT-proBNP ≤ 3500 pg/mL

Baseline Characteristics by Study

Variable mean / %	RHEOS HOPE4HF	HFpEF Registry
NYHA: Class II / III	37% / 58%	17% / 83%
SBP (mmHg)	143	187
DBP (mmHg)	74	102
LVEF (%)	57%	58%
NT-proBNP (pg/mL)	Mean: 1416	Mean: 4533 Median: 585

HFpEF Registry Results (single arm)

	SBP Change 3M / 6M	DBP Change 3M / 6M	NT-proBNP Relative Change 3M /6M	NYHA % Improved 3M / 6M
Median	-10 / -38	-11 / -18	-10% / -35%	60% / 80%
Mean	-13 / -26	-10 / -15	-27% / -28%	

RHEOS HOPE4HF Results (randomized controlled)

	Device	Control	Difference
Repeated Measures (6 and 12 months)	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**
Aortic SP (bpm)	-21.7 ± 4.8	-3.3 ± 4.8	-18.5 ± 6.7
LV Mass Index	5.6 ± 10.0	14.5 ± 7.1	-8.8 ± 12.3
NT proBNP	422.1 ± 585.6	1027.7 ± 562.7	-605.6 ± 812.1
SBP (mmHg)	-16.3 ± 6.8	-9.8 ± 7.3	-6.5 ± 9.9
DBP (mmHg)	-5.3 ± 4.4	1.0 ± 4.7	-6.3 ± 6.4

Does Neuromodulation Using Baroreflex Activation Therapy have Potential Application in HFpEF?

- **Autonomic dysfunction occurs in HFpEF and constitutes a feasible target for BAT**
- **HFpEF Preliminary Clinical Studies Data suggests beneficial effects**
- **Future Applications of BAT should include patients with:**
  - **Hypertension**
  - **HFpEF**
  - **HFpEF in patients with hypertension**