

# Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction

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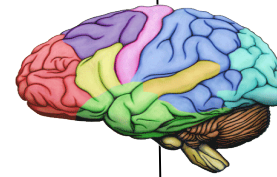
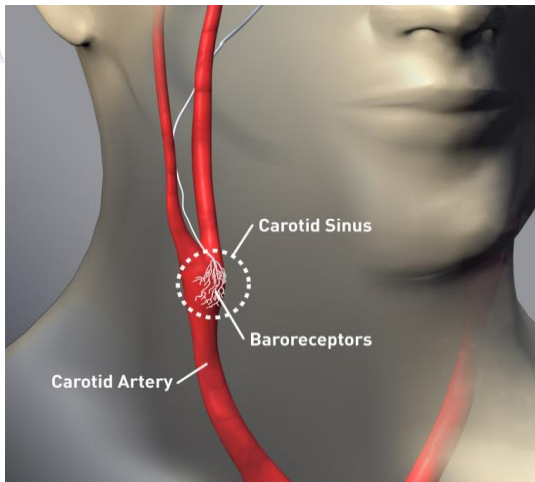
## Background

- Increased sympathetic and decreased parasympathetic activity contribute to heart failure symptoms and disease progression
- Baroreflex activation therapy (BAT) results in centrally mediated reduction of sympathetic outflow and increased parasympathetic activity
- Preliminary observations suggest that BAT improves clinical status and outcomes in patients with heart failure and a reduced ejection fraction (HFrEF)<sup>1</sup>

<sup>1</sup>Gronda E, et al. Eur J Heart Fail 2014; 16:977-983.

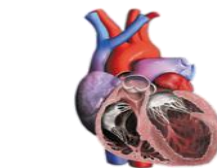
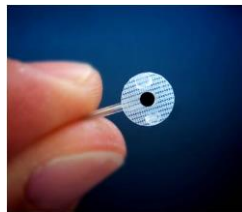
# The Baroreflex as a Therapeutic Target

## Carotid Baroreceptor Stimulation



### **Integrated Autonomic Nervous System Response**

Inhibits **Sympathetic** Activity  
Enhances **Parasympathetic** Activity



↓ HR  
↓ Remodeling



↑ Vasodilation  
↓ Elevated BP



↑ Diuresis  
↓ Renin secretion

## BAT for HFrEF: Study Objective and Design

- Objective: Evaluate the efficacy and safety of the CVRx *neo*<sup>TM</sup> Baroreflex Activation Therapy System in subjects with chronic heart failure and reduced ejection fraction
- Design: Multi-national, prospective, randomized controlled trial
  - Subjects randomized 1:1 to receive BAT plus optimal medical therapy or optimal medical therapy alone
  - Enrollment in the US, Germany, Italy, France and Canada

## BAT for HFrEF: Key Enrollment Criteria

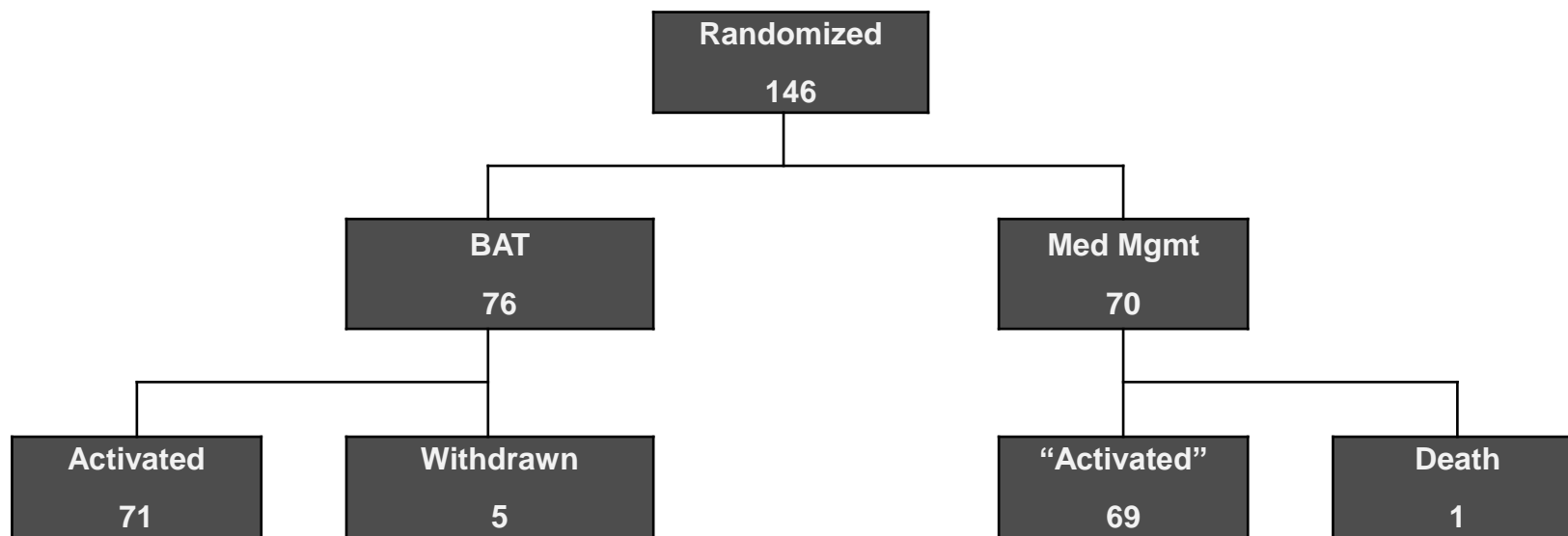
- NYHA Functional Class III
- Left ventricular ejection fraction  $\leq 35\%$
- Six-minute hall walk distance 150 - 400 m
- On stable optimal medical therapy for at least 4 weeks prior to baseline assessment
- No restriction on QRS, concomitant devices\*, or AF

\*  $\geq 6$  months of CRT therapy in patients with CRT

## BAT for HFrEF: Trial Oversight

Oversight	Details
Data Monitoring Committee (DMC)	Full review every 6 months
Heart Failure Steering Committee	Biweekly meetings
Independent Clinical Monitors	100% source verification
Clinical Events Committee	Hospitalization adjudication
Independent Biostatistician	All statistical analyses
Adverse Event Committee	Adverse event adjudication

## BAT for HFrEF: Subject Disposition



- To receive a randomization assignment, the intended date of BAT initiation was identified as the “activation date”
- The activation date determined the schedule for all follow-up visits for both Med Mgmt and BAT group

## BAT for HFrEF: Baseline Demographics

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

\*Median [IQR]

†p≤0.05 between groups



## BAT for HFrEF: Baseline Medications

Variable	BAT (n=71)	Med Mgmt (n=69)
Number of Meds	4.8	4.4
ACE/ARB	80%	81%
Beta-Blocker	87%	85%
Calcium Channel Blocker	6%	9%
Digitalis	21%	10%
Diuretic†	93%	78%
Ivabradine	4%	2%
MRA	59%	50%
CRT	34%	30%
ICD	89%	86%

†p≤0.05 between groups



## BAT for HFrEF: Primary Safety Endpoint

System- or Procedure-Related Major Adverse Neurological or Cardiovascular Events (MANCE) at 6 months

97% Event-Free Rate  
71 Subjects Implanted

2 Pocket hematomas (1 and 7 days from implant)

# Other System- or Procedure-Related Complications

- No death, stroke, or cranial nerve injury
- All but one\* occurred within 7 days of implant and recovered with no residual effect:

## General Surgical

- 2 Urinary retention / urinary tract infection
- 1 Pneumothorax due to improper subcutaneous needle placement
- 1 Cervical Neuralgia\*

## Cardiovascular (All events began during or within 24 hours of implant)

- 2 Non-sustained atrial arrhythmias
- 1 Transient bradycardia
- 1 Transient hypotension
- 1 Transient worsening heart failure



## BAT for HFrEF: Other Safety Observations

- BAT does not cause hypotension in patients with advanced heart failure
  - No reports of symptomatic hypotension
  - SBP significantly increased in BAT group; DBP unchanged
- BAT is compatible with co-existing cardiac rhythm management devices

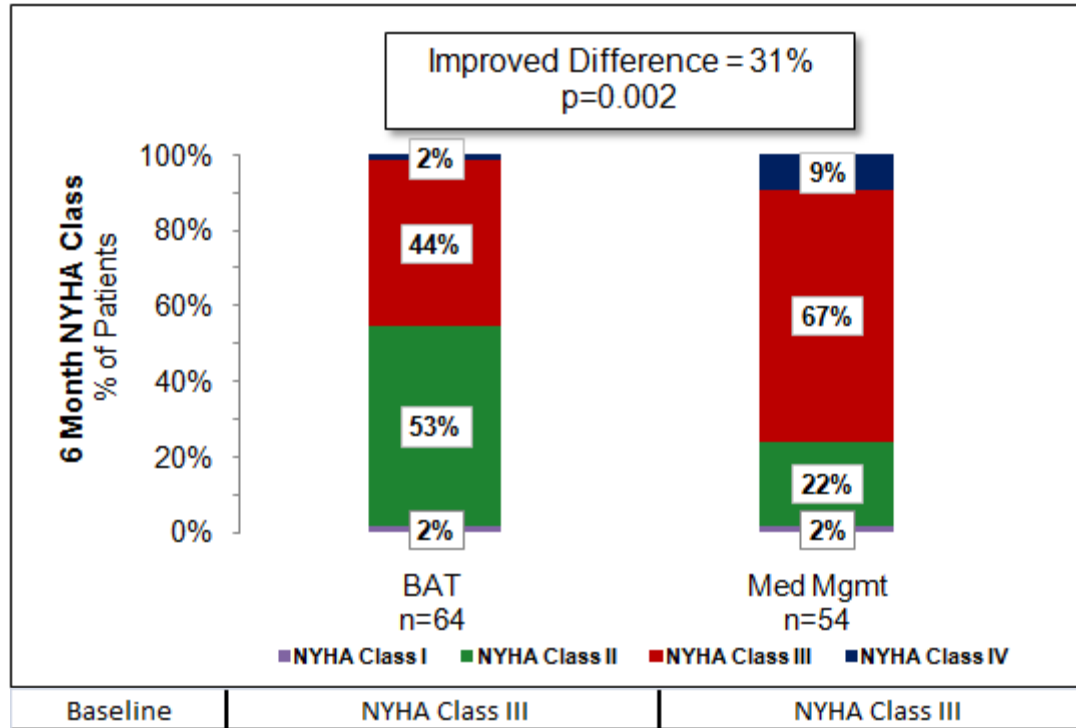


## BAT for HFrEF: Efficacy Endpoints

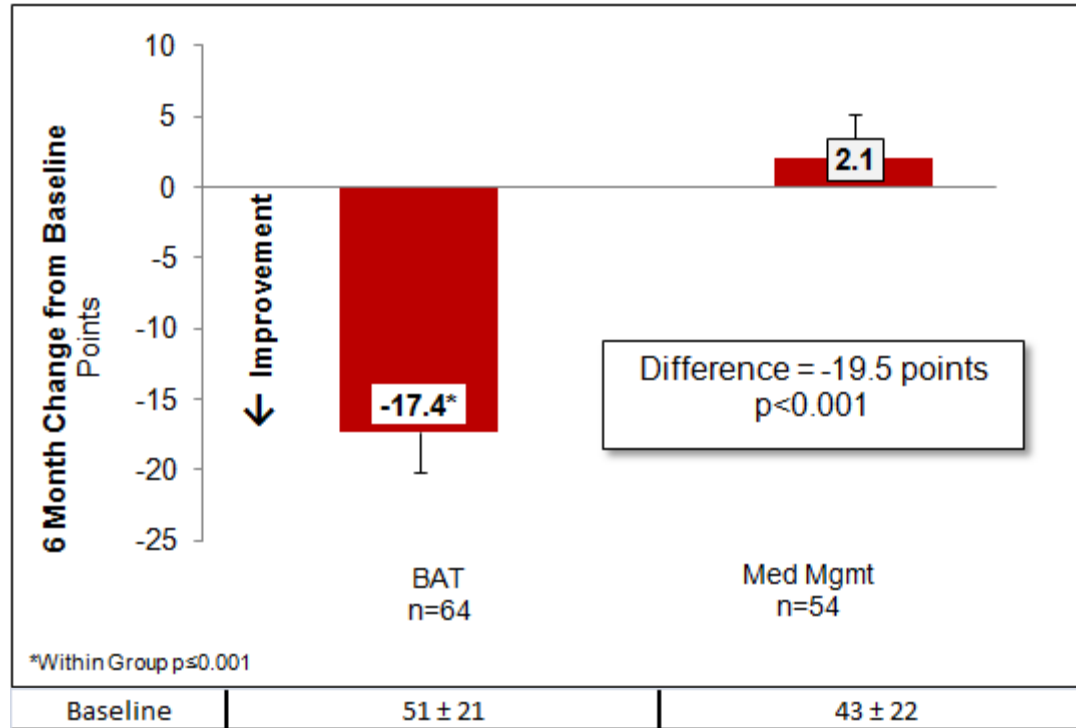
- Change from baseline to 6 months in
  - New York Heart Association Functional Class Rank
  - Minnesota Living with Heart Failure Quality of Life Score
  - Six-Minute Hall Walk (6-MHW) Distance
  - Serum Biomarker (NT-proBNP)
  - Left Ventricular Ejection Fraction
  - Hospitalizations (Days) for Worsening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

\*Baseline defined as 6 months prior to enrollment

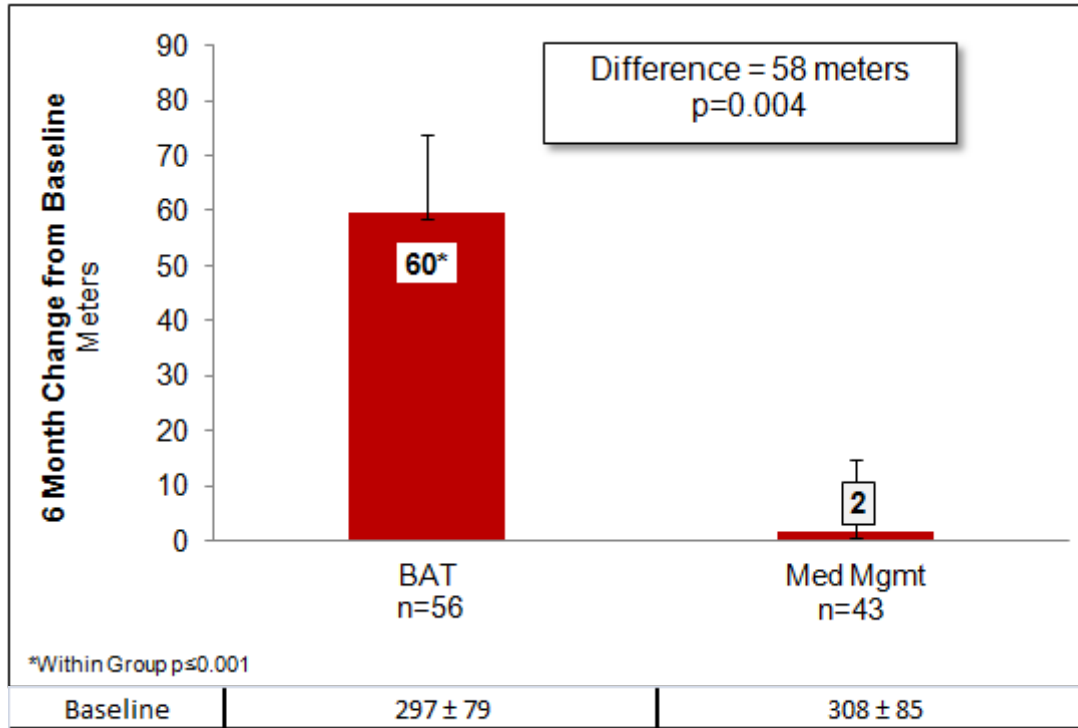
# BAT Significantly Improves NYHA Class



# BAT Significantly Improves Quality of Life Score

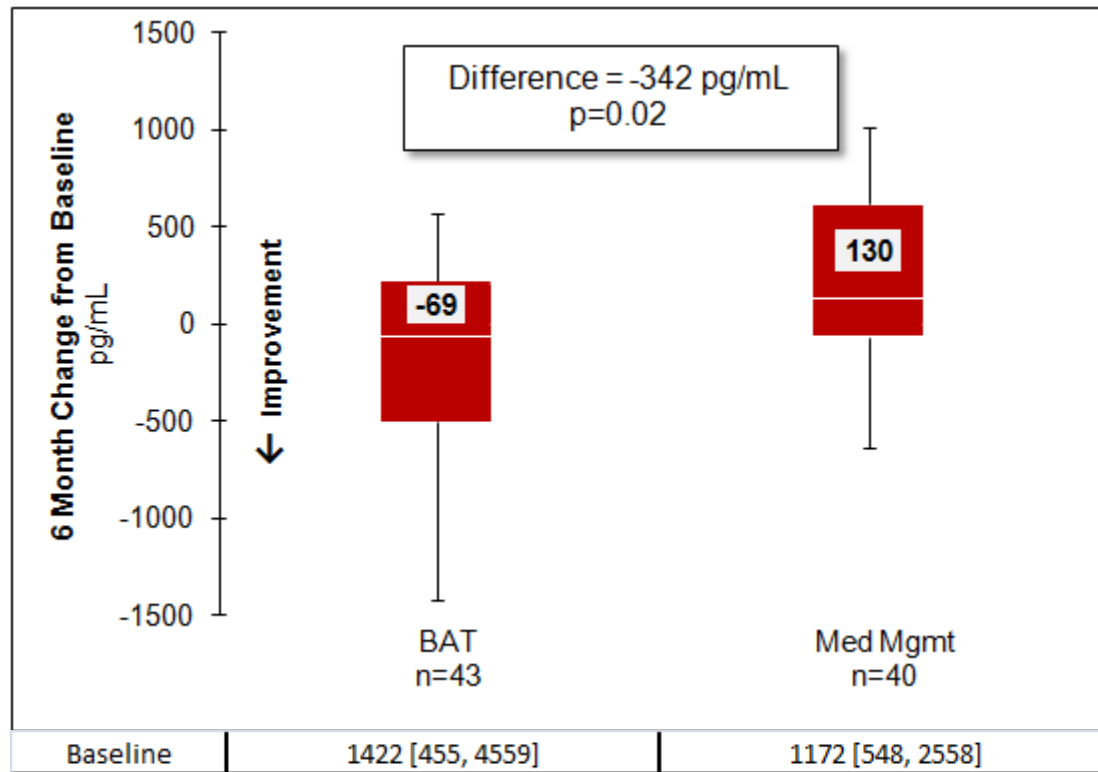


# BAT Significantly Improves 6-MHW Distance



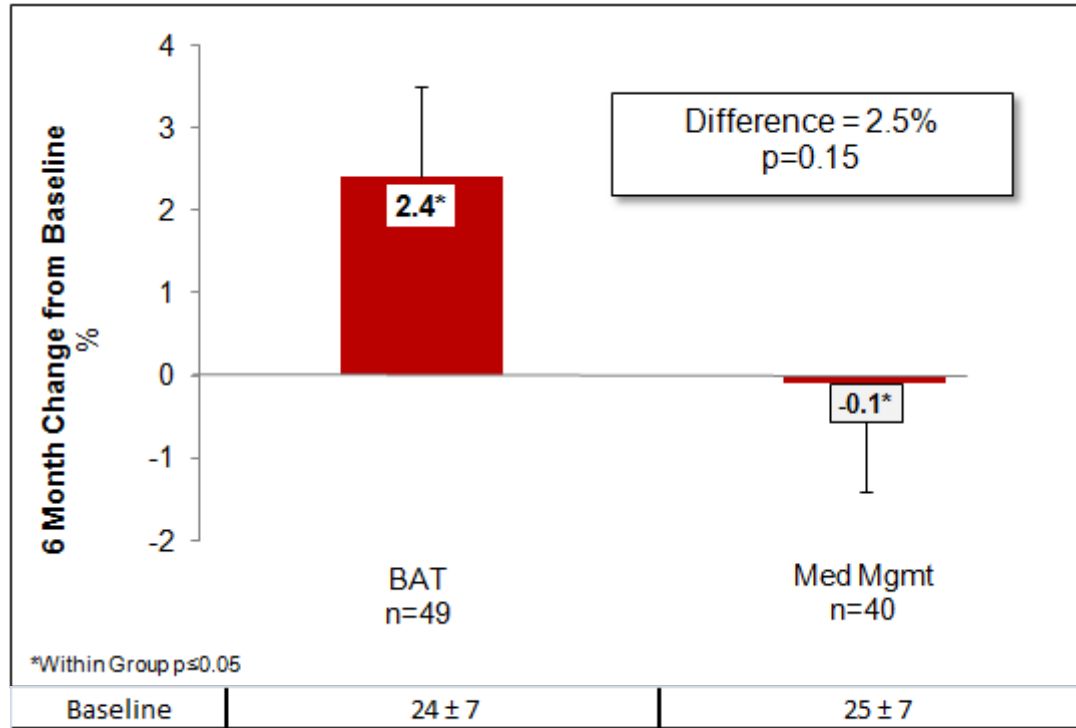


# BAT Significantly Reduces NT-proBNP Levels



Non-parametric (median [IQR])

# Effect of BAT on LV Ejection Fraction



# Effect of BAT on Number of Hospitalization Days for Heart Failure

Variable	BAT (n=57)	Med Mgmt (n=50)	Difference Mean $\pm$ SE
HF Hospitalization Days per Year			
6 Months Pre-Enrollment	6.95 $\pm$ 20.7	2.40 $\pm$ 8.6	4.55 $\pm$ 34
6 Months Post Enrollment	0.67 $\pm$ 2.5	2.48 $\pm$ 7.4	-1.82* $\pm$ 1
Change from Pre to Post	-6.28** $\pm$ 2.7	0.08 $\pm$ 1.7	-6.36** $\pm$ 3
Negative Binomial 6M Post	0.38	2.10	82% RR <sup>†</sup> *

\*p $\leq$ 0.10; \*\*p $\leq$ 0.05

<sup>†</sup>RR – Relative Reduction adjusted for 6 months Pre-Enrollment Heart Failure Hospitalizations (Negative Binomial Model)

# Concordance of Results Support BAT Efficacy in HFrEF


	Difference	p value	Favors
NYHA (% improved)	31	< 0.01	BAT
MLWHF QoL Score (points)	20	<0.001	BAT
6-MHW Distance (m)	58	<0.01	BAT
NT-proBNP (pg/ml)*	342	0.02	BAT
LVEF (absolute %)	2.5	0.15	BAT
Hospitalization Days for Worsening HF (days/pt/yr)	6.4	0.05	BAT

\* Median



## BAT for HFrEF: Summary

- Baroreflex Activation Therapy is safe in HFrEF patients
  - No system- or procedure-related deaths
  - Few and short-lived complications; complication rate comparable to established HF device therapies
  - No hypotension
- BAT significantly improves NYHA Class, quality of life score, exercise capacity, NT-proBNP, and possibly the burden of heart failure hospitalizations
- If these observations are confirmed in a larger study, BAT may offer a new addition for the treatment of advanced HFrEF patients



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Manuscript online today at *JACC Heart Failure*  
<http://heartfailure.onlinejacc.org>