

Evidence of Baroreflex Activation Therapy's Mechanism of Action

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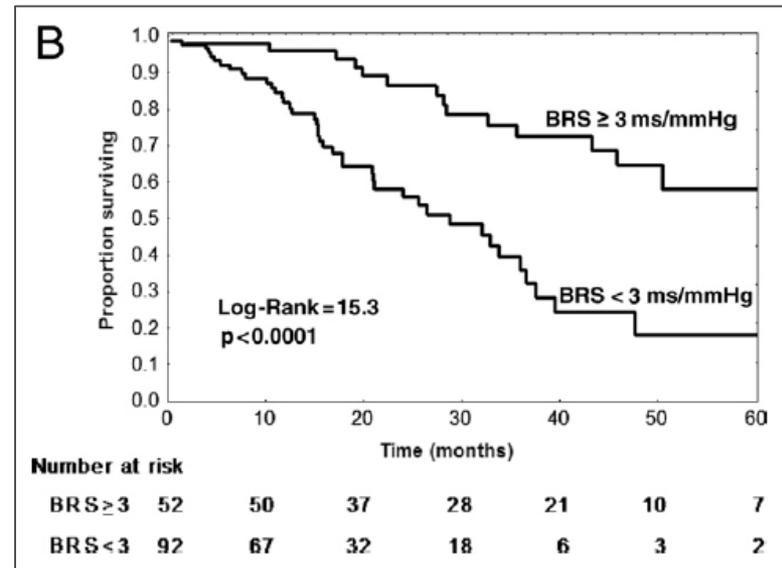
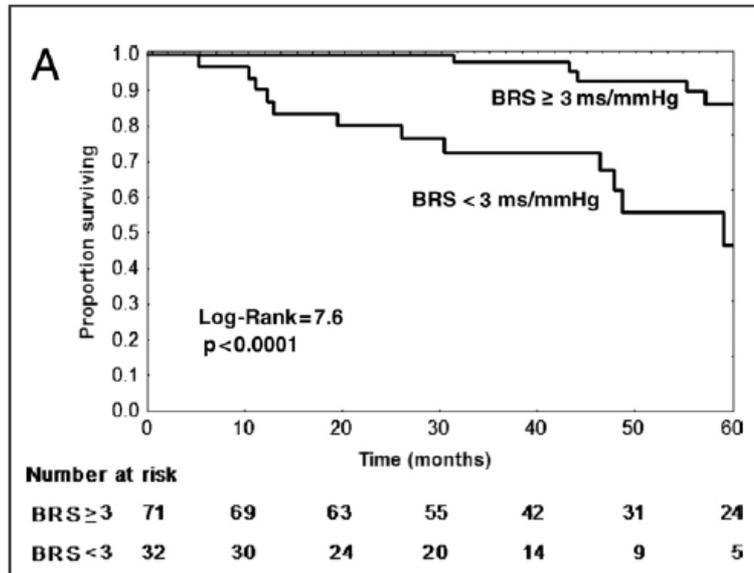
Agenda

- 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



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Baroreflex Sensitivity (BRS) and HF Mortality: PREDICTIVE VALUE PRESERVED WITH β BLOCKADE

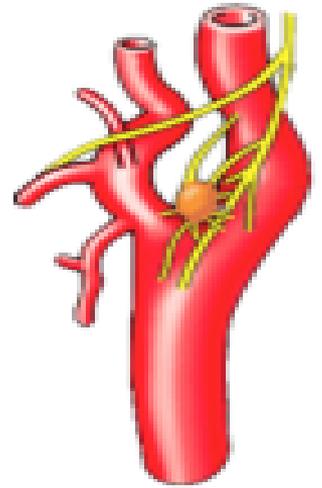


Kaplan-Meier survival curves according to dichotomized baroreceptor-heart rate reflex sensitivity (BRS) in patients (A) taking and (B) not taking beta-blockers.

La Rovere MT JACC 2011

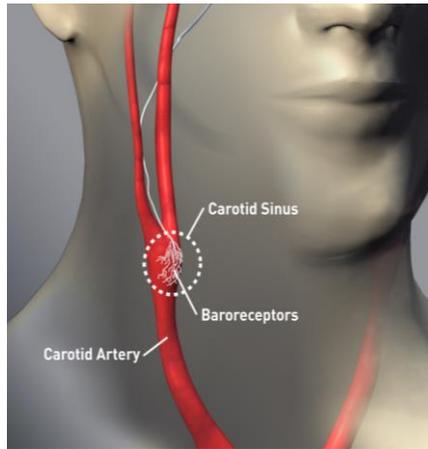
Is the baroreceptor a valuable target for HF treatment?

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.



Floras JS JACC 2009

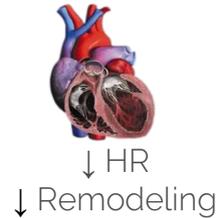
The baroreflex is a therapeutic target



Carotid Baroreceptor Stimulation



Integrated Autonomic Nervous System Response
Inhibits **Sympathetic** Activity
Enhances **Parasympathetic** Activity



↑ Vasodilation
↓ Elevated BP



↑ Diuresis
↓ Renin secretion

Agenda

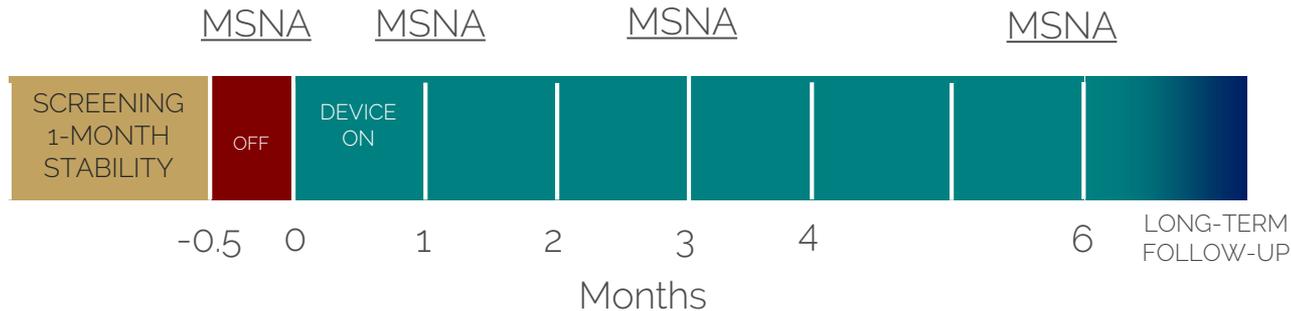
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Proof of Concept Investigation: DESIGN

- Single-center, open label study conducted in Milan, Italy
- Optimal, Stable Medical Therapy:
 - Prescribed β -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



Proof of Concept Investigation:

MAIN INCLUSION CRITERIA

- NYHA Class III 
- Left Ventricular EF $\leq 40\%$
- 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:

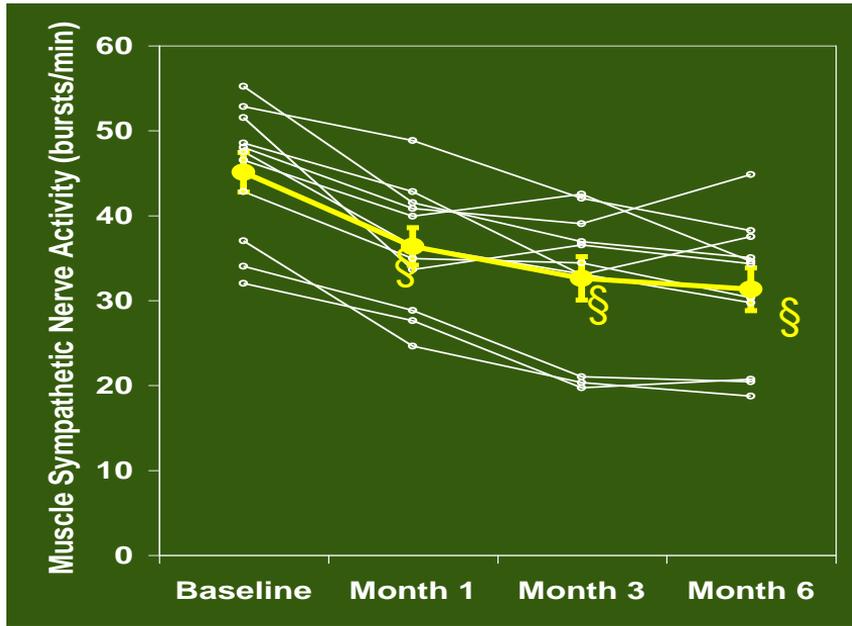
HF POPULATION BASELINE CHARACTERISTICS

Characteristic (N=11)	N (%) or Mean \pm SD
Race, Caucasian	10 (91%)
Sex, Female	3 (27%)
History of Atrial Fibrillation	3 (27%)
Age (years)	67 \pm 9
BMI (kg/m ²)	26 \pm 5
LV Ejection Fraction (%)	31 \pm 7

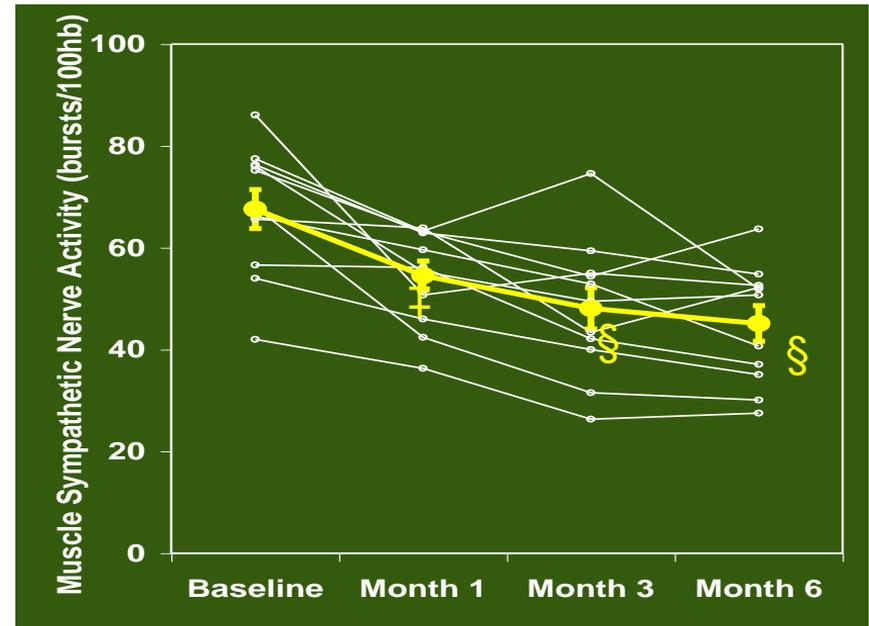
HF Medication	N (%) of Patients
ACE-Inhibitor or ARB	10 (91%)
β -blocker	10 (91%)
Diuretic – loop	11 (100%)
Diuretic – thiazide	1 (9%)
Diuretic – other	3 (27%)
Other	7 (64%)

BAT showed a positive impact on Muscle Sympathetic Nerve Activity (MSNA)

MSNA: bursts /minute



MSNA: bursts /100 heartbeats

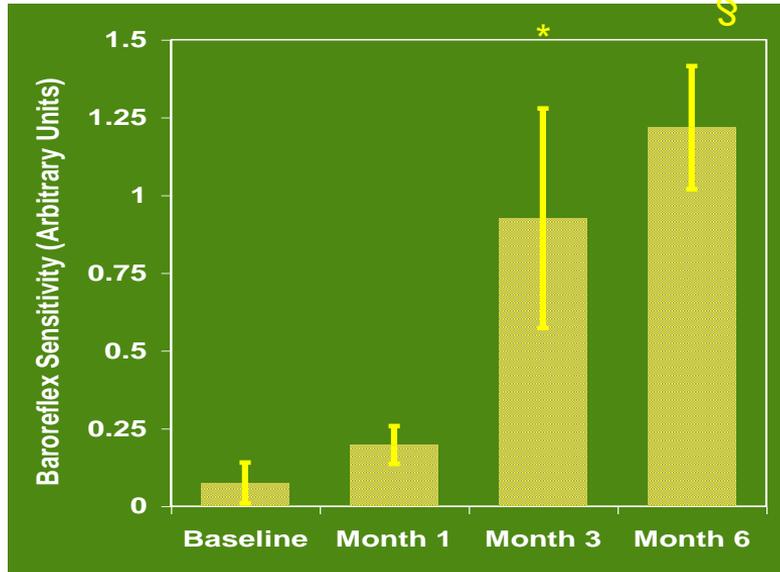


Gronda E et al. EJHF 2014

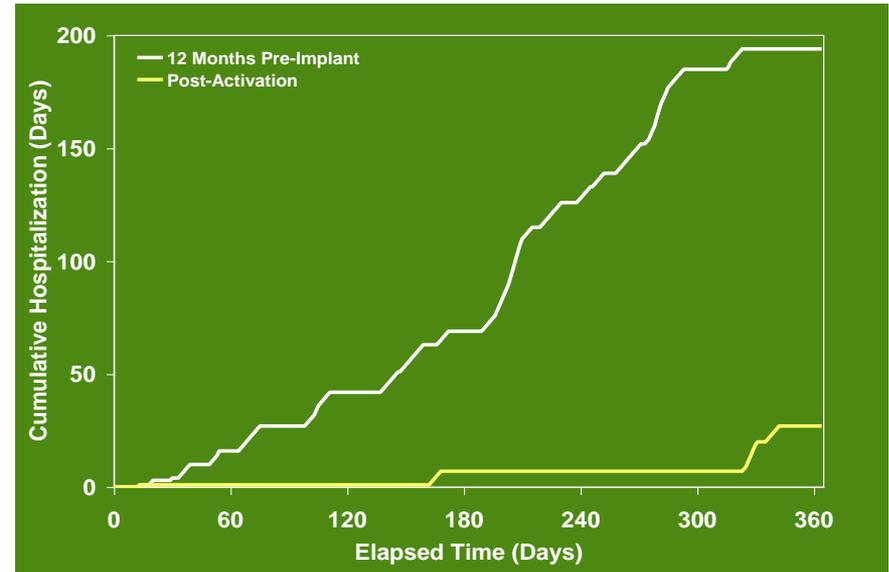
N=11; Mean \pm SE; † $p < 0.005$, § $p < 0.001$ vs. Baseline

Baroreflex Sensitivity was restored & mirrored by a striking reduction in hospital admission rates

Baroreflex Sensitivity



Hospital Resource Utilization



Gronda E et al. EJHF 2014

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

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- Current Baroreflex Activation Therapy Placement in HFrEF Patient Management



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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

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

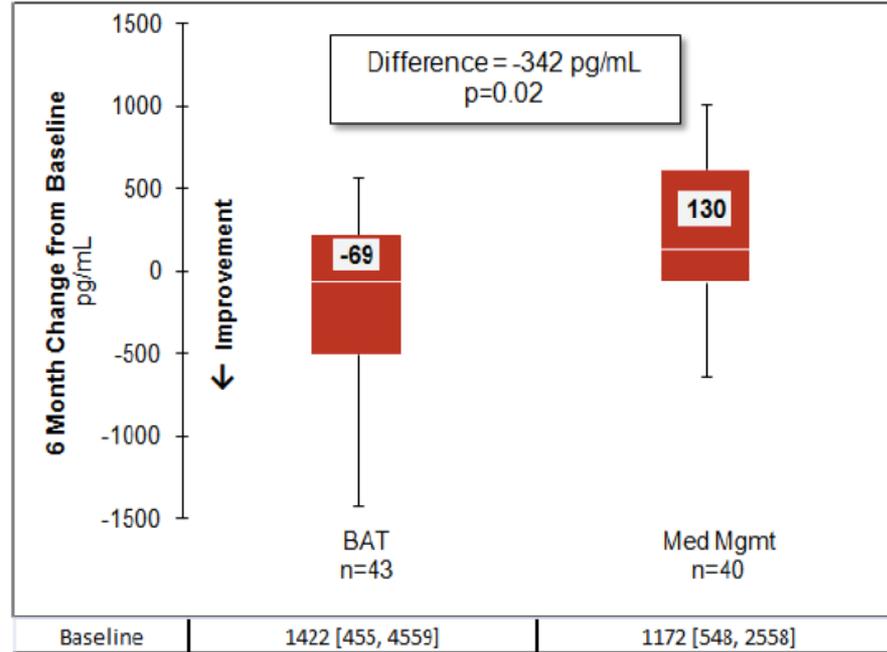
*Median [IQR]; †p<0.05 between groups

BAT for HFrEF Randomised Controlled Trial: 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 significantly reduces NT-proBNP levels



Abraham WT JACC-HF 2015 Non-parametric (median [IQR])

Concordance of results supports 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

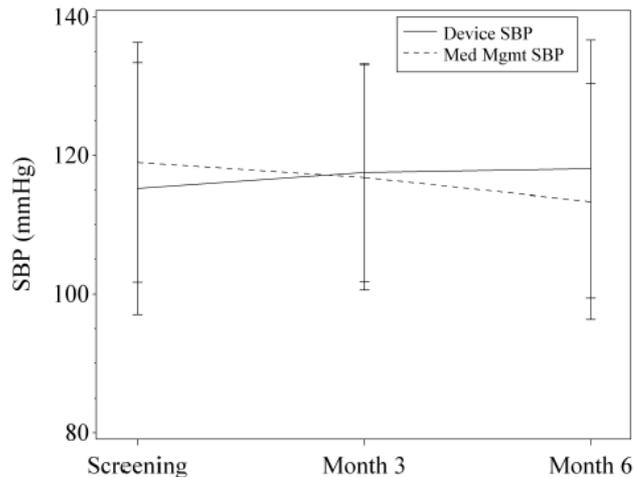
Abraham WT et al. JACC-HF 2015

* Median

Are blood pressure results consistent across HFrEF and resistant hypertension?

HFrEF

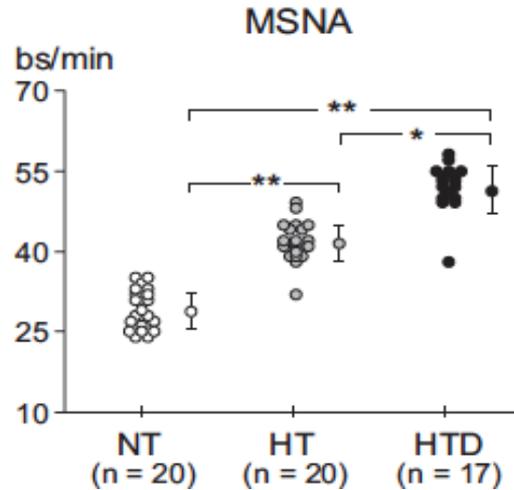
SBP SIGNIFICANTLY INCREASED IN BAT ARM



Abraham WT et al. JACC-HF 2015

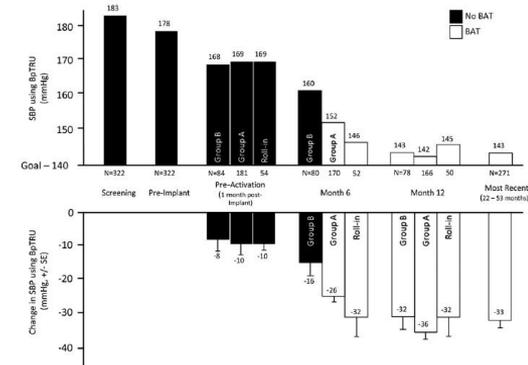
rHTN

MSNA TRAFFIC IS SIGNIFICANTLY GREATER IN HYPERTENSIVE SUBJECTS



Grassi G et al. Hypertension. 2009

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

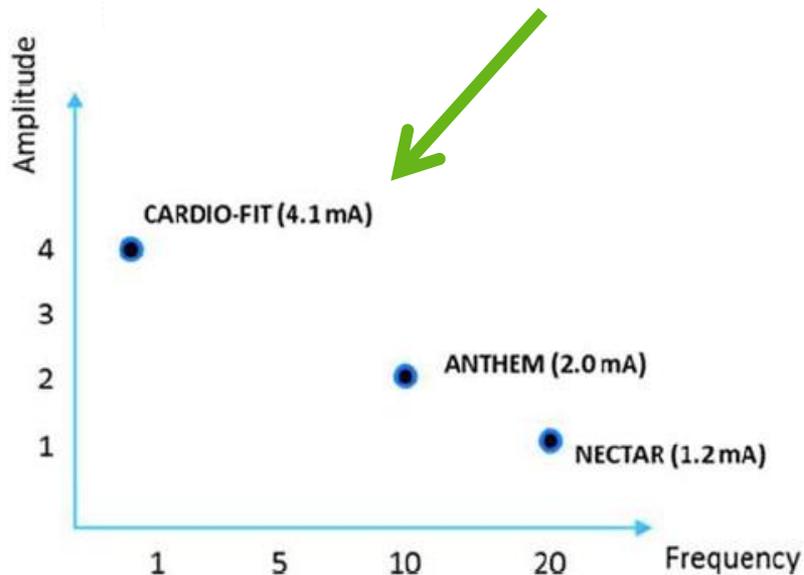


Bakris GL et al. JASH 2012

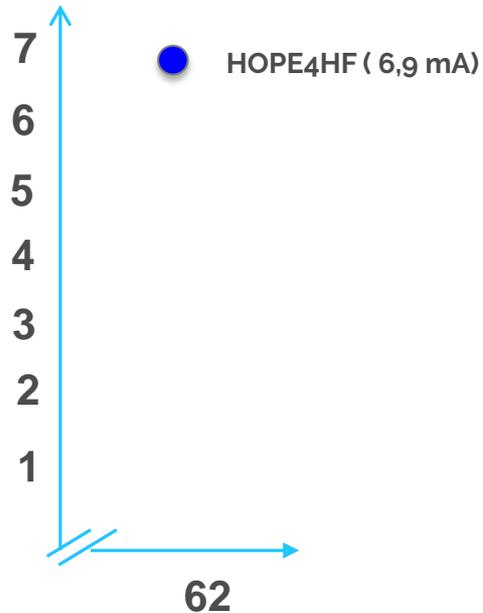
The Dose-Response Concept:

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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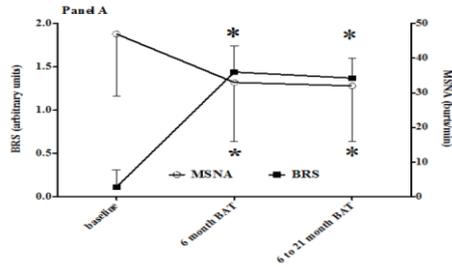


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BAT in HF Proof of Concept Investigation showed sustained effects after 21 & 42 months

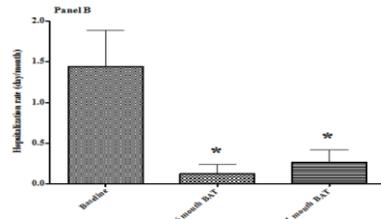
AFTER 21 MONTHS

MSNA, BRS



Gronda E J Hypertension 2016

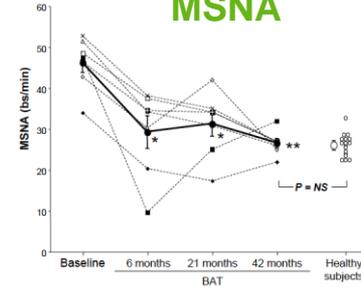
HF HOSPITALIZATION DAYS/MONTH



Gronda E JH 2015

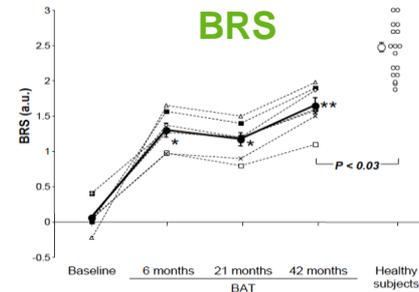
AFTER 42 MONTHS

MSNA



Dell'Oro R J Hypertension 2017

BRS



Gronda E ESC-HF 2017

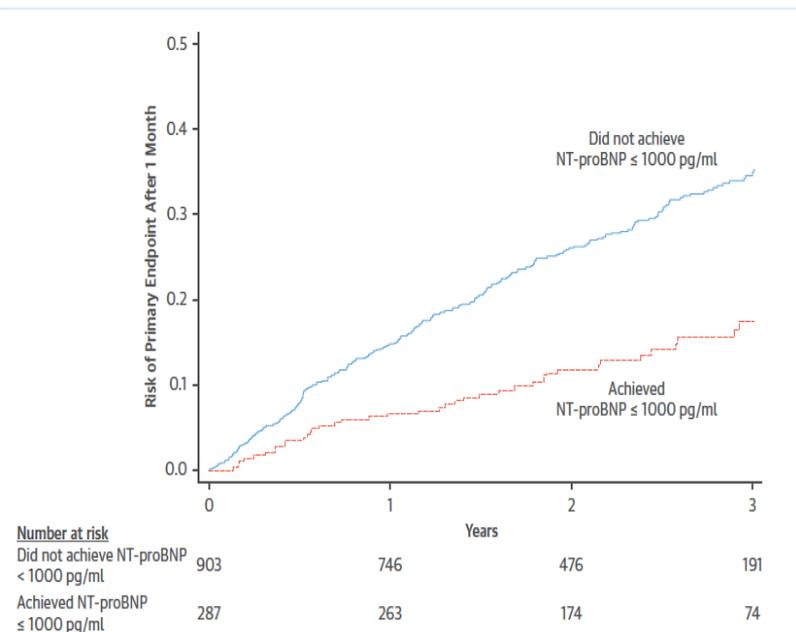
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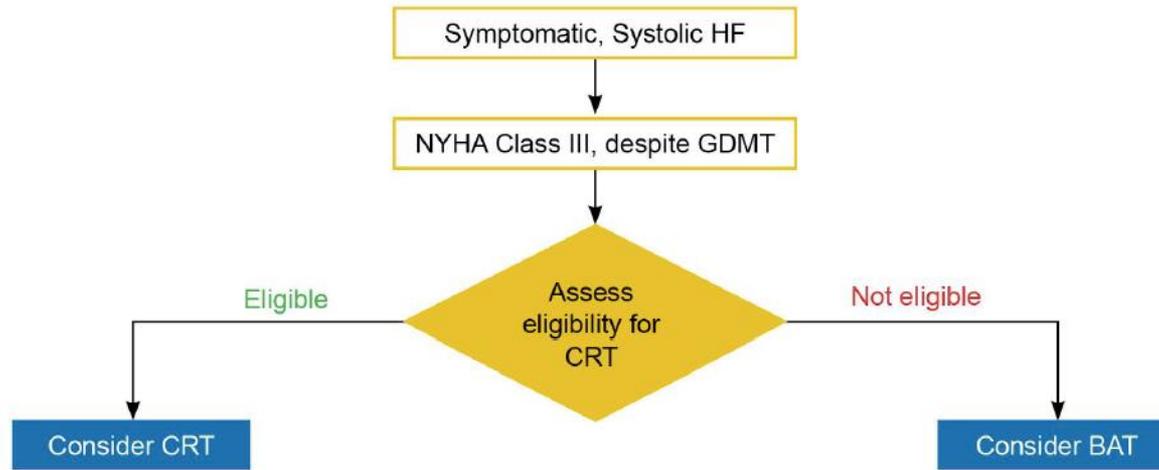
HF patients with NT-proBNP > 1000 pg/ml after 1 month of GDMT are under great risk...



Zile M et al JACC 2016

...therefore it is important to assess and treat them rapidly...

...WHERE BAT IS AN EXCELLENT TREATMENT OPTION



Gronda E J Cardiovasc Med 2017

Thank you.



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