HFSA 2023

ANNUAL SCIENTIFIC MEETING

WHERE **HEART FAILURE TEAMS** GATHER

Huntington Convention Center, Cleveland, OH | October 6-9, 2023

Endovascular Ablation of the Right Greater Splanchnic Nerve in HFpEF: Primary Analysis of the REBALANCE-HF Randomized Trial

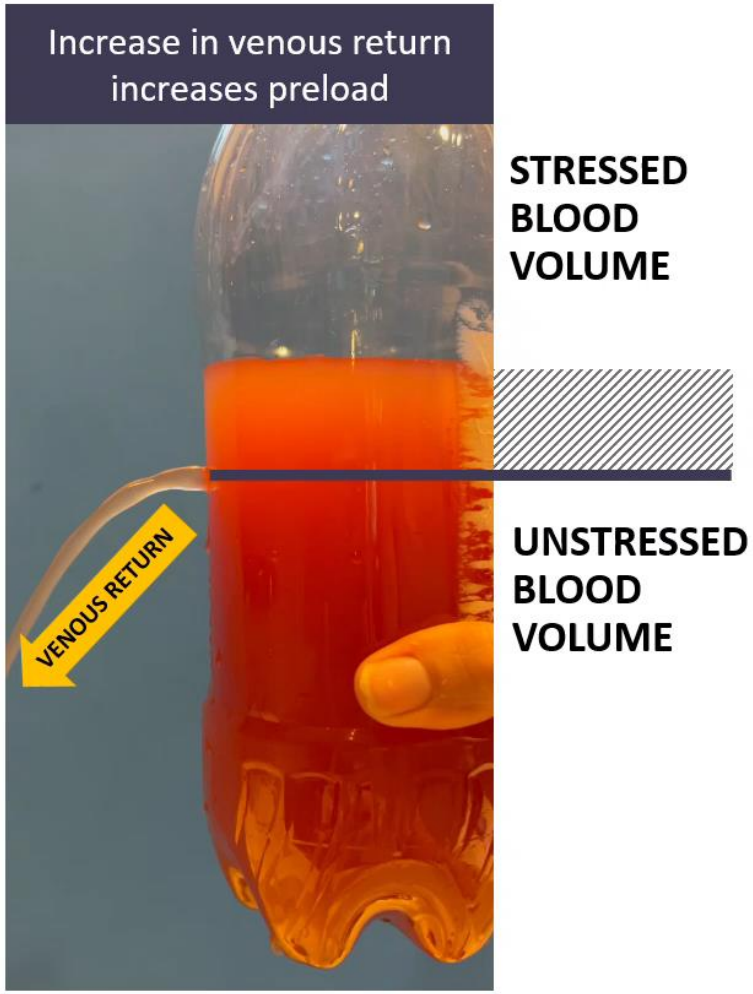
Sanjiv J. Shah, Sheldon Litwin, Peter Fail, Teona Zirakashvili, Tamaz Shaburishvili, Parag Goyal, Scott Hummel, Rajeev C. Mohan, Matthew J. Price, Ravi B. Patel, Vivek Y. Reddy, Daniel Burkhoff, Sami I. Somo, Manesh R. Patel, Barry Borlaug,
and **Marat Fudim**
on behalf of the REBALANCE-HF investigators

Declaration of interests

Research contracts:
Study was supported by Axon Therapies

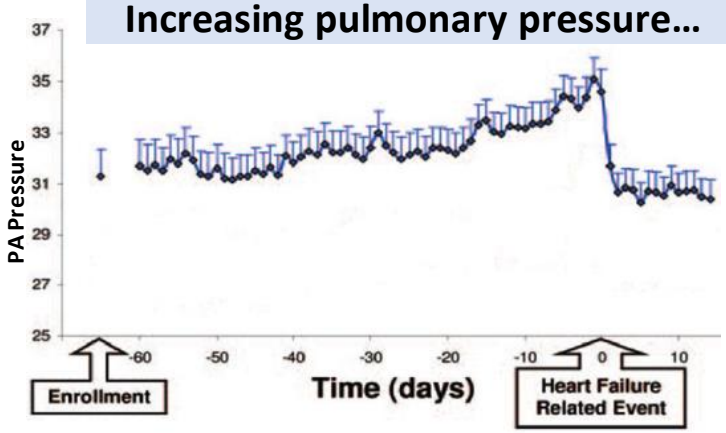
Consulting/Royalties/Owner/Stockholder of a healthcare company:
Axon Therapies

Hyperactive SNS Results in Acute/Chronic Venoconstriction

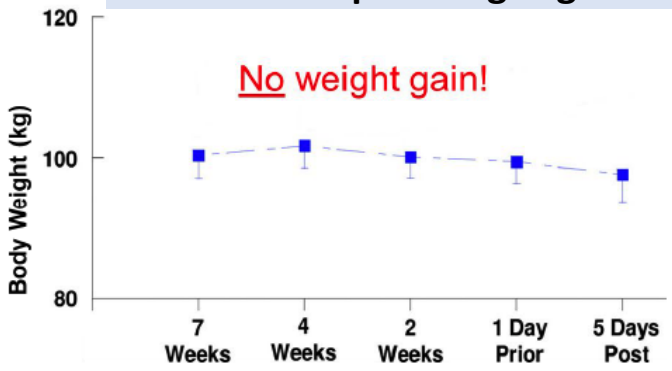


50% of patients had increase in pressure but no change in weight

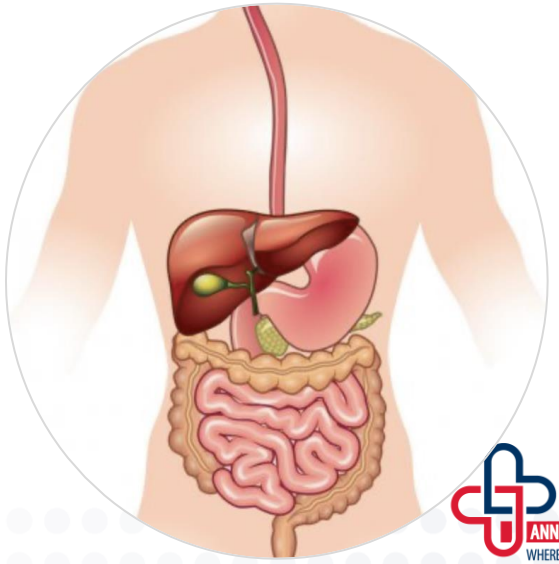
Increasing pulmonary pressure…



does not equal weight gain

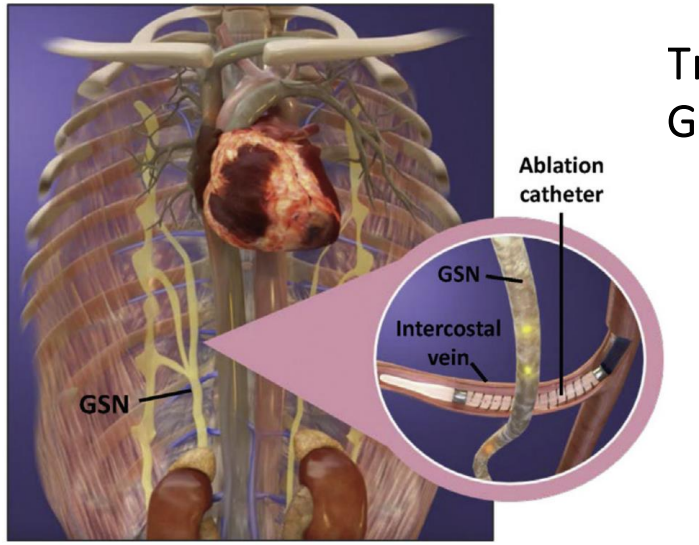


- The **body's main blood volume reservoir** or "buffer"
- **25% of all blood in the body** is in the **liver** and **spleen** alone
- **Activation of the sympathetic nervous system (SNS)** recruits blood from the splanchnic bed into central circulating volume



Fudim et al. JACC 2022; Birch et al. J Vasc Res 2008

Evidence to Date for GSN Ablation in HF



Transvenous right-sided GSN ablation procedure

Temporary Anesthetic GSN block

- **Splanchnic HF-1** (2018) n=11, Hospitalized HFrEF
- **Splanchnic HF-2** (2020) n=15, Ambulatory HFrEF

Surgical: Permanent GSN Ablation

- **Malek, et al.** (2021) n=11, Ambulatory HFpEF

Long-Term Anesthetic GSN Block

- **Splanchnic HF-3** (ongoing) n=5, Ambulatory HF

Catheter: Permanent GSN Ablation

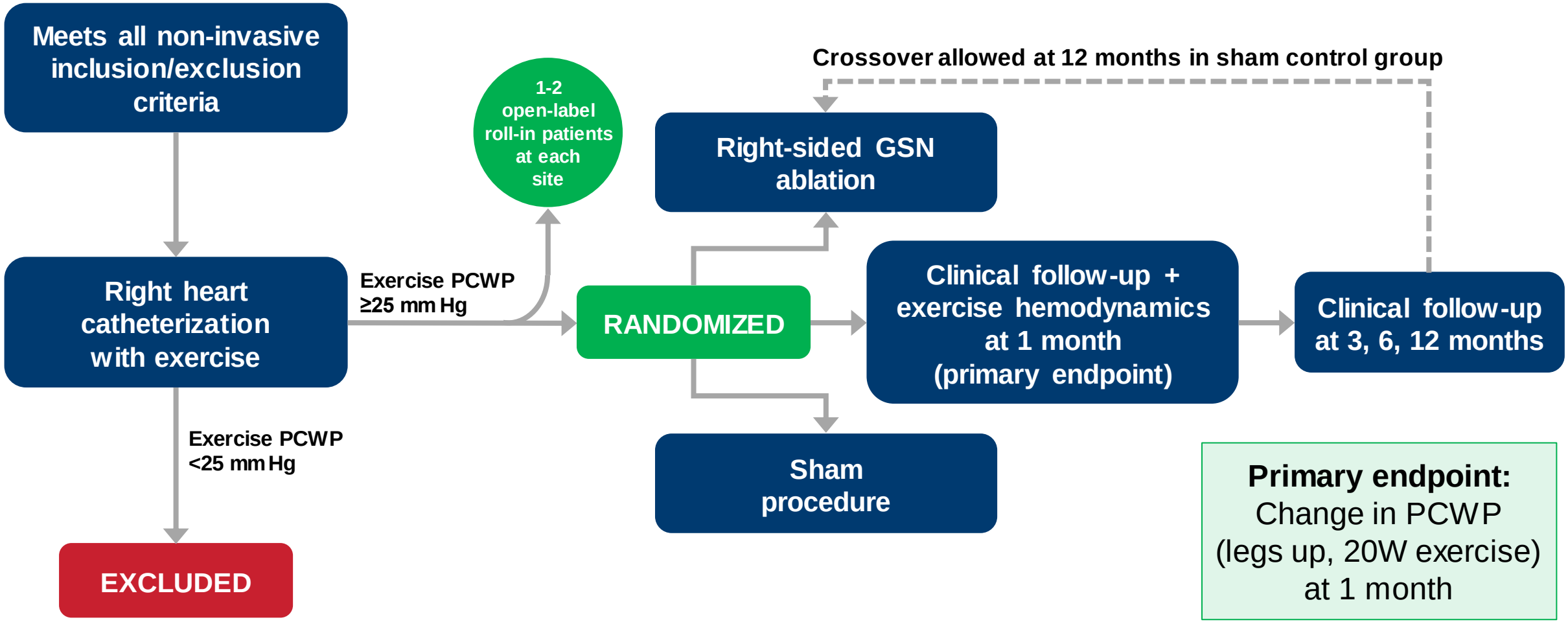
- **SAVM Feasibility** (2021) n=11, Ambulatory HFpEF
- **SAVM Pilot** (2021) n=10, Ambulatory HFrEF
- **REBALANCE HF** (ongoing) Exploratory Feasibility RCT n=90, Ambulatory HFpEF

Fudim et al. JACC BTS 2022

Study Objectives for REBALANCE-HF

- **Establish safety of Splanchnic Ablation for Volume Management (SAVM)**
- **Ensure replicability of the procedure and technical success at multiple sites with multiple operators**
- **<u>Feasibility Study: Identify the responder subgroups for future studies</u>**

REBALANCE-HF Feasibility Study: Design



Primary endpoint:
Change in PCWP (legs up, 20W exercise) at 1 month

Key Inclusion and Exclusion Criteria

Key inclusion criteria:

- ✓ **NYHA class II to ambulatory class IV**
- ✓ **At least 1 of the following:**
  - ≥1 HF hospitalization within prior 12 months
  - IV diuretics of intensification of oral diuresis for worsening HF within prior 12 months
  - NTproBNP >150/>450 pg/ml (NSR/AF) or BNP >50/150 pg/ml (NSR/AF)
- ✓ **LVEF ≥50% in the past 3 months**
- ✓ **Ongoing stable HF GDMT and diuretics for >30 days**
- ✓ **Exercise PCWP ≥25 mmHg**

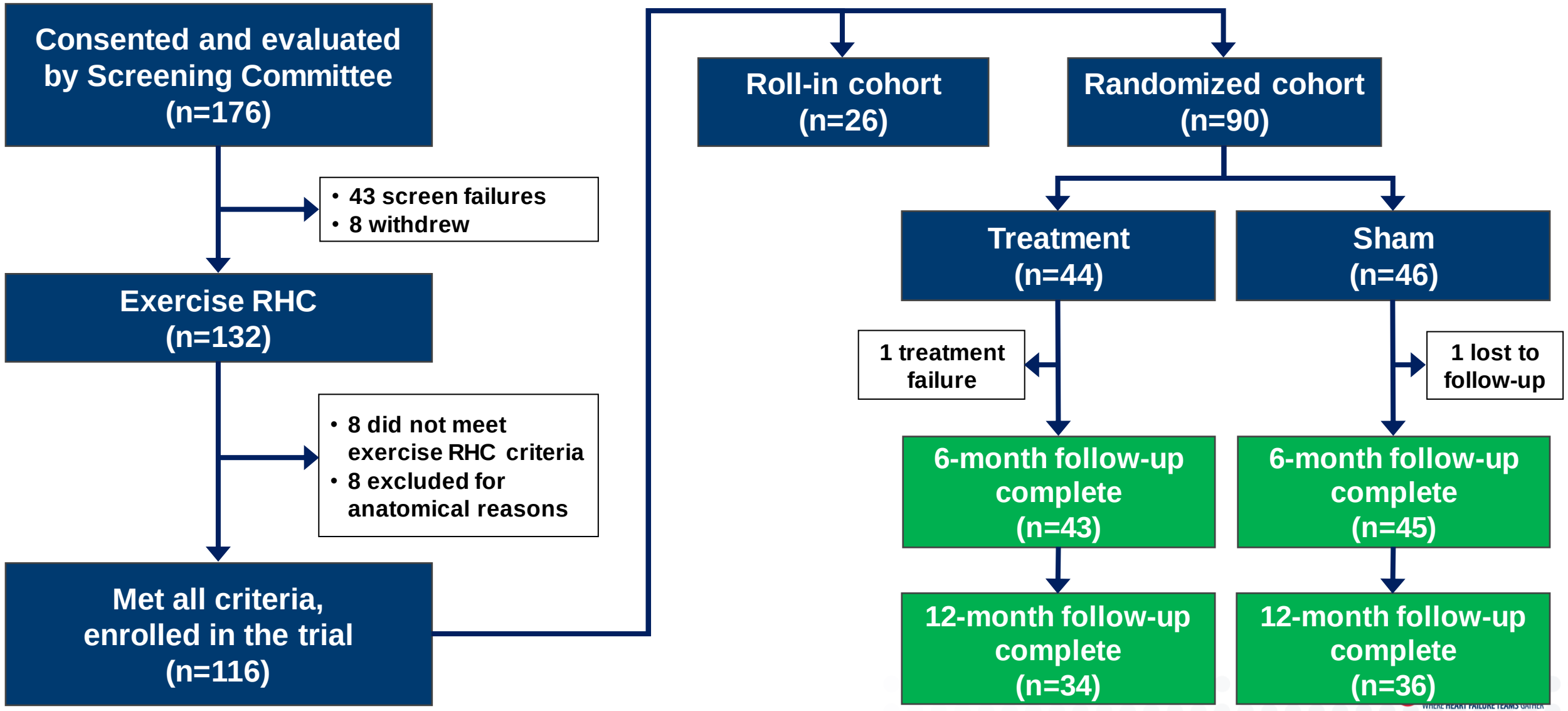
Key exclusion criteria:

- ✕ **Advanced HF, defined by:**
  - Stage D HF, non-ambulatory class IV HF
  - Cardiac index <2.0 L/min/m^2
- ✕ **Orthostatic hypotension:**
  - ↓Systolic BP >30 mmHg or ↑HR >20 bpm supine→standing
- ✕ **Significant valve disease**
- ✕ **Obstructive HCM, restrictive CM, constrictive pericarditis, cardiac amyloid, or other infiltrative CM**

Screening Committee:
Actively reviewed all patients prior to RHC procedure

HFSA 2023 ANNUAL SCIENTIFIC MEETING
WHERE HEART FAILURE TEAMS GATHER

Consort Diagram



Baseline Characteristics of Overall Population

Variable	Treatment N=44	Sham N=46
Age	72 (64, 79)	71 (60, 77)
Female	54.5%	73.9%
White	85%	91%
BMI, kg/m2	33(29.3, 36.9)	35.5(30.1, 38.7)
Prior HFH	22.7%	23.9%
Comorbidities		
Sleep Apnea	54.5%	65.2%
Atrial Fibrillation	54.5%	47.8%
Hypertension	84.1%	91.3%
Diabetes	40.9%	39.1%
COPD	6.8%	21.7%
CKD	20.5%	30.4%
Therapies		
Coronary Revasc	34.1%	32.6%
Ablation for Afib	25%	30.4%
Cardio Mems	6.8%	2.2%
Beta Blocker	54.5%	69.6%
MRA	50%	80.4%
Diuretic	82%	91%
SGLT2i	43.2%	43.5%
Lab		
eGFR	65 (52.8, 81)	59 (45, 76)

Variable	Treatment N=44	Sham N=46
Echo		
LVEF	60 (57.8, 64)	59.5 (55.8, 61.3)
E/e'	12.2 (10, 16.9)	12.1 (9.9, 17.2)
Tricuspid Regurg (mild/mod)	56.8%	30.4%
RVFAC	36 (32, 40.1)	37.7 (35.3, 40.7)
TAPSE, mm	1.9 (1.6, 2.2)	1.8 (1.6, 2)
Hemodynamics		
HR, bpm	71.5 (65.8, 80)	72.5 (65, 78.8)
BP systolic, mmHg	127 (117.8, 134.3)	122 (115.3, 134)
RAP(resting), mmHg	10 (6.5, 13)	9 (5.5, 12)
PAD (resting), mmHg	19.5 (16.3, 22.8)	19 (14.8, 22.3)
PAS (resting), mmHg	38.5 (34, 44.8)	38 (31.8, 46.3)
PCWP (resting), mmHg	17 (13, 22)	17 (14.5, 22)
PCWP (peak), mmHg	36 (31, 44)	36 (31, 43)
CO, L/min	5.3 (4.6, 6.7)	5.1 (4.8, 7)
CI, L/min/m2	2.57 (2.4, 3.0)	2.57 (2.3, 3.2)
PVR (resting)	1.4 (1.1, 2.4)	1.6 (1.1, 2.1)
Prognosis		
NYHA III/IV	89%	93%
KCCQ-OSS	42.5 (27.4, 53.3)	44 (28.2, 52.3)
6MWD, m	316.5 (216.3, 381)	283.5 (205, 343.8)
NT-proBNP, pg/ml	250 (103, 516.3)	304.5 (128.5, 447.5)

Results

Procedural Data

Metric	Treatment N=44
Procedure Time (min)	53 (43, 61)
Treatment Success	43 (98%)
Anesthesia	
General anesthesia	28 (64%)
Moderate conscious sedation	14 (32%)
TIVA with preserved spontaneous ventilation	2 (4.5%)
Contrast volume (mL)	60 (48, 100)

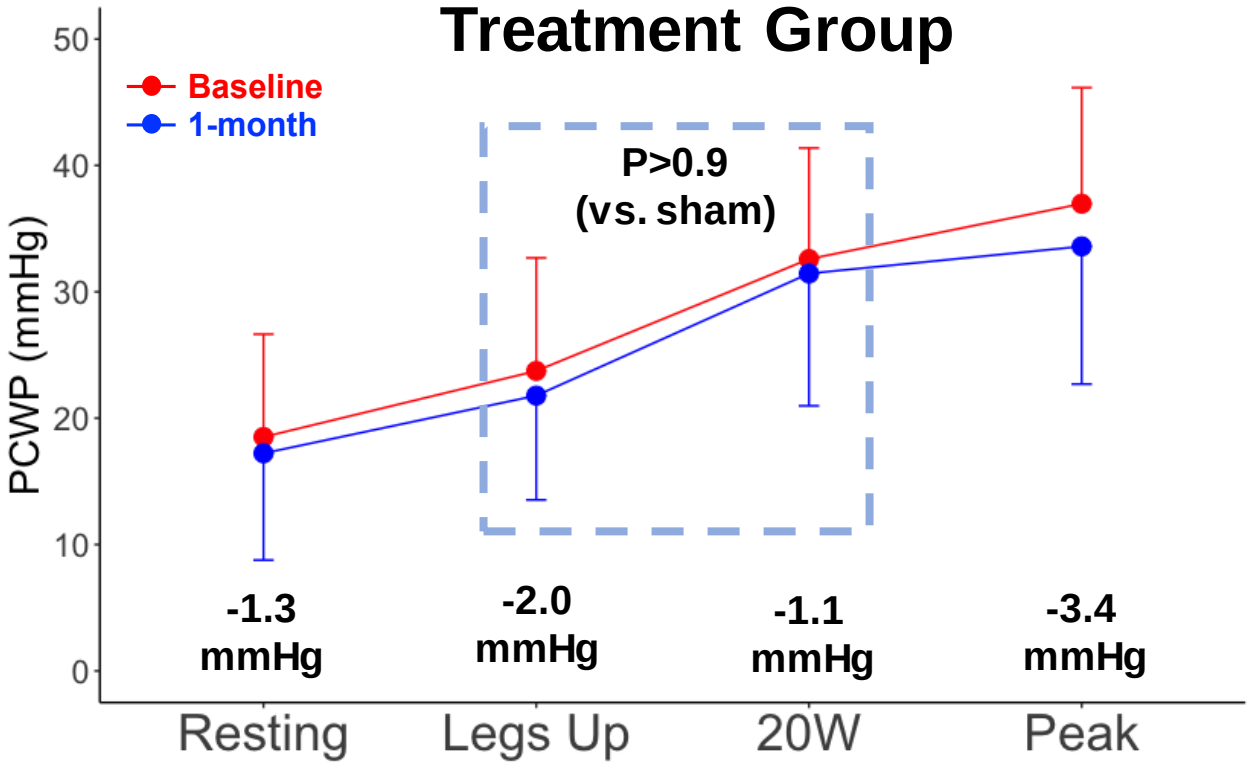
Continuous variables are presented as median (25^{th}, 75^{th} percentile)
Categorical variables are presented as n (%)

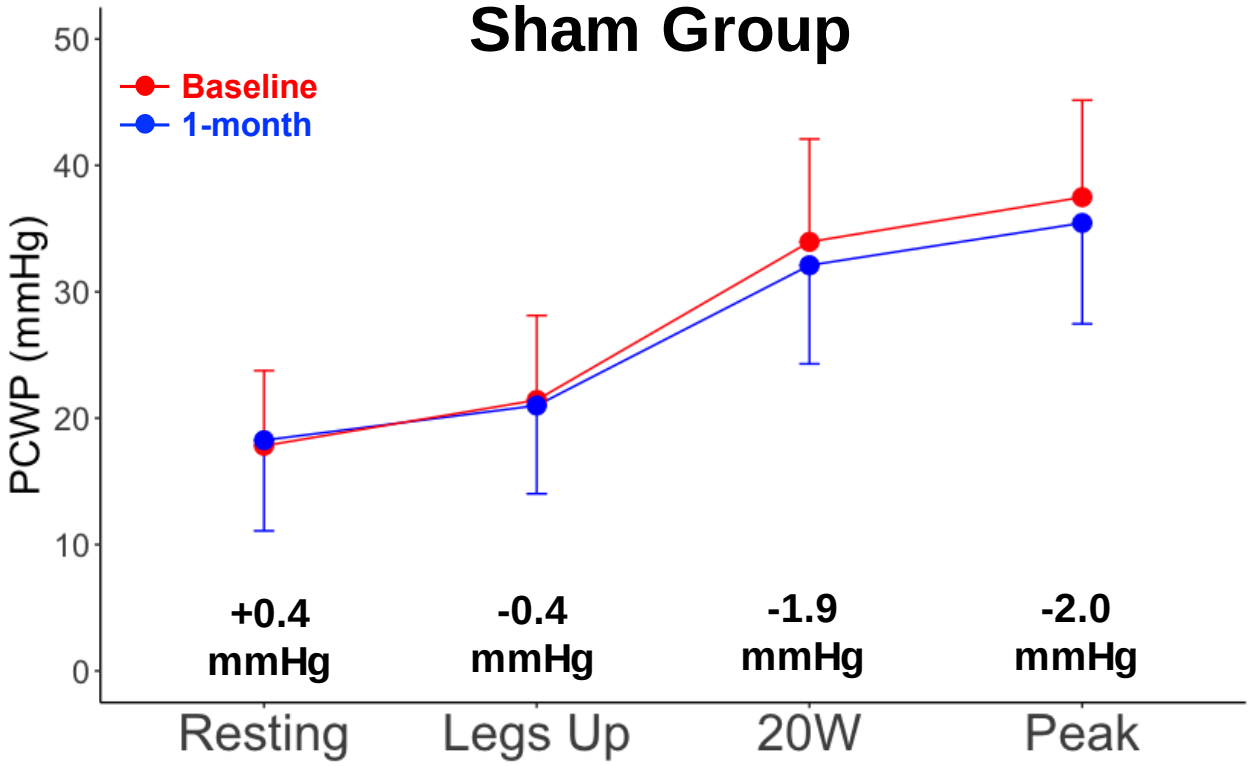
Primary Safety Endpoint

CEC Adjudicated Adverse Events	Treatment (N=44)		Sham (N=46)		P-value
	No. of Events	No. of Pts (%)	No. of Events	No. of Pts (%)	
Primary Safety Outcomes at 1-month					
Device or procedure related SAE	3	3 (7%)	1	1 (2%)	0.3
Aspiration during anesthesia	1	1 (2%)	1	1 (2%)	1.0
Pain*	2	2 (5%)	0	0 (0%)	0.2
Secondary Safety Outcomes up to 12-months					
Serious device-related or vascular event	0	0 (0%)	0	0 (0%)	—
Acute kidney injury requiring renal replacement Rx	0	0 (0%)	0	0 (0%)	—
Worsening GFR >50%	0	0 (0%)	0	0 (0%)	—
All adverse events	24	18 (41%)	22	12 (26%)	0.2
Serious	7	7 (16%)	7	6 (13%)	0.8
Serious—related to device or procedure	0	0 (0%)	0	0 (0%)	—
Non-serious	17	15 (34%)	15	9 (20%)	0.2
Orthostasis	5	5 (11%)	3	3 (7%)	0.5
Nausea / bloating	1	1 (2%)	1	1 (2%)	1.0
Heart failure hospitalization	1	1 (2%)	3	3 (7%)	0.6
All-cause mortality (Non-cardiovascular mortality)#	1	1 (2%)	0	0 (0%)	0.5

*Procedural pain was transient and resolved in all cases
#Trip and fall with no evidence of hypotension or stroke

Primary Efficacy Endpoint: PCWP





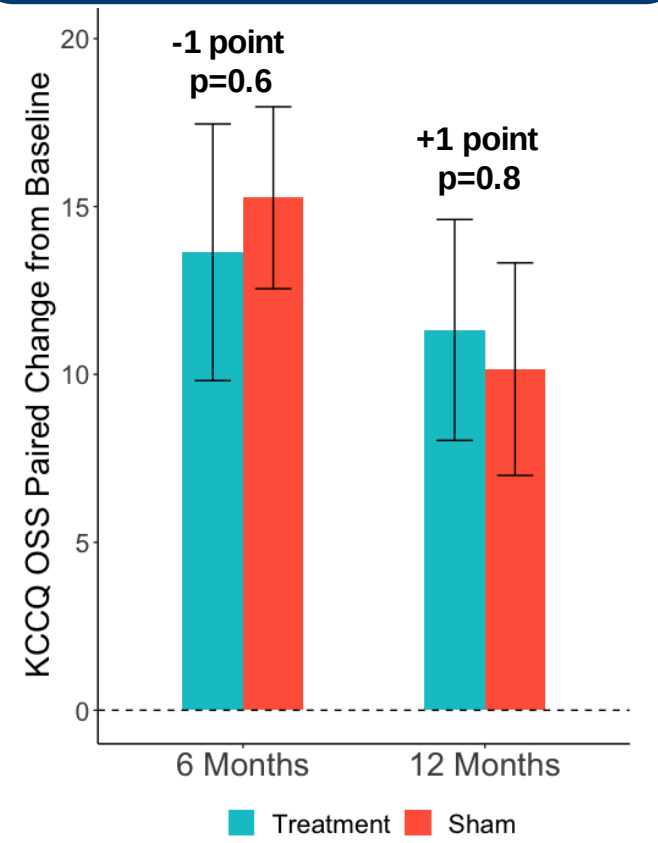
Lower Work Index PCWP (Δ-9 mmHg/W/kg p=0.3) and longer exercise duration (Δ35 seconds; p=0.1) in the Treatment Group vs Sham Group

No significant differences in ΔPCWP, ΔRA pressure, or ΔPA pressures between Treatment and Sham groups

HFSA 2023 ANNUAL SCIENTIFIC MEETING WHERE HEART FAILURE TEAMS GATHER

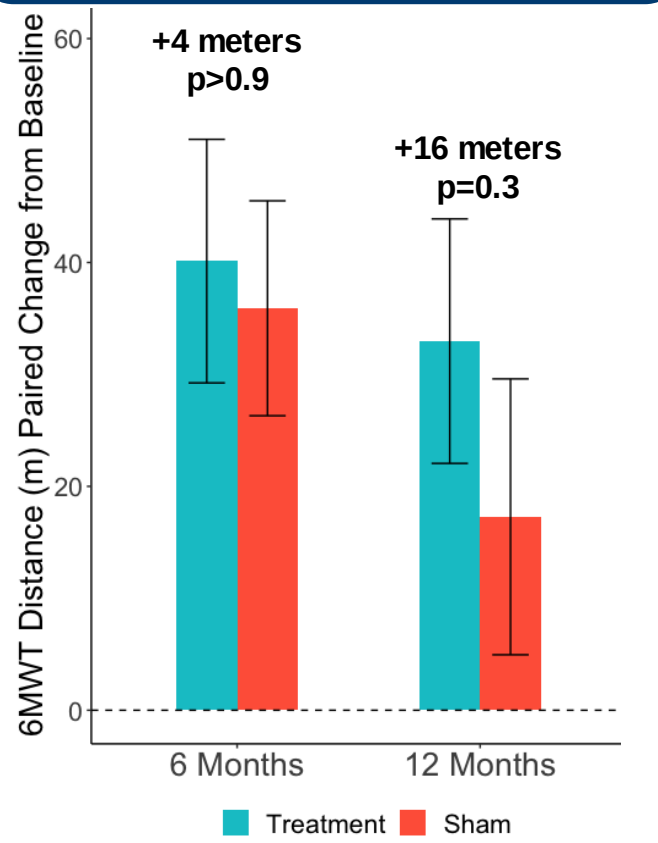
Secondary Efficacy Endpoints:
KCCQ, 6MWT, NTproBNP

KCCQ Overall Summary Score



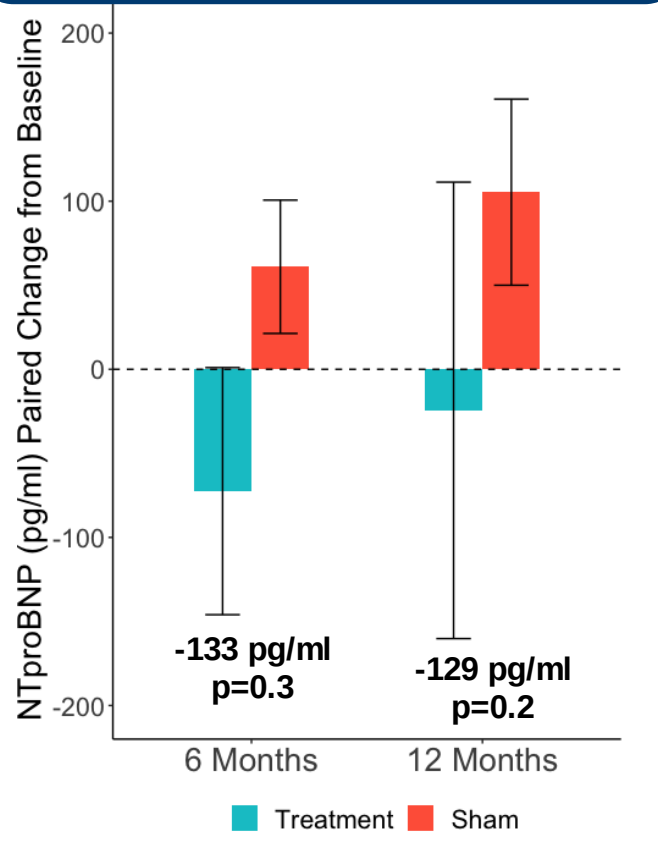
Treatment	n=43	n=34
Sham	n=45	n=36

6 Minute Walk Test



Treatment	n=41	n=34
Sham	n=44	n=36

NTproBNP



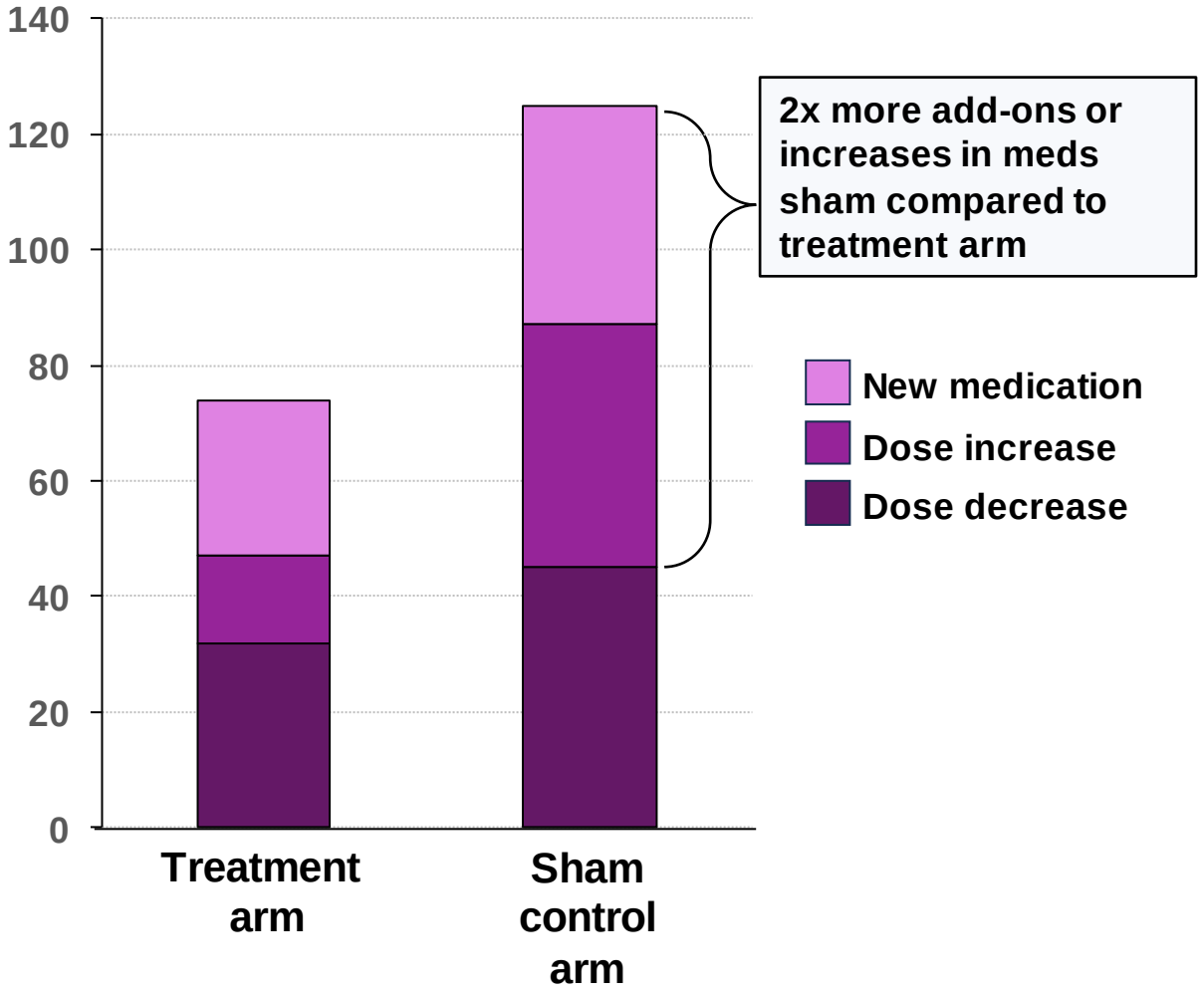
Treatment	n=42	n=33
Sham	n=45	n=34

No significant differences in Δ KCCQ, Δ 6MWT, or Δ NTproBNP between GSN ablation and sham groups

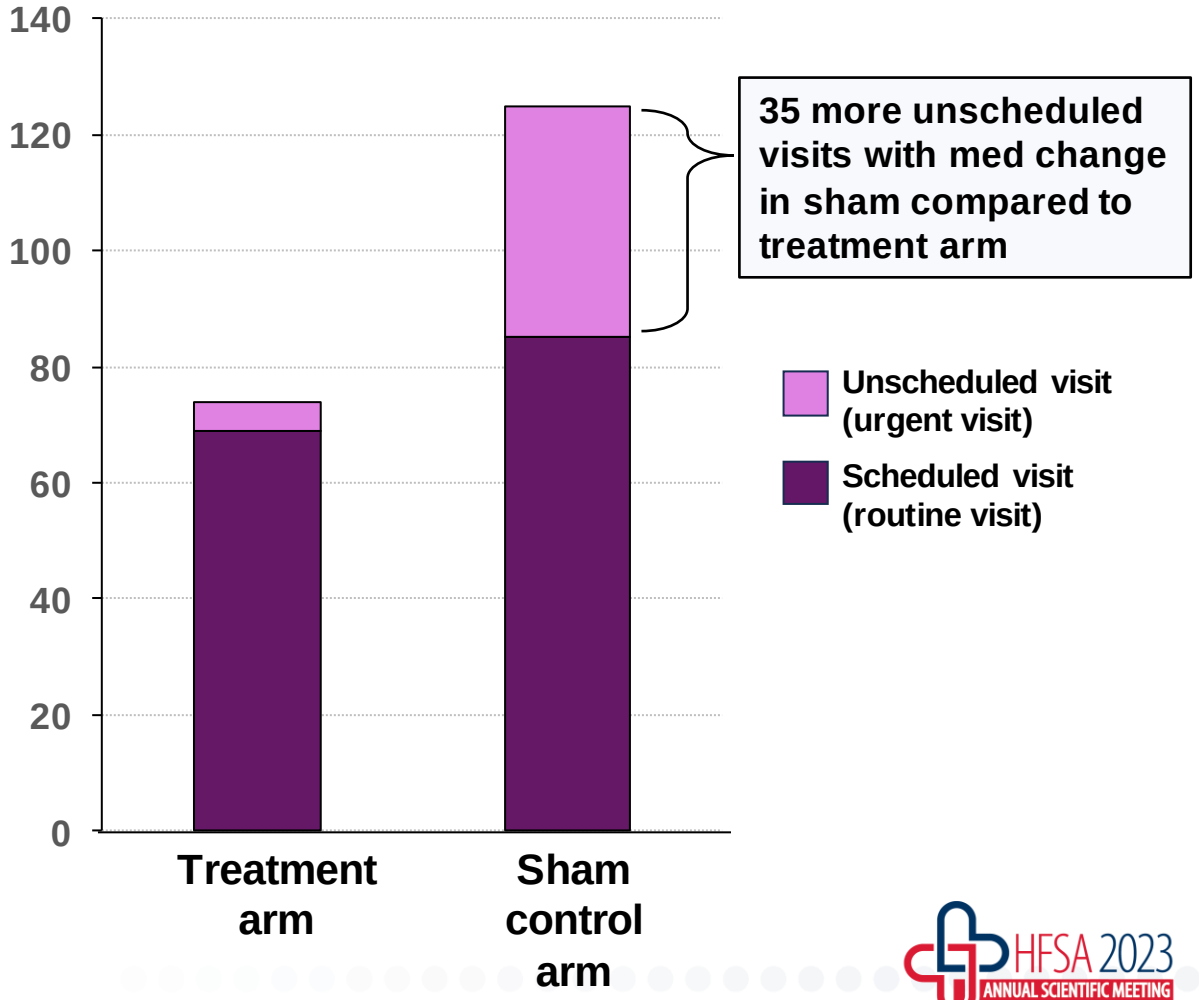
HFSA 2023 ANNUAL SCIENTIFIC MEETING WHERE HEART FAILURE TEAMS GATHER

Medication changes during the trial

Frequency of medication changes



Timing of medication changes



HFSA 2023 ANNUAL SCIENTIFIC MEETING WHERE HEART FAILURE TEAMS GATHER

Responder Analysis Overview

Responder Analysis: Z-score method

Outcomes

$$Z = \frac{x - \mu}{\sigma}$$

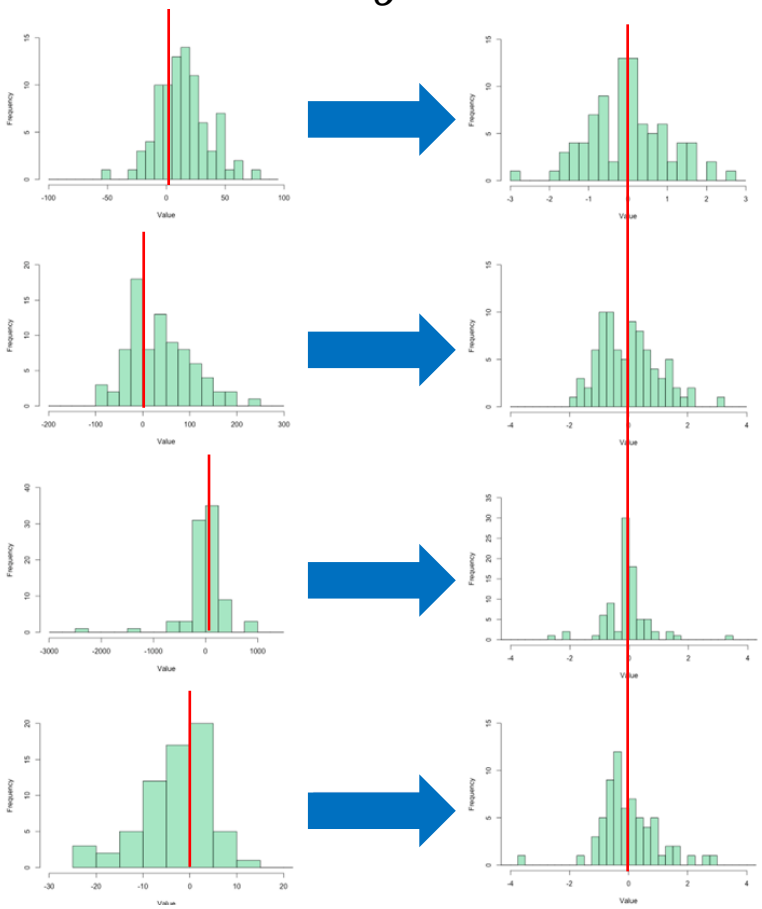
Mean = 0
SD = 1

KCCQ

6MWT

NTproBNP

Peak PCWP



Histogram (original)

Histogram (after standardization)

- **Z-score standardizes magnitude of response so multiple outcomes can be combined and compared together on a single, uniform scale**
- **Treatment effect (change in Z-score) was evaluated in the following subgroups:**

Clinical:
- Age
- Gender
- BMI
- History of Afib/flutter
- CKD
- Diabetes
- Prior HFH

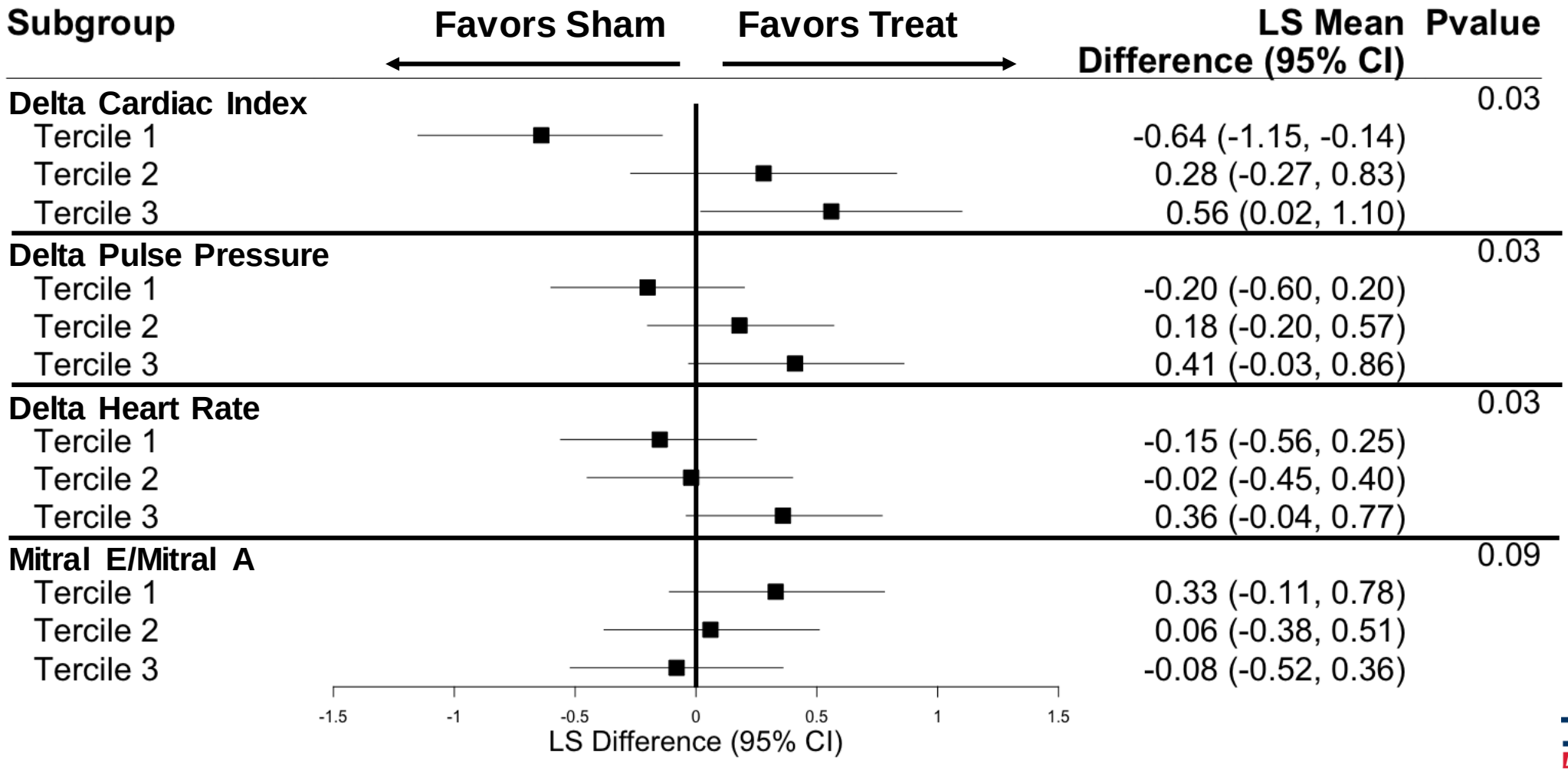
Echo:
- LVEF
- LVESV
- LVEDV
- E/A ratio
- E/e' ratio
- LA size
- LV, LA strain
- TAPSE
- RVFAC

Hemodynamic / Stress:
- Rest and peak exercise:
  - ⇢ RA pressure
  - ⇢ PA systolic pressure
  - ⇢ PCWP
  - ⇢ Heart rate
  - ⇢ Cardiac output
- PVR
- Orthostatic pulse pressure change

*Continuous variables evaluated in terciles

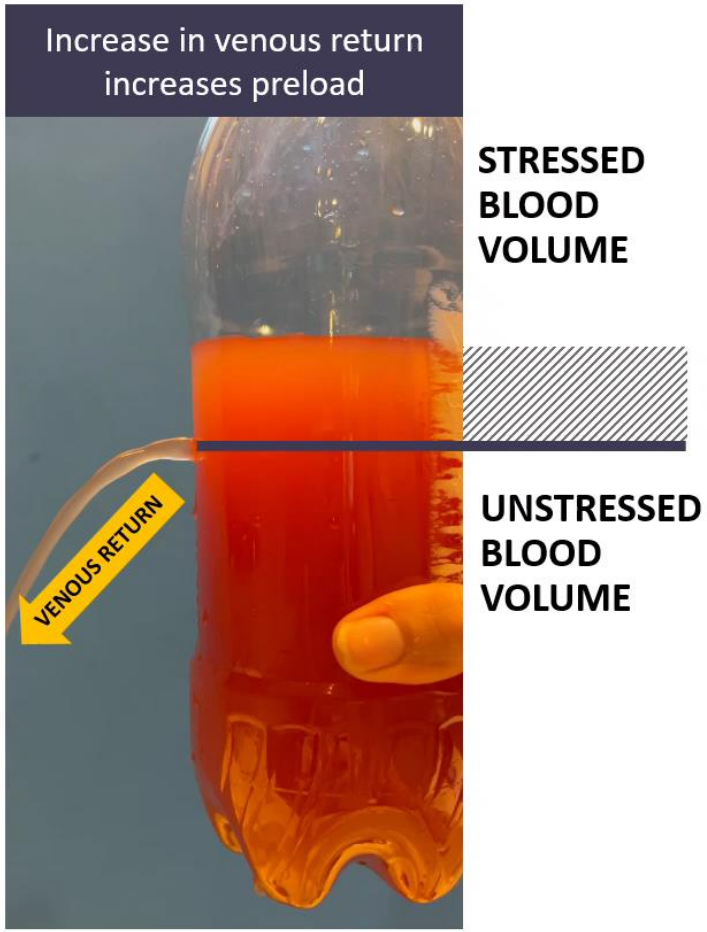
Subgroup for Combined Outcomes by Z-score

Z-score for combined KCCQ, 6MWT, NTproBNP, PCWP



Responder Group

Target Mechanism

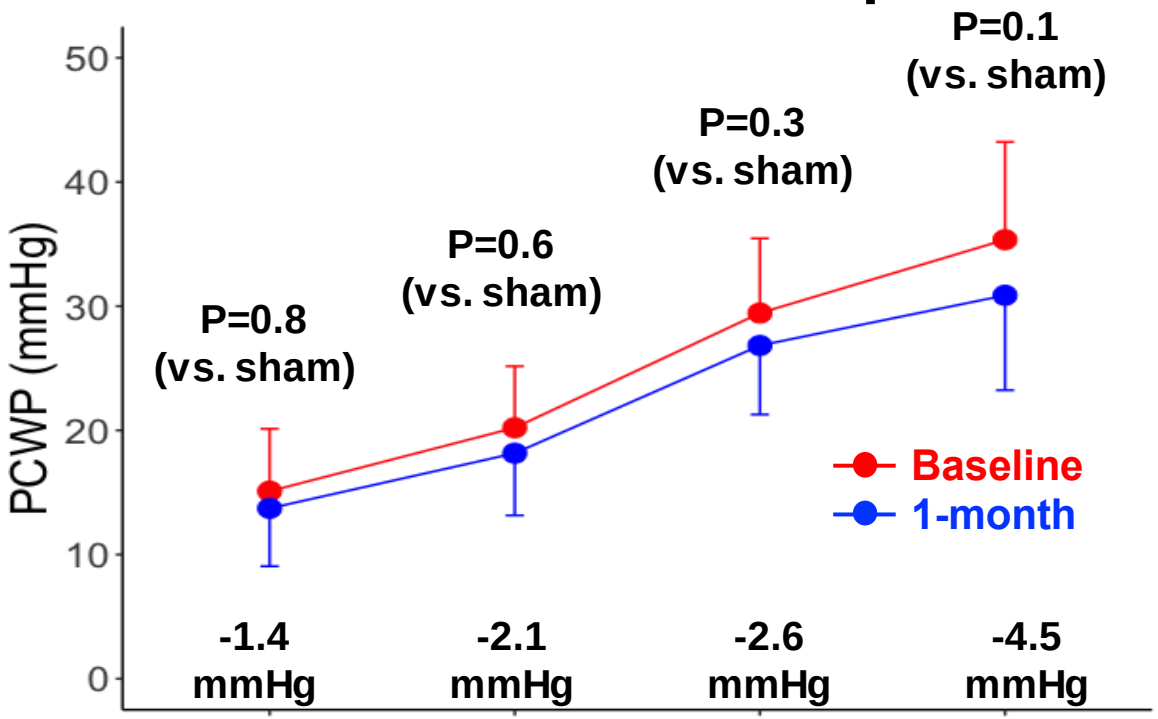


Responders

1. Preserved Cardiac Output with <u>Exercise</u> or <u>Standing</u>
2. Ability to Augment Heart Rate
3. Absence of Advanced Structural Disease

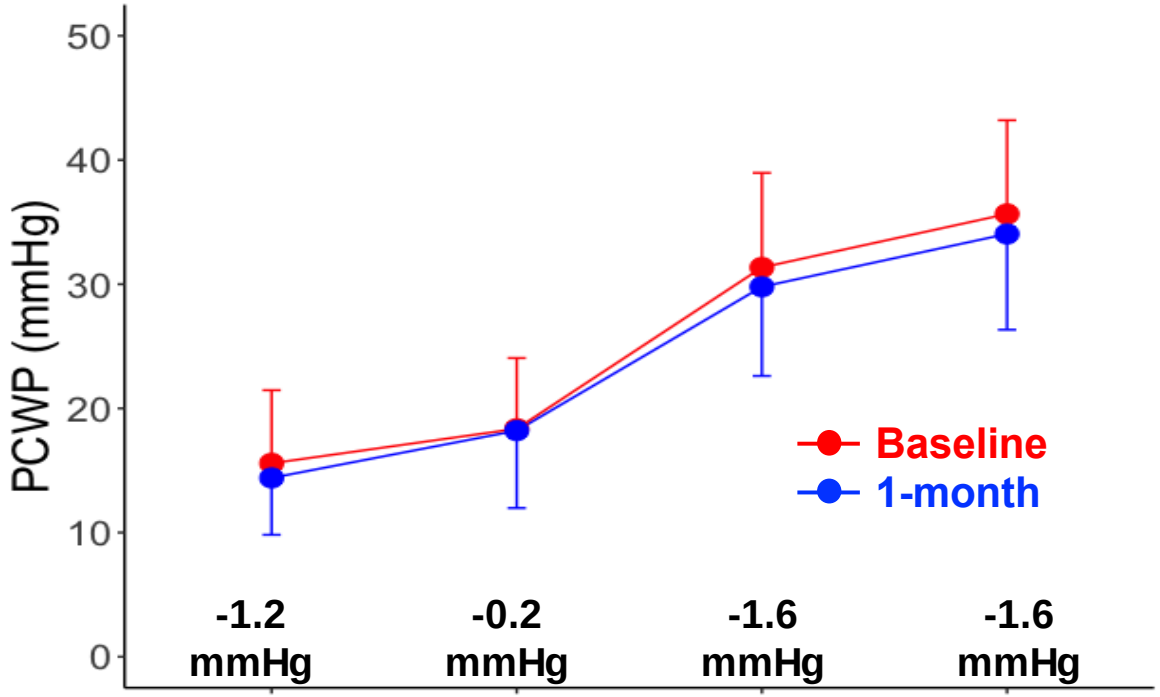
Primary Efficacy Endpoint: Responder Group

Treatment Group



	Resting	Legs Up	20 Watts	Peak
Baseline	n=20	n=19	n=18	n=17
1 Month	n=18	n=19	n=18	n=16

Sham Group



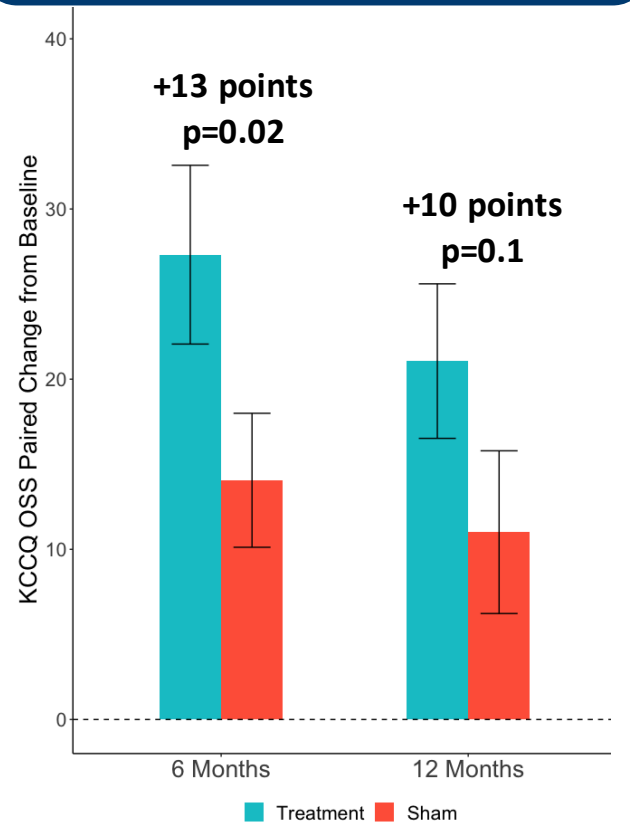
	Resting	Legs Up	20 Watts	Peak
	n=26	n=25	n=16	n=26
	n=25	n=24	n=24	n=21

Δ-18 mmHg/W/kg (p=0.02) in Work Index PCWP
Δ +95 seconds (p=0.02) in Exercise Duration

53% of the Population

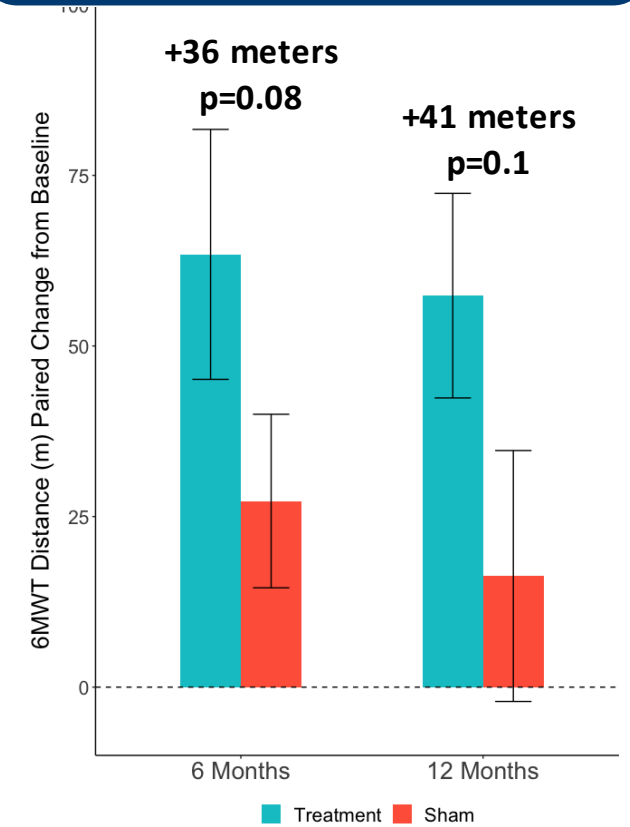
Responder Patient Population Individual Outcomes

KCCQ Overall Summary Score



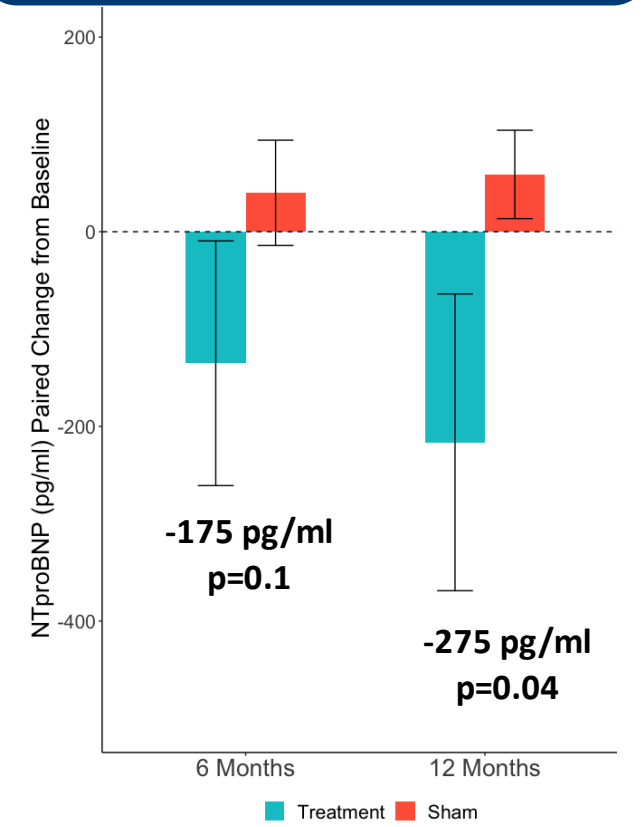
	6 Months	12 Months
Treatment	n=20	n=16
Sham	n=26	n=21

6 Minute Walk Test



	6 Months	12 Months
Treatment	n=19	n=16
Sham	n=26	n=21

NTproBNP



	6 Months	12 Months
Treatment	n=20	n=16
Sham	n=26	n=19

Conclusions

- SAVM (right-sided GSN ablation) is quick to perform and appears safe and well-tolerated
- In a population of broad inclusion/exclusion criteria with HFpEF, SAVM had limited impact on hemodynamics (at 1 month) or clinical outcomes (at 6 and 12 months)
- Potential responder group identified:
  - →Rise in cardiac output when going from supine → standing position and during exercise
  - →Not limited by chronotropic insufficiency
  - →Not limited by advanced (structural/restrictive) heart disease
- Additional prospective clinical studies are needed to confirm the potential benefits of SAVM in the identified responder group
- Deeper dive into REBALANCE-HF responder group will be presented later today @12:15 pm (poster session)

Thank you to all the Investigators and their Teams

Cardiovascular Institute of the South Peter Fail, MD Vinod Nair, MD	Virginia Commonwealth University Keyur Shah, MD Zachary Gertz, MD	Cardiology P.C. Farrell O. Mendelsohn, MD Rayan Saab, MD
Cornell Medical Center Parag Goyal, MD Luke Kim, MD	University of Michigan Scott Hummel, MD Victor Moles, MD Ahmed Abdel-Latif, MD	Prairie Cardiovascular Krishna Rocha-Singh, MD Gabor Matos, MD
Northwestern Medical Center Ravi Patel, MD Keith Benzuly, MD	The Ohio State University Ralph Augostini, MD Ramesh Emani, MD	University of California San Francisco Liviu Klein, MD Richard Cheng, MD
Mount Sinai Sumeet Mitter, MD Abhishek Mann, MD	University of Chicago Mark N. Belkin, MD John Blair, MD	Arizona Cardiology Institute Vijendra Swarup, MD Sudarone Thihalolipavan, MD
Columbia Nir Uriel, MD Sanjum Sethi, MD	Scripps Rajeev Mohan, MD Matthew Price, MD	St Vincent's Ascension Ashwin Ravichandran, MD Brian Bigelow, MD
Medical University of South Carolina Sheldon Litwin, MD Christoper D. Nielson	Mayo Clinic Barry Borlaug, MD Rajiv Gulati, MD	
Duke University Marat Fudim, MD Manesh Patel, MD	Tbilisi Heart and Vascular Clinic Tamaz Shaburishvili, MD Teona Zirakashvili, MD	

HFSA 2023 ANNUAL SCIENTIFIC MEETING
WHERE HEART FAILURE TEAMS GATHER