Endovascular Ablation of the Right Greater Splanchnic Nerve in Heart Failure with Preserved Ejection Fraction: Early Results of the REBALANCE-HF Trial Roll-in Cohort

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Trial Registration: ClinicalTrials.gov Identifier: NCT04592445
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ABSTRACT

Background: In heart failure with preserved ejection fraction (HFpEF), excessive redistribution of blood volume into the central circulation leads to elevations of intracardiac pressures with exercise limitations. Splanchnic ablation for volume management (SAVM) has been proposed as a therapeutic intervention.

Aims: Here we present preliminary safety and efficacy data from the initial roll-in cohort of the REBALANCE-HF trial.

Methods: The open-label (roll-in) arm of REBALANCE-HF will enroll up to 30 patients, followed by the randomized, sham-controlled portion of the trial (up to 80 additional patients). Patients with HF, LVEF ≥50%, and invasive peak exercise PCWP ≥25 mmHg underwent SAVM. Baseline and follow-up assessments included resting and exercise PCWP, NYHA class, Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk test, and NTproBNP. Efficacy and safety were assessed at 1 and 3 months.

Results: Here we report on the first 18 patients with HFpEF have been enrolled into the roll-in, open-label arm of the study across 9 centers; 14 (78%) female; 16 (89%) NYHA class III; and median (IQR) age 75.2 (68.4-81) years, LVEF 61.0 (56.0-63.2)%, and average (SD) 20W exercise PCWP 36.4 (±8.6) mmHg. All 18 patients were successfully treated. Three non-serious moderate device/procedure-related adverse events were reported. At 1-month, the mean PCWP at 20W exercise decreased from 36.4 (±8.6) to 28.9 (±7.8) mmHg ($p<0.01$), NYHA class improved by at least 1 class in 33% of patients ($p=0.02$) and KCCQ score improved by 22.1 points (95% CI 9.4-34.2) ($p<0.01$).

Conclusion: The preliminary open-label results from the multi-center REBALANCE-HF roll-in cohort support the safety and efficacy of SAVM in HFpEF. The findings require confirmation in the ongoing randomized, sham-controlled portion of the trial.

Background

Elevated intra-cardiac filling pressures at rest and specifically during activity cause exertional dyspnea, impaired aerobic capacity, and are associated with increased mortality in patients with heart failure (HF) and preserved ejection fraction (HFpEF).[1-3] Accordingly, many cardiovascular therapies target reduction in intra-cardiac filling pressures to improve exertional capacity, quality of life, and cardiovascular morbidity in patients with HFpEF.[4] The excessive distribution of blood volume from the extra-thoracic compartments into the thorax is a central contributor to elevated filling pressures in HF patients.[4, 5] A substantial proportion of the intravascular blood volume is located in the splanchnic vascular compartment. Preclinical and clinical investigations support the critical role of the sympathetic nervous system in modulating the capacitance and compliance of the splanchnic vascular bed via modulation of the greater splanchnic nerve (GSN). GSN stimulation induces an increase in cardiac preload and afterload with resultant cardiopulmonary pressure elevation.[6-8]

The short-term blockade of the GSN via anesthetic agents demonstrated the feasibility, acute safety and efficacy of the intervention to reduce intracardiac pressures (HF with reduced ejection fraction [HFrEF], bilateral, N=11, NCT03453151[9] and chronic HFrEF, bilateral and unilateral, N=15, NCT02669407)[10]. Long-term blockade of the GSN via surgical ablation in HFPEF (N=11, NCT03715543)[11] extended these findings and supported the long-term safety and persistent efficacy of the intervention out to 12 months. A novel, minimally invasive, endovascular, transvenous procedure was developed to ablate the right-sided GSN (Splanchnic Ablation for Volume Management [SAVM] procedure), and has been shown to be beneficial in a small, single-center open-label pilot trial.[12]

Aims

The ongoing multicenter REBALANCE-HF randomized, sham-controlled trial is evaluating the novel SAVM treatment paradigm to determine whether it safely improves hemodynamics, health

status (symptoms and quality of life), and exercise tolerance compared to sham control in patients with HFpEF. Here, we present preliminary safety and efficacy data from the initial roll-in cohort of the REBALANCE-HF trial.

Methods

The open-label (roll-in) arm of REBALANCE-HF will enroll up to 30 patients, followed by the randomized, sham-controlled portion of the trial (up to 80 additional patients). As part of the roll-in cohort individual sites were allowed to treat up to 3 patients in an unblinded fashion prior to commencing randomization of patients into the trial. These participants are not considered part of the intention-to-treat (ITT) population for the eventual randomized, sham-controlled portion of the trial. Participants included in the roll-in cohort underwent the same procedures and follow up as participants who are being enrolled in the ITT population trial, but with the exception of randomization; however, these participants will not be included in the analyses of the primary efficacy endpoint and acute procedural success data for the overall REBALANCE-HF trial.

Eligible patients with chronic HFpEF (LVEF of ≥50%, with an elevated PCWP at rest or exertion (≥25 mmHg) were required to meet clinical eligibility criteria and as well as qualifying hemodynamic selection criteria on the day of the treatment (**Supplemental Table 1**). All patients were independently evaluated by a dedicated screening committee to confirm eligibility and optimal management of HFpEF with clinical stability for >30 days.

The right GSN was ablated via a transvenous SAVM procedure (Axon Therapies, Santa Clara, CA) (**Figure 1**).[12] Using routine femoral venous access, the right GSN was approached from the right azygos vein and branching intercostal veins where the target nerve and veins cross at the 10th and 11th thoracic levels. The location of the ablation was determined based on anatomical landmarks using fluoroscopic imaging. The SAVM procedure delivers radiofrequency energy (≥ 90 secs) and is continuously cooled by saline injection through the catheter at the ablation site. Baseline and follow-up assessments included resting and exercise

PCWP, NYHA class, Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk test (6MWT), and NTproBNP. The primary efficacy endpoints were a reduction in PCWP at rest, legs up, and 20W exercise at 1 month. The primary safety endpoint was serious device- or procedure-related adverse events at 1 month (see **Supplemental Tables 3-4** for a complete list of protocol-defined potential procedure- and device-related adverse events). Patient data before and at various time-points after the SAVM procedure (1 and 3 months) were compared using Wilcoxon Signed Rank test (SAS v9.4 for Windows, SAS Institute Inc., Cary, NC, USA), exercise hemodynamics were compared between baseline and 1 month using a mixed model repeated measures (MMRM) analysis. Continuous variables within a visit are presented as median [Q1, Q3]. A p-value <0.05 was considered statistically significant. The trial was registered (NCT04592445). The REBALANCE-HF trial is funded by Axon Therapies, Inc. The steering committee designed the protocol with the study sponsor.

Results

To date, 18 patients with HFpEF across 9 centers have been enrolled into the roll-in portion of the study. Of them, 14 (78%) are female, mean age 74±9 years, median [IQR] body mass index of 35.3 [27.6, 37.2] kg/m^2, 16 (89%) NYHA class III, and left ventricular ejection fraction (LVEF) 61 [56-63] % (**Table 1**). All patients were successfully treated. Three non-serious device-related adverse events were reported, including acute HF decompensation due to high periprocedural intravenous volume use and diuretic withholding, transient hypertension during ablation procedure and back pain following ablation (**Supplemental Table 2**). All patients completed their follow up visits out to 3 months.

The 20W PCWP decreased from a mean 36.4 [SD ± 8.6] to 29.9 [SD ± 7.8] (p<0.01) and the peak exercise PCWP decreased from 39.5 [SD ± 6.9] to 31.9 [SD ± 8.4] (p=0.01) at 1 month

after the SAVM procedure (**Figure 2**). The exercise duration on the supine ergometers changed from a median 6 [4, 9] min to 7 [5, 10] min (p=0.51) and the highest achieved resistance on the ergometer (W) was 40 [20, 60] at baseline and 40 [40, 60] at 1 month (p=0.56). At 1 month and 3 months post SAVM procedure 39% and 50% patients experienced at least one NYHA class improvement compared to baseline (p=0.02 and p<0.01), respectively (**Figure 3**). The KCCQ overall summary score improved by 22.1 points (95% CI 9.4-34.2) (p<0.01) at 1 month and 18.3 points (95% CI 9.0-27.7) at 3 months (p<0.01) (**Figure 3**). The median NT-proBNP was 334 [148, 698] pg/ml at baseline, 262 [171, 396] pg/ml at 1 month and 291 [187, 519] pg/ml at 3 months (all p>0.05) (**Figure 3**). The 6-minute walk distance changed from 283 [215, 322] m at baseline to 276 [239, 373] m at 1 month and 342 [257, 370] m at 3 months after the SAVM procedure (**Figure 3**). There were no significant changes in echocardiographic measures of left ventricular systolic function (LVEF), diastolic function (E/A, E/e'), left atrial volume or left ventricular mass at 3 months when compared to baseline values (all p>0.05).

Conclusions

The preliminary open-label results from the REBALANCE-HF roll-in cohort support the safety and efficacy of SAVM in HFpEF. GSN ablation treatment was associated with a reduction in PCWP during exercise and improvement in symptoms and health status without a statistically significant difference in exercise capacity. The treatment procedure was associated with 3 moderate, non-serious device/procedure-related adverse events but no serious adverse events, and learnings from these events in the roll-in portion of the trial have informed the conduct of the randomized portion of the trial (e.g., periprocedural intravenous fluids are now being minimized). The greater reduction in PCWP is notable and consistent with recent data showing that abnormalities in venous capacitance importantly contribute to hemodynamic perturbations that develop during exercise in HFpEF.[13] These results are limited by the single-arm, open-label design; thus, the results are subject to treatment and observation bias. To avoid confounding by

pharmacological medical management on the endpoints of interest, a stable medical HF medical regimen 30 days before and 3 months after the SAVM procedure was required. The findings presented here require confirmation in the ongoing randomized, sham-controlled portion of the REBALANCE-HF trial.

Tables and Figures:

Table 1. Baseline characteristics of the study cohort.

Number of patients	18
Age (years)	75.2 [68.4, 81]
Gender (% female)	78
Race - Black (%), White (%)	11, 89
Comorbidities	
History of Atrial Fibrillation or atrial flutter (%)	56
Hypertension (%)	89
Diabetes (%)	33
Coronary Artery Disease (%)	39
Previous Myocardial Infarction (%)	0
HF or HTN Medication	
Loop Diuretic (%)	83
ACE or ARB (%)	33
Beta-Blocker (%)	56
Mineralocorticoid receptor antagonist (%)	67
Calcium channel blocker (%)	39
Sacubitril/valsartan (%)	6
SGLT2 inhibitors	17
Biometrics	
Body mass index (kg/m^2)	35.3 [27.6, 37.2]
Left Ventricular Ejection Fraction (core lab measured) (%)	61.0 [56.0-63.2]
NYHA Class II/III (%)	II: 5.6, III: 88.9, IV: 5.6
Systolic Blood Pressure (mmHg)	123.5 [114.5-135.8]
Diastolic Blood Pressure (mmHg)	71.5 [66.2-78.8]
Resting Heart Rate (beats/min)	73.5 (69.2-80.8)
NT-proBNP (pg/mL)	334 [148, 698]
Creatinine (mg/dL)	0.94 [0.9, 1.3]
Estimated glomerular filtration rate (ml/min/1.73 m^2)	60.5 (45.2-66.8)
Echocardiography	
Left Ventricular Ejection Fraction (core lab measured) (%)	61.0 [56.0-63.2]
Left ventricular mass index (g/m^2)	80.5 [67.7-93.1]
LA end-diastolic volume index (mL/m^2)	19.4 [13.9-25.8]
LV end-diastolic volume index (mL/m^2)	40.4 [37.6-45.7]
E/e' (septal) (unitless)	15.8 [11.3-21.8]
Mitral E velocity/Mitral A velocity (unitless)	1.0 [0.8-1.8]
Baseline invasive exercise hemodynamics	
Resting PCWP (mmHg)	17.0 [4.0-34.0]
Legs up PCWP (mmHg)	24.0 [11.0-33.0]

20W PCWP (mmHg)	35.0 [22.0-50.0]
Peak PCWP (mmHg)	37.0 [26.0-50.0]
Exercise duration (minutes)	6.0 [4.0-9.0]
Peak workload (Watts)	40.0 [20.0-60.0]

Abbreviations: ACE =angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI=body mass index; CVP=central venous pressure; KCCQ=Kansas City Cardiomyopathy Questionnaire; LVEF=left ventricular ejection fraction; NT-proBNP=N terminal pro brain natriuretic peptide; NYHA=New York Heart Association; SGLT2 = sodium glucose like transporter 2; medians and interquartile range is provided unless otherwise specified.

Figure 1. Splanchnic ablation for volume management (SAVM) system. Ablation catheter (A); access to greater splanchnic nerve via venous system (B).

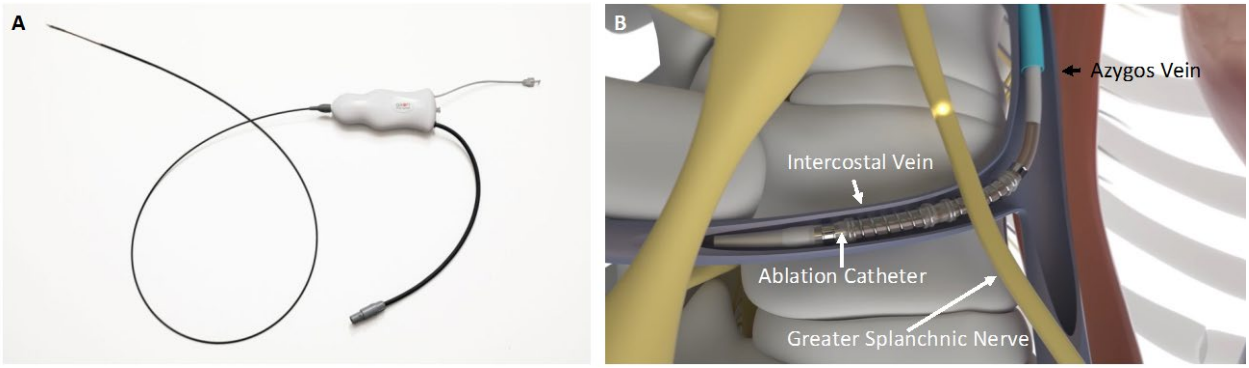


Figure 2. Change in pulmonary capillary wedge pressure at baseline and 1 month after greater splanchnic nerve ablation. Discrepancy in case numbers between baseline and 1 month is explained by either missed or uninterpretable recordings. Means and standard deviation are presented. * Indicates a comparison between baseline and 1 month using a mixed model repeated measures (MMRM) analysis with a p-value < 0.05.

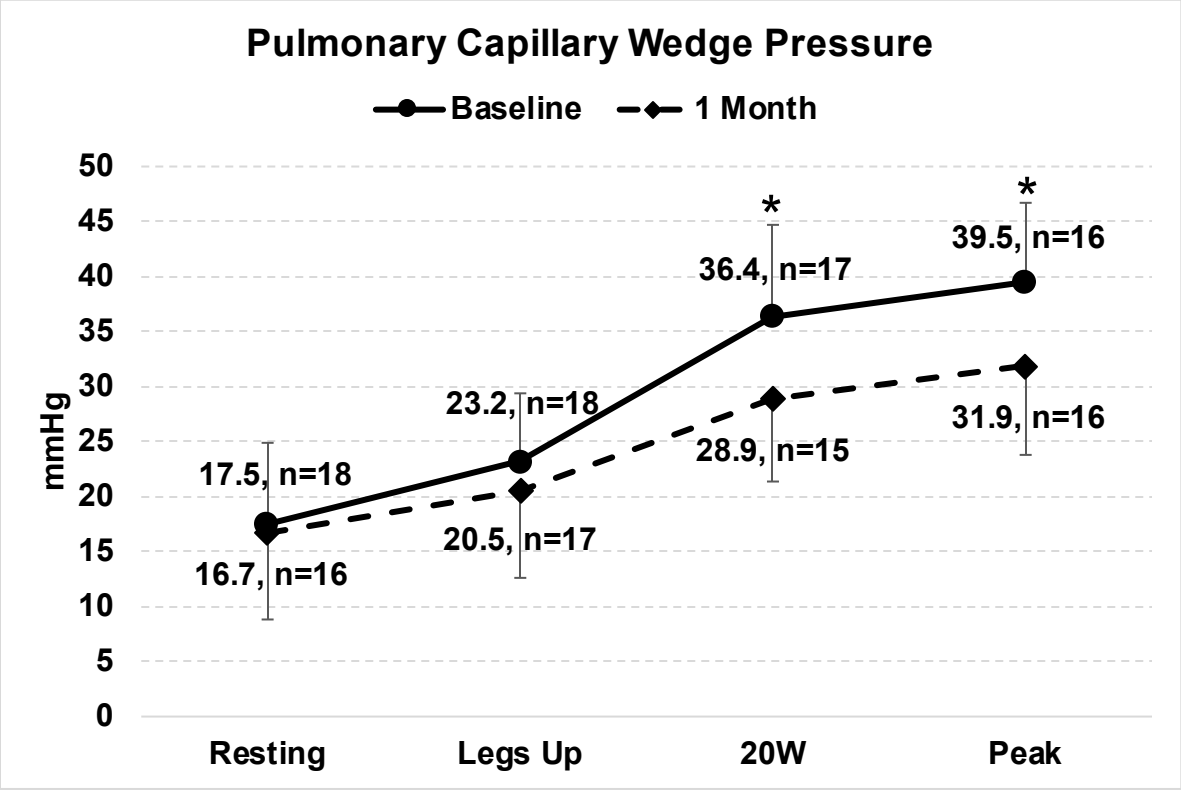
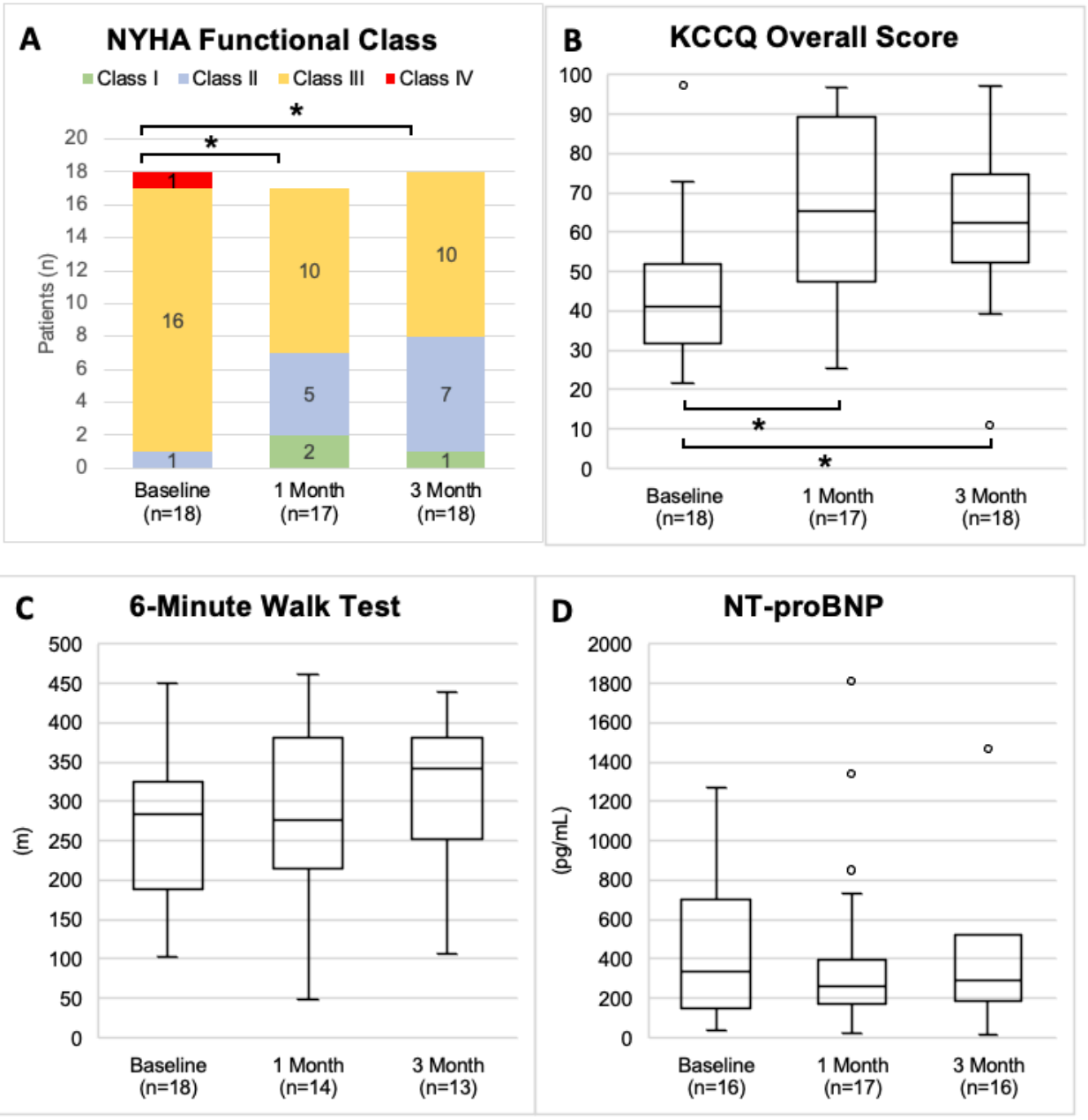


Figure 3. Comparison of baseline New York Heart Association Functional (NYHA) Class (A), Kansas City Cardiomyopathy Questionnaire (KCCQ) (B), 6-minute walk distance (C) and N-terminal pro natriuretic peptide (NT-proBNP) (D) compared to 1 month after greater splanchnic nerve ablation. Medians and interquartile range are provided unless otherwise specified. * Indicates a Wilcoxon signed rank test (compared to Baseline) p-value < 0.05.



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