



# Corporate Presentation

April 2026

# Forward-Looking Statements

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## Disclaimers

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# Derisked Phase 3 Program

WITH PROOF-OF-CONCEPT CLINICAL DATA AND WELL-ESTABLISHED SAFETY PROFILE

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1

TNX-103, or Oral Levosimendan, is a potential first-in-class PH-HFpEF treatment

2

Levosimendan brings a well-established safety profile and MOA uniquely suited to treating PH-HFpEF

3

Randomization target (230 patients) achieved in Phase 3 LEVEL study, topline data expected in Q3 of 2026

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Global Phase 3 LEVEL-2 study initiated, enrollment completion estimated by end of 2027

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Company funded through 2027

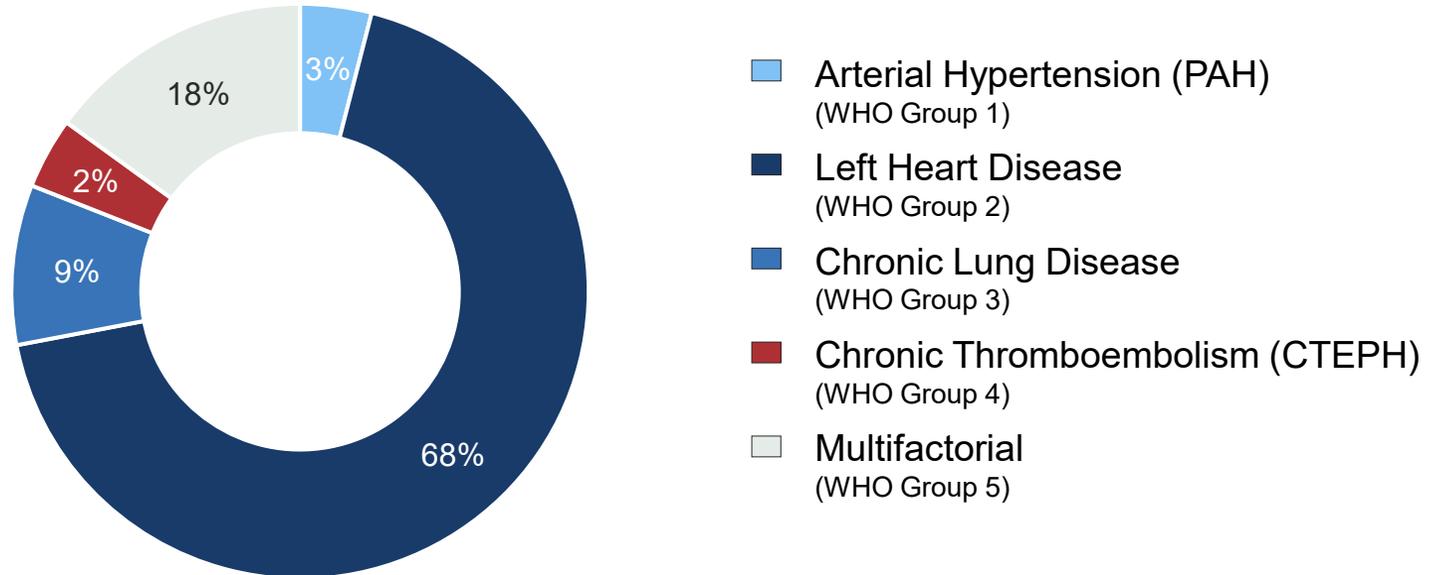
# Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction (PH-HFpEF)

## Group 2 Pulmonary Hypertension (Left Heart Disease)

### PH-HFpEF is the most common form of PH

- Patients present with shortness of breath, leg edema, and poor exercise capacity
- A progressive, debilitating and often fatal disease
- No approved treatment is recommended by current guidelines

## Pulmonary Hypertension Global Prevalence

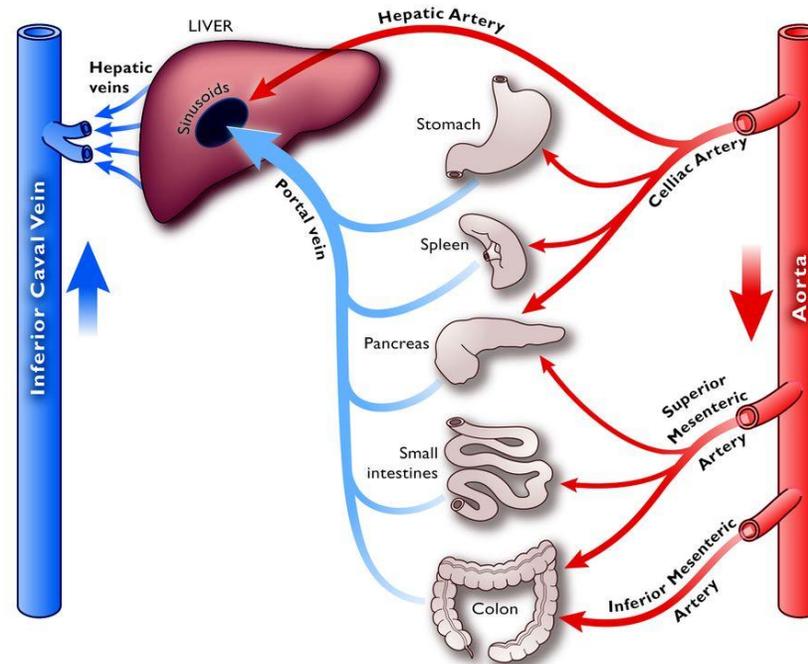


**~50% of Group 2 patients have PH-HFpEF, a large patient population with significant unmet need**

PH: pulmonary hypertension; PH-HFpEF: pulmonary hypertension in heart failure with preserved ejection fraction; WHO: World Health Organization.  
Strange G, et al. *Heart (British Cardiac Society)* vol. 98,24 (2012): 1805-11.

# The Fundamental Role of the Splanchnic Reservoir

35% of circulating blood is in the systemic veins

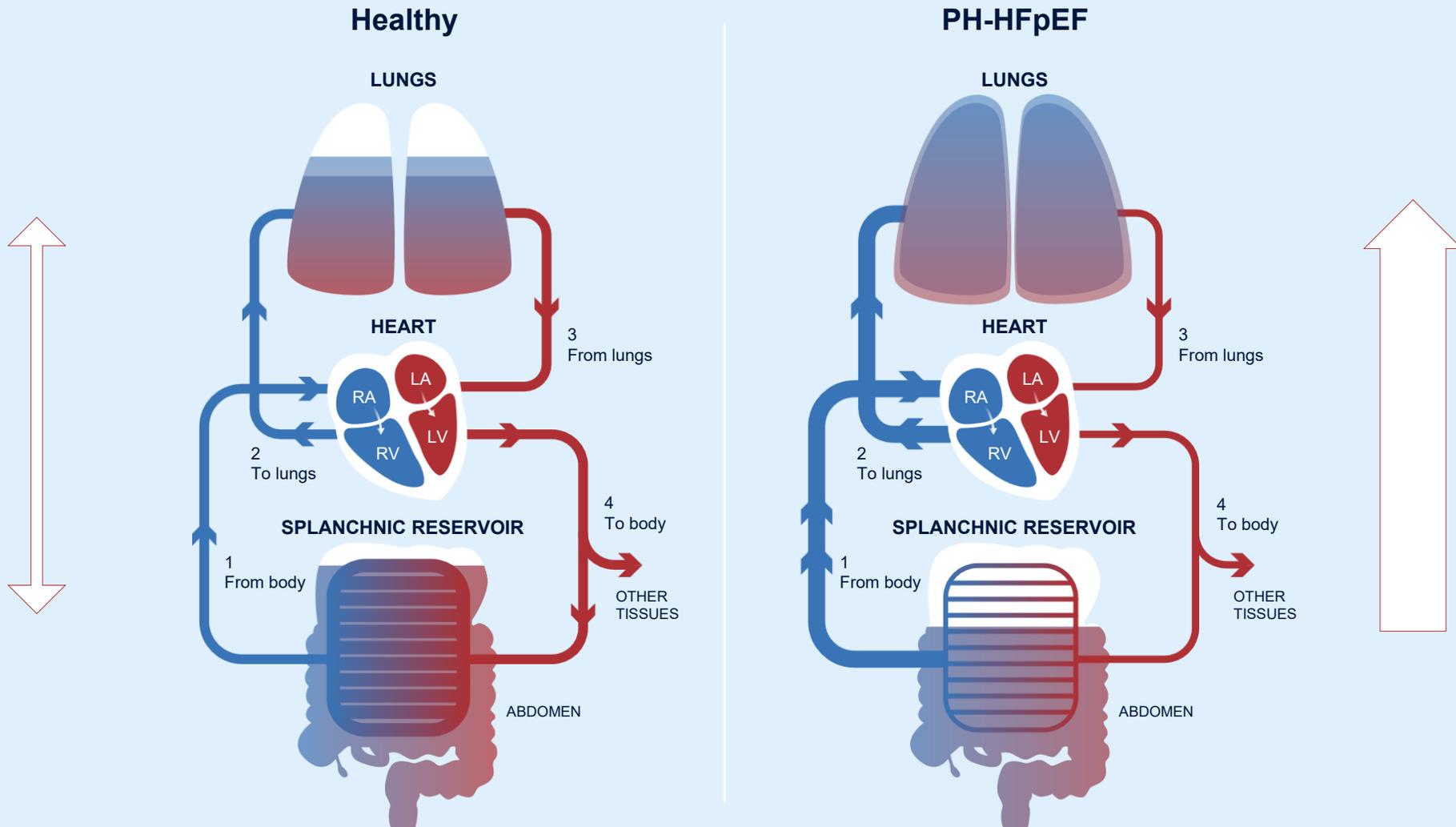


35% of circulating blood is in the systemic arteries

30% of circulating blood is in the splanchnic vascular reservoir

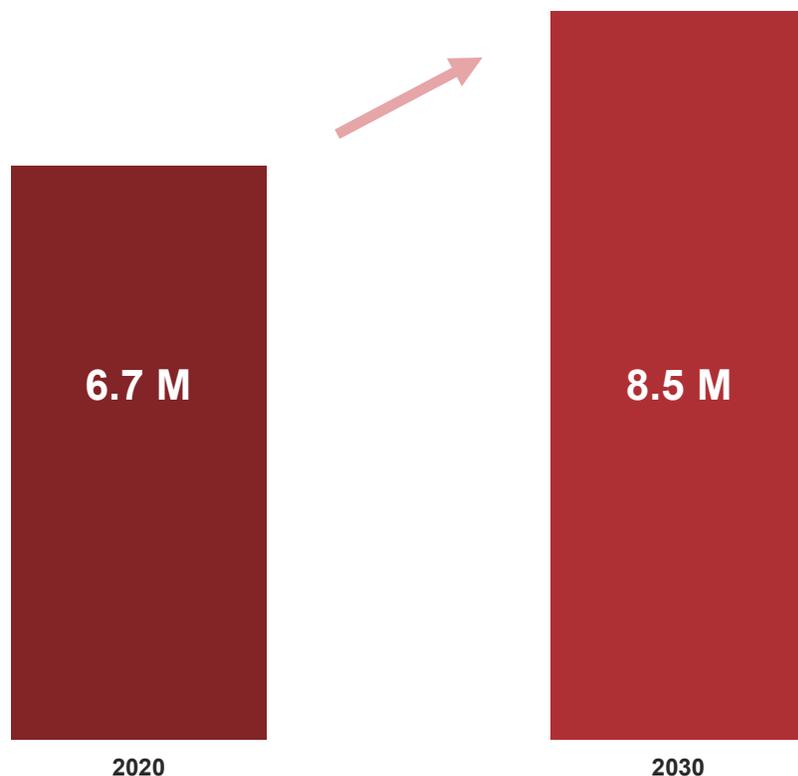
# Blood Volume Distribution

## REDUCING BLOOD VOLUME TO LOWER VENOUS AND PULMONARY PRESSURE

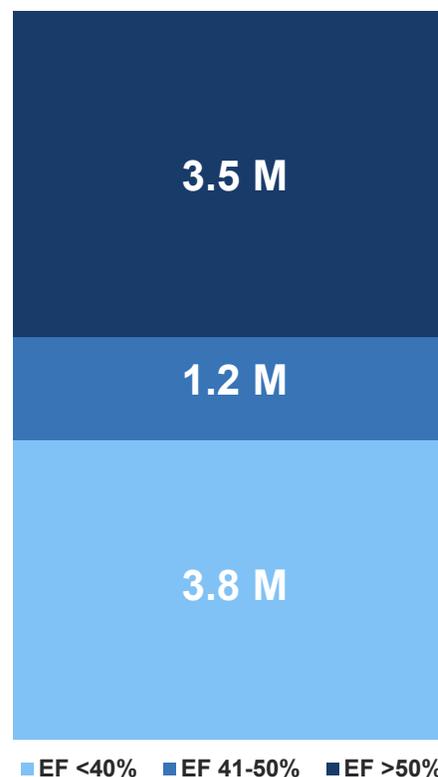


# PH-HFpEF: Large and Growing Market with No Approved Therapies to Date

### Estimated US HF Prevalence



### EF% Distribution



### Estimated US PH-HFpEF Prevalence in 2030

~50-80% of HF patients with EF >40% have PH

That translates to around 2.2-3.7M PH-HFpEF patients in the US by 2030

HF: heart failure; EF: ejection fraction; PH: pulmonary hypertension; PH-HFpEF, pulmonary hypertension in heart failure with preserved ejection fraction.

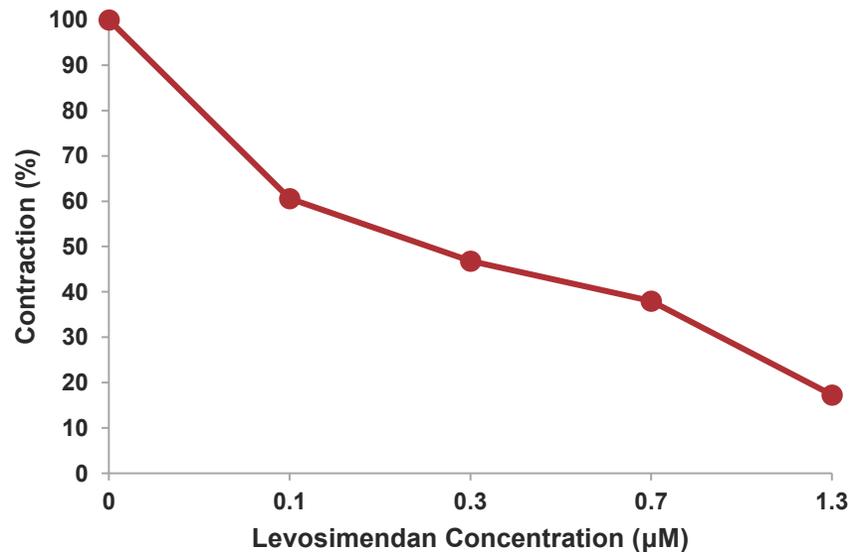
Bozkurt B, et al. *Journal of cardiac failure* vol. 31,1 (2025): 66-116.; Guazzi M. *Circulation. Heart failure* vol. 7,2 (2014): 367-77.; Lam CSP, et al. *Journal of the American College of Cardiology* vol. 53,13 (2009): 1119-26.

# Oral Levosimendan (TNX-103)

# Levosimendan's MOA is Uniquely Suited to Treat PH-HFpEF

NOVEL, POTENTIAL FIRST-IN-CLASS K-ATP CHANNEL ACTIVATOR AND CALCIUM SENSITIZER

## Dose-dependent dilation of human portal vein with levosimendan



### Vein Becomes Less Contracted as Concentration of Levosimendan Increases

- ❖ Human portal vein placed in tissue bath
- ❖ Vein is contracted with norepinephrine to mimic human physiology
- ❖ Levosimendan is then progressively added to tissue bath

# Proof-of-Concept Established in Phase 2 HELP Study

STUDY DEMONSTRATED SAFETY AND EFFICACY OF LEVOSIMENDAN IN PH-HFPEF

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## Phase 2 HELP Study

- Open-label study to evaluate IV levosimendan (TNX-101), specifically the effects on hemodynamics at rest and exercise after 24 hours
- 37 PH-HFpEF patients with initial responses were then enrolled into randomized, double-blinded treatment with once weekly IV infusions for 6 weeks
- Final assessment after 6 weeks of 6-minute walk distance and hemodynamics study

## Summary of Results

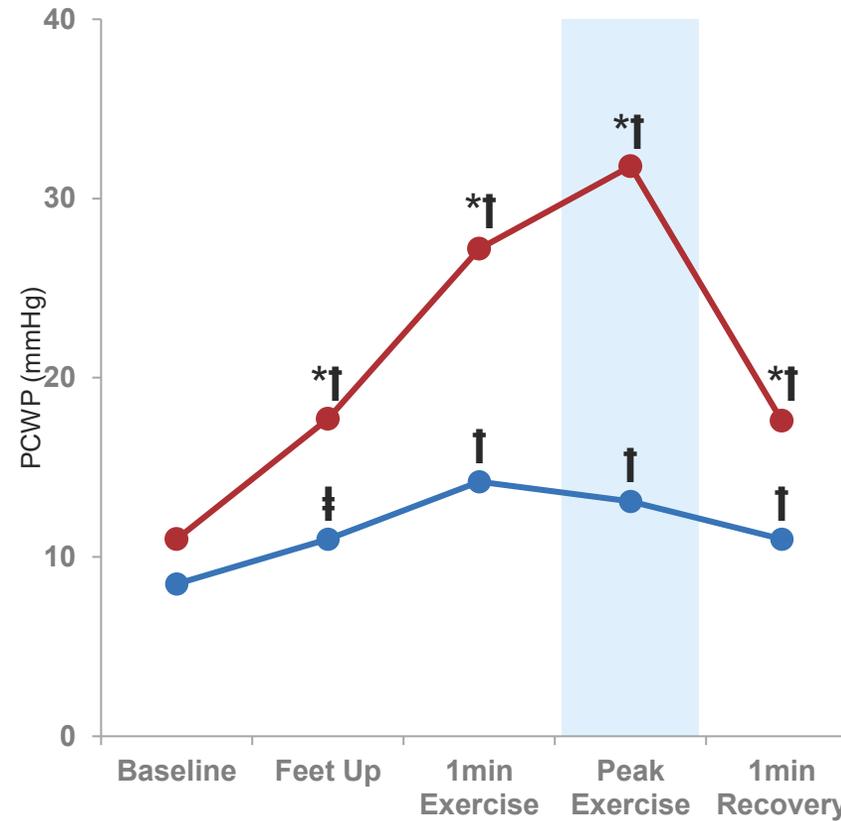
- ❖ Confirmed academia-oriented hypothesis of levosimendan's effectiveness in treating PH-HFpEF
- ❖ First study in any HFpEF population to show improvement in 6MWD
- ❖ Follow-up OLE established PoC for oral levosimendan

# Overview of PH-HFpEF Hemodynamics

## Exercise hemodynamics data from HELP study confirm diagnosis

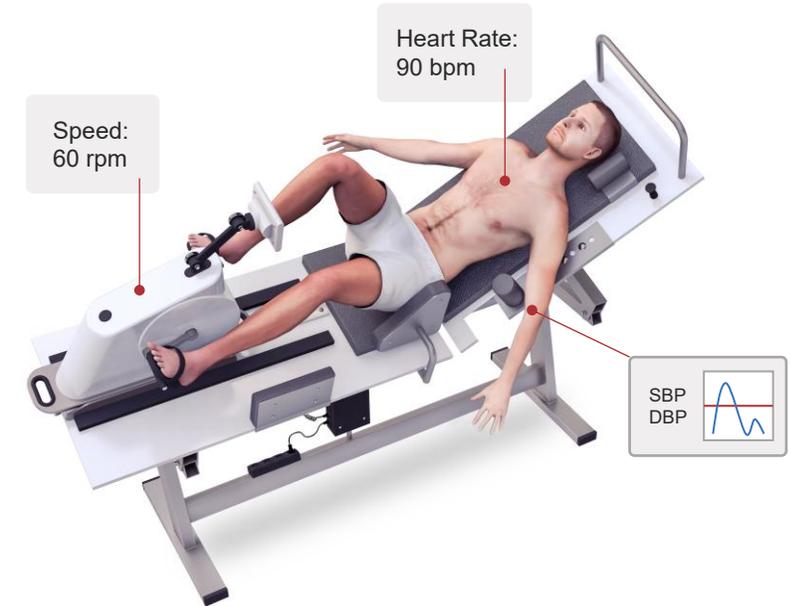
- Increase in PCWP during exercise is the defining impairment in PH-HFpEF
- No known treatment has been able to prevent increase in PCWP during exercise

**ΔPCWP at Rest and Exercise**



● NCD ● HFpEF  
 \* p<0.0001 for ΔPCWP (vs NCD)  
 † p<0.001 vs base (within group)  
 ‡ p<0.01 vs base (within group)

**Experimental Set Up During Isometric Leg Exercise**



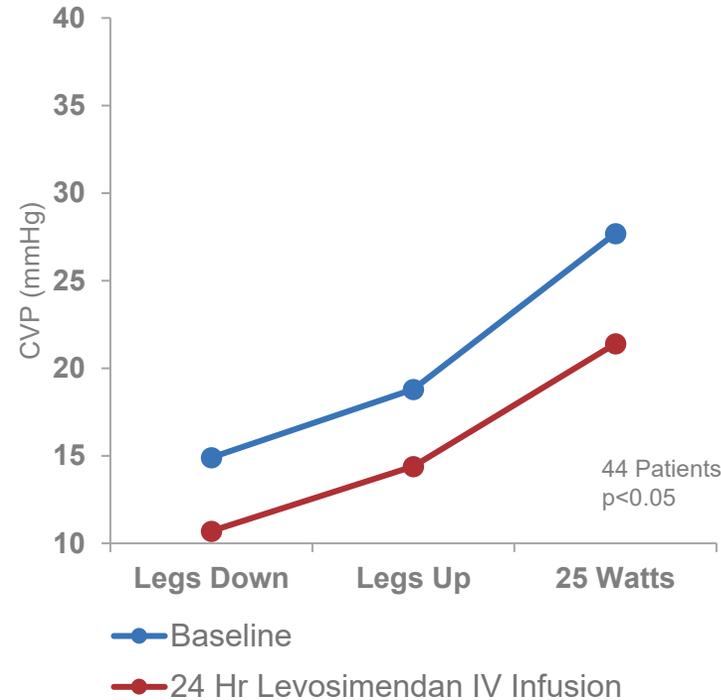
DBP: diastolic blood pressure; NCD: noncardiac dyspnea; PCWP: pulmonary capillary wedge pressure; SBP: systolic blood pressure. Borlaug BA, et al. *Circulation. Heart failure* vol. 3,5 (2010): 588-95.

# IV Levosimendan Improves CVP and PCWP After 24 Hour Infusion

- Improvements seen at rest and with exercise
- 85% of patients enrolled responded with robust decrease (>4mm Hg) in exercise PCWP

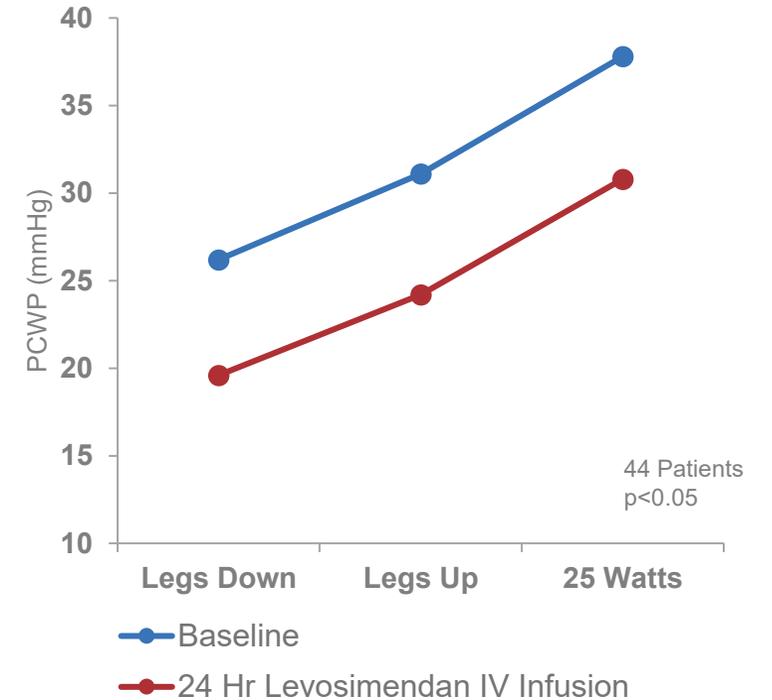
### CVP Improvement

Levosimendan-Treated Patients



### PCWP Improvement

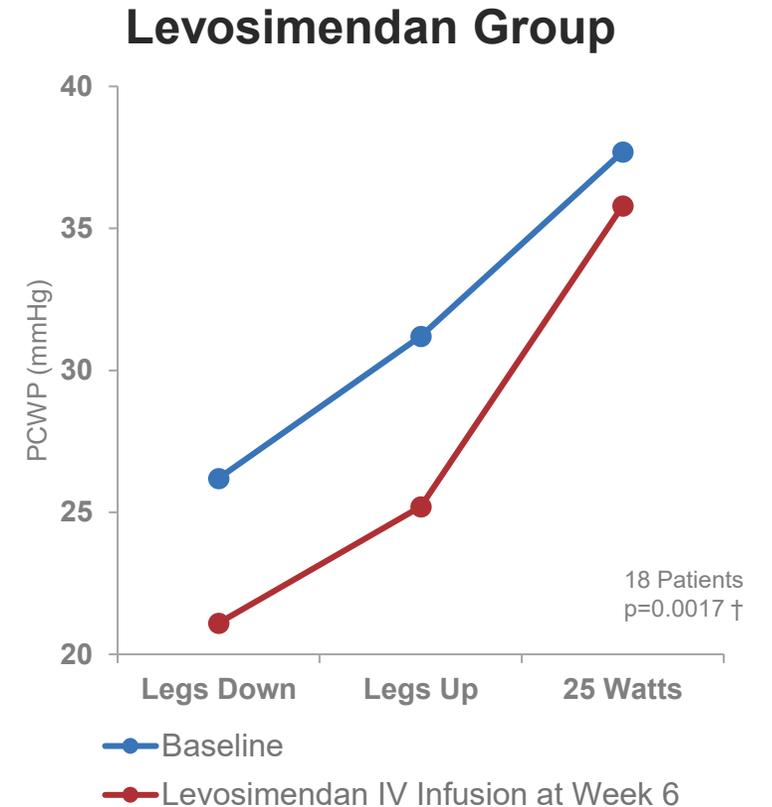
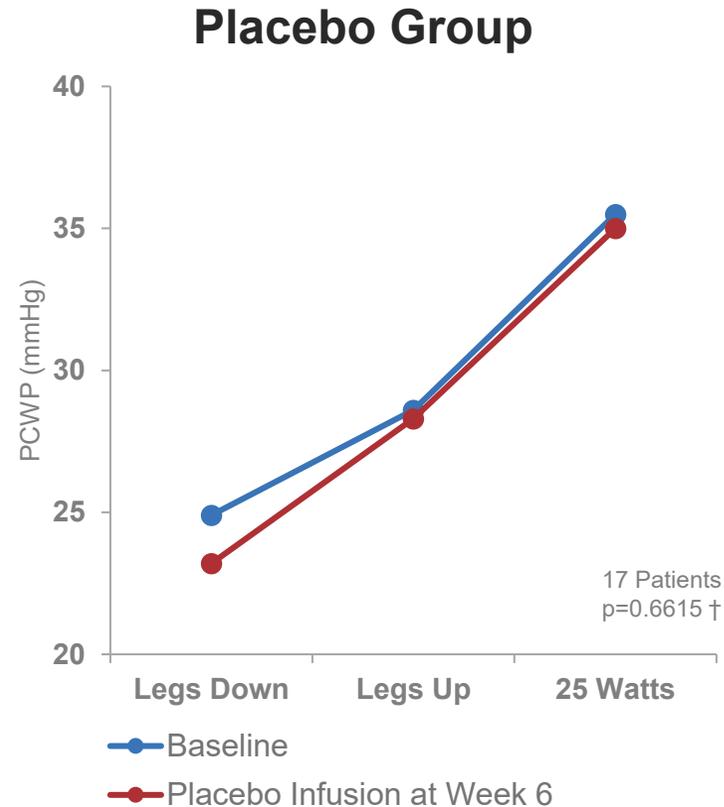
Levosimendan-Treated Patients



CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure. Burkhoff D, et al. *JACC. Heart failure* vol. 9,5 (2021): 360-370.

## IV Levosimendan Significantly Improves PCWP After 6 Weeks

- Following randomization for 6 weeks at trough, placebo patients experienced no change
- Meanwhile, pressure in patients treated with IV levosimendan markedly improved in 3 positions (as assessed by right heart catheterization)

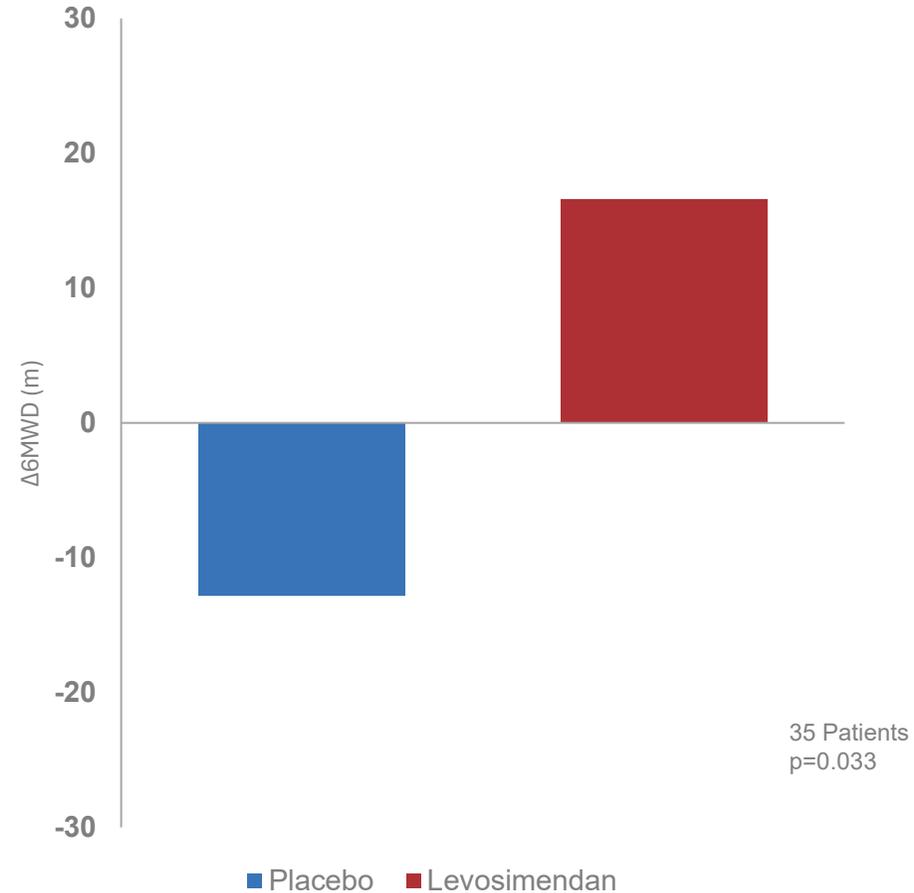


† Tested in a mixed effect model using treatments as factors and position as a random effect.  
PCWP: pulmonary capillary wedge pressure.  
Burkhoff D, et al. *JACC. Heart failure* vol. 9,5 (2021): 360-370.

## IV Levosimendan Improves Exercise Capacity After 6 Weeks at Trough

- 29m improvement in 6MWD
- Levosimendan is the first drug to improve 6MWD in any HFpEF patient population

### 6-Minute Walk Distance (6MWD)



37 patients met hemodynamic criteria and were randomized, of these, 2 patients dropped out due to palpitations and COVID-19 infection, both were in the placebo arm.  
Burkhoff D, et al. *JACC. Heart failure* vol. 9,5 (2021): 360-370.

# OLE Established Safety, Efficacy and Dosing for Oral Levosimendan

PATIENTS IN OLE WERE TRANSITIONED FROM IV TO ORAL LEVOSIMENDAN (TNX-103)

## Study Objectives

- ❖ Safely transition patients from weekly IV to daily oral levosimendan over 6-8 week period to continue providing open-label treatment with TNX-103
- ❖ Confirm safety and tolerability of oral levosimendan (TNX-103)
- ❖ Determine effective dose to maintain safety and efficacy of IV levosimendan

Previous IV Infusion	Week 0* (Office)	Week 2 (Home)	Week 4 (Home)	Week 6 (Office)
<b>0.10 µg/kg/min</b>	1 mg QD (1 mg total daily dose)  Morning	1 mg BID (2 mg total daily dose)  Every 12 hr	1 mg TID (3 mg total daily dose)  Every 8 hr	Patient evaluated for further titration <sup>†</sup>

\*5-7 days after the last IV levosimendan infusion.; <sup>†</sup>The oral dose was increased every 2 weeks by 1 mg/day to a maximum of 4 mg/day over an 8-week period. The highest daily dose was determined by the investigator based on clinical assessments of symptoms and side effects.

BID: twice daily; IV: intravenous; OLE: open-label extension; TID: 3 times daily; QD: every day.

Thenappan T, et al. *J Card Fail.* Vol. 29,4 (2023): 714-715.

# Oral Levosimendan (TNX-103): Safe and Effective as IV Formulation

RESULTS FROM HELP OLE IV-TO-ORAL TRANSITION SUBSTUDY

## Exercise capacity



**+ 7 meters**

6MWD was improved by 7 meters

## Cardiac function



**↓ 23% over IV**

BNP/NT-proBNP improved by 23%

## Patient-reported outcomes

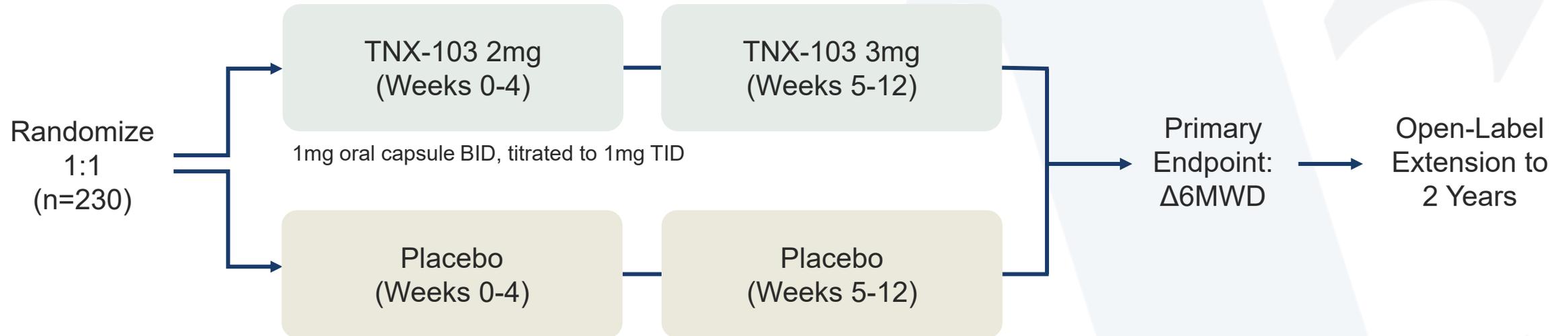


**↑ in 6 of 7 domains**

KCCQ improved further in 6 of 7 different domains

# LEVEL Study

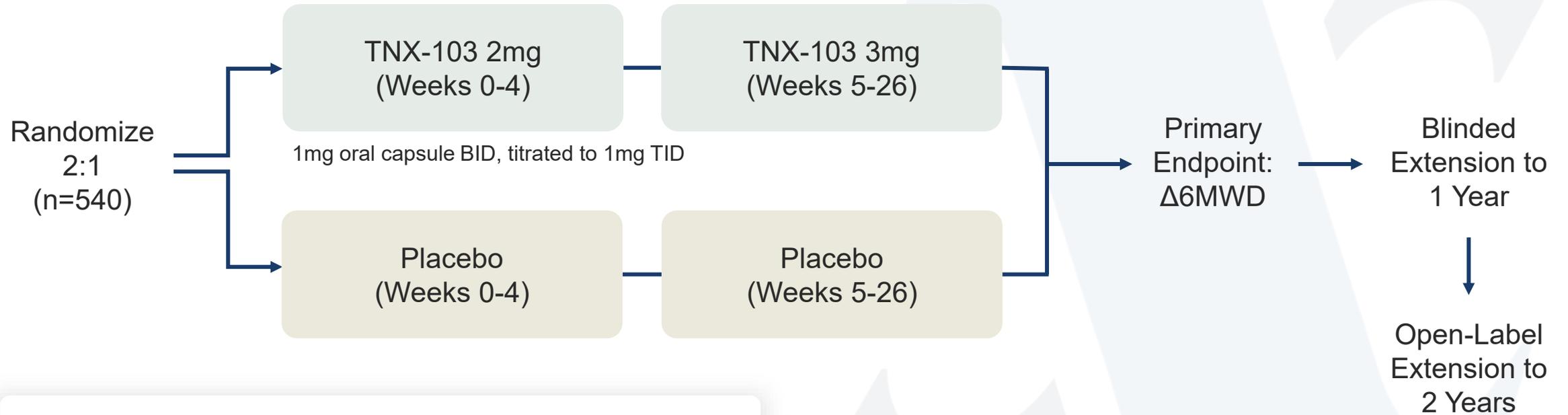
ONGOING PHASE 3 REGISTRATIONAL TRIAL IN US AND CANADA



- Prespecified BSSR demonstrated trial is powered at well over 90% to detect 25m change in 6MWD at 12-weeks (primary endpoint)
- Randomization target (230 patients) achieved
- Topline data expected in Q3 of 2026

# LEVEL-2 Study

## SECOND GLOBAL PHASE 3 REGISTRATIONAL TRIAL



- Same patient selection criteria and dosing as LEVEL
- Primary endpoint: 6MWD at 26 weeks
- Blinded extension for 150 subjects
- Enrollment completion expected by end of 2027

# IP Portfolio Protects Global Rights to Levosimendan Use in PH-HFpEF

- ❖ US patents for oral (TNX-103), IV, expanded dose and combination use through 2040
- ❖ Global protection pending across potential markets
- ❖ All patents have continuation applications pending

## United States:

**US 11,213,524**, issued January 4, 2022, **expires November 14, 2039** (SC Formulation/Use)

**US 11,607,412**, issued March 21, 2023, **expires December 15, 2040** (IV Use)

**US 11,701,355**, issued July 18, 2023, **expires December 15, 2040** (Oral Use)

**US 11,969,424**, issued April 30, 2024, **expires December 15, 2040** (Expanded dose & CV drug combo use)

Pending US Patent Application, USPTO has issued Notice of Allowance (SC Use)

**All patents have continuation applications pending**

## Europe

**EP 4076398 B1** issued February 18, 2026, **expires December 15, 2040**

## Japan/Canada/New Zealand/Australia/Thailand/ Malaysia/Singapore:

Regional stage applications filed (PCT/US2020/065166)

Canadian Patent Application No. 3,161,960 – Allowed

## Other PCT Applications:

**PCT/US2022/080708**, filed November 30, 2022 (Combination use of levosimendan and SGLT-2 in HF)

**PCT/US2022/082561**, filed December 29, 2022 (Oral Levosimendan use in PH-HFpEF)

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Developing a  
therapy uniquely  
suited for PH-HFpEF

# Appendix

# Drug Development Veterans Joined By Preeminent PH Experts



**Chris Giordano**  
President & CEO



**Stuart Rich, MD**  
CMO



**Thomas McGauley**  
Interim CFO



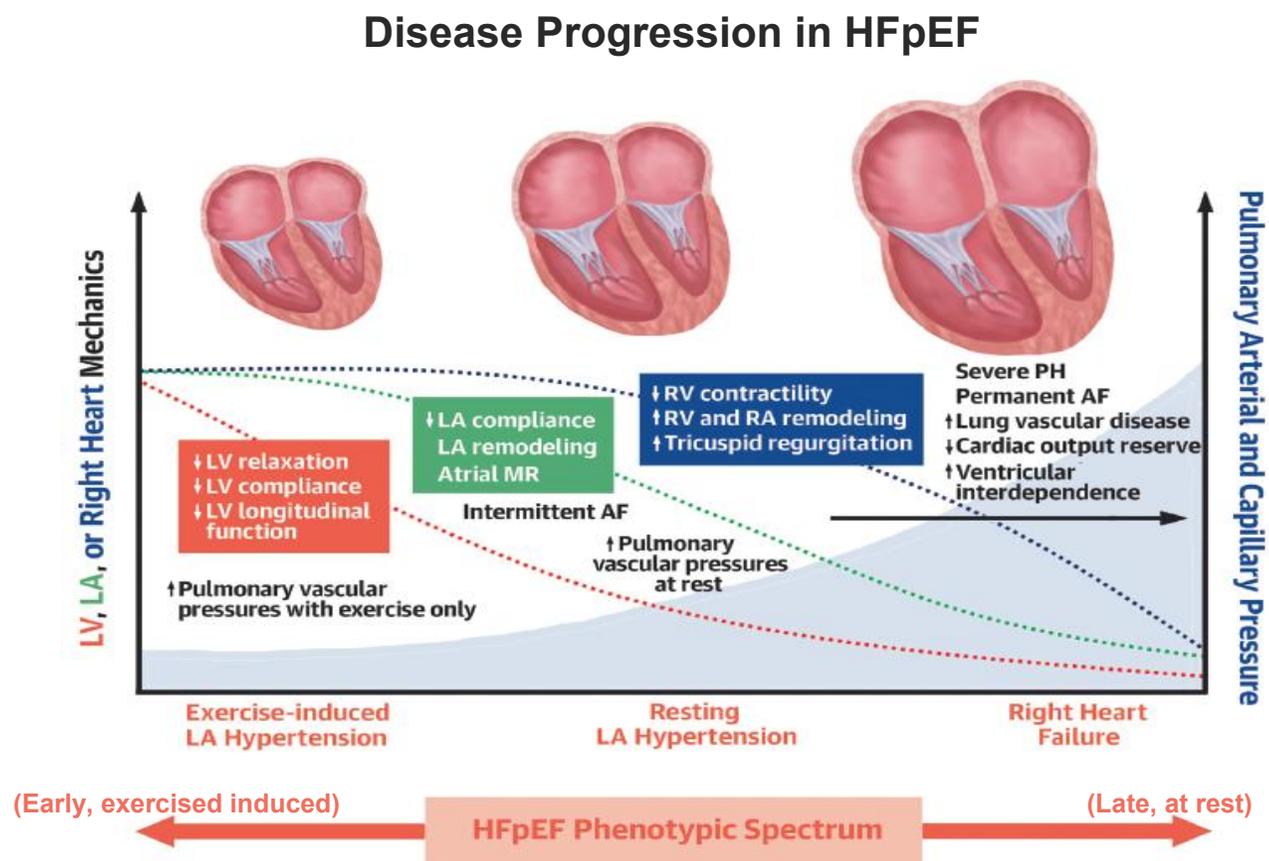
**Doug Randall**  
CBO



## Board of Directors

- Gerry Proehl (Chairman)
- Michael Davidson, MD
- June Almenoff, MD
- Declan Doogan, MD
- Robyn Hunter
- Chris Giordano
- Stuart Rich, MD

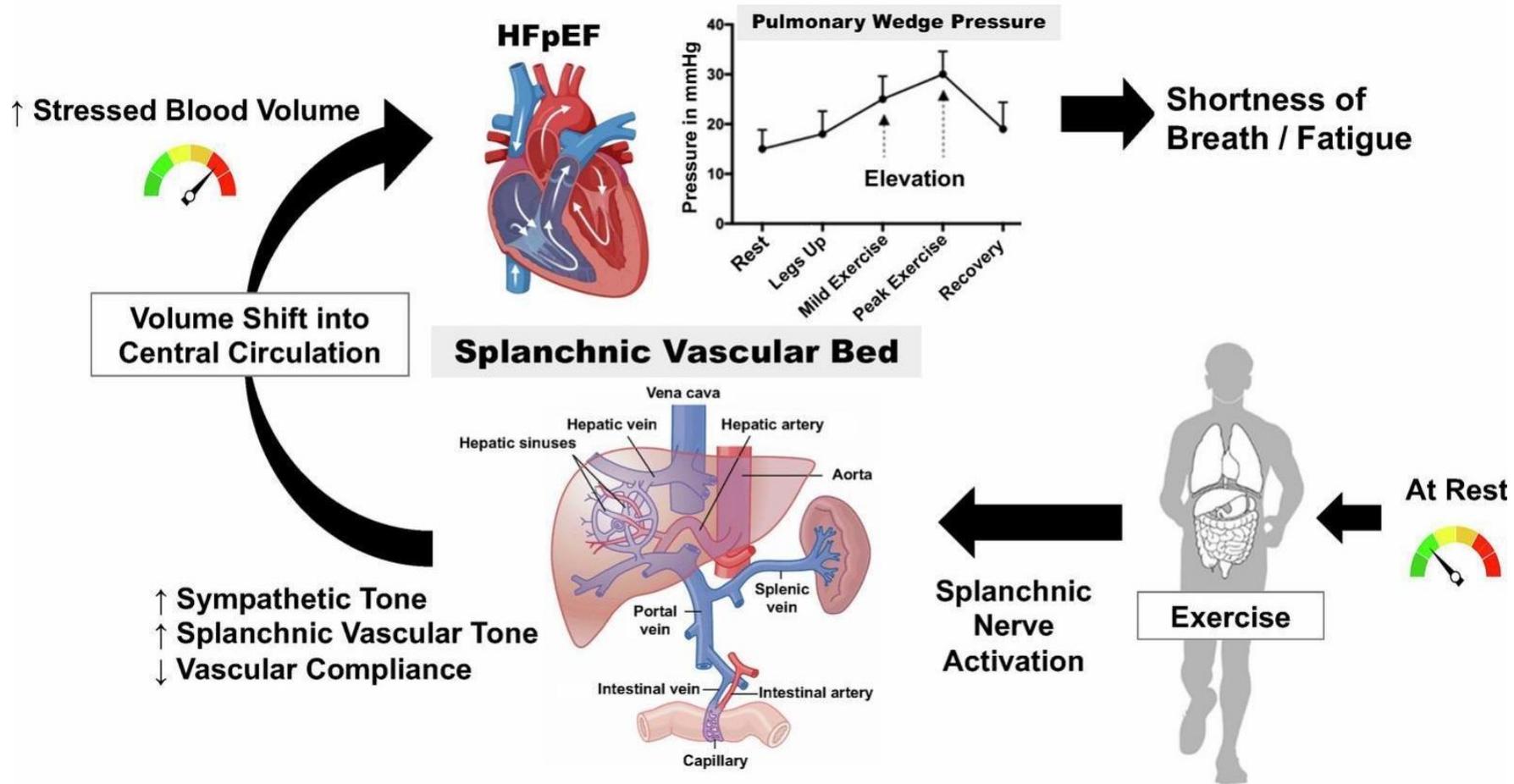
# Pulmonary Hypertension Can Present Across HFpEF Phenotypic Spectrum



>80% of patients with HFpEF are estimated to have pulmonary hypertension

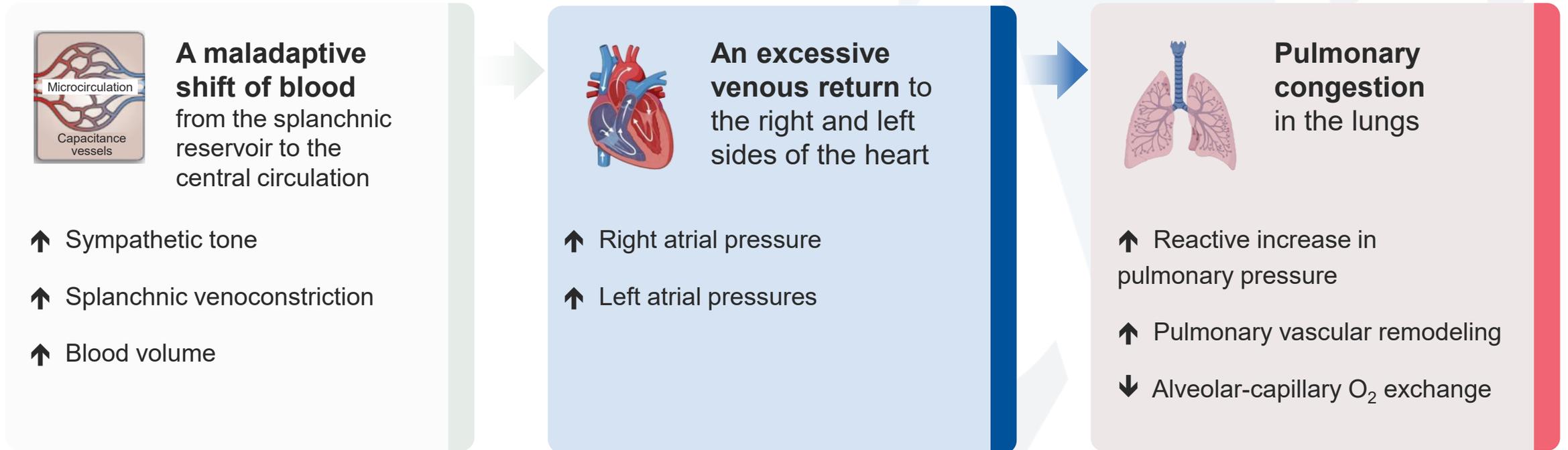
# Splanchnic Circulation

## VOLUME REDISTRIBUTION



# Chronic Constriction of the Splanchnic Circulation in PH-HFpEF

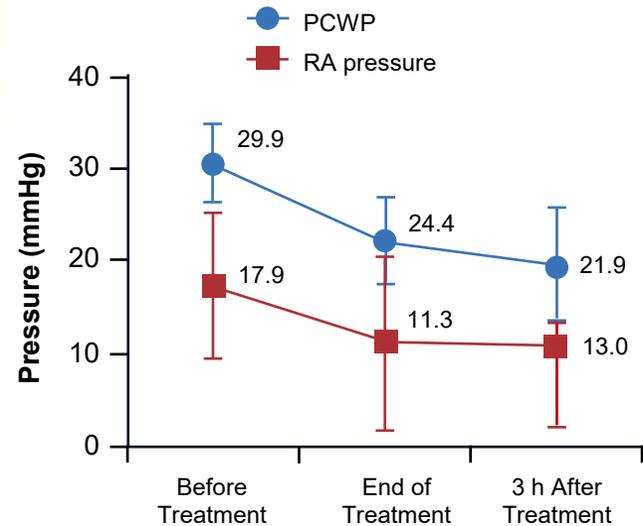
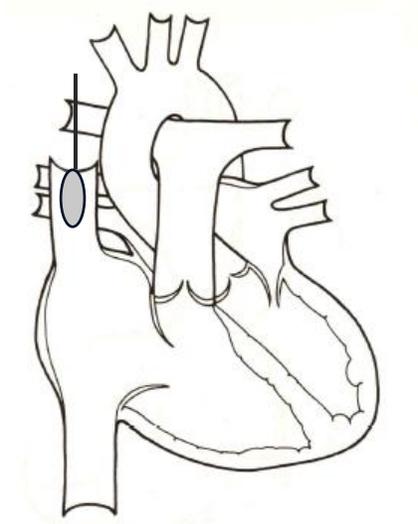
## ALTERS BLOOD VOLUME AND CARDIOPULMONARY FUNCTION



# Mechanical Preload Reducing Device

## PROOF-OF-CONCEPT FOR VENOUS MODULATING THERAPIES

### SVC Balloon Occlusion

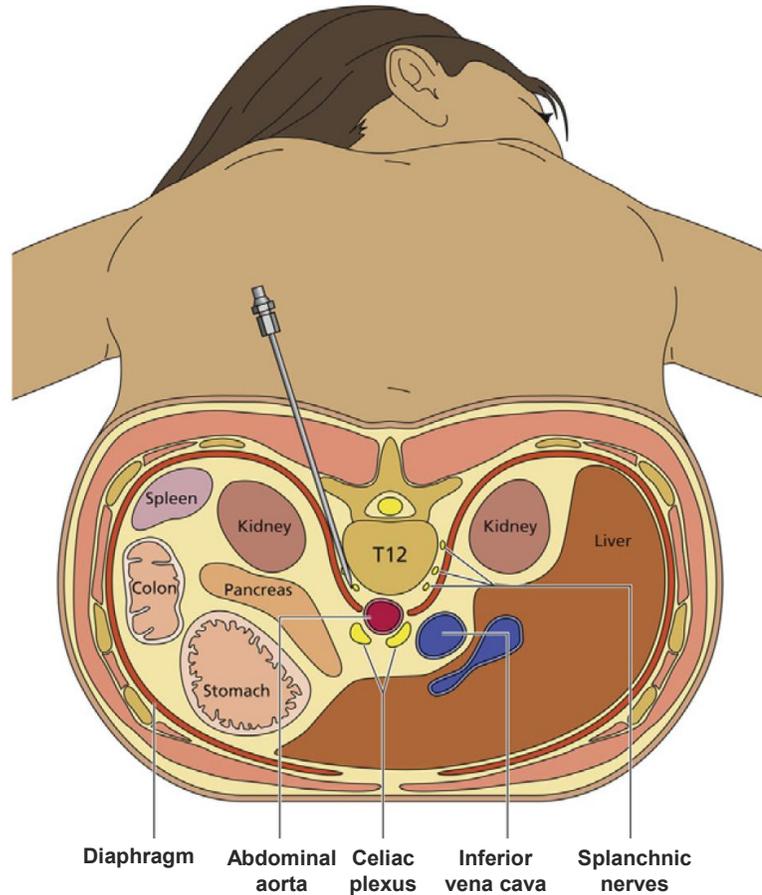


### Acute decompensated HF with LVEF <40%

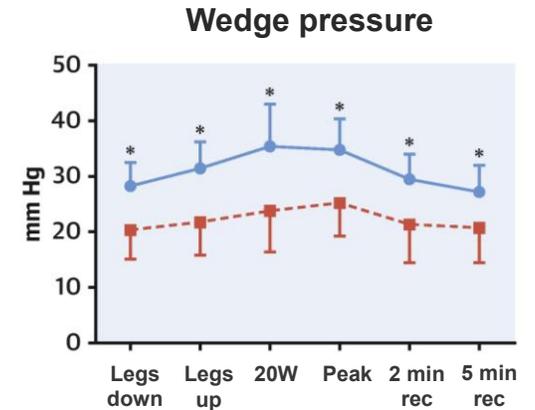
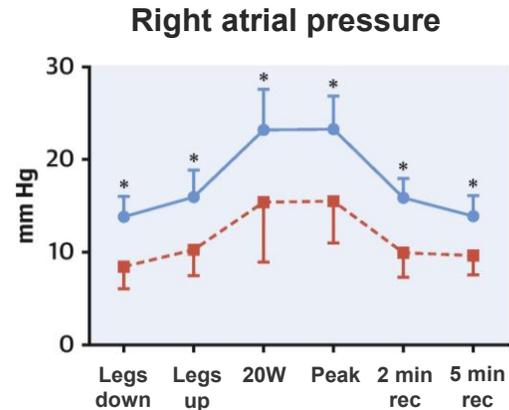
- Mean PAP 40.8 to 33.3 mmHg;  $p < 0.0001$
- PVR had no change;  $p = 0.472$
- Cardiac Index had no change;  $p > 0.99$
- Urine output increased 3.1L;  $p < 0.001$

# Splanchnic Nerve Block

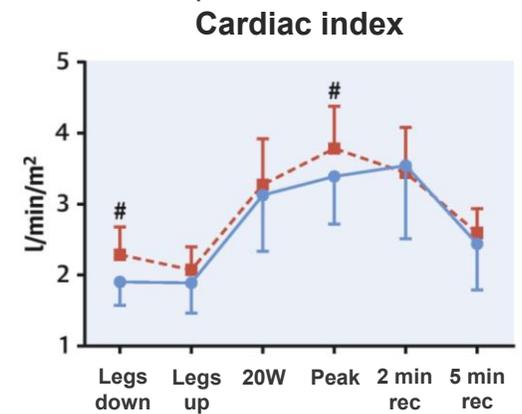
## PROOF-OF-CONCEPT FOR VENOUS MODULATING THERAPIES



Splanchnic nerve block provides proof of concept for benefit of volume modulating therapies



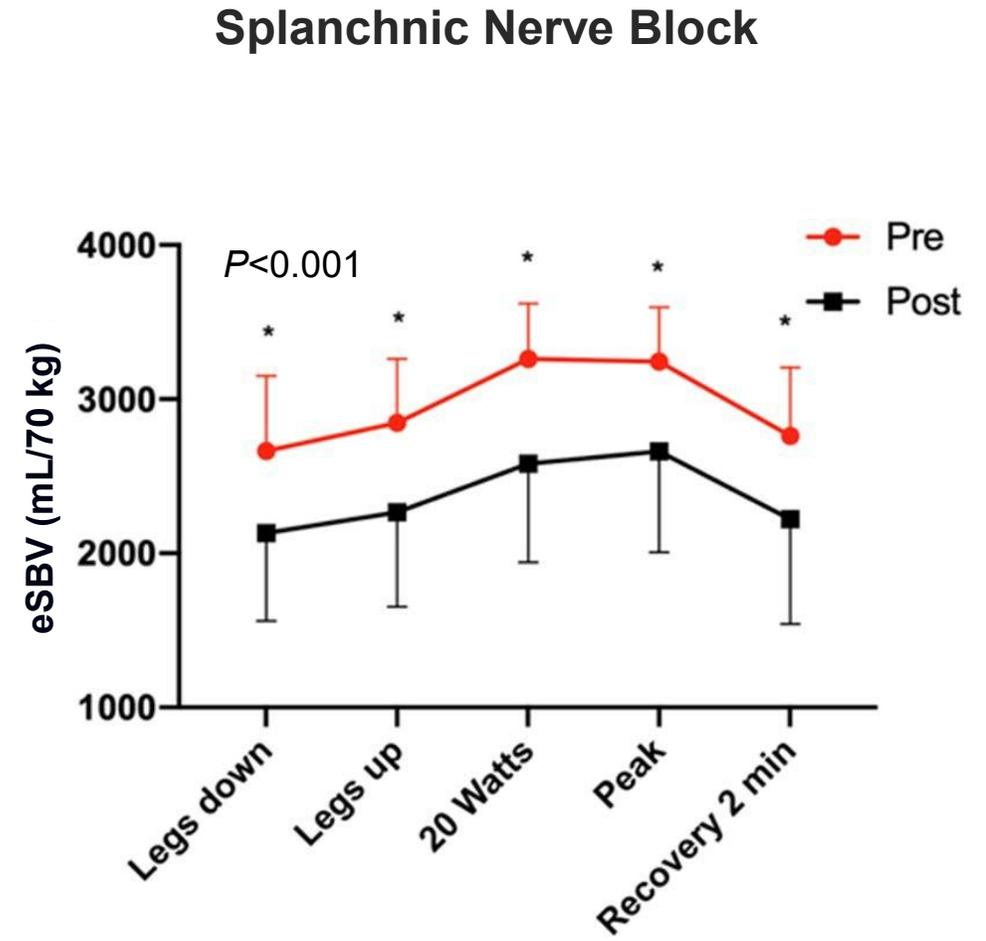
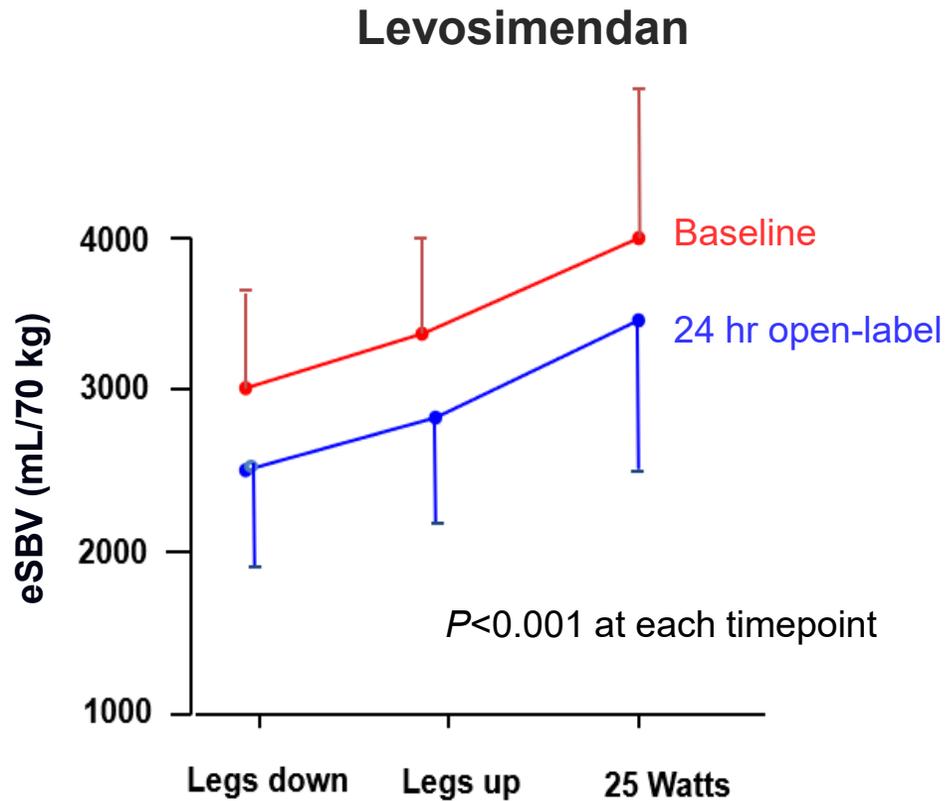
■ Post-nerve block  
■ Baseline



\*Adjusted P<0.01 for a pairwise comparison with the pre-SNB value; #Unadjusted P<0.05, adjusted P>0.05.  
 rec: recovery after peak exercise; SNB: splanchnic nerve block; W: watt.  
 Fudim M, et al. *JACC. Heart failure* vol. 8,9 (2020): 742-752.

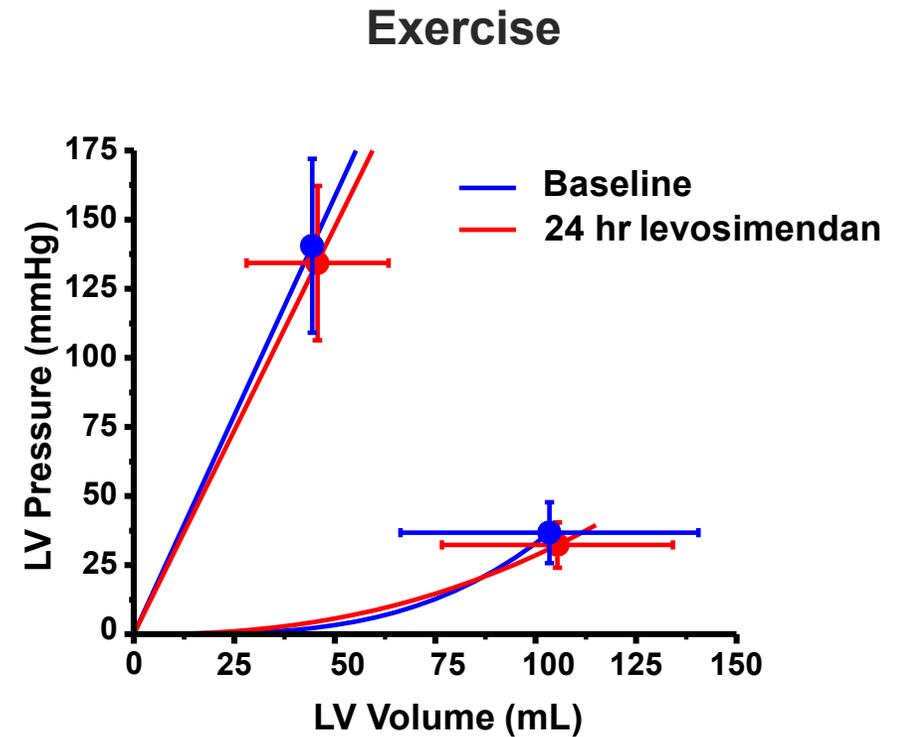
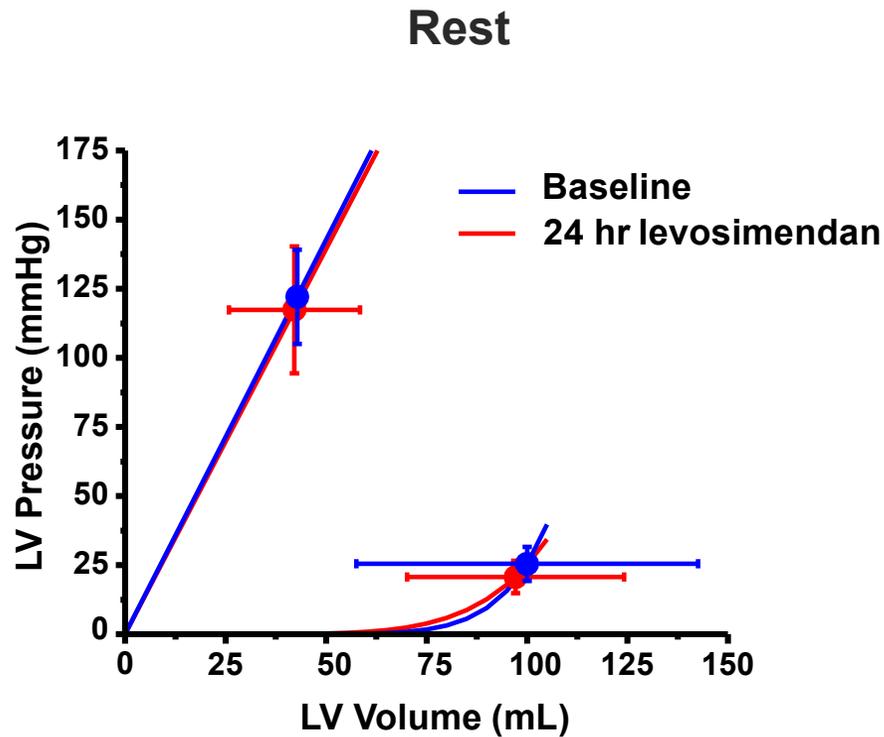
# Levosimendan vs Splanchnic Nerve Block

## EFFECT ON REDUCING BLOOD VOLUME PROVIDES PROOF-OF-CONCEPT

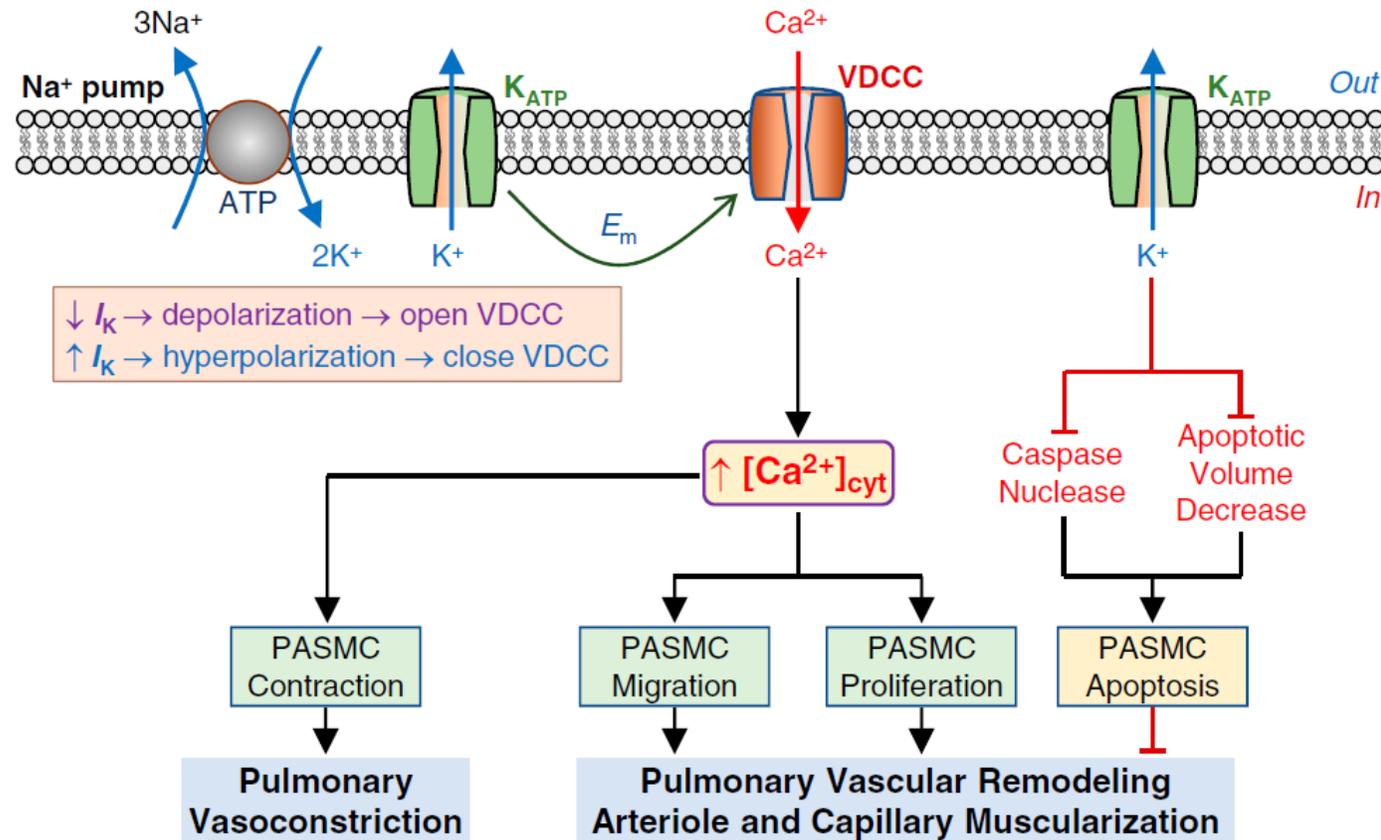


# Baseline vs 24-Hour Levosimendan Infusion on LV Contractility

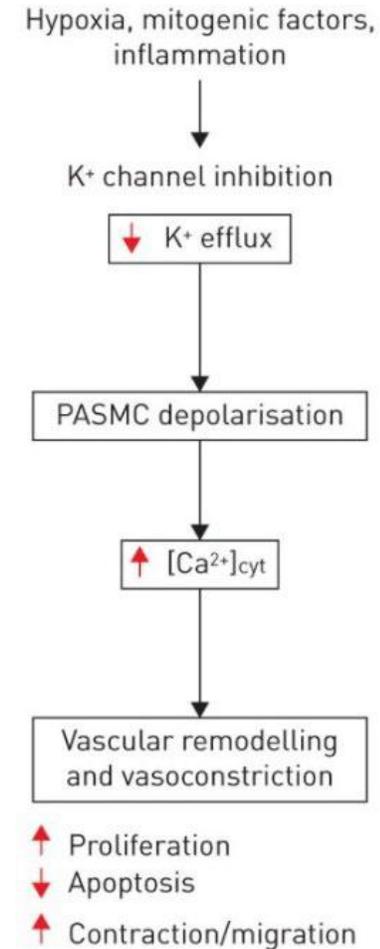
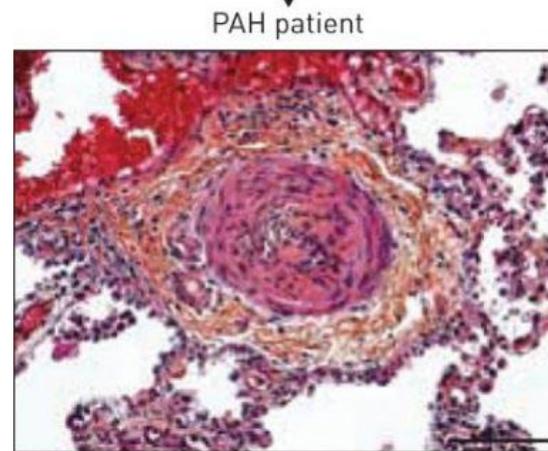
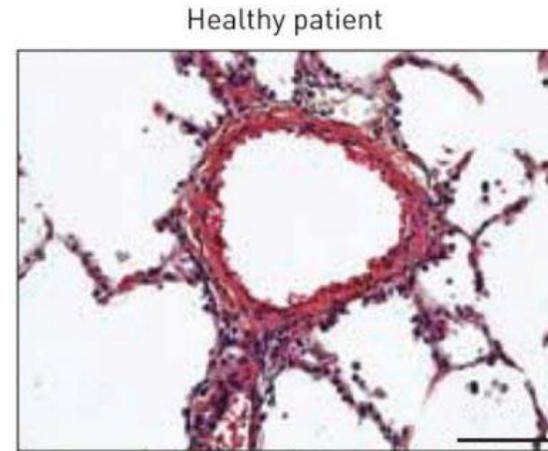
NO EVIDENCE OF INCREASED CONTRACTILITY AT REST OR WITH EXERCISE



# Pulmonary Vascular Remodeling in PH is Associated with Downregulation of K-ATP Channels

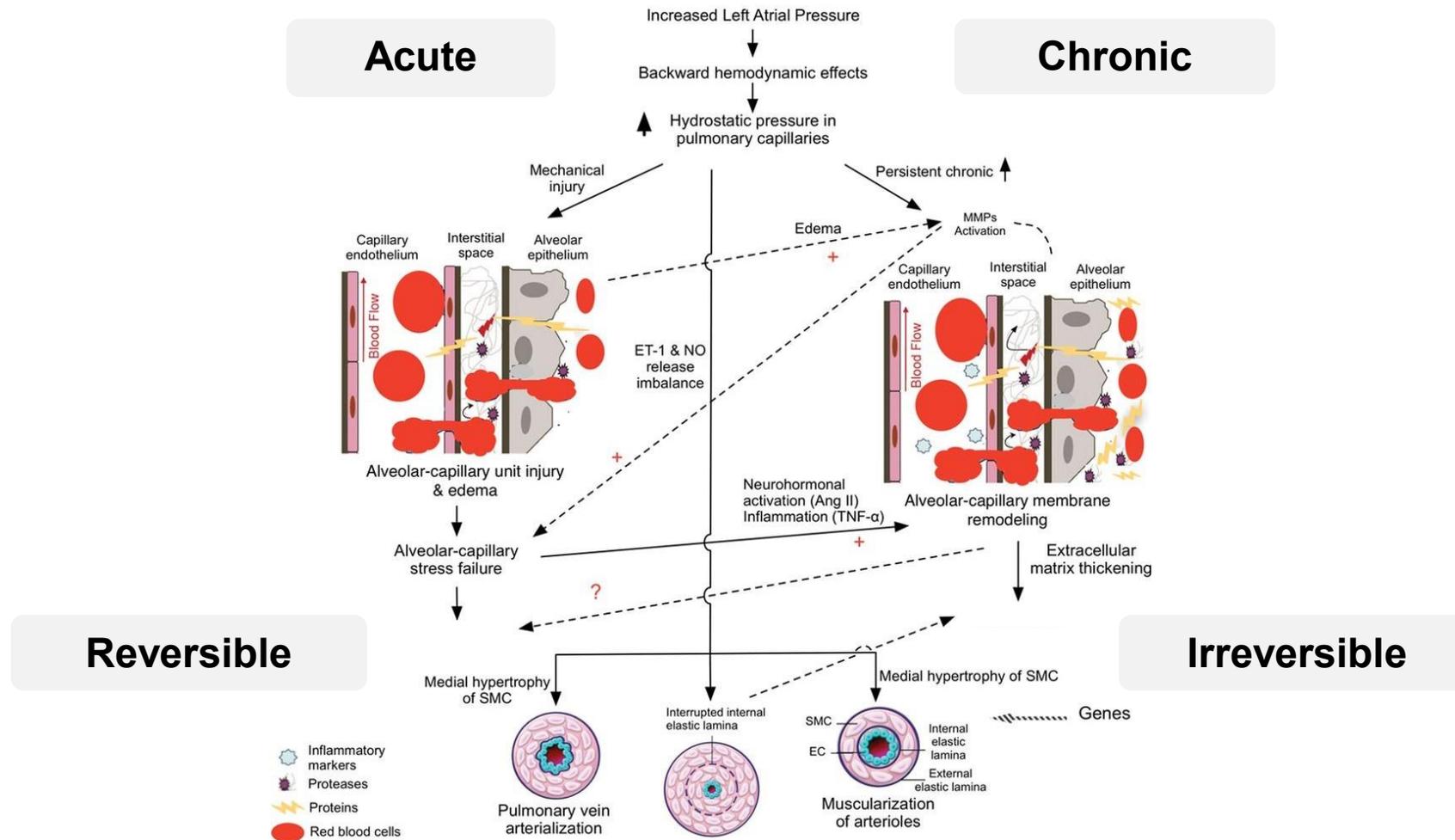


# Altered K-ATP/K Channel Signaling Associated with Pulmonary Vasculopathies



# Pulmonary Vascular Component

## PATHWAYS FROM INCREASED PCWP TO PULMONARY HYPERTENSION

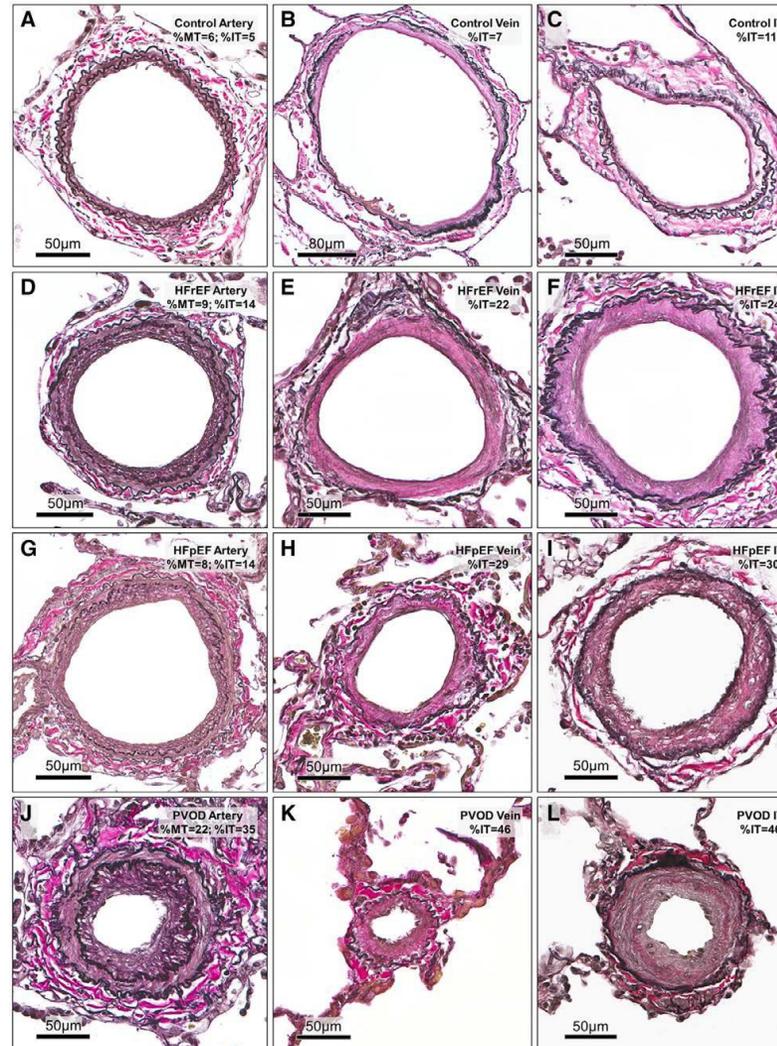


# PH-HFpEF Has Distinct Pathology

## ORIGINAL RESEARCH ARTICLE

### Global Pulmonary Vascular Remodeling in Pulmonary Hypertension Associated With Heart Failure and Preserved or Reduced Ejection Fraction

- Involvement of the pulmonary arteries, pulmonary veins, and arteriole/venule interface.
- Triggered via the increased pressure within the left atrium and/or pulmonary veins.
- The signaling pathway is uncertain.



# Levosimendan: Potential Ideal Treatment for PH-HFpEF

## PROBLEM

Excessive venous return (increased venous blood volume) causing marked elevations in PCWP and RA pressure



## PROPERTY

K<sup>+</sup>ATP channel activation with direct vasodilation of the splanchnic circulation reducing venous blood volume and lowering the PCWP and RA pressure

Remodeling of the pulmonary arteries resulting in elevations in PA pressure



K<sup>+</sup>ATP channel activation with antiproliferative effects on the pulmonary vasculature to lower PA pressure

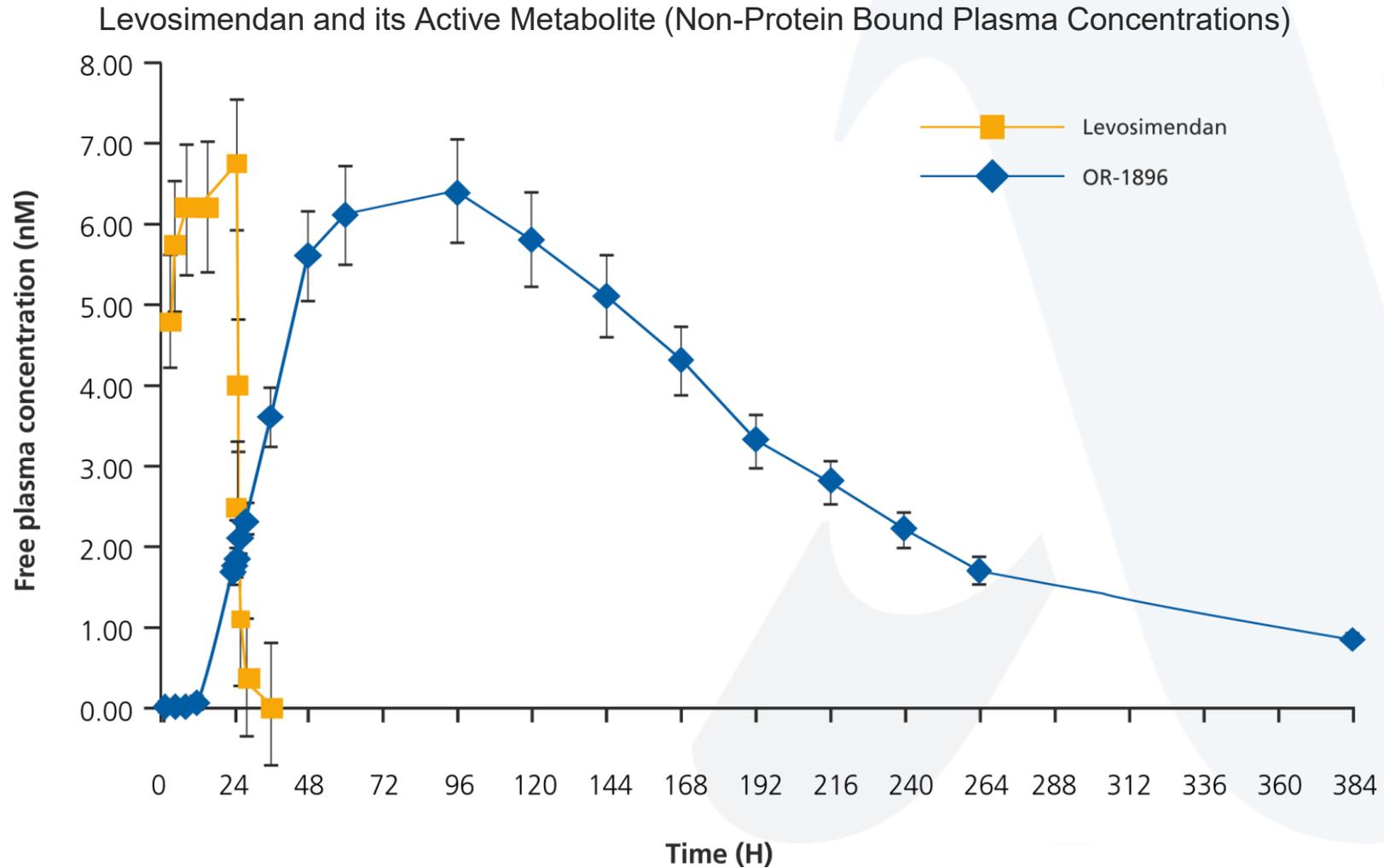
Right ventricular failure from the chronic pulmonary hypertension



Ca<sup>2+</sup> sensitization of cardiac myocytes to improve right ventricular function

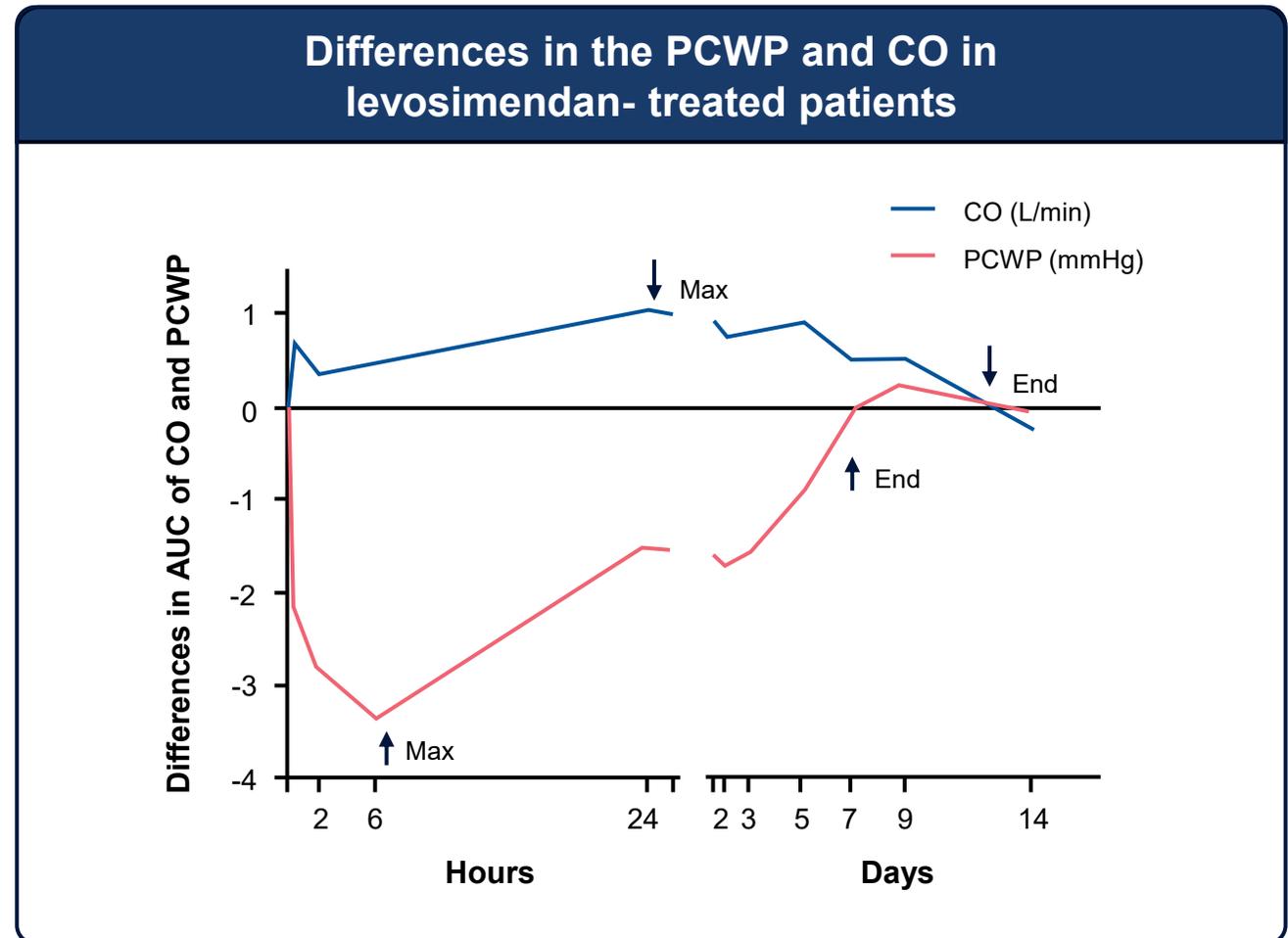
# Rationale for Oral Dose Selection

24-HOUR IV INFUSION OF 0.2  $\mu\text{G}/\text{KG}/\text{MIN}$  (AS COMPARED TO 0.1  $\mu\text{G}/\text{KG}/\text{MIN}$  USED IN HELP)



# Changes in Cardiac Output and PCWP Over Time From Levosimendan in Patients With HFrEF

- Levosimendan produced a marked, rapid fall in the PCWP that preceded the increase in cardiac output
  - Attributed to a reduction in venous blood volume



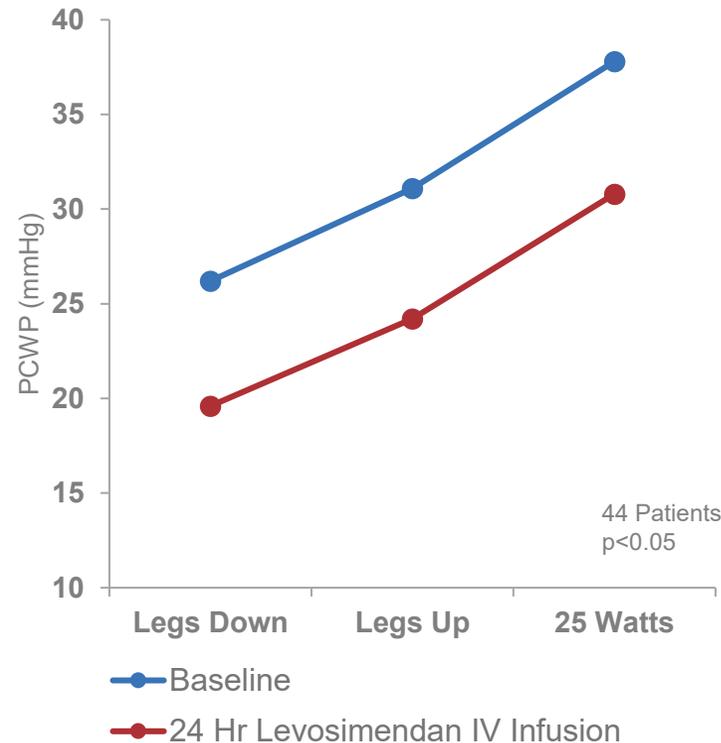
# PCWP Improvement in Levosimendan-Treated Patients

## Effect of IV Levosimendan on PCWP

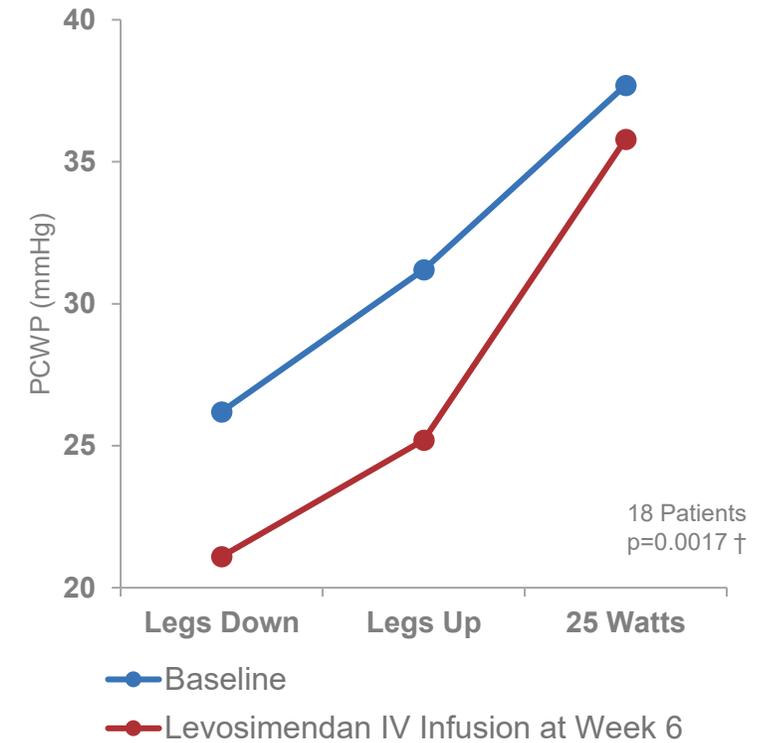
### After 24 Hours vs. After 6 Weeks

- After 24 hour infusion, PCWP was measured at rest, with legs up, and with exercise when concentration of OR-1896 was high
- Following randomization for 6 weeks, right heart catheterization was performed *at end of week following infusion*, with concentration of OR-1896 at trough

### 24 Hours (Open Label)



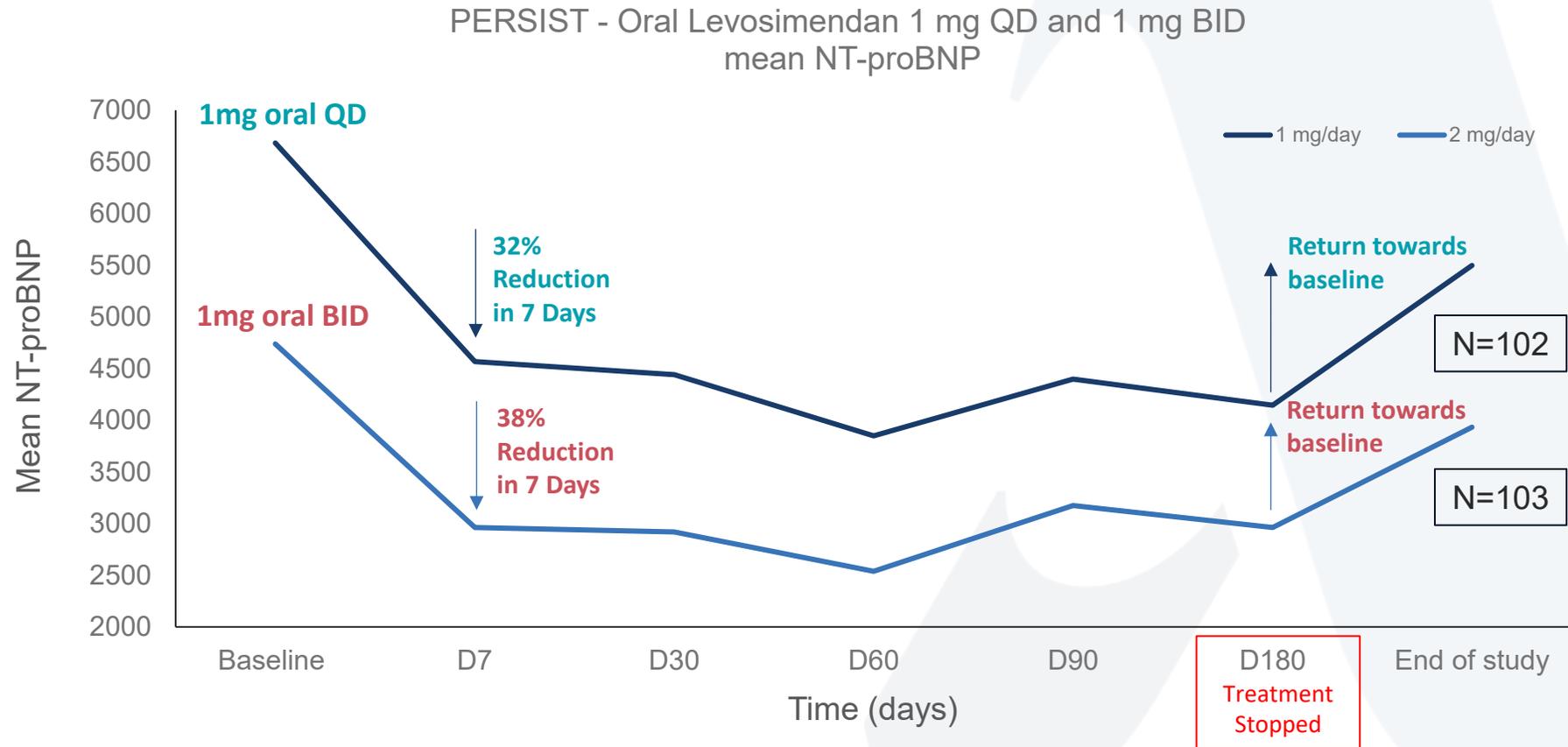
### 6 Weeks (Randomized)



† Tested in a mixed effect model using treatments as factors and position as a random effect.  
PCWP: pulmonary capillary wedge pressure.  
Burkhoff D, et al. *JACC. Heart failure* vol. 9,5 (2021): 360-370.

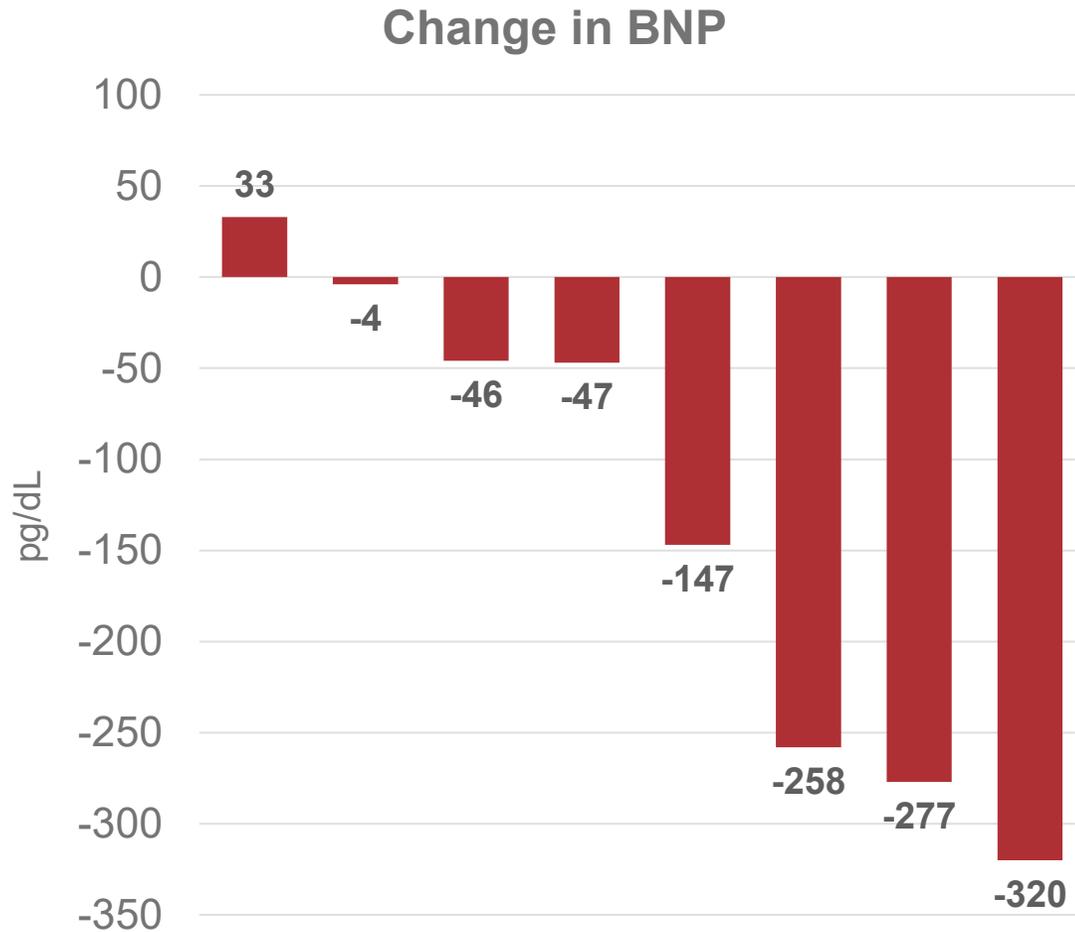
# Oral Levosimendan Causes Rapid, Sustained Reduction in NT-proBNP

DATA FROM PERSIST TRIAL

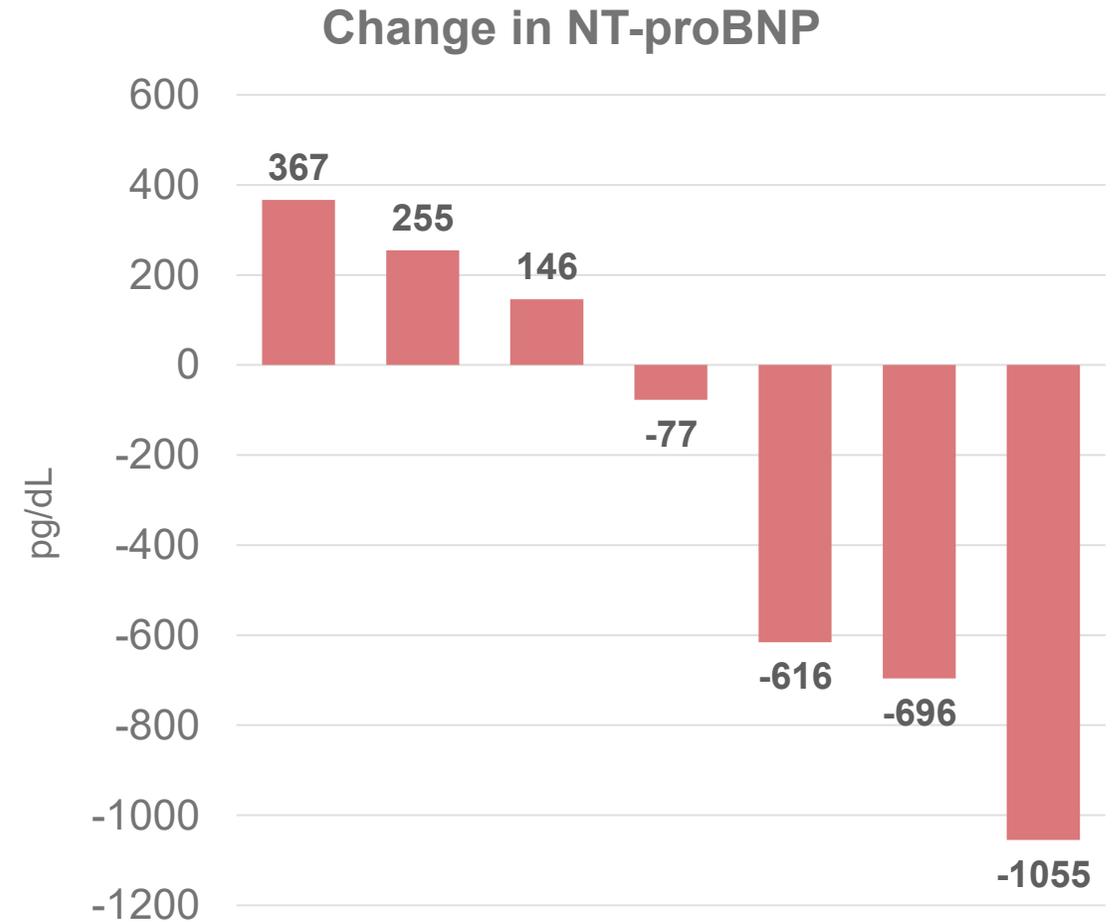


# BNP or NT-proBNP (Collected per Institutional Standard)

DATA FROM HELP OLE



Mean = 133.3 pg/dL



Mean = 239.4 pg/dL

# Oral Levosimendan Drives Sustained Reduction in PCWP in CHF

DATA FROM PERSIST TRIAL

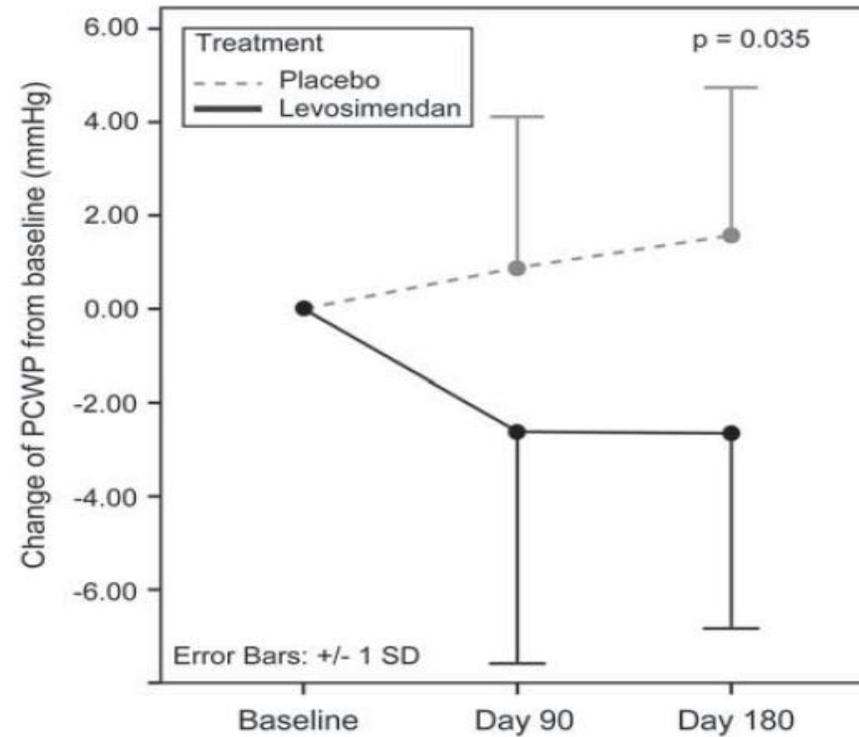


Figure 2. Change of echocardiographic PCWP from baseline to day 180 in placebo and levosimendan treated patients analysed by repeated measures ANOVA ( $p = 0.035$ ).

# Targeting PVR in PH-HFpEF Has Not Proven Successful

## Multicenter Trials of Pulmonary Vasodilators in PH-HFpEF Patients

Drug	Multicenter Trial	PCWP/PAWP Change vs Placebo	PVR Change vs Placebo	6MWD or CPET Change vs Placebo	Safety	Conclusion
<b>Bosentan</b>	BADDHY	Not Reported	Not Reported	No Difference (6MWD)	Questionable, study stopped early	<b>Ineffective</b>
<b>Macitentan</b>	MELODY	No Difference	No difference	No Difference (6MWD)	Questionable, fluid retention	<b>Ineffective</b>
<b>Riociguat</b>	DYNAMIC	No Difference	Decreased	No Difference (6MWD)	Questionable, increased dropouts for AEs in drug arm	<b>Ineffective</b>
<b>Tadalafil</b>	PASSION	Not Reported	Not Reported	No Difference (6MWD)	Questionable, all-cause death was higher (HR, 5.10 [95% CI, 1.10–23.69]; <i>P</i> =0.04)	<b>Ineffective</b>
<b>Sildenafil</b>	Hoendermis <i>et al</i>	Reduction in favor of placebo	No Difference	No Difference (CPET)	No concerns	<b>Ineffective</b>

PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; PAWP: pulmonary artery wedge pressure; 6MWD: 6-minute walk distance; CPET: cardiopulmonary exercise test.  
 Koller B, et al. *Heart, lung & circulation* vol. 26,5 (2017): 433-441.; Mascherbauer J, et al. *Wien Klin Wochenschr* vol. 128 (2016): 882-889.; Vachiéry JL, et al. *The European respiratory journal* vol. 51,2 (2018): 1701886.; Hoeper MM, et al. *Circulation* vol. 150,8 (2024): 600-610.; Hoendermis ES, et al. *European heart journal* vol. 36,38 (2015): 2565-73.