

**Levosimendan Improves Hemodynamics  
and Submaximal Exercise Capacity in PH-  
HFpEF: *Primary Results from the **HELP-  
PH-HFpEF** Multicenter Randomized  
Controlled Trial***

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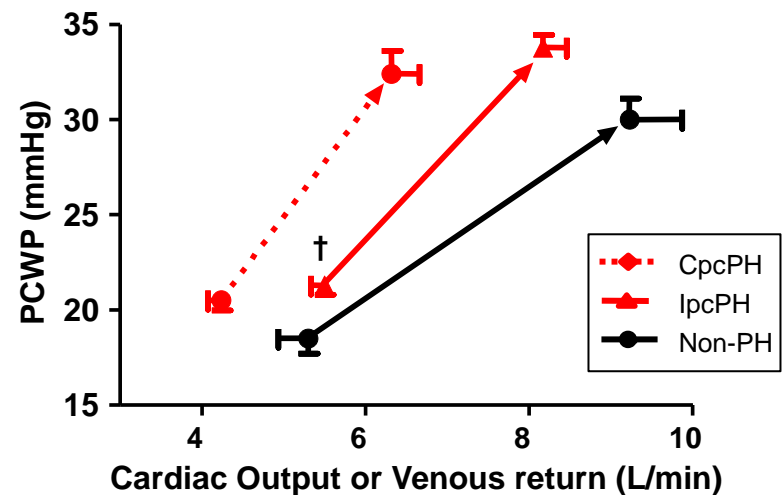
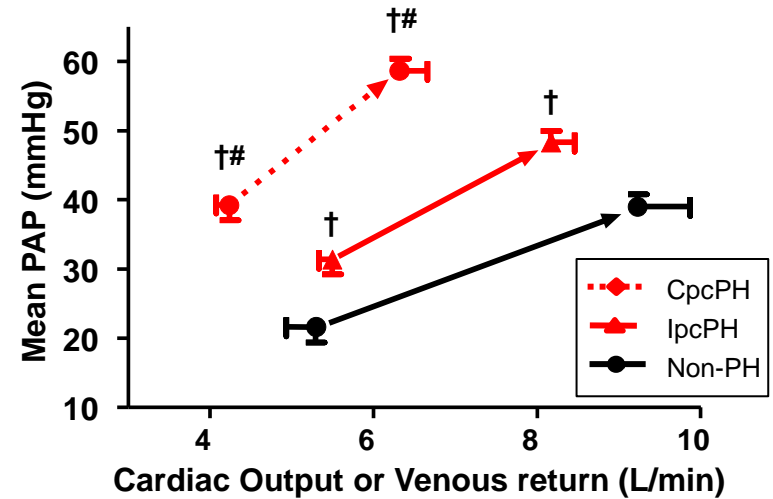
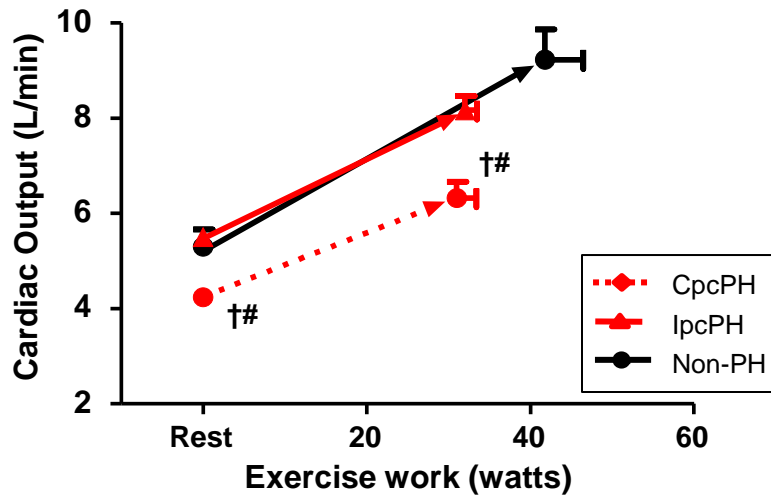
# Background

- HFpEF affects ~50% of all patients with HF, no unequivocally proven effective treatment
- Approximately 70% of patients with HFpEF have PH, and ~30% have RVD
- PH-HFpEF represents more severe phenotype
  - Higher risk of death compared to HFpEF without PH
  - Poorer outcomes compared to WHO Group 1 PH, but no established treatment

Vanderpool...Simon *JAMA Cardiol* 2018

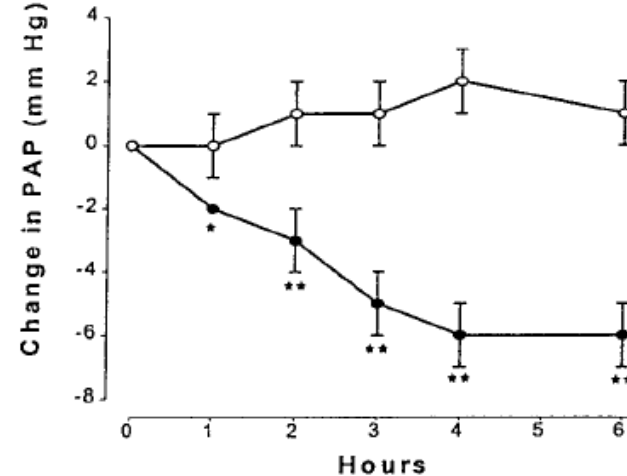
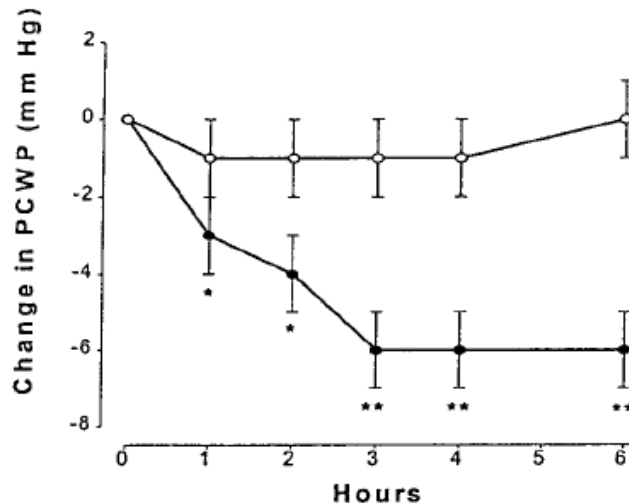
Wijeratne...Archer *Circ Cardiovasc Qual Outcomes* 2018

# Exercise Hemodynamics Severely Deranged in PH-HFpEF



# Levosimendan (LEVO)

- Combined Ca sensitizer,  $K_{ATP}$  channel activator, PDE3 inhibitor
- IV LEVO approved in >60 countries for decompensated HFrEF



- $t_{1/2}$  for LEVO is ~1 hour, but its active metabolite (OR-1896) has  $t_{1/2}$  ~75 hours enabling once weekly dosing

# Hypothesis

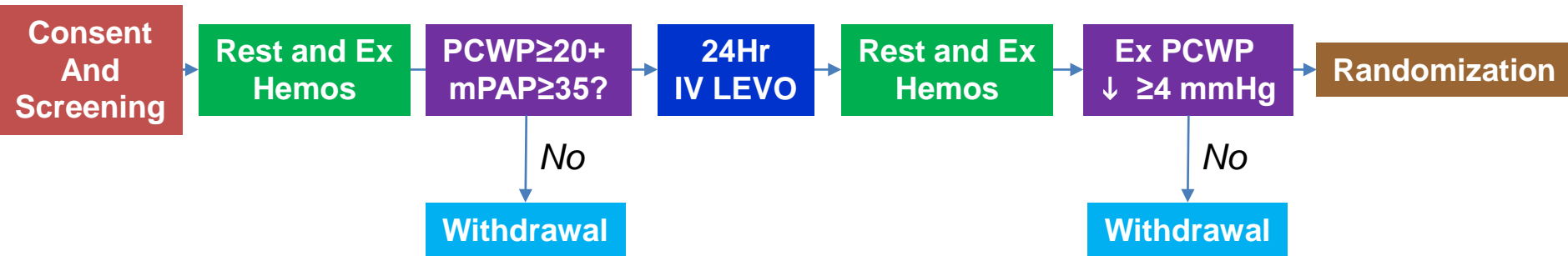
- As compared to placebo, 6 weeks treatment with once weekly home infusion of IV LEVO will reduce pulmonary capillary wedge pressure (PCWP) at rest and during exercise, and improve exercise capacity

# Study population: HFpEF with PH

- Group 2 PH due to HF with  $EF \geq 40\%$
- NYHA class II-IV symptoms
- $PCWP \geq 20$  *and*  $mPAP \geq 35$  mmHg
- Key exclusion criteria
  - Coronary disease unless negative perfusion scan
  - Significant mitral and aortic valve disease
  - $SBP < 100$  mmHg
  - Other causes of PH (lung, congenital)
  - Planned transplant or cardiac surgery

# Study Design: Randomized, double-blind, placebo controlled trial

## Phase 1



## Phase 2



# Trial Endpoints

- Primary

  - Change in PCWP at 25 W exercise at 6 weeks

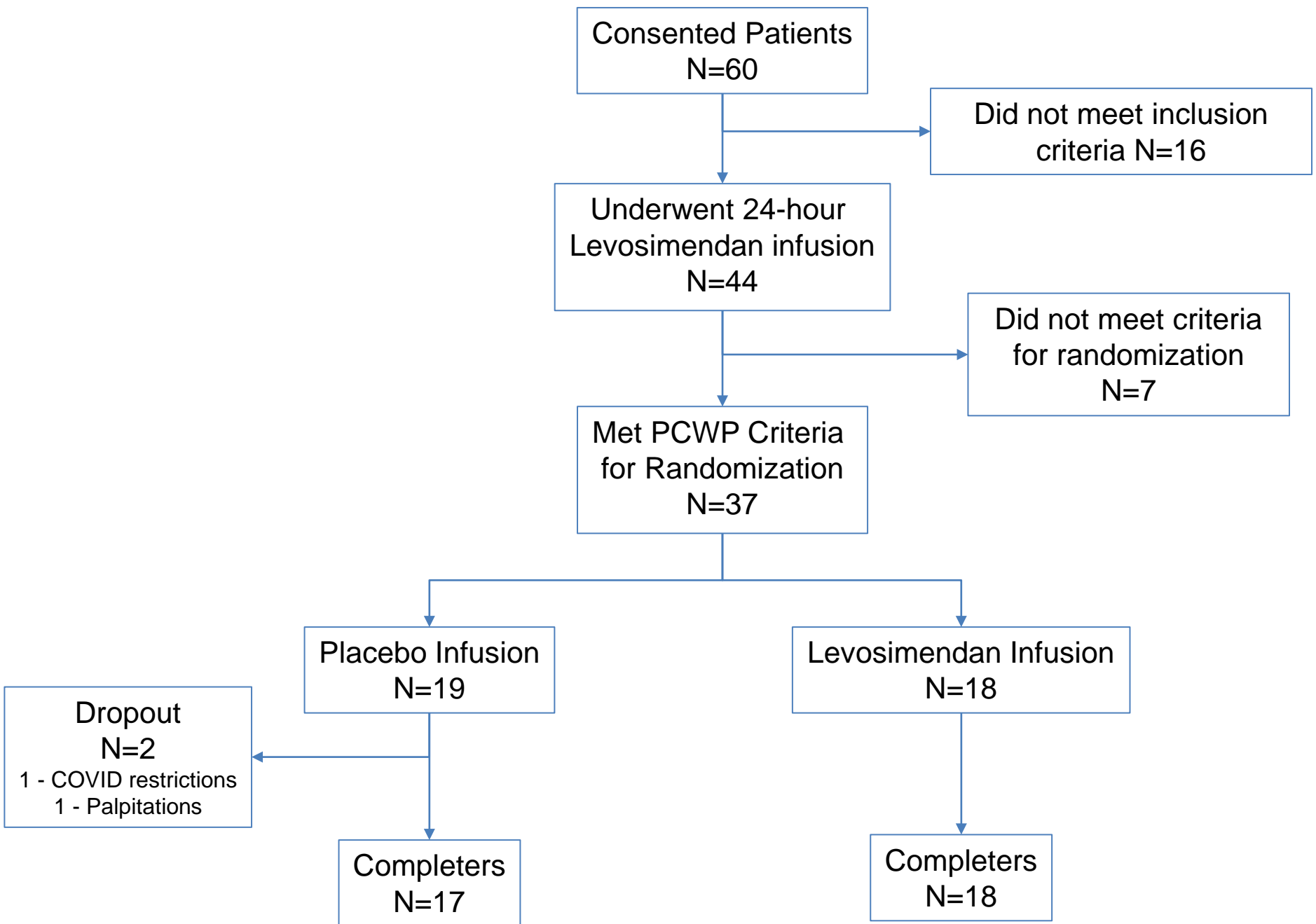
- Secondary

  - Change in PCWP incorporating rest, PLR and exercise using a mixed effect model with repeated measures (MMRM)
  - Change in 6 minute walk distance
  - Change in RAP, mPAP, CI, PVR at rest and with exercise
  - Change in NYHA class
  - Change in patient global assessment
  - Composite of death or hospitalization



# Statistical Analysis

- Intention to treat
- ANOVA: Treatment Effect ( $\Delta\text{levo}-\Delta\text{placebo}$ )
- MMRM: leg position & group as factors + leg position as the repeated term
- N=36 predicted to provide 80% power to detect a difference treatment difference  $\geq 4.9$  mmHg in exercise PCWP assuming SD 5 mmHg at  $\alpha=0.05$



# Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
Age (years)	67 (11)	69 (8)
Women (%)	68	56
White (%)	84	89
BMI (kg/m <sup>2</sup> )	33.0 (7.2)	35.6 (9.2)
Atrial fibrillation (%)	63	89
Hypertension (%)	52	50
Coronary disease (%)	26	33
Diabetes (%)	11	22
Chronic kidney disease (%)	26	33

*Mean values (SD) or % shown*

*All p > 0.05*

# Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
Systolic BP (mmHg)	130 (16)	131 (17)
NYHA class III (%)	84	89
6 minute walk distance (m)	280 (85)	290 (127)
Ejection fraction (%)	59 (8)	58 (7)
Ejection fraction <50% (%)	11	11

*Mean values (SD) or % shown*

*All p > 0.05*

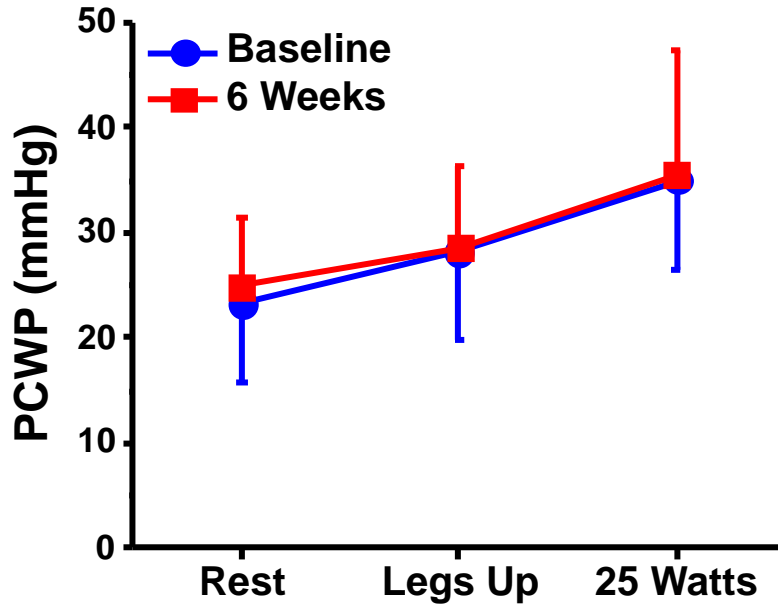
# Hemodynamics at Baseline

Characteristic	Placebo (n=19)	Levo (N = 18)
Right atrial pressure (mmHg)	17 (5)	15 (5)
Mean PA pressure (mmHg)	42 (11)	41 (9)
PCWP (mmHg)	25 (7)	26 (5)
Cardiac index (l/min/m <sup>2</sup> )	2.3 (0.6)	2.7 (1.0)
PVR (WU)	4.1 (3.6)	2.7 (1.5)

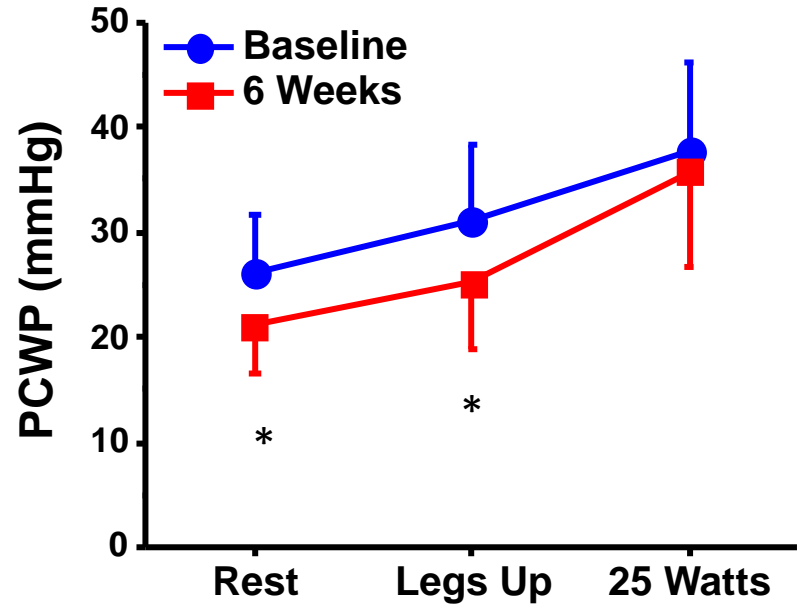
*Mean values (SD) or % shown*

*All p > 0.05*

## Placebo



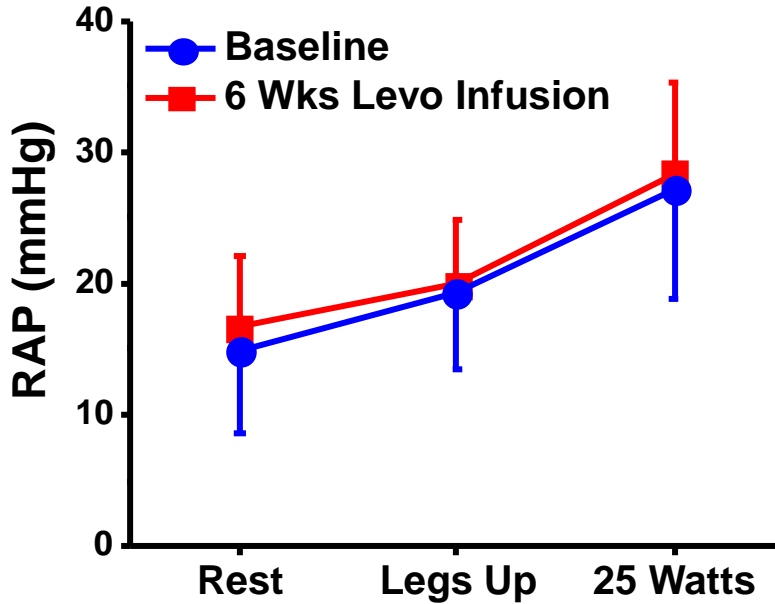
## Levosimendan



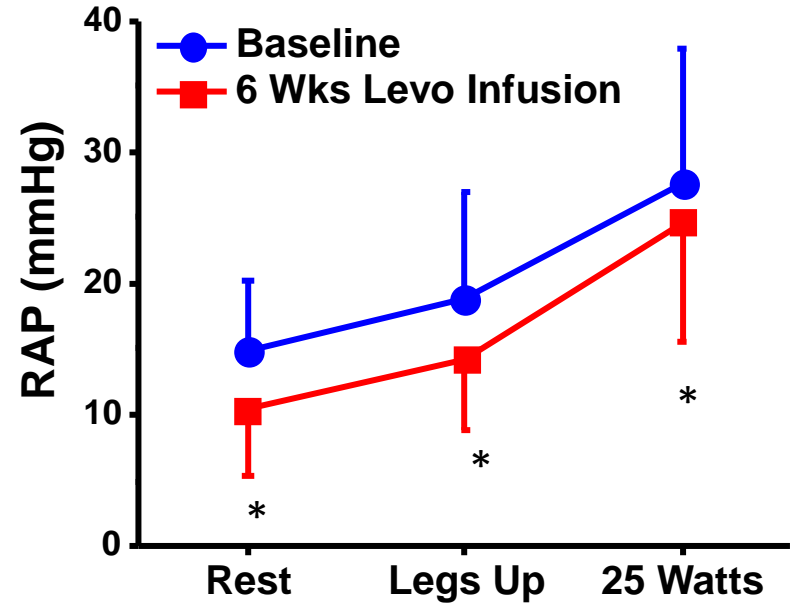
Primary Endpoint ex PCWP (-1.4 mmHg, 95% CI, -7.7 to 4.8, p=0.65)

Mixed-effect repeated measure regression analysis incorporating rest, PLR, and EX stages, LEVO reduced PCWP by  $3.9 \pm 2.0$  mmHg as compared to placebo (p=0.047)

## Placebo

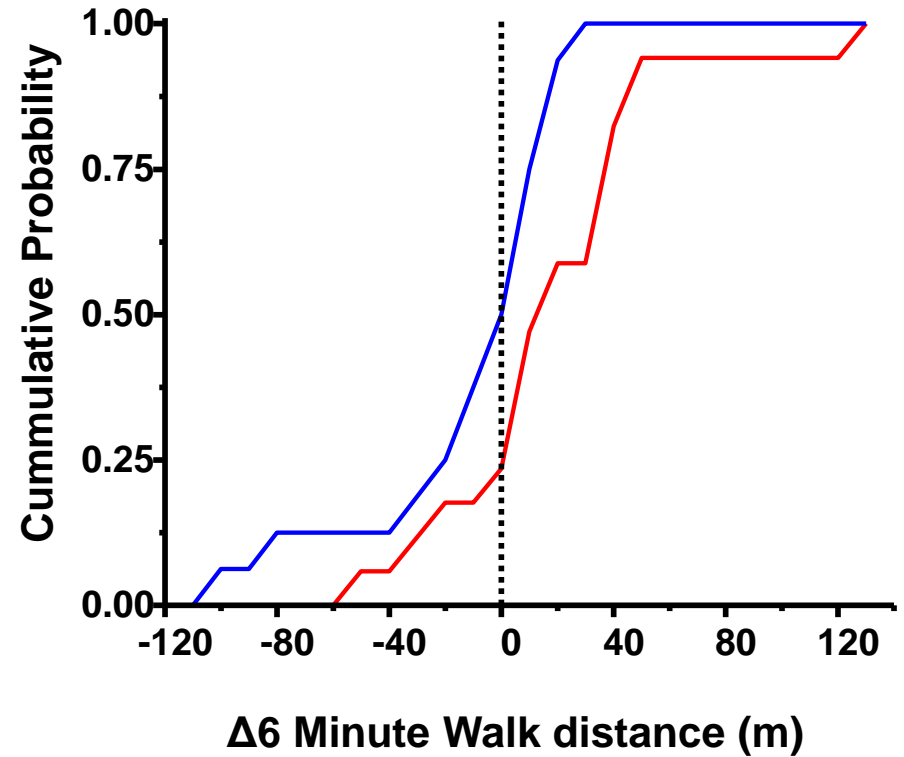
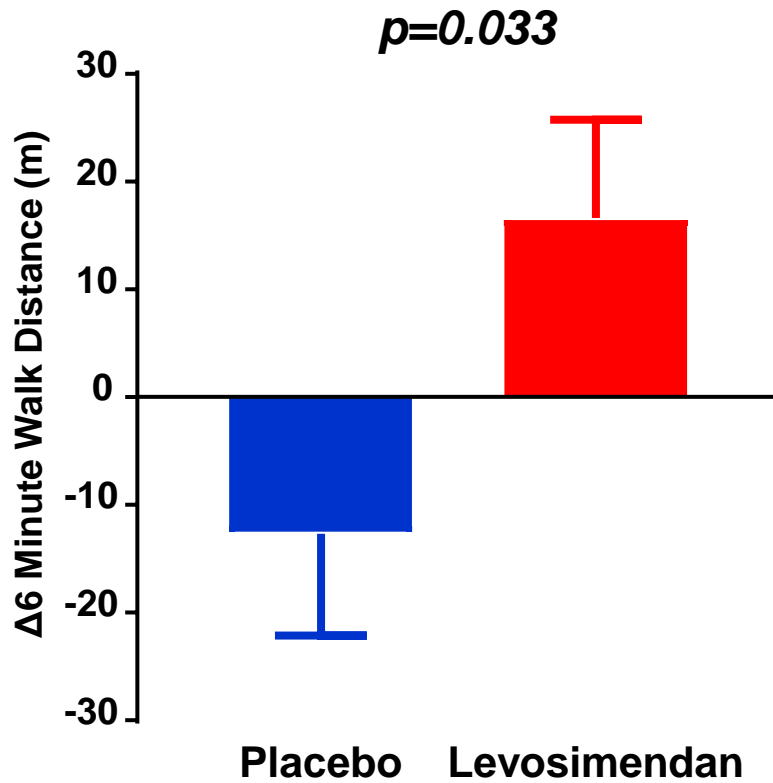


## Levosimendan



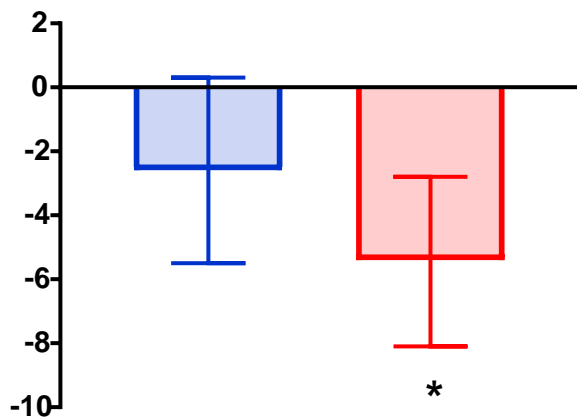
Mixed effect repeated measures model  
-2.9 (95% CI [-6.4, 0.6]) mmHg, p=0.10

# Effects on 6 minute walk distance

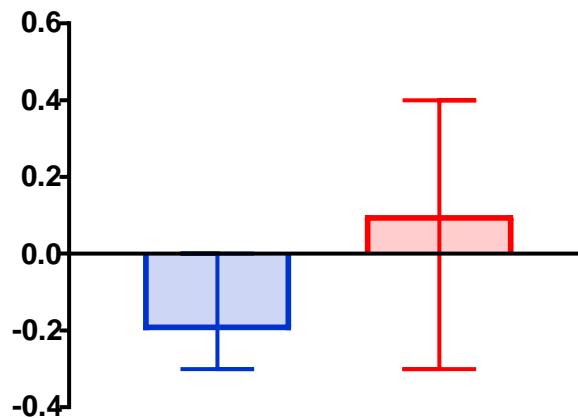




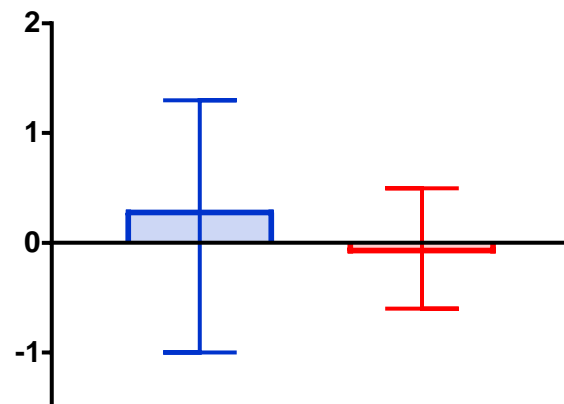
**Mean PA pressure  
(mmHg)**



**Cardiac Index  
(l/min/m<sup>2</sup>)**



**PVR  
mmHg/l/min**



# Safety

Characteristic	Placebo (n=18)	LEVO (n=19)
Discontinued study drug	2	0
PICC Line Infection	0	2
Arrhythmia	0	0
Worsening HF	1	2
Stroke	0	0
Syncope	0	0
SAE - Death	0	0
SAE - Any	2	4

*All p > 0.05*

# Conclusions

- As compared to placebo, once weekly treatment with IV levosimendan did not reduce the primary endpoint of PCWP during exercise
- IV levosimendan did reduce an integrated measure of PCWP across rest and exercise stages, and improved 6 minute walk distance
- These data support conduct of a Phase 3 trial of levosimendan in PH-HFpEF

**Thank you for your attention**