Helping PH-HFpEF Patients Walk Further with Levosimendan

Barry A. Borlaug, MD

ACC Scientific Sessions 2022

Disclosure

Financial Relationships

Research Support:

NIH/NHLBI, Axon, AstraZeneca, Corvia, Medtronic, GlaxoSmithKline, Mesoblast, Novartis, Tenax Therapeutics

Consulting/Advisory Board:

Actelion, Amgen, Aria, Boehringer Ingelheim, Edwards, Eli Lilly, Imbria, Janssen, Merck, Novo Nordisk, VADovations

Off-Label/Investigational Uses

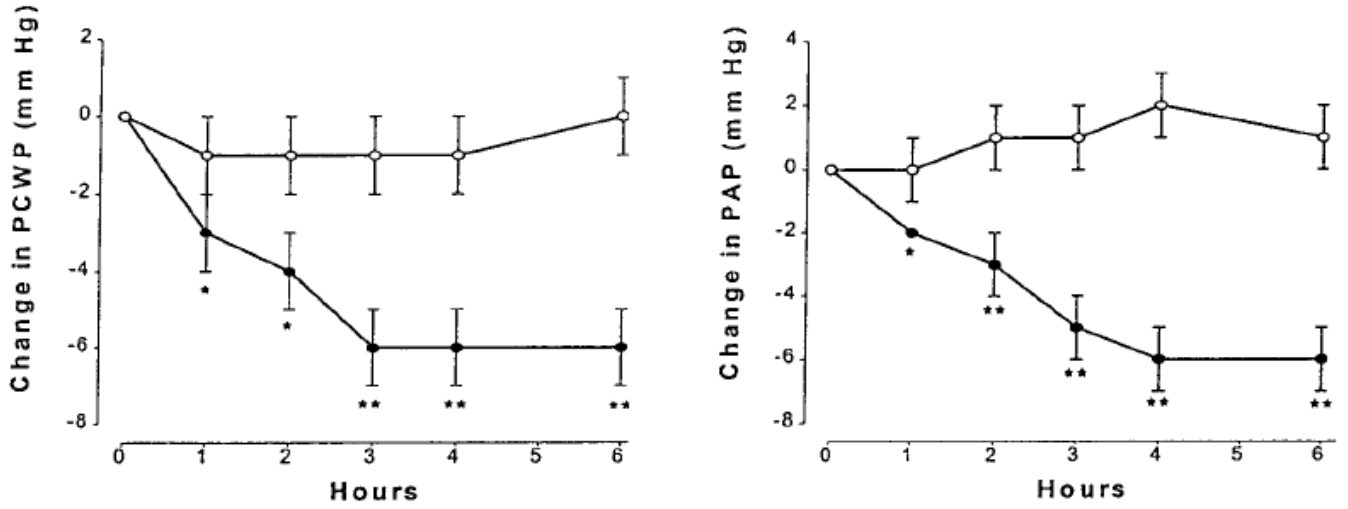
Levosimendan for PH-HFpEF

Background

- ~50% of all patients with HF have HFpEF, there are few effective treatments
- PH is common in HFpEF
- PH-HFpEF represents more severe phenotype
  - Poorer exercise capacity
  - Higher risk of hospitalization & death
- ↑PCWP at rest and during play central role in pathophysiology

Levosimendan (LEVO)

- Combined Ca sensitizer + K_{ATP} channel activator
- 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

Slawsky…Smith *Circulation* 2000

JACC: HEART FAILURE VOL. 9, NO. 5, 2021

Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF

Results of the Randomized Placebo-Controlled HELP Trial

Daniel Burkhoff, MD, PhD,[a] Barry A. Borlaug, MD,[b] Sanjiv J. Shah, MD,[c] Ronald Zolty, MD,[d] Ryan J. Tedford, MD,[e] Thenappan Thenappan, MD,[f] Roham T. Zamanian, MD,[g] Jeremy A. Mazurek, MD,[h] Jonathan D. Rich, MD,[c] Marc A. Simon, MD,[i] Eugene S. Chung, MD,[j] Farhan Raza, MD,[k] David T. Majure, MD,[l] Gregory D. Lewis, MD,[m] Ioana R. Preston, MD,[n] Stuart Rich, MD[c]

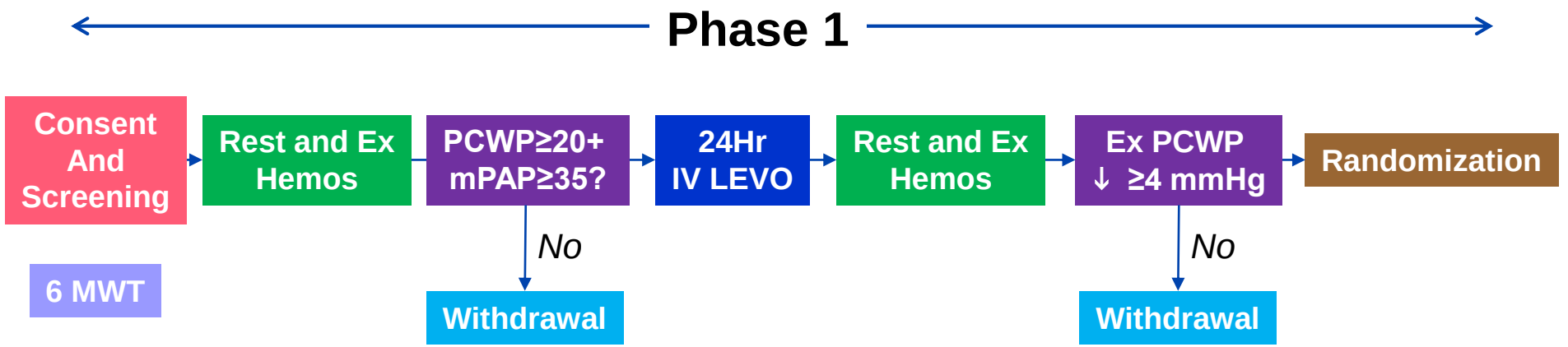
Hypothesis

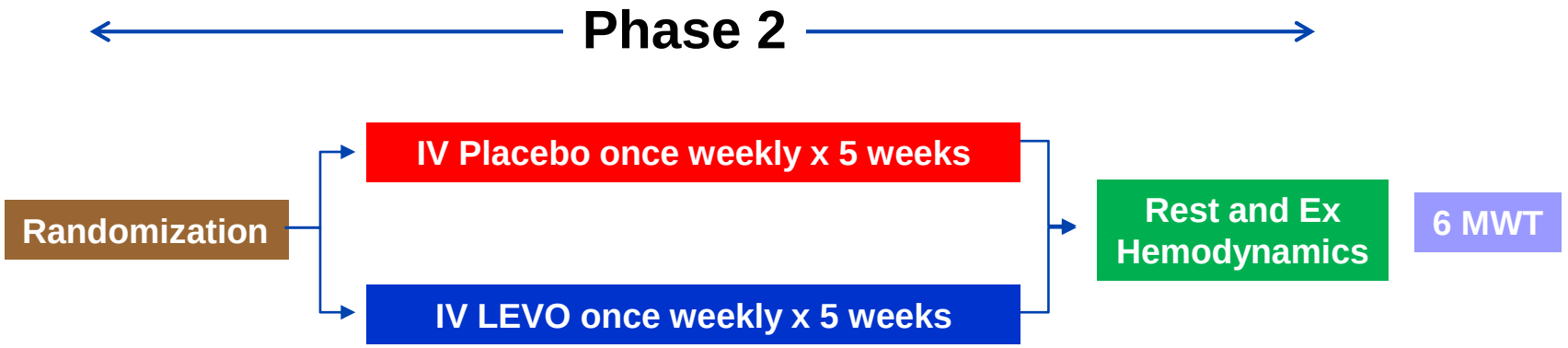
- As compared to placebo, 6 weeks treatment with once weekly home infusion of IV LEVO will reduce pulmonary capillary wedge pressure (PCWP) at rest and during exercise, and improve exercise capacity

Study population: HFpEF with PH

- Group 2 PH due to HF with EF≥40%
- NYHA class II-III symptoms
- PCWP≥20 *and* mPAP≥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





Trial Endpoints

- Primary

  Change in PCWP at 25 W exercise at 6 weeks

- Secondary
  - Change in 6 minute walk distance
  - Change in PCWP incorporating rest, PLR and exercise using a mixed effect model with repeated measures (post hoc)

Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
Age (years)	67 (11)	69 (8)
Women (%)	68	56
White (%)	84	89
BMI (kg/m^2)	33.0 (7.2)	35.6 (9.2)
Atrial fibrillation (%)	63	89

Mean values (SD) or % shown

Baseline Characteristics

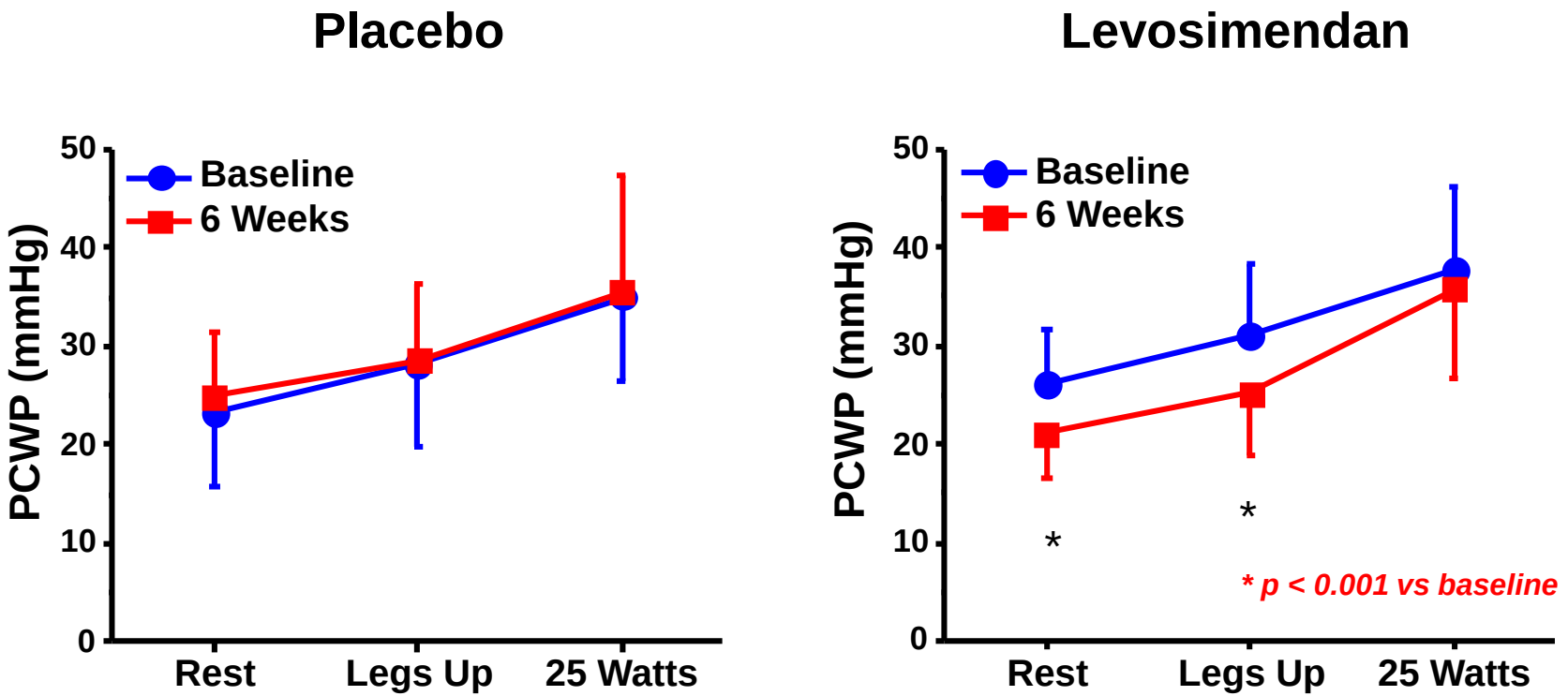
Characteristic	Placebo (n=19)	Levo (N = 18)
NYHA class II/III (%)	16/84	11/89
6 minute walk distance (m)	280 (85)	290 (127)
Ejection fraction (%)	59 (8)	58 (7)

Mean values (SD) or % shown

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^2)	2.3 (0.6)	2.7 (1.0)
PVR (WU)	4.1 (3.6)	2.7 (1.5)

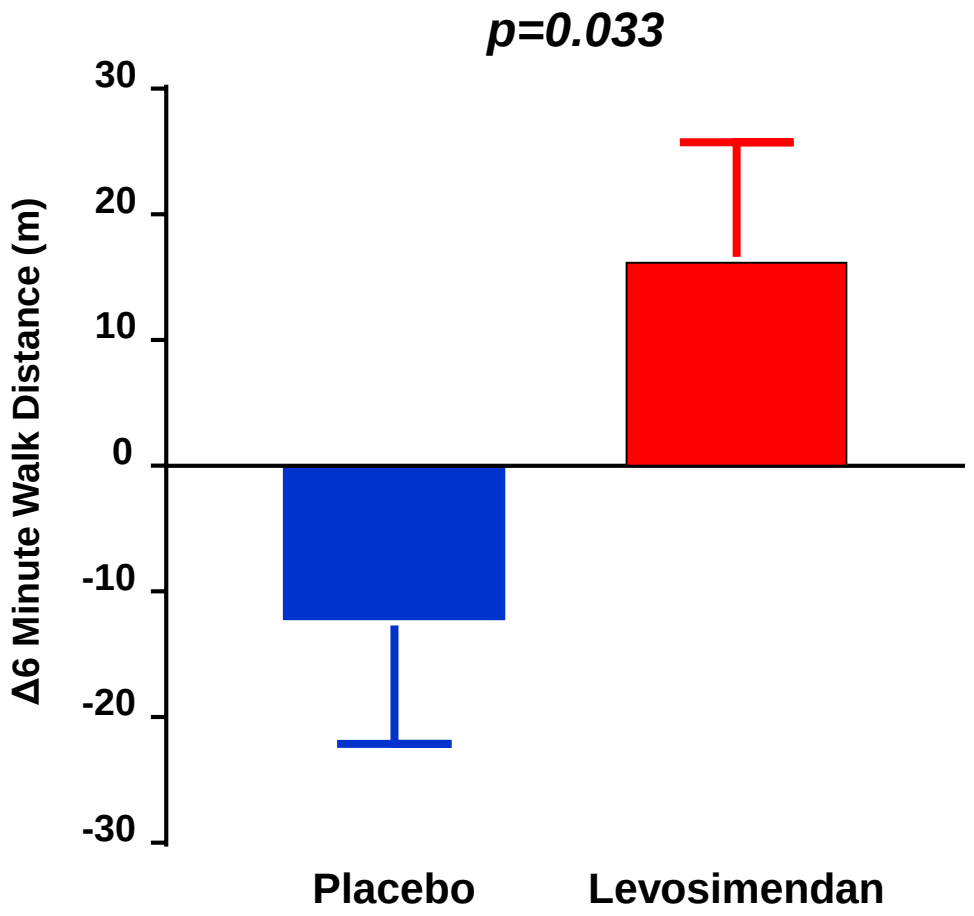
Mean values (SD) or % shown



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

Mixed-effect repeated measure regression analysis: -3.9±2.0 mmHg as compared to placebo (p=0.047)

Effects on 6-minute walk distance



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

Conclusions

- As compared to placebo, once weekly treatment with IV levosimendan did not reduce the primary endpoint of PCWP during exercise in PH-HFpEF
- IV levosimendan reduced PCWP across rest and exercise stages
- IV levosimendan improved 6-minute walk distance
- These data support conduct of a Phase 3 trial of levosimendan in PH-HFpEF
- Pilot study with oral formulation suggests similar benefits, well-tolerated

Thank you for your attention

