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Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF

Results of the Randomized Placebo-Controlled HELP Trial

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ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the effects of intravenous levosimendan on hemodynamics and 6-min walk distance (6MWD) in patients with pulmonary hypertension and heart failure with preserved ejection fraction (PH-HFpEF).

BACKGROUND There are no proven effective treatments for patients with PH-HFpEF.

METHODS Patients with mean pulmonary artery pressure (mPAP) ≥35 mm Hg, pulmonary capillary wedge pressure (PCWP) ≥20 mm Hg, and LVEF ≥40% underwent 6MWD and hemodynamic measurements at rest, during passive leg raise, and supine cycle exercise at baseline and after an open-label 24-h levosimendan infusion (0.1 μg/kg/min). Hemodynamic responders (those with ≥4 mm Hg reduction of exercise-PCWP) were randomized (double blind) to weekly levosimendan infusion (0.075 to 0.1ug/kg/min for 24 h) or placebo for 5 additional weeks. The primary end point was exercise-PCWP, and key secondary end points included 6MWD and PCWP measured across all exercise stages.

RESULTS Thirty-seven of 44 patients (84%) met responder criteria and were randomized to levosimendan (n = 18) or placebo (n = 19). Participants were 69 ± 9 years of age, 61% female, and with resting mPAP 41.0 ± 9.3 mm Hg and exercise-PCWP 36.8 ± 11.3 mm Hg. Compared with placebo, levosimendan did not significantly reduce the primary end point of exercise-PCWP at 6 weeks (−1.4 mm Hg; 95% confidence interval [CI]: −7.8 to 4.8; p = 0.65). However, levosimendan reduced PCWP measured across all exercise stages (−3.9 ± 2.0 mm Hg; p = 0.047). Levosimendan treatment resulted in a 29.3 m (95% CI: 2.5 to 56.1; p = 0.033) improvement in 6MWD compared with placebo.

CONCLUSIONS Six weeks of once-weekly levosimendan infusion did not affect exercise-PCWP but did reduce PCWP incorporating data from rest and exercise, in tandem with increased 6MWD. Further study of levosimendan is warranted as a therapeutic option for PH-HFpEF. (Hemodynamic Evaluation of Levosimendan in Patients With PH-HFpEF [HELP]; NCT03541603) (J Am Coll Cardiol HF 2021;■:■-■) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CO = cardiac output

CVP = central venous pressure

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

MMRM = mixed-effects model with repeated measurements

PCWP = pulmonary capillary wedge pressure

PH = pulmonary hypertension

PH-HFpEF = pulmonary hypertension in the setting of heart failure with preserved ejection fraction

PVR = pulmonary vascular resistance

SVR = systemic vascular resistance

Pulmonary hypertension (PH) associated with heart failure (HF) with preserved ejection fraction (PH-HFpEF) is a debilitating form of PH with an estimated US prevalence exceeding 1.5 million. Pathology studies characterize changes in the pulmonary circulation as having features similar to pulmonary veno-occlusive disease with involvement in arterial and venous vascular beds. PH-HFpEF patients display marked impairments in exercise capacity associated with elevation in pulmonary capillary wedge pressures (PCWPs) at rest and during exercise (1). Over time, sustained exposure to these hemodynamic abnormalities leads to development of right-side HF, with all of its signs and symptoms, including markedly reduced exercise tolerance and increased mortality (2).

There are currently no approved therapies for PH-HFpEF. Studies of pharmacologic treatments have been largely neutral. Reduction in pulmonary arterial (PA) pressures, predominantly through use of diuretics, decreases the risk of HF hospitalization (3). Therefore, society guidelines acknowledge that the only accepted pharmacologic target is a reduction of PCWP with the use of diuretics to treat congestion.

Levosimendan is a unique drug whose properties include potassium channel activation, myofilament calcium sensitization, and phosphodiesterase-3 inhibition (4). In patients with acute decompensated HF with reduced ejection fraction (HFrEF), levosimendan produces dose-dependent increases of cardiac output (CO) and decreases of PCWP, central venous pressure (CVP), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR) (5). We hypothesized that these effects would potentially be beneficial in patients with PH-HFpEF, particularly during exercise where hemodynamic abnormalities become accentuated (1). Although the half-life of intravenous levosimendan is ~1 h, its metabolite (OR-1896) has similar biological effects and has a half-life of ~75 h, making periodic levosimendan infusions suitable for longer-term use (6).

Accordingly, the purpose of this phase 2 clinical trial was to determine the acute and intermediate-term (6-week) hemodynamic effects of levosimendan and its metabolite in PH-HFpEF, as well as the effects of levosimendan treatment on exercise tolerance as measured by 6-min walk distance (6MWD).

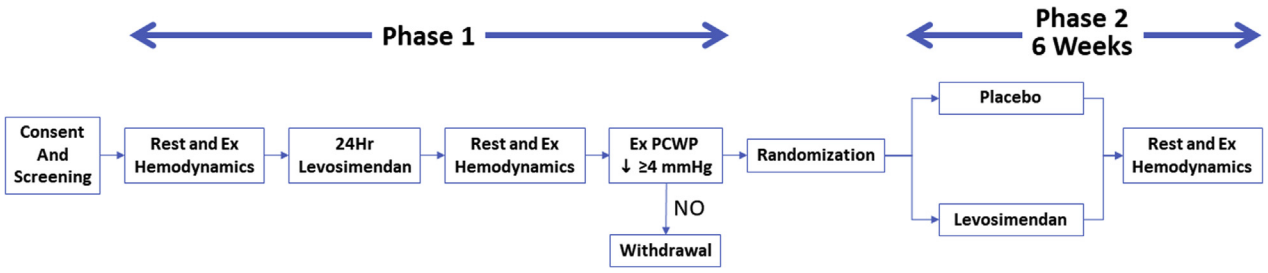
METHODS

STUDY DESIGN AND PARTICIPANTS. This study was approved by the institutional review board of each participating center, and every patient provided informed consent. The inclusion and exclusion criteria for the study are summarized in Supplemental Table 1. In brief, patients were required to have PH-HFpEF based on: 1) mean pulmonary arterial pressure (mPAP) ≥35 mm Hg and baseline PCWP ≥20 mm Hg (both measured by right heart catheterization with legs elevated into pedals of a supine cycle ergometer); 2) New York Heart Association (NYHA) functional class II or III; and 3) LVEF ≥40% according to echocardiography within 3 months of enrollment. All cardiac and pulmonary medications were required to be stable for ≥30 days before enrollment. Concomitant use of pulmonary vasodilators was not allowed. Major exclusion criteria included clinically significant parenchymal lung disease, active myocardial ischemia, untreated hemodynamically significant valvular disease, congenital heart diseases, hypotension (systolic blood pressure <100 mm Hg), and estimated glomerular filtration rate <30 ml/min/1.73 m^2. To evaluate potential proarrhythmic effects from the chronic administration of levosimendan, all patients underwent ambulatory cardiac monitoring for 72 h with a BioTel patch within 2 weeks of the initial hemodynamic assessment and after 5 weeks of treatment.

The trial consisted of 2 phases (**Figure 1**). After meeting initial study entry criteria, including results of rest and exercise hemodynamic measurements, study phase 1 consisted of a 24-h open-label infusion of levosimendan (0.10 μg/kg/min) to identify patients most likely to respond to a longer-term course of treatment. At the end of the 24-h infusion, rest and exercise hemodynamic measurements were repeated. To qualify for randomization in phase 2, patients were required to demonstrate a ≥4 mm Hg reduction of PCWP during 3 min of exercise at 25 W, with no more than a 10% decrease of cardiac index after the 24-h open-label infusion of levosimendan; these criteria defined a levosimendan "responder."

RANDOMIZATION AND BLINDING. Patients exhibiting the required hemodynamic response in phase 1 progressed to phase 2, where they were randomized (1:1, double blind) to receive intermittent (weekly) levosimendan or placebo study drug infusions at home. Study drug was administered over 24 h weekly from week 2 through week 5 via a peripherally

FIGURE 1 Overview of The 2-Phase Study



An initial unblinded levosimendan infusion was used to identify levosimendan responders, defined as those with a ≥4 mm Hg reduction of pulmonary capillary wedge pressure (PCWP) during 25 W exercise (Ex). This was followed by a subsequent randomized double-blind phase.

inserted central catheter (PICC) line using a continuous ambulatory delivery device pump. Placebo solutions were prepared in a manner identical to active drug so that study nurses were also blinded to treatment group.

Study drug concentrated solution (2.5 mg/ml) of levosimendan or placebo was mixed with diluent and administered via the PICC line at 0.075 μg/kg/min over 24 h. Patients had a dose escalation between weeks 3 and 4 to 0.10 μg/kg/min over 24 h, unless there were meaningful drops of blood pressure or increases of heart rate. Infusion rates were allowed to be reduced to 0.05 μg/kg/min if the existing dose was not well tolerated at any time during the study. The dosing schedule is detailed in Supplemental Table 2.

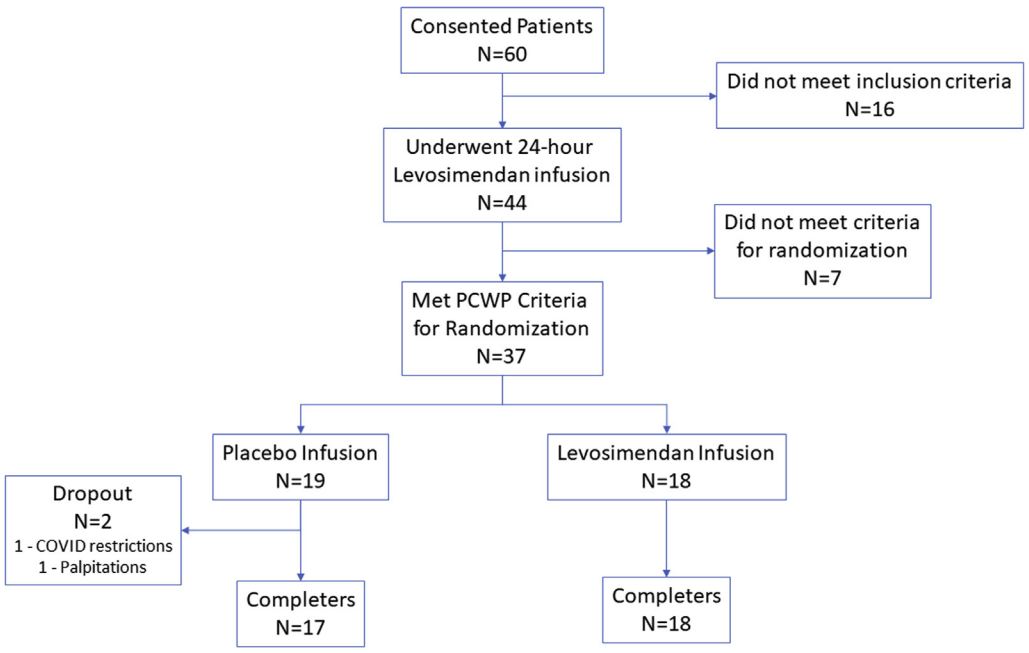
STUDY PROCEDURES. A detailed schedule of events is provided in Supplemental Table 3. In brief, in patients satisfying the study inclusion criteria, invasive hemodynamics with exercise testing was performed at baseline, 24 h after levosimendan, and 6 weeks after randomization. This testing consisted of a standard right heart catheterization via the right internal jugular vein with measurements of CVP, systolic (PAS) and diastolic (PAD) arterial pressures as well as mPAP, PCWP, and CO by means of thermodilution. Procedures were standardized across sites through training that emphasized proper zeroing at midchest and calibration of pressure transducers. Measurements were made with the patient supine at rest, with the legs raised into the pedals of a supine cycle ergometer for 5 min and during 3 min of exercise at 25 W. For patients who developed marked dyspnea before 3 min, repeated measures were made at the earlier time point and noted, so that all subsequent exercise measurements could be made at the same duration of exercise. All pressure recordings were printed on paper, scanned, and submitted for blinded analysis at a hemodynamic core laboratory. Pressure measurements were taken at end-expiration.

Levosimendan "responders" were randomized to receive weekly infusions of active drug or placebo on study weeks 2, 3, 4, and 5 administered at home by a visiting nurse who also assessed vital signs and monitored for the occurrence of adverse events. Patients were seen in the clinic between week 3 and week 4 for an interim medical history, physical examination, NYHA functional class assessment, and 6MWD. The final visit occurred at the end of study week 6, at which time an interim medical history, laboratory tests, echocardiography, assessment of NYHA functional class, 6MWD, and invasive hemodynamic exercise test were all repeated. This trial was registered at NCT03541603.

STATISTICAL CONSIDERATIONS. All efficacy analyses were based on the full analysis set, that is, including all randomized subjects who received any blinded study drug and completed the study with the week 6 office visit. All statistical tests were 2-sided hypothesis tests performed at the 5% level of significance; 2-sided 95% confidence intervals (CIs) were reported.

The primary efficacy end point was defined as the between-group difference in the change of PCWP during 25-W cycle exercise from baseline to 6 weeks as analyzed by means of an analysis of variance (ANOVA) model with change from baseline to week 6 in PCWP as a dependent variable and treatment group as a factor. The sample size was estimated for the primary comparison of levosimendan and placebo with the use of SAS (version 9.4) for Windows procedure PROC POWER. A total of 36 randomized subjects (at 1:1 levosimendan vs. placebo) were predicted to provide 80% power to detect a difference at the 2-sided 0.05 level, assuming an SD of 5 mm Hg in PCWP and a treatment difference of ≥4.9 mm Hg.

FIGURE 2 CONSORT Diagram Showing Flow of Patients Through the Entire Study



Of 60 patients providing informed consent, 44 met study entry criteria and underwent open-label levosimendan infusion. Of those, 37 met criteria as being levosimendan responders and proceeded to the double-blind randomized phase of the study. PCWP = pulmonary capillary wedge pressure.

In addition to analyzing the primary end point of PCWP at peak exercise, we also evaluated the impact of levosimendan on PCWP, incorporating measurements at rest, with legs up, and at 25 W, with the use of a mixed-effects model with repeated measurements (MMRM) for change from baseline, with treatment group and leg position as factors and leg position as the repeated term in the MMRM. Between-group differences in changes in 6MWD were assessed by means of ANOVA. NYHA functional class at baseline and week 6 was assessed by means of Pearson's chi-square test.

To provide further insight into the hemodynamic effects of levosimendan in HFpEF, several additional exploratory analyses were performed. First, hemodynamic responses during the initial prerandomization open-label infusion were summarized using descriptive statistics. Additional efficacy analyses included assessment of treatment effects on a complement of directly measured and derived hemodynamic measurements (PA compliance, right ventricular [RV] stroke work, PVR, and SVR, as defined in Supplemental Table 4). Safety was assessed by tabulating and comparing the number of adverse events between groups.

ROLE OF THE FUNDING SOURCE. The HELP study was designed jointly by an academic steering committee and the sponsor. TENAX Therapeutics funded the study. Data collection and analyses were done by MedPace Clinical Pharmacology (Cincinnati, Ohio). The sponsor had no role in the collection, analysis, interpretation of data, or the decision to submit for publication.

RESULTS. A total of 60 patients provided informed consent and underwent baseline testing (Figure 2). Forty-four of these patients met study inclusion criteria and underwent a 24-h infusion of levosimendan (0.10 μg/kg/min). Three patients experienced a protocol-defined hypotensive episode during the first 24-h infusion. In 1 patient this required only a transient (~6 h) down-titration to 0.075 μg/kg/min, after which the 0.1 μg/kg/min dosing was resumed. In the second and third participants, the doses were down-titrated and maintained at 0.075 and 0.050 μg/kg/min for the remainder of the study (including the randomized phase).

Following the open-label levosimendan infusion in phase 1, 7 patients did not meet the criteria for phase 2 (5 owing to failure to meet the PCWP criterion, 1 owing to the CO criterion, and 1 owing to both PCWP

and CO criteria). Thirty-seven patients were randomized and had a PICC line inserted for drug infusions: 19 were randomized to placebo and 18 to active drug. Two patients withdrew from the placebo arm: One patient experienced palpitations and did not want to continue, and the other was unable to return for follow-up owing to COVID-19-related restrictions. Accordingly, 35 patients completed the study, of which 17 received placebo and 18 received levosimendan.

Baseline characteristics for all randomized patients are summarized in **Table 1**, and baseline background medical therapies are summarized in Supplemental Table 5. Characteristics were balanced between groups, and there were no significant differences in any parameter or medical therapy. Characteristics of the 7 patients who were not randomized are summarized in Supplemental Table 6; other than less decrease of PCWP, the only significant difference was a higher resting heart rate in levosimendan nonresponders (83.4 ± 27.9) compared with responders (71.2 ± 10.8; p = 0.05).

TABLE 1 Baseline Characteristics Among Randomized Patients

	All Randomized (N = 37)	Placebo (n = 19)	Treatment (n = 18)	p Value, Placebo vs. Treatment
Age, yrs	68.1 ± 9.3	67.4 ± 11.0	68.8 ± 7.5	0.65
Age, yrs	43-81	43-81	54-80	
Male	14 (37.8)	6 (31.6)	8 (44.4)	0.42
Race				0.51
White	32 (86.5)	16 (84.2)	16 (88.9)	
Black or African American	3 (8.1)	2 (10.5)	1 (5.6)	
American Indian or Alaska Native	1 (2.7)	1 (5.3)	0 (0.0)	
Other	1 (2.7)	0 (0.0)	1 (5.6)	
Weight, kg	98.2 ± 20.5	95.9 ± 20.8	100.6 ± 20.4	0.50
Height, cm	169.9 ± 10.21	170.5 ± 9.27	169.3 ± 11.36	0.72
BSA	2.14 ± 0.25	2.12 ± 0.25	2.16 ± 0.23	0.6
BMI, kg/m^2	34.3 ± 8.2	33.0 ± 7.2	35.6 ± 9.2	0.35
Medical history				
Atrial fibrillation, % of time	29.7 ± 46.3	15.8 ± 37.4	44.4 ± 51.1	0.06
Atrial fibrillation, history	28 (75.7)	12 (63.2)	16 (88.9)	0.07
Obesity	8 (21.6)	4 (21.1)	4 (22.2)	0.93
DM	6 (16.2)	2 (10.5)	4 (22.2)	0.33
HTN	19 (51.4)	10 (52.6)	9 (50.0)	0.87
CAD	11 (29.7)	5 (26.3)	6 (33.3)	0.64
CKD	11 (29.7)	5 (26.3)	6 (33.3)	0.64
Obstructive sleep apnea	24 (64.9)	12 (63.2)	12 (66.7)	0.82
COPD	7 (18.9)	2 (10.5)	5 (27.8)	0.18
Interstitial lung disease	2 (5.4)	0 (0.0)	2 (11.1)	0.14
Pulmonary embolism/DVT	2 (5.4)	2 (10.5)	0 (0.0)	0.16
NYHA functional class				
I	0 (0.0)	0 (0.0)	0 (0.0)	0.68
II	5 (13.5)	3 (15.8)	2 (11.1)	
III	32 (86.5)	16 (84.2)	16 (88.9)	
Vital signs				
HR	71.2 ± 10.76	68.5 ± 10.36	74.1 ± 10.71	0.12
SBP	130.3 ± 16.47	129.9 ± 16.12	130.7 ± 17.30	0.89
DBP	69.2 ± 11.02	70.4 ± 11.40	67.9 ± 10.78	0.50
RR	16.9 ± 2.17	17.4 ± 1.98	16.4 ± 2.30	0.17
6-min walk distance	284.6 ± 106.24	279.8 ± 85.24	289.7 ± 127.12	0.78
Echocardiography				
LVEF	58.4 ± 7.5	58.8 ± 8.2	58.1 ± 6.9	0.80
LA dimension	92.0 ± 40.1	82.4 ± 33.3	102.2 ± 44.9	0.13
TAPSE	1.8 ± 0.4	1.7 ± 0.5	1.8 ± 0.3	0.76

Values are mean ± SD, range, or n (%).

BSA = body surface area; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; DM = diabetes mellitus; DVT = deep vein thrombosis; HR = heart rate; HTN = hypertension; LA = left atrial; LVEF = left ventricular ejection fraction; RR = respiratory rate; SBP = systolic blood pressure; TAPSE = tricuspid annular plane systolic excursion.

OPEN-LABEL 24-H LEVOSIMENDAN HEMODYNAMIC EFFECTS (PHASE 1). The major hemodynamics effects of phase 1 included significant reductions in CVP, PCWP (**Central Illustration**), and PA pressures and an increase of heart rate at rest, with leg raise, and during exercise. Additional details of hemodynamic effects are summarized in **Table 2** and Supplemental Table 7. Notably, there were no significant changes in arterial pressure, CO, SVR, PVR, or other measures of pulmonary vascular properties.

DOUBLE-BLIND 6-WEEK LEVOSIMENDAN EFFECTS (PHASE 2). All patients in phase 2 completed the 6-week study. As the primary efficacy end point, the between-group difference in the change of PCWP at 25 W from baseline to 6 weeks averaged −1.4 mm Hg (95% CI: −7.8 to 4.8) and was not statistically significant (p = 0.65). However, when analyzed with the use of MMRM, which included baseline values, study group, and leg position (rest, legs up, 25 W) as factors, there was a statistically significant between group difference in PCWP amounting to an average reduction of −3.9 mm Hg (95% CI: −7.9 to 0.0) (p = 0.048) (**Central Illustration**). A detailed summary of all hemodynamic parameters at baseline and their changes at the 6-week visit are detailed in **Table 3**. Interestingly, the effects of levosimendan on CVP and PCWP at rest and during passive leg raise that were observed after the initial 24-h infusion were quantitatively similar to the point estimates of these effects at the end of the 6-week infusion period (**Central Illustration, C and D**). It was only PCWP with legs up that reached statistical significance with an average −5.6 mm Hg (95% CI: −10.3 to −1.0) mm Hg between-group difference. Importantly, there were no significant changes between baseline and 6 weeks (either within groups or between groups) in systemic arterial pressure, CI, SVR, PVR, other measures of pulmonary vascular properties, or RV stroke work in either group (**Table 3**) (additional parameters summarized in Supplemental Table 7).

TABLE 2 Acute (24-h) Effects of Open-Label Levosimendan (N = 44)

	Baseline			Δ 24 h (95% CI)		
	Legs Down	Legs Up	25 W	Legs Down	Legs Up	25 W
HR, beats/min	69.6 ± 16.4	71.0 ± 15.9	86.3 ± 18.0	+5.7 (2.9 to 8.4)*	+6.7 (3.6 to 9.7)*	+4.8 (0.2 to 9.3)*
CVP, mm Hg	15.5 ± 5.2	18.9 ± 6.5	27.1 ± 8.6	−3.9 (−5.3 to −2.6)*	−3.3 (−4.8 to −1.7)*	−4.7 (−6.8 to -2.6)*
PAS, mm Hg	64.9 ± 18.4	73.5 ± 18.2	89.5 ± 22.1	−6.4 (−9.7 to −3.1)*	−6.2 (−9.6 to −2.8)*	−2.4 (−7.2 to 2.4)
PAD, mm Hg	29.0 ± 6.3	32.8 ± 7.4	41.2 ± 9.9	−3.0 (−5.0 to −1.1)*	−3.4 (−5.6 to −1.3)*	−3.1 (−5.7 to −0.4)*
PA mean, mm Hg	41.0 ± 9.3	46.4 ± 9.6	57.3 ± 13.3	−4.2 (−6.4 to −1.9)*	−4.3 (−6.6 to −2.1)*	−2.7 (−5.9 to 0.4)
PCWP, mm Hg	25.7 ± 6.3	29.7 ± 7.8	36.8 ± 11.3	−4.9 (−7.0 to −2.9)*	−5.3 (−7.3 to −3.3)*	−3.9 (−6. to −0.9)*
AoS, mm Hg	135.0 ± 18.8	138.4 ± 18.7	155.7 ± 34.7	−4.7 (−12.2 to 2.8)	−1.4 (−8.5 to 5.7)	−7.2 (−17.5 to 3.1)
CI, l/min/m	2.5 ± 0.8	2.6 ± 0.9	3.2 ± 1.1	0.1 (−0.0 to 0.3)	0.1 (−0.0 to 0.3)	0.2 (−0.0 to 0.4)
SVR, WU	15.5 ± 4.2	15.3 ± 5.2	12.5 ± 5.6	−1.1 (−2.2 to 0.0)	−0.4 (−1.8 to 1.0)	−1.0 (−2.7 to 0.8)
PVR, WU	3.3 ± 2.6	2.7 ± 1.6	3.6 ± 2.9	−0.1 (−0.6 to 0.3)	0.2 (−0.3 to 0.7)	0.0 (−0.4 to 0.5)

Values are mean ± SD, unless otherwise indicated. *p < 0.05 compared with baseline.

AoS = arterial systolic pressure; CI = cardiac index; CVP = central venous pressure; HR = heart rate; PAD = pulmonary artery diastolic pressure; PAS = pulmonary artery systolic pressure; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

6-MINUTE WALK DISTANCE. As summarized in Figure 3A, 6MWD increased by 16.6 m (95% CI: −2.1 to 35.2) in the levosimendan group and decreased by 12.7 m (95% CI: −32.0 to 6.5) m in the placebo group, so that the mean treatment effect was 29.3 m (95% CI: 2.5 to 56.1; p = 0.033). When individual changes in 6MWD were plotted in rank order (Figure 3B), more levosimendan patients increased and fewer decreased their 6MWD.

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION. In the placebo group, NYHA functional class was unchanged in 15 patients and improved in 2 patients from class III to class II. In the levosimendan group, NYHA functional class was unchanged in 10 patients, improved in 7 patients (from class III to class II), and worsened (from class II to III) in 1 patient. The differences in these shifts of NYHA functional class were not statistically significant.

OTHER MEASUREMENTS. There were no meaningful changes in any echocardiographic parameters, including changes in LVEF, global longitudinal strain, RV free wall strain, tricuspid annular plane systolic excursion, and left atrial conduit strain. There were also no changes in blood tests (Supplemental Table 8). Finally, there were no increases in the occurrence or amount of ectopy (atrial or ventricular) noted in either group as assessed by comparing BioTel patch recordings between baseline and study week 5.

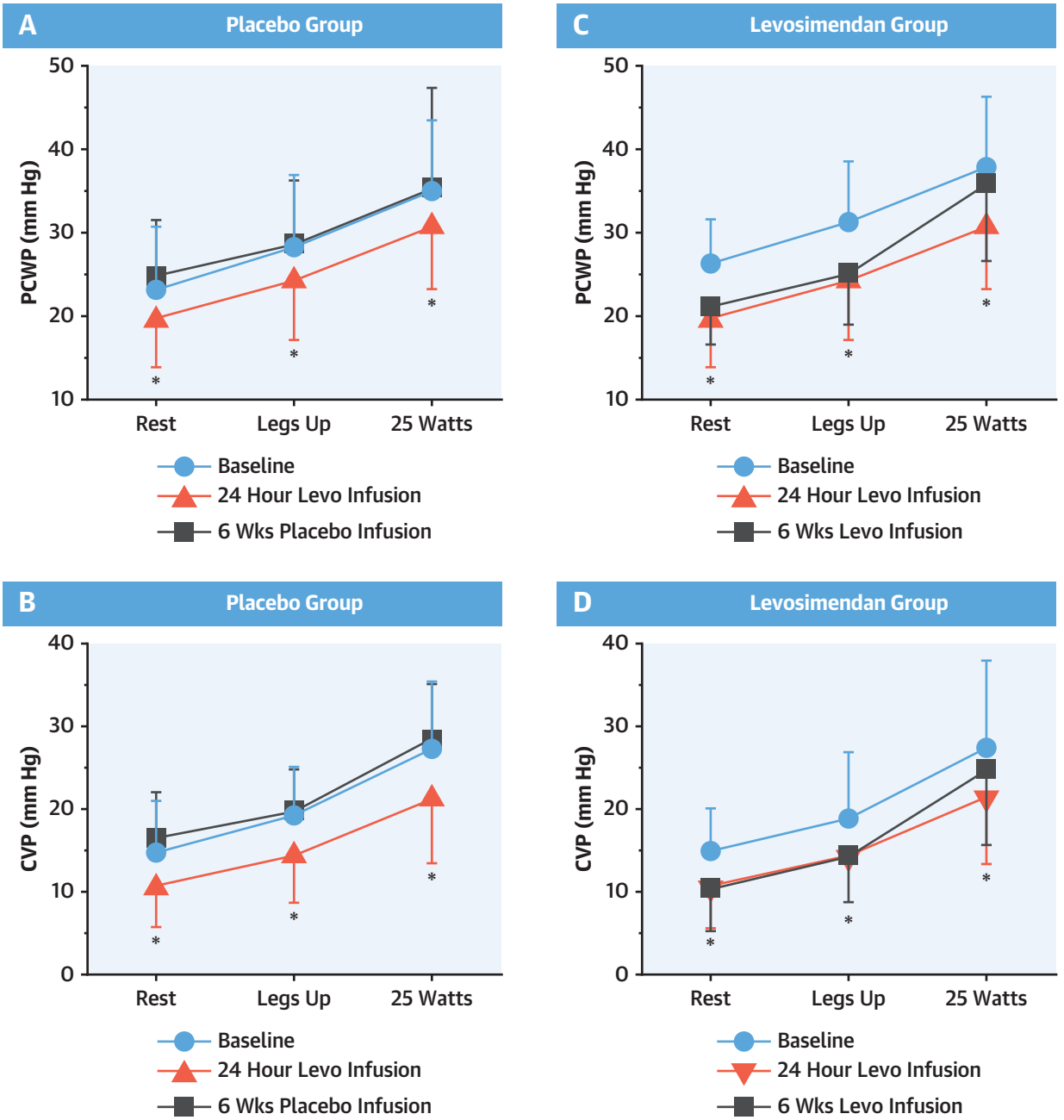
ADVERSE EVENTS. Based on investigator reports, there were 15 nonserious adverse events during the initial 24-h levosimendan infusion (Supplemental Table 9), including headache (n = 7), tachycardia (n = 2), palpitations (n = 2), dyspnea (n = 2) and hypotension (n = 2). Adverse events reported during the 6-week randomized phase (Supplemental Table 10) were generally balanced between the levosimendan and placebo groups, including headache, tachycardia, fatigue, acute heart failure, dyspnea, access site pain, muscle spasms, and hypokalemia. Among these, 6 events in 4 patients (1 placebo, 3 levosimendan) were considered to be serious (Supplemental Table 11). These included right-side HF and cardiogenic shock in 1 placebo patient, 2 instances of acute heart failure in 2 levosimendan patients, and 2 instances of infection related to the PICC line in 2 levosimendan patients.

DISCUSSION

In this prospective multicenter study of patients with PH-HFpEF, a 24-h infusion of levosimendan significantly decreased PCWP and CVP at rest, during a leg-raise volume challenge, and during 25 W supine exercise. In the randomized double-blind phase of the study, once-weekly infusions of levosimendan did not significantly reduce the between-group differences in PCWP during exercise, but did reduce PCWP when measurement at rest and during passive leg raise as well as during exercise were incorporated into the analysis. Submaximal exercise capacity was improved with levosimendan, evidenced by a 29-m placebo-corrected improvement in 6MWD, an effect size that is similar to that of approved pulmonary vasodilators for PH (7). Levosimendan was well tolerated, with no difference in the adverse event profile between treatment and placebo and no evidence of proarrhythmia.

PH-HFpEF is a subset of the group 2 World Health Organization PH classification. A key distinction from group 1 PH, with which it shares a similar clinical

CENTRAL ILLUSTRATION **Effects of Levosimendan on PCWP and CVP**



Burkhoff, D. et al. J Am Coll Cardiol HF. 2021;■(■):■-■.

Comparison of **(A, C)** pulmonary capillary wedge pressure (PCWP) and **(B, D)** central venous pressure (CVP) between baseline, 24 h, and 6 weeks at rest, with legs up, and during 25 W exercise. **(A, B)** Placebo group; **(C, D)** levosimendan group. Note that both groups received open-label levosimendan during the first 24 h. *$p < 0.05$ for comparison between respective baseline and 24-h measurements.

presentation, is elevated PCWP. It also has a distinctive pathology characterized by pulmonary venous and pulmonary arteriolar changes, reflecting the increase in both pulmonary venous and arterial pressure, and limitations in exercise reserve related to elevated filling pressures in both sides of the heart (1). PH-HFpEF is associated with a 5-year survival of 50%, exceeding the mortality of PH (8). No treatments

TABLE 3 Baseline and 6-Week Hemodynamic Parameters Values for All Randomized Patients (n = 18 Placebo and 17 Levosimendan Treatment Patients)*

		Baseline			Placebo-Corrected Effect of Change From Baseline at 6 Weeks, LS Mean (95% CI)		
	Group	Legs Down	Legs Up	25 W	Legs Down	Legs Up	25 W
HR, beats/min	Placebo	66.6 ± 9.6	66.8 ± 10.0	79.1 ± 11.2	4.1 (−0.4 to 8.7)	2.8 (−3.5 to 9.2)	9.3 (−0.4 to 19.0)
	Treatment	70.6 ± 14.4	70.7 ± 15.0	88.3 ± 18.4			
CVP, mm Hg	Placebo	16.6 ± 5.4	19.9 ± 5.0	28.4 ± 6.8	−3.1 (−6.4 to 0.3)	−3.9 (−8.2 to 0.4)	−3.0 (−8.1 to 2.1)
	Treatment	14.9 ± 5.2	18.8 ± 8.1	27.7 ± 10.2			
PAS, mm Hg	Placebo	67.2 ± 21.2	75.6 ± 20.9	87.6 ± 24.9	−2.3 (−8.3 to 3.7)	0.4 (−7.1 to 7.9)	−0.9 (−9.7 to 7.9)
	Treatment	64.8 ± 19.0	70.7 ± 18.7	90.7 ± 21.2			
PAD, mm Hg	Placebo	28.9 ± 6.9	32.3 ± 7.0	39.6 ± 10.4	−3.1 (−6.4 to 0.3)	−1.6 (−6.2 to 3.1)	−1.2 (−6.3 to 3.8)
	Treatment	28.6 ± 5.6	32.3 ± 8.17	40.5 ± 6.6			
PA mean, mm Hg	Placebo	41.7 ± 10.8	46.7 ± 11.0	55.6 ± 14.8	−2.9 (−6.7 to 0.1)	−1 (−5.9 to 4.1)	−1.3 (−6.7 to 4.1)
	Treatment	40.7 ± 9.3	45.1 ± 10.1	57.4 ± 10.8			
PCWP, mm Hg†	Placebo	24.9 ± 6.5	28.6 ± 7.6	35.5 ± 11.8	−3.4 (−7.3 to 0.5)	−5.6 (−10.3 to −1.0)†	−1.4 (−7.7 to 4.8)
	Treatment	26.2 ± 5.3	31.1 ± 7.2	37.8 ± 8.3			
AoS, mm Hg	Placebo	141.5 ± 18.4	141.1 ± 16.8	151.4 ± 31.1	1.6 (−11.6 to 14.8)	0.4 (−13.9 to 14.7)	−2.4 (−25.0 to 20.1)
	Treatment	132.4 ± 19.1	137.1 ± 18.1	148.8 ± 30.7			
CI, l/min/m^2	Placebo	2.3 ± 0.6	2.5 ± 0.5	3.0 ± 0.9	0.2 (−0.2 to 0.6)	0.10 (−0.5 to 0.7)	0.2 (−0.4 to 0.8)
	Treatment	2.7 ± 1.0	2.9 ± 1.1	3.5 ± 1.3			
SVR, WU	Placebo	16.8 ± 3.4	15.3 ± 3.2	12.7 ± 3.2	−1.0 (−4.2 to 0.3)	0.04 (−3.5 to 3.5)	−2.1 (−5.0 to 1.1)
	Treatment	14.0 ± 4.8	13.2 ± 4.8	10.8 ± 3.9			
PVR, WU	Placebo	4.1 ± 3.6	2.2 ± 1.0	3.99 ± 3.8	−0.24 (−1.46 to 0.98)	−0.05 (−1.46 to 1.35)	−0.3 (−1.5 to 0.9)
	Treatment	2.7 ± 1.5	2.6 ± 1.5	3.1 ± 1.9			

Values are mean ± SD, unless otherwise indicated. *Least square (LS) means and confidence intervals (CIs) are from analysis of variance model for change from baseline, with treatment group as a factor. †Between-group differences p = 0.04 by mixed-effects repeated measures model.

Abbreviations as in Table 2.

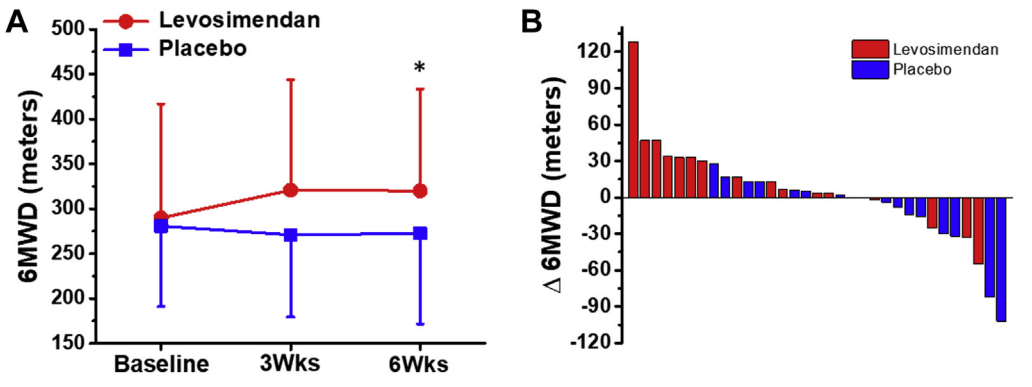
have yet been identified that improve symptoms, quality of life, or survival. Several studies have tested pulmonary vasodilator drugs, almost all without success.

Mechanistically, levosimendan is characterized as an inodilator. (9) Its vasodilating effects are attributed to activation of adenosine triphosphate (ATP)-sensitive potassium (K) channels in arterial and venous smooth muscle cells. The positive inotropic effects are attributed to myofilament calcium sensitization and phosphodiesterase inhibition properties. Other potential effects are mediated by mitochondrial ATP-sensitive K^+ channel opening in cardiomyocytes. In trials of patients with decompensated HFrEF, levosimendan produces dose-dependent reductions in PCWP, which is one reason it became an attractive treatment for use in PH-HFpEF. Although the half-life of levosimendan is only 1 hour, its active metabolite, OR-1896, has a half-life of 75-80 h (4). This long half-life justifies the intermittent dosing used in this and previous studies (summarized in Supplemental Tables 12 and 13). This is the first time that chronic, weekly, 24-h infusions of levosimendan have been investigated in a randomized study, and the sustained hemodynamic effects through 6 weeks provide further support for intermittent dosing. Furthermore, the fact that the 24-h hemodynamic effects of intravenous levosimendan were similar to those measured at 6 weeks supports the similarity between levosimendan and its metabolite.

Several novel features were included in the design of the HELP study. First, previous studies of levosimendan in HFrEF patients used higher doses to achieve increases in CO and reductions of SVR and PVR (Supplemental Tables 12 and 13). In contrast, the present study used an infusion rate ~50% lower than the maximum infusion rate used in most previous trials. In addition, this is the first study to evaluate chronic use of a parenterally administered drug, the first to employ a weekly 24-h intravenous infusion at patients' homes, and the first to evaluate the hemodynamic effects of levosimendan at rest and during exercise. Finally, by including an open-label initial phase to test response to a 24-h levosimendan infusion, it was assumed that the study would be enriched with patients more likely to respond to long-term treatment.

The original rationale for selecting the PH-HFpEF population for the HELP study included potential positive inotropic effects on RV function and pulmonary and systemic vasodilation, which are key targets for PH-HFpEF (1). Yet, one of the most striking findings of the present study is that the acute and chronic reductions of CVP and PCWP were achieved

FIGURE 3 Impact of Levosimendan on 6MWD Compared With Placebo



(A) Comparison of 6-min walk distance (6MWD) in treatment and control groups. *$p < 0.05$. **(B)** Rank-ordered listing of changes in 6MWD for each patient designated by group assignment. More patients in the treatment group had increased 6MWD, whereas more patients in the control group had decreased 6MWD.

without systemic or pulmonary arterial vasodilation, positive inotropic effects, or increases of CO. One potential mechanism that could account for these findings is relatively selective venodilation at the doses used (10). Venodilation causes a shift of blood from the central circulation to the peripheral (mainly splanchnic) circulation, which would reduce venous pressures of both the systemic and the pulmonary circulation. Venodilatory effects of levosimendan have been documented in preclinical studies of isolated venous vascular rings and appears to be related to levosimendan's activation of K channels (11). In addition, we cannot rule out that systemic arterial vasodilation could also be contributory; changes in SVR at both 24 h and 6 weeks just missed statistical significance and might have become significant with a larger sample size.

The observed increase of 6MWD is significant because such changes have been strongly correlated with improvements of quality of life in HFpEF patients (12). Indeed, increased 6MWD (a measure of submaximal exercise tolerance) may be linked to reductions of CVP and PCWP at rest and during leg raise, which signifies increased capacity to deal with a low-intensity hemodynamic stress. It is also noteworthy that reductions of resting CVP and mPAP are both predictors of improved survival in patients with PH (13), and reduction of resting PAP is also a predictor of improved survival in the HFpEF population in general (14). Notably, the HELP study is the first to show significant beneficial effects on hemodynamics and exercise tolerance in PH-HFpEF in a double-blind multicenter study.

STUDY LIMITATIONS. The results of this study need to be interpreted within the context of several limitations. The main limitation relates to the timing of hemodynamic measurements relative to levosimendan dosing in the chronic study phase. Whereas the immediate effects of levosimendan on exercise PCWP and CVP were measured at peak concentrations at the end of the initial 24-h infusion and showed reductions at rest, with passive leg raise, and during exercise, the effects at 6 weeks (representing activity of OR-1896) were measured 1 week after the final levosimendan infusion at week 5. Thus, hemodynamic effects at 6 weeks represents effects of OR-1896 at trough levels, and greater effects might have been observed with earlier assessment.

Another limitiation is the small sample size, which left several of the comparisons underpowered to detect what could have been statistically significant between-group differences in PCWP and CVP at rest and during leg raise at 6 weeks. This appeared to be due to greater than anticipated variability of changes in these parameters. Indeed, point estimates of changes of PCWP and CVP at rest and with legs raised were nearly identical to the effects measured at the end of the open-label 24-h levosimendan infusion. These findings deserve further exploration in a future study.

Finally, because no previous study evaluated chronic levosimendan in PH-HFpEF, we chose a low dose out of an abundance of caution. Because there is a dose-dependent response to levosimendan in both CO increase and PCWP reduction, it remains possible that higher doses may be more effective in selected patients.

CONCLUSIONS

The HELP PH-HFpEF trial shows that levosimendan produces significant acute hemodynamic effects at rest and during exercise. Although levosimendan treatment for 6 weeks did not significantly lower exercise PCWP, it showed effects at rest and with legs raised. In addition, it is the first treatment to produce favorable hemodynamic changes in PH-HFpEF and to improve exercise tolerance. These findings justify further study of levosimendan in PH-HFpEF, a population without any approved therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: There are no effective treatments for patients with pulmonary hypertension in the setting of heart failure with preserved ejection fraction (PH-HFpEF).

COMPETENCY IN MEDICAL KNOWLEDGE 2: Increased pulmonary capillary wedge pressure (PCWP) during exercise is thought to be one factor that limits exercise tolerance; there is evidence that PCWP normalized to workload during exercise is prognostic of clinical outcomes.

TRANSLATIONAL OUTLOOK 1: A 24-h infusion of levosimendan reduced PCWP at rest, during leg raise, and at 25 W of supine cycle exercise, thus suggesting that this drug could have hemodynamic benefits in PH-HFpEF.

TRANSLATIONAL OUTLOOK 2: Although the study included a small number of patients and the primary end point was not met: 1) an analysis including data at rest, during leg raise, and at 25 W showed a significant decrease of PCWP; and 2) there was a significant increase in 6-min walk distance. Both findings support further study of levosimendan in PH-HFpEF.

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KEY WORDS exercise, heart failure with preserved ejection fraction (HFpEF), hemodynamics, levosimendan, pulmonary hypertension

APPENDIX For supplemental tables, please see the online version of this paper.