Levosimendan in Patients with PH-HFpEF: Results of the LEVEL Trial

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on behalf of the LEVEL Trial Investigators

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LEVEL: NCT05983250

Disclosures

- **LEVEL was funded by Tenax Therapeutics:**
  - ⇢ The sponsor designed and conducted the trial in close collaboration with the academic steering committee; all statistical analyses were done by Allucent, Inc.
  - ⇢ **SJS had full access to participant-level data; independently validated all results**
- **SJS: Research funding:**
  - ⇢ NIH U54 HL160273, X01 HL169712; UG3 HL182948; AHA # 24SFRNPCN1291224
  - ⇢ AstraZeneca, Boston Scientific, Corvia, Pfizer, Tempus, Arma Biosciences
- **SJS: Consulting / advisory board / steering committee:**
  - ⇢ 35Pharma, Abbott, Alleviant, AstraZeneca, Amgen, Axon Therapies, BaroPace, Bayer, Boehringer-Ingelheim, Boston Scientific, BMS, Corvia, Cytokinetics, Edgewise, Edwards, Ensho Health, Eidos, Gordian, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, Metabolic Flux, Novartis, Novo Nordisk, OrbiMed, Pfizer, Prothena, Regeneron, Rivus, SalubrisBio, Sardocor, Secretome, Shifamed, Tectonic, Tenax, Tenaya, Ultromics

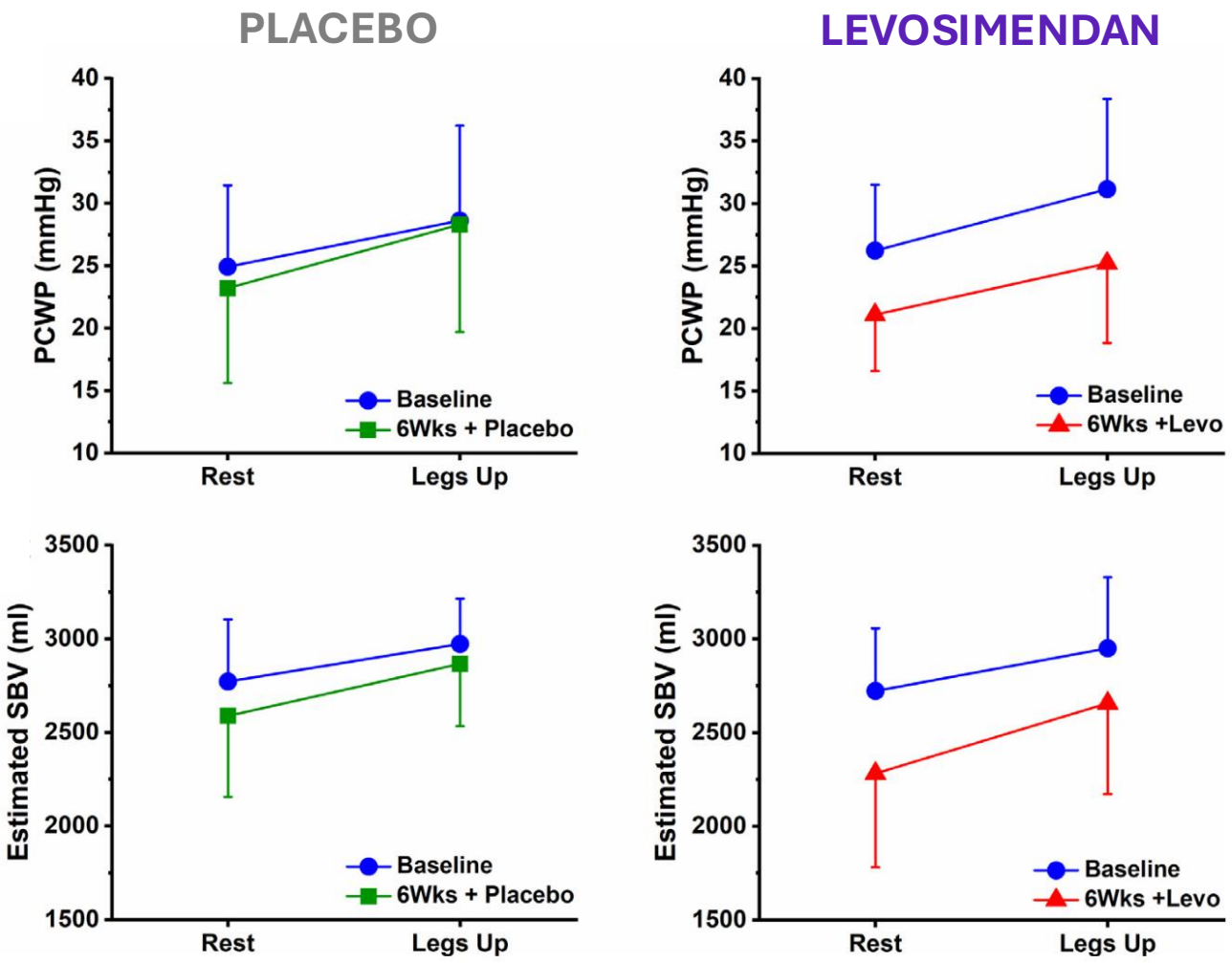
Background and rationale

- **Pulmonary hypertension is common in HFpEF:**
  - ⇢ 70-80% of patients with HFpEF have pulmonary hypertension (PH)
  - ⇢ Associated with AF, TR, cardiorenal syndrome, and poor outcomes
- **Pulmonary vasodilators haven't worked in PH-HFpEF:**
  - ⇢ PDE5 inhibitors, sGC stimulators, endothelin receptor antagonists (ERAs), and relaxin agonists have all been neutral or harmful in PH-HFpEF
  - ⇢ Activin pathway inhibition (sotatercept) ↓PVR in the CADENCE trial, with ↑6MWD in the low-dose arm, but required PVR >4 WU (minority of PH-HFpEF)
- **New treatment strategies are needed for PH-HFpEF:**
  - ⇢ Splanchnic vasodilation + RV contractile support is an attractive target
  - ⇢ **Goal:** reduce cardiopulmonary congestion while maintaining cardiac output

Lam CS, et al. JACC 2009; Shah SJ. JAMA 2012; Brittain EL, et al. Circulation 2022
Gomberg-Maitland M, et al. Circulation 2026; Yaku H, Fudim M, Shah SJ. J Cardiol 2024

Levosimendan for PH-HFpEF

- **Levosimendan:**
  - **K^+-ATP channel opener:** splanchnic and pulmonary vasodilator
  - **Calcium sensitizer:** RV contractile support
- **Phase 2 HELP PH-HFpEF trial:**
  - IV levosimendan vs. placebo in patients with PH-HFpEF (n=37)
  - Reduced cardiac filling pressures and stressed blood volume
  - Improved 6MWD (+29 meters)
  - Open-label extension study with oral levosimendan: well-tolerated



Burkhoff D, et al. ESC Heart Fail 2021; Burkhoff D, et al. JACC Heart Fail 2021
Brener MI, et al. J Card Fail 2021; Thenappan T, et al. J Card Fail 2023

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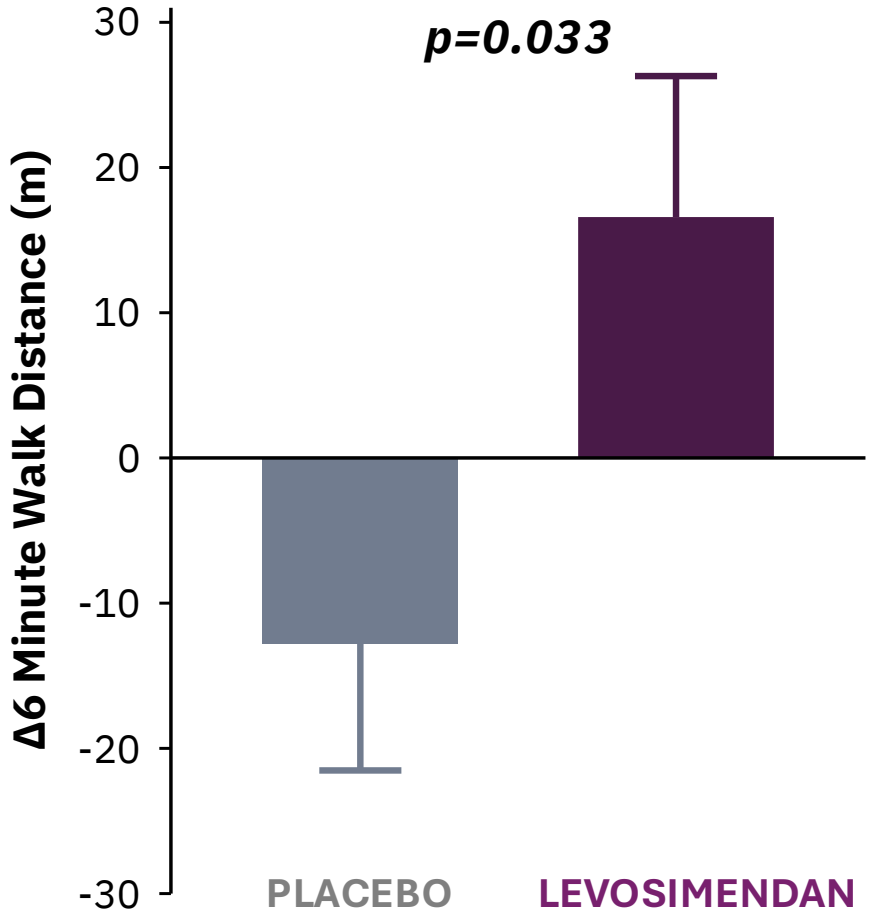

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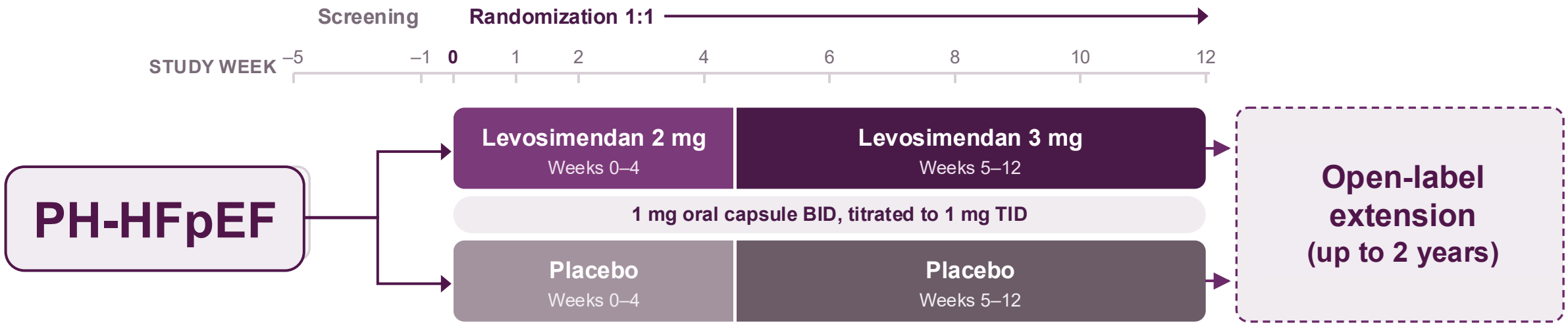
LEVEL: Trial design

LEVEL trial design: Phase 3 RCT in PH-HFpEF



OUTCOME ASSESSMENTS	Baseline	Week 4	Week 8	Week 12
6-minute walk test	◆	◆	◆	◆
KCCQ, PGI scales	◆	◆	◆	◆
NTproBNP	◆	◆	◆	◆
NYHA functional class	◆	◆	◆	◆
Echocardiography	◆			◆
Rhythm monitoring (patch)	◆ (screening)	◆ (Week 3)		◆ (Week 11)

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LEVEL trial design: Phase 3 RCT in PH-HFpEF

Key eligibility criteria:

- **Age** 18-85 years old
- **NYHA** class II, III, or ambulatory IV
- **LVEF ≥40%** confirmed by echo core lab
- **WHO group 2 PH**, confirmed by RHC:

Condition	RAP	mPAP	PCWP
Rest *or*	≥8	≥30	≥18
Legs up *or*	≥8	≥32	≥20
Exercise	≥10	≥35	≥25

- **6MWD** 100-450 m, limited by dyspnea
- **Excluded:** PAH-specific therapy, group 1/3/4/5 PH, SBP <100 mm Hg

Randomization and treatment:

- **Assigned 1:1 to levosimendan or matching placebo**
- **Stratified by** rhythm and LV ejection fraction (40-49% vs. ≥ 50%)
- **Dose:** 1 mg BID for 4 weeks, then titrated to 1 mg TID from week 5 onwards (dose reduction permitted for tolerability at discretion of site PI)
- Patients, investigators, site staff, and sponsor **blinded to treatment assignment**

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LEVEL trial design: Phase 3 RCT in PH-HFpEF

Endpoints (Baseline to Week 12):

- **Primary:** 6MWD
- **Secondary (hierarchical):** KCCQ total symptom score → NYHA class → # of clinical worsening events → time to first clinical worsening event
- **Exploratory:** NTproBNP, RVSP (estimated by echo), PGIS, PGIC, % change in 6MWD

Statistical analyses:

- **Sample size n=230:** >90% power to detect a 25-meter difference between groups in 6MWD at α=0.05 (based on Δ6MWD SD = 55 meters)
- **Primary endpoint analysis:** MMRM with baseline 6MWD, randomization strata, group, visit, and group × visit included in the statistical model

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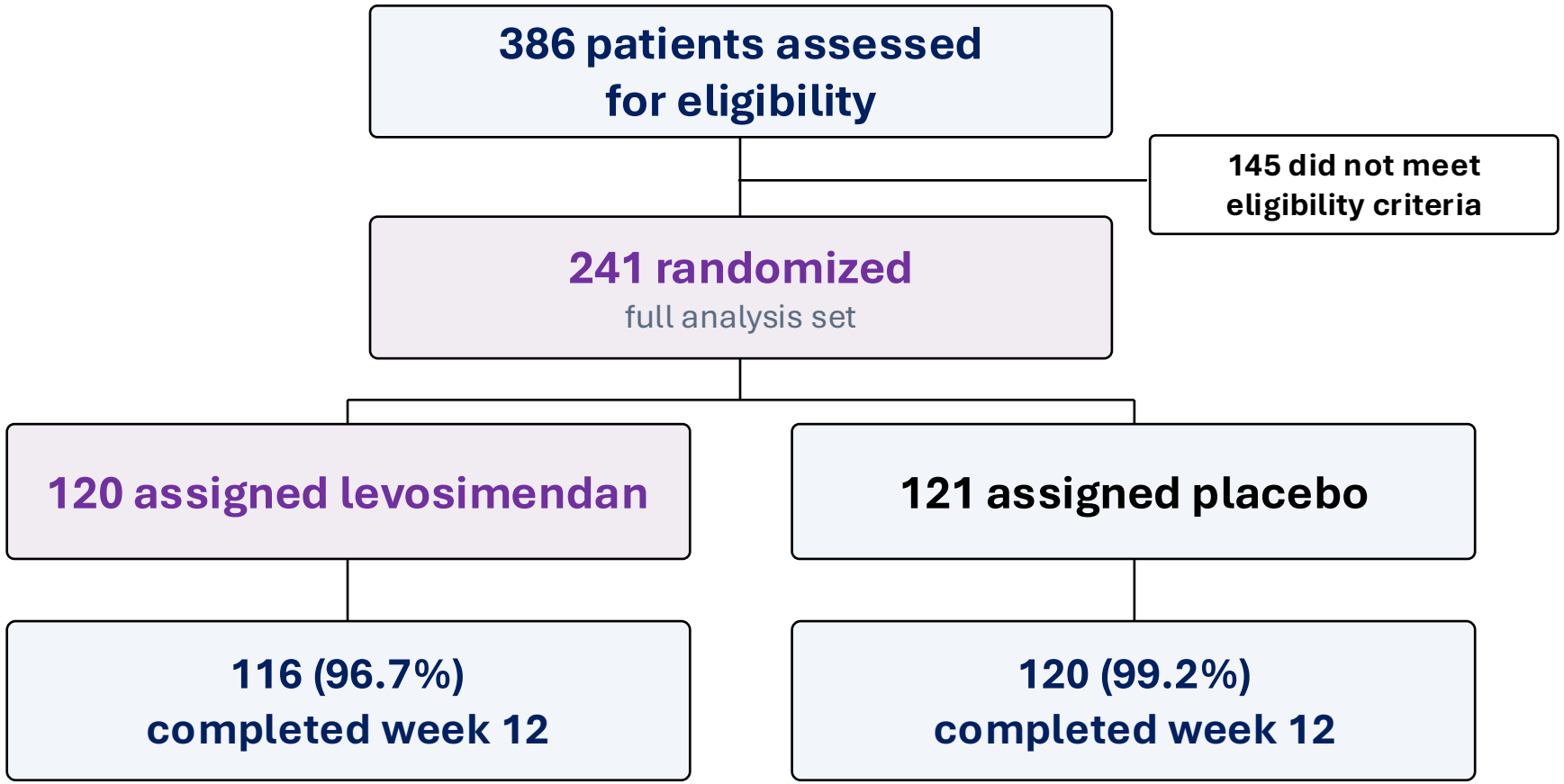
LEVEL: Results

Participant disposition



All 241 randomized patients were included in the full analysis set and safety analysis

Baseline characteristics

Characteristic	Levosimendan (n=120)	Placebo (n=121)
Age — years	69.8 ± 9.7	68.5 ± 10.0
Female sex — no. (%)	86 (71.7)	86 (71.1)
Body-mass index — kg/m^2	33.2 ± 5.8	32.9 ± 6.6
NYHA class III or IV — no. (%)	67 (55.8)	66 (54.5)
Atrial fibrillation or flutter — no. (%)	59 (49.2)	55 (45.5)
Coronary artery disease — no. (%)	49 (40.8)	46 (38.0)
Diabetes mellitus — no. (%)	33 (27.5)	38 (31.4)
Estimated GFR — $mL/min/1.73\ m^2$	70.2 ± 19.1	68.9 ± 22.5
6-minute walk distance — m	317 ± 87	323 ± 83
KCCQ total symptom score	61.5 ± 22.1	61.5 ± 20.1
NT-proBNP — pg/mL, median (IQR)	308 (137–984)	249 (116–623)
Ejection fraction ≥50% — no. (%)	115 (95.8)	115 (95.0)
Loop diuretic — no. (%)	83 (69.2)	79 (65.3)
SGLT2 inhibitor — no. (%)	80 (66.7)	93 (76.9)
MRA — no. (%)	68 (56.7)	76 (62.8)
GLP-1 receptor agonist — no. (%)	36 (30.0)	32 (26.5)

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Older, female-predominant, symptomatic, with multiple comorbidities, majority (>95%) with LVEF ≥50%, and well-treated with HFpEF GDMT (SGLT2i, MRA)
6MWD: mean 320 m, higher than HELP (mean 248 m)

Baseline echo + invasive hemodynamics

Characteristic	Levosimendan (n=120)	Placebo (n=121)
Echocardiography		
LV ejection fraction — %-units	61.1 ± 5.9	60.7 ± 5.6
Global longitudinal strain — %-units	18.8 ± 3.7	18.8 ± 3.3
Left atrial volume index — mL/m^2	29.9 ± 15.3	28.9 ± 15.3
E/e' ratio	10.2 ± 3.5	10.2 ± 3.2
RV systolic pressure (peak TR gradient) — mm Hg	34.8 ± 13.9	34.5 ± 16.2
Resting hemodynamics		
Right atrial pressure — mm Hg	9.7 ± 4.3	10.2 ± 4.4
Mean PA pressure — mm Hg	30.2 ± 11.7	31.0 ± 10.5
PCWP — mm Hg	17.2 ± 5.9	17.8 ± 6.1
Cardiac output — L/min	5.1 ± 1.4	5.2 ± 1.4
PVR — Wood units	3.0 ± 2.6	2.8 ± 2.1
Supine exercise hemodynamics (n=124)		
Mean PA pressure — mm Hg	42.3 ± 6.6	43.7 ± 8.8
PCWP — mm Hg	28.8 ± 4.2	29.5 ± 5.3

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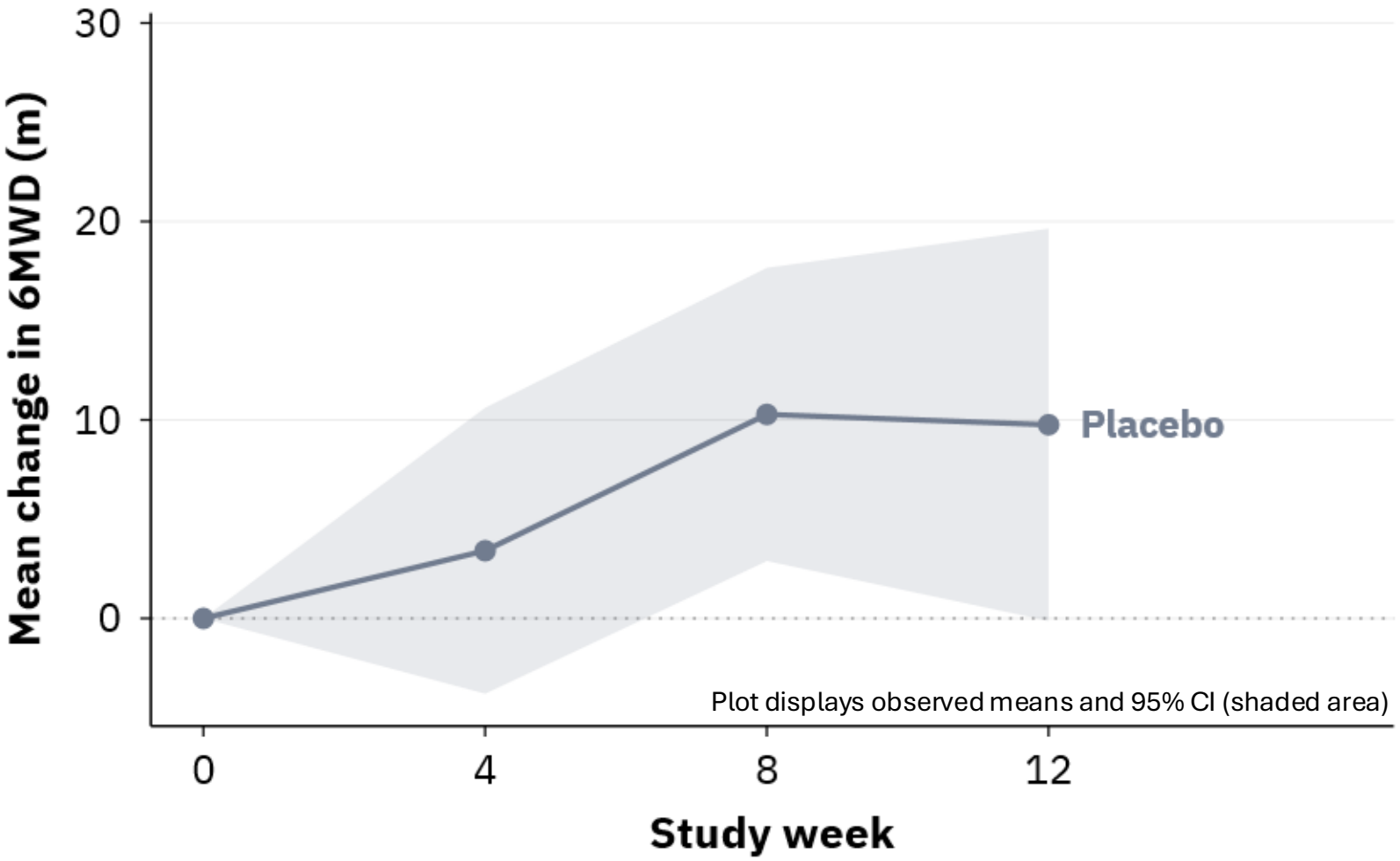
E/e' ratio	10.2 ± 3.5	10.2 ± 3.2
Mean PA pressure — mm Hg	30.2 ± 11.7	31.0 ± 10.5
PCWP — mm Hg	17.2 ± 5.9	17.8 ± 6.1
Cardiac output — L/min	5.1 ± 1.4	5.2 ± 1.4
PVR — Wood units	3.0 ± 2.6	2.8 ± 2.1
Supine exercise hemodynamics (n=124)		
Mean PA pressure — mm Hg	42.3 ± 6.6	43.7 ± 8.8
PCWP — mm Hg	28.8 ± 4.2	29.5 ± 5.3

Invasively proven PH-HFpEF across the range of IpcPH + CpcPH
~60% qualified based on provoked (legs up or exercise) hemodynamics


Primary endpoint: 6MWD

6MWD: Baseline to Week 12



PLACEBO

+10.4 meters*

95% CI: −4.5 to 25.3

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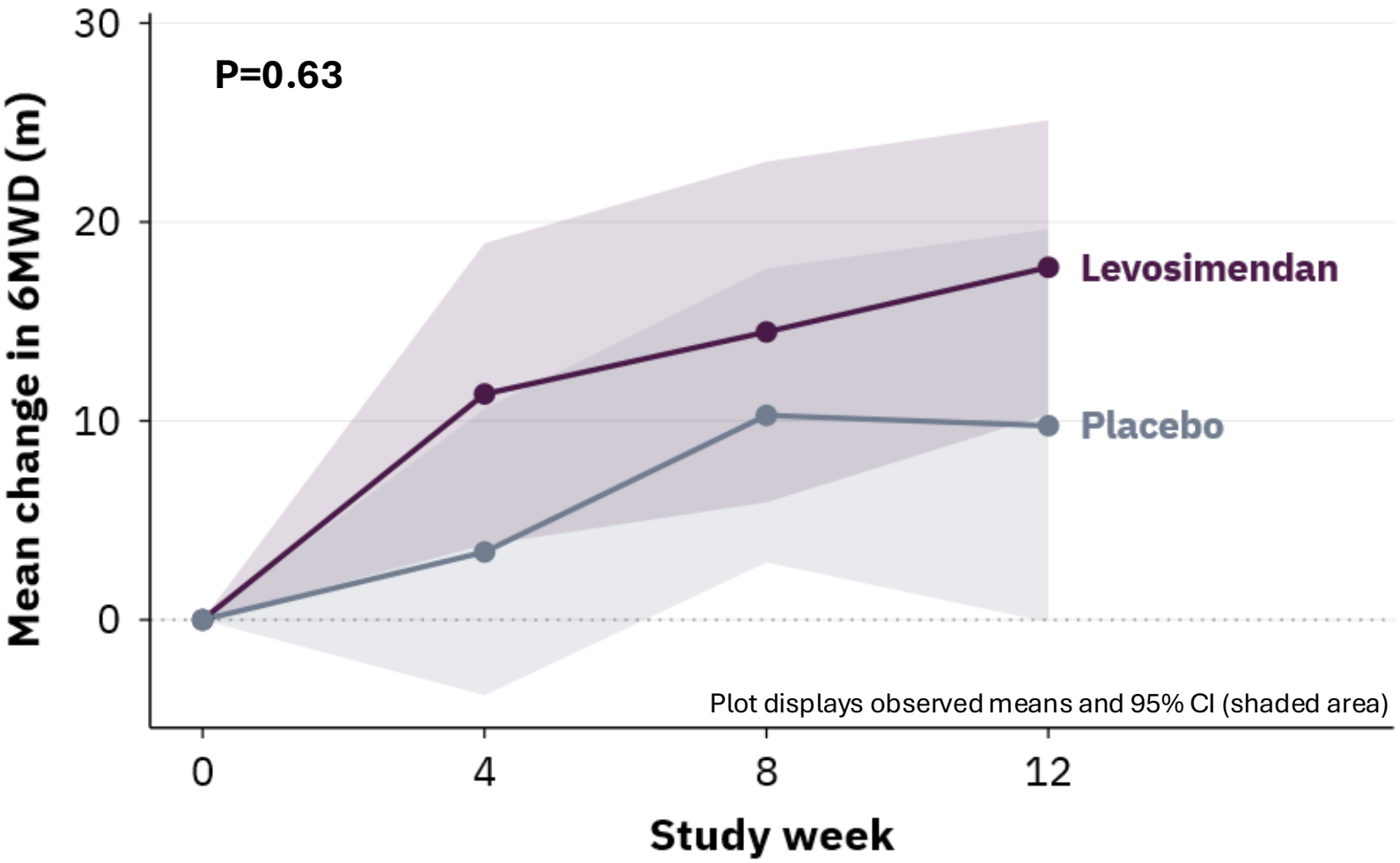
***Least squares mean values (by MMRM)**

6MWD: Baseline to Week 12



LEVOSIMENDAN

+14.0 meters*

95% CI: −1.1 to 29.0

PLACEBO

+10.4 meters*

95% CI: −4.5 to 25.3

TREATMENT DIFFERENCE

+3.5 meters*

95% CI: −10.7 to 17.8

***Least squares mean values (by MMRM)**

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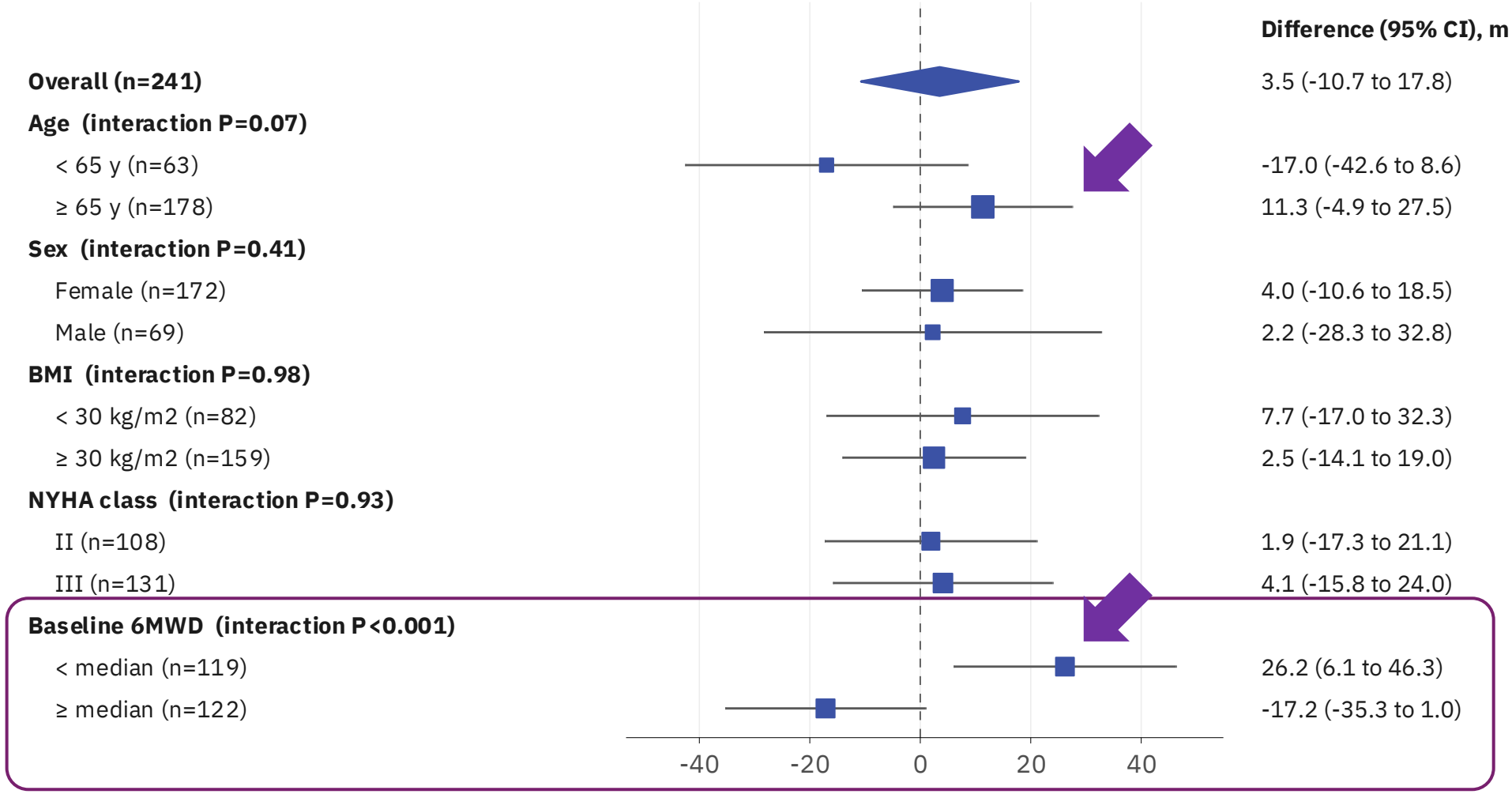
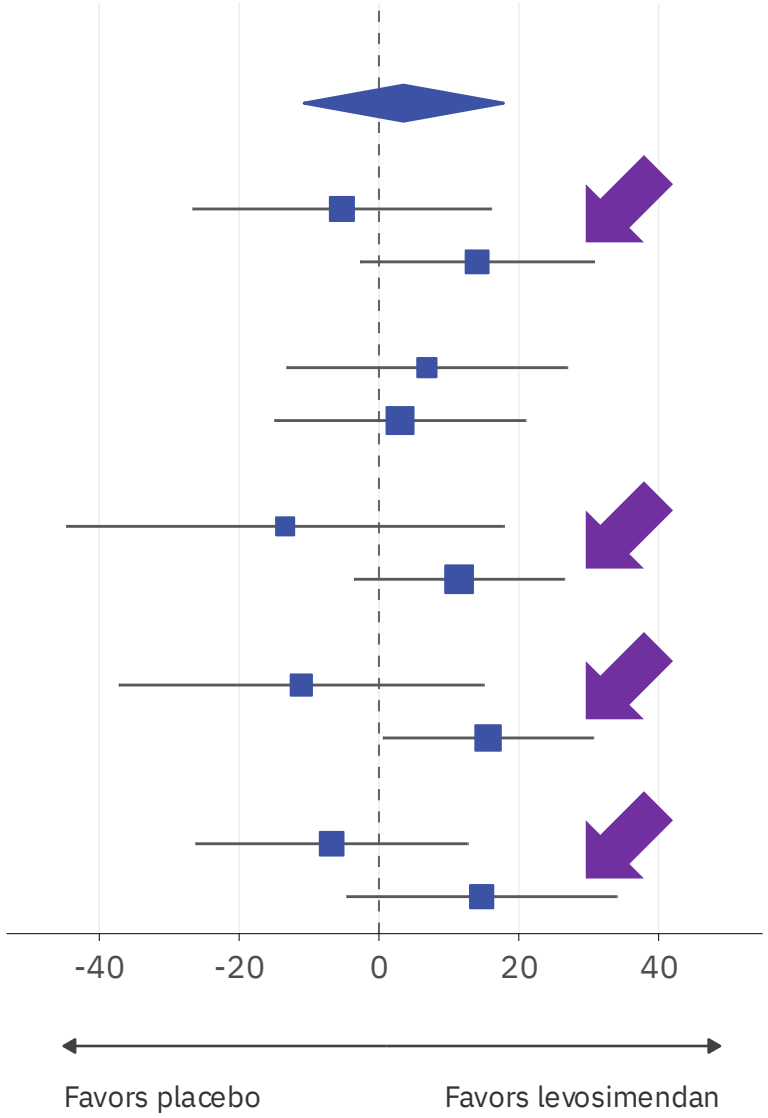
6MWD: Pre-specified subgroup analyses



Responders:

- ↓6MWD
- ↑Age
- Sicker

6MWD: Pre-specified subgroup analyses



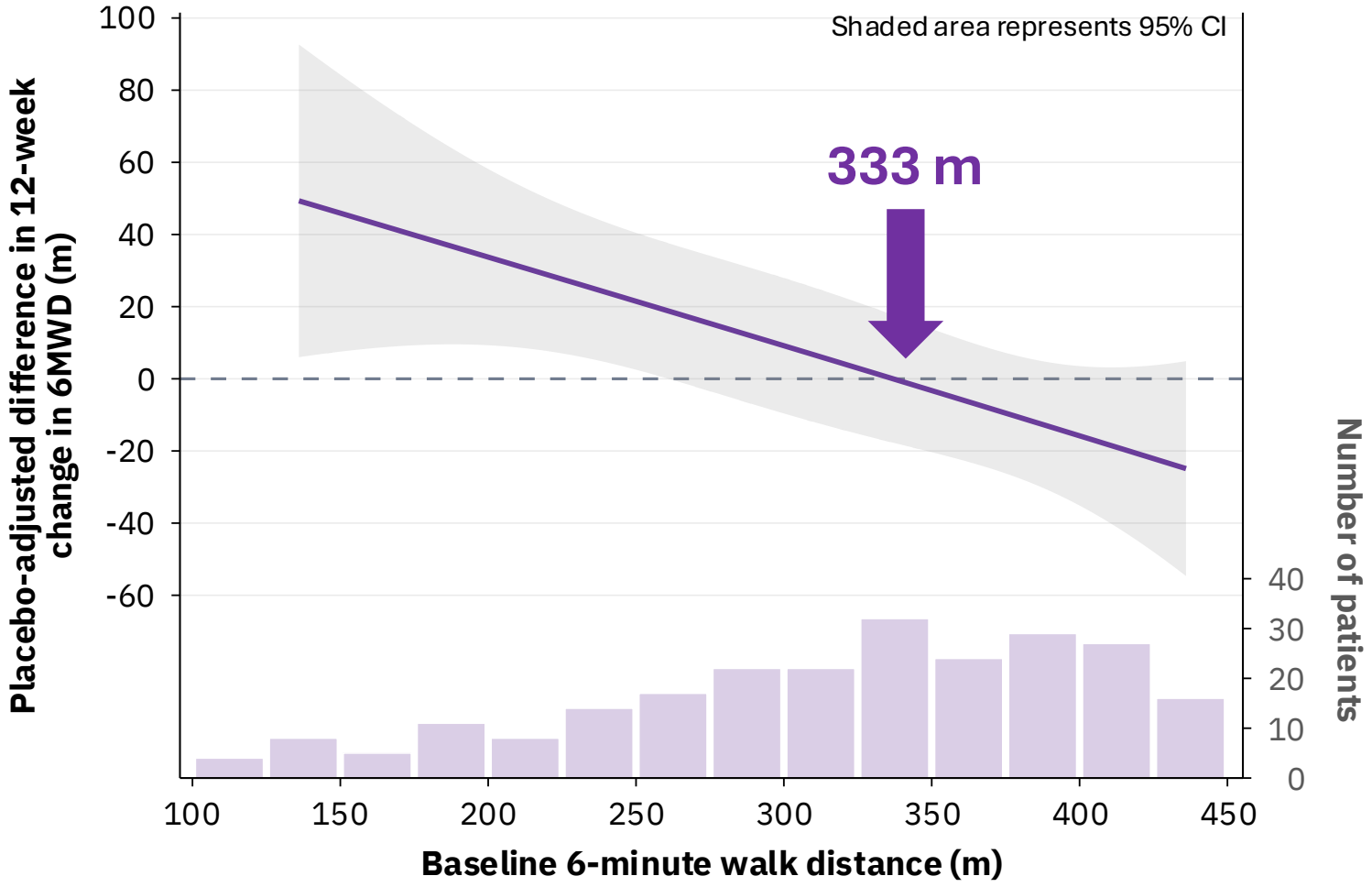
	Difference (95% CI), m
Overall (n=241)	3.5 (-10.7 to 17.8)
Atrial fibrillation (interaction P=0.19)	
No (n=127)	-5.3 (-26.7 to 16.0)
Yes (n=114)	14.0 (-2.7 to 30.8)
Loop diuretic (interaction P=0.77)	
No (n=78)	6.9 (-13.2 to 26.9)
Yes (n=163)	3.0 (-14.9 to 21.0)
SGLT2 inhibitor (interaction P=0.27)	
No (n=68)	-13.4 (-44.7 to 17.9)
Yes (n=173)	11.5 (-3.6 to 26.5)
MRA (interaction P=0.13)	
No (n=97)	-11.1 (-37.2 to 15.0)
Yes (n=144)	15.6 (0.6 to 30.7)
Baseline NT-proBNP (interaction P=0.18)	
At or below median (n=123)	-6.8 (-26.2 to 12.7)
Above median (n=118)	14.7 (-4.6 to 34.0)

Change in 6-minute walk distance at week 12 (m)

Responders:

- **↓6MWD**
- **↑Age**
- **Sicker**

Lower 6MWD → greater benefit



- Inverse linear relationship between baseline 6MWD and treatment effect
- Not explained by regression to the mean (placebo-adjusted)
- In LEVEL, levosimendan-treated patients whose baseline 6MWD matched HELP and CADENCE (274-285 m) had a ~20-meter placebo-adjusted improvement in 6MWD

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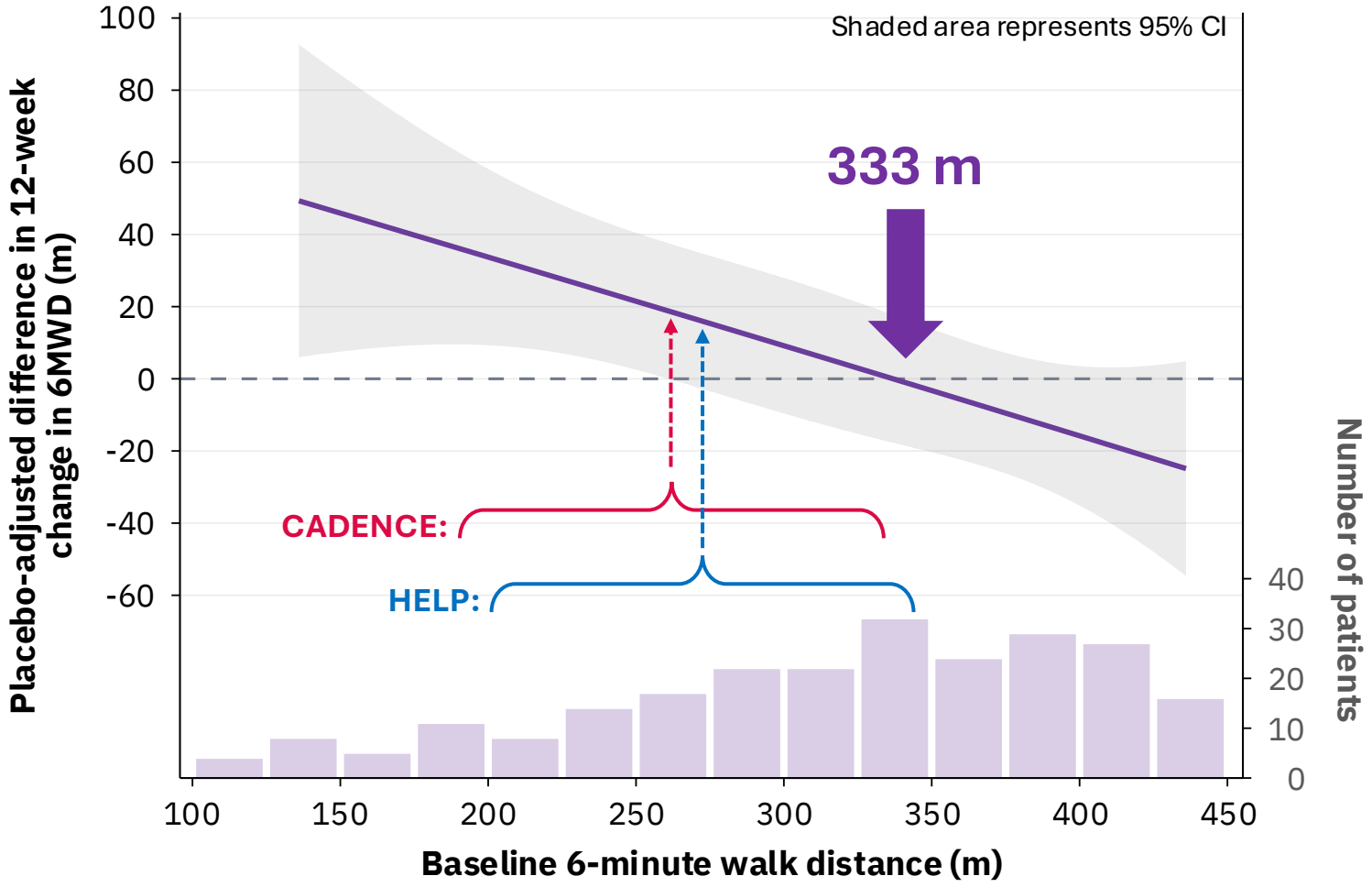

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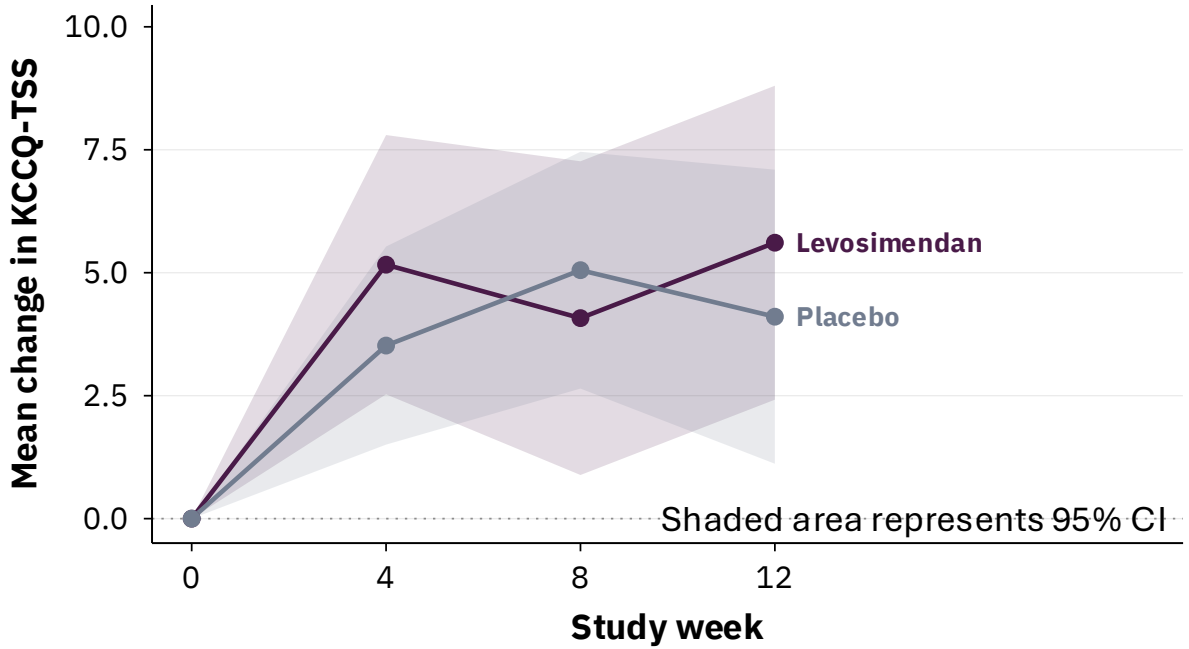
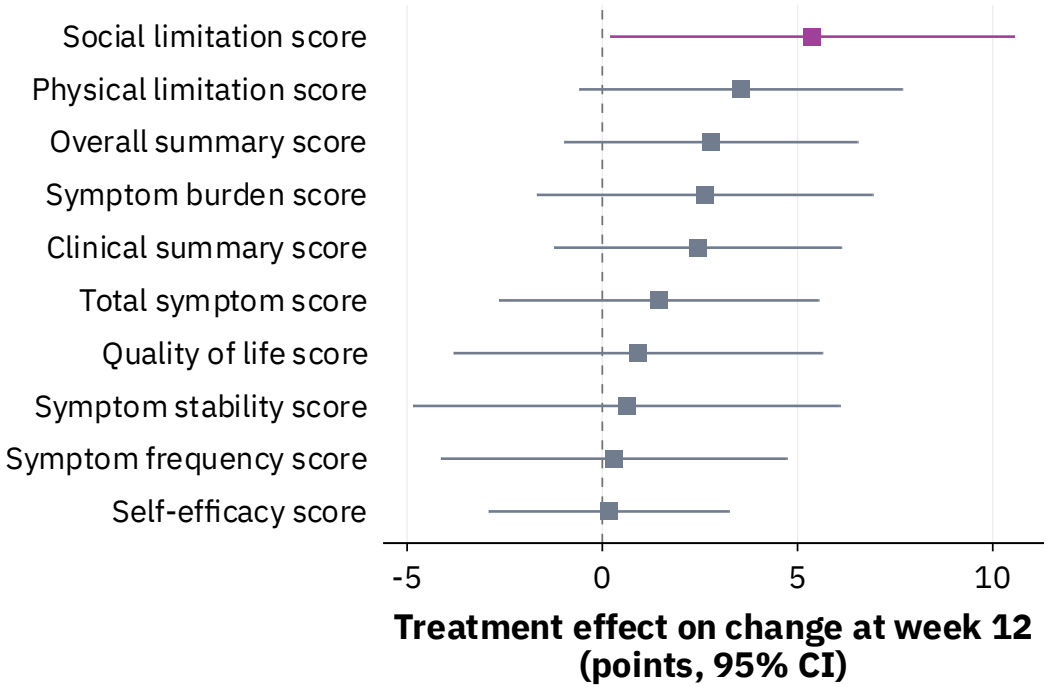
Secondary endpoints: KCCQ-TSS, NYHA class, clinical worsening events

Secondary endpoint results

Endpoint	Levosimendan (n=120)	Placebo (n=121)	Difference (95% CI)	P-value
KCCQ-TSS — points	+6.6	+6.5	0.1 (−4.3 to 4.5)	0.97
Improved NYHA class — no. (%)	28 (23.3)	27 (22.3)	1.0 (−10.4 to 12.4)	0.88
Clinical worsening events — no.	3	3	—	—

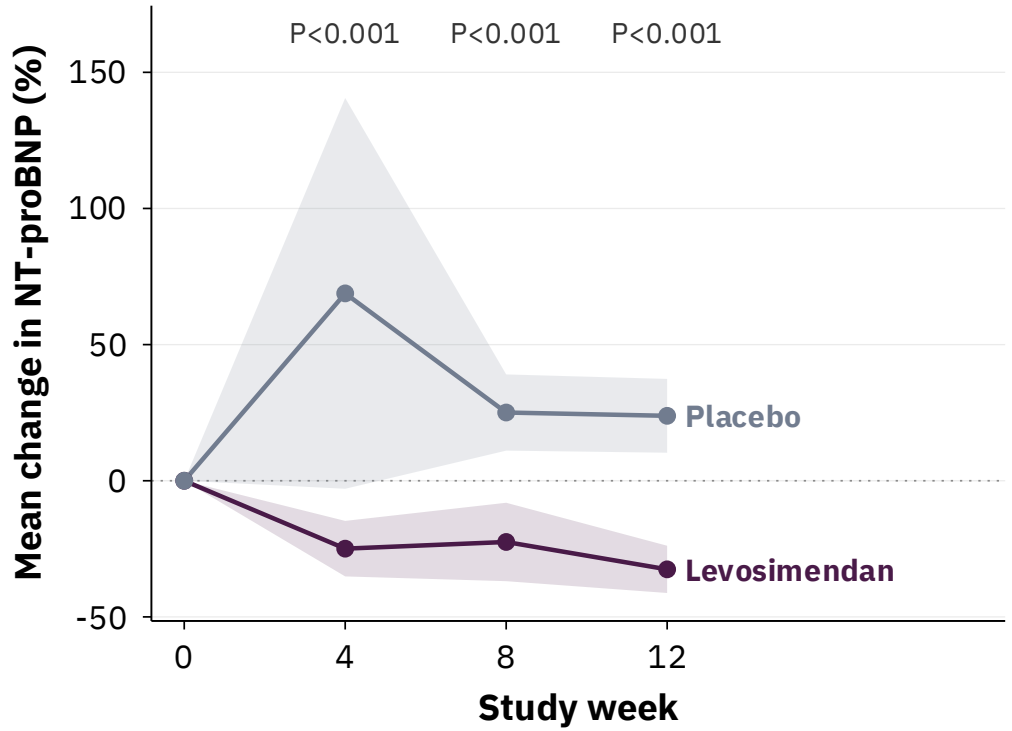


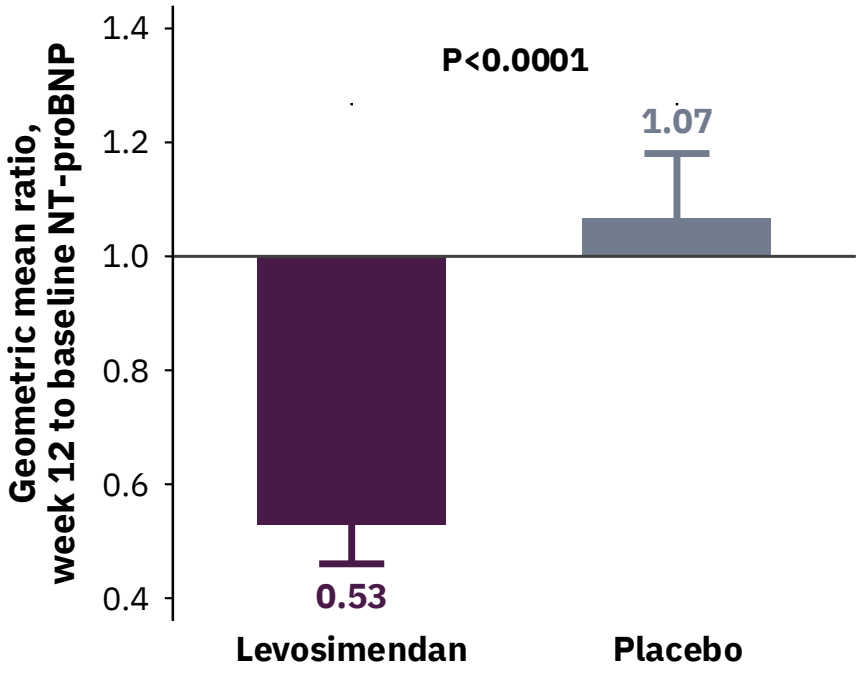


Exploratory endpoints: NTproBNP, RVSP, PGI scales

Levosimendan lowered NTproBNP by ~50%

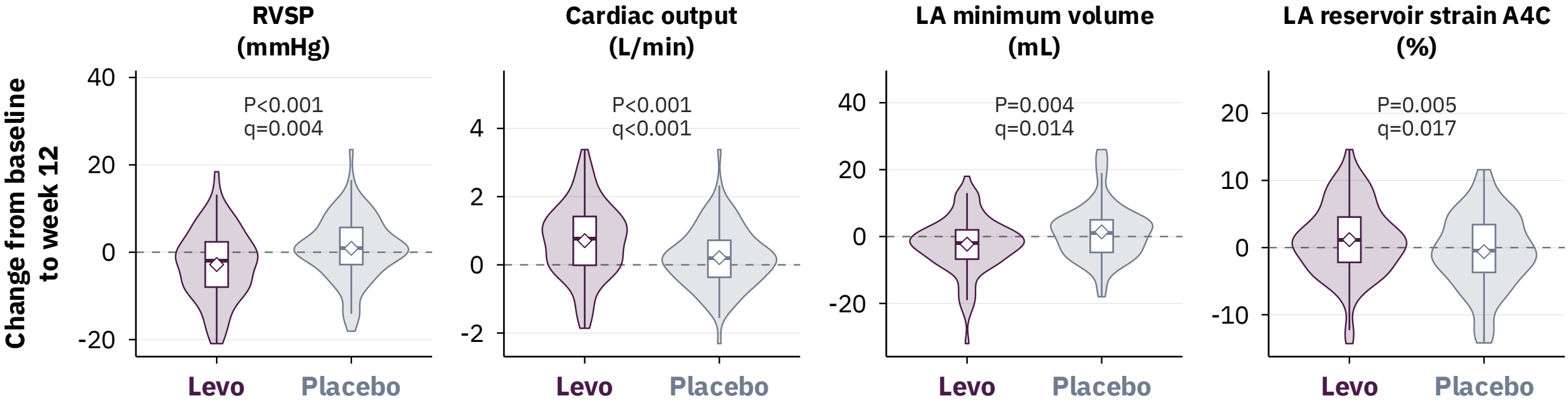
Endpoint	Levosimendan (n=120)	Placebo (n=121)	Mean difference (95% CI)	P-value
Geometric mean ratio of Week 12 to baseline NTproBNP	0.53	1.03	0.51 (0.43 to 0.60)	<0.0001





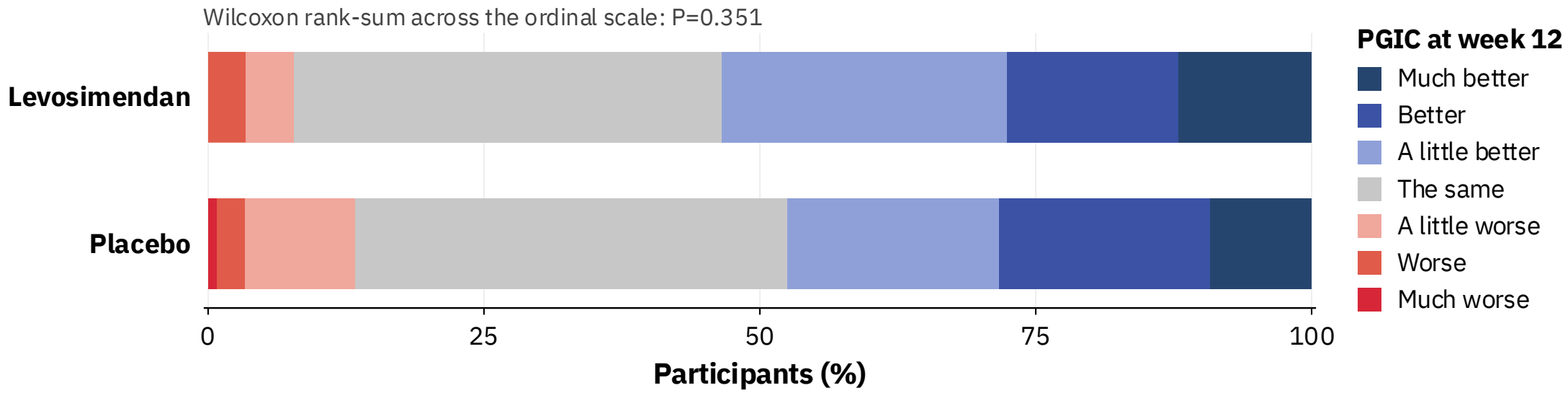
Levosimendan lowered RVSP by 3.5 mmHg

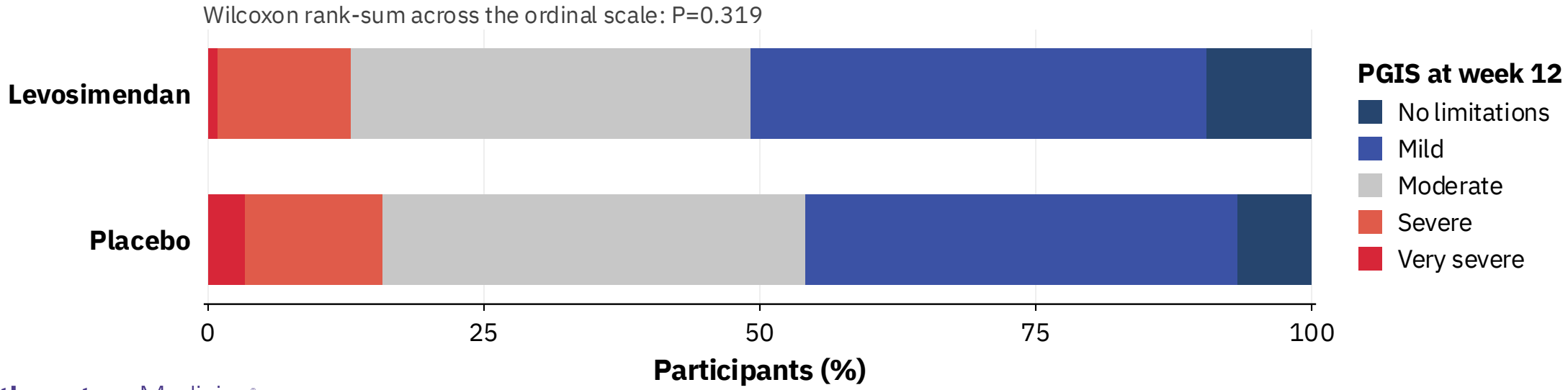
Endpoint	Levosimendan (n=120)	Placebo (n=121)	Mean difference (95% CI)	P-value
Change in RVSP — mm Hg	−3.6 ± 9.8	+0.5 ± 8.2	−3.5 (−6.0 to −1.1)	0.0045



LV structure, LV systolic function, LV diastolic function, LA size/function, RV systolic function, RV diastolic function, and RA size: all improved with levosimendan compared to placebo (P<0.05, corrected for multiple comparisons)

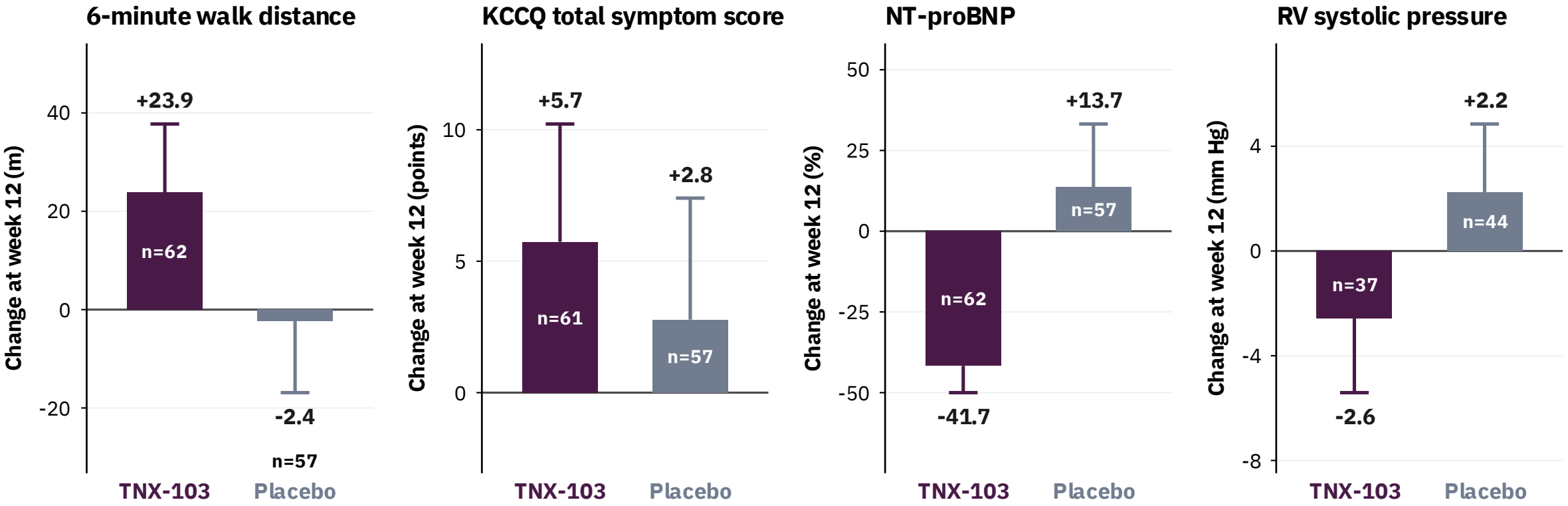
Patient global impression scales





Pre-specified subgroup:
Baseline 6MWD <333 meters

Baseline 6MWD below median (<333 m) subgroup



Metric	6MWD	KCCQ-TSS	NTproBNP	RVSP
Difference	+26.2 m	+3.0 points	Ratio 0.51	-4.8 mmHg
95% CI	+6.1, +46.3	-3.5, +9.4	0.41, 0.64	-8.7, -1.0
P-value	P=0.011	P=0.36	P<0.001	P=0.015

Safety results

Adverse events

Event – no. (%)	Levosimendan (n=120)	Placebo (n=121)
Any adverse event	104 (86.7)	87 (71.9)
Any serious adverse event	**13 (10.8)**	**13 (10.7)**
Related to trial drug	46 (38.3)	21 (17.4)
Led to dose reduction	18 (15.0)	5 (4.1)
Led to discontinuation	10 (8.3)	2 (1.7)
Death from any cause	**2 (1.7)**	**0**
Adverse events of special interest	11 (9.2)	7 (5.8)
New atrial fibrillation	4 (3.3)	1 (0.8)
Hypotension	3 (2.5)	5 (4.1)
Most common adverse events		
Headache	25 (20.8)	17 (14.0)
Palpitations	16 (13.3)	9 (7.4)
Diarrhea	15 (12.5)	5 (4.1)
Dizziness	14 (11.7)	9 (7.4)
Peripheral edema	12 (10.0)	6 (5.0)

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ePatch rhythm monitoring:

No differences between groups in ventricular arrhythmias or AF burden >1%

Levosimendan: Heart rate +6.7 bpm (95% CI 4.0 to 9.4) (placebo-corrected)

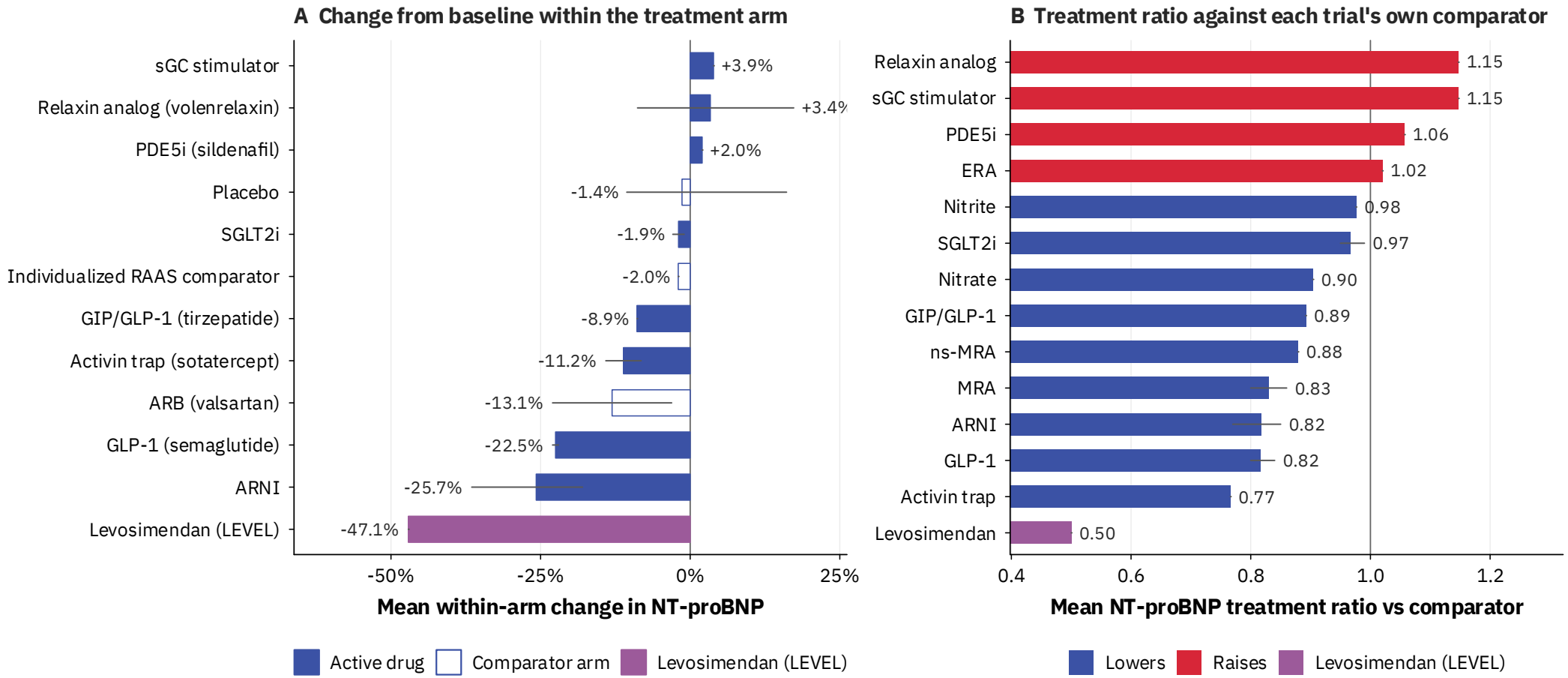

LEVEL: Conclusions

Conclusions

- **LEVEL enrolled a broad range of patients with symptomatic PH-HFpEF, with ↑PA pressures by invasive hemodynamics**
- **Over 12 weeks, levosimendan did not improve 6MWD or KCCQ-TSS, but ↓NTproBNP by ~50% and ↓RVSP by 3.5 mmHg**
  - ⇢ **Largest reduction in NTproBNP to date in a HFpEF RCT**
  - ⇢ **Magnitude of ↓NTproBNP and ↓PA pressure: Predicted to be associated with ↓↓HF events**

Conclusions

LEVEL: Largest ↓NTproBNP to date in HFpEF



Conclusions

- LEVEL
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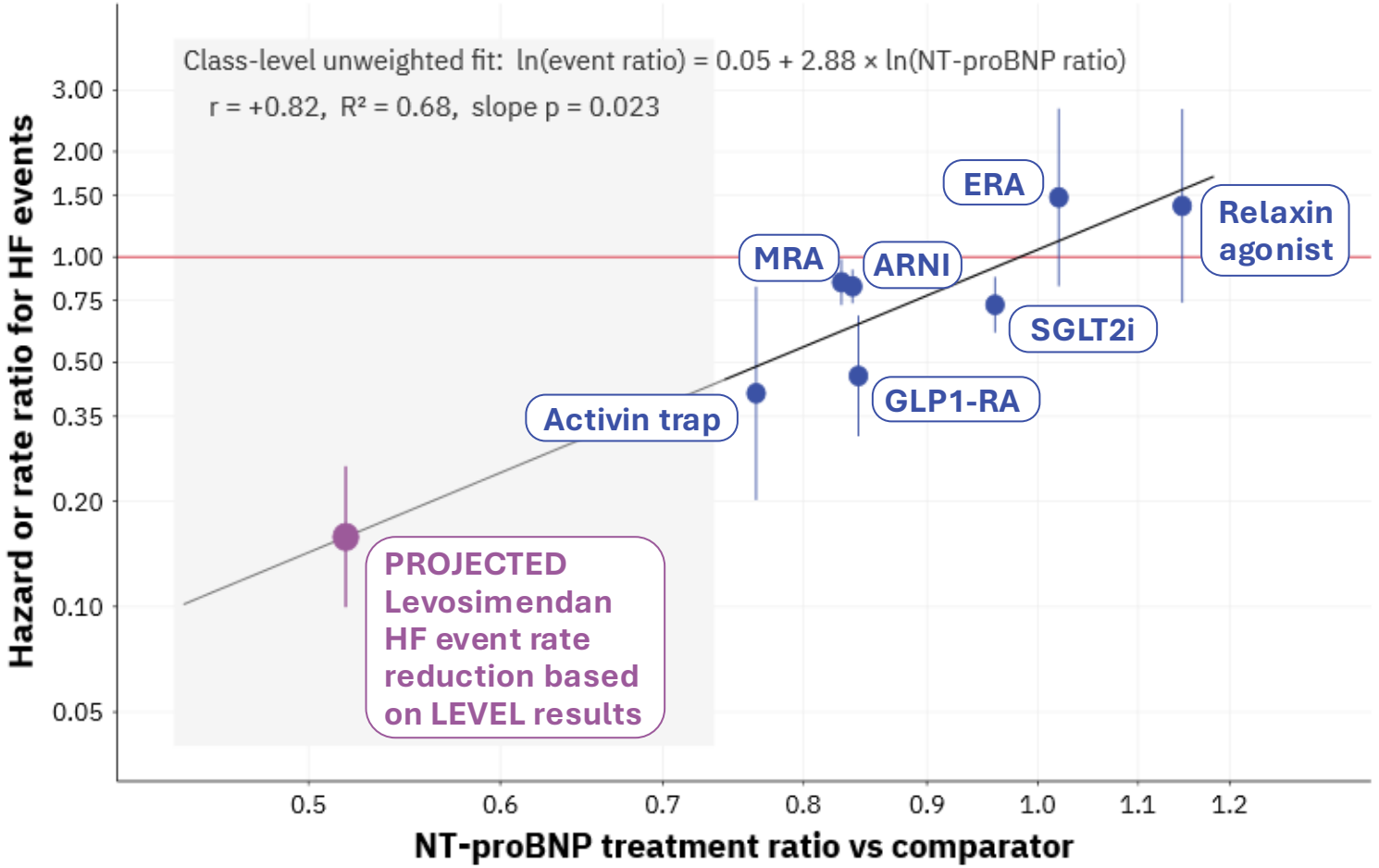
↓NTproBNP: Predicted effect on ↓HF events



Conclusions

- **Inverse linear relationship → baseline 6MWD vs. Δ6MWD:**
  - ⇢ **Lower baseline 6MWD = ↑levosimendan treatment effect**
- **Levosimendan:**
  - ⇢ **No excess of severe adverse events, no significant arrhythmias**
  - ⇢ **↑Adverse events, discontinuations compared to placebo**
  - ⇢ **↑Heart rate: likely therapeutic in PH-HFpEF**
- **Follow-up phase 3 LEVEL-2 RCT in PH-HFpEF is ongoing:**
  - ⇢ **Larger trial (n=540), 2:1 levosimendan/placebo**
  - ⇢ **Longer-follow-up (26 weeks for primary 6MWD endpoint)**
  - ⇢ **Additional follow-up to 52 weeks for events analysis**

LEVEL-2: NCT07288398

Thank you

- **LEVEL trial participants**
- **Site investigators and study teams**
- **Academic steering committee members:**

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