Pathophysiological Rationale and Clinical Evidence for Neurohormonal Modulation in Heart Failure with Preserved Ejection Fraction

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Supplementary Material

Supplementary Table 1: Phase II and III Clinical Trials on Neurohormonal Modulation Pharmacological Therapies in Heart Failure with Preserved Ejection Fraction.

Study acronym[ref]	Intervention Sample size Median follow-up	Main inclusion criteria	Main efficacy results	Effects on symptoms
Angiotensin converting-enzyme inhibitors				
PEP-CHF[1]	Perindopril (4 mg q.d.) vs. placebo n=850 Median f-up: 26.2 m	LV wall motion index ≥1.4 (~LVEF ≥40%), diastolic dysfunction, symptomatic HF treated with diuretics, CV hospitalisation <6 m, age ≥70 y	Primary endpoint (all-cause death, HHF): HR 0.92, 95% CI 0.70 to 1.21, p=0.545 Perindopril at 1 y follow-up: trend towards ↓primary endpoint (HR 0.69, 95% CI 0.47 to 1.01, p=0.055), ↓HF hospitalisations (HR 0.63, 95% CI 0.41 to 0.97, p=0.033)	Perindopril: ↓NYHA class (p=0.030) and ↑6MWD (p=0.011) at 1 y follow-up
Angiotensin receptor blockers				
CHARM-Preserved[2]	Candesartan (32 mg q.d.) vs. placebo n=3023 Median f-up: 36.6 m	LVEF >40%, NYHA II-IV, history of hospitalisation for cardiac reasons	Primary endpoint (CV death, HHF): HR 0.86, 95% CI 0.74 to 1.00, p=0.051, mainly driven by ↓HHF in candesartan group (230 vs. 279, p=0.017) Composite secondary endpoint (CV death, HHF, MI, stroke):	N/A

			HR 0.86, 95% CI 0.75 to 0.99, p=0.037	
I-PRESERVE[3]	Irbesartan (300 mg q.d.) vs. placebo n= 4128 Median f-up: 49.5 m	LVEF ≥45%, NYHA III-IV or NYHA II with HHF <6 m, age ≥60 y	Primary endpoint (all-cause death, CV hospitalisation): HR 0.95, 95% CI 0.86 to 1.05, p=0.35	Irbesartan: no improvement in MLHFQ
Mineralocorticoid receptor antagonists				
Aldo-DHF[4]	Spironolactone (25 mg q.d.) vs. placebo n=422 Median f-up: 12 m	LVEF ≥50%, NYHA II-III, peak VO_2 <25 mL/min/kg, diastolic dysfunction or AF, age ≥50 y	Co-primary endpoint (change in E/e'): adjusted mean difference -1.5, 95% CI -2.0 to -0.9, p<0.001 Co-primary endpoint (change in peak VO_2): adjusted mean difference +0.1 mL/min/kg, 95% CI -0.6 to +0.8, p=0.81 Spironolactone: ↓LVMi (p=0.009), ↓NT-proBNP (p=0.03)	Spironolactone: ↓6MWD (p=0.03), no improvement in NYHA class or QoL
TOPCAT[5]	Spironolactone (up to 45 mg q.d.) vs. placebo	LVEF ≥45%, ≥1 HF sign, ≥1 HF symptom, HHF <12 m or BNP ≥100 ng/L or NT-	Primary endpoint (CV death, aborted cardiac arrest, HHF):	N/A

	n=3445 Median f-up: 40 m	proBNP ≥360 ng/L, age ≥50 y	HR 0.89, 95% CI 0.77 to 1.04, p=0.14 Spironolactone: ↓HHF (HR 0.83, 95% CI 0.69 to 0.99, p=0.04)	
Angiotensin receptor-neprilysin inhibitors				
PARAMOUNT[6]	S/V (up to 97/103 mg b.i.d.) vs. valsartan (up to 160 mg b.i.d.) n=301 Median f-up: 36 w	LVEF ≥45%, NYHA II-III, NT-proBNP >400 ng/L	Primary endpoint (ΔNT-proBNP up to 12 w): ratio 0.77, 95% CI 0.64 to 0.92, p=0.005 S/V: ↓LA dimension (p=0.03) and ↓LA volume index (p=0.007)	S/V: improvement in NYHA class at 36 w (p=0.05), no improvement in KCCQ score
PARAGON-HF[7]	S/V (up to 97/103 mg b.i.d.) vs. valsartan (up to 160 mg b.i.d.) n=4822 Median f-up: 35 m	LVEF ≥45%, NYHA II-IV, NT-proBNP >300 ng/L (>900 if in AF; >200 or >600 if hospitalised within 9 months in SR or AF)	Primary endpoint (CV death, HHF): RR 0.87, 95% CI 0.75 to 1.01, p=0.06 S/V: trend towards ↓HHF (RR 0.85, 95% CI 0.72 to 1.00), ↑nephroprotection (composite of ≥50% eGFR reduction, ESRD, death from renal causes: HR 0.50, 95% CI 0.33 to 0.77, p=0.001)	S/V: ↑NYHA (OR 1.45, 95% CI 1.13 to 1.86), ↓KCCQ-CSS decline (between-group difference 1.0 points, 95% CI 0.0 to 2.1)

PARALLAX[8]	S/V (up to 97/103 mg b.i.d.) vs. either placebo or enalapril (up to 10 mg b.i.d) or valsartan (up to 160 mg b.i.d) n=2572 Median f-up: 24 w	LVEF ≥40%, NYHA II-IV, structural heart disease, NT-proBNP >220 ng/L (>600 if in AF)	Primary endpoint (ΔNT-proBNP at 12 w): adjusted geometric mean ratio 0.84, 95% CI 0.80 to 0.88, p<0.001	S/V: no improvement in 6MWD at 24 w (co-primary endpoint), KCCQ-CSS or NYHA class
Cyclic guanosine monophosphate modulators				
NEAT-HFpEF[9]	ISMN (30 mg daily up to 120 mg daily) vs. placebo n=110 Median f-up: 6 w	LVEF >50%, objective evidence of HF	Primary endpoint (daily activity level as average daily accelerometer units): −381 accelerometer units, 95% CI −780 to 17, p=0.06 ISMN: ↓hours of daily activity (p=0.02); ↓activity levels progressively with increased doses	ISMN: no improvement in 6MWD and QoL scores
RELAX[10]	Sildenafil (20 mg t.i.d. up to 60 mg b.i.d.) vs. placebo	LVEF ≥50%, NYHA II-IV, peak VO_2 ≤60% of reference values, NT-proBNP ≥400	Primary endpoint (Δpeak VO_2 at 24 w): -0.20 (1.70 to 1.11) vs. -0.20 (0.70 to 1.00), p=0.90	Sildenafil: no improvement in 6MWD and clinical status rank score

	n=216 Median f-up: 24 w	ng/L or PCWP >20 mmHg at rest (>25 mmHg with exercise)		
DILATE-1[11]	Riociguat (0.5, 1, 2 mg) vs. placebo n=36 Median f-up: 6 h	LVEF >50%, mPAP ≥25 mmHg, PCWP >15 mmHg	Primary endpoint (ΔmPAP at 6 h): difference riociguat 2 mg vs. placebo 1.2 mmHg, 95% CI -2.9 to 5.2, p=0.60 Riociguat 2 mg: ↑SV (p=0.04), ↓SBP (p=0.03), ↓RV end-diastolic area (p=0.04). No significant changes in heart rate, PCWP, transpulmonary pressure gradient, PVR	N/A
SOCRATES-PRESERVED[12]	Vericiguat (1.25 mg or 2.5 mg q.d. or 10 mg q.d.) vs. placebo n=477 Median f-up: 12 w	LVEF ≥45%, NYHA II-IV, ≤4 weeks from HF decompensation, BNP ≥100 ng/L (≥200 if in AF) or NT-proBNP ≥300 ng/L (≥600 if in AF), LA enlargement	Co-primary endpoint (ΔNT-proBNP at 12 w): mean difference 1.15 ng/L, 90% CI 0.96 to 1.37, p=0.20 Co-primary endpoint (ΔLA volume at 12 w): mean difference 1.63 mL, 90% CI -1.36 to 4.62, p=0.37	Vericiguat: ↑KCCQ at 12 w (mean difference: 9.2 points, p=0.02)

VITALITY-HFpEF[13]	Vericiguat (10 mg q.d or 15 mg q.d.) vs. placebo n=789 Median f-up: 24 w	LVEF ≥45%, NYHA II-III, ≤6 months from HF decompensation, BNP ≥100 ng/L (≥200 if in AF) or NT-proBNP ≥ 300 ng/L (≥ 600 if in AF), LA enlargement or LVH	Primary endpoint (ΔKCCQ-PLS at 24 w): least-squares mean difference for vericiguat 15 mg −1.5 points (95% CI −5.5 to 2.5, p=0.47), for vericiguat 10 mg −0.5 points (95% CI −4.6 to 3.5,p=0.80)	Vericiguat: no improvement in 6MWD at 24 w

6MWD = 6-minute walking distance; AF = atrial fibrillation; b.i.d = *bis in die* (twice daily); BNP = B-type natriuretic peptide; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; f-up = follow-up; HF = heart failure; HHF = heart failure hospitalisation; HR = hazard ratio; ISMN = isosorbide mononitrate; KCCQ-CCS/PLS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score/Physical Limitation Score; LA = left atrial; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMi = left ventricular mass index; MI = myocardial infarction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; mPAP = mean pulmonary artery pressure; N/A = not available; NT-proBNP = N-terminal fraction of pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; q.d. = *quaque die* (once daily); QoL = quality of life; RR = risk ratio; RV = right ventricle; SBP = systolic blood pressure; SR = sinus rhythm; S/V = sacubitril/valsartan; SV = stroke volume.

References

1. Cleland JGF, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;27:2338–45. https://doi.org/10.1093/eurheartj/ehl250; PMID: 16963472.

2. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777–81. https://doi.org/10.1016/S0140-6736(03)14285-7; PMID: 13678871.

3. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;359:2456–67. https://doi.org/10.1056/NEJMoa0805450; PMID: 19001508.

4. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;309:781–91. https://doi.org/10.1001/jama.2013.905; PMID: 23443441.

5. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;370:1383–92. https://doi.org/10.1056/NEJMoa1313731; PMID: 24716680.

6. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;380:1387–95. https://doi.org/10.1016/S0140-6736(12)61227-6.

7. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;381:1609–20. https://doi.org/10.1056/NEJMoa1908655; PMID: 31475794.

8. Pieske B, Wachter R, Shah SJ, et al. Effect of Sacubitril/Valsartan vs standard medical therapies on plasma NT-proBNP concentration and submaximal exercise capacity in patients with heart failure and preserved ejection fraction: the PARALLAX randomized clinical trial. *JAMA* 2021;326:1919–29. https://doi.org/10.1001/jama.2021.18463; PMID: 34783839.

9. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015;373:2314–24. https://doi.org/10.1056/NEJMoa1510774; PMID: 26549714.

10. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013;309:1268–77. https://doi.org/10.1001/jama.2013.2024; PMID: 23478662.

11. Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. Acute hemodynamic effects of Riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. *Chest* 2014;146:1274–85. https://doi.org/10.1378/chest.14-0106; PMID: 24991733.

12. Pieske B, Maggioni AP, Lam CSP, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (Socrates-PRESERVED) study. *Eur Heart J* 2017;38:1119–27. https://doi.org/10.1093/eurheartj/ehw593; PMID: 28369340.

13. Armstrong PW, Lam CSP, Anstrom KJ, et al. Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. *JAMA* 2020;324:1512–21. https://doi.org/10.1001/jama.2020.15922; PMID: 33079152.