**A roadmap for therapeutic discovery in pulmonary hypertension associated with left heart failure. A scientific statement of the Heart Failure Association (HFA) of the ESC and the ESC Working Group on Pulmonary Circulation & Right Ventricular Function**

Ameri P, Mercurio V, Pollesello P, Anker MS, Backs J, Bayes-Genis A, Borlaug BA, Burkhoff D, Caravita S, Chan SY, De Man F, Giannakoulas G, Gonzalez A, Guazzi M, Hassoun PM, Hemnes AR, Maack C, Madden B, Melenovsky V, Müller OJ, Papp Z, Pullamsetti SS, Rainer PP, Redfield MM, Rich S, Schiattarella GG, Skaara H, Stellos K, Tedford RJ, Thum T, Vachiery JL, van der Meer P, Van Linthout S, Pruszczyk P, Seferovic P, Coats AJS, Metra M, Rosano G, Rosenkranz S, Tocchetti CG

**Supplementary material**

**Supplementary Table 1.**

**Clinical trials evaluating HF drugs for treatment of PH-LHF.**

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| --- | --- | --- | --- | --- | --- | --- |
| First author, year, acronym,  NCT | Study intervention | Study  design and duration | N. of pts/ LHF type | PH definition for inclusion | Primary and  secondary outcomes | Main  results |
| Zern EK, 2021  [1] | Sacubitril/ valsartan 24/26 mg BID  Oral | Monocentric,  single-arm,  open-label | 5 pts /  end- stage HFrEF awaiting transplantation | sPAP >60 mmHg and/or PVR >3 WU at RHC  RHC data: yes | Efficacy of ARNI in patients with end-stage HFrEF and PH awaiting transplantation; probability of developing PH after heart transplantation | Reduction of sPAP and PVR  4/5 patients received heart transplantation and did not developed PH after surgery |
| Zhao Y, 2021  [2] | Sacubitril/ valsartan 24/26 mg BID vs enalapril 10 mg OD  Oral | Two-center,  randomized,  open-label /  6 mo | 97 pts / LVEF <40% | sPAP >50 mmHg and/or peak TRV >3.4 m/s at TTE  RHC data: no | Primary: changes in TAPSE/sPAP ratio and in TAPSE  Secondary: SAE  Ancillary: changes in TTE parameters, 6MWD, and NT-proBNP | Improvement in TAPSE/sPAP ratio, TAPSE, and LVEF  Improvement in 6MWD and NT-proBNP  NS differences in SAE |
| Codina P, 2022  [3] | CardioMEMS implantation → sacubitril/ valsartan, mean dose 282 ± 127 mg daily  Oral | Single‐arm, interventional /  18 weeks (6 weeks after CardioMEMS implantation, 6 weeks of ARNI treatment, 6 weeks after ARNI suspension) | 14 pts /  LVEF >45% | mPAP >20 mmHg during the 7 days prior enrollment, including ≥5 measurements per day  RHC data: no  (but data from CardioMEMS) | Primary: changes in mPAP  Secondary: changes in systolic and diastolic PAP, E/e′ and left atrium diameter index; changes in daily diuretic dose; changes in 6MWD, B‐line sum at lung ultrasonography, changes in KCCQ and EQ‐VAS questionnaire; changes in NT‐proBNP, CA‐125, ST2, and hs‐TnT | Decrease in mPAP Improvement in 6MWD, B‐lines, and quality of life  NS differences in diuretic dose |
| Ge T, 2022  [4] | Dapaglifozin + sacubitril/ valsartan  vs sacubitril/ valsartan  (doses not specified)  Oral | Monocentric, randomized, double-blind /  6 months | 120 pts / left heart disease | Not specified  RHC data: not specified | Changes in TTE parameters (such as LV end-diastolic and end-systolic diameters), 6MWD and serum levels of ET-1, NO, NT-proBNP, C-reactive protein, IL-6, and TNF-α | Both groups had improvement in LVEF, LV morphology, pulmonary hemodynamics, exercise capacity and serum biomarkers, but amelioration of LV volumes, LVEF, mPAP, sPAP, decrease in ET-1, NT-proBNP, C-reactive protein, IL-6, TNF-α, and increase in plasma NO were greater in the dapagliflozin + ARNI group |

6MWD, 6-minute walking distance; ARNI, angiotensin receptor‐neprilysin inhibitor; BID, bis in die (twice a day); EQ-VAS, EuroQol visual analogue scale; ET-1, endothelin-1; HFrEF, heart failure with reduced ejection fraction; hs-TnT, high-sensitivity troponin T; IL-6, interleukin-6; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; mo, months; mPAP, mean pulmonary arterial pressure; NCT, identifier number on clinicaltrials.gov; NO, nitric oxide; NS, non-significant; NT-proBNP, N-Terminal pro-B-type natriuretic peptide; OD, once a day; pts, patients; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SAE, severe adverse event; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TNF-α, tumor necrosis factor alpha; TRV, tricuspid regurgitation velocity; TTE, transthoracic echocardiography; WU, Wood units.

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