**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 BIDOral | Monocentric,single-arm,open-label | 5 pts / end- stage HFrEF awaiting transplantation | sPAP >60 mmHg and/or PVR >3 WU at RHCRHC 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 ODOral | Two-center, randomized, open-label / 6 mo | 97 pts / LVEF <40% | sPAP >50 mmHg and/or peak TRV >3.4 m/s at TTERHC data: no | Primary: changes in TAPSE/sPAP ratio and in TAPSESecondary: SAEAncillary: changes in TTE parameters, 6MWD, and NT-proBNP | Improvement in TAPSE/sPAP ratio, TAPSE, and LVEFImprovement in 6MWD and NT-proBNP NS differences in SAE |
| Codina P, 2022[3] | CardioMEMS implantation → sacubitril/ valsartan, mean dose 282 ± 127 mg dailyOral | 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 mPAPSecondary: 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 lifeNS differences in diuretic dose |
| Ge T, 2022[4] | Dapaglifozin + sacubitril/ valsartanvs 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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