JMS Journal of Medical Science

Pulmonary Resistance Modification under treatment with Sacubitril/valsartan in Patients with Heart Failure with reduced ejection fraction (PRESENT-HF) - Study protocol and rationale for a multicentre randomised controlled trial

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https://doi.org/10.20883/medical.e1332

Keywords: HFrEF, ARNI, sacubitril/valsartan, pulmonary hypertension, pulmonary hypertension due to left heart disease

Received 2025-07-01
Accepted 2025-10-10
Published 2025-12-31

How to Cite: Straburzyńska-Migaj E, Dudek M, Migaj J, Bartczak-Rutkowska A, Hiczkiewicz J, Cygański P, Tycińska A, Gierlotka M, Kozielska-Nowalany E, Kubica J, Tomaszewska M, Sawiński P, Paluszkiewicz L, Lesiak M, Kałużna-Oleksy M. Pulmonary Resistance Modification under treatment with Sacubitril/valsartan in Patients with Heart Failure with reduced ejection fraction (PRESENT-HF) - Study protocol and rationale for a multicentre randomised controlled trial. Journal of Medical Science. 2025 December;94(4);e1332. https://doi.org/10.20883/medical.e1332

ABSTRACT

Introduction. Heart failure with reduced ejection fraction (HFrEF) remains a major clinical challenge, partly due to suboptimal implementation of guideline-directed medical therapy and complications such as pulmonary hypertension (PH) that worsen symptoms and prognosis.

Material and methods. PRESENT-HF (ClinicalTrials.gov Identifier: NCT05487261, https://clinicaltrials.gov/ct2/show/NCT05487261) is a multicenter, randomised, double-blind, comparator-controlled clinical trial investigating whether sacubitril/valsartan, compared to enalapril, lowers pulmonary artery pressure and pulmonary vascular resistance as measured by right heart catheterisation in patients with HFrEF and secondary PH. The study will recruit approximately 230 patients, with a 1:1 randomisation to either sacubitril/valsartan or enalapril, and a 52-week follow-up that includes both in-hospital and out-of-hospital treatment phases.

Results. The primary endpoint is the change from baseline in mean pulmonary artery pressure and pulmonary vascular resistance; secondary outcomes include clinical events, quality of life, functional capacity, and safety.

Conclusions. This trial will offer new insights into targeted strategies for improving outcomes in patients with HFrEF complicated by PH, potentially expanding treatment options and informing future guidelines.

Introduction

Despite massive progress in the treatment of heart failure with reduced ejection fraction (HFrEF), prognosis and quality of life (QoL) are still poor. The reasons for this situation are multiple, including poor implementation of guideline-directed medical therapy (GDMT) and multimorbidity in many patients. A special problem in many patients is pulmonary hypertension (PH) associated with heart failure (HF), the true prevalence of which is unknown. It is estimated primarily based on indirect echocardiographic assessment [1,2]. Pulmonary hypertension related to left heart disease (PH-LHD) is the most prevalent among patients with PH and is related to a worse prognosis. A critical issue is PH in patients being evaluated for heart transplantation, as high pulmonary vascular resistance (PVR) is a contraindication for the procedure. Pulmonary hypertension in HFrEF has garnered the interest of numerous researchers investigating its pathophysiology and potential treatment. It is known that specific pharmacological agents used for Pulmonary Arterial Hypertension are contraindicated in the PH-LHD study, which aims to assess the effects of angiotensin receptor-neprilysin inhibitor (ARNI) treatment on RHC parameters in patients with HFrEF and secondary PH.

Methods and analysis

Trial design

PRESENT-HF is a multicenter, randomised, double-blind, comparator-controlled clinical trial that will include patients with chronic HFrEF (ClinicalTrials.gov Identifier: NCT05487261). Approximately 260 participants will be screened, resulting in around 230 patients being randomised across five centres. Subjects will be randomised to receive either an investigational medicinal product – sacubitril/valsartan or a comparator, enalapril.

The study will consist of 5 phases:

- Screening (Vs),
- Randomisation (V0 – day 0) – the eligible patients will be randomly assigned (1:1) to the intervention or comparator arms,
- In-hospital initiation of therapy (with wash-out strategy) (from day 0 to the day of discharge),
- Out-of-hospital phase – increasing the dose of the drug (up-titration phase),
- Out-of-hospital and hospital phase – follow-up on the target dose.

The observation period will span 52 weeks, consisting of a 4-week active up-titration phase followed by 48 weeks of follow-up (see **Figure 1**). Functional capacity is assessed by 6-minute walk distance, New York Heart Association

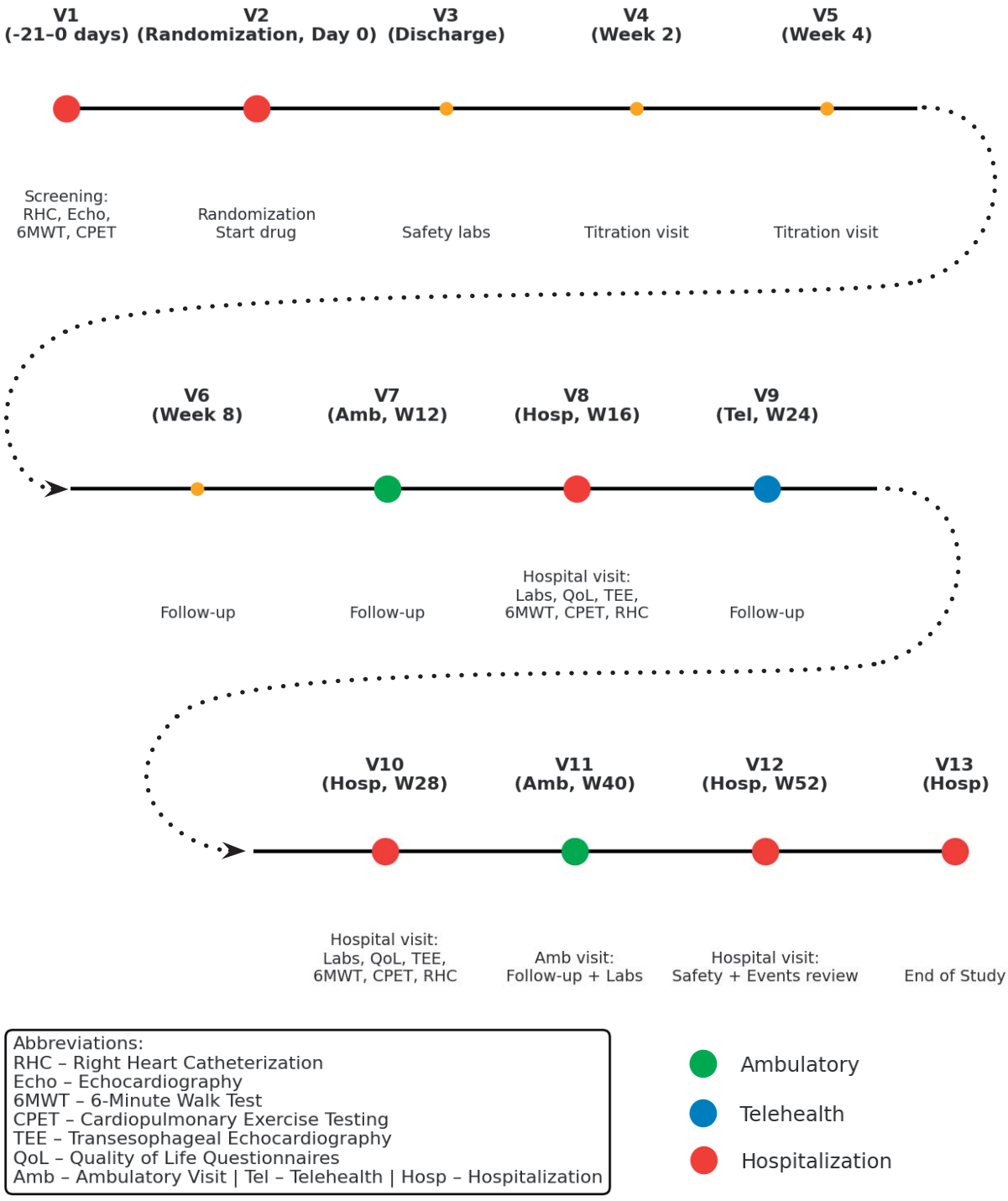

Figure 1. Present-HF: Visit Schedule (V1-V13) with Abbreviations Legend.

(NYHA) class (secondary endpoints) and cardiopulmonary exercise testing (CPET) as exploratory outcomes, with centralised analysis.

Primary and secondary objectives

The trial's objective is to assess the effect of sacubitril/valsartan therapy in comparison to angiotensin-converting enzyme inhibitors (ACE--I) – enalapril, on the parameters of right heart catheterisation in terms of reduction of pulmonary artery pressure (PAP) and PVR in patients with developed PH due to HfrEF.

Secondary objectives are to assess the treatment efficacy as evaluated by the incidence

of major adverse cardiac and cerebrovascular events (MACCE) as a composite endpoint, and separately, to determine the quality of life, and treatment safety and tolerance – assessment of Adverse Events (AE) and Serious Adverse Events (SAE) and their assessment in terms of severity and relationship to the tested substance. Additionally, as part of the exploratory part of the study, the influence of therapy on the selected biomarkers will be analysed.

The primary endpoint for efficacy assessment will be the change from baseline in mean pulmonary artery pressure (mPAP) and PVR.

Secondary endpoints:

1. Change from baseline in pulmonary wedge pressure (PWP) – measured by RHC.
2. Change from baseline in the diastolic pressure gradient (DPG; where DPG = diastolic mPAP – mean PWP).
3. Change meters from baseline in the 6-minute walk test (6MWT).
4. Evaluation of the parameters of the cardiopulmonary exercise test – peak VO_2, VE/VCO_2 slope.
5. Assessment of echocardiographic parameters (LVEF, LV volumes, TAPSE, RV function indices, estimated sPAP).
6. The incidence of the composite endpoint of MACCEs, such as death from all causes, cardiac death, hospitalisation due to worsening/decompensation of HF, heart transplantation, and the need for a left ventricular or biventricular assist device.
7. Hospitalisation or an unplanned visit to an Emergency Department or an unplanned outpatient visit related to HF.
8. The need for an unplanned intravenous administration of diuretics and/or an unplanned hospitalisation, an outpatient visit due to the need to administer intravenous diuretics or requiring an increase in the dose of diuretics >50% from baseline.
9. Quality of life assessment will be conducted between 0-52 weeks – Kansas City Cardiomyopathy Questionnaire (KCCQ-12), WHO (WHOQOL-BREF), SF-36 questionnaire, EQ-5D-3L questionnaire.
10. Assessment of the New York Heart Association (NYHA) classes – change from baseline.

Sample size calculation

Estimating the proportion of patients meeting the study criteria in the general population is difficult. According to the 2016 report of the Heart Failure Section of the Polish Cardiac Society, there are about 1.2 million patients with HF in Poland (2.6% of the population), with 220,000 new cases annually. Pulmonary hypertension occurs in 12–38% of HF patients, nearly half due to HfrEF, giving an estimated study-eligible population of up to 200,000 (0.5–1% of the general population).

Sample size calculations were based primarily on the primary endpoint, PVR (expected reduction from 2 to 1 Wood unit, SD 1), giving a minimum of 23 patients. Additional calculations were performed for 6MWT (n = 86 for a 50 m improvement) and for MACCE analysis using survival models (n = 89 for survival 0.90 vs. 0.70, expected deaths = 35). Taking all endpoints and potential data loss into account, the required sample size was set at 230 patients (including 5% dropout)

Study population – inclusion and exclusion criteria

The study population will consist of patients of both sexes aged 18 years or older with HFrEF in NYHA class II-IV functional classes, who have been diagnosed and treated for at least 3 months before inclusion in the study, and in whom the suspicion of PH has been confirmed based on right heart catheterisation. Participants will be recruited from five tertiary referral cardiology centres in Poland. Eligible patients are identified during routine care or planned hospitalisations for HF diagnostic evaluation. Before randomisation, all participants must undergo right heart catheterisation (RHC) to confirm pulmonary hypertension (PH). Recruitment will be coordinated centrally to ensure standardised screening, consent, and data collection procedures across sites. Patients will meet all inclusion criteria and do not meet any exclusion criteria (see **Supplementary Table 1**). The original definition of PH used a mean pulmonary artery pressure (mPAP) ≥25 mmHg; hence, according to the ESC 2022 guidelines, PH is diagnosed when mPAP is >20 [3].

Treatment protocol – interventional methods

Randomisation process will be performed centrally via an electronic automatic system IVRS as a part of eCRF. Numbered study treatment packs

will contain either IMP (S/V) or comparator (enalapril) according to a computer-generated randomisation plan. Each eligible subject will be randomly assigned to either active treatment (S/V) or comparator (enalapril) using a validated, centralised procedure via eCRF, which automates the random assignment of treatment groups to randomisation numbers (see **Figure 2**). Subject randomisation (1:1) will be determined by an algorithm including a random variable and accounting for the following stratification factors: sex, age (<70 years/≥70 years), HF aetiology (ischemic/ non-ischemic), HF duration (newly diagnosed at Index hospitalisation/known documented HF before Index hospitalisation). Eligible participants are randomised 1:1 to receive either sacubitril/valsartan (S/V) or enalapril. For patients previously treated with ACE inhibitors, a 36-hour washout is mandatory before the first S/V dose (see **Figure 2**). After the patient's last dose of the current therapy, randomisation occurs at Visit 2 (V2). A 36-hour washout period is required before the patient takes the first dose of the new investigational product (IP). Discharge is possible at least six hours after the first IP administration.

Dose adjustments are based on blood pressure, renal function, and potassium levels, which are assessed at each visit. Temporary down-titration is permitted for symptomatic hypotension, worsening renal function, or hyperkalemia.

Administration

Study medications are given orally, twice daily, in the morning and evening, preferably at the exact times each day. Patients are instructed to take doses with water, with or without food.

Follow-Up Schedule

- **In-hospital phase:** Initiation under supervision, with discharge allowed ≥6 hours after first dose if stable.
- **Outpatient phase:** Visits at 2 and 4 weeks for dose titration, then every 3 months until week 52.

Background therapy

All enrolled patients will be treated in accordance with the current ESC guidelines and receive standard chronic HF treatment. GDMT includes beta-blockers, diuretics, ACE-I or ARB, mineralocor-

Dosing and Up-Titration

Study Arm	Starting Dose	Titration Schedule	Target Dose
Sacubitril/Valsartan	24/26 mg twice daily (or 49/51 mg twice daily if baseline SBP ≥110 mmHg and eGFR ≥60 mL/min/1.73m²)	Dose doubled every 2 weeks as tolerated	97/103 mg twice daily
Enalapril	2.5–5 mg twice daily	Dose doubled every 2 weeks as tolerated	10 mg twice daily

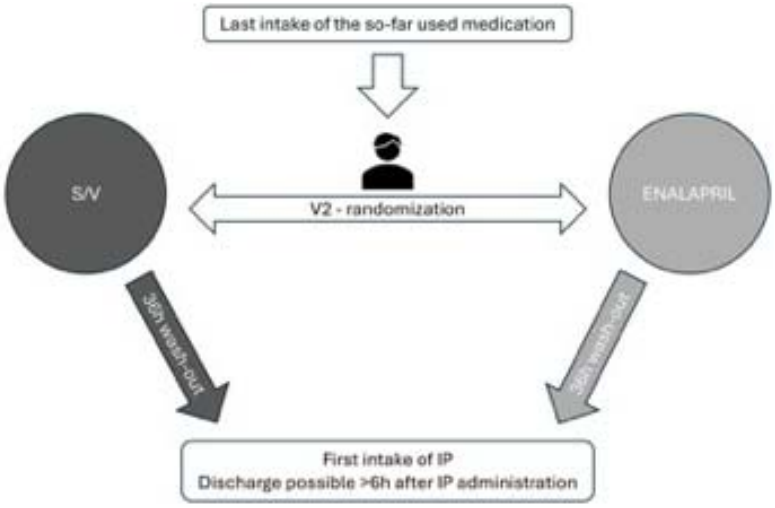

Figure 2.

ticoid receptor antagonists (MRA), and sodium--glucose cotransporter-2 inhibitors (SGLT2-I), if those above are not contraindicated. In patients with atrial fibrillation and/or coronary artery disease, the current standard therapy will be continued.

Ethical issues

This clinical trial received approval from the Ethics Committee of the Medical University of Poznań, Poland (approval number: 77/21, 4 Feb 2021).

The study will be conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, European Directive 2001/20/EC, the Act of 6 September 2001 on Pharmaceutical Law in Poland, and applicable local health laws and authorities, as well as the Ethics Committee requirements.

Results

Statistical analysis

All data collected will be analysed descriptively. Standard descriptive statistical methods, including the number of patients, arithmetic mean, standard deviation, upper and lower quartiles, minimum, median and maximum, will be applied. For categorical variables, tables of frequencies (both absolute and relative) will be presented. The number of patients for whom the data are missing will be provided where appropriate.

Reported adverse events and comorbidities will be coded using the MedDRA dictionary (a version current at the time of the study initiation), and all adverse event summaries will present preferred terms and System Organ Class.

All data up to the time of study completion or withdrawal will be included in the analysis, regardless of treatment duration.

Results will be compared between study arms. For continuous outcomes, distribution will be first tested for normality using the Shapiro-Wilk test. Then, Student's t-test will be used to compare the distribution of normally distributed variables between study arms, and the Mann-Whitney test will be used otherwise. For categorical outcomes, Fisher's exact test of chi-squared test will be used, depending on the expected sizes of the categories. Time-to-event data will be analysed using survival analysis methods. Specifically, survival curves will be estimated using the Kaplan-Meier method and compared between study arms using the log-rank test.

Additionally, the effect of treatment (study arm) on the risk of event occurrence will be assessed using Cox regression. The level of statistical significance will be set at 0.05. Two-sided tests will be used.

Safety monitoring

All patients involved in the study will be monitored according to the visit schedule. On each visit, the patient will have blood samples taken for laboratory tests, among others, for creatinine and electrolytes. The dose level received by the patient will depend on the mean values of the systolic blood pressure (SBP), which is assessed on each visit.

The administration of the study medication will be stopped when any of the following occurs: significant, symptomatic and persistent hypotension (SBP<=90 mmHg), worsening of renal function (defined as an increase in serum creatinine ≥0.5 mg/dL and/or worsening of eGFR ≥ 25%) or development of hyperkaliemia (defined as K ≥ 5.5mEq/L/L). All adverse events that could be potentially associated with the drug will be identified and reported in the form of AE and SAE reports, in accordance with the ICH guideline for Good Clinical Practice. Additionally, the study will be monitored by an Independent Data Monitoring Committee (IDMC), which will also provide a therapy safety assessment throughout the entire study duration.

Discussion

Pulmonary hypertension associated with HFrEF influences symptoms, QoL and prognosis. The original definition of PH used a mean pulmonary artery pressure (mPAP) ≥25 mmHg. Findings from extensive studies have shown, for the first time, that a significant increase in mortality and hospitalisation risk arises in patients with mPAP > 20 mmHg. Hence, according to the ESC 2022 guidelines, PH is diagnosed when mPAP is greater than 20 mmHg [7]. However, despite this, there is still no specific treatment for PH-LHD. One of

the promising drugs is sacubitril/valsartan. S/V combines the effects of an angiotensin receptor blocker with a neprilysin inhibitor, which enhances the activity of the natriuretic peptide system and other vasoactive peptides, thus strengthening the protective effect of endogenous natriuretic peptides in the treatment of HF, an ARNI, functions as an activator of particulate guanylyl cyclase, leading to increased levels of vasoactive peptides and belongs to the peptide signal cascade through cyclic guanosine monophosphate (cGMP), producing significant antimitogenic and vasodilatory effects [10,11].

The main clinical confirmation of the effectiveness of S/V was provided by the PARADIGM--HF study from 2014, which showed that S/V was superior to enalapril in reducing the risk of death and hospitalisation for heart failure. It received the first class of recommendation, hence it constitutes the basic treatment for patients with HFrEF. However, no study has confirmed the influence of ARNI on PH that can complicate the course of HFrEF. There is no specific treatment for PH in HF.

According to the Prospective comparison of an ARNI with an ACE-I to Determine the Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF)[10] trial, the S/V in comparison with enalapril showed a robust 20% relative risk reduction in cardiovascular mortality and hospitalization due to worsening of HF among the ambulatory HF patients with a left ventricular ejection fraction (LVEF) ≤40% (i.e., changed to ≤35% by an amendment to the protocol midtrial) and New York Heart Association functional class II-IV symptoms.

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with S/V had been crossed, resulting in a reduction in the primary outcome in the study group.

Scientific reports indicate that S/V, in the absence of targeted therapy for PH-LHD, appears to improve outcomes in these patients significantly. The beneficial effects of NPs occur through a complex signalling system, which induces direct vasodilation, increases glomerular filtration, promotes natriuresis, reduces renin secretion, and exhibits antihypertrophic and antifibrotic myocardial effects.

Most of the evidence supporting the effects of S/V on PH derives from experimental and echocardiographic studies, mostly retrospective. In experimental studies of pulmonary hypertension in rats, treatment with S/V, but not valsartan, resulted in a significant reduction in right ventricular (RV) pressure (62 ± 4 vs. 46 ± 5 mmHg) compared with the placebo. This was associated with reduced pulmonary vascular wall thickness, increased lung levels of atrial natriuretic peptide, brain natriuretic peptide, and cGMP, and decreased plasma endothelin-1 levels. S/V reduces pulmonary pressures, vascular remodelling, and RV hypertrophy in a rat model of PH. It is suggested that it may be appropriate for the treatment of pulmonary hypertension and RV dysfunction [5].

In another experimental study in which rats were treated with monocrotaline or a hypoxic environment for 14 days to induce PH, S/V was given thereafter for the next 14 days. This study indicated that S/V reduced pulmonary pressure, adverse vascular remodelling and right ventricular hypertrophy in rats [14].

In the retrospective observational study of 93 patients with HFrEF with RV dysfunction based on echocardiographic parameters, it was found that S/V treatment was associated with significant improvements in the following RV function indicators: tricuspid annular plane systolic excursion, tri, including cuspid annular s' peak velocity (S'), RV fractional area change, and pulmonary artery systolic pr[15]. The authors suggested that this improvement may be independent of left heart dysfunction, and in patients with RV dysfunction and HFrEF, S/V may improve RV remodelling.

The systematic review and meta-analysis by Zhang et al. confirmed that S/V significantly enhances proper ventricular function and reduces PH in patients with HFrEF [16]. Across 10 observational studies involving 875 patients (mean age 62.2 years, 74% men), S/V led to significant improvements in key parameters: tricuspid annular plane systolic excursion increased by 1.26 mm (95% CI, 0.33–2.18 mm; P = 0.008), tricuspid annular peak systolic velocity rise by 0.85 cm/s (95% CI, 0.25–1.45 cm/s; P = 0.005), and estimated systolic pulmonary arterial pressure decreased by 7.21 mm Hg (95% CI, 5.38–9.03 mm Hg; P < 0.001). These improvements suggest that S/V positively affects proper ventricular performance and pulmonary pressures, effects that

are not solely dependent on left ventricular reverse remodelling.

The prospective observational study by Polito et al. evaluated the effects of S/V on clinical outcomes and echocardiographic parameters in a real-world cohort of 90 patients with HFrEF [17]. Over a 12-month follow-up, S/V treatment significantly reduced the risk of the composite primary outcome (cardiac death and HF rehospitalisation) with a hazard ratio (HR) of 0.31 (95% CI, 0.11–0.83; P = 0.019). S/V also lowered the risk of HF rehospitalisation (HR: 0.27; 95% CI, 0.08–0.94; P = 0.039) compared to a control group of patients receiving standard medical therapy. Additionally, improvements were observed in NYHA class, LVEF and systolic PAP at 6 months. Importantly, S/V preserved renal function and reduced the need for furosemide at 6 and 12 months. These findings suggest that S/V offers significant clinical benefits in reducing adverse outcomes and improving functional and echocardiographic parameters in patients with HFrEF.

Another prospective study by Yamaguchi et al., based on echocardiographic assessments after the 6MWT, examined the effects of ARNI on pulmonary circulation in 39 HF patients [18]. Significant improvements were observed in LV volume (160.7 ± 49.6 mL vs 136.0 ± 54.3 mL, P < 0.001) and LVEF (37.6 ± 11.3% vs 44.9 ± 11.5%, P < 0.001) for the 31 patients who completed both baseline and follow-up assessments. Follow-up 6MWT stress echocardiography revealed an increase in the 6MWT distance from 380 m to 430 m (P = 0.003). Significantly, the ratio of mean PAP to cardiac output decreased with ARNI treatment (6.9 mmHg/L/min vs 2.8 mmHg/L/min, P = 0.002), indicating improved pulmonary pressure-flow dynamics. These findings suggest that ARNI treatment not only enhances LV function and exercise capacity but also optimises the pulmonary pressure-flow relationship in heart failure patients.

In the two cases reported by De Simone et al., the use of ARNI was noted in patients with advanced HFrEF. This has resulted in an improvement in pH, as measured during RHC, and, consequently, in both clinical status and prognosis. These two cases demonstrate that natriuresis and vasodilation may play a crucial role in reducing pulmonary pressures [19].

ARNIMEMS-HFpEF was a single-arm interventional study with a short observation period (7 days), investigating patients with heart failure with preserved ejection fraction (HFpEF), [20]. The sample size consisted of 14 patients. The results indicated a significant reduction in mPAP by 4.14 ± 5.7 mmHg after 7 days of S/V treatment (P = 0.019), as assessed using the CardioMEMS device. Furthermore, a notable improvement in functional capacity was observed in the 6MWT, with distances increasing from 270.6 ± 101.3 meters to 298.3 ± 88.4 meters (P < 0.001) following the ARNI therapy.

Another retrospective case series involved 18 patients with HFrEF and pulmonary pressures as measured using the CardioMEMS device over 5 days after S/V initiation [7]. The study showed a significant reduction in median (interquartile range) mPAP by −3.6 mmHg (−9.8, −0.7) post-ARNI initiation. Additionally, the baseline median (interquartile range) PVR was significantly higher at 357 (320, 548) dyn/s/cm^5 compared to 137 (73, 172) dyn/s/cm^5 (P = 0.001), suggesting a marked reduction in pulmonary resistance following treatment. These studies emphasise the early hemodynamic benefits of S/V, including cuts in pulmonary pressures and improvements in functional capacity, which contribute to a broader understanding of S/V therapeutic effects in both HFpEF and HFrEF populations.

Conclusions

Pulmonary hypertension secondary to HFrEF remains a major contributor to symptom burden, hospitalisations, and adverse prognosis, yet no specific pharmacological treatment has been proven to modify its course. Sacubitril/valsartan, a cornerstone therapy for HFrEF, has demonstrated robust clinical benefits in reducing mortality and hospitalisations for heart failure. Evidence from preclinical models, echocardiographic studies, and limited invasive hemodynamic data suggests that sacubitril/valsartan may also reduce pulmonary pressures, improve proper ventricular function, and favorably remodel the pulmonary vasculature.

The PRESENT-HF trial is the first randomised, double-blind, controlled study to prospectively investigate the effect of sacubitril/valsartan on invasively measured pulmonary artery pressures and pulmonary vascular resistance in patients

with HFrEF and confirmed PH. By combining gold-standard hemodynamic assessment with clinical, functional, and quality-of-life endpoints, this trial aims to address a critical knowledge gap and expand the therapeutic role of ARNI therapy to include the management of PH-LHD.

Declarations

Conflict of interest

Ewa Straburzyńska-Migaj received consultancy fees and/or honoraria from Novartis, Boehringer Ingelheim, Pfizer, Bayer, Abbott, Servier, AstraZeneca, and Bausch Health; Agnieszka Tycińska – consultancy fees and/or honoraria from Abiomed, Boehringer Ingelheim, Pfizer, Bayer, Servier, AstraZeneca, and Bausch Health; Marta Kałużna-Oleksy's education and lecture collaboration with Novartis; Magdalena Dudek, Jacek Migaj, Agnieszka Bartczak-Rutkowska, Jarosław Hiczkiewicz, Piotr Cygański, Marek Gierlotka, Ewa Kozielska-Nowalany, Jacek Kubica, Małgorzata Tomaszewska, Piotr Sawiński, Lech Paluszkiewicz, and Maciej Lesiak declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors contribiution

Conceptualization, E.S.-M., M.K.-O., M.D.; methodology, E.S.-M., M.K.-O., J.M., M.D.; software, J.M., validation, M.D., M.K.-O.; formal analysis, M.D., M.K.-O.; investigation, E.S.-M., M.D, A.T, M.K.-O, A.B.-R., J. H., P.C, M.G., E. K.-N., J.K., M.T., P.S, L.P., M.L.; resources, M.D.; data curation, M.D. and J.M.; writing—original draft preparation, E.S.-M., M.K.-O, M.D.; writing—review and editing, E.S.-M., M.D, A.T, M.K.-O, A.B.-R., J. H., P.C, M.G., E. K.-N., J.K., M.T., P.S, L.P., M.L; visualization, E.S.-M., M.K.-O., M.D.; supervision, E.S.-M. and M.L.; project administration, E.S-M., M.K.-O. All authors have approved the final version of the manuscript.

Funding

This research received financial support from the Medical Research Agency, Poland (project no. 2019/ABM/01/00078-00).

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Supplementary Table 1. Inclusion and exclusion criteria for the PRESENT-HF study.

Inclusion criteria	Exclusion criteria
1. Age ≥18 years of age who are able to complete and sign the informed consent form. 2. HF patients in NYHA II-IV in whom RHC reveals post-capillary pulmonary hypertension; both IpcPH as well as CpcPH(Humbert et al., 2022) 3. Stable patients haemodynamics, which is defined as no change in diuretic use for at least 4 weeks prior to study entry. 4. HF during optimal treatment with ACE-I/ ARB, beta-blocker, MRA, SGLT2-I except in cases where the above-mentioned treatment was contraindicated or not tolerated. 5. Understanding and acceptance of the research assumptions and methods, and signing the informed consent by the patient.	1. Current treatment with S/V. 2. Cardiogenic shock. 3. Current treatment with sildenafil. 4. Patients ineligible or contraindicated for treatment with S/V. 5. Patients with a history of angioedema. 6. Patients who have had a heart transplant or have had a circulatory support device. 7. Patient on the urgent list for heart transplantation. 8. Isolated right HF secondary to lung disease. 9. Documented untreated significant ventricular arrhythmia with syncope within the previous 3 months. 10. Symptomatic bradycardia or second or third degree atrioventricular block not protected by a pacemaker. 11. Factors that prevent RHC testing (e.g. very serious condition of the patient that makes it impossible to lie down, cardiogenic shock, allergy to contrast agents, etc.). 12. Pregnant or lactating women. 13. Women of childbearing age, defined as the physiological possibility of becoming pregnant, unless using two methods of contraception. 14. Acute coronary syndrome, including myocardial infarction (STEMI, NSTEMI), a ondition with carotid revascularization or major cardiovascular surgery in the last 30 days. 15. Stroke or TIA within the last 3 months. 16. Previous CRT implantation in the last 3 months or planning for CRT implantation. 17. Life expectancy < 6 months. 18. Severe renal failure, eGFR < 30 ml / min / 1.73 m2 (calculated according to the MDRD formula). 19. Serum potassium > 5.2 mEqL. 20. Liver failure or elevated liver transaminases (total bilirubin > 3 mg / dL and/or ALT and/or AST ≥3x ULN). 21. A major surgery planned within 6 months of randomization. 22. Planned coronary angioplasty or pacemaker/ICD/CRT implantation within the next 6 months. 23. Severe primary valve disease (NOT secondary mitral regurgitation) or obstructive hypertrophic cardiomyopathy. 24. The presence of a malignant neoplasm of any organ system, i.e. clinical signs or no stable remission for at least 3 years after the end of the last treatment, with the exception of non-invasive basal cell carcinoma, squamous cell carcinoma of the skin or cervical epithelial dysplasia. 25. Diseases that significantly reduce physical performance: – a) severe COPD putting off oxygen therapy, – b) severe asthma, – c) morbid obesity (BMI>40 kg/m^2), – d) significant lower limb atherosclerosis with intense intermittent claudication. 26. Uncontrolled hypertension (SBP>170 mmHg and / or DBP>100 mmHg). 27. Symptomatic hypotension (SPB < 90 mmHg). 28. Any situation that may make it impossible to perform the research in accordance with the protocol or express written consent in the opinion of the researcher, including abuse of alcohol, drugs or other psychoactive substances. 29. Participation in a study with a device or medicinal product within 3 months prior to randomization or 5 half-lives, whichever is longer, prior to the screening visit.

Abbreviations: ACE-I – Angiotensin-Converting Enzyme Inhibitors; ALT – Alanine Aminotransferase; ARB – Angiotensin Receptor Blockers; AST – Aspartate Aminotransferase; BMI – Body Mass Index; CpcPH – Combined Post- and Pre-capillary Pulmonary Hypertension; COPD – Chronic Obstructive Pulmonary Disease; CRT – Cardiac Resynchronization Therapy; DBP – Diastolic Blood Pressure; eGFR – Estimated Glomerular Filtration Rate; ESC – European Society of Cardiology; HF – Heart Failure; ICD – Implantable Cardioverter-Defibrillator; IpcPH – Isolated Post-capillary Pulmonary Hypertension; MDRD – Modification of Diet in Renal Disease; MRA – Mineralocorticoid Receptor Antagonists; NSTEMI – Non-ST-Elevation Myocardial Infarction; NYHA – New York Heart Association; mPAP – Mean Pulmonary Artery Pressure; PAWP – Pulmonary Artery Wedge Pressure; PH – Pulmonary Hypertension; PVR – Pulmonary Vascular Resistance; RHC – Right Heart Catheterization; S/V – Sacubitril/Valsartan (sakubitryl/walsartan); SBP – Systolic Blood Pressure; SGLT2-I – Sodium-Glucose Cotransporter-2 Inhibitors; STEMI – ST-Elevation Myocardial Infarction; TIA – Transient Ischemic Attack; ULN – Upper Limit of Normal; WU – Wood Units.