LETTER TO THE EDITOR

Designing the right trial for sacubitril / valsartan in heart failure with preserved ejection fraction–related pulmonary hypertension

Gianluca Pagnoni[1], Aurora Vicenzi[2], Francesca Coppi[3]

1 Cardiology Unit of Emergency Department, Guglielmo da Saliceto Hospital, Piacenza, Italy
2 National Institute for Cardiovascular Research (INRC), Bologna, Italy
3 Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy

To the editor We read with great interest the research letter by Niemiec et al[1] on the use of sacubitril / valsartan in patients with pulmonary hypertension (PH) due to heart failure with preserved ejection fraction (HFpEF), and we would like to offer several critical remarks and proposals for future studies.

The authors report a 5-case series (age range, 74–80 y) treated for 3 months with a sacubitril / valsartan dose of 24/26 mg twice daily without uptitration, describing improvement in the New York Heart Association class in all patients, reductions in N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, and favorable hemodynamic signals at right heart catheterization (RHC), including, in some cases, a marked fall in mean pulmonary artery pressure and pulmonary vascular resistance. These are preliminary findings but they are consistent with the hypothesis that angiotensin receptor–neprilysin inhibition (ARNI) in the HFpEF-PH phenotype is beneficial.[1]

While we appreciate this contribution in an area of unmet needs, the descriptive nature, extremely small sample size, as well as absence of a control group and statistical inference expose the results to regression to the mean, placebo effects and selection bias, making it difficult to determine the extent to which the observed changes exceeded the intrinsic variability of RHC. The presence of mild respiratory comorbidities in some cases also suggests phenotypic heterogeneity. Further hemodynamic characterization (eg, pulmonary diastolic pressure, vascular compliance, or pulmonary artery wedge pressure [PAWP] waveform analysis) and integration with right-ventricular imaging would help clarify mechanisms of response, distinguishing the post-capillary from the combined component.

Recent evidence in HFpEF shows that prediabetes-related inflammatory biomarkers, particularly C–C motif chemokine ligand 5 (CCL5), and indices of insulin resistance (estimated glucose disposal rate) are independently associated with diastolic dysfunction and adverse outcomes, reinforcing the need for a metabolic-inflammatory phenotyping approach in patients with HFpEF-PH.[2] Moreover, observations in systemic sclerosis cohorts document that vitamin D insufficiency is associated with higher pulmonary artery pressures (PAPs) and worse right-ventricle pulmonary circulation coupling (tricuspid annular plane systolic excursion / PAPs), suggesting that inflammatory-metabolic and endothelial axes may modulate pulmonary vascular load beyond congestion alone—an additional rationale to include biomarkers and vascular phenotyping in future ARNI trials in HFpEF-PH.[3]

Supporting the need for a structured assessment of diastolic dysfunction, a recent study by Urbanowicz et al[4] in patients with HFpEF and stable angina showed that the combination of septal e′ below 7 cm/s, E/e′ above 14, and tricuspid regurgitation peak gradient below 31 mm Hg identifies the risk of coronary artery disease and predicts its significance, underscoring how left-sided filling parameters and tricuspid gradients can serve as accessible markers of occult ischemia and pulmonary pressure load.

Finally, the most recent literature highlights sex-specific differences in the pathophysiology and clinical presentation of HFpEF, with distinct

Correspondence to:
Aurora Vicenzi, MA,
National Institute for Cardiovascular Research (INRC), Via Irnerio 48, 40126 Bologna, Italy,
phone: +3458584138,
email: aurora.vicenzi@gmail.com
Received: October 2, 2025.
Accepted: October 3, 2025.
Published online: January 29, 2026.
Pol Arch Intern Med. 2026;
136 (1): 17211
doi:10.20452/pamw.17211
Copyright by the Author(s), 2026

prevalence and phenotypic profiles in postmenopausal women. These elements strengthen the case for study designs that incorporate sex stratification and targeted assessments of ventriculo-arterial interaction and diastolic reserve, including relationships with responses to concomitant treatments, such as sodium-glucose cotransporter 2 inhibitors (SGLT2is) and potential add-on therapies.[5]

Although cotherapies are reported as stable, unmeasured fluctuations in adherence, sodium intake, or volemia may have influenced NT-proBNP and PAWP. Moreover, the prudent decision not to uptitrate beyond the starting dose limits the exploration of a dose-response relationship and tolerability margins (hypotension, renal function, and potassium)—aspects that would merit more granular monitoring.

In this context, a recent meta-analysis of randomized controlled trials documented that the initial estimated glomerular filtration rate "dip" after SGLT2i initiation is generally a benign phenomenon, sometimes associated with better cardiovascular outcomes for mild reductions (approximately ≤11.8%), whereas a similar dip in placebo-controlled groups correlates with worse prognosis: evidence useful for safely interpreting SGLT2i coprescription in older adults with HFpEF-PH.[6]

It should also be emphasized that functional outcomes remain underreported: the 6-minute walk test was largely uninformative, and systematic measurements of quality of life (eg, Kansas City Cardiomyopathy Questionnaire) and cardiopulmonary exercise testing—elements crucial to translate hemodynamic signals into patient-perceived clinical benefits—were lacking.[1]

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING None.

CONFLICT OF INTEREST None declared.

AI STATEMENT Artificial intelligence was not used in the preparation of this manuscript.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing anyone to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, including commercial purposes, provided the original work is properly cited.

HOW TO CITE Pagnoni G, Vicenzi A, Coppi F. Designing the right trial for sacubitril/valsartan in heart failure with preserved ejection fraction–related pulmonary hypertension. Pol Arch Intern Med. 2026; 136: 17211. doi:10.20452/pamw.17211

REFERENCES

1 Niemiec M, Grabka M, Niemiec R, et al. The impact of angiotensin receptor-neprilysin inhibitor on clinical status and hemodynamic parameters in patients with pulmonary hypertension due to heart failure with preserved left ventricular ejection fraction: a case series analysis. Pol Arch Intern Med. 2025; 135: 17120.

2 Yu Z, Wang J, Zheng F, et al. Prediabete-srelated inflammatory biomarkers modulate left ventricular diastolic function in patients with heart failure with preserved ejection fraction. Pol Arch Intern Med. 2025; 135: 17021.

3 Pagnoni G, Giuggioli D, de Pinto M, et al. Vitamin D insufficiency and cardiovascular involvement in systemic sclerosis: association with echocardiographic parameters and risk factors. Int J Cardiol Cardiovasc Risk Prev. 2025; 27: 200502.

4 Urbanowicz T, Spasenenko I, Banaszkiewicz M, et al. Can we predict coronary artery disease in patients with heart failure with preserved ejection fraction based on echocardiographic parameters of diastolic dysfunction? A preliminary report. Pol Arch Intern Med. 2025; 135: 16930.

5 Coppi F, Pagnoni G, Grossule F, et al. Gender-specific differences in diastolic dysfunction and hfpef: pathophysiology, diagnosis, and therapeutic strategies. J Cardiovasc Dev Dis. 2025; 12: 213.

6 Urban S, Biegus J, Błaziak M, et al. Placebo-adjusted effect of the initial estimated glomerular filtration rate decline following sodium-glucose cotransporter 2 inhibitor initiation: a systematic review and meta-analysis. Pol Arch Intern Med. 2025; 135: 16981.