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Methodology and Design

Angiotensin Receptor Neprilysin Inhibitor in Heart Failure With Preserved Ejection Fraction and Secondary Mitral Regurgitation: Design and Rationale of the PRAISE-MR Trial

SEBASTIAAN DHONT, M.D.[1,2] SARA MOURA FERREIRA, M.D.[2,3] XAVIER GALLOO, M.D.[4,5]
PIETER MARTENS, M.D., M.Sc., Ph.D.[1,2] EVELYNE MEEKERS, M.D.[1,2] KATRIEN TARTAGLIA, M.Sc.[2]
SÉBASTIEN DEFERM, M.D., Ph.D.[1,2] LIEVEN HERBOTS, M.D., Ph.D.[2,3]
WILFRIED MULLENS, M.D., Ph.D.[1,2] FREDERIK H. VERBRUGGE, M.D., M.Sc., Ph.D.[4,5]
JAN VERWERFT, M.D.,[2,3] and PHILIPPE B. BERTRAND, M.D., Ph.D.[1,2]

Genk, Hasselt, and Jette, Belgium

ABSTRACT

Background: Secondary or functional mitral regurgitation (FMR) of atrial origin is prevalent in heart failure with preserved ejection fraction (HFpEF) and portends a worse clinical course. Unlike ventricular FMR, it lacks evidence-based treatment and is often overlooked. Sacubitril-valsartan may provide benefit in this HFpEF phenotype.

Objective: To assess the impact of sacubitril-valsartan on exercise hemodynamics in patients with HFpEF and atrial FMR.

Methods: This multicenter, prospective, randomized, open-label trial with blinded endpoint assessment enrolls patients with stable HFpEF and at least moderate FMR documented within 1 year prior to enrollment. Participants are randomly assigned to sacubitril-valsartan plus standard medical therapy or to standard therapy alone, consisting of a mineralocorticoid receptor antagonist and a sodium-glucose cotransporter-2 inhibitor. Cardiopulmonary exercise testing with echocardiography is performed at baseline and after 6 months, with interval 24-hour home blood pressure monitoring to ensure blood pressure control in both arms. The primary endpoint is the change in exercise-induced pulmonary hypertension, assessed by the change in the mean pulmonary arterial pressure to cardiac output slope. This slope reflects total pulmonary resistance driven by both pre- and postcapillary factors, capturing key HFpEF features, including myocardial properties, vascular remodeling and the overall impact of (dynamic) atrial FMR. Secondary endpoints include changes in FMR severity, peak oxygen consumption, natriuretic peptide levels, left atrial size and function, and patient-reported outcomes. Prespecified adverse events include hypotension, renal failure, hyperkalemia, and angioedema.

Conclusion: The PRAISE-MR (Sacubitril-Valsartan in Heart Failure with **P**reserved Ejection Fra**c**tion and **Se**condary **M**itral Valve **R**egurgitation) trial will evaluate whether sacubitril-valsartan, an angiotensin receptor neprilysin inhibitor, is beneficial in patients with HFpEF and atrial FMR. (*J Cardiac Fail 2026;32:1041–1049*)

Key Words: Atrial function mitral regurgitation, heart failure with preserved ejection fraction, sacubitril-valsartan, clinical trial.

From the [1]Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium; [2]Doctoral School of Medicine and Life Sciences, Limburg Clinical Research Center, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium; [3]Department of Cardiology, Jessa Hospital, Hasselt, Belgium; [4]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Jette, Belgium and [5]Centre for Cardiovascular Diseases, University Hospital Brussels, Jette, Belgium.

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Reprint requests: Sebastiaan Dhont, M.D., Cardiology department, ZOL, 3600 Genk, Belgium. Tel: 32 471 62 60 94. E-mail: Sebastiaan.Dhont@zol.be

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Introduction

Heart failure with preserved ejection fraction (HFpEF) remains a significant therapeutic challenge, particularly due to the complex interplay of comorbidities that complicate its diagnosis and management.[1] Phenotyping HFpEF supports tailored therapies for subtypes, such as obesity- or atrial fibrillation-related disease.[2,3]

Concomitant secondary or functional mitral regurgitation (FMR) is observed in 25% of patients with HFpEF, resulting primarily from atrial and annular enlargement and age-related structural valve degeneration.[4,5] Although even mild atrial FMR in the context of HFpEF has been linked to poor outcomes, it remains unclear whether FMR is a causal factor or merely a marker of atrioventricular disease severity.[6,7] Moreover, unlike FMR in heart failure with reduced ejection fraction (HFrEF), therapeutic strategies for managing the FMR-HFpEF subtype remain insufficiently studied.

To address this gap, the PRAISE-MR trial (Sacubitril-Valsartan in Heart Failure with **P**reserved Ejection Fra**c**tion and **S**econdary **M**itral Valve **R**egurgitation) was designed. Patients with HFpEF and at least moderate atrial FMR documented within the year prior to enrollment will be randomized to sacubitril-valsartan or standard care to assess the impact of sacubitril-valsartan on exercise hemodynamics, on FMR severity and on cardiopulmonary exercise performance.

Patient Selection

In the management of patients with HFpEF and atrial FMR, it is recommended to optimize fluid balance with diuretics, aim for sinus rhythm in the setting of atrial fibrillation (AF), optimize HFpEF treatment according to current guidelines, and subsequently reassess FMR severity.[4,5,8] In symptomatic patients with persistent severe atrial FMR, a mitral valve-centered approach may be considered.

However, current guidelines do not specifically address the management of atrial FMR in the context of HFpEF.[9,10] Although transcatheter interventions have shown promise in reducing FMR severity and improving symptoms, comparative studies evaluating outcomes against optimized medical therapy are lacking. Furthermore, the majority of patients present with mild to moderate atrial fibrillation mitral regurgitation, for which randomized trials in this expanding HFpEF population remain an unmet need.

Adding to this complexity is the typically dynamic nature of atrial FMR in HFpEF, with worsening regurgitation during periods of volume overload or rhythm disturbances. The contribution of dynamic FMR to exercise hemodynamics and exertional symptoms in HFpEF remains incompletely understood. Within this rationale, the PRAISE-MR (Sacubitril-Valsartan in Heart Failure with **P**reserved Ejection Fra**c**tion and **S**econdary **M**itral Valve **R**egurgitation) trial was designed to enroll patients with HFpEF who had at least moderate FMR documented on echocardiography within the past year, with an exercise-based endpoint selected to capture the functional impact of dynamic FMR.

Intervention: Angiotensin-Neprilysin Inhibition

Sacubitril-valsartan (LCZ696), through dual inhibition of the renin-angiotensin-aldosterone system (RAAS) and neprilysin, carry a class I recommendation in HFrEF, with proven reductions in hospitalizations and cardiovascular mortality rates.[11,12] Neprilysin inhibition enhances vasoactive peptides, including natriuretic peptides and bradykinin but necessitates concurrent angiotensin receptor blockade due to increased angiotensin II.[13] In HFrEF with ventricular FMR, sacubitril-valsartan demonstrated beneficial effects in the PRIME (Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation) trial.[14–16]

In HFpEF, sacubitril-valsartan reduces NT-proBNP, left atrial (LA) size and cardiac and vascular stiffness and improves New York Heart Association class when compared to valsartan (Table 1).[17–19] However, in the PARAGON-HF (Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction) trial, it narrowly missed the primary composite endpoint (RR 0.87; 95% CI 0.75–1.01; $P = 0.06$).[20] Still, it led to Federal Drug Administration approval as the first treatment for HFpEF and a class II guideline recommendation in the United States in the American guidelines.[21] Pooled data show benefit in patients with EF 40%–60%, including reductions in worsening HF events, renal outcomes and cardiovascular death.[22,23] Given the heterogeneity of HFpEF, more targeted phenotyping is needed.

Atrial FMR may represent a subtype where sacubitril-valsartan offers therapeutic potential (Fig. 1). It reduces preload and afterload via natriuretic peptide–mediated vasodilation and diuresis—key determinants of FMR severity. Additionally, it may limit atrial remodeling; PROVE-HF (Prospective study of biomarkers, symptom improvement and ventricular remodeling during Entresto therapy for heart failure) showed a significant reduction in indexed LA volume after 6 months (minus 5 mL/m^2).[14,16,24] Sacubitril-valsartan may also affect mitral leaflet adaptation. Inadequate leaflet growth relative to annular dilation worsens FMR, driven partly by mechanical stress and TGF-β–mediated fibrotic remodeling.[4,25] Animal studies with losartan suggest that RAAS inhibition can preserve adaptive leaflet growth while reducing fibrosis.[26]

Primary Outcome: mPAP/CO Slope

The mean pulmonary arterial pressure over cardiac output (mPAP/CO) slope has emerged as a measure for evaluating flow-dependent total pulmonary resistance during exercise. By reflecting both pre- and postcapillary

components, it captures critical HFpEF features, including myocardial stiffness, vascular remodeling and the impact of (dynamic) atrial FMR during exercise. Assessing the severity of mitral regurgitation at rest requires the integration of various parameters, making evaluation during exercise particularly difficult. The slope serves as a reliable parameter to reflect the effects of sacubitril-valsartan on both FMR and myocardial properties during exercise. A slope > 3 mmHg/L/min is strongly linked to worse outcomes (all-cause mortality and hospitalizations due to HF) and is now recognized in the European Society of Cardiologists pulmonary hypertension guidelines.[27–29]

Cardiopulmonary exercise testing (CPET) enables detailed evaluation of exercise physiology, identifies functional phenotypes and predicts outcomes in HFpEF.[30] When combined with exercise echocardiography, it offers a comprehensive assessment of biventricular function, valvular integrity and pulmonary hemodynamics.[31] Noninvasive assessment of the mPAP/CO slope during CPETecho was shown to be feasible and reliable; details and guidance on the noninvasive mPAP/CO slope measurement are extensively described elsewhere and are summarized in Fig. 2.[27,32]

The PRAISE-MR Trial

Trial Design. The PRAISE-MR (Sacubitril-Valsartan in Heart Failure with **P**reserved Ejection Fra**c**tion and **Se**condary **M**itral Valve **R**egurgitation) trial is a multicenter, investigator-initiated, prospective, randomized, open-label trial with a blinded endpoint. Patient inclusion occurs at 2 centers in Belgium. Ethical-committee approval has been obtained at each participating center and at the Federal Agency for Medicines and Health Products (EudraCT Number: 2023-506634-70-00). The study is being conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients are required to provide written informed consent prior to study initiation. The PRAISE-MR trial is registered at clinicaltrials.gov, identifier NCT05991284. It is an academic study conducted without direct external financial support. The authors and the sponsor (Ziekenhuis Oost-Limburg) are responsible for the design and conduct of this trial, all study analyses, the drafting and editing of this article, and its final contents.

Study Population and Sample Size. To be eligible for inclusion, participants must be ≥ 40 years of age, have a clinical diagnosis of HF, be classified as New York Heart Association functional (NYHA) class II or III, and have an LVEF ≥ 50%. The diagnosis of HFpEF is based on the European Society of Cardiology (ESC) HFpEF criteria and confirmed by expert adjudication, considering all baseline investigations, previous HF hospitalization(s), congestion with positive responses to diuretic therapy, and previous natriuretic peptide levels. Additionally, participants had to have at least moderate FMR as assessed by echocardiography documented within the year prior to enrollment. Atrial FMR is defined as FMR with the following characteristics: (1) normal left ventricular (LV) size and function without papillary muscle displacement; (2) mitral annular and LA dilation; and (3) loss of normal systolic leaflet concavity toward the LV.[5] Patients with (mixed) primary mitral valve disease are excluded; inclusion and exclusion criteria are summarized in Table 2. No data from clinical trials exist to estimate the primary endpoint, so retrospective data from our cohort of patients with HFpEF with varying degrees of FMR undergoing CPETecho were used. This analysis revealed a baseline mPAP/CO slope of 4 ± 1 mmHg/L/min. After discussions with the advisory team, a treatment difference of minus 0.5 mmHg/L/min after 6 months was

Table 1 Completed trials of sacubitril-valsartan in heart failure with preserved ejection fraction

	Phase 2 trials	Phase 3 trials		
	PARAMOUNT	PARALLAX	PARAGON-HF	PARAGLIDE-HF
Population	HFpEF (LVEF ≥ 45%), elevated NT-proBNP	HFpEF (LVEF > 40%), elevated NT-proBNP	HFpEF (LVEF ≥ 45%), elevated NT-proBNP	HFpEF (LVEF > 40%), recently hospitalized for heart failure
Sample size	301	2572	4822	466
Target dosage	97/103 mg twice daily	97/103 mg twice daily	97/103 mg twice daily	97/103 mg twice daily
Comparator	Valsartan	Enalapril, valsartan or placebo	Valsartan	Valsartan
Follow-up	36 weeks	24 weeks	Median 35 months	Median 8 months
Primary endpoint	Change in NT-proBNP levels.	Change in NT-proBNP levels at week 12 and in the 6-minute walk distance at week 24	Composite of total HF hospitalizations and cardiovascular death	Change in NT-proBNP levels
Summary of the primary results	Significantly reduced NT-proBNP and improved left atrial size compared to valsartan	Significantly reduced NT-proBNP at 12 weeks but did not significantly improve 6-minute walk distance at 24 weeks	Missed statistical significance for primary endpoint (rate ratio, 0.87; 95% CI, 0.75–1.01; $P = 0.06$)	Significant NT-proBNP reduction compared to placebo

HF, heart failure; HFpEF, heart failure with preserved ejection fraction, LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

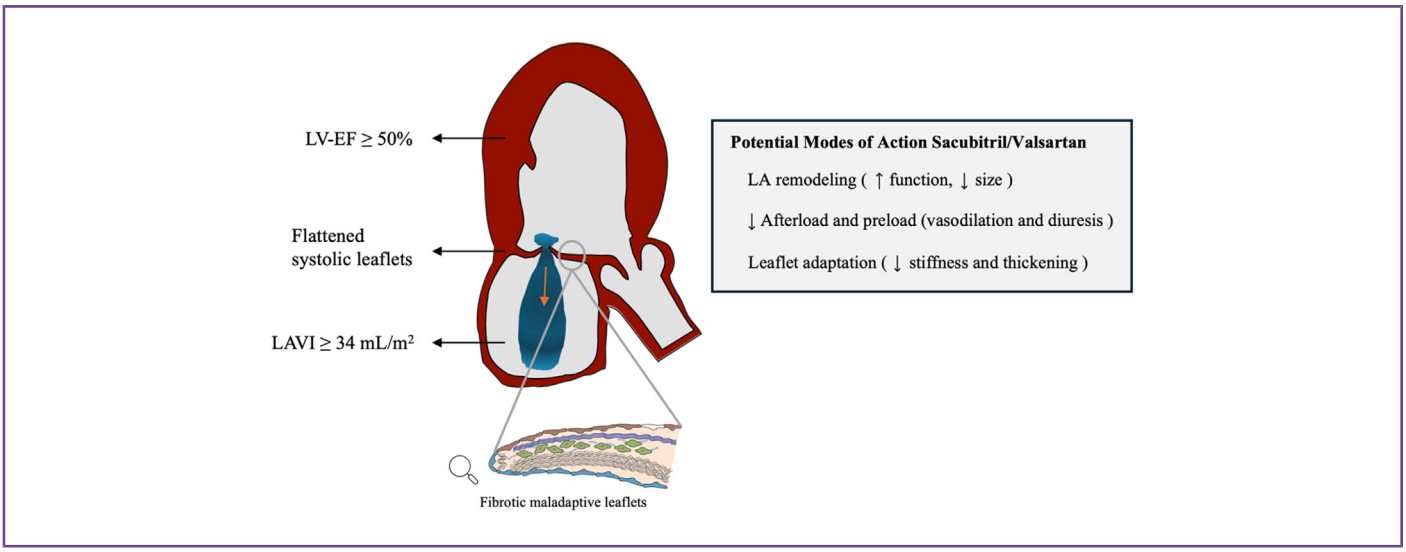


Fig. 1. Mechanisms of sacubitril-valsartan in atrial FMR. Illustration of how sacubitril-valsartan may improve LA remodeling and atrial FMR severity in HFpEF. FMR, functional mitral regurgitation; LA, left atrium; LAVI, left atrial volume index; LV-EF, left ventricular ejection fraction.

assumed. Assuming a power of 80%, a 2-sided alpha of 0.05, and accounting for a 10% dropout rate, the final sample size was set at 110 patients.

Study Protocol. During the screening phase, eligible patients will be assessed, and treatment with an SGLT-2 inhibitor (empagliflozin or dapagliflozin) and a mineralocorticoid receptor antagonist (spironolactone, finerenone or eplerenone) will be initiated if not already started or if contraindicated (Fig. 2). Following 3 months of stable HFpEF therapy, CPETecho will be scheduled. After the first CPETecho, participants are randomized 1:1, using internet-based software (CASTOR edc) stratified by center, to receive either sacubitril-valsartan in addition to

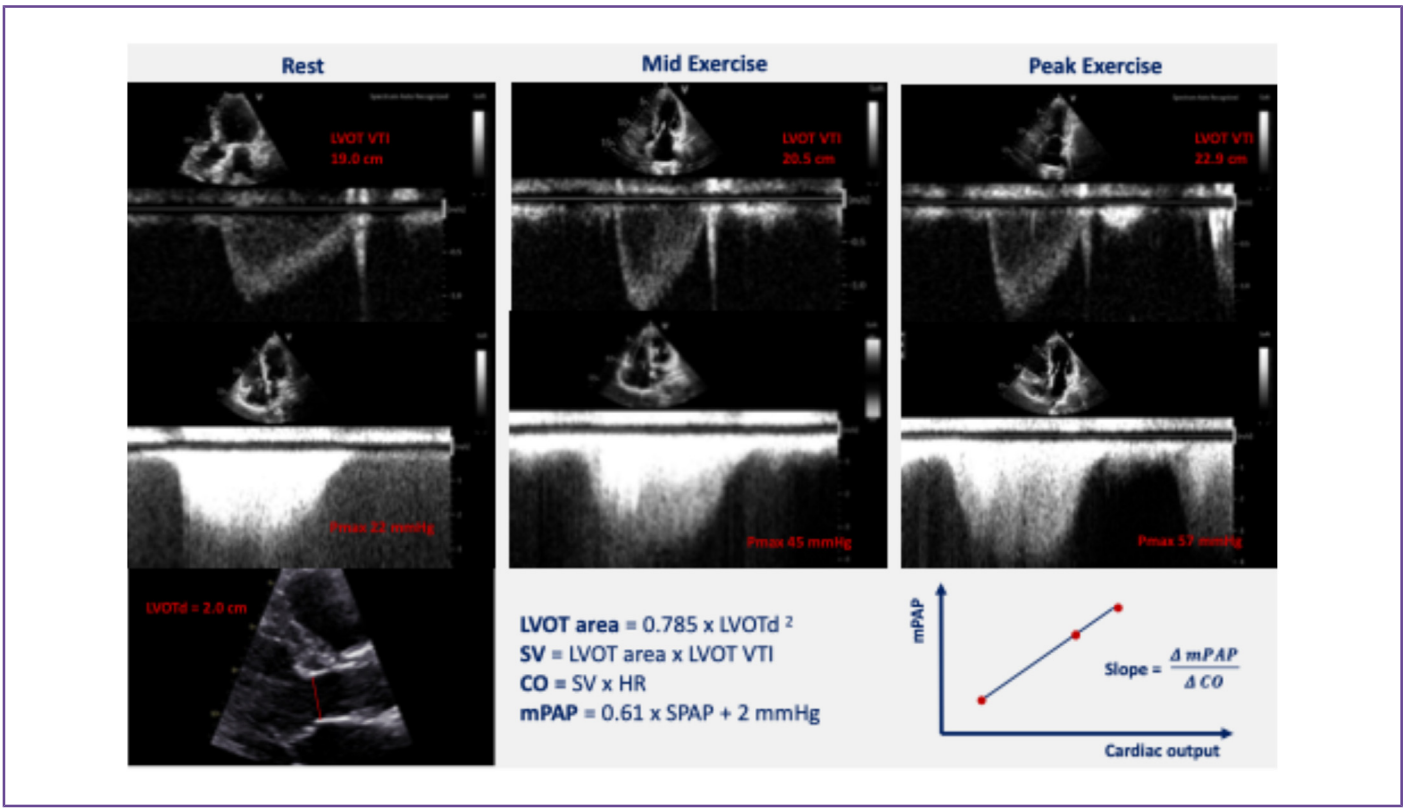


Fig. 2. Noninvasive assessment of the mPAP/CO slope. A case example of exercise mPAP/CO slope calculation using echocardiographic and CPET data. CPET, CO, cardiac output; LVOT, left ventricular outflow tract; mPAP, mean pulmonary artery pressure; VTI, velocity time integral. (Used with the permission of Dhont et al.[27])

Table 2 Eligibility criteria for the PRAISE-MR trial

Key Inclusion Criteria	Key Exclusion Criteria
Age ≥ 40 years	Systolic blood pressure < 100 mmHg
NYHA class II−IV	Potassium > 5.4 mmol/L
Signs and symptoms of heart failure	eGFR ≤ 30 mL/min/1.73m^2
Left ventricular ejection fraction ≥ 50%	History of angioedema or intolerable side effects from ACE inhibitors or ARBs.
Evidence of cardiac structural or functional abnormalities indicating LV diastolic dysfunction or elevated filling pressure	Structural mitral valve disease or previous mitral valve intervention
≥ Moderate atrial FMR assessed by TTE within the previous year	Liver insufficiency, biliary cirrhosis and cholestasis
Written informed consent	Severe concomitant valvular heart disease
	Severe comorbidity with life expectancy < 24 months or inability to perform CPETecho

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CPETecho, cardiopulmonary exercise testing with echocardiography; eGFR, estimated glomerular filtration rate; FMR, atrial functional mitral regurgitation; LV, left ventricle; NYHA, New York Heart Association; TTE, transthoracic echocardiography.

standard care or standard care alone. Participants complete the Kansas City Cardiomyopathy Questionnaire (KCCQ) and undergo blood sampling, including NT-proBNP levels (Elecsys NT-proBNP assay by Roche Diagnostics). The intervention arm initiates sacubitril-valsartan at 24/26 mg twice daily, followed by a clinical visit at 2 weeks, including 24-hour blood pressure measurements, assessment of side effects and lab testing. If well tolerated—defined as absence of symptomatic hypotension (< 90/50 mmHg), hyperkalemia (> 5.4 mmol/L) and a serum creatinine increase ≤ 1.5 × baseline, creatinine ≤ 2.0 mg/dL, and no reported side effects—the dosage is uptitrated to 49/51 mg twice daily for 2 weeks and, subsequently, to the target dosage of 97/103 mg twice daily, as tolerated. Dosage reduction is permitted in the case of intolerance. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be discontinued according to guidelines before starting sacubitril-valsartan. A 24-hour home blood-pressure measurement is also performed in the control group and is used to optimize standard-of-care antihypertensive therapy, aiming to minimize between-group blood pressure differences. The target mean blood pressure is < 130/80 mmHg in both arms. In the case of atrial fibrillation, it is required that a decision regarding rhythm management be made prior to study inclusion. Specifically, the arrhythmia must be accepted either as permanent or, if a rhythm-control strategy is pursued, it should be implemented—including any planned catheter ablation—before enrollment. Rhythm-control interventions, such as electrical cardioversion, initiation of antiarrhythmic therapy or catheter ablation, are discouraged during the 6-month study period unless clinically necessary. Patients are followed for 6 months, after which the CPETecho, KCCQ, 24-hour home blood pressure measurements, and blood sampling are repeated.

CPETecho. Experienced sonographers dedicated to the trial will perform a standardized CPETecho protocol as previously described.[33,34] Briefly, a maximal, symptom-limited bicycle ergometry test is performed in a semisupine position on a tiltable ergometer with simultaneous echocardiography and breath-by-breath ventilation analysis. A ramp protocol is initiated with a first hold stage at low-intensity exercise, identified mainly by a heart rate of 85−100 bpm to avoid E/A fusion when in sinus rhythm. After acquiring a complete set of images, patients are encouraged to reach maximal exertion, at which the second hold stage is performed. Echocardiographic studies are stored digitally in the Digital Imaging and Communication in Medicine format and are transferred to the echocardiography core laboratory, where measurements will be performed using an offline digital review workstation by an investigator blinded to patient data, treatment allocation, study sequence, and previous measures in each patient. All measurements will be averaged over 3 cardiac cycles, or 5 cycles in the case of atrial fibrillation.

Study Endpoints

The primary endpoint of the study is the change in the mPAP/CO slope as assessed by CPETecho from baseline to 6-month follow-up. All echocardiographic measures will be conducted by an external certified echocardiography laboratory (echo core lab) blinded to patient randomization and outcomes. Secondary endpoints include the change from baseline to 6 months in: (1) atrial FMR severity at rest and during exercise; (2) LA volume, and function; (3) NTproBNP levels; (4) the clinical summary score of the KCCQ; and (5) peak VO_2 and VE/VCO_2 slope. An overview of the key echocardiographic study endpoints and their corresponding measurement methods is provided in Table 3. Instead of the mPAP/CO slope, the mPAP/CO ratio will be explored as a point measurement at mid and peak exercise for comparison. Hypotension, renal failure, hyperkalemia, and angioedema are prespecified adverse events.

Statistical Plan

Baseline characteristics will be summarized as mean ± standard deviation for normally distributed continuous variables or as median with interquartile range (IQR) for skewed distributions. Categorical variables will be reported as counts and percentages. Between-group comparisons at baseline will be conducted using

Table 3 Echocardiography outcome measures for the PRAISE-MR trial

Endpoint	Measurement Methods
mPAP/CO Slope	Noninvasive estimation of mPAP from TR velocity using the Chemla formula and cardiac output from LVOT VTI × heart rate; mPAP/CO slope from linear regression at rest, mid and peak exercise (see Fig. 2)
MR Severity	Multiparametric approach according to guidelines with focus on EROA using PISA method at rest and during exercise, when feasible
LA Volume	LAVI derived from biplane Simpson method using apical 2- and 4-chamber views, normalized for body surface area (Mosteller formula)
LA function	LA reservoir strain measured by 2D speckle-tracking echocardiography during the reservoir phase, referenced to end-diastole (QRS onset) in 4-chamber LA-focused view

EROA, effective regurgitant orifice area; LA, left atrium; LA res, left atrial reservoir strain; LAVI, left atrial volume index; LVOT, left ventricular outflow tract; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; PISA, proximal isovelocity surface area; PRAISE, Sacubitril-Valsartan in Heart Failure with **P**reserved Ejection Fraction and **S**econdary Mitral Valve **R**egurgitation trial; TR, tricuspid regurgitation; VTI, velocity-time integral.

independent samples *t* tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed variables, and ^{2} or Fisher exact tests for categorical variables, as appropriate.

All efficacy analyses will follow the intention-to-treat principle, whereas safety analyses will be based on the as-treated population. The primary endpoint—change in the mPAP/CO slope from baseline to 6-month follow-up—will be evaluated using analysis of covariance (ANCOVA), adjusting for baseline values. This approach improves statistical power by accounting for baseline variability. Model assumptions, including normality and homoscedasticity of residuals, will be assessed using diagnostic plots and formal tests. If assumptions are violated, appropriate data transformations will be applied (Fig. 3).

Secondary continuous outcomes will be evaluated by using linear mixed-effects models with random intercepts for subjects to account for repeated measures. Fixed effects will include treatment arm, time (baseline vs 6 months) and the treatment-by-time interaction. Covariates prespecified for adjustment include the baseline value of the dependent variable, age, sex, baseline NT-proBNP level, atrial fibrillation status, and systolic blood pressure. The covariance structure will be prespecified as unstructured; if convergence issues occur, compound symmetry or first-order autoregressive structures will be evaluated based on the lowest Akaike Information Criterion. Assumptions of linearity, independence and normality of residuals will be assessed using residual diagnostics. Binary secondary endpoints and adverse events at follow-up will be compared using the Fisher exact test. For repeated categorical outcomes (eg, NYHA class), generalized linear mixed-effects models with a logit link function will be used, incorporating random intercepts for participants and adjusting for the same covariates as in the linear mixed-effects models.

Missing data will be addressed by using multiple imputation with control-based pattern imputation strategies for continuous outcomes. All statistical tests will be 2-sided with a significance threshold of $\alpha = 0.05$. Effect sizes will be presented with 95% confidence intervals. Analyses will be performed using IBM SPSS Statistics, version 22 (IBM, Chicago, IL) and, where needed, supplemented by R (R Foundation for Statistical Computing, Vienna, Austria) for advanced modeling.

Discussion

Atrial FMR is strongly associated with mortality and HF hospitalizations in patients with HFpEF.[6,7,35] As the prevalence of these interconnected conditions rises, the need for effective therapies becomes increasingly urgent. FMR is notably dynamic and load-dependent, which adds complexity to therapeutic decision making. Surgical and percutaneous interventions may reduce severe atrial FMR, but their impact on survival remains unproven in this group.[9,10] In contrast to ventricular FMR in HFrEF—where treatment focuses on LV optimization—atrial FMR remains underexplored.[36] It stems from progressive LA remodeling and annular dilation in the course of HFpEF.[4] The PRAISE-MR trial enrolls patients with HFpEF and recently documented at least moderate mitral regurgitation (MR), aiming to identify a phenotype that may particularly benefit from sacubitril-valsartan therapy.

Although sacubitril-valsartan is approved by the Food and Drug Administration, its incremental benefit in patients with HFpEF remains a subject of debate, because the PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) trial narrowly missed its primary endpoint.[20] Nonetheless, its proven ability to reduce NT-proBNP levels, LA size and LV filling pressures in patients with HFpEF, coupled with its favorable effects on FMR in HFrEF, suggest a strong physiological rationale for its potential efficacy in atrial FMR and HFpEF.[16,17,22] Myocardial remodeling is considered the primary mechanism underlying its benefits, but sacubitril-valsartan may also have a distinctive effect on the mitral leaflets' pathophysiology by suppressing the overexpression of TGF-β, further enhancing its therapeutic profile.[26] Unlike the PARAGON-HF trial, this study does not include a run-in phase, making the design more reflective of real-world clinical practice. It adopts a more pragmatic approach and includes fewer clinical visits.

In this relatively small, investigator-initiated exploratory trial, a blinded hemodynamic endpoint was selected and evaluated using CPETecho. Integrating CPET with stress echocardiography represents a novel and comprehensive

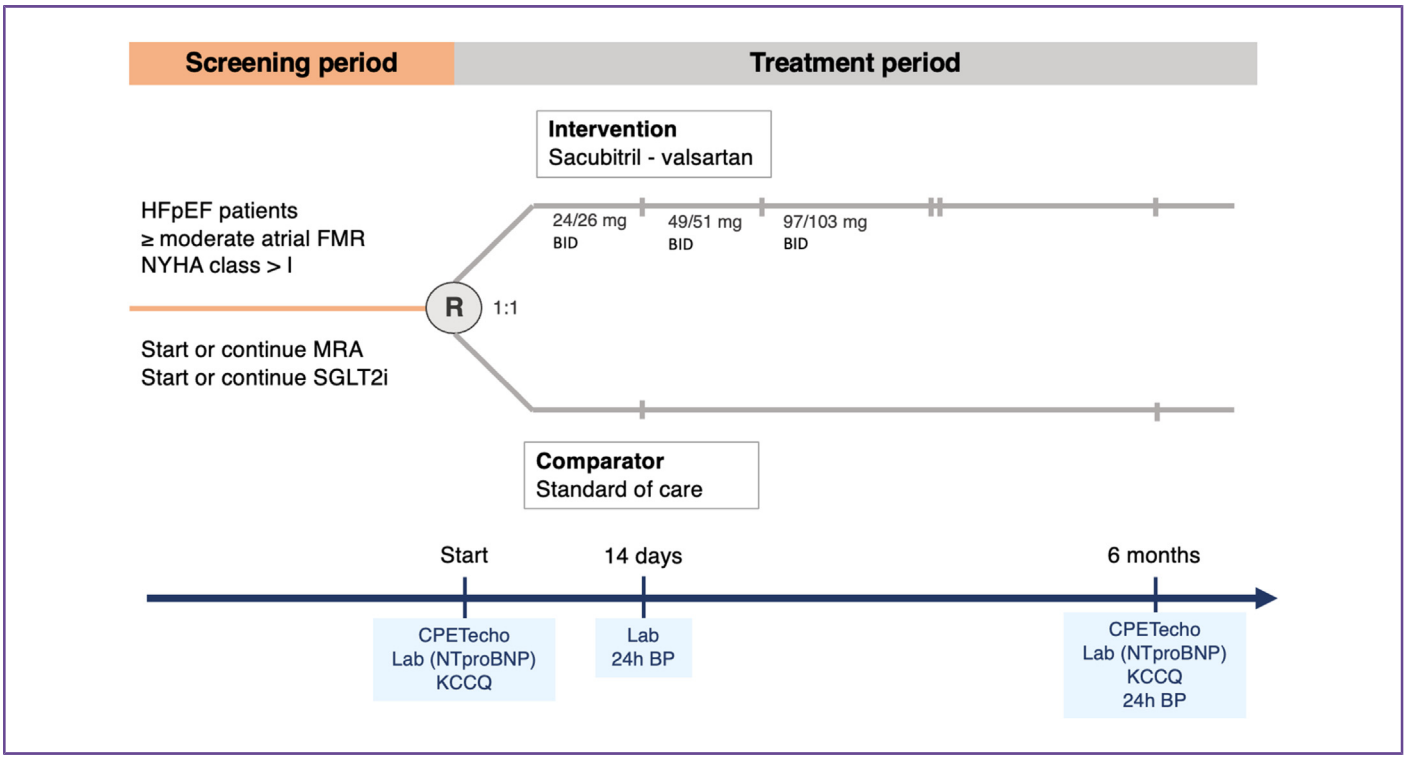


Fig. 3. PRAISE-MR trial design. Study timeline from baseline therapy to 6-month follow-up with key assessments. CPETecho, cardiopulmonary exercise test with echocardiography; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire.

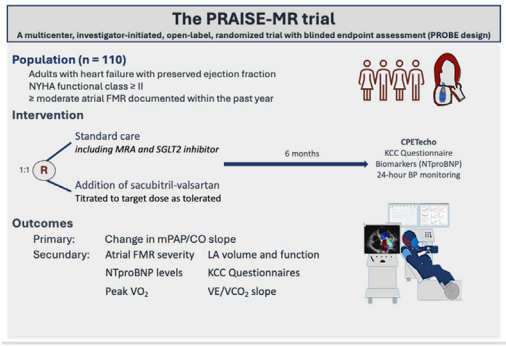
approach to symptom assessment and risk stratification in patients with atrial FMR and HFpEF.[34] This combined methodology enables a more detailed understanding of the interplay between (dynamic) MR and overall cardiopulmonary function, offering a thorough evaluation and potentially uncovering novel pathophysiological insights. The mPAP/CO slope may reflect both the underlying HFpEF physiology and the contribution of MR to total pulmonary resistance. By combining exercise capacity, ventilation analysis and resting and exercise echocardiography, this approach provides a robust assessment of the mechanisms of action of sacubitril-valsartan. Its non-invasive nature further enhances its applicability across a broad range of clinical settings. However, the findings will have to be validated in a larger study with clinical endpoints.

Patients are included on the basis of the presence of at least moderate FMR in the previous year, which may have occurred during episodes of arrhythmia or congestion. Given the load-dependency of FMR, MR severity may be less pronounced or quantifiable at the time of enrollment due to concomitant use of MRAs, SGLT2 inhibitors or decongestive therapy. For this reason, changes in FMR severity are included only as a secondary study endpoint. Importantly, by assessing patients both at rest and during exercise, this study also aims to determine the dynamic nature of FMR in HFpEF and its clinical impact.

The short duration of follow-up may result in an underestimation of the extent of remodeling. However, reductions in both left atrial volume index and E/e' have been reported in other studies after 6 months of treatment.[14,16,24] Notably, the majority of NT-proBNP reductions occurred early after the initiation of sacubitril-valsartan and during a period when most patients were on the lowest dosage of the drug.[14,16] The absence of an active comparator is justified by the lack of evidence supporting the routine use of RAAS inhibitors in patients with HFpEF. To minimize potential differences in blood pressure control between groups, scheduled home-based blood pressure monitoring and treatment adjustments targeting < 130/80 mmHg are implemented.

Limitations

This study has several limitations. First, as a relatively small, exploratory, investigator-initiated trial, it may be underpowered to detect modest clinical effects or to support definitive conclusions. Second, the open-label design and absence of a placebo-controlled arm may introduce bias, although blinded endpoint assessment and standardized protocols aim to mitigate this. Third, the trial evaluates surrogate physiological endpoints, such as the mPAP/CO slope and echocardiographic parameters, rather than hard clinical outcomes, such as hospitalization or mortality. In addition, the follow-up duration may be insufficient to fully capture reverse remodeling or long-term clinical benefit. Last, the inclusion of patients based on a historical diagnosis of FMR—despite its dynamic nature—may result in heterogeneity in baseline MR severity at enrollment.



Visual Take-Home Graphic: Overview of the PRAISE-MR trial protocol. Schematic representation of the PRAISE-MR study design, showing patient eligibility, treatment allocation, drug-titration schedule, and timing of key assessments over the 6-month follow-up period. CPETecho, cardiopulmonary exercise testing with echocardiography; FMR, functional mitral regurgitation; HFpEF, heart failure with preserved ejection fraction; KCC, Kansas City Cardiomyopathy; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor; R, randomization.

Conclusion

Sacubitril-valsartan has a unique pharmacological profile that may exert both leaflet-targeted and atrial-targeted effects in HFpEF with atrial FMR, potentially decreasing FMR severity and improving exercise hemodynamics. The PRAISE-MR trial is designed specifically to test this hypothesis.

Lay summary

Patients with heart failure with preserved ejection fraction (HFpEF) often experience leaking of the mitral valve (atrial functional mitral regurgitation; FMR), which worsens their symptoms and outcomes. However, no proven medical treatments specifically target this problem. The PRAISE-MR trial studies whether the heart-failure drug sacubitril-valsartan can improve heart function and reduce valve leakage in these patients. In this study, participants with HFpEF and atrial FMR are randomly assigned to receive either sacubitril-valsartan or usual care. Researchers will measure changes in heart and lung function during exercise after 6 months. The goal is to find out whether sacubitril-valsartan can ease the strain on the heart and lungs during activity, potentially leading to better treatment options for these patients.

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Disclosures

None.

CRediT authorship contribution statement

SEBASTIAAN DHONT: Writing – original draft, Project administration, Funding acquisition, Visualization, Methodology, Conceptualization, Resources, Investigation. **SARA MOURA FERREIRA:** Writing – review & editing. **XAVIER GALLOO:** Writing – review & editing, Methodology. **PIETER MARTENS:** Writing – review & editing, Methodology, Conceptualization. **EVELYNE MEEKERS:** Writing – review & editing. **KATRIEN TARTAGLIA:** Writing – review & editing, Conceptualization. **SÉBASTIEN DEFERM:** Writing – review & editing, Conceptualization. **LIEVEN HERBOTS:** Writing – review & editing. **WILFRIED MULLENS:** Writing – review & editing, Writing – original draft, Conceptualization. **FREDERIK H. VERBRUGGE:** Writing – review & editing, Conceptualization. **JAN VERWERFT:** Conceptualization, Writing – review & editing. **PHILIPPE B. BERTRAND:** Supervision, Investigation, Data curation, Project administration, Funding acquisition, Conceptualization, Writing – review & editing, Methodology, Formal analysis.

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