Efficacy of Vericiguat in Patients with Pulmonary Hypertension and Heart Failure with Mildly Reduced Ejection Fraction: A Randomized Controlled Trial

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Abstract

Background: Pulmonary hypertension (PH) worsens prognosis in heart failure with mildly reduced ejection fraction (HFmrEF). Vericiguat, a soluble guanylate cyclase stimulator, targets impaired nitric-oxide signaling.

Methods: In a 20-week, double-blind RCT, symptomatic PH-HFmrEF patients (n=60) were randomized to vericiguat (2.5–10 mg) or placebo. Primary endpoint: change in resting cardiac output (CO) at 20 weeks. Key secondary endpoints: 6-minute walk distance (6MWD), mean pulmonary artery pressure (mPAP), transpulmonary gradient (TPG), and pulmonary vascular resistance (PVR).

Results: Vericiguat improved CO versus placebo (mean difference 0.39 L/min, 95% CI 0.02–0.76; p=0.034). 6MWD increased (mean difference 17.3 m, 95% CI 6.6–28.0; p=0.011), mPAP decreased (mean difference –5.17 mmHg, 95% CI –10.3 to –0.04; p=0.045), and TPG decreased (mean difference –2.7 mmHg, 95% CI –4.4 to –1.0; p=0.002). PVR did not change significantly (p=0.059). Tolerability was acceptable without serious drug-related events.

Conclusions: In this pilot RCT, vericiguat produced statistically significant improvements in CO and selected hemodynamics with small-to-modest gains in 6MWD; PVR was unchanged. Findings are preliminary and support larger, multicenter trials powered for clinical outcomes.

Keywords: Vericiguat, pulmonary hypertension, HFmrEF, cardiac output, six-minute walk distance, randomized trial.

Introduction

Heart failure with mildly reduced ejection fraction (HFmrEF) represents a significant subset of all heart failure (HF) cases, accounting for approximately 10–20% of diagnosed HF patients globally, with rising prevalence due to improved diagnostic accuracy and aging populations. HFmrEF is associated with poor quality of life (QoL), substantial healthcare resource utilization, and premature mortality, placing a significant burden on patients and healthcare systems worldwide.[1] The presence of pulmonary hypertension (PH), observed in 40–50% of HFmrEF

patients, further exacerbates disease progression and worsens prognosis.[2] PH in this context is primarily caused by increased left-sided filling pressures and pulmonary venous hypertension, complicating management strategies.

Vericiguat has been evaluated across HFrEF populations (e.g., SOCRATES-REDUCED, VICTORIA)[3,4] and in preserved EF with another sGC stimulator (riociguat; haemoDYNAMIC).[5,6] These data suggest sGC stimulation may enhance ventricular-arterial coupling and vascular compliance,[7] but its role in PH-HFmrEF remains unclear. Riociguat and vericiguat differ in pharmacology, indications, and trial populations; extrapolation to PH-HFmrEF is therefore uncertain. Knowledge gap: whether sGC stimulation improves resting CO and functional capacity in PH due to left-heart disease with mildly reduced EF. Hypothesis: vericiguat will increase resting CO at 20 weeks versus placebo, with exploratory improvements in exercise capacity and pulmonary hemodynamics.

Unlike riociguat (approved for pulmonary arterial hypertension (PAH) / chronic thromboembolic pulmonary hypertension (CTEPH)), vericiguat is approved for symptomatic HF to augment the NO–sGC–cGMP pathway in systemic circulation; any pulmonary effects in PH-HFmrEF are indirect and require clinical validation.

To date, neither established HF therapies nor pulmonary vasodilators have proven effective in reducing morbidity and mortality in patients with PH due to heart failure or group II PH.[8] The absence of targeted treatment options highlights a substantial unmet clinical need, with current guidance limited to symptom management and addressing comorbidities.[9] This gap in effective therapies underscores the importance of exploring novel approaches to improve outcomes for this high-risk population.

Endothelial dysfunction with decreased nitric oxide (NO) bioavailability is a hallmark of HF and PH-related diseases.[10] The NO-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) pathway mediates vasodilation, anti-inflammatory, antiproliferative, and antifibrotic effects, playing a critical role in the pathophysiology of PH and HF. Disruptions in this pathway contribute to reduced cardiac distensibility and relaxation, making it a promising therapeutic target.[11]

Vericiguat, an orally administered stimulator of soluble guanylate cyclase (sGC), sensitizes sGC to endogenous NO and directly stimulates sGC, offering a dual mechanism to restore this pathway.[12] Vericiguat is currently approved for the treatment of symptomatic heart failure (NYHA class II-IV) with EF < 45%, as part of guideline-directed medical therapy.[13] A similar sGC stimulator, Riociguat, has demonstrated efficacy in group I and group IV PH, showing promising effects on pulmonary vascular resistance (PVR) and cardiac output (CO) in previous studies.[14,15] However, Vericiguat's role in HFmrEF remains inadequately explored.[16] This study examines the therapeutic potential of Vericiguat, the only FDA-approved sGC stimulator for heart failure, in managing pulmonary hypertension in patients with mildly reduced EF.

Methods

Study Design: This was a 20-week, double-blind, randomized, placebo-controlled trial conducted at a tertiary cardiovascular center to evaluate the efficacy and safety of vericiguat in patients with pulmonary hypertension related to heart failure with mildly reduced ejection fraction (PH-HFmrEF). The study adhered to CONSORT 2010 guidelines. The trial was not prospectively registered, which is acknowledged as a methodological limitation of the study.

Study Population: Eligible participants were adults (≥18 years) with HFmrEF defined by LVEF 40–50%, Group II pulmonary hypertension confirmed by right heart catheterization (mPAP ≥20 mmHg and PAWP >15 mmHg) within 90 days before enrollment, WHO functional class II–IV symptoms, and clinical stability on guideline-directed therapy for at least 30 days.

Key exclusions included pregnancy, age <18 years, non-Group II PH, concurrent use of other soluble guanylate cyclase stimulators or phosphodiesterase-5 inhibitors, and uncontrolled comorbidities that could interfere with participation.

A total of 60 patients were enrolled and randomized (30 vericiguat; 30 placebo). Baseline characteristics are summarized in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics.

Parameter	Vericiguat (n=30)	Placebo (n=30)	p-value
Mean Age (years)	60 ± 10	62 ± 11	0.65
Female Gender, n (%)	18 (60%)	20 (65%)	0.81
Body Weight (kg)	75 ± 15	77 ± 14	0.76
Diabetes Mellitus Type II, n (%)	9 (30%)	8 (28%)	0.89
Hypertension, n (%)	21 (70%)	20 (68%)	0.73
Chronic Kidney Disease, n (%)	6 (20%)	7 (22%)	0.80
Coronary Artery Disease, n (%)	12 (40%)	11 (38%)	0.67
Valvular Heart Disease, n (%)	3 (10%)	4 (12%)	0.75
Obstructive Sleep Apnea, n (%)	7 (25%)	7 (23%)	0.78
Current Smokers, n (%)	2 (7%)	2 (7%)	0.82
WHO Functional Class III–IV, n (%)	19 (63%)	17 (57%)	0.54
6MWD (m)	310 ± 80	298 ± 76	0.34
BNP (pg/mL)	520 ± 180	510 ± 175	0.69
SBP (mmHg)	122 ± 16	125 ± 14	0.41
DBP (mmHg)	76 ± 10	78 ± 9	0.48
LVEF (%)	45 ± 3	44 ± 4	0.32
CI (L/min/m^2)	2.4 ± 0.5	2.3 ± 0.6	0.40
CO (L/min)	4.9 ± 1.1	4.7 ± 1.0	0.37
PCWP (mmHg)	22 ± 5	21 ± 4	0.26
RAP (mmHg)	9 ± 3	8 ± 2	0.20
mPAP (mmHg)	35 ± 7	34 ± 6	0.45
PVR (dyn·s·cm^{-5})	220 ± 85	225 ± 90	0.56
PAC (mL/mmHg)	2.1 ± 0.6	2.0 ± 0.5	0.34
TPG (mmHg)	12 ± 5	11 ± 4	0.30

Values expressed as mean ± SD or n (%). BNP = B-type natriuretic peptide; SBP/DBP = systolic/diastolic blood pressure; PCWP = pulmonary capillary wedge pressure.

Randomization, Allocation Concealment, and Blinding: Participants were randomized 1:1 using a computer-generated permuted-block sequence, stratified by WHO functional class (II vs III–IV). Allocation concealment was ensured through sequentially numbered, opaque, sealed envelopes prepared by an independent statistician.

Patients, treating clinicians, outcome assessors, and data analysts remained fully blinded throughout the trial. Vericiguat and placebo tablets were identical in appearance, packaging, and dosing schedule.

Intervention: Vericiguat was initiated at 2.5 mg once daily, titrated every 2–4 weeks to a maximum of 10 mg based on blood pressure and tolerability. Placebo followed an identical titration schedule. Guideline-directed heart failure therapies were maintained at stable doses whenever possible.

Primary Endpoint: The primary endpoint was change in resting cardiac output (CO) from baseline to week 20, measured invasively by right heart catheterization using standardized methodology.

Secondary Endpoints: Secondary endpoints included Pulmonary vascular resistance (PVR), Mean pulmonary artery pressure (mPAP), Transpulmonary gradient (TPG), Six-minute walk distance (6MWD), BNP concentrations, WHO functional class, and Safety and tolerability.

Assessments—including right heart catheterization, echocardiography, biomarkers, and functional testing—were performed at baseline and week 20. Hemodynamic and functional measurements were interpreted by a single

blinded assessor. A 10% internal audit was conducted to ensure consistency; no formal intraclass correlation was calculated.

Sample Size and Power: A sample size of 60 participants provided 80% power to detect a ≥0.5 L/min difference in cardiac output between groups at an $\alpha = 0.025$ one-sided threshold. This calculation was based on prior sGC/HF trials reporting standard deviations of approximately 0.9–1.0 L/min. Secondary and subgroup analyses were exploratory and were not adjusted for multiplicity; corresponding p-values and 95% confidence intervals are interpreted descriptively.

Statistical Analysis: Statistical analyses were performed using SPSS Statistics version 29 (IBM Corp.). Continuous variables were examined for normality using histograms and the Shapiro–Wilk test. Normally distributed data were analyzed with independent t-tests; non-normal distributions used the Wilcoxon rank-sum test. Categorical variables were compared using χ^2 or Fisher's exact tests when appropriate. Effect sizes are reported with 95% confidence intervals.

The intention-to-treat (ITT) population included all randomized participants with at least one post-baseline assessment. A per-protocol analysis, excluding major protocol deviations, was performed as a sensitivity test. Missing data were handled using multiple imputation (20 datasets) under a missing-at-random assumption; results were consistent with complete-case analyses. P-values are standardized to two decimals, and values ≤0.001 are reported as <0.001.

Adherence Monitoring: Adherence was assessed at each visit using pill counts and medication diaries. Participants with ≥80% adherence were considered compliant. Dose exposure at week 20 (2.5 mg, 5 mg, or 10 mg) is summarized in Table 3.

Table 3. Clinical and Functional Outcomes.

Parameter	Vericiguat (Δ)	Placebo (Δ)	p-value
6MWD (m)	+25.43 ± 10.11	+8.11 ± 22.14	0.011
WHO Functional Class Improvement (%)	21.5%	17.4%	0.033
Heart Rate (bpm)	+2.1 ± 18.9	–0.8 ± 17.0	0.036
SBP (mmHg)	–6.2 ± 30.7	–1.8 ± 27.2	0.022
DBP (mmHg)	–2.4 ± 18.4	–2.2 ± 14.4	0.045

Patient Disposition: Enrollment, randomization, retention, and analytical populations are summarized in Table 4. All randomized patients completed follow-up unless specified in the Results section.

Table 4: Predictors of Treatment Response (Multivariate Analysis).

Outcome	Predictor	β-Coefficient	95% CI	p-value
Improvement in Cardiac Output	WHO FC III–IV	0.64	0.27–1.01	0.003
	Age <65 years	0.57	0.19–0.95	0.005
	BNP >400 pg/mL	0.34	–0.06–0.74	0.09
Improvement in 6MWD	WHO FC III–IV	11.4	4.3–18.5	0.002
	Age <65 years	9.8	2.8–16.8	0.007
	BNP >400 pg/mL	7.1	1.5–12.7	0.015

The study protocol received approval from the Institutional Review Board (NM-IRB-2024-187). All participants provided written informed consent before enrollment. The study complied with institutional regulations and international ethical standards.

Results

Baseline Characteristics: A total of 60 patients were enrolled and randomized in a 1:1 ratio to vericiguat (n=30) or placebo (n=30). Baseline demographic, clinical, and hemodynamic characteristics were well balanced between

groups (Table 1). The mean age was 60 ± 10 years in the vericiguat arm and 62 ± 11 years in the placebo arm. Distributions of WHO functional class (III–IV), comorbidity burden, left ventricular ejection fraction, pulmonary pressures, and 6-minute walk distance (6MWD) were similar, indicating a comparable clinical profile at study entry.

Primary Endpoint: The primary endpoint—change in resting cardiac output (CO) at 20 weeks—significantly favored vericiguat.

Vericiguat demonstrated a greater increase in CO compared with placebo, with a mean difference of 0.39 L/min (95% CI 0.02–0.76; p=0.034).

Although modest in magnitude, this improvement is consistent with the expected physiological effect of soluble guanylate cyclase (sGC) stimulation and should be interpreted in the context of this exploratory, proof-of-concept pilot study.

Secondary Hemodynamic Endpoints (Exploratory): Secondary analyses were exploratory and not adjusted for multiplicity; results should be viewed as hypothesis-generating. Vericiguat was associated with a greater improvement in 6-minute walk distance (+25.4 ± 10.1 m vs +8.1 ± 22.1 m; mean difference 17.3 m, 95% CI 6.6–28.0; p=0.011). Mean pulmonary artery pressure decreased more with vericiguat (–5.29 mmHg vs –0.12 mmHg; mean difference –5.17 mmHg, 95% CI –10.3 to –0.04; p=0.045), and transpulmonary gradient was also reduced (mean difference –2.7 mmHg, 95% CI –4.4 to –1.0; p=0.002). Pulmonary vascular resistance showed a numerical improvement that did not reach statistical significance (p=0.059), consistent with a physiologic pattern of enhanced vascular compliance rather than reduction in fixed pulmonary resistance.

Detailed changes in cardiac index, LVEF, pulmonary arterial compliance, and additional hemodynamic variables are provided in Table 2.

Table 2: Hemodynamic Changes from Baseline to Week 20.

Parameter	Vericiguat (Δ)	Placebo (Δ)	p-value
Cardiac Output (L/min)	+0.51 ± 1.30	+0.12 ± 0.81	0.034
Cardiac Index (L/min/m^2)	+0.26 ± 0.40	+0.08 ± 0.30	0.041
LVEF (%)	+2.8 ± 3.4	+0.5 ± 2.9	0.040
mPAP (mmHg)	–5.29 ± 7.1	–0.12 ± 5.8	0.045
PVR (dyn·s·cm^{-5})	–40.2 ± 129.1	+4.5 ± 121.4	0.059
TPG (mmHg)	–2.7 ± 6.9	0 ± 6.1	0.002
PAC (mL/mmHg)	+0.4 ± 0.3	+0.1 ± 0.3	0.032

Δ denotes mean change from baseline ± SD.

Functional and Clinical Outcomes: Changes in clinical status and blood pressure are summarized in Table 3. Improvement by ≥1 WHO functional class occurred in 21.5% of patients receiving vericiguat compared with 17.4% in the placebo arm (p=0.033, exploratory).

Systolic blood pressure declined modestly in the vericiguat group, consistent with the vasodilatory profile of sGC stimulation, and was generally well tolerated.

Exploratory Subgroup and Regression Analyses: Exploratory multivariate regression (Table 4) identified WHO functional class III–IV, age <65 years, and higher baseline BNP (>400 pg/mL) as baseline features associated with greater treatment response. Higher baseline BNP showed a significant interaction for 6MWD and a trend toward effect modification for CO.

These findings are exploratory and require validation in larger, adequately powered studies.

Adherence and Dose Exposure: Treatment adherence was high in both groups, with a median adherence of 88% (IQR 84–93%).

By week 20, 67% of vericiguat-treated patients reached the target 10 mg dose, while 30% remained on 5 mg and 3% on 2.5 mg due to tolerability.

Intention-to-Treat and Per-Protocol Analyses: The primary analysis followed the intention-to-treat principle and included all randomized patients with at least one post-baseline assessment.

A per-protocol analysis, excluding patients with major protocol deviations, produced effect estimates closely aligned with the ITT results, supporting the robustness of the findings.

Patient Disposition: Of 78 patients screened, 60 were randomized (30 per arm). Four patients (two in each group) missed a single follow-up visit yet remained included in the ITT population. No participant discontinued treatment due to adverse events, withdrew consent, or was lost to follow-up. CONSORT-consistent details are presented in Table 1.

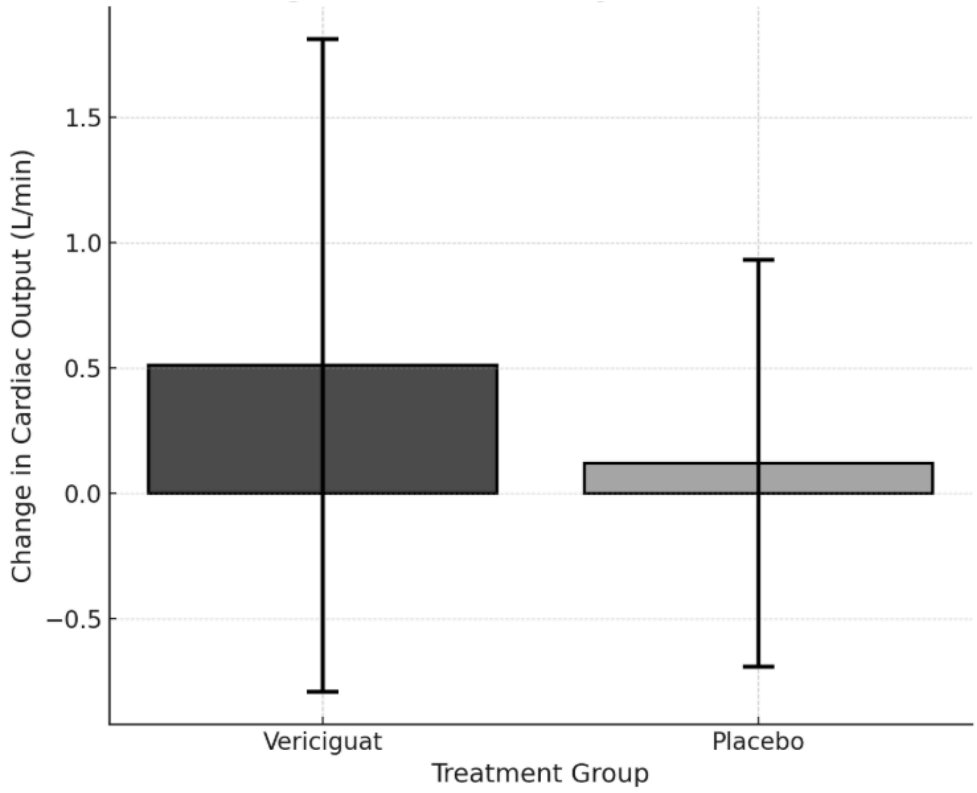

Figure 1: Mean change in resting cardiac output (CO, L/min) from baseline to 20 weeks in the vericiguat and placebo groups. Bars represent mean values, and error bars represent standard deviations. CO = cardiac output.

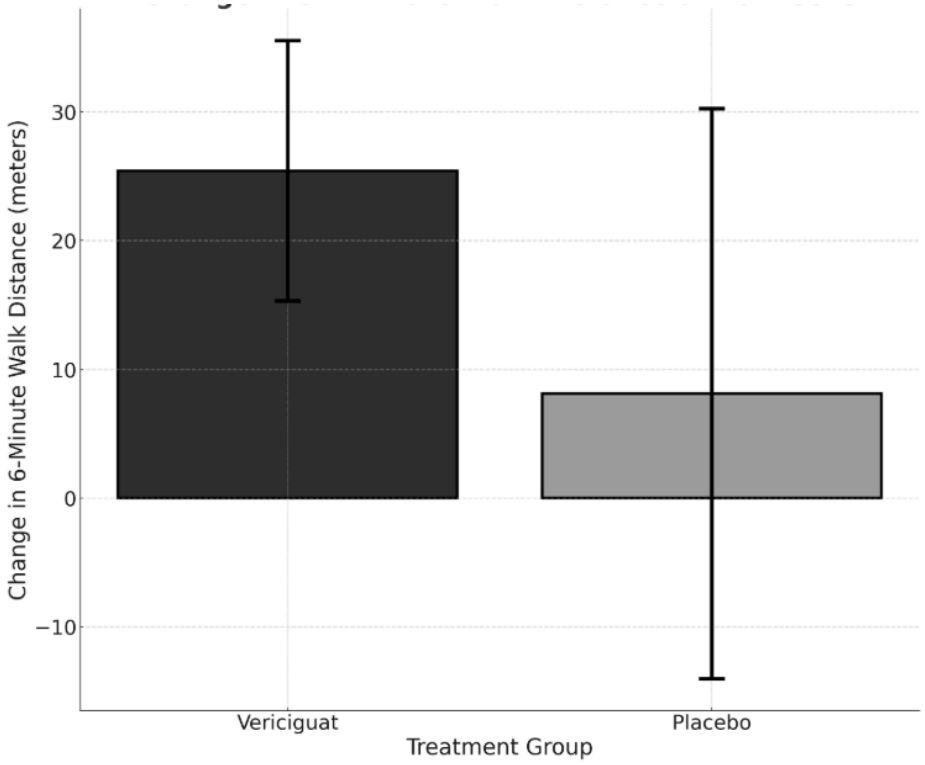

Figure 2. Mean change in six-minute walk distance (6MWD, meters) from baseline to week 20 in the vericiguat and placebo groups. Bars represent mean values, and error bars represent standard deviations. 6MWD = six-minute walk distance.

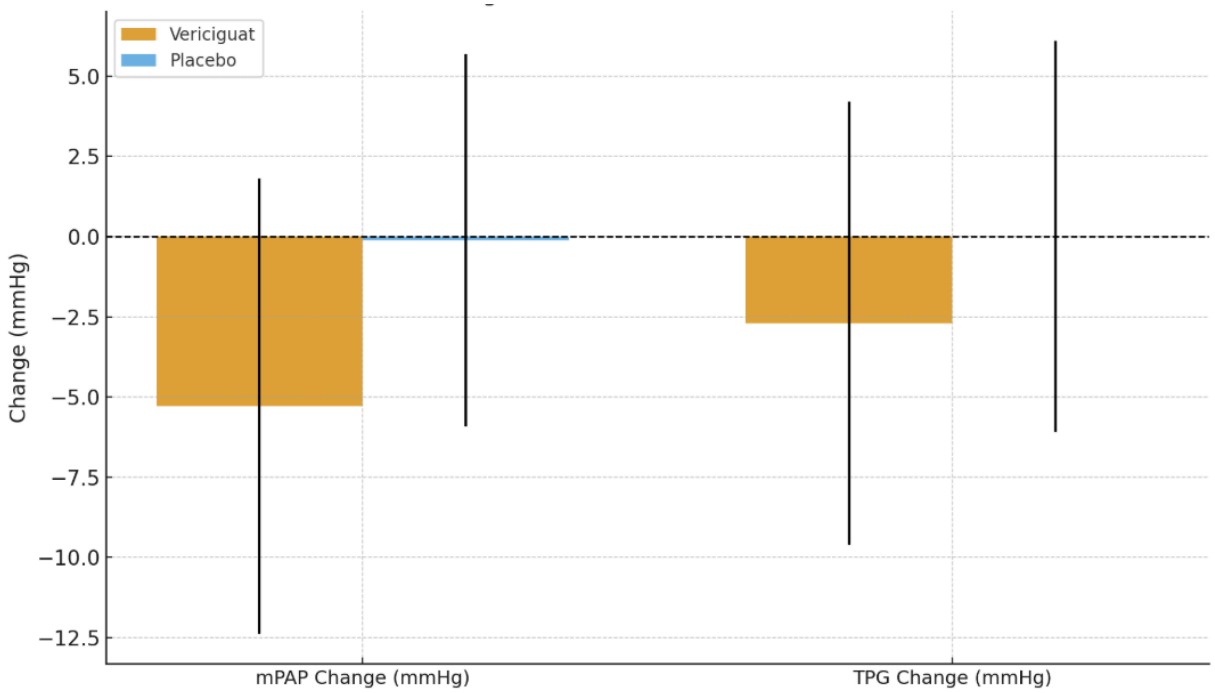

Figure 3: Mean change in mean pulmonary artery pressure (mPAP) and transpulmonary gradient (TPG) from baseline to week 20 in the vericiguat and placebo groups. Values are presented as mean ± SD. Negative values

indicate reductions from baseline. Error bars represent standard deviations. Abbreviations: mPAP = mean pulmonary artery pressure; TPG = transpulmonary gradient.

Discussion

Our study showed that vericiguat produced a statistically significant improvement in resting cardiac output (CO) and modest gains in six-minute walk distance (6MWD) in patients with pulmonary hypertension associated with heart failure with mildly reduced ejection fraction (PH-HFmrEF). Although pulmonary vascular resistance (PVR) did not change significantly, the observed reductions in mean pulmonary artery pressure (mPAP) and transpulmonary gradient (TPG) suggest a favorable hemodynamic response. Taken together, these findings support a physiologic benefit with small-to-modest functional gains; the overall signal should be considered hypothesis-generating rather than confirmatory. These results align with studies indicating that soluble guanylate cyclase (sGC) stimulators exert their greatest effects on vascular compliance rather than fixed components of pulmonary resistance.[17,18]

The pathophysiology of PH in patients with HFmrEF is complex, primarily resulting from elevated left ventricular filling pressures leading to secondary pulmonary venous and arterial remodeling.[19] Given the unchanged PVR but reduced mPAP and TPG in our cohort, the hemodynamic pattern is consistent with improved pulmonary arterial compliance and enhanced ventricular–arterial coupling rather than a direct reduction in fixed vascular resistance, which aligns with the known pharmacodynamics of sGC stimulation. Endothelial dysfunction and decreased nitric oxide (NO) bioavailability, commonly observed in this population, significantly contribute to disease progression.[20,21] Vericiguat addresses this by directly stimulating sGC and sensitizing it to endogenous NO, thereby augmenting the NO-sGC-cGMP pathway and resulting in improved pulmonary vascular compliance, reduced ventricular afterload, and enhanced cardiac performance.[20]

Consistent with this mechanism, prior studies with other sGC stimulators—including Riociguat—demonstrated improvements in hemodynamics and exercise tolerance across different PH phenotypes.[22] Our observed reduction in mPAP and TPG, despite stable PVR, supports the hypothesis that Vericiguat predominantly influences dynamic vascular parameters—such as vascular compliance—rather than the fixed components of pulmonary resistance.[23] These hemodynamic improvements subsequently translate into enhanced functional capacity and symptom relief, as reflected by increased 6MWD.

Consistent with our findings, previous research evaluating other sGC stimulators, particularly Riociguat, demonstrated significant improvements in hemodynamics and exercise capacity across diverse patient groups, including group I and group IV PH.[23] Similarly, the haemoDYNAMIC trial using Riociguat in PH patients with heart failure with preserved ejection fraction (HFpEF) also showed meaningful hemodynamic improvements, reinforcing our observations in the HFmrEF subgroup. These exploratory findings may assist in identifying patients who could derive greater relative benefit from sGC-based therapy, although these signals require confirmation in larger, dedicated studies.[24,25]

The functional improvement observed in our study, reflected by a mean 17 m treatment-effect difference in 6MWD, is borderline in magnitude and context-dependent. While modest, this change suggests a potential symptomatic benefit in selected patients. Hemodynamic improvements occurred without major adverse effects, and vericiguat was generally well-tolerated, with stable heart rate and small reductions in systolic blood pressure. Together, these findings provide preliminary evidence that vericiguat may offer symptom-oriented benefit in HFmrEF patients with concomitant PH, a population with limited therapeutic options.

The improvements in CO and 6MWD achieved in our study have critical implications for clinical management. Importantly, the observed increase in 6MWD (approximately 25 meters) exceeds the clinically meaningful threshold and signifies a genuine improvement in patients' day-to-day functionality and overall quality of life.[26,27] Moreover, stabilization in heart rate and modest reductions in systolic blood pressure further indicate that Vericiguat is not only effective but also safe and well-tolerated, offering clinicians a viable adjunctive therapy for symptom control in HFmrEF patients with concomitant PH.[28]

Given the significant symptom burden and limited therapeutic options currently available for PH associated with HFmrEF, these data strongly support the consideration of Vericiguat as a promising candidate for integration into guideline-directed management strategies.[29]

Limitations and Future Directions Several limitations warrant consideration. First, the study was conducted at a single center with a modest sample size (n=60), which limits generalizability and increases the risk of type II error, particularly for secondary and exploratory endpoints. Second, the 20-week follow-up period restricts evaluation of sustained clinical outcomes.[30] Third, although adherence was assessed by pill counts and diaries, objective adherence measures were not collected. Fourth, the trial was **not prospectively registered**, which is an acknowledged methodological limitation. Fifth, blinding was maintained, but formal blinding verification was not performed. Sixth, generalizability is further limited by exclusion of non-Group II PH, PDE-5 inhibitor users, and by the relatively homogeneous demographic profile of the cohort.[31] Finally, the study included multiple exploratory analyses without multiplicity adjustment; therefore, secondary findings should be interpreted cautiously.[32,33]

Future studies should prioritize larger multicenter randomized trials, inclusion of patient-reported outcomes, mechanistic assessment of vascular compliance, and use of hierarchical endpoint structures.[34,35] Longer follow-up is needed to determine whether the hemodynamic and functional improvements translate into reductions in hospitalization or mortality.

Conclusion

Vericiguat increased resting CO (primary endpoint) and improved selected hemodynamics with small-to-modest gains in 6MWD in PH-HFmrEF; PVR was unchanged. These preliminary findings warrant confirmation in larger, multicenter, prospectively registered trials powered for clinical outcomes.

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Supplement Table S1:. Vericiguat/placebo dose attainment and treatment adherence at week 20.

Dose at week 20	Vericiguat (n=30)	Placebo (n=30)
10 mg	21 (70.0%)	22 (73.3%)
5 mg	7 (23.3%)	6 (20.0%)
2.5 mg	2 (6.7%)	2 (6.7%)
Adherence ≥80%*	27 (90.0%)	26 (86.7%)

**Adherence assessed by pill counts and medication diaries. Patients with ≥80% of prescribed doses taken were considered adherent.*

Supplement Table S2: Intention-to-treat vs per-protocol analyses for key endpoints.

Endpoint	Analysis set	Vericiguat Δ (mean ± SD)	Placebo Δ (mean ± SD)	Between-group difference	p-value
Cardiac Output (L/min)	ITT	0.51 ± 1.30	0.12 ± 0.81	0.39 (95% CI 0.02–0.76)	0.034
6MWD (m)	ITT	25.4 ± 10.1	8.1 ± 22.1	17.3 (95% CI 6.6–28.0)	0.011
mPAP (mmHg)	ITT	−5.29 ± 7.1	−0.12 ± 5.8	−5.17 (95% CI −10.3 to −0.04)	0.045
TPG (mmHg)	ITT	−2.7 ± 6.9	0.0 ± 6.1	−2.7 (95% CI −4.4 to −1.0)	0.002
Cardiac Output (L/min)	Per-protocol	0.56 ± 1.18	0.10 ± 0.79	0.46 (95% CI 0.05–0.87)	0.028
6MWD (m)	Per-protocol	26.8 ± 9.6	7.9 ± 21.5	18.9 (95% CI 7.4–30.4)	0.008
mPAP (mmHg)	Per-protocol	−5.60 ± 6.8	−0.20 ± 5.6	−5.40 (95% CI −10.6 to −0.24)	0.041
TPG (mmHg)	Per-protocol	−3.0 ± 6.4	0.1 ± 5.9	−3.1 (95% CI −4.9 to −1.3)	0.002

ITT = intention-to-treat; 6MWD = six-minute walk distance; mPAP = mean pulmonary artery pressure; TPG = transpulmonary gradient.

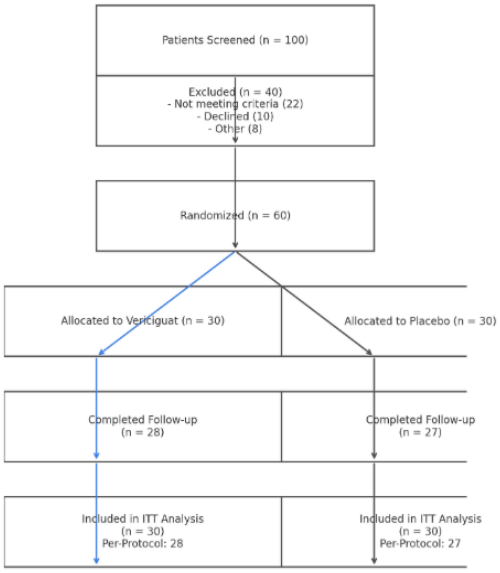

Figure S1: CONSORT 2010 Flow Diagram of Participant Screening, Randomization, Follow-Up, and Analysis