THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Association Between Different Vericiguat Dose Exposures, Concomitant Quadruple Heart Failure Therapy, and Myocardial Fibrosis Burden in Older Adults with Worsening Heart Failure with Reduced Ejection Fraction

ABSTRACT

Background: Older adults with worsening heart failure with reduced ejection fraction (HFrEF) remain high risk despite quadruple guideline-directed medical therapy (GDMT-4). Whether vericiguat exposure relates to change in myocardial fibrosis is unknown.

Methods: A single-center, prospective cohort of patients ≥65 years with HFrEF [left ventricular ejection fraction (LVEF) ≤40%] after a recent worsening event (enrollment from January 2022 to December 2023 with 12-month follow-up) was conducted. Vericiguat exposure was modeled as time-updated, lagged dose across intervals. Baseline therapy was quantified with a GDMT-4 Index (0-7). Co-primary endpoints were 12-month change in cardiovascular magnetic resonance extracellular volume (ECV, %) and a serum fibrosis composite z-score. Extracellular volume used weighted models with observation weights. Multiplicity for co-primary endpoints was controlled by Holm–Bonferroni. Recurrent rehospitalizations used Andersen–Gill and marginal structural models.

Results: Of 268 screened, 210 enrolled and 198 formed the analysis set. Paired ECV was available for 146 (73.7%). High vs. low exposure was associated with greater ECV reduction (−1.3 percentage points; 95% CI −2.1 to −0.5; Holm-adjusted $P = .002$) and serum composite improvement (−0.23 SD; 95% CI −0.37 to −0.09; Holm-adjusted $P = .004$). Secondary endpoints favored higher exposure (global longitudinal strain +1.1%, N-terminal pro-B-type natriuretic peptide geometric mean ratio 0.84, 12-item Kansas City Cardiomyopathy Questionnaire +6.1; $q \leq 0.045$). The exposure × GDMT-4 interaction for ΔECV ($P = .031$) showed larger benefit at higher GDMT-4. Over 195 person-years, 52 rehospitalizations occurred; high exposure was associated with fewer events (Hazard ratio 0.74, 95% CI 0.53–1.03; exploratory). Safety events were infrequent and balanced.

Conclusions: Greater time-updated vericiguat exposure was linked to less fibrosis and an exploratory reduction in rehospitalizations, especially with higher GDMT-4.

Keywords: Cardiac MRI, extracellular volume, guideline-directed therapy, heart failure with reduced ejection fraction, marginal structural models, myocardial fibrosis, vericiguat

INTRODUCTION

Older adults with worsening heart failure with reduced ejection fraction (HFrEF) remain at high risk despite optimized quadruple guideline-directed medical therapy (GDMT-4), which includes angiotensin receptor–neprilysin inhibitor (ARNI)/angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), β-blocker, mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter 2 inhibitor (SGLT2i). The persistence of high risk is evident from several studies that highlight the challenges and limitations of current treatment strategies. Patients with a history of worsening heart failure events are particularly vulnerable, experiencing higher rates of hospitalizations and mortality compared to those without such a history, even when on comprehensive GDMT-4.[1,2] The effectiveness of GDMT-4 in real-world settings is often compromised by suboptimal adherence and dosing, with many patients not receiving the full

ORIGINAL INVESTIGATION

Liyong Ge[1,2]
Guoqiu Wang[1,2]
Anning Zeng[2]
Wei Li[3]

[1]*Clinical College of Guizhou Medical University, Guiyang, Guizhou, China*
[2]*Department of Cardiology II, The People's Hospital of Qiannan Prefecture, Duyun, Guizhou, China*
[3]*Department of Cardiovascular Medicine, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China*

Corresponding author:
Wei Li
✉ gliwei5089@163.com

Received: November 18, 2025
Accepted: February 17, 2026
Available Online Date: April 2, 2026

Cite this article as: Ge L, Wang G, Zeng A, Li W. Association between different vericiguat dose exposures, concomitant quadruple heart failure therapy, and myocardial fibrosis burden in older adults with worsening heart failure with reduced ejection fraction. *Anatol J Cardiol.* 2026;XX(X):1-9.

DOI: 10.14744/AnatolJCardiol.2026.5960

recommended doses due to clinical inertia, adverse effects, or comorbidities.[3-5] Furthermore, older adults, who are frequently underrepresented in clinical trials, face unique challenges in heart failure management due to multimorbidity and frailty, which complicate the application of standard therapies and may shift the risk-benefit balance unfavorably.[6,7] Despite the proven efficacy of GDMT-4 in reducing morbidity and mortality, the residual risk remains significant, underscoring the need for additional therapeutic strategies and personalized care approaches to address the complex needs of older adults with HFrEF.[8,9] The ongoing high rates of hospitalizations and mortality among these patients highlight the necessity for innovative interventions and improved adherence to GDMT-4 to better manage heart failure in this high-risk population.[2,10] The study focused on older adults (≥65 years) because they comprise a large proportion of patients with worsening HFrEF in routine practice, have substantial multimorbidity and frailty that can complicate optimization of guideline-directed therapies, and remain underrepresented in many pivotal HFrEF trials.[6,7] In addition, real-world data suggest that achieving target vericiguat doses is less frequent in older patients, making dose–exposure relationships particularly relevant in this population.[15]

Vericiguat, an oral soluble guanylate cyclase stimulator, is recommended for patients with HFrEF following recent decompensation, yet the real-world dose exposure-biomarker relationships remain unclear. The VICTORIA trial demonstrated vericiguat's efficacy in reducing cardiovascular mortality and hospitalizations in high-risk HFrEF patients.[11,12] In real-world settings, studies like the VERISEC registry and the VeriChange survey have shown that vericiguat is often initiated after a heart failure decompensation event, with a significant proportion of patients achieving the target dose of 10 mg/day.[13,14] However, the up-titration to the maximum dose is less frequent among women and older patients.[15] Biomarker analyses, such as those involving NT-proBNP levels, suggest that patients with lower levels may derive more benefit from vericiguat.[11] Furthermore, studies have shown that vericiguat can lead to cardiac reverse remodeling and improvements in left ventricular ejection fraction when combined with optimal GDMT-4.[16] Despite these benefits, the optimal timing for initiating vericiguat remains debated, with evidence suggesting that earlier initiation, before multiple hospitalizations, may yield better outcomes.[17] Hemodynamic studies have also demonstrated vericiguat's potential to improve cardiac performance by reducing pulmonary artery wedge pressure.[18] Overall, while vericiguat shows promise in reducing adverse outcomes in HFrEF patients, further research is needed to optimize its use and understand the dose-biomarker relationships in diverse patient populations.[19,20]

HIGHLIGHTS

- In older adults with recent worsening heart failure with reduced ejection fraction (HFrEF), greater time-updated vericiguat exposure was independently associated with less 12-month progression of myocardial fibrosis (lower cardiovascular magnetic resonance-extracellular volume and improved serum fibrosis composite).
- The antifibrotic association of vericiguat was stronger at higher background quadruple guideline-directed therapy intensity, supporting biological complementarity with optimized quadruple guideline–directed medical therapy.
- Higher vericiguat exposure was associated with better cardiac mechanics (absolute GLS), lower NT-proBNP, and higher KCCQ-12 scores, aligning mechanistic and patient-reported benefits.
- In marginal structural Andersen–Gill models, higher vericiguat exposure showed an exploratory association with fewer recurrent heart failure rehospitalizations over 12 months.
- Vericiguat was well tolerated in this older, recently decompensated HFrEF cohort, with low and similar rates of symptomatic hypotension and anemia across exposure categories.

The relationship between higher vericiguat exposure and the progression of myocardial fibrosis, as assessed by cardiovascular magnetic resonance (CMR) extracellular volume (ECV) and serum fibrosis composites, remains inadequately defined, particularly in the context of time-related biases and GDMT-4 intensity. Studies indicate that myocardial fibrosis, quantified through ECV, is a significant predictor of adverse outcomes, including hospitalization for heart failure and mortality, with higher ECV correlating with increased risk.[21,22] Furthermore, while vericiguat has shown promise in improving heart failure outcomes and reducing hospital admissions, its specific impact on myocardial fibrosis progression has not been thoroughly investigated.[23] The interplay between myocardial inflammation and fibrosis complicates the interpretation of ECV as a reliable marker, suggesting that the presence of inflammation may alter ECV readings, thus affecting the assessment of fibrosis progression.[24] Therefore, further research is necessary to clarify these associations and control for confounding factors such as GDMT-4 intensity.[25]

The objective was to quantify dose–response associations between time-updated, lagged vericiguat exposure and 12-month change in myocardial fibrosis, measured by CMR-derived ECV (%) and a prespecified serum fibrosis composite (z-score), in older adults with worsening HFrEF, while explicitly accounting for background quadruple guideline-directed therapy (GDMT-4) intensity and time-varying confounding. Secondarily, the study aimed to evaluate whether higher exposure related to fewer recurrent heart-failure rehospitalizations over 12 months and to characterize safety (symptomatic hypotension and anemia).

METHODS

Study design

A single-center, prospective, non-interventional cohort of older adults with HFrEF was conducted to evaluate associations between time-updated, lagged vericiguat exposure

and 12-month change in myocardial fibrosis, assessed by CMR ECV and a serum fibrosis composite, while explicitly addressing time-related biases and background guideline-directed medical therapy intensity. Enrollment occurred from January 2022 to December 2023 with 12-month follow-up. The protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of The People's Hospital of Qiannan Prefecture (Approval No. 2024-qnzy-31) on 24 October 2021. All participants provided written informed consent prior to any study procedures.

Participants

Eligible patients were ≥65 years with chronic HFrEF (LVEF ≤40%) following a recent worsening heart failure event (unscheduled intravenous diuretics or hospitalization within 6 months) who were initiated or continued on vericiguat at clinician discretion. Standard contraindications to CMR or barriers to follow-up were excluded. Of 268 screened, 210 enrolled and 198 formed the full analysis set used for inferential modeling.

Exposure Assessment and Adherence

Vericiguat dose history (start/stop dates, daily dose) was abstracted from medication records, pharmacy fills, and interviews; adherence was summarized as the proportion of days covered (PDC). For description, a 12-month time-weighted average (TWA) daily dose was computed and exposure was categorized as low (≤5 mg), medium (>5-<10 mg), or high (≥10 mg). For inferential analyses, exposure was time-updated and lagged in 3 prespecified intervals (0-3, 3-6, and 6-12 months). For continuous endpoints assessed at 12 months (ECV, serum composite, GLS, KCCQ-12, NT-proBNP), the primary exposure was the cumulative lagged TWA dose over 0-12 months, computed as the average of the interval-specific lagged means (weighted by days contributed), ensuring exposure temporally preceded the 12-month outcome; effects were estimated for high vs. low and per 5-mg increments. For event analyses, exposure remained time-varying at each interval.

Concomitant Quadruple Therapy Intensity (GDMT-4 Index)

Background therapy intensity was quantified longitudinally using a GDMT-4 Index (0-7) that sums dose-tier scores for ARNI/ACEI/ARB (0=none, 1=sub-target, 2=target/maximally tolerated), β-blocker (0–2), SGLT2 inhibitor (0–2), and mineralocorticoid receptor antagonist (0=none, 1=present); the index was updated at each visit and entered all models as a time-varying covariate. A prespecified exposure × GDMT-4 interaction was evaluated for ΔECV to test effect modification.

Outcomes

Co-primary endpoints were change from baseline to 12 months in global ECV (%) and a serum fibrosis composite z-score (negative change indicates improvement). Exploratory secondary endpoints were change in absolute GLS (%; higher magnitude is better), NT-proBNP expressed as a geometric mean ratio (GMR), and change in 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) overall score. Exploratory recurrent HF rehospitalizations within 12 months were captured as counting-process events. Safety endpoints were symptomatic hypotension and anemia, summarized overall and by descriptive exposure categories.

Biomarker Acquisition

Serum biomarkers were collected at baseline and 12 months and used to construct a prespecified fibrosis composite reflecting complementary pathways of myocardial fibrotic remodeling. The composite included procollagen type I C-terminal propeptide and procollagen type III N-terminal propeptide as markers of collagen synthesis; tissue inhibitor of metalloproteinases-1 as a marker of extracellular-matrix regulation favoring net matrix accumulation; and galectin-3 and soluble ST2 (sST2) as markers of fibro-inflammatory activation and adverse remodeling. Biomarkers were log-transformed if skewed and standardized to z-scores. The fibrosis composite at each time point was calculated as the unweighted mean of the component z-scores, and the co-primary endpoint was the change in this composite from baseline to 12 months (negative change indicates improvement). Laboratory staff were blinded to vericiguat exposure. Echocardiographic GLS and KCCQ-12 were obtained at the same time points, and NT-proBNP was assayed in a Clinical Laboratory Improvement Amendments-certified laboratory and log-transformed for analysis.

Follow-up, Covariates, and Data Structure

Study visits were scheduled at baseline, 3, 6, and 12 months. Interim events and medication changes were extracted from the EHR. Prespecified baseline covariates included age, sex, ischemic etiology, LVEF, systolic blood pressure (BP), estimated glomerular filtration rate (eGFR), and hemoglobin; time-varying covariates updated at each interval included systolic BP, eGFR, hemoglobin, NT-proBNP, hypotension/anemia episodes, and the contemporaneous GDMT-4 Index. For continuous outcomes, the dependent variable was the 12-month change (Δ) because the primary estimand was within-participant progression over 12 months. Change-score models provide an intuitive interpretation as an adjusted mean difference in change and reduce between-person baseline heterogeneity. Because Δ already incorporates the baseline value, and to avoid collinearity and over-adjustment, baseline values of the same outcome were not additionally included in the primary Δ-models. As a prespecified sensitivity analysis, ANCOVA models were also fit (12-month outcome level adjusted for baseline) and concordant inferences were found. Timestamps were aligned to preserve temporal ordering between lagged exposure, covariates, and outcomes.

Statistical Analysis

For continuous endpoints, linear mixed-effects models with subject-level random intercepts were fit to estimate adjusted mean differences for high vs. low and per-5-mg dose effects, each with 95% CIs and 2-sided *P*-values. Given 1 Δ per participant, these models reduce to (weighted) linear regression but were retained for consistency across endpoints. Observation weights addressed selective completion of the 12-month CMR and were applied only to ECV models. The serum composite and other secondary continuous endpoints showed minimal missingness and were modeled

without observation weights. The co-primary family (ECV and serum composite) was controlled for multiplicity via Holm–Bonferroni (familywise $\alpha = 0.05$); per-5-mg slopes were prespecified supportive analyses and reported with nominal *P*-values. Exploratory recurrent hospitalizations were modeled using an Andersen–Gill Cox approach with time-varying, lagged exposure and GDMT-4. To address time-varying confounding affected by prior treatment, marginal structural models (MSMs) were implemented as stabilized-weight Andersen–Gill Cox models. For exploratory endpoints and the exposure × GDMT-4 interaction, nominal *P*-values and Benjamini–Hochberg false discovery rate (FDR) q-values were reported. Robust (sandwich) standard errors were used throughout.

Missing Data, Bias Mitigation, and Diagnostics

To address missing 12-month CMR, inverse-probability-of-observation weights were estimated from logistic models informed by baseline and time-varying predictors of repeat imaging and applied in ECV models under a missing-at-random assumption. Pattern-mixture (δ) analyses were performed shifting unobserved ECV by clinically plausible offsets to probe missing-not-at-random mechanisms. Stabilized marginal structural model (MSM) weights for exposure, observation, and censoring included the time-varying covariates listed above; weights were examined for positivity, truncated at extremes, and applied with robust variance. Prespecified lagging of exposure relative to outcomes and explicit time-varying adjustment were used to limit immortal-time and reverse-causation biases and confounding by indication.

RESULTS

Of 268 individuals screened, 210 enrolled and 198 comprised the full analysis set (FAS) (Figure 1). Paired CMR suitable for ECV analysis was obtained at baseline and 12 months in 146/198 (73.7%), and follow-up accrued 195 person-years with 52 HF rehospitalizations recorded as recurrent events. These totals align with the prespecified exposure intervals and lagging strategy and underpin the descriptive distribution of exposure categories displayed in Figure 1 and baseline summaries in Table 1.

At enrollment, the cohort had a median age of 74 years (IQR 69-80), 32.8% were women, 57.1% had ischemic etiology, and mean LVEF was 32% ± 7%, with GDMT-4 Index median 5 (IQR 4-6). Clinical features including hemodynamics, renal function, NT-proBNP, KCCQ-12, and paired-ECV availability were well balanced across the descriptive low, medium, and high TWA dose categories, with no statistically significant differences by χ^2/ANOVA/Kruskal–Wallis testing (Table 1). These similarities support reliance on the time-updated, lagged exposure formulation and covariate adjustment for inferential analyses rather than cross-sectional group comparisons.

Over 12 months, 27.0% (n = 53) were categorized descriptively as low, 34.8% (n = 69) as medium, and 38.4% (n = 76) as high exposure, with median PDC 84% (IQR 71%-93%). These distributions

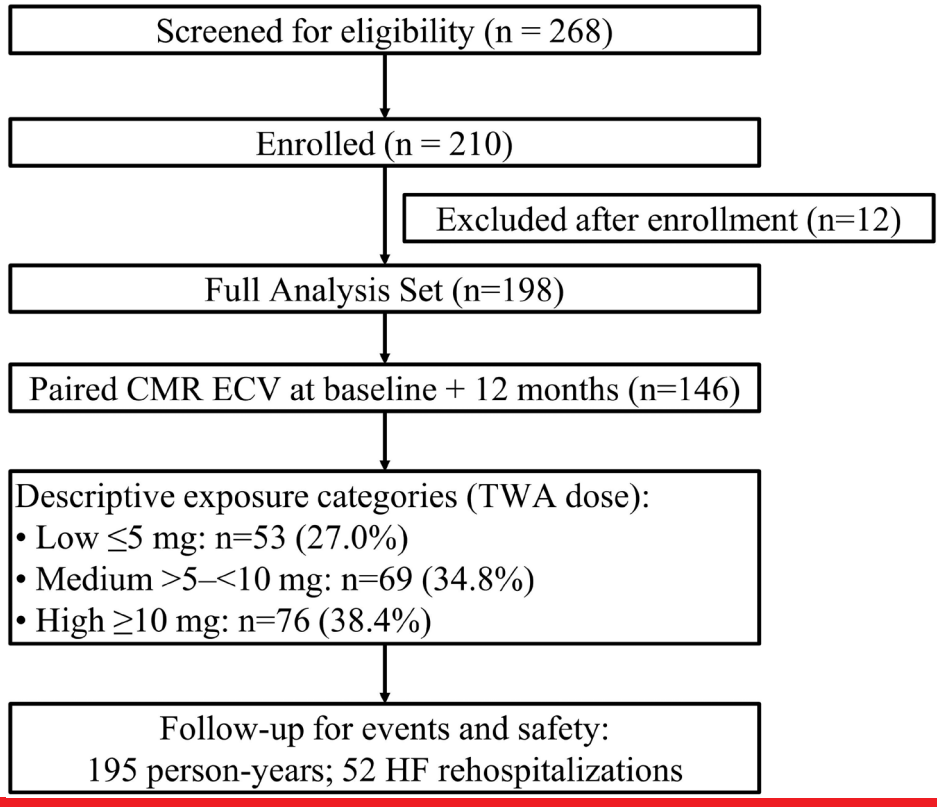

Figure 1. Study flow and analysis sets. Flow of participants from screening (n = 268) to the full analysis set (n = 198), paired cardiovascular magnetic resonance extracellular volume availability (n = 146; 73.7%), descriptive exposure distribution (low 26.8%, medium 34.8%, high 38.4%), and accrued follow-up (195 person-years; 52 rehospitalizations).

Table 1. Baseline Characteristics by Vericiguat Exposure Category (full analysis set, n = 198)

Characteristic	Low ≤5 mg (n = 53)	Medium >5-<10 mg (n = 69)	High ≥10 mg (n = 76)	*P*
Age (years), median (IQR)	75 (70-81)	74 (69-79)	73 (68-79)	.31
Female, n (%)	16 (30.2)	23 (33.3)	26 (34.2)	.78
Ischemic etiology, n (%)	30 (56.6)	39 (56.5)	44 (57.9)	.98
LVEF (%), mean ± SD	31 ± 7	32 ± 6	33 ± 7	.24
Systolic BP (mmHg), mean ± SD	119 ± 15	118 ± 13	117 ± 14	.58
eGFR (mL/min/1.73 m²), mean ± SD	57 ± 17	59 ± 19	58 ± 18	.76
NT-proBNP (pg/mL), median (IQR)	1,700 (920–3,400)	1,600 (880-3,100)	1,620 (900-3,200)	.40
KCCQ-12 (points), mean ± SD	57 ± 20	59 ± 18	58 ± 19	.74
GDMT-4 Index (0–7), median (IQR)	5 (4-6)	5 (4-6)	5 (4-6)	.67
Paired ECV available, n (%)	38 (71.7)	51 (73.9)	57 (75.0)	.78
Adherence (PDC, %), median (IQR)	82 (70-92)	84 (72-94)	85 (73-93)	.41

ECV, extracellular volume; IQR, interquartile range; PDC, proportion of days covered.

provided adequate variability for modeling the cumulative lagged TWA exposure for 12-month continuous endpoints and time-varying exposure for recurrent events (Figure 1, Table 1).

In linear mixed-effects models of 12-month change that incorporated inverse-probability-of-observation weights for ECV and prespecified covariates, higher time-updated vericiguat exposure was associated with less progression of myocardial fibrosis. The adjusted high vs. low contrast yielded an ECV reduction of −1.3 percentage points (pp) (95% CI −2.1 to −0.5; Holm-adjusted *P* = .002), and the per-5-mg dose effect was −0.6 pp (95% CI −1.0 to −0.2; nominal *P* = .003). The serum fibrosis composite improved by −0.23 SD for high vs. low (95% CI −0.37 to −0.09; Holm-adjusted *P* = .004) (Figure 2), and δ-pattern-mixture sensitivity analyses for ECV did not materially alter inferences.

As prespecified, the exposure × GDMT-4 interaction for ΔECV indicated larger anti-fibrotic associations at higher background quadruple therapy intensity (Figure 3). The adjusted high vs. low contrasts were −0.6 pp (95% CI −1.3 to 0.1) for GDMT-4 ≤3, −1.2 pp (95% CI −2.0 to −0.4) for GDMT-4 = 4-5, and −1.8 pp (95% CI −2.8 to −0.8) for GDMT-4 ≥6, with p_interaction = 0.031 under FDR-guided, exploratory interpretation, consistent with enhanced benefit when background therapy is more complete.

Exploratory endpoints were directionally consistent with the co-primary findings (Table 2). High vs. low exposure was associated with improved absolute GLS by +1.1% (95% CI +0.3 to +1.9; *P* = .008; *q* = .020), a lower NT-proBNP GMR of 0.84 (95% CI 0.72–0.98; *P* = .029; *q* = 0.045), and a higher KCCQ-12 score by +6.1 points (95% CI +2.0 to +10.2; *P* = .004; *q* = 0.020). Per-5-mg slope estimates showed consistent directions of effect with q ≤ 0.046 across endpoints, reinforcing internal coherence.

Over 195 person-years, 52 rehospitalizations occurred (26.7 per 100 person-years), and the cumulative mean function demonstrated separation favoring higher exposure over time (Figure 4). In marginal structural Andersen–Gill Cox models with stabilized weights to account for time-varying confounding and adherence dynamics, high vs. low exposure was associated with fewer rehospitalizations (HR 0.74, 95% CI 0.53–1.03; nominal *P* = .072), an exploratory signal concordant with fibrosis and functional outcomes but not meeting conventional significance thresholds.

Adverse events were infrequent and balanced across descriptive exposure categories (Table 3). Symptomatic hypotension occurred in 9.6% and anemia in 12.6% of participants, corresponding to overall rates of 9.7 and 12.8 per 100 person-years, respectively; χ^2 tests across low, medium, and

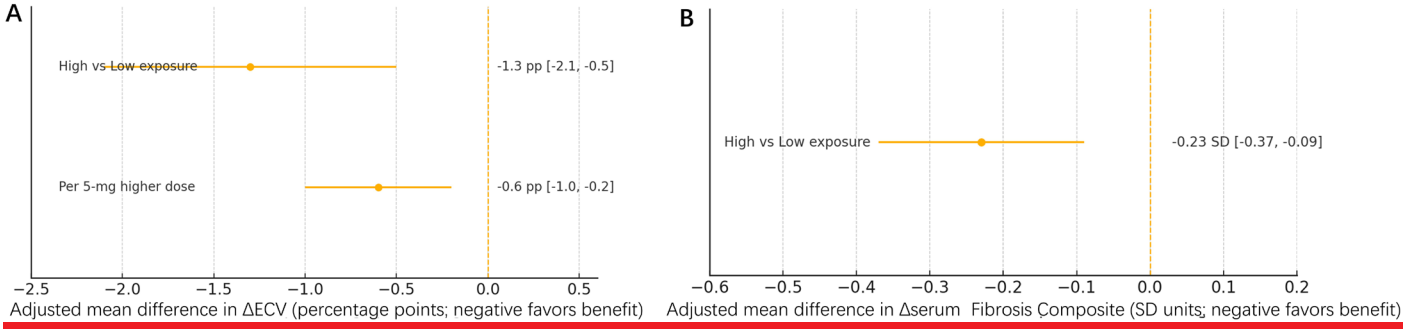

Figure 2. A) Co-primary endpoint—extracellular volume (ECV) vs. time-updated vericiguat exposure. Adjusted contrasts from weighted mixed models show high vs. low exposure associated with −1.3 percentage points (pp) greater ECV reduction (95% CI −2.1 to −0.5; Holm-adjusted *P* = .002); per-5-mg dose effect −0.6 (95% CI −1.0 to −0.2). Negative values favor benefit. B) Co-primary endpoint—serum fibrosis composite vs. exposure. Adjusted high vs. low contrast shows −0.23 SD improvement (95% CI −0.37 to −0.09; Holm-adjusted *P* = .004).

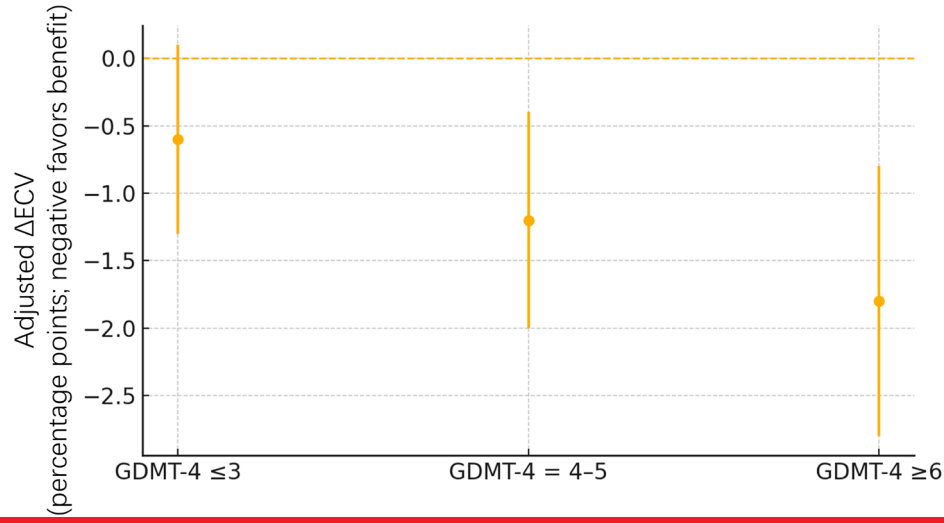

Figure 3. Effect modification by quadruple guideline-directed medical therapy (GDMT-4) intensity. Adjusted extracellular volume (ECV) differences (pp, high vs. low) across strata indicate larger benefit with greater background therapy intensity: GDMT-4 ≤3: −0.6 pp (95% CI −1.3 to 0.1); GDMT-4 = 4-5: −1.2 pp (95% CI −2.0 to −0.4); GDMT-4 ≥6: −1.8 pp (95% CI −2.8 to −0.8); interaction *P* = .031. pp, percentage-point.

Table 2. Secondary Outcomes (Adjusted, Exploratory) and False Discovery Rate Control

Outcome (Direction)	Contrast	Adjusted Effect (95% CI)	*P*	False Discovery Rate q (10%)
Global longitudinal strain, absolute % (higher = better)	High vs. low	+1.1 (+0.3 to +1.9)	.008	0.020
	Per 5-mg higher dose	+0.5 (+0.1 to +0.8)	.012	0.024
NT-proBNP, geometric mean ratio (lower = better)	High vs. low	0.84 (0.72-0.98)	.029	0.045
	Per 5-mg higher dose	0.92 (0.85-0.99)	.034	0.046
KCCQ-12, points (higher = better)	High vs. low	+6.1 (+2.0 to +10.2)	.004	0.020
	Per 5-mg higher dose	+2.7 (+0.8 to +4.7)	.006	0.020

Figure 4. Exploratory recurrent HF rehospitalizations (Andersen–Gill/MSM). Cumulative mean hospitalizations per patient over 12 months show separation favoring higher exposure. Overall 52 events across 195 person-years (26.7 per 100 person-years). Time-varying MSM yielded HR 0.74 (95% CI 0.53–1.03).

Table 3. Safety Events by Exposure Category (full analysis set, n = 198; 195 person-years total)

Adverse Event	Overall	Low ≤5 mg (n = 53)	Medium >5-<10 mg (n = 69)	High ≥10 mg (n = 76)	Rate per 100 person-years (Overall)	*P*
Symptomatic hypotension, n (%)	19 (9.6)	5 (9.4)	7 (10.1)	7 (9.2)	9.7	.91
Anemia, n (%)	25 (12.6)	7 (13.2)	8 (11.6)	10 (13.2)	12.8	.58

high groups were not significant (P = .91 and P = .58). These findings support acceptable tolerability in an older, recently decompensated HFrEF cohort.

DISCUSSION

In this single-center, prospective cohort of older adults with worsening HFrEF, greater time-updated, lagged vericiguat exposure was independently associated with less progression of myocardial fibrosis over 12 months. High exposure yielded greater reduction in CMR-derived ECV and improvement in a serum fibrosis composite. The antifibrotic association was stronger at higher GDMT-4 intensity, supporting biological complementarity with optimized quadruple therapy. Collectively, these results support diligent titration and persistence of vericiguat alongside optimized GDMT-4 to mitigate fibrotic remodeling in older adults after decompensation, while acknowledging the need for multicenter confirmation.

In this prospective cohort of older adults with worsening HFrEF, higher time-updated, lagged vericiguat exposure was associated with less progression of myocardial fibrosis over 12 months—ECV −1.3 pp (95% CI −2.1 to −0.5) and serum fibrosis composite −0.23 SD (95% CI −0.37 to −0.09)—with a per-5-mg dose effect of −0.6 pp for ECV and a larger benefit where background GDMT-4 was more intense (interaction P = .031), while secondary signals favored higher exposure (GLS, NT-proBNP, KCCQ-12) and safety was acceptable. These findings are biologically coherent with nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate–protein kinase G signaling that oxidative stress and impaired NO reduce sGC activity and cGMP generation in heart failure, promoting fibroblast activation and extracellular-matrix accumulation; sGC stimulation restores cGMP-PKG signaling and counters fibrosis and ventricular stiffening, providing a mechanistic rationale for the observed antifibrotic associations in HfrEF.[26,27] CMR-derived ECV is a histologically validated surrogate of diffuse interstitial fibrosis and shows robust prognostic associations. For example, higher ECV has been independently associated with subsequent heart-failure hospitalization and death.[21] Accordingly, the observed −1.3 pp difference in ECV is modest-to-moderate in absolute terms yet potentially clinically meaningful, and it is similar in magnitude to ECV reductions reported with therapies that favorably modify remodeling.[36] Meanwhile, circulating collagen-turnover panels provide complementary but less specific information, together supporting a multidimensional readout of antifibrotic biology in HfrEF.[28-30]

The real-world, dose–response data extend randomized evidence that vericiguat, when added after recent decompensation, reduces the composite of cardiovascular death or first HF hospitalization and is recommended for patients with worsening HFrEF despite GDMT-4.[31,32] The observed KCCQ-12 improvement of +6.1 points with higher exposure exceeds the contemporary 5-point benchmark for clinically important change, aligning a mechanistic antifibrotic signal with patient-reported benefit.[33-37]

The study sought to limit bias by defining exposure as time-updated and lagged to preserve temporal ordering, modeling recurrent hospitalizations with Andersen–Gill processes, and applying marginal structural models with stabilized inverse-probability weights to address time-varying confounding affected by prior treatment—choices aligned with best practices for recurrent HF outcomes and causal inference in observational settings.[38,39] While the rehospitalization association was exploratory and underpowered, its directionality was consistent with the antifibrotic and functional endpoints, and the use of ECV, a surrogate linked to adverse outcomes, helps anchor the biological plausibility of benefit.[21,28,40] These findings should also be interpreted in the context of contemporary heart failure registries that continue to show substantial long-term mortality and rehospitalization despite advances in therapy.[41] Residual confounding and single-center generalizability remain limitations, and missing 12-month CMR was addressed with observation weights and pattern-mixture sensitivity analyses. Nevertheless, the convergence of mechanistic rationale, validated fibrosis readouts, patient-reported improvement, and a favorable safety profile supports diligent titration and persistence of vericiguat alongside optimized GDMT-4 in older adults with worsening HFrEF, and motivates multicenter confirmation.

Principal limitations of this study include the single-center setting and non-randomized dosing, leaving scope for residual confounding despite advanced adjustment. Paired ECV in 146/198 raises potential selection bias even with observation weighting; the limited number of clinical events and an HR of 0.74 reduce precision and render event analyses exploratory, and generalizability is constrained to older adults with worsening HFrEF managed in a tertiary care environment. Importantly, the study did not have a contemporaneous untreated control group; thus, the findings address exposure–response associations among treated patients rather than the effect of initiating vericiguat versus no vericiguat. The placebo-controlled VICTORIA trial provides the randomized estimate of vericiguat initiation on clinical outcomes,[31] whereas the study complements it by probing dose exposure in relation to fibrosis endpoints in routine care. Future work should pursue multicenter confirmation across diverse care settings, pragmatic titration studies that test strategy and persistence on top of optimized GDMT-4, and trials that integrate imaging and serologic fibrosis endpoints

as mechanistic surrogates alongside recurrent-event outcomes to validate causal effects and guide implementation in routine practice.

In conclusion, among older adults with recent worsening HFrEF, greater time-updated, lagged vericiguat exposure was independently associated with less progression of myocardial fibrosis over 12 months. The convergence of mechanistic plausibility and multidimensional antifibrotic signals supports diligent titration and persistence of vericiguat alongside optimized GDMT-4 after decompensation, and motivates multicenter confirmation and pragmatic titration trials that integrate imaging and serologic fibrosis endpoints with recurrent-event outcomes.

Data Availability Statement: Data sets generated during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: The protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of The People's Hospital of Qiannan Prefecture (approval No. 2024-qnzy-31) on 24 October 2021. All participants provided written informed consent prior to any study procedures.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: The authors confirm contribution to the paper as follows: study conception and design: W.L.; data collection: L.G., G.W., A.Z.; analysis and interpretation of results: L.G., G.W., A.Z.; draft manuscript preparation: L.G., G.W., A.Z., W.L. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This study was supported by the Guizhou Provincial Science and Technology Foundation (No. gzwjkj2023-1-069).

Artificial Intelligence–Assisted Technologies Usage Statement: The authors affirm that no artificial intelligence (AI)–assisted technologies (including but not limited to large language models, chatbots, or AI-based image generation tools) were used in the writing, editing, data analysis, figure creation, or any other part of the preparation of this manuscript.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639. [CrossRef]
2. Clephas PRD, Malgie J, Schaap J, et al. Guideline implementation, drug sequencing, and quality of care in heart failure: design and rationale of TITRATE-HF. *ESC Heart Fail*. 2024;11(1):550-559. [CrossRef]
3. Greene SJ, Gaggin HK, Zhou M, et al. Treatment patterns of patients with worsening heart failure with reduced ejection fraction. *ESC Heart Fail*. 2024;11(4):1932-1946. [CrossRef]
4. Okumura T, Murohara T. Overcoming the clinical inertia behind inadequate adherence to guideline-directed medical therapy. *Cardiology*. 2024;149(3):225-227. [CrossRef]
5. Barry AR, Grewal M, Blain L. Use of guideline-directed medical therapy in patients aged 80 years or older with heart failure with reduced ejection fraction. *CJC Open*. 2023;5(4):303-309. [CrossRef]
6. Van der Linden L, Tsuyuki R. Between Scylla and Charybdis: navigating heart failure management in complex older adults. *Br J Clin Pharmacol*. 2025;91(2):306-309. [CrossRef]
7. Araújo CS, Marco I, Restrepo-Córdoba MA, Vila Costa I, Pérez-Villacastín J, Goirigolzarri-Artaza J. An observational study of evidence-based therapies in older patients with heart failure with reduced ejection fraction: insights from a dedicated heart failure clinic. *J Clin Med*. 2024;13(23):7171. [CrossRef]
8. McDonagh TA, Metra M, Adamo M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639. [CrossRef]
9. Wahid M, Aghanya V, Sepehrvand N, Dover DC, Kaul P, Ezekowitz J. Use of guideline-directed medical therapy in patients aged ≥ 65 years after the diagnosis of heart failure: a Canadian population-based study. *CJC Open*. 2022;4(12):1015-1023. [CrossRef]
10. Beldhuis IE, Voors AA, Tromp J. Rapid uptitration: what's the evidence? *Eur J Heart Fail*. 2023;25(2):223-225. [CrossRef]
11. Pieske B, Pieske-Kraigher E, Lam CSP, et al. Effect of vericiguat on left ventricular structure and function in patients with heart failure with reduced ejection fraction: the Victoria echocardiographic substudy. *Eur J Heart Fail*. 2023;25(7):1012-1021. [CrossRef]
12. González-Juanatey JR, Anguita-Sánchez M, Bayes-Genis A, et al. Vericiguat en insuficiencia cardíaca: de la evidencia científica a la práctica clínica. *Rev Clin Española*. 2022;222(6):359-369. [CrossRef]
13. Esteban-Fernández A, Recio-Mayoral A, López-Vilella R, et al. Clinical profile of an unselected population with heart failure treated with vericiguat in real life: differences with the Victoria trial. *Front Cardiovasc Med*. 2025;11:1504427. [CrossRef]
14. Araújo CS, Marco I, Restrepo-Córdoba MA, Vila Costa I, Pérez-Villacastín J, Goirigolzarri-Artaza J. An observational study of evidence-based therapies in older patients with heart failure with reduced ejection fraction: insights from a dedicated heart failure clinic. *J Clin Med*. 2024;13(23):7171. [CrossRef]
15. Kerwagen F, Ohlmeier C, Evers T, et al. Real-world characteristics and use patterns of patients treated with vericiguat: a nationwide longitudinal cohort study in Germany. *Eur J Clin Pharmacol*. 2024;80(6):931-940. [CrossRef]
16. Pieske B, Pieske-Kraigher E, Lam CSP, et al. Effect of vericiguat on left ventricular structure and function in patients with heart failure with reduced ejection fraction: the Victoria echocardiographic substudy. *Eur J Heart Fail*. 2023;25(7):1012-1021. [CrossRef]
17. Hida Y, Imamura T, Kinugawa K. Optimal timing of vericiguat therapy in patients with heart failure with reduced/mildly reduced ejection fraction for improving mortality and heart failure re-hospitalization rate. *J Clin Med*. 2025;14(16):5856. [CrossRef]
18. Kinoshita H, Sugino H, Fujita K, et al. Examination of the suitability of vericiguat in non-heart failure with preserved ejection fraction patients with improved ejection fraction. *J Clin Med*. 2024;13(17):5264. [CrossRef]
19. Russo P, Vitiello L, Milani F, et al. New therapeutics for heart failure worsening: focus on vericiguat. *J Clin Med*. 2024;13(14):4209. [CrossRef]
20. Iniesta Manjavacas ÁM, López-Lluva MT, de Juan Bagudá J, et al. Vericiguat en el abordaje actual del paciente con insuficiencia cardiac. *REC, Cardioclinics*. 2023;58(4):314-323. [CrossRef]
21. Schelbert EB, Piehler KM, Zareba KM, et al. Myocardial fibrosis quantified by extracellular volume is associated with

subsequent hospitalization for heart failure, death, or both across the spectrum of ejection fraction and heart failure stage. *J Am Heart Assoc*. 2015;4(12):e002613. [CrossRef]
22. Mandawat A, Chattranukulchai P, Mandawat A, et al. Progression of myocardial fibrosis in nonischemic DCM and association with mortality and heart failure outcomes. *JACC Cardiovasc Imaging*. 2021;14(7):1338-1350. [CrossRef]
23. Numata G, Takimoto E. Cyclic GMP and PKG signaling in heart failure. *Front Pharmacol*. 2022;13:792798. [CrossRef]
24. Lurz JA, Luecke C, Lang D, et al. CMR-derived extracellular volume fraction as a marker for myocardial fibrosis: the importance of coexisting myocardial inflammation. *JACC Cardiovasc Imaging*. 2018;11(1):38-45. [CrossRef]
25. Pichler G, Redon J, Martínez F, et al. Cardiac magnetic resonance-derived fibrosis, strain and molecular biomarkers of fibrosis in hypertensive heart disease. *J Hypertens*. 2020;38(10):2036-2042. [CrossRef]
26. Numata G, Takimoto E. Cyclic GMP and PKG signaling in heart failure. *Front Pharmacol*. 2022;13:792798. [CrossRef]
27. Kansakar S, Guragain A, Verma D, et al. Soluble guanylate cyclase stimulators in heart failure. *Cureus*. 2021;13(9):e17781. [CrossRef]
28. Scully PR, Bastarrika G, Moon JC, Treibel TA. Myocardial extracellular volume quantification by cardiovascular magnetic resonance and computed tomography. *Curr Cardiol Rep*. 2018;20(3):15. [CrossRef]
29. Diao KY, Yang ZG, Xu HY, et al. Histologic validation of myocardial fibrosis measured by T1 mapping: a systematic review and meta-analysis. *J Cardiovasc Magn Reson*. 2016;18(1):92. [CrossRef]
30. López B, González A, Ravassa S, et al. Circulating biomarkers of myocardial fibrosis: the need for a reappraisal. *J Am Coll Cardiol*. 2015;65(22):2449-2456. [CrossRef]
31. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883-1893. [CrossRef]
32. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18):e895-e1032. [CrossRef]
33. Spertus JA, Jones PG, Butler J, Arnold SV. Minimally important Kansas City cardiomyopathy Questionnaire changes across the spectrum of heart failure severity. *JACC Heart Fail*. 2025;13(9):102587. [CrossRef]
34. Cleland JGF, Ferreira JP, Mariottoni B, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the Heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J*. 2021;42(6):684-696. [CrossRef]
35. Zile MR, O'Meara E, Claggett B, et al. Effects of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFrEF. *J Am Coll Cardiol*. 2019;73(7):795-806. [CrossRef]
36. Mason T, Coelho-Filho OR, Verma S, et al. Empagliflozin reduces myocardial extracellular volume in patients with type 2 diabetes and coronary artery disease. *JACC Cardiovasc Imaging*. 2021;14(6):1164-1173. [CrossRef]
37. Zuo C, Li X, Guan Y, et al. Influence of aging on outcomes of sacubitril/valsartan in hypertensive patients with heart failure: a multicenter retrospective study. *Anatol J Cardiol*. 2024;28(4):194-200. [CrossRef]
38. Rogers JK, Pocock SJ, McMurray JJV, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail*. 2014;16(1):33-40. [CrossRef]
39. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. [CrossRef]
40. Treibel TA, Fridman Y, Bering P, et al. Extracellular volume associates with outcomes more strongly than native or post-contrast myocardial T1. *JACC Cardiovasc Imaging*. 2020;13(1 Pt 1):44-54. [CrossRef]
41. Şabanoğlu C, Sinan ÜY, Akboğa MK, et al. Long-term prognosis of patients with heart failure: follow-up results of Journey HF-TR study population. *Anatol J Cardiol*. 2023;27(1):26-33. [CrossRef]