REVIEW ARTICLE

Impact of vericiguat on mortality and hospitalization in HFrEF: a systematic review, meta-analysis, and meta-regression

Ihab Suliman[1], Noor Yousef Al-Mohaimeed[2], Hisham Ali Hendi Alghamdi[3], Saja Abdullah Alharbi[4], Leen Ghazi Alahmadi[5], Sabah Hussein Alkharboush[6], Layan Tareq Aldhowayan[2*], Manahel Hayder H Alawami[7], Abdulrahman Mohammed H M Aldousari[8], Salah J. S A A Alrashidi[9], Rahaf Mohammed Alansari[6]

ABSTRACT

Background: Patients with heart failure with reduced ejection fraction (HFrEF) remain at high risk despite guideline-directed therapy. Vericiguat, an oral soluble guanylate cyclase stimulator, has emerged as a novel option. We conducted a systematic review and meta-analysis to evaluate its efficacy and safety.

Methods: Randomized, double-blind, placebo-controlled trials of vericiguat in adults with chronic HFrEF were identified through November 2025. The primary outcome was cardiovascular (CV) death or heart failure (HF) hospitalization; secondary outcomes included CV death, HF hospitalization, all-cause mortality, and safety endpoints.

Results: Three trials enrolling >11,000 patients were analyzed. Vericiguat reduced the composite of CV death or HF hospitalization (RR 0.91, 95% CI 0.86-0.97) and lowered HF hospitalization risk, including recurrent events. All-cause mortality showed modest reduction, while CV mortality alone was not significantly reduced. Safety analyses revealed slightly higher risks of hypotension and anemia, but no excess syncope or kidney injury.

Conclusion: Vericiguat offers modest but clinically relevant benefits in reducing HF hospitalizations and composite CV outcomes in HFrEF. Its safety profile is generally acceptable, with only slight increases in hypotension and anemia. These findings support its role as an adjunctive therapy for selected high-risk patients.

Keywords: Vericiguat, heart failure with reduced ejection fraction (HFrEF), heart failure hospitalization, cardiovascular outcomes, meta-analysis.

Introduction

In 2021, the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, and Japanese Heart Failure Society proposed a universal definition of heart failure (HF). HF is defined as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion [1]. When the left ventricular

Correspondence to: Asma Alomary
*College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.
Email: asmaalomary90@gmail.com
Full list of author information is available at the end of the article.
Received: 06 October 2026 | **Revised:** XX XXXX XX | **Accepted:** 21 October 2026

OPEN ACCESS
This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license: https://creativecommons.org/licenses/by/4.0/) which permits any use, Share — copy and redistribute the material in any medium or format, Adapt — remix, transform, and build upon the material for any purpose, as long as the authors and the original source are properly cited. © The Author(s) 2026.

ejection fraction (LVEF) is 40% or lower, it is known as HF with reduced ejection fraction (HFrEF). It is characterized by increasing dilatation of the left ventricle and unfavorable cardiac remodeling. An estimated 64 million individuals are affected by HF globally, which is regarded as a pandemic [2]. The prevalence of HF is projected to increase due to the aging population. The most recent projections for the US suggest an increase in the prevalence of HF of approximately 46% from 2012 to 2030, with a corresponding increase in healthcare costs of approximately 127% [3].

Clinical results have significantly improved with current guideline directed medical therapy (GDMT), which includes angiotensin converting enzyme inhibitors or angiotensin receptor neprilysin inhibitors, beta blockers, mineralocorticoid receptor antagonists, and sodium glucose cotransporter2 inhibitors. Nonetheless, a significant percentage of patients still have poor prognoses, repeated decompensation, and progressive illness, suggesting the continued need for innovative treatment approaches that target different pathophysiological pathways [4]. Poor nitric oxide soluble guanylate cyclase cyclic guanosine monophosphate signaling is a key factor in the pathogenesis of HFrEF, as it causes endothelial dysfunction, vascular stiffness, myocardial remodeling, and decreased cardiac contractility [5]. A recent treatment approach that targets this disturbed signaling pathway is vericiguat, an orally administered soluble guanylate cyclase stimulator that increases cGMP synthesis regardless of nitric oxide availability [6].

Despite the growing body of evidence supporting the use of vericiguat in HFrEF, there are still questions about the consistency of its benefits across patient subgroups, clinical outcomes, and safety precautions. Current randomized studies may not have sufficient power to identify variations in occasional adverse events or secondary outcomes. Therefore, a meta analysis is necessary to summarize the available data and elucidate the overall effects of vericiguat in HFrEF. The composite of cardiovascular (CV) death or HF hospitalization, individual risks of CV death and HF hospitalization, all cause mortality, total HF events, and important safety outcomes such as serious adverse events, symptomatic hypotension, anemia, syncope, and acute kidney injury in patients with reduced ejection fraction were examined in this study. In accordance with the TITAN Guidelines 2025 for transparent use of AI in scholarly communication, no AI tools were used in the research design, data collection, analysis, or interpretation; AI assistance was limited solely to language refinement during manuscript preparation [7].

Methods

The study protocol was registered with PROSPERO to ensure methodological rigor and minimize potential biases. The work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [8]. The study also adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. By applying these guidelines, we ensured that our methods were clearly documented, which enhanced the reliability and reproducibility of our results, thereby bolstering the credibility of our conclusions.

Databases and search strategy

We performed an extensive electronic literature search across PubMed (MEDLINE), the Cochrane Library, ScienceDirect, and ClinicalTrials.gov and additionally searched Google Scholar as a supplementary source, with no time restrictions applied at the lower limit and extending through November 20, 2025. This approach ensured the incorporation of all current literature accessible at the time of our analysis, with November 2025 marking the publication of the last included study. Language was not used as an exclusion criterion. Additionally, we manually examined the bibliographies of the selected studies and associated review articles and explored clinical trial registries to locate further relevant research. Comprehensive search protocols, including exact search queries and retrieval dates for all databases, are detailed in the Supplementary Table 1.

Study selection and eligibility criteria

We employed Mendeley software to eliminate duplicate entries from the database search results, followed by screening in two sequential stages. First, titles and abstracts were independently screened by two reviewers to exclude clearly ineligible reports (non-randomized designs, populations outside chronic HFrEF, non-vericiguat interventions, and non-placebo comparators). The full texts of potentially eligible studies were then retrieved and independently assessed in duplicate against the inclusion and exclusion criteria. Discrepancies were resolved through discussion and, when necessary, by consultation with a third reviewer. Multiple reports from the same trial were collated and treated as a single study using the most complete and recent dataset for quantitative synthesis.

Studies were eligible for inclusion if they met all of the following criteria: (1) employed a randomized controlled trial; (2) enrolled adults (≥18 years) with chronic HF and reduced ejection fraction (LVEF generally ≤40%-45%) and NYHA class II-IV symptoms on guideline-directed medical therapy; (3) evaluated oral vericiguat once daily, titrated toward higher doses (up to 10 mg), compared with matching placebo; and (4) reported at least one prespecified efficacy outcome of interest (e.g., CV or all-cause mortality, HF hospitalization, or composite CV endpoints). Studies were excluded if they met any of the following criteria: (1) observational, quasi-experimental, single-arm, crossover, or otherwise non-randomized designs; (2) primarily included patients without HFrEF (e.g., preserved or mildly reduced EF) without a separately analyzable reduced EF subgroup; and (3) did not report sufficient data for the extraction of at least one of the prespecified outcomes of interest.

Data extraction and outcomes

Two reviewers independently extracted the key data elements to ensure accuracy and reduce extraction bias.

Table 1A. *Study Characteristics*

Study	Clinical trial no	Trial name	Patient category	Dose	Total sample	Sample size		Study design	Primary outcome
						Vericiguat	Placebo		
Butler et al. [14]	NCT05093933	Victor	Adults (≥18 years) with heart failure (LVEF ≤40%) and NYHA class II-IV symptoms.	2·5 mg of vericiguat, titrated to 5 mg at day 14 and to 10 mg at day 28 after randomization.	6105	3053	3052	Double-blind, placebo-controlled, phase 3 trial.	The composite of time from randomization to the first occurrence of cardiovascular death or hospitalization for heart failure.
Armstrong et al. [13]	NCT02861534	Victoria	Adults ≥18 years of age and had chronic heart failure (New York Heart As sociation [NYHA] functional class II, III, or IV)	2.5 mg of vericiguat doses were increased to 5 mg and ultimately to the target dose of 10 mg once daily	5050	2526	2524	Phase 3, randomized, double-blind, placebo-controlled trial.	Composite of death from cardiovascular causes or first hospitalization for heart failure.
Gheorghiade et al. [15]	NCT01951625	Socrates-reduced	Adults with worsening chronic HF (LVEF <45%), recent hospitalization or IV diuretics, congestion, and elevated NT-proBNP/BNP levels.	1.25mg	465	91	92	Multicenter, randomized, double blind, placebo controlled.	change from baseline to week 12 in log-transformed level of N-terminal pro-B-type natriuretic peptide (NT-proBNP).
				2.5mg		91			
				2.5 to 5 mg		91			
				2.5 to 10mg		91			

The extracted information included trial characteristics (year, phase, sample size, follow-up duration, and setting), patient characteristics (age, sex, LVEF, NYHA class, natriuretic peptide levels, recent worsening status, and background guideline-directed medical therapy), intervention details (vericiguat dosing regimen, titration schedule, and duration), comparator details (placebo regimen), and outcome data. Disagreements were addressed through mutual discussion, and a third reviewer provided a final resolution when a consensus could not be achieved. When published articles lacked the necessary data, we contacted the study authors to acquire the missing information. Individual participant data or full study datasets were requested from investigators or accessed through reputable data-sharing repositories, wherever possible. The primary outcome was a composite of CV death or hospitalization for HF. Key secondary outcomes focused on clinical efficacy included CV death, hospitalization for HF (first events), all-cause mortality, and total HF hospitalization (first and recurrent events). Safety outcomes included serious adverse events, overall adverse events, symptomatic hypotension, syncope, anemia, and acute kidney injury, which were evaluated to characterize the tolerability and safety of vericiguat.

Risk of bias and quality assessment

The risk of bias for each included study was independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials [10]. This tool evaluates bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Disagreements were resolved through discussion or consultation with a third reviewer.

Statistical analysis

Statistical analyses were conducted using RevMan software (version 5.4.1; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark, 2020). The Mantel–Haenszel approach was used to calculate risk ratios (RR) for dichotomous outcomes, whereas mean differences for continuous outcomes were calculated using the generic inverse variance method. All results are presented with 95% confidence intervals (CIs). A random-effects model was applied to combine the data, and heterogeneity was evaluated using Higgins' I^2 statistic [11]. Heterogeneity was classified as low if I^2 was <50%, moderate between 50% and 75%, and high if >75%. Statistical significance was set at $p \leq 0.05$.

Subgroup analyses were additionally performed according to vericiguat dose (1.25 mg, 2.5 mg, 2.5–5 mg, and 2.5-10 mg once daily) and follow-up duration (≤16 weeks *vs*. >16 weeks), using the same random-effects modeling approach for each stratum to explore potential effect modification by dosing intensity and exposure time. Meta-regression analyses for the primary outcome (CV death or hospitalization for HF) were conducted to explore whether between-study differences in baseline characteristics modified the vericiguat treatment effect. Meta-regression was performed using comprehensive

meta-analysis (CMA) software. The prespecified moderators included mean age, mean body mass index, comorbidities (prevalence of diabetes, atrial fibrillation, and hypertension), background medical therapy (use of loop diuretics, β-blockers, mineralocorticoid receptor antagonists, implantable cardioverter-defibrillators, and cardiac resynchronization therapy), baseline systolic blood pressure, LVEF, and estimated glomerular filtration rate (eGFR, ml/min per 1.73 m²).

Results

Study selection

A total of 4,757 records were identified: 957 from electronic databases and registers (PubMed/MEDLINE, n = 247; ScienceDirect, n = 598; Cochrane Library, n = 100; ClinicalTrials.gov, n = 12) and 3,800 from Google Scholar, which was searched as a supplementary source. After removing 491 duplicate records, 4,266 records underwent title and abstract screening, of which 4,197 were excluded for irrelevance to the eligibility criteria. The remaining 69 articles were assessed through full-text screening, leading to the exclusion of 66 studies due to non-compliance with the predefined PICO or eligibility criteria. Ultimately, three studies met all inclusion requirements and were included in the final review [12-15]. The complete selection process is depicted in the PRISMA flow diagram (Figure 1).

Study characteristics

Three randomized, double-blind, placebo-controlled multicenter trials were included: VICTOR, VICTORIA, and SOCRATES-REDUCED, enrolling adults with chronic or worsening HF and reduced ejection fraction who had recent decompensation and elevated NT-proBNP levels. Across the three studies, a total of 6,105 patients were randomized in VICTOR, 5,050 in VICTORIA, and 465 in SOCRATES-REDUCED, with vericiguat titrated from low starting doses (1.25-2.5 mg) up to target doses of 10 mg once daily versus matching placebo, and primary outcomes focusing on time to first CV death or heart-failure hospitalization, CV mortality or heart-failure hospitalization, or change in log-transformed NT-proBNP, respectively. Detailed study characteristics are presented in Table 1A.

Baseline characteristics were broadly similar between treatment groups within each trial. Mean age ranged from approximately the mid-60s to early-70s years, with a predominance of male participants and most patients in NYHA functional class II or III; class IV patients constituted a small minority. Comorbidities such as diabetes, hypertension, atrial fibrillation, and use of contemporary guideline-directed medical therapy (including beta-blockers, ACE inhibitors/ARBs/ARNI, mineralocorticoid receptor antagonists, loop diuretics, and device therapy where applicable) were common and balanced across vericiguat and placebo arms, while baseline NT-proBNP concentrations, systolic blood pressure, LVEF, and renal function (eGFR) indicated a population with advanced but hemodynamically stable HF. Detailed baseline characteristics are summarized in Table 1B.

Risk of bias in included studies

Risk of bias for the three included randomized trials was evaluated using the Cochrane RoB 2 tool, which assesses potential bias across domains related to the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. All studies were rated as having low risk of bias in each RoB 2 domain, indicating that concerns regarding selection, performance, detection, attrition, and reporting bias were minimal. Consequently, the overall risk of bias for each trial was judged to be low, supporting the internal validity of the synthesized estimates in this meta-analysis. The detailed summary of risk-of-bias judgments is presented in Figure 2A and Figure 2B, with a comprehensive table provided in the supplementary file (Supplementary Table 2).

Primary Outcome

Cardiovascular death or hospitalization for heart failure

Across three studies, vericiguat significantly reduced the composite risk of CV death or hospitalization for HF. The pooled risk ratio (RR) was 0.91 (95% CI 0.86–0.97; Z = 3.11; p = 0.002), with 1,484 events in the vericiguat group and 1,628 in the placebo group. Between-study heterogeneity was absent (I^2 = 0%), indicating consistent effects across studies (Figure 3).

Secondary Outcomes

Cardiovascular death

Three studies (n = 11,620) reported CV mortality. Vericiguat did not significantly reduce CV death, with a pooled RR of 0.90 (95% CI 0.79–1.02; p = 0.09). There were 432 deaths in the vericiguat group and 483 in the placebo group. Heterogeneity was minimal (I^2 = 0%). Although not statistically significant, the confidence interval is consistent with the possibility of a modest relative risk reduction (Figure 4).

Hospitalization for heart failure (first events)

Three studies contributed data on first HF hospitalizations. Vericiguat was associated with a statistically significant reduction in hospitalizations, with a pooled RR of 0.93 (95% CI 0.86-1.00; p = 0.04). A total of 1,089 events occurred in the vericiguat group compared with 1,173 in the placebo group. Heterogeneity was negligible (I^2 = 0%) (Figure 5).

All-cause mortality

Three studies reported all-cause mortality. The pooled RR was 0.91 (95% CI 0.84-0.99; Z = 2.21; p = 0.03). There were 919 deaths in the vericiguat group and 1,010 in the placebo group. Low heterogeneity (I^2 = 9%) suggests consistent findings across studies (Figure 6).

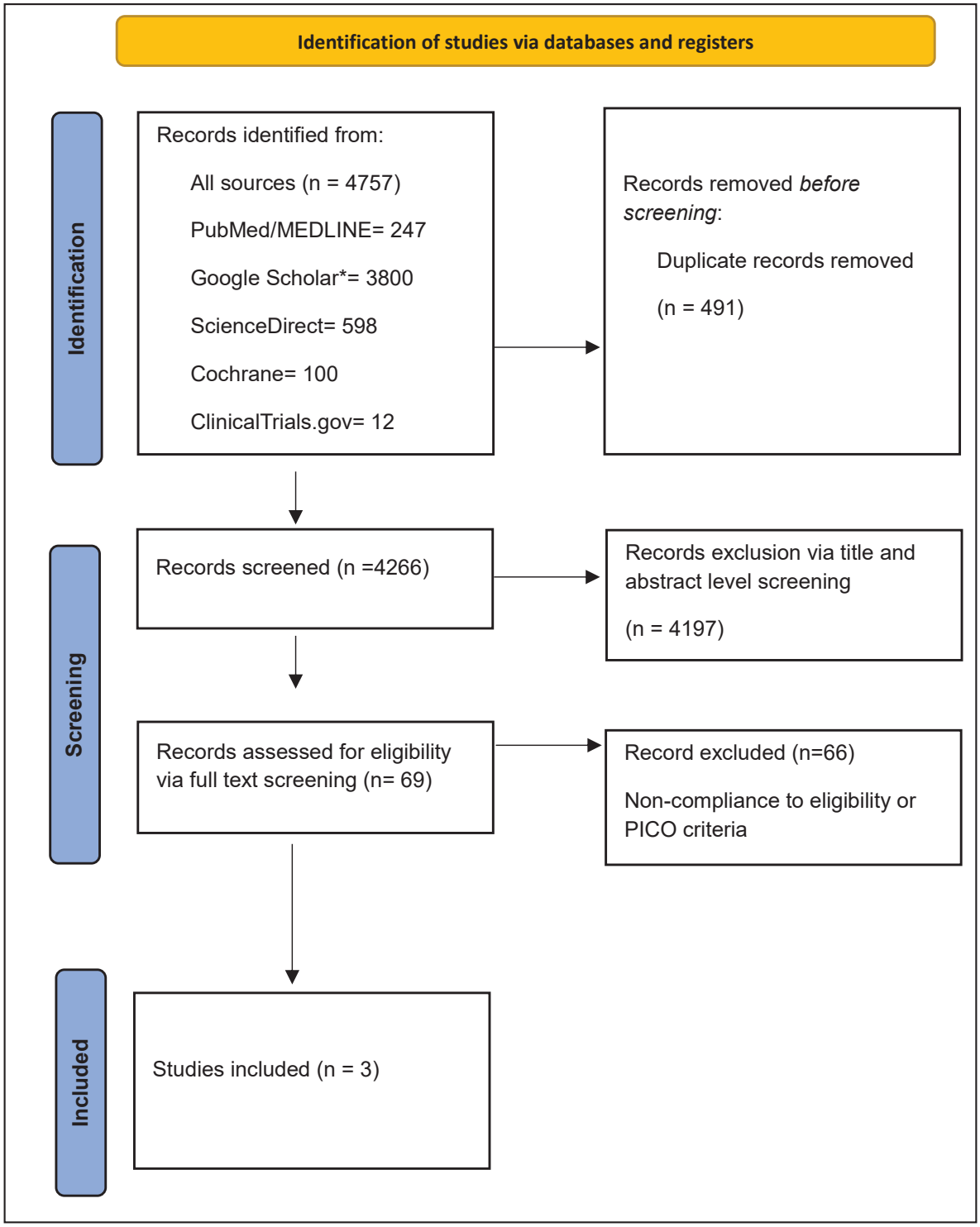


Figure 1. *PRISMA Flow Diagram. *Google Scholar was searched as a supplementary source; records from all sources were pooled before de-duplication.*

Total heart failure hospitalization events (first and recurrent events)

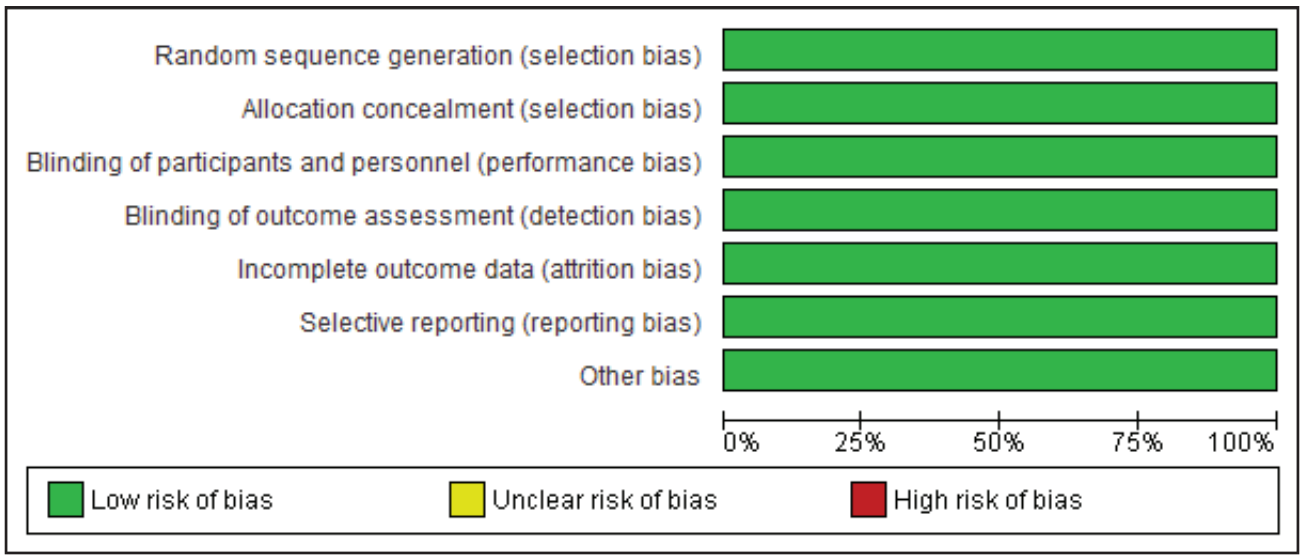
Two studies provided data on total HF hospitalization events. Vericiguat significantly reduced event rates, with a pooled RR of 0.92 (95% CI 0.87-0.96; $Z = 3.57$; $p = 0.0004$). Across studies, 1,772 total events occurred in the vericiguat group versus 1,933 in the placebo group. Heterogeneity was absent ($I^2 = 0\%$) (Supplementary Figure 1).

Safety outcomes

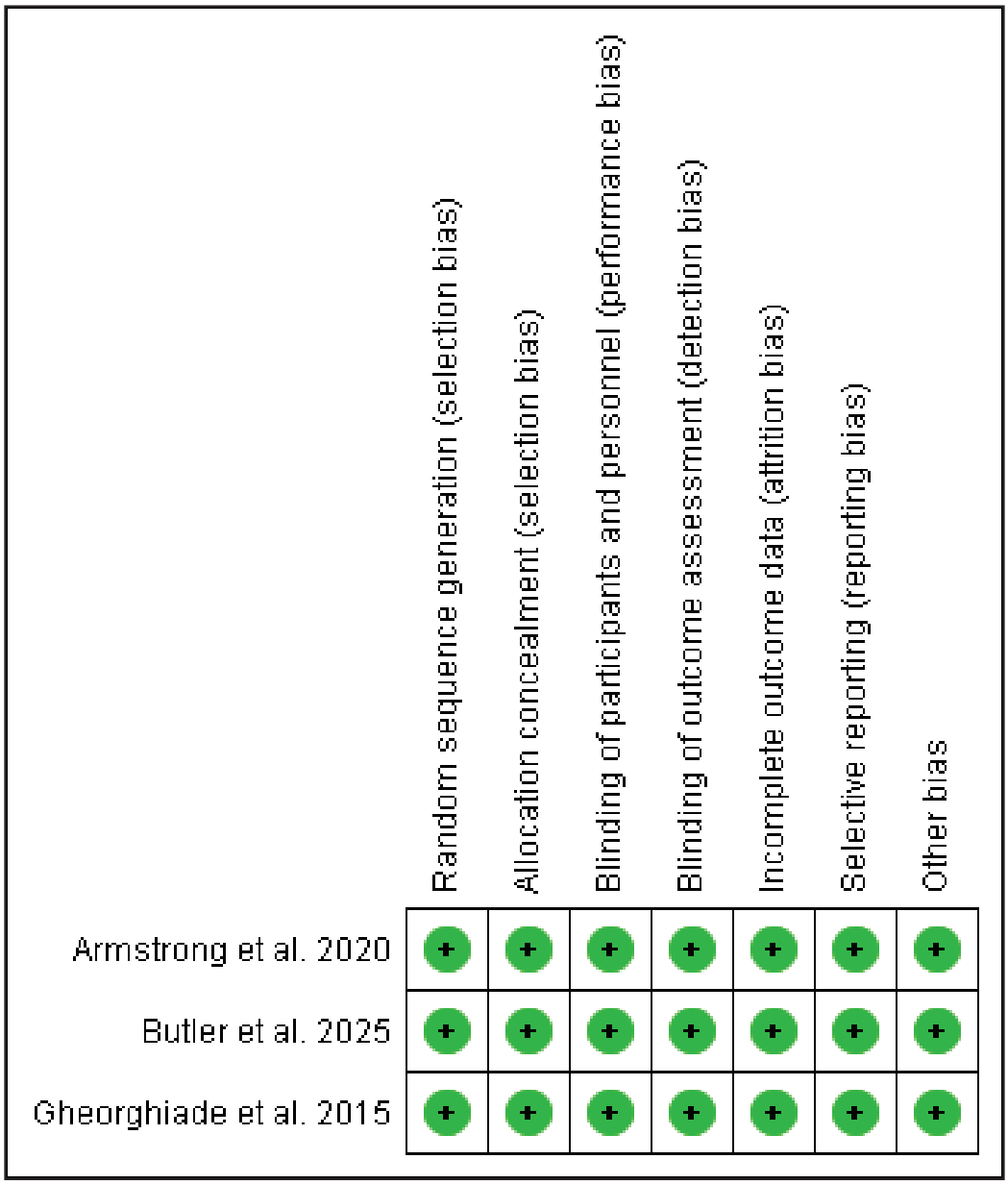
Across the included studies, vericiguat demonstrated an overall acceptable safety profile with specific adverse events showing differential effects. In three studies reporting serious adverse events, vericiguat modestly reduced risk compared with placebo (RR 0.94, 95% CI 0.89-0.99; $p = 0.03$), with 1,662 versus 1,771 events, and no heterogeneity ($I^2 = 0\%$) (Supplementary Figure 2). Across the same three studies, overall adverse events did

Table 1B. *Demographic and baseline characteristics.*

Characteristics		Armstrong et al. [13]		Butler et al. [14]		Gheorghiade et al. [15]				
		Vericiguat	Placebo	Vericiguat	Placebo	Vericiguat 1.25 mg	Vericiguat 2.5 mg	Vericiguat 2.5 to 5 mg	Vericiguat 2.5 to 10 mg	Placebo
Sample size		(*N* = 2526)	(*N* = 2524)	(*N* = 3053)	(*N* = 3052)	(*N* = 91)	(*N* = 91)	(*N* = 91)	(*N* = 91)	(*N* = 92)
Mean age - yr		67.5±12.2	67.2±12.2	68·0 (61·0-75·0)	68·0 (61·0-75·0)	68(13)	68(12)	67(12)	69(12)	67(13)
Sex - no. (%)	Male	1921 (76.0)	1921 (76.1)	2326 (76·2%)	2339 (76·6%)	70(76.9)	72(79.1)	74(81.3)	77(84.6)	73(79.3)
	Female	605 (24.0)	603 (23.9)	727 (23·8%)	713 (23·4%)	N/A	N/A	N/A	N/A	N/A
Mean body mass index		27.7±5.8	27.9±6.1	27·5 (24·3-31·3)	27·7 (24·7-31·4)	28(6)	28(5)	29(5)	28(5)	27(5)
NYHA class - no. / total no. (%)	I	0	2/2523 (0.1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	II	1478/2523 (58.6)	1497/2523 (59.3)	2411 (79·0%)	2411 (79·0%)	N/A	N/A	N/A	N/A	N/A
	III	1010/2523 (40.0)	993/2523 (39.4)	635 (20·8%)	633 (20·7%)	N/A	N/A	N/A	N/A	N/A
	IV	35/2523 (1.4)	31/2523 (1.2)	7 (0·2%)	8 (0·3%)	N/A	N/A	N/A	N/A	N/A
	I/II	N/A	N/A	N/A	N/A	44(48.4)	47(51.7)	44(48.4)	51(56.0)	54(58.7)
	III/IV	N/A	N/A	N/A	N/A	47(51.6)	44(48.4)	47(51.7)	40(44.0)	38(41.3)
Comorbidities	Diabetes	N/A	N/A	1274 (41·7%)	1311 (43·0%)	36(39.6)	54(59.3)	39(42.9)	49(53.8)	41(44.6)
	Atrial fibrillation	N/A	N/A	1135 (37·2%)	1182 (38·7%)	32(35.2)	30(33.0)	30(33.0)	32(35.2)	30(32.6)
	Hypertension	N/A	N/A	2153 (70·5%)	2176 (71·3%)	71(78.0)	70(76.9)	68(74.7)	78(85.7)	70(76.1)
Medical therapy	Loop diuretics	N/A	N/A	2131 (69·8%)	2129 (69·8%)	82(90.1)	87(95.6)	84(92.3)	91(100.0)	86(93.5)
	β blockers	N/A	N/A	2886 (94·5%)	2880 (94·4%)	77(84.6)	79(86.8)	86(94.5)	86(94.5)	83(90.2)
	Mineralocorticoid receptor antagonist	N/A	N/A	2358 (77·2%)	2390 (78·3%)	51(56.0)	61(67.0)	58(63.7)	64(70.3)	50(54.3)
	Implantable cardioverter defibrillator	N/A	N/A	993 (32·5%)	1016 (33·3%)	19(20.9)	18(19.8)	23(25.3)	15(16.5)	20(21.7)
	Cardiac resynchronization therapy	N/A	N/A	464 (15·2%)	440 (14·4%)	6(6.6)	10(11.0)	7(7.7)	3(3.3)	6(6.5)
NT-proBNP, pg/ml		N/A	N/A	1370 (826-2338)	1381 (828-2430)	3670 (1483-8382)	2721 (1500-8467)	2644 (1432-4687)	2805 (1526-6255)	4043 (1962-6712)
Systolic blood pressure, mm Hg		N/A	N/A	120·6 (15·8)	121·5 (16·3)	125.8(13.8)	124.6(11.8)	125.3(12.6)	128.4(14.6)	123.9(14.3)
LVEF, %		N/A	N/A	30·5% (7·0)	30·4% (7·0)	29.5(8.6)	29.2(8.2)	31.5(8.5)	29.3(8.3)	28.6(8.5)
eGFR, ml/min per 1·73 m^2		N/A	N/A	70·9 (23·8)	70·8 (24·3)	57.2(21.0)	56.9(19.1)	60.1(20.2)	60.0(19.6)	57.8(17.4)



350 ***Figure 2A.*** *Risk of bias graph.*



351 ***Figure 2B.*** *Risk of bias summary.*

not differ between groups (RR 1.00, 95% CI 0.96-1.04; p = 0.93; I^2 = 24%) (Supplementary Figure 3).

Vericiguat was associated with an increased risk of symptomatic hypotension, as shown in three studies (RR 1.19, 95% CI 1.06-1.33; p = 0.003), with 592 versus 499 events and no heterogeneity (I^2 = 0%) (Supplementary Figure 4). In contrast, two studies assessing syncope found no significant difference (RR 1.19, 95% CI 0.90-1.55; p = 0.24) (Supplementary Figure 5).

Two studies reporting anemia demonstrated a significant increase with vericiguat (RR 1.26, 95% CI 1.10-1.45; p = 0.0009), with 425 versus 336 events (I^2 = 0%) (Supplementary Figure 6). Acute kidney injury, evaluated in two studies, did not differ significantly between groups (RR 1.05, 95% CI 0.83-1.31; p = 0.70) (Supplementary Figure 7).

Subgroup analysis by dosage

Subgroup analyses according to vericiguat dosage showed generally consistent effects across dose regimens. Efficacy signals for the composite of CV death or HF hospitalization (RR 0.91, 95% CI 0.86-0.97), all-cause mortality (RR 0.91, 95% CI 0.84-0.99), and serious adverse events (RR 0.94, 95% CI 0.89-1.00) were primarily observed with the titrated 2.5-10 mg regimen, whereas lower or intermediate doses did not demonstrate clear benefits. Symptomatic hypotension was more frequent with the titrated regimen (RR 1.21, 95% CI 1.07-1.35), while no evident dose-related pattern was seen for overall adverse events, syncope, or acute kidney injury. No statistically significant interaction was detected between dose and treatment effect for any outcome, suggesting that the benefits and risks of vericiguat were not clearly dose-dependent within the studied range. Detailed results are provided in Supplementary Figures 8(A)-8(I).

Subgroup Analysis by Follow-up Duration

Subgroup analyses according to follow-up duration (≤16 *vs.* >16 weeks) showed broadly consistent effects across outcomes. Vericiguat was associated with modest reductions in the composite of CV death or HF hospitalization, all-cause mortality, and serious adverse events, and with an increased risk of symptomatic hypotension, while showing no clear effect on overall adverse events, syncope, or acute kidney injury. For no outcome was there a statistically significant interaction between treatment effect and follow-up duration, indicating that follow-up length did not materially modify the effect of vericiguat. Detailed results are provided in Supplementary Figures 9(A)-9(I).

Meta-Regression

Exploratory random-effects meta-regression was performed to assess whether study-level characteristics modified the effect of vericiguat on the composite of CV death or HF hospitalization. Mean age, mean body mass index, diabetes, and β-blocker use were not significantly associated with the treatment effect (all p > 0.05). In contrast, a higher prevalence of atrial fibrillation and use of mineralocorticoid receptor antagonists, implantable cardioverter-defibrillators, or cardiac resynchronisation

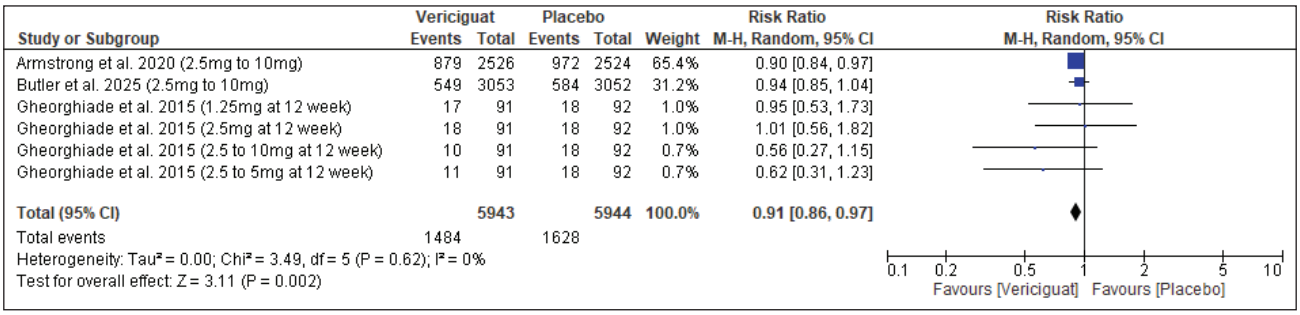


Figure 3. *Forest plot of cardiovascular death or hospitalization for heart failure.*

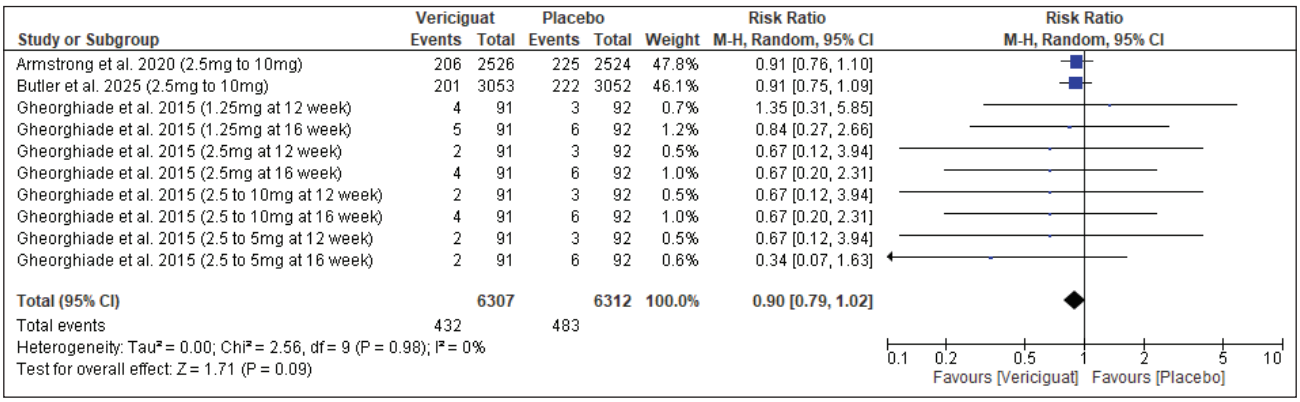


Figure 4. *Forest plot of cardiovascular death.*

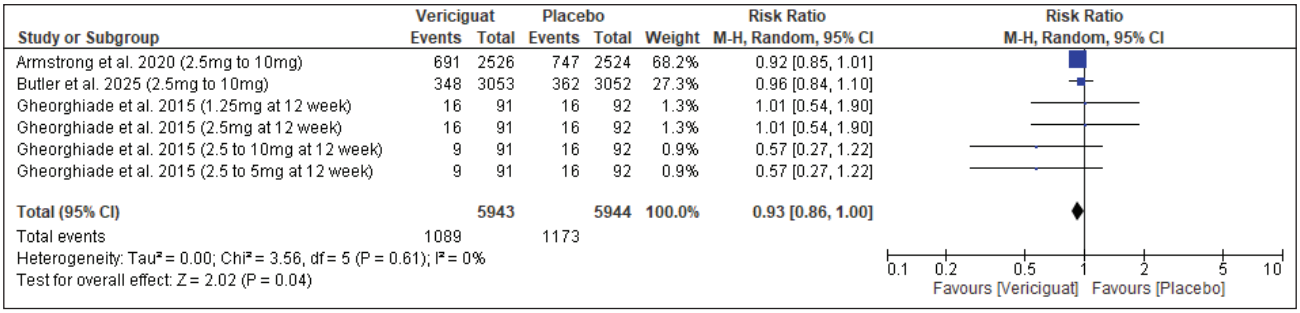


Figure 5. *Forest plot of hospitalization for heart failure.*

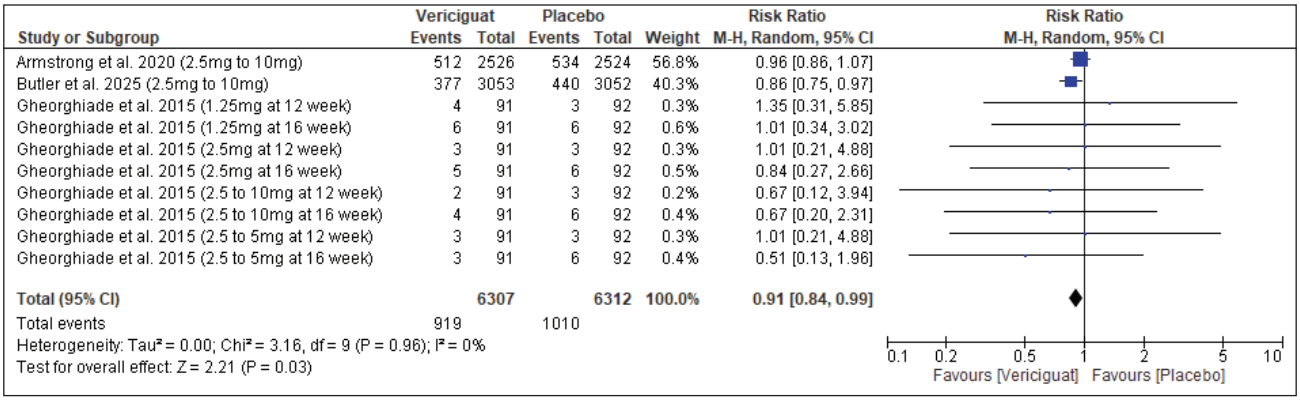


Figure 6. *Forest plot of all-cause mortality.*

therapy were associated with a less favorable observed effect of vericiguat, whereas higher proportions of hypertension and loop-diuretic use, higher baseline eGFR, and lower systolic blood pressure were associated with a more favorable effect (all $p < 0.01$). Higher baseline LVEF was also associated with attenuation of benefit ($p = 0.03$). These analyses are based on a small number of studies and should be interpreted as hypothesis generating, and they did not materially change the low between-study heterogeneity seen in the primary meta-analysis. Detailed coefficients and graphical displays of these relationships are provided in Supplementary Table 3 and Supplementary Figure 10(A)-10(M).

Discussion

Vericiguat consistently improves clinical outcomes for patients with HF and reduced ejection fraction, according to this meta-analysis, mainly by reducing the incidence of recurring or worsening HF episodes. Vericiguat was associated with a slight increase in overall survival and decreased overall burden of HF hospitalizations across all included studies, both for first events and total occurrences. The pattern of results indicates a potential but limited effect, even though there was no discernible decrease in CV mortality.

The risk of adverse outcomes in patients with HFrEF remains high despite treatment with renin angiotensin aldosterone inhibitors, betablockers, and sodium glucose cotransporter 2 inhibitors, particularly after a worsening HF event [16]. Approximately 1 in 6 patients with HFrEF experience worsening HF events an average of 18 months after diagnosis. In this context, therapies such as vericiguat have been evaluated to reduce the burden of recurrent HF events.

When comparing vericiguat with placebo, we observed a substantial decrease in the number of hospitalizations. Vericiguat significantly reduced the total HF hospitalization occurrences (first and recurring episodes) compared to placebo; however, a new study conducted to support this finding revealed a substantial reduction in first events compared to recurrent events. Vericiguat appeared to be more beneficial for patients with lower NT proBNP levels than for those with very high NT proBNP levels in the same trial [12].

According to our meta analysis, vericiguat has a small but significant effect on the composite endpoint of CV death or HF hospitalization. In our investigation, the impact of vericiguat alone on CV mortality was not significant. These findings are consistent with the changing understanding of the role of vericiguat in HFrEF. VICTORIA (published in 2020) showed no change in CV death but a significant decrease in the composite endpoint (HR 0.90) [13]. VICTOR (presented in 2025) enrolled more stable outpatients; it showed fewer CV fatalities (HR 0.83; 95% CI 0.71-0.97) but did not reach the composite goal (HR 0.93; $p = 0.22$) [14]. These were reconciled by our meta analysis; as we discovered, integrating the two trials results in a considerable composite benefit, which probably explains why pooled CV death attained significance in larger analyses.

Crucially, the outcomes aligned with the guidelines' recommendations. Vericiguat has a Class IIb

recommendation in the 2022 ACC/AHA HF Guideline, meaning it "may be considered" to lower HF hospitalization and CV death in high risk HFrEF patients [17]. This cautious recommendation is supported by our results, which show that vericiguat has only a slight impact on survival while providing incremental event reduction in addition to that of conventional therapy. The function of vericiguat throughout a wide HF band is further highlighted by the ESC and other expert communications. Vericiguat, for instance, decreased the risk of CV death, HF related hospitalizations, and all cause mortality in a wide variety of patients, according to a pooled individual participant data analysis of VICTORIA and VICTOR [18]. Vericiguat enhances outcomes, mostly by reducing HF hospitalizations, according to recent data (particularly the VICTOR trial and pooled analysis), despite earlier meta analyses being neutral [19]. Confidence in the outcome was increased by the absence of heterogeneity and agreement with extensive trial data.

Overall, vericiguat showed a good safety profile; patient withdrawals and major adverse events occurred somewhat less frequently than with placebo, but the overall rate of adverse events was approximately the same for both groups. In the VICTORIA study, symptomatic hypotension was recorded in 9.1% of patients compared to 7.9% on placebo (p = 0.12), as would be predicted for a vasodilator; a pooled analysis indicated a slight but substantial increase (RR≈1.19) [13]. Clinically, this resulted in a mere 1-2 mmHg drop in average blood pressure and a marginally increased incidence of hypotensive symptoms or dizziness, whereas syncope remained rare (4.0% *vs*. 3.5%, RR≈1.19, P≈0.24). Another noteworthy observation was that 10% of individuals receiving vericiguat had mild anemia compared with 7% of patients receiving a placebo (RR≈1.26). Crucially, no statistically significant changes were observed between the groups, and vericiguat did not increase the risk of renal dysfunction, acute kidney damage, or electrolyte imbalances [20]. When combined, these findings indicate that, aside from slight elevations in anemia and hypotension, vericiguat is generally well tolerated and has safety results comparable to those of a placebo.

Vericiguat was started at 2.5 mg daily in clinical studies and titrated to 10 mg, which is the target dose utilized in the VICTORIA trial [13]. Patients who reached 10 mg demonstrated primary efficacy signals, which were decreases in all-cause mortality (RR ≈ 0.91) and CV death or HF hospitalization; lower fixed doses had neutral outcomes. Titration to 10 mg is recommended as the normal regimen because the overall safety and efficacy did not indicate strong dosage dependence, although symptomatic hypotension was somewhat more common at the maximal dose (RR ≈ 1.21).

According to an exploratory meta regression, most baseline factors, including age, BMI, diabetes, and betablocker use, did not significantly change the effects of vericiguat. Patients with hypertension, improved kidney function, reduced systolic blood pressure, and increased diuretic use, on the other hand, seemed to benefit more than those with atrial fibrillation or any other advanced intervention. Reduced benefits were associated with a higher ejection fraction. Because these patterns are exploratory, care should be taken when interpreting them.

Limitations

This meta analysis has several notable limitations. The available evidence base is small and largely driven by the VICTORIA and VICTOR trials, making pooled estimates particularly for CV mortality susceptible to the influence of individual studies. Differences between trials in patient clinical stability, baseline NT proBNP levels, and background guideline directed therapy introduce clinical heterogeneity and may limit generalizability. Variability in dosing strategies, follow-up duration, and event adjudication could also affect effect estimates and hinder evaluation of long-term outcomes. In addition, the analysis relies on study level rather than individual patient data, which restricts adjustment for confounding factors and introduces a risk of ecological bias in meta regression findings. Finally, limited power for uncommon safety outcomes and the possibility of reporting or publication bias may have influenced the observed safety profile.

Conclusion

Vericiguat provides a modest but clinically meaningful reduction in HF hospitalizations and improves the composite endpoint of CV death or HF hospitalization in patients with HFrEF. Its effect on CV mortality alone is limited, though pooled data suggest a small survival signal. Safety is acceptable overall, with modest increases in symptomatic hypotension and mild anemia that warrant monitoring. These findings support vericiguat as an adjunct for high risk or recently decompensated HFrEF patients, with benefits most evident in selected subgroups.

Acknowledgments

None.

List of Abbreviations

HFrEF	Heart Failure with Reduced Ejection Fraction
HF	Heart Failure
CV	Cardiovascular
RR	Risk Ratio
CI	Confidence Interval
RCTs	Randomized Controlled Trials
GDMT	Guideline-Directed Medical Therapy
sGC	Soluble Guanylate Cyclase

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The authors received no extramural funding for the study.

Consent for publication

Not applicable.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Availability of data and materials statement

The datasets supporting the conclusions of this article are included in this article.

Peer review and provenance statement

This manuscript was not commissioned.

Clinical trial number

Not applicable.

Author details

Ihab Suliman[1], Noor Yousef Al-Mohaimeed[2], Hisham Ali Hendi Alghamdi[3], Saja Abdullah Alharbi[4], Leen Ghazi Alahmadi[5], Sabah Hussein Alkharboush[6], Layan Tareq Aldhowayan[2], Manahel Hayder H Alawami[7], Abdulrahman Mohammed H M Aldousari[8], Salah J. S A Alrashidi[9], Rahaf Mohammed Alansari[6]

1. Cardiology, King Abdulaziz Medical City, King Abdulaziz Cardiac Center, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
2. College of Medicine, Qassim University, Buraydah, Saudi Arabia
3. Faculty of Medicine, Al Baha University, Al Baha, Saudi Arabia
4. College of Medicine, Majmaah University, Majmaah, Saudi Arabia
5. College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
6. Faculty of Medicine, University of Tabuk, Tabuk, Saudi Arabia
7. College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
8. Department of Internal Medicine, Farwaniya Hospital, Ministry of Health, Farwaniya, Kuwait
9. Department of Internal Medicine, Al Sabah Medical Hospital, Ministry of Health, Kuwait City, Kuwait

Supplementary material, if any, is available online.

References

1. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure: endorsed by the Canadian heart failure society, heart failure association of India, cardiac society of Australia and New Zealand, and Chinese heart failure association. Eur J Heart Fail. 2021;23(3):352–80. https://doi.org/10.1002/ejhf.2115
2. GBD. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018;392(10159):1789–858. https://doi.org/10.1016/s0140-6736(18)32279-7
3. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation. 2021;143(8):e254–e743. https://doi.org/10.1161/cir.0000000000000950
4. Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction: a review. JAMA. 2020;324(5):488–504. https://doi.org/10.1001/jama.2020.10262
5. D'Elia S, Gentile C, Solimene A, Franzese R, Luisi E, Caiazzo A, et al. The NO pathway as a target in patients with stable and advanced heart failure: an additional arrow in our quiver! Biomolecules. 2025;15(10):1420. https://doi.org/10.3390/biom15101420
6. Xia J, Hui N, Tian L, Liang C, Zhang J, Liu J, et al. Development of vericiguat: the first soluble guanylate cyclase (sGC) stimulator launched for heart failure with reduced ejection fraction (HFrEF). Biomed Pharmacother. 2022;149:112894. https://doi.org/10.1016/j.biopha.2022.112894
7. Agha RA, Mathew G, Rashid R, Kerwan A, Al-Jabir A, Sohrabi C, et al. Transparency in the reporting of artificial intelligence - the TITAN guideline. PJS. 2025:100082. https://doi.org/10.70389/pjs.100082
8. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. https://doi.org/10.1136/bmj.j4008
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
11. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557
12. Mentz RJ, Stebbins A, Butler J, Chiang CE, Ezekowitz JA, Hernandez AF, et al. Recurrent hospitalizations and response to vericiguat in heart failure and reduced ejection fraction. JACC Heart Fail. 2024;12(5):839–46. https://doi.org/10.1016/j.jchf.2023.12.005
13. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med. 2020;382(20):1883–93.
14. Butler J, McMullan CJ, Anstrom KJ, Barash I, Bonaca MP, Borentain M, et al. Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2025;406(10510):1341–50. https://doi.org/10.1016/s0140-6736(25)01665-4
15. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CSP, Maggioni AP, et al. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial. JAMA. 2015;314(21):2251–62. https://doi.org/10.1001/jama.2015.15734
16. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, et al. Clinical course of patients with worsening

heart failure with reduced ejection fraction. J Am Coll Cardiol. 2019;73(8):935–44. https://doi.org/10.1016/j.jacc.2018.11.049

17. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM. Correction to: 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):e1033. https://doi.org/10.1161/cir.0000000000001073

18. Zannad F, O'Connor CM, Butler J, McMullan CJ, Anstrom KJ, Barash I, et al. Vericiguat for patients with heart failure and reduced ejection fraction across the risk spectrum: an individual participant data analysis of the VICTORIA and VICTOR trials. Lancet. 2025;406(10510):1351–62. https://doi.org/10.1016/s0140-6736(25)01682-4

19. Ma J, Guo S, Jiang H, Li B. Efficacy and safety of vericiguat in heart failure: a meta-analysis. J Int Med Res. 2023;51(3):3000605231159333. https://doi.org/10.1177/03000605231159333

20. Chiles R, Al-Horani RA. Vericiguat: a new hope for heart failure patients. Cardiovasc Ther. 2022;2022:1554875. https://doi.org/10.1155/2022/1554875