International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	VERICIGUAT: MODERN THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5325
RECEIVED	05 February 2026
ACCEPTED	15 April 2026
PUBLISHED	04 May 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

© The author(s) 2026.
This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

VERICIGUAT: MODERN THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE

Dominik Bylica
Zespół Szpitali Miejskich w Chorzowie, Medical University of Silesia, Chorzów, Poland
ORCID ID: 0000-0001-8131-2863

Anna Kaźmierska *(Corresponding Author, Email: ania.kazmierska43@gmail.com)*
Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Poland
ORCID ID: 0009-0005-2625-6260

Radosław Szydłowski
Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Poland
ORCID ID: 0009-0000-5771-3990

Magdalena Bodera
Wojewódzki Szpital Specjalistyczny nr 5 im. św. Barbary w Sosnowcu, Medical University of Silesia, Sosnowiec, Poland
ORCID ID: 0009-0002-8890-214X

Sonja Rozmus
Wojewódzki Szpital Specjalistyczny nr 5 im. św. Barbary w Sosnowcu, Medical University of Silesia, Sosnowiec, Poland
ORCID ID: 0009-0000-8747-9605

ABSTRACT

Vericiguat is the first oral soluble guanylate cyclase (sGC) stimulator developed to reduce the risk of cardiovascular death and heart failure–related hospitalizations in patients with chronic heart failure with reduced left ventricular ejection fraction (HFrEF). sGC dysfunction, resulting in impaired synthesis of cyclic guanosine monophosphate (cGMP), may play a keyrole in the pathophysiology of heart failure by affecting myocardial function, vascular tone, and peripheral tissue perfusion. Vericiguat exerts its therapeutic effect by enhancing intracellular cGMP levels, leading to improved cardiac function and vasodilation. Consequently, the drug represents a promising treatment option for patients with HFrEF, particularly those with recent decompensation, requiring intravenous diuretic therapy, or at high risk for rehospitalization due to disease exacerbation.

Clinical efficacy of vericiguat was demonstrated in the VICTORIA trial, which enrolled 6,857 patients with HFrEF following recent decompensation. After a median follow-up of 10.8 months, treatment with vericiguat significantly reduced the risk of the composite endpoint of cardiovascular death or heart failure related hospitalization compared with placebo. Patients with more advanced disease also exhibited reductions in NT-proBNP levels, suggesting a potential biomarker of therapeutic response. Vericiguat is generally well tolerated. The most commonly reported adverse events are hypotension and syncope. The drug can be safely administered to patients with mild to moderate renal or hepatic impairment, although data in severe organ dysfunction are lacking. Dose adjustments are not required based on age or body weight. The introduction of vericiguat into the management of HFrEF represents a meaningful advancement in therapy. While the drug does not significantly extend overall survival, its use is associated with a substantial reduction in the risk of recurrent hospitalizations, which may have important clinical and prognostic implications in this patient population.

KEYWORDS

Vericiguat, Soluble Guanylate Cyclase (sGC) Stymulator, Heart Failure, Pharmacological Treatment, Cardiovascular Outcomes

CITATION

Dominik Bylica, Anna Kaźmierska, Radosław Szydłowski, Magdalena Bodera, Sonja Rozmus. (2026) Vericiguat: Modern Therapy for the Treatment of Chronic Heart Failure. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5325

COPYRIGHT

© The author(s) 2026. This article is published as open access under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**, allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

Introduction

Heart failure (HF) represents one of the most significant challenges in contemporary medicine, imposing a substantial burden on healthcare systems worldwide. Its increasing prevalence is driven by population aging and improved survival following acute cardiovascular events. Despite advances in diagnosis and management, the prognosis of patients with symptomatic HF remains poor, with epidemiological data indicating that approximately 40% of patients die within the first year of diagnosis and 60–70% within five years, primarily due to progressive heart failure or sudden cardiac death (SCD). The predominant clinical manifestations of HF include dyspnea, exercise intolerance, and fluid retention, presenting as pulmonary congestion and peripheral edema.

According to current classification, three main HF phenotypes are distinguished:

- HF with preserved ejection fraction (HFpEF) – LVEF ≥ 50%,
- HF with mildly reduced ejection fraction (HFmrEF) – LVEF 40–49%,
- HF with reduced ejection fraction (HFrEF) – LVEF < 40%.

Although understanding of HF pathophysiology has advanced, the mechanisms underlying HFpEF remain incompletely elucidated. Increasing evidence suggests that impaired cyclic guanosine monophosphate (cGMP) signaling plays a critical role in the dysregulation of pathophysiological pathways contributing to HF development and progression.

Preclinical and clinical studies indicate that activation of the nitric oxide (NO)–soluble guanylate cyclase (sGC)–cGMP pathway represents a promising therapeutic strategy in chronic, progressive HF. Under physiological conditions, cGMP regulates cardiomyocyte energetics, myocardial contractility, and endothelial function. In HF, oxidative stress, inflammation, and endothelial dysfunction reduce NO bioavailability, resulting in decreased cGMP synthesis. This deficiency impairs coronary, systemic, and renal microcirculation, exacerbating myocardial injury and promoting disease progression.

Vericiguat, a novel oral sGC stimulator, offers an innovative therapeutic approach in HF by directly increasing cGMP synthesis and restoring sGC responsiveness to endogenous NO, thereby improving endothelial function, systemic hemodynamics, and cardiac performance. The drug has been approved for use in adult patients with symptomatic, chronic HFrEF to reduce the risk of cardiovascular death and recurrent hospitalizations following a decompensation episode. As the first agent of its class, vericiguat has the potential to favorably influence the clinical course of HF, slowing disease progression and enhancing patients ’quality of life.

Aims

The present study provides a comprehensive evaluation of the effects of vericiguat on all cause and cardiovascular mortality. In addition, the safety and tolerability profile of the therapy was characterized, and the optimal dosing strategy of the soluble guanylate cyclase stimulator (vericiguat) was determined in patients with chronic heart failure with preserved left ventricular ejection fraction (HFpEF).

Methods

The SOCRATES-PRESERVED and VICTOR trials represent complementary, randomized, double-blind, placebo-controlled studies designed to evaluate the safety, tolerability, and efficacy of vericiguat in patients with distinct heart failure phenotypes. In the Phase 2b SOCRATES-PRESERVED study, patients with HFpEF (ejection fraction ≥45%) received vericiguat once daily at fixed doses of 1.25 mg or 2.5 mg, or at 5 mg and 10 mg titrated from a 2.5 mg starting dose, or placebo, for 12 weeks. The primary endpoints included changes from baseline in log-transformed NT-proBNP levels and left atrial volume (LAV).

The VICTOR trial enrolled 6,105 ambulatory patients with HFrEF without recent clinical worsening, who were randomized to vericiguat or placebo. In both studies, participants continued contemporary guideline-directed heart failure therapy, enabling the simultaneous assessment of the pharmacodynamic and clinical

effects of vericiguat on cardiac biomarkers, structural cardiac parameters, and cardiovascular outcomes across heterogeneous populations of patients with chronic heart failure.

Mechanism of Action of Vericiguat

The nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) signaling pathway plays a central role in the regulation of cardiovascular function, maintaining vascular tone and endothelial homeostasis. Under physiological conditions, NO produced by endothelial cells diffuses into adjacent vascular smooth muscle cells, where itbinds to the heme moiety of sGC. This binding induces a conformational change in the enzyme, activating its catalytic function and promoting the conversion of GTP to cGMP. Elevated cGMP levels trigger the activation of protein kinase G and downstream signaling cascades, resulting in smooth muscle relaxation and vasodilation.

In heart failure, the NO–sGC–cGMP axis is profoundly impaired. Progressive oxidative stress, reduced NO bioavailability, and endothelial dysfunction lead to attenuated sGC stimulation, resulting in cGMP deficiency and enhanced vascular inflammation, thereby exacerbating cardiovascular dysfunction.

In this context, sGC stimulators have emerged as a therapeutic strategy, with vericiguat representing the first oral agent of this class approved for the treatment of heart failure. Vericiguat has been designed to modulate the cGMP pathway even under conditions of limited NO availability. The drug acts both independently of NO and synergistically with it, directly and indirectly activating sGC by increasing its sensitivity to NO. Interaction with the heme-containing functional form of sGC enhances cGMP synthesis, improving endothelial function, systemic hemodynamics, and myocardial contractility.

Preclinical studies demonstrate that vericiguat exerts a robust and selective stimulatory effect on sGC even under low NO conditions characteristic of heart failure, while its activity is markedly potentiated in the presence of NO, highlighting a synergistic mechanism of action.

Compared with existing heart failure therapies, vericiguat's mechanism is unique. Conventional treatments, including β-blockers, renin–angiotensin–aldosterone system inhibitors, and SGLT2 inhibitors, do not modulate the NO–sGC–cGMP pathway. While most standard therapies target maladaptive neurohormonal signaling, emerging agents such as vericiguat activate protective signaling cascades specifically, the NO–sGC–cGMP pathway and the natriuretic peptide system providing an innovative and complementary therapeutic approach in heart failure management.

Clinical Development of Vericiguat

Four pivotal clinical trials have played a key role in the clinical development of vericiguat: two phase II studies – SOCRATES-REDUCED and SOCRATES-PRESERVED and two phase III studies – VICTORIA and VITALITY-HFpEF.

The SOCRATES program included multicenter, randomized, placebo-controlled trials that assessed the pharmacodynamics, pharmacokinetics, safety, and tolerability of different vericiguat doses over 12 weeks of treatment. In SOCRATES-REDUCED (patients with LVEF < 45%), the primary endpoint was the change in NT-proBNP levels, whereas in SOCRATES-PRESERVED (LVEF ≥ 45%), the primary endpoints were NT-proBNP and left atrial volume. Although no significant differences were observed compared with placebo, a dose–response relationship in NT-proBNP reduction was noted, and vericiguat was well tolerated. In SOCRATES-PRESERVED, vericiguat improved patients 'quality of life while maintaining good tolerability.

The VITALITY-HFpEF study evaluated the effect of vericiguat on physical limitations using the Kansas City Cardiomyopathy Questionnaire (KCCQ) in patients with HFpEF. In this trial of over 700 patients, vericiguat did not improve KCCQ scores compared with placebo.

The phase III VICTORIA trial included 5,050 patients with HFrEF (LVEF < 45%, NYHA class II–IV) following a recent worsening of heart failure. Patients were randomized to vericiguat or placebo in addition to standard therapy. The primary endpoint was the composite of cardiovascular death or first heart failure hospitalization. Treatment was initiated at 2.5 mg vericiguat and gradually uptitrated to 10 mg once daily based on systolic blood pressure and clinical symptoms. Pre-specified adverse events of interest included symptomatic hypotension and syncope.

VICTORIA demonstrated that vericiguat significantly reduced the incidence of the primary composite outcome compared with placebo (897/2,526 vs. 972/2,524; HR = 0.90; 95% CI: 0.82–0.98; P = 0.02), along with a reduction in hospitalizations and a favorable effect on cardiovascular mortality.

Interactions

Available pharmacokinetic data indicate that co-administration of omeprazole reduces systemic exposure to vericiguat, as reflected by decreased AUC and Cmax values. A similar effect has been observed with antacid formulations containing magnesium hydroxide and aluminum hydroxide. In contrast, co administration with ketoconazole results in only a slight increase in plasma concentrations of vericiguat. Enzyme inducers such as rifampicin reduce vericiguat AUC and Cmax by 29% and 9%, respectively, whereas mefenamic acid, a weak UGT1A9 inhibitor, produces only a minimal increase in AUC. No clinically relevant pharmacokinetic changes have been observed when vericiguat is co-administered with warfarin, digoxin, or acetylsalicylic acid. Co-administration with sacubitril/valsartan results ina minor, clinically insignificant reduction in AUC and Cmax, while sildenafil, regardless of dose, has minimal impact on vericiguat pharmacokinetics. Furthermore, vericiguat does not significantly affect midazolam metabolism, indicating no relevant interaction with CYP3A4 activity.

Despite the observed reduction in vericiguat absorption associated with omeprazole and certain antacids, interaction studies confirm a favorable safety profile and predictable pharmacokinetics, supporting its suitability as a therapeutic option for patients with heart failure, particularly those receiving multiple concomitant medications. Caution is warranted in patients concurrently treated with long-acting nitrates, sGC stimulators, or PDE5 inhibitors due to an increased risk of hypotension and syncope. Additionally, vericiguat is not recommended in patients with severe anemia, as it may further reduce hemoglobin levels.

Adverse effects

In clinical trials, vericiguat demonstrated a favorable safety profile, with hypotension being the most frequently reported adverse event. In the VICTORIA trial population, hypotensive episodes occurred in 9.1% of patients receiving vericiguat compared with 7.9% in the placebo group, with the majority of events occurring during the initial months of therapy. The incidence of syncope was similar between the groups (4.0% vs. 3.5%), whereas severe symptomatic hypotension remained rare (0.4% vs. 0.3%). The most common mechanism related adverse events included hypotension, syncope, and anemia.

Less specific adverse events, such as headache, dizziness, nausea, dyspepsia, and diarrhea, are attributed to the vasodilatory and smooth muscle relaxing effects of the drug. Anemia occurred in 7.6% of patients treated with vericiguat and 5.7% of those receiving placebo, with severe cases being uncommon (1.6% vs. 0.9%). A mild increase in heart rate was also observed in some patients, interpreted as a reflex compensatory response to reduced blood pressure.

Renal safety analyses revealed no significant differences between the vericiguat and placebo groups regarding the progression of renal dysfunction, suggesting that dose adjustments are not required in patients with mild increases in serum creatinine or potassium levels.

Conclusions

Vericiguat represents an important adjunct to contemporary pharmacological management of patients with HFrEF, particularly in the post-decompensation population, where the risk of recurrent hospitalizations remains high. Although the drug does not demonstrate a significant impact on overall survival, its beneficial effect in reducing hospitalization rates, along with favorable clinical tolerability, underscores the role of vericiguat in optimizing therapy for patients with advanced heart failure.

The clinical efficacy of vericiguat was confirmed in the VICTORIA trial, which enrolled over 5,000 high-risk patients with HFrEF. Treatment with vericiguat significantly reduced the risk of the composite endpoint of cardiovascular death or heart failure related hospitalization.

Vericiguat exhibits a favorable safety profile. The most frequently reported adverse events were hypotension, syncope, and anemia, generally of mild to moderate severity. Dose adjustments were not required in elderly patients or in those with mild to moderate renal or hepatic impairment. The drug demonstrates a low potential for pharmacological interactions; however, caution is advised when co-administered with long-acting nitrates, PDE5 inhibitors, or other sGC stimulators.

Incorporation of vericiguat into standard HFrEF therapy constitutes a meaningful addition to guideline directed treatment. While it does not affect overall survival, vericiguat significantly reduces the risk of recurrent hospitalizations, with important clinical and prognostic implications for patients with advanced and progressive heart failure.

Author's contribution:
Conceptualization– Dominik Bylica, Anna Kaźmierska
Formal analysis– Radosław Szydłowski, Magdalena Bodera
Investigation – Sonja Rozmus
Data curation– Dominik Bylica, Sonja Rozmus
Writing rough preparation– Dominik Bylica, Anna Kaźmierska, Radosław Szydłowski
Writing review and editing– Dominik Bylica, Anna Kaźmierska, Radosław Szydłowski
Visualization– Dominik Bylica, Anna Kaźmierska, Radosław Szydłowski, Magdalena Bodera

All authors have read and agreed with published version of the manuscript.

Data availability statement: The authors confirm that the data supporting this study are available in the article's references.

Conflict of interest: Authors declare no conflict of interest.

REFERENCES

1. Armstrong, P. W., Pieske, B., Anstrom, K. J., Ezekowitz, J., Hernandez, A. F., Butler, J., et al. (2020). Vericiguat in patients with heart failure and reduced ejection fraction. *New England Journal of Medicine, 382*(20), 1883–1893. https://doi.org/10.1056/NEJMoa1915928
2. Gheorghiade, M., Greene, S. J., Butler, J., Filippatos, G., Lam, C. S. P., Maggioni, A. P., et al. (2015). Effect of vericiguat on NT-proBNP and clinical outcomes in patients with worsening chronic heart failure and reduced ejection fraction: The SOCRATES-REDUCED randomized trial. *JAMA, 314*(21), 2251–2262. https://doi.org/10.1001/jama.2015.15734
3. Pieske, B., Maggioni, A. P., Lam, C. S. P., Pieske-Kraigher, E., Butler, J., Filippatos, G., et al. (2017). Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: Results of the SOCRATES-PRESERVED study. *European Heart Journal, 38*(15), 1119–1127. https://doi.org/10.1093/eurheartj/ehw593
4. Armstrong, P. W., Lam, C. S. P., Anstrom, K. J., Ezekowitz, J., Hernandez, A. F., O'Connor, C. M., et al. (2020). Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: The VITALITY-HFpEF randomized clinical trial. *JAMA, 324*(15), 1512–1521. https://doi.org/10.1001/jama.2020.15922
5. Voors, A. A., Mulder, H., Reyes, E., et al. (2021). Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: Insights from the VICTORIA trial. *European Journal of Heart Failure, 23*(8), 1313–1321. https://doi.org/10.1002/ejhf.2221
6. Butler, J., Fioretti, F., McMullan, C. J., Anstrom, K. J., Barash, I., Bonaca, M. P., et al. (2026). Vericiguat and mortality in heart failure and reduced ejection fraction: The VICTOR trial. *European Heart Journal, 47*(6), 683–697. https://doi.org/10.1093/eurheartj/ehaf655
7. Tian, J., Dong, M., Sun, X., Jia, X., Zhang, G., Zhang, Y., Lin, Z., Xiao, J., Zhang, X., & Lu, H. (2024). Vericiguat in heart failure with reduced ejection fraction patients on guideline-directed medical therapy: Insights from a 6-month real-world study. *International Journal of Cardiology, 417*, 132524. https://doi.org/10.1016/j.ijcard.2024.132524
8. Falco, L., Brescia, B., Catapano, D., Martucci, M. L., Valente, F., Gravino, R., Contaldi, C., Pacileo, G., & Masarone, D. (2023). Vericiguat: The fifth harmony of heart failure with reduced ejection fraction. *Journal of Cardiovascular Development and Disease, 10*(9), 388. https://doi.org/10.3390/jcdd10090388
9. González-Juanatey, J. R., Anguita-Sánchez, M., Bayes-Genís, A., Comín-Colet, J., García-Quintana, A., Recio-Mayoral, A., et al. (2022). Vericiguat in heart failure: From scientific evidence to clinical practice. *Revista Clínica Española (English Edition), 222*(6), 359–369. https://doi.org/10.1016/j.rceng.2021.12.006
10. Dies, R. M., Jackson, C. N., Flanagan, C. J., Sinnathamby, E. S., Spillers, N. J., Potharaju, P., Singh, N., Varrassi, G., Ahmadzadeh, S., Shekoohi, S., & Kaye, A. D. (2023). The evolving role of vericiguat in patients with chronic heart failure. *Cureus, 15*(12), e49782. https://doi.org/10.7759/cureus.49782
11. Lam, C. S. P., Mulder, H., Lopatin, Y., Vazquez-Tanus, J. B., Siu, D., Ezekowitz, J., Pieske, B., O'Connor, C. M., Roessig, L., Patel, M. J., Anstrom, K. J., Hernandez, A. F., Armstrong, P. W., & VICTORIA Study Group. (2021). Blood pressure and safety events with vericiguat in the VICTORIA trial. *Journal of the American Heart Association, 10*(22), e021094. https://doi.org/10.1161/JAHA.121.021094
12. Sahana, U., Wehland, M., Simonsen, U., Schulz, H., & Grimm, D. (2023). A systematic review of the effect of vericiguat on patients with heart failure. *International Journal of Molecular Sciences, 24*(14), 11826. https://doi.org/10.3390/ijms241411826

13. Fritsch, A., Meyer, M., Blaustein, R. O., Trujillo, M. E., Kauh, E., Roessig, L., Boettcher, M., & Becker, C. (2024). Clinical pharmacokinetic and pharmacodynamic profile of vericiguat. *Clinical Pharmacokinetics, 63*, 751–771. https://doi.org/10.1007/s40262-024-01384-1
14. Vannuccini, F., Campora, A., Barilli, M., & Palazzuoli, A. (2022). Vericiguat in heart failure: Characteristics, scientific evidence and potential clinical applications. *Biomedicines, 10*(10), 2471. https://doi.org/10.3390/biomedicines10102471
15. Vyas, A., & Onteddu, N. (2025). Vericiguat. In *StatPearls*. StatPearls Publishing.
16. Russo, P., Vitiello, L., Milani, F., Volterrani, M., Rosano, G. M. C., Tomino, C., & Bonassi, S. (2024). New therapeutics for heart failure worsening: Focus on vericiguat. *Journal of Clinical Medicine, 13*(14), 4209. https://doi.org/10.3390/jcm13144209
17. Chiles, R., & Al-Horani, R. A. (2022). Vericiguat: A new hope for heart failure patients. *Cardiovascular Therapeutics, 2022*, 1554875. https://doi.org/10.1155/2022/1554875
18. Trujillo, M. E., Ayalasomayajula, S., Blaustein, R. O., & Gheyas, F. (2023). Vericiguat, a novel sGC stimulator: Mechanism of action, clinical, and translational science. *Clinical and Translational Science, 16*(12), 2458–2466. https://doi.org/10.1111/cts.13677
19. Rao, V. N., Diez, J., Gustafsson, F., Mentz, R. J., Senni, M., Jankowska, E. A., & Bauersachs, J. (2023). Practical patient care considerations with use of vericiguat after worsening heart failure events. *Journal of Cardiac Failure, 29*(3), 389–402. https://doi.org/10.1016/j.cardfail.2022.10.431
20. Vohra, M., Amir, M., Osoro, I., Sharma, A., & Kumar, R. (2023). Impact of vericiguat on heart failure with reduced ejection fraction: A review. *Global Health Journal, 7*(3), 123–129. https://doi.org/10.1016/j.glohj.2023.07.004
21. European Society of Cardiology. (2022, May 4). *Zalecenia ESC 2021 dotyczące diagnostyki i leczenia ostrej i przewlekłej niewydolności serca*. https://www.escardio.org
22. Stasch, J. P., Schlossmann, J., & Hocher, B. (2015). Renal effects of soluble guanylate cyclase stimulators and activators: A review of the preclinical evidence. *British Journal of Pharmacology, 172*(2), 300–311. https://doi.org/10.1111/bph.12974
23. Markham, A., & Duggan, S. (2021). Vericiguat: First approval. *Drugs, 81*, 721–726. https://doi.org/10.1007/s11096-021-03240-1
24. Aimo, A., Castiglione, V., Vergaro, G., Panichella, G., Senni, M., Lombardi, C. M., & Emdin, M. (2021). The place of vericiguat in the landscape of treatment for heart failure with reduced ejection fraction. *Heart Failure Reviews, 26*(4), 567–577. https://doi.org/10.1007/s10741-021-10122-9