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
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ARTICLE TITLE	USE OF VERCIGUAT IN THE TREATMENT OF HEART FAILURE
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4937
RECEIVED	19 January 2026
ACCEPTED	26 March 2026
PUBLISHED	30 March 2026
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USE OF VERCIGUAT IN THE TREATMENT OF HEART FAILURE

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ABSTRACT

Heart failure remains a major challenge in contemporary cardiology, characterized by high morbidity, frequent hospitalizations, and an unfavorable prognosis despite substantial advances in guideline-directed therapy. Although modern multidrug treatment has improved clinical outcomes, a considerable proportion of patients continue to experience disease progression and recurrent exacerbations, particularly in high-risk populations.

Vericiguat is a novel oral agent used in the treatment of heart failure and represents an adjunct to standard therapy in selected patients. To date, clinical studies have evaluated the efficacy and safety of vericiguat in patients with both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Available evidence suggests that the clinical effects of vericiguat vary depending on the heart failure phenotype and the clinical context, including disease stability and the risk of further deterioration.

This paper provides a comprehensive review of current data on the use of vericiguat across different heart failure phenotypes, with particular emphasis on clinical trial outcomes, therapeutic efficacy, and safety profile. The limitations of existing evidence are discussed, along with the potential role of vericiguat within contemporary treatment strategies. Overall, current findings indicate that vericiguat should not be regarded as a universal therapy for all patients with heart failure, but rather as a complementary treatment option for carefully selected individuals, in whom additional therapeutic strategies may be required.

KEYWORDS

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

CITATION

Radosław Szydłowski, Magdalena Bodera, Anna Kaźmierska, Hanna Porwolik, Sonja Rozmus, Dominik Bylica. (2026) Use of Vericiguat in the Treatment of Heart Failure. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4937

Introduction

Heart failure (HF) represents one of the most serious challenges in contemporary cardiology, being a clinical syndrome with increasing prevalence, high morbidity, and an unfavorable prognosis. It is estimated that this condition affects more than 64 million people worldwide, and its global prevalence continues to rise as a result of population aging and improved survival following acute cardiovascular events, such as myocardial infarction (Shahim et al., 2023). In Europe, the prevalence is estimated at approximately 17 per 1,000 individuals, with substantial regional variation between countries (Yan et al., 2025). Heart failure remains one of the leading causes of hospitalization among the elderly population and constitutes a significant burden for both patients and healthcare systems (McDonagh et al., 2021; Tsao et al., 2023). Despite significant advances in diagnostics and treatment, including the implementation of multidrug therapy with proven benefits in terms of survival and reduction of hospitalizations, a substantial proportion of patients continue to experience disease progression and recurrent exacerbations requiring rehospitalization. Although current therapeutic strategies have improved patient prognosis, their effectiveness in subpopulations at very high risk remains limited (Shahim et al., 2023). The limitations of existing therapeutic strategies, particularly in patients who have experienced recent clinical deterioration, have prompted the search for new treatment options to complement standard management. In this context, vericiguat—a novel oral agent used in the treatment of heart failure—has attracted particular interest and has been evaluated in several clinical trials, including the VICTORIA study. The results of these studies indicate that vericiguat may provide clinical benefits in selected patients, especially those at high risk of cardiovascular events and following recent clinical worsening (Armstrong, Pieske, et al., 2020). The aim of this study is to present current data on the use of vericiguat in the treatment of heart failure, with particular emphasis on the results of clinical trials, as well as the efficacy and safety of the therapy, and to define the role of this drug within current therapeutic strategies.

Heart failure – definition

Heart failure is a clinical syndrome resulting from structural and/or functional impairment of the myocardium, in which the heart is unable to provide an adequate cardiac output to meet the metabolic demands of the tissues, or is able to do so only at the expense of elevated ventricular filling pressures. (Kemp & Conte, 2012; McDonagh et al., 2021). In the pathophysiology of HF, a key role is played by both systolic and diastolic dysfunction, as well as chronic activation of neurohormonal mechanisms, including the sympathetic nervous system and the renin–angiotensin–aldosterone system, which are initially compensatory but ultimately lead to cardiac remodeling and disease progression over time (McDonagh et al., 2021). The contemporary classification of heart failure is based, among other factors, on left ventricular ejection fraction. According to the current guidelines of the European Society of Cardiology, heart failure with reduced ejection fraction is defined by a left ventricular ejection fraction below 40%, whereas heart failure with preserved ejection fraction is characterized by a left ventricular ejection fraction of at least 50% (McDonagh et al., 2021; Ponikowski et al., 2016). Heart failure with reduced ejection fraction is characterized by primary impairment of myocardial systolic function, most commonly resulting from ischemic heart disease or dilated cardiomyopathy, whereas heart failure with preserved ejection fraction is mainly associated with diastolic dysfunction, increased left ventricular stiffness, and the frequent coexistence of metabolic and vascular comorbidities such as arterial hypertension, diabetes mellitus, and obesity (Borlaug & Paulus, 2011). This classification is of significant clinical importance, as the heart failure phenotype determines both prognosis and the effectiveness of therapeutic strategies (McDonagh et al., 2021).

Symptoms of heart failure

The symptoms of heart failure result from inadequate cardiac output and blood congestion in the pulmonary and/or peripheral circulation and include both subjective complaints and signs identified on clinical examination (McDonagh et al., 2021). The most common symptoms include dyspnea, initially exertional and in more advanced stages also at rest and nocturnal, reduced exercise tolerance, and easy fatigability (Ziaeian & Fonarow, 2016). During the course of the disease, orthopnea, palpitations, nocturia, and weight gain related to fluid retention are also frequently observed (McDonagh et al., 2021). Physical signs include lower extremity edema, jugular venous distension, crackles over the lung fields, hepatomegaly, and tachycardia (Ponikowski et al., 2016). In left ventricular failure, symptoms of pulmonary congestion predominate, whereas in right ventricular failure, signs of venous congestion in the peripheral circulation prevail; the severity of symptoms increases with disease progression, significantly affecting patients' quality of life and prognosis (McDonagh et al., 2021).

Risk factors for heart failure

The most common factors contributing to the development of heart failure are coronary artery disease and a previous myocardial infarction, which lead to permanent myocardial damage and impairment of its pumping function (Farmakis et al., 2015). Arterial hypertension is also a significant risk factor, causing chronic overload of the left ventricle and its remodeling, which promotes the development of heart failure (Farmakis et al., 2015). Heart valve diseases, in turn, may lead to significant hemodynamic disturbances which, over the long term, predispose to the development of heart failure (Zhang et al., 2023). Other cardiac factors include arrhythmias, particularly atrial fibrillation (Chamberlain et al., 2020), as well as various forms of cardiomyopathy, such as dilated or hypertrophic cardiomyopathy. (Khatibzadeh et al., 2013). Among metabolic factors, diabetes mellitus plays an important role, increasing the risk of heart failure through the exacerbation of atherosclerotic processes and metabolic disturbances (Park, 2021), as well as excess body weight, which constitutes an additional burden on the cardiovascular system (Carbone et al., 2022). It has also been demonstrated that chronic kidney disease is an independent risk factor for the development of heart failure (Dhingra et al., 2011). This risk increases with age, particularly in individuals over 65 years of age (Sukhbaatar et al., 2023). Genetic factors also play a significant role in the predisposition to heart failure (Czepluch et al., 2018), and biological sex influences the clinical course and phenotype of the disease (Regitz-Zagrosek, 2020). Moreover, modifiable lifestyle factors such as tobacco smoking, low physical activity, and unhealthy dietary habits significantly increase the risk of developing heart failure (Agha et al., 2014; Ding et al., 2022; Sharifi-Rad et al., 2020).

Current treatment of heart failure

Contemporary management of heart failure is multidirectional and includes pharmacological therapy, non-pharmacological interventions, and—in selected cases—device-based and interventional treatment. The therapeutic strategy depends on the patient's clinical presentation, the stage of disease progression, and left ventricular ejection fraction, with the main goals being symptom reduction, improvement of quality of life, reduction in hospitalization rates, and decreased mortality (McDonagh et al., 2021). The cornerstone of treatment for heart failure with reduced ejection fraction (HFrEF) is currently the so-called four-drug therapy, which includes angiotensin-converting enzyme inhibitors or angiotensin receptor–neprilysin inhibitors (ARNIs), β-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 (SGLT2) inhibitors. The effectiveness of this approach has been confirmed in numerous clinical trials, which have demonstrated a significant reduction in the risk of cardiovascular death and hospitalization for heart failure (McDonagh et al., 2021; McMurray et al., 2019; Packer et al., 2020). Diuretics, although they do not affect prognosis, play a key role in symptomatic treatment by enabling control of fluid overload and improving patient comfort (Mullens et al., 2019). In selected patients, adjunctive therapies such as ivabradine, digoxin, or the combination of hydralazine and nitrates are also used (Behnoush et al., 2022; McDonagh et al., 2021). For many years, the treatment of heart failure with preserved and mildly reduced ejection fraction (HFpEF and HFmrEF) was largely limited to symptom control and management of comorbidities such as arterial hypertension, diabetes mellitus, or atrial fibrillation. Currently, a significant advancement is the introduction of SGLT2 inhibitors, which are the first class of drugs to demonstrate a prognostic benefit also in these heart failure phenotypes (Anker et al., 2021; Solomon et al., 2022). Therapeutic management in this group of patients also focuses on optimizing symptom control and preventing disease exacerbations (Shams et al., 2025). Therapeutic management in heart failure involves not only disease-modifying treatment but also optimization of symptom control and measures aimed at preventing

exacerbations and hospitalizations, which constitute one of the main goals of comprehensive care for patients with HF in accordance with current therapeutic strategies (Sapna et al., 2023). In patients with advanced heart failure who meet specific clinical and electrocardiographic criteria, device-based therapies such as implantation of an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) are used; these interventions reduce the risk of sudden cardiac death and improve cardiac function (Cleland et al., 2005; Ponikowski et al., 2016). In end-stage disease, mechanical circulatory support or heart transplantation is considered as definitive therapy (Fang et al., 2015).

Vericiguat – a novel drug in the treatment of heart failure

Despite significant advances in the treatment of heart failure and the implementation of multidrug therapy with proven prognostic benefit, a substantial proportion of patients continue to experience disease progression and recurrent exacerbations requiring hospitalization. The limitations of existing therapeutic strategies, particularly in patients with advanced or unstable heart failure, have prompted the search for new molecular targets and the development of innovative drugs to complement standard management. In recent years, agents modulating the nitric oxide–guanylate cyclase–cGMP pathway have attracted particular interest, including vericiguat, which represents a novel therapeutic option for selected patients with heart failure (Armstrong, Pieske, et al., 2020; Trujillo et al., 2023).

Mechanism of action of vericiguat

Vericiguat is a novel oral drug used in the treatment of heart failure and belongs to the class of soluble guanylate cyclase (sGC) stimulators (Armstrong, Pieske, et al., 2020). Its mechanism of action is based on modulation of the nitric oxide–sGC–cyclic guanosine monophosphate (cGMP) signaling pathway, which is significantly impaired in patients with heart failure as a result of endothelial dysfunction, oxidative stress, and reduced nitric oxide bioavailability (Pieske et al., 2017; Trujillo et al., 2023). Vericiguat directly stimulates soluble guanylate cyclase and increases its sensitivity to endogenous nitric oxide, leading to an increase in intracellular cGMP levels (Armstrong, Pieske, et al., 2020). Activation of this pathway results in favorable hemodynamic and cellular effects, including vasodilation, reduction of afterload, anti-inflammatory and antifibrotic actions, and attenuation of adverse myocardial remodeling (Pieske et al., 2017; Trujillo et al., 2023). Consequently, vericiguat serves as an adjunct to standard heart failure therapy, targeting pathophysiological mechanisms that are insufficiently modified by currently used drugs, particularly in patients at high risk of disease progression (Armstrong, Pieske, et al., 2020).

Use of vericiguat in heart failure with reduced ejection fraction

One of the most important studies evaluating vericiguat is the VICTORIA trial, which included 5,050 participants. The study assessed the effect of the drug in patients with heart failure with reduced ejection fraction. Participants were randomized into two groups—one receiving vericiguat and the other placebo. The results of the trial indicate that vericiguat is an effective adjunct to standard therapy in patients with chronic heart failure with reduced ejection fraction who experienced clinical worsening requiring hospitalization or urgent intervention. Treatment with vericiguat was associated with a significant reduction in the incidence of the composite primary endpoint of cardiovascular death or hospitalization for heart failure. This effect emerged relatively early, after approximately three months of treatment, and was sustained throughout the follow-up period. Although the relative risk reduction was moderate, the very high baseline risk of the study population translated this effect into a clinically meaningful absolute reduction in events, as reflected by a low number needed to treat to prevent one adverse outcome. The therapeutic benefit was driven mainly by a reduction in heart failure hospitalizations, whereas the effect on cardiovascular mortality was less consistent, and no significant reduction in all-cause mortality was demonstrated. This may be related to the relatively short follow-up period and the advanced stage of disease in the studied population. The trial enrolled patients at particularly high risk, with more advanced heart failure and higher NT-proBNP levels than those included in previous large clinical trials (McMurray et al., 2014, 2019). This explains the high event rate observed in this population and underscores that vericiguat is primarily applicable in clinically unstable patients. The treatment was administered as an add-on to guideline-directed medical therapy, indicating that vericiguat does not replace standard medications but rather represents an additional therapeutic option for patients who continue to experience recurrent exacerbations despite optimized treatment. The unique mechanism of action of vericiguat, involving modulation of the nitric oxide–cyclic GMP pathway, distinguishes it from other heart failure therapies and makes it a potentially valuable adjunct in patients with advanced, high-risk heart failure,

in whom the primary therapeutic goals are clinical stabilization and reduction in hospitalization rates. (Armstrong, Pieske, et al., 2020). However, in another study—the VICTOR trial—no efficacy was demonstrated in reducing the primary composite endpoint of cardiovascular death or hospitalization for heart failure in stable, ambulatory patients with heart failure with reduced ejection fraction who had not experienced recent clinical worsening. This indicates that in well-controlled patients receiving intensive, guideline-directed medical therapy, the addition of vericiguat did not confer additional benefit in preventing hospitalizations nor did it significantly affect the primary study endpoint. Despite failure to meet the primary endpoint, secondary and post hoc analyses showed numerically fewer cardiovascular deaths and all-cause deaths in the vericiguat group. This effect was consistent across subgroups, including patients receiving full guideline-directed therapy, suggesting a potential beneficial impact of the drug on mortality. The lack of effect on heart failure hospitalizations may be explained by the characteristics of the study population, which was intentionally at low risk for events. Most patients were in NYHA class II, nearly half had never been hospitalized for heart failure, and the proportion of patients receiving contemporary therapies (ARNI, SGLT2 inhibitors, CRT) was exceptionally high. In such a well-treated and clinically stable population, the potential for further reduction in hospitalizations was limited, which may have masked any possible effect of vericiguat. An important conclusion is that the benefits of vericiguat appear to be dependent on the clinical context. In contrast to the VICTORIA trial, the VICTOR study suggests a lack of meaningful benefit in stable ambulatory patients. This indicates that vericiguat is not a “universal” therapy for all patients with HFrEF, but rather a potentially targeted treatment for high-risk patients following decompensation (Butler et al., 2025). The VICTOR trial indicates that vericiguat should not be routinely used in stable, well-treated ambulatory patients with HFrEF, but may retain potential value in patients with recent clinical worsening, a hypothesis that requires further appropriately designed clinical trials. The SOCRATES-REDUCED study demonstrated good tolerability of vericiguat in patients with chronic heart failure with reduced ejection fraction (HFrEF) during a period of clinical deterioration, without an increased incidence of serious adverse events compared with placebo. Although the study did not meet its primary endpoint in the main analysis (no significant difference in NT-proBNP reduction after 12 weeks in the pooled higher-dose groups), prespecified secondary analyses revealed a dose–response relationship, with a more pronounced decrease in NT-proBNP at higher vericiguat doses. The strongest signal of potential efficacy was observed at the dose of 10 mg once daily, where reductions in NT-proBNP and improvements in left ventricular ejection fraction were noted without significant changes in blood pressure or heart rate. This suggests that the beneficial effects of vericiguat may result from a direct impact on the myocardium and remodeling processes rather than from hemodynamic effects. Preclinical data support this hypothesis, indicating reductions in fibrosis, improvement in endothelial function, and preservation of renal function in a blood pressure–independent manner. A numerically lower incidence of heart failure hospitalizations and deaths was also observed in the higher-dose vericiguat groups, further strengthening the signal of potential clinical benefit. (Gheorghiade et al., 2015). In patients with hypertensive heart failure with reduced ejection fraction, treatment with vericiguat was associated with a significant improvement in cardiac function, as evidenced by a reduction in left ventricular dimensions (LVESD, LVEDD), an increase in left ventricular ejection fraction (LVEF), and improved exercise tolerance assessed by the 6-minute walk test. Vericiguat demonstrated a beneficial effect on endothelial function and the vascular system by stabilizing the circadian rhythm of blood pressure and limiting target organ damage, which is particularly important in patients with hypertensive heart failure, in whom disturbances of nocturnal blood pressure dipping are frequently observed. Vericiguat also reduced levels of markers of myocardial overload and injury (NT-proBNP, cTnI), indicating a reduction in hemodynamic stress and an improvement in myocardial condition. At the same time, the observed decrease in endothelin-1 concentrations and increase in nitric oxide levels confirm the favorable effect of the drug on vascular homeostasis and cardiac remodeling processes. Additionally, vericiguat exhibited anti-inflammatory effects, as demonstrated by a reduction in C-reactive protein (CRP) levels. Since inflammation plays a significant role in the pathogenesis and progression of heart failure, this effect may have both therapeutic and prognostic relevance, particularly in the early stages of the disease (Cao et al., 2024).

Use of vericiguat in heart failure with preserved ejection fraction

The effect of vericiguat on heart failure with preserved ejection fraction may be different. In the SOCRATES-PRESERVED trial, no efficacy was demonstrated with regard to the primary endpoints in patients with heart failure with preserved ejection fraction (HFpEF), as after 12 weeks of treatment there was no reduction in NT-proBNP levels or left atrial volume compared with placebo. This indicates that, in the short term, the drug does not affect objective surrogate markers of disease severity in this patient population. At the same time, exploratory analyses showed an improvement in patient-reported symptoms and quality of life assessed using the KCCQ questionnaire, particularly at higher doses of vericiguat (especially 10 mg), a finding that was not confirmed in the VITALITY-HFpEF trial (Pieske et al., 2017; Armstrong, Lam, et al., 2020). Exploratory echocardiographic data indicate a possible improvement in left ventricular diastolic function independent of blood pressure reduction, suggesting a potential direct myocardial effect of vericiguat. Moreover, the observed reduction in heart rate, correlated with improved quality of life, may reflect enhanced diastolic filling or an overall improvement in clinical status, although the underlying mechanism remains unclear (Pieske et al., 2017). In the VITALITY-HFpEF trial, vericiguat did not demonstrate efficacy in patients with heart failure with preserved ejection fraction (HFpEF) after recent clinical worsening. Neither the 10 mg nor the 15 mg daily dose significantly improved quality of life assessed by the KCCQ questionnaire or physical capacity measured by the 6-minute walk test. However, a significant improvement in KCCQ scores was observed in the placebo group, suggesting that the natural recovery of quality of life following hospitalization for HFpEF is substantial and may mask a potential treatment effect. This also highlights the limited predictability of quality-of-life changes in this population and the challenges in selecting appropriate endpoints in HFpEF trials (Armstrong, Lam, et al., 2020). Overall, the available studies indicate that vericiguat should not be considered an effective therapeutic option in HFpEF, due to the heterogeneity of this form of heart failure and the need for further research into other pathophysiological mechanisms and treatment strategies in this patient population.

Discussion

Despite the documented clinical benefits of vericiguat, its place in the treatment of heart failure requires critical evaluation, particularly in the context of its adverse event profile and in comparison with other modern drugs used in this disease entity (Armstrong, Lam, et al., 2020; Pieske et al., 2017; Trujillo et al., 2023). In contrast to SGLT2 inhibitors or mineralocorticoid receptor antagonists, which demonstrate a favorable prognostic effect with a relatively low risk of clinically significant hemodynamic adverse events, vericiguat—due to its vasodilatory mechanism of action—is associated with a tangible risk of arterial hypotension and syncope (Armstrong, Pieske, et al., 2020; Vannuccini et al., 2022; Zhang et al., 2023). This limits its use in patients with low baseline systolic blood pressure, in whom treatment tolerance may be insufficient and the risk of clinical complications, such as falls or impaired organ perfusion, is increased (Trujillo et al., 2023). Additionally, the higher incidence of anemia observed in clinical trials in the vericiguat-treated group raises questions regarding the long-term safety of the therapy, particularly in patients with chronic kidney disease or coexisting hematological disorders, who already constitute a particularly vulnerable population at baseline (Armstrong, Pieske, et al., 2020; Zhang et al., 2023). It is also worth emphasizing that vericiguat has not demonstrated a clear effect on reducing all-cause mortality, and that its clinical benefits are primarily focused on reducing the rate of hospitalizations due to heart failure, which distinguishes it from therapies with a stronger disease-modifying effect (Armstrong, Pieske, et al., 2020). Moreover, the VICTORIA trial population consisted of patients at very high risk of cardiovascular events, which on the one hand highlights the potential usefulness of the drug in this group, but on the other hand limits the possibility of extrapolating the results to patients with a milder course of heart failure (Pieske et al., 2017). In this context, vericiguat should be regarded primarily as an adjunctive therapy intended for carefully selected patients after recent decompensation, in whom standard therapy has already been optimized and further options for improving prognosis are limited. Such an approach allows the risk of adverse events to be minimized while simultaneously maximizing the potential clinical benefits derived from the use of this drug.

Conclusions

This paper presents current issues related to the pathophysiology and treatment of heart failure, with particular emphasis on new therapeutic options. Current strategies of pharmacological treatment and their limitations are discussed, as well as the role of innovative drugs as an adjunct to standard therapy. Special attention is devoted to vericiguat—a novel soluble guanylate cyclase stimulator—by analyzing its mechanism of action, clinical efficacy, and safety profile. The discussion indicates that vericiguat may provide benefits for selected patients with heart failure who are at high risk of disease progression; however, its use requires careful patient selection and an individualized assessment of the benefit–risk ratio. The conclusions highlight the importance of further research into new therapeutic strategies to improve prognosis and quality of life in patients with heart failure.

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