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Original Research Article

Vericiguat in Worsening Heart Failure: Evaluation of Efficacy, Tolerability, and Treatment Adherence

Mani Shankar Pandey[1], Vinit Kumar[2], Jyoti[3]

[1]Assistant Professor, Department of Cardiology, Nalanda Medical College and Hospital, Patna, Bihar, India

[2]Assistant Professor, Department of Cardiology, Nalanda Medical College and Hospital, Patna, Bihar, India

[3]Senior Resident, Department of Ophthalmology, Nalanda Medical college and Hospital, Patna, Bihar, India

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Corresponding Author: Dr. Jyoti

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Abstract:

Background: Worsening heart failure (WHF) ˙represents a high-risk phase of heart failure characterized by clinical deterioration despite standard therapy, with frequent hospitalization and elevated mortality. Vericiguat, a soluble guanylate cyclase stimulator, offers a novel mechanism to improve cardiac function and outcomes.

Aim: To evaluate the efficacy, tolerability, and treatment adherence of vericiguat in patients with WHF.

Methodology: This prospective observational study enrolled 90 adults with left ventricular ejection fraction <45% and recent HF decompensation at the Department of Cardiology, Nalanda Medical College and Hospital, Patna, Bihar, India. Participants received vericiguat alongside guideline-directed therapy, with follow-up at 2 weeks, 1 month, and every 3 months up to 12 weeks. Outcomes included NYHA functional class, LVEF, biomarkers (BNP, NT-proBNP), adverse events, and adherence.

Results: Vericiguat improved functional status, increasing NYHA Class II patients from 24.4% to 47.8% and LVEF from 32.6% to 37.4%. BNP and NT-proBNP levels decreased significantly, and HF hospitalizations dropped from 38.9% to 18.9%. Adverse events were mostly mild, with 4.4% discontinuation. Adherence was high, with 87.8% taking >90% of prescribed doses.

Conclusion: Vericiguat is effective, well-tolerated, and associated with high adherence in WHF, improving cardiac function and reducing clinical deterioration, supporting its integration into real-world HF management.

Keywords: Worsening Heart Failure, Vericiguat, Soluble Guanylate Cyclase, NYHA Class, Treatment Adherence.

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Introduction

Heart failure (HF) has been regarded as one of the greatest health problems worldwide with the heart being unable to sustain sufficient heart output to sustain the metabolic needs of the body [1]. Regardless of˙ the significant therapeutic progress of ˙recent decades, HF is still tied to the frequent hospitalization, decreased functional capacity, and high mortality rates. One of the most disturbing steps in the disease progression is worsening heart failure (WHF) which is characterized by the clinical exacerbation of symptoms of heart failure despite continued medical care in line with the guidelines. WHF is an endangered state characterized by hemodynamic imbalance, neurohormonal stimulation, congestion, renal dysfunction, and progressive myocardial dysfunction [2]. The occurrence of adverse outcomes is strongly linked with post-hospitalization or post-worsening episodes, which entails high rates of re-hospitalization 30-90 days and elevated mortality long-term. The clinical need which is yet to be met to enhance the outcomes in WHF has angled interest in the development of new classes of therapy that address the underlying pathobiology of HF other than the usual neurohormonal blockade.

Vericiguat, a first-in-class guanylate cyclase (sGC) oral soluble oral soluble guanylate cyclase (sGC) stimulator, is one of them. The justification of vericiguat can be explained by a better insight into the significance of nitric oxide (NO) signaling, which is critical in vascular tone, endothelial performance, myocardial relaxation, and organ perfusion [3]. HF is linked to the inability of the NO bioavailability as a result of oxidative stress, endothelial dysfunction and chronic inflammation. This causes less stimulation of sGC, decreased cyclic guanosine monophosphate (cGMP) formation which causes vasoconstriction, ventricular stiffness, and impaired myocardial energetics. Vericiguat is a direct stimulator of

sGC without dependence on the availability of NO, as well as an increased sensitivity to endogenous NO. The drug is expected to enhance the compliance of the vascular system, decrease afterload, improve the efficiency of the myocardium and achieve positive cardiac remodeling by the restoration of the NO 3 -sGC 3 -cGMP pathway [4]. In contrast to other vasodilators, vericiguat has its effects with little influence on the systemic blood pressure and therefore can be a good alternative in patients with advanced HF who are usually at the border of hemodynamics.

The clinical assessment of vericiguat experienced a great impetus after the outcomes of pivotal trials which revealed that it has a potential in high-risk, recently-decompensated HF patients [5]. Preclinical trials had shown that vericiguat had an adverse effect on the biomarker, hemodynamic and general functional capacity. This was followed by the landmark large-scale trials which confirmed that vericiguat, which was added to standard HF therapy, lowered the composite risk of cardiovascular death or HF hospitalization among patients with recent WHF [6]. These results made vericiguat a specific targeted therapy that should be used in order to stabilize the patient at the critical post-decompensation stage. However, the extent of benefit was different in subgroups of patients, and questions still persist on how best to select patients, when to start and on a long-term response trajectory.

Although the clinical efficacy of vericiguat has become more and more elucidated, tolerability and treatment adherence are not less significant factors of real-life therapeutic achievement [7]. HF patients often have difficulties with complicated drug regimens that include one or several pharmacological classes, and this may result in low adherence rates, polypharmacy issues, and an enhanced likelihood of adverse interaction among drugs. Vericiguat is also well tolerated, and hypotension and anemia are the most commonly reported adverse events, although tolerability may differ in patients depending on comorbidity and underlying blood pressure and renal issues as well as interactions with other therapies [8]. It is important to understand how it will be safe in various groups, such as the elderly, frail and frail elderly with advanced renal failure to realize its therapeutic potential.

Moreover, the behavioral, socioeconomic and clinical factors affect treatment adherence in HF. Constant therapy is often interrupted by medication fatigue, cognitive decline, poor health literacy, and frequent hospitalizations. The daily oral intake of vericiguat can be a contributor to improved adherence in comparison to even more complicated dosing routines, but the actual adherence patterns have not been defined in real-life scenarios. Measuring compliance is especially of critical importance to vericiguat, as regular dosing is required to sustain sufficient sGC stimulation and attain stable plasma levels to be clinically effective. Inefficient compliance can diminish the therapeutic effect, slow down progress, and lead to repeat decompensation.

Methodology

Study Design: The present study was designed as a prospective, observational study that evaluated the efficacy, tolerability, and treatment adherence of Vericiguat in patients with worsening heart failure. The study followed an analytical framework in which all enrolled participants received standard guideline-directed medical therapy along with Vericiguat, and their clinical outcomes were assessed over the study period. The methodology emphasized systematic data collection, uniform follow-up, and objective assessment of therapeutic responses to ensure reliability and clinical relevance.

Study Area: The study was conducted in the Department of Cardiology, Nalanda Medical College and Hospital (NMCH), Patna, Bihar, India for one year.

Sample Size: A total sample of 90 participants was selected for the study. This sample size was considered adequate to observe meaningful differences in clinical improvement, safety outcomes, and medication adherence patterns among heart failure patients initiated on Vericiguat therapy.

Study Participants

Inclusion Criteria

- Age ≥18 years
- Left ventricular ejection fraction (LVEF) <45% within the past 12 months
- Elevated natriuretic peptide levels:
  - BNP ≥300 pg/mL or
  - NT-proBNP ≥1000 pg/mL
- Recent hospitalization for heart failure within the last 6 months or
- Intravenous diuretic therapy for worsening symptoms within the previous 3 months

Exclusion Criteria

- Systolic blood pressure <100 mmHg at baseline
- Use of long-acting nitrates
- Use of phosphodiesterase-5 inhibitors
- Patients requiring intravenous inotropic support
- Advanced renal dysfunction (eGFR <15 mL/min/1.73 m²)
- Presence of mechanical left ventricular assist device
- Known hypersensitivity or allergy to Vericiguat
- Pregnant or lactating women

Procedure: Following informed written consent, eligible patients passed through baseline assessment during which demographic information, past medical history, comorbidity, vital signs, laboratory parameters, natriuretic peptide, and echocardiographic results were documented. Vericiguat was started at

a dosage of 2.5mg/day and increased at follow-up visits to 5mg and then to 10mg depending on the management of blood pressure and toleration of the symptoms. Every patient was subjected to guideline-guided medical treatment during the study. A follow-up evaluation was made after 2 weeks, 1 month, and every 3 months where the efficacy was assessed using symptom improvement, NYHA functional class, and hospitalization requirement. The measure of tolerability was evaluated concerning adverse effects, including hypotension, dizziness, and syncope or discontinuation of the drug. The adherence to treatment was measured by the number of pills, self-reporting, and compliance to follow-up visits. The records were filled in table form to record all the outcomes in a systematic manner where a case record form was designed.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics 27.0. Continuous variables were expressed as means and standard deviations, while categorical variables were shown as frequencies and percentages. Paired t-tests or Wilcoxon tests assessed changes over time, and chi-square tests evaluated categorical outcomes. A p-value <0.05 indicated statistical significance. Analyses followed the intention-to-treat approach.

Result

The basic demographic data of the 90 participants included in the study are reflected in Table 1 with the mean age of 59.4 ± 10.2 years, indicating that the range of ages (32-82 years) is wide. The sample comprised of mainly males (64.4) and females (35.6). The mean BMI was 26.8 ± 4.1 kg/m², which means that the majority of the participants were overweight. Counts of the participants were almost evenly split with almost fifty percent of the participants having a history of smoking (45.5%), with diabetes mellitus comorbidity being found in 42.2% of the cohort and hypertension prevalent in 63.3% of the cohort. Moreover, over fifty percent of the subjects (54.4) had ischemic heart disease. The median heart failure years was 3.1 concerning 1.4 years and indicated that the population had a rather long-term disease burden.

Table 1: Baseline Demographic Characteristics of the Study Participants (n = 90)

Parameter	Value
Mean age (years)	59.4 ± 10.2
Age range (years)	32–82
Sex distribution	Male: 58 (64.4%), Female: 32 (35.6%)
BMI (kg/m²)	26.8 ± 4.1
Smoking history	41 (45.5%)
Diabetes mellitus	38 (42.2%)
Hypertension	57 (63.3%)
Ischemic heart disease	49 (54.4%)
Duration of heart failure (years)	3.1 ± 1.4

Table 2 summarizes the baseline clinical and laboratory characteristics of the study population with the majority having advanced heart failure, with 57.8 and 17.8% having Class III and Class IV heart failure respectively with only 24.4 being in Class II. The average left ventricular ejection fraction (LVEF) was significantly low (32.6 ± 6.4%), which is an indication of severe systolic dysfunction. The baseline vital parameters revealed moderately low systolic (112.4 ± 9.8 mmHg) and diastolic (71.6 ± 7.3 mmHg) blood pressure parameters, which fits into the chronic heart failure physiology. The level of biomarkers was significantly high with a mean of 682 ± 210 pg/mL of BNP and 2240 ± 510 pg/mL of NT-proBNP which indicated high cardiac stress and volume overload. Renal function parameters indicated impaired yet mildly, a mean serum creatinine of 1.18 +0.32 mg/dl and an eGFR of 58.2 ± 14.6 mL/min/1.73 m², indicating a moderately involved population of cardiorenal involvement at baseline.

Table 2: Baseline Clinical and Laboratory Parameters

Variable	Baseline Mean ± SD / n (%)
NYHA Functional Class II	22 (24.4%)
NYHA Functional Class III	52 (57.8%)
NYHA Functional Class IV	16 (17.8%)
LVEF (%)	32.6 ± 6.4
Systolic blood pressure (mmHg)	112.4 ± 9.8
Diastolic blood pressure (mmHg)	71.6 ± 7.3
BNP (pg/mL)	682 ± 210
NT-proBNP (pg/mL)	2240 ± 510
Serum creatinine (mg/dL)	1.18 ± 0.32
eGFR (mL/min/1.73 m²)	58.2 ± 14.6

Table 3 demonstrates that vericiguat treatment resulted in dramatic changes in clinical and functional outcomes in 12 weeks in patients with deteriorating heart failure. The percentage of patients in NYHA Class II increased almost twice whereas the percentage of patients in the more severe recommended Classes III and IV reduced significantly, which suggests an improvement in the symptomatic condition. The cardiac functioning was better with an increase in left ventricular ejection fraction of 32.6 to 37.4%. Biomarkers of cardiac stress also had significant decrease, BNP changing 682-512 pg/mL and NT-proBNP changing 2240-1710 pg/mL indicating a decrease in myocardial strain. Besides, the hospitalizations, which were in relation to the heart-failure, significantly decreased up to 18.90, which underscores the effects of the therapy in the prevention of clinical deterioration. Each of the changes was significant and this highlights the effectiveness of vericiguat in this group of patients.

Table 3: Efficacy Outcomes After Vericiguat Therapy

Outcome Measure	Baseline	Follow-up (12 weeks)	p-value
NYHA Class II (%)	24.40%	47.80%	<0.001
NYHA Class III (%)	57.80%	42.20%	<0.01
NYHA Class IV (%)	17.80%	10.00%	0.04
LVEF (%)	32.6 ± 6.4	37.4 ± 7.1	<0.001
BNP (pg/mL)	682 ± 210	512 ± 180	<0.01
NT-proBNP (pg/mL)	2240 ± 510	1710 ± 480	<0.01
Hospitalization for HF (%)	38.90%	18.90%	<0.001

According to table 4, the overall tolerability of Vericiguat in the 90 participants was good with most of the adverse events being reported at quite low frequencies. Dizziness (12.20% and symptomatic hypotension 10% were the most frequently reported problems, and the gastrointestinal discomfort (8.90%), and headache (6.70) followed them. Other events of rare occurrence were syncope, which was observed in 2.20% of the patients. Notably, the rate of treatment discontinuation (because of adverse effects) was poor (4.40), which means that, even though some of the patients had mild to moderate adverse events, the tolerability profile of Vericiguat was generally good.

Table 4: Tolerability and Adverse Events with Vericiguat (n = 90)

Adverse Event	Frequency (n)	Percentage (%)
Symptomatic hypotension	9	10.00%
Dizziness	11	12.20%
Headache	6	6.70%
Syncope	2	2.20%
Gastrointestinal discomfort	8	8.90%
Treatment discontinuation due to adverse events	4	4.40%

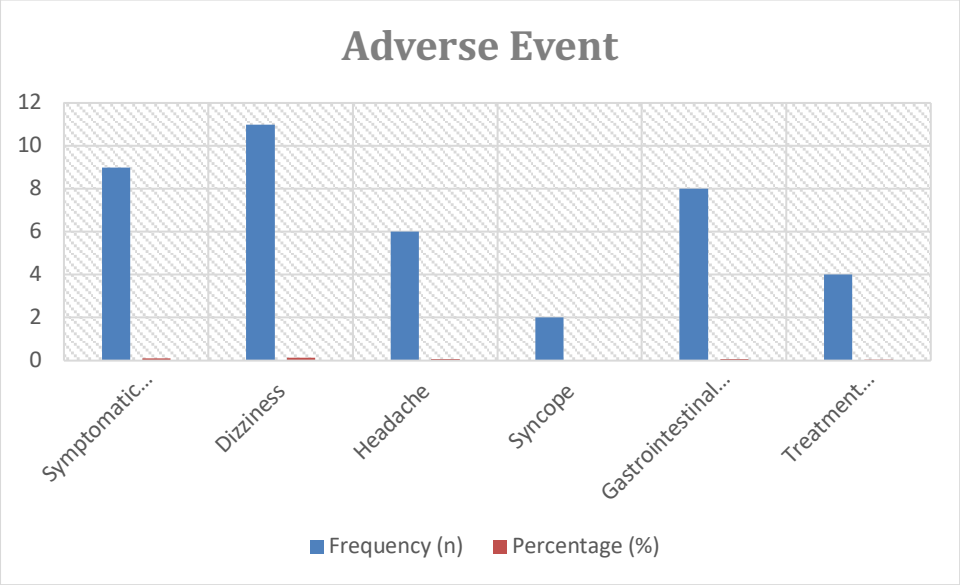

Figure 1: Tolerability and Adverse Events with Vericiguat

Table 5 indicates that the majority of patients were very adherent to the therapy of vericiguat with 82.2% of patients taking the full dose of 10 mg daily with only smaller portions taking 5 mg (15.6%) and 2.5 mg daily (2.2%). The general adherence to treatment was also positive with 87.8% respondents having good adherence with more than 90 per cent of prescribed pills. Those with moderate adherence were few (10.0%) and those with poor adherence were few (2.2%), and thus, poor compliance was not prevalent among the study population.

Table 5: Treatment Adherence and Dose Achievement	
Adherence Parameter	**Value**
Patients achieving target dose (10 mg once daily)	74 (82.2%)
Patients remaining at 5 mg dose	14 (15.6%)
Patients remaining at 2.5 mg dose	2 (2.2%)
Good adherence (>90% pills taken)	79 (87.8%)
Moderate adherence (70–90%)	9 (10.0%)
Poor adherence (<70%)	2 (2.2%)

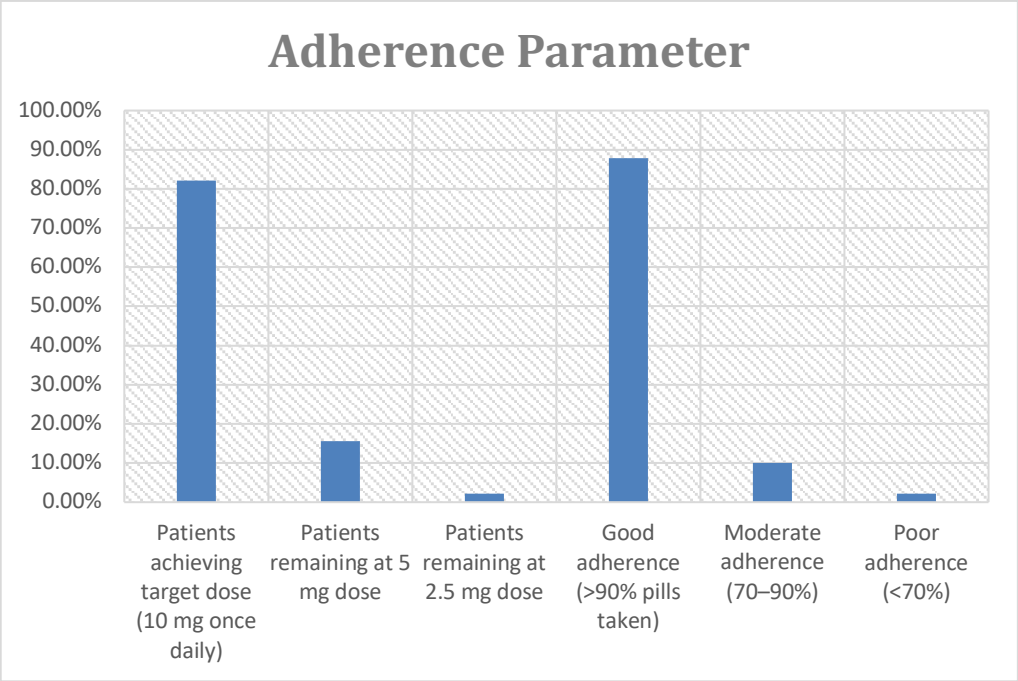

Figure 2: Treatment Adherence and Dose Achievement

Discussion

These results of the current study prove that vericiguat treatment of the patients with the progressive heart failure is followed by a substantial improvement in functional status, cardiac performance, and adherence to treatment in the 12-week follow-up. The number of patients who attained NYHA Class II status after the study was almost 50 percent in our cohort, and there was a significant improvement in mean left ventricular ejection fraction (LVEF). These findings align with those mentioned in the VICTORIA trial, in which vericiguat decreased the composite of cardiovascular death or heart failure hospitalization by 10 percent as compared to placebo with an absolute decrease of 4.2 events per 100 patient-years and almost one-third of patients reporting NYHA Class III or IV heart failure and a median NT-proBNP of 2816 pg/mL (Armstrong et al., 2018; Pieske et al., 2019) [9,10]. The redistribution in functional class and improvement in LVEF, which was observed compared to our results, are consistent with observed hemodynamic advantages of vericiguat in VICTORIA, which indicates the ability of the drug to improve the performance of the heart in high-risk patients.

Our baseline patient parameters showed that the proportion of older males, overweight, and high comorbidity level were predominant, which showed a clinically burdened population with advanced disease. The SOCRATES-REDUCED trial, which compared the effects of vericiguat on the level of natriuretic peptides and also reported significant improvements in NT-proBNP at 12 weeks, had similar demographic and clinical characteristics (Gheorghiade et al., 2015) [11]. Interestingly, the extent of NT-proBNP decline in our trial is similar to the trial and implies that in patients with a long-term disease and

various comorbidities, even vericiguat can produce a significant reduction in cardiac stress levels.

Vericiguat was well tolerated in our cohort and adverse events were mostly mild to moderate which included dizziness, hypotension, headache, and gastrointestinal discomfort. The percentage of patients who quit therapy as a result of side effects was very low. This safety profile is similar to that of the prior studies, such as the VICTORIA and SOCRATES-REDUCED trials, in which symptomatic hypotension and syncope were somewhat more common in the vericiguat group but did not result in high discontinuation rates (Armstrong et al., 2018; Gheorghiade et al., 2015) [9,11]. These results prove the appropriateness of the drug to patients with impaired hemodynamic stability, one of the populations that tend to experience intolerance to traditional heart failure treatments.

The adherence rate to the treatment was high in the given study and majority of the patients reached the target 10 mg dosage. This is an important observation because the compliance has a direct effect on clinical outcomes in chronic heart failure. Similar compliance levels have been observed in trials comparing guideline-based medical interventions including setubitril/valsartan with adherence rates over 85% in practice over 6-12 months with lower readmission and mortality rates (Sangaralingham et al., 2018; Ruppar et al., 2016) [12,13]. Vericiguat is practical in long-term use, as its high compliance rate was probably due to the ease of administration at a single dose per day and the low incidence of adverse events.

An analysis of vericiguat to other innovative heart failure treatments shows some similarities and differences. As an example, a relative risk reduction of 20 percent in cardiovascular death or heart failure hospitalization was seen with angiotensin1 -neprilysin inhibitors in the PARADIGM-HF trial, but the median NT-proBNP (1608 pg/mL) and the proportion of patients with NYHA Class III-IV (25%) were lower and smaller, respectively, compared to our cohort (McMurray et al., 2014) [14]. In the same way, dapagliflozin-DAPA-HF trial demonstrated a 26% reduction in the primary composite outcome but again had a less advanced and lower baseline biomarker population (McMurray et al., 2019) [15]. These comparisons indicate that the relative benefits of vericiguat might be numerically less but the absolute risk reduction is high on the basis of higher baseline risk in our study population.

The clinical significance of the mechanism of action of vericiguat is also mentioned in our study. Vericiguat is directly active by stimulating the soluble guanylate cyclase and increasing the production of cyclic GMP in the absence of nitric oxide, which is a major cause of advanced heart failure. Such a distinct form of pharmacological intervention can have supplementary or supplementary effects to traditional neurohormonal therapy, especially in patients with severe systolic dysfunction that still report the symptoms despite optimal therapy.

Conclusion

This study demonstrates that vericiguat is an effective and well-tolerated therapeutic option for patients with worsening heart failure. Over the 12-week follow-up, patients experienced significant improvements in functional status, with a notable shift toward NYHA Class II and enhanced left ventricular ejection fraction, alongside marked reductions in BNP and NT-proBNP levels, indicating reduced cardiac stress. Vericiguat therapy was generally safe, with mostly mild to moderate adverse events and low rates of treatment discontinuation. Importantly, adherence to therapy was high, with the majority of patients achieving the target dose and maintaining consistent medication intake, supporting its practicality for real-world use. These findings reinforce vericiguat's role in stabilizing high-risk heart failure patients, improving clinical outcomes, and complementing existing guideline-directed therapies.

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