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REVIEW ARTICLE

Vericiguat for heart failure with reduced ejection fraction (HFrEF): A review of its potential benefits in Pakistan

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Abstract

Heart failure (HF) is categorized by left ventricular ejection fraction (LVEF) into three groups. HF with reduced ejection fraction (HFrEF) is one of these groups characterized by the heart's inability to pump sufficient blood to meet the body's needs, resulting from the left ventricle's impaired ability to contract effectively. The Canadian Cardiovascular Society (CCS) guidelines recommend vericiguat for hospitalized patients experiencing worsening symptoms of HFrEF. This article reviews vericiguat's efficacy and potential benefits in Pakistani patients with HFrEF. A literature search from 2013 to 2024 was conducted using PubMed, ScienceDirect, and Google Scholar, employing keywords such as guidelines, heart failure, Pakistan, and reduced ejection fraction. Soluble guanylate cyclase (sGC) stimulators, like vericiguat, have shown benefits in patients with left ventricular hypertrophy and fibrosis by reducing afterload through vasodilation. Vericiguat (2.5 – 10 mg taken orally once daily) shows promise in reducing cardiovascular mortality and hospitalization in adults with LVEF ≤45%. Vericiguat may alleviate Pakistan's growing cardiovascular disease burden. Expedited access to this innovative therapy can be achieved through collaborative efforts among policymakers, healthcare authorities, and international research centers, potentially reducing hospitalization rates in Pakistani HFrEF patients.

Keywords: Vericiguat; Heart failure with reduced ejection fraction; Pakistan; Soluble guanylate cyclase stimulator; Cardiovascular disease

1. Introduction

Heart failure (HF) is a multifaceted clinical condition characterized by dyspnea or exertional limitation due to impaired ventricular filling, impaired blood ejection, or a

combination of both.[1] HF affects an average of 64.3 million people worldwide, making it a significant global cardiac pathology.[2] As the population ages and the outcomes of acute cardiovascular events improve, the prevalence of HF has increased.[2] Despite new therapies and management strategies, individuals with HF still face a poor prognosis, with a 5-year survival rate estimated at around 50% following the initial diagnosis.[2] Recurrent hospital stays and the need for additional parenteral therapy during exacerbations further indicate worse prognoses and lower quality of life.[2] HF with reduced ejection fraction (HFrEF) is a condition where the heart is unable to pump enough blood to meet the body's needs due to an inability of the left ventricle to contract sufficiently.[1] This leads to clinical manifestations such as shortness of breath and fatigue. Ejection fraction (EF), which measures the amount of blood pumped out with each contraction, is normally 55% and above, whereas HFrEF is defined by an ejection fraction of 40% or less.[1,3] The HF is categorized into HF with preserved ejection fraction (HFpEF, ejection fraction ≥50%),[4] mid-range ejection fraction (HFmrEF, EF: 40 – 49%),[5] and reduced ejection fraction (HFrEF, ejection fraction ≤40%).[1,3] HFrEF poses a significant health challenge globally and is particularly prevalent in Pakistan, where approximately 2.8 million people are affected by congestive heart failure (CHF).[5] The prevalence of CHF is higher in urban areas and among older adults, driven by high rates of diabetes, hypertension, and obesity.[5] In Pakistan, HFrEF management involves a combination of lifestyle modifications – such as quitting smoking, exercising regularly, and adhering to a healthy diet – alongside pharmacological treatments including diuretics, angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) In severe cases, surgical interventions such as implantable cardioverter-defibrillators (ICDs) or cardiac resynchronization therapy (CRT) are considered.[6] Recent advancements in HFrEF management, such as vericiguat, provide hope for improving outcomes in these patients. Vericiguat is an oral soluble guanylate cyclase stimulator that enhances the activity of cyclic guanosine monophosphate (cGMP), which plays a critical role in regulating cardiovascular, renal, and metabolic functions.[1] The VICTORIA trial specifically targeted a higher-risk population with HFrEF, characterized by elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, lower EFs, and recent hospitalizations for HF.[1] The trial demonstrated that vericiguat significantly reduced the composite outcome of cardiovascular death or first HF hospitalization in these patients (35.5% vs. 38.5%; hazard ratio, 0.90 [95% confidence interval, 0.82 – 0.98]), primarily driven by a reduction in HF hospitalization, over a median follow-up of 10.8 months.[1] Table 1 summarizes the key outcomes of the VICTORIA trial, comparing Vericiguat and placebo groups in terms of cardiovascular events, mortality, and adverse effects. However, the reduction in cardiovascular death was not statistically significant (16.4% vs. 17.5%; hazard ratio, 0.93 [95% confidence interval, 0.81–1.06]).[1] This suggests that vericiguat is particularly beneficial for HFrEF patients with worsening symptoms who remain clinically unstable despite being on guideline-directed medical therapy (GDMT), as evidenced by high NT-proBNP levels and frequent hospital admissions. The findings of the VICTORIA study can be contrasted with those of the EMPEROR-Reduced study,[7] which focused on a slightly different patient population. The EMPEROR-Reduced study included patients with a broader range of baseline ejection fractions and NT-proBNP levels, which may explain the different outcomes observed between the studies.[7] In addition, the treatment protocols in the EMPEROR-reduced study emphasized the comprehensive use of GDMT, whereas, in the VICTORIA trial, a significant portion of the cohort was not optimally managed according to current guidelines. This discrepancy highlights the need for precise patient selection and optimization of background therapy when evaluating the efficacy of novel treatments like vericiguat in real-world settings.[7] Evidence from the VICTORIA study, supported by additional analyses, suggests that the ideal candidates for vericiguat are HFrEF patients with an ejection fraction of 40% or less, elevated NT-proBNP levels, and a history of recent HF hospitalizations or outpatient intravenous diuretic use. These patients typically exhibit worsening symptoms despite being on maximally tolerated doses of standard therapies, including ACE inhibitors, ARBs, beta-blockers, and MRAs.[7] As such, vericiguat should be considered an adjunctive therapy for patients at high risk of adverse outcomes to reduce the likelihood of further hospitalizations and potentially improve survival, in line with European and American HF management guidelines.[7] This review evaluates the efficacy of vericiguat and its potential benefits for Pakistani patients with HFrEF.

2. Methodology

For this review, relevant articles were searched on electronic databases including PubMed, Science Direct, and Google Scholar from 2013 to 2024 using keywords such as guidelines, HF, Pakistan, and reduced ejection fraction. Inclusion criteria include article types such as cross-sectional studies, narrative reviews, systematic reviews, meta-analyses, and case reports that met the study's objectives, written in the English language, conducted

Table 1. Outcomes of cardiovascular events, mortality, and adverse effects in heart failure patients (vericiguat-treated group versus placebo) based on VICTORIA Trials

Outcome	Vericiguat group (n=2526)	Placebo group (n=2524)	HR	*P*-value	References
Primary outcome (CV death or HF hospitalization)	897 (35.5%)	972 (38.5%)	0.90	0.02	7
Cardiovascular death	414 (16.4%)	442 (17.5%)	0.92	0.27	7
All-cause death	513 (20.3%)	535 (21.2%)	0.95	0.38	7
Heart failure hospitalization	691 (27.4%)	747 (29.6%)	0.90	0.048	7
Serious adverse events	828 (32.8%)	878 (34.8%)	-	-	7
New anemia occurrence	344 (13.6%)	266 (10.5%)	-	<0.001	7

Abbreviations: CV: Cardiovascular; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

in Pakistan, and focused on the Pakistani population diagnosed with HF. However, we excluded article types such as editorials, commentaries, and perspectives that did not meet the study's objectives, were written from other countries, and focused on other populations diagnosed with HF.

3. Results

3.1. Preclinical evidence about therapeutic benefits of vericiguat

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) (NO-sGC-cGMP) pathway is crucial for cardiovascular function but becomes impaired in HF, diminishing the heart's natural protective mechanisms.[8] This disruption is due to reduced NO availability and changes in the redox state of sGC, making it less responsive to NO.[8] Vericiguat, an sGC stimulator, enhances sGC sensitivity to endogenous NO, offering a more physiological effect compared to sGC activators like cinaciguat, which bypass NO but elevate risk of hypotension.[8] In preclinical studies, vericiguat demonstrated efficacy in restoring NO/sGC signaling across various animal models of HF, leading to improved cardiac function and hemodynamic.[9] The effects of vericiguat were dose-dependent, with higher doses leading to increased cGMP levels and enhanced heart function, emphasizing the importance of determining optimal dosing for clinical applications.[9] In addition, preclinical safety data indicated that vericiguat was well-tolerated in animal models, showing no significant adverse effects at therapeutic doses.[9] These promising results laid the groundwork for human trials, including the VICTORIA Phase 3 trial, where vericiguat showed potential in improving clinical outcomes for HF patients.[9] In summary, preclinical studies highlight vericiguat's mechanism of action, efficacy in restoring NO-sGC-cGMP signaling, dose-dependent effects, and favorable safety profile, strongly supporting its therapeutic role in chronic HF and possibly other cardiovascular conditions.[9]

3.2. Global trials of vericiguat in patients with heart failure and reduced ejection fraction

Various potential benefits of sGC stimulators have been recognized, including the capacity to prevent or even reverse left ventricular hypertrophy and fibrosis, as well as decrease left ventricular afterload due to systemic and pulmonary vasodilation.[10] Consequently, restoring adequate NO-sGC-cGMP signaling is and recognized as an essential treatment objective for HF, with vericiguat enhancing sGC sensitivity to endogenous NO.[10] A study that explored the potential of vericiguat as the fifth cornerstone in the treatment of HFrEF, found that the drug yielded promising treatment outcomes.[11] The promising results demonstrated by vericiguat in high-risk HF patients indicate its potential as a valuable therapeutic option for HFrEF treatment, possibly leading to the recommendation of quintuple therapy, in addition to standard optimal medical therapy.[11] A study on eligibility for vericiguat in a real-world HF population included patients from the Sweden HF registry, who were aged 18 or older, with their ejection fraction and HF duration recorded between May 2000 and December 2018.[12] Using the VICTORIA trial eligibility criteria, only 21% of patients with chronic HFrEF were eligible for vericiguat, while 47% met the criteria based on guidelines and regulatory labelling.[12] Prior hospitalization for HF was the most restrictive factor in determining eligibility, resulting in the exclusion of 49% of patients with chronic HFrEF. The eligibility criteria for vericiguat set by the VICTORIA trial, guidelines, and regulatory labeling were designed to target a high-risk population with HFrEF in a real-world setting.[12] A consensus statement from India, based on expert opinions regarding the identification and pharmacological management of worsening HF, concluded that vericiguat effectively reduces the risk of cardiovascular death and hospitalization for adults with symptomatic chronic HF and an ejection fraction of <45%.[13] This medication is recommended for individuals who have been recently hospitalized for HF or require outpatient intravenous diuretics.[13] The initial dose of

vericiguat is 2.5 mg, taken orally once daily with food; this dose should be increased approximately every 2 weeks until it reaches the target maintenance dose of 10 mg once daily, as tolerated by the patient.[13] African Americans were significantly underrepresented in the VICTORIA trial, accounting for only 4.9% of the vericiguat arm and 5% of the placebo arm.[14] However, this underrepresentation should be considered in the context of the trial's global nature, with the majority of trial sites located in Eastern Europe and the Asia Pacific region – have low populations of the African diaspora.[14] It is worth noting that other recent positive HF trials, such as PARADIGM-HF and DAPA-HF, also had low representation of African Americans, with percentages ranging between 4.4% and 5.1%.[14] Table 2 shows the eligibility criteria for inclusion of HFrEF patients in vericiguat clinical trials.

At present, clinical trial data on vericiguat in Pakistan are scarce, raising concerns given the increasing prevalence of cardiovascular diseases in the country. Conducting a clinical trial of vericiguat in Pakistan would be a significant step forward in addressing the management of HFrEF among the Pakistani population. Such a trial would not only benefit the local population but also contribute to enhancing global HF care. Figure 1 shows the role of vericiguat in HFrEF.

3.3. Potential benefits of vericiguat for HF management in Pakistan

Among FDA-approved medications between 2021 and 2022, vericiguat was notable, with the most commonly reported side effects of hypotension and anemia – both exceeding 5% of reported incidents.[14] Using sacubitril/valsartan in the Pakistani population with HFrEF is generally safe and well-tolerated, as indicated by stable hemodynamic parameters and a notable improvement in left ventricular function and functional class.[15] Thus, this therapy can be considered as a primary treatment option for patients with HFrEF, with a gradual dose escalation over a 6-week timeframe.[15]

The benefit of vericiguat in heart failure with reduced ejection fraction (HFrEF) was studied in patients experiencing worsening heart failure events.[13] This population includes those with a history of decompensation events leading to emergency department visits and hospitalizations. The focus is on optimizing treatment for high-risk patients, particularly those who have not responded adequately to standard therapies.[13] In Pakistan, HF is a major public health issue, and further research is needed to explore the use and role of vericiguat in patients with HFrEF.

3.4. Safety profile of vericiguat and its adverse effects

A study has shown that vericiguat has proven effective in reducing cardiovascular mortality and hospitalization rates for HF patients with reduced ejection fraction (HFrEF), but did not demonstrate a therapeutic benefit for those with preserved ejection fraction (HFpEF).[16] The treatment showed a favorable safety profile, with common adverse events including hypotension, syncope, and anemia.[17] Consequently, vericiguat is indicated for HFrEF patients with a minimum systolic blood pressure of 100 mmHg, particularly those experiencing symptom worsening despite optimal medical therapy, including ACE inhibitors, beta-blockers, spironolactone, and SGLT2 inhibitors.[16]

Another study found that vericiguat significantly lowered the risk of cardiovascular death or hospitalization due to HF in high-risk patients, showcasing its positive impact on clinical outcomes.[16]

3.5. Flaws and limitations of VICTORIA'S trial

The VICTORIA trial demonstrated that vericiguat significantly reduced the risk of cardiovascular death and hospitalization for heart failure compared to placebo, with a hazard ratio of 0.90 for the primary composite outcome (Table 1). Hospitalization rates were slightly lower in the Vericiguat group (35.5%) versus placebo (38.5%), indicating a modest benefit (Table 1). However, this marginal reduction may reflect suboptimal baseline therapy among participants, suggesting Vericiguat's full potential could be greater under optimized conditions. While generally well-tolerated, Vericiguat was associated with a higher incidence of new anemia (Table 1). The

Table 2. Eligibility criteria for inclusion of heart failure with reduced ejection fraction patients in vericiguat clinical trials

Eligibility Criteria	Description	Reference (s)
Symptoms despite optimal medical care	HFrEF patients experiencing symptoms despite receiving optimal medical care.	12-14
Worsening heart failure	HFrEF patients with worsening condition despite receiving treatment.	12-14
Usage of nitrates	HF patients using nitrates.	12-14
Increased NT-proBNP levels	Patients with elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), indicating HF severity.	12-14 12-14

Abbreviations: HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

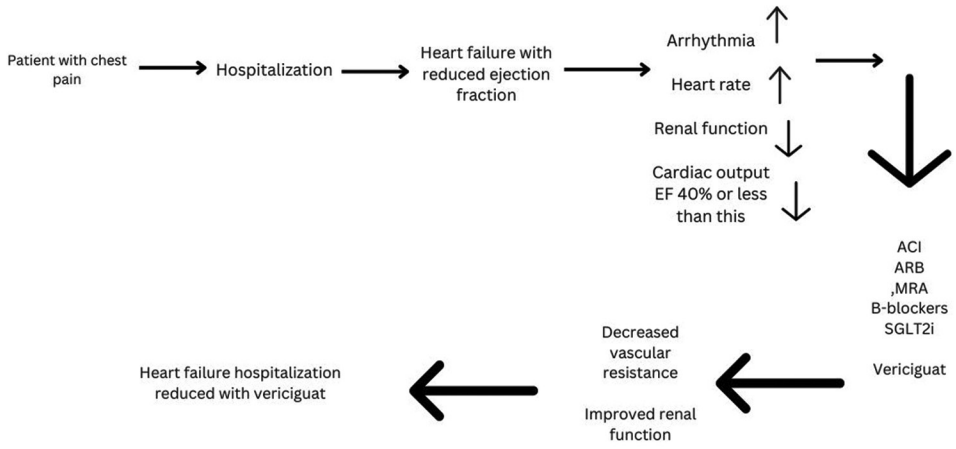


Figure 1. The role of vericiguat in heart failure with reduced ejection fraction. Image created by authors.
Abbreviations: ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; B-blockers: Beta-blockers; cGMP: Cyclic guanosine monophosphate; EF: Ejection fraction; GTP: Guanosine triphosphate; HFrEF: Heart failure with reduced ejection fraction; MRA: Mineralocorticoid receptor antagonists; NO: Nitric oxide; sGC: Soluble guanylate cyclase; SGLT2i: Sodium-glucose cotransporter-2 inhibitors.

inclusion of the *post hoc* analysis by Senni *et al.* and other relevant studies adds depth to the discussion of these flaws.[7] Senni's analysis, for example, underscores the importance of patient stratification and tailored therapy in HF management, particularly in assessing new treatments like vericiguat.[7] The analysis found significant variations in treatment efficacy based on baseline risk factors, which aligns with the concerns raised about the mixed population and subgroup differences in the current study.[7] In addition, studies focusing on the importance of adhering to GDMT in clinical trials highlight the need for rigorous application of existing guidelines to ensure new therapies are evaluated against a standard of care that reflects best practices in HF management.[7]

3.5.1. Mixed population

The inclusion of a diverse patient population in the study, characterized by variations in age, NT-proBNP levels, ejection fraction, and other clinical parameters, presents both strengths and limitations for the study's generalizability and interpretation.[7] While a heterogeneous cohort can offer a broad perspective on the potential benefits of vericiguat across different subgroups, it also complicates the ability to generalize findings to specific patient populations with HFrEF.[7] For instance, the variation in NT-proBNP levels, a biomarker for HF severity, could lead to differing responses to therapy and skewed outcomes.[7] Patients with higher NT-proBNP levels typically have a worse prognosis; if these patients were unevenly distributed across the study groups, it might impact the findings regarding the vericiguat's effectiveness.[7]

Moreover, age and ejection fraction differences among the participants can significantly affect the outcomes, as older patients or those with lower ejection fractions often have different comorbidities and treatment responses.[7] This diversity makes it challenging to draw robust conclusions about the efficacy of vericiguat for the general HFrEF population without a more nuanced stratification of results by these variables.[7] Previous studies, including a *post hoc* analysis by Senni *et al.*, have highlighted the importance of patient selection and stratification in evaluating HF therapies, suggesting that more uniform populations may provide clearer insights into drug efficacy and safety profiles in clinical practice.[7]

3.5.2. Inadequate guideline-directed medical therapy

A study[18] failed to ensure that a substantial portion of the cohort received GDMT, specifically the recommended triple therapy comprising an ACEi or ARB, a beta-blocker, and an MRA, which undermines its claims about the effectiveness of vericiguat. GDMT is the cornerstone of HFrEF management, and its omission or underuse could confound the study results, making it difficult to isolate the true impact of vericiguat.[18] Patients not receiving full GDMT may have had worse baseline characteristics or more severe disease, leading to poorer outcomes regardless of additional therapies like vericiguat.[18]

The lack of adherence to GDMT also limits the study's[18] applicability to real-world settings, where adherence to guidelines is crucial for improving patient outcomes.[18] Previous research has shown that patients who receive comprehensive GDMT have significantly better outcomes, including reduced mortality and hospitalization rates, compared to those who do not.[18] Thus, the observed benefits of vericiguat treatment in this study[18] may reflect an effect on a population that is not optimally managed, rather than

the additive benefit of the drug itself.[18] To better assess the efficacy of new drugs, future studies should ensure that all participants are on full GDMT before introducing additional therapies.[18]

3.5.3. Subgroup differences between quartiles

The presence of notable differences between quartiles (e.g., Q1 – Q3 vs. Q4) in terms of baseline characteristics and outcomes suggests potential biases in the study design[7] that may limit its ability to deliver robust conclusions about the general HFrEF population.[7] For example, if patients in Q4 had higher baseline NT-proBNP levels or worse kidney function compared to those in Q1 – Q3, the overall outcomes could be skewed by these more severe cases, making the treatment appear less effective than it might be in a more homogenous population.[7]

This variability highlights the need for more precise stratification in the study[7] design to ensure comparability across different patient subgroups.[7] The *post hoc* analysis by Senni *et al.* emphasizes that subgroup analysis is critical in interpreting clinical trial results for HF treatments.[7] Their findings suggest that patients with high-risk profiles or more advanced disease stages may not benefit as much from certain therapies, which could explain the differences observed between quartiles in the current study.[7] Thus, while the study provides valuable insights on the use of vericiguat, its design limits the applicability of its findings to the broader HFrEF population, necessitating further research with more homogeneous patient groups.

3.6. Challenges faced in the treatment of HFrEF

Studies have shown that patients with HFrEF in Pakistan are not receiving the optimal medication dosages, resulting in suboptimal treatment outcomes.[3] This is likely due to a variety of factors, including a lack of awareness about optimal dosages, a lack of access to medications, and poor adherence to the treatment regimen. The main challenges faced in the treatment of HFrEF are poor adherence to the treatment plan and side effects from the medications. Adherence can be a challenge because some of the medications need to be taken multiple times a day and must be continued for life.[6] Side effects of the medications can include dizziness, fatigue, cough, and headaches. Some people may also experience low blood pressure and kidney problems. Another challenge can be the cost, as some HF medications are expensive.

Depression is a common comorbidity in patients with CHF in general, and it is associated with increased morbidity and mortality.[19] While this has been studied in high-income countries, the prevalence and impact of depression in CHF patients in low- and middle-income countries like Pakistan is less well-understood.[19] A study showed that the clinical assessment of CHF symptoms, as determined by the NYHA classification, did not accurately reflect the severity of the disease.[17] It was also found that many CHF patients with reduced ejection fraction were not being prescribed the appropriate medications, such as ACE inhibitors and beta blockers, as recommended by clinical guidelines. This indicates a need for improved assessment and treatment of CHF in Pakistan.[20]

3.7. Consideration when administering or using medications for HFrEF

There are a few considerations when using the above medications to treat HFrEF; the patient's other health conditions and risk factors should be considered before administering the drugs. For example, if a patient has diabetes or kidney problems, some of these medications may not be suitable for them.[21] Another consideration is the patient's age and overall health. Beta-blockers, for example, may not be suitable for elderly patients or those with a history of heart block or asthma.[21] It is also important to consider whether the patient is pregnant or breastfeeding, as some of these medications can be harmful to the fetus or baby.[21] Table 3 presents potential challenges and considerations for vericiguat implementation in Pakistan.

3.8. Current guidelines of vericiguat and its implications in Pakistan

In patients with HFrEF, vericiguat, a new oral sGC activator, has demonstrated promise in lowering the risk of cardiovascular death and HF hospitalizations.[22,23] For instance, vericiguat stimulates the biochemical pathways of cGMP and NO, which are impaired in patients with HF.[24] Therefore, patients with HFrEF who are experiencing symptoms even after receiving the best medical care and whose HF is worsening may consider vericiguat as a new treatment option. Patients with HFrEF who fit specific criteria might consider receiving vericiguat medication. Based on the guidelines and trial conditions, the eligibility to receive vericiguat varies; about 21.4% of patients with HFrEF would be eligible for vericiguat treatment based on the VICTORIA trial's criteria.[12] The most significant factors influencing this eligibility include the usage of nitrates, increased NT-proBNP levels, and recent hospitalization for HF.[24] The VICTORIA study, a prospective, randomized, double-blind, placebo-controlled study, evaluated the efficacy and safety of vericiguat in patients with HF.[24] The study found that vericiguat supplementation, at a target dose of 10 mg twice a day, reduced cardiovascular death and hospitalization for HF in patients with clinical manifestations of chronic HF and reduced ejection fraction.[12] In Pakistan, the introduction of vericiguat may have an impact on the management of

Table 3. Challenges and considerations in implementing vericiguat therapy for heart failure with reduced ejection fraction in Pakistan: accessibility, education for healthcare providers, and regulatory approval

Challenges and Considerations	Description	References
Accessibility and affordability	Ensuring that vericiguat is readily available and affordable to patients in Pakistan by taking into account the economic factors and accessibility of healthcare infrastructures.	21
Education for healthcare providers	Providing information and training to healthcare professionals in Pakistan on the appropriate use of vericiguat as a treatment for heart failure.	21
Regulatory approval process	Navigating the regulatory approval process in Pakistan to ensure that vericiguat meets safety and efficacy standards for use in heart failure treatment.	21

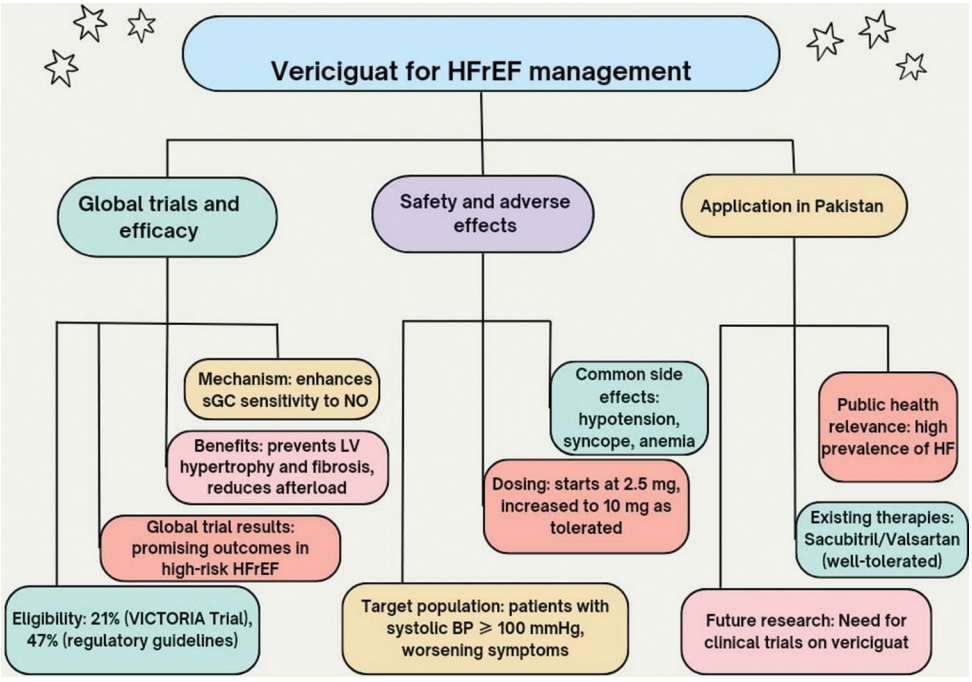


Figure 2. Summary flowchart for the efficacy, safety, and application of vericiguat for the management of heart failure with reduced ejection fraction. Image created by authors.
Abbreviations: BP: Blood pressure; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; LF: Left ventricle; NO: Nitric oxide; sGC: Soluble guanylate cyclase.

HFrEF.[24] In individual patients with HFrEF, particularly those at higher risk for HF hospitalization, the addition of vericiguat to the treatment regimen may be considered.[25] However, the effectiveness of the combination of vericiguat with sacubitril and valsartan in HFrEF is currently unknown.[26] In Pakistan, the use of vericiguat could enhance cardiac disease management by exerting a targeted pharmacological effect, specifically by increasing the sensitivity of soluble guanylate cyclase (sGC) to endogenous nitric oxide (NO), thereby improving heart function.[23] Vericiguat has the potential to improve outcomes for individuals with HFrEF, especially in terms of lowering hospitalizations and cardiovascular deaths.[1] Its implementation in Pakistan might improve patient outcomes and the management of heart disease. However, to fully comprehend its effectiveness when used with other medications such as valsartan and sacubitril, more research is needed.

4. Future perspective for vericiguat in Pakistan

Considering Pakistan's high rate of HF, integrating vericiguat into clinical practice may have a significant impact on patient outcomes and healthcare systems. HF and other cardiovascular diseases are becoming more common in Pakistan, a situation that calls for creative and practical solutions.[27] Due to its distinct mode of action and encouraging outcomes from clinical trials, vericiguat is a solid contender for inclusion in national HF management

protocols.[27] It is recommended that Pakistani policymakers and healthcare authorities keep a close eye on the ongoing Phase III trials of vericiguat.[27] By incorporating this innovative therapy into existing treatment plans, hospitalization rates may be decreased, and patients with HF may have a higher quality of life.[27] To ensure optimal use and maximize patient benefits, extensive training programs for healthcare providers should be introduced alongside the adoption of vericiguat.[27] Given its demonstrated efficacy and safety in preliminary clinical trials, Pakistan's regulatory bodies ought to think about expediting vericiguat's approval process. Partnerships with foreign pharmaceutical firms and research centers may make this drug more accessible, guaranteeing that Pakistani patients will be among the first to take advantage of this innovative therapy.[27]

In Pakistan, a study showed vericiguat's effectiveness in reducing all-cause mortality, cardiovascular mortality, and HF-related hospitalizations, regardless of atrial fibrillation (AF) status.[28] In 2019, the prevalence and disability rates for HF in Pakistan were 405.12 and 35.80 per 100,000 populations, respectively, with the highest burden in Islamabad and the lowest in Khyber Pakhtunkhwa.[29] Females saw a higher increase in HF prevalence from 1990 to 2019 compared to males, and the burden of HF increased in the 10 – 49 age group.[29] The integration of GDMT and recent pharmacological advancements in Pakistan reflects an effort to align with international standards, although resource constraints pose significant challenges.[30] Access to educational resources, patient education, and improvements in healthcare policy are crucial to enhancing HF outcomes in such settings.[30] Figure 2 shows the flowchart for the adoption of vericiguat in HFrEF management in Pakistan.

5. Conclusion

The use of vericiguat in the treatment of HF in Pakistan is an important topic of discussion that warrants significant attention. The use of this drug would reduce the burden of HF in Pakistan. It is crucial for policymakers and healthcare authorities to demonstrate strong political will and implement effective research and policy strategies to facilitate the adoption of vericiguat in Pakistan.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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References

1. Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction: A review. *JAMA*. 2020;324(5):488.
doi: 10.1001/jama.2020.10262
2. Vannuccini F, Campora A, Barilli M, Palazzuoli A. Vericiguat in heart failure: Characteristics, scientific evidence and potential clinical applications. *Biomedicines*. 2022;10(10):2471.
doi: 10.3390/biomedicines10102471
3. Vancheri F, Longo G, Henein MY. Left ventricular ejection fraction: Clinical, pathophysiological, and technical limitations. *Front Cardiovasc Med*. 2024;11:1340708.
doi: 10.3389/fcvm.2024.1340708
4. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: A review. *JAMA*. 2023;329(10):827-838.
doi: 10.1001/jama.2023.2020
5. Sheikh SA. Heart failure in Pakistan: A demographic survey. *J Cardiac Failure*. 2006;12(8):S157.
doi: 10.1016/j.cardfail.2006.08.069
6. Ashraf T, Ishaq M. Managing heart failure with reduced ejection fraction: What to know? *Pak Heart J*. 2021;54(3):205-206.
doi: 10.47144/phj.v54i3.2192
7. Senni M, Lopez-Sendon J, Cohen-Solal A, *et al*. Vericiguat and NT-proBNP in patients with heart failure with reduced ejection fraction: Analyses from the VICTORIA trial. *ESC Heart Failure*. 2022;9(6):3791-3803.
doi: 10.1002/ehf2.14050
8. Olivella A, Almenar-Bonet L, Moliner P, *et al*. Role of vericiguat in management of patients with heart failure with reduced ejection fraction after worsening episode. *ESC Heart Failure*. 2024;11(2):628-636.
doi: 10.1002/ehf2.14647
9. Follmann M, Ackerstaff J, Redlich G, *et al*. Discovery of

the soluble guanylate cyclase stimulator vericiguat (BAY 1021189) for the treatment of chronic heart failure. *J Med Chem*. 2017;60(12):5146-5161.

doi: 10.1021/acs.jmedchem.7b00449

10. Lombardi CM, Cimino G, Pagnesi M, *et al*. Vericiguat for heart failure with reduced ejection fraction. *Curr Cardiol Rep*. 2021;23(10):144.

doi: 10.1007/s11886-021-01580-6

11. Hammer A, Niessner A, Sulzgruber P. Vericiguat: A fifth cornerstone in the treatment of heart failure with reduced ejection fraction? *ESC Heart Failure*. 2023;10(6):3735-3738.

doi: 10.1002/ehf2.14549

12. Nguyen NV, Lindberg F, Benson L, *et al*. Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria: Data from the Swedish heart failure registry. *Eur J Heart Fail*. 2023;25(8):1418-1428.

doi: 10.1002/ejhf.2939

13. Seth S, Bauersachs J, Mittal S, *et al*. Expert opinion on the identification and pharmacological management of worsening heart failure: A consensus statement from India. *J Pract Cardiovasc Sci*. 2023;9(1):1.

doi: 10.4103/jpcs.jpcs_32_23

14. Ilonze OJ, Guglin M. Vericiguat, organic nitrates, and heart failure in African Americans. *Int J Cardiol*. 2021;338:136-137.

doi: 10.1016/j.ijcard.2021.06.033

15. Khan MN, Soomro NA, Naseeb K, *et al*. Safety and tolerability of Sacubitril/Valsartan in heart failure patient with reduced ejection fraction. *BMC Cardiovasc Disord*. 2023;23(1):133.

doi: 10.1186/s12872-023-03070-9

16. Sahana U, Wehland M, Simonsen U, Schulz H, Grimm D. A systematic review of the effect of vericiguat on patients with heart failure. *Int J Mol Sci*. 2023;24(14):11826.

doi: 10.3390/ijms241411826

17. Effectiveness *of Self-Management Interventions on Mortality, Hospital Readmissions, Chronic Heart Failure Hospitalization Rate and Quality of Life in Patients with Chronic Heart Failure: A Systematic Review*. Available from: https://www.sciencedirect.com/science/article/abs/pii/S073839911000025X [Last accessed on 2024 Dec 27].

18. Zafar R, Haris M, Assad S, *et al*. Core Measures for congestive heart failure in a tertiary care setting in Pakistan. *Cureus*. 2016;8:e728.

doi: 10.7759/cureus.728

19. Husain MI, Chaudhry IB, Husain MO, *et al*. Depression and congestive heart failure: A large prospective cohort study from Pakistan. *J Psychosom Res*. 2019;120:46-52.

doi: 10.1016/j.jpsychores.2019.03.008

20. (PDF) *Factors Associated with Congestive Heart Failure among Patients Presenting with Acute Cardiac Emergencies in Northern Lahore. ResearchGate*; 2024. Available from: https://www.researchgate.net/publication/377306521_factors_associated_with_congestive_heart_failure_among_patients_presenting_with_acute_cardiac_emergencies_in_northern_lahore [Last accessed on 2024 Dec 27].

21. Bolam H, Morton G, Kalra PR. Drug therapies in chronic heart failure: A focus on reduced ejection fraction. *Clin Med (Lond)*. 2018;18(2):138-145.

doi: 10.7861/clinmedicine.18-2-138

22. Siddiqi AK, Greene SJ, Fudim M, Mentz RJ, Butler J, Khan MS. Vericiguat for the treatment of heart failure with reduced ejection fraction. *Expert Rev Cardiovasc Ther*. 2023;21(4):245-257.

doi: 10.1080/14779072.2023.2189101

23. 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.

doi: 10.1177/03000605231159333

24. Nakamura M, Imamura T, Kinugawa K. Initial experience of vericiguat treatment in patients with heart failure and reduced ejection fraction. *JCM*. 2023;12(13):4396.

doi: 10.3390/jcm12134396

25. Aimo A, Castiglione V, Vergaro G, *et al*. The place of vericiguat in the landscape of treatment for heart failure with reduced ejection fraction. *Heart Fail Rev*. 2022;27(4):1165-1171.

doi: 10.1007/s10741-021-10146-1

26. Merriel SWD, Andrews V, Salisbury C. Telehealth interventions for primary prevention of cardiovascular disease: A systematic review and meta-analysis. *Prev Med*. 2014;64:88-95.

doi: 10.1016/j.ypmed.2014.04.001

27. Alfieri M, Bruscoli F, Di Vito L, *et al*. Novel medical treatments and devices for the management of heart failure with reduced ejection fraction. *J Cardiovasc Dev Dis*. 2024;11(4):125.

doi: 10.3390/jcdd11040125

28. Shaikh TG, Jawed S, Rahmat ZS, *et al*. Efficacy and safety of vericiguat for treatment of heart failure: A systematic review. *Curr Probl Cardiol*. 2023;48(5):101586.

doi: 10.1016/j.cpcardiol.2023.101586

29. Jain SS, Li SS, Xie J, *et al*. Clinical and economic burden of obstructive hypertrophic cardiomyopathy in the United States. *J Med Econ*. 2021;24(1):1115-1123.

doi: 10.1080/13696998.2021.1978242

30. Rashid AM, Khan MS, Fudim M, DeWald TA, DeVore A, Butler J. Management of heart failure with reduced ejection fraction. *Curr Problems Cardiol*. 2023;48(5):101596.

doi: 10.1016/j.cpcardiol.2023.101596