Review Article

Practical Patient Care Considerations With Use of Vericiguat After Worsening Heart Failure Events

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ABSTRACT

Vericiguat is a soluble guanylate cyclase stimulator approved by multiple global regulatory bodies and recommended in recently updated clinical practice guidelines to reduce morbidity and mortality in patients with worsening chronic heart failure (HF) with reduced ejection fraction (HFrEF). Despite the growing armaments of evidence-based medical therapy for HFrEF that have demonstrated clinical outcome benefits, there is a need to address residual risk following worsening HF events. When considering therapies aimed to mitigate postevent cardiovascular risk, potential barriers preventing the prescription of vericiguat in eligible patients may include providers' lack of familiarity with it, clinical inertia, limited knowledge about monitoring response to therapy, and concerns about potential adverse effects as well as integration of its routine use during an era of in-person and telehealth hybrid ambulatory care. This review provides an overview of vericiguat therapy and proposes an evidence-based and practical guidance strategy toward implementing its use in various clinical settings. This review additionally summarizes patient counseling points for its initiation and maintenance. (*J Cardiac Fail 2023;29:389–402*)

Key Words: Vericiguat, worsening heart failure, heart failure, medical therapy, evidence-based therapy.

Heart failure (HF) with reduced ejection fraction (HFrEF) contributes to an increasing burden on the health care system worldwide,[1] and it continues to carry a survival rate comparable to that of many cancers; it shows approximately a 50% mortality rate at 5 years after diagnosis.[2] Despite the availability of multiple evidence-based therapies proven to improve quality of life and extend survival,[3] approximately 1 in 6 patients develop worsening HF, including the need for intravenous diuretics in outpatient or hospitalization settings, from the time of HF diagnosis. These patients exhibit an exceedingly high risk for mortality and rehospitalization by as much as 50% within 30 days.[4] Further residual cardiovascular risk persists despite optimized background therapy.[5–7] Thus, an imperative exists to identify and treat patients with HFrEF at high risk of rehospitalization following worsening HF events toward improving clinical outcomes, as well as mitigating heart failure-related health care expenditures.

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Manuscript received March 16, 2022; revised manuscript received October 10, 2022; revised manuscript accepted October 29, 2022.

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See page 400 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2022.10.431

Vericiguat, a novel oral-soluble guanylate cyclase (sGC) stimulator, was a recent introduction to the arsenal for the treatment of HFrEF. In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial, treatment with vericiguat resulted in significantly lower rates of composite HF hospitalization or cardiovascular death when compared to placebo across a high-risk population with HFrEF post-worsening HF events who were optimized on background HF therapy.[8] Results from this trial have supported the addition of vericiguat into the recommended therapies for HfrEF, and it has a IIb recommendation in the most recent guidelines.[3,9,10] In light of the increasing need to address high rates of events in patients with worsening HF, we review the current evidence surrounding treatment of HFrEF with vericiguat and propose a practical framework of its use and monitoring for clinical providers and patients.

Vericiguat in the Context of the Current Heart Failure Pharmacological Therapeutic Landscape

Landmark clinical trials have identified multiple classes of medications that reduce morbidity and mortality rates for patients with HFrEF,[5–7,11] which include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), vericiguat, ivabradine and, most recently, sodium-glucose cotransporter-2 inhibitors (SGLT2is) (Supplementary Fig. 1).[5–8,11–13]

VICTORIA was a phase 3 randomized placebo-control trial that randomized 5050 patients with chronic HFrEF and an ejection fraction of less than 45% once stabilized following a worsening HF event, to receive either vericiguat or placebo, alongside continued optimal medical therapy.[8] Participants were categorized into 3 cohorts based on the timing of the deterioration: within 3 months from an index HF hospitalization (n = 3378, 67%; of whom 11% were in-hospital); within 3–6 months of HF hospitalization (n = 871, 17%); or within 3 months of outpatient worsening HF (n = 801, 16%).[8,14] Over a median of 10.8 months, composite cardiovascular death or HF hospitalization occurred in 35.5% of the vericiguat group and in 38.5% of the placebo group (annualized absolute risk reduction of 4.2%; hazard ratio 0.90 [95% CI 0.82–0.98]; $P = 0.02$). The medication was well tolerated; adverse event rates were similar for syncope (4.0% of the vericiguat group vs 3.5% of the placebo group; $P = 0.30$) and for symptomatic hypotension (9.1% of the vericiguat group vs 7.9% of the placebo group; $P = 0.12$).[8] Patients enrolled in the VICTORIA trial were notably older and sicker, and had longer duration of HF compared to other trial populations for contemporary HFrEF therapies, including sacubitril/valsartan (PARADIGM-HF),[5] SGLT2i therapies (DAPA-HF and EMPEROR-Reduced),[6,7] and omecamtiv mecarbil (GALACTIC-HF)[15] (Table 1). VICTORIA was powered for composite cardiovascular death or first HF hospitalization. As such, event rates were relatively higher and accrued faster in VICTORIA, particularly through first HF hospitalization, than in other contemporary trials, and there was similar overall absolute risk reduction in composite cardiovascular death or first HF hospitalization associated with active drug vs comparator.[6–8] Given these high event rates with varying follow-up times, examination of absolute risk reduction suggests that the outcome benefits are comparable across trials of vericiguat, ARNI, or SGLT2i in HFrEF.[16] Clearly, such comparisons across clinical trials remain complex and should be interpreted with caution due to the enrollment of patients with differing risk profiles.

VICTORIA trial results led to the approval of vericiguat by the U.S. Food and Drug Administration for treatment of worsening chronic HFrEF following hospitalization for HF or need for outpatient intravenous diuretics, and also by the European Medicines Agency for treatment of symptomatic chronic HFrEF in patients who are stabilized after a recent decompensation event requiring intravenous therapy. Professional organizations and guideline committees have incorporated the use of vericiguat into the treatment pathway for patients with HFrEF. For instance, the updated 2021 European Society of Cardiology, 2021 Japanese Circulatory Society/Japanese Heart Failure Society, 2021 Canadian Cardiovascular Society, and 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guidelines for diagnosis and treatment of acute and chronic heart failure recommended that, in addition to background HF therapies, vericiguat may be used in HFrEF for further reduction of cardiovascular mortality rates and hospitalizations due to HF.[3,9,10,17]

Of the recent guideline updates, the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guidelines list the use of vericiguat as a Class 2b recommendation in selected high-risk patients with HFrEF who had recent worsening HF and were already on background evidence-based therapies, which include the Class 1 recommended agents ACEI/ARB/ARNIs, beta-blockers, MRAs, and SGLT2is, as tolerated.[10] Although not explicitly stated in these guidelines, a higher level of recommendation may not have been awarded to vericiguat because the VICTORIA trial showed a significant difference in the composite of cardiovascular death and hospitalization due to HF, but it did not show a difference in the secondary endpoint of

Table 1. Overview of Landscape Trials of Contemporary Therapies in Heart Failure.

Trial Characteristics	PARADIGM HF n = 8442 (5) Sacubitril/valsartan	VICTORIA n = 5050 (8) Vericiguat	DAPA-HF n = 4744 (6) Dapagliflozin	EMPEROR-Reduced n = 3730 (7) Empalgliflozin	GALACTIC-HF n = 8256 (15) Omecamtiv Mecarbil
Drug class	Angiotensin receptor−neprilysin inhibitor	Soluble guanylate cyclase stimulator	SGLT-2 inhibitor	SGLT-2 inhibitor	Selective cardiac myosin activator
Intervention/ control	LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily)	Vericiguat (10 mg once daily) or placebo	Dapagliflozin (10 mg once daily) or placebo	Empagliflozin (10 mg once daily) or placebo	Omecamtiv mecarbil (25 mg, 37.5 mg, or 50 mg twice daily based on drug plasma levels) or placebo
Clinical setting	Outpatient	Outpatient and inpatient	Outpatient	Outpatient	Outpatient and inpatient
Key inclusion criteria	Chronic HF with LVEF ≤40% (functional class II−IV) AND Run-in period with use of ACE inhibitor or ARB for at least 4 weeks AND -NT-proBNP ≥ 600pg/mL OR -NT-proBNP ≥ 400 pg/mL if there was a prior HFH within prior 12 months	Chronic HF (functional class II−IV) with LVEF <45% AND Evidence of worsening heart failure -hospitalization within 6 months -having received IV diuretic therapy without hospitalization within 3 months AND - NTproBNP ≥ 1000 pg/mL OR - NT-proBNP ≥1600 pg/mL if with AF or atrial flutter	Chronic HF with LVEF ≤40% AND NT-proBNP ≥600 pg/mL OR -NT-proBNP ≥400 pg/mL but had HF hospitalizations within prior 12 months OR -NT-proBNP ≥900 pg/mL if with AF or atrial flutter on baseline electrocardiogram	Chronic HF (functional class II−IV) with LVEF ≤40%AND - If LVEF ≤30% • NT-proBNP ≥600 pg/mL if no AF • NT-proBNP ≥1200 pg/mL if with AF - If LVEF 31%−35% • NT-proBNP ≥1000 pg/mL if no AF • NT-proBNP ≥2000 pg/mL if with AF - If LVEF 36−40% • NT-proBNP ≥2500 pg/mL if no AF • NT-proBNP ≥5000 pg/mL if with AF - If LVEF >40% but had HF hospitalizations within prior 12 months, • NT-proBNP ≥600 pg/mL if no AF • NT-proBNP ≥1200 pg/mL if with AF	Chronic HF with LVEF ≤35% who were outpatients with urgent visits to the emergency department or a prior hospitalization for HF within 1 year or visit or currently hospitalized patients AND -NT-proBNP ≥ 400 pg/mL OR -NT-proBNP ≥1200 pg/mL if with AF or atrial flutter on baseline
Key exclusion criteria†	eGFR <30 mL/min/1.73m^2 Symptomatic hypotension and/or systolic blood pressure <100 mmHg at screening or <95 mmHg at randomization Potassium >5.2 mmol/L at screening or >5.4 mmol/L at randomization History of angio-edema or unacceptable side effects during receipt of ACE inhibitors or ARBs	eGFR <15 mL/min/1.73m^2 Symptomatic hypotension and/or systolic blood pressure <100 mmHg Concurrent or anticipated use of long-acting nitrates, soluble guanylate cyclase stimulators, or phosphodiesterase type 5 inhibitors. Use of IV inotropes or implantable left ventricular assist devices	eGFR <30 mL/min/1.73m^2 Symptomatic hypotension and/or a systolic blood pressure < 95 mmHg	eGFR <20 mL/min/1.73m^2 or dialysis Symptomatic hypotension and/or a systolic blood pressure <100 mmHg	Current hemodynamic or clinical instability leading to the use of mechanical support or intravenous medication Systolic blood pressure <85 mmHg eGFR <20 mL/min/1.73m^2
Median NT-proBNP, pg/mL	1608	2816	1437	1906	2001
HFH within 6 mo	31%	84%	16%	NA	NA
eGFR <60 ml/min/1.73m^2	37%	53%	41%	48%	52%
Median follow-up time	27 months	10.8 months	18.2 months	16 months	21.8 months

(*continued on next page*)

Table 1 (*Continued*)

Trial Characteristics	PARADIGM HF n = 8442 (5) Sacubitril/valsartan	VICTORIA n = 5050 (8) Vericiguat	DAPA-HF n = 4744 (6) Dapagliflozin	EMPEROR-Reduced n = 3730 (7) Empagliflozin	GALACTIC-HF n = 8256 (15) Omecamtiv Mecarbil
Primary endpoint	Composite of cardiovascular death or a first hospitalization for HF Enalapril: 13.2 events/100 PY Sacubitril/valsartan: 10.6 events/100 PY Hazard ratio (95% CI): 0.80 (0.73,0.87; $P < 0.001$)	Composite of cardiovascular death or a first hospitalization for HF Placebo: 37.8 events/100 PY Vericiguat: 33.6 events/100 PY Hazard ratio (95% CI): 0.90 (0.82, 0.98; $P = 0.02$)	Composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death Placebo: 15.6 events/100 PY Dapagliflozin: 11.6 events/100 PY Hazard ratio (95% CI): 0.74 (0.65, 0.85; $P < 0.001$)	Composite of cardiovascular death or hospitalization for worsening HF Placebo: 21.0 events/100 PY Empagliflozin 15.8 events/100 PY Hazard ratio (95% CI): 0.75 (0.65, 0.86; $P < 0.001$)	Composite of worsening HF (hospitalization or urgent visit for HF) or cardiovascular death Placebo: 26.3 events/100 PY Omecamtiv Mecarbil: 24.2 events/100 PY Hazard ratio (95% CI): 0.92 (0.86, 0.99; $P = 0.03$)

AF, atrial fibrillation; BP, blood pressure; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal-pro hormone brain natriuretic peptide; PY, person years; SGLT, sodium glucose cotransporter.
†Trials excluded recent acute coronary syndrome, stroke, percutaneous coronary intervention, and coronary-artery bypass surgery within 3 months prior to enrollment.

cardiovascular death. The nature of the trial, including a short follow-up and enrollment of a high-risk population, may explain the failure to meet this secondary endpoint. The ongoing VICTOR trial (NCT05093933) is currently enrolling patients with chronic HFrEF and may provide additional data on the efficacy of vericiguat in patients with and without recent worsening HF events, including patients with broader uses of other Class 1 recommended novel background therapies listed above.

Vericiguat use has been proposed under selected patient scenarios alongside other Class 2a and Class 2b guideline-recommended therapies, but vericiguat is specific to worsening HF.[10] An explicit criterion that promotes the use of vericiguat over other Class 2b agents (ie, digoxin, potassium binders, polyunsaturated fatty acids) to reduce composite cardiovascular death or hospitalization for HF is the worsening HF episode, which is a commonly identifiable moment in patient care. Among the Class 2b agents, only vericiguat proved to reduce the primary endpoint of composite cardiovascular death or hospitalization for HF in a large contemporary randomized trial. Additionally, although ivabradine (Class 2a) has a higher level of recommendation than vericiguat, vericiguat may be considered after a worsening HF episode, especially as providers assess ambulatory heart rates on maximally tolerated beta-blockers prior to initiation of ivabradine in suitable patients. Providers may refer to the following practical guidance for use of vericiguat in populations with HFrEF (Fig. 1).

Guidance for Providers When Initiating Vericiguat After a Worsening HF Event

Given the high event rates of mortality and HF rehospitalizations among patients with worsening HF,[4] there exist differences and advantages of novel therapies for HFrEF that may allow for personalized treatment based on a patient's specific HF risk, clinical characteristics, and comorbidities. Thus, addressing key questions for providers will likely be central to reducing adverse cardiovascular events in high-risk patients with HFrEF after worsening HF[1]: What is the mechanism of action of vericiguat?[2] Who is the candidate patient for vericiguat use in the era of contemporary HF therapies?[3] How should vericiguat be started and uptitrated?[4] and How should patients be followed-up and monitored to prevent adverse effects? We detail responses to these key questions below.

What Is the Mechanism of Action of Vericiguat?

Vericiguat exhibits a unique mechanism of action as a novel direct sGC stimulator, which serves as a key mechanism for generating cyclic guanosine

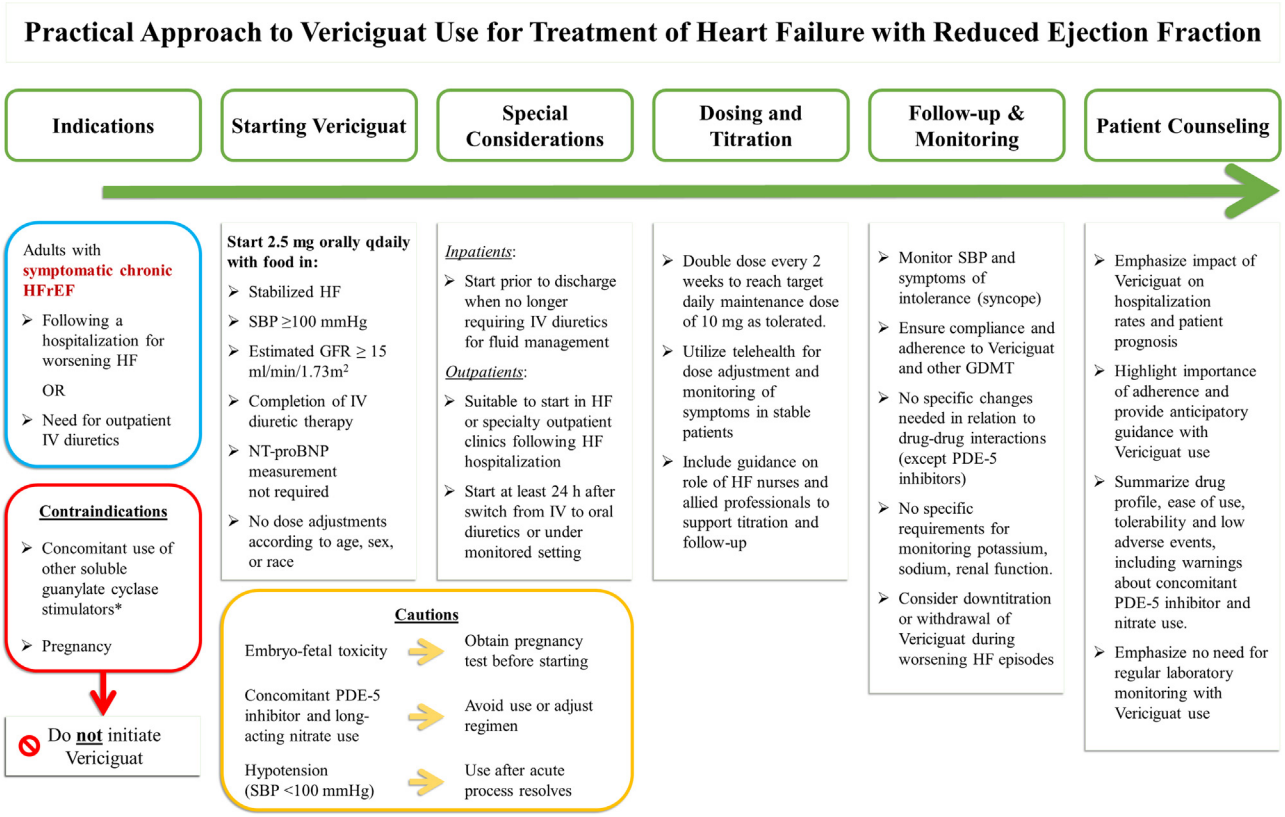


Fig. 1. Central illustration and take-home graphic: stepwise approach to prescription of vericiguat. A proposed pathway of candidate selection, initiation, monitoring, and patient counseling related to prescription of vericiguat in clinical practice. GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide; PDE-5, phosphodiesterase-5; qdaily, once daily; SBP, systolic blood pressure; sGC, soluble guanylate cyclase stimulators. *Other soluble guanylate cyclase stimulators include riociguat.

monophosphate (cGMP), an important second messenger that mediates vasodilation.[18] In HFrEF, the nitric oxide (NO)-sGC-cGMP pathway is impaired, which contributes to endothelial, myocardial, and vascular dysfunction.[19,20] Vericiguat works to restore the NO-sGC-cGMP pathway. This pathway improves cardiac and vascular function in HFrEF, reduces inflammatory and profibrotic mechanisms,[18,19] and reduces cardiomyocyte hypertrophy.[20] Unlike other sGC stimulators such as riociguat, which has been studied for treatment of pulmonary hypertension and exhibits a pharmacokinetic profile requiring 3-times daily dosing, vericiguat exhibits a distinct pharmacokinetic profile allowing for once-daily oral dosing and greater hemodynamic tolerability in HFrEF[20] (Fig. 2).

Other medications may have indirect effects on the NO-sGC-cGMP pathway, including NO donors, phosphodiesterase-5 (PDE-5) inhibitors and ARNIs.[18] NO donors act upstream of this pathway and may exhibit profound vasodilatory responses in HFrEF.[20] PDE-5 inhibitors act downstream of the pathway by inhibiting breakdown of cGMP.[18] ARNIs also increase cGMP levels indirectly by blocking neprilysin-mediated degradation of natriuretic peptides,[18] which stimulate particulate guanylate cyclase in response to increased myocardial wall stress and subsequently increase cGMP.[21,22] Nitrates or PDE-5 inhibitors do not selectively affect cGMP generation.[22] Unlike nitrates, PDE-5 inhibitors and ARNIs, vericiguat uniquely restores cGMP production by working in synergy with endogenous NO, including states of low NO availability, and independent of background neurohormonal-blockade therapies.[18,23] Additionally, vericiguat's production of cGMP restores NO sensitivity, and subsequently decreases arterial constriction and arterial stiffness.[23] Among therapies increasing cGMP, only sacubitril/valsartan and vericiguat have been shown to improve patient outcomes over ACEi/ARBs, beta-blockers and MRAs in HFrEF. The myocardial response to sacubitril/valsartan or vericiguat may be synergic in cGMP upregulation due to their differently activated pathways through natriuretic peptide-mediated particulate guanylate cyclase and vericiguat-mediated sGC.[22] Their concurrent use has shown safety and efficacy in post hoc analyses of the VICTORIA trial.[24]

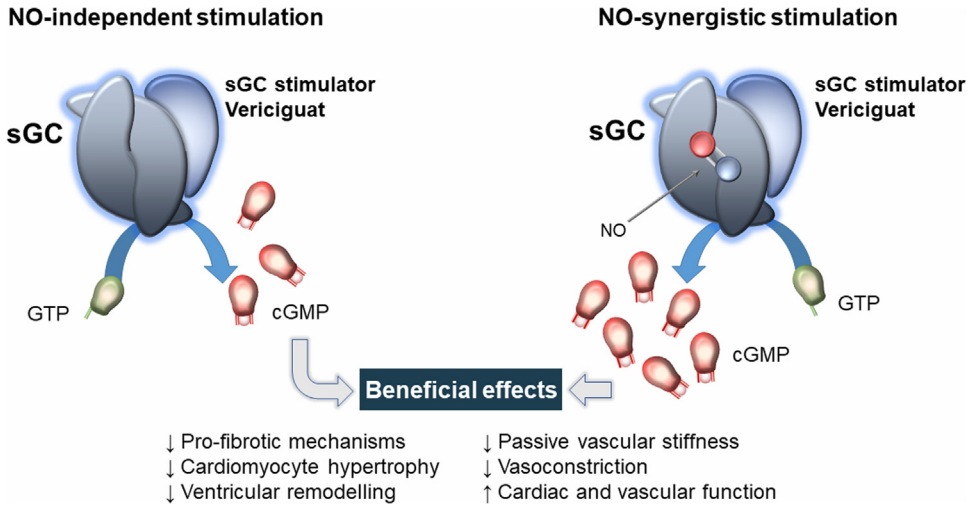


Fig. 2. Mechanism of action of vericiguat in heart failure with reduced ejection fraction. Direct stimulation of native sGC by vericiguat occurs independently from endogenous NO as well as synergistically with endogenous NO, leading, in both scenarios, to increased availability of cyclic guanosine monophosphate and its mediated beneficial cardiac and vascular effects.[18–20,23] cGMP, cyclic guanosine monophosphates; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.

Who Are the Candidate Patients for Vericiguat Use in the Era of Contemporary HF Therapies?

The eligibility criteria for participants in the VICTORIA trial should be used to identify and to estimate the potential clinical benefits of vericiguat use (Table 1). The VICTORIA trial included adults with HFrEF, New York Heart Association functional class II–IV symptoms, elevated natriuretic peptide levels (in patients without established atrial fibrillation, B-type natriuretic peptide (BNP) $\geq$ 300 pg/mL or N-terminal (NT)-pro-BNP $\geq$ 1000 pg/mL; in patients with established atrial fibrillation, BNP $\geq$ 500 pg/mL or NT-proBNP $\geq$ 1600 pg/mL), estimated glomerular filtration rate $\geq$ 15 mL/min/1.73m^2, and evidence of worsening HF events, defined as HF hospitalization within 6 months before randomization (inclusive of in-hospital initiation) and worsening HF episode without hospitalization but requiring intravenous diuretic therapy within the previous 3 months.[8,25] These key discrete events portray elevated risk of subsequent HF events and may facilitate focused attention on and screening for patients who may be eligible for initiation of and monitoring response to vericiguat.

Vericiguat is generally well-tolerated; it results in minimal hypotension and a favorable safety profile, even in patients with more advanced renal disease.[26] In the VICTORIA trial, the mean age of enrolled participants was 67 years.[8] Univariate analyses suggested a favorable signal toward placebo among prespecified older participants (age $\geq$ 75 years).[8] Although older patients with HFrEF may have additional comorbidities that may limit their candidacy for HF therapies, particularly risk for symptomatic hypotension, multivariable analyses revealed that vericiguat was well tolerated by patients with recent worsening HF and with lower baseline blood pressure (systolic blood pressure 100–110 mmHg), even among those of older age ($>$ 75 years) and concurrent use of other HF therapies such as ARNIs.[27] Providers may be reassured when considering the safety and tolerability profile of vericiguat and balancing the expected longer-term therapeutic benefits against potentially withholding therapy due to risk of hypotension in at-risk populations with HFrEF. Additionally, VICTORIA enrolled 10% (n = 506) participants with advanced kidney disease (estimated glomerular filtration rate $\leq$ 30 mL/min/1.73m^2),[8] and vericiguat remained effective and well tolerated across renal groups, as discussed further below.[28]

Other patient characteristics to consider are concomitant use of other sGC stimulators (eg, riociguat), because their coadministration is contraindicated. However, these medications are used relatively uncommonly in patients with HFrEF. Additionally, data from preclinical animal reproductive studies have demonstrated that vericiguat use may result in fetal harm when administered during pregnancy and, therefore, its use is contraindicated in females considering pregnancy or currently pregnant. When considering whether to start vericiguat in women of reproductive potential with HFrEF, providers must recommend using effective forms of contraception during treatment and for 1 month after stopping treatment.

In patients with HF, concomitant use of short-acting nitrates (eg, sublingual nitroglycerin) is well tolerated with vericiguat use. However, vericiguat

coadministration of either PDE-5 inhibitors (eg, sildenafil, vardenafil, and tadalafil) have not been studied in phase 2 or 3 clinical trials in HF. Therefore, vericiguat and PDE-5 inhibitor coadministration is not recommended due to insufficient available safety data on the potential risk for sustained hypotension. Limited experience is available for coadministration of long-acting medications that upregulate the nitric oxide pathway (eg, long-acting nitrates, including isosorbide mononitrate) with vericiguat, but vericiguat and long-acting nitrate coadministration is not yet routinely recommended for the population with HF.[29]

How to Start and Uptitrate Vericiguat?

Vericiguat may be started on top of background HF therapies without the necessity of any discontinuation or washout periods. Eligible patients should receive vericiguat at a starting dosage of 2.5 mg taken orally once daily with food. The dose should be doubled as tolerated every 2 weeks until achieving a target dose of 10 mg once daily.[8,29] Routine baseline assessments for basic metabolic function, including renal function and complete blood count, may be obtained but are not necessary.

No dosage adjustment of vericiguat is recommended in patients with an estimated glomerular filtration rate $\geq$ 15 mL/min/1.73m^2 who are not on dialysis.[29] Although univariate prespecified subgroups in the VICTORIA trial suggested the primary outcome favored the placebo, primary outcomes were consistent across renal function categories, and there was no difference in the trajectory of renal function between vericiguat and placebo based on multivariate analyses.[28] Patients with mild to moderate hepatic impairment also require no dosage adjustment of vericiguat during initiation or titration.[29]

How to Follow-up, Monitor and Prevent Adverse Effects?

Similar to the VICTORIA trial, we recommend following patients on a biweekly basis after vericiguat initiation with dosage titration over 6–8 weeks.[30] Titration must be balanced in the context of other HFrEF drug therapy. Once maximum tolerated dosage has been achieved, the patient can be followed per local protocols. Vericiguat use does not require routine monitoring of renal function or electrolytes, such as sodium or potassium.

Serious adverse events were similar between the vericiguat and placebo groups in the VICTORIA trial.[8] Adverse events related to vericiguat in VICTORIA included symptomatic hypotension and syncope.[8] These findings may reflect the severity of illness in the trial population, particularly in those with recent worsening HF events, and the findings may not be due directly to vericiguat use alone; rates were similar between vericiguat and placebo groups for symptomatic hypotension (9.1% vs 7.9%; $P = 0.12$) and syncope (4% vs 3.5%; $P = 0.30$).[8] Notably, these events did not contribute to a greater discontinuation of drug therapy during follow-up.[8] It is important that providers perform routine monitoring of vitals, but they may be reassured that such events remain low, and vericiguat offered clinical benefits for HF across baseline blood pressure groups.[8,27]

Another observed adverse event related to vericiguat use was anemia, defined as hemoglobin $<$ 13.0 g/dL in men and $<$ 12.0 g/dL in women. Anemia was common in participants in the VICTORIA trial at the time of randomization in the vericiguat and placebo groups (7.6% vs 5.7%).[8] However, lower hemoglobin levels related to vericiguat use did not progress further, nor were they related to the treatment benefit of vericiguat.[8,31] Additionally, lower hemoglobin was associated with greater frequency of clinical events,[31] also suggesting a sicker enrolled population. Thus, it is recommended that providers measure complete blood counts as clinically indicated, but they do not need to specifically monitor blood counts related to vericiguat therapy.

Given that vericiguat initiation and dose titration do not necessarily require face-to-face in-person visits, particularly with frequent laboratory studies or imaging assessments, telehealth care may be suitable for the monitoring of drug tolerance and adverse effects in stabilized patients with normal blood pressures. Pilot studies have described the feasibility of remote optimization of evidence-based HF therapies in HFrEF,[32] as well as patient activation tools to enable self-efficacy and discussion of evidence-based practices for HF prior to scheduled appointments.[33] Additionally, the landscape of patient engagement and health care delivery through digital health strategies continues to grow and evolve.[34] Other ancillary pilot programs consist of HF clinic nurses, advanced practice providers, and pharmacists to support HF clinics and provide algorithmic titration and follow-up monitoring that may have the potential to improve clinical inertia and decrease provider burden when initiating therapies such as vericiguat.[32,35] Visits may focus on maximizing HF therapies, optimizing fluid status, reducing medication burdens that do not improve HF prognosis, and addressing patient- or system-level barriers to long-term drug adherence. Therefore, vericiguat's safety and monitoring profile may allow practices to leverage telehealth and ancillary resources in order to provide focused care for patients at risk of future worsening HF events.

Table 2. Clinical Criteria to Interrupt Vericiguat During Acute Decompensation Episodes.

Vitals Assessment	Dosage Modification
SBP ≥ 100 mmHg AND on vericiguat 10 mg dosage OR SBP ≥90 and < 100 mmHg on any dosage	Maintain current dosage of vericiguat
SBP <90 mmHg Asymptomatic	Consider decreasing vericiguat dosage if the patient is taking vericiguat 5 mg or 10 mg and to pause vericiguat if patient is taking 2.5 mg.
SBP <90 mmHg Symptomatic	Interrupt dosage of vericiguat.
Normotensive resting vitals but with orthostatic hypotension	Assess volume status, adjust/decrease diuretic therapy first, then reduce non-heart failure blood pressure-lowering therapies. If patient continues to remain orthostatic, then reduce vericiguat by 1 dosage level.

Adapted instructions from the VICTORIA trial protocol.[8]
SBP, systolic blood pressure.

Special Considerations

Worsening HF Event or Acute Decompensation Warranting Dose Modification

Patients with recent worsening HF events are at extremely high risk for subsequent events.[4,36] Certain episodes of noncardiovascular or cardiovascular etiologies may result in circumstances in which vericiguat dosage modification may be appropriate. The VICTORIA trial protocol offers insight into how providers may address sustained hypotension during episodes of acute decompensation.[8] If a patient has a resting systolic blood pressure of ≥ 100 mmHg and is taking vericiguat 10 mg, or has a resting systolic blood pressure between ≥ 90 and < 100 mmHg on any dosage of vericiguat, providers are advised to maintain current vericiguat dosing. If a patient is asymptomatic, but resting systolic blood pressure is < 90 mmHg, then providers may consider decreasing the vericiguat dosage if the patient is taking vericiguat 5 mg or 10 mg and to pause vericiguat if the patient is taking 2.5 mg. If the patient is symptomatic and systolic blood pressure is < 90 mmHg, providers are advised to pause vericiguat until resolution of the acute episode (Table 2).

If patients present to the clinic or to acute care with orthostatic hypotension, providers should first evaluate volume status and whether diuretic dosage reduction or changes are necessary. If this maneuver does not result in clinical response, then concomitant medications with blood pressure-lowering effects that do not improve HF prognosis should be stopped. If either of these results in no benefit, then a dosage reduction of vericiguat as described above may be appropriate.[8] Additionally, providers may consider an approach where therapies proven to improve HF prognosis by reducing composite cardiovascular death or HF hospitalization, such as ARNIs and MRAs, be preferentially maintained with demonstration of hemodynamic stability before reintroduction of vericiguat.

Table 3. Instructions for Resumption of Vericiguat Following Brief Interruption.

Dosage at Time of Interruption	Length of Interruption	Restart Dosage
2.5 mg	Any time interval	2.5 mg
5 mg	Any time interval	2.5 mg
10 mg	>5 days	2.5 mg
10 mg	≤5 days	5 mg

Adapted instructions from the VICTORIA trial protocol.[8]

Every effort should be made to resume vericiguat upon temporary interruption of therapy following resolution of acute illness. We advise that patients restart vericiguat at 2.5 mg once daily, unless the patient was taking 10 mg and the duration of interruption was ≤ 5 days, then the patient may restart vericiguat at 5 mg once daily (Table 3). Titration toward target dosing would remain on a biweekly basis, as tolerated.[8] Data from real-world registries may provide further insight into the duration and reinitiation of therapy during noncardiovascular hospitalizations and worsening HF episodes.

Concomitant HF Vasodilator Therapy

No specific changes to medication regimens are needed when initiating vericiguat and considering drug-drug interactions, except for concomitant sGC stimulators, PDE-5 inhibitors, and long-acting nitrate therapies (eg, isosorbide mononitrate). The Vericiguat Drug-drug Interaction Study With Isosorbite Mononitrate in Stable Coronary Artery Disease Patients (VISOR) study was a phase 1b trial that studied vericiguat with isosorbide mononitrate in patients with chronic coronary syndromes, and it did not find additional adverse events with concomitant use than those seen with isosorbide mononitrate alone.[37] Regarding populations with HFrEF, the VICTORIA trial enrolled a modest proportion of Black participants (4.9%), among whom some may also

qualify for HF vasodilator therapies as first-line therapies, including hydralazine and long-acting nitrates.[3,10] Patients with concomitant or anticipated use of long-acting nitrates were excluded from the VICTORIA trial and, thus, the sequencing of vericiguat relative to those with HFrEF who are eligible for HF vasodilator therapies has not yet been defined due to insufficient available safety data. The use of these agents is not specifically excluded in current labeling,[29] but we caution vericiguat use in populations with anticipated or current use of long-acting nitrates. Recruitment for the VICTOR trial (NCT05093933) is ongoing in patients with HFrEF, and it includes patients with concomitant use of long-acting nitrate therapy. Both VICTOR and real-world data will provide additional safety data and insight about vericiguat use in populations most likely to also derive benefit from long-acting nitrates.

Concomitant ARNI and SGLT2i Use

Uncertainty may arise as to whether vericiguat may provide benefit in patients already prescribed contemporary background HF therapies, including ARNIs and SGLT2is. A recently published meta-analysis on landmark HF therapies suggested potential additive benefits of vericiguat alongside novel therapies.[38] In the VICTORIA study, 15% (n = 731) of enrolled participants were prescribed ARNIs, a class that has also been shown to confer N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction as well as improvement in clinical outcomes in both ambulatory and hospitalized patients with HFrEF. A modest number of patients in this trial also received SGLT2is, given the period of trial recruitment and the timng of SGLT2 data in HFrEF, and thus further data are needed to better understand the incremental or synergistic value of all concomitant drug administration for patients at high risk for worsening HF events. No head-to-head comparisons have been performed between these drug classes proven to improve HF prognosis, but vericiguat, ARNI and SGLT2i classes all demonstrated absolute risk reduction in composite HF hospitalization cardiovascular mortality.[5–8] This is particularly important because baseline risk profile and subsequent annualized event rates for the primary outcomes varied across trials, with a much higher event rate in the VICTORIA trial, which was associated with a shorter median follow-up time.[16] In the VICTORIA trial, the treatment effect for primary composite endpoint of cardiovascular death or hospitalization due to HF was similar whether or not patients received sacubitril/valsartan.[8] Additionally, ARNIs were initiated more commonly after randomization in participants in the VICTORIA trial in the placebo group than in the vericiguat group, which would have influenced the primary results toward no difference in the overall population. Concomitant use of ARNIs did not alter the efficacy of vericiguat; there were similar tolerability and safety profiles between both groups. It is worth noting that the interpretation of postrandomization subgroups and nonrandomized therapy is particularly challenging.[24] These data suggest that all 3 classes are safe to use, yet data on specific sequencing are still warranted. In accordance with recently published guidelines, we recommend that eligible patients should be initiated on evidence-based therapies, including ARNIs and SGLT2is, and on vericiguat following worsening HF events, with dosages titrated toward target levels as tolerated for maximal improvement in HF prognosis (Supplementary Fig. 1).

Elevated Natriuretic Peptide Level

Although vericiguat, compared with placebo, reduced the primary outcome of composite cardiovascular death or hospitalization due to HF in patients with HFrEF in the VICTORIA trial, analyses of patients with elevated baseline NT-proBNP levels of $>$ 8000 pg/mL at time of randomization revealed no benefit or potential harm of vericiguat (HR for primary endpoint 1.16 [95% CI: 0.94−1.41).[39] Reduction of the composite primary outcome and its subcomponents of hospitalization due to HF and cardiovascular death were achieved by patients taking vericiguat who had NT-proBNP levels $<$ 8000 pg/mL, with greatest benefit in those with $<$ 4000 pg/mL, at time of randomization. Additionally, higher baseline NT-proBNP levels exhibited a nonlinear relationship with HF prognosis, with greatest adverse incremental risk at values $>$ 4000 pg/mL.[39] Extreme elevation of NT-proBNP levels may be reflective of incompletely stabilized HF[40] or may identify patients progressing toward end-stage HF, and it may prompt providers to further optimize volume status through diuretic therapy before starting vericiguat (Fig. 2). While there is potential of these findings to guide providers in determining ideal candidates for vericiguat therapy, future studies are warranted, given that prior attempts at natriuretic peptide-guided HF therapy implementation have yielded limited efficacy.[41]

Suggested Treatment Sequence and Clinical Scenarios

Clinically, there are certain time points in the disease progression of HFrEF at which initiation of vericiguat may be most favorable for improving the prognosis for those with HF.[14] In patients with a recent hospitalization for HF ($<$ 6 months), there was no statistically significant treatment interaction

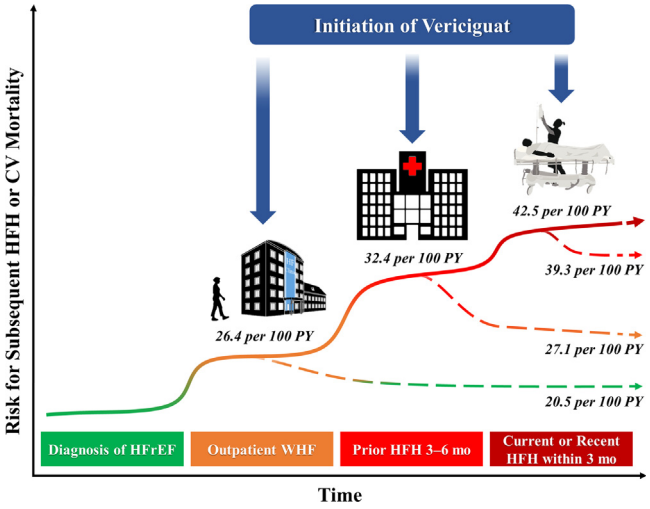


Fig. 3. Patient decline over time after sequential worsening heart failure events and vericiguat initiation time points. The benefit of vericiguat on clinical event rate reduction by episodes of WHF events, in patient-years, as adapted from Lam et al.[14] HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; WHF, worsening heart failure.

with subgroups defined by 30-day intervals for time between hospitalization and vericiguat initiation, including the in-hospital setting (interaction $P = 0.35$).[14] Here we discuss 3 examples of patients and a treatment scheme in which vericiguat should be started to improve downstream outcomes (Fig. 3). This strategy may facilitate the implementation of vericiguat into routine postworsening HF event management of patients with HFrEF with high risk of subsequent worsening HF events.

Patient 1: Established Diagnosis of HFrEF, Now Presenting With Outpatient Worsening HF Event

A 64-year-old woman of non-Black race with a history of type 2 diabetes and nonischemic cardiomyopathy was diagnosed with HFrEF more than 1 year ago (left ventricular ejection fraction of 35%). She was started on a beta-blocker, ARNI, SGLT2i, MRA, and daily furosemide therapy, with uptitration to maximally tolerated dosages of beta-blocker and ARNI 6 months prior to evaluation. She now presents urgently to the clinic with a 5-kg weight gain, lower-extremity swelling, shortness of breath, and requiring 2 pillows to sleep at night. Echocardiography demonstrates no change in cardiac function, and laboratory results reveal normal renal function and elevated NT-proBNP levels of 1723 pg/mL. She is provided intravenous furosemide therapy, resulting in marked improvement in symptoms, and her diuretic regimen is changed to twice-daily torsemide at a comparable higher dosage.

This patient presented with worsening HF as an outpatient. While provider or patients may perceive this as a mild event, but data from the VICTORIA trial demonstrated that worsening HF in outpatients means that they are at moderate risk for subsequent HF hospitalization and cardiovascular mortality rates of 26.4 per 100 patient-years; initiation of vericiguat decreases this risk to 20.5 per 100 paient-years (HR 0.78 [95% CI 0.60−1.02]).[14] This at-risk patient would be an ideal candidate for vericiguat therapy to reduce morbidity and mortality. Vericiguat may be started without the need for prolonged monitoring in a clinic. For those not on background therapy, patients may also be started on evidence-based HF therapies at low dosage in sequence,[30] although initiation of any single HF therapy should not be delayed beyond 1 month due to the high risk for subsequent cardiovascular events.[30] Follow-up clinic visits may be performed biweekly, in person or virtually, with close attention to volume status and uptitration of vericiguat to a target dosage of 10 mg.

Patient 2: Ambulatory Patient With Chronic HFrEF and Advanced Kidney Disease Who Was Recently Hospitalized for HF Within the Prior 6 Months

A 48-year-old man with nonischemic cardiomyopathy and chronic kidney disease presents to clinic. The patient was hospitalized for worsening HF 5 months ago. Since his hospitalization due to HF, the patient was started on beta-blocker and SGLT2i therapy, alongside titration of diuretic therapy. Long-acting nitrates were initiated but withdrawn due to persistent headache. The patient's systolic blood pressures in the clinic have ranged between 100−110 mmHg but without symptoms or orthostatic blood pressure changes. Laboratory studies reveal stable kidney function with estimated glomerular filtration rate of 28 mL/min/1.73m^2.

In this circumstance, vericiguat would be an ideal next therapy to reduce morbidity and cardiovascular events. Consideration of ARNI and MRA use is possible, but concerns at this time about reduced glomerular filtration rate prohibited their use, given that the guidance of current practice pathways noted issues with estimated glomerular filtration rates $<$ 30 mL/min/1.73m^2.[10] In ideal circumstances, these ARNIs and MRAs would have been considered earlier in the patient's clinical course following hospitalization, but this window may have been missed in the setting of advanced kidney disease. Additionally, concomitant hydralazine/long-acting nitrates may be offered in the setting of advanced kidney disease according to the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guidelines, yet this patient exhibited intolerance to these therapies.[10] Post hoc analyses of the VICTORIA trial demonstrated that patients with worsening HFrEF and

advanced kidney disease have displayed cardiovascular benefit with vericiguat use across renal-function categories until estimated glomerular filtration rates of 15 mL/min/1.73m^2 are reached.[28,42] This particular HFrEF population, while now stabilized, also requires focused attention, given their higher risk of subsequent cardiovascular events.[14] Frequent laboratory monitoring is not required beyond routine assessments, especially in patients prone to hyperkalemia, as in this case. Vericiguat may not only be ideal in improving HF prognosis in stabilized HFrEF, but in also potentially allowing for subsequent initiation of foundational evidence-based therapies (Supplementary Fig. 1).

Patient 3: Patient Hospitalized for Worsening HF Who Is Now Stabilized

A 79-year-old man with coronary artery disease and HFrEF is hospitalized for decompensated HF. He receives intravenous diuretic therapy for 4 days and experiences a reduction in weight of 10 kg. His background therapy of beta-blocker ARNI and SGLT2i is restarted prior to discharge. Patients like this are at particularly high risk for subsequent cardiovascular events at an absolute rate of 42.5 per 100 patient-years, with reduction to 39.3 per 100 patient-years following vericiguat initiation. We emphasize that patients should be started on vericiguat therapy during hospitalization once stabilized or immediately postdischarge, but prolonging hospitalization for drug initiation is not necessary in the case of vericiguat therapy, and patient tolerance and drug uptitration may ideally be assessed during the routine posthospitalization follow-up within 7−14 days. An important point worth emphasizing for providers and patients alike is that prior evidence from clinical trials and real-world data about other HF therapies consistently demonstrate that drug initiation should be started (when possible) prior to discharge. As indicated by evidence on in-hospital initiation of beta-blockers, ARNIs or MRAs, patients are more likely to remain adherent in the long term, and deferring the initiation of evidence-based therapies to outpatient care is more likely to result in patients never being prescribed these therapies by as much as 90% through 1 year after hospitalization.[35,43] Cumulative data about other HF therapies suggest a similar likelihood for success in long-term adherence when vericiguat is initiated in eligible patients while they are in the hospital. Additionally, certain patient profiles may be taken into consideration when prioritizing or sequencing HF medical therapy, particularly those with extreme elevations in natriuretic peptide levels,[44] although real-world data are needed to validate suggested practice patterns among patient profiles.

Guidance for Counseling Patients

Increasing the use of vericiguat in patients with recent worsening HF events will involve addressing patient barriers. Providers and health systems should actively work to identify eligible patients with HFrEF and to understand the advantages of initiating vericiguat, either during a hospitalization due to HF or in the outpatient setting after stabilization. Patients should be counseled about potential adverse effects of vericiguat therapy, with particular emphasis on maintaining adherence, with downstream improvements in subsequent urgent HF visits or hospitalizations. Providers may also emphasize the lack of need for regular laboratory monitoring and the possibility of monitoring medication tolerance through more contemporary and virtual-care modalities.

The benefits of starting vericiguat early are clear: (1) it provides critical benefit across worsening HF episode types, highlighting its priority when timing therapy among at-risk groups; (2) it is simple to administer (it is taken as a once-daily tablet, has minimal side effects and does not require laboratory monitoring); and (3) it exhibits no additional adverse blood pressure effects, including greater risk for symptomatic hypotension or syncope, which are important considerations when initiating other background HF therapy.[26,43]

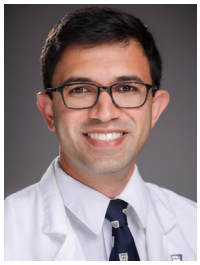
Patients must also be advised against its use and in altering therapy when prescribed other sGC stimulators (eg, riociguat), PDE-5 inhibitors (eg, sildenafil, vardenafil, and tadalafil), or medications that upregulate the NO pathway. Discussion of these drug-drug interactions may also provide opportunities to deprescribe other therapies that provide no change to either HF prognosis or patient quality of life with respect to comorbid conditions.

Having a standardized protocol in place to identify patients with HFrEF who are eligible for vericiguat and to support prescribing it can help to overcome many of the barriers that work against its use. These may also include engaging key stakeholders, such as inpatient providers (including physicians, advanced practice providers, and pharmacists), hospital administration, social workers, and care coordinators, to develop an interdisciplinary team approach, as this may be essential to implementing any sustainable change. Periodic assessment of and alterations to the implementation strategy are also important to changing local practices and eliminating potential barriers.

Conclusion

Vericiguat is an excellent therapy for patients with HFrEF and recent worsening HF events. As medical therapy for HFrEF continues to evolve, patients with worsening HF events will require focused attention

and tailored treatment strategies, given their exceedingly high risk for subsequent events within 30 days. Patient encounters during hospitalization after stabilization or in a clinic will provide key opportunities to mitigate such events by screening for vericiguat eligibility because it carries distinct advantages, including its strong safety and tolerability profile, its minimal to no side effects, and its lack of need for frequent laboratory monitoring. Together, integration of routine vericiguat use, alongside other components of HFrEF therapy, will allow providers and patients alike to develop and match therapeutic goals, including through in-person and telehealth hybrid care.



Lay Summary

Vericiguat is an approved novel medical therapy for the treatment of patients with heart failure with reduced ejection and with recent worsening heart failure events, including hospitalization for heart failure or requiring intravenous diuretics outside the hospital. There may exist potential concerns regarding the use of vericiguat, which may include the providers' lack of familiarity, clinical inertia, limited knowledge of monitoring responses to therapy, and concerns about potential adverse effects, as well as integration of its routine use during an era of in-person and telehealth hybrid ambulatory care. This review provides an overview of vericiguat therapy. It additionally proposes an evidence-based and practical guidance strategy for implementing its use in various clinical settings, and it summarizes counseling points for patients before its initiation and maintenance.

Disclosures

VNR is supported by a National Institutes of Health (NIH) Training Grant (NIH 5T32HL069749-18). JD is an advisor for and receives speaker fees from Bayer, Astra-Zeneca, and Vifor Pharma. FG is an advisor for Bayer, Ionis, Alnylam, Pfizer, and Pharmacosmos; receives speaker's fees from Boehringer-Ingelheim, Novartis, and Orion Pharma. RJM receives research support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Eli Lilly, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Medtronic, Merck, Novartis, Relypsa, Respicardia, Roche, Sanofi, Vifor, Windtree Therapeutics, and Zoll. MS reports consultancy fees from Novartis, Merck, Vifor Pharma, Abbott, Boehringer Ingelheim, Bioventrix, Servier, Novo Nordisk. JB has received honoraria for lectures/consulting from Novartis, Vifor, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, and Corvia; and research support for the department from Zoll, CVRx, and Abiomed. Funding for this manuscript was provided by Bayer AG, Berlin, Germany, according to Good Publication Practice guidelines. Bayer AG, Berlin, Germany, reviewed the paper and provided editorial comments, but the text was drafted and revised with full leadership by the academic authors, and the final submitted text was independent of the sponsors.

Acknowledgments

Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, reviewed the paper for scientific accuracy. Administrative assistance was provided by Evangelia Giannakouri, PhD, of Scion, London, UK, supported by Bayer AG, Berlin, Germany.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.10.431.

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