

# Vericiguat in Heart Failure with a Reduced Ejection Fraction: Patient Selection and Special Considerations

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**Abstract:** With improvement in the understanding of the pathophysiological mechanisms of heart failure with reduced ejection fraction (HFrEF), several drug classes have been developed targeting the renin–angiotensin–aldosterone system, the beta adrenergic system, and to a certain extent the nitric oxide pathway. Recently, the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors has resulted in a reduction in heart failure hospitalizations and cardiovascular death. As a result, SGLT-2 inhibitors are now the fourth drug class recommended as part of guideline-directed medical therapy (GDMT) for HFrEF. Soluble guanylate cyclase (sGC) stimulators, such as vericiguat, are a novel therapy targeting the cyclic guanosine monophosphate (cGMP) pathway with downstream effects including smooth muscle cell relaxation and a reduction in hypertrophy, inflammation, and fibrosis. The recently published VICTORIA trial has demonstrated a reduction in heart failure hospitalizations or cardiovascular death with vericiguat. Patients with a baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) values <8000 pg/mL may identify a sub-group most likely to benefit with addition of vericiguat. The cumulative benefit of quadruple therapy with the addition of sGC stimulators remains unknown. We review the mechanism of action for sGC stimulators, clinical trial data, and their real-world application to HFrEF patients with consideration of quintuple therapy.

**Keywords:** vericiguat, soluble guanylate cyclase stimulators, heart failure with reduced ejection fraction, guideline-directed medical therapy, VICTORIA

## Introduction

Heart failure (HF) remains the number one admission diagnosis identified by the Centers for Medicare and Medicaid, with a projected incidence in the United States of 3% by 2030. The number of patients with HF is expected to further rise from 5.7 million in 2012 to 8 million in the next 8 years.<sup>1</sup> HF with a reduced ejection fraction (HFrEF), defined as patients with a left ventricular ejection fraction (LVEF) of  $\leq 40\%$ , accounts for approximately 50% of overall HF cases.<sup>2</sup> Recent advances in guideline-directed medical therapy (GDMT) for HFrEF, including the use of angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, have resulted in reduced morbidity and mortality when fully optimized.<sup>3–5</sup>

Therapies for HFrEF have not historically addressed endothelial dysfunction or targeted the nitric oxide (NO) pathway. Decompensated HF results in inhibition of the nitric oxide-soluble guanylate cyclase (NO-sGC) pathway, hence restoration of sufficient sGC signaling could help attenuate HF pathology.<sup>6,7</sup> Vericiguat is a novel therapy targeting the cyclic guanosine monophosphate (cGMP) pathway by stimulating sGC leading to downstream effects including the relaxation of smooth muscle cells as well as reduced hypertrophy, inflammation, and fibrosis.<sup>8</sup> A recent Phase 3 trial treating higher risk HF patients with vericiguat demonstrated a significant reduction in a composite end point of cardiovascular (CV) death or first heart failure hospitalization (HFH).<sup>9</sup> The purpose of this review is to present the clinical trials and literature leading to the development of vericiguat with a focus on the clinical application of this drug in addition to GDMT.

## Role of cGMP in the Pathophysiology of HF

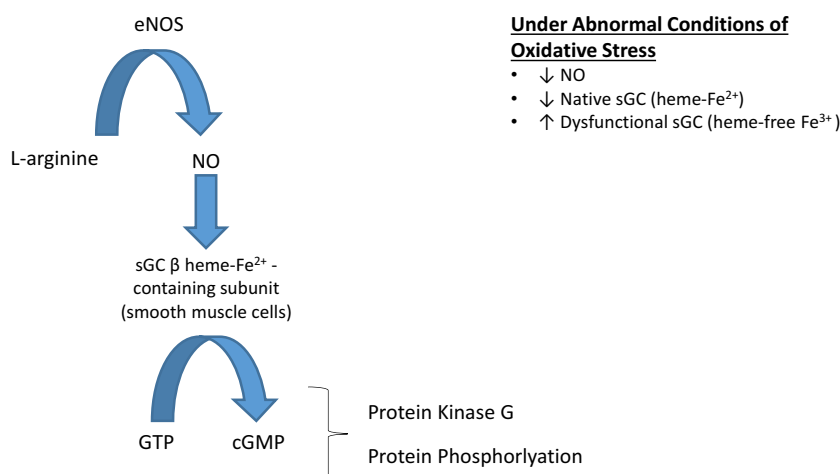
The NO-sGC-cGMP pathway plays an important role in the pathogenesis of HF.<sup>6,7,10</sup> The vascular endothelium normally generates NO which stimulates sGC mediated cGMP production. The endocardial endothelium, in addition to being sensitive to NO, regulates contractility and diastolic function by raising intracellular cGMP. NO is synthesized from L-arginine by 3 different enzymes including endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase, and inducible isoforms of nitric oxide synthase. Under typical physiological conditions, NO is produced by eNOS and diffuses rapidly to the smooth muscle cells in the vasculature, binding with the heme subunit of sGC, thus catalyzing the conversion of guanosine triphosphate (GTP) to the intracellular second messenger, cGMP.<sup>7,10</sup>

Cyclic GMP promotes the activation of the primary effector, protein kinase G (PKG). In cardiac myocytes, impaired PKG signaling has been demonstrated to promote left ventricular stiffness by hypophosphorylation of titin.<sup>11</sup> The stimulation of PKG results in downstream effects such as smooth muscle relaxation, vasodilation, inhibition of hypertrophy, reduction in inflammation and fibrosis, and improvement in cardiac remodeling (Figure 1).<sup>10</sup> In HF, the NO-sGC-cGMP pathway is impaired due to increased inflammation, oxidative stress, and endothelial dysfunction leading to reduced bioavailability of NO and higher conversion of sGC from its native heme-Fe<sup>2+</sup>-containing form, for which NO has a high affinity, to the oxidized, dysfunctional heme-free-Fe<sup>3+</sup>-form of sGC.<sup>7,10</sup> This impaired cGMP pathway in HF is thought to contribute to adverse effects on the heart, kidneys, and vasculature, promoting further disease progression.

## Pharmacology of Vericiguat

Vericiguat acts as a stimulator of sGC, acting synergistically with available NO but also binding to the heme-containing form of sGC, leading to an increase in cGMP levels with subsequent beneficial effects on cardiac and vascular function.<sup>8</sup> Alternatively, sGC activators, such as cinaciguat, act only on dysfunctional sGC independently of endogenous NO. Alterations in the chemical structure of vericiguat, when compared to other sGC stimulators such as riociguat, have resulted in improved pharmacokinetic stability and excellent oral bioavailability with a long half-life, allowing for once daily oral administration (Table 1).<sup>8,12</sup> Due to these unique pharmacokinetic and pharmacodynamic properties, vericiguat has a milder effect on blood pressure, compared with other sGC inducible drugs, with approximate reductions of 2 mm Hg in systolic blood pressure on average.<sup>9,13,14</sup> Adverse events that occurred more frequently in clinical studies with vericiguat compared to placebo include anemia (7.6% vs 5.7%) and symptomatic hypotension (9.1% vs 7.9%).<sup>9,15</sup>

### cGMP Pathway Under Normal Physiological Conditions



**Figure 1** Cyclic guanosine monophosphate (cGMP) pathway.

**Abbreviations:** eNOS, endothelial nitric oxide synthase; NO, nitric oxide; sGC, soluble guanylate cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate.

**Table I** sGC Stimulators and Activators

	Mechanism of Action	Maximum Dosing	Adverse Effects	Indications
<b>Stimulators</b>				
<b>Riociguat</b>	Binds to the heme-Fe <sup>2+</sup> beta subunit of soluble guanylate cyclase (native form of sGC)	2.5 mg PO TID	Hypotension anemia GERD	PAH CTEPH
<b>Vericiguat</b>	Synergistic with endogenous NO	10 mg PO daily	Hypotension anemia	HFrEF
<b>Activators</b>				
<b>Cinaciguat</b>	Binds to dysfunctional heme-free-Fe <sup>3+</sup> sGC regardless of endogenous NO availability	600 mcg/hr IV infusion	Hypotension	Experimental drug, most potent sGC activator

**Abbreviations:** sGC, soluble guanylate cyclase; NO, nitric oxide; TID, three times daily; PO, orally; GERD, gastroesophageal reflux disease; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; HFrEF, heart failure with reduced ejection fraction; IV, intravenous.

## Evolution of GDMT in HFrEF

Pharmacologic treatment of HFrEF has come a long way in the past 50 years. While initial strategies in the 1970s focused on vasodilation, the neurohormonal aspect of heart failure soon became the dominant focus of medical therapy over the subsequent decades.<sup>16</sup> The 1995 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Evaluation and Management of Heart Failure reflect this focus by giving angiotensin converting enzyme (ACE) inhibitors and hydralazine/isosorbide dinitrate a class I recommendation, while beta blockers were given a weaker recommendation.<sup>17</sup> By the time the 2005 guideline updates were written, large-scale randomized controlled clinical trials had cemented beta blockade, renin-angiotensin system (RAS) inhibition, as well as mineralocorticoid receptor antagonism (MRA) as class I therapies in heart failure with systolic dysfunction.<sup>18–23</sup> We are in an era of rapid growth in evidence for the use of therapies with a much wider range of pathophysiological pathways.

Reflecting the ever-changing landscape of medical therapy in this space, the next target to generate guideline changing data was neprilysin. Neprilysin is a naturally occurring peptide that is involved in the degradation of a variety of vasoactive agents including natriuretic peptides and bradykinin.<sup>24</sup> LCZ696 was designed as a combination of sacubitril (a neprilysin inhibitor) and valsartan and was shown in the PARADIGM-HF trial to be superior to enalapril alone in reducing the risk of death or HFH.<sup>4</sup> Of note, the patient population in this trial reflected the strong medical therapy of the time, with 93% of patients receiving beta blockers at the time of enrollment, although only a little more than half of the patients were taking an MRA.

The next evolution of heart failure therapies came with the serendipitous discovery of SGLT2 inhibitors. Found in the root bark of apple trees, phlorizin had been known since the 1930s to increase glucosuria by preventing reabsorption in the renal tubules. Synthetic versions of phlorizin were thought to be a novel therapeutic class for diabetes mellitus, until the EMPA-REG OUTCOME trial unexpectedly found empagliflozin to provide 35% relative risk reduction in heart failure hospitalizations against placebo in patients with diabetes and cardiovascular disease.<sup>25</sup> Two additional SGLT2 inhibitors, dapagliflozin and canagliflozin, also found similar preliminary results.<sup>26,27</sup> These findings ultimately led to the landmark EMPEROR-Reduced and DAPA-HF trials, which cemented these medications as part of the current armamentarium of guideline therapies.<sup>3,5,28</sup>

Despite the overwhelming amount of data supporting their efficacy, GDMT (currently “quadruple therapy,” encompassing a beta blocker, RAS inhibitor, MRA and SGLT2 inhibitor) usage remains infrequent in clinical practice due to a variety of factors including awareness gaps, therapeutic inertia, and side effect profiles.<sup>29</sup> Thus, novel therapies such as vericiguat must contend with both the potency of current medical therapy as well as the ongoing struggles of individualizing patient risk and side effect profiles to increase utilization.

## Clinical Trials Using sGC Stimulators or Activators in HFrEF

Prior to the development of vericiguat, both cinaciguat and riociguat were studied for their hemodynamic effects on patients with HFrEF (Table 2). In a Phase 2b trial, patients with acute decompensated HF who received cinaciguat had a significant reduction in pulmonary capillary wedge pressure (PCWP) at 8 hours compared to placebo; however, a high rate of hypotension in the cinaciguat group led to premature discontinuation of the trial.<sup>13</sup> Riociguat was evaluated in patients with pulmonary hypertension due to LV systolic dysfunction in the phase 2 LEPHT study.<sup>30</sup> Riociguat failed to meet the primary end point, placebo-corrected change from baseline to week 16 in mean pulmonary artery pressure (mPAP), compared to placebo ( $p = 0.10$ ). Two clinical trials (SOCRATES-REDUCED and VICTORIA) have evaluated the safety and efficacy of vericiguat in patients with HFrEF.

The phase 2 SOCRATES-REDUCED trial enrolled 456 patients with an LVEF of  $<45\%$ , a recent worsening HF event, and elevated natriuretic peptide levels.<sup>14</sup> Patients were randomized to placebo or 1 of 4 target doses with vericiguat

**Table 2** Clinical Trials Evaluating Soluble Guanylate Cyclase Stimulators or Activators in Heart Failure with a Reduced Ejection Fraction

Trial Name (Year of Publication)	Trial Design	Sample Size	Inclusion Criteria	Primary Outcomes	Results
COMPOSE programme (2013) <sup>13</sup>	Placebo-controlled, phase 2b, randomized dose ranging study	N=139	Current HFH, PCWP $>18$ mm Hg, LVEF $<40\%$	Change in PCWP at 8 hours	Significant reduction in mean PCWP vs placebo (mean PCWP $-7.7$ mm Hg with cinaciguat vs $-3.7$ mm Hg with placebo [ $p < 0.0001$ ]). High incidence of hypotension with cinaciguat (73%)
LEPHT (2013) <sup>30</sup>	Placebo-controlled, phase 2b, randomized dose ranging study	N=201	LVEF $\leq 40\%$ and mPAP $\geq 25$ mm Hg	Placebo-corrected change from baseline at week 16 in mPAP	No significant difference in mPAP change between riociguat group ( $-6.1 \pm 1.3$ mm Hg) vs placebo ( $-4.0 \pm 1.2$ mm Hg ( $p = 0.10$ ))
SOCRATES-REDUCED (2015) <sup>14</sup>	Placebo-controlled, phase 2b, dose ranging study	N=456	LVEF $<45\%$ , a recent worsening HF event, and elevated natriuretic peptide levels	Reduction in NT-proBNP values at 12 weeks	No significant difference in primary end point between pooled vericiguat group and placebo ( $p = 0.15$ ). Vericiguat 10 mg dose group had a significant reduction in NT-proBNP values compared to placebo group in exploratory secondary analysis ( $p = 0.048$ ). Rates of adverse events similar between placebo and vericiguat groups
VICTORIA (2020) <sup>9</sup>	Phase 3 randomized, placebo-controlled, double blind study	N=5050	LVEF $<45\%$ , NYHA class II–IV symptoms, elevated natriuretic peptide levels, and worsening HF event	Composite CV death or first HFH	Significant reduction in primary end point with vericiguat group (35.5%) versus placebo (38.5%, HR 0.90, $p = 0.019$ ). Vericiguat group had fewer total hospitalizations for heart failure (38.3 events per 100 patient-years) compared to placebo (42.4 events per 100 patient-years; HR 0.91; 95% CI 0.84–0.99; $p = 0.02$ ). No significant difference between treatment groups for CV or all-cause mortality. Similar rates of serious AEs between treatment groups (32.8% with vericiguat group and 34.8% with placebo group) with higher rates of anemia in the vericiguat group.

**Abbreviations:** HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; HF, heart failure; mPAP, mean pulmonary arterial pressure, NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; AE, adverse event.

(1.25 mg, 2.5 mg, 5 mg, or 10 mg once daily). The primary end point, change in log-transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels over 12 weeks, was not significantly different in the pooled vericiguat group compared to the placebo group ( $p = 0.15$ ). An exploratory secondary analysis of the primary end point suggested a dose-response relationship with higher vericiguat doses associated with a larger reduction in NT-proBNP values ( $p < 0.02$ ). A pairwise analysis of the vericiguat 10 mg dose demonstrated a significant reduction in log-transformed NT-proBNP values compared to placebo ( $p = 0.048$ ). Vericiguat therapy was not associated with a significant change in blood pressure or heart rate and overall adverse event rates were similar between placebo and vericiguat groups.

VICTORIA was a randomized, placebo-controlled, double-blind, phase 3 trial ( $n = 5050$ ), assessing the efficacy and safety of vericiguat in patients with HFrEF.<sup>9</sup> Patients were included if they had New York Heart Association (NYHA) functional class II–IV symptoms, elevated natriuretic peptide values, an LVEF of  $<45\%$ , and were hospitalized with HF within the last 6 months or received intravenous (IV) diuretics for decompensated symptoms. For patients who received vericiguat, the starting dose was 2.5 mg daily with the dose doubled every 2 weeks if tolerated to the maximum dose of 10 mg daily. Patients were continued on dose titration if the systolic blood pressure was  $\geq 100$  mm Hg. The dose of vericiguat was maintained if the systolic blood pressure was  $< 100$  mm Hg but  $\geq 90$  mm Hg and the dose was interrupted or decreased if the systolic blood pressure was  $< 90$  mm Hg. The primary end point was a composite of CV death or first HFH.

Over a median follow-up of 10.8 months, patients treated with vericiguat experienced a significant reduction in the primary end point (35.5% vs 38.5% in the placebo group; hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.83–0.98,  $p = 0.02$ ). The number needed to treat with vericiguat for 1 year to avoid one primary end point event was 24. The reduction of primary end point was driven by a reduction in first HFH events (27.4% in the vericiguat group vs 29.6% in the placebo group, HR 0.90; 95% CI 0.81–1.00) with no significant difference between treatment groups in CV or overall mortality. On sub-group analysis, the effect of vericiguat on the primary end point appeared consistent across many sub-groups including sex, geographic region, and NYHA class; however, the benefit appeared to be attenuated in patients with an age  $\geq 75$  years, with the highest quartile of NT-proBNP ( $> 5314$  pg/mL), or with LVEF between 40–45%, although specific  $p$ -values for interaction were not reported. Additional sub-analyses of the VICTORIA trial have demonstrated a consistent treatment effect of vericiguat regardless of baseline estimated glomerular filtration rate (eGFR), index worsening HF event, or history of atrial fibrillation.<sup>31–33</sup> Another sub-analysis of VICTORIA further evaluated the impact of baseline NT-proBNP values on the treatment effect of vericiguat.<sup>34</sup> Patients with baseline NT-proBNP values  $< 8000$  pg/mL treated with vericiguat, compared to placebo, showed a significant reduction in the primary end point (HR 0.85, 95% CI 0.76–0.95) including a reduction in CV mortality (HR 0.84, 95% CI 0.71–0.99), whereas patients with baseline NT-proBNP values  $\geq 8000$  pg/mL experienced no significant benefit in the primary end point with vericiguat treatment (HR 1.16, 95% CI 0.94–1.41).

Overall, vericiguat was well tolerated in VICTORIA with similar adverse event rates compared to placebo. The target dose of 10 mg with vericiguat was achieved in 89% of patients. Rates of symptomatic hypotension were numerically higher with vericiguat (9.1%) compared to placebo (7.9%), although this did not reach statistical significance ( $p = 0.12$ ). There was no significant difference between treatment groups for syncopal events. Rates of anemia occurred more frequently in patients treated with vericiguat (7.6%) compared with placebo (5.7%). At 16 weeks, the mean change in hemoglobin was mild at  $-0.24$  g/dL with vericiguat compared to placebo (95% CI,  $-0.312$  to  $-0.163$ ;  $p < 0.001$ ) and more patients experienced anemia with vericiguat (13.6%) compared to placebo (10.5%,  $p < 0.001$ ).<sup>35</sup> A time-updated analysis of hemoglobin from the VICTORIA trial showed no significant association with the treatment effect of vericiguat on the primary end point compared to placebo.<sup>35</sup>

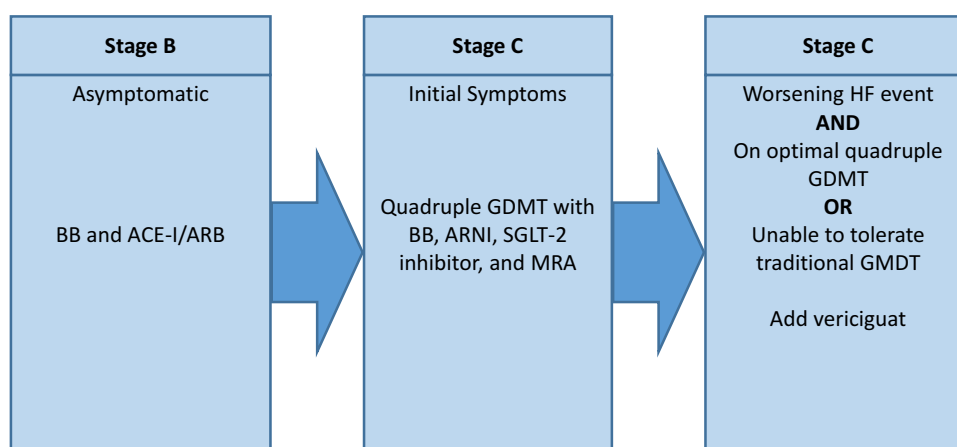
## Vericiguat in Clinical Practice

The VICTORIA trial demonstrated the efficacy and safety of vericiguat in patients with HFrEF with some unique features of this study. By design, VICTORIA included patients who were generally higher risk than those enrolled in previous clinical trials in patients with chronic HFrEF as evidenced by higher median NT-proBNP values (median 2816 pg/mL vs 1608 pg/mL in PARADIGM-HF) and more patients with NYHA class III or IV symptoms at baseline (40% vs 25% in PARADIGM-HF).<sup>4</sup> This is further demonstrated by a considerably higher event rate in VICTORIA (38.5% with

placebo) compared to PARADIGM-HF (26.5% with enalapril) over a shorter follow-up period (11 months in VICTORIA vs 27 months in PARADIGM-HF). The study also required enrollment within 6 months of HFH or within 3 months of IV diuretic therapy with most patients (67%) being enrolled within 3 months of HFH. Patients with a baseline systolic blood pressure < 100 mm Hg or on long-acting nitrates were excluded, and few Black patients (4.9%) and NYHA class IV patients (1.3%) were enrolled, limiting generalizability of results in these patient populations. Notably, 60% of patients were on background triple GDMT therapy, including beta-blockers, RAS inhibitor, and MRA, with low rate of ARNI utilization (15%) and unreported rates of SGLT-2 inhibitor use. Therefore, vericiguat was primarily studied in addition to triple GDMT therapy and further studies are warranted to ascertain additional benefit in combination with SGLT-2 inhibitors and an ARNI. Indeed, neprilysin inhibition enhances guanylate cyclase signaling via particulate guanylate cyclase, but it remains to be seen if this leads to synergistic clinical benefit or enhances the risk of adverse events.<sup>6</sup>

Currently, vericiguat is not addressed in the most recent 2021 update to the ACC Decision Pathway for HF as the medication was not approved by Food and Drug Administration (FDA) at the time of publication.<sup>28</sup> The 2021 European Society of Cardiology (ESC) HF guidelines provide one recommendation on the use of vericiguat, based upon the findings of the VICTORIA trial.<sup>36</sup> Vericiguat may be considered in symptomatic patients with HFrEF who have had worsening HF despite treatment with GDMT to reduce the risk of CV mortality or HFH (Class IIb; Level of Evidence: B).

With the recent advances in GDMT for HFrEF, it remains an ongoing challenge to position newer treatments, such as vericiguat, while understanding that traditional GDMT remains underutilized in clinical practice. Vericiguat joins an increasingly growing list of oral HFrEF medications that have been demonstrated to reduce HFH events without a significant impact on CV mortality, including digoxin, ivabradine, and, most recently, omecamtiv mecarbil.<sup>37–39</sup> Compared to other HF treatments, vericiguat requires only once daily administration, is well-tolerated with minimal hemodynamic impact, and does not require routine laboratory testing or therapeutic drug monitoring for use. Escalating a patient's underlying GDMT to include quadruple therapy, with a focus on ARNI and SGLT-2 inhibitor use, seems most rational in a majority of patients with HFrEF while reserving vericiguat in high risk patients who are already on optimal quadruple GDMT. Patients unable to tolerate traditional quadruple GDMT therapy (i.e chronic kidney disease or hyperkalemia) with a recent HFH may also be candidates for an additional HF medication, including vericiguat (Figure 2). Furthermore, patients with a recent worsening HF event and baseline NT-proBNP value < 8000 pg/mL appear to derive the greatest benefit with vericiguat. Ultimately, taking a personalized approach accounting for baseline risk, patient preference, cost, and pill burden is fundamental to amplifying the potential benefit with vericiguat.



**Figure 2** Place in therapy for vericiguat according to progression through the ACC/AHA stages B and C of heart failure.

**Abbreviations:** BB, beta blocker; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GDMT, guideline-directed medical therapy; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT-2, sodium-glucose cotransporter-2; MRA, mineralocorticoid receptor antagonist.



## Conclusion

Vericiguat is the newest addition to the armamentarium of therapies in the treatment of HFrEF. Clinical studies support the efficacy and safety of vericiguat as an add-on therapy for patients with HFrEF and a recent worsening HF event to reduce the incidence of CV death or HFH. Patients with baseline NT-proBNP values < 8000 pg/mL may derive the greatest benefit from the addition of vericiguat. Recent updates to the ESC HF guidelines endorse the use of vericiguat in patients with HFrEF who have worsening HF despite treatment with GDMT. Vericiguat may be considered in patients with a worsening HF event, despite being on optimal GDMT or in patients who cannot tolerate traditional GDMT.

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Dr. Kassis-George's disclosure includes speaking for Merck. Dr. Kanwar's disclosures include consulting for Bayer, Abiomed, and CareDx. The other authors (Drs. Verlinden and Fu) report no conflicts of interest related to this work.

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