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REVIEW ARTICLE

Soluble guanylate cyclase stimulators in patients with heart failure with reduced ejection fraction across the risk spectrum

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Patients with heart failure with reduced ejection fraction (HFrEF) have a high residual risk of adverse outcomes, even when treated with optimal guideline-directed medical therapy and in a clinically stable state. Soluble guanylate cyclase (sGC) stimulators have the potential to lower this risk by modifying the nitric oxide–sGC–cyclic guanosine monophosphate cascade – a pathophysiological pathway that has been targeted with limited success in HFrEF previously. Vericiguat, an sGC stimulator, was shown to improve outcomes in patients with HFrEF in the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial. However, this trial included patients with recently worsening disease. In this brief review, we discuss the rationale of evaluating sGC stimulators in lower-risk HFrEF patients. First, all key HFrEF medications have been evaluated in both higher- and lower-risk populations, and the treatment effect is not always consistent across the risk spectrum. Second, pre-clinical studies and post-hoc studies of the VICTORIA trial have suggested that sGC stimulators may have cardioprotective effects – these effects may be more apparent when the medication is initiated earlier in the disease process. Third, the effect of vericiguat on cardiovascular mortality remains uncertain and a trial with a longer follow-up in a lower-risk population may allow better assessment of its effect on cardiovascular mortality. Therefore, there is a pertinent need to investigate the effects of vericiguat in optimally treated, low-risk HFrEF patients (i.e. those without recently worsening heart failure).

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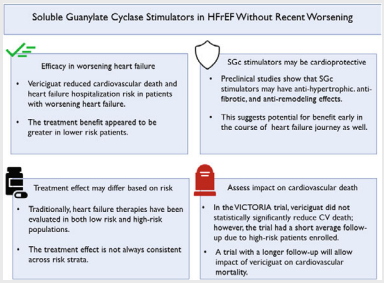
Graphical Abstract



Rationale to evaluate the efficacy of soluble guanylate cyclase (sGC) stimulators in heart failure with reduced ejection fraction (HFrEF) without recent worsening. CV, cardiovascular; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction.

Keywords HFrEF • Soluble guanylate cyclase stimulators • Vericiguat

Patients with heart failure with reduced ejection fraction (HFrEF) have a substantially increased risk of mortality and hospitalization.[1] Early initiation of guideline-directed medical therapy (GDMT) decreases this risk.[2] For patients with HFrEF, quadruple therapy with angiotensin receptor–neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors is now recommended as the standard of care.[3] However, patients with optimal medical therapy continue to have a substantial residual risk of adverse outcomes.[4] In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial, of the 3730 patients randomized, 1863 (50%) were in the empagliflozin arm and were receiving excellent background medical therapy with renin–angiotensin modulators (89%), beta-blockers (95%) and MRAs (70%).[5] Despite widespread quadruple therapy in the SGLT2 treatment arm, the residual 2-year risk of all-cause mortality and hospitalization for heart failure (HHF) was ~20% and ~19%, respectively.[6] This residual risk is much higher than other chronic cardiovascular diseases (*Figure 1*).[4] According to the 2021 European Society of Cardiology guidelines, 50–69-year olds should be considered at 'high risk' if their cumulative 10-year risk of atherosclerotic cardiovascular disease events exceeds 7.5%.[7] In contrast, the annualized mortality rate is 8–9% even in the lowest-risk stratum of HFrEF, that is, well-treated and clinically stable individuals with no prior history of HHF.[8] Many such patients experience sudden cardiac death without a preceding hospitalization. Contextualizing the residual risk associated with HFrEF against other common cardiovascular conditions highlights the need to develop therapies with novel mechanisms of action to further improve outcomes in this population.[4]

The original focus of treatment for HFrEF has been modulating the neurohormonal pathways, but recently alternate mechanisms, for example, SGLT2 inhibition, have been explored. The VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, evaluated the efficacy of vericiguat, a soluble guanylate cyclase (sGC) stimulator, in 5050 patients with recently worsening HFrEF.[9] Vericiguat, compared with placebo, demonstrated a significant reduction in the primary composite outcome of cardiovascular death (CVD) or HHF. However, the results from this trial cannot be extrapolated to a lower-risk HFrEF population without recently worsening disease. The ongoing VICTOR (A Study of Vericiguat [MK-1242] in Participants with Chronic Heart Failure With Reduced Ejection Fraction) trial (NCT05093933) will enroll patients with chronic HFrEF without a HHF in the past 6 months and without outpatient intravenous diuretic use in the past 3 months. In this brief review, we discuss the importance of evaluating sGC stimulators across the risk spectrum in HFrEF, considering its mechanism of action, findings from previous trials, and historical drug development patterns in HFrEF.

Physiology of the nitric oxide pathway, and its impairment in heart failure

The nitric oxide (NO) generated by the endothelium has important biologic effects.[10,11] NO readily diffuses across cell membranes into the vascular smooth muscle cells and binds to heme-containing (active) sGC, which catalyses the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). Downstream, this counteracts vasoconstriction and helps maintain perfusion to vital organs.[12] Expression of sGC is highest in the myocardial cells, and the sGC-generated cGMP causes ventricular relaxation, decreased contractility, and has anti-hypertrophic and anti-fibrotic effects.[13] The myocardial effects of the NO–sGC–cGMP pathway may be due to regulation of titin, a major determinant of myocardial stiffness (*Figure 2*).

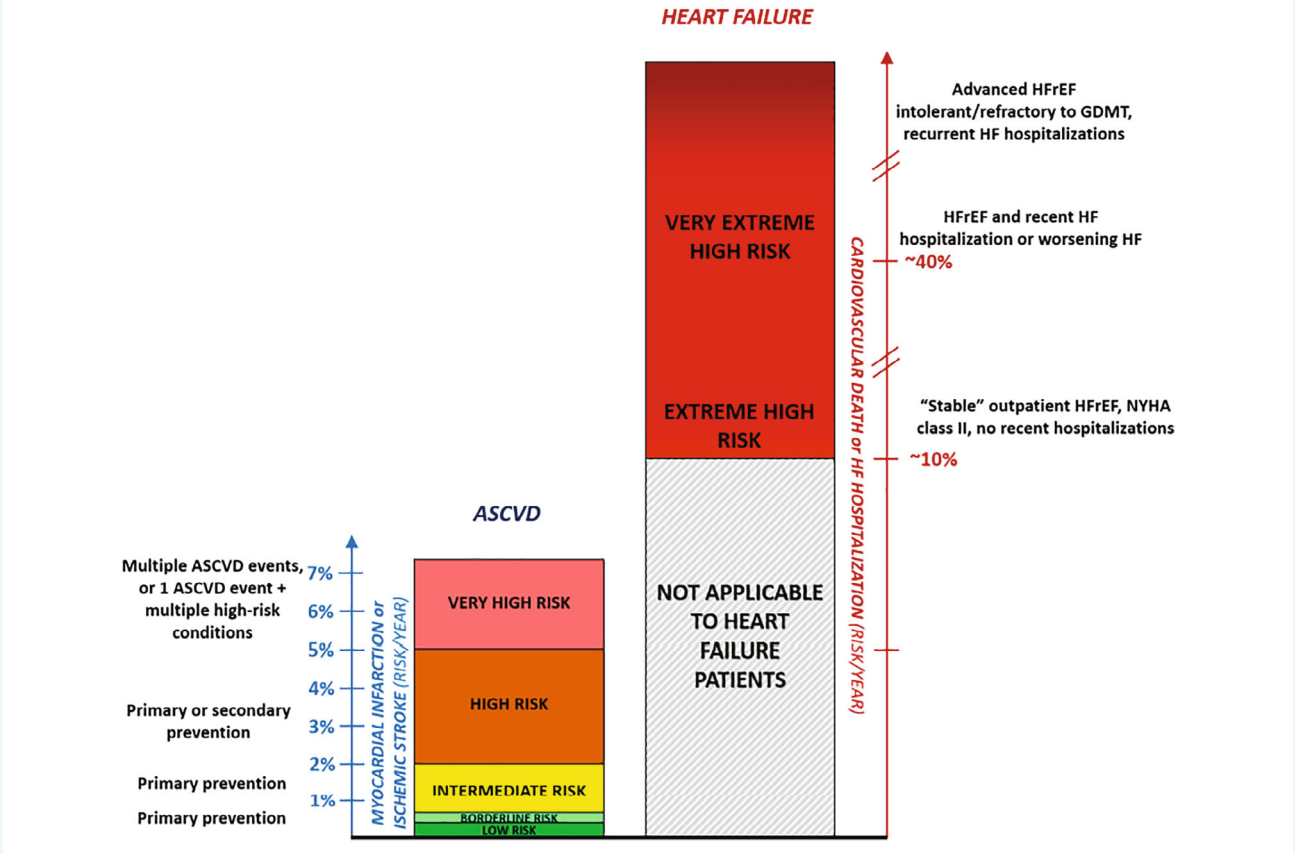


Figure 1 The risk associated with heart failure (HF) with reduced ejection fraction (HFrEF) versus atherosclerotic cardiovascular disease (ASCVD). GDMT, guideline-directed medical therapy; NYHA, New York Heart Association. Reproduced with permission from Greene *et al.*[4]

In HFrEF, the NO–sGC–cGMP pathway is impaired.[14] HFrEF is characterized by neurohormonal activation and systemic vasoconstriction, which overpowers NO–sGC–cGMP mediated vasodilatation. HFrEF is also associated with endothelial dysfunction due to oxidative stress, which results in reduced endothelial NO synthase activity and an absolute insufficiency of NO. The functionality of the NO–sGC–cGMP pathway is dependent on the redox status of the body. Increased oxidative stress in HFrEF disrupts the signalling cascade by varying levels of inactivation of NO, sGC and cGMP.[14] The downstream effects include increased vascular tone, stiffness, afterload, and left ventricular pressures. Coronary microcirculation is impaired, predisposing myocardial cells to ischaemic injury. Impairment of the NO–sGC–cGMP pathway leaves the myocardium vulnerable to hypertrophy and myocardial fibrosis.

Previous attempts to counter nitric oxide signalling abnormalities

The use of nitrates has been tested as a method to up-regulate cGMP levels in HFrEF. However, this approach is limited due to the development of tolerance and the potential for increased rather than decreased oxidative stress.[15] Nitrates appear to be most effective in Black patients in combination with hydralazine.[15] Intracellular cGMP levels may be increased by inhibiting phosphodiesterase, the enzyme responsible for cGMP degradation; however, this relies on sufficient endogenous NO and cGMP production, which is impaired in HFrEF. Clinical trials have not yielded encouraging findings with phosphodiesterase inhibitors in HFrEF and have, in fact, suggested increased morbidity and mortality.[16,17]

Soluble guanylate cyclase as a therapeutic target

Direct sGC stimulators provide an alternative pharmacological modulation of the NO–sGC–cGMP pathway. sGC stimulators bind to the heme-containing (active) form of sGC and stimulate cGMP formation. Also, they act in synergy with NO, increasing the sensitivity of sGC to the NO that is bioavailable. Pre-clinical studies suggested that direct activation of sGC may address several of the pathophysiologic mechanisms in HFrEF, without the adverse effects seen with nitrates and phosphodiesterase inhibitors. In the blood vessels, sGC stimulators may increase compliance and decrease remodelling (*Figure 3*). Increased renal perfusion can subsequently

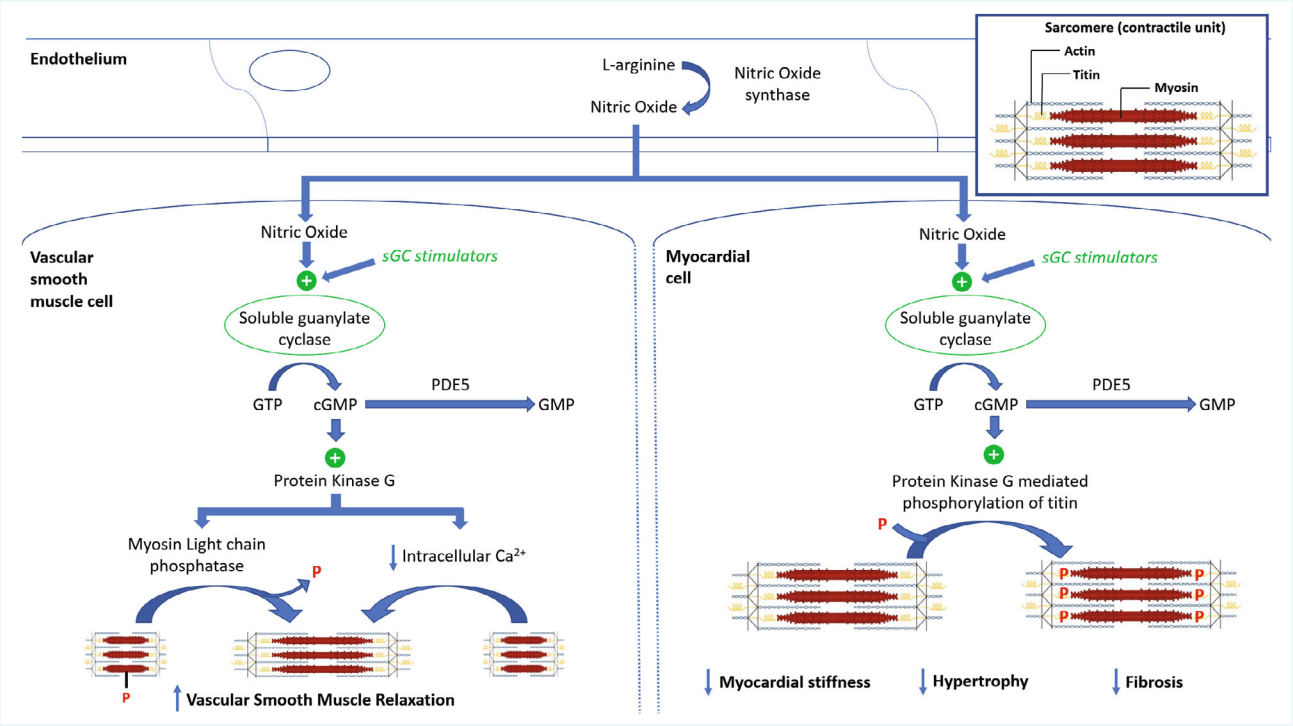


Figure 2 The nitric oxide–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) cascade pathway in vascular smooth muscle cells and myocardial cells, and the action of sGC stimulators. Ca^{2+}, calcium; GTP, guanosine triphosphate; P, phosphate; PDE, phosphodiesterase.

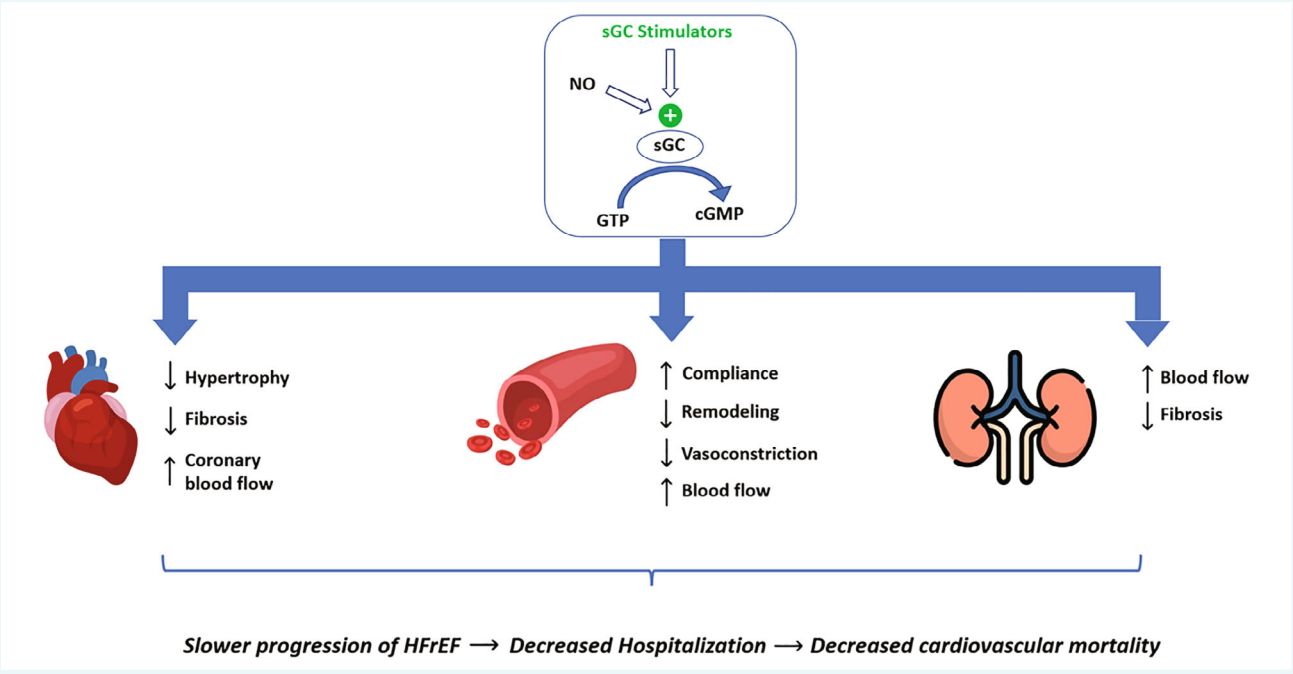


Figure 3 Potential clinical benefits of soluble guanylate cyclase (sGC) stimulators in patients with heart failure with reduced ejection fraction (HFrEF). cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide.

decrease neurohormonal activation and progression to kidney disease. In the myocardium, sGC stimulators may slow or reverse left ventricular hypertrophy and fibrosis. Evidence suggests that these anti-remodelling effects of sGC stimulators are independent of its effect on vascular tone.[18] These beneficial mechanisms of sGC stimulators are unique from neurohormonal blockers and may result in additive or synergistic effects when used simultaneously.

Clinical trials with soluble guanylate cyclase stimulators in heart failure

Following the positive findings in pre-clinical studies, the phase II SOCRATES-REDUCED (Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study) trial evaluated the safety and efficacy of the sGC stimulator vericiguat (tested in four doses ranging from 1.25 to 10 mg daily) in patients with worsening chronic HFrEF. An exploratory secondary analysis of the trial showed a dose–response relationship, with higher vericiguat doses being associated with greater reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) compared to placebo.[19] Subsequently the VICTORIA trial evaluated the safety and efficacy of vericiguat in 5050 patients with worsening HFrEF with either a recent hospitalization within 6 months or outpatient intravenous diuretic treatment within 3 months.[9] Vericiguat demonstrated a significant reduction in the primary composite outcome of CVD/HHF (hazard ratio 0.90; 95% confidence interval 0.82–0.98; $p = 0.02$). The absolute risk reduction in the primary outcome was 4.2 events per 100 patient-years, translating to a number needed to treat of 24 to prevent one CVD/HHF event over a year.

Generalizability of VICTORIA trial results

The VICTORIA trial enrolled a subset of patients with worsening HFrEF.[9] The absolute risks of CVD/HHF and all-cause mortality in the trial population were 38 and 17 per 100 patient-years, respectively, which is considerably higher than in trials that enrolled stable outpatient populations. In the VICTORIA trial, vericiguat led to greater improvement in patients in the lower three quartiles of natriuretic peptide levels at baseline. Another analysis demonstrated a trend towards greater benefit in patients who had a longer duration since their most recent HHF.[20] Thus, amongst patients enrolled in the VICTORIA trial, vericiguat appeared to be more effective in patients who were relatively stable. Thus, SGc stimulators may provide greater benefit in lower-risk patients who were not enrolled in the VICTORIA trial, and this merits evaluation.

The uncertain effect of soluble guanylate cyclase stimulators on cardiovascular mortality

The effect of sGC stimulators on cardiovascular mortality in patients with HFrEF remains unclear. In the VICTORIA trial, CVD events were numerically lower in the vericiguat arm and contributed to the statistical significance of the composite endpoint; however, cardiovascular mortality did not reach statistical significance by itself. One plausible explanation for this is that the follow-up time of VICTORIA (median 10.8 months) was not enough to detect a reduction in mortality. Indeed, a separation of the Kaplan–Meier curve was noted late in the VICTORIA trial (after ~22 months of follow-up), which supports this hypothesis.[21] Evaluating sGC stimulators in a trial with a longer follow-up in patients without worsening heart failure may better elucidate its effects on mortality. Moreover, the potential anti-remodelling effects of sGC stimulators may reduce the incidence of fatal arrhythmias and prevent sudden cardiac death in heart failure. The existence of this effect can be better tested in a lower-risk HFrEF population, which has a higher ratio of sudden cardiac death to pump failure death.[4]

Need for developing evidence across the spectrum of risk

For all key HFrEF pharmacotherapies, randomized trials have generally been conducted in both the higher- and lower-risk populations. The specific criteria used to determine risk have varied, with trials of some agents evaluating risk based on New York Heart Association class (e.g. EMPHASIS-HF vs. RALES),[22,23] while others have utilized time since last HHF (e.g. DAPA-HF vs. SOLOIST-WHF).[6,24] Regardless of the axis of risk used, most agents have been evaluated in populations with low as well as high absolute risk of clinical events (*Figure 4*).[25,26] This is important since difference in risk may modify the treatment effects of a drug. On the one hand, high-risk patients may have more 'opportunity' for improvement. On the other hand, these patients may be too sick to realize benefit from a novel agent. While MRA and angiotensin-converting enzyme inhibitor (ACEi) trials were first conducted in higher-risk patients, beta-blocker, ARNI, and SGLT2 inhibitor trials, first targeted a lower-risk population. The efficacy of beta-blockers and SGLT2 inhibitors was consistent in both low-to-intermediate risk, as well as high-risk HFrEF populations.[5,6,21,27–29] Although by and large GDMT has been beneficial in HFrEF, the degree of benefit has not always been consistent across the risk spectrum, for example, ACEi demonstrated a 27% relative risk reduction in mortality in the higher-risk population in the CONSENSUS trial,[30] but a 16% relative risk reduction in a lower-risk population enrolled in the SOLVD-T trial.[31] Conversely, ARNI improved outcomes in a moderate-risk population, but this was not replicated in the very high-risk HFrEF patients.[8,32]

Need to assess soluble guanylate cyclase modulation in lower-risk patients

Given the above background, there are reasons to evaluate the efficacy of vericiguat in lower-risk patients with HFrEF who have not experienced a recent worsening event (*Graphical Abstract*).

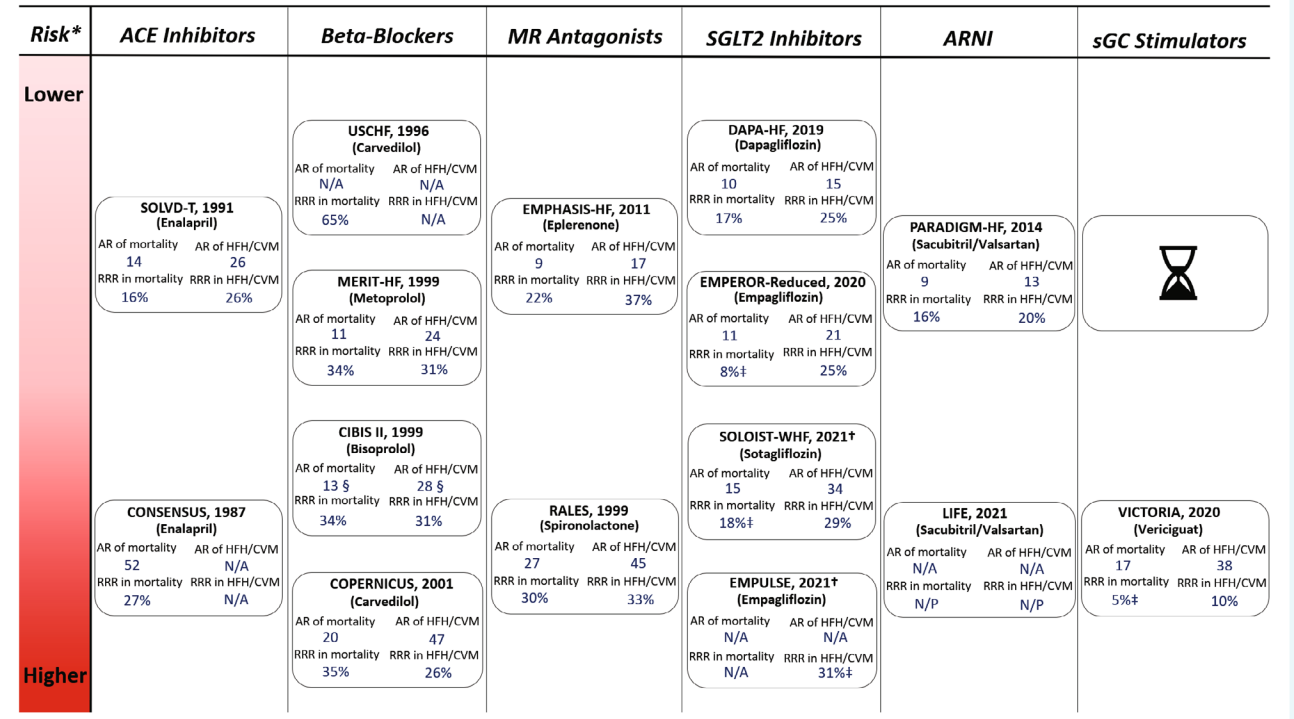


Figure 4 The absolute risk (AR) of populations enrolled in pivotal heart failure with reduced ejection fraction clinical trials with different drug classes. Absolute risks are presented for the entire trial population. Absolute risks are as estimated by Van Spall *et al.*[25] and Skali *et al.*[26] ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor–neprilysin inhibitor; CIBIS II, The Cardiac Insufficiency Bisoprolol Study II; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EMPULSE, Empagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalized for Acute Heart Failure Who Have Been Stabilized; HFH/CVM, composite of first heart failure hospitalization or cardiovascular mortality; LIFE, Entresto™ (LCZ696) in Advanced Heart Failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MR, mineralocorticoid receptor; N/A, not available; N/P, not powered for clinical outcomes; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; RRR, relative risk reduction; sGC, soluble guanylate cyclase; SGLT2, sodium–glucose cotransporter 2; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; SOLVD-T, Studies of Left Ventricular Dysfunction-Treatment; USCHF, U.S. Carvedilol Heart Failure Study; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction. *Not to scale; §ARs available only for the placebo arm; †populations of these trials include patients with both heart failure with reduced and preserved ejection fraction; ‡not statistically significant.

First, not all therapies have shown consistent presence and extent of benefit across the spectrum of risk in HFrEF. Second, post-hoc analyses suggested that the effect of vericiguat was modified by risk within the VICTORIA trial population with an indication of greater benefit in patients at lower risk. Third, mechanism of action as well as benefits of sGC stimulators seen in pre-clinical studies are preventive in nature, such as anti-hypertrophic and anti-fibrotic effects in the heart and anti-remodelling effects in blood vessels. This suggests that the drug may also be useful in preventing the progress of HFrEF if initiated in the low-risk phase. Fourth, a trial of vericiguat with a longer follow-up and a lower-risk population may allow better assessment of its effect on cardiovascular mortality. Fifth, the VICTORIA trial enrolled patients with a recent worsening HFrEF event and was conducted when ARNI therapy was just being introduced into practice, and prior to the demonstration of benefit of SGLT2 inhibitors in HFrEF. Incremental benefit of sGC stimulators on modern standard of care therefore needs to be evaluated.

While it may seem logical that sGC stimulators can further reduce the high residual risk seen even in lower-risk HFrEF, this nevertheless requires testing in a contemporary trial of patients optimally treated with currently accepted GDMT. This is important especially in an era of increasing costs and polypharmacy.

The VICTOR trial

The VICTOR trial is a phase 3, randomized, double-blind, placebo-controlled clinical trial, which will evaluate the safety and efficacy of vericiguat in a lower-risk HFrEF population, compared

with the VICTORIA trial. The VICTOR trial is expected to enrol an estimated 6000 patients. Patients will be eligible for inclusion if they have (i) a history of chronic heart failure (New York Heart Association class II to IV); (ii) a left ventricular ejection fraction ≤40%; (iii) elevated NT-proBNP levels; and (iv) No HHF in the past 6 months and no intravenous diuretic therapy in the past 3 months before randomization. Participants will be randomized to either vericiguat (started at 2.5 mg and titrated to 5 and 10 mg) or matching placebo. The primary outcome of interest is first HHF/CVD. Other outcomes that will be evaluated include first HHF, CVD, total HHF, all-cause mortality and composite of all-cause mortality or HHF. In the higher-risk population of the VICTORIA trial, CVD events comprised of a relatively smaller component of the primary outcome (ratio of HHF:CVD >3) due to the short average follow-up in this cohort with high risk for hospitalization. In contrast, in trials with more stable HFrEF populations, the HHF:CVD ratio is ∼1. Thus, although the VICTOR trial may not be powered to study CVD and the overall CVD event rate may be lower due to advances in background therapy, this outcome is likely to play a more prominent role in the primary endpoint in this particular patient population and will better illustrate the effect of vericiguat on it. Like VICTORIA, VICTOR is an event-driven trial; however, the events will likely take longer to accumulate in the relatively stable population of VICTOR, and thus follow-up times will be longer. The trial is expected to conclude mid-2025.

Conflict of interest: J.B. is a consultant to Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Cardior, CVRx, G3 Pharma, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, and Vifor. K.J.A reports grants from NIH, Merck, Bayer, PCORI, outside the submitted work. R.O.B is a full-time employee of Merck. M.P.B was supported by the American Heart Association Strategically Focused Research Network in Vascular Disease under award numbers 18SFRN3390085 (BWH-DH SFRN Center) and 18SFRN33960262 (BWH-DH Clinical Project). J.A.E reports study funding from Novartis and Servier as well as grants from Merck, Bayer, Trevena, and Amgen. C.F. is a full-time employee of Bayer AG. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the advisory board, steering committee, or executive committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global, Radcliffe Group, and Corpus; and is co-founder and non-executive director of Us2.ai. J.L. has received research support from AstraZeneca, Sensible Medical, and Volumetrix; and has received consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Boston Scientific, CVRx, Cytokinetics, Edwards Lifesciences, Impulse Dynamics, V-Wave, and Vifor. E.F.L. reports research grant support from Novartis; consulting fees from Amgen, Dal-Cor, and Merck. C.J.M. is a full-time employee of Merck. R.J.M. has received 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. M.S. has received personal fees from Novartis during the conduct of the study and personal fees from Bayer, Abbott, Merck, AstraZeneca, Vifor Pharma and Boehringer outside the submitted work. J.U. reported receiving grants from Heartflow, Lantheus Medical Imaging, Abbott Laboratories, and the National Heart, Lung, and Blood Institute and participating in clinical trial committee work for Pfizer/GlaxoSmithKline and HeartFlow outside the submitted work. A.A.V. received honoraria and/or research support from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Bayer, Cytokinetics, Merck, Novartis, Novo Nordisk, Roche Diagnostics. F.Z. reports personal fees from Janssen, Novartis, Boehringer Ingelheim, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer, and Cellprothera; and other support from CVCT and Cardiorenal. All other authors have nothing to disclose.

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