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Soluble Guanylate Cyclase Stimulators in Patients with Heart Failure with Reduced Ejection Fraction Across the Risk Spectrum

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Accepted Article

Abstract

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. Sodium 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 (A Study of Vericiguat in Participants 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, preclinical 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 recent worsening heart failure).

Accepted Article

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 With 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 two-year risk of all-cause mortality and heart failure hospitalization was ~20% and ~19%, respectively (6). This residual risk is much higher than other chronic cardiovascular diseases (Figure 1) (7). 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 (ASCVD) events exceeds 7.5% (8). In contrast, the annualized mortality rate is 8-9% even in the lowest-risk stratum of HFrEF, i.e., well-treated and clinically stable individuals with no prior history of heart failure hospitalization (9). 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 (7).

The original focus of treatment for HFrEF has been modulating the neurohormonal pathways, but recently alternate mechanisms, e.g., SGLT2 inhibition, have been explored. The VICTORIA (A Study of Vericiguat in Participants 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 (10). Vericiguat, compared with placebo, demonstrated a significant reduction in the primary composite outcome of cardiovascular death or hospitalization for HF (CVD/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 with neither a heart failure hospitalization nor outpatient intravenous diuretic use in the past 6 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 NO generated by the endothelium has important biologic effects (11, 12). NO readily diffuses across cell membranes into the vascular smooth muscle cells and binds to heme-containing (active) sGC, which catalyzes the conversion of guanosine triphosphate to cGMP. Downstream, this counteracts vasoconstriction and helps maintain perfusion to vital organs (13). 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 (14). The myocardial effects of the NO-sGC-cGMP pathway may be due to regulation of titin, a major determinant of myocardial stiffness (Figure 2).

In HFrEF, the NO-sGC-cGMP pathway is impaired (15). HFrEF is characterized by neurohormonal activation and systemic vasoconstriction, which overpowers NO-sGC-cGMP mediated vasodilation. HFrEF is also associated with endothelial dysfunction due to oxidative stress, which results in reduced endothelial NOS 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 signaling cascade by varying levels of

inactivation of NO, sGC and cGMP (15). The downstream effects include increased vascular tone, stiffness, afterload, and left ventricular pressures. Coronary microcirculation is impaired, predisposing myocardial cells to ischemic injury. Impairment of the NO-sGC-cGMP pathway leaves the myocardium vulnerable to hypertrophy and myocardial fibrosis.

Previous Attempts to Counter Nitric Oxide Signaling Abnormalities

The use of nitrates has been tested as a method to upregulate 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 (16). Nitrates appear to be most effective in Black patients in combination with hydralazine (16). 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 (17, 18).

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. Preclinical 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 remodeling (Figure 3). Increased renal perfusion can subsequently 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-remodeling effects of sGC stimulators are independent of its effect on vascular tone

(19). 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 preclinical studies, the phase-II SOCRATES-Reduced (Phase IIb Safety and Efficacy Study of Four Dose Regimens of BAY1021189 (vericiguat) in Patients with Heart Failure with Reduced Ejection Fraction Suffering From Worsening Chronic Heart Failure) trial evaluated the safety and efficacy of the sGC stimulator vericiguat (tested in 4 doses ranging from 1.25 mg 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 NT-proBNP compared to placebo (20).

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 (10). Vericiguat demonstrated a significant reduction in the primary composite outcome of CVD/HHF (hazard ratio 0.90; 95% confidence interval: 0.82 to 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 (10). The absolute risks of CVD/HHF and all-cause mortality in the trial population were 17 and 38 per 100-patient years, respectively, which is considerably higher than in trials that enrolled stable outpatient population of patients. 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 HF

hospitalization (21). 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 Inhibitors on Cardiovascular Mortality

The effect of sGC stimulators on cardiovascular mortality in patients with HFrEF remains unclear. In the VICTORIA trial, cardiovascular deaths 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 (25). Evaluating sGC stimulators in a trial with a longer follow-up in patients without worsening HF may better elucidate its effects on mortality. Moreover, the potential anti-remodeling effects of sGC stimulators may reduce the incidence of fatal arrhythmias and prevent sudden cardiac death in HF. 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 (7).

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 has varied, with trials of some agents evaluating risk based on NYHA class (e.g., EMPHASIS-HF vs RALES), while others have utilized time since last HFH (e.g., DAPA-HF vs SOLOIST-WHF). 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). 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 ACEi trials were first conducted in higher risk patients, beta-blocker, angiotensin receptor neprilysin inhibitors (ARNI), and SGLT2i 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, 22-26). Although by and large GDMT has been beneficial in HFrEF, the degree of benefit has not always been consistent across the risk spectrum, e.g., ACEis demonstrated a 27% relative risk reduction in mortality in the higher-risk population in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial, but a 16% relative risk reduction in a lower-risk population enrolled in the SOLVD-T (Studies of Left Ventricular Dysfunction-Treatment) trial. Conversely, ARNI improved outcomes in a moderate-risk population, but this was not replicated in the very high-risk HFrEF patients (9, 27).

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). 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 preclinical studies are preventive in nature, such as anti-hypertrophic and anti-fibrotic effects in the heart and anti-remodeling 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 SGLT2i 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 guideline-directed medical therapy. This is important especially in an era of increasing costs and polypharmacy.

The VICTOR trial

The VICTOR trial, page 11: “VICTOR 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 enroll an estimated 6000 patients. Patients will be eligible for inclusion if they have (i) a history of chronic HF (New York Heart Association Class II to IV); (ii) a left ventricular ejection fraction <40%; (iii) elevated NT-proBNP levels; and (iv) no HFrEF or outpatient IV diuretic therapy in the 3 months before randomization. Participants will be randomized to either vericiguat (started at 2.5mg and titrated to 5mg and 10mg) or matching placebo. The primary outcome of interest is first HFrEF/CV death. Other outcomes that will be evaluated include first HFrEF, CV death, total HFrEF, all-cause mortality and composite of all all-cause mortality or HFrEF. In the higher-risk population of the VICTORIA trial, CV death events comprised of a relatively smaller component of the primary outcome (ratio of HFrEF:CV deaths >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 HFrEF:CV death ratio is ~1. Thus, although the VICTOR trial may not be powered to study CV death and the overall CV death 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.”

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Figure Legends

Figure 1: The risk associated with heart failure with reduced ejection fraction versus atherosclerotic cardiovascular disease

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Figure 2: The NO-sGC-cGMP pathway in vascular smooth muscle cells and myocardial cells, and the action of sGC stimulators.

Abbreviations: sGC: Soluble guanylate cyclase; GTP: Guanosine triphosphate; cGMP: Cyclic guanosine monophosphate; PDE: Phosphodiesterase; Ca²⁺: calcium; P = phosphate

Figure 3: Potential clinical benefits of sGC stimulators in patients with HFrEF.

Abbreviations: sGC: Sodium guanylate cyclase; NO: Nitric oxide; GTP: Guanosine triphosphate; cGMP: Cyclic guanosine monophosphate; HFrEF: Heart failure with preserved ejection fraction

Figure 4: The absolute risk of populations enrolled in pivotal HFrEF clinical trials with different drug classes

Absolute risks are presented for the entire trial population. Absolute risks are as estimated by Spall et al, *EJHF*, May 2021 and Skali et al, *Circulation*, Nov 2006.

Abbreviations: N/A: Not available; N/P: Not powered for clinical outcomes; AR: Absolute risk; RRR: Relative risk reduction;

HFH/CVM: Composite of first heart failure hospitalization or cardiovascular mortality; ACE: Angiotensin converting enzyme; MR:

Mineralocorticoids; SGLT2: Sodium-glucose cotransporter 2; ARNI: Angiotensin receptor/neprilysin inhibitor; SGc: Sodium guanylate cyclase. SOLVD-T: Studies of Left Ventricular Dysfunction – Treatment; CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study; USCHF: U.S. Carvedilol Heart Failure Study; MERIT-HF: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; CIBIS-II: The Cardiac Insufficiency Bisoprolol Study II; COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; RALES: Randomized Aldactone Evaluation Study; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Reduced: EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; SOLOIST-WHF: Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; EMPULSE: EMPagliflozin 10 mg compared to placebo, initiated in patients hospitalised for acUte heart failUre who have been StabilisEd; PARADIGM-HF: Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure; LIFE: EntrestoTM (LCZ696) In Advanced Heart Failure; VICTORIA: A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction.

*Not to scale § Absolute risks available only for the placebo arm † Populations of these trials include patients with both HFrEF and heart failure with preserved ejection fraction ‡ Not statistically significant

Graphical Abstract: Rationale to evaluate the efficacy of SGc stimulators in HFrEF without recent worsening.

Abbreviations: SGC: Sodium guanylate cyclase; HFrEF: heart failure with reduced ejection fraction; VICTORIA: A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction; CV: cardiovascular

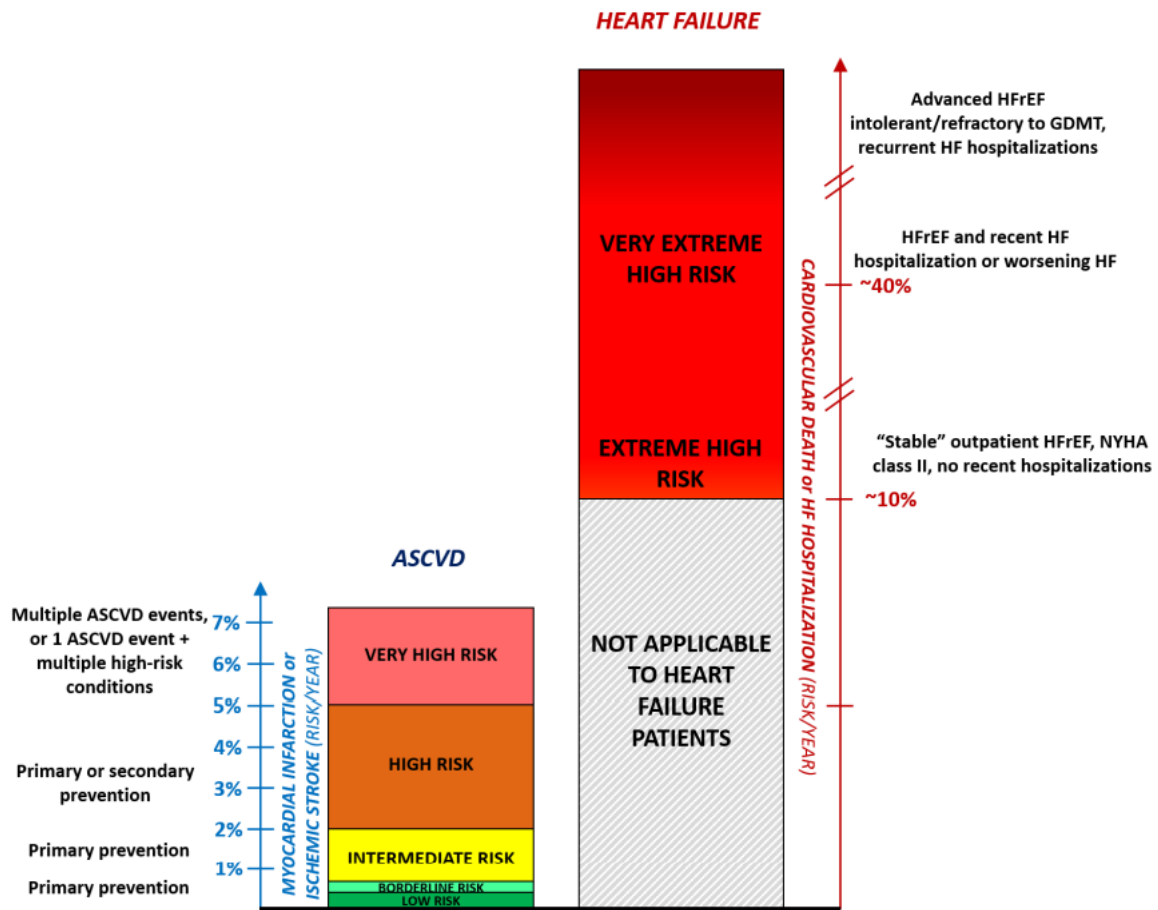
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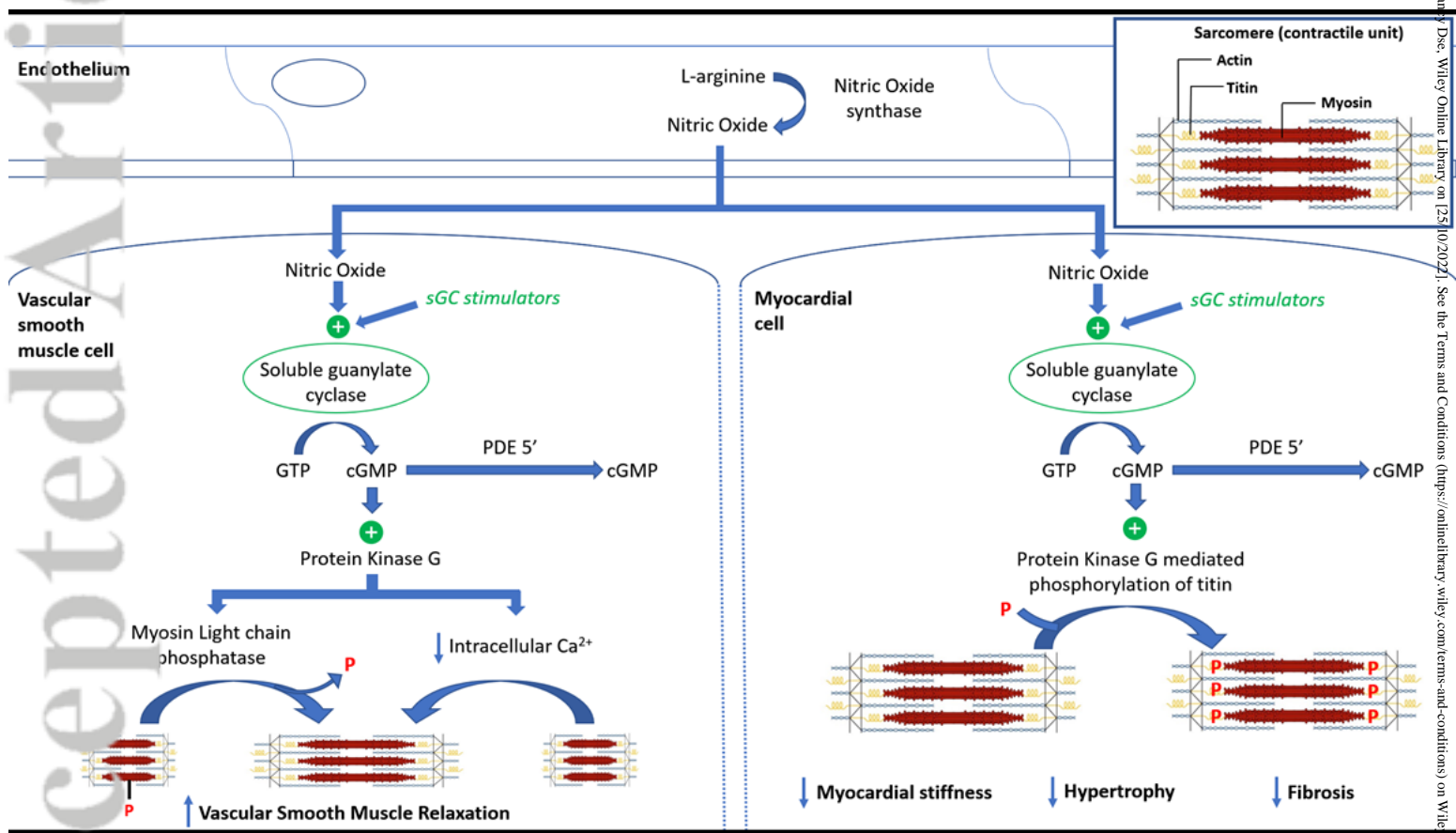
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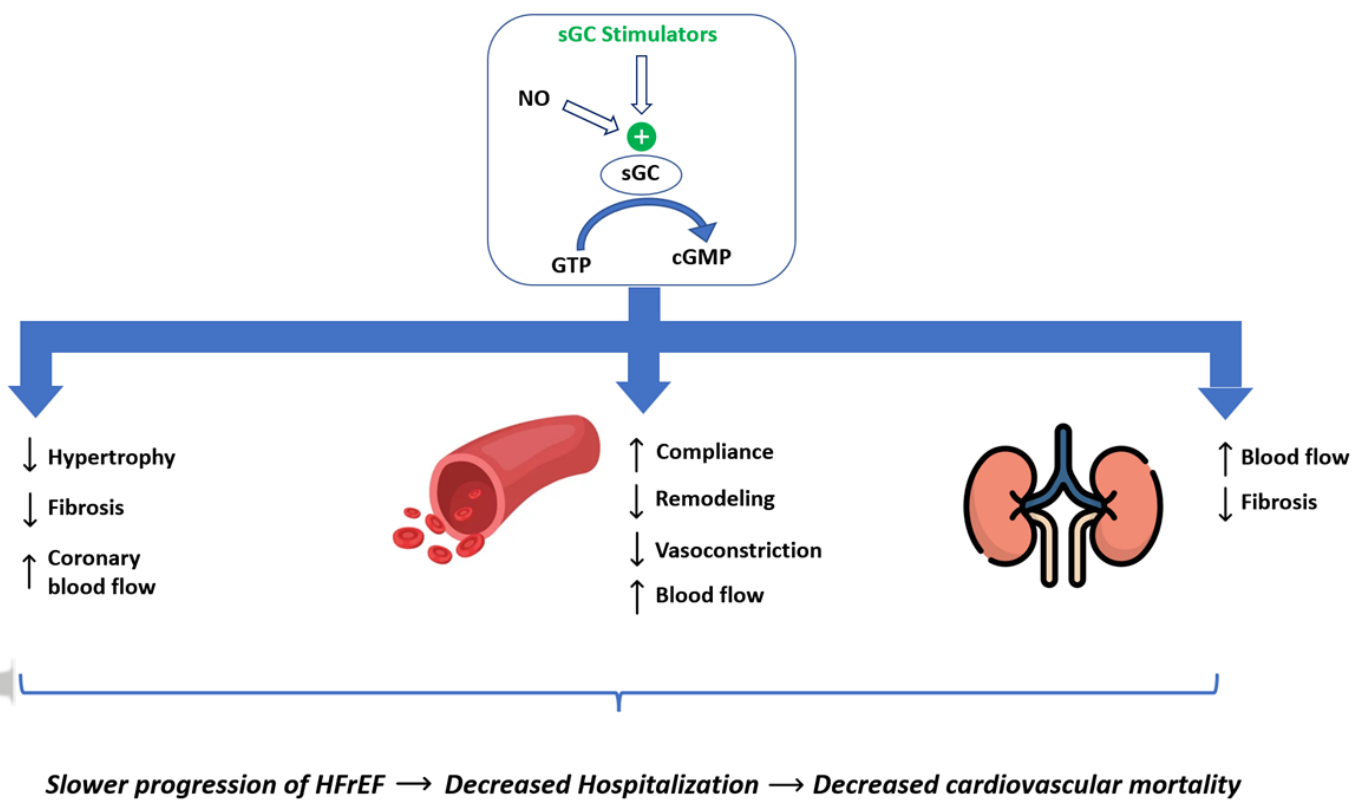
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Accepted Article




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Class	ACE Inhibitors	Beta-Blockers	MR Antagonists	SGLT2 Inhibitors	ARNI	sGC Inhibitors
Lower	<p>SOLVD-T, 1991 (Enalapril)</p> <p>AR of mortality: 14 RRR in mortality: 16%</p> <p>AR of HFH/CVM: 26 RRR in HFH/CVM: 26%</p>	<p>USCHF, 1996 (Carvedilol)</p> <p>AR of mortality: N/A RRR in mortality: 65%</p> <p>AR of HFH/CVM: N/A RRR in HFH/CVM: N/A</p> <p>MERIT-HF, 1999 (Metoprolol)</p> <p>AR of mortality: 11 RRR in mortality: 34%</p> <p>AR of HFH/CVM: 24 RRR in HFH/CVM: 31%</p> <p>CIBIS II, 1999 (Bisoprolol)</p> <p>AR of mortality: 13 § RRR in mortality: 34%</p> <p>AR of HFH/CVM: 28 § RRR in HFH/CVM: 31%</p> <p>COPERNICUS, 2001 (Carvedilol)</p> <p>AR of mortality: 20 RRR in mortality: 35%</p> <p>AR of HFH/CVM: 47 RRR in HFH/CVM: 26%</p>	<p>EMPHASIS-HF, 2011 (Eplerenone)</p> <p>AR of mortality: 9 RRR in mortality: 22%</p> <p>AR of HFH/CVM: 17 RRR in HFH/CVM: 37%</p> <p>RALES, 1999 (Spironolactone)</p> <p>AR of mortality: 27 RRR in mortality: 30%</p> <p>AR of HFH/CVM: 45 RRR in HFH/CVM: 33%</p>	<p>DAPA-HF, 2019 (Dapagliflozin)</p> <p>AR of mortality: 10 RRR in mortality: 17%</p> <p>AR of HFH/CVM: 15 RRR in HFH/CVM: 25%</p> <p>EMPEROR-Reduced, 2020 (Empagliflozin)</p> <p>AR of mortality: 11 RRR in mortality: 8%‡</p> <p>AR of HFH/CVM: 21 RRR in HFH/CVM: 25%</p> <p>SOLOIST-WHF, 2021† (Sotagliflozin)</p> <p>AR of mortality: 15 RRR in mortality: 18%‡</p> <p>AR of HFH/CVM: 34 RRR in HFH/CVM: 29%</p> <p>EMPULSE, 2021† (Empagliflozin)</p> <p>AR of mortality: N/A RRR in mortality: N/A</p> <p>AR of HFH/CVM: N/A RRR in HFH/CVM: 31%‡</p>	<p>PARADIGM-HF, 2014 (Sacubitril/Valsartan)</p> <p>AR of mortality: 9 RRR in mortality: 16%</p> <p>AR of HFH/CVM: 13 RRR in HFH/CVM: 20%</p> <p>LIFE, 2021 (Sacubitril/Valsartan)</p> <p>AR of mortality: N/A RRR in mortality: N/P</p> <p>AR of HFH/CVM: N/A RRR in HFH/CVM: N/P</p>	 <p>VICTORIA, 2020 (Vericiguat)</p> <p>AR of mortality: 17 RRR in mortality: 5%‡</p> <p>AR of HFH/CVM: 38 RRR in HFH/CVM: 10%</p>
Higher						

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Accepted Article

Soluble Guanylate Cyclase Stimulators in HFrEF Without Recent Worsening

Efficacy in worsening heart failure

- Vericiguat reduced cardiovascular death and heart failure hospitalization risk in patients with worsening heart failure.
- The treatment benefit appeared to be greater in lower risk patients.



SGc stimulators may be cardioprotective

- Preclinical studies show that SGc stimulators may have anti-hypertrophic, anti-fibrotic, and anti-remodeling effects.
- This suggests potential for benefit early in the course of heart failure journey as well.

Treatment effect may differ based on risk

- Traditionally, heart failure therapies have been evaluated in both low risk and high-risk populations.
- The treatment effect is not always consistent across risk strata.



Assess impact on cardiovascular death

- In the VICTORIA trial, vericiguat did not statistically significantly reduce CV death; however, the trial had a short average follow-up due to high-risk patients enrolled.
- A trial with a longer follow-up will allow impact of vericiguat on cardiovascular mortality.