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LETTER TO THE EDITOR

Vericiguat: a fifth cornerstone in the treatment of heart failure with reduced ejection fraction?

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a common cardiovascular disease with a significant impact on public health. Its prevalence is estimated to be around 2–3% of the general population in developed countries, increasing with age, and is more prevalent in men than women.[1] Both the incidence and prevalence of HFrEF are currently on the rise due to the aging population and improved survival rates in patients with cardiovascular disease. Risk factors for the development of HFrEF include hypertension, coronary artery disease, diabetes, obesity, and valvular heart disease.[2] HFrEF is associated with high morbidity and mortality rates, with a 5-year mortality rate of around 50% and a high risk of hospitalization.[3,4] It is also a leading cause of hospitalization in people over the age of 65.[4] The economic burden of HFrEF is substantial, with estimated direct and indirect costs of over $30 billion in the United States alone.[4]

The functional and/or structural impairment of the left ventricle, resulting in left ventricular ejection fraction (LVEF) of 40% or less, leads to volume overload and impaired tissue perfusion, which can trigger compensatory mechanisms that ultimately exacerbate heart failure (HF). Approximately 17% of HFrEF patients experience worsening HF within 18 months of initial diagnosis, and about 80% of hospitalizations for HF are due to progressive worsening of the condition.[5]

The management of HFrEF remains a significant challenge for healthcare systems worldwide. Pharmacotherapy is a cornerstone in the management of HFrEF to minimize symptoms, reduce hospitalizations, and improve survival. Currently, neurohormonal modulation plays a critical role in guideline-directed pharmacotherapy for HFrEF.[2] The primary medications used are beta-blockers, renin-angiotensin-aldosterone system inhibitors (including angiotensin-converting enzyme and angiotensin receptor blockers—alternatively angiotensin receptor-neprilysin inhibitor), mineralocorticoid receptor antagonists and most recently the sodium-glucose cotransporter 2 inhibitors. The recently published guidelines on the treatment of HF by the European Society of Cardiology underlined them as the four 'key disease-modifying drugs', which should be initiated as soon and safely as possible in all HFrEF patients.[2] However, given the complex, multifactorial nature of HF, it is important to consider other pharmacotherapeutic approaches alongside the standard treatment. Research has highlighted the significance of a board treatment foundation in HF, as the more comprehensive the approach, the greater the degree of progressive improvement in outcome.[6] Vericiguat is a novel drug that has shown promising results in the treatment of HF.[7] It is a soluble guanylate cyclase (sGC) stimulator that works by increasing the production of cyclic guanosine monophosphate (cGMP), a molecule that promotes vasodilation and reduces oxidative stress and inflammation.[8]

Endothelial NO synthase induces the production of nitric oxide (NO) in response to laminar flow and shear stress. NO diffuses to nearby cells and binds to the haem group of sGC, which in turn produces cGMP, activating protein kinase G. Protein kinase G phosphorylates proteins in the heart and vessels to promote diastolic relaxation, improve coronary blood flow, inhibit inflammation, hypertrophy, and fibrosis in response to cardiac damage, and improve ventricular-arterial coupling.[8] In the heart, there are seven isoforms of phosphodiesterase (PDE) that inactivate cGMP to GMP.[9] PDE3 inhibitors like milrinone and enoximone are used in acute HF, and PDE5 inhibitors such as sildenafil and udenafil improve contractile function in systolic HF, blunt left ventricular hypertrophic remodelling, reduce myocardial infarct size, and suppress ventricular arrhythmias, although neither class of drugs improves the outcome of HF patients.[9] Natriuretic peptides (NPs), particularly atrial NP or B-type NP, act on transmembrane receptors (NR-A and NR-B) with GC activity (particulate GC) to exert their biological effects, while NR-C receptors act as clearance receptors, decreasing plasma NP concentration, together with enzymatic cleavage by vasopeptidases like neprilysin.[10] In HFrEF, impaired left ventricular systolic function leads to tissue hypoperfusion, inflammation, and oxidative stress, resulting in decreased NO bioavailability and cGMP deficiency.[11] This cGMP deficiency has deleterious effects on the heart, kidneys, and vessels (including the pulmonary circulation), which may contribute to HF progression.[12,13] HFrEF patients commonly exhibit a reduced response to NPs, which may be due to various mecha-

nisms, including altered production or clearance of active NPs, their binding to membrane receptors, or intracellular effects.[14] sGC modulators acting on a downstream target of the NO-sGC-cGMP pathway may circumvent NP resistance more effectively than other therapeutic strategies that aim to increase NP concentration, such as the administration of pharmacological doses of recombinant B-type NP (nesiritide and ularitide), which is associated with worsening renal function and no effect on outcome.[8,15,16] The sGC activator cinaciguat increases cGMP levels by directly activating sGC, independent of NO, and has a high risk of hypotension.[8] Conversely, sGC stimulators enhance sGC sensitivity to endogenous NO, which possibly explains their neutral effects on blood pressure.[8] While the sGC stimulator riociguat requires three administrations per day due to its shorter half-life, vericiguat has a more favourable pharmacology, which makes it more feasible for daily use considering drug compliance and adherence.[2,8]

Efficacy and safety of vericiguat in heart failure with reduced ejection fraction

Vericiguat has undergone phase 2 (SOCRATES-REDUCED)[17] and phase 3 (VICTORIA)[7] trials in the context of HFrEF. These studies specifically targeted patients with a high risk of decompensation, as it was anticipated that the diuretic and natriuretic effects resulting from sGC stimulation would yield the greatest advantages.

The SOCRATES-REDUCED trial[17] recruited 456 patients with LVEF $<$ 45% and recent HF decompensation. Patients were randomized to five arms with different doses of vericiguat or placebo. The trial found no significant difference in the change of N terminal pro brain natriuretic peptide (NT-proBNP) between the pooled vericiguat group and the placebo arm over 12 weeks, but a significant difference was observed in the comparison between the highest vericiguat dose and placebo. Patients on the highest vericiguat dose also showed a greater increase in LVEF. Vericiguat therapy was safe and did not affect haemodynamic function, with lower rates of serious AEs than placebo.[17] *Post hoc* analysis showed that vericiguat treatment was associated with a dose-dependent decrease in plasma high-sensitivity C-reactive protein and serum uric acid.[17]

In the VICTORIA trial,[7] patients with an LVEF below 45% HF decompensation requiring hospitalization in the past 6 months and elevated circulating NPs were enrolled. This included the same cutoffs as in the SOCRATES-REDUCED trial. A total of 5050 patients were enrolled, with 76% men and 60% of patients on triple medical therapy including a beta-blocker, mineralocorticoid receptor antagonist, and either an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or sacubitril-valsartan (10%). The patients were randomly assigned to receive vericiguat 2.5 mg once daily, up-titrated to 5 mg and then 10 mg at 2-week intervals, or a placebo. Over a median 10.8-month follow-up, patients taking vericiguat had a lower incidence of cardiovascular death or first HF hospitalization [hazard ratio (HR) 0.90, 95% confidence interval (CI) 0.82–0.98; P = 0.02], with a number needed to treat of approximately 24. The results were mainly driven by a lower incidence of first HF hospitalization (HR 0.90, 95% CI 0.81–1.00), linked to a reduced number of HF hospitalizations (HR 0.91, 95% CI 0.84–0.99; P = 0.02). However, vericiguat appeared to be less effective in patients in the highest quartile of NT-proBNP levels ($>$5314 ng/L), those aged $\geq$ 75 years, with worse renal function [estimated glomerular filtration rate (eGFR) 15–30 mL/min/1.73 m^2], or LVEF 40–45%. It is noteworthy that the trial lacked sufficient statistical power to draw definitive conclusions from these subgroup analyses. The rates of symptomatic hypotension or syncope were similar between patients on vericiguat and placebo. Anaemia occurred more frequently in patients on vericiguat than placebo, although it was rarely categorized as a serious adverse event. Overall, serious AEs occurred in a comparable percentage of patients in both groups. The tolerability of the drug was further verified by an 89% rate of target dose achievement.

A distinctive feature of the VICTORIA study was its incorporation of participants with an eGFR below 30 mL/min/1.73 m^2. Through a subanalysis focusing on the relationship between renal function and vericiguat's efficacy, with no increase in creatinine levels compared with the placebo, vericiguat's effectiveness remained steady across varying eGFR levels.[18] In contrast, pivotal trials of renin-angiotensin-aldosterone system inhibitors in HF encompassed individuals with eGFR $>$ 30 mL/min/1.73 m^2, and these agents are considerably less prescribed in patients with severely impaired renal function.[19–23] Consequently, individuals at the greatest risk are unable to fully profit form standard therapy. Hence, despite substantial advances in managing patients with HFrEF, there remains a demand for innovative treatments, particularly directed towards those with eGFR $<$30 mL/min/1.73 m^2 and severe HFrEF.

In another *post hoc* analysis, the efficacy of vericiguat concerning baseline NT-proBNP levels was investigated.[24] Patients were categorized into ascending quartiles based on their NT-proBNP concentrations. Quartiles 1 to 3 encompassed patients with NT-proBNP levels at or below the 75th percentile ($\leq$5314 pg/mL), while Quartile 4 included those with NT-proBNP levels exceeding this threshold, representing a notably more diseased subgroup.[24] Overall, vericiguat demonstrated clinical benefit by reducing hospitalizations for HF and cardiovascular mortality.[24] Nonetheless, the treatment's efficacy appeared most pronounced in patients below the 75th percentile of NT-proBNP levels.[24] As the authors suggested, a plausible hypothesis is that individuals with severely elevated NT-proBNP values mirror a pa-

tient population that may likely be in an advanced disease stage, burdened with additional comorbidities, or potentially have not achieved adequate clinical stability to fully benefit from vericiguat. Furthermore, other factors such as the potential influence of pharmacokinetic factors might become relevant in patients with extensive cardiac decompensation and far progressed HFrEF.

Conclusion and future perspective

Vericiguat reduced the risk of cardiovascular death or HF hospitalization compared with placebo, when added to standard therapy.[7] Its mechanism of action and clinical trial results suggest that it can improve symptoms and reduce the risk of hospitalization and death in HF patients. Additionally, the treatment was well-tolerated and had a low incidence of adverse effects.

In order to determine whether vericiguat improves patient outcomes when used in conjunction with sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, and omecamtiv mecarbil, further research is necessary. The response of cardiomyocytes to these new treatments may have an additive or synergistic effect, potentially altering the course of HFrEF.

According to recent clinical trials, vericiguat has shown both safety and efficacy in patients with high-risk HF, including a reduced incidence of death from cardiovascular causes or HHF. However, in the spotlight of recent advances in acute and chronic HF therapy, the future role of vericiguat therapy requires clarification. The positive results of vericiguat in high-risk HF patients may open the possibility of adding it as a new therapeutic tool for HFrEF treatment, leading to a potential recommendation of a quintuple therapy in addition to standard optimal medical therapy.

Given the evidence linking comprehensive treatment strategies to improved outcomes in HFrEF, it is clear that a multifaceted approach to treating this condition is beneficial.[6] This further strengthens vericiguat's position as a valuable addition to the treatment arsenal against this complex disease. In order to reduce cardiovascular morbidity and mortality, vericiguat should be initiated as soon and safely as possible in HFrEF patients with recent decompensation (initial oral intake is 2.5 mg per day) and up-titrated every 2 weeks by twice its original amount until it reaches the maintenance dose of 10 mg per day, depending on the patient's tolerance.

Andreas Hammer
Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria

Alexander Niessner
Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria
E-mail: alexander.niessner@meduniwien.ac.at

Patrick Sulzgruber
Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria

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