European Heart Journal Supplements (2023) **25** (Supplement C), C316–C318
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad056

ESC
European Society
of Cardiology

Chronic heart failure: the role of di vericiguat

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KEYWORDS
Heart failure;
Vericiguat;
Hospitalization

The introduction of multiple new pharmacological agents over the past three decades in the field of heart failure with reduced ejection fraction (HFrEF) has led to reduced rates of mortality and hospitalizations, and consequently, the prevalence of HFrEF has increased, and up to 10% of patients progress to more advanced stages, characterized by high rates of mortality and hospitalizations and poor quality of life. Vericiguat, a novel oral soluble guanylate cyclase stimulator, has proved effective in patients with HFrEF who had recently been hospitalized or had received intravenous diuretic therapy. In these patients, vericiguat reduced the primary outcome of death from cardiovascular causes or first hospitalization for heart failure in comparison with placebo. By reducing hospital admissions in a population at a very high risk of re-hospitalization, vericiguat might have a positive impact on healthcare costs for the management of HFrEF.

Introduction

Chronic heart failure (CHF) is a progressive disease characterized by phases of acute exacerbations, interspersed with periods of complete or partial remission of symptoms, and by a progressive evolution toward an end-stage disease and death.[1] About half of HF patients are characterized by a reduced ejection fraction (HFrEF). The treatment of HFrEF has significantly improved in the last 40 years with the introduction of several drugs effective in improving mortality and hospitalization of these patients. Despite this, the survival of HFrEF patients is still similar or even worse than that of some aggressive neoplasms.[2] The disease progression continues even when patients are treated with optimal medical therapy, according to guidelines and recommendations.[3] Every new hospitalization for worsening HF is related to an increased risk of re-hospitalization and death. More frequent are hospitalizations the more the risk of further clinical events and the higher the mortality rate.[4,5] Therefore, there is a need for developing new drugs that act through different mechanisms with respect to the currently available drugs, and that aim to counteract pathophysiological processes involved in the progression of CHF. The recently published Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial[6] has showed that vericiguat, a drug that stimulates the cyclic guanosine monophosphate (cGMP) pathway, improves the prognosis of patients at particularly high risk of clinical events or death.

Clinical events after acute exacerbation of heart failure

While there is a relatively low in-hospital mortality rate during an hospitalization, the immediate period after discharge, corresponding to the first 1–3 months, called the 'vulnerable phase', is characterized by the highest rates of clinical events. During this phase, there is a 30% risk of hospital re-admission and a 10% risk of death. This vulnerable period is therefore the most critical for HF patients from a prognostic point of view, even if they are treated with optimal medical therapy.[7,8]

From a pathophysiological prospective, the persistence of a congestive state ad discharge plays a key role in determining the high rate of clinical events during the vulnerable phase.[9] Currently, about 20% of hospitalized patients still present signs of congestion at the time of

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discharge.[7] Very few drugs have been tested in the earliest phase after hospitalization for worsening HF. Clinical trials on angiotensin-converting-enzyme (ACEs) inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), sacubitril/valsartan, dapaglifozin ed empagliflozin, recruited patients in stable clinical conditions. These patients were often included if their therapy was unchanged for at least 3 months. To date, only few drugs recruited HF patients with recent hospitalization for acute exacerbation of symptoms: VICTORIA, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)[10] and in patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo. In the Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure GALACTIC-HF[11] the administration of omecamtiv mecarbil was a lower incidence of a composite of a heart-failure event or death from cardiovascular causes than placebo.

Mechanism of action of vericiguat

Vericiguat is the first drug approved by the European Medicines Agency, based on the results of the VICTORIA trial, in patients with recent acute exacerbation of HF leading or not to hospitalization, despite being already on optimal therapy.[6] The vericiguat mechanism of action is completely different from the other drugs currently used for the management of HF: it enhances the cGMP pathway by stimulating directly soluble guanylate cyclase. In HF, the generation of the intracellular second messenger cGMP via nitric oxide (NO) is impaired since NO levels are decreased as a consequence of inflammation, oxidative stress, and endothelial dysfunction. Cyclic GMP promotes the activation of the primary effector, protein kinase G (PKG). 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 remodelling.[12]

Role of vericiguat in HFrEF

In the VICTORIA trial, vericiguat significantly decreased the primary endpoint of cardiovascular death and hospitalization for HF, obtaining a 10% of relative risk reduction compared to placebo. It is noteworthy that the vericiguat arm of the VICTORIA study experienced an absolute risk reduction of 4.2% that is more than 50% higher than the correspondent reduction obtained with sacubitril/valsartan in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial.[10] The VICTORIA study confirms that the number of clinical events occurring after an hospitalization for HF exponentially declines after the first months, with most of the events occurring early after discharge.[4] In this trial, patients recruited within 3 months from the hospitalization for worsening HF, showed an incidence of the primary combined endpoint (cardiovascular death or re-hospitalization for worsening HF), of 40.9 events/100 patients/year, which is almost twice compared to that of patients recruited within 3–6 months from the hospitalization (29.6 events/100 patients/year) and of those who received intravenous diuretic therapy, without hospitalization (23.4 events/100 patients/year). The risk was even higher among patients recruited while still hospitalized (50 events/100 patients/year).[13] Despite these considerable differences in the risk among different subgroups in relation to the time of patient randomization in VICTORIA, there were not significant differences in vericiguat-induced benefits among these subgroups. The latter observation suggests that vericiguat could be effective in HF patients regardless of the time that has elapsed since hospitalization.[13]

The VICTORIA trial has showed favourable effects of vericiguat in patients with a recent acute exacerbation of HF. The study enrolled patients with a very high risk of re-hospitalization and death, despite being treated with optimal therapy.[6] The occurrence of the primary endpoint in the group with the highest risk, i.e. those randomized within 3 months from HF hospitalization (40.9 events/100 patients/year), was about two times higher than the correspondents rate observed among similar higher risk patients included in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trial[14] and among participants of the PARADIGM trial[15]. Even when considering the subgroup with the lowest risk (worsening HF without hospitalization), the occurrence of the primary endpoint (23.4 events every 100 patients/year) was more than two times higher than in the correspondent group of the CHARM study while it was more similar to the rate observed in the group at higher risk of the CHARM study. The higher rate of clinical events observed in the VICTORIA trial is probably due to the clinical characteristics of patients included in this study. In fact these patients were more often in NYHA class III–IV and had higher levels of natriuretic peptide than those included in previous trials and were more vulnerable since 84% had been hospitalized for heart failure in the previous 6 months.[6] These results underline that patients treated with diuretics outside the hospital had a similar risk of those who were hospitalized.[16] Vericiguat is the only drug specifically tested in this kind of patients at very high risk and which has proven effective in reducing clinical events. Due to its mechanism of action that differentiates it from others drugs used for HF (neuro-hormon modulators, glifozin) and considering its effectiveness in these high risk patients with recent hospitalization, vericiguat fills a gap in the landscape of available treatments for HF.

In light of the evidences coming from VICTORIA trial, the latest guidelines of the Heart Failure Association (HFA) of the European Society of Cardiology recommend the use of vericiguat as a drug that can be prescribed in patients with NYHA class II–IV which have experienced an acute exacerbation of HF, despite being already treated with ACE-inhibitor (or sacubitril/valsartan), beta-blockers and MRAs, for reducing the risk of cardiovascular death and re-hospitalization for HF (Class IIb; Level of Evidence: B).[3] The role of vericiguat in the treatment of HF has been further defined by an HFA Position Paper in which is stated that the administration of vericiguat can be started immediately at discharge or within the first 3 months after hospitalization.[17]

It has been suggested that vericiguat could become the drug of choice particularly in the highest risk patients with

recent or recurrent hospitalizations despite full background medication.[18] Two main aspects in favour of its use are the high tolerability (the target dose of 10 mg/daily was reached in about 90% of patients of the VICTORIA study) and its safety in patients with reduced renal function. On the contrary, the main limitation that emerges from the VICTORIA study is that, contrary to that observed with omecamtiv mecarbil, the beneficial effects of vericiguat on outcome were shown only in patients in the three lower quartiles of NT-proBNP levels at baseline, which suggests that this drug may be less effective in patients with more advanced HF. Given its effectiveness in reducing hospital admissions in a population at a very high risk of rehospitalization, vericiguat might have a positive impact on healthcare costs. Preliminary assessment of the cost effectiveness of vericiguat performed in the US showed a positive impact of this drug in the management of HFrEF patients.[19]

Conclusions

Vericiguat is the newest drug added to the armamentarium of therapies in the treatment of HFrEF. Current evidences 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 HF hospitalization. Patients with baseline NT-proBNP values <8000 pg/mL may derive the greatest benefit from the addition of vericiguat. Further studies are needed in order to better understand the exact position of vericiguat in the management of CHF.

Funding

None declared.

Conflict of interest: All authors declare no conflict of interest.

Data availability

No new data were generated or analyzed in support of this paper.

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