ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 791–793
doi:10.1002/ejhf.2511

EDITORIAL COMMENT

Is targeting cyclic guanosine monophosphate by vericiguat effective to treat ischaemic heart failure with reduced ejection fraction? Yes, it is

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This article refers to 'Vericiguat in patients with coronary artery disease and heart failure with reduced ejection fraction' by C. Saldarriaga *et al.*, published in this issue on pages 782–790.

Heart failure with reduced ejection fraction (HFrEF) remains a leading cause of morbidity and mortality despite great advances in treatment. Heart failure (HF) is associated with cyclic guanosine monophosphate (cGMP) deficiency and resistance to the cGMP-dependent effects of natriuretic peptides (NPs) which might contribute to disease progression.[1] The nitric oxide (NO)–cGMP–protein kinase G (PKG) pathway exerts numerous beneficial effects at the cardiovascular and renal level by reducing inflammation, fibrosis, hypertrophy, and vasal tone as well as by increasing coronary and renal blood flow, eventually resulting in reduced cardiac and vascular remodelling and improved diuresis, natriuresis and renal protection.[1] Inflammation and oxidative stress are hallmarks of the pathophysiology of HFrEF and contribute to disease progression in part by dysregulating the NO–cGMP–PKG pathway.[2]

Ischaemic aetiology accounts for nearly two thirds of HFrEF cases and is associated with a worse prognosis.[3] Patients with atherosclerotic coronary artery disease (CAD) are characterized by endothelial dysfunction, which manifests with a reduced production of NO.[4] This may suggest a greater benefit of drugs modulating the NO–cGMP–PKG pathway in ischaemic HFrEF.

Vericiguat is an oral drug that enhances the sensitivity of soluble guanylate cyclase (sGC) to endogenous NO, thus increasing the production of cGMP.[5] VICTORIA was a Phase 3 trial enrolling 5050 patients with left ventricular ejection fraction (LVEF) <45%, a recent HF decompensation either requiring hospitalization (<6 months) and/or intravenous diuretics (<3 months), and elevated NPs (B-type natriuretic peptide [BNP] ≥300 ng/L or N-terminal pro-B-type natriuretic peptide [NT-proBNP] ≥1000 ng/L; for patients in atrial fibrillation, BNP ≥500 ng/L or NT-proBNP ≥1600 ng/L). Patients were randomized to vericiguat 2.5 mg once daily (titrated up to 10 mg) or placebo. After a median follow-up of 10.8 months, patients on vericiguat showed a lower incidence of cardiovascular death or first HF hospitalization (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.82–0.98; $p = 0.02$), translating into an absolute event-rate reduction of 4.2 events per 100 patient-years and a number needed to treat with vericiguat for 1 year of about 24. These results were driven by a lower incidence of first HF hospitalizations (HR 0.90, 95% CI 0.81–1.00) in the vericiguat group.[6] The efficacy of vericiguat on the primary outcome was confirmed in numerous subgroups, identified based on sex, age, ethnic group, New York Heart Association (NYHA) class, estimated glomerular filtration rate, and LVEF.[6]

A *post-hoc* analysis of VICTORIA demonstrated that vericiguat reduced risk of the primary outcome as well as all-cause death and HF hospitalization irrespective of the time from previous HF decompensation. Vericiguat showed a trend toward greater benefit with longer duration since index HF hospitalization, although patients closest to their index HF event had the highest risk for the composite endpoint.[7] Another *post-hoc* analysis showed that the effect of vericiguat varied significantly across the spectrum of NT-proBNP at randomization (interaction $p = 0.002$). The superior efficacy of vericiguat over placebo was confirmed for NT-proBNP levels up to 8000 ng/L.[8]

Given that patients with ischaemic HFrEF have a worse outcome, it is important to investigate whether the effects of a new therapy are consistent across the ischaemic and non-ischaemic aetiologies. In this issue of the Journal, Saldarriaga *et al.*[9] evaluated the efficacy and safety of vericiguat in patients with ischaemic versus non-ischaemic HF. More precisely, the authors focused on the history of CAD, defined as a patient-reported history of myocardial infarction (MI, 78.4%), percutaneous coronary intervention (PCI, 62%), and/or coronary artery bypass graft surgery (CABG, 34.5%)

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.2468

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prior to their index HF hospitalization. In the VICTORIA cohort, patients with a history of CAD accounted for 58.3% of the whole population, and had a higher risk of HF hospitalization, cardiovascular and all-cause death compared to the other patients. These differences in outcome were likely not driven by a heterogeneous treatment, although patients with CAD were less likely (55.3% vs. 64.8%) to receive a triple guideline-directed medical therapy and had more often an implantable cardioverter defibrillator (33.5% vs. 21.1%) or a cardiac resynchronization therapy (16.3% vs. 12.8%). A survival benefit from vericiguat over placebo was found both in patients with or without CAD (HR 0.92, 95% CI 0.83–1.03 vs. HR 0.85, 95% CI 0.74–0.98; *p* for interaction = 0.78). No interaction with history of CAD was observed also regarding the individual items of the composite outcome. In addition, vericiguat was well tolerated in both groups. To summarize, patients with HFrEF have a higher risk of cardiovascular outcomes when they have a history of CAD, but they benefit from vericiguat to a similar extent than patients without a history of CAD.

The study investigators should be congratulated for providing novel insight into the efficacy and safety of vericiguat according to HFrEF aetiology. Results from subgroup analyses must always be regarded as hypothesis-generating given the lack of adequate statistical power, but the high interaction *p*-values suggest a real lack of different effects of vericiguat in patients with or without a history of CAD. Interestingly, the benefit of vericiguat over placebo was investigated only in terms of HRs in the two subgroups, and by searching for an interaction.[9] Nonetheless, the study investigators previously compared the results from VICTORIA with other trials also in terms of absolute risk reduction, reporting that 'although the HR may suggest the largest treatment effect in DAPA-HF followed by PARADIGM-HF and then VICTORIA, a comparison of annualized or 12-month event rates for the primary endpoint suggests that the outcome benefits are comparable across trials'.[10] The same combined assessment of relative and absolute risk reduction with vericiguat over placebo could be usefully performed in patients with versus without CAD, also considering the different baseline risk in the two subgroups.[9]

Coming back to the study hypothesis, the authors postulated a more pronounced effect of vericiguat in patients with HFrEF and CAD based on a diminished activity of sGC in these patients. Numerous pre-clinical and clinical studies demonstrated that the NO–cGMP–PKG pathway is downregulated in the presence of CAD, but most of these studies used healthy controls as comparators.[4] HF itself causes endothelial dysfunction, independently of the underlying aetiology, and there is strong evidence suggesting that the NO–cGMP–PKG pathway is downregulated in different models of HF,[1] while there are no data suggesting an additive effect of CAD once HF has already developed. Therefore, future studies should test whether the presence of CAD has any role in reducing NO–cGMP–PKG pathway activity (such as by measuring circulating and urinary cGMP) regardless of HF. Notably, a history of MI, PCI and/or CABG is a rather gross approximation of the presence of CAD, and dedicated studies should include a more thorough assessment of symptoms and imaging evidence of atherosclerotic disease in the coronary arteries (and possibly also in other districts).

Despite these possible issues, this study and similar subgroup analyses are important to better understand which patients might benefit most from vericiguat. Vericiguat has received class IIb/2b, level B recommendations by both the European Society of Cardiology and American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines (ACC/AHA/HFSA).[11,12] Specifically, vericiguat 'may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an angiotensin-converting enzyme inhibitor (or an angiotensin receptor–neprilysin inhibitor, ARNI), a beta-blocker and a mineralocorticoid receptor antagonist'[11] or in 'selected high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy (GDMT)'.[12] As GDMT now includes also sodium–glucose cotransporter 2 (SGLT2) inhibitors, the ACC/AHA/HFSA guidelines seem to open to the combined use of vericiguat and SGLT2 inhibitors, which are very effective drugs to prevent HF hospitalization in patients with HFrEF. The clinical efficacy and molecular effects of combined therapies are other open questions for future research. Subgroup analysis of the VICTORIA trial showed that vericiguat retained its efficacy independently of ARNI administration, although this conclusion was limited by the low number of patients taking both drugs (15%).[6] The NO–cGMP–PKG pathway is the one through which NPs exert their effects on the cell. ARNI increase NP levels, thus stimulating the NO–cGMP–PKG pathway, as demonstrated by the higher urinary cGMP levels following sacubitril/valsartan administration.[13] ARNI and sGC might then act synergistically. Indeed, by acting on a downstream target of the NO–cGMP–PKG pathway, vericiguat might circumvent NP resistance, a common feature in HFrEF.[5] Currently, there are no data on the combined efficacy of sGC stimulators and SGLT2 inhibitors. The precise mechanisms underlying the beneficial cardiovascular effects of SGLT2 inhibitors are still under investigation. Major hypotheses include the restoration of euvolaemia though a greater free water clearance and a shift towards a more energetically advantageous ketogenic metabolism.[14] However, recent pre-clinical data suggest that empagliflozin might directly stimulate the sGC–cGMP–PKG pathway.[15]

In summary, the VICTORIA study investigators remind us that a history of CAD is an important determinant of outcome in HFrEF, but should not affect our decision to prescribe vericiguat. Indeed, vericiguat seemed safe and effective in both patients with and without a history of CAD.

Conflict of interest: none declared.

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