BISKUPSKI, Mikolaj, CYGNAROWICZ, Aleksandra, WOJTAS, Aneta Klaudia, ZABOJSKA, Krystyna, KOROTKO, Urszula, MANDZIUK, Aneta, WITOWSKA, Kinga, TUREMKA, Mariola, HOSSEINNEJAD, Negar and SACHER, Karolina. Vericiguat – possibly next weapon to overcome heart failure. Review of latest literature. Journal of Education, Health and Sport. 2024;76:56619. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.76.56619
https://apcz.umk.pl/JEHS/article/view/56619

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 03.12.2024. Revised: 18.12.2024. Accepted: 18.12.2024. Published: 18.12.2024.

Vericiguat – possibly next weapon to overcome heart failure. Review of latest literature.

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Abstract

Introduction

Heart failure (HF) is a common clinical syndrome characterized by symptoms such as breathlessness and fatigue, affecting 1-2% of adults in developed countries. Standard treatment for heart failure with reduced ejection fraction (HFrEF) includes a "new quadruple" therapy comprising ARNI/ACE-I, beta-blockers, MRAs, and SGLT2i. However, a subset of patients remains inadequately managed, highlighting the need for new therapies like vericiguat. Vericiguat, an oral soluble guanylate cyclase (sGC) stimulator approved by the FDA in January 2021, shows promise for patients with heart failure with reduced ejection fraction (HFrEF). This review highlights vericiguat's pharmacodynamics, including its mechanism that enhances nitric oxide effects and promotes vasodilation, thereby improving hemodynamic status.

Materials and Methods

This review synthesizes recent literature on vericiguat sourced from PubMed and Cochrane databases, including studies published in English between 2023 and 2024. Eight relevant publications were selected based on strict inclusion criteria.

Results

Reviewed studies demonstrate that vericiguat significantly reduces NT-proBNP levels and lowers the risk of composite cardiovascular death or HF hospitalization. Notably, vericiguat showed efficacy in specific subgroups, including patients with chronic kidney disease and those in NYHA class III/IV.

Conclusion

Vericiguat is a promising candidate for inclusion in the "new quadruple" therapy for HF, particularly for patients with severe symptoms or chronic kidney disease. Further research is essential to clarify its benefits in stable HF patients and its comparative efficacy alongside current guideline-directed medical therapy.

Keywords : Vericiguat; heart failure; guanylate cyclase

Introduction

1.1 Heart Failure

Heart failure is defined by 2021 European Society of Cardiology guideline as: "[...] not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema)." [1]. Definition excludes patients with asymptomatic structural disease or myocardium dysfunction, and focus on typical reported symptoms which derive from pulmonary and systemic congestion. Standard further evaluation of a patient with symptoms of heart failure includes transthoracic echocardiography and measurement of natiuretic peptides. [1,2]

Heart failure is a common advanced stage form of most cardiac diseases, although the most prevalent etiologies are coronary arterial disease, arterial hypertension, diabetes, valvular heart diseases, arrhythmias and dilated cardiomyopathy. The prevalence of heart failure among adults in developed countries range from 1.0% to 2.0% and it remains great financial burden for health care system. [3,4,5,6]

The most up-to-date classification of heart failure used in scientific research and clinical situation is based on the differentiation of left ventricular ejection fraction (LVEF). We can differentiate: heart failure with reduced ejection fraction (HFrEF, LVEF $\leq$ 40%), heart failure with mildly reduced ejection fraction (HFmrEF, LVEF from 40% to 49%), heart failure with preserved ejection fraction (HFpEF, LVEF $\geq$ 50%), and heart failure with improved ejection fraction (HFimpEF, with a previous LVEF $\leq$ 40% and a follow-up LVEF > 40% and an increase of $\geq$10% from baseline). [1,2]

Standard treatment of HFrEF, besides of lifestyle changes, contains of so called "new quadruple" therapy which consist of angiotensin receptor-neprilysin inhibitors (ARNI)/ angiotensin-converting enzyme inhibitors (ACE-I), beta blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i). Typical treatment used for reduction of congestion symptoms are oral and intravenous diuretics. Inseparable part of HF treatment in the selected group of patients are implantable devices as cardioverter-defibrillators (ICD) and cardiac resynchronization therapy devices (CRT). In severe cases usage of left ventricular assist devices (LVADs) and heart transplantation may be considered. In HFpEF and HFmrEF baseline of treatment are sodium-glucose cotransporter-2

inhibitors (SGLT2i) and diuretics, when fluid retention is present. In HFmrEF we should consider use of ACE-I/ARNI, MRA, and BB, especially when HF is accompanied by other cardiovascular diseases. [1,2]

However, despite progress in pharmacological treatment, applying pharmacotherapy according to guidelines, there remains a percentage of the heart failure patient population who fail to achieve satisfying and sustained improvement in cardiac function, undergoing frequent hospitalization with high mortality. For this group, research is underway on new drugs among which vericiguat may be a promising candidate to join the "new quadruple". [7,8]

1.2 Vericiguat

Under normal conditions, nitric oxide (NO) produced by the endothelium binds to soluble guanylate cyclase (sGC), catalysing conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Production of intracellular cyclic guanosine monophosphate (cGMP) is important for preserving proper cadiomyocyte contractibility, vascular tone and prevent heart muscle remodeling. In patients with HF, due to inflammation and oxidative stress, generation of nitric oxide (NO) and activity of sGC became impaired. Recognition of NO-sCG-cGMP axis disfunction in heart failure opened opportunities for new drugs with this gripping point. [9,10]

Vericiguat developed by Merck under the brand name VERQUVO® and chemically known as methyl (4,6-diamino-2-(5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate, is oral drug approved by the FDA on January 19, 2021 based on data from SOCRATES-REDUCED and VICTORIA trials. Vericiguat is a direct and indirect stimulator of soluble guanylate cyclase (sGC). It binds directly to a target site bypassing NO-activation. At the same time, vericiguat increases sensitivity of sGC to endogenous nitric oxide, by stabilizing NO binding to the binding site. In the contrary to nitrovasodilator (which are NO donors), vericiguat does not develop tolerance upon long-term use, and due to its long half-life, allows for once daily dosing. In a nutshell, the objective of sGC stimulators, like vericiguat, is restoring proper intracellular concentration of the cyclic guanosine monophosphate (cGMP) in low nitric oxide environment, which results in smooth muscle relaxation, vasodilation, increase of cardiac output, cardiac index and decrease in systemic vascular resistance. [11,12,13,14,15,16]

1.3 SOCRATES-REDUCED trial

SOCRATES-REDUCED is multicenter, randomized, double-blind, placebo-controlled, phase 2, dose-finding trial published in 2015. It was conducted to evaluate the effect on natriuretic

peptide levels and tolerability of 12 weeks of treatment, with 4 different doses of oral Vericiguat. Inclusion criteria were: LV ejection fraction less than 45% and a recent episode of worsening chronic HF (defined as worsening symptoms requiring either hospitalization or outpatient administration of intravenous diuretics, signs of fluid retention and elevated natriuretic peptides [NT-proBNP or BNP]).

The trial included 456 patients (mean age of 68 years) across Europe, North America, and Asia, who were then randomized to 5 groups (1:1:1:1:1). All vericiguat groups (with exclusion of 1,25mg once-daily group) started with initial 2.5 mg once-daily of vericiguat at randomization. Target doses were respectively: 1.25 mg, 2.5 mg, 5 mg, and 10 mg, once-daily.

After 12 weeks, the 3 highest-dose intervention groups were pooled together (the 1.25 mg was assumed to have minimal to no effect) and taken into account to primary analysis. Primary endpoint, specified as a change in log-transformed NT-proBNP level from baseline to 12 weeks, was not significantly different in the pooled vericiguat treatment versus placebo group ($P = 0.15$). However, secondary analysis conducted using linear regression modelling significantly suggested ($P < 0.02$) a negative correlation of higher vericiguat doses with greater reduction in NT-proBNP levels.

Noteworthy is a fact that patients in the two highest doses groups experienced a reduced rate of HF hospitalization (9.9% in the 10 mg and 5 mg vericiguat groups vs. 17.4% in the placebo group), and a favourable but statistically non-significant trend toward reduction of the composite cardiovascular death and HF hospitalization ($P = 0.72$). [16]

1.4 VICTORIA trial

VICTORIA (Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction) is a phase 3, randomized, double-blind, placebo-controlled trial from 2020 involving 5050 adult patients, in the mean age of 67 years, with chronic heart failure (NYHA class II, III, or IV), an ejection fraction of less than 45%, elevated natriuretic peptide level and evidence of worsening heart failure (WHF). WHF was defined as an HF hospitalization within 6 months before randomization or an episode of decompensation with outpatient treatment using intravenous furosemide 3 months before randomization. Patients were then randomly assigned, in a 1:1 ratio, to receive vericiguat or matching placebo. All the patients received guideline-based medical therapy (60% of the patients received triple therapy (BB, MRA, ACE-I/ARNI) and 15% received an ARNI).

Results showed 10% reduction (Hazard Ratio [HR] 0.90 [0.82-0.98], $P = 0.02$) of primary outcome which was defined as death from cardiovascular causes or first hospitalization for heart

failure. If we look at the components of the primary endpoint, only total hospitalization for heart failure were significantly reduced (HR 0.91 [0.84-0.99], P=0.02). Additionally, among the secondary endpoints, the composite of death from any cause or first HF hospitalization reached statistical significance (HR 0.90 [0.83–0.98], P = 0.02). It is worth pointing out that reduction of death from cardiovascular causes (16,4% in vericiguat group and 17,5% in placebo group) did not reached statistical significance. The pre-determined adverse events were symptomatic hypotension (9.1% vericiguat group and 7.9% placebo group [P = 0.12]) and syncope (4.0% vericiguat group and 3.5% placebo group [P = 0.30]). Anaemia developed in more patients in the vericiguat group than in the placebo group (7.6% vs. 5.7%) but it was considered as serious adverse event in 1.6% (in the vericiguat group) and 0.9% (in the placebo group). [15,17]

2. Materials and methods

The article is a result of the review of the latest scientific literature searched by keyword "vericiguat" available in Pubmed and Cochrane databases. Publications were included if they were observational studies or interventional studies or meta-analyses investigating vericiguat use in heart failure with reduced ejection fraction published in English between 2023 and 2024. Publications not strictly related to the topic, duplicates and studies involving animals were excluded. Following the initial search, retrieved studies were screened based on titles and abstracts. Studies that met the inclusion criteria underwent a full-text review. Eight publications were considered for this work.

3. Results

3.1 Meta-Analysis

Several meta-analysis regarding vericiguat have been published in 2023 and 2024. First one by Guofang et al., issued May 2023, is a meta-analysis of 4 Randomized Controlled Trial (RCT) including 2 aforementioned. Total patient sample size was 5947. The primary endpoint was composite outcome of cardiovascular death or heart failure hospitalization. Secondary endpoints included death from cardiovascular causes, hospitalization for heart failure, death from any cause, adverse events, and serious adverse events. Statistical analysis demonstrated notable improvement in composite outcome of cardiovascular death or heart failure hospitalization (Odds Ratio [OR] = 0.87 [0.78-0.97]; P = 0.02) in group treated with vericiguat. However, no significant influence on hospitalization for heart failure (P = 0.05), death from cardiovascular causes (P = 0.48), death from any cause (P = 0.56), adverse events (P = 0.42) or serious adverse events (P = 0.12) has been noted. Authors also bring our attention to the 33.6% annualized rate of the primary composite outcome in the vericiguat group, which was >2 times

higher than seen in the 2 comparator trials: PARADIGM-HF (ARNI vs. ACEI) and the DAPA-HF (SGLT2i). They explain it with percentage of NYHA class III or IV heart failure patient included, which amounts to 41% in VICTORIA in comparison to 24% and 32% respectively in other two. [18, 19, 20]

Published in September 2024 systemic review and network meta-analysis by Lavalle et al. involves 5 RCT studies comparing standard-of-care HF therapy with sacubitril/valsartan, dapagliflozin, empagliflozin, vericiguat, or omecamtiv mecarbil (OM) with overall 30 198 patients enrolled. The aim of the study was to compare the efficacy of different HF drugs in specific subgroups of HFrEF patients, such as patients >65 years, patients >75 years, women, patients with CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min), patients with diabetes, patients in NYHA class III–IV, patients with coronary arterial disease (CAD), and patients on or off ARNI therapy. The primary focus was composite endpoint of cardiovascular death and HF hospitalization. Vericiguat showed significant reduction of primary endpoint in CKD group (RR 0.84 [0.73–0.97]; P= 0.016) and NYHA Class III/IV group (RR 0.87 [0.77-0.98]; P = 0.025). In other groups, despite tendency to reduction in event risk, vericiguat did not reached statistical significance. In discussion section, authors draw our attention to the potential of vericiguat for patient with CKD. It can be safely used by patients with low eGFR (15–30 mL/min) and does not cause hyperkalemia which are common reasons to discontinue renin-angiotensin-aldosterone system inhibitors. Besides vericiguat and OM, no other therapy reached significant reduction of primary endpoint within NYHA class III/IV group. Notably, RCT regarding this two therapies have greater representation of NYHA class III/IV population, compared to the others. [21, 22, 23]

In January 2024 in International Journal of Cardiology appeared meta-analysis by Kang et al. Its aim was to examine non-inferiority of vericiguat to sacubitril/valsartan. Authors compared data from VICTORIA and PARADIGM-HF trials. The non-inferiority margin (ΔHR) was established at 1.24 and the criterion for considering vericiguat as non-inferior to ARNI rested on whether the 95% CI of the HR fell below the designated non-inferiority margin. Network meta-analysis demonstrated that verciguat was not significantly distinct from that of sacubitril/valsartan (HR 0.88 [0.62–1.23]; P = 0.88), as composite outcome of cardiovascular death or HF hospitalization is assessed. Authors pinpoint limitations like variances between the two trials in patient characteristics, study design, and a run-in period, which have to be taken into consideration. [24, 15, 20]

Network meta-analysis by Tang et al., published November 2024 and involving 90 529 participants from 49 RCTs attempts to evaluate the most effective combination of pharmacological therapy in patients with HFrEF. Included treatments were different combination of ACE-I, BB, MRA, SGLT2i, Vericiguat, Ivabradine (Iva), Hydralazine, and Isosorbide Dinitrate. Results show that treatments composed of ACEI + BB + MRA + SGLT2i, ACEI + BB + MRA + Vericiguat and ACEI + BB + MRA + Ivabradine were best approach for reducing the risk of all-cause death, the risk of cardio-vascular death, and HF hospitalizations. The leader in reduction of all-cause death and HF hospitalizations was the therapy including SGLT2i. [25]

Contrary to the above promising results, meta-analysis by Ma et al. from 2023 shows no significant difference in cardiovascular death (RR 0.97 [0.58–1.61], I^2 = 37%), HF hospitalization in HFrEF and HFpEF (RR 0.92 [0.85–1.01], I^2 = 0%), and adverse effects (RR 1.00 [0.97–1.03], I^2 = 0%) between the vericiguat and placebo group. [26]

3.2 RCTs

As in previously published works safety of vericiguat is confirmed by recent studies. Phase Ib, placebo-controlled, doubleblind, multicenter study by Böttcher et al. from January 2023 shows, that during vericiguat treatment there is no significant QT interval prolongation. Additionally, side effects (like hypotension or dizziness) prevalence does not exceed previously reported. [27]

An impact of the vericiguat on echocardiographic measurements was recently addressed by VICTORIA RCT substudy by Pieske et al. published in April 2023. A total of 419 patients (208 in the vericiguat group and 211 in the placebo group) were included. Primary endpoints included in this study were the change in LV end-systolic volume index (LVESVI) and LV ejection faction (LVEF) from baseline to follow-up. After 8-month therapy LVESVI significantly decreased in both the vericiguat (from 60.7±26.8ml/m2 to 56.8±30.4ml/m2; P <0.001) and placebo groups (from 68.2±31.0 ml/m2 to 61.1±29.9ml/m2; P <0.01). The LVEF significantly increased in both the vericiguat (from 33.0±9.4% to 36.1±10.2%; P <0.001) and placebo groups (from 31.8±8.2% to 34.2±9.5%; P <0.01). The absolute change in LVESVI and LVEF between groups did not differ significantly. [28]

3.3 Cohort Studies

The last study reviewed in the article is multicenter, observational cohort study including 200 HFrEF patients by Tian et al. published September 2024. Comparison of baseline characteristics between vericiguat and placebo groups showed no statistically significant differences. The

primary outcome was the proportion of participants with NT- proBNP ≤1000 pg/ml at the 6-month follow-up assessment. Statistical analysis showed vericiguat is an effective factor influencing NT-proBNP status (model 1: OR =2.80 [1.45–5.43], P =0.002; model 2: OR =2.67 [1.24–5.77], P =0.013). Furthermore, vericiguat exhibited greater tendency to improve the NT-proBNP status in patients with non-low systolic blood pressure (SBP), defined as SBP＞105mmHg. Despite above, no improvement in ventricular remodelling revealed as significant. Worth noting that over 85 % of the patients were already on SGLT2i at baseline which distinguishes this study from previous ones (basing on the paradigm of triple therapy consisting of ACEI/ARB/ARNI, BB, and MRA). [29]

4. Conclusion

Despite great advances in the treatment of heart failure in recent years, there is still area for new therapy, especially in a population experiencing frequent exacerbations and hospitalizations. Vericiguat has emerged as a promising candidate for the next pillar of guideline-directed medical therapy (GMDT) as indicated by its inclusion in the 2021 ESC HF treatment guidelines. Following the above, its use may be considered "in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization". [1]

Despite several limitations persist, the numerous trials and meta-analyses confirm a significant effect of vericiguat on the NT-proBNP levels and composite outcome of cardiovascular death or heart failure hospitalization. However, the impact on the outcome of cardiovascular death alone still remains unclear. [18, 21, 24, 25, 26, 28, 29]

A major limitation of the recent studies, from the perspective of current GDMT, is the scarcity of studies directly comparing the "new quadruple" therapy composed of ACE-I/ARNI, MRA, BB and SGLT2i with an additional intervention in the form of vericiguat. Not to be missed is the fact that in real-world clinical practice full GDMT including "new quadruple" is still used too rarely. Assuming an additive effect of drugs with different point of grip, the addition of vericiguat remains a new area to explore. [30]

Results presented in this article suggest that vericiguat may have the greatest impact in patients with more severe HF symptoms (NYHA III/IV), after a recent exacerbation. An interesting target group of patients are also those with CKD because vericiguat can be safely used over a wide range of eGFR (15–30 mL/min). All recent trials confirm the safety of vericiguat with infrequent predictable side effects like hypotension and dizziness. [21, 23, 27]

We wait for the results of further interesting research, including the VICTOR trial, which will assess the efficacy and safety of vericiguat in patients with ejection fraction ≤40%, without recent worsening HF on a background of current foundational HFrEF therapy. As NO-sCG-cGMP axis dysfunction remains an opportunity for treatment, studies are underway to search for new sGC stimulators that may outrun vericiguat in efficacy. [31, 32]

With the permanent entry of SGLT2i into clinical practice for the treatment of heart failure, vericiguat remains one of the next candidates to join the "new quadruple." Despite a number of promising studies showing its effects on NT-proBNP level and the composite outcome of cardiovascular death or heart failure hospitalization in patients with worsening HF, the efficacy in stable patients with chronic HF remains unclear. There is an urgent need for further studies evaluating the efficacy of vericiguat, particularly studies comparing vericiguat addition to current state-of-art GDMT.

Disclosure:

Authors contributions

[MB],**[KS]**: Conceptualization, Writing - rough preparation, Methodology, Investigation, Project administration

[AC], [AKW], [MT], [NH]: Formal Analysis, Visualisation

[KZ], [UK]: Software, Writing – review and editing.

[MB], [AM], [KW]: Methodology, Investigation

[MT], [NH]: Supervision, Resources

[NH], [KS]: Supervision, Data curation

All authors have read and agreed with the published version of the manuscript.

Funding Statement

The study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data presented in this study is available upon request from the corresponding author.

Acknowledgments

Not applicable.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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