New Drugs for Treatment of Heart Failure with Reduced Ejection Fraction: Vericiguat and Omecamtiv Mecarbil

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The last decades have witnessed a decline in the mortality of patients with heart failure with reduced ejection fraction (HFrEF), comparing the periods from 1987 to 1991, from 1992 to 1996, and from 1997 to 2001, but this did not occur when comparing patients with heart failure with preserved ejection fraction (HFpEF) between the same periods.[1] More recently, a study with more than 11,000 hospitalized patients (3 or 6 months) reaffirmed that hospitalization of patients with left ventricular ejection fraction (LVEF) < 45% contributes to increased mortality and morbidity, especially within the first 3 months (56% of hospitalizations). Mortality was 22.5% at 2 years. It became clear once again that the presence of comorbidities increases the occurrence of worsening, and renal dysfunction especially increases the instability of heart failure (HF) 2-fold. In the entire sample, triple therapy was detected in only 14% of patients, and 1 in 6 patients evolved with worsening HF within 18 months of follow-up.[2]

The past 2 or 3 years have seen the development and approval of new therapeutic options, especially drug therapies, which significantly improve survival and significantly reduce hospitalization or readmission of patients with HFrEF (PARADIGM, EMPEROR-Reduced, DAPA-HF).

Nevertheless, there is still a great deal of room for new therapies that improve survival, in addition to reducing the chance of progression to instability and the need for hospitalization or visits to emergency units to treat decongestion, without requiring subsequent hospitalization. In spite of the development and approval of new drugs, devices, and surgical treatments for HFrEF and also very recently for the stability of HFpEF, there is still a need for new means to treat these patients.

In this article, we will address 2 new drugs with new mechanisms of action that have increased our possibility of stabilizing these patients, as well as future evidence of improved prognosis.

Keywords

Insuficiência Cardíaca; Sobrevida; Hospitalização; Omecamtiv Mecarbil; Vericiguat.

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Omecamtiv mecarbil - myosin activator

During the 1980s and 1990s, several attempts at long-term treatment with inotropes in patients with systolic dysfunction almost always resulted in increased mortality or a neutral effect (oral milrinone, intravenous dobutamine infusion), with the exception of levosimendan, when used in intermittent infusions in patients with advanced heart failure, which did not interfere with prognosis and avoided worsening quality of life and readmissions.[3]

Omecamtiv mecarbil is an inotropic agent whose mechanism of action differs from the others, having no relation to increased calcium influx or increased sensitivity to calcium by myocardial fibers. The drug increases cardiac contractility by selectively interacting with cardiac myosin, increasing the number of molecules available to bind to actin and produce greater kinetic energy at the beginning of systole, without increasing calcium and/or oxygen consumption. Omecamtiv mecarbil binds to a site that stabilizes the molecule, promoting a greater number of actin-myosin interactions, increasing the amount of energy generated with each ventricular systole.[4]

Pre-clinical studies have demonstrated a significant improvement in increased cardiac output, improved myocardial tension, decreased end-systolic and end-diastolic volumes, improved LVEF, and reduced natriuretic peptides.[5]

The Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) study[6] evaluated whether oral treatment with omecamtiv mecarbil in patients with HFrEF reduced the risk of HF events and cardiovascular death.

The study included a total 8,256 patients between 18 and 85 years of age, New York Heart Association functional class (NYHA FC) II, III, or IV, and LVEF 35% or lower. Patients were hospitalized for HF, had been treated in the emergency department, or had been hospitalized for HF within 1 year. Patients were required to have N-terminal pro–B-type natriuretic peptide (NT-proBNP) of at least 400 pg/mL or B-type natriuretic peptide (BNP) of at least 125 pg/mL; in those with atrial fibrillation or flutter, the NT-proBNP cut-off level was 1,200 pg/mL, and the BNP cut-off level was 375 pg/mL. Other drug interventions or devices could be indicated according to the investigator.

The primary composite endpoint was a HF event (emergency room visit or hospitalization due to HF) or cardiovascular death, and secondary endpoints were cardiovascular death, change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score, first hospitalization for HF, and all-cause death.

Randomization was 1:1 to placebo or omecamtiv mecarbil at doses of 25 mg, 37.5 mg, or 50 mg twice daily according to the drug plasma level.

Average age of patients was 64 years. A quarter of patients were included during hospitalization; 96% were in NYHA FC II or III. Mean systolic pressure was 116 mmHg; mean LVEF was 26%. NT-proBNP was 2000 pg/mL, and glomerular filtration rate was 58 ml/min/1.73 m^2. The prescription of drugs that change prognosis was high (4% with angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor and 94% with beta-blocker), but sodium-glucose co-transporter 2 inhibitor was still in a small proportion (2.5%). The results demonstrated a reduction in the primary composite outcome of 37% in the omecamtiv mecarbil group and 39% in the placebo group (OR: 0.92; 0.86 to 0.99; p = 0.03), but there was no difference in the secondary outcomes of cardiovascular death (19.6% versus 19.4%; OR: 1.01; 0.92 to 1.11), change in KCCQ, hospitalization for HF, or emergency room visit for HF (27.7% versus 28.7%). The omecamtiv mecarbil group had a 10% reduction in median NT-proBNP (Figure 1).

Post-hoc analysis analyzed the results of the GALACTIC-HF study according to the following LVEF quartiles: ≤ 22% (n = 2,246), from 23% to 28% (n = 2210), from 29% to 32% (n = 2,026), and ≥ 33% (n = 1,750).[7] Patients in the omecamtiv mecarbil group with lower LVEF had a 17% relative risk reduction for the primary outcome (EF ≤ 22%; OR: 0.83; 95% confidence interval: 0.73 to 0.95) compared to patients with EF ≥ 33% (OR: 0.99; 95% confidence interval: 0.84 to 1.16; interaction as EF by quartiles, p = 0.013). However, the most significant finding was the reduction in first HF events in patients with lower LVEF. In patients with EF ≥ 33%, it was 26% versus 24% (OR 1.04; 0.86 to 1.25), and, in patients with LVEF ≤ 22%, it was 31% in the omecamtiv mecarbil group and 37% in the placebo group (OR: 0.81; confidence interval: 0.70 to 0.93).

Conclusion: These results suggest that omecamtiv mecarbil may be a useful drug in patients with more severe disease or patients at greater risk of death or HF instability.

Vericiguat

Drugs that modulate evolution and survival in HF include vasodilators, which stimulate the production of nitric oxide, but they are not the only ones, given that other drugs that also change the evolution used to this end increase production. However, there was no success, for example, with phosphodiesterase-5 inhibitors or with synthetic BNP, and those vasodilators considered effective have the characteristic of inducing tachyphylaxis. New vasodilators can be very useful for patients with HF and, to this end, vericiguat was developed and tested.

Vericiguat is a drug that stimulates soluble guanylate cyclase by binding at a site independent of nitric oxide, increasing the activity of the cyclic guanosine monophosphate pathway and endogenous production of nitric oxide, also stabilizing the binding of nitric oxide to its binding site[8,9] (Figure 2). A drug that increases the availability of nitric oxide tends to have a positive impact on HF, given that NO2 depletion is part of the pathophysiology of ventricular dysfunction, leading to vasoconstriction, vascular stiffness, stimulation of fibrosis, ventricular remodeling, and retention of sodium and water.

The drug then appeared to be a viable and potentially promising alternative; therefore, several studies were developed to study its effect in patients with both HFrEF and HFpEF.

The Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA),[11] evaluated the

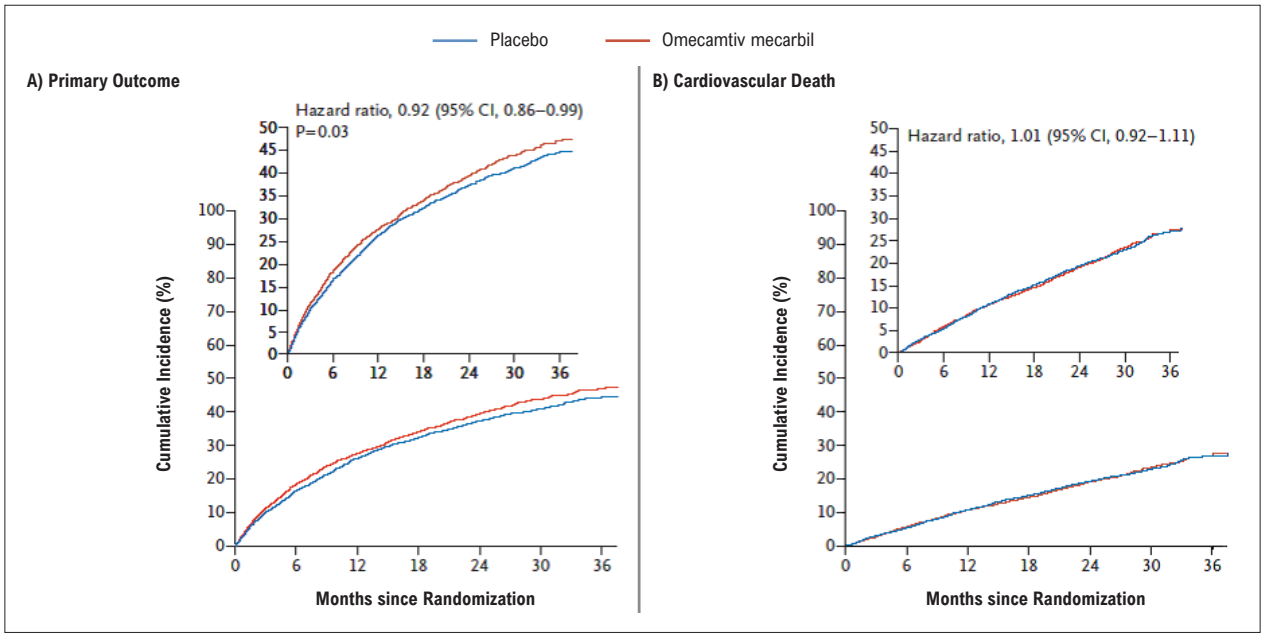

Figure 1 – *Primary and secondary outcomes of cardiovascular death of the GALACTIC-HF study.*

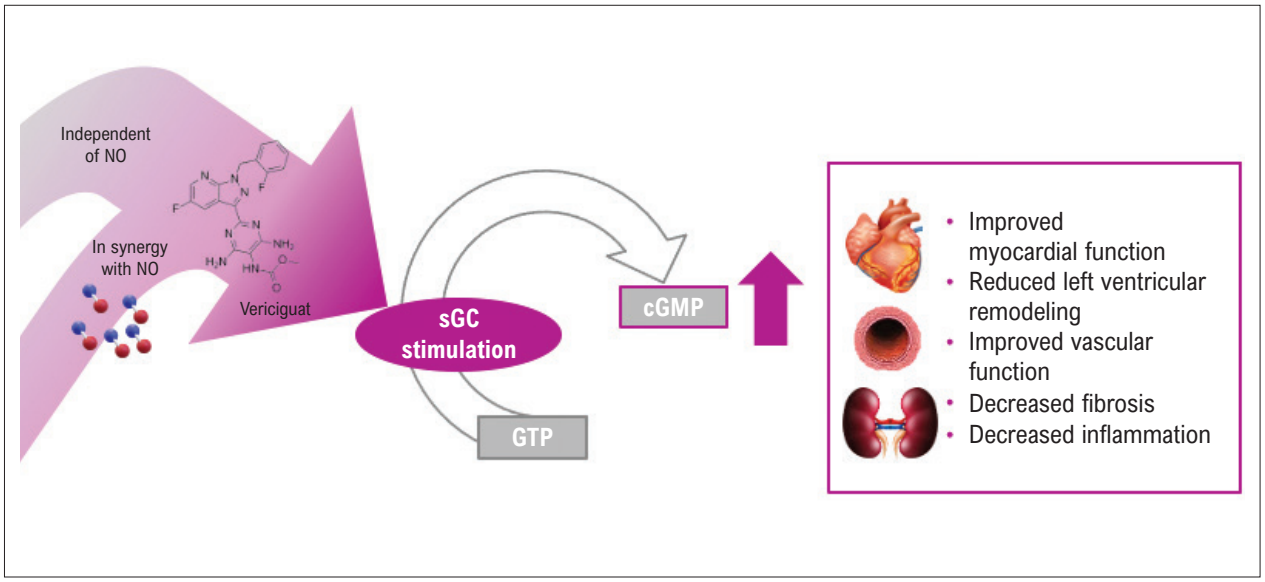

Figure 2 – *Mechanism of action of vericiguat (adapted from Armstrong et al.[9] and Gheorghiade et al.[10])*

efficacy and safety of vericiguat in patients with reduced EF and chronic HF with recent decompensation. They included 5,050 patients over 18 years of age, with HF in NYHA FC II, III, or IV and LVEF below 45% up to 12 months before randomization, BNP of 300 pg/mL or more and NT-proBNP of 1,000 pg/mL or more, and, in patients with atrial fibrillation, BNP of at least 500 pg/mL and NT-proBNP of at least 1,600 pg/mL. Evidence of worsening HF was assessed in the following 3 situations: hospitalized within 3 months before randomization, hospitalized from 3 to 6 months, and received intravenous administration within 3 months, but without hospitalization. Patients with glomerular filtration rate lower than 30 mL/min/1.73 m^2, between 15 and 30, but limited to 15% of the sample, were also included. Patients were randomized 1:1 to receive 2.5 mg vericiguat or placebo; doses increased to 5 mg and finally to the target dose of 10 mg once daily, according to blood pressure and clinical symptoms. Standard drug therapy for HF was balanced in both groups, and 60% of patients were on triple therapy (a beta-blocker, a mineralocorticoid antagonist, and an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor), with 15% using an angiotensin receptor-neprilysin inhibitor. Median dose was 9.2 mg in both the vericiguat and placebo groups, but, at 12 months, about 90% of patients were receiving the target dose of 10 mg.

Median age was 67 years; two thirds of patients were within 3 months of hospitalization; 40% were in NYHA FC III and 59% in NYHA FC II. Mean LVEF was 29%, and mean NT-proBNP level was 2,816 pg/mL.

The primary outcome, cardiovascular death or first hospitalization for HF, occurred in 35.5% in the vericiguat group and 38.5% in the placebo group (OR: 0.90; 0.82 to 0.98; p = 0.02). Cardiovascular death occurred in 16.4% in the vericiguat group and 17.5% in the placebo group (OR: 0.93; 0.81 to 1.06). Hospitalization for HF occurred in 27.4% in the vericiguat group and 29.6% in the placebo group (OR: 0.90; 0.81 to 1.00), but, regarding total hospitalizations and recurrent hospitalizations for HF, there were 1,223 hospitalizations (38.3 events per 100 patient-years) in the vericiguat group and 1,336 hospitalizations (42.4 events per 100 patient-years) in the placebo group (OR: 0.91; 0.84 to 0.99; p = 0.02). All-cause death occurred in 20.3% in the vericiguat group and in 21.2% in the placebo group (OR: 0.95; 0.84 to 1.07; p = 0.38). A secondary outcome, all-cause death or first hospitalization for HF, occurred in 37.9% in the vericiguat group and in 40.9% in the placebo group (OR: 0.90; 0.83 to 0.98; p = 0. 02) (Figure 3).

The benefits were similar in all strata, including different LVEF. Serious adverse events occurred in a considerable number, approximately one third of the patients, but this was the same in the vericiguat and placebo groups; serious and non-serious events also occurred in 80% in both groups, here undoubtedly caused by the severity of the patients included.

A relevant finding is that, in the VICTORIA study, there were more patients with HF in NYHA FC III or IV compared to the PARADIGM and DAPA-HF studies, and the level of NT-proBNP in the patients of the VICTORIA study was almost double, which may have attenuated the benefits.

The results of the VICTORIA study provide us with an additional tool for stabilizing patients with advanced HF, progressive worsening of the disease, or refractory patients.

Other studies with vericiguat include the Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study (SOCRATES-REDUCED), whose primary objective was the reduction of NT-proBNP by week 12.[12] Although there was no benefit in the primary outcome, exploratory analysis suggested that, at the highest doses, there was a significant reduction in NT-proBNP.

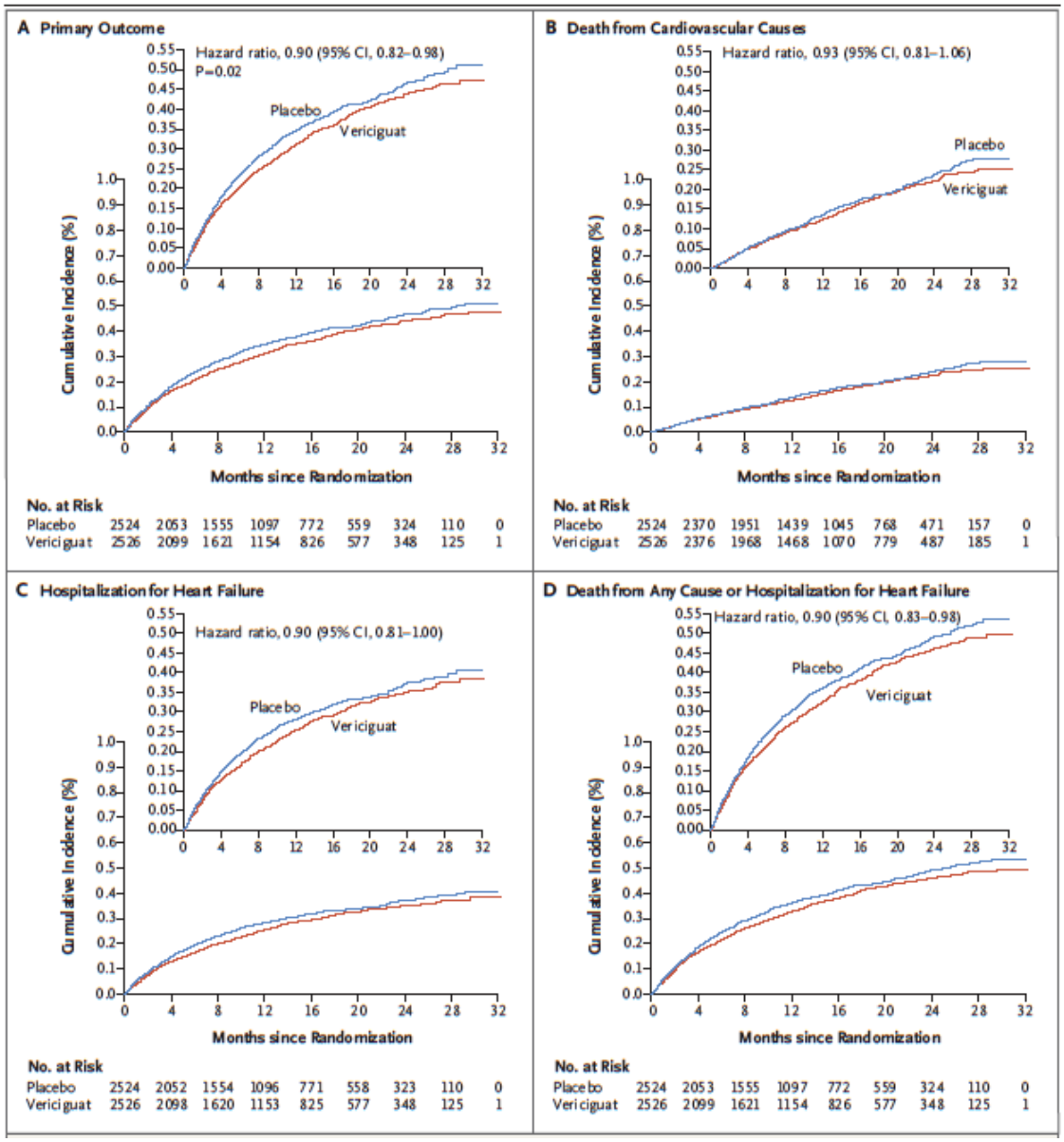

Figure 3 – *Estimates of the incidence of the primary and secondary outcomes.*

Another exploratory analysis, from the VICTORIA study, evaluated the effect of vericiguat on the evolution of renal function, and the authors concluded that the evolution of renal function was similar between patients treated with vericiguat and placebo.[13]

Vericiguat has also been tested in patients with HFpEF. The objective of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED ejection fraction study (SOCRATES-PRESERVED) was to determine the dose of vericiguat in symptomatic patients with LVEF ≥ 45%, with the primary outcome of change in NT-proBNP and left atrial volume. To do this, doses were given once a day at 1.25 or 2.5 mg, or 5 or 10 mg titrated from an initial dose of 2.5 mg, or placebo for 12 weeks. Patients had mean age of 73 years, mean LVEF 57%, and atrial fibrillation 40%. At all dosages, the variation in NT-proBNP and left atrial volume were not different from patients in the placebo group. Vericiguat was well tolerated with little discontinuation. Quality of life was also assessed using the KCCQ and the score improved in the vericiguat 10 mg arm by 19.3 ± 16.3 points compared to baseline (p = 0.016).[13]

Another study, Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction (VITALITY-HFpEF)[14] analyzed 789 patients with mean age

of 73 years, mean LVEF of 56%, and mean NT-proBNP of 1,403 pg/mL. They were randomized to 15 mg or 10 mg daily of vericiguat or placebo, and the KCCQ scores in relation to the baseline and the 6-minute walk test showed no difference after 24 weeks of follow-up. Once again the drug was well tolerated.

Conclusion: Vericiguat is a drug that has shown benefits when used at an adequate dose for patients with HFrEF, and it will certainly be a new therapeutic tool for patients with progressive HF, patients with repeated hospitalizations or emergency room visits, and in patients at a higher risk of death or hospitalization. There is still a lack of data to support its use in patients with HFpEF.

Author Contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Oliveira Jr. MT; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Oliveira Jr. MT, Barretto ACP, Del Carlo CH, Jallad S, Chaud MAS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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