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Vericiguat for the treatment of heart failure: mechanism of action and pharmacological properties compared with other emerging therapeutic options

Jean-Sébastien Hulot, MD[*,1,2]; Jean-Noël Trochu, MD[3]; Erwan Donal, MD, PhD[4]; Michel Galinier, MD[5]; Damien Logeart, MD[6]; Pascal de Groote, MD[7]; Yves Juillière, MD[8]

1 Université de Paris, INSERM, PARCC, F-75006 Paris, France ;
2 CIC1418 and DMU CARTE, AP-HP, Hôpital Européen Georges-Pompidou, F-75015, Paris, France; Email: jean-sebastien.hulot@aphp.fr

3 Université de Nantes, CHU Nantes, CNRS, INSERM, l'institut du Thorax, F-44000 Nantes, France. Email: jeannoel.trochu@chu-nantes.fr

4 LTSI INSERM U1099, Service de Cardiologie et Maladies Vasculaires, Centre Hospitalier Universitaire de Rennes, Université Rennes 1 35000 Rennes, France. Email: erwan.donal@chu-rennes.fr

5 Department of Cardiology, Toulouse-Rangueil University Hospital, Toulouse University School of Medicine, TSA 50032, 31059 Toulouse Cedex 9, France. Email: galinier.m@chu-toulouse.fr

6 Department of Cardiology, Lariboisière Hospital, Paris, France; Université de Paris, Paris, France. Email: damien.logeart@aphp.fr

7 CHU Lille, Service de Cardiologie, F-59000 Lille, France, INSERM U1167, Institut Pasteur de Lille, F-59000 Lille, France. Email: pascal.degroote@chru-lille.fr

8 Centre Hospitalier Universitaire de Nancy Brabois, 54500 Vandoeuvre Lès Nancy, France. Email: yves.juilliere@wanadoo.fr

***Author for correspondence:** Jean-Sébastien Hulot, Hôpital Européen Georges Pompidou, 20 Rue Leblanc, F-75015, Paris, France. Email: jean-sebastien.hulot@aphp.fr

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Abstract

Introduction: The significant morbidity and mortality in patients with heart failure (HF), notably in the most advanced forms of the disease, justify the need for novel therapeutic options. In the last year, the soluble guanylate cyclase (sGC) stimulator, vericiguat, has drawn the attention of the medical community following the report of reduced clinical outcomes in patients with worsening chronic HF (WCHF).

Areas Covered: The authors review the available data on the mechanism of action of vericiguat (cyclic guanosine monophosphate (cGMP) pathway), its clinical development program, its role in HF management, and its future positioning in the therapeutic recommendations.

Expert opinion: cGMP deficiency has deleterious effects on the heart and contributes to the progression of HF. Different molecules, including nitric oxide (NO) donors, phosphodiesterase inhibitors, and natriuretic peptides analogues, target the NO-sCG-cGMP pathway but have yielded conflicting results in HF patients. Vericiguat acts as a sGC stimulator thus targeting the NO-sGC-cGMP pathway by a different mechanism that complements the current pharmacotherapy for HF. Vericiguat has shown an additional statistical add-on therapy efficacy by reducing morbi-mortality in patients with WCHF. A better evaluation of HF severity might be an important determinant to guide the use of vericiguat among the available therapies.

Keywords (5-8): cGMP pathway; heart failure (HF); heart failure hospitalization (HFH); heart failure with reduced ejection fraction (HFrEF); reduced left ventricular ejection fraction (LVEF); soluble guanylate cyclase (sGC); sGC stimulator; ventricular remodeling; vericiguat; worsening chronic heart failure (WCHF).

Article Highlights

- cGMP deficiency is common in HF.
- Different therapies targeting the NO-sGC-cGMP pathway have been evaluated in HF patients but with conflicting results.
- Vericiguat is an sGC stimulator with an original mechanism of action.
- Vericiguat enhances sGC sensitivity to endogenous NO, thus exerts a more physiological action.
- Vericiguat reduces clinical outcomes in patients with worsening chronic HFrEF.

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- At a pharmacological level, vericiguat and ARNIs could have synergistic effects.

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1. Introduction

The economic burden of heart failure (HF) is increasing [1] with more than 26 million people worldwide affected by this condition [2]. After initial diagnosis and therapeutic management, HF patients can present a progressive deterioration of their HF symptoms leading to increased medical needs, intensification of therapies and hospitalization requirements [3,4]. These patients were recently defined as having worsening chronic heart failure (WCHF), and impose a growing healthcare burden because of recurrent medical needs and re-hospitalizations. In addition, quality of life is greatly impaired in patients with HF [5], and to a similar extent in patients with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) [6].

Available pharmacological therapies in HFrEF consist of renin-angiotensin-aldosterone system (RAS) blockers (either angiotensin-converting-enzyme inhibitor [ACEI] or angiotensin receptor blockers [ARB]), or angiotensin receptor-neprilysin inhibitors (ARNIs, such as sacubitril/valsartan) and mineralocorticoid receptor antagonists (MRAs), that are combined to beta-blockers and diuretics including loop diuretics [7]. When required, a cardiac resynchronization therapy ± implantable cardioverter defibrillator are used. While these therapies address the main pathophysiological mechanisms activated in HF, the WCHF population remains at risk of high event rates despite their effectiveness. Consequently, there is a clinical unmet need to provide more therapeutic options investigating new pathways for patients with WCHF.

Among molecules, the impairment and deficiency of soluble guanylate cyclase (sGC) in cyclic guanosine monophosphate (cGMP) in HF is not directly targeted by available HF therapies. Deficiency of cGMP and resistance to the cGMP-dependent tissue effects of natriuretic peptides (NP) have however been reported for a long time in HF. Several drugs modulating the nitric oxide (NO)-cGMP pathways have been evaluated in HF, notably with NO donors (i.e., nitrates) or by reducing cGMP degradation with phosphodiesterase (PDE) inhibitors. More recently, novel drugs have been developed to directly increase the production of cGMP. In this context, novel classes of drugs called sGC stimulators (riociguat and vericiguat) and sGC activators (cinaciguat and ataciguat) were developed as an emerging therapy with a mechanism distinct from other available HF therapies [8], and vericiguat was particularly evaluated in HF patients.

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2. Approved Use

This paper will focus on vericiguat which has been developed and recently tested for the treatment of WCHF in adults with left ventricular ejection fraction (LVEF) below 45% to reduce the risk of cardiovascular (CV) death and heart failure hospitalization (HFH), in combination with other HF therapies.

2.1. Mechanism of Action of Vericiguat

sGC has a key role in generating cGMP [9] with sGC-derived production of cGMP being essential for normal cardiac and vascular function [10-12]. cGMP is indeed a key second messenger to mediate vaso- and cardiac relaxation. In HF, NO availability and functionality of sGC are impaired, resulting in an increased oxidative stress and loss of cGMP production. In other terms, the NO–sGC–cGMP pathway is impaired in HF which may contribute to the progression of cardiovascular disease (CVD) in terms of endothelial, myocardial and vascular dysfunction [11,13]. Notably, a deficiency in cGMP is common to both HFrEF and HFpEF [12]. Oxidative stress can also stimulate autophagy, apoptosis, or necrosis, leading to the loss of cardiomyocytes and their replacement with collagen, and to fibrosis [14,15]. Moreover, left-ventricular remodeling/stiffness is associated with hypophosphorylation of titin found in cardiomyocytes which is associated with an impaired cGMP-dependent protein kinase G (PKG) activity [16-18]. Titin is the third myofilament of the cardiac muscle [19]. By having direct and indirect links with several signaling molecules and having multiple phosphorylation sites in the Z-disk, M-band, and I-band (containing the N2B element) segments, titin is recognized as a major regulator of cardiomyocyte stiffness. For example, the level of phosphorylation of the N2B element, notably through PKG, regulates the myofibrillar stiffness [19].

Vericiguat is an oral drug with a once-daily dosing schedule, that acts as a direct stimulator of the sGC enzyme. Vericiguat was developed to be indicated upon regulatory approval as a first-in-class therapy for WCHF [20]. Vericiguat has an optimized pharmacokinetic profile with a higher half-life as compared with the first sGC stimulator, riociguat, thus allowing the development of a once-daily oral administration regimen [21]. Vericiguat works in synergy with endogenous NO [13,22]

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which is considered as a nitrovasodilator to produce cGMP under low-NO conditions. Accordingly, vericiguat treatment is expected to restore the impaired NO–sGC–cGMP pathway leading to a diversity of pharmacological effects including improvements in cardiac and vascular functions, and reduction in pro-fibrotic and inflammatory pathways [11,20] (Figure 1). By increasing cGMP, vericiguat is also estimated to induce vasorelaxation and improve regulation of vascular tone and myocardial dysfunction [13,23,24]. It would also attenuate left-ventricular remodeling by inducing PKG-mediated phosphorylation of titin following the activation of PKG by cGMP [24]. On the hemodynamic level and based on the CHEST and PATENT studies on riociguat [26,27], vericiguat is believed to improve the cardiac index through its vasodilator effect without exhaustion of this effect in contrast with other vasodilators. As for the extra-cardiac effects of vericiguat, this molecule has antiagregant and antifibrotic (potential benefit in kidney failure) properties [28]. Thus, vericiguat is anticipated to improve myocardial and endothelial functions in patients with HF and potentially with WCHF [9].

Importantly, intracellular cGMP is produced by two independent pathways, the NO-sGC-cGMP and the NP-particulate guanylate cyclase (pGC)-cGMP pathway (Figure 2). While the NO-sGC-cGMP pathway is driven by sGC, the NP-pGC-cGMP pathway is driven by a membrane-bound, pGC. ARNIs such as sacubitril/valsartan are currently available for the treatment of HF, targeting the NP-pGC-cGMP pathway by inhibiting degradation of NP and many other vasoactive mediators. Thus, both vericiguat and sacubitril/valsartan can lead to cGMP augmentation through different pathways with a potentially synergistic effect between both agents, due to the contemporary stimulation of the two cGMP-generating pathways. It is also possible that vericiguat, sacubitril/valsartan, and other therapies that increase cGMP levels could lead to an increase of distinct and specific intracellular pools of cGMP which could then act synergistically. In this respect, a subgroup analysis of patients treated with sacubitril/valsartan in the Phase 3 VICTORIA trial suggested a potential synergistic effect of the vericiguat and sacubitril/valsartan combination [29].

On a different note, the sGC stimulator, vericiguat, differs from current therapies targeting the NO-sGC-cGMP pathway such as NO donors, PDE5 inhibitors, ACEIs/ARBs, and ARNIs (sacubitril/valsartan), with no proven efficacy in HF for some of them (NO donors and PDE5 inhibitors):

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- While NO donors act upstream of the NO-sGC-cGMP pathway, vericiguat restores cGMP production even under low-NO conditions and high oxidative stress.
- Unlike PDE5 inhibitors that act downstream of the NO-sGC-cGMP pathway by preventing the breakdown of cGMP, vericiguat directly stimulates sGC to increase cGMP concentration [8].
- Independent of RAS blockers (i.e. ACEIs/ARBs and ARNIs) and sympathetic nervous system blockers (i.e. beta-blockers), sGC stimulation is a highly effective way to actively restore the NO-cGMP pathway.
- Although ARNIs increase cGMP levels by indirectly blocking neprilysin-mediated degradation of NP, vericiguat directly stimulates sGC to significantly increase intracellular cGMP concentration [6,40,41].

Lastly, vericiguat has been shown to have advantages over sGC activators such as cinaciguat. Cinaciguat was administered as an intravenous infusion in patients with acute decompensated HF but induced hypotension without improving dyspnea or the cardiac index in the COMPOSE trials [42] In contrast to vericiguat, cinaciguat activates sGC irrespective of NO bioavailability, which may support higher vasodilatation effects [43]. Cinaciguat was consequently not further developed for HF patients.

2.2. Clinical Development of Vericiguat in HFrEF

SOCRATES-REDUCED (or Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study) was a Phase 2b dose-finding trial [44]. It aimed to determine the optimal dose and tolerability of vericiguat in 456 clinically stable patients with a LVEF <45% within 4 weeks of a WCHF event. The patients were equally randomized to receive either placebo or 1 of 4 daily doses of oral vericiguat (1.25 mg, 2.5 mg, 5 mg, 10 mg) for 12 weeks. No significant difference between the pooled vericiguat group and placebo was reported for the primary outcome measure which was change in log-transformed level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) between baseline and Week 12. In parallel, HFH tended to be reduced in the 2 highest dose groups (5 and 10 mg), this effect was less visible with CV death. Some hypotension and syncopes were noted after administration of the first doses. However, after this initiation phase, vericiguat showed no effect on blood pressure (BP) although a vasodilatation and reduction of systolic BP were hypothesized given the effect of sGC stimulators such as riociguat on pulmonary hypertension [26,27]. In the vericiguat 10

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mg/day group, treatment-emergent syncope and hypotension were more common although this effect tended to occur within the first 2 weeks of randomization while receiving the 2.5-mg dose.

VICTORIA was a Phase 3 global randomized, double-blind, placebo-controlled trial which evaluated the efficacy and safety of vericiguat in patients with HFrEF with recent decompensated HF. A total of 5,050 eligible patients were randomly assigned to receive vericiguat at 10 mg/day (n=2,526) or placebo (n=2,524), in addition to recommended therapy. The primary endpoint was a composite of CV death or first HFH, and pre-specified safety event of interest were syncope and symptomatic hypotension [29]. Inclusion criteria and baseline characteristics of participants [45] are comparable with the characteristics of participants in SOCRATES-REDUCED study (patients with worsening chronic HFrEF) with the only difference that intravenous diuretics were administered within 24 hours in Phase 2 SOCRATES-REDUCED versus 3 months before randomization in Phase 3 VICTORIA. WCHF was defined as a recent HF event or 'progressively escalating symptoms and signs of HF' requiring treatment in the outpatient, emergency room, or hospital setting and is associated with a 'markedly worse prognosis' [3,4].

Results of Phase 3 VICTORIA were recently published [29]. Patients who received vericiguat had a lower incidence of CV death (n=414; 16.4%) or HFH (n=691; 27.4%) versus those who received placebo (CV death: n=441; 17.5% / HFH: n=747; 29.6%) [29]. Syncope was reported in 4% and symptomatic hypotension in 9.1% of the patients in the vericiguat group versus 3.5% and 7.9% of the patients in the placebo group, respectively, without any significant statistical difference between both treatment groups [29]. The positive data of VICTORIA trial supported the submission of the marketing authorization application to the European Medicines Agency and new drug application to the Ministry of Health, Labor and Welfare in Japan in June 2020 [46]. These regulatory submissions were made for using vericiguat in the treatment of WCHF in adults with LVEF <45% to reduce the risk of CV death and HFH, in combination with other HF therapies.

3. Competitive Environment

3.1. Current and Future Landscape in the Treatment of HFrEF

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Emerging therapeutic options for patients with HFrEF include sacubitril/valsartan, sodium-glucose cotransporter-2 inhibitors (SGLT2i), and omecamtiv mecarbil. This section summarizes the main characteristics of each class as compared to vericiguat.

Sacubitril/valsartan, an ARNI, simultaneously inhibits neprilysin and blocks angiotensin II type-1 receptors [47]. Sacubitril/valsartan has shown a benefit in patients with HFrEF and LVEF<40% in the PARADIGM study. In addition, PIONEER-HF and TRANSITION Phase 4 trials support its initiation during hospitalization as soon as hemodynamic parameters have been stabilized from an acute HF episode in ACEI/ARB-naïve patients [47,48]. Also, sacubitril/valsartan showed encouraging results in terms of a favorable safety profile and reduction of plasma NT-ProBNP levels in patients with HFrEF [48,49]. As previously exposed, both sacubitril/valsartan and vericiguat are increasing cGMP levels, but through two independent pathways. The titration and use of sacubitril/valsartan is hampered by its tolerance on the BP. It is thus anticipated that the combination of sacubitril/valsartan with vericiguat might be revealed difficult into the clinics, especially in patients with WCHF and low BP.

SGLT2i, also called gliflozins such as empagliflozin, canagliflozin, sotagliflozin, and dapagliflozin, are used in the treatment of type 2 diabetes mellitus (T2DM). New guidelines include empagliflozin, canagliflozin, or dapagliflozin in patients with T2DM and CVD, or at high to very high CV risk, to reduce CV events [50]. SGLT2i represent also a promising therapeutic option for patients with HFrEF [51]. The DAPA-HF Phase 3 randomized trial compared effects of dapagliflozin to placebo in 4,744 patients with chronic HF and LVEF ≤40%, with or without diabetes, and showed a significant 26% reduction of the primary endpoint (WCHF event or CV death) [52]. In parallel, the EMPEROR-Reduced Phase 3 trial investigated effects of empagliflozin on time to CV death or first HFH in 3,730 patients with chronic HFrEF (LVEF ≤40%) [53]. Empagliflozin reduced significantly the primary endpoint by 25% (hazard ratio of 0.75; 95% confidence interval: 0.65-0.86, p-value <0.0001) [53]. Lastly, sotagliflozin, a SGLT1 and SGLT2i, was shown to reduce the rate of death from CV causes and HFH (hazard ratio of 0.67; 95% confidence interval: 0.52-0.85; p-value <0.001) in patients with diabetes and recent worsening HF in the SOLOIST-WHF trial [54]. Overall, these clinical trials advocate for a beneficial class effect of SGLT2i in HF patients. SGLT2i stimulate natriuresis and osmotic diuresis which reduces BP and intravascular volume, and thus decreases cardiac preload and afterload [55]. Other potential mechanisms of improved

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cardiac function with SGLT2i are, but not limited to, an increased myocardial energetics, an improved myocardial autophagy, inhibition of cardiac fibrosis, and a reduction in left ventricular mass and in the activity of the calcium/calmodulin-dependent protein kinase II [56]. Given that SGLT2i and vericiguat will be almost simultaneously marketed, cardiologists need to be guided to choose the most appropriate therapeutic option according to the patients' profile. There is especially no evidence from clinical trials of SGLT2i and vericiguat combined together in this setting. On a pharmacological viewpoint, SGLT2i present some additional advantages over vericiguat (Table 1). An important issue relates to the tolerance profile of vericiguat on BP as HF patients are already treated with multiple therapies that lower BP. This issue might not be observed with SGLT2i, which remains to be confirmed in the upcoming clinical trials. Additional benefits of SGLT2i are their kidney-protective effects and their preventive effect in the onset of diabetes.

Omecamtiv mecarbil is a selective cardiac myosin activator that can increase cardiac contractility, reverse ventricular remodeling and reduce NT-ProBNP; without affecting intracellular myocyte calcium concentrations or myocardial oxygen consumption [62]. It thus appears that the overlap in the mechanism of action between omecamtiv mecarbil and vericiguat is limited. The hypothesis on its efficacy in the treatment of HFrEF highlights a different pathway to vericiguat and is being addressed in two Phase 3 trials (GALACTIC-HF and METEORIC-HF). In GALACTIC-HF, omecamtiv mecarbil reduced significantly but weakly the primary endpoint, time to CV death or first HFH, by 8% in patients with chronic HFrEF [61,63]. METEORIC-HF is evaluating its effect on exercise capacity [64] and patient recruitment is still ongoing.

4. Expert Opinion

cGMP deficiency has deleterious effects on the heart and contribute to the progression of HF. Different molecules, including NO donors, PDE inhibitors, and NP analogues, target the NO-sCG-cGMP pathway but have yielded conflicting results in HF patients. Among other effects, ARNIs increase the cGMP levels and significantly improve the prognosis of HF patients with LVEF ≤35%. Vericiguat acts as a sGC stimulator thus targeting the NO-sGC-cGMP pathway by a different mechanism that complements the

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current pharmacotherapy for HFrEF.

In the VICTORIA trial, vericiguat has shown an additional statistical add-on therapy efficacy by reducing morbi-mortality in patients with WCHF. Whether potentiating cGMP signaling might be additive or synergistic with other therapeutic options for HF requires to be better delineated. Notably, as ARNIs increase cGMP levels by indirectly blocking neprilysin-mediated degradation of NP, an open question relates to the efficacy that could be achieved by combining sacubitril/valsartan with vericiguat in patients with HFrEF. Different markers indicate that the patients included in the VICTORIA trial had a higher baseline risk as compared with patients in contemporary trials testing other therapeutic options, including ARNIs, and SGLT2i. A better evaluation of the severity of HF patients might be an important determinant to guide the use of vericiguat among the available therapies. Reciprocally, there is currently limited evidence that vericiguat provides a similar benefit in patients with HFpEF, as exemplified by the lack of significant changes in markers of cardiac remodeling in the SOCRATES-preserved trial [65] or physical activity scores in the VITALITY-HFpEF trial [66]. On a side note, new ESC guidelines on the management of HF are planned for 2021. The current opinion does not aim to anticipate the recommendations to avoid contraindications, in any. However, the guidelines provide a general framework and the expert opinion would allow for a more precise/refined approach on individualized decisions.

Finally, the concept of WCHF is appealing but novel in the realm of HF management which is traditionally organized between acute and chronic stable conditions. Thus, the appropriate identification of such patients might be challenging. As such, WCHF is not defined as decompensated HF, which evokes rather more severe cases who are often hospitalized. In some countries, outpatient management of decompensated patients is not the norm, which justifies the need for an adapted treatment course. From that perspective, defining the profile of patients eligible for vericiguat treatment is important. These include worsening chronic HrEF after a decompensation event (whether or not patients received gliflozins), intolerance to other therapeutic options, and specific comorbidities (e.g. renal failure).

Future directions would potentially focus on establishing HF units and providing funds to enhance specialist nursing to ensure ambulatory follow-up with primary care physicians and cardiologists. Hence, telemedicine is expected to ensure a close but

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remote follow-up of the patients, especially in terms of vericiguat titration and safety through telemonitoring.

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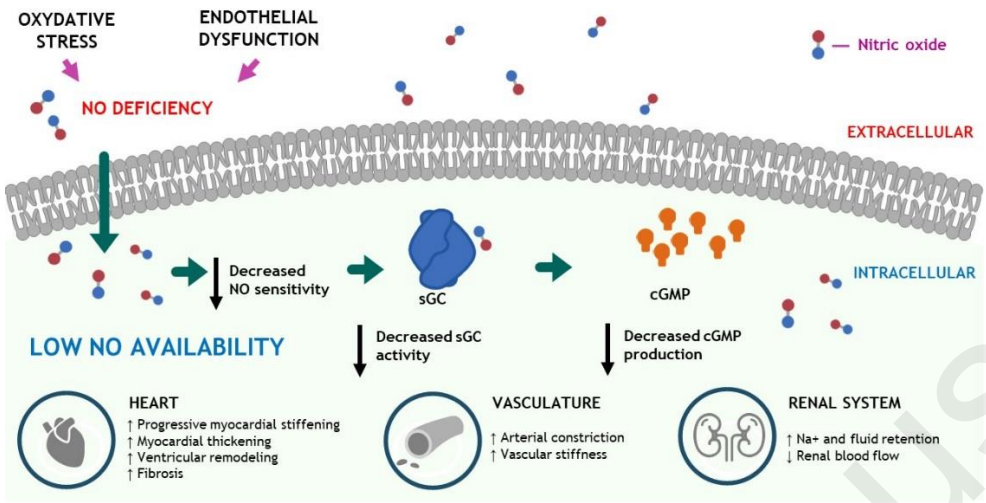
Figure Legends

A.



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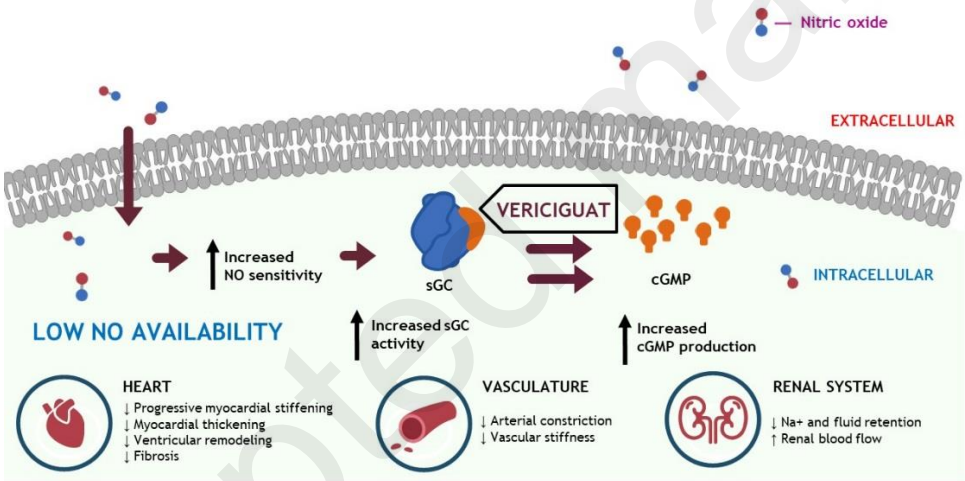

Figure 1. Mechanism of action of vericiguat and related clinical effects [8,20,22,30-34].

A: The NO-sGC-cGMP pathway is not currently medically addressed. Under normal conditions, NO travels through the cell membrane and binds to sGC which in turn leads to an increased availability of cGMP. However, under conditions of oxidative stress and endothelial dysfunction commonly found in patients with HF, there is a significant deficiency in NO. This low NO availability leads to a decreased activity of the sGC as well as a reduction in its sensitivity to NO. Ultimately, this results in a reduction in cGMP production that has deleterious downstream effects for the heart, vasculature and renal system. **B:** Vericiguat helps restore the deficient NO-sGC-cGMP pathway in patients with HF. By directly stimulating the sGC independently, it helps increase its activity independent of endogenous NO, which results in an increased production of cGMP. This in turn leads to a reduction of the deleterious effects of the deficient NO-sGC-cGMP pathway on the heart, vasculature and renal system with a reduction in myocardial and

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vascular stiffening, a reduction in fibrosis of the myocardium etc. Also, by increasing sGC sensitivity to NO, its cGMP output is further improved.

Abbreviations: cGMP: cyclic guanosine monophosphate; HF: heart failure; Na: sodium; NO: nitric oxide; sGC: soluble guanylate cyclase.

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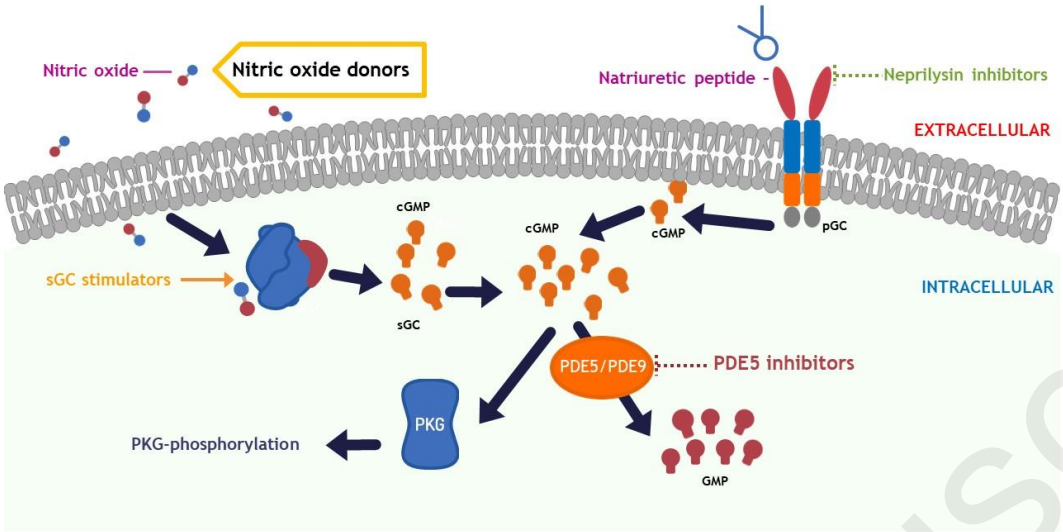

Figure 2. cGMP augmentation through different pathways in the treatment of heart failure with vericiguat (NO-sGC-cGMP pathway) and sacubitril/valsartan described as ARNI (NP-pGC-cGMP pathway) [8,9,13,35,39].

This graph shows the synergistic effect of sGC stimulators and neprilysin inhibitors (e.g. ARNI) in augmenting the cGMP availability via the NO-sGC-cGMP and the particulate CG-cGMP pathways respectively.

Abbreviations: ARNI: angiotensin receptor-neprilysin inhibitor; cGMP: cyclic guanosine monophosphate; GTP: guanosine triphosphate; NO: nitric oxide; NP: natriuretic peptides; pCG: particulate guanylate cyclase; PDE: phosphodiesterase; PKG: protein kinase G; sGC: soluble guanylate cyclase.

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Table 1. Comparison of data between Phase 3 HFrEF studies.

		Sacubitril/valsartan	Gliflozins		Vericiguat	Omecamtiv mecarbil
Mechanism of action		ARB + ARNI (indirect cGMP stimulation)	SGLT2i		cGMP stimulation (direct sGC stimulation)	Cardiac myosin activator
Phase 3 HFrEF study		PARADIGM-HF [57,58]	DAPA-HF [52,59]	EMPEROR-Reduced [53Erreur ! Signet non défini.]	VICTORIA [29,45]	GALACTIC-HF [60,61]
Main criteria	**Inclusion**	• LVEF ≤40% • NT-proBNP ≥600 pg/Ml	• LVEF ≤40% • NT-proBNP≥600 pg/mL (SR); 900 pg/mL (AF) (400 if hospitalized	• LVEF ≤40% • NT-proBNP cut-off according to EF & AF *	• LVEF <45% + worsening HF • NT-proBNP ≥1,000 pg/mL (SR); 1 600 pg/mL (AF)	• LVEF ≤35% + prior HFH • NT-proBNP ≥400 pg/mL (SR); 1,200 pg/mL (AF)
	Exclusion	• eGFR <30 mL/min	• eGFR <30 mL/min	• eGFR <20 mL/min	• eGFR <15 mL/min	• eGFR <20 mL/min
Patients charac-teristics	**Age at baseline (mean)**	63.8 years	66 years	67 years	67 years	65 years
	NT-proBNP (median)	1,615 pg/Ml	1,437 pg/mL	1,887 pg/mL	2,821 pg/mL	1,988 pg/mL
	HFH within 6 months	37%	16.4%	NA	84%	NA
	AF	36.2-37.4%	38%	35.6-37.8%	45%	27%
	Diabetes	34.7%	41.8%	49.8%	47.1%	40.1%
	eGFR	Serum creatinine (no eGFR): 1.09-1.17 mg/dL	66 mL/min	62 mL/min	61.5 mL/min	58.8 mL/min
Primary endpoint (comparator arm)	*** HFH + CV death ** HFH / urgent visit + CV death**	13.2%*	15.6%**	21%*	37.8%*	39.1%**

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	Sacubitril/valsartan	Gliflozins		Vericiguat	Omecamtiv mecarbil
Median follow-up time (months)	27	18.2	16	10.8	21.8
Prescription information	Bid; titration (mean dose: 375 mg in Paradigm-HF)	Od; no titration		Od; titration (90.3% at target dose in VICTORIA)	Bid; titration
Safety profile	Higher proportions of patients with hypotension and non-serious angioedema versus the enalapril group	No difference in the frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia between treatment groups (versus placebo)	• Slower annual rate of decline in the eGFR with empagliflozin versus placebo • Lower risk of serious renal outcomes with empagliflozin • More frequent uncomplicated genital tract infection with empagliflozin	• Symptomatic hypotension: 9.1% in the vericiguat group versus 7.9% in the placebo group (*p*-value-0.12) • Syncope: 4% in the vericiguat group versus 3.5% in the placebo group • More frequent anemia in the vericiguat group (7.6%) versus the placebo group (5.7%)	• No difference in the frequency of adverse events related to cardiac ischemic events • Similar rates of arrhythmic events
What to monitor	Blood pressure, kidney function, and electrolytes				

* NT-proBNP ≥1,000 pg/mL for EF 31-35%; ≥2,500 pg/mL for EF 36-40%, ≥ 600 pg/mL for EF <30%. These NT-proBNP thresholds were doubled in patients with AF.
Abbreviations: AF: atrial fibrillation; ARB: angiotensin receptor blocker; ARNI: receptor-neprilysin inhibitor; Bid: bis in die (twice a day); cGMP: cyclic guanosine monophosphate; CV: cardiovascular; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HFH: heart failure hospitalization; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NA: not applicable; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OD: *omne in die* (once a day); sGC: soluble guanylate cyclase; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SR: sinus rhythm.

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