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ANMCO position paper on vericiguat use in heart failure: from evidence to place in therapy

Stefania Angela Di Fusco[1]*, Alessandro Alonzo[1], Alberto Aimo[2], Andrea Matteucci[1], Rita Cristina Myriam Intravaia[3], Stefano Aquilani[1], Manlio Cipriani[4], Leonardo De Luca[5], Alessandro Navazio[6], Serafina Valente[7], Michele Massimo Gulizia[8], Domenico Gabrielli[5,9], Fabrizio Oliva[10], and Furio Colivicchi[1]

[1]U.O.C. Cardiologia Clinica e Riabilitativa, Presidio Ospedaliero San Filippo Neri—, ASL Roma 1, 00135, Italy; [2]Interdisciplinary Center for Health Science, Scuola Superiore Sant'Anna, Piazza Martiri della Libertà 33, Pisa, 56127, Italy; [3]Cardiologia 4-Diagnostica e Riabilitativa, Dipartimento Cardiotoracovascolare 'A. De Gasperis', ASST Grande Ospedale Metropolitano Niguarda, Piazza dell'Ospedale Maggiore, 3, Milan, 20162, Italy; [4]U.O. Cardiologia, Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione-ISMETT, Via Ernesto Tricomi 5, Palermo, 90127, Italy; [5]U.O.C. Cardiologia, Dipartimento Cardio-Toraco-Vascolare, Azienda Ospedaliera San Camillo Forlanini, Circonvallazione Gianicolense 87, Rome, 00152, Italy; [6]S.O.C. Cardiologia Ospedaliera, Presidio Ospedaliero Arcispedale Santa Maria Nuova, Azienda USL di Reggio Emilia—IRCCS, Viale Risorgimento 80, Reggio Emilia, 42123, Italy; [7]Dipartimento Cardio-Toracico, A.O.U. Senese, Ospedale Santa Maria alle Scotte, Viale Mario Bracci 16, Siena, 53100, Italy; [8]U.O.C. Cardiologia, Ospedale Garibaldi-Nesima, Azienda di Rilievo Nazionale e Alta Specializzazione 'Garibaldi', Via Palermo 636, Catania, 95122, Italy; [9]Fondazione per il Tuo cuore—Heart Care Foundation, Via Alfonso la Marmora 36, Firenze, 50121, Italy; and [10]Cardiologia 1-Emodinamica, Dipartimento Cardiotoracovascolare 'A. De Gasperis', ASST Grande Ospedale Metropolitano Niguarda, Piazza dell'Ospedale Maggiore, 3, Milan, 20162, Italy

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In the growing therapeutic armamentarium for heart failure (HF) management, vericiguat represents an innovative therapeutic option. The biological target of this drug is different from that of other drugs for HF. Indeed, vericiguat does not inhibit neuro-hormonal systems overactivated in HF or sodium-glucose co-transporter 2 but stimulates the biological pathway of nitric oxide and cyclic guanosine monophosphate, which is impaired in patients with HF. Vericiguat has recently been approved by international and national regulatory authorities for the treatment of patients with HF and reduced ejection fraction who are symptomatic despite optimal medical therapy and have worsening HF. This ANMCO position paper summarises key aspects of vericiguat mechanism of action and provides a review of available clinical evidence. Furthermore, this document reports use indications based on international guideline recommendations and local regulatory authority approval at the time of writing.

Introduction

Heart failure (HF) has a significant socio-economic impact on the healthcare system due to its high prevalence (1% in the population aged <55 years and >10% in the population aged >70 years)[1] and the associated high frequency of hospitalization (one per year after initial diagnosis).[2] Despite significant progress in the treatment of cardiovascular diseases, the number of individuals affected by HF is expected to increase, particularly among the elderly population. Therefore, research efforts have focused on developing new therapeutic options to reduce hospitalization and mortality risk in HF

*Corresponding author. Tel: 0039 3491500982, Fax: 0039 0633062489, Email: doctstefania@hotmail.com

patients. Although significant pharmacological and non-pharmacological advances in the field of HF have improved both quality and life expectancy, particularly in HF with reduced ejection fraction (HFrEF), the prognosis remains unfavourable. In addition to the beta-blockers, mineralocorticoid receptor antagonists, sacubitril/valsartan, and sodium–glucose co-transporter 2 (SGLT2) inhibitors recommended as medical therapy in international HF guidelines,[1,3] vericiguat is an emerging further therapeutic option. Vericiguat is a new drug for HF treatment that has been developed as part of an intensive scientific research programme investigating therapeutic agents that target oxidative stress and endothelial dysfunction, two mechanisms that are closely linked and involved in HF pathophysiology.[4] Unlike other drugs that have been shown to alter the prognosis of patients with HF by inhibiting the neuro-hormonal system or the SGLT2 enzyme, vericiguat stimulates the activity of an enzyme, soluble guanylate cyclase (sGC), and promotes the synthesis of cyclic guanosine monophosphate (cGMP), a mediator of several beneficial effects in HF patients. This document of the Italian Association of Hospital Cardiologists (ANMCO) describes the mechanism of action of this new drug and its biological effects, reports the main clinical evidence supporting its use in patients with HF, and discusses the current recommendations of international guidelines. Lastly, the document provides a practical guidance on appropriate clinical use to maximise its benefits and minimise the risk of potential adverse effects.

Mechanism of action and biological effects

In several cardiovascular diseases, including HF, inflammation and vascular dysfunction can decrease the bioavailability of nitric oxide (NO), leading to reduced cGMP synthesis. This reduction in cGMP levels can contribute to the progression of cardiovascular and renal damage. Vericiguat stimulates sGC similarly to riociguat, which was the first stimulator with a clinical application. However, vericiguat differs from riociguat due to the longer half-life, which allows once a day oral administration.[5] Acting as a nitrovasodilator, vericiguat promotes cGMP production even when NO levels are low and acts in synergy with endogenous NO by stimulating sGC. Unlike other nitrovasodilators, vericiguat does not cause long-term tolerance.[6] NO is a key mediator of several cardiovascular system functions, including the regulation of vascular tone and myocardial performance. The decreased activity of the NO-sGC-cGMP pathway, and consequently reduced cGMP synthesis, leads to endothelial dysfunction. In HF, endogenous NO levels are reduced due to decreased bioavailability of l-arginine, increased arginase activity, downregulation or uncoupling of endothelial NO synthase (eNOS), and inactivation of NO by superoxide anions. Furthermore, in the HF setting there is an increase in plasma concentrations of the endogenous eNOS inhibitor and a reduced affinity of the oxidised form of sGC for NO.[7] Overall, the beneficial effects of vericiguat, mediated by its action on the NO-sGC-cGMP pathway, which is impaired in HF, include cardiac and vascular function improvement and a reduction in fibrosis (*Figure 1*).

Increased cGMP levels lead to reduced vascular tone and counteract the increased afterload of both ventricles, due to systemic and pulmonary vascular constriction. High cGMP levels also counteract renal and coronary vessel incongruous regional vasomotor response, which is a common phenomenon in HF due to the insufficient activity of the NO-sGC-cGMP pathway.[8,9] Furthermore, increased cGMP production induces titin phosphorylation by protein kinase G, improves the cardiac index, and attenuates left ventricular remodelling.[8] Extracardiac effects of vericiguat that may have a favourable impact in HF include a possible nephroprotective effect through renal fibrosis inhibition.[10] It should be noted that also sacubitril/valsartan leads to an increase in cGMP levels mediated by natriuretic peptides, which are activators of cGMP. Therefore, strong arguments support the No-sGC-cGMP pathway as a therapeutic target for HF treatment.[11]

Efficacy and safety evidence

To evaluate vericiguat safety, tolerability, and pharmacokinetic and pharmacodynamic profiles at different dosages, it was tested in Phase 1 clinical trials.[5] Overall, these clinical trials demonstrated that vericiguat is well tolerated at a dose ≤10 mg and that its bioavailability is greater and with a less variability of the pharmacokinetic profile when taken with food.[5] Vericiguat pharmacokinetic characteristics are shown in *Table 1*.

In addition, no significant drug interactions were observed, and no dose adjustments were required in patients with polypharmacy and multiple comorbidities, such as patients with HF.[12]

The first evidence on vericiguat use in patients with HF was provided by the Phase 2 SOCRATES-REDUCED trial. The aim of the study was to verify the optimal dose and tolerability of the drug in patients with chronic HF and reduced ejection fraction (EF <45%).[13] The study did not achieve the primary endpoint of reducing amino-terminal fragment pro-B-type natriuretic peptide (NT-proBNP) levels. However, this study provided relevant data on its efficacy and safety. The exploratory secondary analysis demonstrated a dose-dependent relationship, with a statistically significant reduction in NT-proBNP values and increase in EF with a dosage of 10 mg. In addition, in the vericiguat group, a reduction in the composite endpoint of cardiovascular death or hospitalization for HF was observed, although the trial was not powered to test clinical endpoints. Finally, the study also demonstrated that the drug was safe and well tolerated in all groups on active treatment.[13]

On this basis, the Phase 3 randomised controlled and double-blinded VICTORIA study[14] was devised. It represents the cornerstone of clinical evidence on vericiguat in HF. A total of 5050 patients with HF and New York Heart Association (NYHA) functional Class II-IV and EF <45% were randomised to receive vericiguat (starting from a dose of 2.5 mg/day to a target dose of 10 mg/day) or placebo, in addition to optimal medical therapy. The primary composite endpoint was cardiovascular death and hospitalization for HF. The clinical and demographic characteristics of the study population delineated a high clinical risk population with

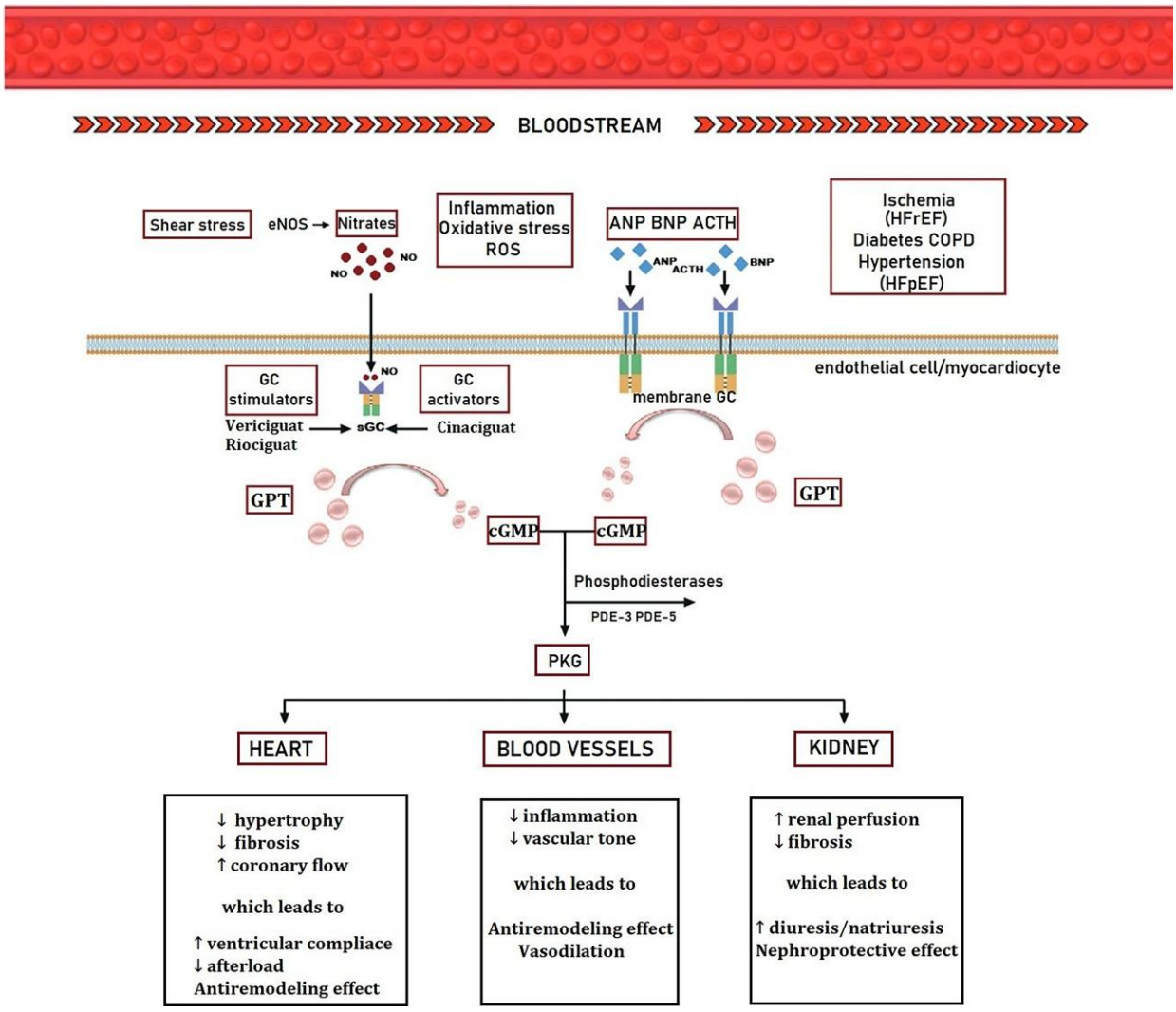

Figure 1 Nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate pathway and vericiguat biological effects in the heart, vessels, and kidney. On the left, the activation of the soluble guanylate cyclase receptor by nitric oxide and activators/stimulators of the receptor itself are reported. On the right, the activation of the guanylate cyclase membrane receptor by natriuretic atrial peptides and adreno-corticotropic hormone is shown. Both pathways produce cyclic guanosine monophosphate from guanosine triphosphate and lead to the activation of protein kinase G. ACTH, adreno-corticotropic hormone; ANP, atrial natriuretic peptide; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; cGMP, cyclic guanosine monophosphate; eNOs, endothelial nitric oxide synthase; GTP, guanosine triphosphate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NO, nitric oxide; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylate cyclase.

Table 1 Vericiguat pharmacokinetic characteristics

Parameter	
Time to steady state	6 days
Bioavailability when taken with meals	98%
Average distribution volume in healthy individuals	44 L
Plasma protein binding	98%
Half-life in heart failure patients	30 h

a mean age of 67 years, mostly men, a median NT-proBNP value of 2816 ng/L, and a median EF of 29%.

During the median follow-up of 10.8 months, a reduction in the incidence of the primary endpoint was observed in patients on active treatment [hazard ratio (HR) 0.90; 95% confidence interval (CI), 0.83–0.98; $P = 0.02$], driven by a lower number of hospitalizations (HR 0.9; 95% CI, 0.81–1.00). Cardiovascular death occurred in 16.4% of patients in the vericiguat group and in 17.5% of patients in the placebo group (HR 0.93; 95% CI, 0.81–1.06). The efficacy of vericiguat was confirmed in all prespecified subgroups, except for elderly patients (>75 years) and in the quartile with higher NT-proBNP values (>5314 pg/mL).[14] The incidence of adverse events, such as symptomatic hypotension and syncope, was similar in the two groups, confirming the good safety profile of the drug.

After the VICTORIA trial data publication, several *post-hoc* analyses were performed with the aim of verifying and integrating the new evidence. Ezekowitz *et al.*[15] identified the threshold value of 8000 ng/L of

NT-proBNP, beyond which the use of vericiguat does not result in significant clinical benefit. This finding can be explained considering that these high NT-proBNP values identify a population that has a higher clinical risk, is older and more symptomatic, and has worse renal function. By analysing the time interval between randomization and last hospitalization for HF, a recent hospitalization was associated with a higher risk of adverse outcomes, leading to a reduced benefit of vericiguat treatment.[16] Conversely, the presence of atrial fibrillation (AF), reported in about 50% of the VICTORIA study population, does not influence the positive impact of vericiguat treatment.[17] Further data from *post-hoc* analyses suggest a possible detrimental effect of vericiguat on haemoglobin (Hb) levels. In fact, a significant, albeit mild, reduction in Hb levels (-0.38 ± 1.27 g/dL) in the active treatment group compared with the control group (0.14 ± 1.30 g/dL) was observed. However, an in-depth analysis showed that this effect occurs only in the first 16 weeks of treatment and does not affect the benefits of vericiguat.[18] A further analysis demonstrated that both patients with and without coronary artery disease (CAD) benefit equally from the treatment, although those with CAD have a significantly worse prognosis.[19] A further *post-hoc* analysis examined the clinical efficacy of vericiguat in chronic kidney disease. In patients with estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease formula [$\text{eGFR} = 175 \times (\text{creatinine serum}) - 1.154 \times (\text{age}) \quad -0.203 \times 0.742$ (if female) $\times 1.212$ (if African ethnicity)] < 30 mL/min/1.73 m^2, the treatment benefit was maintained across the entire spectrum of eGFR values, starting with a eGFR $\geq$15 mL/min, which was the minimum value for trial inclusion.[20] Finally, a further analysis confirmed both the safety and efficacy of vericiguat in patients with a high risk of hypotensive events, such as the elderly and those treated with sacubitril/valsartan.[21]

Comparing the patient characteristics of the VICTORIA trial with those of the Phase 3 trials evaluating sacubritil/valsartan[22] and glyflozines,[23,24] recently introduced into clinical practice and recommended for the treatment of HFrEF, it is evident that patients enrolled in VICTORIA had a different risk profile (*Table 2*). The higher event rate in the VICTORIA study allowed a shorter follow-up (median follow-up 11 months vs. 27, 18, and 16 months in the PARADIGM-HF, DAPA-HF, and EMPEROR-Reduced studies, respectively) to reach the number of primary endpoint events required to obtain a significant difference in the event rate between the placebo and the active treatment group (37.8% vs. 33.6% events).[14]

Finally, clinical evidence of vericiguat is not limited to HFrEF patients. In recent years, data have also emerged on its use in HF with preserved EF (HFpEF). In this context, the first published study was SOCRATES-PRESERVED, a Phase 2b clinical trial designed to determine the optimal dose and tolerability of the drug in patients with HF and EF >45%.[25] The study failed to demonstrate a reduction in NT-proBNP levels and left atrial volume at 12 weeks, which were the two primary endpoints. However, vericiguat was well tolerated and associated with improved quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score. Nevertheless, the VITALITY-HFpEF trial, which enrolled a larger population (789 patients) with similar characteristics to those included in the SOCRATES-PRESERVED study who were followed for 24 weeks,[26] did not demonstrate a benefit of vericiguat treatment in terms of physical limitation improvement, as assessed by the KCCQ physical limitation score or by the distance travelled with the 6 minutes' walk test. However, further and larger studies with longer follow-up and more robust clinical endpoints are needed to verify the efficacy of vericiguat in the HFpEF setting.

The main evidence of vericiguat in both patients with HFrEF and patients with HFpEF is summarised in *Table 3*.

Current indications and future perspectives

The European Society of Cardiology 2021 guidelines recommend considering vericiguat therapy when a patient with HFrEF (defined as an EF <40%, although the cut-off in the VICTORIA trial was 45%)[14] has an NYHA functional Class II–IV and decompensation despite angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker, beta-blocker, and aldosterone blocker therapy (Class IIb, level of evidence B).[1] This recommendation reflects the VICTORIA trial design.[14] The ACC/AHA/HFSA guidelines advise considering vericiguat therapy in patients who are at high risk of rehospitalization and already on 'guideline recommended medical therapy'.[3] Interestingly, such medical therapy would also include SGLT2-inhibitors, although there is currently no evidence of the additional benefit of vericiguat compared with a therapeutic combination including an SGLT2-inhibitor. Neither guideline explicitly mentions sacubitril/valsartan due to the small number of patients receiving this drug in the VICTORIA trial (731 out of 5040 at the time of randomization, 425 thereafter).[27] It seems very unlikely that Phase 3 trials evaluating the efficacy of vericiguat as an add-on to therapy including sacubitril/valsartan and an SGLT2-inhibitor will ever be conducted. Overall, it seems reasonable to consider vericiguat therapy in patients with: (i) HFrEF, (ii) optimised medical therapy (i.e. taking an ACE inhibitor or possibly sacubitril/valsartan, a beta-blocker, and an aldosterone blocker at the recommended target dose or maximally tolerated dose, and dapagliflozin or empagliflozin unless contraindicated), (iii) a high risk of rehospitalization for HF despite optimal medical therapy. The risk of rehospitalization should preferably be defined according to VICTORIA study inclusion criteria as elevated natriuretic peptide values (BNP $\geq$300 ng/L or NT-proBNP $\geq$1000 ng/L in patients in sinus rhythm, BNP $\geq$500 ng/L or NT-proBNP $\geq$1600 ng/L in patients in AF), hospitalization for HF in the previous 6 months, or use of intravenous diuretic therapy in the previous 3 months (*Figure 2*).[14] In a retrospective study that included a cohort of 9948 patients with HFrEF, more than 50% had a decompensation event during the median follow-up of 5.8 years, and of these 38.3% had all inclusion criteria of the VICTORIA study.[28] Based on a sub-analysis of the VICTORIA trial, vericiguat could determine a prognostic benefit (in terms of the composite endpoint 'cardiovascular death and hospitalization for HF') up to

Table 2 Characteristics of patients enrolled in Phase 3 clinical trials that tested sacubitril/valsartan, dapagliflozin, empagliflozin, and vericiguat and primary endpoint comparison

	PARADIGM HF[22]		DAPA-HF[23]		EMPEROR-Reduced[24]		VICTORIA[14]	
Study characteristics								
	Control Enalapril	Tested drug Sacubitril/Valsartan	Control Placebo	Tested drug Dapagliflozin	Control Placebo	Tested drug Empagliflozin	Control Placebo	Tested drug Vericiguat
No. of patients	8399		4744		3730		5050	
Median follow-up (months)	27		18		16		11	
Patient characteristics at baseline								
EF %	≤35%		≤40%		≤40%		<45%	
NT-proBNP, pg/mL	≥600 or ≥ 400		≥600 or ≥400		Variable on the basis of EF		≥1000 SR; ≥1600 AF	
eGFR, mL/min/1.73 m^2	≥30		≥30		≥20		≥15	
Recent HF decompensation	NO		NO		Chronic HF ≥ 3 months		Hospitalization for HF in the previous 6 months or use of IV diuretics in the previous 3 months	
NT-proBNP (average), pg/mL	1608		1437		1906		2816	
NYHA Class III or IV %	25		32		25		41	
Hospitalization for HF < 3 months, %	19		8		NR		67	
Hospitalization for HF < 6 months, %	31		16		NA		84	
eGFR < 60 mL/min/1.73 m^2, %	37		41		48		53	
Major events								
Primary endpoint	First hospitalization for HF or CV death		Worsening HF or CV death		First hospitalization for HF or CV death		First hospitalization for HF or CV death	
Primary endpoint, HR (95%)	0.80 (0.73-0.87)		0.74 (0.65-0.85)		0.750.92 (0.75-1.12) (0.65-0.86)		0.90 (0.82-0.98)	
CV death, HR (95% CI)	0.80 (0.71-0.89)		0.82 (0.69-0.98)		0.92 (0.75-1.12)		0.93 (0.81-1.06)	
First hospitalization for HF, HR (95% CI)	0.79 (0.71-0.89)		0.70 (0.59-0.83)		0.69 (0.59-0.81)		0.90 (0.81-1.00)	
Annualised event rate, *n* events per 100 patient-years at risk								
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8	37.8	33.6
ARR primary endpoint	2.7		4		5.2		4.2	
CV death	7.5	6.0	7.9	6.5	8.1	7.6	13.9	12.9
ARR CV death	1.5		1.4		0.5		1	
First hospitalization for HF	NA	NA	9.8	6.9	NA	NA	29.1	25.9
ARR first admission for HF	1.6		2.9		NA		3.2	

AF, atrial fibrillation; ARR, absolute reduction of the risk of events/year with the tested drug; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; IV, intravenous; NA, not applicable/not available; NT-proBNP, amino-terminal fragment of brain natriuretic peptide; NYHA, New York Heart Association; SR, sinus rhythm.

Table 3 Clinical studies on vericiguat in heart failure

Study	Number of patients	Inclusion criteria	Study design	Primary endpoint	Results	Safety
Clinical studies on vericiguat in heart failure with reduced ejection fraction >45%						
SOCRATES-REDUCED[13]	351	HF with EF <45% and a recent episode of decompensated HF, defined as worsening of symptoms that requires hospitalization or i.v. diuretic use and elevated NT-proBNP levels	1:1:1:1:1 randomization Maximum target dose vericiguat 1.25 mg, 2.5 mg, 5 mg, 10 mg/day or placebo	NT-proBNP level reduction at 12 weeks	No statistically significant difference [Δlog(NT-proBNP) from baseline to 12 weeks ($P = 0.15$)] between vericiguat 'pooled' and placebo groups	Adverse event rates: 71.4% vericiguat 10 mg vs. 77.2% placebo (ns)
VICTORIA[14]	5050	HF with EF < 45% (NYHA II-IV), BNP ≥300 ng/L (≥500 ng/L if AF) or NT-proBNP ≥1000 ng/L (≥1600 ng/L if AF) and hospitalization in the previous 6 months or i.v. diuretic use in the previous 3 months	1:1 randomization vericiguat (dose target 10 mg) vs. placebo	Composite endpoint: CV mortality and hospitalization for HF CV mortality Hospitalization for HF	37.9% in vericiguat group vs. 40.9% in placebo group (HR, 0.90; 95% IC, 0.83-0.98; $P = 0.02$) 16.4% in vericiguat group vs. 17.5% in placebo group (HR, 0.93; 95% IC, 0.81-1.06) 27.4% in vericiguat vs. 29.6% in placebo group (HR, 0.90; 95% IC, 0.81-1.00)	Adverse event rates: 80.5% in the vericiguat group vs. 81% in the placebo group (ns) Serious adverse event rates: 32.8% in the vericiguat group vs. 34.8% in the placebo group (ns)
Clinical studies on vericiguat in heart failure with ejection fraction >45%						
SOCRATES-PRESERVED[25]	477	HF with EF >45%, previous HF diagnosis (NYHA II-IV), BNP ≥100 ng/L (≥200 ng/L if AF) or NT-proBNP ≥300 ng/L (>600 ng/L if AF) at randomization, left atrial enlargement assessed on echocardiogram, and a recent decompensated HF episode (within 4 weeks) defined as worsening symptoms requiring hospitalization or use of i.v. diuretic	1:1:1:1:1 randomization Maximum dose target 1.25, 2.5, 5, and 10 mg/die or placebo	NT-proBNP levels and LAV (mL) reduction at 12 weeks	No statically significant difference [Δlog(NT-proBNP) and VAS (mL) from baseline to week 12 ($P = 0.15$)] between the pooled vericiguat and placebo groups	Adverse event rates: 69.8% in the vericiguat group vs. 73.1% in the placebo group (ns) Serious adverse event rates: 25% in the vericiguat 10 mg group vs. 28% in the placebo group (ns)
VITALITY-HFpEF[26]	789	HF with EF >45% (NYHA II-IV), BNP ≥100 ng/L (≥200 ng/L if AF) or NT-proBNP	1:1:1 randomization vericiguat 15, 10 mg or placebo	Change in physical limitations, assessed with KCCQ PLS, from	No statistically significant difference in the three groups	Adverse event rates: 65.2% in the vericiguat 15 mg

Continued

Table 3 Continued

Clinical studies on vericiguat in heart failure with reduced ejection fraction >45%						
Study	**Number of patients**	**Inclusion criteria**	**Study design**	**Primary endpoint**	**Results**	**Safety**
		≥300 ng/L (>600 ng/L if AF) within 30 days from randomization, left atrial enlargement or left ventricular hypertrophy evaluated on echocardiogram within 12 months from randomization and a recent HF decompensated episode (within 6 months) defined as worsening symptoms requiring hospitalization or use of i.v. diuretic without hospitalization		baseline to 24 weeks		group, 62.2% in the vericiguat 10 mg group and 65.6% in the placebo group (ns)

AF, atrial fibrillation; BNP, B natriuretic peptide CI, confidence interval; EF, ejection fraction; HF, heart failure; HR, hazard ratio; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAV, left atrial volume; NT-proBNP, amino-terminal fragment pro-B-type natriuretic peptide; NYHA, New York Heart Association; ns, non-significant; PLS, physical limitation score.

NT-proBNP values of 8000 ng/L.[15] There was no evidence of a different efficacy of vericiguat in the subgroup of patients receiving sacubitril/valsartan nor interactions with a history of CAD or with haemoglobin levels. Therefore, all these variables should not be taken into consideration when a therapy with vericiguat is considered. Vericiguat is not recommended in patients with HF and mildly reduced (40–49%) or preserved (≥50%) EF as it was not superior to placebo in improving quality of life in patients with EF ≥45%.

Patients with cardiac amyloidosis often tolerate traditional HF therapies poorly because of restrictive haemodynamics (whereby cardiac output is sustained by increased heart rate) and are prone to conduction disturbances.[29] On the other hand, these patients often have frequent HF decompensations. Furthermore, patients with cardiac transthyretin amyloidosis and NYHA functional Class III are not candidates for tafamidis therapy due to an apparent increased risk of hospitalizations in the ATTR-ACT trial.[30] In this context, as a drug with no significant effects on haemodynamics that is capable of reducing the risk of hospitalization for HF, vericiguat could be an interesting therapeutic option.[31] However, there is no evidence for the use of vericiguat in patients with cardiac amyloidosis, who were excluded from the VICTORIA study. Dedicated studies should be conducted in the future. The use of vericiguat in other clinical contexts that were exclusion criteria in the VICTORIA study, i.e. acute conditions such as acute myocarditis or Takotsubo syndrome or late-stage HF requiring inotropic support or ventricular assist devices, appears less promising.

Implementation in clinical practice

According to Italian Medicines Agency indications, vericiguat can be used for the treatment of chronic symptomatic HF in adult patients with clinically stable HFrEF after a recent exacerbation event which required intravenous therapy.[32] Before initiating treatment with vericiguat, a comprehensive assessment of the patient is mandatory and special attention must be paid to blood volume in order to be sure that the patient has achieved a phase of effective clinical stability after the exacerbation event. NT-proBNP levels should be evaluated, since very high values are associated with a greater risk of adverse events. Treatment must not be initiated in patients with symptomatic hypotension or systolic blood pressure values <100 mmHg since there is no evidence in this group of patients. Recommended

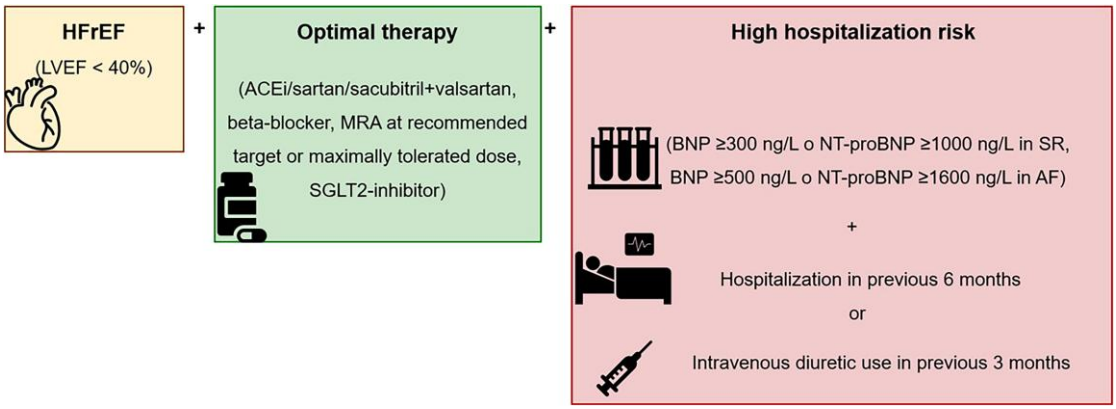

Figure 2 Current indications for vericiguat therapy. ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; BNP, B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal fragment of the BNP precursor; SR, sinus rhythm.

starting dose is 2.5 mg/day. Vericiguat dose should be titrated according to patient tolerability, doubling the dosage after approximately 2 weeks until the target dose of 10 mg/day is reached. It should be noted that one year after enrolment in the Phase 3[14] clinical study, approximately 90% of patients reached the target dose of 10 mg/day. Since drug absorption is reduced in a fasting state, vericiguat should always be taken with food. If signs or symptoms of poor treatment tolerance appear, such as symptomatic hypotension or systolic blood pressure <90 mmHg, it is recommended to reduce the dose or withdraw the treatment. No dose adjustment is necessary in elderly patients or patients with impaired renal function if the eGFR is >15 mL/min/1.73 m^2 and the patient is not on dialysis. Furthermore, in the VICTORIA study hyperkalaemia was not an exclusion criterion and treatment with vericiguat was not associated with significant changes in serum potassium levels.[20] For this reason, use of vericiguat does not require periodic monitoring of serum electrolytes and can be considered safe even in patients with an increased risk of hyperkalaemia. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. However, vericiguat is not recommended in severe hepatic impairment since it has not been studied in this setting. Vericiguat is contraindicated in patients treated with other sGC stimulants, such as riociguat.

Conclusions

Within the scope of HF management, vericiguat represents a therapeutic option with an innovative mechanism of action compared with all currently available drugs. Indeed, it does not directly inhibit neuro-hormonal systems nor other molecular mechanisms. Conversely, it has a stimulating action on the NO-sGC-cGMP pathway, which is impaired in patients with HF. This treatment is indicated in patients with symptomatic HFrEF despite optimal medical therapy and with a recent episode of decompensation. Treatment with vericiguat is targeted to patients who have a high risk of adverse events. In this setting, it has been shown to reduce the incidence of the primary composite endpoint of cardiovascular death and hospitalization for HF by 10%.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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