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Vericiguat in heart failure – who benefits the most?

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Introduction

Heart failure is a chronic and progressive clinical syndrome induced by structural or functional cardiac abnormalities displaying either reduced (HFrEF) or preserved (HFpEF) left ventricular ejection fraction (LVEF). The substantial reduction in short-term mortality in patients with several acute cardiac conditions and the relevant improvement in long-term survival in HFrEF patients treated with beta-blockers, angiotensin converting-enzyme inhibitors and mineralocorticoid receptor antagonists, combined with several demographic changes, have sharply increased the number of patients living with heart failure [1]. In developed countries, heart failure has become a substantial public health problem, affecting 2% of the adult population, and the number of hospital admissions related to heart failure has tripled since the 1990s [2]. Nowadays, acute heart failure is the most frequent cause of unplanned hospital admission in patients of >65 years of age and is still associated with poor outcomes, with 90-day readmission rates and 1-year mortality reaching 10–30% [3]. It is estimated that only 50% of patients survive 5 years beyond their initial diagnosis and, perhaps even more importantly, repeated hospitalisations or emergency visits to receive supplemental parenteral diuretics, markedly impair the quality of life [4]. Thus, there is an urgent need for new treatment approaches to improve survival and reduce the risk of hospital readmissions for heart failure.

In recent years, massive efforts have been deployed to discover new therapeutic options to reduce mortality and hospitalisations, and improve the quality of life in HFrEF. Several novel drugs (e.g., the angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril/valsartan [5], the sodium-glucose cotransporter 2 inhibitors (SGLT2i) dapagliflozin and empagliflozin [6, 7], and the soluble guanylate cyclase (sGC) stimulator vericiguat [8]) have been shown to improve clinical course of HFrEF patients compared with standard treatment. Because these new therapies have abruptly taken centre stage, and their effects have been tested simultaneously, rather than sequentially as for previous drug classes, the interpretation of the results and the correct use of these new drugs might be challenging [9]. This article aims to provide concise insight into one of these promising heart failure drugs, the oral sGC stimulator vericiguat.

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Vericiguat – an oral soluble guanylate cyclase stimulator

Heart failure leads to the activation of several compensatory mechanisms that may contribute to acute decompensations and long-term disease progression. Under the effect of an activated renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), the second messenger cyclic adenylate monophosphate (cAMP) is increased at a cellular level [10]. Cyclic guanosine monophosphate (cGMP) is another key intracellular second messenger that counteracts the detrimental effects of cAMP in heart failure, mediating protective cardiovascular, renal, neurohumoral and metabolic actions [11]. Endothelial nitric oxide (NO) is an endogenous relaxing factor, which in physiological conditions activates soluble guanylate cyclase (sGC), which in turn stimulates the production of the effector molecule cGMP [12]. In addition to the NO pathway, cGMP is also enhanced by natriuretic peptides (NPs, e.g., atrial natriuretic peptide, B-type natriuretic peptide, and C-type natriuretic peptide) through activation of membrane-bound guanylate cyclase (particulate guanylate cyclase, pGC) [12]. In heart failure, both the NO-sGC-cGMP and the NP-pGC-cGMP signalling pathways are impaired as a result of impaired production and/or excessive degradation of NO, and inadequate release and/or excessive inactivation of natriuretic peptides as pGC ligands, respectively [13].

In this context, therapeutic strategies to augment cGMP have been evaluated for the treatment of heart failure. Phosphodiesterase (PDE)-3 inhibitors such as milrinone and enoximone and PDE-5 inhibitors such as sildenafil reduce degradation of cGMP to GMP and induce favourable haemodynamic effects in heart failure. However, to date, no randomised clinical trial has shown improvement in patient outcome with the use of PDE inhibitors [14]. Therapeutic options to enhance the NP-pGC-cGMP pathway include synthetic NPs and NP analogues (e.g., nesiritide, ularitide), as well as the ARNi sacubitril/valsartan. ARNis reduce the degradation of NPs [15], and have been shown to markedly improve outcome in heart failure [5]. The modulation of the NO-sGC-cGMP axis may be achieved

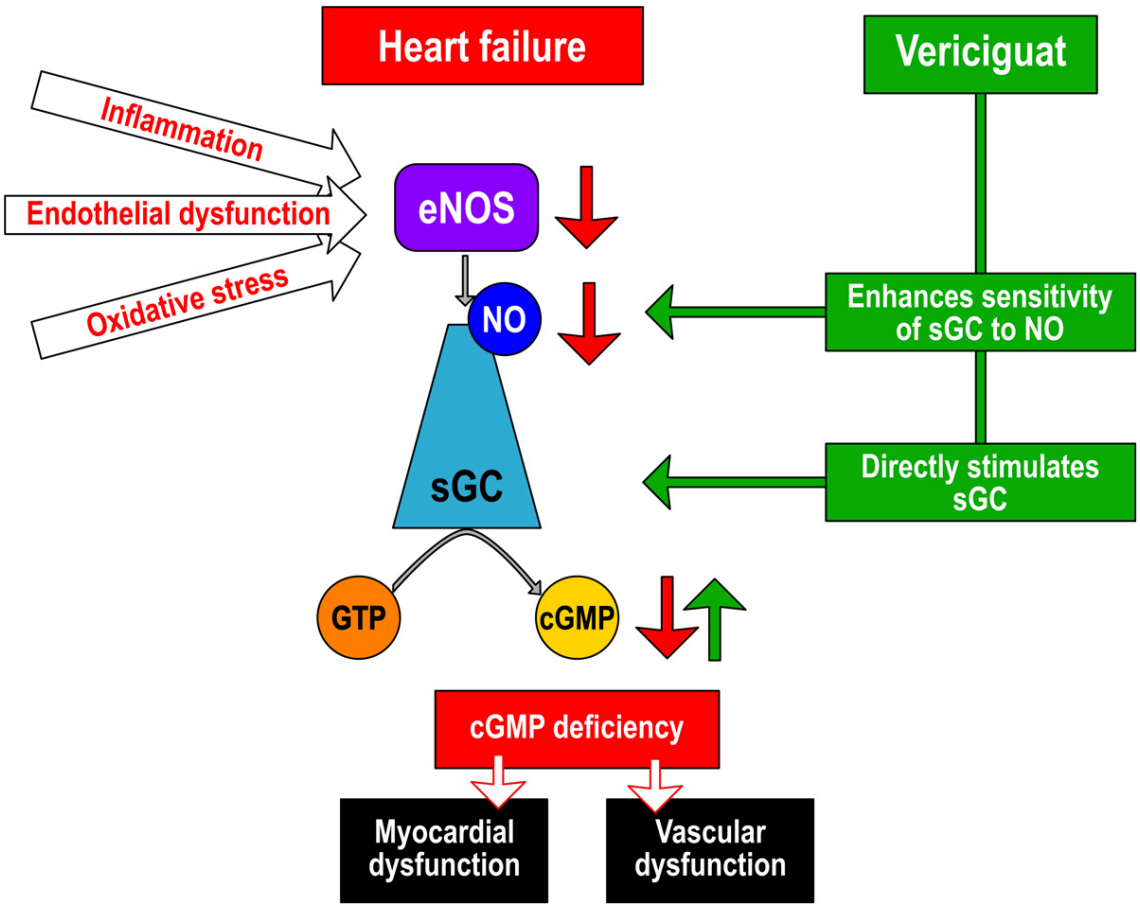
by using organic nitrates or NO-donors; however, the use of such compounds is limited by potential tolerance / lack of response and – even more importantly – lack of evidence that such treatment improves outcome [13]. Therefore, compounds that increase cGMP by activating sGC in a NO-independent manner may provide an interesting approach for treating heart failure patients.

Vericiguat is an oral drug with once-daily administration that stimulates sGC by enhancing the sensitivity of the enzyme to endogenous NO and directly in a NO-independent manner, resulting in increased formation of cGMP (fig. 1). Vericiguat has a small risk of drug interactions and, unlike nitrates, does not induce tolerance. The beneficial properties of sGC stimulators on the cardiovascular system include systemic and pulmonary vasodilation, which induces decongestion, improves ventricular-arterial coupling, and increases coronary blood flow [13]. Anti-inflammatory, antiproliferative and antifibrotic properties of sGC stimulators reduce myocardial hypertrophy, remodelling and fibrosis, and decrease platelet activation [13]. Furthermore, sGC stimulation has reno-protective effects, reducing renal fibrosis and increasing diuresis and natriuresis [13]. In the phase II, dose-finding, placebo-controlled randomised clinical trial (SOCRATES-REDUCED), vericiguat was investigated in patients with stable HFrEF [17]. The drug appeared safe and did not worsen haemodynamic parameters. Although the primary endpoint (reduction in N-terminal pro-B-type natriuretic peptide [NT-proBNP] from baseline at week 12) was not met, an exploratory analysis suggested a dose-response relationship in which higher doses of vericiguat were associated with greater reductions in circulating NT-proBNP [17]. In light of these observations, the phase III Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) was designed.

The VICTORIA trial results

The phase III VICTORIA trial examined the efficacy of vericiguat in patients at high risk of heart failure decompensation. The trial enrolled patients with HFrEF (LVEF <45%), a previous heart failure decompensation requiring outpatient intravenous diuretics or hospitalisation during the past 6 months and elevated circulating NPs (NT-proBNP ≥1000 ng/l if the patient was in sinus rhythm or ≥1600 ng/l with atrial fibrillation) [16]. Patients considered unstable, with arterial hypotension (i.e., systolic blood pressure <100 mm Hg), or in whom the use of nitrates or PDE-5 inhibitors was planned were excluded. Patients were randomised to receive a placebo on a background of optimal medical heart failure therapy or vericiguat with a target

Figure 1: Mechanisms of action of vericiguat. Heart failure is a condition characterised by endothelial dysfunction, inflammation and oxidative stress, which cause decreased nitric oxide (NO) bioavailability and insufficient activation of intracellular soluble guanylate cyclase (sGC), red arrows. The resulting cyclic guanosine monophosphate (cGMP) deficiency is associated with myocardial dysfunction and impaired vascular regulation, white arrows. Vericiguat stimulates sGC by enhancing the sensitivity of the enzyme to endogenous NO and directly in a NO-independent manner, resulting in increased formation of cGMP, green arrows. eNOS = endothelial nitric oxide synthase. Adapted from Armstrong et al. [16]



dose of 10 mg once daily. The study was event-driven, with an estimated duration of 18 months. The primary endpoint was a composite of death from cardiovascular cause or first hospitalisation for heart failure [16].

A total of 5050 patients with advanced symptomatic HFrEF were included (table 1). Their mean age was 67 years, 76% of patients were men, 41% were in New York Heart Association (NYHA) class III–IV, and 67% had been hospitalised because of heart failure in the 3 months before enrolment. The mean LVEF and eGFR were 29% and 61 ml/min/1.73m^2, respectively. The median baseline NT-proBNP was 2821 ng/l. Background medical heart failure therapy consisted of beta-blockers (93%), RAAS blockers (88%: 73% angiotensin converting-enzyme inhibitors / angiotensin receptor blockers, 15% ARNi), and mineralocorticoid receptor antagonists (70%). Patients in the vericiguat arm received a median dose of 9.2 mg over a median follow-up of 10.8 months.

The incidence of the primary endpoint was significantly lower in patients receiving vericiguat than in those receiving placebo (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.82–0.98; p = 0.02), with a number needed to treat of 24 [8]. However, the result was mainly driven by a lower incidence of heart failure hospitalisations in the vericiguat group (HR 0.90, 95% CI 0.81–1.0), without a difference in regard to mortality. Vericiguat generally had a favourable side-effect profile and 89% of patients achieved the target dose; mean systolic blood pressure at baseline was 121 mm Hg in both study arms, without significant difference during follow-up across the groups. Symptomatic hypotension and syncope were numerically higher in patients receiving vericiguat, without statistical significance. The results were consistent in most of the prespecified subgroups, except for patients with the highest quartile of baseline NT-proBNP (>5314 ng/l), in whom the positive effects of vericiguat appeared to be blunted.

Translating trial results into clinical practice: which patients benefit the most?

The VICTORIA trial showed a modest relative reduction in the composite endpoint of cardiovascular mortality and heart failure hospitalisation in patients treated with vericiguat. The result was mainly driven by a lower incidence of heart failure hospitalisations in the vericiguat group. Some points should be considered before drawing conclusions for clinical practice.

First, determination of the relative impact of therapies by comparing HRs across different trials is incorrect and potentially misleading [9]. The efficacy of different therapies should best be assessed with head-to-head trials, but such studies are often not performed. An alternative approach is to consider study inclusion criteria, baseline characteristics of the included patients, follow-up durations, event rates and absolute risk reductions, as summarised in table 1 [9]. Patients included in VICTORIA were markedly older and sicker compared with the study populations of other contemporary heart failure trials (e.g., PARADIGM-HF, DAPA-HF) and reported a long history of heart failure (mean time from diagnosis to randomisation 4.8 years). A higher proportion of patients in VICTORIA were in NYHA class III–IV and circulating NT-proBNP levels were markedly higher (table 1). Accordingly, the event rate in the control group of VICTORIA is twice as high as in PARADIGM-HF and DAPA-HF [18].

In light of these observations, the “modest” relative reduction in the primary endpoint (expressed as HR) translates into absolute reductions of the annualised event rate that are in line with those of other contemporary heart failure trials (−4.2 events per 100 patient-years for vericiguat compared with −4.0 for dapagliflozin in DAPA-HF and −2.7 for sacubitril/valsartan in PARADIGM-HF). Similarly, the absolute rate reductions of the individual components of the primary endpoint (cardiovascular death and

Table 1: Comparison of characteristics and outcomes of recent clinical trials in heart failure.

	PARADIGM-HF [5]		DAPA-HF [6]		VICTORIA [8]	
Trial and patient characteristics						
Number of patients	8399		4744		5050	
Follow-up (months)	27		18		11	
Comparator	Active (enalapril)		Placebo		Placebo	
Age (years)	64		66		67	
LVEF (%)	29		31		31	
eGFR (ml/min/1.73m^2)	68		66		61	
NT-proBNP (ng/L)	1615		1437		2821	
NYHA class III–IV (%)	25		33		41	
Hazard ratio and 95% confidence interval						
Primary combined endpoint	0.80 (0.73–0.87)		0.74 (0.65–0.85)		0.90 (0.82–0.98)	
Cardiovascular death	0.80 (0.71–0.89)		0.82 (0.69–0.98)		0.93 (0.81–1.06)	
First heart failure hospitalisation	0.79 (0.71–0.89)		0.70 (0.59–0.83)		0.90 (0.81–1.00)	
Annualised event rate (n events per 100 patient-years at risk)						
Primary combined endpoint	13.2	10.5	15.6	11.6	37.8	33.6
– Absolute rate reduction	2.7		4.0		4.2	
Cardiovascular death	7.5	6.0	7.9	6.5	13.9	12.9
– Absolute rate reduction	1.5		1.4		1.0	
First HF hospitalisation	NA	NA	9.8	6.9	29.1	25.9
– Absolute rate reduction	1.6		2.9		2.7	

eGFR = estimated glomerular filtration rate; LVEF = left-ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association
Values are reported as mean or median, as appropriate. Adapted from Butler et al. [9]

first heart failure hospitalisation) were similar across recent trials (table 1).

Second, as previously mentioned, heart failure hospitalisations were significantly reduced in the vericiguat arm compared with placebo, and cardiovascular mortality showed a similar trend without achieving statistical significance [9]. The reasons for missing the survival endpoint are speculative. Perhaps vericiguat can effectively reduce hospitalisations but has no impact on survival in this population of advanced HFrEF patients, who are simply too sick to benefit from this intervention. Supporting this hypothesis, the authors showed a meaningful interaction between baseline NP levels and treatment effect, with patients with the highest quartile of NT-proBNP displaying no benefit in regard to the primary endpoint from vericiguat [18]. Similar observations came from a post-hoc analysis examining the potential interaction of disease severity (expressed as NP levels) and treatment effect; in patients with baseline NT-proBNP <8000 ng/l, there was a significant reduction in both cardiovascular death and heart failure hospitalisation in the vericiguat arm, whereas in patients with NT-proBNP >8000 ng/l, no effect of vericiguat on cardiovascular death or heart failure hospitalisation was observed [19]. Maybe in patients with very high baseline NT-proBNP it is too difficult to prevent the inevitable decline [18].

Third, VICTORIA was an event-driven trial, and the high event rate in the high-risk study population was associated with a shorter median follow-up to acquire the total number of events needed than in other heart failure trials (table 1). Perhaps the limited median exposure time enabled a reduction in readmissions, but was insufficient to impact survival.

Forth, many more points need to be elucidated to establish the potential role of vericiguat in clinical practice. Based on the results of VICTORIA, vericiguat improves outcomes in patients with advanced HFrEF, except in those with markedly elevated NPs. Future trials should investigate the prognostic effect of vericiguat in patients with less severe forms of HFrEF, in particular with mildly reduced LVEF and with lower NT-proBNP. Even more importantly, the role of vericiguat in combination with the novel heart failure drugs, in particular ARNis, should be addressed. Indeed, it would be very interesting to understand whether targeting both GC (i.e., sGC with vericiguat and pGC indirectly with sacubitril/valsartan) would further improve the outcome of patients or would increase the incidence of adverse events such as arterial hypotension. The low proportion of patients concomitantly treated with an ARNi in VICTORIA does not allow a definitive answer. Finally, further studies may elucidate a potential role for refined patient selection based on biomarkers (e.g., patients with low cGMP? patients with low NO or low bioactive natriuretic peptides?) [12].

In summary, vericiguat – a sGC stimulator increasing intracellular cGMP – is a new oral treatment for heart failure and provides a novel approach to tackle the pathophysiology of heart failure. Treatment with vericiguat is associated with a significant reduction in the combined endpoint of cardiovascular mortality and heart failure hospitalisation, mainly driven by a reduction in hospital admissions. Patients with advanced HFrEF and a recent history of acute decompensation despite optimal medical heart failure therapy are optimal candidates for starting treatment with vericiguat. The potential role of vericiguat in the milder and in the most severe forms of HFrEF and its use in combination with other novel HFrEF treatments need to be elucidated in further studies.

Key points

- Reduced cGMP activity resulting from ineffective stimulation of soluble guanylate cyclase (sGC) due to endothelial dysfunction plays a key role in the pathophysiology of heart failure and contributes to disease progression.
- Therapeutic strategies to augment cGMP have been evaluated in patients with heart failure with reduced ejection fraction (HFrEF), including stimulation of sGC.
- Vericiguat is an oral sGC stimulator enhancing the sensitivity of sGC to endogenous NO and directly stimulating it in a NO-independent manner, resulting in increased formation of cGMP.
- Vericiguat has been shown to reduce the composite endpoint of cardiovascular mortality and hospitalisations in HFrEF patients. The result was mainly driven by a lower incidence of heart failure hospitalisations in the vericiguat group.
- Patients with advanced HFrEF with a recent history of acute decompensation despite optimal medical therapy are optimal candidates for starting treatment with vericiguat.

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