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ORIGINAL ARTICLE

Eligibility for vericiguat in a real-world, contemporary heart failure population

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Abstract

Aims Vericiguat is a soluble guanylate cyclase stimulator and improves survival in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and an increased risk of decompensation. As real-world data on how many patients could be eligible for vericiguat therapy derive from outdated registries, we aimed to assess eligibility in a prospective cohort of patients with HF.

Methods and results Data from consecutive HF patients undergoing an elective ambulatory visit at five university hospitals from 3 July to 28 July 2023 were collected. Independent investigators assessed which patients (i) met the eligibility criteria of the VICTORIA trial, (ii) complied with HF guideline recommendations, (iii) met regulatory agency criteria, or (iv) met criteria for refundability according to the Italian regulatory agency. Patients (n = 346, 72% men, median age 69 years) had HFrEF in 57% of cases, left ventricular ejection fraction $<$ 45% in 68%, and New York Heart Association class II–IV symptoms in 76%. Patients meeting the eligibility criteria of the VICTORIA trial or European and American HF Guideline recommendations were 9% and 13%, respectively. Patients meeting Food and Drug Administration (FDA) or European Medicines Agency (EMA) label criteria were 19% and 17%, respectively. Drug costs would be covered by the Italian National Health System in 10% of patients [if a sodium-glucose cotransporter-2 inhibitor (SGLT2i) is not mandatory] or in 8% (if an SGLT2i is requested).

Conclusions In a real-world study, 9% of patients met the eligibility criteria of the VICTORIA trial, but up to 13% complied with guideline recommendations and up to 19% met FDA or EMA criteria. In Italy, drug costs would be covered by up to 10% of patients.

Keywords Vericiguat; Heart failure; Therapy; Guidelines; Population

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Introduction

Despite advances in treatment, the prognosis of heart failure (HF) with reduced ejection fraction (HFrEF) remains poor, particularly in patients with a recent worsening event.[1–3] Vericiguat acts as a stimulator of the enzyme soluble guanylate cyclase (sGC), thus activating the same signalling pathways as nitric oxide and natriuretic peptides.[4] In the phase 3 Vericiguat Global Study in Subjects with Heart Failure and Reduced Ejection Fraction (VICTORIA) trial, vericiguat reduced by 10% the composite endpoint of cardiovascular death or first HF hospitalization in patients with HFrEF and increased the risk of HF decompensation.[5] Based on these results, the European Society of Cardiology (ESC)[6] and American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA)[7] Guidelines recommended vericiguat therapy in HFrEF patients considered 'at high risk' with a class of recommendation IIb and a level of evidence B. Vericiguat also gained approvals from the Food and Drug Administration (FDA) and the European Medicines

Agency (EMA) in 2021.[8,9] As a result, this drug is becoming available in current clinical practice.

A few studies have investigated how many patients from real-world HF cohorts may be eligible to vericiguat therapy based on VICTORIA trial criteria, most notably a study conducted on the Korean Acute HF (KorAHF) Registry[10] and another one on the Swedish HF Registry.[11] The large scale of the cohorts investigated (n = 5625 and 23 573 patients, respectively)[10,11] is the main strength of these analyses. On the other hand, all patients in KorAHF were enrolled during an HF decompensation,[10] and the Swedish HF Registry included both inpatients and outpatients,[11] whereas VICTORIA enrolled only stable patients with a higher risk of decompensation.[5] Moreover, patients in both the KorAHF and Swedish HF Registries were enrolled several years ago (from 2011 to 2014 and from 2000 to 2018, respectively),[10,11] which is a possible limitation considering the profound changes in HF therapy over the last two decades, from the acceptance of the neurohormonal model of HF to the four pillars of HFrEF treatment.[12,13] The shifting epidemiology of HF may affect patient characteristics, including, for example, the risk of HF decompensation,[13] and then the estimate of how many patients meet the eligibility criteria of the VICTORIA trial. Furthermore, the percentage of HFrEF patients on triple therapy with renin–angiotensin system blockers, beta-blockers, and mineralocorticoid receptor antagonists (MRAs) has increased over the years following the adoption of guideline recommendations in clinical practice. Guideline-directed medical therapy (GDMT) should now also include a sodium-glucose cotransporter-2 inhibitor (SGLT2i), first recommended in the 2021 ESC Guidelines[6] and then by the AHA/ACC/HFSA in 2022.[7]

Based on these considerations, we gathered information from a prospective cohort of HF patients evaluated in July 2023 at five university hospitals in Italy. We considered how many patients met the eligibility criteria of VICTORIA, guideline recommendations, as well as FDA and EMA label criteria, and how many patients could have vericiguat therapy refunded according to Italian regulation.

Methods

Survey

The study was promoted by an initiative of the Italian Society of Cardiology. We conducted a survey in five university hospitals in Tuscany and Umbria [Fondazione Toscana Gabriele Monasterio (FTGM), Pisa; Azienda Ospedaliera Universitaria Pisana (AOUP), Pisa; Azienda Ospedaliera Universitaria Careggi (AOUC), Florence; Azienda Ospedaliera Universitaria Senese (AOUS); and Azienda Ospedaliera di Perugia]. Data from consecutive HF patients undergoing an elective ambulatory visit over 4 weeks (from 3 July to 28 July 2023) were collected with a dedicated web-based survey (Supporting Information, *Table S1*). Eligibility for vericiguat therapy was established by independent investigators (A. A. and G. V.) based on the data collected at the five sites.

Consent

The institutional ethics committee approved the study and waived the acquisition of informed consent as fully de-identified data were collected.

VICTORIA trial criteria

Eligibility criteria for vericiguat from the VICTORIA trial were applied to our cohort, as reported in *Table 1*. Patients with HFrEF were also evaluated separately.

Guideline recommendations

According to the 2021 ESC[6] and 2022 AHA/ACC/HFSA[7] Guideline recommendations, vericiguat may be considered in patients fulfilling the following criteria: (i) age $\geq$ 18 years; (ii) chronic HFrEF; (iii) New York Heart Association (NYHA) class II–IV symptoms; (iv) recent worsening HF; and (v) on GDMT, defined as concomitant use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors (ACE-Is/ARBs/ARNIs), beta-blockers, and MRAs, unless contraindicated or not tolerated.

Regulatory agency criteria

According to the FDA product label, vericiguat is indicated 'following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%'[8] (*Table 2*). The timing of the previous HF hospitalization or the need for outpatient intravenous diuretics is not specified. The only contraindications specifically mentioned are concomitant use of other sGC stimulators and pregnancy.[8]

In the EMA label, vericiguat is indicated 'for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy'[9] (*Table 2*). The left ventricular ejection fraction (LVEF) cut-off is not specified.[9] In the present analysis, we interpreted the definition of 'reduced ejection fraction' as HFrEF according to ESC HF Guidelines,[6] as in the study on the Swedish HF Registry.[11] The contraindications reported on the label are severe renal disease or

Table 1 Patients meeting the inclusion and exclusion criteria of the VICTORIA trial

Criteria	Patient number (%)	
	All cohort $n = 346$	HFrEF (LVEF < 40%) $n = 198$
Inclusion criteria		
Informed consent[a]	346 (100)	198 (100)
Age ≥ 18 years	346 (100)	198 (100)
Chronic HF (HF duration ≥ 6 months)	346 (100)	198 (100)
NYHA class II–IV	262 (76)	187 (84)
Prior HF hospitalization ≤6 months prior to baseline	87 (25)	62 (31)
NT-proBNP criterion	153 (44)	109 (55)
LVEF < 45%	237 (69)	198 (100)
Is not of reproductive potential[a]	346 (100)	198 (100)
Patients meeting all the inclusion criteria	50 (14)	47 (24)
Exclusion criteria		
SBP < 100 mmHg at baseline	29 (8)	25 (13)
Nitrate, PDE5-i, or sGC stimulator use at baseline	5 (0)	4 (2)
Allergy to any sGC stimulator	0 (0)	0 (0)
Implanted VAD within 5 years before and after baseline; heart transplantation within 5 years since baseline	14 (4)	13 (7)
Valvular surgery ≤3 months prior to baseline	17 (5)	6 (3)
History of amyloidosis or sarcoidosis; obstructive HCM; Takotsubo cardiomyopathy or acute myocarditis within 30 days prior to baseline; post-heart transplant cardiomyopathy; tachycardia-induced cardiomyopathy	30 (9)	16 (8)
Unstable angina, STEMI and NSTEMI, PCI, CABG, carotid stenosis, TIA, or stroke ≤2 months prior to baseline	12 (3)	6 (3)
History of congenital heart disease	0 (0)	0 (0)
Endocarditis or constrictive pericarditis ≤3 months prior to baseline	0 (0)	0 (0)
eGFR < 15 mL/min/1.73 m^2 at baseline	0 (0)	0 (0)
Chronic dialysis ≤3 months prior to baseline	0 (0)	0 (0)
Hepatic failure or hepatic encephalopathy ≤1 year prior to baseline	0 (0)	0 (0)
Secondary cancer (metastases) or primary cancer with very poor prognosis	3 (1)	2 (1)
PAH within 1 year prior to baseline	0 (0)	0 (0)
Drug/alcohol abuse ≤1 year prior to baseline	0 (0)	0 (0)
Participation in another trial[a]	0 (0)	0 (0)
Unable to provide informed consent[a]	0 (0)	0 (0)
Mental disorders ≤1 year prior to baseline	0 (0)	0 (0)
Direct involvement with the trial[a]	0 (0)	0 (0)
Interstitial lung disease ≤1 year prior to baseline	3 (1)	3 (2)
Is pregnant or breastfeeding or plans to become pregnant or to breastfeed[a]	0 (0)	0 (0)
Patients not meeting any exclusion criteria	94 (27)	58 (29)
Patients meeting all the inclusion criteria and none of the exclusion criteria	32 (9%)	31 (16)

CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary artery hypertension; PCI, percutaneous coronary intervention; PDE5-i, phosphodiesterase-5 inhibitor; SBP, systolic blood pressure; sGC, soluble guanylate cyclase; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack; VAD, ventricular assist device.
[a]Assumed.

dialysis, severe liver disease, hypersensitivity to the active substance or to any of the excipients, and concomitant use of other sGC stimulators.[9]

Italian refundability criteria

Eligibility criteria for refundability according to the Italian regulatory agency [Agenzia Italiana del Farmaco (AIFA)] are listed in *Table 3*. The 'tolerated optimal medical treatment' was not further specified. At the time of the survey (July 2023), ACE-Is, ARBs, ARNIs, beta-blockers, and MRAs had class IIb recommendations for use in patients with LVEF 41–45%, whereas no recommendation was available for SGLT2is.[6] SGLT2is received a class I indication for these patients in August 2023.[14] For the purposes of this survey, we considered as optimal medical therapy the combination of ACE-Is/ARBs/ARNIs, beta-blockers, and MRAs, and we performed a separate analysis considering also SGLT2is as part of the optimal medical therapy.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 24). The normal distribution was assessed through the Shapiro–Wilk test. All continuous variables were non-normally distributed and were then expressed as the median and interquartile range. Categorical variables were expressed as numbers and percentages.

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Results

Patient population

The survey included 346 HF outpatients from five centres (FTGM, *n* = 120, 35%; AOUP, *n* = 82, 24%; AOUS, *n* = 57, 17%; AOUC, *n* = 51, 15%; and Azienda Ospedaliera di Perugia, *n* = 36, 10%). Men accounted for 72% of the cohort; the median age was 69 years (interquartile range 59–78); and 76% had NYHA class II–IV symptoms. The majority of patients (*n* = 198, 57%) had LVEF ≤ 40% (i.e. HFrEF). Patients on triple therapy (ACE-I/ARB/ARNI, beta-blocker, and MRA) were 247 (71%); 175 (51%) were on quadruple therapy (also including an SGLT2i).

Table 2 Patients meeting the Food and Drug Administration (FDA) and European Medicines Agency (EMA) label criteria

Criteria	Patient number (%)
Age ≥ 18 years	346 (100)
Chronic HF	346 (100)
NYHA class II–IV	262 (76)
LVEF < 45%	237 (69)
Hospitalization for heart failure or need for outpatient IV diuretics[a]	87 (25)
Concomitant use of other sGC stimulators	0 (0)
Pregnancy[b]	0 (0)
FDA eligibility	65 (19)
Age ≥ 18 years	346 (100)
Chronic HF	346 (100)
NYHA class II–IV	262 (76)
LVEF ≤ 40%	198 (57)
Hospitalization for heart failure or need for outpatient IV diuretics[a]	87 (25)
eGFR < 15 mL/min/1.73 m^2 or dialysis	0 (0)
Severe liver disease (Child–Pugh class C)	0 (0)
Hypersensitivity to the active substance or to any of the excipients	0 (0)
Concomitant use of other sGC stimulators	0 (0)
EMA eligibility	59 (17)

eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; sGC, soluble guanylate cyclase.
[a]Criterion adjudicated as in VICTORIA.
[b]Assumed.

Eligibility according to VICTORIA trial criteria

The majority of patients (*n* = 237, 68%) had an LVEF < 45%, as in the VICTORIA trial.[5] Patients meeting inclusion criteria were 50 (14%), while 94 (27%) met at least one exclusion criterion (*Table 1*). Overall, 32 patients (9%) were eligible to vericiguat based on trial criteria. Among them, 17 (53%) had N-terminal pro-B-type natriuretic peptide (NT-proBNP) values < 8000 ng/L, a threshold below which the drug seemed more effective based on a subgroup analysis.[15]

When patients with HFrEF (*n* = 198) were considered separately, 31 (16%) met the eligibility criteria of the VICTORIA trial (*Table 1*).

Status post/anticipated heart transplantation or other specific diagnosis (e.g. obstructive hypertrophic cardiomyopathy, tachycardia-induced cardiomyopathy, uncontrolled tachyarrhythmia, complex congenital heart disease, acute myocarditis, amyloidosis, sarcoidosis, Takotsubo syndrome, active endocarditis, and constrictive pericarditis) and hypotension represented the most common exclusion criteria (9% and 8%, respectively) (*Table 1*).

Table 3 Refundability criteria according to Italian regulation

Refundability criteria	Patient number (%)
NYHA class II–IV	262 (76)
LVEF < 45%	237 (69)
No primary valve disease requiring repair or replacement or valve repair/replacement during the previous 12 weeks	329 (95)
No obstructive HCM, previous heart transplant, tachycardia-induced cardiomyopathy, uncontrolled tachyarrhythmia, complex congenital heart disease, acute myocarditis, amyloidosis, sarcoidosis, Takotsubo syndrome, active endocarditis, constrictive pericarditis	316 (91)
No acute coronary syndrome (either unstable angina or myocardial infarction) or percutaneous or surgical coronary revascularization in the previous 60 days or an indication to coronary revascularization	334 (97)
No symptomatic coronary artery stenosis, transient ischaemic attack, or stroke in the previous 60 days	334 (97)
Persistence or worsening of symptoms after an HF hospitalization <6 months or need for intravenous diuretic therapy <3 months	87 (25)
OMT for HF (as tolerated) for ≥3 months = ACE-I/ARB/ARNI, beta-blocker, MRA	247 (71)
OMT for HF (as tolerated) for ≥3 months = ACE-I/ARB/ARNI, beta-blocker, MRA + SGLT2i	175 (51)
Systolic artery pressure ≥ 100 mmHg	317 (92)
eGFR ≥ 15 mL/min/1.73 m^2	346 (100)
No severe liver disease (Child–Pugh class C)	346 (100)
No pregnancy or breastfeeding	346 (100)
Refundable drug (if OMT = ACE-I/ARB/ARNI, beta-blocker, MRA)	34 (10)
Refundable drug (if OMT = ACE-I/ARB/ARNI, beta-blocker, MRA + SGLT2i)	28 (8)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OMT, optimal medical therapy; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
See the text for further details.

Guideline recommendations

As stated above, the ESC[6] and AHA/ACC/HFSA[7] Guidelines recommend vericiguat therapy in adult patients with chronic HFrEF (*n* = 198, 75% in our cohort) meeting the following criteria: NYHA class II–IV symptoms (*n* = 167, 84%), recent HF worsening (*n* = 62, 31%, according to the VICTORIA trial criterion),[5] and on GDMT (defined as renin–angiotensin system inhibitors/ARNIs, beta-blockers, and MRAs, unless contraindicated or not tolerated; *n* = 159, 80%). Overall, 46 patients (13%) complied with guideline recommendations.

When SGLT2is were included as part of GDMT, unless contraindicated or not tolerated, 38 patients (11%) complied with guideline recommendations.

Regulatory agency criteria

Sixty-five patients (19%) were eligible to vericiguat based on FDA label criteria, and 59 (17%) based on EMA label criteria (*Table 2* and *Figure 1*).

Italian reimbursement criteria

According to AIFA criteria, 34 patients (10%) could have the costs of vericiguat therapy covered by the Italian National Health System. If quadruple therapy was considered the optimal medical therapy for all patients (i.e. including those with LVEF 41–45%), vericiguat therapy could be refunded in 28 patients (8%). Details are provided in *Table 3*.

Discussion

Following the recent evidence from the VICTORIA trial and the latest recommendations from both the European and American guidelines, vericiguat is expected to enter the clinical routine in the next few months and to represent an additional pillar in selected patients with HF, namely, those deemed at higher risk for decompensation. Previous studies have made an attempt to retrospectively estimate from large registries the proportion of patients potentially eligible for therapy with vericiguat. Conversely, this is the first prospective investigation of a real-world, contemporary prospective HF population. Our findings show that 9% of the HF population met the eligibility criteria of the VICTORIA trial, but up to 15% complied with guideline recommendations and up to 19% with EMA (*Figure 2*) or FDA criteria. In Italy, drug costs would be covered by up to 10% of patients. These findings highlight that, in real-world settings, the population potentially receiving vericiguat may be much wider, and likely different, from the trial population.

Figure 1 Venn diagram showing the distribution of patients fulfilling criteria for eligibility for vericiguat therapy. Patient eligibility has been assessed according to the criteria of the VICTORIA trial, the European Society of Cardiology (ESC) guidelines (GLs), and the European Medicines Agency (EMA). HF, heart failure.

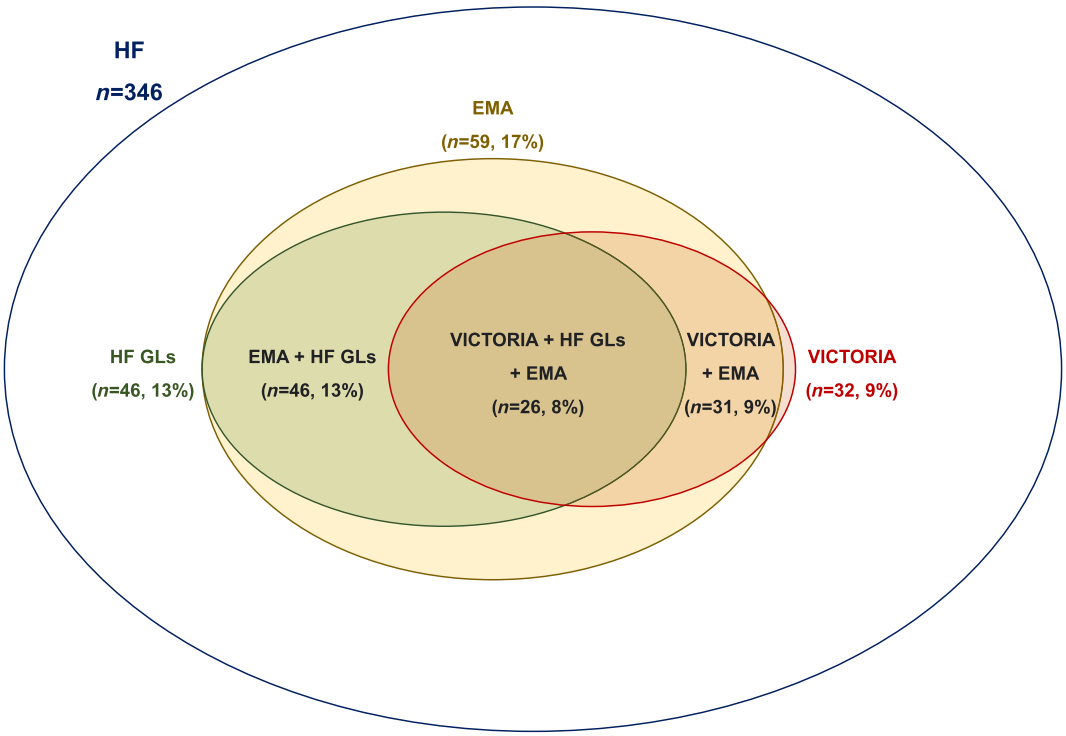

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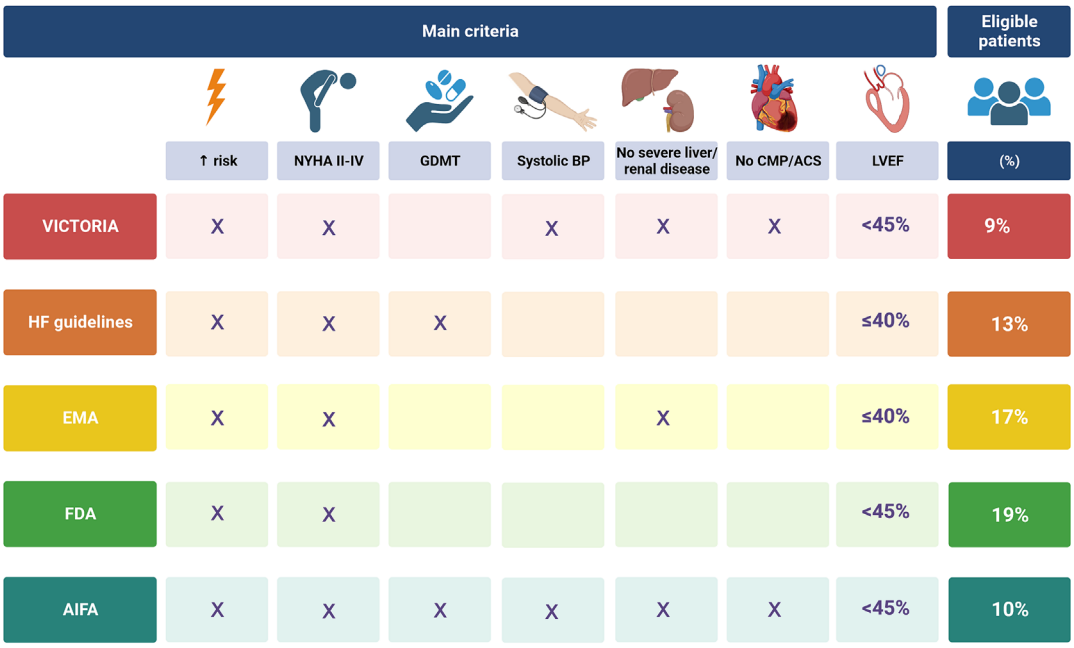
Figure 2 Patients meeting the different criteria for eligibility for vericiguat therapy. See the text for details. ACS, acute coronary syndrome; AIFA, Agenzia Italiana del Farmaco; BP, blood pressure; CMP, cardiomyopathy; EMA, European Medicines Agency; FDA, Food and Drug Administration; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure and Reduced Ejection Fraction.



In our study, fewer patients were found to be eligible compared with the SwedeHF Registry, in which 21% met the eligibility criteria.[11] Such a discrepancy may be related to the inclusion in the Swedish Registry of both inpatients and outpatients, with the former fulfilling by definition one of the entry criteria and likely accounting for a more severe population.

In the VICTORIA trial, inclusion criteria were chosen to select a population with evidence of worsening HF, although there is no general consensus on its definition. Some data suggest that vericiguat may be more effective in patients with relatively lower NT-proBNP levels[15] and, therefore, is expected to have a less severe disease. Testing vericiguat in patients at lower risk may extend the eligibility well above the 9% we have reported. Interestingly, when the clinicians participating in the present survey were asked, in a conclusive item of the survey, if the patient was deemed to have benefited from therapy with vericiguat, they answered affirmatively in 169/346 (49%) cases. In the whole study population, the post-heart transplantation status or other specific diagnosis, such as obstructive hypertrophic cardiomyopathy, tachycardia-induced cardiomyopathy, uncontrolled tachyarrhythmia, complex congenital heart disease, acute myocarditis, amyloidosis, sarcoidosis, Takotsubo syndrome, active endocarditis, and constrictive pericarditis, represented the most common exclusion criteria (9%), followed by hypotension (systolic blood pressure $<$ 100 mmHg; 8%). The same criteria were the most common reasons for exclusion in the cohort of patients with HFrEF (8% and 13%, respectively). Unfortunately, we pooled together specific aetiologies to limit the number of items in the survey; thus, we are not able to report the prevalence of each individual diagnosis. The number of patients potentially excluded due to low blood pressure was similar to those reported in previous studies exploring the real-world eligibility for sacubitril/valsartan.[16] On one side, serial monitoring of blood pressure is mandatory for the introduction and the titration of the therapy; on the other hand, this enforces the need for a careful evaluation of pharmacotherapy and for the withdrawal of drug classes with blood-pressure-lowering effects that are contraindicated or sometimes unnecessary (e.g. calcium channel and alpha-blockers).

We performed a prospective assessment of consecutive patients, representative of a contemporary HF population treated at Italian tertiary centres, and on up-to-date pharmacological and non-pharmacological therapy, including, when indicated, therapy with sacubitril–valsartan and SGLT2i. Indeed, in the whole study population (which was not restricted to HFrEF), up to 71% of patients were receiving ACE-Is/ARBs/ARNIs, beta-blockers, and MRAs, and up to 51% were receiving ACE-Is/ARBs/ARNIs, beta-blockers, MRAs, and SGLT2is. We also limited our study to ambulatory patients, as hospitalized patients were excluded from the VICTORIA trial, and following guideline recommendations, we applied to 'stable' HF patients. We could recruit a relatively small cohort from university hospitals, which may not

accurately mirror the real-world experience of smaller centres. Moreover, detailed data on patient characteristics, including the doses of pharmacological therapy, could not be collected.

In conclusion, in a prospective, consecutive, contemporary, real-world cohort of patients with stable HF, eligibility for vericiguat is 9% according to the VICTORIA trial criteria. Eligibility for vericiguat was higher following European and American HF Guidelines (13% of patients), FDA and EMA label criteria (19% and 17%, respectively), and according to Italian National Health System reimbursement criteria (up to 10% of patients), thus suggesting that the population eligible for vericiguat in clinical practice may be much wider than expected from the VICTORIA trial entry criteria.

Conflict of interest

None declared.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Items of the questionnaire used for the survey on eligibility for vericiguat.

References

1. Roger VL. Epidemiology of heart failure: A contemporary perspective. *Circ Res* 2021;**128**:1421-1434. doi:10.1161/CIRCRESAHA.121.318172
2. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;**3**:7-11. doi:10.15420/cfr.2016:25:2
3. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;**22**:1342-1356.
4. Emdin M, Aimo A, Castiglione V, Vergaro G, Georgiopoulos G, Saccaro LF, *et al*. Targeting cyclic guanosine monophosphate to treat heart failure: JACC review topic of the week. *J Am Coll Cardiol* 2020;**76**:1795-1807. doi:10.1016/j.jacc.2020.08.031
5. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, *et al*. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**:1883-1893. doi:10.1056/NEJMoa1915928
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4-131. doi:10.1002/ejhf.2333
7. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e876-e894. doi:10.1161/CIR.0000000000001062
8. Verquvo [Package Insert]. Leverkusen, Germany: Merck Sharp and Dohme Corp. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214377s000lbl.pdf. Accessed 8 Sep 2023
9. European Medicines Agency. Verquvo. https://www.ema.europa.eu/en/medicines/human/EPAR/verquvo. Accessed 8 Sep 2023
10. Oh J, Lee CJ, Park JJ, Lee SE, Kim MS, Cho HJ, *et al*. Real-world eligibility for vericiguat in decompensated heart failure with reduced ejection fraction. *ESC Heart Fail* 2022;**9**:1492-1495.
11. Nguyen NV, Lindberg F, Benson L, Ferrannini G, Imbalzano E, Mol PGM, *et al*. Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2023;**25**:1418-1428.
12. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: A review. *JAMA* 2020;**324**:488-504. doi:10.1001/jama.2020.10262
13. Greene SJ, Bauersachs J, Brugts JJ, Ezekowitz JA, Lam CSP, Lund LH, *et al*. Worsening heart failure: Nomenclature, epidemiology, and future directions: JACC review topic of the week. *J Am Coll Cardiol* 2023;**81**:413-424. doi:10.1016/j.jacc.2022.11.023
14. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2023 focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;**44**:3627-3639. doi:10.1093/eurheartj/ehad195
15. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, *et al*. N-terminal pro-B-type natriuretic peptide and clinical outcomes: Vericiguat Heart Failure With Reduced Ejection Fraction Study. *JACC Heart Fail* 2020;**8**:931-939. doi:10.1016/j.jchf.2020.08.008
16. Simpson J, Benson L, Jhund PS, Dahlström U, McMurray JJV, Lund LH. "Real world" eligibility for sacubitril/valsartan in unselected heart failure patients: Data from the Swedish Heart Failure Registry. *Cardiovasc Drugs Ther* 2019;**33**:315-322. doi:10.1007/s10557-019-06873-1