

University of Groningen

Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria

Nguyen, Ngoc V.; Lindberg, Felix; Benson, Lina; Ferrannini, Giulia; Imbalzano, Egidio; Mol, Peter G.M.; Dahlström, Ulf; Rosano, Giuseppe M.C.; Ezekowitz, Justin; Butler, Javed

Published in:
European Journal of Heart Failure

DOI:
[10.1002/ejhf.2939](https://doi.org/10.1002/ejhf.2939)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Nguyen, N. V., Lindberg, F., Benson, L., Ferrannini, G., Imbalzano, E., Mol, P. G. M., Dahlström, U., Rosano, G. M. C., Ezekowitz, J., Butler, J., Lund, L. H., & Savarese, G. (2023). Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria: Data from the Swedish Heart Failure Registry. *European Journal of Heart Failure*, 25(8), 1418-1428.
<https://doi.org/10.1002/ejhf.2939>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria: Data from the Swedish Heart Failure Registry

Ngoc V. Nguyen¹, Felix Lindberg², Lina Benson², Giulia Ferrannini², Egidio Imbalzano³, Peter G.M. Mol⁴, Ulf Dahlström⁵, Giuseppe M.C. Rosano⁶, Justin Ezekowitz⁷, Javed Butler^{8,9}, Lars H. Lund^{2,10}, and Gianluigi Savarese^{2,10*} 

¹Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; ²Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; ³Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; ⁴Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ⁵Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; ⁶IRCCS San Raffaele Roma, Rome, Italy; ⁷Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada; ⁸University of Mississippi Medical Center, Jackson, MS, USA; ⁹Baylor Scott and White Institute, Dallas, TX, USA; and ¹⁰Heart, Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden

Received 23 February 2023; revised 29 May 2023; accepted 8 June 2023; online publish-ahead-of-print 29 June 2023

Aim

We investigated the eligibility for vericiguat in a real-world heart failure (HF) population based on trial, guideline and label criteria.

Methods and results

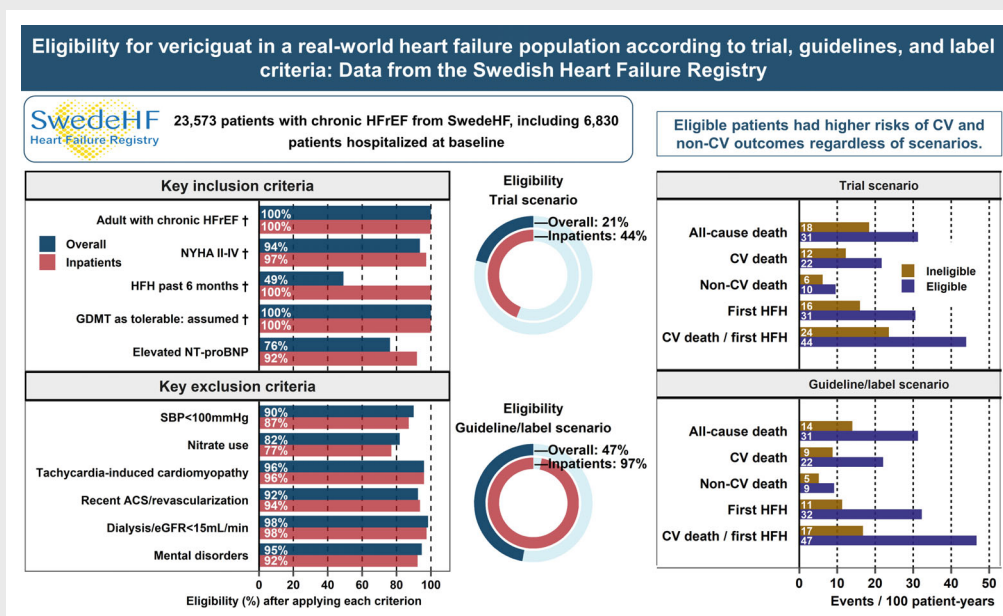
From the Swedish HF registry, 23 573 patients with HF with reduced ejection fraction (HFrEF) enrolled between 2000 and 2018, with a HF duration ≥ 6 months, were considered. Eligibility for vericiguat was calculated based on criteria from (i) the Vericiguat Global Study in Subjects with Heart Failure and Reduced Ejection Fraction (VICTORIA) trial; (ii) European and American guidelines on HF; (iii) product labelling according to the Food and Drug Administration and European Medicines Agency. Estimated eligibility for vericiguat in the trial, guidelines, and label scenarios was 21.4%, 47.4%, and 47.4%, respectively. Prior HF hospitalization within 6 months was the criterion limiting eligibility the most in all scenarios (met by 49.1% of the population). In the trial scenario, other criteria meaningfully limiting eligibility were elevated N-terminal pro-B-type natriuretic peptide levels and nitrate use. In all scenarios, eligibility was higher among patients hospitalized for HF at baseline (44.3% vs. 21.4% [trial scenario] and 97.3% vs. 47.4% [guideline/label scenarios] for hospitalized vs. non-hospitalized patients). Overall, eligible patients were older, had more severe HF, more comorbidities, and consequently higher cardiovascular mortality and HF hospitalization rates compared with ineligible patients across all scenarios.

Conclusion

In a large and contemporary real-world HFrEF cohort, we estimated that 21.4% of patients would be eligible for vericiguat according to the VICTORIA trial selection criteria, 47.4% based on guidelines and labelling. Eligibility for vericiguat translated into the selection of a population at high risk of morbidity/mortality.

*Corresponding author. Division of Cardiology, Department of Medicine, Karolinska Institutet, Norrbacka S3:00, 171 76, Stockholm, Sweden. Email: gianluigi.savarese@ki.se
 Ngoc V. Nguyen and Felix Lindberg Equally contributed as first authors.

Graphical Abstract



Proportion and outcomes of patients eligible for vericiguat according to trial, guideline, and label criteria in patients with chronic HFrEF. ACS, acute coronary syndrome; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure. Criteria labelled with a dagger were considered in the guideline and label scenarios.

Keywords Heart failure • Vericiguat • Eligibility • Randomized controlled trial • Guidelines • Label

Introduction

Despite advances in treatment, the prognosis of heart failure (HF) with reduced ejection fraction (HFrEF) remains poor, especially in patients with a recent worsening event.¹⁻³ Targeting patients with worsening HF and an ejection fraction (EF) <45%, the Vericiguat Global Study in Subjects with Heart Failure and Reduced Ejection Fraction (VICTORIA) trial showed a reduction in risk of cardiovascular (CV) death or HF hospitalization with the soluble guanylate cyclase stimulator vericiguat compared with placebo.⁴ Accordingly, the 2021 HF guidelines from the European Society of Cardiology (ESC) as well as the 2022 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend that vericiguat may be considered in patients with symptomatic worsening HFrEF (Class IIb).^{5,6} Vericiguat gained approvals from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2021.^{7,8}

Randomized controlled trials (RCTs) in HF apply selection criteria to ensure the correct identification of the study population, to enrich for the CV outcomes of interest, and to minimize competing risks from non-CV events. As a result, trial populations may have a higher risk of CV but a lower risk of non-CV events compared with the real-world HF population.^{9,10} Thus, the stringent

selection of patients in RCTs might limit the generalizability of trials' findings to the HF patients encountered in daily clinical practice.¹¹ This has also major implications in terms of regulatory approval, product labelling, guideline recommendations, reimbursement criteria, clinical acceptance, and implementation of novel interventions.¹²⁻¹⁴

Therefore, in a large and unselected real-world HF population, we aimed to (i) assess the proportions of patients eligible for receiving vericiguat based on trial, guidelines, and label criteria, and (ii) explore the differences in patient characteristics and prognosis by eligibility status.

Methods

Data sources

The Swedish HF registry (SwedeHF) has been described previously.¹⁵ It is a voluntary national quality registry founded in 2000 (www.swedehf.se). The inclusion criterion was a clinician-judged diagnosis of HF until April 2017, which has been thereafter redefined according to the International Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, I13.2. Currently, 20 of 21 regions and 69 of 76 hospitals in Sweden participate, with a prevalent HF coverage of 30.4%.¹⁶

For this analysis, SwedeHF was linked with other national registries: (1) the National Patient Register to extract comorbidities and cause-specific hospitalization outcomes¹⁷; (2) Statistics Sweden to obtain socioeconomic variables; (3) the Cause of Death Register to obtain cause-specific mortality outcomes.¹⁸

A complete variable list and corresponding data sources are reported in online supplementary Table S1. The establishment of SwedeHF and its linkage with the other registries were approved by the Swedish Ethical Review Authority.

Study population and design

The present study included patients enrolled in SwedeHF between May 2000 and December 2018, aged >18 years, with recorded data on EF and HF duration. Patients were considered potentially eligible, and thereby included in the denominator for eligibility calculations, if they had chronic HF (defined as having had a HF diagnosis ≥ 6 months) and an EF <40% for the main analysis or <50% for the trial sensitivity analysis. These two specific cut-offs for EF were chosen due to the fact that, in SwedeHF, EF is a categorical variable (<30%, 30–39%, 40–49%, $\geq 50\%$), which did not allow for an exact match with the EF criterion used in the trial (<45%), guidelines ($\leq 40\%$), and labels (EMA: $\leq 40\%$, FDA: <45%). Index date was defined as the date of the latest registration in SwedeHF to better represent contemporary care. End of follow-up for the outcome analysis was 31 December 2019 in the main analysis. Patient selection is detailed in online supplementary Figure S1.

Eligibility criteria for vericiguat in the trial, guidelines, and label scenarios

Eligibility criteria for vericiguat from the VICTORIA trial⁴ were applied to SwedeHF as reported in Table 1. According to the 2021 ESC and 2022 AHA/ACC guideline recommendations,^{5,6} vericiguat may be considered in patients fulfilling the following criteria: (1) adult; (2) chronic HFrEF; (3) New York Heart Association (NYHA) class II–IV; (4) recent worsening HF; (5) on guideline-directed medical therapy (GDMT), defined as concomitant use of a renin–angiotensin system inhibitor (RAS)/angiotensin receptor–neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA). In the FDA/EMA product labelling information,^{7,8} vericiguat was approved for patients fulfilling the following criteria: (1) adult; (2) chronic HF with EF <45% (FDA) or EF $\leq 40\%$ (EMA); (3) NYHA class II–IV; (4) a recent hospitalization for HF or need for outpatient intravenous diuretics. The full list of original criteria along with their respective definitions in SwedeHF are reported in online supplementary Tables S2 (trial scenario), S3 (guideline scenario), and S4 (label scenario).

In this analysis, a worsening event was defined as a HF hospitalization according to the diagnostic codes in online supplementary Table S1. Outpatient intravenous diuretic therapy (considered in VICTORIA) could not be assessed due to lack of data, and consequently was not included in the definition, but is deemed overall rare in Swedish clinical practice. The timeframe for a worsening event in the trial was defined as within 6 months prior to randomization,⁴ whereas no timeframe was specified in the guidelines or labels.^{5–8} Therefore, we defined 6 months prior to or at the index date as the relevant timeframe for the main analysis and performed a sensitivity analysis in the guideline and label scenarios considering a 3-month timeframe. For the guideline scenario criterion of GDMT, we hypothesized that in clinical practice ~ 6 months since an HF diagnosis would allow for

the initiation and up-titration of medical therapy. Thus, in the main analysis we assumed that all patients were on GDMT since our study only included patients with HF duration ≥ 6 months. In a sensitivity analysis, a literal interpretation of GDMT was used considering as eligible only those patients on RAS/ARNI + beta-blocker + MRA, which is rarely observed in real-world clinical practice mainly due to the limited implementation of MRA.¹⁹ Furthermore, we conducted a ‘renal function’ sensitivity analysis for the guideline and label scenarios, where patients with an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m² or dialysis were considered as ineligible.

Statistical analysis

Eligibility proportions were reported as percentages and represented the eligible cohort after applying the respective inclusion/exclusion criteria. Eligibility proportions were calculated for each criterion individually in the overall cohort, as well as in the subgroup of patients hospitalized due to HF at the index date. Patient characteristics according to eligibility were presented as frequencies (percentages) for categorical variables and as medians (interquartile range [IQR]) for continuous variables, with comparisons across groups performed by Chi-square test and Wilcoxon–Mann–Whitney test or *t*-test, respectively.

Nine outcomes were considered: all-cause death, CV death, non-CV death, time to first all-cause hospitalization, time to first CV hospitalization, time to first non-CV hospitalization, time to first HF hospitalization, a composite of CV death or first HF hospitalization, and a composite of all-cause death or first HF hospitalization. Incidence rates with 95% confidence intervals (CI) (per 100 person-years) were calculated according to the eligibility status. Rates were compared between eligible and ineligible patients using the exact Poisson test and presented as incidence rate ratios (IRR) with 95% CI. Kaplan–Meier curves were reported accordingly.

Two sensitivity analyses were performed to achieve better comparability between the VICTORIA trial cohort and the contemporary real-world setting: (i) an additional outcome analysis censored at 10.8 months (the median follow-up time in VICTORIA); (ii) separate eligibility and event rate calculations in patients with an index date during the last 2 years of the enrolment period (2017–2018).

Missing data were handled by single imputation (R package *mice*),²⁰ stratified by EF (<40% and 40–49%). The variables included in the imputation models were those reported in online supplementary Table S5 along with all-cause mortality as a Nelson–Aalen estimator. In addition, we performed two consistency analyses, namely: (1) a *complete-case analysis* where we excluded patients with any missing entries for the variables needed for eligibility calculation; (2) a *missing as eligible analysis* where we considered patients with missing entries for the variables needed for eligibility calculation eligible for the corresponding criteria. All analyses were performed in R 4.1.2. The significance level was set at 5%, two-sided.

Results

Between May 2000 and December 2018, 23 573 patients with chronic HF and EF <40% were enrolled in the SwedeHF. The median age was 76 years (IQR 68–83) and 73% were male. The majority of patients was encountered in an outpatient setting (71%) and had NYHA class III–IV (54%). Most patients were treated with a beta-blocker (92%), a RAS/ARNI (89%), and an MRA (44%). Use of devices was low, that is, 12% with cardiac resynchronization

Table 1 Eligibility for vericiguat after applying the trial inclusion/exclusion criteria (missing values imputed)

Eligibility criteria	EF <40%		EF <50% (n = 34 399)
	Total (n = 23 573)	Hospitalized patients (n = 6830)	
Inclusion criteria			
Number of patients eligible (fulfilling the respective inclusion criteria) (%)*			
1. Informed consent (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
2. Age ≥18 years	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
3. Chronic HF (HF duration ≥6 months)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
4. NYHA class II–IV	22 060 (93.6)	6647 (97.3)	31 542 (91.7)
5. Prior HF hospitalization within 6 months	11 565 (49.1)	6830 (100)	15 429 (44.9)
6. NT-proBNP criterion	17 954 (76.2)	6280 (91.9)	24 723 (71.9)
7. EF criterion	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
8. Is not of reproductive potential (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
Trial eligibility, only inclusion criteria	9856 (41.8)	6127 (89.7)	12 954 (37.7)
Exclusion criteria			
Number of patients eligible (not fulfilling the respective exclusion criteria) (%)*			
1. SBP <100 mmHg at baseline	21 205 (90.0)	5947 (87.1)	31 550 (91.7)
2. Nitrate use at baseline	19 300 (81.9)	5257 (77.0)	28 285 (82.2)
3. PDE5-i use at baseline	23 461 (99.5)	6782 (99.3)	34 206 (99.4)
4. sGC stimulator use at baseline	23 461 (99.5)	6782 (99.3)	34 206 (99.4)
5. Allergy to any sGC stimulator (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
6. Implanted VAD within 5 years before and after baseline; heart transplantation within 5 years since baseline	23 531 (99.8)	6813 (99.8)	34 353 (99.9)
7. Valvular surgery within 3 months prior to baseline	23 427 (99.4)	6797 (99.5)	34 169 (99.3)
8. History of hypertrophic obstructive cardiomyopathy	23 479 (99.6)	6798 (99.5)	34 253 (99.6)
9a. History of amyloidosis, sarcoidosis	23 484	6799	34 270
9b. Takotsubo cardiomyopathy or acute myocarditis within 30 days prior to baseline	(99.6)	(99.5)	(99.6)
10. Has post-heart transplant cardiomyopathy (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
11. History of tachycardia-induced cardiomyopathy	22 640 (96.0)	6566 (96.1)	33 248 (96.7)
12. Unstable angina, STEMI and NSTEMI, PCI, CABG, within 2 months prior to baseline	21 806 (92.5)	6403 (93.7)	32 011 (93.1)
13. Carotid stenosis, TIA or stroke within 2 months prior to baseline	23 276 (98.7)	6717 (98.3)	33 996 (98.8)
14. History of congenital heart disease	23 443 (99.4)	6797 (99.5)	34 204 (99.4)
15. Endocarditis or constrictive pericarditis within 3 months prior to baseline	23 526 (99.8)	6811 (99.7)	34 322 (99.8)
16a. eGFR <15 ml/min/1.73 m ² at baseline	23 198	6656	33 873
16b. Chronic dialysis within 3 months prior to baseline	(98.4)	(97.5)	(98.5)
17. Hepatic failure or hepatic encephalopathy within 1 year prior to baseline	23 476 (99.6)	6778 (99.2)	34 278 (99.6)
18. Secondary cancer (metastases) or primary cancer with very poor prognosis. The diagnosis has to be in first position appearing twice within 7 months prior to baseline.	23 449 (99.5)	6802 (99.6)	34 233 (99.5)
19. PAH within 1 year prior to baseline	23 461 (99.5)	6782 (99.3)	34 206 (99.4)
20. Drug/alcohol abuse within 1 year prior to baseline	22 998 (97.6)	6621 (96.9)	33 675 (97.9)
21. Participation in another trial (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
22. Unable to provide informed consent (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
23. Mental disorders within 1 year prior to baseline	22 330 (94.7)	6306 (92.3)	32 715 (95.1)
24. Direct involvement with the trial (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
25. Interstitial lung disease within 1 year prior to baseline	23 371 (99.1)	6755 (98.9)	34 081 (99.1)
26. Is pregnant or breastfeeding or plans to become pregnant or to breastfeed (assumed 100%)	23 573 (100.0)	6830 (100.0)	34 399 (100.0)
Trial eligibility, only exclusion criteria	13 808 (58.6)	3461 (50.7)	20 993 (61.0)
Trial eligibility, overall	5039 (21.4)	3029 (44.3)	6814 (19.8)

Definitions of eligibility criteria are provided in online supplementary Table S2.

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

*Eligibility proportions represent the eligible cohort after applying the respective inclusion/exclusion criteria.

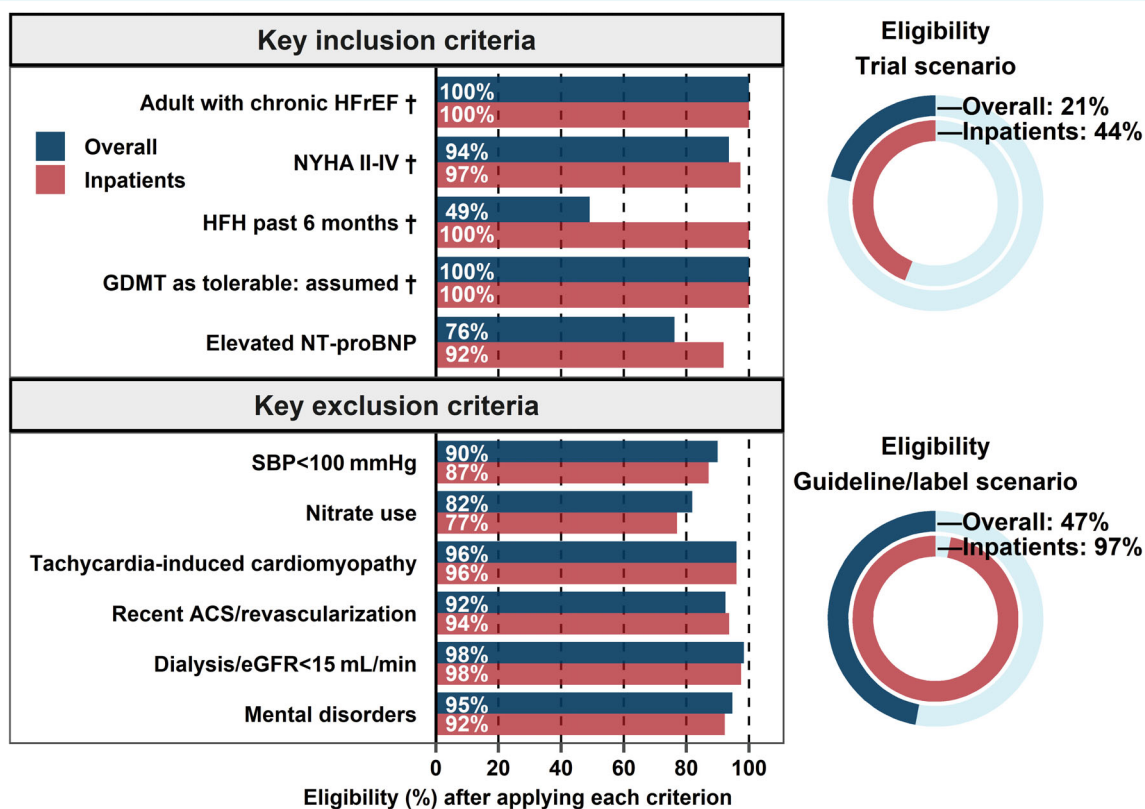


Figure 1 Eligibility for vericiguat according to trial, guideline, and label criteria in the overall population, and only in inpatients. Criteria marked with † were applied in the guideline/label scenario and in the trial scenario. Unmarked criteria were applied only in the trial scenario. All applied eligibility criteria are outlined in detail in Table 1 (trial scenario) and Table 2 (guideline/label scenario). ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; HFH, heart failure hospitalization; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

therapy and 7% with implantable cardioverter-defibrillator (these estimates do not consider that not all patients had an indication for these devices). The most common comorbidities were hypertension (64%) and atrial fibrillation (59%). A full description of the study population is reported in online supplementary Table S5.

Eligibility assessment

Of 23 573 patients, 5039 (21%) were eligible for vericiguat based on the trial criteria (Table 1, Figure 1). Inclusion criteria (met by 42% of the population) had a greater impact on eligibility than exclusion criteria (59% were eligible after considering only exclusion criteria). The major inclusion criteria limiting eligibility were a recent HF hospitalization (within 6 months prior to or at the index date), elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) and NYHA class II–IV (met by 49%, 76%, and 94%, respectively). The exclusion criteria that most limited eligibility were nitrate use, recent acute coronary syndromes, and low systolic blood pressure (82%, 92% and 90% were eligible after applying individually these exclusion criteria, respectively). In the sensitivity analysis on patients with EF < 50%, overall trial eligibility was consistent (20%),

and the influence of individual criteria on the overall eligibility was similar.

In the guideline and label scenarios (which considered the same criteria as in the main analysis), 11 179 (47%) were eligible for vericiguat (Table 2, Figure 1). The criteria affecting eligibility the most were a recent HF hospitalization and NYHA class II–IV (49% and 94% eligible after applying individually these criteria, respectively). In the sensitivity analysis 1 for the guideline and label scenarios using a stricter timeframe for defining a recent HF hospitalization (3 instead of 6 months), this criterion was met by slightly fewer patients (44% vs. 49% when a 6-month timeframe was used), which resulted in a slightly lower overall eligibility proportion (43% vs. 47%). In the sensitivity analysis 2 for the guideline scenario using a literal interpretation of GDMT (RAS/ARNI + beta-blockers + MRA), the GDMT criterion was met by 37%, and eligibility was markedly lower (18%). Guideline/label eligibility was slightly lower (46%) when patients with eGFR < 15 ml/min/1.73 m² or dialysis were considered ineligible (~1.6% of patients fulfilled this criterion).

In the subgroup analysis of hospitalized patients, who fulfilled per definition the criterion of a recent HF hospitalization, eligibility

Table 2 Eligibility for vericiguat after applying the guideline and label criteria (missing values imputed)

Guideline/label criteria	EF <40%, Number of patients (%)*	
	Total (n = 23 573)	Hospitalized patients (n = 6830)
1. EF <40%	23 573 (100.0)	6830 (100.0)
2. Age ≥18 years	23 573 (100.0)	6830 (100.0)
3. NYHA class II–IV	22 060 (93.6)	6647 (97.3)
4. Recent HF hospitalization		
4a. Previous HF hospitalization within 6 months	11 565 (49.1)	6830 (100.0)
4b. Previous HF hospitalization within 3 months	10 374 (44.0)	6830 (100.0)
5. Guideline-directed medical therapy		
5a. HF duration >6 months	23 573 (100.0)	6830 (100.0)
5b. GDMT (RAS/ARNI + beta-blocker + MRA)	8811 (37.4)	2228 (32.6)
6. eGFR ≥15 ml/min/1.73 m ² and not on dialysis	23 198 (98.4)	6656 (97.5)
Guideline eligibility – Main analysis (criteria 1, 2, 3, 4a, 5a)	11 179 (47.4)	6647 (97.3)
Guideline eligibility – Sensitivity analysis 1 (criteria 1, 2, 3, 4b, 5a)**	10 075 (42.7)	6647 (97.3)
Guideline eligibility – Sensitivity analysis 2 (criteria 1, 2, 3, 4a, 5b)†	4186 (17.8)	2160 (31.6)
Label eligibility – Main analysis (criteria 1, 2, 3, 4a)	11 179 (47.4)	6647 (97.3)
Label eligibility – Sensitivity analysis (criteria 1, 2, 3, 4b)**	10 075 (42.7)	6647 (97.3)
Guideline/label eligibility – Sensitivity analysis including renal criterion (criteria 1, 2, 3, 4a, 5a, 6)	10 946 (46.4)	6474 (94.8)

Definitions criteria are provided in online supplementary Tables S3 and S4.

ARNI, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAS, renin–angiotensin system inhibitor.

*Eligibility proportions represent the eligible cohort after applying the respective criteria.

**Sensitivity analysis 1: Consider a 3-month frame for the HF hospitalization event instead of 6 months as in the main analysis.

†Sensitivity analysis 2: Literally apply the definition of GDMT considering the use of RAS/ARNI + beta-blocker + MRA instead of using a HF duration of >6 months as a surrogate.

for vericiguat was more than two-fold higher in all scenarios as compared to the overall population (44%, 97%, and 97% for trial, guideline, and label scenarios, respectively) (Tables 1 and 2). In the 2017–2018 subgroup, a lower proportion of patients had been enrolled in an inpatient setting (11%); fewer patients fulfilled the criterion of recent HF hospitalization (32%); overall eligibility was lower (trial scenario: 15%, guideline/label scenario: 31%) compared to the total cohort. When assessed in the subgroup of patients hospitalized for HF at baseline, the eligibility estimates in the 2017–2018 cohort were consistent with the main analysis (online supplementary Tables S6 and S7).

Consistency analyses considering different methods for handling missing data, that is, complete case analysis and missing as eligible, eligibility estimates were overall consistent with the main analyses (online supplementary Tables S8 and S9).

Patient characteristics according to the eligibility status

Patient characteristics by eligibility status are presented in Figure 2 and online supplementary Table S10. In all scenarios, eligible patients were ~3–4 years older, more likely female, less likely referred to specialty care, had a lower education level, and more severe HF (i.e. higher NYHA class, higher NT-proBNP levels, more often recently hospitalized for HF and/or encountered in an inpatient setting). They were less likely treated with RAS/ARNI and

beta-blockers, but more likely with digoxin and diuretics. Use of MRA was similar between eligible and ineligible patients in the trial scenario, but higher in the first versus the latter in the guideline and label scenarios. Regardless of the scenario, eligible patients had higher prevalence of most CV comorbidities (e.g. hypertension, stroke, and atrial fibrillation), but less history of coronary revascularization, and, in the trial scenario, myocardial infarction. Non-CV comorbidities, including anaemia, diabetes, renal disease, and lung disease were also more common in eligible patients across scenarios. Liver disease was more frequent among eligible patients in the guideline/label scenario but less prevalent among eligible patients in the trial scenario.

Outcome rates according to the eligibility status

Over a median follow-up of 2.09 years (IQR 0.84–4.27), mortality rate was 21 deaths per 100 patient-years in the overall cohort. Outcome rates compared by eligibility status are presented in online supplementary Tables S11–S14 and Figure 3, by Kaplan–Meier curves in online supplementary Figures S2–S6. Eligible versus ineligible patients had higher rates of all the investigated outcomes in the trial scenario (i.e. all-cause mortality: 31.3 vs. 18.4 deaths per 100 patient-years; IRR [95% CI] 1.70 [1.64–1.76]) and the guideline/label scenarios (i.e. all-cause mortality: 31.3 vs. 14.0 deaths per 100 patient-years; IRR [95% CI] 2.24 [2.16–2.31]). The IRRs

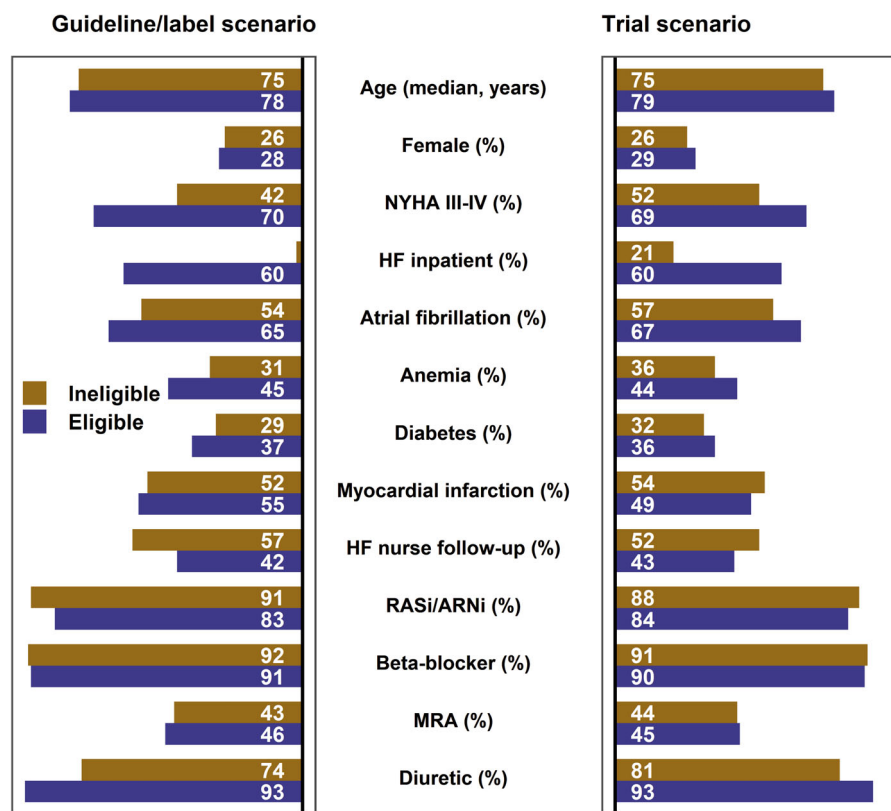


Figure 2 Key characteristics of the study population by eligibility status in trial, guideline, and label scenarios. A full depiction of patient characteristics according to trial and guideline/label eligibility are presented in detail in online supplementary Table S10. ARNi, angiotensin receptor–neprilysin inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor.

for all outcomes seemed to be higher in the guideline/label scenarios compared to the trial scenario. Across scenarios, the IRRs for CV outcomes tended to be higher than those for non-CV outcomes. Sensitivity analyses yielded overall similar findings, with the following exceptions: IRRs were overall lower in the guideline sensitivity analysis 2 where the GDMT criterion was interpreted literally (online supplementary Table S12); IRRs were consistent, but the event rates were higher in the outcome analysis censored at 10.8 months (e.g. all-cause mortality: 51.0 and 28.6 deaths per 100 patient-years in the overall cohort and in the 2017–2018 cohort, respectively) (online supplementary Tables S13 and S14).

Discussion

In this real-world cohort of chronic HFrEF patients, eligibility for vericiguat was 21% according to the selection criteria of the VICTORIA trial, and 47% according to the guideline recommendations and regulatory labelling. In all scenarios, the criterion limiting eligibility the most was the history of a prior hospitalization, which led to the exclusion of 49% of patients. Consistently, eligibility was more than two-fold higher (trial: 44%, guideline/label: 97%) in the subgroup of patients hospitalized for HF at the index date.

Eligible patients were characterized by older age, more comorbidities, more severe HF, and a markedly higher risk of CV outcomes as well as, although to a lesser degree, of non-CV outcomes (Graphical Abstract).

Eligibility according to the trial, guideline and label scenarios

Few previous analyses assessed eligibility for vericiguat in real-world populations. In a Korean cohort of patients hospitalized for decompensated HFrEF, overall eligibility according to the trial protocol was 58%.²¹ Their modestly higher trial eligibility than ours in patients hospitalized for HF (44%) might be explained by the application of fewer eligibility criteria compared with our analysis (e.g. NYHA class, blood pressure, NT-proBNP, kidney function). In a more recent analysis from the US Get With The Guidelines-Heart Failure registry, trial eligibility for vericiguat was 38% in patients hospitalized for HF.²² This estimate was slightly lower than in our hospitalized cohort (44%), which might be due to considering *de novo* HF as an exclusion criterion in the US study, while we calculated eligibility in a population with chronic HF (i.e. *de novo* HF was not considered in the denominator of

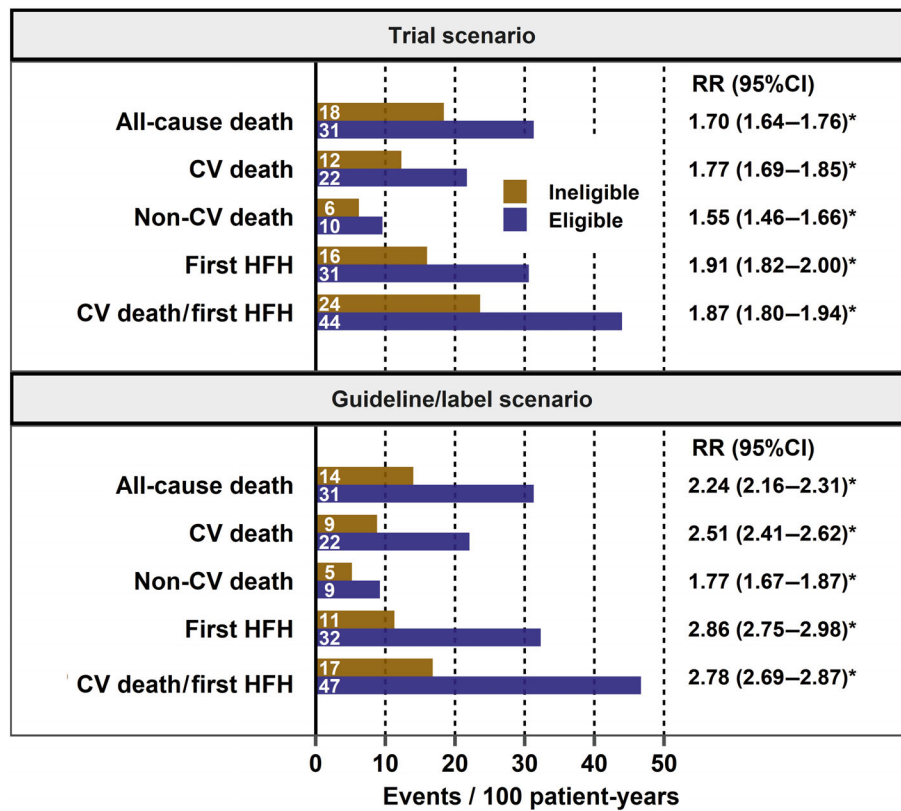


Figure 3 Event rates and incidence rate ratios for outcomes comparing eligible to ineligible patients selected in each scenario. * $p < 0.05$. CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; RR, rate ratio.

our calculations). Another study recently assessed eligibility for VICTORIA in Alberta's healthcare databases.²³ That study, unlike ours, only included patients who had ever been hospitalized for HF after receiving the diagnosis, which likely contributed to a higher estimated eligibility (39%) than ours (21%).

A recent HF decompensation and elevated NT-proBNP levels are among the strongest predictors of poor outcomes in patients with HFrEF.^{24–26} Consistently, the high NT-proBNP cut-off in the VICTORIA trial (>1000 pg/ml) and the requirement of a recent HF hospitalization successfully enriched for the occurrence of clinical outcomes, contributing to the achievement of a sufficient power for detecting differences in event rates across the arms in a relatively short follow-up period (median 10.8 months).^{4,27} However, our study showed that these criteria also led to the exclusion of half and one-quarter of patients, respectively, limiting eligibility. Accordingly, our estimated eligibility for vericiguat was mostly lower than previous eligibility estimates for other HF therapies, such as sodium–glucose cotransporter 2 inhibitors (trial eligibility: 39–52%^{28–31}; label eligibility: 86%³⁰) and sacubitril/valsartan (trial eligibility: 24–38%^{32–36}; label eligibility: 84%³⁵), but higher than ivabradine (trial eligibility: 14%).³⁷ These findings highlight the difficulties in balancing enrichment strategies against feasibility of enrolment when designing trials. Across all the scenarios, the subgroup of patients hospitalized for HF at the index date had markedly

higher eligibility for vericiguat than the overall population, since already fulfilling the requirement of having a prior HF hospitalization. This shows that the in-hospital setting might be the setting where vericiguat treatment is more likely to be initiated.

Guideline recommendations and regulatory labelling include fewer criteria as compared with the long list considered by the VICTORIA trial (e.g. there is no requirement in terms of NT-proBNP or exclusion of patients due to several comorbidities).^{4–8} Accordingly, eligibility for vericiguat was >2 times higher (47%) according to the labels and guidelines as compared with the trial scenario. This implies that in the real world, there is a large proportion of patients having an indication who might receive vericiguat differing from the population tested in the trial. This highlights the often-raised concern related to the external validity of trial findings, which might limit the implementation of novel drugs in daily clinical practice.

A literal interpretation of the guideline criterion of achieving GDMT before initiating vericiguat made >60% of patients ineligible. This shows both the difficulty in achieving GDMT in clinical practice, due to contraindications or tolerability issues,^{19,38} and the potential underuse of life-saving treatments due to clinical inertia. In an analysis of the ESC HF Long-Term registry, 12–28% of an HF outpatient cohort was eligible for sacubitril/valsartan based on guideline recommendations, and these low estimates were

mainly due to a literal interpretation of the GDMT criterion, which rendered 60–82% of patients ineligible.³⁵

Patient characteristics and outcomes in eligible versus ineligible patients

Randomized controlled trials in HF generally enrol younger patients with less non-cardiac comorbidities than real-world patients.^{9,10} In the current study, eligible patients were older and had overall higher CV as well as non-CV comorbidity burden. Previous SwedeHF analyses on trial eligibility for sacubitril/valsartan and dapagliflozin/empagliflozin showed similar findings.^{32,39} This might be explained by the association of such patient characteristics (i.e. older age, multi-comorbidity) with more severe HF, which was the target population for the VICTORIA trial and also, to a less extent, for sacubitril/valsartan and dapagliflozin/empagliflozin RCTs.^{5,6}

Notably, compared with the VICTORIA trial population,⁴ our SwedeHF trial-eligible patients were ~12 years older, and had higher NYHA classes and NT-proBNP. Furthermore, compared with the placebo arm of the VICTORIA trial, our eligible patients who were enrolled in 2017–2018 and had a similar follow-up duration as VICTORIA, had markedly worse outcomes, with higher rates of CV death or HF hospitalization (70.0 vs. 37.8 per 100 person-years) and all-cause death (28.6 vs. 16.9).⁴ This might imply an even more pronounced absolute benefit in specific subpopulations of real-world patients (i.e. an even lower number needed to treat than in VICTORIA) with vericiguat, and might be partially attributable to the differences in study settings, where VICTORIA enrolled patients from different countries with heterogeneous healthcare systems, whereas our study was based on Swedish national data. Moreover, there has been evidence indicating the underuse of guideline-recommended medications and devices for patients, especially the older, in SwedeHF, which could partially explain the observed worse outcomes.^{19,40} Another explanation might be that the investigators exert a certain degree of subjective selectivity while screening and enrolling patients in trials, that is, not all potentially eligible patients might be screened for enrolment. This might be partially due to well-reasoned factors that make trial participation unsuitable but that are not captured by the eligibility criteria. Nonetheless, an important implication is that some degrees of generalizability might be lost not only while designing a trial and setting eligibility criteria, but also at the site of enrolment. In contrast to our findings, an analysis from the PINNACLE registry reported similar characteristics in patients with a worsening HF event defined as in the VICTORIA trial as compared with the trial population. This could be explained by their inclusion of ~30% of patients with NYHA class I, which would be likely to contribute to a lower comorbidity burden as compared to patients considered as eligible in the present study.⁴¹

The event rates in VICTORIA were higher than in the other HF trials. Consequently, although the relative risk reduction with vericiguat was modest (10%), the absolute rate reduction (4.2 events per 100 person-years) and the number needed to treat were comparable to other landmark HF trials that demonstrated greater reductions in relative risk.^{4,42–44} Accordingly, pharmacoeconomic

studies have estimated vericiguat to be cost-effective.^{45,46} In our study, the enrichment criteria applied in the VICTORIA trial successfully targeted a population at high risk of CV outcomes even in a real-world setting. Indeed, our VICTORIA-eligible 'real-world' population had considerably higher rates of CV events. Additionally, they had also higher rates of non-CV events. While trial eligibility criteria aim to enrich for CV and not for non-CV events, this finding might reflect the higher comorbidity burden associated with more severe HF and older age (i.e. the median age of 76) in our population, which is also linked with a higher risk of non-CV outcomes. Consistently, risk factors that are perceived as specific for HF and CV disease, such as high NT-proBNP levels, have been shown to be associated with increased risks of not only CV but also non-CV events.²⁷

In the main analysis of our study, the difference in risk of outcomes between eligible and ineligible patients was greater in the guideline/label scenarios versus the trial scenario. One potential explanation is that the guideline/label eligible patients seemed to be overall sicker than the patients who were eligible according to the trial criteria (i.e. higher NYHA class and comorbidity burden). This might be due to the fact that the trial employed an extensive set of criteria excluding many specific comorbidities (e.g. recent myocardial infarction, stroke, and dementia) that were not adopted by guidelines/labels. However, when the GDMT criterion was strictly applied for the guideline scenario, instead of using the 6-month duration as proxy (guideline sensitivity analysis 2), the IRRs became more similar or even lower than those in the trial scenario. This likely reflects the efficacy of GDMT (triple therapy) as shown in numerous RCTs,⁴⁷ as well as the fact that poor tolerance to GDMT in HF often reflects advanced disease.

Strengths and limitations

The primary strength of the current study was the use of a large and well-characterized real-world HF population that enabled a detailed application of trial/guideline/label criteria and assessment of cause-specific outcomes according to the eligibility status. However, some limitations deserve to be acknowledged. First, eligibility was assessed cross-sectionally while eligibility status might change over the course of HF for each patient. Evolving characteristics over time may also affect eligibility on a cohort level, as highlighted in a separate analysis on only those patients registered 2017–2018, revealing a modestly lower eligibility due to fewer patients fulfilling the criterion of recent HF hospitalization. However, when assessing eligibility only among inpatients, the 2017–2018 cohort reported findings that were consistent with the overall analysis. Second, certain criteria needed to be adapted to the SwedeHF setting with the use of surrogates. However, several sensitivity analyses provided consistent results. Third, certain trial selection criteria could not be evaluated due to unavailability of data and were assumed to lead to 100% eligibility (e.g. inclusion criteria: outpatient intravenous diuretic therapy, informed consent; exclusion criteria: pregnancy, post-heart transplant cardiomyopathy, intravenous inotropes). However, these criteria are expected to be highly uncommon in our cohort, and thus, the magnitude of overestimation/underestimation should be

negligible. Nonetheless, generalizability to other healthcare settings where the unassessed criteria are more common might be limited. Moreover, when assessing the GDMT criterion, we did not consider the dosing or adherence of individual drugs due to data unavailability. Lastly, although less selected than RCT populations, the SwedeHF cohort has better prognosis and fewer comorbidities than the general HF population,⁴⁸ potentially limiting generalizability.

Conclusions

In a large and contemporary real-world cohort of patients with chronic HFrEF, estimated eligibility for vericiguat was 21% according to the VICTORIA trial eligibility criteria, and 47% according to guidelines and regulatory labelling. The criterion of prior HF hospitalization was the most limiting determinant of eligibility, leading to the exclusion of 49% of patients with chronic HFrEF. The eligibility criteria for vericiguat used in the VICTORIA trial, guidelines, and regulatory labelling translated into targeting a HFrEF population at higher risk of CV outcomes in a real-world setting.

Supplementary Information

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

Funding

This study received support through a personal grant from Bayer to Dr. Savarese's institution, the Horizon Europe programme (project number 101095479-More-EUROPA), and the Swedish Heart and Lung Foundation (project number 20220680). The grant sources had no role in the design or analysis, nor in the interpretation of results, manuscript preparation, or decision to submit.

Conflict of interest: G.F. has received research grants from the Erling-Perssons family foundation and the Swedish Heart and Lung Foundation and speaker fees from the European Society of Cardiology, AstraZeneca, CSL Vifor and Novartis. U.D. reports grants from Pfizer, AstraZeneca, Vifor, Boehringer Ingelheim, Boston Scientific, Roche Diagnostics and honoraria/consultancies from Amgen, Pfizer and AstraZeneca, all outside the submitted manuscript. J.B. reports consulting fees from Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Cardior, CVRx, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, and Vifor Pharma. L.H.L. reports outside the submitted work, grants, consulting, honorari: Abbott, Alleviant, AstraZeneca, Bayer, Biopetetics, Boehringer Ingelheim, Boston Scientific, Corteria, Edwards, FineHeart, Medscape/WebMD, Merck/MSD, Novartis, Novo Nordisk, OrionPharma, Pharmacosmos, Radcliffe Cardiology, Roche, Sanofi, Servier, Translational Medicines Academy, Vifor; Stock ownership: AnaCardio. G.S. received financial support from Bayer for performing this investigator-initiated study; he reports grants and personal fees from Vifor, Boehringer Ingelheim, AstraZeneca, Novartis, Cytokinetics, PHARMACOSMOS, personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Medtronic, grants from Boston Scientific, Merck, outside the submitted work. All other authors have nothing to disclose.

References

- Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail.* 2020;**22**:1342–1356. <https://doi.org/10.1002/ehf.1858>
- Roger VL. Epidemiology of heart failure: A contemporary perspective. *Circ Res.* 2021;**128**:1421–1434. <https://doi.org/10.1161/CIRCRESAHA.121.318172>
- Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev.* 2017;**3**:7–11. <https://doi.org/10.15420/cfr.2016.25.2>
- Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al.; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2020;**382**:1883–1893. <https://doi.org/10.1056/NEJMoa1915928>
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Böhm M, et al. 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.
- 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: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;**145**:e895–e1032. <https://doi.org/10.1161/CIR.0000000000001063>
- Verquvo [Package Insert]. Leverkusen, Germany: Merck Sharp and Dohme Corp; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214377s000lbl.pdf Accessed 15 June 2023.
- European Medicines Agency. Verquvo. <https://www.ema.europa.eu/en/medicines/human/EPAR/verquvo>. Accessed 15 June 2023.
- Ezekowitz J, Mentz RJ, Westerhout CM, Sweitzer NK, Givertz MM, Piña IL, et al. Participation in a heart failure clinical trial: Perspectives and opportunities from the VICTORIA trial and VICTORIA simultaneous registry. *Circ Heart Fail.* 2021;**14**:e008242. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.008242>
- Ezekowitz JA, Hu J, Delgado D, Hernandez AF, Kaul P, Leader R, et al. Acute heart failure: Perspectives from a randomized trial and a simultaneous registry. *Circ Heart Fail.* 2012;**5**:735–741. <https://doi.org/10.1161/CIRCHEARTFAILURE.112.968974>
- Kostis JB, Dobrzynski JM. Limitations of randomized clinical trials. *Am J Cardiol.* 2020;**129**:109–115. <https://doi.org/10.1016/j.amjcard.2020.05.011>
- US Food and Drug Administration. *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry.* Maryland: US Food and Drug Administration FDA; November 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial>. Accessed 15 June 2023.
- Rothwell PM. Factors that can affect the external validity of randomised controlled trials. *PLoS Clin Trials.* 2006;**9**:e9. <https://doi.org/10.1371/journal.pct.0010009>
- Murad MH, Katabi A, Benkhadra R, Montori VM. External validity, generalisability, applicability and directness: A brief primer. *BMJ Evid Based Med.* 2018;**23**:17–19. <https://doi.org/10.1136/ebmed-2017-110800>
- Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: A living, ongoing quality assurance and research in heart failure. *Ups J Med Sci.* 2019;**124**:65–69. <https://doi.org/10.1080/03009734.2018.1490831>
- 2021 Tabellbilaga Riksvikt Årsrapport. <https://www.ucr.uu.se/riksvikt/om-riksvikt/arsrapporter/arsrapporter/2021-tabellbilaga-riksvikt-arsrapport>. Accessed 15 June 2023.
- Ludvigsson JF, Andersson E, Ekblom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* 2011;**11**:450. <https://doi.org/10.1186/1471-2458-11-450>
- Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish Cause of Death Register. *Eur J Epidemiol.* 2017;**32**:765–773. <https://doi.org/10.1007/s10654-017-0316-1>
- Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, et al. Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail.* 2022;**24**:1047–1062. <https://doi.org/10.1002/ehf.2483>
- van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *J Stat Softw.* 2011;**45**:1–67. <https://doi.org/10.18637/jss.v045.i03>
- 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. <https://doi.org/10.1002/ehf2.13837>
- Khan MS, Xu H, Fonarow GC, Lautsch D, Hilkert R, Allen LA, et al. Applicability of vericiguat to patients hospitalized for heart failure in the United States. *JACC Heart Fail.* 2023;**11**:211–223. <https://doi.org/10.1016/j.jchf.2022.11.007>

23. Sepehrvand N, Islam S, Dover DC, Kaul P, McAlister FA, Armstrong PW, et al. Epidemiology of worsening heart failure in a population-based cohort from Alberta, Canada: Evaluating eligibility for treatment with vericiguat. *J Card Fail.* 2022;**28**:1298–1308. <https://doi.org/10.1016/j.cardfail.2022.04.015>
24. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JVV, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J.* 2006;**27**:65–75. <https://doi.org/10.1093/eurheartj/ehi555>
25. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J.* 2018;**39**:1770–1780. <https://doi.org/10.1093/eurheartj/ehy005>
26. Shah KS, Xu H, Matsouka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol.* 2017;**70**:2476–2486. <https://doi.org/10.1016/j.jacc.2017.08.074>
27. Savarese G, Orsini N, Hage C, Vedin O, Cosentino F, Rosano GMC, et al. Utilizing NT-proBNP for eligibility and enrichment in trials in HFpEF, HFmrEF, and HFrEF. *JACC Heart Fail.* 2018;**6**:246–256. <https://doi.org/10.1016/j.jchf.2017.12.014>
28. Maltês S, Cunha GJL, Rocha BML, Presume J, Guerreiro R, Henriques C, et al. Dapagliflozin in a real-world chronic heart failure population: How many are actually eligible? *Cardiology.* 2021;**146**:201–206. <https://doi.org/10.1159/000512432>
29. Håkansson E, Norberg H, Sjölander S, Lindmark K. Eligibility of dapagliflozin and empagliflozin in a real-world heart failure population. *Cardiovasc Ther.* 2021;**2021**:1894155. <https://doi.org/10.1155/2021/1894155>
30. Monzo L, Ferrari I, Cicogna F, Tota C, Calò L. Sodium-glucose co-transporter-2 inhibitors eligibility in patients with heart failure with reduced ejection fraction. *Int J Cardiol.* 2021;**341**:56–59. <https://doi.org/10.1016/j.ijcard.2021.08.035>
31. Angelini G, Albanese M, Ursi R, Lisi F, Bellino MC, Amato L, et al. Eligibility of outpatients with chronic heart failure for sodium-glucose co-transporter-2 inhibitors. *ESC Heart Fail.* 2021;**8**:2951–2958. <https://doi.org/10.1002/ehf2.13380>
32. Savarese G, Hage C, Benson L, Schrage B, Thorvaldsen T, Lundberg A, et al. Eligibility for sacubitril/valsartan in heart failure across the ejection fraction spectrum: Real-world data from the Swedish Heart Failure Registry. *J Intern Med.* 2021;**289**:369–384. <https://doi.org/10.1111/joim.13165>
33. Norberg H, Bergdahl E, Lindmark K. Eligibility of sacubitril-valsartan in a real-world heart failure population: A community-based single-centre study. *ESC Heart Fail.* 2018;**5**:337–343. <https://doi.org/10.1002/ehf2.12251>
34. Simpson J, Benson L, Jhund PS, Dahlström U, McMurray JVV, 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. <https://doi.org/10.1007/s10557-019-06873-1>
35. Kapelios CJ, Lainscak M, Savarese G, Laroche C, Seferovic P, Ruschitzka F, et al.; Heart Failure Long-Term Registry Investigators. Sacubitril/valsartan eligibility and outcomes in the ESC-EORP-HFA Heart Failure Long-Term Registry: Bridging between European Medicines Agency/Food and Drug Administration label, the PARADIGM-HF trial, ESC guidelines, and real world. *Eur J Heart Fail.* 2019;**21**:1383–1397. <https://doi.org/10.1002/ehf.1532>
36. Chen X, Schaufelberger M, Fu M. The eligible population of the PARADIGM-HF trial in a real-world outpatient clinic and its cardiovascular risk between 2005 and 2016. *J Cardiovasc Med (Hagerstown).* 2020;**21**:6–12. <https://doi.org/10.2459/JCM.0000000000000889>
37. Das D, Savarese G, Dahlström U, Fu M, Howlett J, Ezekowitz JA, et al. Ivabradine in heart failure: The representativeness of SHIFT (Systolic Heart Failure Treatment with the IF Inhibitor Ivabradine Trial) in a broad population of patients with chronic heart failure. *Circ Heart Fail.* 2017;**10**:e004112. <https://doi.org/10.1161/CIRCHEARTFAILURE.117.004112>
38. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlström U, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: An analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2018;**20**:1326–1334. <https://doi.org/10.1002/ehf.1182>
39. Thorvaldsen T, Ferrannini G, Mellbin L, Benson L, Cosentino F, McMurray JVV, et al. Eligibility for dapagliflozin and empagliflozin in a real-world heart failure population. *J Card Fail.* 2022;**28**:1050–1062. <https://doi.org/10.1016/j.cardfail.2022.04.011>
40. Lund LH, Braunschweig F, Benson L, Ståhlberg M, Dahlström U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: Results from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2017;**19**:1270–1279. <https://doi.org/10.1002/ehf.781>
41. Butler J, Djathe LM, Lautsch D, Yang L, Patel MJ, Mentz RJ. Representativeness of the VICTORIA trial population in clinical practice: Analysis of the PINNACLE registry. *J Card Fail.* 2021;**27**:1374–1381. <https://doi.org/10.1016/j.cardfail.2021.06.019>
42. McMurray JVV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-nepriylsin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;**371**:993–1004. <https://doi.org/10.1056/NEJMoa1409077>
43. McMurray JVV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;**381**:1995–2008. <https://doi.org/10.1056/NEJMoa1911303>
44. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al.; EMPEROR-reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;**383**:1413–1424. <https://doi.org/10.1056/NEJMoa2022190>
45. Alsumali A, Djathe LM, Briggs A, Liu R, Diakite I, Patel D, et al. Cost effectiveness of vericiguat for the treatment of chronic heart failure with reduced ejection fraction following a worsening heart failure event from a US Medicare perspective. *Pharmacoeconomics.* 2021;**39**:1343–1354. <https://doi.org/10.1007/s40273-021-01091-w>
46. Alsumali A, Lautsch D, Liu R, Patel D, Nanji S, Djathe LM. Budget impact analysis of vericiguat for the treatment of chronic heart failure with reduced ejection fraction following a worsening event. *Adv Ther.* 2021;**38**:2631–2643. <https://doi.org/10.1007/s12325-021-01681-2>
47. Burnett H, Earley A, Voors AA, Senni M, McMurray JVV, Deschaseaux C, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: A network meta-analysis. *Circ Heart Fail.* 2017;**10**:e003529. <https://doi.org/10.1161/CIRCHEARTFAILURE.116.003529>
48. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, et al. Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail.* 2017;**19**:1107–1116. <https://doi.org/10.1002/ehf.762>