ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 1492–1495
Published online 9 February 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13837

SHORT COMMUNICATION

Real-world eligibility for vericiguat in decompensated heart failure with reduced ejection fraction

Jaewon Oh[1], Chan Joo Lee[1], Jin Joo Park[2], Sang Eun Lee[3], Min-Seok Kim[3], Hyun-Jai Cho[4], Jin-Oh Choi[5], Hae-Young Lee[4], Kyung-Kuk Hwang[6], Kye Hun Kim[7], Byung-Su Yoo[8], Dong-Ju Choi[2], Sang Hong Baek[9], Eun-Seok Jeon[5], Jae-Joong Kim[3], Myeong-Chan Cho[6], Shung Chull Chae[10], Byung-Hee Oh[11] and Seok-Min Kang[1]*

[1]*Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Cardiovascular Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Korea;* [2]*Division of Cardiology, Seoul National University Bundang Hospital, Seongnam, Korea;* [3]*Division of Cardiology, Asan Medical Center, Seoul, Korea;* [4]*Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea;* [5]*Department of Internal Medicine, Sungkyunkwan University College of Medicine, Seoul, Korea;* [6]*Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea;* [7]*Department of Internal Medicine, Chonnam National University, Gwangju, Korea;* [8]*Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea;* [9]*Department of Internal Medicine, Catholic University of Korea, Seoul, Korea;* [10]*Department of Internal Medicine, Kyungpook National University College of Medicine, Daegu, Korea; and* [11]*Department of Internal Medicine, Mediplex Sejong Hospital, Incheon, Korea*

Abstract

Aims In 2021, vericiguat was approved by the US Food and Drug Administration (FDA) and the European Commission (EC) for reducing cardiovascular mortality and heart failure (HF) hospitalizations in patients with HF with reduced ejection fraction (HFrEF) based on the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial. However, there has been no report for characterizing the generalizability of vericiguat to real-world clinical practice.

Methods and results The Korean Acute Heart Failure (KorAHF) registry is a multicentre prospective cohort study. A total of 5625 patients who were admitted for HF decompensation were consecutively enrolled. We excluded the patients without left ventricular ejection fraction (LVEF) quantification, patients with LVEF $>$ 45%, patients with in-hospital death or urgent heart transplantation, and patients without natriuretic peptide measurement. Among a total of 3014 enrolled patients, there were 21.9% patients with lower systolic blood pressure (SBP) ($<$100 mmHg) and 20.1% patients without elevated natriuretic peptide. Regarding chronic kidney disease (CKD) status, 5.1% patients had CKD Stage V [estimated glomerular filtration rate (eGFR) $<$15 mL/min/1.73 m^2] and 11.8% patients had CKD Stage IV (15 $\leq$ eGFR $<$ 30 mL/min/1.73 m^2). When we analysed these criteria sequentially, 21.9% were excluded from lower SBP, 15.9% were excluded from elevated natriuretic peptide, and 4.2% were excluded from advanced CKD Stage V (9.6% for CKD Stages IV and V). Among the KorAHF registry patients, we found two main reasons for not meeting the inclusion criteria of the VICTORIA trial such as low SBP and non-elevated natriuretic peptide.

Conclusions Among the Korean hospitalized HFrEF patients, 94.9% met the FDA/EC label criteria, while 58% met the inclusion criteria of the VICTORIA trial. Our findings suggest the need for better strategies to integrate up-to-date HF treatment in a real-world HF population, especially decompensated HF patients with low SBP and non-elevated natriuretic peptide.

Keywords Vericiguat; Heart failure; Eligibility; Clinical pharmacology; Registries

Received: 10 August 2021; Revised: 4 January 2022; Accepted: 26 January 2022
**Correspondence to: Seok-Min Kang, Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Cardiovascular Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. Tel: 82-2-2228-8450; Fax: 82-2-2227-7732. Email: smkang@yuhs.ac*

Introduction

In January 2021, vericiguat was approved by the US Food and Drug Administration (FDA) for reducing cardiovascular mortality and heart failure (HF) hospitalizations in HF patients with left ventricular ejection fraction (LVEF) $<$45%, requiring outpatient intravenous diuretic therapy or hospitalization, based on the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial.[1] In July 2021, the European Commission (EC)

also approved vericiguat for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring intravenous therapy. Vericiguat can stimulate soluble guanylate cyclase to produce cyclic guanosine monophosphate and restore nitric oxide sensitivity. It is another first-in-class drug in HF with reduced ejection fraction (HFrEF).[2]

Methods

The Korean Acute Heart Failure (KorAHF) registry is a multicentre prospective cohort study from March 2011 to February 2014.[5,6] A total of 5625 patients who were admitted for HF decompensation were consecutively enrolled in 10 tertiary university hospitals in Korea. After excluding 522 patients without LVEF quantification, 1648 patients with LVEF $>$ 45%, 154 patients with in-hospital death or urgent heart transplantation, and 287 patients without natriuretic peptide measurement, 3014 patients were finally analysed. Continuous data were presented as mean ± standard deviation or median [inter-quartile range], as appropriate. Categorical data were presented as proportions.

Results

In the VICTORIA trial, 22.4% Asians were enrolled (100% Asians in our registry). To compare the baseline characteristics between two studies, we collected the clinical and laboratory parameters from discharge after hospitalization or the first outpatient visit in KorAHF registry (*Table 1*). The patients in Korean registry were similar with those in the VICTORIA trial regarding age, LVEF, and serum sodium and potassium level. However, the patients enrolled in the VICTORIA trial were more male and had higher prevalence for ischaemic origin HF, diabetes, hypertension, chronic obstructive pulmonary disease, and atrial fibrillation, higher body mass index, systolic blood pressure (SBP), and haemoglobin level, and lower estimated glomerular filtration rate (eGFR) and N-terminal pro-brain natriuretic peptide (NT-proBNP) compared with those in our registry. Regarding HF treatments, the patients from the VICTORIA were more likely to use medical treatments such beta-blockers and mineralocorticoid receptor antagonists compared with those from our registry.

Table 2 showed the eligibility for the inclusion criteria of the VICTORIA trial in KorAHF registry. Among a total of 3014 patients, there were 21.9% patients with lower SBP ($<$100 mmHg) and 20.1% patients without elevated natriuretic peptide [brain natriuretic peptide (BNP) $\geq$300 pg/mL

Table 1 Baseline characteristics in KorAHF registry and VICTORIA patients

Characteristics	KorAHF (N = 3014)	VICTORIA (N = 5050)
Male (%)	58.4%	76.4%
Age (years)	67 ± 15	67 ± 12
BMI (kg/m^2)	23.2 ± 3.8	27.8 ± 5.9
Ischaemic origin (%)	41.8%	58.3%
Diabetes (%)	36.2%	46.9%
Hypertension (%)	56.2%	79.1%
COPD (%)	10.4%	17.2%
Atrial fibrillation (%)	29.8%	44.9%
Systolic blood pressure (mmHg)	114 ± 19	121 ± 16
Diastolic blood pressure (mmHg)	67 ± 13	73 ± 11
Heart rate (b.p.m.)	81 ± 17	73 ± 13
LVEF (%)	28.7 ± 8.7	28.9 ± 8.3
eGFR (mL/min/1.73 m^2)	68.2 ± 34.0	61.5 ± 27.2
$>$60 (%)	58.7%	47.1%
$>$30 to $\leq$60 (%)	29.5%	42.7%
$\leq$30 (%)	11.8%	10.2%
Haemoglobin (g/dL)	12.7 ± 2.2	13.4 ± 1.9
Sodium (mmol/L)	138.4 ± 3.8	139.9 ± 3.4
Potassium (mmol/L)	4.5 ± 0.6	4.5 ± 0.5
BNP (pg/mL)	1040 [544–1730]	
NT-proBNP (pg/mL)	3544 [1875–8052]	2816 [1556–5314]
Heart failure treatments		
ACEi/ARB/ARNI (%)	77.2%	87.9%
BB (%)	58.3%	93.1%
MRA (%)	51.2%	70.3%

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; KorAHF, Korean Acute Heart Failure registry; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction.

DOI: 10.1002/ehf2.13837

Table 2 The individual and sequential impact of each eligibility criterion according to VICTORIA in KorAHF registry population with complete information for eligibility assessment

VICTORIA criteria	Prevalence	
	Individually (%)	Sequentially (%)
1. Age ≥18 years	100%	
2. LVEF ≤ 45%	100%	
3. Prior HF hospitalization within 6 months	100%	
4. SBP ≥ 100 mmHg	78.1%	78.1%
5. Elevated natriuretic peptide[a]	79.9%	62.2%
6. eGFR ≥ 15 mL/min/1.73 m^2	94.9%	58.0%
7. eGFR ≥ 30 mL/min/1.73 m^2	88.2%	52.5%

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; KorAHF, Korean Acute Heart Failure registry; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction.
[a]BNP ≥ 300 pg/mL or NT-proBNP ≥ 1000 pg/mL for sinus rhythm and BNP ≥ 500 pg/mL or NT-proBNP ≥ 1600 pg/mL for atrial fibrillation.

or NT-proBNP ≥ 1000 pg/mL for sinus rhythm and BNP ≥ 500 pg/mL or NT-proBNP ≥ 1600 pg/mL for atrial fibrillation]. Regarding chronic kidney disease (CKD) status, 5.1% patients had CKD Stage V (eGFR < 15 mL/min/1.73 m^2) and 11.8% patients had CKD Stage IV (15 ≤ eGFR < 30 mL/min/1.73 m^2). When we analysed these criteria sequentially, 21.9% were excluded from lower SBP, 15.9% were excluded from elevated natriuretic peptide, and 4.2% were excluded from advanced CKD Stage V (9.6% for CKD Stages IV and V). Among the KorAHF registry patients, we found two main reasons for not meeting the inclusion criteria of the VICTORIA trial such as low SBP and non-elevated natriuretic peptide. However, these two factors were not mentioned in the FDA/EC approval label. When we compared clinical characteristic between patients who meet the FDA/EC label and inclusion criteria of the VICTORIA trial (*Table 3*), the prevalence of ischaemic origin HF, hypertension, and diabetes history was higher and eGFR level was lower in the patients who can meet the inclusion criteria.

Aims

Considering the difference in clinical characteristics of HF patients from between randomized clinical trial and registry or real world,[3,4] the study for evaluating candidacy for vericiguat should be warranted for encouraging administration rate of evidence-based HF medical treatment. However, there has been no report for characterizing the generalizability of vericiguat to real-world clinical practice. Therefore, we aimed to assess the real-world eligibility for vericiguat based on the inclusion criteria of the VICTORIA trial for the first time in decompensated HF patients.

Table 3 Baseline characteristics according to the FDA/EC label and VICTORIA inclusion criteria

Characteristics	FDA/EC label (*N* = 2861)	VICTORIA inclusion criteria (*N* = 1748)
Male (%)	58.4%	56.2%
Age (years)	67 ± 15	69 ± 14
BMI (kg/m^2)	23.2 ± 3.8	23.1 ± 3.8
Ischaemic origin (%)	40.9%	46.2%
Diabetes (%)	35.0%	39.1%
Hypertension (%)	54.9%	61.8%
COPD (%)	10.5%	10.7%
Atrial fibrillation (%)	30.4%	27.8%
Systolic blood pressure (mmHg)	113 ± 19	120 ± 16
Diastolic blood pressure (mmHg)	67 ± 13	70 ± 11
Heart rate (b.p.m.)	81 ± 17	81 ± 17
LVEF (%)	28.6 ± 8.7	28.9 ± 8.7
eGFR (mL/min/1.73 m^2)	71.4 ± 32.0	67.4 ± 32.0
>60 (%)	61.8%	55.8%
>30 to ≤60 (%)	31.1%	34.7%
≤30 (%)	7.1%	9.6%
Haemoglobin (g/dL)	12.9 ± 2.2	12.6 ± 2.2
Sodium (mmol/L)	138.4 ± 3.8	138.7 ± 3.7
Potassium (mmol/L)	4.5 ± 0.5	4.6 ± 0.6
BNP (pg/mL)	1020 [523–1670]	1010 [553–1615]
NT-proBNP (pg/mL)	3476 [1848–7883]	3334 [1862–7584]
Heart failure treatments		
ACEi/ARB/ARNI (%)	77.8%	76.0%
BB (%)	58.3%	57.5%
MRA (%)	53.3%	49.9%

EC, European Commission; FDA, Food and Drug Administration. Other abbreviations in *Table 1*.

Conclusions

The clinical evidence for HF guideline-directed medical therapy (GDMT) in CKD population was limited especially in patients with advanced CKD (Stages IV and V, eGFR $<$ 30 mL/min/1.73 m^2). The recent pivotal clinical trials such as the PARADIGM-HF and DAPA-HF also excluded these advanced CKD patients. However, many CKD patients have administered GDMT like as non-CKD HF patients in real world. In our study, only 5.1% patients were ineligible for the VICTORIA inclusion criteria based on advanced CKD (eGFR $<$ 15 mL/min/1.73 m^2). Our data from a large, contemporary HF patients suggest that almost 90% patients with hospitalized HF (LVEF $<$ 45%) would be candidates for initiation of vericiguat, supporting its broad generalizability to real-world clinical practice, especially in advanced CKD patients with HF decompensation. However, other potential confounding factors such as ethnical difference between the VICTORIA trial (22.4% Asians) and the KorAHF registry (100% Asians), lower HF GDMT prescription rates, and other components in the exclusion criteria of the VICTORIA trial should be considered.

This is the first study to assess the eligibility for vericiguat according to the inclusion criteria of the VICTORIA trial in a large, real-world decompensated HF population. Among the Korean hospitalized HFrEF patients, 94.9% met the FDA label criteria, while 58% met the inclusion criteria of the VICTORIA trial. Therefore, our findings highlight the need for better strategies to integrate up-to-date GDMT in a real-world HF population, especially decompensated HF patients with low SBP and non-elevated natriuretic peptide. Another ongoing vericiguat study, the VICTOR (NCT05093933) trial which has a plan to enroll the outpatient HFrEF patients with lower NT-proBNP level than the VICTORIA trial, will answer this question.

Conflict of interest

None declared.

Funding

None.

References

1. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM, VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020; **382**: 1883–1893.
2. Butler J, Anstrom KJ, Armstrong PW. Comparing the benefit of novel therapies across clinical trials: insights from the VICTORIA trial. *Circulation* 2020; **142**: 717–719.
3. Vaduganathan M, Greene SJ, Zhang S, Grau-Sepulveda M, DeVore AD, Butler J, Heidenreich PA, Huang JC, Kittleson MM, Joynt Maddox KE, McDermott JJ, Owens AT, Peterson PN, Solomon SD, Vardeny O, Yancy CW, Fonarow GC. Applicability of US Food and Drug Administration labeling for dapagliflozin to patients with heart failure with reduced ejection fraction in US clinical practice: the Get With the Guidelines-Heart Failure (GWTG-HF) registry. *JAMA Cardiol* 2021; **6**: 267–275.
4. Oh J, Lee CJ, Park JJ, Lee SE, Kim M-S, Cho H-J, Choi J-O, Lee H-Y, Hwang K-K, Kim KH, Yoo B-S, Choi D-J, Baek SH, Jeon E-S, Kim J-J, Cho M-C, Chae SC, Oh B-H, Kang S-M. Real-world eligibility for sacubitril/valsartan in heart failure with reduced ejection fraction patients in Korea: data from the Korean Acute Heart Failure (KorAHF) registry. *Int J Heart Fail* 2019; **1**: 57–68.
5. Lee SE, Lee HY, Cho HJ, Choe WS, Kim H, Choi JO, Jeon ES, Kim MS, Kim JJ, Hwang KK, Chae SC, Baek SH, Kang SM, Choi DJ, Yoo BS, Kim KH, Park HY, Cho MC, Oh BH. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF). *Korean Circ J* 2017; **47**: 341–353.
6. Lee SE, Cho HJ, Lee HY, Yang HM, Choi JO, Jeon ES, Kim MS, Kim JJ, Hwang KK, Chae SC, Seo SM, Baek SH, Kang SM, Oh IY, Choi DJ, Yoo BS, Ahn Y, Park HY, Cho MC, Oh BH. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. *Eur J Heart Fail* 2014; **16**: 700–708.