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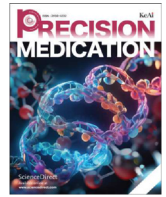
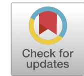


Quality evaluation of the guidelines for vericiguat treatment of heart failure with reduced ejection fraction



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ABSTRACT

Background: Heart failure (HF) bears a heavy disease burden, and vericiguat is the only guanylate cyclase stimulator proved to improve its prognosis. However, its clinical use needs a further improvement.
Objective: To evaluate the quality of the guidelines for vericiguat treatment of heart failure with reduced ejection fraction (HFrEF) using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument, thus providing references for clinical decision-making.
Methods: Clinical guidelines for vericiguat treatment of HFrEF published before 31st March, 2024 were systematically searched in online databases, including the CNKI, Wanfang, VIP, SinoMed, Cochrane Library, Pubmed, and Embase. Eligible articles were screened out by two investigators independently. Quality of the guidelines for vericiguat treatment of HFrEF was evaluated by four investigators from different professional groups using the AGREE II instrument.
Results: A total of seven guidelines for vericiguat treatment of HFrEF were enrolled for quality evaluation. Among them, the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure* graded the highest score, followed by the *2021 CCS/CHFS Heart Failure Guidelines Update*, and the *2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure*. The *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023* graded in a moderate level. Significant differences were observed in scores of the stakeholder involvement, rigor of development, and editorial independence. Generally, guidelines for vericiguat treatment of HFrEF shared similar contents, with a moderate quality of evidence. Except for the *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023*, and the *Korean Society of Heart Failure Guidelines for the Management of Heart Failure 2023* evaluated with a stronger recommendation, the remaining guidelines for vericiguat treatment of HFrEF were equipped with a weaker recommendation.
Conclusion: Referring to guidelines with higher quality, vericiguat is an option for HFrEF patients with a short-term aggravation. Existing recommodations for vericiguat treatment of HFrEF are formulated highly dependent on the findings from the VICTORIA trial, leading to potential biases. More clinical trials are needed for validating the efficacy and safety of vericiguat in treating HFrEF.

Introduction

Heart failure (HF) is a complex syndrome of impaired ventricular filling or ejection caused by abnormalities in the heart structure or function, serving as the end stage of various heart diseases. Due to the aging population, advanced medical techniques, and increased survival of cardiovascular diseases, the prevalence of HF keeps increasing.[1] Currently, the in-depth research provides new insights into the design and synthesis of drugs against HF. In addition to the conventional quadruple therapy for heart failure with reduced ejection fraction (HFrEF), agents targeting the signaling pathway involving the nitric oxide (NO),-soluble guanylate cyclase (sGC),-cyclic guanosine

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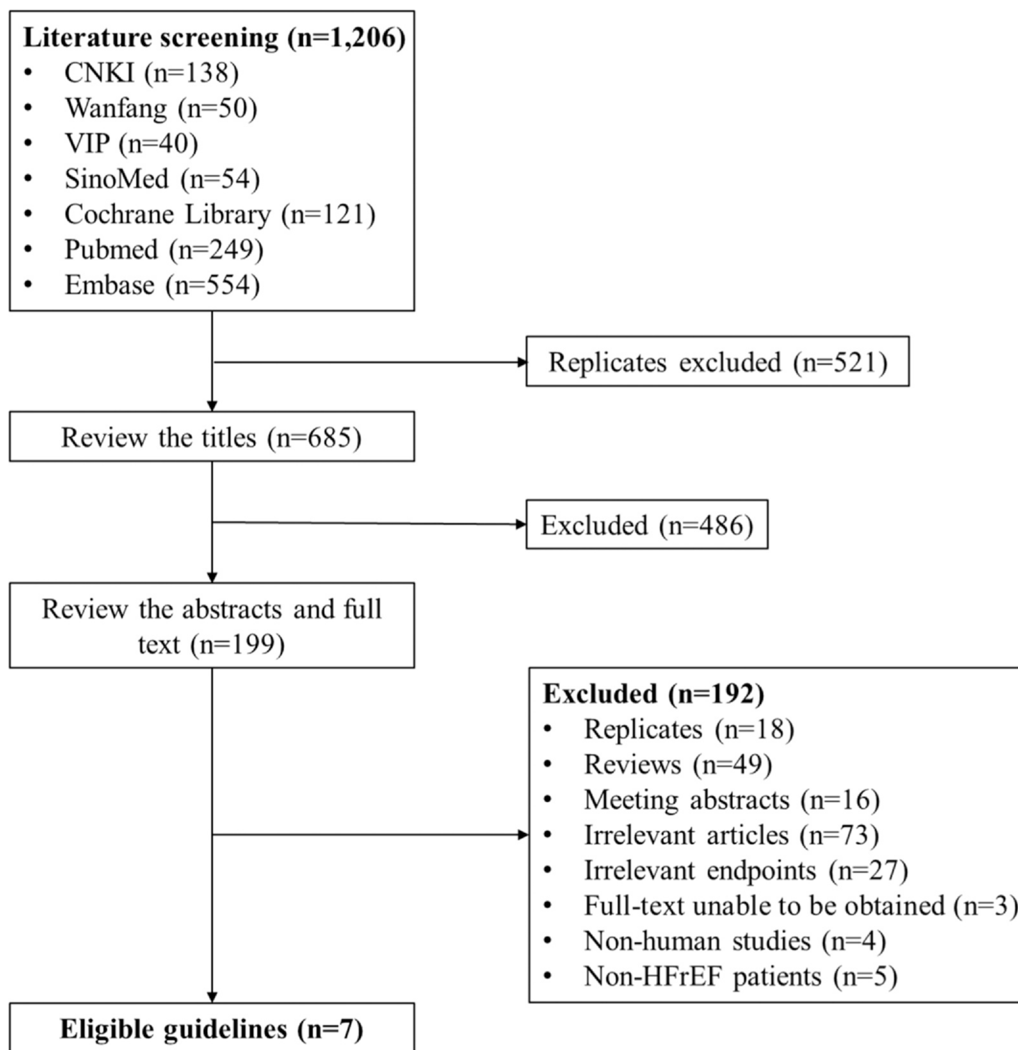

Fig. 1. A flow chart of literature screening. Note: CNKI: China national knowledge infrastructure; VIP: VIP journal.

monophosphate (cGMP) are rising stars for their potential in treating HF.

NO is widely distributed in human tissues, and endogenous NO is dominantly produced by vascular endothelial cells. sGC, as the only receptor for cellular NO, binds to NO that freely passes through the cell membrane.[2] cGMP acts as a second messenger to activate the cGMP-dependent protein kinase pathway, endowing it with the properties of anti-inflammation, vascular dilation, anti-fibrosis, anti-myocardial hypertrophy, and improving ventricular remodeling and ventricular remodeling.[3,4] Production and utilization rate of endogenous NO decrease in chronic HF patients because of the inflammatory response, and vascular endothelial damage. Insufficiency in sGC and decreased synthesis of cGMP synergistically lead to vasodilation dysfunction, myocardial fibrosis, and ventricular remodeling, forming a vicious cycle to aggravate the condition of HF. Novel sGC agonists act on repairing the NO/sGC/cGMP signaling pathway by increasing the sensitivity of sGC to endogenous NO via stabilizing the binding sites between NO and sGC. Moreover, they are excellent at directly stimulating sGC to produce cGMP in an NO-independent manner.[5] Existing sGC agonists on the market consist of vericiguat, riociguat, and praliciguat. Currently, vericiguat is the only sGC agonist approved to treat HFrEF, and validated for its efficacy in improving the prognosis.[6] It is available on the market in China, and a phase III clinical trial confirmed the potential of vericiguat in lowering the hospitalization risk of HF.[7] Superior to the quadruple therapy for HFrEF, vericiguat offers outstanding prognostic benefits to affected people. However, clinical experience of vericiguat treatment of HFrEF is scant. This study aims to evaluate the quality of guidelines for vericiguat treatment of HFrEF using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument, thus providing references for clinical decision-making.

Methods

Literature screening

Guidelines for reporting vericiguat in treating HFrEF released before 31st March, 2024 were searched in online databases, including CNKI, Wanfang, VIP, SinoMed, Cochrane Library, Pubmed, and Embase using the following key words in both the Chinese and English languages: "heart failure or cardiac insufficiency or cardiac functional insufficiency" and "soluble guanylate cyclase stimulators or vericiguat or Verquvo". In addition, guidelines were searched in the websites of the National Institute for Clinical Excellence (NICE), American Heart Association (AHA), and European Society of Cardiology (ESC) by searching "heart failure". Replicates, translations or interpretations of the guidelines were excluded.

Quality evaluation

Two investigators were independently responsible for extracting useful information in eligible guidelines, including: guideline developmental organization, year of publication, country/region, target population, recommendations for vericiguat, grading of recommendations, and level of evidences. Methodological quality of guidelines for

vericiguat treatment of HFrEF was independently evaluated by four investigators (2 cardiology pharmacists, 1 cardiologist, and 1 epidemiological researcher) using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument.[8,9] The AGREE II is a 23-item system consisting of 6 domains of the scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence, followed by 2 global rating items. Each domain is rated from 1 point (strongly disagree) to 7 points (strongly agree). The sum of each item within the certain domain is standardized to a percentage of the total possible points for that domain, and a higher percentage indicates a better quality.

Statistical analysis

Statistical analysis was performed using SPSS 21.0. The consistency of methodological evaluation of guidelines by four investigators was quantified via the intraclass correlation coefficient (ICC), and classified into good reliability ($ICC \geq 0.75$), moderate reliability ($0.40 \leq ICC < 0.75$), and poor reliability ($ICC < 0.40$).

Results

Screening of eligible guidelines

A total of 1206 articles were initially screened out, and 685 were obtained by excluding replicates. Through reviewing the titles, abstracts, and full text, 7 guidelines were finally selected.[10–16] The process of literature screening was listed in Fig. 1.

All the included guidelines were released from 2021 to 2024, including 1 domestic guideline and 6 international guidelines issued in the United States, Canada, Europe, Saudi Arabia, Thailand, and South Korea. The *2021 CCS/CHFS Heart Failure Guidelines Update*, the *2023 NHC/SHA Guidelines for the Management of Heart failure*, and the *2022 HFCT Heart Failure Guidelines* were updates of the former versions. ICC values of all the 7 guidelines ranged from 0.787 to 0.951, suggesting a good reliability in evaluating the methodological quality (Table 1).

Table 1
Guide quality evaluation consistency test.

Guideline	ICC	95 %CI
AHA/ACC/HFSA 2022	0.787	(0.604, 0.898)
CCS/CHFS 2021	0.836	(0.694, 0.922)
ESC 2021	0.896	(0.805, 0.950)
NHC/SHA 2023	0.951	(0.908, 0.976)
KSHF 2023	0.920	(0.851, 0.962)
HFCT 2022	0.942	(0.893, 0.973)
Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023	0.907	(0.827, 0.956)

Note: AHA: American Heart Association; ACC: American College of Cardiology; HFSA: Heart Failure; CCS: Canadian Cardiovascular Society; CHFS: Canadian Heart Failure Society; ESC: European Society of Cardiology; NHC: National Heart Center; SHA: Saudi Heart Association; KSHF: Korean Society of Heart Failure; HFCT: Heart Failure Council of Thailand; ICC: Intraclass Correlation Coefficient; CI: Confidence Interval.

Scope and purpose

Baseline characteristics and methodological evaluation of the seven domains using the AGREE II instrument were summarized (Tables 2, 3). In the domain of scope and purpose, clear statements of overall objective of the guideline, health question covered by the guideline, and target populations were evaluated. All the seven guidelines scored similar, ranging from 86.1 % to 97.2 %. The 2022 *AHA/ACC/HFSA Guideline for the Management of Heart Failure* graded the highest score, offering descriptions of the overall objective and health question in independent chapter.

Stakeholder involvement

The rationality of members involved in the guideline development, and target users of the guideline were evaluated. The quality of the stakeholder involvement varied considerably, ranging from 34.7 % to 94.4 %. The *2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure*, in the leading place, specifically listed the authors, reviewers, members of the European Society of Cardiology (ESC) Clinical Practice Guidelines, two patient representatives, and one methodology expert in each guideline development. There was a clear statement of members engaged in the formulation of the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure*, including cardiologists, heart failure specialists, physicians, interventional physicians, electrophysiologists, surgeons, pharmacists, senior nurses, and 2 public/patient representatives. The lowest score was detected in the *2022 HFCT Heart Failure Guidelines*, where the majority of members of guideline development are cardiac/cardiovascular specialists. Public/patient opinions and preferences were not mentioned. The *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023* placed moderately in this domain, only stating the guideline development group members, while their professional groups and public/patient preferences were not provided.

Rigor of development

Summary, update, and methods for formulating the recommendations were evaluated, grading 40.6 %-94.8 %. The *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure*, and the *2021 CCS/CHFS Heart Failure Guidelines Update* obtained the highest scores in this domain, both clearly describing the methods for formulating the recommendations, individuals engaged in the external review and the process, and procedures for updating guidelines. They also outperformed in the statements of the criteria for selecting the evidence, as well as the strengths and limitations of the body of evidence. In detail, the former guideline thoroughly described the key words, searching time, databases, and summary of evidence in the appendix, and the latter also made a description of searching strategy. On the contrary, the *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023*, the *2022 HFCT Heart Failure Guidelines*, and the *2023 KSHF Guidelines for the Management of Heart Failure* did not depict the methods for evidence searching and formulating the recommendations, as well as the criteria for

Table 2
Baseline characteristics of guidelines.

Guideline	Country/region	Type
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure	U.S.	Original
2021 CCS/CHFS Heart Failure Guidelines Update	Canada	Update
2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure	Europe	Original
2023 NHC/SHA Guidelines for the Management of Heart failure	Saudi Arabia	Update
2023 KSHF Guidelines for the Management of Heart Failure	South Korea	Original
2022 HFCT Heart Failure Guidelines	Thailand	Update
Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023	China	Original

Table 3
Methodological evaluation using the AGREE II instrument.

Guideline	AGREE II instrument						Total score	Grading of recommendation
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence		
2022 AHA/ACC/HFSA	97.2 %	86.0 %	94.8 %	93.1 %	85.4 %	100.0 %	26	Recommended
2021 CCS/CHFS	95.8 %	68.1 %	93.2 %	91.7 %	87.5 %	100.0 %	25	Recommended
2021 ESC	90.3 %	94.4 %	79.2 %	97.2 %	89.6 %	100.0 %	24	Recommended
2023 NHC/SHA	91.7 %	58.3 %	52.1 %	88.9 %	83.3 %	18.8 %	21	Use after being modified
2023 KSHF	94.4 %	61.1 %	45.4 %	93.1 %	88.5 %	43.8 %	19	Use after being modified
2022 HFCT	86.1 %	34.7 %	45.3 %	88.9 %	66.7 %	41.7 %	19	Not recommended
Chinese Guidelines	93.1 %	58.3 %	40.6 %	95.8 %	80.2 %	47.9 %	20	Use after being modified

Note: AGREE II: Appraisal of Guidelines for Research & Evaluation II.

selecting the evidence. External review and procedures for updating the guideline were not mentioned in the former two guidelines. Although members responsible for external review were listed in the *2023 KSHF Guidelines for the Management of Heart Failure*, they were overlapped with individuals for guideline development.

Clarity of presentation

Description of recommendations, applicable conditions and difficulty of identification were scored 88.9 %-97.2 %, showing a similar performance. Each guideline made recommendations clear and unambiguous. Opinions for recommendations, in most of evaluated guidelines, were emphasized in black boxes, separate paragraph listing, concise tables, or flow charts. Specific recommendation summary, recommendation update summary or important information chapters were stated in some of the guidelines.

Applicability

Similar performances in the facilitators and barriers to its application, advice and/or tools on how the recommendations can be put into practice, potential resource implications of applying the recommendations, and monitoring and/or auditing criteria were seen in all the seven guidelines, ranging from 66.7 % to 89.6 %. Slideshows, posters, and manuals were available on the website that released the *2021 CCS/CHFS Heart Failure Guidelines Update*. Similar tools, such as videos, slideshows, and guidance software were provided by the official websites where the *2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure*, and the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure* were issued.

Editorial independence

Descriptions of the conflicting interests, funding source, and disclaimer were evaluated, ranging largely from 18.8 % to 100 %. The *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure* graded the highest score, the *2021 CCS/CHFS Heart Failure Guidelines Update*, and the *2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure* had the maximum points in this domain. All of them clearly stated the funding from the associations, rather than commercial grants. Additionally, they provided contacts of members of guideline development with pharmaceutical companies, such as the lecture fees, consultation fees, or related positions. The remaining guidelines, however, were graded low in this domain, only with a rough description of "the authors declare no conflict of interest."

Recommendations for vericiguat treatment of HFrEF

Recommendations for vericiguat treatment of HFrEF, grading of recommendations, and levels of evidence were summarized in Table 4. Similarly in the enrolled seven guidelines, vericiguat was recommended for treating HFrEF patients with a history of using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs), or HFrEF patients in the New York Heart Association (NYHA) Functional Classification II-IV and suffer from a short-term aggravation after guideline-recommended medications. Evidence of recommendations in all the seven guidelines was referred by the VICTORIA trial, with a moderate level of evidence. Except for the *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023* and the *2023 KSHF Guidelines for the Management of Heart Failure* were evaluated as Class IIa recommendations, the remaining was graded in Class IIb/2b/week recommendation.

Table 4
Grading of recommendations for vericiguat treatment of HFrEF.

Guidelines	Recommendations	Grading of recommendations
2022 AHA/ACC/HFSA	Oral sGC stimulators (e.g., vericiguat) are optional to high-risk HFrEF patients who have received guidelines-oriented medications but have recently worsened their condition, thus decreasing the risk of HF-induced hospitalization and cardiovascular disease-associated mortality.	Class 2b, B-R
2021 CCS/CHFS	Combination of vericiguat with the optimal anti-HF treatment regimen is optional to patients whose symptoms worsen within the past 6 months and hospitalized for HF, thus decreasing the risk of re-hospitalization for HF.	Moderate
2021 ESC	Vericiguat is optional to HFrEF patients in NYHA Grade II-IV with worsening conditions, thus decreasing the risk of HF-induced hospitalization and cardiovascular disease-associated mortality.	Class IIb, B
2023 NHC/SHA	Vericiguat is optional to HFrEF patients in NYHA Grade II-IV with worsening conditions even after medications of ACEIs, ARNIs, beta-blockers, and MRAs, thus decreasing the risk of HF-induced hospitalization and cardiovascular disease-associated mortality.	May be reasonable to perform, and the usefulness and effectiveness have not been fully affirmed by evidence and expert opinions.
2023 KSHF	Vericiguat is optional to high-risk HF patients (LVEF $< 45\%$) who have received guidelines-oriented medications but have recently worsened their condition, thus decreasing the risk of HF-induced hospitalization and cardiovascular disease-associated mortality.	Class IIa, LOE B
2022 HFCT	Combination of vericiguat with the optimal anti-HF treatment regimen is optional to patients whose symptoms worsen or recently hospitalized for HF, thus decreasing the risk of re-hospitalization for HF.	Class IIb, B
Chinese Guidelines	Vericiguat can be applied earlier in the combination of the optimal anti-HF treatment regimen to symptomatic HF patients in NYHA Grade II-IV, with recent aggravated HF events, and LVEF $< 45\%$, thus decreasing the risk of HF-induced hospitalization and cardiovascular disease-associated mortality.	Class IIa, B

Note: HFrEF: heart failure with reduced ejection fraction; sGC: soluble guanylate cyclase; HF: heart failure; NYHA: New York Heart Association; ACEIs: angiotensin-converting enzyme inhibitors; ARNIs: angiotensin receptor-neprilysin inhibitors; MRAs: mineralocorticoid receptor antagonists; LVEF: left ventricular ejection fraction; LOE: levels of evidence.

Discussion

Ju et al.[17] evaluated guidelines and expert consensus on the chronic HF released from 1st January 2011–31 st December 2020, including the *2017 AHA/ACC/HFSA Guideline for the Management of Heart Failure* graded the highest score, followed by the *2017 CCS/CHFS Heart Failure Guidelines Update*, the *2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure*, and the *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018*. These guidelines, although being praised for the scope and purpose, and clarity of presentation, are graded low in the remaining four domains of the AGREE II. In addition, their findings showed that guidelines published in English language have an overall better methodology than those published in other languages. In our study, the quality of the seven guidelines for vericiguat treatment of HFrEF rated in a higher place. The reason may due to the updated methodological quality in guidelines published after 2021. In addition to the guideline document in full, we also reviewed the websites releasing the guidelines, guideline developer policy statement, separate technical report, appendix and conflicts of interest when grading scores. For example, item 14 in the domain of rigor of development describes the procedure for updating the guideline, which was not described in the guideline document in some of the guidelines, but mentioned in the guideline developer policy statement.

There has a noticeable disparity in the methodological quality of guidelines, especially in the domains of stakeholder involvement, rigor of development, and editorial independence. Guidelines graded high in the domain of stakeholder involvement were formulated with the involvement of individuals from all relevant professional groups, and target populations of patients and public. On the contrary, those graded low in this domain were formulated or reviewed by individuals from a narrow spectrum of professions, and views and preferences have not been sought. Excluding evidence was not clearly stated in guidelines graded low in the domain of rigor of development. Besides, they did not thoroughly describe search terms used, sources consulted, and dates of the literature covered, and external review. The biggest disparity was found in the domain of editorial independence. Guideline development group members can have close connections to pharmaceutical companies, and many guidelines are developed with external funding. Consequently, competing interests form the dominant source of biases during guideline formulations.[18] In the present study, the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure* graded the highest score, the *2021 CCS/CHFS Heart Failure Guidelines Update*, and the *2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure* outperformed in the editorial independence. Members engaged in the guideline formulation and review had open and transparent contacts with pharmaceutical companies, and stated clearly in lecture fees, consultation fees, or related positions. The remaining guidelines, however, were graded low in this domain, only with a rough description of "the authors declare no conflict of interest."

Grading of recommendations and levels of evidence of the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure* were specifically referred by the associations, while those of the *2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure*, the *2022 HFCT Heart Failure Guidelines*, and the *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023* were referred by the global consensus. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the quality of evidence and making recommendations on the *2021 CCS/CHFS Heart Failure Guidelines Update*. Levels of evidence, however, was not described in the *2023 NHC/SHA Guidelines for the Management of Heart failure*. The *2023 KSHF Guidelines for the Management of Heart Failure* did not mention the evaluation method of grading of recommendations and levels of evidence. Recommendations of vericiguat for treating HFrEF were made largely dependent on the VICTORIA trial, which had limitations.[19,20] Consequently, all the evaluated guidelines were graded in the moderate level of evidence. The strength of recommendation for vericiguat was “IIb/2b/weak recommendation” only in *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023* and the *2023 KSHF Guidelines for the Management of Heart Failure* and were graded in Class IIb/2b/week recommendation in the remaining guidelines, suggesting that the usefulness or efficacy was less well established by evidence. The *2021 CCS/CHFS Heart Failure Guidelines Update*, the *2021 ESC Guidelines for the Diagnosis and Treatment of Acute*

and Chronic Heart Failure, and the *2023 NHC/SHA Guidelines for the Management of Heart failure* all demonstrated that vericiguat did not decrease the risk of all-cause or cardiovascular mortality in HF patients. Both the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure*, and the *2021 CCS/CHFS Heart Failure Guidelines Update* illustrated that HF patients with the highest N-terminal pro B-type natriuretic peptide (NT-proBNP) levels did not benefit from vericiguat, and the former also suggested the association between vericiguat and increased risks of symptomatic hypotension and syncope. The *2022 HFCT Heart Failure Guidelines* pointed out that the efficacy of vericiguat in general HF has not been determined, and it has not been launched in Thailand at the time of the guideline issued. The *Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023* and the *2023 KSHF Guidelines for the Management of Heart Failure* only described the efficacy of vericiguat in treating HF, while other conditions and the reasons for recommendations grade were not mentioned.

Conclusion

The methodological quality of guidelines for vericiguat treatment of HFrEF is generally in a moderate-to-high place. The Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2023, although graded moderate in the methodological quality, lag behind guidelines released by developed countries, particularly in the stakeholder involvement, rigor of development, and editorial independence. We suggested a detailed disclosure of professional backgrounds of guideline development members, sources of evidence, specific procedures for forming the recommendations, funding source, and connection between guideline development members and pharmaceutical companies in domestic guidelines.

Based on our findings, we propose the following suggestions on the use of vericiguat in HF patients. First, high-quality guidelines can be referred, and vericiguat can be applied to HFrEF patients in NYHA Grade II-IV with worsening conditions even after guidelines-oriented medications. Second, benefits and disadvantages of vericiguat treatment are still in mystery, and its clinical use should be cautious after fully considering the individualized conditions. Third, HF patients should be informed prior to the medication that vericiguat is beneficial to lowering the risk of hospitalization, rather than the mortality.

Finally, the evidence of vericiguat treatment of HFrEF is single-sourced, and its clinical efficacy needs to be validated by more clinical evidence. Due to the properties of low renal function requirements and less impact on blood potassium, vericiguat may be promising in HFrEF patients who cannot tolerate ACEIs/ARNIs, and MRAs. Its efficacy and safety should be further validated in this population.

Declarations

Not applicable.

Authors' contributions

Q. Cai: Conceptualization, methodology, and supervision. T. Li: Methodology, data curation, and writing. L. Chen: Methodology, formal analysis, and investigations. Q. Chen, Z. Wei: Investigations.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declarations of Competing interests

The authors declare that they have no competing interests.

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Authors' other information

Not applicable.

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