REVIEWERS' COMMENTS

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a very interesting topic. There are so many factors that influence EF, thus it is not enough to divide heart failure just by EF. I hope that in the future there will be more comprehensive indicators to distinguish heart failure.

Authors: We are grateful to this Reviewer for the encouraging comments and we totally agree with his/her comments.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In this manuscript, the authors discussed the limitations related to the current LVEF based classification of HF and provided examples of erroneous conclusions that could be drawn, especially in HF patients at the higher end of the HF spectrum. The author's focus is very novel and important, and puts forward very meaningful opinions on the current diagnostic criteria and classification of heart failure. I think this problem is worthy of attention..

Authors: We are grateful to Reviewer 2 for the supportive comments.

Furthermore, I hope the author can try to explain the potential reasons for this difference according to literature review and analysis, which may be more enlightening for us to understand this problem.

Authors: We thank Reviewer 2 for the comment. This is indeed a very important question:

"The LVEF based classification of HF was initially applied a few decades ago in the clinical trials of neurohormonal inhibitors in which LVEF cutoffs of <35% or 40% were chosen **arbitrarily** to define patients with HF perceived to be at greatest risk (HFrEF). Several years later, clinical trials with similar agents and end points were conducted in patients with HF with LVEF of ≥40% to 50% (HFpEF), but they were considered unsuccessful for diverse reasons. Recently, another HF phenotype (HFmrEF) was added on the basis of **under-representation** of patients with HF with an LVEF of 40% to 50% in clinical trials." Therefore, for example a patient with a LVEF of 45% was considered to have HFpEF in older studies and HFmrEF in more recently ones. In addition, some scientific societies adopted the HFmrEF phenotype (i.e. European Society of Cardiology) whereas others did not (i.e. Australian and New Zealand). This led to confusion and major disputes about LVEF cut offs

(for example please see “Border Disputes Between Heart Failure Phenotypes”, Circulation. 2022 May 3;145(18):1374-1376)

In addition, the author's keywords need to be modified. The all of six keywords listed at present do not represent the key points and importance of the content.

Authors: We agree with the Reviewer. Accordingly, keywords have been updated

“Arbitrary; Cut off; Guidelines; Limitations; Normal left ventricular ejection fraction range; Phenotypic persistence”

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have expressed their opinion on the validity on LVEF as the basis for classification of congestive heart failure. Although it is true there are minor variations in the definitions of various categories of CHF, most guidelines agree with the definition of HFrEF as LVEF of <40% with a notable exception of guidelines from Australia and New Zealand. In general, an LVEF of >55% is considered normal in most guidelines. The authors bring out a good point that there may be sexual variations in normal ranges for LVEF based on studies pointed by the authors, although the differences are between normal ranges are minor (5-10%). It is also being recognized in recent studies that hyperdynamic LVEF may also have adverse prognostic implications. The classification of CHF based on LVEF has worked well in coordinating management of CHF patients over the past couple of decades with multiple high quality studies documenting improvement in survival with medication and device therapies for HFrEF. CHF is a worldwide problem responsible for considerable morbidity and mortality worldwide. The authors seem to suggest that it is time to eject LVEF from CHF classification but do not suggest any viable alternatives for classification that would help cardiologists and heart failure specialists manage patients with CHF effectively. Would recommend the authors to suggest those ideas in this letter as well.

Authors: We are grateful to Reviewer 3 for the helpful and instructive comments.

“LVEF based classification of HF phenotypes has served as well over all of these years. However, HF is such a complex syndrome that no single marker can be used to classify those patients. Accumulating data from recent studies show that markers of contractility such as the longitudinal strain and cardiac power outperform the LVEF. The incorporation of artificial intelligence (AI) in diagnostic modalities, outcome-predictions, and management of HF (individualized precision medicine) constitutes a major development in the field of cardiovascular medicine. In this regard, developing and validating universally accepted scoring systems based on AI would be a fruitful area of research” (Please see also answer to Reviewer 5)

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear authors, The paper represents a letter to the editor concerning a concept of heart failure with reduced, mildly reduced or preserved left ventricular ejection fraction. The article is written with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly.

Authors: We are grateful to Reviewer 4 for the encouraging comments.

The most discussable options in the article are: 1) Would you please kindly correct all your minor typos and grammar errors throughout the manuscript.

Authors: The manuscript has been reviewed by a native English speaker. Minor typos and grammar errors have been corrected.

2) I would strongly suggest you to avoid any strong judgements. All the revealed facts are of interest and very well-known being usually discussed during big conferences, but it might be better to deliver the certain message and not merely declaring something false. This is still a scientific journal and I would carefully ask you to harmonize the way how you judge the findings. Please underline the difference in the studied populations and conditions, maybe certain bias, but without abuse.

Authors: Thank you for your comment. Please see below:

(Page 5, 1st paragraph, last sentence) "Thus, the LVEF based terminology for HF classification is unjustified based on recent evidence", has been replaced with: "Thus, the LVEF based terminology for HF classification is challenged based on recent evidence."

(Page 5, 2nd paragraph, 1st sentence) "It is, therefore, not surprising that the LVEF based classification often leads to erroneous conclusions when interpreting the results of the various studies enrolling HF patients at the upper end of LVEF spectrum", ***has been replaced with:*** "It is, therefore, not surprising that the LVEF based classification might lead to erroneous conclusions when interpreting the results of the various studies enrolling HF patients at the upper end of LVEF spectrum"

(Page 5, last paragraph, last sentence) "Thus, when interpreting these two HFpEF studies it would be irrational to extrapolate the findings of the one to the other and, therefore, no meaningful conclusions can be drawn regarding the effectiveness of empagliflozin or phenotypic persistence in HFpEF." Has been replaced with: "Thus, when interpreting these two HFpEF studies it would be challenging to extrapolate the findings of the one to the other. Therefore, no firm conclusions can be drawn regarding the effectiveness of empagliflozin or phenotypic persistence in HFpEF."

3) Regarding cut offs, it sounds now not entirely scientific. The reason for any cut-off is essentially a result of any trial. Would you please kindly build a Table with the Guidelines (that you analyzed, as from Figure 1) and relevant trials (that were a reason for a particular cut-off). In that case we can appreciate all the arguments about reasoning.

Authors: Thank you for this important comment. Please see table below:

Table 1. Heart failure studies including patients with mildly reduced and preserved LVEF

Study	Drug	LVEF cut off
Registries		
ADHERE Yancy CW, et al. J Am Coll Cardiol. 2006; 47:76–84	-	≥40
OPTIMIZE-HF Fonarow GC, et al. J Am Coll Cardiol. 2007; 50:768–777	-	≥40% ≥50%
GWTG-HF Steinberg BA, et al. Circulation. 2012; 126:65–75	-	≥50% 40-50%
Randomized Controlled Trials		
CHARM-PRESERVED Yusuf S, et al. Lancet. 2003; 362:777–781	Candesartan	>40%
PEP-CHF Cleland JG, et al. Eur Heart J. 2006; 27:2338–2345	Perindopril	>40%
I-PRESERVE Massie BM, et al. N Engl J Med. 2008; 359:2456–2467	Irbesartan	≥45%
SENIORS van Veldhuisen DJ, et al. J Am Coll Cardiol. 2009; 53:2150–2158	Nebivolol	>35%
RELAX Trial Redfield M, et al. JAMA. 2013; 309:1268–1277	Phosphodiesterase-5 inhibitors	≥50
J-DHF Yamamoto K, et al. Eur J Heart Fail. 2013; 15:110–118	Carvedilol	>40%
DIG-PEF Ahmed A, et al. Circulation. 2006;114(5):397-403	Digitalis	>45%
TOPCAT Pitt B, et al. N Engl J Med. 2014; 370:1383–1392	Spironolactone	≥45%
PARAMOUNT Solomon SD, et al. Lancet. 2012;380(9851):1387-95	Sacubitril/Valsartan	≥45%
PARAGON HF Solomon SD, et al. N Engl J Med. 2019;381(17):1609-1620	Sacubitril/Valsartan	≥45%

SOCRATES-PRESERVED Pieske B, et al. Eur Heart J. 2017;38(15):1119-1127	Vericiguat	≥45%
VITALITY-HFpEF Armstrong PW, JAMA. 2020;324(15):1512-1521	Vericiguat	≥45%
EMPEROR-PRESERVED Anker S, et al. N Engl J Med. 2021. In Press	Empagliflozin	>40%
DELIVER trial Solomon SD, et al. Eur J Heart Fail. 2021;23(7):1217-1225	Dapagliflozin	>40%
Meta-analyses		
MAGGIC Meta-analysis Global Group in Chronic Heart Failure. Eur Heart J. 2012;33:1750-1757	-	≥50
SYSTEMATIC REVIEW AND META-ANALYSIS Zheng SL, et al. Heart. 2018;104(5):407-415	Neurohormonal inhibitors	≥40%

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Overall nice concise manuscript highlighting current HF and ejection fraction directed classifications Edits: In first paragraph " lucking" I think it meant to say " lacking" In second paragraph European society classification HFrEF should be less then or equal to 40

Authors: We are grateful to Reviewer 5 for the supportive comments. Typos have been corrected.

Suggestions: Authors should write a paragraph or two on what alternative options might be to consider in classifying CHF and need for validation studies and possibly developing universally accepted scoring system (something like MELD scoring for liver failure)

Authors: This is an important comment.

"LVEF based classification of HF phenotypes has served as well over all of these years. However, HF is such a complex syndrome that no single marker can be used to classify those patients. Accumulating data from recent studies show that markers of contractility such as the longitudinal strain and cardiac power outperform the LVEF. The incorporation of artificial intelligence (AI) in diagnostic modalities, outcome-predictions, and management of HF (individualized precision medicine) constitutes a major development in the field of cardiovascular medicine. In this regard, developing and validating universally accepted

scoring systems based on AI would be a fruitful area of research" (Please see also answer to Reviewer 3)

EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

The authors discuss the limitations related to the LVEF cut offs used for HF classification in this letter. This letter is nicely structured and well written. However, I have several comments about this letter. Please consider the following comments. (Comments) 1. Page 5, lines 5-7 I think this sentence should be tone done, for example, "the LVEF based classification often might lead to erroneous conclusion" or "LVEF based classification often could lead to erroneous conclusion". Just consider.

Authors: We are grateful to the Editor for the valuable comments. Accordingly, sentence has been replaced: "It is, therefore, not surprising that the LVEF based classification might lead to erroneous conclusions when interpreting the results of the various studies enrolling HF patients at the upper end of LVEF spectrum" (Please also see answer to Reviewer 4)

2. Page 11, Figure 1 The authors probably make several mistakes. 2018 Australia and New Zealand guidelines: the border line of the bar graph is at the position of LVEF 45%. 2015 ASE and EACVI recommendations: (Females, mildly abnormal) Correct "41-51%" to "41-53%". 2013 ACC/AHA guidelines: (HF with preserved LVEF) Correct ">50%" to "≥50%".

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade C (Good)

Authors: We thank the Editor for these important comments. Accordingly, figure has been corrected.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Cardiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or

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Authors: We are grateful to the Company editor-in-chief for the important comments. Figure 1 is original (Copyright ©The Author(s) 2022). For figures 2 and 3 the authors have received permissions to be re-published; and have correctly indicated the reference source and copyrights. Related articles from World Journal of Cardiology have been referenced in the manuscript.