

# World Journal of *Cardiology*

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## Heart failure with reduced, mildly reduced, or preserved left ventricular ejection fraction: Has reasoning been lost?

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### Abstract

Left ventricular (LV) ejection fraction (LVEF), defined as LV stroke volume divided by end-diastolic volume, has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF is classified as HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cutoffs. A prerequisite for using this LVEF-based terminology is knowledge of the LVEF normal range, which is lacking and may lead to erroneous conclusions in HF, especially at the higher end of the LVEF spectrum.

**Key Words:** Arbitrary; Cut off; Guidelines; Limitations; Normal left ventricular ejection fraction range; Phenotypic persistence

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**Core Tip:** Left ventricular ejection fraction (LVEF) has been consistently used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF is classified as HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cutoffs. A prerequisite for using this terminology is knowledge of the LVEF normal range, which is lacking and may lead to erroneous conclusions, especially at the higher end of the LVEF spectrum.

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## TO THE EDITOR

Left ventricular (LV) ejection fraction (LVEF), defined as LV stroke volume divided by LV end-diastolic volume, is the only biomarker that has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades[1]. Accordingly, HF has been classified into HF with reduced LVEF (HFrEF), HF with midrange or mildly reduced LVEF (HFmrEF), and HF with preserved LVEF (HFpEF) using various, continuously changing LVEF cutoffs. A mandatory prerequisite for the use of this LVEF-based terminology is the definition of the normal LVEF range, which is lacking. From this perspective, we discuss the limitations related to the current LVEF-based classification of HF and provide examples of erroneous conclusions that can be drawn, especially in HF patients at the higher end of the HF spectrum.

The LVEF-based classification of HF was initially applied several 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 endpoints were conducted in patients with HF with an LVEF of  $\geq 40\%$ -50% (HFpEF), but they were considered unsuccessful for various reasons[2,3]. Recently, another HF phenotype (HFmrEF) was added based on the underrepresentation of patients with HF with an LVEF of 40%-50% in clinical trials. The LVEF cutoffs used for HF classification have varied continuously in the guidelines issued by scientific societies (Figure 1)[4]. The 2013 American College of Cardiology Foundation/American Heart Association guidelines defined HFrEF by an LVEF of  $\leq 40\%$ , borderline HFpEF by an LVEF of 41%-49%, and HFpEF by an LVEF of  $\geq 50\%$ [5]. By contrast, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines defined HFrEF and HFpEF by an LVEF of < 50% and  $\geq 50\%$ , respectively, and did not recognize borderline HFpEF or HFmrEF as a distinct entity[6]. Furthermore, in the recent Universal Definition and Classification of Heart Failure[7], which was adopted by the European Society of Cardiology[8], HF classification includes HFrEF with an LVEF of  $\leq 40\%$ , HFmrEF with an LVEF of 41%-49%, and HFpEF with an LVEF of  $\geq 50\%$ . Subsequently, another classification of HF was proposed, which defines HFrEF by an LVEF of < 40%, HFmrEF by  $40\% \leq \text{LVEF} < \text{normal}$ , and HF with normal EF by an LVEF of  $\geq 55\%$  in men and  $\geq 60\%$  in women[9]. LVEF can be reduced, mildly reduced, preserved, or normal; however, what is the normal LVEF range? According to the 2015 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging, the normal reference range for LVEF is 52%-72% for males and 54%-74% for females[10]. The latest guidelines from the British Society of Echocardiography define LVEF  $\geq 55\%$  as normal (preserved)[11]. However, several recent studies have raised serious concerns regarding the normal LVEF range as proposed by echocardiographic societies. Wehner *et al*[12] investigated the relationship between LVEF and survival by linking physician-reported LVEF on 403977 echocardiograms obtained from 203135 patients to all-cause mortality in the United States, and validated their findings in a dataset including 45531 echocardiograms and 35976 patients from New Zealand. During follow-up, unadjusted hazard ratios for mortality showed a U-shaped relationship for LVEF with a nadir of risk at an LVEF of 60%-65% in both datasets. The results were similar after adjusting for conditions associated with an elevated LVEF, including mitral regurgitation, increased wall thickness, and anemia and when restricted to patients reported to have HF at the time of the echocardiogram (Figure 2). Slightly different but trending in the same direction were the findings of another study including approximately 500000 participants, which reported that in both women and men, mortality was lowest at an LVEF of 65.0%-69.9%[13]. However, in the same study, sex-dependent differences in the relationship between LVEF and mortality were observed. In women, an increased risk of cardiovascular-related mortality persisted to an LVEF of 60.0%-64.9%, whereas in men, the equivalent LVEF was lower (55.0%-59.9%) (Figure 3)[13]. Sex-related differences were also reported in 4632 patients from coronary computed tomography angiography evaluation for clinical outcomes, namely, an international multicenter registry in which LVEF was measured by cardiac computed tomography and participants were categorized according to LVEF (low < 55%, normal 55%-65%, and high > 65%) [14]. After 6 years of follow-up, no difference in mortality was observed in patients with high LVEF in the overall cohort. However, when data were stratified by sex, women with high LVEF died more often from any cause compared to women with normal LVEF, while an opposite trend was observed in men [14]. Thus, the LVEF-based terminology for HF classification is challenged based on recent evidence.

Therefore, it is not surprising that the LVEF-based classification might lead to erroneous conclusions when interpreting the results of various studies enrolling HF patients at the upper end of the LVEF spectrum (Table 1). A typical example is the recently published Empagliflozin outcome trial in patients with chronic HF with preserved EF (EMPEROR-preserved trial), which reported a benefit with



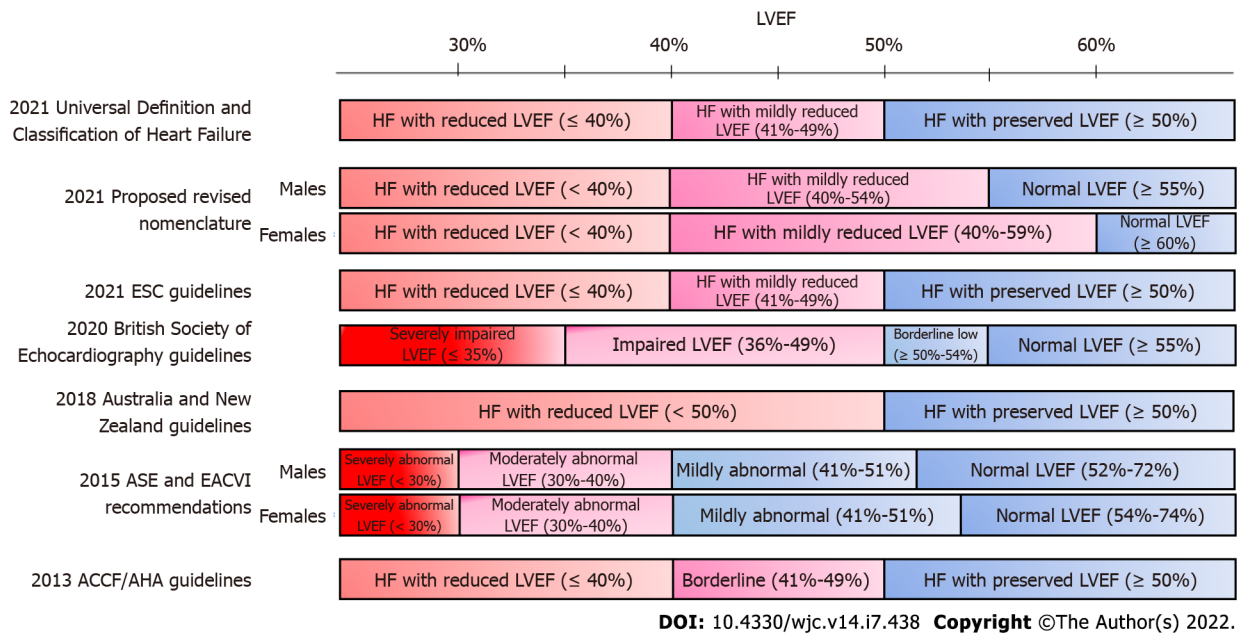
**Table 1 Heart failure studies including patients with mildly reduced and preserved left ventricular ejection fraction**

Ref.		Drug	LVEF cut off
Registries			
Yancy <i>et al</i> [22]	ADHERE	-	≥ 40
Fonarow <i>et al</i> [23]	OPTIMIZE-HF	-	≥ 40%; ≥ 50%
Steinberg <i>et al</i> [24]	GWTH-HF	-	≥ 50%; 40%-50%
Randomized controlled trials			
Yusuf <i>et al</i> [25]	CHARM-PRESERVED	Candesartan	> 40%
Cleland <i>et al</i> [26]	PEP-CHF	Perindopril	> 40%
Massie <i>et al</i> [27]	I-PRESERVE	Irbesartan	≥ 45%
van Veldhuisen <i>et al</i> [28]	SENIORS	Nebivolol	> 35%
Redfield <i>et al</i> [29]	RELAX Trial	Phosphodiesterase-5 inhibitors	≥ 50
Yamamoto <i>et al</i> [30]	J-DHF	Carvedilol	> 40%
Ahmed <i>et al</i> [31]	DIG-PEF	Digitalis	> 45%
Pitt <i>et al</i> [32]	TOPCAT	Spironolactone	≥ 45%
Solomon <i>et al</i> [33]	PARAMOUNT	Sacubitril/Valsartan	≥ 45%
Solomon <i>et al</i> [34]	PARAGON HF	Sacubitril/Valsartan	≥ 45%
Pieske <i>et al</i> [35]	SOCRATES-PRESERVED	Vericiguat	≥ 45%
Armstrong <i>et al</i> [36]	VITALITY-HFpEF	Vericiguat	≥ 45%
Anker <i>et al</i> [15]	EMPEROR-PRESERVED	Empagliflozin	> 40%
Solomon <i>et al</i> [37]	DELIVER trial	Dapagliflozin	> 40%
Meta-analysis			
Meta-analysis Global Group in Chronic Heart Failure[38]	MAGGIC	-	≥ 50
Zheng <i>et al</i> [39]	Systematic review and meta-analysis	Neurohormonal inhibitors	≥ 40%

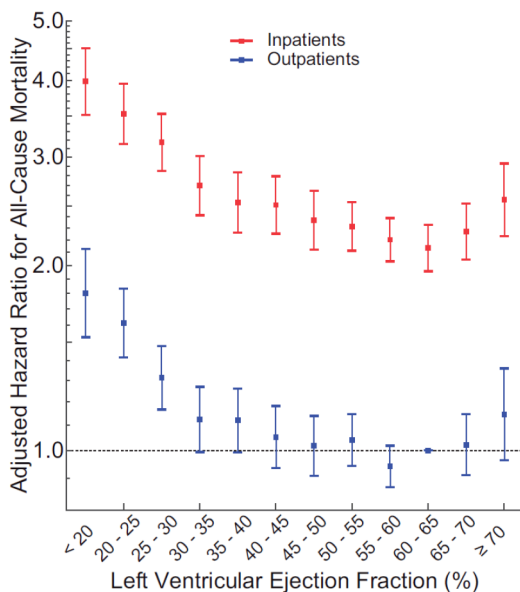
LVEF: Left ventricular ejection fraction.

empagliflozin (compared with placebo) in HFpEF defined by an LVEF > 40%[15,16] which is different from the 50% cutoff recommended in the Universal Definition and Classification of Heart Failure[7]. It is noteworthy that in the EMPEROR-preserved trial, ~90% of the patients suffered from hypertension, ~49% from diabetes, and ~51% from atrial fibrillation. By contrast, in a study by Lupon *et al*[17], which was used as evidence supporting phenotypic persistence in HFpEF[18], an LVEF cutoff of 50% was used and the patient characteristics were entirely different from those in the EMPEROR-preserved trial with approximately 12% of the participants suffering from hypertrophic cardiomyopathy and 36% from valvular heart disease. Thus, when interpreting these two HFpEF studies, it would be challenging to extrapolate the findings of one to the other. Therefore, no firm conclusions can be drawn regarding the effectiveness of empagliflozin or phenotypic persistence in HFpEF.

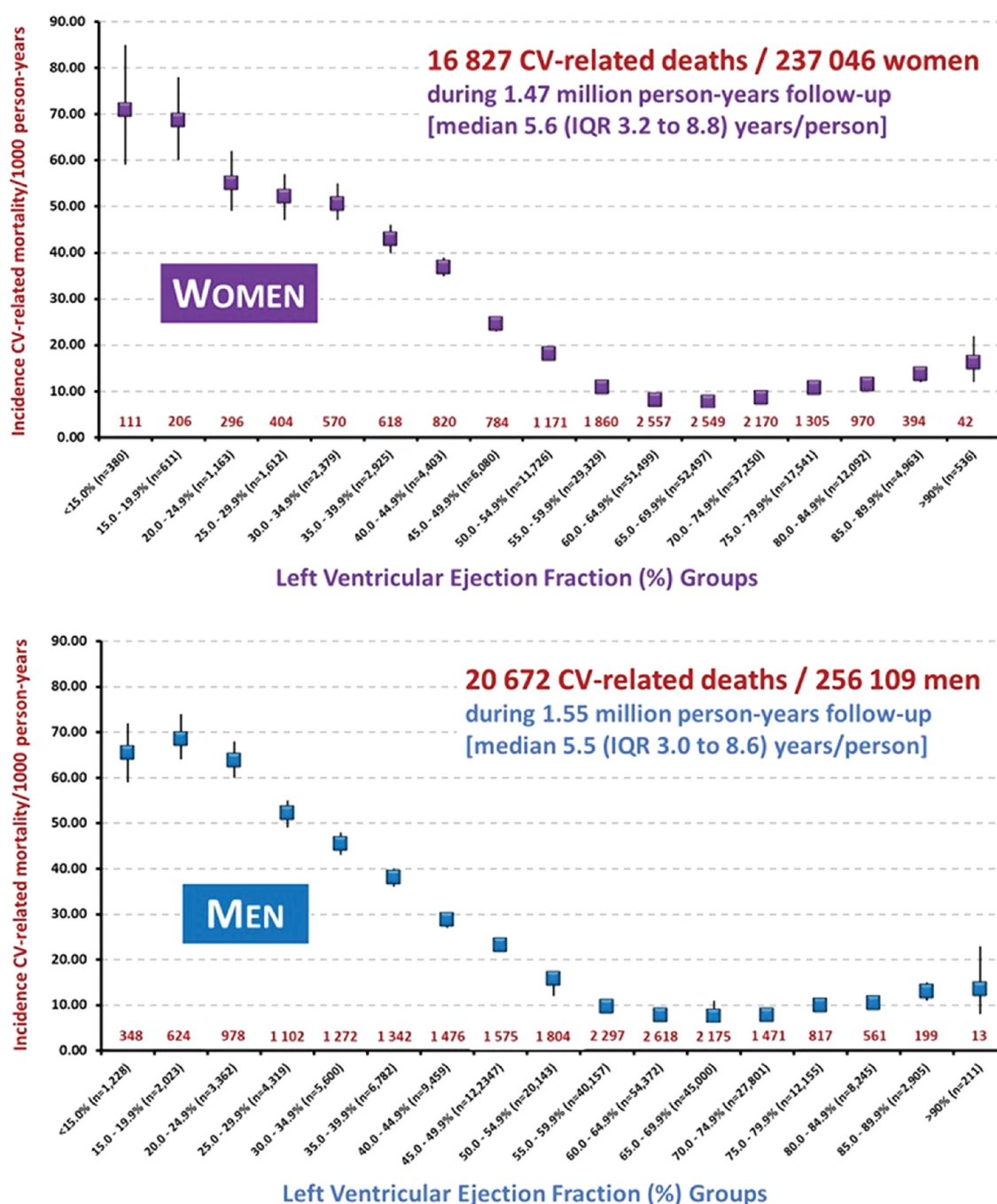
LVEF-based classification of HF phenotypes has served well over the years. However, HF is such a complex syndrome that no single marker can be used to classify those patients. Accumulating data from recent studies show that markers of contractility such as longitudinal strain[19] and cardiac power[20] 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. The LVEF has been considered the holy grail for HF classification treatment guidance for years. The time for change has come, unless one wants to justify those claiming that most published research findings are false[21].



**Figure 1** There is significant discordance in the normal values of left ventricular ejection fraction reported by several major scientific societies and associations. This makes the classification of heart failure based on the left ventricular ejection fraction problematic. ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ASE: American Society of Echocardiography; EACVI: European Association of Cardiovascular Imaging; ESC: European Society of Cardiology.



**Figure 2** Left ventricular ejection fraction adjusted hazard ratios in patients with heart failure (number of echocardiograms = 40616). Left ventricular ejection fraction (LVEF) intervals are inclusive of the lower threshold. Error bars represent the 95%CI. The referent group was outpatients with an LVEF of 60%-65%. While 51192 echocardiograms were performed on patients with heart failure in the primary analysis, only 40616 echocardiograms are represented in this figure due to excluding echocardiograms missing measurements of end-diastolic volume index or wall thicknesses, for which adjustments were made in the analysis. Citation: Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020; 41(12): 1249-1257. Copyright ©The Author(s) 2019. Published by the European Society of Cardiology.



**Figure 3 Incident rate of cardiovascular-related mortality.** The rate of cardiovascular (CV)-related mortality per 1000 person-years is presented separately for women (top graph) and men (bottom) according to 5-unit increments in the left ventricular ejection fraction. The total number of deaths contributing to the rate of mortality in each group (red numerals) is provided above the horizontal axis. IQR: Interquartile range. Citation: Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, Codde J, Strange G; NEDA Investigators. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. *Eur J Heart Fail* 2021; 23(3): 406-416. Copyright ©The Author(s) 2020. Published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

## FOOTNOTES

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