Classification of Heart Failure According to Ejection Fraction JACC Review Topic of the Week

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JACC REVIEW TOPIC OF THE WEEK

Classification of Heart Failure According to Ejection Fraction

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ABSTRACT

The recent U.S. Food and Drug Administration expanded indication for sacubitril/valsartan introduces a new potential taxonomy for heart failure, with no reference to "preserved" ejection fraction but referring to "below normal" ejection fraction as those most likely to benefit. This review summarizes the evolution of nomenclature in heart failure and examines evidence showing that patients with ejection fraction in the "mid range" may benefit from neurohormonal blockade similar to those with more severely reduced (<40%) ejection fraction. Furthermore, prominent sex differences have been observed wherein the benefit of neurohormonal blockade appears to extend to a higher ejection fraction range in women compared to men. Based on emerging evidence, revised nomenclature is proposed defining heart failure with "reduced" (<40%), "mildly reduced," and "normal" (≥55% in men, ≥60% in women) ejection fraction. Such nomenclature signals consideration of potentially beneficial therapies in the largest group of patients with reduced or mildly reduced ejection fraction. (J Am Coll Cardiol 2021;77:3217–25) © 2021 by the American College of Cardiology Foundation.

There have been recent landmark events in heart failure (HF). For the first time, HF societies around the world have agreed on a universal definition of HF as "a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion," with a universal classification into HF with reduced ejection fraction (EF) (HFrEF) (left ventricular [LV] EF [LVEF]: ≤40%), HF with mildly reduced EF (HFmrEF) (LVEF: 41% to 49%), HF with preserved EF (HFpEF) (LVEF: ≥50%), and HF with improved EF (1). Also for the first time, the U.S. Food and Drug Administration has approved an expanded indication for sacubitril/valsartan "to reduce the risk of cardiovascular death and hospitalization for HF in adult patients with chronic HF," with benefits "most clearly evident in patients with LVEF below normal" (2)—a decision based on efficacy data across the spectrum of LVEF in the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) and PARAGON-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction) trials (**Figure 1**)—and a label that introduces a new potential taxonomy for HF. Of note, the indication removes all reference to "reduced" or "preserved" EF, which have become

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ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

FDA = U.S. Food and Drug Administration

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

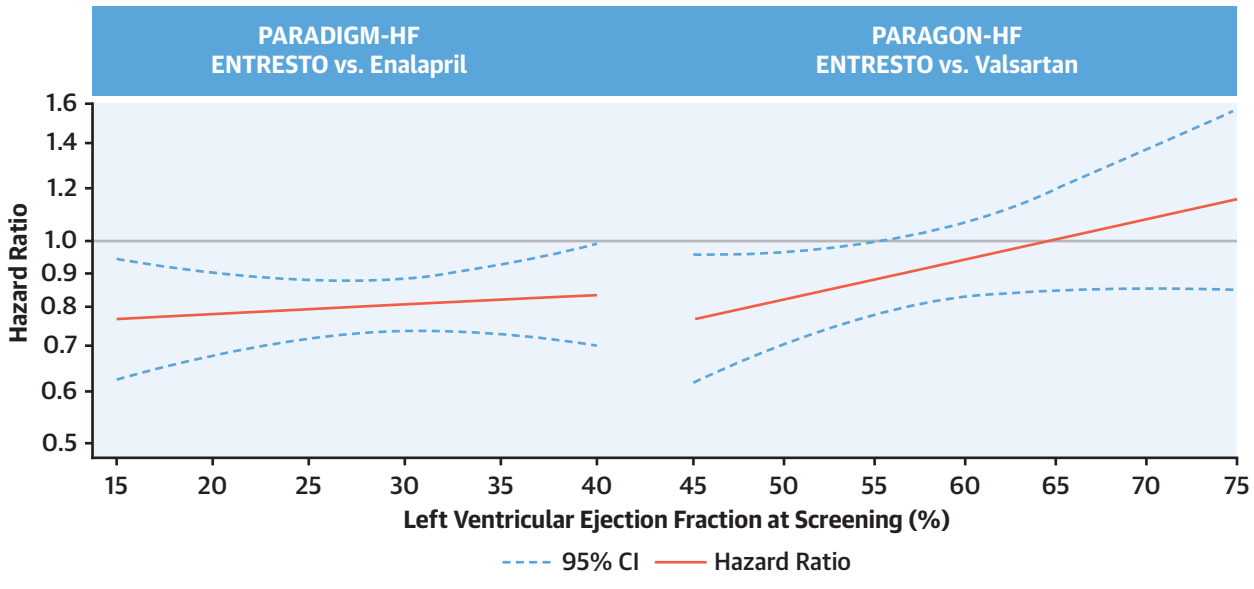
standard components of our HF lexicon over the past several decades. At the same time, the indication refers to "below normal" as the group of patients who will most likely benefit from angiotensin receptor-neprilysin inhibition. These changes are bound to cause confusion among clinicians. To untangle these issues, it behooves us to examine the history of the nomenclature for the condition of HF without overt reduction in LVEF (<40%) (Table 1).

Both the universal definition of HF (1) and the traditional pathophysiological definition as "an inability of the heart to pump blood to the body at a rate commensurate with its needs, or to do so only at the cost of high filling pressures" (3) are importantly LVEF agnostic and are based fundamentally on the presence of hemodynamic congestion that results in the clinical syndrome of HF regardless of LVEF. However, in the 1980s and 1990s, the diagnosis of HF became synonymous with the presence of reduced LVEF largely because of the advent of major randomized clinical trials in HF, which included an upper LVEF exclusion criterion. The focus on patients with reduced LVEF was understandable given their higher mortality rates, providing the power to demonstrate mortality benefit with neurohormonal antagonists in the early

HIGHLIGHTS

- Emerging data suggest that patients with heart failure and ejection fraction in the mid range between "reduced" and "preserved" may benefit from neurohormonal blockade, like those with lower ejection fractions.
- There are important differences based on patient sex, with women with heart failure benefiting from neurohormonal blockade at higher ejection fractions than men.
- Recent data support defining heart failure with reduced ejection fraction as <40%, mildly reduced ejection fraction, and normal ejection fraction (≥55% for men and ≥60% for women).

FIGURE 1 Treatment Effect for the Composite Endpoint of Time to First Heart Failure Hospitalization or Cardiovascular Death by Left Ventricular Ejection Fraction in the PARADIGM-HF and PARAGON-HF Trials



The relationship between left ventricular ejection fraction and the composite endpoint of time to first heart failure hospitalization or cardiovascular death in PARADIGM-HF and PARAGON-HF showed that patients with lower ejection fraction ("below normal") experienced greater risk reduction with sacubitril/valsartan. Reprinted with permission from Novartis (2). CI = confidence interval; PARADIGM-HF = Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAGON-HF = Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction.

trials, which then translated to physicians characterizing patients by low LVEF to qualify for life-saving HF medications. Isolated case reports and small case series in the 1980s served as reminders that HF could occur in the absence of overt reduction in LVEF (4–6). However, this syndrome received little attention until the more widespread use of noninvasive assessments of LVEF provided robust epidemiological evidence of the magnitude of the problem of HF in the absence of reduced LVEF. Collectively, these early epidemiological data from the Helsinki Ageing Study (7), Olmsted County study (8–10), Framingham Heart Study (11), Strong Heart Study (12), Cardiovascular Health Study (13,14), and Ontario study (15) showed that approximately one-half of patients with HF did not have a markedly reduced LVEF and that these patients had a significantly increased risk of death and hospitalization.

TABLE 1 Evolution of Nomenclature for Heart Failure Without Overt Reduction in Ejection Fraction

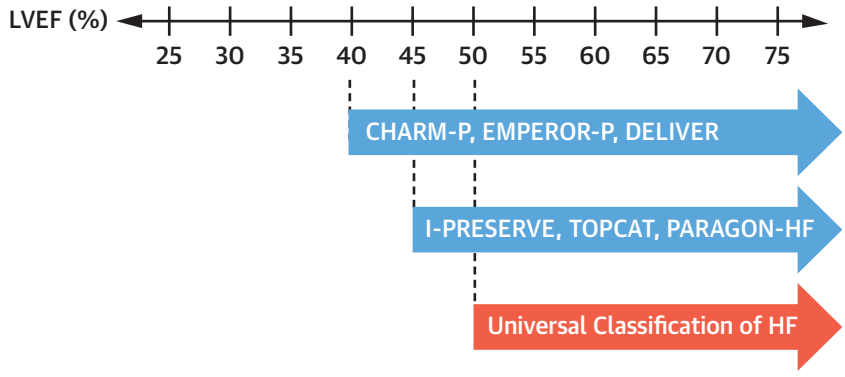
Terminology	Comment
Hypertensive hypertrophic cardiomyopathy of the elderly	Described in isolated case series
Diastolic heart failure	Diastolic dysfunction is common in asymptomatic older patients without heart failure and even more common in "systolic" heart failure
Heart failure with normal systolic function	Subtle systolic dysfunction (myocardial contractile dysfunction) exists even in the absence of overt reduction of ejection fraction
Heart failure with normal ejection fraction	Normal ejection fraction varies with age, sex, and ethnicity
Heart failure with preserved ejection fraction	Originally coined in the CHARM-P trial to refer to patients with heart failure and ejection fraction of >40% who qualified as having neither "reduced" (<40%) nor completely "normal" ejection fraction

CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity–Preserved.

With recognition of the importance of the syndrome of HF in the absence of reduced LVEF came efforts to understand the condition, with its nomenclature evolving with our deepening understanding (**Table 1**). The term "hypertensive hypertrophic cardiomyopathy of the elderly" was used to describe 21 elderly, predominantly female hypertensive patients with HF symptoms, LV hypertrophy, high LVEF, and LV diastolic dysfunction (6). With seminal work establishing the hallmark of a leftward-shifted LV pressure/volume relationship, indicating LV diastolic dysfunction in most, if not all, patients, the term "diastolic HF" was coined. The systolic/diastolic HF distinction was popular because it conveniently divided the HF population into 2 halves, reflecting the key pathophysiological factor believed to cause each syndrome. However, consistent with the pathophysiological definition of HF, wherein increased LV filling pressure was present regardless of LVEF in HF, population-based studies showed that patients with "systolic HF" were even more likely to have LV diastolic dysfunction compared to those with so-called "diastolic HF"; furthermore, in the absence of HF, LV diastolic dysfunction was present in a large proportion of older adults (9,16). Thus emerged the term "HF with normal systolic function"—a term that did not make assumptions regarding underlying pathophysiological mechanisms and could accommodate the emerging evidence of mechanisms extending beyond LV diastolic dysfunction to left atrial (17), vascular (18,19), right-sided (20,21), and noncardiac (e.g., renal, pulmonary) organ dysfunction (22). However, reports emerged showing that systolic function was not necessarily normal in these patients and that myocardial contractile dysfunction was present despite normal overall chamber pump function (18,23,24).

The term "HF with normal EF" was then adopted in guidelines (25). The emphasis on LVEF was practical given the ease and convenience of its noninvasive assessment, as well as clinicians' familiarity with and acceptance of LVEF as a standard measurement of LV function in HF. However, there remained controversy regarding the cutoff of LVEF to define "normal." LVEF is a continuous variable with a normal distribution within the general population—a distribution that changes with age and sex, thus challenging a single precise threshold for "normal." Indeed, although HF guidelines used a cutoff of 50%, echocardiography guidelines used a threshold of 55% to define normal LVEF. For HF clinical trialists, using an LVEF cutoff of 50% left a gap in the "middle range" of LVEF of 40% to 50% where patients would qualify as having neither "reduced" (<40%) LVEF based on inclusion criteria of prior large HF outcomes trials nor completely "normal" LVEF. The need to address the evidence gap in such patients led investigators of the CHARM (Candesartan in HF Assessment of Reduction in Mortality and Morbidity) program (26) to design the CHARM "preserved" component using an LVEF of >40%, complementing the other components of the program including patients with an LVEF of ≤40% and thus allowing the most pragmatic approach of randomizing patients with HF, regardless of LVEF, into 1 of 3 components of the umbrella program. The use of the term "HF with preserved EF" (HFpEF) in this major outcomes trial, along with continued uncertainties about what constitutes a truly "normal" LVEF in HF, led to the widespread adoption of the term "HFpEF" to this day (**Table 1**). Although now widely

FIGURE 2 LVEF Cutoffs Used as Inclusion Criteria in Clinical Trials and in the Universal Definition of HF



CHARM-P = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity–Preserved; DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; EMPEROR-P = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure With Preserved Systolic Function; LVEF = left ventricular ejection fraction; PARAGON-HF = Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

used, the term "HFpEF" has been applied with varying LVEF cutoffs of 40% or 45% in clinical trials (**Figure 2**) and defined using a cutoff of ≥50% in HF guidelines, including the universal definition (1,27–29).

The guidelines definition using an LVEF cutoff of 40% for HFrEF and 50% for HFpEF leaves a "gray zone" of LVEF between 40% and 50%. The 2016 European Society of Cardiology HF Guidelines adopted the term "HF with mid-range EF (HFmrEF)" to refer to patients with an LVEF of 40% to 50%, whereas the 2013 American College of Cardiology/American Heart Association HF guidelines used "borderline" to describe this group. Importantly, this new nomenclature led to an upsurge of publications related to this previously neglected subgroup of HF (30) and a relook at prior HF trials randomizing patients over a board range of LVEFs (**Table 2**). In aggregate, these retrospective analyses suggested that patients with LVEF in the lower portion of the HFpEF range, including those in the HFmrEF category, may benefit from mineralocorticoid antagonists (31), beta-blockers (32), angiotensin receptor blockers (33), digoxin (34), and, most recently, angiotensin receptor-neprilysin inhibitors (35), similar to patients with an LVEF of <40% and distinct from patients with higher LVEF values. Based on these observations, it has been proposed that HFmrEF be renamed from "HF with mid-range EF" to "HF with mildly reduced EF" (1,36), thus preserving the acronym "HFmrEF" yet reminding clinicians that such patients may benefit from established HF therapies traditionally reserved for those with more severely reduced LVEF (**Central Illustration**).

Importantly, the "normal" distribution of LVEF increases with age, is higher in women than men, and varies with ethnicity in the general population (37). This makes sense when considering that LVEF is a fraction in which the denominator, LV end-diastolic volume, becomes smaller with age-related remodeling or in women versus men. Thus, a common LVEF cutoff for "normal" of 50%, regardless of age or sex, would end up including elderly women who actually have relatively reduced EF for their age and sex. Indeed, in the PARAMOUNT (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Receptor Blockers on Management of Heart Failure With Preserved Ejection Fraction) trial, there was subtle evidence of more LV systolic dysfunction, despite a higher LVEF, in women compared to men with HFpEF (38). Furthermore, in combined analyses of PARAGON-HF and PARADIGM-HF data, sex-specific treatment effect splines across the entire LVEF spectrum showed efficacy of sacubitril/valsartan in the 40% to 50% EF range in both sexes, with the upper 95% confidence interval boundary of the rate ratio for sacubitril/valsartan versus comparator renin-angiotensin blockade remaining below 1.0 (indicating benefit with sacubitril/valsartan) up to higher LVEFs in women compared to men (39). When such sex-EF interaction analyses were extended in pooled patient-level data analyses from trials of angiotensin receptor blockers

TABLE 2 Results of Post Hoc Analyses of Trials Including Patients With Left Ventricular Ejection Fraction Between 40% and 50%

Medication	Trial	Results
Mineralocorticoid antagonists	TOPCAT (31)	Although overall results showed a nonsignificant 11% risk reduction in the primary composite endpoint with spironolactone versus placebo, LVEF modified the treatment effect, particularly in the patients in the Americas, with larger estimated benefits of spironolactone in those with lower LVEF. For those with LVEF of 45% to 50%, evidence of benefit was present, with a HR for spironolactone versus placebo of 0.72 (95% CI: 0.50 to 1.05), in contrast to those with LVEF of ≥60% (HR: 0.97; 95% CI: 0.76 to 1.23).
Beta-blockers	Beta-Blockers in Heart Failure Collaborative Group (32)	Individual patient-level meta-analysis of the effect of beta-blockers across the spectrum of LVEF in 18,637 patients, who participated in 11 different randomized trials, showed that beta-blockers improved mortality in sinus rhythm in lower LVEF categories up to and including LVEF of 40% to 49% but not in LVEF of ≥50%.
Angiotensin receptor blockers	CHARM Programme (33)	Across the spectrum of LVEF in HF, the benefit of candesartan versus placebo for the primary outcome was more evident in those with lower LVEF, including those with LVEF of 40% to 49% (HR for candesartan vs. placebo: 0.76; 95% CI: 0.61 to 0.96) but not in those with LVEF of ≥50% (HR: 0.95; 95% CI: 0.79 to 1.14).
Digoxin	DIG (34)	Digoxin reduced HF hospitalization to a greater extent in those with lower LVEF. The HR for digoxin versus placebo was 0.71 (95% CI: 0.65 to 0.77) in those with LVEF of <40%, 0.80 (95% CI: 0.63 to 1.03) in those with LVEF of 40% to 49%, and 0.85 (95% CI: 0.62 to 1.17) in those with LVEF of ≥50%.
Angiotensin receptor–neprilysin inhibitors	PARAGON-HF (50)	Although PARAGON-HF just missed statistical significance for its primary endpoint of total HF hospitalizations and cardiovascular death (rate ratio: 0.87; 95% CI: 0.75 to 1.01; p = 0.059), a pre-specified analysis showed significant therapeutic heterogeneity based on LVEF, with patients at the lower end of the LVEF spectrum demonstrating greater benefit from sacubitril/valsartan compared with valsartan. Among patients with LVEF at or below the median of 57%, benefit was evident in the HR for sacubitril/valsartan versus valsartan of 0.78 (95% CI: 0.64 to 0.95) but not in those with LVEF of <57% (HR: 1.00; 95% CI: 0.81 to 1.23).

CI = confidence interval; CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; DIG = Digitalis Investigation Group; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; PARAGON-HF = Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

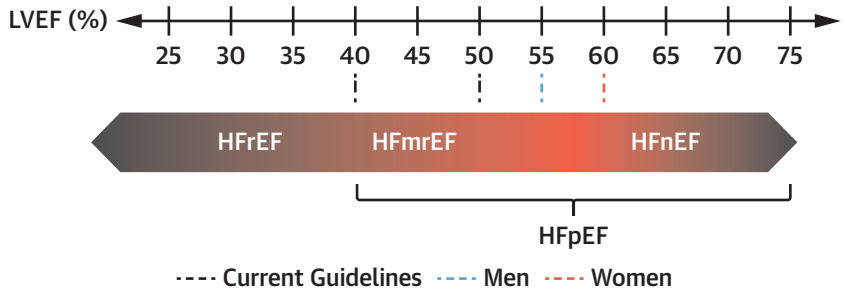
and mineralocorticoid antagonists across the entire LVEF spectrum of HF, similar patterns were observed (**Figure 3**) (40). Treatment with neurohormonal blockade was found to be beneficial beyond the upper limit of LVEF eligibility used in contemporary HFrEF clinical trials (40%), with benefit extending to the 40% to 50% EF range. Of note, the benefit of each treatment seemed to extend to a higher LVEF in women compared to men (**Figure 3**) (40).

How may these data inform our LVEF classification or nomenclature in HF? Most straightforward may be a simple dichotomy of "reduced" versus not reduced LVEF. However, combining patients with "mildly reduced" and more severely reduced LVEF into 1 "reduced" group would fail to acknowledge the important differences in prognosis, magnitude of treatment effect, risk-benefit ratio, and strength of trial evidence in HFmrEF versus those with lower LVEFs. Thus, preserving a distinction between "mildly reduced" versus more severely reduced LVEF appears warranted.

This still leaves the questions of which LVEF cutoff should be used to define the nonreduced group and which name should be used to refer to this group. The emerging data from HF trials (31,33,35) and recent large echocardiographic registries inclusive of HF (41,42) suggest that the LVEF cutoff of 50% is too low and that cutoffs of 55% or 60% may be more appropriate, based on the LVEF value below which mortality risk increases or at which the protective effect of neurohormonal blockade becomes evident. Notably, a higher cutoff of 55% would coincide with LVEF values used to define "normal" in the general population, as recommended in echocardiography guidelines. Indeed, guidelines from the American Society of Echocardiography and European Society of Echocardiography define a normal EF as >55% (43). Importantly, the overwhelming evidence, from both HF trials and general population studies, indicates that sex differences exist, supporting the consideration of sex-specific cutoffs in nomenclature (**Central Illustration**). Finally, with a new LVEF cutoff of 55% (men) or 60% (women) approximating the definition of "normal" in the general population, it may be time to return full circle to the term "HF with normal LVEF" (**Central Illustration**).

There are several important clinical implications of the proposed LVEF thresholds and nomenclature for HF with "mildly reduced EF" and "normal EF" (**Central Illustration**). First, the extended LVEF range covered by "mildly reduced" (<55%) means a larger proportion of patients potentially qualifying for

CENTRAL ILLUSTRATION Proposed Nomenclature in Heart Failure



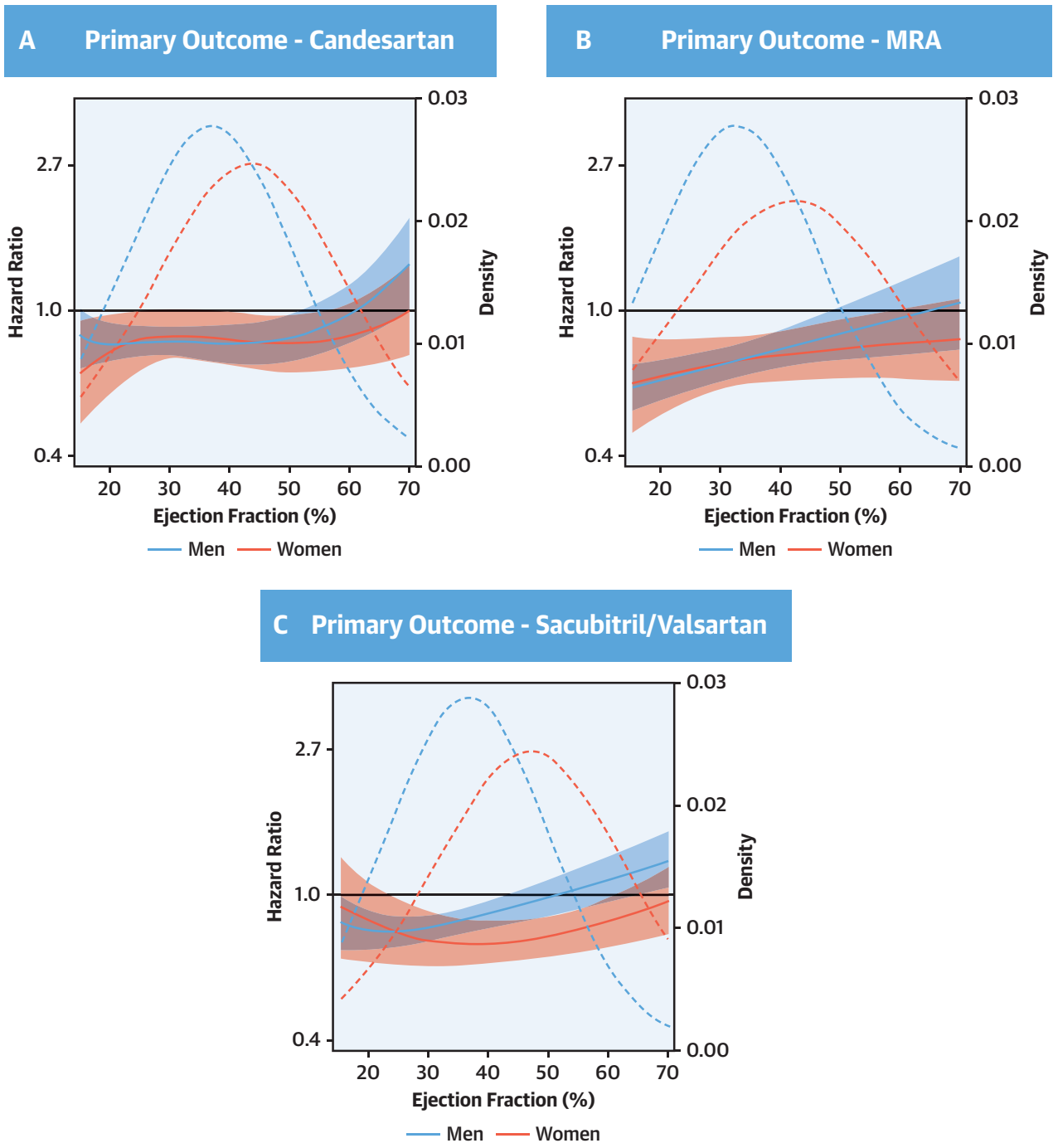
Lam, C.S.P. et al. J Am Coll Cardiol. 2021;77(25):3217-25.

The proposed nomenclature based on left ventricular ejection fraction defines "heart failure with reduced ejection fraction" (HFrEF) as LVEF of <40%, "heart failure with mildly reduced ejection fraction" (HFmrEF) as 40% ≤ LVEF < normal, and "heart failure with normal ejection fraction" (HFnEF) as LVEF of ≥55% in men and ≥60% in women. The term "heart failure with preserved ejection fraction" (HFpEF) for LVEF of >40%, as originally coined in the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) program, thus overlaps with HFmrEF and HFnEF.

proven treatments currently limited to HF with more severely reduced LVEF. This approach gives the most patients the benefit of the doubt, reducing the risk that patients with mildly reduced LVEF, especially women, may be deprived of potentially beneficial therapies. Correspondingly, this nomenclature unambiguously calls out the population of HF with normal EF (≥55% in men and ≥60% in women) in whom we still have no proven therapies. It is critical that, in referring to this group as "HF with normal EF," the term "normal" is not misconstrued as referring to healthy individuals who do not have HF—that is, individuals not needing therapy. Instead, this is the group that should be specifically recognized as being in urgent need of future research and still requiring the basic HF management of decongestion, hemodynamic control, and search for underlying treatable causes (e.g., amyloidosis, hypertrophic cardiomyopathy, or high-output syndromes).

It is likely that our ability to identify therapies for HF with LVEF of >40% has been hampered by the nomenclature we have used to describe this syndrome. We propose allowing the nomenclature to be driven by the science and not the other way around. Future approaches to HF may consider replacing LVEF with other measurements of systolic function (e.g., strain) (44,45) or using completely different methods to classify HF meaningfully (e.g., by etiology or biomarker profiling) (46). The limitations of LVEF as a measure of systolic function are well known (47)—it is load dependent, insensitive to subtle reductions in contractility, and only moderately reproducible by echocardiography, with interobserver and intraobserver variability of up to 21% and 13%, respectively (48). Moreover, the clinical methods by which LVEF is assessed do not necessarily provide comparable measurements, and LVEF can change over time in the same patient with HF (49), leading to confusion in LVEF-based classification. Recognizing the prognostic implications of longitudinal LVEF change in a patient with HF, the universal definition specifically accounts for LVEF trajectory in its classification (1). Despite shortcomings, LVEF remains the most widely accepted marker of systolic function in clinical practice, and clinical trials that form the basis of evidence-based treatment recommendations in guidelines are all predicated on LVEF cutoffs. A shift away from LVEF to an alternative metric (e.g., strain) would be challenged by the burden of evidence generation required to override the existing evidence base, as well as the need to change clinicians' perceptions and practice. The future performance of "umbrella" HF trials covering the entire LVEF spectrum and the retrospective analysis of past trials (**Table 2**)—although fraught with the perils of post hoc subgroup analyses—may represent our best current approach because it would be infeasible to repeat all past trials with new criteria. The recent U.S. Food and Drug Administration approval of sacubitril/valsartan for HF in general, without specifically calling out HFrEF or HFpEF—but with the caveat that "benefits are most clearly evident in patients with LVEF below normal" and "LVEF is a variable measure, so use clinical judgment

FIGURE 3 Interaction Between LVEF, Sex, and Neurohormonal Modulators in HF



Solid lines show a continuous hazard ratio for the primary composite outcome (HF hospitalization/cardiovascular death) stratified by sex (men in **blue** and women in **red**) and according to treatment group in the range of LVEF included in respective trials, with **shaded areas** representing the 95% CIs. **Dotted curves** represent the normalized distribution of LVEF by sex. In all 3 graphs there is evidence of benefit (hazard ratio: <1.0) with the active treatment—**(A)** candesartan versus placebo, **(B)** mineralocorticoid receptor antagonist versus placebo, and **(C)** sacubitril/valsartan versus renin-angiotensin-aldosterone system inhibitor—extending to the ejection fraction range of 40% to 50% and extending to a higher LVEF in women compared to men. Adapted from Dewan et al. (40). MRA = mineralocorticoid receptor antagonist; other abbreviations as in Figures 1 and 2.

in deciding whom to treat" (2)—also represents a welcome step away from rigid LVEF cutoffs and ambiguous nomenclature. This new approval, and mounting evidence, of beneficial therapies in this group of patients behooves the HF clinical community to reconsider the existing nomenclature and embrace potential new approaches that may facilitate clinical implementation and future research.

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REFERENCES

1. Bozkurt B, Coats A, Tsutsui H. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail 2021;23:352–80.

2. Novartis. Entresto (sacubitril and valsartan) tablets, for oral use. Prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207620s018lbl.pdf. Accessed February 28, 2021.

3. Braunwald E. Heart Disease: A Textbook of Cardiovascular Medicine. 4th edition. Philadelphia: W.B. Saunders, 1992.

4. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol 1984;54:778–82.

5. Soufer R, Wohlgelernter D, Vita NA, et al. Intact systolic left ventricular function in clinical congestive heart failure. Am J Cardiol 1985;55:1032–6.

6. Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. N Engl J Med 1985;312:277–83.

7. Kupari M, Lindroos M, Iivanainen AM, Heikkila J, Tilvis R. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med 1997;241:387–94.

8. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.

9. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.

10. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

11. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.

12. Devereux RB, Roman MJ, Liu JE, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000;86:1090–6.

13. Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001;87:413–9.

14. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002;137:631–9.

15. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.

16. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

17. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol 2007;49:198–207.

18. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. J Am Coll Cardiol 2009;54:410–8.

19. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 2010;56:845–54.

20. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–26.

21. Thenappan T, Shah SJ, Gomberg-Maitland M, et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. Circ Heart Fail 2011;4:257–65.

22. Lam CS, Lyass A, Kraigher-Krainer E, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 2011;124:24–30.

23. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36–46.

24. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail 2009;15:782–9.

25. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/

American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. J Am Coll Cardiol 2005;46:e1–82.

26. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.

27. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

28. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239.

29. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

30. Nauta JF, Hummel YM, van Melle JP, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail 2017;19:1569–73.

31. Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37:455–62.

32. Kotecha D, Flather MD, Altman DG, et al. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. J Am Coll Cardiol 2017;69:2885–96.

33. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 2018;20:1230–9.

34. Abdul-Rahim AH, Shen L, Rush CJ, et al. Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. Eur J Heart Fail 2018;20:1139–45.

35. Solomon SD, Vaduganathan M, Claggett BL, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 2020;141:352–61.

36. Lam CSP, Voors AA, Piotr P, McMurray JJV, Solomon SD. Time to rename the middle child of heart failure: heart failure with mildly reduced ejection fraction. Eur Heart J 2020;41:2353–5.

37. Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL study. J Am Coll Cardiol Img 2015;8:656–65.

38. Gori M, Lam CS, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur J Heart Fail 2014;16:535–42.

39. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. Circulation 2020;141:338–51.

40. Dewan P, Jackson A, Lam CSP, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. Eur J Heart Fail 2020;22:898–901.

41. Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? Eur Heart J 2020;41:1249–57.

42. Stewart S, Playford D, Scalia GM, et al. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. Eur J Heart Fail 2021;23:406–16.

43. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

44. Reimer Jensen AM, Zierath R, Claggett B, et al. Association of left ventricular systolic function with incident heart failure in late life. JAMA Cardiol 2021;6:509–20.

45. Yancy CW, Fonarow GC. Is the left ventricular ejection fraction measurement still preeminent? New measures to quantify subclinical systolic dysfunction. JAMA Cardiol 2021;6:521.

46. Tromp J, Ouwerkerk W, Demissei BG, et al. Novel endotypes in heart failure: effects on guideline-directed medical therapy. Eur Heart J 2018;39:4269–76.

47. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J 2016;37:1642–50.

48. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. Am Heart J 2003;146:388–97.

49. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail 2012;5:720–6.

50. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609–20.

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