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REVIEW TOPIC OF THE MONTH

Left Ventricular Ejection Fraction and the Future of Heart Failure Phenotyping

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HIGHLIGHTS

- Heart failure is a complex syndrome categorized by LVEF.
- Although flawed, LVEF is prognostic for adverse events and predicts response to some medical therapies.
- Simplified LVEF terminology may improve utilization of heart failure medical therapy.
- Novel therapies should be characterized across the entire LVEF spectrum to best determine their utility.

ABSTRACT

Heart failure (HF) is a complex syndrome traditionally classified by left ventricular ejection fraction (LVEF) cutpoints. Although LVEF is prognostic for risk of events and predictive of response to some HF therapies, LVEF is a continuous variable and cutpoints are arbitrary, often based on historical clinical trial enrichment decisions rather than physiology. Holistic evaluation of the treatment effects for therapies throughout the LVEF range suggests the standard categorization paradigm for HF merits modification. The multidisciplinary Heart Failure Collaboratory reviewed data from large-scale HF clinical trials and found that many HF therapies have demonstrated therapeutic benefit across a large range of LVEF, but specific treatment effects vary across that range. Therefore, HF should practically be classified by association with an LVEF that is reduced or not reduced, while acknowledging uncertainty around the precise LVEF cutpoint, and future research should evaluate new therapies across the continuum of LVEF. (J Am Coll Cardiol Case Rep 2024;12:451–460) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

HF = heart failure

HFimpEF = heart failure with improved ejected fraction

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

SGLT2i = sodium glucose co-transporter 2 inhibitor

Left ventricular ejection fraction (LVEF) measurement remains a staple of heart failure (HF) research, classification, and clinical management. The recently updated Canadian, European, and United States HF guidelines elaborate the growing evidence for the treatment of patients with HF without a reduced LVEF distinctly from those with a reduced LVEF.[1-3] The guidelines organize HF into categories based on LVEF, including heart failure with reduced ejection fraction (HFrEF) with LVEF ≤40%, heart failure with a preserved ejection fraction (HFpEF) with LVEF ≥50%, heart failure with mildly reduced (formerly, mid-range) ejection fraction (HFmrEF) with LVEF 41% to 49%, and heart failure with improved ejection fraction (HFimpEF) with LVEF >40% but previous LVEF ≤40% (**Figure 1**).

LVEF is useful in clinical care and for research because it is broadly prognostic of adverse events in patients with HF and can predict response to many HF medical therapies. As foundational inclusion criteria for multiple practice-changing clinical trials, traditional LVEF cutoffs are tied to lifesaving clinical advances and are straightforward to apply in routine clinical practice. However, LVEF is a continuous rather than a dichotomous variable and only one of many biomarkers that may help phenotype patients with HF to improve their clinical care.

In addition, although the guidelines currently describe the category of HF without a reduced LVEF as "preserved," or HFpEF, this terminology intimates that myocardial structure and function are not altered. In contrast, a "normal" LVEF does not imply normal myocardial function and substantial evidence demonstrates that patients with HF but without a reduced LVEF have decreased myocardial strain, elevated ventricular filling pressures, and increased risk of adverse outcomes.[4,5]

The Heart Failure Collaboratory is a multistakeholder consortium composed of clinical investigators, physicians, payers, patients, and representatives from industry, the Food and Drug Administration, and other government agencies. The HF-ARC (Heart Failure Collaboratory convened the Heart Failure–Academic Research Consortium) forum to review data from multiple landmark clinical trials, discuss potential limitations of the current classification of HF based on LVEF, and provide consensus recommendations. Although prior publications have commented on the utility or disutility of LVEF, this expert panel consensus updates the discussion with the most recent sodium glucose co-transporter 2 inhibitor (SGLT2i) clinical trial data, and provides novel concise recommendations for clinical and research use of LVEF in the context of the latest HF guidelines.

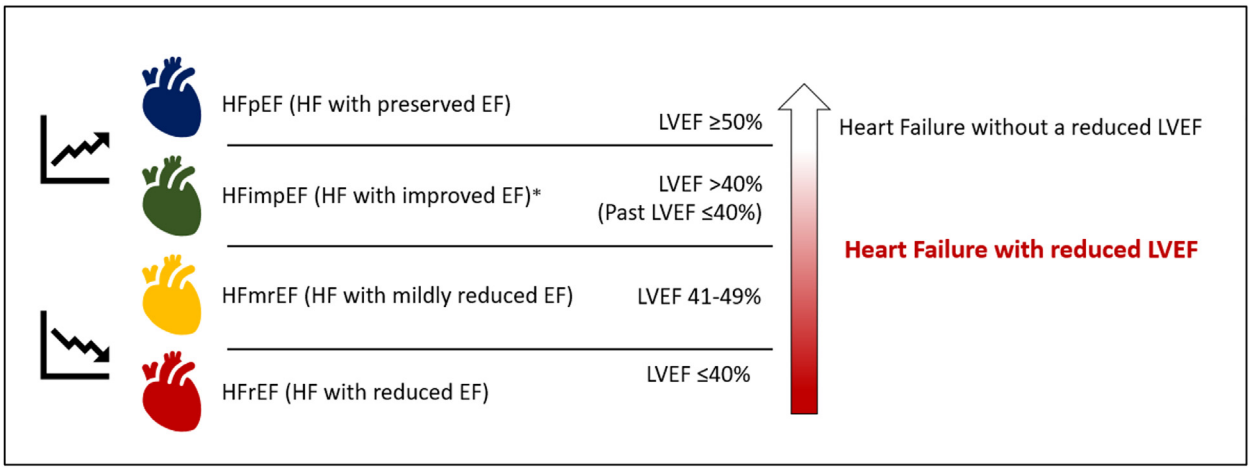
Until more precise and nuanced biomarkers are available for HF classification, we argue that pragmatically, LVEF remains flawed but useful for HF clinical management and research. Clinically, HF should be divided into 2 broad categories based on LVEF: heart failure with reduced ejection fraction (HFrEF) and HF without a reduced LVEF (**Figure 1**). We acknowledge that there is a region of overlap between these syndrome populations, and thus uncertainty of assignment for patients with LVEF measurements that lie within generally accepted normal population values. "HF without a reduced LVEF" appropriately acknowledges the heterogeneity of disease processes that cause the HF syndrome in this population, and omitting a precise cutoff between the groups recognizes the evidentiary uncertainty around that breakpoint due to measurement and physiologic variability. Nevertheless, although these 2 LVEF groups generally signal the therapeutic benefits clinicians can reasonably expect patients to experience, novel therapies should continue to be investigated for utility across the entire continuum of LVEF to facilitate evidence generation among all patients with HF.

LVEF: IMPERFECT BUT USEFUL

LVEF is imperfect because it can vary by imaging modality, hemodynamic loading conditions, heart rhythm, and on repeat measures even by the same modality for a single individual.[6] On a population level, LVEF assessment also varies by age, race, and sex, as women have a slightly higher normal range.[7-9] Despite these limitations, decades of clinical trial evidence support classification of HF by LVEF, and LVEF will remain useful until HF can be better phenotyped using proteomics, genomics, other imaging modalities such as strain echocardiography, or perhaps additional biomarkers currently under investigation. Although the strengths of LVEF are discussed in the following, improved phenotyping of and individualized treatment for patients with HF remains critically important as an essential mechanism to advance clinical care.

LVEF is valuable in HF because it possesses both prognostic utility (identifies patients likely to have a disease-related event) and predictive capabilities (identifies patients likely to respond to an intervention).[10] Patients with lower LVEF are at greater risk of adverse events, including higher absolute rates of

FIGURE 1 Current HF Classification and the New Proposed Conceptualization of LVEF



Current (2022) guidelines for the classification of heart failure (HF) by left ventricular ejection fraction (LVEF) from the European Society of Cardiology and the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA), contrasted with our proposed way of thinking about HF and LVEF.[1,3] Heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with improved ejected fraction (HFimpEF) should be treated as subclassifications of heart failure with reduced ejection fraction (HFrEF). Patients respond proportionally to their degree of LVEF reduction to typical therapies used for the treatment of HFrEF, and patients with improved LVEF should continue to be treated as HFrEF. *HFimpEF appears only in the ACC/AHA/HFSA guidelines. HFpEF = heart failure with preserved ejection fraction.

cardiovascular mortality, hospitalization, and sudden cardiac death. This was among the reasons that clinical trials initially, and now pervasively, used LVEF as an enrollment and enrichment criterion: lower LVEF meant higher event rates, greater statistical power, and better opportunity to demonstrate a treatment benefit for a novel therapeutic. Although clinical trials have used varied LVEF cutpoints for enrollment (Figure 2), the impact of these historical decisions was to limit evidence generation to patients only with LVEF in these ranges.

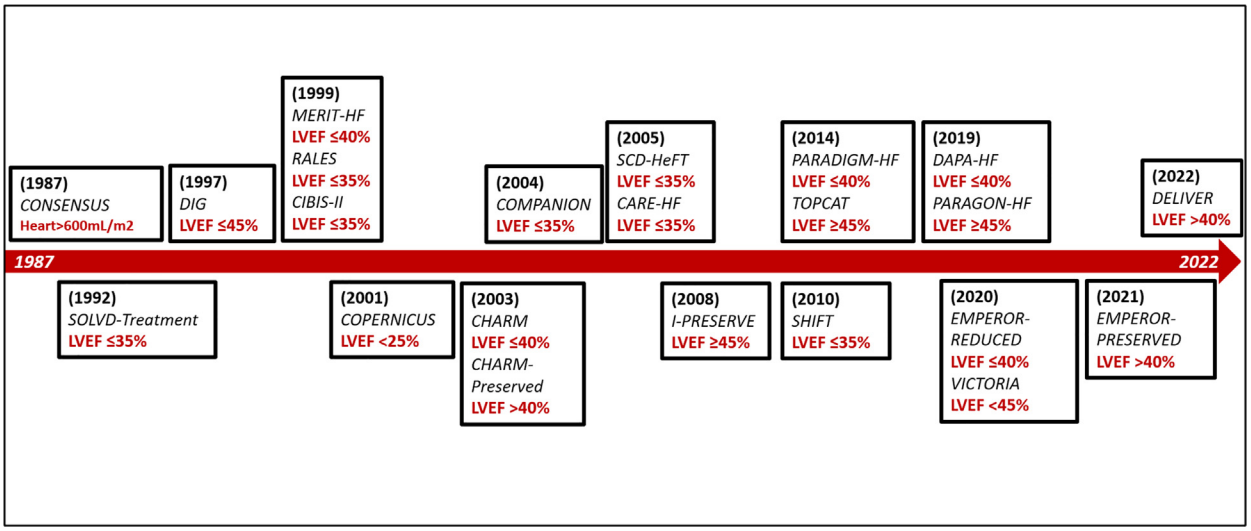
LVEF predicts both the expected treatment effect and magnitude across its continuum, but only for some therapies, and not as a dichotomous instrument. For neurohormonal antagonists of the renin-angiotensin-aldosterone system, LVEF captures the likelihood of therapeutic effect as a response variable until LVEF passes above values generally regarded as the lower limit of normal, in the range of 50% to 55%.[8,9] Nonetheless, their effectiveness is variable for patients with higher values of LVEF, as some are effective into the LVEF range above 55% and many are not (Central Illustration, Table 1).

SPECIFIC HF THERAPEUTICS ACROSS THE RANGE OF LVEF

Multiple medications used for the treatment of HFrEF have been studied for effectiveness across the range of LVEF. In post hoc analysis of the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, candesartan benefited patients across the continuous range of LVEF up to above 60%.[21] However, because the overall incidence of cardiovascular morbidity and mortality declined for patients with LVEF closer to or in the normal range, the treatment benefit on morbidity and mortality also declined in those patients. In addition, the relative benefit of candesartan varied by outcome over the range of LVEF: the benefit on mortality was principally seen at lower LVEF values, whereas the benefit on hospitalization extended into the normal range of LVEF.

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial enrolled patients with LVEF ≥45%. Although the trial did not meet its primary endpoint, post hoc analyses suggested greater therapeutic benefit for spironolactone at the lower end of the included LVEF spectrum, and a reduction in the primary endpoint of cardiovascular death, HF hospitalization, or aborted cardiac arrest and HF hospitalization was observed up to an LVEF of 50%.[22] A combined analysis of trials with spironolactone and eplerenone suggested that, similar to candesartan, the overall therapeutic benefit with mineralocorticoid receptor antagonists extends into the normal range of LVEF, again with the effect on cardiovascular

FIGURE 2 Clinical Trial Inclusion Criteria for LVEF Over the Past 35 Years



Left ventricular ejection fraction (LVEF) inclusion criteria published in the primary results paper from contemporary heart failure clinical trials from 1987 to 2022. Data taken from CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study, 1987), SOLVD (Studies of Left Ventricular Dysfunction, 1991), DIG (Digitalis Investigation Group, 1997), MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, 1999), RALES (Randomized Aldactone Evaluation Study, 1999), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II, 1999), COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival, 2001), CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity, 2003), COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure, 2004), SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial, 2005), CARE-HF (Cardiac Resynchronization-Heart Failure, 2005), I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study, 2008), SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial, 2010), PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity, 2014), TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist, 2014), DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure, 2019), PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction, 2019), EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction, 2020), VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction, 2020), EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction, 2021), and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure, 2022).

mortality more apparent at lower LVEF, and the effect on hospitalization extending farther into the normal LVEF range.[23]

A meta-analysis of 11 beta-adrenergic receptor antagonist trials showed that, although the treatment effect was most pronounced in patients with LVEF <40%, beta-blockers reduced morbidity and mortality for patients with LVEF <50%, but with diminished evidence for a treatment effect at higher LVEF.[24]

Evidence for the treatment benefit of the cardiac glycoside digoxin is greatest at the lower end of the LVEF spectrum, below LVEF of 45%. The ancillary arm of the DIG (Digitalis Investigation Group) trial enrolled patients with LVEF >45% but the relative risk reduction in cardiovascular death and HF hospitalization was smaller in magnitude and did not meet statistical significance.[19] The cardiac myosin activator omecamtiv mecarbil was only studied in patients with an LVEF ≤35%. Although the overall study demonstrated a modest treatment benefit, a larger treatment effect was found for patients with LVEF <28% in post hoc analyses, and it may have greatest potential utility in only this lower range of LVEF.[25,26]

Post hoc analyses of sacubitril/valsartan trials also showed effectiveness across the range of HFrEF and for patients above LVEF 50% to 55%. A prespecified pooled analysis from the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trials demonstrated a beneficial treatment effect for the composite of total HF hospitalization or cardiovascular death for sacubitril/valsartan up to an LVEF of 55%.[27] Similar to other neurohormonal agents, the effect on mortality was less prevalent at higher LVEF than the effect on morbidity. Along with other neurohormonal

antagonists, the relative and absolute risk reduction with treatment diminishes at the higher range of LVEF, particularly above LVEF 50% to 55%.

SGLT2i also demonstrated therapeutic benefit across the spectrum of LVEF. Empagliflozin reduced hospitalizations across the range of LVEF extending up to 65% in a pooled analysis of nearly 10,000 patients from the EMPEROR-Reduced and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure) program, but there was no evidence of benefit above LVEF of 65%.[28] A prespecified pooled analysis of individual patient data from more than 11,000 patients from 2 clinical trials, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure), revealed a similar treatment benefit across the range of LVEF, with no evidence of treatment effect modification based on LVEF.[29] Dapagliflozin thus stands in contrast to the neurohormonal antagonists with apparent effectiveness that reliably extends into and above the normal range of LVEF.

These data support that for currently available HF medical therapies in clinical practice, LVEF can be practically dichotomized into reduced and nonreduced. In patients with the HF syndrome and LVEF below the normal range expected for their demographics, treatment with neurohormonal antagonists and SGLT2i can be anticipated to reduce risk of morbidity and mortality. For patients with LVEF closer to the lower limits of normal, the relative and absolute treatment benefits attenuate, as the overall risk of death and hospitalization and the magnitude of benefit are proportional to the decrement in LVEF. For neurohormonal antagonists in patients with normal or supranormal LVEF, the expected treatment responses are distinct, with little effect on mortality and diminishing effects on morbidity, except for SGLT2i.

In contrast, the clinical use of the more recently and arbitrarily defined category HFmrEF is not supported by independent clinical trial data, and the utility of therapies in this range can only be extrapolated from their adjacent trends. Specifically, the HRs for benefit with 95% CIs for beta-blockers, spironolactone, and sacubitril/valsartan in the LVEF range of 40%-49% span 0.60-1.13, 0.50-1.05, and 0.73-1.10, respectively (**Table 1**). It is only when the context of the rest of the LVEF spectrum is accounted for that their utility in the HFmrEF range can be surmised. The lack of utility of HFmrEF may be because LVEF measurements are dynamic and demonstrate operator-dependent variability on repeat assessment and are thus impractical over the narrow LVEF range of HFmrEF. In addition, data supportive of HFmrEF as a phenotype come only from post hoc analyses of large trials and observational analyses from registries, but no clinical trials have tested interventions separately in this population. Finally, use of HFmrEF as a clinical concept does not augment implementation of effective HF medications except when lumped together with HFrEF and may confuse clinicians otherwise seeking to use more HF medical therapy. Therefore, we advise the elimination of HFmrEF as a phenotypic category because of its impracticality, lack of evidence of utility, and potential for harm.

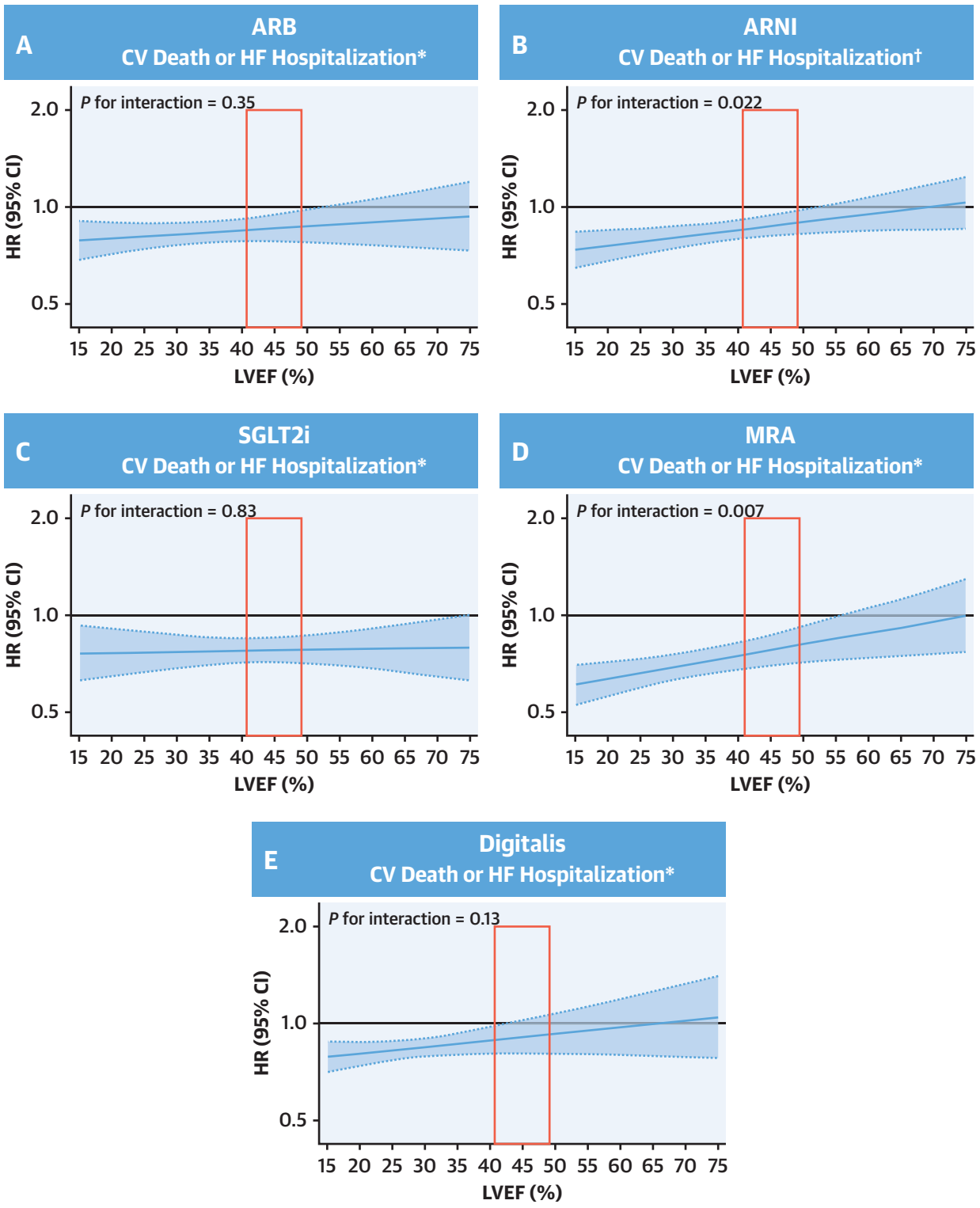
HFimpEF is another subcategory of HFrEF that for clinical simplicity should be included and treated under the HFrEF rubric. The TRED-HF (Therapy withdrawal in REcovered Dilated cardiomyopathy trial) demonstrated that patients with prior HFrEF that had improvement with appropriate HF medical therapy would frequently relapse with removal of that medical therapy.[30] In addition, molecular and biomarker testing of hearts with improved LVEF treated with medical, electrophysiologic device, or mechanical circulatory support device therapies demonstrate persistent myocardial abnormalities that support the concept of myocardial remission rather than recovery in response to these therapies.[31] Therefore, as patients with HFimpEF have HFrEF on a molecular level and remain at elevated risk of adverse events if taken off therapy, HFimpEF should be conceptualized and treated as HFrEF.

Future trials should enroll patients across a wide range of LVEF. In this way, the benefits of SGLT2i are a guide for the future: if SGLT2i had not been studied across the full range of LVEF, numerous patients would not currently be able to reap their rewards. Novel HF therapies should be evaluated across the continuum of LVEF because treatment benefits are unlikely to stop at artificial borders imposed by traditional LVEF cutoffs while the pathophysiologic targets for therapies likely span the range of LVEF.

HF DEVICES ACROSS THE RANGE OF LVEF

Evidence from HF device development reinforce the LVEF lessons learned from drug development. HF devices demonstrate conceptually similar differences in effectiveness across the range of LVEF, and some have been developed for use only in specific subranges of LVEF, while others for all patients with HF. Guidelines recommend implantable cardioverter-defibrillators in symptomatic patients at highest risk, typically those with LVEF ≤35%, or in those with

CENTRAL ILLUSTRATION **Treatment Effect of Medications for Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction**



Dimond MG, et al. J Am Coll Cardiol HF. 2024;12(3):451-460.

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LVEF ≤30% and a recent myocardial infarction.[3] The evidence for benefit from cardiac resynchronization therapy (CRT) is primarily for high-risk patients with LVEF ≤35% and a wide left bundle branch block pattern. However, similar to the growing appreciation of neurohormonal antagonism benefit at higher LVEF, the BLOCK-HF (Biventricular verses Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) trial suggests a treatment effect for CRT in patients with LVEF 35% to 50%; however, the MIRACLE EF study (NCT01735916) of CRT with higher LVEF was unable to recruit.[32,33] Uniquely, cardiac contractility modulation is only approved for patients with LVEF between 25% and 45% who are not candidates for CRT, although investigation of cardiac contractility modulation therapy for patients with LVEF of 40% to 60% is ongoing.[34] In contrast, utilization of the CardioMEMS device (Abbott Cardiovascular) reduces HF hospitalization regardless of LVEF.[35]

THE FUTURE OF LVEF AND NOVEL HF PHENOTYPING

Because of the described variable effectiveness of some therapies across LVEF, it is prudent to measure LVEF at baseline in HF clinical trials and to identify LVEF as a defining predictor of interest, including in prespecified subgroups. Furthermore, the trajectory of LVEF over time as a response to a new treatment could provide additional insight into the effect on cardiac remodeling. Although LVEF is a crude biomarker, the relationship between the degree of pathologic eccentric molecular and structural remodeling and drug response should remain a research focus for all novel therapies, because it may facilitate discovery of better phenotyping characteristics. Currently available HF data do not rule out qualitative molecular differences within the spectrum of LVEF that could dictate differential responses in some ranges to some therapies. Ongoing diligence may help meet the critical need for novel biomarkers that better phenotype patients into prognostic and predictive groups. Perhaps the implementation of "umbrella" trials to test multiple interventions across a broad spectrum of patients, and to sub-phenotype them using non-LVEF biomarkers, would allow collection of sufficient data to conclusively characterize expected treatment benefits of particular therapies throughout the continuum of HF.[36]

Nevertheless, improved phenotyping methodologies are likely to be complex and unlikely to replace LVEF in the near future. It is improbable that any single undescribed biomarker will identify treatment responders across all classes of HF therapies, and more plausible that biomarkers will vary by treatment modality. Useful phenotypic characteristics may include both pathophysiologic biomarkers such as aldosterone levels, and indicators of disease severity such as ST2 gene expression, or N-terminal pro-B-type natriuretic peptide levels for both. Furthermore, pathophysiologic biomarkers for newly developed therapies such as SGLT2i may yet be unknown.

Cardiac amyloidosis will hopefully serve as a roadmap for how improved HF phenotyping can lead to the identification of pathophysiologically distinct disease processes currently housed under HF that may be effectively treated with targeted molecular therapies. Individuals with cardiac amyloidosis most commonly present with the HF syndrome but without a reduced LVEF and are frequently undiagnosed. It is presumed that substantial proportions of patients enrolled in HFpEF clinical trials have likely had cardiac amyloidosis and their inclusion may have altered trial results because these patients often do not tolerate HF medications.[37] Yet patients with

CENTRAL ILLUSTRATION Continued

Association between left ventricular ejection fraction (LVEF) and the effects of selected heart failure (HF) medications on cardiovascular death or HF hospitalization, assuming a linear relationship with 95% CI around the HR. Interactions between LVEF and drug treatment effect were evaluated using a likelihood ratio test. All analyses were performed using STATA version 17.0 (Stata Corp). Data come from (A) results of the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) trial;[11] (B) PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity) and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction);[12,13] (C) DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure);[14,15] (D) RALES (Randomized Aldactone Evaluation Study, 1999), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist);[16-18] and (E) the DIG (Digitalis Investigation Group) trial.[19] The treatment effects for each class of HF therapy differ across the continuum of LVEF, with zones of unclear benefit (where the 95% CI for treatment benefit crosses an HR of 1.0) that vary by medication class but are typically above LVEF 50%, which is the upper end of the typical heart failure with mildly reduced ejection fraction (HFmrEF) range (red boxes), which supports consolidation of HFmrEF into heart failure with reduced ejection fraction (HFrEF). For most medication classes whose benefits appear to wane at higher LVEF values, the zone of unclear benefit occurs similarly around an LVEF of 50% to 55%, the typical lower limit of normal LVEF. *Compared with placebo. †Compared with enalapril or valsartan. ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CV = cardiovascular; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium glucose co-transporter 2 inhibitor.

TABLE 1 Medication Treatment Effect on Cardiovascular Death or Hospitalization for HF

	<40%	40%-49%	50%-60%	>60%
Beta-blockers	0.74 (0.62-0.88)	0.83 (0.60-1.13)	0.66 (0.38-1.15)	–
Spironolactone	0.69 (0.58-0.82)	0.72 (0.50-1.05)	0.85 (0.61-1.18)	0.97 (0.76-1.23)
Candesartan	0.82 (0.75-0.91)	0.76 (0.61-0.91)	0.95 (0.79-1.14)	–
Sacubitril-Valsartan	0.81 (0.69-0.94)	0.89 (0.73-1.10)	0.89 (0.74-1.06)	1.03 (0.80-1.32)
Empagliflozin	0.75 (0.65-0.86)	0.71 (0.57-0.88)	0.80 (0.64-0.99)	0.87 (0.69-1.10)
Dapagliflozin	0.74 (0.65-0.85)	0.87 (0.72-1.04)	0.79 (0.65-0.97)	0.78 (0.62-0.98)

HRs (95% CI) have been stratified by left ventricular ejection fraction cutpoints. Adapted from Ferreira et al.[20]
HF = heart failure.

amyloidosis respond to directly targeted disease-modifying therapies that have no effect on other patients with HF. Technetium pyrophosphate scintigraphy, genetic testing, and molecular diagnostics have facilitated noninvasive diagnosis and treatment, and effectively transformed care for patients with cardiac amyloidosis and lifted it from under the mantle of HF.

CONCLUSIONS

The wealth of data that support differential HF treatment effects by LVEF, or the lack thereof for some therapies, argue for the following proposed changes in the conceptualization and use of LVEF as a biomarker and updated guidelines for the classification and management of HF based on LVEF. Simplified and practical terminology to group patients by LVEF will hopefully facilitate improved utilization of HF medical therapy, known colloquially as guideline-directed medical therapy, by all clinicians and thereby improve care and outcomes for patients with HF. If the LVEF is below the generally accepted normal range of 50% to 55%, treat with therapies for HFrEF (**Figure 1**, **Central Illustration**). In contrast, if the LVEF is not reduced, then more individualized and personalized diagnostic and treatment paradigms are needed, including shared decision-making, and often specialty referral. HFmrEF should be eliminated from the guidelines and clinical practice, and HFimpEF should be classified and treated as a subtype of HFrEF. Although medications conventionally indicated for HF with a reduced LVEF such as spironolactone and sacubitril/valsartan should be considered to prevent hospitalizations for patients in the border zone around normal LVEF, such a regimen should not be considered sufficient and additional treatment modalities should be developed in addition or as alternatives because the likelihood and magnitude of response in this region are diminished. In contrast, ongoing characterization of the effectiveness of novel therapies across the entire spectrum of LVEF and improved phenotyping with development of additional targeted therapeutics for patients with HF without a reduced LVEF remain the challenging research target.

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REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24(1):4–131. https://doi.org/10.1002/ejhf.2333

2. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol*. 2021;37(4):531–546. https://doi.org/10.1016/j.cjca.2021.01.017

3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):1757–1780.

4. Ma C, Luo H, Fan L, Liu X, Gao C. Heart failure with preserved ejection fraction: an update on pathophysiology, diagnosis, treatment, and prognosis. *Braz J Med Biol Res*. 2020;53(7):e9646. https://doi.org/10.1590/1414-431X20209646

5. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction: understanding mechanisms by using noninvasive methods. *J Am Coll Cardiol Img*. 2020;13(1 Pt 2):245–257. https://doi.org/10.1016/j.jcmg.2018.12.034

6. Pellikka PA, She L, Holly TA, et al. Variability in ejection fraction measured by echocardiography, gated single-photon emission computed tomography, and cardiac magnetic resonance in patients with coronary artery disease and left ventricular dysfunction. *JAMA Netw Open*. 2018;1(4):e181456. https://doi.org/10.1001/jamanetworkopen.2018.1456

7. Galderisi M, Cosyns B, Edvardsen T, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18(12):1301–1310. https://doi.org/10.1093/ehjci/jex244

8. 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(6):656–665. https://doi.org/10.1016/j.jcmg.2015.02.014

9. 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):1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003

10. U.S. FDA. Enrichment strategies for clinical trials to support determination of effectiveness of human drugs and biological products. *March*. 2019. Accessed April 12, 2023. https://www.fda.gov/media/121320/download

11. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362(9386):777–781. https://doi.org/10.1016/S0140-6736(03)14285-7

12. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077

13. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609–1620. https://doi.org/10.1056/NEJMoa1908655

14. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303

15. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387(12):1089–1098. https://doi.org/10.1056/NEJMoa2206286

16. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709–717. https://doi.org/10.1056/NEJM199909023411001

17. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11–21. https://doi.org/10.1056/NEJMoa1009492

18. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383–1392. https://doi.org/10.1056/NEJMoa1313731

19. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336(8):525–533. https://doi.org/10.1056/NEJM199702203360801

20. Ferreira JP, Packer M, Butler J, Zannad F. Reconsidering the ejection fraction centric view of pharmacologic treatment for heart failure. *Eur J Heart Fail*. 2022;24(7):1148–1153. https://doi.org/10.1002/ejhf.2457

21. 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(8):1230–1239. https://doi.org/10.1002/ejhf.1149

22. 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(5):455–462. https://doi.org/10.1093/eurheartj/ehv464

23. 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(5):898–901. https://doi.org/10.1002/ejhf.1776

24. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39(1):26–35. https://doi.org/10.1093/eurheartj/ehx564

25. Felker GM, Solomon SD, Claggett B, et al. Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure: a post hoc analysis of data from the GALACTIC-HF randomized clinical trial. *JAMA Cardiol*. 2022;7(1):26–34. https://doi.org/10.1001/jamacardio.2021.4027

26. Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med*. 2021;384(2):105–116. https://doi.org/10.1056/NEJMoa2025797

27. Solomon SD, Vaduganathan M, L Claggett B, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141(5):352–361. https://doi.org/10.1161/CIRCULATIONAHA.119.044586

28. Butler J, Packer M, Filippatos G, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J*. 2022;43(5):416–426. https://doi.org/10.1093/eurheartj/ehab798

29. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. 2022;28(9):1956–1964. https://doi.org/10.1038/s41591-022-01971-4

30. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393(10166):61–73. https://doi.org/10.1016/S0140-6736(18)32484-X

31. Basuray A, French B, Ky B, et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation*. 2014;129(23):2380–2387. https://doi.org/10.1161/CIRCULATIONAHA.113.006855

32. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med*. 2013;368(17):1585–1593. https://doi.org/10.1056/NEJMoa1210356

33. Linde C, Curtis AB, Fonarow GC, et al. Cardiac resynchronization therapy in chronic heart failure with moderately reduced left ventricular ejection fraction: lessons from the Multicenter InSync Randomized Clinical Evaluation MIRACLE EF study. *Int J Cardiol*. 2016;202:349–355. https://doi.org/10.1016/j.ijcard.2015.09.023

34. About AIM HIGHer clinical trial. Impulse Dynamics Web site. Accessed April 7, 2023. https://impulse-dynamics.com/aim-higher/for-patients/

35. Zile MR, Mehra MR, Ducharme A, et al. Hemodynamically-guided management of heart failure across the ejection fraction spectrum: the GUIDE-HF trial. *J Am Coll Cardiol HF*. 2022;10(12):931–944. https://doi.org/10.1016/j.jchf.2022.08.012

36. Ahmad T, Wilson FP, Desai NR. The trifecta of precision care in heart failure: biology, biomarkers, and big data. *J Am Coll Cardiol*. 2018;72(10):1091–1094. https://doi.org/10.1016/j.jacc.2018.07.009

37. Oghina S, Bougouin W, Bézard M, et al. The impact of patients with cardiac amyloidosis in HFpEF trials. *J Am Coll Cardiol HF*. 2021;9(3):169–178. https://doi.org/10.1016/j.jchf.2020.12.005

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