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Heart Failure With Improved Ejection Fraction

Definitions, Epidemiology, and Management

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ABSTRACT

Heart failure with improved ejection fraction (HFimpEF) has gained increasing recognition as a distinct phenotype within the spectrum of heart failure, characterized by previously reduced left ventricular ejection fraction (≤40%) that subsequently improves to >40%. HFimpEF remains relatively understudied, and uncertainty persists regarding its long-term prognosis and optimal management. Contemporary registries and clinical trials suggest a rising prevalence, likely reflecting both the increased implementation of guideline-directed medical therapy and evolving consensus definitions for its identification. Despite left ventricular ejection fraction recovery, patients with HFimpEF remain at risk for adverse outcomes, and their management remains an area of active investigation. The aim of this review is to provide an in-depth evaluation of HFimpEF, including its epidemiology, pathophysiology, prognosis, and treatment strategies. The authors also highlight existing clinical gaps and propose future research directions to refine risk stratification and therapeutic approaches for this evolving population. (JACC. 2025;85:2401-2415) © 2025 by the American College of Cardiology Foundation.

Heart failure with improved ejection fraction (HFimpEF) has emerged as a distinct clinical phenotype within the spectrum of heart failure (HF), characterized by a prior left ventricular ejection fraction (LVEF) ≤40% followed by subsequent improvement to >40%. Although LVEF improvement is associated with better outcomes compared with persistent HF with reduced ejection fraction (HFrEF), it does not equate to full recovery, as these patients remain at risk for recurrent HF events.[1-3] Since the publication of the *JACC* scientific expert panel,[4] HFimpEF has gained widespread recognition as a distinct HF phenotype, leading to the adoption of a universal definition and incorporation into recent clinical practice guidelines. Recent studies have refined our understanding of the mechanisms driving LVEF improvement, including genetic predisposition, biomarker trajectories, and advanced

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CV = cardiovascular

GDMT = guideline-directed medical therapy

GLS = global longitudinal strain

HF = heart failure

HFimpEF = heart failure with improved ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-brain natriuretic peptide

RR = reverse remodeling

imaging parameters. Additionally, major HF randomized clinical trials have now enrolled HFimpEF patients, providing new insights into disease progression, long-term risk, and therapeutic optimization. This review synthesizes these recent advancements, offering a contemporary perspective on HFimpEF epidemiology, prognosis, and management, while identifying critical gaps for future studies.

DEFINITION

The universal definition of HFimpEF, established by the Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society in 2021, requires a baseline LVEF ≤40%, a subsequent absolute increase of ≥10 points, and a follow-up LVEF >40% (**Central Illustration**).[1] However, even since the publication of the universal definition of HFimpEF, guideline definitions continue to vary. The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guideline for the management of HF defines HFimpEF as prior LVEF ≤40% with a follow-up LVEF >40%, without specifying the degree of improvement.[3] Neither the 2021 European Society of Cardiology guidelines for the management of HF nor the 2023 focused update explicitly defines HFimpEF, but both suggest that patients with prior LVEF ≤40% and subsequent LVEF ≥50% with persistent symptoms should be considered to have HFimpEF rather than HF with preserved ejection fraction (HFpEF).[2]

Although LVEF improvement is central to HFimpEF classification, LVEF trajectory is not always linear, and some patients experience transient or permanent declines over time.[5] Additionally, echocardiographic variability can introduce misclassification, further complicating risk assessment. Despite these challenges, LVEF >40% in patients with prior HFrEF is widely accepted as a marker of favorable reverse remodeling (RR), defining a phenotype with distinct biological and clinical characteristics.

EPIDEMIOLOGY AND OUTCOMES

Given the historical lack of a unified definition of HFimpEF, its true prevalence remains uncertain (**Table 1**).[6-23] In addition, the timing of follow-up assessments of LV function is often not standardized, which may affect the identification of HFimpEF. In a systematic review and meta-analysis of 9 studies including 9,491 HF patients, the pooled prevalence of HFimpEF was estimated at about 23% over an average follow-up period of 3.8 years.[14] However, these estimates are influenced by heterogenous HFimpEF definitions and study populations.

RISK FOR LVEF DECLINE AND HF PROGRESSION. Prior studies have suggested that up to 50% of HFimpEF patients with nonischemic cardiomyopathy will experience LVEF decline within 3.5 years of improvement.[24-26] Although the DELIVER (Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction) trial did not include routine serial LVEF assessments, a post hoc analysis of investigator-reported data suggested that among HFimpEF patients with at least 1 HF hospitalization, two-thirds experienced declines in LVEF.[27] However, these findings should be interpreted with caution, as LVEF was not systematically measured during hospitalizations, introducing the potential for ascertainment bias.

In a study of 1,160 patients with HF, LVEF improvement was typically sustained for about a decade before a gradual decline, reinforcing the need for long-term surveillance and continued guideline-directed medical therapy (GDMT).[28] Importantly, patients who experience LVEF deterioration after improvement appear to have a higher risk for mortality, heart transplantation, or left ventricular (LV) assist device implantation than those with persistent HFimpEF.[19,25,26]

OUTCOMES COMPARED WITH HFrEF. HFimpEF is associated with significantly better outcomes than persistent HFrEF, with an approximately 60% lower risk for mortality or hospitalization.[14] This was confirmed in the MECKI (Metabolic Exercise Cardiac Kidney Indexes) study, in which HFimpEF patients had a cardiovascular (CV) mortality rate of 26.6 vs 46.9 per 1,000 person-years compared with persistent HFrEF.[15] Similar improved survival and lower hospitalization rates were observed in the BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) trial and the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry.[23] Furthermore, HFimpEF patients have a lower risk for arrhythmic events compared with those with persistent HFrEF, with one study reporting almost 60% lower odds of ventricular arrhythmias.[29] However, this risk is not eliminated, as sudden cardiac death and ventricular arrhythmias can still occur, raising ongoing uncertainties regarding implantable cardioverter-defibrillator (ICD) management, particularly the need for generator replacement or long-term device therapy in patients with LVEF improvement.

CENTRAL ILLUSTRATION **Definition, Factors Associated With Reverse Remodeling, Management, Prognosis, and Clinical Uncertainty of HFimpEF**

Heart Failure With Improved Ejection Fraction (HFimpEF)

HFA/HFSA/JHFS universal HF definition:
HF with baseline LVEF ≤40%, a ≥10 point increase, and a second measurement of LVEF >40%

ACC/AHA/HFSA guidelines:
HF with baseline LVEF ≤40%, and a second measurement of LVEF >40%

ESC guidelines:
HF with baseline LVEF ≤40%, and a second measurement of LVEF ≥50%

Reverse remodeling associations

- Younger age, non-ischemic etiology, shorter disease duration
- ↑ Myocardial function on imaging (LV structure and function)
- ↓ Biomarkers levels (NT-proBNP)
- Better kidney function, few comorbidities
- CRT, M-TEER and GDMT
- Female sex
- ↓ Fibrosis

Prognosis vs persistent HFrEF

- >50% lower risk of HF hospitalization
- >50% lower risk of death
- Lower arrhythmic risk
- But up to 50% will have EF decline within 3.5 years of improvement

Management

- SGLT2i (dapagliflozin) and finerenone are the only therapies tested in clinical trials for symptomatic HFimpEF, showing a lower risk of adverse CV events
- Continue GDMT leading to improved LVEF per TRED-HF trial
- Identification of patients at high risk for recurrence (phenotype + biomarkers + advanced imaging + genetic testing)

Clinical uncertainty

- Consensus definition for HFimpEF
- Consensus timeline for LVEF monitoring and follow-up
- Benefit of selective GDMT de-escalation based on risk assessment
- Benefit of ICD generator replacement
- Role of biomarkers in therapy titration/discontinuation
- Role of CMR/strain echocardiography/other imaging tools

Ongoing clinical trials

- Sacubitril/Valsartan vs Valsartan in Heart Failure with Improved Ejection Fraction (PROSPER-HF) - NCT04803175
- Tapering HF medication in patients with recovered EF - NCT06724653
- Withdrawal of Treatment for Heart Failure Patients with Recovery from Tachycardia-Induced Cardiomyopathy (WEAN-HF) - NCT06128980
- Withdrawal of Spironolactone Among Heart Failure with Improved Ejection Fraction (With-HF) - NCT04367051

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CMR = cardiac magnetic resonance; CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; GLS = global longitudinal strain; HF = heart failure; HFimpEF = heart failure with improved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; M-TEER = mitral transcatheter edge-to-edge repair; TAVR = transcatheter aortic valve replacement.

TABLE 1 Prevalence and Prognosis of Patients With HFimpEF

First Author	HFimpEF Definition	Prevalence	Outcome
Basuray et al[6]	LVEF ≥50% but prior LVEF <50%	9.7%	↓ Risk for death, HTx, LVAD placement, and all-cause hospitalization compared with patients with HFrEF and HFpEF
Kalogeropoulos et al[11]	LVEF ≤40% recovered to LVEF >40%	16.2%	↓ Risk for all-cause hospitalization and HF hospitalizations compared with patients with HFrEF and HFpEF
Nadruz et al[7]	LVEF 40%-55% but previously <40%	22.89%	↓ Risk for HF hospitalizations and CV death compared with patients with HFrEF
Agra Bermejo et al[10]	LVEF ≤40% recovered to LVEF >40%	52.07%	↓ Risk for mortality and hospitalization compared with patients with HFrEF and HFpEF
Trullàs et al[8]	LVEF >50% and an absolute increase >5% from baseline LVEF <50%	25%	↓ Risk of death compared with patients with HFpEF and HFrEF
Chang et al[9]	LVEF <35% to >40%	18.55%	↓ Risk for mortality, first HF hospitalization, and recurrent HF hospitalization compared with patients with HFrEF
Martínez-Mateo et al[12]	LVEF <40% to >50% at follow-up	26.91%	↓ Risk for mortality compared with patients with HFrEF
Lupón et al[13]	LVEF <45% at baseline and ≥45% at 1 y	24.8%	↓ Risk for CV death and HF hospitalization compared with patients with HFrEF and HFpEF
He et al[14]	Various definition depending on study	22.64%	↓ Risk for mortality and CV hospitalization compared with patients with HFrEF and HFpEF
Agostoni et al[15]	Prior LVEF ≤40% and a follow-up measurement of LVEF >40%	20%	↓ Risk for mortality compared with patients with HFrEF.
Florea et al[16]	Prior LVEF ≤35% and second assessment >40%	9.1%	↓ Risk for mortality compared with patients with HFrEF
Choi et al[17]	Prior LVEF ≤45% and an absolute increase in LVEF ≥20% or ≥10% in patients with follow-up LVEFs ≥50% and a decrease in LVEDD index ≥10% or an LVEDD index ≤33 mm/m^2	38%	↓ Risk for HF hospitalization, cardiac death, and HTx compared with patients with HFrEF
Ghimire et al[18]	Prior LVEF ≤40% and an absolute improvement ≥10% at follow-up	37.6%	↓ Risk for mortality, all-cause hospitalization, HTx, and LVAD implantation compared with patients with HFrEF
Manca et al[19]	Baseline LVEF ≤40% and second evaluation showing both a ≥10 percentage point increase from baseline LVEF and LVEF >40%	57%	↓ Risk for death, HTx, and LVAD compared with patients with HFrEF
Merlo et al[20]	LVEF increase of ≥10% or LVEF ≥50% and a decrease in LVEDD index of ≥10% or LVEDD index ≥33 mm/m^2	37%	↓ Risk for death compared with patients with HFrEF
Romero et al[21]	Baseline LVEF ≤40% and second evaluation showing both a ≥10 percentage point increase from baseline LVEF and LVEF >40%	39%	↓ Risk for death compared with patients with HFrEF
Huang et al[22]	Baseline LVEF ≤40% and second evaluation showing both a ≥10percentage point increase from baseline LVEF and LVEF >40%	35.7%	↓ Risk for all-cause mortality compared with patients with HFrEF
Stępień et al[42]	Baseline LVEF ≤40% and second evaluation showing both a ≥10percentage point increase from baseline LVEF and LVEF >40%	17.9%	↓ Risk for all-cause mortality compared with patients with HFrEF
Cao et al[23]	Baseline LVEF ≤40% and second evaluation at 9 mo showing LVEF >40% and a ≥10% increase	20%-30%	BIOSTAT-CHF: ↓ risk for all-cause mortality, and HF hospitalization compared with patients with HFrEF ASIAN-HF: ↓ risk for all-cause mortality and HF hospitalization compared with patients with HFrEF

ASIAN-HF = Asian Sudden Cardiac Death in Heart Failure; BIOSTAT-CHF = Biology Study to Tailored Treatment in Chronic Heart Failure; CV = cardiovascular; HF = heart failure; HFimpEF = heart failure with improved ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTx = heart transplantation; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction.

OUTCOMES COMPARED WITH HFpEF. Observational studies have suggested that HFimpEF may have a more favorable prognosis than HFpEF. In a prospective cohort study, HFimpEF patients had lower rates of HF hospitalization and death compared with HFpEF patients.[27] Similarly, other studies suggest that HFimpEF patients have a lower incidence of HF readmission and all-cause mortality.[30] The DELIVER trial also provided new insights into the prognosis of HFimpEF relative to HFpEF. Patients with HFimpEF had similar event rates of HF hospitalization and death compared with those with

LVEF consistently >40%.[31] However, they experienced greater in-hospital morbidity, requiring intensified management and higher resource use beyond standard diuretic therapy compared with patients with HF and LVEF consistently >40%.[32] However, this discrepancy may be because DELIVER enrolled high-risk HFimpEF participants, as patients needed to be symptomatic with elevated natriuretic peptides to meet study criteria, so the HFimpEF patients enrolled in DELIVER may not be representative of the general HFimpEF population (**Table 1**, **Central Illustration**).

Taken together, these findings highlight HFimpEF as a dynamic condition, distinct from both HFrEF and HFpEF, with heterogeneous long-term trajectories. Although outcomes are better than in persistent HFrEF, there remains a substantial risk for relapse and adverse events, necessitating ongoing risk assessment, individualized management, and long-term follow-up strategies.

LEFT VENTRICULAR REVERSE REMODELING

Pathologic cardiac remodeling results primarily from microscopic cardiomyocyte alterations, including cellular hypertrophy, metabolic dysregulation, disrupted protein expression, impaired cellular signaling, and dysregulated apoptotic processes.[33,34] Concurrent extracellular matrix remodeling leads to fibrosis and altered myocardial architecture, collectively driving structural alterations in the heart.[33,34]

LV RR refers to the restoration of cardiac myocyte size and consequent LV chamber geometry resulting in improvement or normalization of LVEF.[33] Although the biological basis of LV RR is not completely understood, it is a dynamic process facilitated by GDMT, device therapy, and surgical interventions. It can also occur spontaneously after resolution of the inciting stress that impaired myocardial function, such as stress cardiomyopathy, cardiotoxicity (chemotherapy, alcohol), myocarditis, or peripartum cardiomyopathy. Despite LV RR, LVEF improvement does not equate to complete myocardial normalization. Persistent dysregulation of transcriptomes, metabolomes, and proteomes of cardiac myocytes as well as a progressive erosion of the native 3-dimensional organization of the extracellular matrix surrounding the cardiac myocytes remain.[34] As such, HFimpEF represents a state of remission rather than recovery, with patients susceptible to recurrent LV dysfunction in response to hemodynamic, neurohormonal, or environmental stressors.[4,19,35] This concept has important clinical implications for the long-term management of these patients, reinforcing the need for ongoing surveillance and sustained medical therapy to mitigate residual risk and prevent disease recurrence.

PREDICTORS ASSOCIATED WITH RR. LVEF improvement in HFrEF is highly variable, raising key questions about which patients are most likely to experience RR (**Central Illustration**, **Table 2**).[8,10,12,13,15-23,30,36-42] Evidence suggests that younger age, female sex, nonischemic cardiomyopathy, shorter duration of disease, higher blood pressure, GDMT use, lower biomarker levels, absence of an ICD, and fewer comorbidities (including preserved renal function) are all associated with a higher likelihood of improvement of LVEF (**Table 2**).[4,43] These predictors have major clinical implications, particularly for risk stratification, follow-up intensity, and device therapy decisions. Patients with a high probability of LVEF improvement may require close follow-up during the first few years to confirm sustained improvement, followed by annual monitoring to assess long-term stability. Conversely, those with a low likelihood of improvement may need more frequent assessment to identify those who could benefit from advanced therapies.

LVEF trajectory also plays a critical role in determining the timing and necessity of ICD placement. For patients unlikely to achieve LVEF >35%, early primary prevention ICD placement may be warranted. In contrast, for those with a higher probability of LVEF improvement, extending the duration of GDMT optimization before committing to ICD placement may be a reasonable approach. This strategy could lead to a more personalized and cost-effective approach to ICD therapy, potentially reducing unnecessary procedures while ensuring appropriate protection against arrhythmic risk.[44,45]

ETIOLOGIES

The etiologies associated with HFimpEF are heterogeneous, influencing prognosis, management, and long-term risk for relapse. Certain conditions are more likely to achieve LVEF improvement, whereas others carry a higher risk for recurrence despite initial improvement.

ISCHEMIC HEART DISEASE. Patients with ischemic heart disease have a lower likelihood of LVEF recovery, which might be related to the extent and degree of myocardial damage and scar. However, in chronic coronary syndrome, identifying and revascularizing hibernating myocardium may improve the likelihood of LV RR.[46] Conversely, in acute myocardial infarction, early revascularization reduces infarct size and preserves LV function, whereas delayed revascularization leads to fibrosis, LV dilation, and poor

TABLE 2 Key Factors Associated With Left Ventricular Reverse Remodeling in HFimpEF

	Characteristic Associated With Reverse Remodeling	Notes
Age	✓ Younger age	Higher probability of reverse remodeling[8,10,12,18,19,22,36,39,40]
Sex	✓ Female	Consistently associated with better reverse remodeling[13,15,18,21,23,37,40]
HF etiology	✓ Nonischemic cardiomyopathy	Better prognosis compared with ischemic etiology[10,13,15,16,22,23,36-39,42]
Duration of disease	✓ Short duration	Early intervention improves likelihood of recovery[13,38,39]
Blood pressure	✓ Higher blood pressure	Associated with reverse remodeling probably for greater chance of holding up to maximum doses to the GDMT[15-18,20,22,30,39-41]
Left ventricular dimension	✓ Less dilated ventricle	Higher probability of reverse remodeling [15-17,19,22,23,41]
Comorbidities	⊘ Fewer	Particularly absence of diabetes, atrial fibrillation, and chronic kidney disease[8,15,36,42]
Treatment	✓ Complete GDMT	Associated with higher probability of reverse remodeling[10,12,16,17,22,30,39,41]
ICD	⊘ No previous implantation	Associated with better reverse remodeling, possibly reflecting a less severe clinical presentation[10,19,38]
Biomarkers	✓ Low baseline troponin levels and reduction in NT-proBNP levels	Predictive of better remodeling[15,16]

GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-brain natriuretic peptide.

prognosis.[47] Postmyocardial infarction cardiac rehabilitation may further facilitate LV RR.[48,49]

NONISCHEMIC CARDIOMYOPATHY. Nonischemic cardiomyopathy has a higher probability of LV RR compared with ischemic heart disease.[10,13,15,16,22,23,36-39,42] Specific conditions associated with favorable remodeling include the following:

- Alcohol-induced cardiomyopathy, for which alcohol cessation and GDMT can restore LV function.[50]
- Inflammatory cardiomyopathies (including myocarditis), for which resolution of inflammation may lead to LVEF improvement. In this population, higher NYHA functional class, type of myocarditis (eg, giant cell, lymphocytic, eosinophilic), genetic predisposition, and signs of myocardial inflammation on histology are generally accepted as independent predictors of poor LV RR.[49] Additionally, persistence fibrosis or edema on cardiac magnetic resonance (CMR) predicts a higher relapse risk.[51]
- Dilated cardiomyopathy. Gene mutations occur in up to 40% of patients with dilated cardiomyopathy, and finding a pathogenic gene variant could inform prognosis and device therapy decisions.[2] In a large retrospective cohort study of 1,005 patients, having positive results on genetic testing was associated with a lower occurrence of LV RR (40% vs 46%). Patients with *TTN* mutations had higher rates of LV RR (53%) compared with those with desmosomal mutations (11%).[52] A correlation between positive genetic results and the absence of LV RR has also been observed in other studies.[53,54]
- Tachycardia-induced cardiomyopathy or arrhythmia-induced HF, which has a favorable prognosis with sinus rhythm restoration or rate control.[55] However, persistent structural changes may predispose patients to recurrent LV dysfunction if arrhythmias recur. The optimal duration of GDMT postrecovery is unknown, through therapy may be safely de-escalated in select patients in stable sinus rhythm.
- Stress cardiomyopathy, which is now recognized as a condition with persistent myocardial dysfunction despite LVEF normalization rather than a benign process.[56] Patients may continue to have ongoing symptoms and remain at risk for recurrent episodes affecting long-term prognosis. There is still no evidence-based treatment to provide symptomatic or survival benefits for these patients.
- Valvular heart disease, for which early intervention may facilitate LV RR. For instance, in a meta-analysis of mitral transcatheter edge-to-edge repair trials, significant LV volume reduction and LVEF improvement were observed postintervention.[57]
- Peripartum cardiomyopathy, thought to be a vascular associated HF syndrome, affects women during pregnancy or in the early postpartum period.[58] Studies suggest that LVEF can improve within 36 months, though complete recovery varies, with studies reporting about 50% to 65%,

depending on the region.[2] Elevated levels of natriuretic peptides and high-sensitivity troponin immediately after delivery have been identified as predictors of poorer LV RR.[59,60]

ROLE OF ADVANCED IMAGING

Advanced imaging is playing an increasingly important role in identifying patients with a higher likelihood of LVEF recovery and in refining risk stratification as our understanding of HFimpEF evolves.

ECHOCARDIOGRAPHY. Global longitudinal strain (GLS) is a major echocardiographic predictor of LV RR.[61] Better baseline LV GLS has been shown to correlate significantly with greater LVEF improvement over time.[62] For instance, abnormal GLS (≤−16%) demonstrated high sensitivity (88%) for predicting a subsequent >5% LVEF decline during follow-up, though with limited specificity (46%).[63] In nonischemic cardiomyopathy, GLS ≥8% was associated with a nearly 4-fold higher odds of LVEF improvement.[64] Additionally, in 289 patients with HFimpEF, each 1% increase in GLS on index echocardiography was associated with a lower risk for CV mortality and HF hospitalization.[65]

Left atrial function parameters could also predict LV RR.[66] Left atrial strain is an independent predictor of HFimpEF even after adjustment for sex and LVEF, with values >10.8% more than quadrupling the likelihood of LVEF improvement in patients with HFrEF, with high sensitivity (96%) and specificity (82%).[67] Notably, improvements in GLS and left atrial strain after sacubitril/valsartan initiation have been associated with lower risk for CV death and HF hospitalization.[68] These findings highlight the potential of advanced strain-based imaging to guide GDMT optimization and timing interventions such as ICD placement.

CMR. CMR imaging complements echocardiography by offering detailed assessment of myocardial viability and fibrosis.[69] Additionally, T1 mapping and extracellular volume assessment are emerging as valuable tools for predicting LV RR, guiding drug titration, assessing cardiac resynchronization therapy benefit, and informing long-term surveillance.[70,71]

ROLE OF BIOMARKERS

Biomarkers are emerging as valuable tools for predicting LV RR, guiding therapy titration and risk stratification in HFimpEF.

NATRIURETIC PEPTIDES. N-terminal pro-brain natriuretic peptide (NT-proBNP) has been consistently associated with LV RR prediction and monitoring. In an echocardiographic substudy of the PROTECT (ProBNP Outpatient Tailored Chronic Heart Failure) study, higher final NT-proBNP levels over 10 months of follow-up were associated with increased LV volumes and lower LVEF, whereas reduction in NT-proBNP correlated with LV RR.[72] Similar results were observed in the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study, in which lowering NT-proBNP levels to <1,000 ng/L regardless of treatment strategy was associated with more extensive LV RR determined by lower LV volumes and greater LVEF improvements and improved outcomes.[73] The PROVE-HF (Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes) study further supported this, demonstrating that NT-proBNP reductions appeared as early as 2 weeks after sacubitril/valsartan initiation, preceding echocardiographic improvements at 6 months.[74]

MARKERS OF REMODELING AND FIBROSIS. Soluble suppression of tumorigenicity 2 reflects fibrosis and LV hypertrophy in HF and provides additional prognostic value beyond NT-proBNP.[75,76] It has previously been shown that a soluble suppression of tumorigenicity 2 level >48 ng/mL was associated with a lower likelihood of LV RR, likely reflecting an increased myocardial fibrotic burden.[77] Troponin T, a marker of myocardial injury, has also been linked to LV RR, with troponin T <11 ng/L associated with a higher incidence of recovery.[78] Other potential predictors of LV RR include galectin-3 and big endothelin 1, both involved in myocardial fibrosis.[79]

INFLAMMATORY AND METABOLIC MARKERS. Emerging data suggest that biomarkers related to inflammation and cardiac metabolism may also predict LV RR. In an echocardiography substudy of the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial, reductions tumor necrosis factor superfamily member 13B, growth differentiation factor-15, and insulin-like growth factor binding protein 7 were associated with greater LV RR.[80]

CLINICAL IMPLICATIONS OF BIOMARKERS AND IMAGING PARAMETERS. Integrating biomarkers with advanced imaging may improve risk stratification, ICD replacement decisions, GDMT titration, and long-term surveillance in patients with HFimpEF. Elevated soluble suppression of tumorigenicity 2 levels (>48 ng/mL), indicative of diffuse myocardial fibrosis, combined with late gadolinium enhancement on CMR may help justify ICD generator replacement despite apparent LVEF recovery and may help in

identifying patients with underlying arrhythmic risk. Conversely, the absence of fibrosis on CMR and no prior ICD therapy may support a more conservative approach in select patients. Similarly, NT-proBNP reductions, when paired with improvements in GLS and left atrial strain on echocardiography, may help identify patients who could tolerate cautious GDMT de-escalation. However, persistent subclinical dysfunction on strain imaging or residual fibrosis on CMR despite NT-proBNP improvement may suggest higher risk for relapse, reinforcing the need for continued therapy. Additionally, elevated NT-proBNP or troponin, combined with worsening GLS or left atrial strain, may serve as an early marker of LVEF deterioration, prompting closer surveillance and earlier intervention. By incorporating biomarkers, echocardiography, and CMR, clinicians could adopt a personalized approach to ICD management, GDMT decisions, and long-term monitoring, ensuring that high-risk patients receive timely interventions while avoiding unnecessary procedures in lower risk individuals. However, these de-escalation strategies require prospective evaluation in randomized clinical trials.

HF MEDICAL THERAPY

Pharmacologic therapy remains the cornerstone of HFrEF management, with GDMT playing a critical role in promoting LV RR. Although individual drug classes have been extensively studied for their effects on LVEF improvement, their collective impact on long-term HFimpEF management remains less defined (Table 3).[2]

NEUROHORMONAL BLOCKADE AND RR. Renin-angiotensin-aldosterone system inhibitors play a central role in LV RR, with early evidence from the SOLVD (Effects of Enalapril on Survival in Patients With Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure) trial, in which enalapril was associated with reduced LV volumes.[81] Similarly, participants treated with valsartan in the Val-HeFT (Valsartan Heart Failure Trial" showed a decrease in LV volumes and improvement.[82] Mineralocorticoid receptor antagonists further enhance LV RR.[83-85] Finally, angiotensin receptor neprilysin inhibitors have emerged as the most potent renin-angiotensin-aldosterone system–modulating therapy for RR. Sacubitril/valsartan has demonstrated greater structural and functional LV improvements compared with angiotensin-converting enzyme inhibitors, as shown in PROVE-HF and EVALUATE-HF (Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction), with meta-analyses confirming its superior LV RR effects.[86,87]

β-BLOCKERS. β-Blockers play a critical role in LV RR. In an echocardiographic substudy of the Australia/New Zealand Collaborative Group, carvedilol significantly reduced LV volumes and improved LVEF compared with placebo.[88] The MOCHA (Carvedilol in Heart Failure) trial further demonstrated dose-dependent improvements in LVEF and survival with carvedilol in patients with chronic HF.[89] Last, an echocardiographic substudy from CIBIS I (Cardiac Insufficiency Bisoprolol Study) showed that after 5 months of bisoprolol therapy, LV end-systolic dimensions decreased significantly, but LV end-diastolic dimensions remained unchanged.[90]

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS. Sodium-glucose cotransporter 2 inhibitors showed beneficial effects on LV RR, including LV volume reduction and LVEF improvement, as demonstrated in the EMPA-TROPISM (Empagliflozin in Non-Diabetic Heart Failure Patients With Reduced Ejection Fraction study,[91] SUGAR-DM-HF (Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure),[92] the EMPIRE HF (Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction trial,[93] and the DAPA-MODA (Impact of Dapagliflozin on Cardiac Remodelling in Patients With Chronic Heart Failure) trial.[94]

OTHER HF THERAPIES. Soluble guanylate cyclase stimulators, such as vericiguat, and myosin activators, such as omecamtiv mecarbil, have shown improvements in LVEF.[95-97] Iron repletion with ferric carboxymaltose may also enhance LV RR, particularly in iron-deficient patients with HF, as demonstrated in the IRON-CRT (Effect of Intravenous Ferric Carboxymaltose on Reverse Remodelling Following Cardiac Resynchronization Therapy) trial.[98]

CRT AND LEFT BUNDLE BRANCH PACING. Cardiac resynchronization therapy has been associated with robust LV RR. An analysis of BLOCK-HF (Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction)[99] and a meta-analysis including the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction), and MIRACLE ICD II (Multicenter InSync ICD Randomized Clinical Evaluation II) trials, among others, showed that cardiac resynchronization therapy was associated with a robust decrease in LV volumes and

TABLE 3 Impact of Medical and Device Therapy on Left Ventricular Reverse Remodeling

	Key Studies	Main Findings
ACE inhibitors	SOLVD (enalapril vs placebo)[81]	↓ LVEDV, ↓ LVESV
Angiotensin receptor blockers	Val-HeFT (valsartan vs placebo)[82]	↓ LVEDV, ↑ LVEF
Mineralocorticoid receptor antagonists	Vizzardi et al[83] (spironolactone vs. placebo) Naser et al[85] (eplerenone vs spironolactone)	Spironolactone: ↓ LVEDV, ↓ LVESV, ↑ LVEF Eplerenone: ↓ LVESV, ↑ LVGLS, = LVEDV
ARNIs	PROVE-HF (ARNI vs placebo)[86] EVALUATE-HF (ARNI vs enalapril)[87]	↑ LVEF, ↓ LVEDVi, ↓ LVESVi
β-blockers	ANZ (carvedilol vs. placebo)[88] MOCHA (carvedilol vs. placebo)[89] CIBIS I (bisoprolol vs. placebo)[90]	Carvedilol: ↑ LVEF, ↓ LVEDVi, ↓ LVESVi Bisoprolol: ↓ LVESD, = LVEDD
SGLT2 inhibitors	EMPA-TROPISM (empagliflozin vs placebo)91 SUGAR-DM-HF (empagliflozin vs placebo)[92] EMPIRE HF (empagliflozin vs placebo)[93] DAPA-MODA (dapagliflozin vs. placebo)[94]	Empagliflozin: ↓ LVEDV, ↓ LVESV, ↑ LVEF Dapagliflozin: ↓ LVEDV, ↓ LVESV vs placebo
Other medical therapies	SOCRATES-REDUCED (vericiguat vs. placebo)[95] VICTORIA (vericiguat vs. placebo)[97] COSMIC-HF (omecamtiv mecarbil vs placebo)[96] IRON-CRT (carboxymaltose ferric vs placebo)[98]	Vericiguat: =/↑ LVEF, = LVEDV, = LVESVi Omecamtiv mecarbil: ↓ LVESD, ↓LVEDD Carboxymaltose ferric: ↑ LVEF, ↓ LVESV, = LVEDV
CRT	REVERSE (CRT-D vs medical therapy)[100] MADIT-CRT (CRT-D vs ICD)[100] MIRACLE ICD II (CRT-D vs ICD)[100] BLOCK-HF (BIV vs non-BIV pacing)[99]	↑ LVEF, ↓ LVEDVi, ↓ LVESVi
M-TEER	Meta-analysis (M-TEER vs placebo)[57]	↑ LVEF, ↓ LVEDV, ↓ LVESV

ACE = angiotensin-converting enzyme; ARNI = angiotensin receptor neprilysin inhibitor; ANZ = Australia/New Zealand Heart Failure Research Collaborative Group; BIV = biventricular; BLOCK-HF = Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction; CIBIS I = Cardiac Insufficiency Bisoprolol Study; COSMIC-HF = Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; DAPA-MODA = Impact on Atrial Remodeling of Dapaglifozin in Patients With Heart Failure; EMPA-TROPISM = Empagliflozin in Non-Diabetic Heart Failure Patients With Reduced Ejection Fraction; EMPIRE HF = Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction; EVALUATE-HF = Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction; IRON-CRT = Effect of Intravenous Ferric Carboxymaltose on Reverse Remodelling Following Cardiac Resynchronization Therapy; LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-diastolic diameter; LVESV = left ventricular end-systolic volume; LVESVi = left ventricular end-systolic volume index; LVGLS = left ventricular global longitudinal strain; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; MIRACLE ICD II = Multicenter InSync ICD Randomized Clinical Evaluation II; MOCHA = Carvedilol in Heart Failure; M-TEER = mitral transcatheter edge-to-edge repair; PROVE-HF = Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes; REVERSE = Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; SGLT2 = sodium-glucose cotransporter 2; SOCRATES-REDUCED = Phase IIb Safety and Efficacy Study of Four Dose Regimens of BAY1021189 in Patients With Heart Failure With Reduced Ejection Fraction Suffering From Worsening Chronic Heart Failure; SOLVD = Effects of Enalapril on Survival in Patients With Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure; SUGAR-DM-HF = Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure; Val-HeFT = Valsartan Heart Failure Trial; VICTORIA = Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction; other abbreviations as in Tables 1 and 2.

increased LVEF.[100] Similarly, left bundle branch area pacing has emerged as a promising alternative, with studies reporting improved LVEF and LV volumes in patients with HFrEF.[101]

PRACTICAL CONSIDERATIONS FOR MANAGEMENT

MANAGEMENT OF PATIENTS WITH SYMPTOMATIC HFimpEF: INSIGHTS FROM DELIVER AND FINEARTS-HF. There is limited evidence on the optimal management of patients with symptomatic HFimpEF, with DELIVER and FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Compared to Placebo in Patients With Heart Failure) providing the only dedicated randomized data in this population.[102,103] Interestingly, a post hoc analysis of the DELIVER trial revealed substantial variability in HF medical therapy among patients with HFimpEF, with nearly 25% receiving either no or only 1 medication at baseline, 44% on 2 agents, and 35% on 3 agents.[104] In DELIVER, dapagliflozin reduced the primary composite outcome of worsening HF or CV death, and the treatment effect was consistent in 1,151 patients with HFimpEF regardless of sex or background GDMT use.[104-106] Meanwhile, FINEARTS-HF provided evidence supporting finerenone in 307 patients with HFimpEF, showing significant reductions in HF events and CV death compared with placebo. These findings suggest that beyond continuation of GDMT in HFimpEF, further optimization of medical therapy with therapies such as sodium-glucose cotransporter 2 inhibitors and nonsteroidal mineralocorticoid receptor antagonists may be important in symptomatic HFimpEF, though further studies are needed to define long-term treatment strategies. In addition, HFimpEF is heterogeneous, and management should be tailored to the underlying etiology and risk profile.

MANAGEMENT OF ASYMPTOMATIC HFimpEF PATIENTS: GDMT DE-ESCALATION AND ICD REPLACEMENT. The TRED-HF (Withdrawal of Pharmacological Treatment

for Heart Failure in Patients With Recovered Dilated Cardiomyopathy) trial, the Quinapril Heart Failure Trial, and an analysis of the EMPEROR (Empagliflozin Outcome Trials in Chronic Heart Failure) program demonstrated a high risk for relapse following drug withdrawal,[107-109] but carefully monitored down-titration may be feasible in select patients with reversible causes (eg, stress cardiomyopathy, peripartum cardiomyopathy, tachycardia-induced cardiomyopathy). Notably, TRED-HF was a small study limited to dilated cardiomyopathy, underscoring the need for larger trials to assess the safety and long-term outcomes of GDMT de-escalation in the heterogeneous HFimpEF population. Additional insights into the risks associated with drug withdrawal are expected from forthcoming analyses of the FINEARTS-HF trial.

ICD management remains a key challenge. Although patients with HFimpEF have a lower risk for arrhythmic events than those with persistent HFrEF, the risk is not eliminated.[31] Conversely, ICD generator replacement carries a 4% risk for potentially major complications (eg, lead dislodgement, infection) and a 7% risk for minor complications (eg, hematoma) within 6 months.[110] Decisions regarding generator replacement should rely solely on LVEF improvement, as fibrosis on CMR may indicate persistent arrhythmic risk. Meanwhile, patients who never experienced ICD interventions during the initial implantation period may have a lower need for ongoing defibrillator protection.[29] Future studies are needed to refine risk stratification strategies for ICD management in HFimpEF.

PHENOTYPE-SPECIFIC CONSIDERATIONS

In ischemic HFimpEF, optimal coronary artery disease management remains essential, including guideline-directed revascularization, antiplatelet therapy, and lipid-lowering therapy. Assessing for hibernating myocardium may help identify patients with potential for further recovery.[46] Dilated cardiomyopathy presents heterogeneity in response to GDMT and arrhythmic risk; patients with pathogenic gene variants linked to arrhythmias may still benefit from ICD therapy, while those with persistent myocardial fibrosis on CMR may require closer monitoring and prolonged GDMT to mitigate LVEF decline.[52,111] In tachycardia-mediated cardiomyopathy, particularly in the context of atrial fibrillation, a common comorbidity in HFimpEF, rate vs rhythm control strategies should be individualized, with catheter ablation considered in select patients. Given the high risk of LVEF relapse with recurrent atrial fibrillation, maintaining sinus rhythm is likely critical. If tachycardia is the sole cause of LV dysfunction, some patients may tolerate gradual weaning of HF therapy with careful monitoring.

THE ROLE OF GENETIC TESTING

Genetic testing may not be universally required in HFimpEF but holds major clinical implications for patients with idiopathic or familial forms. Those carrying pathogenic variants (eg, *TTN*, *LMNA*, *FLNC*) face an increased risk for late LVEF deterioration, reinforcing the need for prolonged GDMT even after apparent recovery.[52] Certain mutations, such as *LMNA*, *FLNC*, and *RBM20*, confer high arrhythmic risk, potentially warranting ICD placement despite LVEF normalization. Additionally, identifying a pathogenic variant allows cascade genetic testing, facilitating early screening and intervention for at-risk relatives. Patients with HFimpEF with high-risk genetic mutations may benefit from closer surveillance, including frequent echocardiography, CMR, or ambulatory rhythm monitoring. Given these implications, genetic testing should be integrated into phenotype-specific risk stratification rather than viewed as a stand-alone diagnostic tool.

ONGOING TRIALS

Several ongoing trials were designed to address critical knowledge gaps in HFimpEF management. PROSPER-HF (Sacubitril/Valsartan Versus Valsartan in Heart Failure With Improved Ejection Fraction; NCT04803175) is evaluating the safety and efficacy of sacubitril/valsartan vs valsartan specifically in patients with HFimpEF. Additionally, a trial investigating GDMT tapering in HFimpEF (NCT06724653) is set to begin, while WEAN-HF (Withdrawal of Treatment for Heart Failure Patients With Recovery From Tachycardia-Induced Cardiomyopathy; NCT06128980) is already assessing the safety of HF therapy withdrawal in patients recovering from tachycardia-induced cardiomyopathy. The ongoing With-HF (Pilot Study on Withdrawal of Spironolactone Among Heart Failure With Improved Ejection Fraction; NCT04367051) will test the impact of spironolactone treatment withdrawal among patients with HFimpEF, and an upcoming secondary analysis from FINEARTS-HF will evaluate the impact of finerenone withdrawal after the randomized phase.

Beyond HFimpEF-specific trials, several ongoing studies of HF with mildly reduced ejection fraction and HFpEF (NCT04435626, NCT05636176, NCT04847557)

are now including patients with prior LVEF ≤40%, which may provide additional insights into treatment strategies for this evolving HF phenotype.

CLINICAL UNCERTAINTY AND ONGOING CONTROVERSY

Despite growing recognition, HFimpEF remains a poorly understood and understudied HF phenotype with key clinical questions that require further investigation:

- What is the optimal LVEF improvement threshold to define HFimpEF? LVEF trajectory is often nonlinear, with potential fluctuations over time. Although the universal HF definition of HFimpEF requires a ≥10% increase in LVEF from a baseline value ≤40%, it remains unclear whether smaller LVEF gains or alternative imaging modalities such as CMR could better define clinically meaningful improvement. Additionally, the optimal timing for follow-up LVEF assessments to establish HFimpEF remains unclear.
- Should GDMT be continued in all patients with HFimpEF? Current evidence, based largely on the TRED-HF trial, suggest that GDMT withdrawal is associated with high relapse risk.[107,112] However, that trial was small and focused on dilated cardiomyopathy. It remains uncertain whether specific HFimpEF subgroups could safely tolerate de-escalation.
- Should GDMT be further intensified after LVEF has improved? Although discontinuation of GDMT seems to increase the risk for LVEF deterioration in patients with HFimpEF,[107,112] it is unclear whether continued up-titration of GDMT beyond baseline targets is necessary once LVEF has improved and in the absence of symptoms.
- How should ICD and cardiac resynchronization therapy generator replacement decisions be approached in HFimpEF? Risk stratification for ICD replacement in patients with HFimpEF remains challenging. Given that arrhythmic risk may persist despite LVEF improvement, further studies are needed to delineate the role of advanced imaging, biomarkers, and genetic testing in ICD decision making. Additionally, the role of electrophysiological testing in refining ICD indications is uncertain.[113]
- What is the long-term trajectory of these patients? HFimpEF is increasingly recognized as a dynamic state, with LVEF decline occurring in up to 50% of cases. However, the optimal surveillance strategy remains undefined. Current practice suggests follow-up every 6 months during the first 3 years, with periodic clinical assessments, NT-proBNP measurement, and echocardiography.[114]
- What is the role of biomarkers, imaging, and genetic testing in patients with HFimpEF? Biomarkers, imaging, and genetic testing may refine risk stratification and guide management in HFimpEF, but their roles remain uncertain. NT-proBNP increases have been linked to LVEF relapse after GDMT withdrawal, potentially useful for therapy monitoring. CMR can identify fibrosis and extracellular volume expansion, which may help predict relapse and inform ICD management, though routine use is limited. Genetic testing, particularly in idiopathic HFimpEF, may identify patients at high risk for arrhythmic events despite EF recovery. Future studies should assess whether combining these tools can optimize GDMT tapering, surveillance, and ICD decision making.

CONCLUSIONS

HFimpEF represents a dynamic HF phenotype characterized by LVEF improvement with persistent risk for deterioration and adverse outcomes. Although achieving LV RR is associated with a better prognosis than persistent HFrEF, these patients remain vulnerable to relapse, underscoring the need for ongoing surveillance and sustained GDMT. Emerging data from DELIVER and FINEARTS-HF provide the first evidence for further drug therapy optimization in symptomatic HFimpEF, yet major knowledge gaps remain regarding long-term management, risk stratification, and the role of GDMT de-escalation. Future research integrating biomarkers, advanced imaging, and genetic profiling will be essential to refining individualized treatment strategies and improving long-term outcomes in this evolving HF population.

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