



# Clinical Perspective of Myocardial Recovery and Improvement: Definitions, Prevalence, and Relevance

REVIEW

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## ABSTRACT

Partial or complete imaging resolution of left ventricular (LV) systolic dysfunction in patients with heart failure with reduced ejection fraction (HFrEF) has gone by many names in the past few decades, including LV recovery, remission, reverse remodeling, and, most recently, improvement. This phenomenon has been described in a variety of clinical scenarios, including removal of an acute myocardial insult, unloading with durable LV assist devices, and treatment with various devices as well as pharmacotherapies, termed guideline-directed medical therapy (GDMT). Irrespective of definition, systolic improvement is associated with improved clinical outcomes compared to persistent systolic dysfunction. In the past few years, systolic improvement has been distinguished from HFrEF as a new clinical entity referred to as HF with improved EF (HFimpEF). Given the relative novelty of this condition, there is a paucity of data with regard to the clinical trajectory and management of this population. In this review, we describe the history of myocardial improvement terminology and explore notable findings that have led to the delineation of HFimpEF. Additionally, we highlight the importance of understanding LV trajectory and the potential opportunity for new GDMT management for clinicians when treating patients with HFimpEF.

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## INTRODUCTION

Myocardial recovery, where there are demonstrable changes in left ventricular (LV) structure and systolic function on imaging, is often thought of as the holy grail of the subspecialty of advanced heart failure (HF). The term has commonly been associated with reversal of HF syndrome and normalization of ventricular function with mechanical unloading from LV assist devices (LVADs). The sometimes-controversial debate of “recovery versus remission” has become less relevant in recent clinical settings, and the notion of plotting a trajectory in a particular patient’s myocardial recovery (recently redefined as improvement) course has become more useful. Here we discuss the concepts of myocardial recovery and remission as they relate to HF with improved ejection fraction (HFimpEF). Additionally, we explore the prevalence of myocardial improvement in various clinical scenarios and the significance of delineating responders from nonresponders as it relates to patient care and potential future research endeavors.

## HISTORICAL PERSPECTIVES AND DEFINITIONS

The observation of myocardial recovery was historically associated with spontaneous LV recovery after transient severe LV dysfunction due to an acute neurohormonal insult, tachyarrhythmia (with resolution of systolic dysfunction with sinus rhythm restoration), or hyperthyroidism.<sup>1,2</sup> The thought, at that time, was that following these short-lived insults, the cardiac structure returned to normal, both intrinsically at the level of the myocyte and extrinsically regarding LV volumes and global function. In a seminal paper over a decade ago, Mann and Burkoff put forth the idea that partial recovery of the HF with reduced EF (HFrEF) phenotype consisted of EF improvement between 40% and 50% with residual abnormalities at the (1) myocyte, (2) extracellular matrix, and (3) ventricular structure and performance levels, but true cardiomyopathy recovery included normalization of all three components and a resultant EF > 50%.<sup>3</sup>

However, contrary to this theory, subsequent evidence demonstrated that the previously determined “fully-recovered” cardiomyopathies indeed were not normal. A classic example is the case of Takotsubo cardiomyopathy; Scally and others have shown that, despite a return to normal LVEF and normalization of serum biomarkers, there are persistent abnormalities in apical circumferential and global longitudinal strain (GLS) in those patients considered to be “recovered.” Increased native T1 mapping values on cardiac magnetic resonance (CMR) imaging persist as

well, reinforcing the concept of myocardial remission as a distinct clinical and pathobiological entity.<sup>4</sup>

Since then, numerous studies have examined the underlying basis of remission, frequently termed LV reverse remodeling (LVRR). While this topic is outside the scope of this article, the current understanding of LVRR is not simply a “replica in reverse” of the molecular and cellular pathways that become dysregulated during forward/maladaptive LV remodeling. Rather, LVRR represents a distinct, multilevel process that leads to a less pathological myocardial steady state.<sup>5,6</sup>

The experience with the acute cardiomyopathies paved the way for expanded clinical scenarios of recovery/remission, most notably with regard to chronic LV unloading with durable LVADs. After years of studying LV unloading and strategies for recovery, the dedicated Remission from Stage D Heart Failure (REStage-HF) trial added intensive neurohormonal therapy for HF plus LV unloading and demonstrated a 40% recovery rate sufficient to meet the primary outcome, defined as sufficient improvement of myocardial function; this allowed for LVAD explantation within 18 months with sustained remission from death/mechanical circulatory support/heart transplantation at 12 months.<sup>7</sup> This was a culmination of sorts of over a decade of clinical experience and discovery by Birks and colleagues with LV unloading with durable LVADs.

In addition, it is now widely recognized that, when exposed to highly effective neurohormonal therapies (collectively termed guideline-directed medical therapy [GDMT]), a subset of HFrEF patients undergo LVRR and functional improvement.<sup>8,9</sup> Further, LVRR has been observed in patients who have received guideline-indicated implantable devices, especially cardiac resynchronization therapy (CRT).<sup>10,11</sup> In clinical trials, CRT receipt is associated with significant reduction in LV volumes and improvement in LVEF.<sup>12,13</sup> This subset of GDMT and device “responders” is now referred to as HFimpEF, previously known as recovered EF (HFrecEF),<sup>14</sup> and has recently been recognized as a distinct clinical entity in the American Heart Association/American College of Cardiology/Heart Failure Society of America’s (AHA/ACC/HFSA) clinical guideline.<sup>15</sup>

Despite our knowledge of the phenomenon of myocardial recovery/improvement in clinical practice, it was only recently that a consensus statement definition was put forth for HFrecEF, which included: (1) a documented history of HFrEF with LVEF ≤ 40%, (2) ≥ 10% absolute increase in LVEF, and (3) resultant LVEF > 40% with an accompanied reduction in LV volumes.<sup>14</sup> This delineation has garnered support from a recent consensus statement on the universal definition of HF from the HFSA/European Society of Cardiology/Japanese Heart Failure Society, with an iteration in terminology from HFrecEF to HFimpEF. This change was based on totality of the evidence that there

is a persistent HF risk in this population, and remission/improvement is the more accurate description.<sup>16</sup> A now contemporary term, the HFimpEF classification, is also supported by the most recent AHA/ACC/HFSA HF guidelines.<sup>15</sup> Notably, these guidelines do not specify a criterion for an absolute increase in LVEF.

## CURRENT UNDERSTANDING OF IMPROVEMENT

### PREVALENCE

A potential reason for HFimpEF only recently becoming incorporated into the guidelines is the varying estimates of the proportion of patients with improved LVEF. Due to

the heterogeneity in clinical populations and variable definitions in both observational and clinical trial datasets, improvement rates range widely (Table 1).<sup>9,17-36</sup> Over a decade ago, work from the IMPROVE-HF study—a large observational cohort of outpatients with HFrEF enrolled in a performance measure intervention—demonstrated that partial improvement was possible with current available pharmacotherapies, which at the time included only angiotensin-converting enzyme inhibitors and beta blockers. However, despite not being exposed to either angiotensin receptor/neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist, or sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapies, almost one-third of patients experienced meaningful improvement of myocardial function, with nearly a doubling of LVEF function

| FIRST AUTHOR                 | PUBLICATION YEAR | STUDY SIZE (n) | POPULATION                                 | BASELINE THERAPIES (> 70%)    | IMPROVEMENT EF CUTOFF   | FREQUENCY OF IMPROVEMENT (%) |
|------------------------------|------------------|----------------|--------------------------------------------|-------------------------------|-------------------------|------------------------------|
| Cioffi <sup>18</sup>         | 2004             | 110            | Chronic HFrEF (EF < 40%)                   | Digoxin, diuretics            | > 51%                   | 18%                          |
| McNamara <sup>19</sup>       | 2011             | 373            | Recent onset DCM & myocarditis (EF ≤ 40%)  | ACE, BB                       | ≥ 50%                   | 25%                          |
| Merlo <sup>20</sup>          | 2011             | 242            | Chronic DCM                                | ACE, BB, digoxin              | Increase ≥ 10% or ≥ 50% | 37%                          |
| Wilcox <sup>21</sup>         | 2012             | 3,994          | Chronic HFrEF (EF ≤ 35%)                   | ACE, BB                       | Increase > 10%          | 29%                          |
| Dunlay <sup>22</sup>         | 2012             | 674            | Chronic HF (EF < 50%)                      | Not given                     | ≥ 50%                   | 39%                          |
| Merlo <sup>24</sup>          | 2015             | 408            | DCM (EF < 50%)                             | ACE/ARB, BB                   | ≥ 50%                   | 15%                          |
| Florea <sup>9</sup>          | 2016             | 4,410          | Chronic HFrEF (EF < 35%)                   | ACE, diuretics                | > 40%                   | 9%                           |
| Kalogeropoulos <sup>25</sup> | 2016             | 2,166          | Chronic HFrEF (EF ≤ 40%)                   | ACE/ARB, BB                   | > 40%                   | 16%                          |
| Lupon <sup>26</sup>          | 2017             | 940            | Chronic HF (EF < 45%)                      | ACE/ARB, BB, diuretics        | ≥ 45%                   | 25%                          |
| Agra Bermejo <sup>27</sup>   | 2018             | 242            | Chronic HFrEF (EF ≤ 40%)                   | ACE/ARB, BB, diuretics        | > 40%                   | 52%                          |
| Chang <sup>28</sup>          | 2018             | 318            | African-American, Chronic HFrEF (EF < 35%) | ACE/ARB, BB, diuretics        | > 40%                   | 19%                          |
| Ghimire <sup>29</sup>        | 2019             | 3,124          | Chronic HFrEF (EF ≤ 40%)                   | ACE, BB                       | Increase ≥ 10%          | 38%                          |
| He <sup>30</sup>             | 2021             | 9,491          | Meta-analysis Chronic HFrEF                | Varied                        | Varied                  | 23%                          |
| Zhang <sup>31</sup>          | 2021             | 1,160          | Chronic HFrEF (EF < 40%)                   | ACE/ARB, BB, MRA <sup>†</sup> | > 40% & increase ≥ 10%  | 25%                          |
| Yang <sup>32</sup>           | 2022             | 262            | Chronic HFrEF (EF ≤ 40%)                   | BB, MRA                       | > 40% & increase ≥ 10%  | 46%                          |
| Goh <sup>33</sup>            | 2023             | 407            | Chronic HFrEF (NICM; EF ≤ 40%)             | ACE/ARB, BB                   | > 40% & increase ≥ 10%  | 34%                          |
| Liu <sup>34</sup>            | 2023             | 573            | Chronic HFrEF (EF ≤ 40%)                   | ACE/ARB/ARNI, BB              | > 40% & increase ≥ 10%  | 37%                          |
| Mohebi <sup>36</sup>         | 2023             | 416            | Chronic HFrEF (EF < 35%)                   | ARNI, BB                      | ≥ 35%                   | 61%                          |
| Romero <sup>35</sup>         | 2024             | 1,307          | Chronic HFrEF (EF ≤ 40%)                   | ACE/ARB/ARNI                  | > 40% & increase ≥ 10%  | 39%                          |

**Table 1** Prevalence of improvement from observational cohorts and subgroup analyses of clinical trials.\* Modified from Gulati and Udelson.<sup>17</sup> EF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; DCM: dilated cardiomyopathy; ACE: angiotensin-converting enzyme inhibitor; BB: beta blocker; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor/neprilysin inhibitor.

\*Select studies presented and not intended to be an exhaustive list.

†MRA only > 70% in persistent HFrEF patients

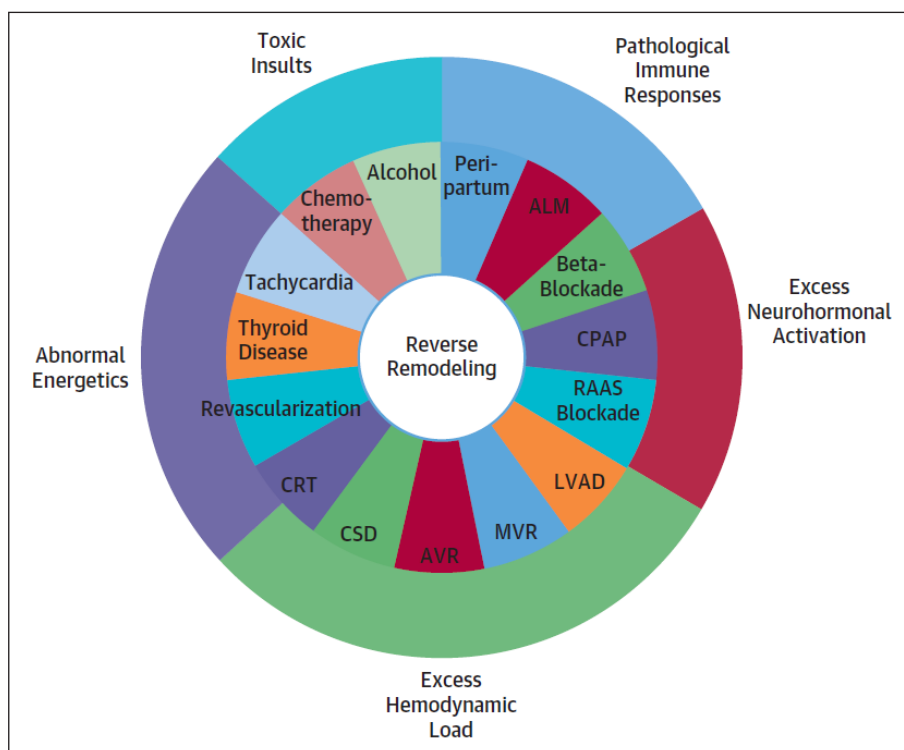
(from 25% to 46%).<sup>21</sup> In a meta-analysis, when multiple definitions of myocardial recovery/improvement are combined, the prevalence estimate was lower at 22.6% at a mean follow-up of 3.8 years.<sup>30</sup> The prevalence of HFimpEF is likely somewhere between currently available estimates. Further, multicentered, diverse analyses are necessary to refine these estimates by duration of HF, cardiomyopathy type, and type and duration of HF therapies.

### IMPORTANCE OF UNDERLYING ETIOLOGY AND CLINICAL PREDICTORS

Determining the etiology of myocardial dysfunction is crucial to estimating the probability of achieving myocardial remission or HFimpEF status. Simply stated, the “etiology of the cardiomyopathy matters,” and the nature and duration of the myocardial insult modulate improvement status. In reality, it is often challenging in clinical practice to determine the exact inciting myocardial insult, which results in many patients being labeled as idiopathic nonischemic cardiomyopathy. Figure 1 shows many of the toxin, inflammation, and abnormal energetic insults that, when removed, frequently result in spontaneous improvement in LV function and LVRR.<sup>1</sup>

In clinical practice, the improvement in ventricular function is often highest in cases of adverse metabolic

or energetic milieu, such as the case of tachycardia-mediated and abnormal thyroid-associated (both hyperthyroidism and hypothyroidism) LV dysfunction. Cardiomyopathies due to abnormal immune responses, such as peripartum cardiomyopathy (PPCM), also have higher rates of improvement compared to idiopathic dilated cardiomyopathy (DCM). In one large European-based registry analysis, 46.5% of 465 patients with PPCM had myocardial recovery, defined as baseline LVEF  $\leq$  45% and follow-up LVEF  $\geq$  50% at 6 months.<sup>37</sup> Similarly, in their analysis of the IMAC2 registry, Cooper et al. demonstrated that 48% of PPCM patients achieve an LVEF  $\geq$  50% from a baseline of  $\leq$  40%, which was significantly higher at 6 months than rates in other groups (19% in men; 34% in non-PPCM women,  $P = .002$ ).<sup>38</sup> Improvement in LV function also can be seen after the discontinuation of cardiotoxic agents, including alcohol<sup>39</sup> and monoclonal antibodies.<sup>40</sup> For example, in one small Spanish analysis, > 40% of patients with alcohol-associated cardiomyopathy developed LVEF recovery (defined as follow-up LVEF  $\geq$  40% and increase in absolute LVEF by  $\geq$  10%) with a reduction in or abstinence of alcohol intake.<sup>41</sup> In addition to etiology, a number of other clinical, imaging, and biochemical markers are linked to varying degrees of LVRR (Table 2), although their description is outside the scope of this review.



**Figure 1** Categorization of frequently encountered myocardial insults in clinical practice. The outer ring represents pathobiologic insults that can result in left ventricular ejection fraction reduction. The middle ring represents either treatments that can result in left ventricular reverse remodeling (LVRR) or scenarios where LVRR can occur if the insult is removed. Used with permission from Hellawell and Marguiles.<sup>1</sup> ALM: acute lymphocytic myocarditis; CPAP: continuous positive airway pressure; RAAS: renin-angiotensin-aldosterone system; LVAD: left ventricular assist device; MVR: mitral valve repair/replacement; AVR: aortic valve replacement; CSD: cardiac support device; CRT: cardiac resynchronization therapy

| PREDICTOR CATEGORY         | PREDICTORS OF REVERSE LV REMODELING                                                        |
|----------------------------|--------------------------------------------------------------------------------------------|
| <b>Clinical parameters</b> | Nonischemic etiology                                                                       |
|                            | Shorter duration of HF                                                                     |
|                            | Female sex                                                                                 |
|                            | No LBBB                                                                                    |
|                            | LBBB in CRT                                                                                |
| <b>Genetic factors</b>     | Pathogenic gene variants not involving structural cytoskeletal proteins or Z-disk proteins |
| <b>Echo/CMR imaging</b>    | Greater contractility on strain imaging                                                    |
|                            | LGE absence                                                                                |
| <b>Biomarkers</b>          | Lower NT-proBNP                                                                            |
|                            | Lower troponin                                                                             |
|                            | Lower sST2                                                                                 |
|                            | Galectin-3, emerging biomarkers (mimecan, miRNAs, orexin)                                  |

**Table 2** Clinical predictors of myocardial recovery. Used with permission from Wilcox et al.<sup>14</sup> LV: left ventricular; HF: heart failure; LBBB: left bundle branch block; Echo: echocardiography; CRT: cardiac resynchronization therapy; CMR: cardiac MRI; LGE: late gadolinium enhancement; NT-proBNP: N-terminal pro-b-type natriuretic peptide; sST2: solute suppression of tumorigenicity 2

## CLINICAL RELEVANCE

### WHY DO WE CARE ABOUT MYOCARDIAL RECOVERY/IMPROVEMENT IN CLINICAL PRACTICE?

Regardless of the specific criteria or thresholds used to categorize HFimPEF, the trend remains consistent: LVRR leads to favorable clinical outcomes compared with persistently reduced LVEF.<sup>26,27,35</sup> Myocardial improvement is associated with substantially improved clinical outcomes, including reduction in hospitalization rates and death, when compared with persistent HFREF. For example, compared to patients with myocardial improvement defined as LVEF < 40% to > 40% with an absolute increase in LVEF of  $\geq 10\%$ , those with persistent HFREF have a near two-fold increased risk of all-cause mortality (HR 1.973; 95% CI, 1.206-3.226,  $P = .007$ ) and of all-cause hospitalization (HR 1.740; 95% CI, 1.336-2.267,  $P = .000$ ).<sup>31</sup> Hence, myocardial improvement is an important target for therapy and is a defined, shared goal for the clinician and their patient. The inability to achieve LVRR or persistent HF symptoms offers the clinician the ability to identify patients at risk for progressive, or ACC/AHA stage D, HFREF and thereby who may be candidates for advanced therapies.

### WHY IS THE DISTINCTION OF CLINICAL MYOCARDIAL REMISSION IMPORTANT?

The concept of recovery versus remission from HF in DCM led to the seminal Therapy withdrawal in REcovered Dilated cardiomyopathy-Heart Failure (TRED-HF) trial, arguably the only dedicated clinical trial that was performed in what was thought to be a truly “recovered” patient population at

the time. In this small but well-powered study, 51 patients with prior DCM and LVEF  $\leq 40\%$  who had recovered LVEF to  $\geq 50\%$ , were asymptomatic, on GDMT, had normal LV end-diastolic volume (LVEDV) index by CMR imaging, and normal biomarker profiles (normal N-terminal pro-B-type natriuretic peptide [NT-proBNP]) were randomized to GDMT withdrawal. Importantly, within 6 months of GDMT withdrawal, 40% of patients met the primary outcome of relapsing HF (defined as either reduction in LVEF > 10% to < 50%, increase in LVEDV > 10% to higher than the normal range, two-fold rise in NT-proBNP, or clinical evidence of HF). Notably, 13 of the 20 individuals who met the primary study end point did so within 16 weeks of treatment withdrawal.<sup>42</sup> Given this high relapse rate of LV dysfunction, the field of myocardial recovery could have paused, but most clinicians in the field leaned into the idea of remission as a laudable goal for patients as the primary lesson of TRED-HF and remain steadfast in trying to understand the biology of remission/recovery.

As previously mentioned, an example of this commitment to remission from HF was the combination of LV unloading with LVAD support and high-dose GDMT utilized in the RESTAGE-HF trial. In this prospective multicenter study, 36 of 40 randomized patients with advanced HF secondary to nonischemic cardiomyopathy, age < 60 years, with starting LVEF < 25%, and short duration of HF ( $\leq 5$  years) underwent protocolized LVAD speed optimization with the goal of maximal LV unloading. Subjects simultaneously underwent aggressive, protocolized titration of multiple pharmacological agents (lisinopril, carvedilol, spironolactone, digoxin, and losartan) to maximally tolerated doses. Within 18 months, 50% ( $n =$

18/36) of patients who completed the study protocol met criteria for LVAD explantation, including an LVEF > 45% and reduction in LV dimensions, with an additional patient meeting criteria after 18 months.<sup>7</sup> Through this analysis, Birks and colleagues demonstrated that when remission is a clinical target and the population is enriched, remission is achievable. Learnings from TRED-HF reinforce the concept that GDMT must be continued among LVAD explant patients in addition to close monitoring with biomarkers and serial echocardiography imaging.

Another recent area of clinical inquiry relates to the timing of LVEF improvement, which is likely very different based on the individual patient, and most patients do not demonstrate improvement at the same rate.<sup>43</sup> Especially within the first year of de novo diagnosis of HFrEF, there is heterogeneity in response to GDMT, potential for spontaneous improvement in LVEF, and the possibility of early versus later improvement. Additionally, it has been observed that a substantial proportion of patients develop LVEF improvement beyond 1 year, with some demonstrating improvement after 2 years.<sup>44</sup>

Building on this observation that the timing of improvement can be highly variable is a subgroup analysis from the Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes (PROVE-HF) trial.<sup>36</sup> In the original PROVE-HF trial, patients exposed to sacubitril/valsartan (ARNI) demonstrated improvement in LVEF at 6 months and further improvement at 12 months.<sup>45</sup> In a subgroup analysis of 416 patients, 61.3% of those eligible for implantable cardioverter-defibrillator (ICD) implantation (LVEF < 35%) at trial inclusion improved their LVEF to  $\geq$  35% after 12 months of ARNI exposure. In their model, the most significant factors that predicted lack of LVEF improvement were lower baseline LVEF, higher LV mass index, longer duration of HF, younger age, lower baseline, and 14-day change in NT-proBNP (area under the curve [AUC] for predicting lack of LVEF improvement of 0.92 and 0.86 in the training and validation cohorts, respectively).<sup>36</sup> Current guidelines suggest ICD implantation if LVEF remains < 35% after 90 days of maximally tolerated GDMT, but this subgroup analysis is an important reminder that LVRR is highly variable, and many patients may still experience remodeling and LVEF improvement even out to 12 months from new therapy introduction.

From this arises a major clinical unmet need: lack of available models to predict an individual patient's disease trajectory, and, if they have LVEF improvement, the time necessary to achieve improvement. Based on current available data and our clinical experience, we have previously proposed that there are at least three trajectories for systolic progression in the HFimpEF population: continued LVEF

improvement, LVEF stability/remission, and LVEF decline.<sup>46</sup> However, the factors associated with these trajectories are not well-delineated. There is some evidence that imaging markers, specifically GLS, may be useful in predicting eventual LVEF deterioration and adverse cardiovascular outcomes.<sup>47</sup> It remains to be determined if these factors are clinically modifiable to improve outcomes. Additionally, further analysis is necessary to elucidate the time course to achieving these trajectories and to determine if different subclasses of patients may experience these trajectories at different time points.

### SHOULD WE MANAGE PATIENTS WITH SOME DEGREE OF REMISSION ANY DIFFERENTLY?

The real question may be: Should we escalate therapy? (For instance, we may ask, "Do you add an SGLT2i in HFimpEF?") While the TRED-HF trial solidified that most patients who experience improvement from HFrEF after exposure to GDMT should remain on lifelong therapies, the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial<sup>48</sup> demonstrated that addition of the SGLT2i dapagliflozin is beneficial even in the HFimpEF population. In this trial, patients with an LVEF > 40% were randomized to dapagliflozin or placebo. Importantly, the inclusion criteria encompassed patients with LVEF improvement by the ACC/AHA/HFSA guidelines (defined as prior LVEF  $\leq$  40% and improved to > 40%).<sup>15</sup>

In a secondary analysis of the trial, patients with LVEF improvement demonstrated substantial benefit from dapagliflozin compared with placebo with lower risk of the primary composite outcome of cardiovascular death and worsening HF requiring admission or urgent HF evaluation (HR 0.74; 95% CI, 0.56-0.97). Additionally, these patients experienced improved HF-related symptom burden while on dapagliflozin.<sup>49</sup> There was also an observed reduction in cardiovascular death compared to placebo (HR 0.62; 95% CI, 0.41-0.96), which was attributed to decreased rates of sudden cardiac death.<sup>50</sup> Despite these promising findings, it is not currently known if SGLT2i therapy will result in further improvements in LVEF in this group or if it may mitigate risk of future LVEF decline among the HFimpEF population. Irrespective, the DELIVER trial represents a step toward targeted therapy in HFimpEF.

To this notion, subclinical effects of SGLT2i in addition to the HFimpEF GDMT regimen on myocardial structure and mechanics are unknown. Additionally, in one small prospective trial of SGLT2i (in this case empagliflozin) in patients with diabetes mellitus and no known cardiovascular disease, SGLT2i prescription was associated with improvements in GLS at 1- and 6-month intervals in



those with baseline abnormal GLS (< 16.5%).<sup>51</sup> It is feasible that the benefits of SGLT2i use in the HFimpEF population observed in the DELIVER trial may be partly related to similar reverse remodeling mechanisms. However, further endeavors into this concept are needed before definitive conclusions can be drawn.

## CONCLUSION

Myocardial improvement remains a highly relevant target for therapy. Although the prevalence varies widely and is influenced by underlying etiology of cardiomyopathy, understanding the predictors and mechanisms of systolic improvement can aid in better patient selection for future clinical studies. Recent clinical trials have given clinicians insight into initial management strategies for the HFimpEF population. Future endeavors must now be aimed at understanding long-term remission in HFimpEF, categorizing LVEF trajectory, and preventing recurrent systolic decline and, thereby, adverse outcomes in this population.

## KEY POINTS

- The current understanding of myocardial improvement has come a long way in the past few decades, but further analyses are needed to understand the factors driving different trajectories in heart failure with improved ejection fraction (HFimpEF).
- Rigorous use of the accepted definition of HFimpEF is required to help streamline future knowledge acquisition of this condition.
- Patients with HFimpEF should be continued on their guideline-directed medical therapy regimens indefinitely, and the addition of an SGLT2i should be considered in this patient population.

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## COMPETING INTERESTS

Dr. Wilcox is a consultant for Abbott, Abiomed, Astra Zeneca, and Boehringer Ingelheim. The other authors have no competing interests to declare.

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## REFERENCES

1. **Hellawell JL, Margulies KB.** Myocardial Reverse Remodeling. *Cardiovasc Ther.* 2012 Nov 25;30(3):172-181. doi:[10.1111/j.1755-5922.2010.00247.x](https://doi.org/10.1111/j.1755-5922.2010.00247.x)
2. **Givertz MM, Mann DL.** Epidemiology and Natural History of Recovery of Left Ventricular Function in Recent Onset Dilated Cardiomyopathies. *Curr Heart Fail Rep.* 2013 Dec;10(4):321-330. doi:[10.1007/s11897-013-0157-5](https://doi.org/10.1007/s11897-013-0157-5)
3. **Mann DL, Burkhoff D.** Is Myocardial Recovery Possible and How Do You Measure It? *Curr Cardiol Rep.* 2012 Jun;14(3):293-298. doi:[10.1007/s11886-012-0264-z](https://doi.org/10.1007/s11886-012-0264-z)
4. **Scally C, Rudd A, Mezincescu A, et al.** Persistent Long-Term Structural, Functional, and Metabolic Changes After Stress-Induced (Takotsubo) Cardiomyopathy. *Circulation.* 2018 Mar 6;137(10):1039-1048. doi:[10.1161/CIRCULATIONAHA.117.031841](https://doi.org/10.1161/CIRCULATIONAHA.117.031841)
5. **Hnat T, Veselka J, Honek J.** Left Ventricular Reverse Remodelling and Its Predictors in Non-Ischaemic Cardiomyopathy. *ESC Heart Fail.* 2022 Aug;9(4):2070-2083. doi:[10.1002/ehf2.13939](https://doi.org/10.1002/ehf2.13939)
6. **Boulet J, Mehra MR.** Left Ventricular Reverse Remodeling in Heart Failure: Remission to Recovery. *Structural Heart.* 2021 Sep;5(5):466-481. doi:[10.1080/24748706.2021.1954275](https://doi.org/10.1080/24748706.2021.1954275)
7. **Birks EJ, Drakos SG, Patel SR, et al.** Prospective Multicenter Study of Myocardial Recovery Using Left Ventricular Assist Devices (RESTAGE-HF [Remission from Stage D Heart

- Failure)): Medium-Term and Primary End Point Results. *Circulation*. 2020 Nov 24;142(21):2016-2028. doi:[10.1161/CIRCULATIONAHA.120.046415](https://doi.org/10.1161/CIRCULATIONAHA.120.046415)
8. **Nauta JF, Santema BT, van der Wal MHL**, et al. Improvement in Left Ventricular Ejection Fraction After Pharmacological Up-Titration in New-Onset Heart Failure with Reduced Ejection Fraction. *Neth Heart J*. 2021 Jul;29(7-8):383-393. doi:[10.1007/s12471-021-01591-6](https://doi.org/10.1007/s12471-021-01591-6)
  9. **Florea VG, Rector TS, Anand IS, Cohn JN**. Heart Failure With Improved Ejection Fraction: Clinical Characteristics, Correlates of Recovery, and Survival: Results From the Valsartan Heart Failure Trial. *Circ Heart Fail*. 2016 Jul;9(7):e003123. doi:[10.1161/CIRCHEARTFAILURE.116.003123](https://doi.org/10.1161/CIRCHEARTFAILURE.116.003123)
  10. **Brambatti M, Guerra F, Matassini MV**, et al. Cardiac Resynchronization Therapy Improves Ejection Fraction and Cardiac Remodelling Regardless of Patients' Age. *EP Europace*. 2013 May;15(5):704-710. doi:[10.1093/europace/eus376](https://doi.org/10.1093/europace/eus376)
  11. **Antonio N, Teixeira R, Coelho L**, et al. Identification of 'Super-Responders' to Cardiac Resynchronization Therapy: The Importance of Symptom Duration and Left Ventricular Geometry. *Europace*. 2009 Mar;11(3):343-349. doi:[10.1093/europace/eup038](https://doi.org/10.1093/europace/eup038)
  12. **Linde C, Abraham WT, Gold MR**, et al. Randomized Trial of Cardiac Resynchronization in Mildly Symptomatic Heart Failure Patients and in Asymptomatic Patients with Left Ventricular Dysfunction and Previous Heart Failure Symptoms. *J Am Coll Cardiol*. 2008 Dec 2;52(23):1834-1843. doi:[10.1016/j.jacc.2008.08.027](https://doi.org/10.1016/j.jacc.2008.08.027)
  13. **St John Sutton MG, Plappert T, Abraham WT**, et al. Effect of Cardiac Resynchronization Therapy on Left Ventricular Size and Function in Chronic Heart Failure. *Circulation*. 2003 Apr 22;107(15):1985-1990. doi:[10.1161/01.CIR.0000065226.24159.E9](https://doi.org/10.1161/01.CIR.0000065226.24159.E9)
  14. **Wilcox JE, Fang JC, Margulies KB, Mann DL**. Heart Failure With Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2020 Aug 11;76(6):719-734. doi:[10.1016/j.jacc.2020.05.075](https://doi.org/10.1016/j.jacc.2020.05.075)
  15. **Heidenreich PA, Bozkurt B, Aguilar D**, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022 May 3;145(18):e895-e1032. doi:[10.1161/cir.0000000000001063](https://doi.org/10.1161/cir.0000000000001063)
  16. **Bozkurt B, Coats AJS, Tsutsui H**, et al. 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 Mar;23(3):352-380. doi:[10.1002/ehjhf.2115](https://doi.org/10.1002/ehjhf.2115)
  17. **Gulati G, Udelson JE**. Heart Failure with Improved Ejection Fraction: Is It Possible to Escape One's Past? *JACC Heart Fail*. 2018 Sep;6(9):725-733. doi:[10.1016/j.jchf.2018.05.004](https://doi.org/10.1016/j.jchf.2018.05.004)
  18. **Cioffi G, Stefenelli C, Tarantini L, Opasich C**. Chronic Left Ventricular Failure in the Community: Prevalence, Prognosis, and Predictors of the Complete Clinical Recovery with Return of Cardiac Size and Function to Normal in Patients Undergoing Optimal Therapy. *J Card Fail*. 2004 Jun;10(3):250-257. doi:[10.1016/j.cardfail.2003.10.002](https://doi.org/10.1016/j.cardfail.2003.10.002)
  19. **McNamara DM, Starling RC, Cooper LT**, et al. Clinical and Demographic Predictors of Outcomes in Recent Onset Dilated Cardiomyopathy: Results of the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 Study. *J Am Coll Cardiol*. 2011 Sep 6;58(11):1112-1118. doi:[10.1016/j.jacc.2011.05.033](https://doi.org/10.1016/j.jacc.2011.05.033)
  20. **Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G**. Prevalence and Prognostic Significance of Left Ventricular Reverse Remodeling in Dilated Cardiomyopathy Receiving Tailored Medical Treatment. *J Am Coll Cardiol*. 2011 Mar 29;57(13):1468-1476. doi:[10.1016/j.jacc.2010.11.030](https://doi.org/10.1016/j.jacc.2010.11.030)
  21. **Wilcox JE, Fonarow GC, Yancy CW**, et al. Factors Associated with Improvement in Ejection Fraction in Clinical Practice Among Patients with Heart Failure: Findings from IMPROVE HF. *Am Heart J*. 2012 Jan;163(1):49-56 e2. doi:[10.1016/j.ahj.2011.10.001](https://doi.org/10.1016/j.ahj.2011.10.001)
  22. **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 Nov;5(6):720-726. doi:[10.1161/CIRCHEARTFAILURE.111.966366](https://doi.org/10.1161/CIRCHEARTFAILURE.111.966366)
  23. **Basuray A, French B, Ky B**, et al. Heart Failure with Recovered Ejection Fraction: Clinical Description, Biomarkers, and Outcomes. *Circulation*. 2014 Jun 10;129(23):2380-2387. doi:[10.1161/CIRCULATIONAHA.113.006855](https://doi.org/10.1161/CIRCULATIONAHA.113.006855)
  24. **Merlo M, Stolfo D, Anzini M**, et al. Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: does real healing exist? *J Am Heart Assoc*. 2015 Jan 13;4(1):e001504. doi:[10.1161/JAHA.114.000570](https://doi.org/10.1161/JAHA.114.000570)
  25. **Kalogeropoulos AP, Fonarow GC, Georgiopoulos V**, et al. Characteristics and Outcomes of Adult Outpatients with Heart Failure and Improved or Recovered Ejection Fraction. *JAMA Cardiol*. 2016 Aug 1;1(5):510-518. doi:[10.1001/jamacardio.2016.1325](https://doi.org/10.1001/jamacardio.2016.1325)
  26. **Lupón J, Díez-Lopez C, de Antonio M**, et al. Recovered Heart Failure with Reduced Ejection Fraction and Outcomes: A Prospective Study. *Eur J Heart Fail*. 2017 Dec;19(12):1615-1623. doi:[10.1002/ehjhf.824](https://doi.org/10.1002/ehjhf.824)
  27. **Agra Bermejo R, Gonzalez Babarro E, Lopez Cano JN**, et al. Heart Failure with Recovered Ejection Fraction: Clinical



- Characteristics, Determinants and Prognosis. CARDIOCHUS-CHOP Registry. *Cardiol J*. 2018;25(3):353-362. doi:10.5603/CJ.a2017.0103
28. **Chang KW, Beri N, Nguyen NH**, et al. Heart Failure with Recovered Ejection Fraction in African Americans: Results from the African-American Heart Failure Trial. *J Card Fail*. 2018 May;24(5):303-309. doi:10.1016/j.cardfail.2017.09.005
  29. **Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA**. Frequency, Predictors, and Prognosis of Ejection Fraction Improvement in Heart Failure: An Echocardiogram-Based Registry Study. *Eur Heart J*. 2019 Jul 1;40(26):2110-2117. doi:10.1093/eurheartj/ehz233
  30. **He Y, Ling Y, Guo W**, et al. Prevalence and Prognosis of HFimpEF Developed from Patients with Heart Failure with Reduced Ejection Fraction: Systematic Review and Meta-Analysis. *Front Cardiovasc Med*. 2021 Nov 25;8:757596. doi:10.3389/fcvm.2021.757596
  31. **Zhang X, Sun Y, Zhang Y**, et al. Characteristics and Outcomes of Heart Failure with Recovered Left Ventricular Ejection Fraction. *ESC Heart Fail*. 2021 Dec;8(6):5383-5391. doi:10.1002/ehf2.13630
  32. **Yang CD, Pan WQ, Feng S**, et al. Insulin Resistance Is Associated with Heart Failure with Recovered Ejection Fraction in Patients Without Diabetes. *J Am Heart Assoc*. 2022 Oct 4;11(19):e026184. doi:10.1161/JAHA.122.026184
  33. **Goh ZM, Javed W, Shabi M**, et al. Early Prediction of Left Ventricular Function Improvement in Patients with New-Onset Heart Failure and Presumed Non-Ischaemic Aetiology. *Open Heart*. 2023;10(2):e002429. doi:10.1136/openhrt-2023-002429
  34. **Liu D, Hu K, Schregelmann L**, et al. Determinants of Ejection Fraction Improvement in Heart Failure Patients with Reduced Ejection Fraction. *ESC Heart Fail*. 2023 Aug;10(2):1358-1371. doi:10.1002/ehf2.14303
  35. **Romero E, Baltodano AF, Rocha P**, et al. Clinical, Echocardiographic, and Longitudinal Characteristics Associated with Heart Failure with Improved Ejection Fraction. *Am J Cardiol*. 2024 Jan 15;211:143-152. doi:10.1016/j.amjcard.2023.10.086
  36. **Mohebi R, Liu Y, Felker GM**, et al. Prediction of Left Ventricular Ejection Fraction Change Following Treatment With Sacubitril/Valsartan. *JACC Heart Fail*. 2023 Jan;11(1):44-54. doi:10.1016/j.jchf.2022.09.009
  37. **Jackson AM, Goland S, Farhan HA**, et al. A Novel Score to Predict Left Ventricular Recovery in Peripartum Cardiomyopathy Derived from the ESC EORP Peripartum Cardiomyopathy Registry. *Eur Heart J*. 2024 Apr 21;45(16):1430-1439. doi:10.1093/eurheartj/ehad888
  38. **Cooper LT, Mather PJ, Alexis JD**, et al. Myocardial Recovery in Peripartum Cardiomyopathy: Prospective Comparison with Recent Onset Cardiomyopathy in Men and Nonperipartum Women. *J Card Fail*. 2012 Jan;18(1):28-33. doi:10.1016/j.cardfail.2011.09.009
  39. **Dominguez F, Adler E, Garcia-Pavia P**. Alcoholic cardiomyopathy: an update. *Eur Heart J*. 2024 Jul 9;45(26):2294-2305. doi:10.1093/eurheartj/ehae362
  40. **Ewer MS, Vooletich MT, Durand JB**, et al. Reversibility of Trastuzumab-Related Cardiotoxicity: New Insights Based on Clinical Course and Response to Medical Treatment. *J Clin Oncol*. 2005 Nov 1;23(31):7820-7826. doi:10.1200/JCO.2005.13.300
  41. **Amor-Salamanca A, Guzzo-Merello G, Gonzalez-Lopez E**, et al. Prognostic Impact and Predictors of Ejection Fraction Recovery in Patients With Alcoholic Cardiomyopathy. *Rev Esp Cardiol (Engl Ed)*. 2018 Aug;71(8):612-619. doi:10.1016/j.rec.2017.11.032
  42. **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 Jan 5;393(10166):61-73. doi:10.1016/S0140-6736(18)32484-X
  43. **Negi PC, Gupta A, Thakur P**, et al. Incidence, Determinants, and Outcomes of Recovered Left Ventricular Ejection Fraction (LVEF) in Patients with Non-Ischemic Systolic Heart Failure: A Hospital-Based Cohort Study. *Indian Heart J*. 2023 Mar-Apr;75(2):128-132. doi:10.1016/j.ihj.2023.02.003
  44. **Manca P, Stolfo D, Merlo M**, et al. Transient Versus Persistent Improved Ejection Fraction in Non-Ischaemic Dilated Cardiomyopathy. *Eur J Heart Fail*. 2022 Jul;24(7):1171-1179. doi:10.1002/ehf.2512
  45. **Januzzi JL Jr, Prescott MF, Butler J**, et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment with Cardiac Structure and Function in Patients with Heart Failure with Reduced Ejection Fraction. *JAMA*. 2019 Sep 17;322(11):1085-1095. doi:10.1001/jama.2019.12821
  46. **Pensa AV, Khan SS, Shah RV, Wilcox JE**. Heart Failure with Improved Ejection Fraction: Beyond Diagnosis to Trajectory Analysis. *Prog Cardiovasc Dis*. 2024 Jan-Feb;82:102-112. doi:10.1016/j.pcad.2024.01.014
  47. **Janwanishstaporn S, Cho JY, Feng S**, et al. Prognostic Value of Global Longitudinal Strain in Patients with Heart Failure with Improved Ejection Fraction. *JACC Heart Fail*. 2022 Jan;10(1):27-37. doi:10.1016/j.jchf.2021.08.007
  48. **Solomon SD, McMurray JJV, Claggett B**, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022 Sep 22;387(12):1089-1098. doi:10.1056/NEJMoa2206286
  49. **Vardeny O, Fang JC, Desai AS**, et al. Dapagliflozin in Heart Failure with Improved Ejection Fraction: A Prespecified Analysis of the DELIVER Trial. *Nat Med*. 2022 Dec;28(12):2504-2511. doi:10.1038/s41591-022-02102-9

50. **Vardeny O, Desai AS, Jhund PS**, et al. Dapagliflozin and Mode of Death in Heart Failure with Improved Ejection Fraction: A Post Hoc Analysis of the DELIVER Trial. *JAMA Cardiol*. 2024 Mar 1;9(3):283-289. doi:10.1001/jamacardio.2023.5318
51. **Nesti L, Pugliese NR, Sciuto P**, et al. Effect of Empagliflozin on Left Ventricular Contractility and Peak Oxygen Uptake in Subjects with Type 2 Diabetes Without Heart Disease: Results of the EMPA-HEART Trial. *Cardiovasc Diabetol*. 2022 Sep 12;21(1):181. doi:10.1186/s12933-022-01618-1

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