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Heart Failure With Improved Ejection Fraction

Is it Possible to Escape One's Past?

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ABSTRACT

Among patients with heart failure with reduced ejection fraction, investigators have repeatedly identified a subgroup whose left ventricular ejection fraction and structural remodeling can improve to normal or nearly normal levels with or without medical therapy. This subgroup of patients with "heart failure with improved ejection fraction" has distinct clinical characteristics and a more favorable prognosis compared with patients who continue to have reduced ejection fraction. However, many of these patients also manifest clinical and biochemical signs of incomplete resolution of heart failure pathophysiology and remain at some risk of adverse outcomes, thus indicating that they may not have completely recovered. Although rigorous evidence on managing these patients is sparse, there are several reasons to recommend continuation of heart failure therapies, including device therapies, to prevent clinical deterioration. Notable exceptions to this recommendation may include patients who recover from peripartum cardiomyopathy, fulminant myocarditis, or stress cardiomyopathy, whose excellent long-term prognoses may imply true myocardial recovery. More research on these patients is needed to better understand the mechanisms that lead to improvement in ejection fraction and to guide their clinical management. (J Am Coll Cardiol HF 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

Since the earliest studies of vasodilator therapy in patients with heart failure (HF) with reduced ejection fraction (HFrEF), it has been noted that left ventricular (LV) ejection fraction (LVEF) can improve during the course of therapy (1). As new medical and device-based therapies for HFrEF have been developed, investigators have repeatedly identified a subset of patients who have substantial improvement of LVEF with or without therapy (2). The characteristics and clinical outcomes of this subgroup of HF patients have only recently been outlined, although optimal management strategies have not been prospectively studied.

In this review, we explore the nomenclature, epidemiology, clinical characteristics, and outcomes of this group of patients. Mechanisms that may underlie improvement of LVEF are reviewed, and current published reports regarding management of these patients are summarized. Finally, current knowledge gaps are highlighted, and priorities for further investigation are identified.

DEFINITION AND NOMENCLATURE

Although it is acknowledged that a distinct cohort of patients with improved or recovered LVEF exists, there is currently no consensus definition of this cohort. Current American College of Cardiology/American Heart Association guidelines define a cohort of "HFpEF, improved" patients as those who have LVEF >40% but who previously had LVEF ≤40% (3). European Society of Cardiology guidelines introduced a category called "HF with midrange EF" (HRmrEF) (LVEF 40% to 49%) but do not distinguish

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

CRT = cardiac resynchronization therapy

HF = heart failure

HFiEF = heart failure with improved ejection fraction

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

LV = left ventricular

LVEF = left ventricular ejection fraction

PPCM = peripartum cardiomyopathy

between patients who previously had lower LVEF and those who have never had HFrEF (4). Other investigators have defined a cohort of patients with HF with recovered EF (HFrecEF) or HF with better EF (HFbetterEF) as those who have LVEF ≥50% but with a previously documented LVEF <50% (5,6). HF with improved EF (HFiEF) has been proposed to define patients with LVEF >40% with a previously documented LVEF <35% (7).

We propose using the term HFiEF to define patients who had LVEF <40% and who have experienced any improvement in LVEF beyond the reproducibility and variability of the imaging techniques. We favor this definition because it acknowledges that varying degrees of improvement can exist and that the magnitude of change likely has prognostic implications. For HFiEF patients whose need for ongoing HF therapy is uncertain and whose physicians have questions regarding the need for ongoing HF therapy in these patients, we discuss recommendations later. We also use the term "improved" rather than "recovered" because it highlights 2 important features of this clinical entity: 1) despite having very improved or even normalized LVEF, these patients may continue to have clinical HF and abnormal biomarker signs of functional impairment; and 2) the improvement experienced by these patients does not necessarily reflect recovery from their underlying structural cardiomyopathic process. Moreover, improvement in LVEF is generally considered a surrogate for the underlying process of reverse remodeling occurring at the myocardial and ventricular structural and functional levels, and therefore it should be accompanied by a reduction in LV volumes (8).

EPIDEMIOLOGY OF HFiEF

FREQUENCY OF LVEF IMPROVEMENT. For some patients, such as those with stress cardiomyopathy (Takotsubo), LVEF improvement may occur rapidly, even in the absence of medical therapy. For others, medical therapy may be partially or wholly responsible for LVEF improvement. What is clear, however, is that the frequency of LVEF improvement depends on the cause of the underlying cardiomyopathy. In a comprehensive review, Givertz et al. (9) documented rates of LVEF improvement (to LVEF >50%) of 60% to 100% when considering causes of cardiomyopathy such as tachycardia, Takotsubo, and hyperthyroidism among patients with recent onset (<6 months) cardiomyopathy. Rates of LVEF improvement are lower in cohorts of patients with chronic HF. In a tertiary care center cohort of over 1,800 patients with HF, only 10% of patients had HFiEF (to LVEF ≥50%) (5). Similarly, only 9% of the nearly 4,500 patients selected for analysis from Val-HeFT (Valsartan Heart Failure Trial) went on to experience LVEF improvement to ≥40% during the first 12 months of follow-up (7).

Rates of LVEF improvement in patients receiving cardiac resynchronization therapy (CRT) are also variable. In MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), 79% of patients had partial improvement in LVEF (to 36% to 50% from a baseline of 30%), but only 7.3% of patients were "super-responders" and had LVEF improvement to >50% (10). In smaller cohorts, rates of super-response ranged from 12% to 17% (11,12). The existence of CRT super-responders suggests that in these patients, unlike other HFrEF patients, LV dyssynchrony was a predominant cause of LV dysfunction.

Table 1 summarizes selected studies that have reported on LVEF improvement as a consequence of various therapies and have reported baseline predictors of improvement. The frequency of improvement is variable, in part because of differing definitions of HFiEF, but also because of heterogeneity of study populations regarding HF origin, duration, and underlying medical therapy. Ideally, frequency of LVEF improvement would be assessed in patients with new onset HFrEF; in these patients, initiation of full guideline-directed medical therapy would provide a purer assessment of the incidence of LVEF improvement with contemporary management. When considering data from clinical trials of HFrEF patients whose inclusion criteria include stability on background medical therapy, patients who have already had LVEF improvement are selected out, and any subsequent improvement observed is to a large degree a consequence of the new therapy being evaluated (7).

FACTORS THAT PREDICT LVEF IMPROVEMENT. Despite differences in HFiEF definition, several demographic and clinical characteristics are repeatedly identified as being associated with greater likelihood of improved LVEF (Table 1). These include female sex, nonischemic cause of HF, shorter duration of HF, and less severe adverse cardiac remodeling at initial evaluation. These factors have also been associated with super-response to CRT (13). However, although the presence of left bundle branch block (LBBB) is also predictive of CRT response, LBBB is associated with attenuated LVEF improvement or lack of LVEF

TABLE 1 LVEF Improvement in HFrEF Patients

First Author (Ref.)	Publication Year	Study Size (n)	Population	Baseline Medical Therapy (>70% Use)	Definition of LVEF Improvement	Frequency of LVEF Improvement (%)	Baseline Characteristics Associated With LVEF Improvement
Cioffi (Online Ref. 9)	2004	110	Chronic HFrEF	Digoxin, diuretics	LVEF >51%	18	Absence of diabetes, higher SBP, shorter duration of HF, nonischemic origin
McNamara (Online Ref. 10)	2011	373	ROCM	ACE, BB	LVEF ≥50%	25	Smaller LVIDs, higher SBP, race other than black, higher NYHA class
Merlo (14)	2011	242	Chronic HFrEF	ACE, BB, digoxin	Increase in LVEF >10%	37	Higher SBP, absence of LBBB
Biteker (Online Ref. 11)	2011	24	PPCM	ACE, diuretics	LVEF >50%	46	Smaller LVIDd, smaller LVIDs, higher LVEF, smaller LA diameter
Wilcox (Online Ref. 12)	2012	3,994	Chronic HFrEF	ACE, BB	Increase in LVEF >10%	Not given	Female, nonischemic origin, higher LVEF, higher SBP, no digoxin use
Dunlay (Online Ref. 13)	2012	674	Chronic HFrEF	ACE, BB	LVEF ≥50%	39	Not given
Basuray (5)	2014	1,821	Chronic HFrEF	ACE, BB, diuretics	LVEF ≥50%	Not given	Female, nonischemic origin
McNamara (Online Ref. 14)	2015	100	PPCM	ACE, BB	LVEF ≥50%	72	Smaller LVIDs, nonblack race
Florea (7)	2016	4,410	Chronic HFrEF	ACE, diuretics	LVEF ≥40%	9	Female, nonischemic origin, higher DBP, smaller LVIDd, BB therapy, valsartan therapy
Bermejo (Online Ref. 15)	2017	242	Chronic HFrEF	ACE, BB, diuretics	LVEF >40%	52	Younger age, higher NYHA class, ACE/BB use, nonischemic origin, lack of ICD placement
Chang (Online Ref. 16)	2017	318	African-American chronic HFrEF	ACE, BB, diuretics	LVEF ≥40%	19	Higher LVEF, shorter duration of HF, no digoxin use, use of I/H
Lupón (22)	2017	940	Chronic HFrEF	ACE, BB, diuretics	LVEF ≥45%	25	Younger age, female, nonischemic origin, nondiabetic, shorter duration of HF, higher NYHA class
Kim (Online Ref. 17)	2017	90	Takotsubo CM	None	LVEF ≥50%	70	Younger age, absence of hypothyroidism, shorter QT interval, ACE or ARB use

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CM = cardiomyopathy; DBP = diastolic blood pressure; HFrEF = heart failure with reduced ejection fraction; I/H = isosorbide dinitrate and hydralazine; ICD = implantable cardioverter-defibrillator; LA = left atrium; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; NYHA = New York Heart Association; PPCM = peripartum cardiomyopathy; Ref. = reference; ROCM = recent onset cardiomyopathy; SBP = systolic blood pressure.

improvement with optimal medical therapy alone (14,15). This discrepancy again highlights the importance of dyssynchrony in maintaining LV dysfunction in some patients.

There are also data on the influence of genetics on LVEF improvement. Activating mutations in the angiotensin-converting enzyme (ACE) or β_1-adrenergic receptor genes have been linked to a less favorable LVEF response to medical therapy (16). Mutations in sarcomeric proteins may also play a role because patients with truncating mutations in the titin-A gene have a higher frequency of LVEF improvement (of >10%) compared with patients with idiopathic dilated cardiomyopathies or those with *LMNA* mutations when these patients are treated with guideline-directed therapies (17). However, in a study of 172 patients with peripartum cardiomyopathy (PPCM), patients with truncating titin-A mutations were less likely to demonstrate normalization of LVEF at 1 year than patients without such mutations (18).

CHARACTERISTICS OF HFiEF PATIENTS FOLLOWING IMPROVEMENT. Patients who have LVEF improvement may continue to have a distinct clinical and biochemical profile compared with both HFrEF patients and the general population. In an early study, Punnoose et al. (2) cross-sectionally analyzed 358 patients from a tertiary care HF center and identified 177 patients with LVEF ≥40% who would conventionally have had a diagnosis of HFpEF. Of these, 121 patients (68%) previously had LVEF <40%, representing the HFiEF cohort. These investigators compared characteristics of HFiEF patients with those who had HFrEF (LVEF <40%) at the time of analysis. On average, HFiEF patients were younger and less likely to have coronary disease compared with those with HFrEF, whereas rates of atrial fibrillation, hypertension, and diabetes were similar (2). HFiEF patients had higher systolic blood pressures and smaller LV volumes than HFrEF patients. Interestingly, LV volumes were larger in HFiEF patients than in HFpEF patients, a finding suggesting some degree of residual adverse remodeling despite improvement of LVEF (2). B-type natriuretic peptide and troponin levels were also lower in HFiEF patients than in HFrEF patients, although levels were still supra-normal in approximately one-half of HFiEF patients, thus indicating ongoing neurohormonal

TABLE 2 HFrEF Recurrence in HFiEF Patients

First Author (Ref.)	Publication Year	Study Size (n)	Median Follow-Up (Months)	Frequency of HFrEF Recurrence (%)	Factors Associated With HFrEF Recurrence
Cioffi (Online Ref. 9)	2004	20	17	40	Not available
Moon (44)	2009	42	48	19	Discontinuation of HF therapy
Park (25)	2014	85	50	39	Older age, longer duration of HF before improvement, diabetes, larger LVIDd
de Groote (21)	2014	174	96	22	Lower LVEF, LBBB, larger LVIDd, slower heart rate
Nadruz (19)	2016	123	32	29	Older age, HTN, lower GFR

GFR = glomerular filtration rate; HRiEF = heart failure with improved ejection fraction; HTN = hypertension; other abbreviations as in Table 1.

activation and myocardial stress and injury (5). Exercise capacity of HFiEF patients also appears to be reduced relative to healthy controls, with average peak oxygen consumption reported as 17 to 18 ml/kg/min (53% predicted) (19). Finally, although HFiEF patients reported better quality of life than HFrEF patients (20), 25% to 75% still reported HF symptoms despite good adherence to medical therapy (2,5,19).

In summary, following LVEF improvement, the clinical, biomarker, and functional characteristics of HFiEF patients are more favorable than those of HFrEF patients. However, HFiEF patients as a group are distinct from healthy controls. Their phenotypic improvement does not necessarily reflect full recovery from adverse structural remodeling or remission of HF.

CLINICAL OUTCOMES IN HFiEF PATIENTS

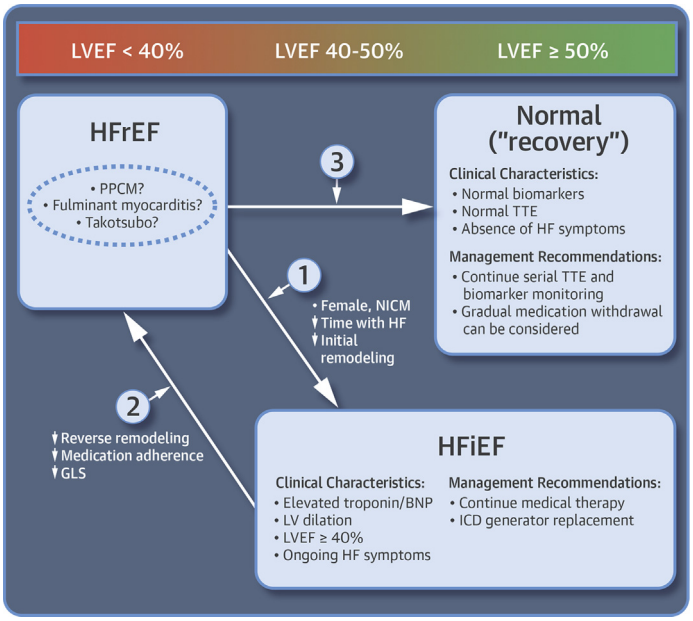
Reflecting their biochemical profiles, HFiEF patients have more favorable clinical outcomes than HFrEF patients. Several moderate-sized HFiEF cohorts have reported 5-year survival rates of 80% to 90%, compared with 65% to 75% in HFrEF patients (19,21,22). Although patients whose LVEF normalizes have the most favorable outcomes, even those who experience partial improvement in LVEF (to 41% to 49% from <35%) have more favorable survival relative to patients whose LVEF is persistently 41% to 49% (19). LVEF improvement remains independently associated with freedom from death or heart transplantation, even after accounting for differences in baseline LVEF, HF duration, New York Heart Association functional class, and treatment with β-blockers (14), a finding suggesting that it is the reverse remodeling itself that leads to increased survival (23). Hospitalizations are also decreased in HFiEF patients compared with patients with HFrEF (5,24). However, overall survival is still worse than in healthy controls (21).

Natural history studies have shown that HFiEF patients remain at some risk of developing HFrEF again; several of these studies are summarized in Table 2. Just as more severe LV remodeling is associated with lower rates of LVEF improvement, HFiEF patients with larger LV size appear to be at higher risk of future deterioration in LVEF (21,25). LV deformation mechanics may also be used to identify patients at risk for recurrent HFRef. A recent study showed that less negative global longitudinal strain at the time of LVEF improvement predicted a higher risk of future declines in LVEF (26). The mean global longitudinal strain in the HFiEF population in this study was −14.4%, which is less negative than currently accepted normal values for global longitudinal strain (−17% to −20%), again indicating that there remain subtle but detectable myocardial abnormalities in HFiEF patients. One study also identified the presence of LBBB as an independent risk factor for HFrEF recurrence (21). However, although some risk factors have been identified that are associated with a higher likelihood of HFrEF recurrence, it remains difficult to predict accurately which individual HFiEF patients are at risk.

MECHANISMS OF LVEF IMPROVEMENT

Although a complete discussion of the mechanisms of reverse remodeling is beyond the scope of this review, the link between adherence to HF therapy and LVEF improvement suggests that the pathways targeted by HF therapies may provide mechanistic insight into the process of LVEF improvement. Up-regulated angiotensin II signaling, similar to the neurohormonal activation seen in HFrEF patients, leads to deleterious myocyte hypertrophy mediated by transforming growth factor-β and endothelin-1 (27). ACE inhibitors down-regulate this pathway by suppressing fibroblast signaling and collagen deposition (28), thereby reducing myocardial fibrosis. ACE inhibitors and angiotensin receptor blockers (ARBs) also reduce the effect of β-adrenergic stimulation by enhancing myocardial nitric oxide

CENTRAL ILLUSTRATION **Definitions and Management of Patients With HFrEF With LVEF Improvement**



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Patients with heart failure with reduced ejection fraction (HFrEF) and left ventricular ejection fraction (LVEF) improvement often have signs of ongoing neurohormonal activation, structural abnormalities, and heart failure symptoms, and they should be considered to have heart failure with improved ejection fraction (HFiEF). Factors associated with left ventricular ejection fraction improvement are indicated (1). These patients remain at some risk of developing recurrent cardiomyopathy and should continue guideline-directed medical therapy. Characteristics associated with heart failure with reduced ejection fraction recurrence are indicated (2). In contrast, it is possible that some patients with heart failure with reduced ejection fraction who have certain cardiomyopathies such as peripartum cardiomyopathy (PPCM), fulminant myocarditis, or Takotsubo cardiomyopathy who experience left ventricular ejection fraction normalization may have true structural and functional recovery and become "normal," although this paradigm has been challenged by recent data. These patients may be candidates for medication withdrawal but should continue to be monitored with serial echocardiograms and biomarker assessment (3).
GLS = global longitudinal strain; ICD = implantable cardioverter-defibrillator; NICM = nonischemic cardiomyopathy; TTE = transthoracic echocardiogram.

production (29), which attenuates the positive inotropic effects of β-agonists (30). Adrenergic receptor stimulation results in myocyte hypertrophy and eventual development of HF, mediated through G-protein-coupled receptor pathways (31,32). β-blockers restore normal G-protein-coupled receptor function and enhance myocardial contractility (33). They also restore normal calcium signaling by normalizing ryanodine receptor function, resulting in increased contractility (34).

Electrophysiological processes also play key roles in reverse remodeling. The gene expression profile of contractile proteins is altered in CRT responders, with increased expression of α-myosin heavy chain and phospholamban and decreased expression of β-myosin heavy chain (35,36). Structural changes are induced by CRT as well, with restoration of normal T-tubule and ryanodine receptor organization in a canine HF model with LBBB (37). The presence of atrial fibrillation also can inhibit reverse remodeling. Restoration of sinus rhythm by catheter ablation can lead to high rates of normalization of LVEF in HFrEF patients, a phenomenon seen less frequently with rate control alone (38,39). The molecular mechanisms underlying this improvement are still unclear. Nonetheless, whether by attenuation of abnormal neurohormonal or electrical activity, the structural changes induced by HF therapies shed some light on the mechanisms of reverse remodeling.

MANAGEMENT OF HFiEF PATIENTS

There are currently no randomized trials comparing management strategies in HFiEF patients. However,

the observation that HFiEF patients may maintain a biochemical profile suggestive of ongoing neurohormonal activation (5) and remain at risk for HF recurrence and adverse cardiovascular outcomes (21,22) implies that continuation of neurohormonal blockade would be generally beneficial for HFiEF patients.

There are data from small prospective studies to support continuation of β-blocker therapy in HFiEF patients. One of the earliest reports describes a group of 15 patients with HFiEF who were previously treated with β-blockers for 6 to 50 months, whose LVEF had increased to a mean of 46%, and who were then subjected to β-blocker withdrawal. LVEF deteriorated in 11 of the 13 patients who had follow-up data (to a mean of 35%), and 40% had recurrence of HF symptoms (40). These findings were later confirmed in a cohort of 26 patients who had median LVEF improvement from 25% to 41% after a median of 16 months of β-blocker therapy. Withdrawal of therapy resulted in a decrease in LVEF to 32% and a decline in New York Heart Association functional class within 1 year. Furthermore, resuming β-blocker therapy resulted in a partial clinical and echocardiographic improvement back to the pre-withdrawal baseline (41). Similar results were seen in a subsequently reported Japanese cohort (Online Ref. 1).

Few data exist regarding withdrawal of ACE inhibitors or ARBs in patients with HFiEF. Early studies of ACE inhibitor use in chronic HF have shown prevention of progressive LV dilation and remodeling (42), and ACE inhibitor withdrawal leads to clinical deterioration in patients with chronic HF (43). Withdrawal of ACE inhibitors for 2 to 3 weeks after almost 3 years of treatment in the context of the SOLVD (Studies of Left Ventricular Dysfunction) trial led to some loss of the favorable remodeling changes that had been observed compared with placebo (42). However, it is still unknown what effect ACE inhibitor withdrawal would have in a patient whose LVEF had more substantially improved. Observational data supporting continuation of ACE inhibitor therapy in HFiEF come from a Korean study of a cohort of 42 patients with HFiEF (defined as improved LVEF from a mean of 26 ± 7% to ≥40% and ≥10% absolute LVEF increase) who were followed for a median of 41 months after improvement of LVEF. Twenty percent of patients developed recurrent systolic dysfunction, and discontinuation of HF therapies, including ACE inhibitors, was the only risk factor associated with HF recurrence on multivariable analysis (44).

SPECIFIC CARDIOMYOPATHIES. Although the previous discussion applies to HFiEF patients in general, patients with certain specific cardiomyopathies may better tolerate medication withdrawal if their LVEF has improved or normalized. In a small cohort of 22 patients with PPCM with improved LVEF (to >50%), one-half of patients discontinued either ACE inhibitor or β-blocker therapy, and 5 patients had discontinued both medications. None of these 16 patients experienced recurrent LV dysfunction at a median of 29 months of follow-up (45). Importantly, none of these patients had a subsequent pregnancy during the follow-up period. Recurrent pregnancy is associated with high risk of recurrence of LV dysfunction in patients with prior PPCM, even in those who had previously experienced complete normalization of LVEF, and patients should discuss any subsequent desired pregnancies with their cardiologist and obstetrician (Online Refs. 2 and 3). Still, there is reason to be cautious because a significant minority of PPCM patients has mutations in genes associated with dilated cardiomyopathy (18), which may confer persistent risk of HF. It is yet unknown whether these patients represent a distinct subset of PPCM patients that should be considered to have genetic dilated cardiomyopathy. Given the lack of data, discontinuation of HF medications after recovery from PPCM should be a shared decision between patient and clinician. One possible approach is to taper 1 medication at a time, each separated by a 6-month period of clinical monitoring and serial echocardiograms (46).

Similar considerations may apply to patients who recover from fulminant myocarditis. Despite presenting with profound cardiovascular compromise, these patients often experience LVEF improvement if they survive their acute illness, with excellent long-term outcomes (Online Refs. 4 and 5). Patients with Takotsubo cardiomyopathy also frequently have normalization of LVEF and excellent long-term survival (47). Although a recent study has suggested that subtle yet persistent phenotypic abnormalities may be present in these patients (48), more data are necessary before strong conclusions can be drawn.

DEVICE THERAPY. In the subset of HFiEF patients who previously received implantable cardioverter-defibrillators (ICDs) for prevention of sudden cardiac death, the need for ongoing ICD therapy is uncertain. A recent meta-analysis of studies of HFiEF patients with primary prevention ICDs demonstrated that improvement in LVEF is associated with lower rates of appropriate ICD therapy (49). However, it is clear that some arrhythmic risk remains despite improvement in LVEF. A recent analysis of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) showed that the reduction in mortality associated with ICD therapy was similar in patients with LVEF improvement

to ≥35% and in patients without such improvement (50). Results are similar among secondary prevention patients, where improvement of LVEF is associated with a significant reduction in appropriate ICD therapies, although 29% of patients with HFiEF still experienced arrhythmias (Online Ref. 6).

For patients with an indication for CRT, improvement of LVEF is also associated with reduced rates of ventricular arrhythmias (1.7 to 2.3 vs. 7.2 to 8.2 events per 100 person-years) (51). There appears to be a relationship between the degree of LVEF improvement and the risk reduction, with 1 study finding that patients with LVEF ≥50% had the lowest rates of ICD therapies, followed by those with LVEF 36% to 50% (10). Again, however, there remains residual arrhythmic risk in this population. Current Appropriate Use Criteria for generator replacement in patients with LVEF ≥50% state that ICD replacement may still be appropriate, and that although continuation of CRT-defibrillator therapy in patients with prolonged QRS complex duration is appropriate, replacement of CRT-defibrillator with CRT-pacemaker therapy may also be appropriate (Online Ref. 7). Current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines do not address this group of patients (Online Ref. 8).

CONCLUSIONS

The group of patients with HF who experience improvement of LVEF to nearly normal or even normal levels represents a unique cohort of HF patients. Unfortunately, despite improvement of LVEF, the underlying myocardial and biochemical abnormalities may not completely resolve. Such patients often have evidence of ongoing HF symptoms and may continue to have signs of neurohormonal activation, an abnormal biomarker profile, and detectable functional abnormalities. Furthermore, they remain at risk of deterioration of LV function, HF hospitalization, and death. Therefore, despite a relative lack of high-quality data, it seems prudent to continue HF therapy after LVEF improvement (6). However, in unique patient subgroups, such as patients with PPCM, Takotsubo cardiomyopathy, and recovered fulminant myocarditis, it may be possible to discontinue HF medications slowly under close supervision (**Central Illustration**).

Much remains to be learned about HFiEF patients. Although clinical factors associated with a higher likelihood of LVEF improvement have been identified, the actual positive and negative predictive values are too low to be used as prognostic tools for individual patients. Improved biomarker and genetic phenotyping is needed to correlate baseline characteristics of HFiEF patients with clinical outcomes and to aid in prognostication. Investigation into the mechanisms of LVEF improvement can shed new light on the remodeling process and may identify unique therapeutic targets to promote LVEF improvement.

Finally, management of HFiEF patients remains challenging. More studies comparing management strategies, including medication withdrawal, are required before definitive recommendations can be made. Furthermore, clinicians need additional data to guide decision making around continuation of device therapy after LVEF improvement. These may be ideal scenarios for registry-based comparative effectiveness outcomes studies across multiple centers. When conducting such studies, importance should be paid to the cause of HF because it is possible that not all HFiEF patients will benefit from the same management strategy. Only with ongoing careful investigation can this subgroup of patients be optimally managed.

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REFERENCES

1. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.

2. Punnoose LR, Givertz MM, Lewis EF, Pratibhu P, Stevenson LW, Desai AS. Heart failure with recovered ejection fraction: a distinct clinical entity. J Card Fail 2011;17:527–32.

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

4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–2200m.

5. Basuray A, French B, Ky B, et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. Circulation 2014;129:2380–7.

6. Stevenson LW. Heart failure with better ejection fraction: a modern diagnosis. Circulation 2014;129:2364–7.

7. 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;9:e003123.

8. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects

on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol 2010;56:392–406.

9. Givertz MM, Mann DL. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. Curr Heart Fail Rep 2013;10:321–30.

10. Ruwald MH, Solomon SD, Foster E, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy. Circulation 2014;130:2278–86.

11. António 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;11:343–9.

12. Tian Y, Zhang P, Li X, et al. True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. Europace 2013;15:1499–506.

13. Proclemer A, Muser D, Facchin D. What we can learn from "super-responders". Heart Fail Clin 2017;13:225–32.

14. 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;57:1468–76.

15. Sze E, Samad Z, Dunning A, et al. Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. J Am Coll Cardiol 2018;71:306–17.

16. Rigolli M, Cicoira M, Bergamini C, Chiampan A, Rossi A, Vassanelli C. Progression of left ventricular dysfunction and remodelling under optimal medical therapy in CHF patients: role of individual genetic background. Cardiol Res Pract 2011;2011:1–6.

17. Jansweijer JA, Nieuwhof K, Russo F, et al. Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy. Eur J Heart Fail 2017;19:512–21.

18. Ware JS, Li J, Mazaika E, et al. Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 2016;374:233–41.

19. Nadruz W, West E, Santos M, et al. Heart failure and midrange ejection fraction: implications of recovered ejection fraction for exercise tolerance and outcomes. Circ Heart Fail 2016;9:e002826.

20. Joyce E, Chung C, Badloe S, et al. Variable contribution of heart failure to quality of life in ambulatory heart failure with reduced, better, or preserved ejection fraction. J Am Coll Cardiol HF 2016;4:184–93.

21. de Groote P, Fertin M, Duva Pentiah A, Goéminne C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β-blocker therapy. Circ Heart Fail 2014;7:434–9.

22. Lupón J, Díez-López C, de Antonio M, et al. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. Eur J Heart Fail 2017;19:1615–23.

23. Udelson JE, Konstam MA. Ventricular remodeling: fundamental to the progression (and regression) of heart failure. J Am Coll Cardiol 2011;57:1477–9.

24. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. JAMA Cardiol 2016;1:510–8.

25. Park J-S, Kim J-W, Seo K-W, et al. Recurrence of left ventricular dysfunction in patients with restored idiopathic dilated cardiomyopathy. Clin Cardiol 2014;37:222–6.

26. Adamo L, Perry A, Novak E, Makan M, Lindman BR, Mann DL. Abnormal global longitudinal strain predicts future deterioration of left ventricular function in heart failure patients with a recovered left ventricular ejection fraction. Circ Heart Fail 2017;10:e003788.

27. Gray MO, Long CS, Kalinyak JE, Li HT, Karliner JS. Angiotensin II stimulates cardiac myocyte hypertrophy via paracrine release of TGF-β1and endothelin-1 from fibroblasts. Cardiovasc Res 1998;40:352–63.

28. Hale TM. Persistent phenotypic shift in cardiac fibroblasts: impact of transient renin angiotensin system inhibition. J Mol Cell Cardiol 2016;93:125–32.

29. Wittstein IS, Kass DA, Pak PH, Maughan WL, Fetics B, Hare JM. Cardiac nitric oxide production due to angiotensin-converting enzyme inhibition decreases beta-adrenergic myocardial contractility in patients with dilated cardiomyopathy. J Am Coll Cardiol 2001;38:429–35.

30. Hare JM, Loh E, Creager MA, Colucci WS. Nitric oxide inhibits the positive inotropic response to beta-adrenergic stimulation in humans with left ventricular dysfunction. Circulation 1995;92:2198–203.

31. D'Angelo DD, Sakata Y, Lorenz JN, et al. Transgenic Galphaq overexpression induces cardiac contractile failure in mice. Proc Natl Acad Sci USA 1997;94:8121–6.

32. Engelhardt S, Hein L, Wiesmann F, Lohse MJ. Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. Proc Natl Acad Sci U S A 1999;96:7059–64.

33. Böhm M, Deutsch HJ, Hartmann D, La Rosée K, Stäblein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. J Am Coll Cardiol 1997;30:992–6.

34. Reiken S, Wehrens XHT, Vest JA, et al. Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. Circulation 2003;107:2459–66.

35. Iyengar S, Haas G, Lamba S, et al. Effect of cardiac resynchronization therapy on myocardial gene expression in patients with nonischemic dilated cardiomyopathy. J Card Fail 2007;13:304–11.

36. Vanderheyden M, Mullens W, Delrue L, et al. Myocardial gene expression in heart failure patients treated with cardiac resynchronization therapy responders versus nonresponders. J Am Coll Cardiol 2008;51:129–36.

37. Sachse FB, Torres NS, Savio-Galimberti E, et al. Subcellular structures and function of myocytes impaired during heart failure are restored by cardiac resynchronization therapy. Circ Res 2012;110:588–97.

38. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;7:31–8.

39. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol 2017;70:1949–61.

40. Swedberg K, Hjalmarson A, Waagstein F, Wallentin I. Adverse effects of beta-blockade withdrawal in patients with congestive cardiomyopathy. Br Heart J 1980;44:134–42.

41. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 1989;80:551–63.

42. Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. Circulation 1993;88:2277–83.

43. Pflugfelder PW, Baird G, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawl in chronic heart failure: a double-blind, placebo-controlled study of quinapril. The Quinapril Heart Failure Trial Investigators. J Am Coll Cardiol 1993;22:1557–63.

44. Moon J, Ko Y-G, Chung N, et al. Recovery and recurrence of left ventricular systolic dysfunction in patients with idiopathic dilated cardiomyopathy. Can J Cardiol 2009;25:e147–50.

45. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. Am Heart J 2006;152:509–13.

46. Hilfiker-Kleiner D, Haghikia A, Nonhoff J, Bauersachs J. Peripartum cardiomyopathy: current management and future perspectives. Eur Heart J 2015;36:1090–7.

47. Sharkey SW, Windenburg DC, Lesser JR, et al. natural history and expansive clinical profile of stress (Tako-tsubo) cardiomyopathy. J Am Coll Cardiol 2010;55:333–41.

48. Scally C, Rudd A, Mezincescu A, et al. Persistent long-term structural, functional, and metabolic changes after stress-induced (Takotsubo) cardiomyopathy. Circulation 2018;137:1039–48.

49. Smer A, Saurav A, Azzouz MS, et al. Meta-analysis of risk of ventricular arrhythmias after improvement in left ventricular ejection fraction during follow-up in patients with primary prevention implantable cardioverter defibrillators. Am J Cardiol 2017;120:279–86.

50. Adabag S, Patton KK, Buxton AE, et al. Association of implantable cardioverter defibrillators with survival in patients with and without improved ejection fraction secondary analysis of the sudden cardiac death in heart failure trial. JAMA Cardiol 2017;2:767–74.

51. Chatterjee NA, Roka A, Lubitz SA, et al. Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review. Eur Heart J 2015;36:2780–9.

KEY WORDS HFrEF, left ventricular ejection fraction, management, outcomes

APPENDIX For supplemental references, please see the online version of this paper.