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JACC SCIENTIFIC EXPERT PANEL

Heart Failure With Recovered Left Ventricular Ejection Fraction

JACC Scientific Expert Panel

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ABSTRACT

Reverse left ventricular (LV) remodeling and recovery of LV function are associated with improved clinical outcomes in patients with heart failure with reduced ejection fraction. A growing body of evidence suggests that even among patients who experience a complete normalization of LV ejection fraction, a significant proportion will develop recurrent LV dysfunction accompanied by recurrent heart failure events. This has led to intense interest in understanding how to manage patients with heart failure with recovered ejection fraction (HFrecEF). Because of the lack of a standard definition for HFrecEF, and the paucity of clinical data with respect to the natural history of HFrecEF patients, there are no current guidelines on how these patients should be followed up and managed. Accordingly, this *JACC* Scientific Expert Panel reviews the biology of reverse LV remodeling and the clinical course of patients with HFrecEF, as well as provides guidelines for defining, diagnosing, and managing patients with HFrecEF. (J Am Coll Cardiol 2020;76:719–34) © 2020 by the American College of Cardiology Foundation.

OVERVIEW OF HEART FAILURE WITH A RECOVERED LEFT VENTRICULAR EJECTION FRACTION

The recognition that left ventricular ejection fraction (LVEF) improves substantially in a subset of heart failure (HF) patients with reduced ejection fraction (HFrEF) who are treated with evidenced-based medical and device therapies has led to intense interest in their outcomes and clinical management, as well as raised interest in understanding how these patients differ from those with more modest to little positive change in LVEF (nonresponders). Improvements in LVEF with guideline-directed medical therapy (GDMT) can lead to a complete normalization of LVEF (i.e., >50%) or a partial normalization of LVEF (40% to 50%) (**Figure 1**). Estimates of the proportion of patients with improved LVEF range widely (e.g., 10% to

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CRT = cardiac resynchronization therapy

DCM = dilated cardiomyopathy

ECG = electrocardiogram

GDMT = guideline-directed medical therapy

HF = heart failure

HFmrEF = heart failure mid-range ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrecEF = heart failure with recovered ejection fraction

HFrEF = heart failure with reduced ejection fraction

ICD = implantable-cardioverter defibrillator

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SCD = sudden cardiac death

40%) due to variable definitions and the use of both observational and clinical trial datasets. There is no consensus definition currently available for identifying HFrEF patients with a recovered LVEF.

Although increases in LVEF may occur "spontaneously" in some forms of dilated cardiomyopathy (DCM), the changes generally occur in the setting of the use of guideline-directed medical and device therapy (1). Moreover, it is usually not possible to clearly discern the spontaneous component of the improvement in myocardial function, as most patients are treated with GDMT. It is important to recognize that the subgroup of HFrEF patients with a recovered LVEF are clinically distinct from patients with heart failure with a preserved EF (HFpEF), who also have an LVEF >50% along with the presence of HF signs and symptoms (2,3). The issue of modest recovery of LVEF with a resultant LVEF that falls between 40% and 50% has resulted in the proliferation of new nomenclatures, including HF improved EF (4), HFpEF, borderline HFpEF (1), HF recovered EF (HFrecEF) (3,5), and HF mid-range EF (HFmrEF) (6). In the absence of prior documentation of LVEF, one can only speculate as to whether LVEF is either rising or falling in this group of patients, which emphasizes the need to follow the LVEF trajectory in this group of patients by performing serial assessments of LVEF over time. Indeed, previous studies have shown that patients with mid-range LVEF between 40% and 50% (HFmrEF) are heterogeneous in nature and represent an admixture of HFrEF patients with improved LVEF and patients with HFpEF whose LVEF has declined (7,8). Although HFmrEF is endorsed by the European Society of Cardiology (6) as a new category of HF, we suggest that, absent knowledge of the LVEF trajectory, HFmrEF patients should be considered neither biologically nor clinically synonymous with HFrEF patients with a recovered LVEF.

Given the complexity and heterogeneity of patients with heart failure with a recovered EF (HFrecEF), it is not surprising that there is little or no consensus with respect to how to define, diagnose, and manage this growing population of HF patients. Accordingly, the current *JACC* Scientific Expert Panel reviews the biology and clinical course of HFrecEF patients, as well as provides guidelines for defining, diagnosing, and managing this group of patients.

HIGHLIGHTS

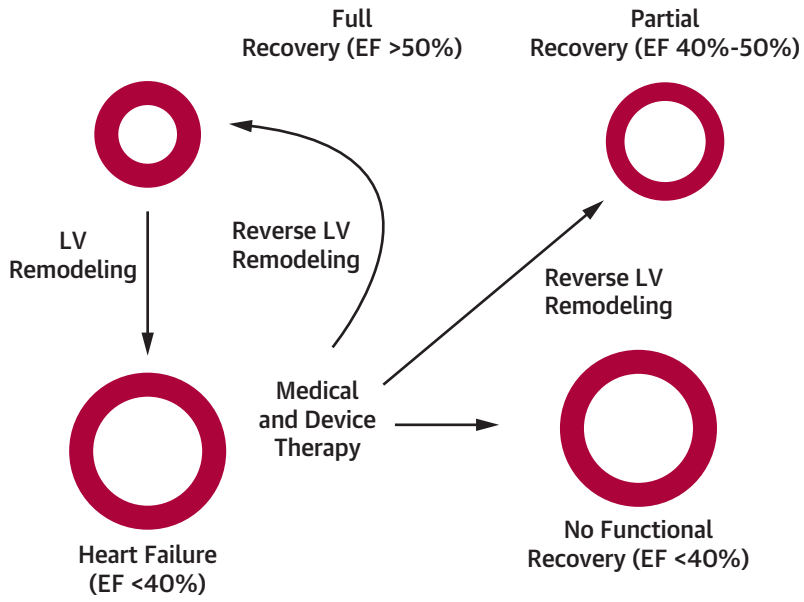
- This consensus document was created because there are no guidelines for the management of patients with HFrecEF.
- A working definition of HFrecEF that is consistent with the majority of studies in the literature includes the following: 1) documentation of a decreased LVEF <40% at baseline; 2) ≥10% absolute improvement in LVEF; and 3) a second measurement of LVEF >40%.
- Guideline-directed medical and device therapy for patients with HFrecEF should be continued indefinitely until the biology and clinical epidemiology of HFrecEF is better understood.
- HFrecEF patients should have close clinical follow-up due to the high risk of heart failure relapse.

BIOLOGY OF REVERSE REMODELING AND RECOVERY OF VENTRICULAR FUNCTION

Insofar as the calculation of LVEF incorporates LV end-diastolic volume in the denominator of the equation, improvements in LVEF are associated with a reciprocal decrease in LV end-diastolic volume, which has been referred to as reverse LV remodeling. In the context of the present discussion, reverse LV remodeling refers to the restoration of more normal cardiac myocyte size and LV chamber geometry, resulting in a leftward shift of the end-diastolic pressure volume relationship toward normal values (9,10). Importantly, reverse LV remodeling is associated with improved myocyte contractility and improved LV chamber contractility (11–13). It is important to recognize that reverse LV remodeling is associated with fewer HF hospitalizations and decreased cardiovascular mortality, and that there is a direct correlation between the extent of reverse LV remodeling and the improvement in cardiac survival (14).

MECHANISMS OF REVERSE LV REMODELING. Although the biological basis for reverse LV remodeling and recovery of LV function is incompletely understood, several general concepts have emerged. The most prominent theme is that cardiac remodeling is a dynamic process that occurs in a bidirectional

FIGURE 1 **Changes in LVEF With GDMT in Patients With Heart Failure With a Reduced EF**



Patients with heart failure with recovered ejection fraction (HFrecEF) treated with guideline-directed medical and device therapies (GDMT) may have a complete recovery of left ventricular ejection fraction (LVEF) >50%, partial recovery of LVEF (EF 40% to 50%), or no functional recovery of LVEF (EF <40%).

manner (i.e., forward and reverse) and that cardiac remodeling involves the coordinated regulation of multiple molecular and cellular changes that contribute to phenotypic changes in the size, shape, and function of the heart. Basic and clinical studies have consistently shown that many of the cellular and anatomic changes that occur during forward LV remodeling revert toward the normal less pathologic phenotype during reverse LV remodeling. A complete description of the molecular changes that occur during reverse LV remodeling has been the subject of several reviews (15–17).

Table 1 shows that pharmacological and device therapies that lead to reverse LV remodeling are accompanied by salutary changes in the biology of the cardiac myocyte, the composition of the extracellular matrix, and the chamber properties of the left ventricle. Moreover, studies that have examined serial changes in gene expression during reverse LV remodeling have shown that the normalization of gene transcription related to myocyte contractility occurs before changes in genes related to the extracellular matrix, suggesting that return of myocyte function is required for reversal of the changes in LV geometry in the failing heart (18). In addition to changes in adult cardiac myocytes during reverse LV remodeling, there are a number of important changes that occur within the myocardial extracellular matrix (15). A second important theme, which has direct bearing on the concept of myocardial remission (discussed later), is that many of the multilevel molecular changes that occur during forward LV remodeling remain dysregulated in reverse remodeled hearts, despite improvements in structural and functional abnormalities. Transcriptional profiling of reverse remodeled hearts reveals the emergence of new sets of genes that belong to ontogenies that are not expressed in nonfailing hearts (19). Viewed together, these findings suggest that reverse LV remodeling is not simply a mirror image of the molecular and cellular pathways that become dysregulated during forward LV remodeling but rather that reverse LV remodeling represents a coordinated multilevel process that allows the heart to adopt a new, less pathological steady state that is associated with enhanced pump function and improved clinical prognosis.

Given the multilevel adaptations associated with reverse remodeling and the diversity of clinical contexts in which it occurs, it is reasonable to speculate about whether there are primary drivers of reverse remodeling that enable the activation of other secondary downstream processes. In this regard, there is strong evidence supporting the concept of biomechanical load as one such primary driver (20). The

TABLE 1 Cellular and Molecular Determinants of Recovery of LV Function

	Beta-Blocker	ACE Inhibitor	ARB	Aldosterone Antagonists	LVAD	CRT	CSD
Myocyte defects							
Hypertrophy	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Fetal gene expression	Decreased	Decreased	Decreased	ND	Decreased	Decreased	Decreased
Myocytolysis	Decreased	ND	ND	ND	Decreased	ND	ND
Beta-adrenergic desensitization	Decreased	Decreased	Decreased	ND	Decreased	Decreased	Decreased
EC coupling	Increased	Increased	Increased	ND	Increased	Increased	Increased
Cytoskeletal proteins	ND	ND	ND	Increased	Increased	ND	Increased
Myocardial defects							
Myocyte apoptosis	Decreased	Decreased	Decreased	ND	Decreased	Decreased	Decreased
MMP activation	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Fibrosis	Decreased	Decreased	Decreased	Decreased	Increased*	Decreased	Decreased
Angiogenesis	Increased	Increased	Increased	Increased	Decreased	Increased	Increased
LV dilation	Decreased	Stabilized	Stabilized	Stabilized	Decreased	Decreased	Decreased

Reproduced with permission from Mann et al. (17)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; CSD = cardiac support device; EC = excitation-contraction; LV = left ventricular; LVAD = left ventricular assist device; MMP = matrix metalloproteinase; ND = not done.

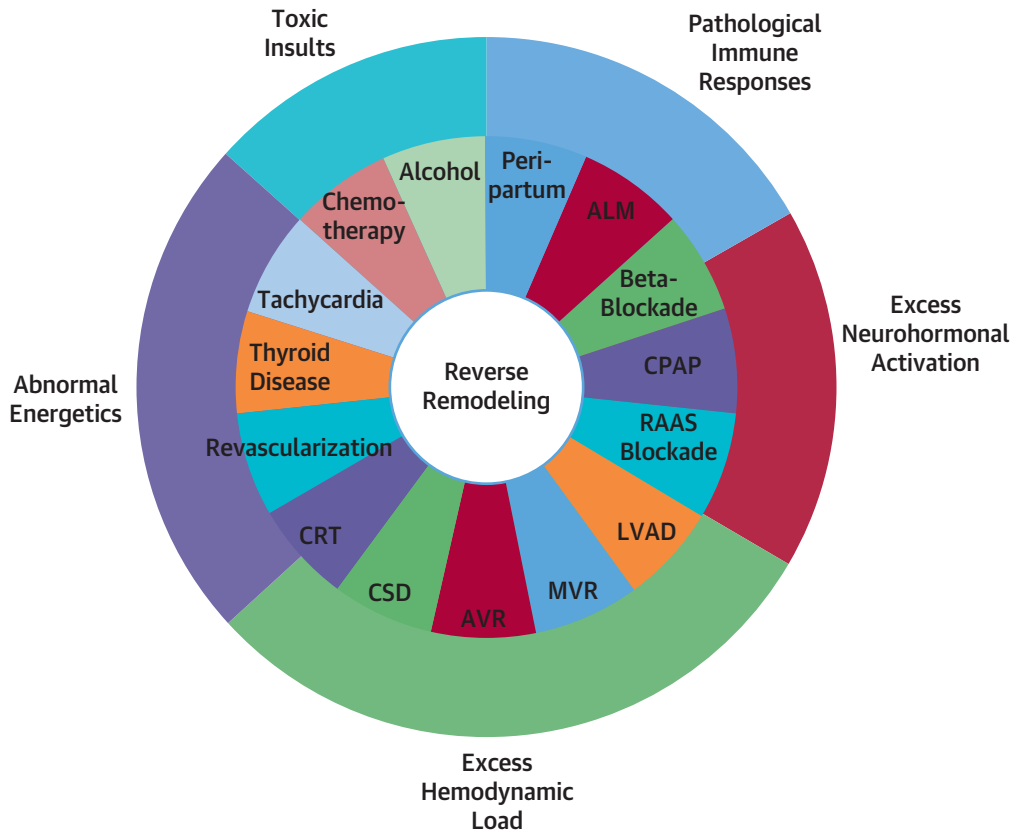
pathological hypertrophy resulting from a discrete process such as aortic stenosis ultimately entrains a wide variety of pathological signaling processes that contribute to the resultant structural and functional abnormalities; myocardial unloading likewise invokes varied and potent reverse LV remodeling signaling pathways. This is particularly evident in studies of hearts supported by a LV assist device (19,21) but also apparent after cardiac resynchronization therapy (CRT) (22), in which decreased cellular and chamber hypertrophy are accompanied by changes in gene expression that regulate different functional domains of the cell; these include the sarcomere, ß-adrenergic signaling, excitation contraction coupling, metabolism, and the cytoskeleton.

EPIDEMIOLOGY OF REVERSE LV REMODELING AND RECOVERY OF LV FUNCTION

Reverse LV remodeling with recovery of LV function can occur spontaneously in a variety of different clinical settings (**Figure 2**). These clinical observations provide clues to the underlying biology of reverse LV remodeling. Remarkably, recovery of LV function occurs in a significant proportion of individuals even when the severity of HF or cardiac dysfunction is severe. Spontaneous recovery of LV function most commonly occurs after resolution of the inciting stress that compromised myocardial function. As shown in **Figure 2**, 3 major etiologies of myocardial injury are associated with spontaneous recovery of LV function and reverse LV remodeling: abnormal energetics, toxic insults, and inflammation. The highest rates of recovery of LV function have been associated with amelioration of adverse metabolic or energetic circumstances known to compromise cardiac function such as chronic tachycardia, hyperthyroidism, and hypothyroidism (16,23). The second highest rates of recovery of LV function have been associated with dilated cardiomyopathies that are associated with immune responses, such as peripartum cardiomyopathy, acute lymphocytic myocarditis, and the systemic inflammatory response syndrome. Recovery of LV function has also been associated with the discontinuation of cardiotoxins, most commonly ethanol and cancer chemotherapies, including anthracyclines, tyrosine kinase inhibitors, and monoclonal antibodies (16). There also seem to be differences in recovery of LV function in DCM among women and men, as well as White and Black patients, with greater recovery of LV function and event-free survival in women and White patients (24).

A large body of evidence shows reverse LV remodeling and recovery of LV function after implementation of evidence-based medical, device-based, and surgical interventions in patients with chronic HFrEF. Because this topic has been reviewed extensively elsewhere (16,25), it is discussed here only briefly. Numerous studies in patients with ischemic heart disease have shown that there is substantial potential for reverse LV remodeling after coronary artery revascularization (26). Although the role of myocardial viability testing in this setting remains uncertain, multiple studies have reported that there is a greater likelihood of improved LV function, functional capacity, and survival after revascularization when viable myocardial segments are present.

FIGURE 2 Recovery of LVEF in Clinical Settings



The segments of the outmost ring highlight pathophysiological processes implicated by reverse left ventricular remodeling, in particular clinical settings that comprise the middle ring. Reproduced with permission from Hellawell et al. (16). ALM = acute lymphocytic myocarditis; AVR = aortic valve replacement; CPAP = continuous positive airway pressure; CRT = cardiac resynchronization therapy; CSD = cardiac support device; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MVR = mitral valve repair/replacement; RAAS = renin-angiotensin-aldosterone system.

Pharmacological inhibition of the sympathetic nervous system and the renin-angiotensin-aldosterone system have also been associated with reverse LV remodeling, improved LV function, and improved clinical outcomes. Among the different evidence-based neurohormonal antagonists, the use of beta-adrenergic blockers are most strongly associated with reverse LV remodeling. Although there is substantial evidence that antagonism of the renin-angiotensin-aldosterone system prevents forward LV remodeling, the evidence for regression of established LV remodeling is less definitive for angiotensin-converting enzyme inhibitors and aldosterone antagonists (25). However, treatment with angiotensin receptor blockers is associated with significant reductions in LV internal diastolic diameter and increases in LVEF (4). More recently, treatment with sacubitril/valsartan was shown to induce reverse LV remodeling and improve LV function in patients with HFrEF (27). Viewed together, these studies implicate adrenergic and renin-angiotensin-aldosterone system signaling in the pathogenesis of forward LV remodeling and indicate that mitigating these mechanisms favors reverse LV remodeling. **Table 2** summarizes established clinical predictors of reverse remodeling.

The prevalence of HFrecEF has been gleaned primarily from retrospective single-center reports or aggregated from a few centers with research databases. In one of the first reports to carefully characterize such patients, Punnoose et al. (28) noted that the prevalence of heart failure with a recovered LVEF was 34% in their center; notably, 70% of patients labeled as HFpEF had documentation of prior HFrEF. Patients with HFrecEF with a baseline LVEF <40% that improved to an LVEF >40% were younger, less likely to have coronary artery disease, and had fewer

TABLE 2 Predicting Reverse LV Remodeling Among Patients With HFrEF

	Predictors of Reverse LV Remodeling
Clinical parameters	Nonischemic etiology Lower duration of HF Female No LBBB LBBB in CRT
Genetic factors	Pathogenic gene variants not involving structural cytoskeletal proteins or Z-disk proteins
Echocardiography/CMR imaging	Lower LVEF, greater contractility on strain imaging Greater LV diameters LGE absence
Biomarkers	Lower NT-proBNP Lower troponin Lower sST2 Galectin-3, emerging biomarkers (mimecan, microRNAs, orexin)

Modified with permission from Aimo et al. (58).

CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with a reduced ejection fraction; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST2 = soluble ST (suppression of tumorigenicity) 2.

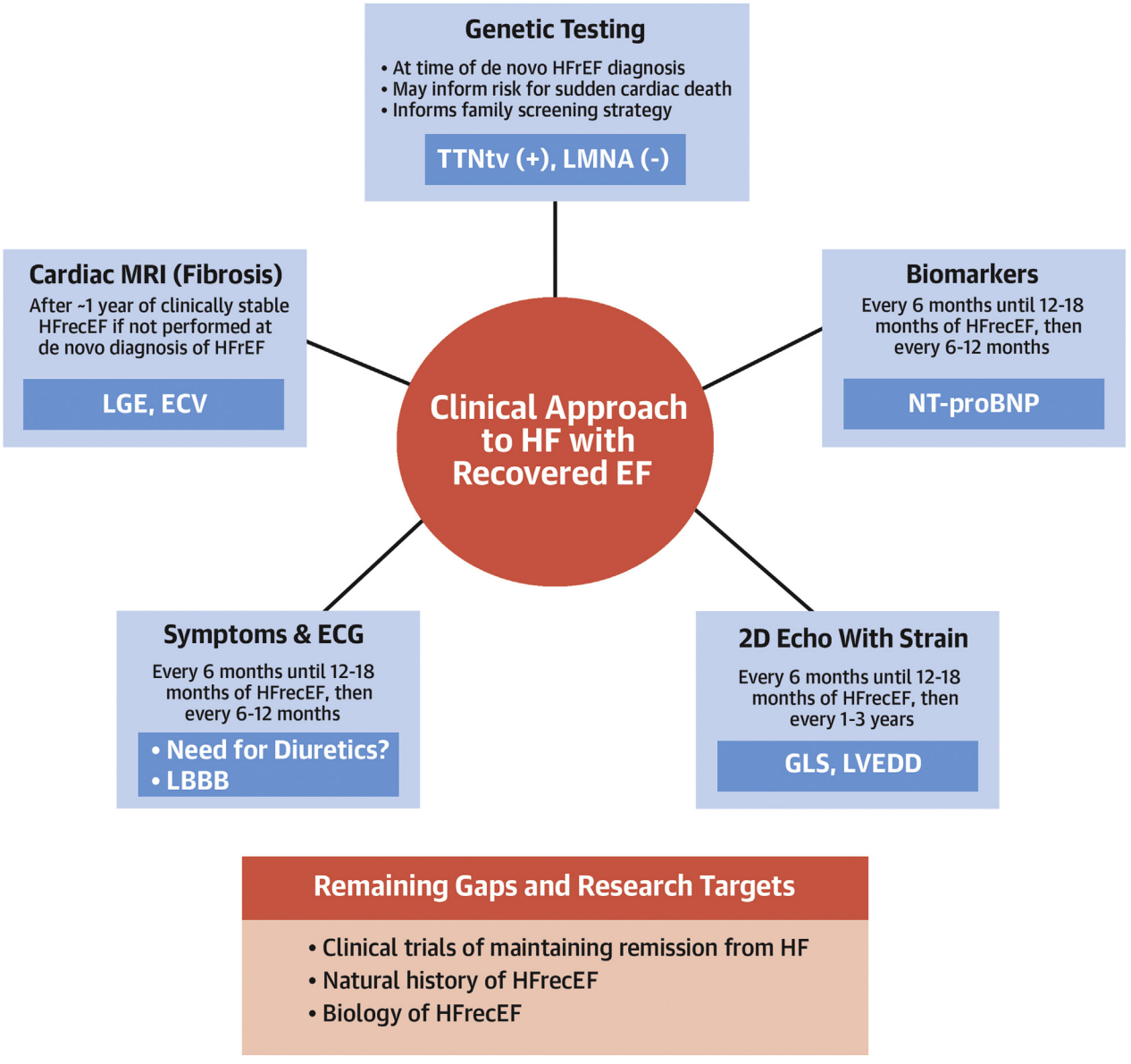
comorbidities. Basuray et al. (3) extended these preliminary findings in the 3-center collaborative Penn Heart Study, which followed up HF patients for almost 9 years. These authors defined HFrecEF as an LVEF >50% with prior documentation of an LVEF <50%. Of the entire cohort, only 10% (n = 176 of 1,821) were classified as HFrecEF, with an average improvement in LVEF of 28% over a mean of 29 months. Similar to the report by Punnoose et al. (28), the HFrecEF patients were younger and had less coronary disease with fewer comorbidities and symptoms. Importantly, HFrecEF patients were on comparable GDMT compared with HFrEF patients. The hazard ratio for all-cause death, cardiac transplantation, or left ventricular assist device placement in the HFrEF group versus the HFrecEF group was 4.1 (95% confidence interval: 2.4 to 6.8; $p < 0.001$), whereas the unadjusted hazard ratio for HFpEF versus HFrecEF was 2.3 (95% confidence interval: 1.2 to 4.5; $p = 0.013$). Intriguingly, the patients with HFrecEF had a risk of HF hospitalizations that was similar to that of patients with HFpEF (1.3; 95% confidence interval: 0.9 to 2.0; $p = 0.15$), as well as persistent biomarker evidence of inflammatory, neurohormonal, and myocardial injury. These findings were also confirmed in the prospective registry to Improve the Use of Evidence-Based Medical Therapies in the Outpatient Setting (IMPROVE-HF), which enrolled 3,994 patients (29), in which almost one-third (29%) of patients experienced a 10% absolute increase in LVEF (24.5% to 46.2%) over a 24-month follow-up. In this series, female sex, nonischemic etiology, and lack of myocardial infarction were associated with improvement in LVEF.

Larger, more contemporary series have generally confirmed these early observations and provided additional insights (30). In a prospective consecutive series of 1,057 patients from a university program in Spain with baseline and follow-up echocardiograms at 1 year, one-quarter of patients with a baseline LVEF <45% experienced an average increase of 21% in their LVEF. In addition to female sex, nonischemic etiology, and younger age, the investigators found that shorter duration of HF and absence of left bundle branch block predicted reverse LV remodeling and recovery of LVEF (31). In a cohort of ambulatory patients studied at Emory University, ~16% of patients with a baseline LVEF <50% recovered their LVEF >50% on GDMT. Patients with a recovered LVEF >50% had a decreased risk of HF hospitalizations, as well as all-cause and cardiovascular mortality compared with HFpEF and HFrEF cohorts (5). In the Heart Muscle Disease Registry of Trieste (32), Merlo et al. reported that 38 (9%) of 408 DCM patients recovered their LVEF >50% and normalized their LV end-diastolic dimension on GDMT. Importantly, ~40% of this subgroup experienced a subsequent decline in LVEF, and 5% required heart transplantation or died after 15 ± 4.7 years of follow-up.

Clinical trial data provide important insights into recovery of LVEF on GDMT insofar as the data are drawn from multiple centers in a prospective manner and are therefore less subject to survival bias than single-center studies. In the Val-HeFT (Valsartan Heart Failure Trial), 9% of patients (n = 3,517) with an LVEF <35% had an improved LVEF >40% at 1 year (4). Seven variables (male sex [odds ratio (OR): 0.69], ischemic origin [OR: 0.41], body mass index [OR: 0.96], diastolic blood pressure [OR: 1.01], left ventricular internal diameter/body surface area [OR: 0.5], baseline beta-blocker therapy [OR: 1.9], and valsartan treatment [OR: 1.5]) were independently associated with HFrecEF. However, even in the presence of all 7 factors, only a few of the patients had substantial recovery in LV function (median probability of HFrecEF: 0.15 [95% CI: 0.08 to 0.22]; area under the curve: 0.76 [95% confidence interval: 0.72 to 0.79]).

Dramatic responses among some HFrEF patients to cardiac resynchronization therapy (CRT), so-called super-responders, can also provide insight into HFrecEF (33). Patients with nonischemic HF, very wide QRS with left bundle branch block morphology, female sex, and echocardiographic evidence of dyssynchrony responded favorably to CRT. Notably, a small prospective randomized experience showed that 78% of super-responders experienced a deterioration in clinical and echocardiographic parameters within 12 months after CRT deactivation (34).

CENTRAL ILLUSTRATION **Clinical Assessment of Patients With Recovered Left Ventricular Ejection Fraction**



Wilcox, J.E. et al. J Am Coll Cardiol. 2020;76(6):719–34.

Clinical assessment of symptoms and electrocardiogram (ECG) can identify patients with heart failure with recovered ejection fraction (HFrecEF) at higher risk of relapse. The need for persistent diuretics and left bundle branch block (LBBB) represents higher risk subgroups. Absence of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging is a strong predictor of recovery or remodeling and is associated with improved prognosis. Elevated extracellular volume (ECV) values (suggested of edema or fibrosis) can also improve diagnostic understanding of specific cardiomyopathies. Higher absolute global longitudinal strain (GLS) (e.g., >16%) is associated with stability of left ventricular ejection fraction over short-term follow-up and higher GLS even among dilated hearts is associated with HFrecEF status. Prognosis in genetic dilated cardiomyopathy varies, with truncating variants of the titin gene (TTNtv) more likely to respond favorably to guideline-directed medical therapy and achieve HFrecEF status, and LMNA mutations less likely to respond and confer high risk for sudden cardiac death despite HFrecEF status. Greater reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) with neurohormonal heart failure (HF) therapy is associated with greater improvements in left ventricular structure and function, as well as improved clinical outcomes. A rise in NT-proBNP in HFrecEF patients may precede HF relapse. Gaps remain with regard to development of inception cohorts to better understand the natural history of HFrecEF, and additional clinical trials are needed to define which elements of clinical care are important for maintaining clinical remission, as well as basic studies to better define the biology of HFrecEF in order to develop new therapeutic targets. Echo = echocardiography; HFrEF = heart failure with reduced ejection fraction; LVEDD = left ventricular end diastolic dimension; MRI = magnetic resonance imaging.

TABLE 3 Recommended Interval Follow-Up for HFrecEF

Interval Follow-Up Time Period (After Meeting the HFrecEF Definition)	Clinical Examination and ECG	Holter Monitoring (24 h)	NT-pro BNP	Echocardiography With Mechanics (Strain)	CMR
Every 6 months (until 12–18 months of HFrecEF).	X		X	X	
After ~1 yr of "clinically stable" HFrecEF					X*
Every 6–12 months (at minimum).	X		X		
Optimal interval of echocardiography/imaging is unknown. It is reasonable clinical practice to assess durability every 1–3 yrs after stable recovery depending on etiology.				X	
Every 1–2 yrs for certain genetic cardiomyopathies at risk of atrial dysrhythmias (e.g., *TTN*).		X			

*Consider CMR if one was not performed at de novo diagnosis of HFrEF.
CMR = cardiac magnetic resonance; ECG = electrocardiogram; HFrecEF = heart failure with recovered ejection fraction; other abbreviations as in Table 2.

In summary, regardless of the definition of HFrecEF, the preponderance of data suggests that younger age, female sex, nonischemic etiology, shorter duration of disease, and fewer comorbidities are associated with higher likelihood of recovery of LVEF. Moreover, the clinical outcomes of HFrecEF patients are also improved compared with patients with HFrEF and HFpEF with respect to death. However, HF events still occur and symptoms remain present in HFrecEF patients, although they may be less frequent than in patients with HFrEF (31). A number of limitations of the available data should be recognized, including survival bias, the imprecise nature of quantitative data in the clinical setting, missing data, treatment disparities, and variable clinical protocols with respect to surveillance testing and therapeutic management.

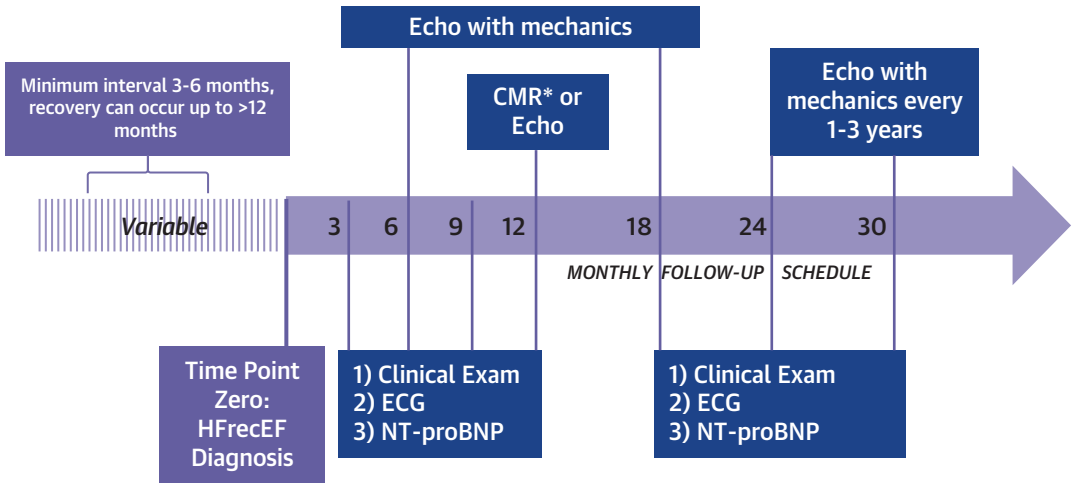
NATURAL HISTORY OF RECOVERED LVEF

Although reverse LV remodeling and recovery of LV function are associated with improved clinical outcomes, there is a growing body of evidence suggesting that, even among patients who experience a complete normalization of LV structure and function after implementation of GDMT, a significant proportion will develop recurrent LV dysfunction accompanied by recurrent HF events (3,32). The biological explanation for why some patients who have improved LV structure and function remain free from HF events ("myocardial remission") and why other patients who have a similar improvement in LV structure and function continue to have recurrent HF events is not known. One plausible explanation for this phenomenon, which is based on the consistent finding that the reverse remodeled heart retains many of the molecular features of the failing heart, is that reverse LV remodeling represents a transition to a new less pathological "steady state" that allows the heart to maintain LV pump function under normal conditions; however, this adaptation has less biological and contractile reserve capacity, and is therefore more prone to redevelop LV dysfunction in response to hemodynamic, neurohormonal, or environmental stress. Although the precise biological motifs that are responsible for this loss of reserve capacity are not known, it is likely that progressive loss of cardiac myocytes, persistent dysregulation of the transcriptome, metabolome, and proteome of cardiac myocytes, and the progressive erosion of the native 3-dimensional organization of the extracellular matrix surrounding the cardiac myocytes contribute to the stability of the reverse LV remodeled heart (17). This point of view is supported by the observation that the great majority of clinical examples of spontaneous recovery of LV function associated with durable clinical stability occur after transient injury (e.g., energetic defects or myocardial toxins), rather than more long-standing and/or permanent injury (e.g., myocardial infarction, genetic abnormalities).

ETIOLOGY OF THE CARDIOMYOPATHY MATTERS

Understanding the pathophysiological basis for HF is essential for understanding the prognosis and management of patients with HFrecEF. Indeed, management of specific types of cardiomyopathies is a burgeoning field, especially in the cardio-oncology arena, such as with trastuzumab-related ventricular dysfunction, and inflammatory responses to immune-checkpoint inhibitors (35). Monoclonal antibodies that block ErbB2 (HER2/neu) signaling (e.g., trastuzumab) disrupt cardiac homeostasis and myocardial repair and cause systolic and diastolic dysfunction. In a seminal paper, Narayan et al. (36) showed in a prospective cohort of 277 patients with breast cancer that trastuzumab therapy resulted in early LVEF

FIGURE 3 Sample Follow-Up and Clinical Testing Schedule for an HFrecEF Patient Deemed High-Risk for Recurrence of HF



Patients with heart failure with recovered ejection fraction (HFrecEF) at high risk of relapse (persistent left bundle branch block, genetic dilated cardiomyopathy, higher biomarker profiles, or more comorbidities) require close clinical follow-up, with biomarker and imaging, with shorter intervals immediately following HFrecEF diagnosis out to 12 months, and longer intervals thereafter. Abnormal or worsening global longitudinal strain (GLS) may identify patients at higher risk of HF relapse. *Consider CMR if was not performed at de novo time of HFrEF diagnosis. CMR = cardiac magnetic resonance; ECG = electrocardiogram; Echo = echocardiography; HF = heart failure; HFrEF = heart failure with a reduced ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

declines and incomplete recovery (e.g., persistent subclinical dysfunction) at 3 years. The echocardiographic parameters most consistently associated with LVEF decline were LV volumes, longitudinal and circumferential strain, arterial load, and the ventricular arterial coupling ratio.

Takotsubo cardiomyopathy has previously been considered a transient period of profound LV dysfunction brought on by emotional distress that resolves with absolute recovery of LVEF. However, Scally et al. (37) recently highlighted that in fact, despite a return to normal LVEF and normalization of serum biomarkers, patients with previous Takotsubo cardiomyopathy experienced persistent reduced apical circumferential strain and reduced global longitudinal strain on speckle-tracking echocardiography, as well as increased native T_1 mapping values on cardiac magnetic resonance (CMR). This persistent subclinical cardiac dysfunction is also characterized by a low-grade chronic inflammatory state with a myocardial macrophage inflammatory infiltrate and an increase in systemic proinflammatory cytokines (38). Moreover, recent data from the InterTAK Registry highlight the morbidity of Takotsubo cardiomyopathy, with long-term outcomes similar to those with acute coronary syndromes (39). However, at the time of manuscript writing, the proportion of patients with Takotsubo cardiomyopathy who will develop an HFrEF phenotype is unknown, nor is it clear whether these patients will benefit from continued GDMT.

Patients with alcohol-induced cardiomyopathy often have significant LV reverse remodeling following cessation of alcohol consumption (40). One observational study suggests improved durability of recovery over 15 years of follow-up among subjects with alcohol-induced cardiomyopathy compared with other HF etiologies; however, survival bias limits interpretation. Ware et al. (41) have reported a shared genetic predisposition in alcohol-induced cardiomyopathy and DCM, mostly due to truncating variants in *titin* (*TTN*). Given the cohort data showing similar prognosis compared with DCM (42), and other studies limited by survival bias, we recommend that medical therapy for HF generally be continued, even in HFrecEF patients with alcohol-induced cardiomyopathy.

Fulminant myocarditis is a relatively uncommon syndrome that is associated with excellent 11-year transplant-free survival of >90%, if patients survive the initial episode, which often requires acute mechanical support for cardiogenic shock (43). In a clinicopathological study from Johns Hopkins, a more

catastrophic clinical presentation was associated with higher likelihood of complete myocardial recovery in survivors of the acute episode (44). The biology of the fulminant presentation of myocarditis is likely different from the biology of acute myocarditis without fulminant presentation, given that these 2 conditions have dramatically different survival curves. In one study, nonfulminant acute myocarditis was associated with a 45% 11-year transplant free survival rate. In contrast, data from an international registry of fulminant and nonfulminant myocarditis revealed that cardiac death or transplantation occurred more frequently among adults with fulminant lymphocytic myocarditis compared with those with nonfulminant lymphocytic myocarditis at 60 days (19.5% vs. 0%; $p = 0.005$) and at 7 years of follow-up (41.4% vs. 3.1%; $p = 0.0004$) (45). Because of the conflicting nature of the long-term clinical outcomes for fulminant and nonfulminant myocarditis patients, we believe that it is prudent to continue GDMT therapy for both of these subpopulations of HFrecEF patients, pending additional long-term outcome data.

WORKING DEFINITION OF HFrecEF

Patients with HFrecEF represent a distinctly responsive subset of patients with HFrEF whose biological substrate for HF and clinical course are distinct from patients with HFrEF and HFpEF. We propose that these patients be referred to as HFrecEF, to denote that they were initially HF patients with a remodeled (e.g., dilated) left ventricle. This terminology also avoids confusing these patients with patients with HFpEF who have an LVEF >50%, as well as with patients with an intermediate LVEF (40% to 50%), which may represent HFpEF patients with deteriorating LVEF. As noted earlier, one of the major hurdles toward our understanding of this unique group of patients is the lack of standardization with regard to the definition of HFrecEF. A second limitation is that there are no current guidelines with respect to how these patients should be followed up. Accordingly, we propose the following general recommendations to guide clinical care:

- When identifying patients with HFrecEF, it is important to focus on the LVEF "trajectory" of the patient, recognizing that changes in LVEF integrate a number of different variables, including the nature and extent of myocardial injury, the degree and duration of LV remodeling, and the type of therapy that is being initiated.
- A working definition of HFrecEF that is consistent with the majority of studies in the literature includes: 1) documentation of a decreased LVEF <40% at baseline; 2) ≥10% absolute improvement in LVEF; and 3) a second measurement of LVEF >40%. These improvements in LVEF are typically accompanied by a reduction in LV volumes.
- Measurement of the changes in LVEF to ascertain HFrecEF should be obtained at least 3 to 6 months after the baseline LVEF, when the patient is stable hemodynamically, to avoid acute changes in LVEF that are secondary to changes in heart rate or loading conditions.

MANAGEMENT OF PATIENTS WITH RECOVERED CARDIOMYOPATHY

Despite an improvement in outcomes, patients with HFrecEF are still at risk for subsequent HF hospitalization and death relative to patients without HF and hence are not "normal" or truly cured from their HF (3,5,28). As discussed earlier, despite substantial reverse LV remodeling in certain patients, even with normalizing their LVEF and LV size, these improvements most often represent myocardial "remission" rather than a true cure of HF. Optimal clinical management of this significant population, albeit with a less severe phenotype, remains unclear due to lack of robust prospective data. In fact, there has only been one randomized-controlled clinical trial (discussed later) in 50 patients with nonischemic HFrecEF to assess the safety of weaning GDMT in this patient population (46). Using best available evidence, putative mechanistic insights, and clinical practice experience, we propose the following framework for assessment, surveillance, and treatment that can help inform the answers to these questions (**Central Illustration**).

CLINICAL EXAMINATION, SYMPTOMATOLOGY, AND ELECTROCARDIOGRAM. Jugular venous distension and signs of volume overload are particularly concerning in HFrecEF. Patients with HFrecEF who still require loop diuretics for symptom relief may represent a higher risk population, suggesting that they are at higher risk of recurrent HF events (i.e., relapse). Moreover, persistent exertional dyspnea is common, although usually less severe, and may reflect resting or exertional increases in pulmonary capillary wedge pressure, chronotropic incompetence, pulmonary hypertension, lack of systemic vasodilator reserve, and/or microvascular dysfunction.

The electrocardiogram (ECG) is also a cost-effective modality to risk-stratify patients with HFrecEF. Although left bundle branch block is predictive of

CRT response, it is associated with lower likelihood of improvement with GDMT alone (47). In addition, parameters of repolarization heterogeneity on surface ECG (e.g., QRST angle, QT dispersion) are associated with myocardial recovery among patients with acute HF and nonischemic cardiomyopathy (48). In the absence of a complete normalization of the ECG, it should be assumed that myocardial disease remains present.

FAMILY HISTORY OF DCM AND EVALUATION OF UNDERLYING GENETIC RISK. A thorough 3-generation family history is always recommended among patients with nonischemic DCM, regardless of the LVEF or clinical trajectory, insofar as there are implications for the patient's prognosis and recovery as well as offspring and other first-degree relatives. All first-degree relatives of a DCM proband are recommended to undergo clinical screening with echocardiography, ECG, and clinical examination (49). In addition, we recommend that clinicians should have low threshold to perform genetic testing even among those with recovered DCM, because the results may inform prognosis about durability of recovery, risk for HF relapse or sudden death, and risk for atrial arrhythmias, in addition to informing HF risk for family members. Herman et al. (50) published seminal findings in 2012 that 15% to 25% of cases of DCM were associated with rare truncating *TTN* variants. In addition, Ware et al. (51) have shown that 15% of women with *peripartum cardiomyopathy* carried truncations in *TTN*. Titin is the largest protein in the heart, spanning the length of the sarcomere, from the Z disc to the M band, and it functions as a molecular spring that regulates contraction. In contrast to other known genetic etiologies of DCM, truncating variants in *TTN* are compatible with recovery after exposure to GDMT (52,53) and left ventricular assist device unloading; however, it should be emphasized that the sustainability of these improvements are not well characterized.

Another important consideration in the care of the HFrecEF patient is determining the risk of sudden cardiac death (SCD), a risk that still persists in certain underlying genetic cardiomyopathies, despite recovery of LVEF. For example, pathogenic mutations in *DSP, SCN5A, LMNA,* and *FLNC* carry a significantly higher risk of malignant arrhythmias compared with other genetic and nongenetic etiologies of DCM (54–57) despite therapy with GDMT and improvements in LVEF.

BIOMARKERS. Circulating biomarkers are influenced by intrinsic myocardial properties as well as peripheral and local metabolic factors. Because they reflect generally distinct mechanistic pathways of myocardial injury and repair, biomarkers such as natriuretic peptides (ventricular remodeling), troponin (myocardial injury), ST2 (inflammation), and galectin-3 (fibrosis) can provide independent additive prognostic information in HFrEF (58). Relevant to HFrecEF, a greater reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) with GDMT is associated with greater improvements in LVEF and greater reduction in LV volumes as well as improved clinical outcomes (59). A subsequent study showed that multiple biomarkers are associated with improvements in LVEF (60). Because there is a risk of recurrent LV dysfunction in HFrecEF (61,62), consideration should also be given to performing serial measurements of specific biomarkers over time, in conjunction with regular surveillance provider visits and selected imaging modalities.

2-DIMENSIONAL ECHOCARDIOGRAPHY. In addition to clinical status, responder status to GDMT is ultimately determined by 2-dimensional echocardiography. Specific echocardiographic features are characteristic of HFrecEF, including decreases in LV end-systolic and end-diastolic volumes, improvements in functional mitral regurgitation, and the lack of right ventricular dysfunction (27,63). Despite improvements in gross myocardial functioning, global longitudinal strain and diastolic function rarely normalize in HFrecEF (62). However, among HFrecEF patients, higher global longitudinal strain (e.g., >16% absolute global longitudinal strain) is associated with stability of LVEF over short-term follow-up (~2 years). Swat et al. (64) further showed that higher baseline absolute longitudinal strain (e.g., >8%) is associated with HFrecEF status in a retrospective cohort of DCM patients with acute decompensated HF, even among patients with larger left ventricular dimensions.

CMR IMAGING. CMR is best utilized to characterize the myocardial substrate around the time of de novo diagnosis of HFrEF to provide insights into etiology. For example, the pattern of late gadolinium enhancement can be very suggestive of specific cardiomyopathies, such as sarcoidosis and certain muscular dystrophies (65,66). The presence and extent of late gadolinium enhancement are also predictors of response to neurohormonal HF therapy and risk prediction in both ischemic (67) and nonischemic (68,69) conditions. In nonischemic cardiomyopathy, the absence of late gadolinium enhancement is a strong predictor of recovery or remodeling and is associated with improved prognosis (70). The use of T_1 mapping to measure extracellular volume and

interstitial fibrosis (71) shows promise as another predictor of response to therapy and improved prognostication in HF (72). However, the utility of CMR after some degree of LV remodeling or recovery has occurred is largely unknown.

CLINICAL SCENARIOS. Within the framework of the information and the limitations discussed here, we propose the following answers to frequently asked clinical questions in managing patients with HFrecEF.

1. Can any or all of the HF medications be stopped in HFrecEF? Is there a "signature" for cure? In the open-label randomized pilot TRED-HF (Withdrawal of Pharmacological Treatment for Heart Failure in Patients With Recovered Dilated Cardiomyopathy) trial, the investigators tested the hypothesis that GDMT could be withdrawn in asymptomatic HFrEF patients if the LVEF rose from <40% to >50%, the left ventricular end-diastolic volume normalized, and NT-proBNP was <250 ng/l after treatment (46). After screening 936 patients, 51 patients were randomized to either a phased withdrawal protocol of the HF GDMT or continued therapy with GDMT; the participants initially randomized to continued therapy also had their medications weaned. Within 6 months, 11 (44%) of 25 from the first withdrawal group and 9 (36%) of 25 from the second group experienced a recurrence of HF, defined by a fall in LVEF >10% to <50%, an increase in left ventricular end-diastolic volume >10% to greater than the normal range, a doubling of the NT-proBNP to >400 ng/l, or clinical evidence of HF. Importantly, there were no deaths. Based on this single randomized trial and clinical reports reviewed herein, we recommend not stopping GDMT in patients with HFrecEF unless there are mitigating circumstances. In this regard it is notable that in TRED-HF, the recurrence of HF occurred over months, rather than days or weeks, after weaning GDMT. Accordingly, if patients with HFrecEF stop neurohormonal antagonists for several days due an intercurrent illnesses or for some other clinical reason, it is unlikely that they will redevelop recurrent HF in the immediate short term.

Cessation of diuretic agents is encouraged among recovered-EF patients; indeed, the ability to tolerate the lack of diuretics may be indicative of a lower risk of recrudescent HF in HFrecEF (73). We recommend that if a patient with HFrecEF continues to require diuretics, then further titration of GDMT (to target doses) should be considered. In addition, consideration should be given to substituting an angiotensin receptor neprilysin inhibitor for an angiotensin-converting enzyme inhibitor. Recent pooled analyses of the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Global Mortality and Morbidity in Heart Failure) and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trials revealed that the therapeutic effects of sacubitril/valsartan, compared with a RAS inhibitor alone, seem to extend to patients with HF and mildly reduced EF (74). It is likely that most patients with HFmrEF in current clinical practice have HFrecEF, which likely explains why there is a therapeutic benefit for continued neurohormonal blockade in HFmrEF (74,75). In our experience, if there is uncertainty around whether to continue GDMT in a particular patient, medications should be continued because of the clinical observation that, among patients who experience a relapse and recurrent decline in LVEF, there is a higher likelihood of recurring myocyte injury and a diminished ability to recover LVEF the second time around.

2. How should these patients be followed up? What should be the frequency of follow-up? Table 3 summarizes our consensus recommendation for interval testing to guide management in HFrecEF patients. Once patients with HFrecEF are deemed "stable" for at least 1 year by the treating provider, we recommend that they should be seen every 6 months for at least 3 years, then every year at minimum due to the risk of relapse and HF hospitalization (3,5,28,76). Such a practice ensures regular laboratory surveillance (e.g., biomarker data), review of symptoms and signs of HF, and to encourage compliance with polypharmacy, a well-known limitation in chronic conditions, particularly when such conditions are asymptomatic.

Follow-up imaging is clearly part of surveillance to assess for durability of recovery, and the interval of imaging is patient and risk dependent. The current echocardiographic-appropriate use criteria do not discuss this patient population (77). Based on available data (acknowledging its limitations) and our clinical experience, we suggest that echocardiography be performed annually for the first 2 years at a minimum to assess durability of recovery (62), or earlier if signs and/or symptoms of HF develop. Imaging intervals can be lengthened after a period of stability; however, the optimal frequency is unclear at the time of this writing. Given that the durability of LV function in HFrecEF is uncertain, we recommend that patients should be imaged at least every 3 to 5 years until further longitudinal data can be obtained on this patient population. Patients at higher risk (e.g., those with persistent left bundle branch block, genetic DCM, higher biomarker profiles, more comorbidities) may be

selected for a shorter interval of imaging follow-up. In addition, patients with long-term HFrecEF may relapse due to a newly acquired condition, such as coronary disease, or new onset of atrial fibrillation that was not present when diagnosed at an earlier time point or the appearance of a new arrhythmia. HFrecEF patients should be vigilantly followed up as described earlier, and clinicians should recognize that not all recrudescent HF is "failure of GDMT," and new concurrent cardiac conditions may be an underlying explanation. **Figure 3** shows an example of a follow-up schedule for an HFrecEF patient deemed to be higher risk for HF relapse.

3. Is implantable-cardioverter defibrillator generator change indicated in HFrecEF patients? It is unclear if the subset of HFrecEF patients who had an implantable-cardioverter defibrillator (ICD) placed for primary prevention of SCD when the LVEF was ≤35% continue to benefit from ICD therapy after the LVEF has improved. However, the greater duration of documented LV dysfunction may place the HFrecEF subgroup with an ICD in an inherently higher risk SCD category than an HFrecEF patient who recovered to an LVEF >35% to 40% within a relatively short time frame, and therefore did not meet appropriate use criteria for ICD implantation (78). A recent meta-analysis supports the notion that there is persistent arrhythmic risk among recovered EF patients, with a 3.3% per year rate of appropriate ICD therapy among those with LVEF ≥45% (79). An analysis of SCD HeFT (Sudden Cardiac Death in Heart Failure Trial) showed that patients who had an improvement in EF to >35% during follow-up accrued a similar mortality benefit with an ICD as those whose EF remained at ≤35% (80).

Device therapy in HFrecEF patients is not specifically addressed in current practice guidelines (81). However, guidelines do mention that ICD therapy may be appropriate for patients who carry certain pathogenic genetic mutations associated with high arrhythmia risk regardless of LVEF if clinical HF is present (49). Because fatal arrhythmias may occur despite normalization of LVEF, considerations for prophylactic placement of an ICD have been recommended independent of EF for specific mutations in genes such as *LMNA, SCN5A,* and *FLNC* (82–84).

There are no prospective trials of ICD therapy among HFrecEF populations; however, based on the best evidence to date, the data would support ICD generator change for most patients with HFrecEF (85), especially if a deleterious genetic mutation associated with high arrhythmia risk is present, history of appropriate shocks is documented, or the ECG remains abnormal. As a rule, CRT should be maintained because electrical dyssynchrony and forward LV remodeling are known to recur with loss of resynchronization (33,86).

GAPS IN KNOWLEDGE/FUTURE PERSPECTIVES

We have learned a great deal about the biology, epidemiology, clinical predictors, and outcomes of reverse LV remodeling and recovery of LV function over the past 2 decades. Unfortunately, far less is known about the biology, natural history, and the long-term clinical outcomes for HFrecEF patients. This knowledge gap represents a significant unmet clinical need, insofar as it is directly relevant to the reemergence of clinical HF in this seemingly stable patient population. Until recently, these HF readmissions have been ascribed to inadequate clinical care. As discussed in the current review, the redevelopment of HF in patients with HFrecEF likely has more to do with our lack of understanding with respect to how to manage HFrecEF than to inadequate clinical care.

We believe that future research in this area will benefit from improved phenotyping of HFrEF patients to guide care, developing inception cohorts of HFrecEF patients to better understand the natural history of HFrecEF and additional clinical trials to define which elements of clinical care are important for maintaining clinical remission, as well as basic studies to better define the biology of HFrecEF. The goal is to develop new therapeutic targets that will enable patients with HFrecEF to experience a durable remission from HF.

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