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STATE-OF-THE-ART REVIEW

Management of Heart Failure With Improved Ejection Fraction

Current Evidence and Controversies

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HIGHLIGHTS

- Current guidelines recommend sustained and indefinite treatment of HFimpEF due to concerns of relapse.
- Patients with HFimpEF are likely heterogeneous, with unique underlying etiology and pathophysiology rendering differential prognosis.
- Relapse risk could be further assessed using advanced imaging, natriuretic peptides, genetic testing, and electrocardiogram findings.
- Partial de-escalation of GDMT might be safe in patients with low risk of relapse, although large trials are needed.

ABSTRACT

Heart failure with improved ejection fraction (HFimpEF) is defined by improved left ventricular ejection fraction (LVEF) among patients who previously had reduced LVEF. HFimpEF is associated with improved prognosis, albeit with persistent risk of relapse and adverse events in some patients. Current guidelines thus recommend sustained and indefinite guideline-directed medical therapy (GDMT) for all patients with HFimpEF. Emerging clinical experience suggests that heart failure arising from acute etiologies that fully resolve along with complete LVEF recovery may have a favorable prognosis with lower risk of relapse. Indeed, cohort and case series studies have demonstrated the feasibility of safe de-escalation of GDMT in select patients with specific etiologies, with multiple small trials ongoing. Future studies should investigate whether advanced imaging or blood biomarkers could aid in risk stratifying patients with recovered LVEF, whether partial de-escalation of GDMT could be safe and feasible, and whether implantable cardioverter-defibrillator therapy can be safely discontinued. (JACC Heart Fail. 2025;13:537–553) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HFimpEF = heart failure with improved ejection fraction

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

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

RAS = renin-angiotensin system

SGLT2i = sodium-glucose cotransporter 2 inhibitor

Among patients with heart failure (HF) with reduced ejection fraction (HFrEF), defined by left ventricular ejection fraction (LVEF) ≤40%, roughly 10% to 60% experience improvement of LVEF (**Figure 1**, Supplemental Table 1); this may occur either spontaneously or because of treatment with guideline-directed medical therapy (GDMT).[1,2] This phenomenon has recently been termed "heart failure with improved ejection fraction (HFimpEF)," which is defined by an absolute improvement of LVEF by ≥10% to >40%.[1,2] HFimpEF is associated with improved prognosis compared with persistent HFrEF, although evidence suggests persistent risk of relapse and adverse events in some patients (**Figure 2**).[1,2] In recent years, a greater understanding of the pathophysiologic processes underlying myocardial dysfunction has shaped our current conceptual framework that full myocardial recovery might be unlikely in many patients with HFimpEF, drawing a distinction between full recovery and mere remission.[2] This current framework was supported by the TRED-HF (Withdrawal of Pharmacological Treatment for Heart Failure in Patients with Recovered Dilated Cardiomyopathy) trial, which found that complete de-escalation of GDMT resulted in relapse in a subset of patients who had previously achieved complete LVEF recovery.[3] Consequently, the latest clinical guidelines recommend that all patients with HFimpEF should continue to receive full-dosage GDMT indefinitely.[4] Nevertheless, there is ongoing debate as to whether *all* patients require indefinite full-dosage GDMT to prevent relapse, or whether certain patients might be able to safely de-escalate GDMT, at least partially. This question is of great clinical significance because it weighs the benefits of decreased medication burden and side effects as well as potentially reduced financial costs against the risks of relapse and adverse events.

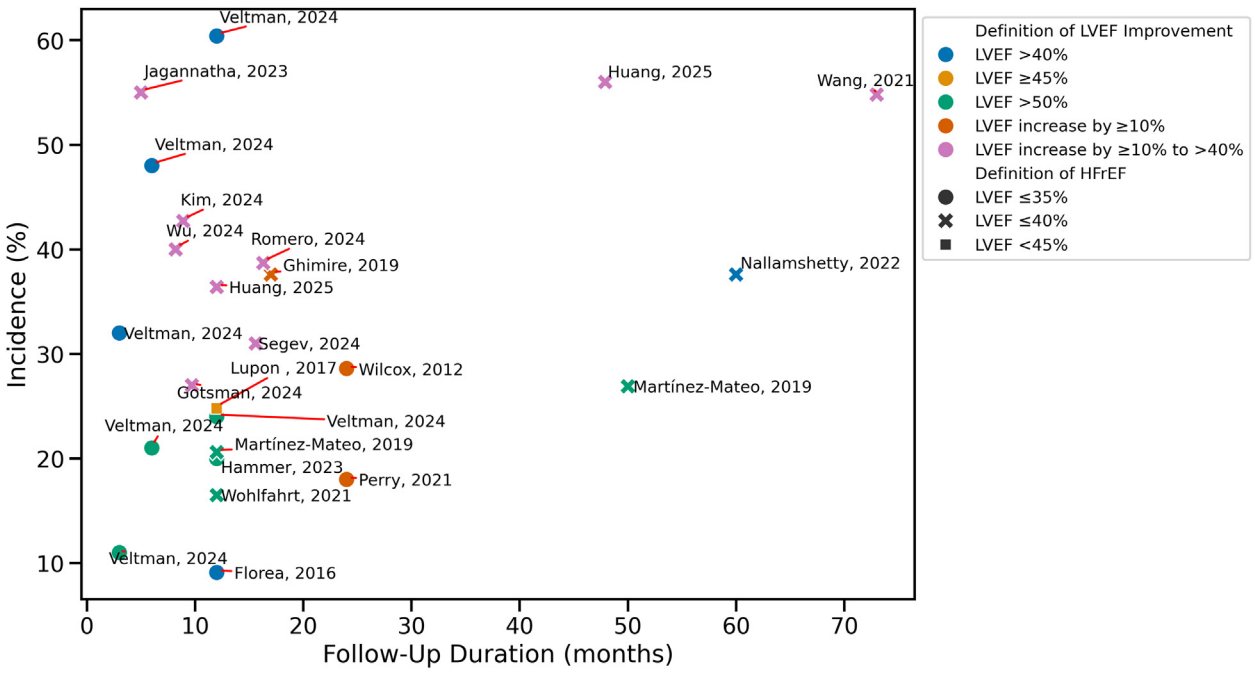
Herein, we first critically review the evidence supporting the current management recommendations for HFimpEF. We then discuss the existing knowledge gaps, including limitations of current diagnostic assessments and the current definition of HFimpEF, as well as uncertainty regarding management of GDMT and implantable cardioverter-defibrillator (ICD) therapy. Finally, we conclude by describing evidence from cohort studies, case series studies, and clinical trials investigating de-escalation of GDMT based on various etiologies of HFrEF. In doing so, we highlight not only the promises of these studies but also the limitations, emphasizing the need for more robust data from large-scale clinical trials with long-term follow-up before routine de-escalation of GDMT can potentially be considered.

PHARMACOLOGIC MANAGEMENT OF HFimpEF: CURRENT EVIDENCE AND NEW INSIGHTS

FINDINGS FROM THE TRED-HF TRIAL. The TRED-HF trial investigated whether GDMT could be safely withdrawn in 51 adult patients who had dilated cardiomyopathy (DCM) and previously had LVEF <40% with subsequent complete LVEF recovery (≥50%) for at least 6 months, normalization of left ventricular end-diastolic volume, reduction of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels to <250 ng/L, and were deemed asymptomatic (**Table 1**).[3] Notably, the patient cohort had a relatively low burden of comorbidities. Eligible patients were randomized to either stepwise withdrawal of GDMT (n = 25) or continuation (n = 26). After 6 months, patients in the GDMT continuation arm crossed over to the withdrawal arm as part of a single-arm crossover methodology. Over 6 months of follow-up, relapse of DCM occurred in 20 patients (40%), along with reinitiation of treatment in 25 patients (50%). Interestingly, relapse was mostly asymptomatic, as independently adjudicated. Of the 20 patients who relapsed, 17 (85%) maintained or re-achieved LVEF >50% upon reinitiation of medication. Overall, these results strongly suggest that many patients with DCM who experience improvement of myocardial function are merely in remission rather than having achieved full recovery, which is consistent with prior studies demonstrating persistent neurohormonal activation among many patients with LVEF recovery.[5]

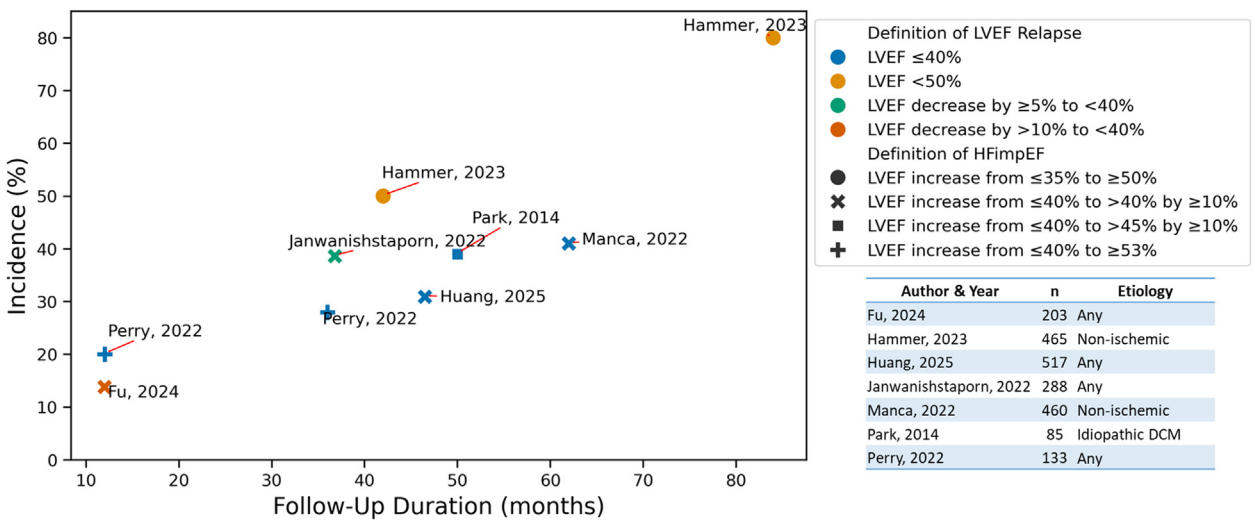
A recent prospective follow-up study of the 51 patients in TRED-HF found that 9 patients experienced recurrent relapse and 13 patients experienced new relapse at 5 years following trial completion (43%), despite the fact that participants were recommended to restart pharmacotherapy (**Table 1**).[6] Notably, the average intensity of pharmacotherapy was found to be reduced among patients during long-term follow-up compared with at trial enrollment, with 7 of the 13 patients who experienced new relapse being on low-intensity pharmacotherapy and 4 not being on any pharmacotherapy at all. Overall, 33 of 51 patients (65%) experienced at least 1 episode of relapse over a median follow-up of 6 years post enrollment into TRED-HF. Interestingly, 5 patients (10%) remained free from relapse throughout the entire follow-up duration while also remaining free of pharmacotherapy.

FIGURE 1 **Reported Estimated Incidence of LVEF Improvement Among Patients With HFrEF**



Listed for each study is the first author and year as well as the definitions for HFrEF and LVEF improvement. Note that the exact LVEF definitions used in studies by Florea, Hammer, Wilcox, Nallamshetty, and Wohlfahrt have been slightly adapted to simplify the figure. Full study details and references can be found in Supplemental Table 1. HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

FIGURE 2 **Reported Estimated Incidence of LVEF Relapse Among Patients With HFimpEF**



Author & Year	n	Etiology
Fu, 2024	203	Any
Hammer, 2023	465	Non-ischemic
Huang, 2025	517	Any
Janwanishstaporn, 2022	288	Any
Manca, 2022	460	Non-ischemic
Park, 2014	85	Idiopathic DCM
Perry, 2022	133	Any

Listed for each study is the first author and year, the definitions for HFimpEF and LVEF relapse, and the sample size. Note that the exact LVEF definitions used in studies by Janwanishstaporn, Park, and Perry have been slightly modified to simplify the figure. Full study details and references can be found in Table 2. DCM = dilated cardiomyopathy; HFimpEF = heart failure with improved ejection fraction; other abbreviation as in Figure 1.

TABLE 1 Key Findings From the TRED-HF Trial and Its Follow-Up Studies

TRED-HF Study Design	Cohort	Substudy	Key Findings
Pilot, open-label, randomized, controlled, single-arm crossover trial investigating phased and total withdrawal of HF medications (including beta-blockers, RAS inhibitors, MRA, and loop diuretic agents), with all patients ultimately undergoing total medication withdrawal over a follow-up period of 6 mo	51 adult patients with a history of HF meeting the following inclusion and exclusion criteria: Key inclusion criteria: • Previous DCM and LVEF <40% with subsequent LVEF recovery to ≥50% for at least 6 mo • Normalization of left ventricular end-diastolic volume as assessed by CMR • Reduction of NT-proBNP levels to <250 ng/L • Asymptomatic Key exclusion criteria: • Arrhythmia requiring treatment with beta-blockers • Advanced chronic kidney disease • Advanced valvular disease • Uncontrolled hypertension In terms of etiology, 35 patients had idiopathic DCM, 7 had familial DCM, and 9 had DCM secondary to an environmental insult or other medical condition; 11 patients had a likely pathogenic truncating mutation in the *TTN* gene	Trial results[3]	• At 6 mo of follow-up, 20 of 51 patients (~40%) experienced relapse of DCM, as defined by either a reduction in LVEF of >10% to <50%, an increase in left ventricular end-diastolic volume by >10% and to greater than normal range, a 2-fold rise in NT-proBNP levels to >400 ng/L, or clinical evidence of HF • Relapse was mostly asymptomatic, as independently adjudicated • Medication was reinitiated in 25 patients overall, including the 20 patients who experienced relapse • Of the 20 patients who experienced relapse, 17 (85%) maintained or re-achieved LVEF >50% upon reinitiation of medication • Baseline characteristics associated with increased risk of relapse included older age, higher NT-proBNP levels, lower peak global radial strain, treatment with MRA, and treatment with more than 2 HF medications
		Post hoc analysis[14]	• Increases in mean heart rate and blood pressure were among the earliest clinical predictors of relapse, with changes in these markers occurring as quickly as within 4 to 8 wks following initiation of treatment withdrawal • Changes in NT-proBNP levels were found to be a delayed predictor of relapse
		Prospective cohort follow-up study[6]	• At long-term follow-up of 5 y following completion of TRED-HF, 9 patients experienced recurrent relapse and 13 patients experienced new relapse • Despite all patients being advised to restart and continue pharmacotherapy post-trial, the average intensity of pharmacotherapy was reduced among patients at long-term follow-up compared with at trial enrollment, with 7 patients who experienced new relapse being on low-intensity pharmacotherapy and 4 not being on any pharmacotherapy at all • Of the overall 22 episodes of relapse during the long-term follow-up period, roughly one-third were attributable to an identifiable trigger, including arrhythmia, pregnancy, hypertension, or infection • A history of atrial fibrillation was associated with reduced risk of relapse • Notably, 5 patients remained free from relapse throughout the entire long-term follow-up duration while also remaining free of pharmacotherapy • Overall, 33 of 51 patients (65%) experienced at least 1 episode of relapse over a median follow-up of 6 y post enrollment into TRED-HF

CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RAS = renin-angiotensin system; TRED-HF = Withdrawal of Pharmacological Treatment for Heart Failure in Patients with Recovered Dilated Cardiomyopathy.

NEW INSIGHTS INTO THE TRED-HF TRIAL. Although a pilot study such as TRED-HF cannot provide definitive evidence for the safety of treatment withdrawal, it can certainly provide definitive evidence of harm. Thus, despite the limitations of TRED-HF, such as the unblinded, single-center study design with a small sample size and short-term follow-up, this trial demonstrates that routine withdrawal of GDMT in patients with DCM and recovered LVEF should currently be avoided unless necessary. Nevertheless, there are some interesting observations that warrant identifying more accurate definitions of full recovery, more sensitive predictors of relapse, and safer and more feasible strategies for de-escalation of GDMT. First, and often overlooked, is that a relatively large proportion of patients in TRED-HF (60%) did not experience relapse during the study period at 6 months of follow-up, despite being off of all GDMT.[3] Moreover, during long-term follow-up at 6 years post enrollment, some patients were able to remain free from relapse without requiring pharmacotherapy.[6] It is therefore conceivable that a subset of patients with

HFimpEF with normalization of cardiac structure and function may have sufficient physiologic myocardial recovery (ie, full recovery as opposed to remission) that allows for safe de-escalation of GDMT. Second, the TRED-HF investigators identified some baseline clinical markers that could potentially distinguish between patients who are merely in remission vs those who have fully recovered, including modestly elevated NT-proBNP levels and the potential presence of pathogenic genetic variants in those who experienced relapse.[3,6] This implies that complete myocardial recovery should be better defined beyond using contemporary imaging measures alone, and that more stringent criteria that also account for underlying substrate vulnerabilities and the specific etiology of HFrEF should be considered. This is especially important given that LVEF measurements derived from 2-dimensional echocardiography may be subject to inter- or intra-assessor variability of up to 10% in absolute terms, which is some cases may result in misclassification of patients from HFrEF to HFimpEF or vice versa.[7] Moreover, clinical characteristics and biomarkers could be used to further risk stratify patients with HFimpEF based on risk of relapse (**Table 2**). Interestingly, even simple clinical characteristics such as duration to LVEF recovery from the onset of HFrEF diagnosis might offer unique insight into the degree to which myocardial damage is reversible (with a shorter duration to LVEF recovery presumably portending a more favorable prognosis).[8] Third, the protocol of total GDMT de-escalation was structured to be completed within an overall 16-week period with 50% reduction in the dosage of each drug across 2-week intervals, with the large majority of cases of relapse occurring within the first 8 weeks.[3] Whether a slower pace of de-escalation or a partial de-escalation strategy might be safer and more feasible are questions of interest. Also, although it is reassuring that there were no major adverse cardiovascular events during the 6-month study period, the long-term adverse consequences following even a brief episode of relapse remain largely uncertain, albeit recent data suggest that a longer duration of sustained LVEF recovery may be associated with improved survival.[9]

CONTROVERSIES AND UNANSWERED QUESTIONS REGARDING MANAGEMENT OF HFimpEF

LIMITATIONS OF LVEF FOR ASSESSING MYOCARDIAL RECOVERY AND RELAPSE. Imaging-derived measures obtained via modalities such as echocardiogram and cardiac magnetic resonance (CMR) are most frequently used to assess HFimpEF. Yet, despite being most frequently used, conventional measures derived from these modalities such as LVEF may not be sensitive enough to detect *subclinical* myocardial defects indicative of persistent pathology, as evidenced by the TRED-HF trial in which roughly 40% of patients experienced relapse.[3] In this context, it is noteworthy that the LVEF cutoff points currently used to categorize HF have been somewhat arbitrarily established over the years, even varying across the world.[10] Indeed, historically clinical trials used LVEF-based categorizations primarily for logistical purposes such as to enhance statistical power and reduce trial costs by targeting enrollment of patients who had reduced LVEF and, in turn, higher event rates.[10] Granted, such LVEF-based categorizations have demonstrated utility given that many pharmacologic therapies have demonstrated morbidity and mortality benefit in patients with reduced LVEF but not those with preserved LVEF.[10] Nevertheless, the current paradigm that relies almost exclusively on LVEF-based categorizations for differential assessment and management of HF has hindered our ability to gain deeper insights into the heterogeneity of this disease, including unique biological phenotypes.[10]

ADVANCED IMAGING FOR ASSESSING MYOCARDIAL RECOVERY AND RELAPSE. Advanced imaging-derived measures beyond LVEF could potentially offer greater insight into subclinical myocardial dysfunction. One such measure is global longitudinal strain, which is a more sensitive marker of systolic function than LVEF, with a normal or higher absolute value of strain portending a more favorable prognosis.[2] Another measure is the magnitude of late gadolinium enhancement via CMR, which assesses the presence and extent of myocardial fibrosis, with a lower degree of enhancement reflecting less fibrosis and thus increased likelihood of reverse remodeling.[2] Notably, late gadolinium enhancement may be combined with other features of tissue characterization such as T1 mapping to gain additional insight into myocardial fibrosis along with extracellular volume.[2]

With rapid advancements in imaging technology, there are likely also emerging subclinical CMR features or other advanced imaging parameters that may better illuminate the presence of subclinical myocardial defects. One such example is the myocardial microstructural feature known as E2A mobility, which is measured by diffuse tensor CMR and is a measure of the degree to which functional units of cardiomyocytes known as myocardial sheetlets are capable of reorienting themselves throughout the cardiac cycle between diastole and systole.[11]

TABLE 2 Incidence and Clinical Predictors of LVEF Relapse in HFimpEF

First Author, Year	Design	Cohort Definition	Definition of LVEF Relapse	Follow-Up Duration	Incidence of LVEF Relapse, %	Baseline Clinical Predictors of LVEF Relapse
Hammer et al,[9] 2023 (N = 465)	Retrospective cohort study	Previous LVEF ≤35% secondary to nonischemic etiology with subsequent recovery to ≥50%	Decrease in LVEF to <50%	7 y	50 (at 3.5 y), 80 (at 7 y)	• Younger age (<40 y) • Higher left ventricular internal diameter at end diastole • Hypertension • Atrial fibrillation
McElderry et al,[49] 2023 (N = 7,070)	Retrospective cohort study	Previous LVEF ≤40% with subsequent increase by ≥10% to >40%	Decrease in LVEF to a value less than the HFimpEF-defining LVEF	15.9 mo	–	• Male • Black • Atrial fibrillation or flutter • Coronary artery disease • History of myocardial infarction • Discontinued use of RAS inhibitor • Use of loop diuretic agents • Presence of ICD • Lowest quartile for LVEF or highest quartile for left ventricular end-diastolic or end-systolic volume
Huang et al,[50] 2025 (N = 517)	Retrospective cohort study	Previous LVEF ≤40% with subsequent increase by ≥10% to >40%	Decrease in LVEF to ≤40%	46.5 mo	30.9	• Longer duration of HFrEF • Ischemic etiology • Absence of valvular etiology • Lower LVEF • Higher left atrial and ventricular dimensions • Higher bilirubin levels • Higher NT-proBNP levels • Higher uric acid levels
Janwanishstaporn et al,[51] 2022 (N = 288)	Retrospective cohort study	Previous LVEF <40% with subsequent increase by ≥10% to >40%	Decrease in LVEF by ≥5% to <40%	36.8 mo	38.6	• Lower absolute value of GLS
Fu et al,[53] 2024 (N = 203)	Prospective cohort study	Previous LVEF ≤40% with subsequent increase by ≥10% to >40%	Decrease in LVEF by >10% to <40%	1 y	13.8	• Ischemic cardiomyopathy • Atrial fibrillation • Higher left ventricular end-diastolic diameter index • Higher potassium levels • Lack of SGLT2i treatment
Manca et al,[52] 2022 (N = 460)	Retrospective cohort study	Previous LVEF ≤40% secondary to nonischemic etiology with subsequent increase by ≥10% to >40%	Decrease in LVEF to ≤40%	62 mo	41	• Older age • Lower LVEF • Longer duration of HFrEF (>6 months)
Jiang et al,[54] 2024 (N = 162)	Retrospective cohort study	Previous LVEF ≤40% with subsequent increase to >40%	Decrease in LVEF to ≤40%	–	30.2	• Female • Lower high-density lipoprotein cholesterol levels • Higher urea levels
Park et al,[55] 2014 (N = 85)	Retrospective cohort study	Previous LVEF <40% secondary to idiopathic DCM with subsequent increase by ≥10% to >45%	Decrease in LVEF to <40%	50 mo	39	• Older age • Diabetes • Higher left ventricular end-diastolic diameter
Perry et al,[56] 2022 (N = 133)	Retrospective cohort study	Previous LVEF <40% with subsequent recovery to ≥53%	Decrease in LVEF to <40%	3 y	20 (at 1 y), 28 (at 3 y)	• Ischemic etiology

GLS = global longitudinal strain; HFimpEF = heart failure with improved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; SGLT2i = sodium-glucose cotransporter 2 inhibitor; other abbreviations as in Table 1.

Recently, it was observed that E2A mobility was reduced in patients with DCM, but that patients with recovered DCM (defined as complete recovery of LVEF, complete normalization of left ventricular size, and symptomatic improvement) had significant improvement of E2A mobility, albeit persistent impairment compared with healthy controls.[11,12] These findings suggest that the degree of E2A mobility varies across the spectrum of disease progression and, therefore, that E2A mobility and similar myocardial microstructural features could potentially risk stratify patients with HFimpEF beyond conventional macrostructural measures.

NATRIURETIC PEPTIDES FOR ASSESSING MYOCARDIAL RECOVERY AND RELAPSE. Blood biomarkers such as NT-proBNP may especially be important predictors of clinical relapse, as well as for distinguishing between mere remission and full recovery. In the TRED-HF trial, higher baseline NT-proBNP levels were associated with increased risk of relapse, both during the study period as well as over a long-term follow-up of

6 years.[3,6] Hence, NT-proBNP could be a useful marker for stratifying patients with HFimpEF based on risk of relapse and adverse events. Indeed, a secondary analysis of the REDEAL-HF (Relationships and Differences Analysis in Heart Failure) trial found that elevated baseline NT-proBNP (>1,153 pg/mL) was the strongest independent predictor of future cardiovascular events among patients with HFimpEF.[2,13] These results suggest that elevated NT-proBNP reflects residual myocardial dysfunction that persists despite improved cardiac structure and function. Hence, NT-proBNP could potentially serve as an important surveillance tool to guide management of GDMT in patients with HFimpEF. That said, it should be noted that in the TRED-HF trial, changes in NT-proBNP levels were found to be a relatively delayed predictor of relapse, leading the authors to argue that serial measurement of NT-proBNP is probably not the most effective means of detecting relapse.[14] However, this finding might have been due to the fact that the NT-proBNP cutoff used for enrollment into this trial was relatively high (<250 ng/L) and not sufficiently stringent, with in fact half of the patients who relapsed having a baseline NT-proBNP level ≥125 ng/L.[3] In addition, recent epidemiologic data have shed light on the importance of considering body mass index (BMI) when assessing NT-proBNP levels, with a higher BMI associated with lower NT-proBNP levels such that patients with obesity have a higher risk of developing HF at any given NT-proBNP level.[15] As such, NT-proBNP cutoffs should be adjusted for BMI when monitoring patients with HFimpEF for early signs of relapse (eg, <50 pg/mL for BMI ≥35 kg/m^2),[15] albeit this diagnostic approach needs to be prospectively validated.

MANAGEMENT OF GDMT: THE CASE FOR REASSESSING RISK-BENEFIT ANALYSIS AND PARTIAL DE-ESCALATION. There is clear evidence that GDMT should be continued unabated and indefinitely in patients with HFimpEF who have features of persistent myocardial dysfunction (eg, clinical signs or symptoms, elevated NT-proBNP levels).[16] However, it is not as clear whether the risk-benefit analysis continues to favor indefinite prescription of full-dosage GDMT in patients who appear to have potentially achieved full recovery by meeting all of the following criteria: asymptomatic without clinical signs or symptoms, complete LVEF recovery (≥50%), normalized echocardiogram and CMR parameters, normalized BMI-adjusted NT-proBNP and other cardiac biomarkers, absence of electrocardiogram abnormalities, absence of pathogenic genetic variants, and an etiology of HF with a relatively favorable prognosis (eg, takotsubo cardiomyopathy). For patients who meet all of these criteria, there are several important considerations when assessing the risk-benefit analysis of indefinite full-dosage GDMT. First, it should be emphasized that GDMT medications are not without their side effects (eg, hypotension, fatigue, hyperkalemia, dehydration), especially as the number of GDMT medications has grown over the past few years. Second, currently there are limited to no data demonstrating continued benefit from GDMT in patients who no longer meet the clinical indications for which they were prescribed medication in the first place. This is especially the case given that almost all the pivotal trials for GDMT medications have been conducted with an average follow-up duration of merely 2 to 4 years and, as such, there are scant data on whether these medications continue to provide benefits at longer follow-up. Third, the financial burden of full-dosage and indefinite GDMT should not be underestimated, especially with the addition of newer medication classes, albeit this should also be weighed against the financial costs of treating potential relapse upon de-escalation of GDMT. Overall, it can be theoretically argued that the risk-benefit analysis of GDMT for select patients with HFimpEF may evolve over time as a given patient's functional status and clinical profile normalizes, which may warrant continual reassessment and shared decision-making to allow for individualized care. Granted, it should be emphasized that there are currently insufficient data to support routine de-escalation of GDMT at this time.

For patients with HFimpEF and full resolution of abnormal myocardial features, there is an emerging hypothesis that *partial* de-escalation of GDMT could potentially be safe and feasible. Current GDMT entails quadruple therapy comprising a beta-blocker, renin-angiotensin system (RAS) inhibitor, mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter 2 inhibitor (SGLT2i).[4] Ongoing trials are testing the hypothesis that partial de-escalation of GDMT could potentially be safe and feasible in highly selective patients who have achieved full LVEF recovery along with amelioration of symptoms and biomarker levels.[19] The ongoing BONFIRE (Beta-blOckers discontinuation in Patients Presenting Heart Failure With Recovered Left Ventricular Ejection Fraction; NCT06518694) trial is a phase 3 trial investigating partial de-escalation of GDMT via withdrawal of beta-blockers. The ongoing TRED-HF2 (Therapy to Maintain Remission in Dilated Cardiomyopathy; NCT06091475) trial is a pilot study investigating stepwise withdrawal of

MRA and SGLT2i. It is important to emphasize that larger trials with longer follow-up duration and noninferiority study design will ultimately be needed to confirm or refute the results of pilot trials such as TRED-HF2. Such trials should also investigate how to best monitor sustained remission, as well as whether prompt reinitiation of GDMT upon detecting relapse can readily restore remission without adverse long-term consequences. While multiple GDMT medications are being investigated as part of a partial de-escalation protocol, it is noteworthy that continued treatment with beta-blockers and or RAS inhibitors has been shown to be necessary in many patients with HFimpEF to prevent relapse or manage comorbidities (eg, arrhythmia, hypertension).[3,18]

ADDITIONAL UNANSWERED QUESTIONS REGARDING LONG-TERM EFFECTS AND MANAGEMENT OF GDMT. Aside from de-escalation, other questions remain regarding the appropriate long-term management of GDMT in patients with HFimpEF. For example, it remains unclear whether GDMT should be escalated and up-titrated to maximally tolerated dosages in patients with HFimpEF. Recent evidence from a prespecified secondary analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial suggests that initiating SGLT2i may offer benefit in patients with HFimpEF who remain symptomatic and have elevated NT-proBNP levels.[19] Whether this is also true for other GDMT medications remains to be determined. Relatedly, it remains unclear whether and to what degree GDMT use—or lack thereof—is associated with the gradual, long-term (>10 years follow-up) decline in LVEF that has been observed among some patients with HFrEF who initially experience LVEF improvement.[20] Interestingly, a recent study found that a higher medication score was not associated with a longer duration of sustained LVEF recovery among 172 patients with nonischemic HF who had achieved complete LVEF recovery.[9] Granted, this study has limitations including the low utilization of newer medications such as angiotensin receptor-neprilysin inhibitor and SGLT2i among the patient cohort, as well as relatively low medication scores for most patients, resulting in limited ability to identify a relationship between GDMT use and duration of sustained LVEF recovery. It is also unclear whether reinitiating and uptitrating GDMT among patients with HFimpEF who experience relapse over the long term can prevent and reverse LVEF deterioration and disease progression.

ICD THERAPY. Another unanswered question is whether patients with HFimpEF and LVEF ≥50% require continued ICD therapy, especially among those with nonischemic cardiomyopathy. In particular, there is currently no clinical guidance as to whether low-risk patients with LVEF ≤35% who have received an ICD for primary prevention of sudden cardiac death due to ventricular arrhythmia but have experienced improvement of LVEF (and thus no longer meet the criteria for prophylactic ICD therapy) should have their ICD generator replaced at the end of its battery life.[21] Despite the lack of trial evidence, the available clinical observational data suggest that continuation of ICD therapy may be warranted in many patients. This is because although patients with HFimpEF appear to have decreased risk of ventricular tachyarrhythmias, they still have a nontrivial risk, with an estimated risk of 2% to 5% per patient-year.[21-23] Notably, this risk appears to be inversely related to the degree of LVEF improvement, with a recent meta-analysis of 41 studies (N = 38,572) reporting that the annual rate of arrhythmic events was 6.2% among patients with partial recovery of LVEF (>35% but <50%) vs 2.7% among those with complete recovery of LVEF (≥50%).[23] Moreover, a separate meta-analysis of 16 studies (N = 3,959) found that although patients with improved LVEF (>35%) had a lower rate of appropriate ICD therapy than those with low LVEF (≤35%), patients with improved LVEF nonetheless had a notable rate of appropriate therapy (3.3% per year), with the rate of inappropriate ICD therapy being similar among both groups.[21,24] Regarding effects on survival, a retrospective analysis of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) found that ICD therapy had similar mortality benefit in both patients with improvement of LVEF to >35% and those whose LVEF remained ≤35%.[21,25,26] Taken together, these findings support the current clinical understanding that ICD therapy may continue to offer benefit in some patients with improved LVEF and, therefore, should be continued—including generator replacement as needed—insofar as the risk is acceptable.[21,22] This is especially true for patients who, at baseline, already have risk factors for ventricular arrhythmias, such as predisposing genetic variants (eg, *LMNA*, *SCN5A*, *FLNC*).[21] For some patients, however, the risks of ICD therapy—including chronic anxiety and psychological trauma, device infections, and periprocedural complications[22]—may outweigh the benefits, particularly those in whom LVEF has completely recovered (≥50%) and thus the risk of ventricular arrhythmias is minimal. A future clinical trial will hopefully provide more guidance, but in the meantime, physicians should inform patients about

the benefits and risks of continued ICD therapy to allow for shared decision-making (Figure 3).

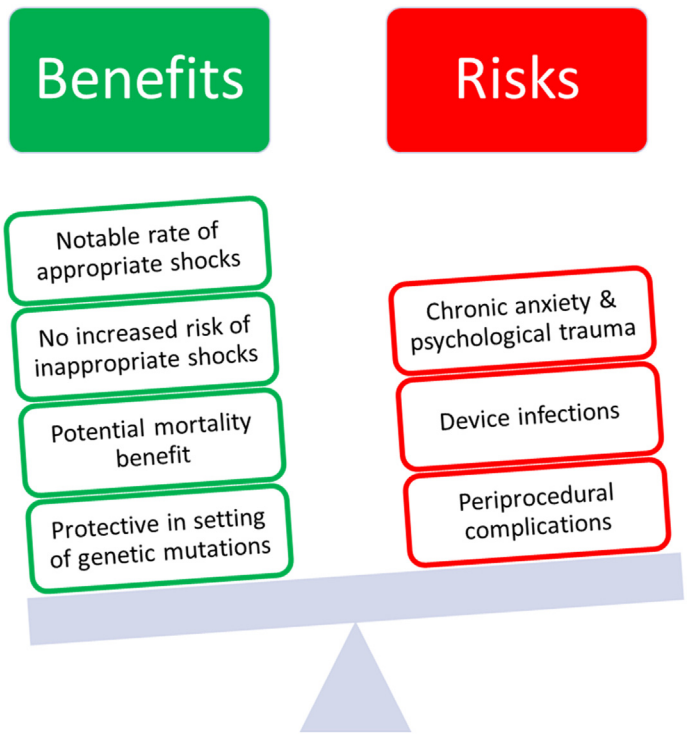
DE-ESCALATION OF PHARMACOTHERAPY IN SPECIFIC CARDIOMYOPATHIES: ETIOLOGY MATTERS

Cardiomyopathies of varying and distinct etiologies can precipitate the onset of HFrEF, and it has been recognized that the specific underlying etiology can influence the unique long-term trajectory of LVEF in these patients.[20] This in turn highlights the importance of viewing and studying HFrEF as a heterogeneous condition with distinct manifestations based on the unique underlying etiology and pathophysiology. Accordingly, one concept to entertain is that some etiologies of HFrEF may be more or less amenable to de-escalation of GDMT following recovery of myocardial function. Here, we discuss the current evidence for de-escalation of GDMT in specific cardiomyopathies, specifically once the primary driver of cardiac dysfunction has been resolved along with normalization of left ventricular function (Table 3). Of note, most of the evidence discussed here is derived from observational studies or trials with small sample size, necessitating more robust data from large randomized controlled trials with long-term follow-up to guide clinical management.

PERIPARTUM CARDIOMYOPATHY. Peripartum cardiomyopathy is a form of idiopathic systolic dysfunction that engenders HF at the end of pregnancy or in the months immediately following delivery.[27] The rate of LVEF recovery among patients with peripartum cardiomyopathy is estimated to range from 35% to 72% depending on the patient cohort, definition of recovery, and follow-up time used, with recovery most frequently occurring within 3 to 6 months following diagnosis.[27-29] Recently, a predictive model yielding a score known as the ESC EORP PPCM Recovery Score was developed to predict the probability of LVEF recovery at 6 months of follow-up among women diagnosed with peripartum cardiomyopathy.[29] Although patients with peripartum cardiomyopathy who experience LVEF recovery have improved outcomes, they still remain at risk of adverse events and relapse, either spontaneously or in the face of stressors (eg, future pregnancy), presumably because of decreased contractile reserve.[27,28] A small retrospective cohort study found that withdrawal of beta-blockers and/or angiotensin-converting enzyme inhibitors was not associated with LVEF deterioration at 29 months of follow-up in 15 patients with prior peripartum cardiomyopathy but subsequent LVEF recovery.[30] Similarly, another retrospective cohort study found that among 18 patients with peripartum cardiomyopathy and subsequent LVEF recovery who underwent tapering of beta-blockers and RAS inhibitors over a mean duration of 3.3 years, 17 remained free from relapse and adverse events at a long-term follow-up of 7.9 years.[31] Despite the limitations of these studies, these findings suggest that it might be possible to cautiously de-escalate GDMT in select patients with peripartum cardiomyopathy who have complete LVEF recovery for at least 6 to 12 months.[27] However, it is prudent to not de-escalate GDMT in patients with high-risk features that make them prone to relapse (eg, plans for future pregnancy, preeclampsia or pregnancy-induced hypertension, presence of pathogenic DCM genetic variants).[27]

DYSSYNCHRONY-INDUCED CARDIOMYOPATHY FOLLOWING CARDIAC RESYNCHRONIZATION THERAPY. In cases in which left ventricular dyssynchrony due to left bundle branch block is a key contributing factor to

FIGURE 3 Benefits vs Risks of Continued ICD Therapy for Primary Prevention of Ventricular Arrhythmias and Sudden Cardiac Death in Patients With HFimpEF



Based on available observational evidence, most patients should continue ICD therapy, although some may elect to discontinue via shared decision-making. ICD = implantable cardioverter-defibrillator; other abbreviation as in Figure 2.

TABLE 3 Completed or Ongoing Studies Investigating De-Escalation of GDMT Following Normalization of Left Ventricular Function in Specific Cardiomyopathies

First Author, Year OR Ongoing Trial Name	Design	Cohort	Key Findings or Planned Endpoints
Peripartum cardiomyopathy			
Amos et al,[30] 2006 (N = 15)	Retrospective cohort study	Peripartum cardiomyopathy with subsequent LVEF recovery to ≥50%	• Withdrawal of beta-blockers and/or ACEIs was not associated with LVEF deterioration in any patients at an average follow-up of 29 mo
Barasa et al,[31] 2018 (N = 18)	Retrospective cohort study	Peripartum cardiomyopathy with subsequent LVEF recovery to ≥50%	• Tapering of beta-blockers and RAS inhibitors over a mean duration of 3.3 y was safely achieved in 17 of 18 patients, with only 1 patient experiencing worsening of HF, which was promptly resolved with reinitiation of medication • No long-term adverse events were observed in any patient at a mean follow-up of 7.9 y
Dyssynchrony-induced cardiomyopathy			
Nijst et al,[17] 2020 (N = 80)	Randomized controlled pilot trial utilizing a 2x2 factorial design to investigate whether neurohumoral blockers including beta-blockers and RAS inhibitors can be safely withdrawn following cardiac resynchronization therapy	Nonischemic HF with recovery of LVEF (≥50%) and left ventricular volumes following initiation of cardiac resynchronization therapy for a Class I indication (ie, left bundle branch block and prolonged QRS interval duration)	• At 24 mo of follow-up, there was an overall low incidence of the primary endpoint of recurrence of pathologic remodeling (n = 6) (7.5%), as well as the secondary composite endpoint of all-cause mortality, HF-related hospitalizations, and incidence of ventricular arrhythmias (n = 4) (5%) • In patients who did experience recurrence of pathologic remodeling, immediate reinitiation of therapy resulted in recovery of LVEF in all patients within 6 mo • Overall, most patients (62%) were able to safely withdraw neurohormonal blockers without relapse of HF at 24-months of follow-up, albeit several patients required reinitiation of treatment to manage uncontrolled comorbidities, with 16 patients reinitiating a beta-blocker for supraventricular arrhythmias and 1 patient reinitiating a RAS inhibitor for hypertension
Tachycardia-induced cardiomyopathy			
Segan[36] 2024 (N = 60) (Preliminary results presented at the 2024 ESC Congress)	Randomized controlled, double-arm crossover trial investigating whether HF pharmacotherapy can be withdrawn while maintaining LVEF recovery (≥50%)	History of atrial fibrillation–induced cardiomyopathy with subsequent control and normalization of heart rhythm along with LVEF recovery to ≥50%	• 55 of 60 patients (91.7%) were able to safely withdraw HF pharmacotherapy at 6 mo of follow-up • Of the 5 patients who relapsed during the study period, none developed clinical HF or required hospitalization • At 12 mo following study completion, 45 of 55 patients (81.8%) remained off HF pharmacotherapy while maintaining LVEF recovery (median LVEF of 60%)
Domínguez-Rodríguez, et al[35] 2024 (N = 188)	Single-center, retrospective cohort study	Arrhythmia-induced cardiomyopathy with either subsequent complete recovery of LVEF (≥50%) or partial improvement of LVEF (increase by ≥10% to ≥40%)	• 89 (47.3%) patients experienced HF relapse, with a median time to relapse of 26.5 mo • Use of beta-blockers and RAS inhibitors was associated with lower risk of relapse
WEAN-HF (Withdrawal of Treatment for Heart Failure Patients With Recovery From Tachycardia-induced Cardiomyopathy; NCT06128980) (N = 342)	Open-label, randomized, controlled, noninferiority trial determining whether incremental weaning of GDMT is noninferior to continuous GDMT	History of tachycardia-induced cardiomyopathy due to underlying atrial fibrillation or flutter with subsequent recovery of LVEF (≥50%) and left ventricular volumes following initiation of GDMT along with adequate control of atrial fibrillation or flutter via termination (ablation or conversion) or rate control	Primary endpoint • Freedom from HF deterioration at 1 y post randomization Notable secondary endpoints • Hospitalization for HF • Cardiovascular death • All-cause death • Change in MLHFQ score

Continued on the next page

TABLE 3 Continued

First Author, Year OR Ongoing Trial Name	Design	Cohort	Key Findings or Planned Endpoints
Chemotherapy-induced cardiomyopathy			
Fadol, et al[43] 2016 (N = 20)	Prospective cohort pilot study investigating whether HF medications could be safely withdrawn without worsening of LVEF	History of chemotherapy-induced cardiomyopathy (mainly due to anthracycline agents) with subsequent LVEF recovery to ≥50%	• None of the 12 patients who remained in the study through 6 mo of follow-up experienced significant reduction of LVEF, rise in cardiac biomarkers, or development of symptoms
Yu, et al[44] 2024 (N = 20)	Retrospective matched cohort study	History of breast cancer with mild cardiac dysfunction (LVEF reduction of ≥10% to <53% but >40%) because of sequential treatment with anthracyclines and trastuzumab, but with subsequent improvement of LVEF (>53%) following treatment with beta-blockers and RAS inhibitors	• None of the 10 patients who discontinued neurohormonal antagonists experienced relapse over a median follow-up of roughly 2.5 y
Park, et al[57] 2024 (N = 134)	Retrospective analysis of a single-center prospective cohort study	History of cancer therapeutics-related cardiac dysfunction with subsequent improvement in LVEF by ≥10% following initiation of cardioprotective therapy	• Of 134 patients, 44 withdrew cardioprotective therapy while 90 continued it • Patients who withdrew therapy had a higher risk of the primary composite endpoint of HF hospitalization or reduction in LVEF by ≥10% • Among patients with baseline LVEF <45%, withdrawal of therapy was associated with a lower final LVEF compared with continuation of therapy
COP-RCT (Cessation Of Pharmacotherapy In Recovered Chemotherapy-induced cardioToxicity; ANZCTR12621000928819) (N = 70)	Multicenter, open-label, randomized, controlled pilot trial investigating whether ceasing cardioprotective therapy is safe and feasible	Low-risk patients with a history of cancer therapeutics-related cardiac dysfunction with subsequent LVEF recovery to ≥50%	Primary endpoint • Change in LVEF as assessed by CMR at 6 mo post randomization Notable secondary endpoints • Hospitalization for HF • Change in KCCQ score
HER-SAFE (Safety of Withdrawal of Pharmacological Treatment for Recovered HER2 Targeted Therapy Related Cardiac Dysfunction; NCT05880160) (N = 90)	Multicenter, open-label, randomized, controlled trial investigating total withdrawal of HF medications	Low-risk patients with a prior diagnosis of human epidermal growth factor receptor 2 therapy-related cardiac dysfunction who are currently treated with HF medications and have achieved recovery of cardiac function as defined by the following: asymptomatic, LVEF ≥50%, and NT-proBNP <125 ng/L for at least 6 mo	Primary endpoint • Relapse in cardiotoxicity at 12 mo as defined by any of the following: ○ Reduction in LVEF by ≥10% to <50% ○ Reduction in LVEF by ≥5% to <50% *and* 1 of the following: relative decline in GLS by >15% or significant rise in cardiac biomarkers (>2-fold rise in NT-proBNP to >400 ng/L or rise in high-sensitivity troponin to >99th percentile) ○ Recurrence of signs or symptoms of HF *and* 1 of the following: reduction in LVEF by ≥5%, relative decline in GLS by >15%, significant rise in cardiac biomarkers (as described earlier), or development of new arrhythmia Notable secondary endpoints: • Change in KCCQ and MLHFQ scores
STOP-MED (STOPping Cardiac MEDications in Patients With Normalized Cancer Therapy Related Cardiac Dysfunction; NCT06183437) (N = 335)	Multicenter, open-label, noninferiority, randomized, controlled trial investigating total withdrawal of HF medications	Patients with previous asymptomatic and moderate cancer therapy-related cardiac dysfunction (due to either anthracyclines or human epidermal growth factor receptor 2 therapy-targeted therapy) who received treatment with HF medications and subsequently achieved recovery of cardiac function as defined by the following: asymptomatic, LVEF ≥55%, normalized left ventricular volumes as assessed by CMR, and normalized NT-proBNP levels	Primary endpoint: • Relapse of cancer therapy-related cardiac dysfunction at 1 y as defined by either of the following: ○ LVEF <50% ○ Development of signs and symptoms of HF Notable secondary endpoints: • Cost-effectiveness analysis • Changes in CMR parameters • Change in KCCQ score

ACEI = angiotensin-converting enzyme inhibitor; ESC = European Society of Cardiology; GDMT = guideline-directed medical therapy; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living with Heart Failure Questionnaire; other abbreviations as in Tables 1 and 2.

HF, cardiac resynchronization therapy may engender complete recovery of left ventricular function.[21] The STOP-CRT (Systematic Withdrawal of Neurohumoral Blocker Therapy in Optimally Responding CRT Patients) trial was a randomized, controlled pilot trial that used a 2 × 2 factorial design to investigate whether neurohormonal blockers including beta-blockers and/or RAS inhibitors could be safely withdrawn in 80 patients with nonischemic HF who had achieved complete recovery of LVEF (≥50%) and left ventricular volumes following initiation of cardiac resynchronization therapy due to a Class I indication (ie, left bundle branch block and prolonged QRS interval duration).[17] At 24 months of follow-up, there was an overall low incidence of the primary endpoint of recurrence of pathologic remodeling (n = 6, 7.5%), as well as the secondary composite endpoint of all-cause mortality, HF-related hospitalizations, and incidence of ventricular arrhythmias (n = 4, 5%). Notably, in patients who did experience recurrence of pathologic remodeling, immediate reinitiation of therapy resulted in recovery of LVEF in all patients within 6 months. Overall, most patients (62%) were able to safely withdraw neurohormonal blockers without relapse of HF at 24 months of follow-up, albeit several patients required reinitiation of treatment to manage uncontrolled comorbidities, with 16 patients reinitiating a beta-blocker for supraventricular arrhythmias and 1 patient reinitiating an RAS inhibitor for hypertension. Given that all patients enrolled into this trial had left bundle branch block, withdrawal of neurohormonal blockade presumably did not result in relapse in most patients because cardiac resynchronization therapy corrected the primary contributing factor driving the remodeling process (namely left ventricular dyssynchrony). These findings suggest that neurohormonal blockers can be safely weaned in most patients with dyssynchrony-induced cardiomyopathy that fully resolves with cardiac resynchronization therapy, although neurohormonal blockers may need to be continued in some cases to manage comorbid conditions such as arrhythmias and hypertension.

TAKOTSUBO CARDIOMYOPATHY. Takotsubo cardiomyopathy is a type of transient, stress-induced left ventricular systolic dysfunction that is thought to arise from a surge in catecholamines in response to various stressors.[28,32] Although some patients have persistent cardiac symptoms, in most cases the prognosis is favorable, with a relatively low 5-year recurrence rate estimated to range from 5% to 22%,[32] along with a lack of permanent myocardial damage and no increased risk of mortality based on available data.[28,32] That said, recent evidence suggests that patients with takotsubo cardiomyopathy who experience a longer time to LVEF recovery (≥10 days) following the inciting event may have reduced short- and long-term survival compared with those who have a shorter time to recovery (<10 days).[8] Although there have been some reports of lower rates of recurrence of left ventricular dysfunction with beta-blocker treatment, it is currently unclear whether sustained treatment with HF medications such as beta-blockers and angiotensin-converting enzyme inhibitors reduces the risk of recurrence or improves long-term prognosis.[28,32,33] Hence, long-term management of these patients should be individualized based on patient risk factors and clinical judgment.

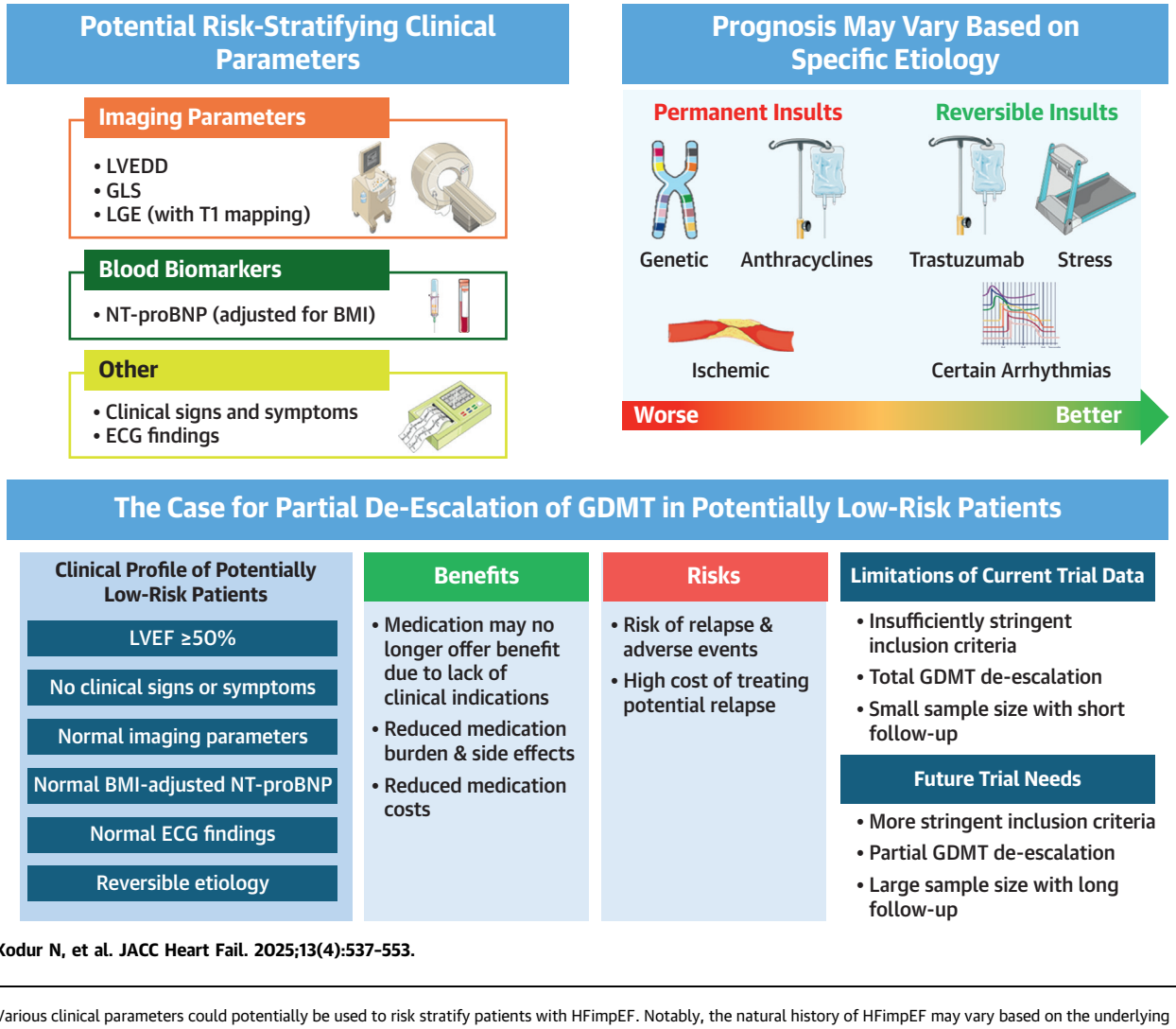
TACHYCARDIA-INDUCED CARDIOMYOPATHY TREATED WITH ABLATION. Tachycardia-induced cardiomyopathy is a condition in which an arrhythmia (eg, atrial fibrillation or flutter, supraventricular tachycardia, premature ventricular contractions) is the presumed primary cause of left ventricular dysfunction and HF.[28,34] Among the first-line treatments for tachycardia-induced cardiomyopathy is catheter ablation, which, if successful, eliminates the underlying tachyarrhythmia and in turn resolves left ventricular dysfunction and HF within a few months.[34] However, many patients remain at risk of relapse of HF in response to recurrent arrhythmias or other triggers, presumably because of permanent myocardial damage such as diffuse myocardial fibrosis resulting from prolonged tachyarrhythmia.[28,34] Indeed, a recent retrospective analysis of 188 patients with a history of arrhythmia-induced cardiomyopathy but subsequent LVEF improvement found that 89 (47.3%) patients experienced relapse, with use of beta-blockers and RAS inhibitors being associated with lower risk of relapse.[35] Hence, patients with tachycardia-induced cardiomyopathy who achieve recovery of left ventricular function should nonetheless continue to receive GDMT unabated and indefinitely.[34] This recommendation, however, may change based on findings from ongoing clinical trials such as WEAN-HF (Withdrawal of Treatment for Heart Failure Patients With Recovery From Tachycardia-induced Cardiomyopathy; NCT06128980). Indeed, preliminary results from the single-center Australian WITHDRAW-AF (WITHDRAWal of Heart Failure Pharmacotherapy in Patients with Normalized Left Ventricular Function After AF Rhythm Control in Arrhythmia Induced Cardiomyopathy; ACTRN12621000896875) study presented at the 2024 European Society of Cardiology Congress showed that

among 60 patients who had a history of atrial fibrillation-induced cardiomyopathy but subsequently achieved LVEF recovery (≥50%), most (>90%) had GDMT successfully withdrawn without relapse at 6 months of follow-up, with judicious monitoring of LVEF via CMR and proper rhythm control.[36] It is also important to note that the risk of relapse may vary depending on the specific underlying arrhythmia. For instance, although premature ventricular contraction-induced cardiomyopathy may be amenable to ablation therapy with immediate improvement of LVEF in some cases, in other cases it may be associated with genetic factors or chronic inflammatory cardiomyopathies that portend an increased risk of relapse.[37]

COMPLICATED ACUTE MYOCARDITIS. Myocarditis is an inflammatory condition of the heart arising from various etiologies, including viral infections, autoimmune conditions, and drugs and vaccines.[38] Most patients who develop myocarditis have an uncomplicated course with preserved cardiac function or transient cardiac dysfunction that resolves promptly and, therefore, may not even warrant GDMT initiation in the first place, or long-term continuation if initiated.[38] However, roughly 25% of patients develop complicated myocarditis, which may entail left ventricular dysfunction along with the onset of HFrEF in some patients, thus warranting GDMT to slow and even reverse DCM progression.[38] Previously, it was suggested that patients with fulminant myocarditis might have a better long-term prognosis than those with nonfulminant myocarditis, and that patients in the former group might therefore be candidates for de-escalation of GDMT.[28] However, this was challenged by a retrospective cohort study using an international registry containing 220 patients with acute myocarditis that found that fulminant myocarditis was associated with poorer long-term prognosis, with a rate of cardiac death and heart transplantation of 47.7% at 7 years of follow-up.[39] Although patients with nonfulminant myocarditis fared better, they too had a relatively high rate of 10.4%, suggesting persistent risk. A more recent retrospective cohort study using a nationwide registry from Japan found that among 214 patients with biopsy-proven fulminant myocarditis, patients who had an LVEF <50% at discharge had a higher adjusted probability of mortality or cardiac transplantation at 4 years of follow-up compared with those who had an LVEF ≥50%.[40] Taken together, these findings suggest that both patients with fulminant and nonfulminant myocarditis remain at heightened risk of adverse events, thereby warranting indefinite GDMT, irrespective of whether myocardial function recovers. Future studies should investigate whether certain etiologies of myocarditis are associated with a relatively favorable prognosis that may be amenable to de-escalation of GDMT.

CHEMOTHERAPY-INDUCED CARDIOMYOPATHY. Chemotherapy agents that can induce cardiomyopathy and concomitant HFrEF include anthracyclines and trastuzumab.[28] These 2 agents are thought to exert their deleterious myocardial effects via distinct mechanisms and, accordingly, appear to differ with respect to HF prognosis.[28] Anthracycline-induced cardiomyopathy appears to entail permanent myocardial ultrastructural damage such as myofibrillar disarray and necrosis, which is thought to account for its presumed relatively unfavorable long-term prognosis.[28,41] Yet, despite a relatively poor long-term prognosis, when promptly treated with HF medications, some patients with anthracycline-induced cardiomyopathy may experience recovery of myocardial function, at least in the short term. A prospective cohort study of 201 patients with anthracycline-induced cardiomyopathy with LVEF ≤45% found that prompt treatment with enalapril and/or carvedilol following cessation of chemotherapy was associated with complete recovery of LVEF in 85 patients (42%) and a lower rate of cardiac events at a mean follow-up of 36 months, with sooner onset of HF treatment being correlated with a greater degree of LVEF recovery; notably, only patients who were treated within 6 months following cessation of chemotherapy experienced LVEF recovery.[42] Whether patients with complete LVEF recovery can weaned off GDMT is a difficult question given the presumed poor long-term prognosis of anthracycline-induced cardiomyopathy. A prospective cohort study of 20 patients found that, among the 12 patients who remained in the study through 6 months of follow-up, withdrawal of HF medications was not associated with deterioration of LVEF or clinical status.[43] Similarly, in a retrospective matched cohort study of 20 breast cancer patients who experienced mild cardiac dysfunction following sequential treatment with anthracyclines and trastuzumab but subsequently attained improvement of LVEF (>53%) following treatment with neurohormonal antagonists, none of the 10 patients who discontinued neurohormonal antagonists experienced relapse over a median follow-up of roughly 2.5 years.[44] These promising findings notwithstanding, there are major limitations to these studies including the small sample size, observational study design, and relatively short follow-up time. Hence, there is currently no strong evidence to suggest that patients with anthracycline-induced cardiomyopathy who experience LVEF

CENTRAL ILLUSTRATION Current Controversies Regarding Management of HFimpEF



Kodur N, et al. JACC Heart Fail. 2025;13(4):537–553.

Various clinical parameters could potentially be used to risk stratify patients with HFimpEF. Notably, the natural history of HFimpEF may vary based on the underlying etiology. In low-risk patients with complete resolution of abnormal features, partial de-escalation of GDMT could be safe and feasible, although more robust trial data are needed. This figure was created in part using Servier Medical Art (licensed under CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). BMI = body mass index; ECG = electrocardiogram; GDMT = guideline-directed medical therapy; GLS = global longitudinal strain; HFimpEF = heart failure with improved ejection fraction; LGE = late gadolinium enhancement; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

recovery can safely de-escalate GDMT, especially given permanent myocardial structural damage and the potential for reduced myocardial reserve along with subclinical cardiac dysfunction.

In contrast with anthracycline-induced cardiomyopathy, trastuzumab-induced cardiomyopathy is thought to be reversible, with no permanent myocardial ultra-structural changes.[28,41,45] Indeed, a retrospective cohort study of 38 patients with suspected trastuzumab-related cardiotoxicity found that withdrawal of trastuzumab was associated with LVEF recovery at a mean follow-up of 1.5 months, both in 32 patients who received sustained HF treatment as well as 6 patients who did not receive any HF treatment.[45] Moreover, among 25 patients with LVEF improvement who were subsequently rechallenged with trastuzumab while maintaining HF treatment, only 3 patients experienced recurrent left ventricular

dysfunction at a median follow-up of 8.4 months, whereas the other 22 did not. In support of these findings, an analysis of the HERA (Herceptin [Trastuzumab] in Treating Women With Human Epidermal Growth Factor Receptor [HER] 2-Positive Primary Breast Cancer) trial found that, at a median follow-up of 8 years, trastuzumab therapy was associated with a relatively low incidence of cardiac events (including significant deterioration of LVEF and development of severe HF), and that in most cases cardiac dysfunction was reversible.[46] Together, these studies suggest that trastuzumab-induced cardiomyopathy is generally reversible following concurrent withdrawal of trastuzumab and initiation of HF treatment, and may even be reversible in many patients following a strategy of permissive cardiotoxicity (defined as continuation of trastuzumab therapy despite mild cardiotoxicity given the favorable benefit-to-risk ratio). Ongoing trials such as COP-RCT (Cessation Of Pharmacotherapy In Recovered Chemotherapy-induced cardioToxicity; ANZCTR12621000928819), HER-SAFE (Safety of Withdrawal of Pharmacological Treatment for Recovered HER2 Targeted Therapy Related Cardiac Dysfunction; NCT05880160), and STOP-MED (STOPping Cardiac MEDications in Patients With Normalized Cancer Therapy Related Cardiac Dysfunction; NCT06183437) will hopefully provide better evidence to inform management of GDMT in patients with a history of chemotherapy-induced cardiomyopathy who experience LVEF recovery.

ALCOHOL-INDUCED CARDIOMYOPATHY. Alcohol-induced cardiomyopathy is a potentially reversible cause of HFrEF that can subside with abstinence.[28] The prognosis of alcohol-induced cardiomyopathy following adoption of abstinence with concomitant recovery of left ventricular function remains unclear, although most available evidence suggests that patients continue to remain at heightened risk of adverse events.[28,47,48] Coupled with the fact that no studies to date have investigated de-escalation of GDMT in this population, these findings suggest that GDMT should be continued in most patients with alcohol-induced cardiomyopathy who experience LVEF recovery, albeit de-escalation may be attempted in select cases based on clinical judgment.

CONCLUSIONS

Advances in GDMT over the past couple of decades have paved the way for a growing patient population with HFimpEF, yet there is currently limited high-quality evidence to guide long-term clinical management of these patients, particularly the lifelong burden of polypharmacy. Weighing the risks of relapse and adverse events against the burden of lifelong pharmacotherapy for the highly morbid and costly condition that is HF, current treatment guidelines recommend that all patients with HFimpEF should continue to receive GDMT unbated and indefinitely. However, there are ongoing efforts to refine and challenge this one-size-fits-all approach as we begin to gain greater insights into the distinction between mere remission and full recovery, especially among specific etiologies of HFrEF that may favor low risk of relapse (**Central Illustration**). Emerging studies suggest that partial de-escalation of GDMT with careful monitoring could be safe in low-risk patients with acute causes of myocardial dysfunction that are transient and that fully resolve without any permanent structural or molecular defects, although large-scale clinical trials with long-term follow-up are ultimately needed. It is our hope that the findings and insights discussed in this review will spark ideas for future studies and ultimately pave the way for high-quality clinical trials, thereby providing clinicians with better guidance on how to optimally manage patients with HFimpEF, especially those who may have truly recovered.

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REFERENCES

1. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Eur J Heart Fail*. 2021;23(3):352–380.

2. Kodur N, Tang WHW. Myocardial recovery and relapse in heart failure with improved ejection fraction. *Curr Treat Options Cardio Med*. 2024;26(6):139–160.

3. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393(10166):61–73.

4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263–e421.

5. Basuray A, French B, Ky B, et al. Heart failure with recovered ejection fraction. *Circulation*. 2014;129(23):2380–2387.

6. Cheng L, Hammersley D, Ragavan A, et al. Long-term follow-up of the TRED-HF trial: implications for therapy in patients with dilated cardiomyopathy and heart failure remission. *Eur J Heart Fail*. 2025;7(1):113–123.

7. Brandt M, Cotter G, Wenzel P. Delivering more evidence for the specificities of heart failure with improved ejection fraction: new answers, new questions. *Eur J Heart Fail*. 2024;26(12):2541–2543.

8. Almendro-Delia Manuel, López-FL, Uribarri A, et al. Recovery of left ventricular function and long-term outcomes in patients with takotsubo syndrome. *J Am Coll Cardiol*. 2024;84(13):1163–1174.

9. Hammer Y, Yosef M, Khalatbari S, Aaronson KD. Heart failure with recovered ejection fraction in patients with nonischemic cardiomyopathy: characteristics, outcomes, and long-term follow-up. *J Card Fail*. 2023;29(12):1593–1602.

10. Triposkiadis F, Butler J, Abboud FM, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J*. 2019;40(26):2155–2163.

11. Khalique Z, Ferreira PF, Scott AD, et al. Diffusion tensor cardiovascular magnetic resonance of microstructural recovery in dilated cardiomyopathy. *JACC Cardiovasc Imaging*. 2018;11(10):1548–1550.

12. Khalique Z, Ferreira PF, Scott AD, Nielles-Vallespin S, Firmin DN, Pennell DJ. Diffusion tensor cardiovascular magnetic resonance imaging: a clinical perspective. *JACC Cardiovasc Imaging*. 2020;13(5):1235–1255.

13. Liu D, Hu K, Schregelmann L, et al. Determinants of ejection fraction improvement in heart failure patients with reduced ejection fraction. *ESC Heart Fail*. 2023;10(2):1358–1371.

14. Halliday BP, Owen R, Gregson J, et al. Changes in clinical and imaging variables during withdrawal of heart failure therapy in recovered dilated cardiomyopathy. *ESC Heart Fail*. 2022;9(3):1616–1624.

15. Ndumele CE, Matsushita K, Sang Y, et al. NT-proBNP and heart failure risk among individuals with and without obesity: the ARIC study. *Circulation*. 2016;133(7):631–638.

16. Talha KM, Butler J, Packer M. Consequences of discontinuing long-term drug treatment in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2024;84(22):2215–2232.

17. Belfort D. *Carvedilol as single maintenance therapy for heart failure with improved ejection fraction: an open-label randomized clinical trial CATHEDRAL-HF*. London, England, United Kingdom: Paper presented at: ESC Congress 2024; August 31, 2024. https://esc365.escardio.org/presentation/290256

18. Nijst P, Martens P, Dauw J, et al. Withdrawal of neurohumoral blockade after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2020;75(12):1426–1438.

19. Vardeny O, Fang JC, Desai AS, et al. Dapagliflozin in heart failure with improved ejection fraction: a prespecified analysis of the DELIVER trial. *Nat Med*. 2022;28(12):2504–2511.

20. Lupón J, Gavidia-Bovadilla G, Ferrer E, et al. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol*. 2018;72(6):591–601.

21. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart failure with recovered left ventricular ejection fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2020;76(6):719–734.

22. Baman JR, Patil KD, Medhekar AN, Wilcox JE. Primary prevention implantable cardioverter-defibrillator therapy in heart failure with recovered ejection fraction. *J Card Fail*. 2021;27(5):585–596.

23. Al-Sadawi M, Gier C, Tao M, et al. Risk of appropriate implantable cardioverter-defibrillator therapies and sudden cardiac death in patients with heart failure with improved left ventricular ejection fraction. *Am J Cardiol*. 2024;213:55–62.

24. 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(2):279–286.

25. Chen X, Wu M. Heart failure with recovered ejection fraction: current understanding and future prospects. *Am J Med Sci*. 2023;365(1):1–8.

26. 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(7):767–774.

27. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;75(2):207–221.

28. Basuray A, Fang JC. Management of patients with recovered systolic function. *Prog Cardiovasc Dis*. 2016;58(4):434–443.

29. Jackson AM, Goland S, Farhan HA, et al. A novel score to predict left ventricular recovery in peripartum cardiomyopathy derived from the ESC EORP Peripartum Cardiomyopathy Registry. *Eur Heart J*. 2024;45(16):1430–1439.

30. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J*. 2006;152(3):509–513.

31. Barasa A, Goloskokova V, Ladfors L, Patel H, Schaufelberger M. Symptomatic recovery and pharmacological management in a clinical cohort with peripartum cardiomyopathy. *J Matern Fetal Neonatal Med*. 2018;31(10):1342–1349.

32. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on takotsubo syndrome: a position statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(1):8–27.

33. Santoro F, Sharkey S, Citro R, et al. Beta-blockers and renin-angiotensin system inhibitors for takotsubo syndrome recurrence: a network meta-analysis. *Heart*. 2024;110(7):476–481.

34. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-induced cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(18):2328–2344.

35. Domínguez-Rodríguez LM, Dobarro D, Iglesias-Otero C, et al. Guideline-directed medical therapy for heart failure in arrhythmia-induced cardiomyopathy with improved left ventricular ejection fraction. *Eur J Heart Fail*. Published online December 18, 2024. https://doi.org/10.1002/ejhf.3556

36. Segan L. WITHDRAWal of heart failure pharmacotherapy in patients with normalized left ventricular function after AF rhythm control in arrhythmia induced cardiomyopathy—The WITHDRAW-AF Randomized Clinical Trial. Paper presented at: ESC Congress 2024; August 31, 2024; London, England, United Kingdom. https://esc365.escardio.org/presentation/290257

37. Latchamsetty R, Bogun F. Premature ventricular complex-induced cardiomyopathy. *JACC Clin Electrophysiol*. 2019;5(5):537–550.

38. Ammirati E, Moslehi JJ. Diagnosis and treatment of acute myocarditis: a review. *JAMA*. 2023;329(13):1098–1113.

39. Ammirati E, Veronese G, Brambatti M, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2019;74(3):299–311.

40. Kanaoka K, Onoue K, Terasaki S, et al. Changes in cardiac function following fulminant myocarditis. *Circ Heart Fail*. 2024;17(4):e010840.

41. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005;23(13):2900–2902.

42. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2010;55(3):213–220.

43. Fadol AP, Banchs J, Hassan SA, Yeh ETH, Fellman B. Withdrawal of heart failure medications in cancer survivors with chemotherapy-induced left ventricular dysfunction: a pilot study. *J Card Fail*. 2016;22(6):481–482.

44. Yu C, Power C, Sooriyakanthan M, et al. Withdrawal of neurohormonal antagonists in breast cancer patients with cardiotoxicity and improved left ventricular function. *JACC CardioOncol*. 2024;6(2):315–317.

45. Ewer MS, Vooletich MT, Durand J-B, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol*. 2005;23(31):7820–7826.

46. de Azambuja E, Procter MJ, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac events at 8 years of median follow-up in the herceptin adjuvant trial (BIG 1-01). *J Clin Oncol*. 2014;32(20):2159–2165.

47. Gavazzi A, De Maria R, Parolini M, Porcu M. Alcohol abuse and dilated cardiomyopathy in men. *Am J Cardiol*. 2000;85(9):1114–1118.

48. Fauchier L, Babuty D, Poret P, et al. Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy. *Eur Heart J*. 2000;21(4):306–314.

49. McElderry B, O'Neill T, Griffin BP, Kalahasti V, Barzilai B, Brateanu A. Factors associated with maintenance of an improved ejection fraction: an echocardiogram-based registry study. *J Am Heart Assoc*. 2023;12(21):e031093.

50. Huang L, Zhou P, Zhai M, et al. Incidence, progression, and outcomes of heart failure with improved ejection fraction: the added value of longitudinally assessed ejection fraction. *Int J Cardiol*. 2025;420:132759.

51. Janwanishstaporn S, Cho JY, Feng S, et al. Prognostic value of global longitudinal strain in patients with heart failure with improved ejection fraction. *JACC Heart Fail*. 2022;10(1):27–37.

52. Manca P, Stolfo D, Merlo M, et al. Transient versus persistent improved ejection fraction in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail*. 2022;24(7):1171–1179.

53. Fu K, Yang Z, Wang N, et al. Recurrence of left ventricular systolic dysfunction and its risk factors in heart failure with improved ejection fraction patients receiving guideline-directed medical therapy: a trajectory analysis based on echocardiography. *Int J Cardiol*. 2024;415:132370.

54. Jiang Y, Chen X, Zhang X, Dong S, Liu Y. Dynamic trajectories of left ventricular ejection fraction in heart failure with improved ejection fraction. *BMC Cardiovasc Disord*. 2024;24(1):621.

55. Park J-S, Kim J-W, Seo K-W, et al. Recurrence of left ventricular dysfunction in patients with restored idiopathic dilated cardiomyopathy. *Clinical Cardiol*. 2014;37(4):222–226.

56. Perry AS, Mudigonda P, Huang GS, et al. Long-term outcomes and risk stratification of patients with heart failure with recovered ejection fraction. *Am J Cardiol*. 2022;173:80–87.

57. Park H, Lee N, Hwang CH, et al. Prognosis after withdrawal of cardioprotective therapy in patients with improved cancer therapeutics-related cardiac dysfunction. *JACC CardioOncol*. 2024;6(5):699–710.

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