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RESEARCH ARTICLE

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Characteristics, outcomes and the necessity of continued guideline-directed medical therapy in patients with heart failure with improved ejection fraction

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ABSTRACT

Background: Much remains to be learned about patients with heart failure with improved ejection fraction (HFimpEF).

Objective: This study sheds light on the characteristics and clinical outcomes of HFimpEF patients, including the consequences of halting guideline-directed medical therapy (GDMT).

Methods: This retrospective study was conducted on patients diagnosed with heart failure with reduced ejection fraction (HFrEF) who underwent a second echocardiogram at least 6 months apart between January 2009 and February 2023. The primary outcomes were major adverse cardiovascular events (MACEs), including all-cause mortality and heart failure hospitalization. The second outcome was recurrent HFrEF.

Results: Of 4,560 HFrEF patients were included, 3,289 (72.1%) achieved HFimpEF within a median follow-up period of 3.4 years (IQR: 1.8 – 5.9 years). Among these HFimpEF patients, recurrent HFrEF was observed in 941 (28.6%) patients during a median follow-up period of 2.3 years (IQR: 0.8–4.6 years). The proportion of patients who halted GDMT was 70.4%, 53.2%, 59.8% and 63.8% for MRA, beta-blockers, ACEI/ARB/ARNI and SGLT-2 inhibitors. Multivariable Cox analysis revealed ischemic heart disease, chronic kidney disease, coronary heart disease, lower left ventricular ejection fraction, larger left ventricular diastolic dimension and non-use GDMT are associated with recurrent HFrEF. Individuals without GDMT use exhibited lower chances of persistently recovering ejection fraction and high risks of MACEs compared to those who continue use.

Conclusions: HFimpEF is a common condition across all clinical follow-ups. Prevalent discontinuation of GDMT medications may contribute significantly to recurrent HFrEF, placing patients at a higher risk for poor prognosis.

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Introduction

Heart failure with reduced ejection fraction (HFrEF), a complex and usually progressive clinical condition, causes substantial morbidity and mortality [1,2]. Recent advances in medical and device therapies have enabled partial or complete reversal of left ventricular remodelling and dysfunction in a significant proportion of patients, with rates ranging from 10% to 52% [3–5]. This has given rise to a newly recognized category of heart failure known as 'heart failure with improved ejection fraction' (HFimpEF) [6].

Patients with HFimpEF typically exhibit milder clinical symptoms and appear to have a more favourable prognosis [3,7,8]. However, in those patients, the left ventricular ejection fraction (LVEF) may deteriorate

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again after a variable period of stability. The reasons for this functional worsening and subsequent recurrent HF events are not well known, whereas natural history and long-term clinical outcomes for (transient or persistent) HFimpEF have not been explicitly evaluated [9, 10]. Moreover, despite the current recommendation for prolonged administration of 'guideline-directed medical therapy (GDMT)' drugs in individuals with HFimpEF, there exists a limited amount of evidence-based medicine data to substantiate this recommendation [6]. Consequently, both patients and physicians might express hesitation in following this recommendation for long-term medication adherence, which has led to a significant discontinuation rate.

This study has gathered an extensive group of patients with HFimpEF to date and has obtained follow-up data over ten years. The primary objectives of this study are twofold: (1) to provide a thorough description of the characteristics and phenotypes of HFimpEF and the resulting outcomes, and (2) to investigate the impact of GDMT cessation in patients with HFimpEF.

Methods

Study design

The present study involved the sequential enrollment of individuals diagnosed with HFrEF who had undergone repeat echocardiograms at least six months apart after their initial diagnosis. The research was conducted at the First Affiliated Hospital of Wenzhou Medical University from January 2009 to February 2023. This database has been extensively detailed and elucidated in the literature previously published [11–16]. Patient data, including demographic details, medical history, medication records, echocardiographic evaluation details, and follow-up data, was collected from electronic medical records.

The research was conducted according to the Declaration of Helsinki principles, and the First Affiliated Hospital ethics committee of Wenzhou Medical University has approved the study protocol (NO. KY2023-R267). The requirement for informed consent was waived due to the retrospective design of our study.

Study definition

Two-dimensional echocardiography was performed. The report of each echocardiogram was interpreted by the consensus of two experienced readers according to the guidelines [17]. Readers interpreted the echocardiogram and analysed the already existing data. In case of ambiguous data or imaging, experienced readers interpreted the data. The subjects underwent a second echocardiogram at least 6 months apart and were separated into two categories, HFimpEF and non-HFimpEF. HFimpEF was defined as the patients who had met both the following criteria were diagnosed as: (1) the baseline LVEF < 40%; (2) a positive change in ejection fraction greater than or equal to 10%, and (3) a subsequent ejection fraction measurement above 40%, We also divided patients with HFimpEF into two subgroups: transient and persistent HFimpEF. If the LVEF decreases to 40% or below in at least one subsequent echocardiogram assessment after the initial diagnosis of HFimpEF, the patient is classified as transient HFimpEF. While if further measurements, not any LVEF < 40% were conducted following the initial diagnosis of HFimpEF, the patient was classified as persistent HFimpEF. We also classified HFimpEF cases with LVEF greater than 50% as the 'super-improved HFimpEF' group. The aetiology was considered as the diagnosis at discharge. Dilated cardiomyopathy was diagnosed as defined as a reduced LVEF <40% not attributable to known causes such as ischemic, valvular or pacemaker-induced cardiomyopathy, etc.

In adherence to the most recent guidelines, patients were treated with GDMT, such as mineralocorticoid receptor antagonists (MRAs), beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and angiotensin receptor neprilysin inhibitors (ARNI), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors for their medical needs [18, 19]. The use of SGLT-2 inhibitors was not a common practice in prior cases. Despite this, we have seen a significant increase in its use at our hospital following 2020. The drug therapy mentioned above was directed by the guidelines and gradually increased during each follow-up depending on the patient's tolerance [18–20].

Study outcomes

Clinical outcomes were evaluated through the comprehensive examination of clinical follow-up data, which were meticulously gathered from a variety of sources, encompassing both inpatient and outpatient medical records. Periodically, the patients visited the outpatient clinic. The risk of decompensated heart failure and readmission to the hospital determined the timing of follow-up as well as the intensity and type of intervention. The time for a repeated echocardiogram was based on the clinicians' judgment. In real clinical

practice, this time depended on the symptoms and/or signs of worsening HF, the time of the last hospitalization due to decompensated heart failure, and the patient's general health and social status (e.g. the cognitive function, patients' socially isolated, other comorbidities etc.). The primary endpoints were on a composite of major adverse clinical events (MACEs), such as all-cause death or hospitalization due to heart failure. All-cause mortality was defined as any form of death, regardless of its cause. Hospitalization due to heart failure was defined as any admission for ≥24 h with a primary diagnosis of heart failure and worsening symptoms, objective evidence of the HF situation (based on signs or laboratory tests) and augmentation of therapy [21]. The secondary endpoints were recurrent HFrEF. The follow-up period duration was determined from the time of HFimpEF diagnosis until either the final clinical follow-up or the occurrence of time-to-event endpoints, whichever came first. Patients were systematically followed up until April 2023 to assess clinical outcomes for prognostic purposes.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD), while those without a normal distribution were shown as median with interquartile range (IQR). Categorical variables were reported as counts and percentages. Group comparisons utilized the Student's *t*-test for normally distributed continuous variables, the Mann–Whitney U-test for non-normally distributed continuous variables and the Chi-squared test for categorical variables. Furthermore, a Cox proportional hazards model was employed to evaluate the effects of GDMT withdrawal on clinical outcomes over the follow-up period. We have considered various confounding factors as potential variables for inclusion in multivariable analysis. Variables with a p-value of less than 0.1 in the univariate analysis were considered potential risk factors, including age, sex, BMI, current smoking, current drinking, aetiology, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, previous stroke, previous myocardial infarction and chronic kidney disease, and were incorporated into the multivariate Cox regression analysis, ensuring adherence to the proportional hazards assumption. Hazard ratios (HR) and 95% confidence intervals (CI) have been calculated using Cox proportional hazard models. Event-free survival curves were determined using the Kaplan–Meier method, and variance between the curves was assessed using the log-rank test. To mitigate lead-time bias, where individuals with longer survival may have a higher chance of LVEF recovery, we set the start of the follow-up period at 1 year and reevaluated time-to-event analyses. Statistical significance was established at a *P*-value of < 0.05 (two-tailed). Statistical analyses were performed using IBM SPSS software (version 23.0 for Windows).

Results

Study population

The flowchart for the selection and exclusion process of patients is presented in Figure 1. The study initially included 5,137 consecutive patients diagnosed with HFrEF. Of these, 78 patients were excluded from the study as they did not have any information regarding their medications, 354 patients with HFrEF were excluded due to follow-up echocardiography that was less than 6 months, and 145 patients were lost to follow-up and therefore also excluded from the study. Therefore, our research involved a final group of 4,560 participants who met all the necessary criteria.

Clinical characteristics of HFimpEF patients

According to LVEF recovery, at 3.4 years (IQR: 1.8 – 5.9 years) medium follow-up, 3289 (72.1%) patients were assigned to the HFimpEF group, whereas 1271 (27.9%) showed persistent LVEF and were thus categorized under the non-HFimpEF group. A comprehensive summary of their baseline clinical characteristics is presented in Table 1. The comparison between these two groups revealed that: the HFimpEF group consisted of younger patients with more females, had a lower proportion of ischemic heart disease, and a higher percentage of patients with a history of hypertension, dyslipidaemia and atrial fibrillation. Additionally, 661 (20.0%), 1119 (34.0%), 967 (29.4%) and 105 (3.1%) patients were on mono, dual, triple and quadruple therapy, respectively. the HFimpEF group had a higher frequency of beta-blocker use, ACEI/ARB/ARNI and SGLT-2 inhibitors. During the follow-up, the HFimpEF group exhibited an improvement in echocardiographic parameters, with a smaller left ventricular end-diastolic dimension (LVDD), smaller left ventricular end-systolic dimension (LVSD) and left atrial diameter (LAD), as well as a lower proportion of moderate-severe mitral regurgitation and higher LVEF when compared to the non-HFimpEF group (all $p < 0.001$).

Clinical characteristics of transient and persistent HFimpEF patients

Over the course of a median follow-up period of 2.3 years (IQR: 0.8-4.6 years) following HFimpEF

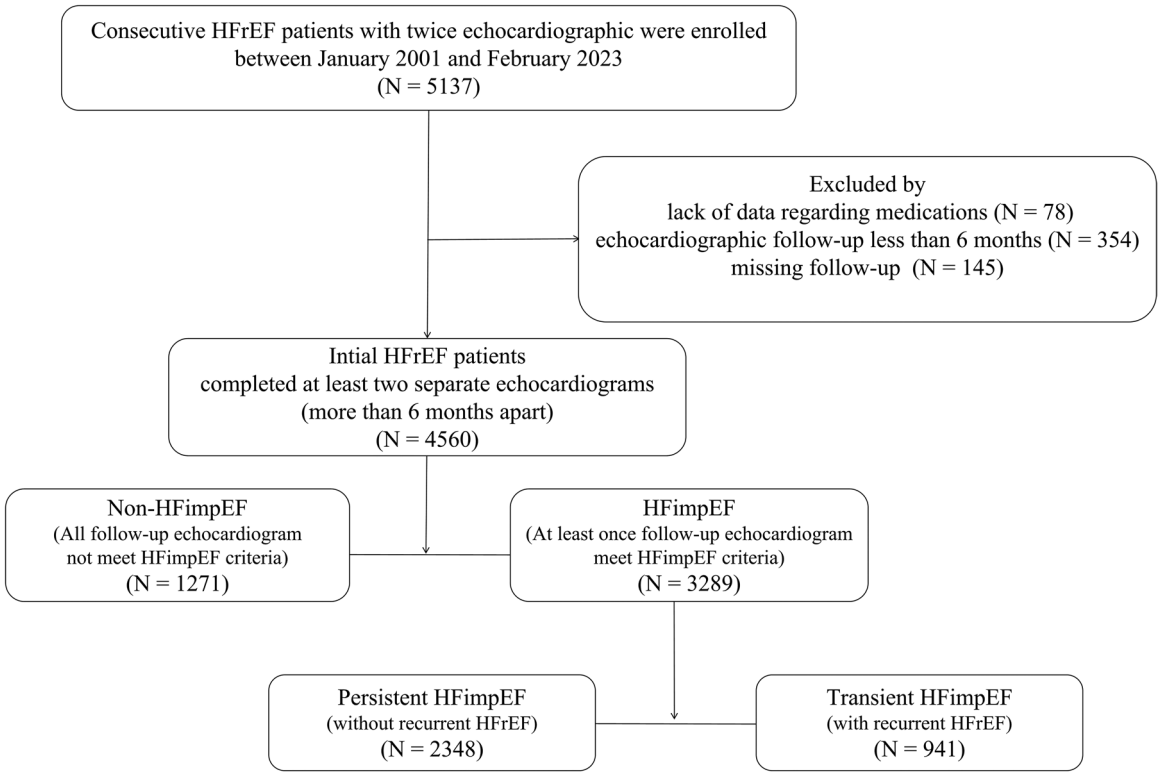

Figure 1. Flow diagram.
Abbreviations: HFrEF, heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction.

diagnosis, it was discovered that in patients with HFimpEF, recovered LVEF was transient in 941 (28.6%) patients, whilst it was observed to be persistent HFimpEF in 2348 (71.4%) patients. Clinical characteristics of HFimpEF patients stratified by transient and persistent HFimpEF can be seen in Table 2. Additionally, it was determined that in transient HFimpEF, the median duration from time of HFimpEF to the decline of LVEF to less than 40% was 11.0 months (IQR: 2.7-27.2 months), and the mean reduction in LVEF was found to be 15.5 ± 8.9%.

Predictive factors of recurrent HFrEF in HFimpEF

To investigate the factors that predict recurrent HFrEF in patients with HFimpEF, we conducted a univariable and multivariable Cox proportional hazard analysis (Table 3). Univariate analysis showed that males, current smoking, current drinking, a history of ischemic heart disease, chronic kidney disease, larger LAD/LVDD/LVSD, lower LVEF at baseline and all echocardiographic parameters at HFimpEF diagnosis were associated with higher risk. In contrast, the use of MRA, ACEI/ARB/ARNI, beta-blocker and SGLT-2 inhibitors was associated with lower risk of recurrent HFrEF in HFimpEF patients. When the multivariable analysis was performed, the history of ischemic heart disease and chronic kidney disease was associated with a higher risk of recurrent HFrEF. In comparison, the use of GDMT was associated with a lower risk of it in HFimpEF patients. Specifically, the use of ACEI/ARB/ARNI resulted in an HR of 0.72 (95% CI: 0.62 − 0.83, $p < 0.001$), while the use of beta-blockers led to an HR of 0.34 (95% CI: 0.29 − 0.40, $p < 0.001$). In addition, SGLT-2 inhibitors were associated with the low risk of recurrent HFrEF significantly, with an HR of 0.41 (95% CI: 0.21 − 0.79, $p = 0.008$).

Predictive factors of MACEs in HFimpEF

A detailed overview of the baseline clinical characteristics of the participants stratified by MACEs was presented in Supplement Table 1. We conducted multivariate Cox proportional hazard analyses to investigate potential risk factors for MACEs in HFimpEF patients (Supplement Table 2). Results from the univariate analysis revealed that age, smoking, drinking, ischemic heart disease, dilated cardiomyopathy, a history of hypertension, diabetes mellitus, chronic kidney disease, larger LAD/LVDD at HFrEF diagnosis, lower LVEF, larger LAD/LVDD/LVSD and their change values were all associated with increased risk of MACEs in HFimpEF patients. Moreover, in the multivariable analysis, we also found that age, a history of hypertension, diabetes mellitus, larger LAD and change value of LVEF were significantly associated with an increased risk of MACEs

Table 1. Baseline characteristics of the study population and stratified by HFimpEF and non-HFimpEF.

	Overall ($n=4560$)	Non-HFimpEF ($n=1271$, 27.9%)	HFimpEF ($n=3289$, 72.1%)	*P* value
Age, years	63.4 ± 13.8	65.2 ± 13.2	62.8 ± 14	<0.001
Male, *n* (%)	3313 (72.7%)	981 (77.2%)	2332 (70.9%)	<0.001
BMI, kg/m^2	23.7 ± 3.6	23.2 ± 3.3	23.9 ± 3.6	<0.001
Current smoking, *n* (%)	2019 (44.3%)	574 (45.2%)	1445 (43.9%)	0.465
Current drinking, *n* (%)	1526 (33.5%)	410 (32.3%)	1116 (33.9%)	0.294
NYHA class III-IV	1163 (25.5%)	345 (27.1%)	818 (24.9%)	0.114
NT-proBNP	1545 (491–4486)	3317 (1544–8444)	1141 (374–3377)	<0.001
Aetiology, *n* (%)				
Ischemic heart disease	2103 (46.1%)	622 (48.9%)	1481 (45%)	0.019
Dilated cardiomyopathy	1008 (20.5%)	333 (26.2%)	675 (20.5%)	<0.001
Others	1449 (31.8%)	316 (24.9%)	1133 (34.4%)	<0.001
Hypertensive	409 (9.0%)	95 (7.5%)	314 (9.5%)	0.028
Valvular	362 (7.9%)	82 (6.5%)	280 (8.5%)	0.021
Tachy-mediated cardiomyopathy	298 (6.5%)	75 (5.9%)	223 (6.8%)	0.281
Takotsubo cardiomyopathy	19 (0.4%)	4 (0.3%)	15 (0.5%)	0.506
Postpartum cardiomyopathy	6 (0.1%)	0 (0.0%)	6 (0.2%)	0.195
Alcohol	50 (1.1%)	13 (1.0%)	37 (1.1%)	0.766
Unknown cause	305 (6.7%)	47 (3.7%)	258 (7.8%)	<0.001
Comorbidities, *n* (%)				
Hypertension	2142 (47%)	544 (42.8%)	1598 (48.6%)	<0.001
Diabetes mellitus	951 (20.9%)	244 (19.2%)	707 (21.5%)	0.088
Dyslipidaemia	1432 (31.4%)	370 (29.1%)	1062 (32.3%)	0.039
Atrial fibrillation	864 (18.9%)	163 (12.8%)	701 (21.3%)	<0.001
Previous stroke	341 (7.5%)	88 (6.9%)	253 (7.7%)	0.414
Previous myocardial infarction	917 (20.1%)	266 (20.9%)	651 (19.8%)	0.387
Chronic kidney disease*	1036 (22.7%)	290 (22.8%)	746 (22.7%)	0.937
LBBB	248 (5.4%)	60 (4.7%)	188 (5.7%)	0.184
Cardiac interventional therapy, *n* (%)				
Cardiac resynchronization therapy	667 (14.6%)	175 (13.8%)	492 (15.0%)	0.308
CRT-D placement	270 (5.9%)	61 (4.8%)	209 (6.4%)	0.046
Coronary revascularization	983 (21.6%)	290 (22.8%)	693 (21.1%)	0.198
AF/AFL ablation	222 (4.9%)	63 (5.0%)	159 (4.8%)	0.863
Valvular interventions	300 (6.6%)	0 (0%)	300 (9.1%)	<0.001
GDMT following HFrEF diagnosis, *n* (%)				
MRA	3512 (77.0%)	955 (75.1%)	2557 (77.7%)	0.065
Beta-blocker	3539 (77.6%)	890 (70.0%)	2649 (80.5%)	<0.001
ACEI/ARB/ARNI	3565 (78.2%)	867 (68.2%)	2698 (82.0%)	<0.001
SGLT-2 inhibitors	284 (6.2%)	44 (3.5%)	240 (7.3%)	<0.001
Baseline echo at HFrEF diagnosis				
LVEF, %	32.8 ± 5.4	31.7 ± 6.0	33.3 ± 5.1	<0.001
LAD, mm	47.2 ± 7.3	48.1 ± 6.9	46.9 ± 7.3	<0.001
LVEDD, mm	61.3 ± 8.5	64.6 ± 8.4	60 ± 8.3	<0.001
LVSDD, mm	50.7 ± 8.8	54.3 ± 8.9	49.3 ± 8.4	<0.001
Moderate-severe MR	237 (5.2%)	75 (5.9%)	162 (4.9%)	0.181
Following echo after HFimpEF diagnosis				
LVEF, %	43.7 ± 10.9	30.6 ± 6.1	48.8 ± 7.6	<0.001
LAD, mm	46.4 ± 7.8	49.8 ± 7.9	45.1 ± 7.3	<0.001
LVDD, mm	59.5 ± 9.1	66.4 ± 8.9	56.9 ± 7.7	<0.001
LVSD, mm	46.2 ± 10.5	56.3 ± 9.5	42.3 ± 8.1	<0.001
Moderate-severe MR	214 (4.7%)	152 (12.0%)	62 (1.9%)	<0.001

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BMI: body mass index; SGLT-2: glucagon-like peptide-2; HFrEF, heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction; LAD: left atrial diameter; LVSD: left ventricular end systolic diameter; LVDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonist;.
*eGFR <60 mL/min/1.73 m^2.

in HFimpEF patients. Additionally, the use of beta-blocker resulted in an HR of 0.51 (95% CI: 0.46 – 0.55, $p < 0.001$), and the use of ACEI/ARB/ARNI led to an HR of 0.63 (95% CI: 0.58 – 0.69, $p < 0.001$) was significantly associated with increased risk of MACEs.

GDMT discontinuation rates and its Effect on clinical outcomes

High discontinuation rates after HFimpEF diagnosis were common regardless of pharmacological class (Figure 2). The proportion of patients who were on GMDT during the diagnosis of HFimpEF and discontinued these agents later was 70.4%, 53.2%, 59.8%, and 63.8% for MRA, beta-blockers, ACEI/ARB/ARNI and SGLT-2 inhibitors respectively. As presented in Table 4, for both beta-blockers and ACEI/ARB/ARNI, as well as SGLT-2 inhibitors, there was a higher likelihood of HFrEF recurrence and a greater incidence of MACEs events observed in the population who never used or discontinued the medication. However, with regard to MRAs, the difference was less evident. Then we

Table 2. Baseline characteristics of HFimpEF patients stratified by persistent and transient HFimpEF.

	Overall HFimpEF ($n=3289$)	Persistent HFimpEF ($n=2348$, 71.4%)	Transient HFimpEF ($n=941$, 28.6%)	*P* value
Age, years	62.8 ± 14.0	62.7 ± 14.3	63 ± 13.2	0.574
Male, *n* (%)	2332 (70.9%)	1612 (68.7%)	720 (76.5%)	<0.001
BMI, kg/m^2	23.9 ± 3.6	23.9 ± 3.7	23.9 ± 3.5	0.653
Current smoking, *n* (%)	1445 (43.9%)	967 (41.2%)	478 (50.8%)	<0.001
Current drinking, *n* (%)	1116 (33.9%)	749 (31.9%)	367 (39%)	<0.001
NT-proBNP	1141 (374-3377)	933 (305-2944)	1579 (624-4695)	<0.001
NYHA class	818 (24.9%)	588 (25%)	230 (24.4%)	0.719
Aetiology, n (%)				
Ischemic heart disease	1481 (45%)	997 (42.5%)	484 (51.4%)	<0.001
Dilated cardiomyopathy	675 (20.5%)	464 (19.8%)	211 (22.4%)	0.094
Others	1133 (34.4%)	887 (37.8%)	246 (26.1%)	<0.001
Hypertensive	314 (9.5%)	257 (10.9%)	57 (6.1%)	<0.001
Valvular	280 (8.5%)	180 (7.7%)	100 (10.6%)	0.006
Alcohol	223 (6.8%)	169 (7.2%)	54 (5.7%)	0.133
Tachy-mediated cardiomyopathy	15 (0.5%)	14 (0.6%)	1 (0.1%)	0.059
Takotsubo cardiomyopathy	6 (0.2%)	5 (0.2%)	1 (0.1%)	0.517
Postpartum cardiomyopathy	37 (1.1%)	28 (1.2%)	9 (1.0%)	0.562
Unknown cause	258 (7.8%)	234 (10%)	24 (2.6%)	<0.001
Comorbidities, n (%)				
Hypertension	1598 (48.6%)	1159 (49.4%)	439 (46.7%)	0.165
Diabetes mellitus	707 (21.5%)	506 (21.6%)	201 (21.4%)	0.925
Dyslipidaemia	1062 (32.3%)	762 (32.5%)	300 (31.9%)	0.773
Atrial fibrillation	701 (21.3%)	530 (22.6%)	171 (18.2%)	0.005
Previous stroke	253 (7.7%)	190 (8.1%)	63 (6.7%)	0.192
Previous myocardial infarction	651 (19.8%)	428 (18.2%)	223 (23.7%)	<0.001
Chronic kidney disease*	746 (22.7%)	473 (20.1%)	273 (29.0%)	<0.001
LBBB	188 (5.7%)	138 (5.9%)	50 (5.3%)	0.529
Cardiac interventional therapy, n (%)				
Cardiac resynchronization therapy	492 (15%)	327 (14%)	165 (18%)	0.009
CRT-D placement	209 (6.4%)	149 (6.3%)	60 (6.4%)	0.974
Coronary revascularization	693 (21%)	474 (20%)	219 (23%)	0.050
AF/AFL ablation	159 (4.8%)	103 (4.4%)	56 (6.0%)	0.059
Valvular interventions	300 (9.1%)	229 (9.8%)	71 (7.5%)	0.047
GDMT before HFrEF diagnosis, n (%)				
MRA	2557 (77.7%)	1781 (75.9%)	776 (82.5%)	<0.001
Beta-blocker	2649 (80.5%)	1890 (80.5%)	759 (80.7%)	0.961
ACEI/ARB/ARNI	2698 (82.0%)	1875 (79.9%)	823 (87.5%)	<0.001
SGLT-2 inhibitors	240 (7.3%)	125 (5.3%)	115 (12.2%)	<0.001
GMDT following HFimpEF diagnosis, n (%)				
MRA	794 (24.1%)	543 (23.1%)	251 (26.7%)	0.034
Beta-blocker	1314 (40.0%)	1088 (46.3%)	226 (24%)	<0.001
ACEI/ARB/ARNI	1133 (34.4%)	851 (36.2%)	282 (30%)	0.001
SGLT-2 inhibitors	113 (3.4%)	104 (4.4%)	9 (1.0%)	<0.001
Baseline echo at intial HFrEF diagnosis				
LVEF, %	33.3 ± 5.1	33.4 ± 5.1	32.8 ± 5.0	0.001
LAD, mm	46.9 ± 7.3	46.7 ± 7.2	47.4 ± 7.6	0.015
LVDD, mm	60 ± 8.3	59.4 ± 8.1	61.7 ± 8.4	<0.001
LVSD, mm	49.3 ± 8.4	48.7 ± 8.2	50.9 ± 8.7	<0.001
Moderate-severe MR	162 (4.9%)	129 (5.5%)	33 (3.5%)	0.016
Baseline echo at HFimpEF diagnosis				
LVEF, %	48.8 ± 7.6	50.1 ± 7.9	45.5 ± 5.8	<0.001
LAD, mm	45.1 ± 7.3	44.7 ± 7.3	46.3 ± 7.1	<0.001
LVDD, mm	56.9 ± 7.7	55.4 ± 7.1	60.5 ± 7.8	<0.001
LVSD, mm	42.3 ± 8.1	40.7 ± 7.4	46.6 ± 8.2	<0.001
Moderate-severe MR	62 (1.9%)	42 (1.8%)	20 (2.1%)	0.570
δLVEF**, %	15.5 ± 8.9	16.7 ± 9.2	12.7 ± 7.3	<0.001
δLAD**, mm	−1.7 ± 5.7	−2.0 ± 5.8	−1.0 ± 5.4	<0.001
δLVDD**, mm	−3.1 ± 6.8	−4.0 ± 6.9	−1.1 ± 6.1	<0.001
δLVSD**, mm	−6.9 ± 8.1	−8.0 ± 8.1	−4.0 ± 7.4	<0.001
Following echo after HFimpEF diagnosis				
LVEF, %	48.7 ± 12.4	54.6 ± 9.0	33.9 ± 4.8	<0.001
LAD, mm	45.9 ± 7.9	45.0 ± 7.7	48.3 ± 7.8	<0.001
LVDD, mm	56.0 ± 8.4	53.6 ± 7.2	62.2 ± 7.9	<0.001
LVSD, mm	41.7 ± 9.8	38.0 ± 7.78	51.3± 8.1	<0.001
Moderate-severe MR	151 (4.6%)	62 (2.6%)	89 (9.5%)	<0.001

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BMI: body mass index; GDMT: guideline-directed medical therapy; SGLT-2: sodium-glucose cotransporter-2; HFrEF: heart failure with reduced ejection fraction; HFimpEF: heart failure with improved ejection fraction; MRA: mineralocorticoid receptor antagonist;.

*eGFR <60 mL/min/1.73 m^2.

**Change value of echo parameter between HFrEF diagnosis and HFimpEF diagnosis.

Table 3. Cox regression analyses for predictors of recurrent HFrEF in HFimpEF patients.

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	1.47 (1.26–1.70)	<0.001		
Current smoking	1.41 (1.24–1.60)	<0.001		
Current drinking	1.28 (1.12–1.46)	<0.001		
Ischemic heart disease	1.44 (1.27–1.64)	<0.001	1.55 (1.34–1.79)	<0.001
Other Aetiology	0.86 (0.82–0.90)	<0.001		
Atrial fibrillation	0.84 (0.72–1.00)	0.044		
Previous myocardial infarction	1.42 (1.22–1.65)	<0.001		
Chronic kidney disease*	1.51 (1.31–1.74)	<0.001	1.36 (1.17–1.58)	<0.001
GDMT following HFimpEF diagnosis**				
MRA	0.81 (0.70–0.94)	0.005		
Beta-blocker	0.29 (0.25–0.34)	<0.001	0.34 (0.29–0.40)	<0.001
ACEI/ARB/ARNI	0.53 (0.46–0.61)	<0.001	0.75 (0.64–0.87)	<0.001
SGLT-2 inhibitors	0.27 (0.14–0.52)	<0.001	0.38 (0.19–0.77)	0.007
Baseline echo at HFrEF diagnosis				
LVEF, per 1%	0.99 (0.97–1.00)	0.018		
LAD, per 1 mm	1.01 (1.00–1.02)	0.009		
LVDD, per 1 mm	1.03 (1.02–1.03)	<0.001	1.04 (1.02–1.07)	<0.001
LVSD, per 1 mm	1.03 (1.02–1.03)	<0.001		
Moderate-severe MR	0.88 (0.62–1.25)	0.486		
Follow-up echo at HFimpEF diagnosis				
LVEF, per 1%	0.91 (0.90–0.92)	<0.001	0.94 (0.93–0.96)	<0.001
LAD, per 1 mm	1.03 (1.02–1.03)	<0.001		
LVDD, per 1 mm	1.07 (1.06–1.08)	<0.001		
LVSD, per 1 mm	1.08 (1.07–1.09)	<0.001	1.02 (1.00–1.05)	0.046
δLVEF***	0.95 (0.94–0.96)	<0.001		
δLAD***	1.03 (1.01–1.04)	<0.001		
δLVDD***	1.06 (1.05–1.07)	<0.001		
δLVSD***	1.05 (1.05–1.06)	<0.001		

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; SGLT-2: sodium-glucose cotransporter-2; HFrEF: heart failure with reduced ejection fraction; HFimpEF: heart failure with improved ejection fraction; LAD: left atrial diameter; LVSD: left ventricular end systolic diameter; LVDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonist;.

*eGFR <60 mL/min/1.73 m^2;.

**Those who never used GDMT were included.

***Change value of echo parameter between HFrEF diagnosis and HFimpEF diagnosis.

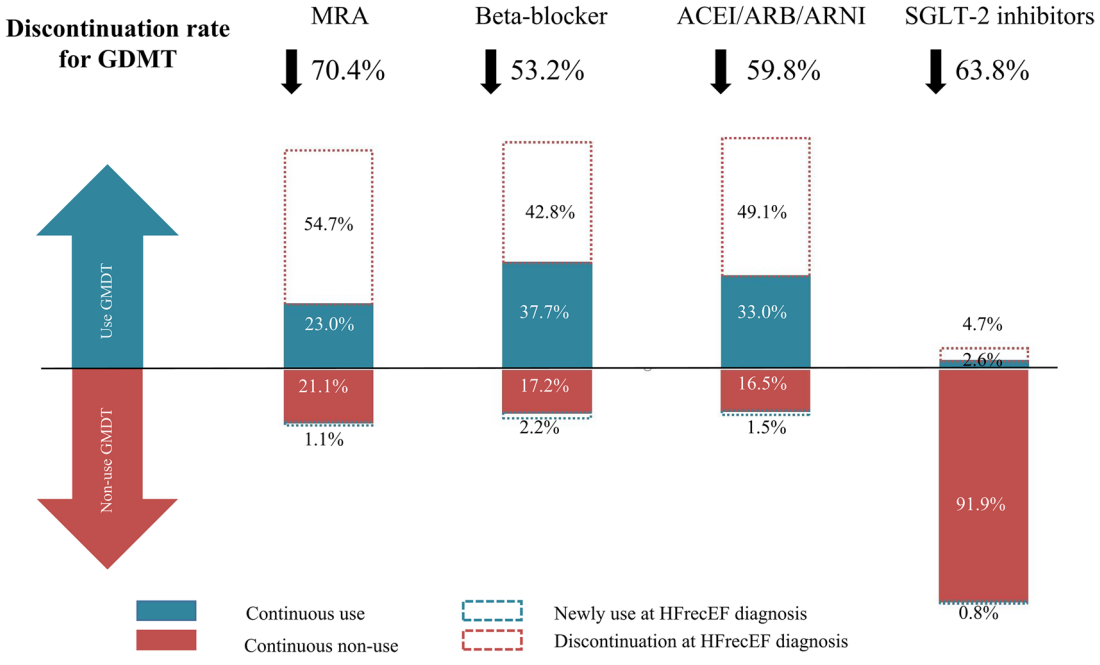

Figure 2. Utilization of GMDT in patients with HFimpEF following their diagnosis.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; GMDT, guideline-directed medical therapy; HFimpEF, heart failure with improved ejection fraction; MACEs, major adverse clinical events; MRA, mineralocorticoid receptor antagonists; SGLT-2, glucagon-like peptide-2.

Table 4. Clinical outcomes of the study population and stratified by GDMT medication.

	Recurrent HFrEF	MACEs	All-cause death	HHF
All subject	941 (28.6%)	1027 (31.2%)	193 (5.9%)	942 (28.6%)
MRA				
Continuous use	235 (31.0%)	244 (32.2%)	43 (5.7%)	225 (29.7%)
Newly use at HFimpEF diagnosis	16 (43.2%)	11 (29.7%)	3 (8.1%)	10 (27.0%)
Discontinuation at HFimpEF diagnosis	541 (30.1%)	610 (33.9%)	118 (6.6%)	561 (31.2%)
Continuous non-use	149 (21.4%)	162 (23.3%)	29 (4.2%)	146 (21.0%)
Beta-blocker				
Continuous use	216 (17.4%)	174 (14.0%)	50 (4.0%)	140 (11.3%)
Newly use at HFimpEF diagnosis	10 (13.7%)	9 (12.3%)	3 (4.1%)	8 (11.0%)
Discontinuation at HFimpEF diagnosis	543 (38.6%)	643 (45.7%)	50 (4.0%)	610 (43.3%)
Continuous non-use	172 (30.3%)	201 (35.4%)	95 (6.7%)	184 (32.5%)
ACEI/ARB/ARNI				
Continuous use	278 (25.6%)	263 (24.3%)	50 (4.6%)	235 (21.7%)
Newly use at HFimpEF diagnosis	4 (8.2%)	7 (14.3%)	4 (8.2%)	6 (12.2%)
Discontinuation at HFimpEF diagnosis	545 (33.8%)	610 (37.8%)	113 (7.0%)	566 (35.1%)
Continuous non-use	114 (21.0%)	147 (27.1%)	26 (4.8%)	135 (24.9%)
SGLT-2 inhibitors				
Continuous use	8 (17.4%)	6 (6.9%)	5 (5.7%)	1 (1.1%)
Newly use at HFimpEF diagnosis	1 (3.8%)	3 (11.5%)	1 (3.8%)	2 (7.7%)
Discontinuation at HFimpEF diagnosis	107 (69.9%)	88 (57.5%)	9 (5.9%)	85 (55.6%)
Continuous non-use	825 (27.3%)	930 (30.8%)	178 (5.9%)	854 (28.3%)

Abbreviations: ACEI: angiotensin converting enzyme inhibitor; ARBs: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; SGLT-2: sodium-glucose cotransporter-2; HFrEF: heart failure with reduced ejection fraction; HFimpEF: heart failure with improved ejection fraction; HHF: hospitalization due to heart failure; MRA: mineralocorticoid receptor antagonist.

conducted an additional Kaplan-Meier analysis to assess the clinical outcomes of HFimpEF patients with GDMT withdrawal compared to those without GDMT withdrawal. The Kaplan–Meier survival curves for all-cause mortality and hospitalization due to heart failure are shown in Figure S3, respectively. The incidence of all-cause death or HF hospitalization, was significantly lower in the group with GDMT use compared to those without use regardless of pharmacological class. Moreover, Supplement Figure 1 presents displays the Kaplan–Meier curves used to assess the cumulative impact of non-use of GDMT drugs across different categories.

Sensitivity analysis excluding 1-year events

It is possible that lead-time bias could affect the outcomes of patients with HFimpEF since they may have survived long enough for their LVEF to improve before being included in the study. To minimize this bias, we decided to limit follow-up to one year and conduct repeated time-to-event analyses. After excluding patients who died or had no follow-up beyond one year ($n=1227$), the final cohort consisted of 2062 patients. As shown in Supplement Figure 2, it can be inferred with certainty that patients with HFimpEF who persist in taking beta-blockers, ACEI/ARB/ARNI medicines, or SGLT-2 inhibitors experience a notable reduction in the risk of MACEs compared to those who discontinue medication (all $p<0.001$). However, individuals who continue using MRA medication exhibit no significant difference in the likelihood of MACEs when compared to those who choose to discontinue ($p=0.066$).

Effect of GDMT discontinuation on clinical outcomes stratified by the underlying cause

We conducted an additional subgroup analysis based on the aetiology of the condition, distinguishing between ischemic and non-ischemic causes (Supplement Figure 3). Our findings presented in Table 5 indicate that patients with ischemic heart disease who continue beta-blocker or ACEI/ARB/ARNI medication are at reduced risk of MACEs compared to those who discontinue medication. Specifically, HR for beta-blockers was 0.20 (95% CI 0.16 – 0.25, $p<0.001$), for ACEI/ARB/ARNI it was 0.54 (95% CI 0.44 – 0.67, $p<0.001$), and for SGLT-2 inhibitors, it was 0.24 (95% CI 0.08 – 0.76, $p=0.015$). However, patients who continued with MRA medication faced a comparable risk of MACEs compared to those who stopped (HR 2.21; 95% CI 1.13 – 4.32). Even in patients with dilated cardiomyopathy, a similar pattern was observed (beta-blocker: HR 2.49, 95% CI 2.19 – 2.84, $p<0.001$; ACEI/ARB/ARNI: HR 0.69, 95% CI 0.49 – 0.96, $p=0.029$; and SGLT-2 inhibitors: HR 0.16, 95% CI, 0.02 – 1.15, $p=0.069$).

Characteristics and incidence of recurrent HFrEF in super-improved HFimpEF patients

In a group of 4,560 people diagnosed with HFrEF, 2,108 (46.2%) individuals achieved super-improved HFimpEF. Supplement Table 3 comprehensively

Table 5. Cox regression analyses for predictors of MACEs in HFimpEF patients stratified by underlying aetiology.

	Adjusted HR (95% CI)	P-value
Ischemic heart disease		
MRA	1.13 (0.92 – 1.40)	0.237
Beta-blocker	0.20 (0.16 – 0.25)	<0.001
ACEI/ARB/ARNI	0.54 (0.44 – 0.67)	<0.001
SGLT-2 inhibitors	0.24 (0.08 – 0.76)	0.015
Dilated cardiomyopathy		
MRA	1.32 (0.94 – 1.85)	0.106
Beta-blocker	0.21 (0.15 – 0.31)	<0.001
ACEI/ARB/ARNI	0.69 (0.49–0.96)	0.029
SGLT-2 inhibitors	0.16 (0.02 – 1.15)	0.069
Other aetiology		
MRA	1.11 (0.85 – 1.45)	0.463
Beta-blocker	0.21 (0.16 – 0.29)	<0.001
ACEI/ARB/ARNI	0.64 (0.5 – 0.82)	0.001
SGLT-2 inhibitors	1.14 (0.47 – 2.77)	0.781

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; GDMT: guideline-directed medical therapy; SGLT-2: glucagon-like peptide-2; HFrEF: heart failure with reduced ejection fraction; HFimpEF: heart failure with improved ejection fraction; LAD: left atrial diameter; LVSD: left ventricular end systolic diameter; LVDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MACEs: major adverse clinical events; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonist;.

Adjusted for age, sex, BMI, current smoking, current drinking, aetiology, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, previous stroke, previous myocardial infarction and chronic kidney disease.

P-value for interaction of MRA, Beta-blocker, ACEI/ARB/ARNI, SGLT-2 inhibitors were 0.99, 0.53, 0.17, 0.05.

summarizes the participants' baseline clinical characteristics, categorized into super-improved HFimpEF and non-super-improved HFimpEF groups. A comparative analysis between these two groups reveals that the cohort with super-improved HFimpEF comprises primarily younger patients, with a higher number of females and a lower prevalence of ischemic heart disease. Additionally, the super-improved group received more frequent treatment with beta-blockers, ACEI/ARB/ARNI, and SGLT-2 inhibitor therapies. Of 2,108 individuals who achieved super-improved HFimpEF, 245 (11.6%) individuals subsequently experienced recurrent HFrEF. The baseline clinical characteristics of patients with super-improved HFimpEF, stratified by recurrent HFrEF and non-recurrent HFrEF, are presented in Supplement Table 4.

Discussion

There are various causes and phenotypes of HFimpEF may have different clinical outcomes and repercussions from the withdrawing GDMT. the present study collected new evidence from a sizable cohort of HFimpEF patients with longitudinal reassessment data in contemporary times. This study's critical findings reveal that:

1. Although approximately 70% of the population with HFrEF experienced HFimpEF throughout the observation period, around 30% of patients with HFimpEF also experienced recurrent HFrEF.
2. After being diagnosed with HFimpEF, a high discontinuation rate for GDMT was observed, ranging from approximately 50-70%, with a higher incidence of adverse outcomes.
3. For patients with HFimpEF who have either ischemic or non-ischemic etiology, it is imperative to maintain long-term usage of GDMT medication.

Prevalence of HFimpEF

In retrospective investigations, it was found that the incidence of LVEF improvement varied from 10% to 57% [3, 9, 22–25]. Additionally, it was discovered that once the root reversible causes were eliminated, there is a chance for up to 40% to 50% [26–29]. In our study, the prevalence of HFimpEF was much higher than cited in the literature. Several reasons may explain this situation. Firstly, due to the retrospective nature and design of the study, any patient who died or did not undergo a second echocardiogram was excluded. Mortality and the proportion of patients without echocardiogram at follow-up are not negligible even in a 6-month follow-up period in studies of heart failure, while mortality is greater in HFrEF [30–32]. Secondly, the majority of the published studies included patients with chronic HFrEF, while most of the patients included in our study belonged to the hospital cohort group and were diagnosed with HFrEF during an episode of acute heart failure [14, 33]. Some interventions can positively impact reverse remodelling of the left ventricle of the patients. Furthermore, it is known that the incidence of HFimpEF decreased in relation to time since diagnosis of HFrEF [34]. Thirdly, our study population had a lower mean age than most of the previous studies, and younger age is a predictor of improvement in left ventricular ejection fraction [35, 36]. Fourthly, prior reported studies have assessed LV response at specific time points such as 1-years. In our study, the timing of the left ventricular reaction to therapeutic interventions has yet to be definitively determined. For HFimpEF diagnosis, following echocardiography was only limited at least 6 months apart, but not limited to the last following echocardiography time. So, a late reverse remodeling could contribute to the higher proportion of HFimpEF [37]. Interestingly, given the results of a study in which they included patients with a new diagnosis of HFrEF and severely reduced EF (24 ± 7%) who they followed closely, the proportion of patients with the early and late recovery of EF might be higher than reported until to this day [38]. Fifth, our population with HFrEF had higher baseline EF than that reported in previous

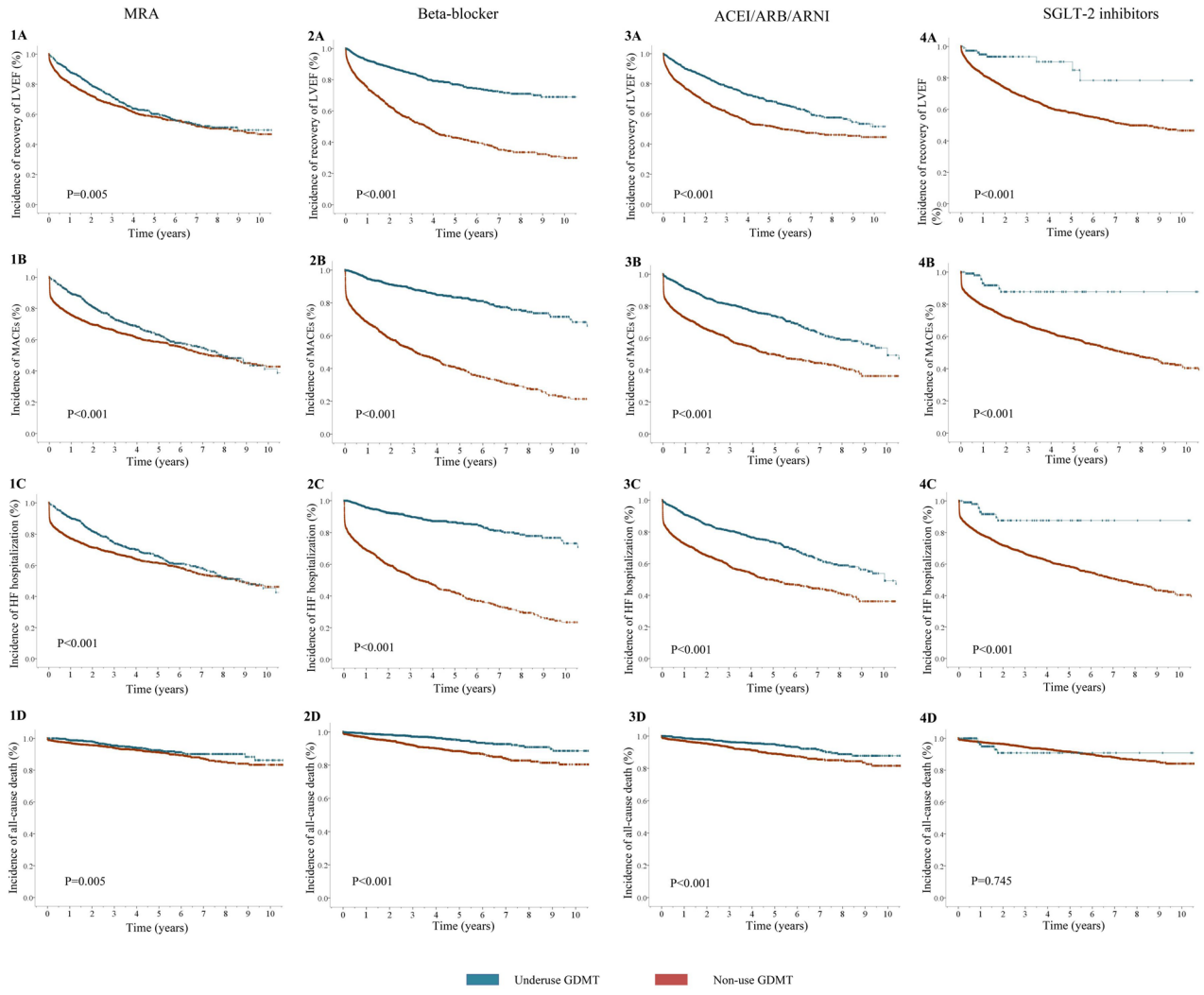

Figure 3. Kaplan-Meier event-free survival curve in patients with HFimpEF according to MRA (1 A-1D), beta-blockers (2 A-2D), ACEI/ARB/ARNI (3 A-3D) and SGLT-2 inhibitors (4 A-4D) use status following their diagnosis: (A) recurrent HFrEF; (B) MACEs; (C) HHF and (D) All-cause death.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; HFrEF, heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction; HHF, hospitalization due to heart failure; MACEs, major adverse clinical events; MRA, mineralocorticoid receptor antagonists; SGLT-2, glucagon-like peptide-2; GMDT, guideline-directed medical therapy.

studies and higher EF is a predictor of HFimprEF [32, 39]. However, despite our efforts to minimize selection bias, it cannot be excluded, mainly due to the retrospective nature of the study.

This is because the timing of the left ventricular reaction to therapeutic interventions has yet to be definitively determined. Prior reported studies have also assessed LV response at specific time points such as 1-years. For example, Manca et al. enrolled 800 consecutive NICM patients with baseline LVEF ≤ 40% enrolled in the Trieste the overall cohort), with a median time to improve LVEF of 13 (IQR 7–25) months. We also found that around 50% of patients with HFrEF experienced improved LVEF at first-year follow-up. However, extended tracking of LVEF over an extended period of observation has rarely been reported. We opted not to limit the response time for LVEF and observed the patients throughout the clinical follow-up period. Additionally, Manca et al. found that recurrent HFrEF was observed in around 40% of improved LVEF patients [25]. We also discovered that around 30% of patients with HFimpEF experienced recurring HFrEF. Even patients with super-improved HFimpEF have a risk for recurrent HFrEF.

Clinical characteristics and predictors of HFimpEF

In our population, patients with HFrEF and afterward improved LVEF (HFimpEF) were younger, with a higher prevalence of female sex, lower prevalence of ischemic heart disease, and better neurohormonal and echocardiographic profile than those without improved LVEF.

These results are consistent with most of the previous studies [3, 8, 40]. Symptoms (the NYHA profile) did not differ, while published results in the literature are conflicting [8, 41, 42]. A recently published meta-analysis showed that the female gender is associated with an increased chance of LVEF improvement by 50% [43]. Regarding therapy, the group of improved LVEF received more frequent GTMD following the diagnosis of HFrEF. From interventional therapies, only CRT-D placement and valvular interventions were associated with LVEF improvement. These parameters and better renal function may also play a role in the maintenance of LVEF improvement. Previous studies have proved the remodelling effects of CRT-D placement [44, 45]. Finally, it is quite difficult from data retrieved from retrospective studies to explain the association of chronic kidney disease with heart remodelling and the course of heart failure and to clarify if the primary injury was in the heart, the kidney or in both systems [46].

Can any or all of GDMT be discontinued in patients with HFimpEF?

HFimpEF among patients may fluctuate considerably because of variations in crucial clinical characteristics and disparities in follow-up periods. Optimal medical therapy positively influences the LVEF in HFrEF patients, partially or completely. According to current expert consensus, it is not recommended to withdraw GDMT in patients with HFimpEF [6]. Our data indicated that 50–70% of patients did not continue to use GDMT, with 40-70% experiencing HFimpEF recurrence. There are several reasons for the discontinued use of GMDT with HFimpEF. Firstly, there is no clear conclusion on whether GMDT should be continued in such cases. Secondly, patients may find it difficult to comply with long-term use of the drug after symptom improvement. Lastly, drug discontinuation may be necessary due to adverse reactions or changes in clinical needs. Moreover, discontinuation of GDMT was associated with a higher risk of adverse events. It is worth noting that no patient can be excluded from the risk of recurrent HFimpEF and the risk is greater after discontinuation of GDMT even in patients with a LVEF above 50% during follow-up periods.

Two theories attempt to explain the apparent therapeutic advantage of continued GDMT [6]. One concept worth mentioning is that a considerable number of multi-molecules that underwent dysregulation during the process of ventricular remodelling continue to remain dysregulated in the heart that underwent reverse remodeling, despite experiencing significant improvements in both shape and function [47, 48]. Thus, those patients are more likely to suffer from recurring myocyte injury and have a reduced ability to recover LVEF in subsequent episodes. Additionally, probably, the majority of patients currently diagnosed with heart failure with mid-range ejection fraction in contemporary clinical settings are suffering from the recovery process, which is not the end of their recovery. Thus, the 2020 Scientific Expert Panel on HFimpEF has expressed the view that in cases where there is uncertainty concerning the decision of whether to continue GDMT, it would be more advisable to continue administering medications [6].

Is it advisable to discontinue GDMT medication depending on the underlying aetiology of patients with HFimpEF?

Although some interventions can positively impact reversing remodelling and restoring LVEF in heart failure patients, the benefits are typically limited to a cardiac remission rather than a complete cure. Patients with HFimpEF may continue to experience sustained neurohormonal activation metabolic syndrome and chronic systemic inflammation, which can leave them vulnerable to HF recurrence and other negative cardiovascular events [11, 49–51]. This question necessitates an evaluation of the underlying etiology, which prompted us to conduct a supplementary subgroup analysis based on this factor. The results revealed consistent findings among ischemic HFimpEF patients and those with dilated cardiomyopathy. However, our data should be extrapolated with caution to HFimpEF of all underlying aetiology of HFimpEF. Other aetiology populations are diverse, with various underlying causes leading to heart failure, which include acute myocarditis, alcoholic cardiomyopathy, perinatal cardiomyopathy, tachycardiomyopathy, drug-induced cardiomyopathy and hyperthyroidism-associated cardiomyopathies. In cases where these underlying causes are identified and addressed, patients may achieve near-complete recovery from the pathophysiology of heart failure [26, 52]. The vast number of individuals involved in the research and our cautious approach have made it challenging to pinpoint a particular disease origin of HFimpEF. The TRED-HF trial (Therapy withdrawal in REcovered Dilated cardiomyopathy trial) aimed to explore the impact of phased withdrawal of heart failure medications in patients with dilated cardiomyopathy and HFimpEF [50]. This open-label, pilot, randomized trial enrolled a total of 51 participants, with 25 assigned to the treatment withdrawal group and 26 to the continued treatment group. During the following 6 months, there were three reported instances of serious adverse events in

the treatment withdrawal group. This led to the conclusion that patients who were considered to have recovered from dilated cardiomyopathy experienced a relapse upon withdrawal of GMDT.

Future research endeavours could concentrate on pinpointing specific patient groups with sustained restoration of myocardial function, allowing for safe discontinuation of certain medications in the long term or the need for continued use of only select medications. According to the consensus previously established, if you are unsure whether the potential hazard has been resolved, it is recommended that you proceed with the GDMT treatment.

Study limitations

Our study report included a few limitations that require acknowledgment. Firstly, the research was conducted retrospectively at a single centre; therefore, it may not be possible to avoid selection bias. Secondly, we acknowledge that there is a possibility of bias due to lead time or survival, as we required eligible patients to undergo two echocardiograms at least six months apart, and the diagnosis of heart failure may not have been based on the first echocardiogram obtained at the time of diagnosis. Thirdly, it was a challenge to determine the duration of heart failure before enrollment, as the patient's diagnosis could have been made at hospitals outside our affiliation, where records are not connected to ours. Fourth, heart failure hospitalization rates may have been underestimated due to the use of electronic medical records, which may have failed to capture hospitalizations of patients admitted to hospitals outside our institution. Fifth, residual confounding and confounding by indication limit the interpretability of the results since the reasons for drug continuation/new initiation/discontinuation are unclear. The effect size of continued GDMT use vs withdrawal appears very high and, along with the directionality of the treatment effect of MRA, suggests that there may be confounding. Sixth, the number of patients on SGLT2i therapy is so small it is difficult to draw confirmed conclusions. Lastly, most of the participants in this study are Asian, and future studies on the clinical outcomes of HFimpEF need to be further established in other ethnic groups.

Conclusions

HFimpEF is a prevalent condition observed throughout clinical follow-ups. However, recurrent HFrEF is also a frequent occurrence among patients with HFimpEF. Prevalent discontinuation of GDMT medications may contribute significantly to recurrent HFrEF, placing patients at a higher risk for poor prognosis.

Contributions

Conceptualization: Q-F Chen, YD Lu, W-H Lin and X-D Zhou;

Data curation: Q-F Chen, YD Lu, YD Peng, JF Sun, MM Li, CY Liu, HX Yao, LY Lian and XF Feng collected data.

Formal analysis: Q-F Chen, LY Lian and X-D Zhou

Funding acquisition: W-H Lin and X-D Zhou;

Investigation: YD Lu, YD Peng, JF Sun, MM Li, CY Liu, HX Yao, and XF Feng

Methodology: Q-F Chen and LY Lian

Project administration: W-H Lin and X-D Zhou;

Resources: X-D Zhou

Software: YD Lu and LY Lian

Supervision: W-H Lin and X-D Zhou;

Validation: Q-F Chen, CS Katsouras and X-D Zhou

Writing – original draft: Q-F Chen, YD Lu and X-D Zhou

Writing-review & editing: Q-F Chen, YD Lu, YD Peng, JF Sun, MM Li, CY Liu, HX Yao, LY Lian, XF Feng and X-D Zhou.

All authors have read and approved the final work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability Statement

The data that support the findings of this study are available from the corresponding author (zhouxiaodong@wmu.edu.cn) upon reasonable request.

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