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ORIGINAL RESEARCH ARTICLE

Cardiac reverse remodelling and health status in patients with chronic heart failure

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Abstract

Aims This study aims to assess long-term changes in left ventricular ejection fraction (LVEF) together with echocardiographic markers of cardiac remodelling and their association with prognosis and patient-reported quality of life (QoL).

Methods and results We conducted a retrospective analysis of serial echocardiograms performed between January 2009 and December 2019 in 1089 patients (median age 63 years, 71.0% men) enrolled in the Mazankowski Heart Function Clinic Registry who had at least two echocardiograms separated by ≥12 months. We classified the patients into four subgroups by their baseline and LVEF trajectories: persistent heart failure with reduced ejection fraction (persistent HFrEF, *n* = 364), recovered ejection fraction (HFrecEF, *n* = 325), transient recovery in ejection fraction (HFtrecEF, *n* = 117), and preserved ejection fraction (HFpEF, *n* = 283); 4490 echocardiograms were included in the present analysis, with 4.1 ± 1.8 echocardiograms available per patient during follow-up. Reductions in echocardiographic markers of cardiac remodelling, including LVIDd [adjusted odds ratio (aOR): 2.22, 95% confidence interval (CI) 1.75–2.86], LVIDs (aOR: 2.44, 95% CI 2.00–2.94), left ventricular mass index (aOR: 1.15, 95% CI 1.09–1.22), E/e′ ratio (aOR: 1.15, 95% CI 1.02–1.30), left atrial volume index (aOR: 1.10, 95% CI 1.03–1.16), along with an increase in the maximum recommended daily dose of renin-angiotensin system inhibitors (aOR: 1.04, 95% CI 1.01–1.07) and mineralocorticoid-receptor antagonists (aOR: 1.06, 95% CI 1.01–1.11) at 2 years, strongly predicted the HFrecEF classification, which was further sustained at 5 years of follow-up. However, changes in these parameters were mostly absent in patients experiencing only a transient recovery in LVEF (HFtrecEF), closely resembling patients with persistent HFrEF. In the multivariable analysis, HFrecEF patients had lower risk of all-cause mortality alone [adjusted hazard ratio (aHR): 0.46, 95% CI 0.23–0.93], and composite all-cause (aHR: 0.59, 95% CI 0.49–0.73), cardiovascular (aHR: 0.47, 95% CI 0.36–0.61), and heart failure (aHR: 0.50, 95% CI 0.35–0.70) related hospitalizations with mortality than patients with persistent HFrEF. QoL assessed through the shortened Kansas City Cardiomyopathy Questionnaire-12 at the end of follow-up was greater in patients with HFrecEF by 5.2, 12.4, and 9.4 points than persistent HFrEF, HFtrecEF, and HFpEF, respectively.

Conclusions Patients with HFrecEF experienced progressive normalization in echocardiographic markers of cardiac remodelling characterized by reductions in left ventricular dimensions and mass in tandem with reductions in left atrial volume and E/e′ ratio, which is associated with better prognosis and QoL.

Keywords Reverse remodelling; Heart failure with reduced ejection fraction; Heart failure with recovered ejection fraction; Kansas City Cardiomyopathy Questionnaire; Prognosis

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Introduction

Left ventricular ejection fraction (LVEF) is an essential parameter for diagnosis, prognostication, classification, management, and surveillance of patients with heart failure (HF).[1] Recovery of LVEF is observed in 10% to 40% (depending on the definition used) of patients with heart failure with reduced ejection fraction (HFrEF),[2–6] and this population is

often referred to as heart failure with recovered ejection fraction (HFrecEF). However, whether this reflects true myocardial recovery remains speculative as recurrence of HF events and relapse in symptoms following the withdrawal of evidence-based medical therapies is prevalent, despite the normalization in LVEF.[7]

Left ventricular ejection fraction recovery is frequently associated with cardiac reverse remodelling marked by the restoration of left ventricular (LV) geometry and global cardiac function accompanied by biomarker, neuroendocrine, genomic, molecular, and cellular changes in settings of optimal medical and device therapies.[5,6,8–10] Patients with HFrecEF experience better prognosis compared with those with persistent HFrEF and heart failure with preserved ejection fraction (HFpEF).[2–5] Furthermore, the trajectories of LVEF in patients with HFrEF remain dynamic, reflective of progression along the HF spectrum, with deteriorations in LVEF following initial recovery observed in a substantial proportion of patients.[11,12] By estimate, approximately 16% of patients with initial recovery in LVEF experience subsequent deteriorations within 1 year.[13]

Accordingly, there is a need to further differentiate HFrecEF from persistent HFrEF and patients experiencing only a transient recovery in LVEF to inform clinical management consistent with the heterogeneity of HF.[6] In this study, we characterized the longitudinal trajectories of echocardiographic parameters associated with cardiac remodelling through serial and detailed evaluation of echocardiograms to delineate the natural history of patients with HFrecEF and understand factors influencing divergent trajectories in LVEF. We further complement these findings with long-term clinical outcomes and quality of life (QoL) assessments from a comprehensive outpatient-based heart function registry at an urban tertiary-care academic centre.

Methods

Study population and design

Since February 2018, 1385 consecutive outpatients with documented cardiologist diagnosed HF visiting the Heart Function Clinic (HFC) at the Mazankowski Alberta Heart Institute (Canada) were enrolled into a prospective HFC registry. The HFC is a tertiary referral centre in Alberta, Canada, with a catchment of approximately two million adults utilizing a specialized multidisciplinary care approach for HF management. All enrolled patients had either pre-existing HF already followed by the HFC or new-onset HF. Patients were followed according to the usual standard-of-care (i.e. without specific treatment algorithms) with QoL assessments conducted using the shortened Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at enrolment and during scheduled follow-ups.[14] There were no specific exclusion criteria identified, except for patients must be ≥18 years of age. Our study was conducted in accordance with the ethical principles of the Declaration of Helsinki with approval from the University of Alberta Health Research Ethics Board (Pro00077124). Written informed consent was obtained from all participants.

Utilizing the HFC registry, we analysed serial 2D echocardiograms performed over 10 years between January 2009 and December 2019 through review of individual electronic medical records. For the present analyses, 1089 patients met the inclusion criteria with ≥2 serial echocardiograms separated by ≥12 months (Supporting Information, *Figure S1*). All echocardiograms examined for this study were performed and interpreted at academic hospitals by certified echocardiographers in accordance with the American Society of Echocardiography guidelines.[15]

Clinical characteristics and outcome assessment

Clinical characteristics, co-morbidities, and risk profiles at baseline were collected through accessing the linked healthcare administrative databases available through Alberta Health Services using the International Classification of Diseases, Tenth Revision codes, Canada (ICD-10-CA) obtained from all hospitalization records in the 4 years prior to the index date (date of the first echocardiogram) as we have carried out previously.[2,16] Individual review of electronic medical records was conducted for patient demographics, primary HF aetiology, and device therapies. ICD-10-CA coding in Alberta has been validated with a positive predictive value >75% and specificity >98% for cardiovascular (CV) conditions.[17] Medication dispensation records and dosages were obtained from the Alberta Pharmaceutical Information Network (capturing details regarding all medication dispensations from community pharmacies within the province since 2008)[18] (Supporting Information, *Table S1*). Clinical outcomes, including all-cause, CV, and HF hospitalizations, were examined together with all-cause mortality, which were obtained from the Discharge Abstract Database and the Provincial Registry database, respectively.

Heart failure classifications

Using baseline and serial echocardiograms, patients were classified based on the working definition proposed by the *JACC* scientific expert panel as (i) persistent HFrEF, if LVEF was persistently <40%, (ii) HFrecEF, if baseline LVEF was <40%, but improved to >40% in serial evaluations, concurrent with an ≥10% absolute improvement in LVEF, and maintained throughout the study (iii) heart failure with transient recovery in ejection fraction (HFtrecEF), if patients experienced a transient recovery in LVEF from <40% to >40%,

concurrent with an ≥10% absolute improvement in LVEF but subsequently deteriorated back to <40% within the study period, (iv) HFpEF, if baseline LVEF is ≥50% with no previous documentation of LVEF <50%.[6] Patients with mid-range ejection fraction (i.e. LVEF 40–49%) were excluded from the current analysis based on the heterogenous LVEF trajectories in this patient cohort (Supporting Information, *Figure S2*).[19] All echocardiograms included in the study were individually reviewed by two members of the study team for verification of patient classification. The mean LVEF value was used for analyses if LVEF was reported as a range.

Statistical analysis

Descriptive statistics were presented as medians with interquartile range (IQR) or mean with standard deviation for continuous data, and between-group comparisons were made using the non-parametric Mann–Whitney *U* or Kruskal–Wallis test when appropriate. Categorical data were presented as absolute numbers with percentages and compared using the χ^2 or Fisher's exact test when appropriate. The longitudinal trajectories in echocardiographic parameters and medication dosages were analysed by loess (locally weighted error sum of squares) curves with 95% confidence intervals (CI) fitted across the pre-defined study cohorts as a non-parametric depiction of changes over time. Linear mixed effect models were used to compare the echocardiographic and medication dosage trajectories in patients across the four HF subcohorts based on pre-specified classifications.

For predictors of LVEF trajectories, multinomial logistic regression was performed for the association between echocardiographic parameters including left ventricular internal diameter end diastole (LVIDd), left ventricular internal diameter end systole (LVIDs), left ventricular mass index (LVMI), E/e′ ratio, left atrial volume index (LAVI), and HF medication dosages through the percentage maximum recommended daily dose (MRDD) with HF classifications. The estimation models were adjusted for age, sex, HF aetiology, diabetes, atrial fibrillation, Charlson co-morbidity index, hospital frailty risk scores, use of HF medications [renin-angiotensin system inhibitors (RASi), mineralocorticoid receptor antagonists (MRA), beta-blockers], K^+ levels, and eGFR. Rates of missingness of data during follow-up were ≤4% for most variables including LVIDd, LVIDs, LVMI, and LAVI, except for E/e′ ratio (missing for 24% of patients). Multiple imputation by chained equations (MICE) algorithm was utilized for imputation of missing predictor values at both 2 and 5 years to minimize the impact of missing data during longitudinal follow-up.[20] First, missing values were replaced with the means of the non-missing values as a place holder. Subsequently, the place holder value was replaced with the results of a regression with the missing value as a dependent variable with the non-missing values as an independent variable. This process was then repeated for each missing value.

Clinical outcomes amongst HF cohorts were compared using the Kaplan–Meier curve and log-rank test over 10 years. Multivariable Cox regression analyses were performed to assess association between HF classifications and changes in echocardiographic parameters with subsequent clinical outcomes. Patients were followed until death or appropriately censored at the end of the study. We adjusted for age, sex, HF aetiology, diabetes, atrial fibrillation, Charlson co-morbidity index, hospital frailty risk scores, and the use of HF medications in this model. KCCQ-12 scores were derived from physical limitations, symptom burdens, social limitations, and QoL domains and summarized to a scale ranging from 0 to 100. Time-varying component of KCCQ-12 from follow-up duration was adjusted for using a multivariable general linear model for between group comparisons. Statistical significance was considered based on two-tailed $P < 0.05$. All statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, New York) and R 3.6.1 (Vienna, Austria).

Results

Baseline characteristics

Amongst the 1089 patients eligible for analyses, we identified four distinct HF cohorts according to our pre-specified classifications. At index echocardiogram, 283 (26.0%) patients had preserved LVEF (≥50%), and 806 patients (74.0%) had reduced LVEF (<40%). Evaluation of serial echocardiograms revealed 364 patients (33.4%) as having persistent HFrEF (median follow-up time of 6.6 years, IQR: 3.4–8.9 years), 325 patients (29.8%) as HFrecEF (5.5 years, IQR: 3.0–8.3 years), and 117 (10.7%) patients as HFtrecEF (7.8 years, IQR: 5.7–9.2 years). A total of 4490 echocardiograms were included in the present analysis (Supporting Information, *Figure S3*). Overall, 4.1 ± 1.8 echocardiograms were available per patient during follow-up, with HFrEF, HFrecEF, HFtrecEF, and HFpEF, having 4.0 ± 1.8, 3.8 ± 1.8, 5.4 ± 1.7, and 4.1 ± 1.8 echocardiograms per patient, respectively (Supporting Information, *Figure S4*). Patients with HFrecEF were characterized by being younger ($P = 0.007$), more likely to be women ($P = 0.03$) with non-ischaemic HF aetiology ($P < 0.001$), better renal function based on eGFR ($P = 0.001$), lower baseline BNP levels ($P = 0.009$), more prescription of MRA ($P = 0.003$), with less prescription of warfarin ($P = 0.001$) and nitrates ($P < 0.001$) compared with patients with persistent HFrEF (*Table* 1). Moreover, HFrecEF tended to have higher prevalence of atrial fibrillation ($P = 0.04$), lower prevalence of diabetes ($P = 0.02$), coronary artery diseases ($P < 0.001$), and an overall lower frailty score

($P = 0.04$) and co-morbidity index ($P < 0.001$). In comparison, patients with HFtrecEF closely resembled those with persistent HFrEF in demographic and clinical characteristics (*Table* 1). Prescription of angiotensin receptor neprilysin inhibitor ($P < 0.001$) and ICD implantation ($P < 0.001$) occurred more frequently in patients with persistent HFrEF and HFtrecEF than in HFrecEF during follow-up.

Trajectories in echocardiographic parameters and heart failure medication dosages

Incidence of cardiac reverse remodelling was only evident in patients with HFrecEF, which is associated with a sustained rise in LVEF over the study period (*Figure 1* and Supporting Information, *Figure S5*). Between baseline and 2 years, LVEF improved by 20.1% (IQR: 10.1–27.5%, $P < 0.001$), LVIDd decreased by 0.5 cm (IQR: 0.1–1.0 cm, $P < 0.001$), LVIDs decreased by 0.8 cm (IQR: 0.3–1.6 cm, $P < 0.001$), LVMI decreased by 17.5 g/m^2 (IQR: 0.2–37.8 g/m^2, $P < 0.001$), LAVI decreased by 5.2 mL/m^2 (IQR: 2.0–12.5 mL/m^2, $P < 0.001$), and E/e′ ratio decreased by 2.3 (IQR: 0.7–6.1, $P < 0.001$) in patients with HFrecEF. For HFtrecEF, only a reduction in LVIDs was observed at 2 years associated with the transient improvement in LVEF. As depicted in *Figure 1*, trajectories in echocardiographic parameters of remodelling were mostly absent or worsened over time in persistent HFrEF and HFtrecEF cohorts, with similar trends observed for the HFpEF cohort.

We next assessed dosages of RASi, MRA, and beta-blockers at baseline and overtime. As shown in *Figure 2*, HFrecEF received a higher %MRDD of RASi and MRA than patients with persistent HFrEF or HFtrecEF. At 2 years, RASi MRDD was 74% vs. 62% vs. 63% for HFrecEF, persistent HFrEF, and HFtrecEF, respectively ($P < 0.001$), and MRA MRDD was 59% vs. 50% vs. 49% ($P < 0.001$); the difference was further maintained at 5 years. In contrast, up-titration of beta-blockers occurred simultaneously and to a comparable extent across the cohorts (*Figure 2* and Supporting Information, *Figure S6*).

Predictors for left ventricular ejection fraction trajectories

After adjusting for relevant clinical covariates, lower LVIDd, LVIDs, and LAVI at baseline remained as independent predictors for HF classifications (*Table* 2). Reduction in LVIDd, LVIDs, LVMI, E/e′ ratio, and LAVI, concurrent with an increase in RASi, MRA, but not beta-blocker %MRDD at both 2 and 5 years served as independent predictors for patients with HFrecEF compared with persistent HFrEF. In contrast, only a reduction in LVIDs at 2 years was characteristic of HFtrecEF compared with persistent HFrEF, while changes or a lack of change in other echocardiographic parameters of cardiac remodelling and HF medication dosages were comparable between the two cohorts.

Clinical and patient self-reported outcomes

During a median follow-up of 6.6 years (IQR: 3.6–9.0 years), 796 patients (73.1%) had an all-cause hospitalization or mortality, 542 patients (49.8%) experienced CV hospitalization or mortality, while 352 patients (32.3%) had HF hospitalization or mortality. Overall, patients with HFrecEF experienced significantly less events than patients with persistent HFrEF, HFtrecEF and HFpEF (*Figure 3A*). Adjusted hazard ratios for adverse events vs. persistent HFrEF were 0.46 (0.23–0.93), $P = 0.03$ for all-cause mortality alone, 0.59 (0.49–0.73), $P < 0.01$ for all-cause hospitalization, 0.47 (0.36–0.61), $P < 0.001$ for CV-related hospitalization and 0.50 (0.35–0.70), $P < 0.001$ for HF-related hospitalization or mortality (*Figure 3B*). However, patients with only a transient LVEF recovery in the HFtrecEF cohort experienced comparable event rates as patients with persistent HFrEF throughout the assessed outcomes (*Figure 3B*). Furthermore, reduction in LVIDd and LVIDs at 2 and 5 years was associated with lower risks for all three composite outcomes in the multivariable analysis (*Figure 4* and Supporting Information, *Table S2*). While an increase in LVEF, and reduction in LVMI were independent predictors of lower CV and HF hospitalization with mortality at 2 years.

Patients in the HFrecEF cohort reported better QoL at the end of study follow-up, with the highest KCCQ-12 scores (80, IQR: 57–94), $P = 0.02$, whereas patients in persistent HFrEF (75, IQR: 55–90), HFtrecEF (68, IQR: 51–86) and HFpEF (71, IQR: 48–90) cohorts reported a much poorer QoL (*Figure 3C*).

Discussion

In our examination of longitudinal trajectories in echocardiographic parameters for 1089 patients with HF, we found that 40% of those with HFrEF at baseline experienced a sustained recovery in LVEF, while another 15% exhibited only a transient recovery in LVEF, with subsequent deterioration to LVEF <40% (the HFtrecEF cohort). The distinguishing feature separating HFrecEF with patients having persistent HFrEF or HFtrecEF is the presence of cardiac reverse remodelling as characterized by a progressive reduction in LVIDd, LVIDs, LVMI, E/e′ ratio, and LAVI. Importantly, patients with HFtrecEF did not manifest a reduction in LVIDd and LVMI, indicative of ongoing injury and adverse LV remodelling, which highlights the importance of assessing related cardiac parameters in addition to LVEF. Furthermore, our findings support the utility of serial evaluations in delineating trajectories of echocardiographic parameters associated with cardiac

Table 1 Patient baseline characteristics and management during follow-up (n = 1089)

	Overall (n = 1089)	Persistent HFrEF (n = 364)	HFrecEF (n = 325)	HFtrecEF (n = 117)	HFpEF (n = 283)
Demographics					
Age (years)	63 (54–72)	62 (54–71)	57 (51–68)	61 (53–69)	68 (59–77)
Sex (% male)	773/1089 (71.0)	282/364 (77.5)	231/325 (71.1)	96/117 (82.1)	164/283 (58.0)
Aetiology					
IHD	374/1089 (34.3)	202/364 (55.5)	82/325 (25.2)	46/117 (39.3)	44/283 (15.5)
Non-IHD	715/1089 (65.7)	162/364 (44.5)	243/325 (74.8)	71/117 (60.7)	239/283 (84.5)
Echocardiography					
LVEF (%)	32.5 (25.0–50.0)	30.0 (22.5–36.9)	27.5 (21.8–33.1)	27.5 (22.5–32.5)	57.5 (54.5–61.2)
IVIDd (cm)	5.6 (5.0–6.2)	5.9 (5.4–6.5)	5.8 (5.3–6.4)	5.8 (5.3–6.4)	4.8 (4.4–5.3)
IVIDs (cm)	4.4 (3.6–5.2)	4.9 (4.2–5.6)	4.7 (4.2–5.3)	4.7 (4.2–5.2)	3.1 (2.7–3.7)
LVMI (g/m^2)	110.6 (90.8–135.4)	118.3 (98.4–142.4)	117.8 (95.6–140.9)	109.4 (90.4–135.0)	94.3 (78.0–115.5)
E-wave velocity (m/s)	84.9 (65.4–104.1)	84.4 (65.4–101.1)	83.9 (62.5–104.6)	81.3 (64.8–100.0)	87.3 (69.3–110.0)
E/A ratio	1.2 (0.8–1.9)	1.4 (0.8–2.0)	1.2 (0.8–1.8)	1.2 (0.8–1.9)	1.1 (0.8–1.5)
e′ velocity (m/s)	6.6 (5.3–8.3)	6.5 (5.0–7.8)	6.5 (5.1–8.2)	6.4 (5.2–8.0)	7.4 (5.8–10.0)
E/e′ ratio	12.5 (9.2–16.5)	13.4 (10.2–17.7)	12.5 (9.0–16.5)	12.3 (9.1–15.0)	11.2 (8.7–15.1)
LAVI (mL/m^2)	34.7 (26.6–44.9)	37.0 (28.1–47.3)	35.0 (26.9–44.2)	35.0 (27.8–49.1)	32.1 (24.1–40.4)
Laboratory tests					
BNP (pg/mL)	548 (221–1086)	759 (379–1213)	478 (221–1157)	588 (232–1253)	285 (118–602)
Cholesterol (mmol/L)	4.08 (3.43–4.97)	3.89 (3.28–4.86)	4.12 (3.48–5.01)	3.92 (3.23–4.91)	4.32 (3.56–5.12)
eGFR (mL/min/1.73 m^2)	63 (57–78)	61 (57–75)	67 (58–82)	59 (55–71)	60 (57–76)
Creatinine (μmol/L)	97 (81–112)	103 (83–113)	92 (78–110)	108 (87–115)	92 (77–108)
Haemoglobin (g/L)	137 (123–150)	137 (121–149)	139 (126–152)	138 (125–150)	136 (120–149)
Non-HDL (mmol/L)	2.89 (2.26–3.84)	2.79 (2.17–3.82)	3.16 (2.40–3.82)	2.71 (2.16–3.85)	2.90 (2.31–3.86)
Sodium (mmol/L)	139 (137–141)	139 (137–140)	139 (137–140)	139 (137–140)	140 (138–141)
Potassium (mmol/L)	4.2 (4.0–4.5)	4.3 (4.0–4.5)	4.2 (4.0–4.5)	4.2 (4.0–4.5)	4.2 (4.0–4.5)
Baseline medications					
ACEI	768/1044 (73.6)	273/345 (79.1)	257/313 (82.1)	89/113 (78.8)	149/276 (54.0)
%MRDD	50.0 (37.5–100.0)	50.0 (31.3–87.5)	56.3 (37.5–100.0)	50.0 (37.5–100.0)	75.0 (50.0–100.0)
ARB	214/1041 (20.6)	64/343 (18.7)	65/312 (20.8)	29/113 (25.7)	56/276 (20.3)
%MRDD	50.0 (25.0–72.9)	50.0 (25.0–50.0)	50.0 (25.0–66.7)	33.3 (25.0–100.0)	50.0 (50.0–94.9)
MRA	494/1074 (46.0)	191/362 (52.8)	206/322 (64.0)	55/117 (47.0)	42/276 (15.2)
%MRDD	50.0 (37.5–50.0)	50.0 (35.4–50.0)	50.0 (37.5–50.0)	50.0 (50.0–50.0)	50.0 (37.5–75.0)
Beta-blocker	916/1074 (85.3)	328/362 (90.6)	298/322 (92.5)	104/117 (88.9)	186/276 (67.4)
%MRDD	50.0 (25.0–64.6)	37.5 (25.0–56.8)	50.0 (25.0–69.5)	45.8 (25.0–58.3)	50.0 (25.0–69.7)
Digoxin	115/1082 (10.6)	31/364 (8.5)	39/325 (12.0)	22/117 (18.8)	23/276 (8.3)
Loop diuretics	772/1082 (71.3)	264/364 (72.5)	261/325 (80.3)	88/117 (75.2)	159/276 (57.6)
NOAC	179/1082 (16.5)	49/364 (13.5)	63/325 (19.4)	20/117 (17.1)	47/276 (17.0)
Warfarin	298/1082 (27.5)	114/364 (31.3)	66/325 (20.3)	37/117 (31.6)	81/276 (29.3)
Nitrate	246/1082 (22.7)	115/364 (31.6)	55/325 (16.9)	27/117 (23.1)	50/276 (18.1)
Implantable devices					
Pacemaker	41/1089 (3.8)	10/364 (2.7)	14/325 (4.3)	6/117 (5.1)	11/283 (3.9)
ICD	68/1089 (6.2)	30/364 (8.2)	23/325 (7.1)	9/117 (7.7)	6/283 (2.1)
CRT-D	9/1089 (0.8)	6/364 (1.6)	2/325 (0.6)	1/117 (0.9)	0/283 (0.0)
Medical history					
Hypertension	621/1085 (57.2)	207/360 (57.5)	177/325 (54.5)	75/117 (64.1)	162/283 (57.2)
Diabetes	358/1085 (33.0)	129/360 (35.8)	89/325 (27.4)	45/117 (38.5)	95/283 (33.6)
CAD	588/1085 (54.2)	247/360 (68.6)	168/325 (51.7)	68/117 (58.1)	105/283 (37.1)
CVD	95/1085 (8.8)	40/360 (11.1)	21/325 (6.5)	9/117 (7.7)	25/283 (8.8)

(*Continues*)

Table 1 (continued)

	Overall (n = 1089)	Persistent HFrEF (n = 364)	HFrecEF (n = 325)	HFtrecEF (n = 117)	HFpEF (n = 283)
Atrial fibrillation	373/1085 (34.4)	100/360 (27.8)	111/325 (34.2)	49/117 (41.9)	113/283 (39.9)
VA	116/1085 (10.7)	48/360 (13.3)	36/325 (11.1)	15/117 (12.8)	17/283 (6.0)
CKD	241/1085 (22.2)	83/360 (23.1)	75/325 (23.1)	26/117 (22.2)	57/283 (20.1)
Cancer	272/1085 (25.1)	90/360 (25.0)	78/325 (24.0)	26/117 (22.2)	78/283 (27.6)
COPD	233/1085 (21.5)	80/360 (22.2)	74/325 (22.8)	30/117 (25.6)	49/283 (17.3)
Anxiety/depression	113/1085 (10.4)	40/360 (11.1)	33/325 (10.2)	12/117 (10.3)	28/283 (9.9)
Dyslipidaemia	396/1085 (36.5)	150/360 (41.7)	99/325 (30.5)	47/117 (40.2)	100/283 (35.3)
Valvular disease	170/1085 (15.7)	45/360 (12.5)	48/325 (14.8)	23/117 (19.7)	54/283 (19.1)
Anaemia	150/1085 (13.8)	56/360 (15.6)	27/325 (8.3)	15/117 (12.8)	52/283 (18.4)
Risk profile					
Hospital frailty risk score	2 (1–3)	2 (1–4)	2 (1–3)	2 (1–4)	2 (1–3)
Charlson co-morbidity index	1.8 (0.0–6.6)	1.9 (0.0–7.4)	0.8 (0.0–4.1)	1.8 (0.0–7.8)	3.3 (0.0–9.2)
Management (follow-up)					
Medications					
ACEI	574/1089 (52.7)	182/364 (50.0)	201/325 (61.8)	60/117 (51.3)	131/283 (46.3)
%MRDD	50.0 (50.0–100.0)	50.0 (31.3–100.0)	100.0 (50.0–100.0)	50.0 (50.0–100.0)	50.0 (43.8–100.0)
ARB	179/1089 (16.4)	51/364 (14.0)	59/325 (18.2)	18/117 (15.4)	51/283 (18.0)
%MRDD	50.0 (25.0–50.0)	25.0 (12.5–50.0)	50.0 (25.0–70.9)	29.2 (25.0–50.0)	50.0 (25.0–75.0)
ARNI	189/1089 (17.4)	100/364 (27.4)	49/325 (15.1)	29/117 (24.8)	11/283 (3.9)
%MRDD	50.0 (25.0–50.0)	25.0 (25.0–50.0)	50.0 (25.0–50.0)	50.0 (25.0–50.0)	50.0 (25.0–50.0)
MRA	640/1089 (58.8)	255/364 (70.1)	207/325 (63.7)	75/117 (64.1)	103/283 (36.4)
%MRDD	50.0 (50.0–50.0)	50.0 (50.0–50.0)	50.0 (50.0–50.0)	50.0 (50.0–50.0)	50.0 (50.0–50.0)
Beta-blocker	973/1089 (89.3)	343/364 (94.2)	309/325 (95.1)	110/117 (94.0)	211/283 (74.6)
%MRDD	50.0 (25.0–100.0)	50.0 (25.0–100.0)	50.0 (37.5–100.0)	50.0 (25.0–100.0)	50.0 (25.0–100.0)
Digoxin	80/1089 (7.3)	30/364 (8.2)	20/325 (6.2)	14/117 (12.0)	16/283 (5.7)
Loop diuretics	647/1089 (59.4)	216/364 (59.3)	176/325 (54.2)	77/117 (65.8)	178/283 (62.9)
NOAC	363/1089 (33.3)	105/364 (28.8)	98/325 (30.2)	45/117 (38.5)	115/283 (40.6)
Warfarin	143/1089 (13.1)	58/364 (15.9)	25/325 (7.7)	16/117 (13.7)	44/283 (15.5)
Nitrate	205/1089 (18.8)	90/364 (24.7)	48/325 (14.8)	26/117 (22.2)	41/283 (14.5)
Implantable devices					
Pacemaker	138/1089 (12.7)	48/364 (13.2)	27/325 (8.3)	13/117 (11.1)	50/283 (17.7)
ICD	225/1089 (20.7)	120/364 (33.0)	54/325 (16.6)	33/117 (28.2)	18/283 (6.4)
CRT-D	69/1089 (6.3)	43/364 (11.8)	19/325 (5.8)	6/117 (5.1)	1/283 (0.4)

Values are given as n (%) or median (interquartile range). Medication doses as % of maximum recommended daily dose (MRDD) shown in parentheses.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillation; CVD, cerebrovascular disease; E, peak mitral inflow during passive filling in early diastole; e', mitral annular velocity during early diastole; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; ICD, implantable cardioverter-defibrillator; IHD, ischaemic heart disease; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; RVD, right ventricular dysfunction; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VA, ventricular arrhythmia.

Figure 1 Long-term trajectories of echocardiographic parameters across heart failure cohorts including persistent HFrEF, HFrecEF, HFtrecEF, and HFpEF depicted by loess curves with 95% confidence intervals. (A) LVEF, $P < 0.001$ for changes in trajectories amongst HF cohorts; (B) LVIDd, $P < 0.001$; (C) LVMI, $P < 0.001$; (D) LVIDs, $P < 0.001$; (E) LAVI, $P < 0.001$; (F) E/e′ ratio, $P = 0.003$. HFrecEF is associated with a sustained increase in LVEF over the 10 year period, accompanied by reduction in LVIDd, LVMI, LVIDs, LAVI, and E/e′ ratio which is most apparent within the first 2 years.

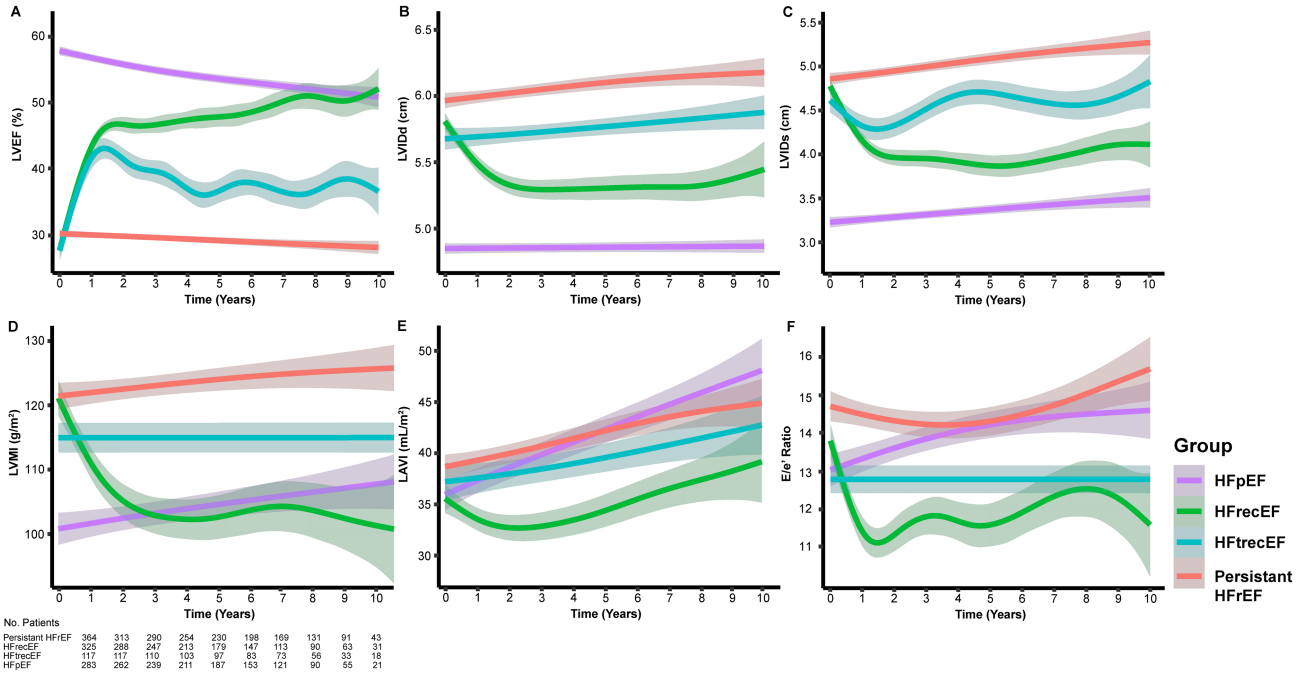
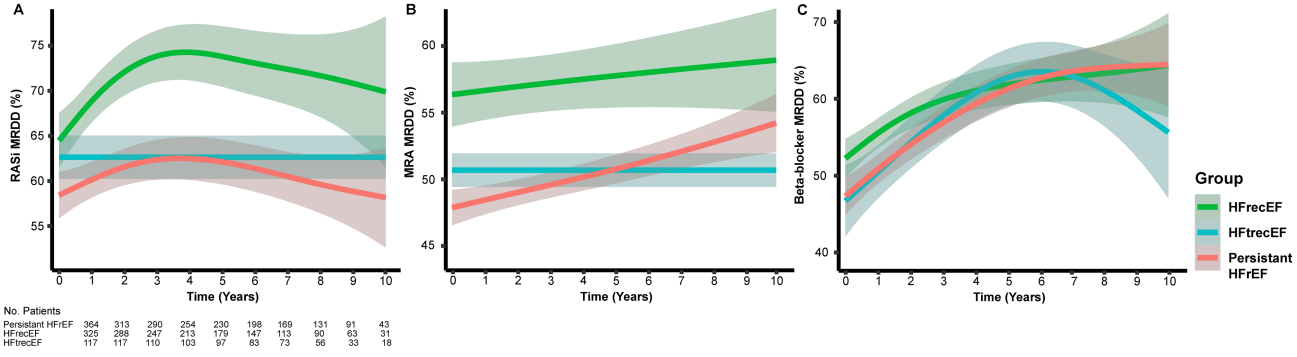


Figure 2 Long-term trajectories of maximum recommended daily dose expressed as percentages of guideline-based medical therapies for HFrEF depicted by loess curves with 95% confidence intervals. (A) Renin-angiotensin system inhibitors (RASi), $P = 0.001$ for changes in trajectories amongst HF cohorts; (B) Mineralocorticoid receptor antagonists (MRA); (C) beta-blockers.



reverse remodelling in the prognostication and management of patients with HFrEF.

We found that patients more likely to experience sustained LVEF recovery are younger, more likely to be female and to have non-ischaemic aetiology, preserved renal function, lower BNP levels with a greater presence of modifiable conditions such as atrial fibrillation, accompanied by an overall lower burden of co-morbidities, which has been shown in several other studies as well.[2–5,21] However, the link to cardiac reverse remodelling has not been established in the HFrecEF population. Lupón *et al*. reported in 304 consecutive patients with HF, younger age (OR: 0.98, 95% CI 0.96–1.00), non-ischaemic aetiology (OR: 5.13, 95% CI 3.07–8.57), and lower NT-proBNP levels (OR: 0.74, 95% CI 0.61–0.91) predicted reverse remodelling after 1 year in an univariate analysis.[22] Non-ischaemic aetiology (aOR: 4.70,

Table 2 Predictive value of echocardiographic parameters and % maximum recommended daily dose of heart failure medical therapy in classification of patients as HFrecEF and HFtrecEF compared with persistent HFrEF

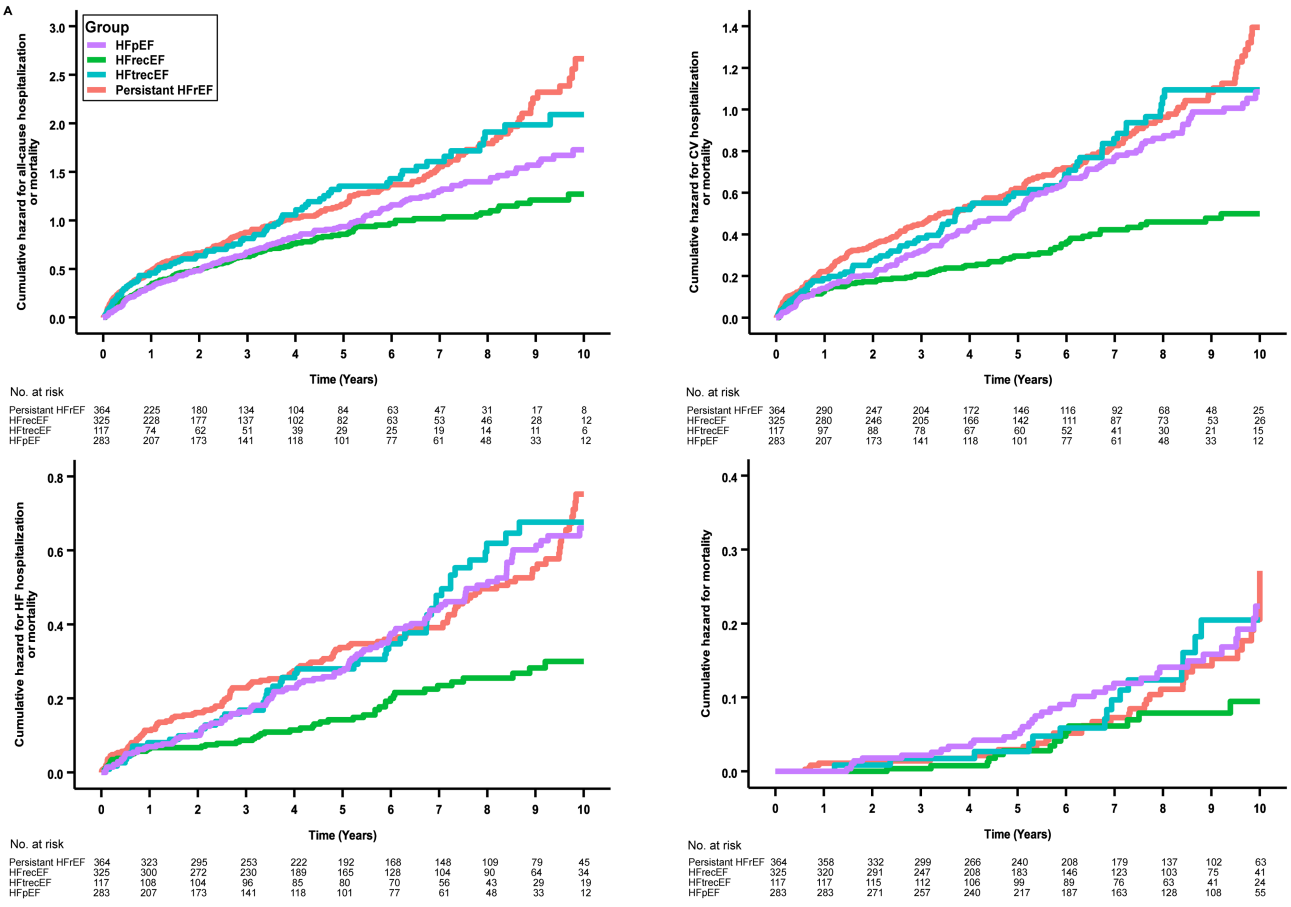
	Baseline		2 years		5 years	
Parameter	aOR (95% CI)	*P*	aOR (95% CI)	p	aOR (95% CI)	*P*
LVEF (per 5% increase)						
HFrecEF	0.96 (0.87–1.05)	0.39	2.11 (1.89–2.36)	<0.001	1.88 (1.70–2.07)	<0.001
HFtrecEF	0.91 (0.81–1.03)	0.15	1.76 (1.56–1.99)	<0.001	1.37 (1.24–1.52)	<0.001
LVIDd (per 1 mm decrease)						
HFrecEF	1.49 (1.20–1.82)	<0.001	2.22 (1.75–2.86)	<0.001	2.22 (1.75–2.86)	<0.001
HFtrecEF	1.54 (1.16–2.00)	0.002	1.16 (0.85–1.59)	0.34	1.05 (0.78–1.43)	0.71
LVIDs (per 1 mm decrease)						
HFrecEF	1.35 (1.12–1.61)	0.001	2.44 (2.00–2.94)	<0.001	2.70 (2.17–3.33)	<0.001
HFtrecEF	1.45 (1.15–1.85)	0.002	1.33 (1.03–1.69)	0.03	1.23 (0.97–1.56)	0.08
LVMI (per 10 g/m^2 decrease)						
HFrecEF	1.01 (0.96–1.05)	0.82	1.15 (1.09–1.22)	<0.001	1.16 (1.11–1.22)	<0.001
HFtrecEF	1.11 (1.03–1.19)	0.004	1.01 (0.93–1.07)	0.86	0.98 (0.92–1.04)	0.54
E/e′ ratio (per 5 units decrease)						
HFrecEF	1.10 (0.97–1.23)	0.13	1.15 (1.02–1.30)	0.02	1.23 (1.10–1.37)	<0.001
HFtrecEF	1.27 (1.05–1.52)	0.01	0.88 (0.76–1.03)	0.12	0.96 (0.83–1.12)	0.64
LAVI (per 5 mL/m^2 decrease)						
HFrecEF	1.09 (1.03–1.16)	0.003	1.10 (1.03–1.16)	0.003	1.09 (1.02–1.15)	0.007
HFtrecEF	1.09 (1.00–1.16)	0.04	1.02 (0.94–1.10)	0.62	1.03 (0.96–1.11)	0.39
RASi %MRDD (per 5% increase)						
HFrecEF	1.02 (1.00–1.05)	0.07	1.04 (1.01–1.07)	0.003	1.04 (1.01–1.07)	0.008
HFtrecEF	1.03 (1.00–1.06)	0.13	0.98 (0.95–1.02)	0.29	0.99 (0.96–1.02)	0.39
MRA %MRDD (per 5% increase)						
HFrecEF	1.03 (0.98–1.08)	0.30	1.06 (1.01–1.11)	0.022	1.12 (1.06–1.19)	<0.001
HFtrecEF	1.04 (0.98–1.10)	0.21	0.97 (0.90–1.04)	0.34	0.96 (0.89–1.04)	0.34
Beta-blocker %MRDD (per 5% increase)						
HFrecEF	1.02 (0.99–1.05)	0.23	1.02 (0.99–1.06)	0.17	1.02 (0.99–1.05)	0.30
HFtrecEF	1.00 (0.96–1.04)	0.94	0.99 (0.95–1.03)	0.57	1.00 (0.96–1.03)	0.89

In the multivariate model, age, sex, heart failure (HF) aetiology, diabetes, atrial fibrillation, Charlson co-morbidity index, hospital frailty risk scores, use of HF medications (RASi, MRA, beta-blockers), K^+ levels and eGFR were included for adjustment.
aOR, adjusted odds ratio; CI, confidence interval; E, peak mitral inflow during passive filling in early diastole; e′, mitral annular velocity during early diastole; HFrecEF, heart failure with recovered ejection fraction; HFtrecEF, heart failure with decompensated ejection fraction; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor.

95% CI 1.87–11.93), baseline LVEF (aOR: 0.93, 95% CI 0.88–0.97), HF duration (aOR: 0.82, 95% CI 0.69–0.98), absence of left bundle branch block (aOR: 4.70, 95% CI 1.87–11.93), and soluble ST2 levels (aOR: 0.69, 95% CI 0.50–0.94) were further associated with reverse remodelling in the multivariate analysis. Aimo *et al*. examined sex-based differences in 927 patients with HF reported 41% women and 27% men demonstrated reverse remodelling defined as ≥15% reduction in LVESV after 12 month, with female sex being an independent predictor of reverse remodelling (aOR: 1.54, 95% CI 1.11–2.14).[23] Furthermore, presence of diabetes, chronic kidney disease, and hypertension are associated with cardiac hypertrophy and increased risk for adverse cardiac remodelling.[24] In accordance with the clinical characteristics, incidence of reverse remodelling was observed solely in the HFrecEF cohort, with the greatest magnitude occurring within 2 years following index echocardiogram. Reduction in LV dimensions, myocardial hypertrophy based on LVMI, LAVI, and E/e′ ratio served as independent predictors for the HFrecEF classification, suggesting that evidence of reverse remodelling from serial echocardiographic evaluations could serve as an additional marker for prediction of patients with either transient or sustained recovery in LVEF.

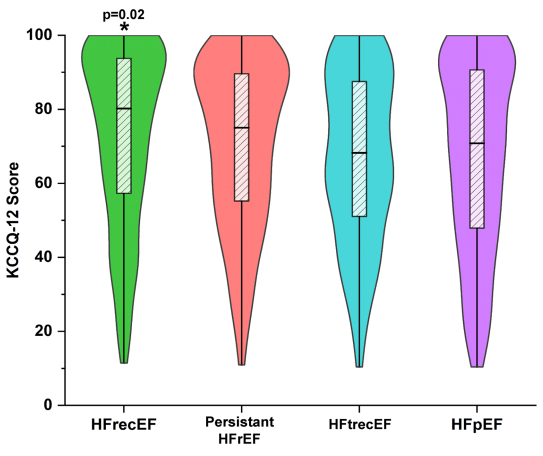
RASi, MRA, and beta-blockers represent the cornerstone of evidence-based guideline directed therapy for HFrEF.[1] Patients with HFrecEF achieved greater %MRDD for RASi and MRA during follow-up, while beta-blockers were up-titrated to a similar extent amongst the HF subtypes. Kramer *et al*. reported an improvement in LVEF accompanied by reductions in LVEDV and LVESV following HF therapy in a meta-analysis of randomized controlled trials, highlighting the pivotal role of medical therapies on reverse remodelling.[10] In the TRED-HF trial, patients with recovered dilated cardiomyopathy experienced adverse LV remodelling upon therapy withdraw as characterized by increased LVMI, cell mass, and reduced LV global longitudinal strain, even in those free from progression in chamber dilation and systolic dysfunction.[25] In our study, a greater ability to further up-titrate RASi and MRA during the clinical course is associated with LVEF recovery and evidence of reverse remodelling in patients with HFrecEF. Interestingly, predictors for the inability to achieve recommended dosages differed between RASi and beta-

Figure 3 Clinical outcomes and patient-reported quality of life according to heart failure (HF) classification. (A) Kaplan–Meier analysis of all-cause mortality alone (log rank $P = 0.09$), all-cause (log rank $P < 0.001$), cardiovascular (log rank $P < 0.001$) and HF-related (log rank $P < 0.001$) hospitalization in composition with mortality. (B) Multivariable Cox regression analysis of composite clinical outcomes adjusting for age, sex, HF aetiology, diabetes, atrial fibrillation, Charlson co-morbidity index, hospital frailty risk scores, and the use of HF medications (RASi, MRA, beta-blockers). (C) Kansas City Cardiomyopathy Questionnaire-12 score assessed at the end of study follow-up amongst HF cohorts. aHR, adjusted hazard ratio; CI, confidence interval.



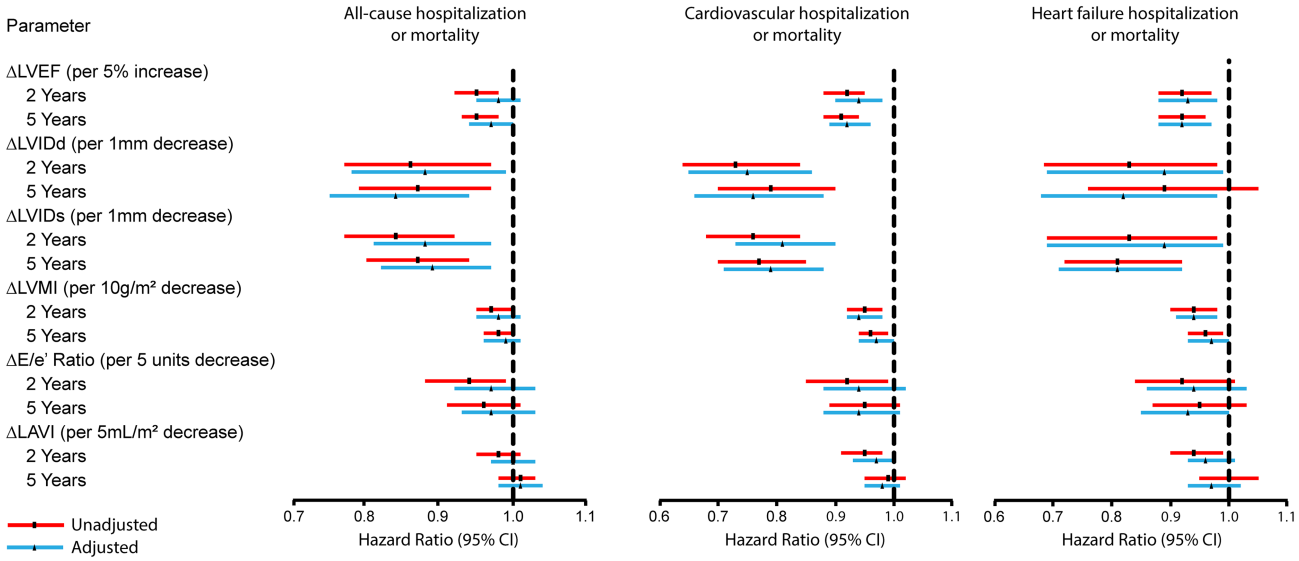
B

	All-cause hospitalization or mortality aHR (95% CI)	CV hospitalization or mortality aHR (95% CI)	HF hospitalization or mortality aHR (95% CI)	All-cause mortality aHR (95% CI)
Persistant HFrEF	Reference	-	-	-
HFrecEF	0.59 (0.49-0.73)	0.47 (0.36-0.61)	0.50 (0.35-0.70)	0.46 (0.23-0.93)
HFtrecEF	0.98 (0.86-1.10)	0.96 (0.84-1.11)	1.01 (0.85-1.19)	0.91 (0.66-1.26)
HFpEF	0.80 (0.64-0.99)	0.94 (0.73-1.21)	0.92 (0.67-1.26)	0.89 (0.50-1.58)



blockers in BIOSTAT-CHF: while women, those with lower BMI and eGFR achieved lower doses of RASi, advanced age, lower heart rate, and diastolic blood pressure were predictors of under-dosing for beta-blockers.[26] Beta-blockers appear to be better tolerated than RASi or MRA,[27] making it possible to achieve higher doses despite

Figure 4 Association between temporal changes in LVEF, LVIDd, LVIDs, LVMI, E/e′ ratio, and LAVI with composite (A) all-cause hospitalization with mortality, (B) cardiovascular hospitalization with mortality, (C) heart failure hospitalization with mortality in patients presenting as HFrEF on index echocardiogram adjusted for age, sex, HF aetiology, diabetes, atrial fibrillation, Charlson co-morbidity index, hospital frailty risk scores, and the use of HF medications (RASi, MRA, beta-blockers). CI, confidence interval.



advanced age and multiple co-morbidities. In context, despite adjusting for relevant demographic and clinical parameters, changes in RASi and MRA %MRDD at 2 and 5 years (but not beta-blockers) remained independent predictors for the HFrecEF classification.

Prognosis of patients with HFrecEF was better than patients with persistent HFrEF. This agrees with previously published studies.[2–5] Patients with HFtrecEF, where only a transient LVEF recovery followed by subsequent deteriorations and lack of reverse remodelling was observed had comparable risks as patients with persistent HFrEF. We found the dynamic changes in LV chamber dimensions (LVIDd and LVIDs) after 2 and 5 years were predictors for all composite outcomes. Moreover, changes in LVEF and LVMI at 2 years demonstrated positive prognostic value for composite CV and HF-related hospitalizations with mortality. Therefore, recovery of LVEF, restoration of LV dimensions, and reduction in myocardial mass in combination contribute towards the better prognosis associated with the HFrecEF cohort. However, the absence of non-reversible myocardial injuries from lower prevalence of ischaemic heart diseases, influence of age, sex, co-morbidity, and frailty burden, along with possible genetic and lifestyle factors, should be considered in delineating the mechanisms leading towards favourable prognosis in HFrecEF.

We are the first to report a greater health-related QoL in patients with HFrecEF than other HF cohorts, even after adjustment for time-varying differences in follow-up duration. Recent analysis of FAIR-HF trial reported the minimal clinically important difference in KCCQ score varies between 0.7 to 4.9 points across the seven domains assessed.[28] In our study, patients with HFrecEF scored 5.2, 12.4, and 9.4 points higher on the KCCQ-12 than patients with persistent HFrEF, HFtrecEF, and HFpEF, respectively. In accordance, Joyce *et al*. found patients with improvement in LVEF to ≥50% from HFrEF reported higher overall QoL scores than patients with persistent HFrEF and HFpEF, and these patients perceived alternative medical or nonmedical factors as dominant contributors to their QoL rather than HF symptoms.[29] Furthermore, in the Alberta HEART cohort, both baseline and changes in KCCQ scores over time were important predictors of cardiovascular outcomes, with changes in LVEF serving as an independent predictor of KCCQ score changes over 12 months.[30] As KCCQ scores are not only associated with HF-related hospitalization and mortality but is also increasingly utilized as outcomes for clinical trials,[31,32] our findings of better QoL in patients with HFrecEF complement the observation of cardiac reverse remodelling and lower risk for hospitalization and mortality in this patient cohort.

The current analysis is limited by its retrospective nature, ascertainment bias (the timing of repeat echocardiograms was at the discretion of the attending physician and not at pre-specified intervals), and survivor bias. As such, serial echocardiograms available for analyses may be influenced by patients' clinical status, which may introduce selection biases especially between patients in the HFtrecEF and HFrecEF cohorts, but also reflects routine clinical practice and management of patients with HF utilizing echocardiography as a non-invasive imaging modality. Furthermore, the detailed time course behind recovery and subsequent

deteriorations cannot be accurately assessed due to time differences between repeat echocardiograms in the present cohort. Additionally, as patients were recruited from a single academic centre, the translatability of our findings may be limited at the population level and subjected to confounding. The present analysis is also limited in the detailed assessments of LV remodelling being unable to distinguish between eccentric and concentric LV hypertrophy derived from different pathophysiology and co-morbid conditions reflected by divergent clinical and biomarker phenotypes, which may translate to variations in the reverse remodelling process and survival benefits associated with up-titration of HF medications.[33] Moreover, despite showing recoveries in LVEF and improvements in LV geometry, patients may still experience persistent subclinical impairment of systolic function reflected through a reduction in global longitudinal strain resulting in subsequent deteriorations in LVEF.[34] Future studies should also examine the relationship between cardiac reverse remodelling with circulating biomarkers to offer mechanistic and therapeutic insights into factors predictive of the sustained LVEF recovery in patients with HFrecEF.

Conclusion

In patients initially presenting with HFrEF, their LVEF trajectory remains dynamic over time with patients having a sustained recovery in LVEF (HFrecEF) having the best 10 year prognosis and QoL. Concurrent assessment of serial echocardiographic parameters associated with cardiac reverse remodelling and changes in patient reported QoL could play a crucial role in prognostication and management of patients with HFrEF.

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Conflict of interest

The authors have no relationships relevant to the contents of this paper to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Heart failure medications and the associated maximum recommended daily dose.
Table S2. Prognostic impacts of temporal changes in echocardiographic parameters.
Figure S1. Study flow chart.
Figure S2. LVEF trajectories in patients with midrange ejection fraction.
Figure S3. Distribution of the number of echocardiograms available for analyses per year.
Figure S4. Distribution of the number of echocardiograms available for analyses per patient.
Figure S5. Temporal changes in echocardiographic parameters across heart failure cohorts presenting as HFrEF on index echocardiogram.
Figure S6. Temporal changes in percentage maximum recommended daily dose of heart failure medical therapies across heart failure cohorts presenting as HFrEF on index echocardiogram.

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